Lung protective ventilation strategy for the acute respiratory distress syndrome (Review)

Petrucci N, Iacovelli W
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Lung protective ventilation strategy for the acute respiratory distress syndrome

Nicola Petrucci¹, Walter Iacovelli²

¹Department of Anaesthesia and Intensive Care, Azienda Ospedaliera Desenzano, Desenzano, Italy. ²Department of Anaesthetics, Azienda Ospedaliera Desenzano, Desenzano, Italy

Contact address: Nicola Petrucci, Department of Anaesthesia and Intensive Care, Azienda Ospedaliera Desenzano, Loc. Montecroce, Desenzano, Brescia, 25015, Italy. n.petrucci@libero.it

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ABSTRACT

Background

Patients with acute respiratory distress syndrome and acute lung injury require mechanical ventilatory support. Acute respiratory distress syndrome and acute lung injury are further complicated by ventilator-induced lung injury. Lung-protective ventilation strategies may lead to improved survival.

Objectives

To assess the effects of ventilation with lower tidal volume on morbidity and mortality in patients aged 16 years or older affected by acute respiratory distress syndrome and acute lung injury. A secondary objective was to determine whether the comparison between low and conventional tidal volume was different if a plateau airway pressure of greater than 30 to 35 cmH₂O was used.

Search strategy

In our original review, we searched databases from inception until 2003. In this updated review, we searched The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library 2006, Issue 3). We updated our search of MEDLINE, EMBASE, CINAHL and the Web of Science from 2003 to 2006. We also updated our search of intensive care journals and conference proceedings; databases of ongoing research, reference lists and ‘grey literature’ from 2003 to 2006.

Selection criteria

We included randomized controlled trials comparing ventilation using either lower tidal volume (VT) or low airway driving pressure (plateau pressure 30 cmH₂O or less), resulting in tidal volume of 7 ml/kg or less versus ventilation that uses VT in the range of 10 to 15 ml/kg, in adults (16 years old or older).

Data collection and analysis

We independently assessed trial quality and extracted data. Wherever appropriate, results were pooled. We applied fixed- and random-effects models.
Main results

We found one new study in this update for a total of six trials, involving 1297 patients, which were eligible for inclusion. Mortality at day 28 was significantly reduced by lung-protective ventilation: relative risk (RR) 0.74 (95% confidence interval (CI) 0.61 to 0.88); hospital mortality was reduced: RR 0.80 (95% CI 0.69 to 0.92); overall mortality was not significantly different if a plateau pressure less than or equal to 31 cm H₂O in control group was used: RR 1.13 (95% CI 0.88 to 1.45). There was insufficient evidence about morbidity and long term outcomes.

Authors' conclusions

Clinical heterogeneity, such as different lengths of follow up and higher plateau pressure in control arms in two trials, make the interpretation of the combined results difficult. Mortality is significantly reduced at day 28 and at the end of hospital stay. The effects on long-term mortality are unknown, although the possibility of a clinically relevant benefit cannot be excluded.

Plain language summary

Patients affected by severe lung failure need a gentler form of mechanical breathing

Critically ill patients affected by severe acute respiratory failure need air to be pumped into their lungs (mechanical ventilation) to survive. Mechanical support buys time for the lungs to heal. Nevertheless, 40 to 50% still die. Several studies suggested that mechanical breathing can also cause lung damage and bleeding. A new lung-protective way of mechanical ventilation was tested in large trials. This systematic review shows that protective ventilation can decrease death in the short term, but the effects in the long term are uncertain or unknown.

Background

Acute respiratory distress syndrome (ARDS) is a common, devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. The first description of ARDS appeared in 1967, when Ashbaugh described 12 patients with acute respiratory distress; cyanosis refractory to oxygen therapy; decreased lung compliance and diffuse infiltrates evident on chest X-ray (Ashbaugh 1967).

Acute lung injury (ALI) is a subset of ARDS with less severe impairment in oxygenation. An estimate by the National Institutes of Health suggested that the annual incidence of ARDS in the USA was 75 per 100,000 population (ARDS Conference 1977). However, a recent study has estimated the incidence of this disease to be between 15 and 34 cases per 100,000 inhabitants per year (Frutos-Vivar 2004). According to a prospective cohort study, the prevalence of ARDS/ALI was about 9% amongst intensive care patients, and 39.6% amongst ventilated patients (Roupie 1999). The mortality rate from ARDS/ALI is approximately 40 to 50% (Lewandowski 1999). There is also short- and long-term morbidity associated with these syndromes. Short-term morbidity leads to a prolonged stay in the intensive care unit and prolonged ventilator dependence (Davidson 1999). Those who survive the illness have a reduced health-related quality of life as well as cognitive impairment and high rates of disability (Dowdy 2006).

Mechanical ventilation (MV) represents the main therapeutic support to maintain acceptable pulmonary gas-exchange whilst treating the underlying disease. Many forms of additional therapies have been considered, including inhaled nitric oxide, prone positioning, and surfactant treatment (Ware 2000). ARDS is known to be associated with abnormal mechanical properties of the respiratory system, with hallmark features of reduction in static compliance (Marini 1990). As a result of this low compliance, high pressures are needed to obtain a sufficient tidal volume. The larger the tidal volume, the higher the pressure required, which may lead to barotrauma, that is, alveolar rupture and radiological evidence of extra-alveolar air. In such patients, mechanical ventilation could lead to injury due to over-distension. This results from the distribution of the increased tidal volume to the high-compliance regions causing stretching and shear forces on the alveolar wall (volutrauma) (Dreyfuss 1998; Parker 1993). Plateau pressure, de-
fined as airway pressure during the end-expiratory pause, roughly reflects the level of alveolar over-distension. Finally, parts of the lung are consolidated, thus not recruitable. This leads to fewer alveoli truly being ventilated; hence, a "normal" tidal volume may not be appropriate for those remaining alveoli.

Animal models demonstrated that, due to the interdependence of alveoli, the fragile lung tissue of non-uniformly expanded lungs is affected not only by applied transpulmonary pressures, but by the shear forces that are present in the interstitium between open and closed alveoli. These shear forces are, to a great extent, responsible for the damage caused by inappropriate modes of artificial ventilation (Parker 1993). Damage caused by MV to the lungs has been termed ventilator induced lung injury (VILI).

Better understanding of the pathophysiology of ARDS and of VILI, along with studies based on animal models, have led to the proposal that airway pressure and tidal volume should be limited in managing the ventilation of ARDS patients (Artigas 1998; Hickling 1990; Hickling 1994). This entails accepting a rise in the arterial partial pressure of carbon dioxide. In addition, cyclic inflation-deflation of injured lung units/alveoli can exacerbate lung injury (Dreyfuss 1998), and medium to high levels of positive end-expiration pressure (PEEP) should be used to keep alveoli open throughout the ventilatory cycle. Overall, this type of approach has been termed lung-protective ventilation strategy (LPVS). The characteristics of LPVS are illustrated in Additional Table 1 (Artigas 1998). Ventilation with lower tidal volumes was also associated with lower levels of systemic inflammatory mediators (Ranieri 1999).

Table 1. Lung protective ventilation strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid distension and barotraumas</td>
<td>Transpulmonary pressure &lt; 30 mmHg/low tidal volume</td>
</tr>
<tr>
<td>Avoid repeated opening/closing of airway</td>
<td>PEEP</td>
</tr>
<tr>
<td>Avoid oxygen toxicity</td>
<td>FiO2 as low as possible</td>
</tr>
</tbody>
</table>

Lowering the tidal volume is possibly not without hazards (Roupie 1995). Severe hypercapnia and acidosis can have adverse effects, including increased intracranial pressure; depressed myocardial contractility; pulmonary hypertension; and depressed renal blood flow (Feihl 1994). The view that these risks are preferable to the higher plateau pressure required to achieve normocapnia represented a substantial shift in ventilatory management.

**OBJECTIVES**

The objective of this systematic review was to compare ventilation with lower tidal volume and ventilation with conventional tidal volume and to determine whether such lung-protective ventilation strategy reduced morbidity and mortality in critically ill adults affected by ALI or ARDS.

**METHODS**

Criteria for considering studies for this review

**Types of studies**
We accepted only randomized, controlled trials (RCTs) to guarantee control of selection bias. We excluded studies that, on closer scrutiny, were determined to be quasi-randomized or cross-over studies.

Types of participants
We included critically ill patients, from 16 years old or older, intubated and ventilated, affected by ARDS or ALI from any cause; and as defined by the North-American-European Consensus Conference on ARDS (NAECC) (Bernard 1994) or by the Lung Injury Severity Score (LISS) (Murray 1988).

Types of interventions
Protective ventilation strategy that used lower tidal volume or low airway driving pressure (plateau 30 cm H₂O or less), or a combination of the two, which resulted in tidal volume of 7 ml/kg or less versus conventional mechanical ventilation that used tidal volume in the range of 10 to 15 ml/kg. Regardless of the strategy used to deliver the interventions, the two study groups had to differ only for the tidal volume, and not for other elements of associated ventilatory strategy. Hypercapnia (as an unavoidable part of the protective ventilation intervention) was accepted as long as the resulting acidosis was controlled and kept within acceptable ranges, and those range were clearly stated.

Types of outcome measures

Primary outcomes
Overall mortality, evaluated at hospital discharge. (If this information was unavailable, mortality was evaluated at the end of the follow-up period scheduled for each trial.)

There is evidence that the cause of death in ARDS is the development of organ failure (Monchi 1998), and that mechanical ventilation might be a factor leading to multiple organ failure (MOF). The duration of mechanical ventilation could also lead to the development of associated infectious diseases that could affect the patients’ overall prognosis, such as ventilator-associated pneumonia (VAP). If mortality is equal, other outcomes become important to the patients such as long-term quality of life and cognitive impairment.

Secondary outcomes
1. development of multi-organ failure;
2. duration of mechanical ventilation and total duration of mechanical support;
3. total duration of stay in intensive care unit and hospital;
4. long-term mortality;
5. long-term health-related quality of life;
6. long-term cognitive outcome;
7. costs.

Search methods for identification of studies
In our original review (Petrucci 2004a) we searched databases from inception until 2003.
In this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2006, Issue 3) (Appendix 1); MEDLINE (2003 to October 2006) (Appendix 2); EMBASE (2003 to October 2006) (Appendix 3); CINAHL (2003 to October 2006) (Appendix 4) and Web of Science (2003 to October 2006), using a combination of MeSH and text words.
We applied no language restrictions.
In addition we hand-searched references lists and abstracts and proceedings of scientific meetings held on the subject.
In our original review, we searched proceedings of the Annual Congress of the European Society of Intensive Care Medicine (ESICM) and of the American Thoracic Society (ATS) from 1993 to 2003. We updated that search to October 2006.
We also searched the following databases: Biological abstracts and Current Contents.
We sought data from unpublished trials and ‘grey’ literature by searching

- The System for Information on Grey Literature in Europe (SIGLE)
- The Index to Scientific and Technical Proceedings (from the Institute for Scientific Information, accessing via BIDS)
- Current Research in Britain (CRIB). This database also includes Nederlanse Onderzoek Databank (NOD), the Dutch current research database
- Web Resources: the meta Register of Controlled Trials (mRCT) (www.controlled-trials.com)

We contacted the original author(s) for clarification about content, study design and missing data, if needed.

Data collection and analysis
We employed the standard methods of The Cochrane Anaesthesia Review Group. We (NP, WI) independently performed trial searches, assessment of methodology and extraction of data, with comparison and resolution of any difference found at each stage. We judged the quality of each trial by whether or not the study design had minimized bias within the scope of the clinical context.
The biases we examined were selection, performance, attrition and detection.
We defined high-quality trials as: controlled, appropriately randomized, having adequate concealment of allocation, and completeness of follow up according to intention-to-treat analysis. We judged the concealment of allocation adequate if the trials took adequate measures to conceal allocation through central randomization, such as serially numbered opaque envelopes or a table of random numbers. We judged the generation of allocation sequence adequate where trials were deemed to have satisfactory sequence generation (random numbers generated by computers, drawing of lots of envelopes).
For the individual trial results, we calculated relative risk (RR) with 95% confidence intervals (CI), and number needed to treat (NNT) for categorical outcomes. We reported mean differences (MD) and 95% CI for continuous variables, if appropriate.
We performed formal exploration of heterogeneity. Statistical tests for heterogeneity have low power especially when there are not many studies. Higgins developed measures of the impact of heterogeneity in a meta-analysis that are independent of the numbers of studies (so called I² statistics) (Higgins 2002). These measures describe the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. We used the statistics I² as an interpretation of the extent of heterogeneity. Values of I² less than 56%, and higher than 31%, account for ‘moderate’ heterogeneity. Meta-analysis with a random-effects model was applied when this happened (Deeks 2001). Otherwise, we performed meta-analysis using a fixed-effect model. However, the possibility of a Type II (false negative) error must be considered and a thorough attempt was made to identify clinical heterogeneity or sources of bias.
For the meta-analysis, we reported relative risk (RR), risk difference (RD) and 95% confidence intervals (CI) for dichotomous outcomes; and weighted mean differences (WMD) for continuous variables. We explored publication bias using a plot of study sample size against relative risk. Publication bias occurs when published more often than negative results. In the absence of published studies are not representative of all studies that have been done, usually because positive results tend to be submitted and published more often than negative results. In the absence of publication bias, a plot of study sample size (or study weight) versus outcome (i.e. log relative risk) should have a bell or inverted funnel shape with the apex near the summary effect estimate (funnel plot).
We planned subgroup analysis to determine whether the results differed by one of the following.

Population
1. Age
2. Severity of disease - ARDS (more severe impairment) or ALI (less severe impairment)
3. Aetiology of ARDS/ALI (i.e. pneumonia, trauma, sepsis, etc)

Concomitant treatment
1. Inhaled nitric oxide
2. Use of the prone position
3. Surfactant treatment

Delivery of interventions
1. To determine whether the comparison between low tidal volume and normal tidal volume is different if a plateau pressure of greater than 30 to 35 cm H₂O was used.
We performed a sub-group analysis based on plateau pressure in control groups; we also performed sensitivity analyses based on whether the outcome assessors were blinded and by imputing values for dropouts.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
In our original review (Petrucci 2004a) we found eight studies that were of potential relevance. We excluded three studies after closer assessment (Esteban 2000; Ranieri 1999; Rappaport 1994) and five studies met our inclusion criteria (Amato 1998; ARDS Network 2000; Brochard 1998; Brower 1999; Stewart 1998). We found an additional two studies of potential relevance from our updated search (2003 to October 2006). We excluded one study (Brower 2004) after a closer assessment. The other study (Villar 2006) met our inclusion criteria.
We therefore found 10 studies in all that were of potential relevance, of which we eventually excluded four studies (Brower 2004; Esteban 2000; Ranieri 1999; Rappaport 1994) (see ‘Characteristics of excluded studies’ table).
Six studies in total met our study inclusion criteria (Amato 1998; ARDS Network 2000; Brochard 1998; Brower 1999; Stewart 1998; Villar 2006) and were assessed for methodological quality (see ‘Characteristics of included studies’ table).
Data from one trial (ARDS Network 2000) were used for subsequent multiple publications (see Additional Table 2). We excluded these papers. All of the included studies were multi-centre ones.
Table 2. Secondary publications

<table>
<thead>
<tr>
<th>Publications</th>
</tr>
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The total number of patients randomized in each study varied from 52 (Brower 1999) to 861 (ARDS Network 2000). All studies included ARDS patients, but some investigations tended to use the LISS definition (Amato 1998; Brochard 1998) and some the NAECC definition of ARDS (ARDS Network 2000; Brower 1999; Villar 2006). The average age at randomization, with standard deviation (SD), varied from 33±13 SD (Amato 1998) to 59±17 SD (Stewart 1998). The European study (Brochard 1998) was unique in the inclusion of patients with single organ failure (lung injury) only. Time that had elapsed from eligibility to randomization ranged from one hour to 36 hours. In one study (Villar 2006), only patients who demonstrated persistent ARDS 24 hours after initially meeting ARDS criteria, were enrolled.

All the trials assessed the baseline risk by combining several prognostic variables into a severity score (APACHE II or APACHE III score), which provides initial risk stratification for severely ill hospitalized patients and risk estimate for hospital mortality for individual ICU patients (Knaus 1985; Knaus 1991). The higher the score, the higher is the relative risk of hospital death. The APACHE II score at baseline was in the range of 17±8 SD (Brochard 1998) to 28±7 SD (Amato 1998). Two trials used the APACHE III score (ARDS Network 2000; Brower 1999). The APACHE III score ranged from 81±28 SD (ARDS Network 2000) to 90±26 SD (Brower 1999). The severity of impairment of lung function was reported according to partial pressure of arterial oxygen to the fraction of inspired oxygen ratio (PaO$_2$/FiO$_2$) (see ‘Characteristics of included studies’ table). Patients with less severe hypoxaemia (as defined by a PaO$_2$/FiO$_2$ ratio of 300 or less) are considered to have ALI, and those with more severe hypoxaemia (as defined by a ratio of 200 or less) are considered to have ARDS (ARDS Conference 1977).

Delivery of interventions for each trial varied. Five trials (ARDS Network 2000; Brochard 1998; Brower 1999; Stewart 1998; Villar 2006) set the tidal volume based on body weight, without the use of a Pressure-Volume (PV) curve. However, in the ARDS Network, Brower, Stewart and Villar trials, the tidal volume was set according to predicted (or ideal) body weight (IBW), which was calculated according to the gender and height of the patient. IBW is, on average, 20% less than measured body weight. When transformed to ml/kg measured body weight, the mean tidal volume in the ARDS Network trial ranged from 9.4 to 9.9 ml/kg in the control group, which was quite similar to values used in the other trials, and 5.2 ml/kg in the low tidal volume group, which was lower than other trials. Two trials (Amato 1998; Villar 2006) compared the effect of a combined strategy composed of a low tidal volume and relatively high PEEP titrated according to the PV curve. Amato added an intermittent recruitment manoeuvre, and used in the control group a ventilatory strategy aimed at normalizing partial pressure of carbon dioxide, without limitation in peak inspiratory pressure. Based on aggregate data, all patients in the lung-
protective ventilation groups received tidal volumes significantly lower than those in the conventional ventilation groups. Limits of airway plateau pressure ranged from 22 to 30 cm H\textsubscript{2}O in the protective arms, and from 31 to 37 cm H\textsubscript{2}O in the conventional arms. Most studies focused on plateau airway pressure, whereas one study focused on peak inspiratory airway pressure (Brochard 1998). Protocols for the management of acidosis using bicarbonate infusions were developed in all trials, although there were some differences. ARDS Network investigators (ARDS Network 2000) were most aggressive in attempting to keep pH greater than 7.30 for all patients and allowed violations of the tidal volume and airway pressure limits when pH fell below 7.15. In contrast, another study (Stewart 1998) did not dictate volume and pressure violations until pH fell to 7.00. Co-interventions were not detailed in the studies. Only one trial (Amato 1998) reported treatments other than ventilation. None of the studies reported use of prone positioning or surfactant. Nitric oxide was used in one trial only (Brochard 1998), and did not appear to be an important feature that imbalanced the trial as it was used in about one-fifth of patients in both groups.

The studies did not report all the considered outcomes. The definition of overall mortality differed between trials. Mortality was measured at a cut-off point of day 60 in one study (Brochard 1998), day 180 in one study (ARDS Network 2000) and at hospital discharge in two studies (Brower 1999; Stewart 1998). In one study (Amato 1998), both mortality at day 28 and at hospital discharge were reported. ICU and hospital mortality were reported in one study (Villar 2006). Importantly, in ARDS Network 2000 patients were followed until discharged home or for 180 days, whichever occurred first. This may be considered equivalent to hospital mortality. Among the secondary outcome measures considered for this review, only three trials reported duration of mechanical ventilation (Brochard 1998; Brower 1999; Stewart 1998) (see Additional Table 3). In the ARDS Network study, this outcome was reported as median number of days, without further description. However, the absence of a strict protocol for weaning in all the trials, apart from the ARDS Network study (ARDS Network 2000), makes this outcome, although important for clinical and economic implications, difficult to evaluate objectively. Similarly, organ failures were reported using different measures. Two trials did not report this outcome at all (Amato 1998; Brower 1999). Brochard 1998 reported that 24 patients in each group suffered from organ failures without further details, whereas Stewart 1998 reported a mean value of two organ failures per patient in each group. ARDS Network 2000 reported the number of days without non-pulmonary organ failure at day 28. Other secondary outcomes considered relevant for this review were not reported in the studies.

### Table 3. Secondary outcomes considered for this review

<table>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Development of MOF</td>
<td>N/A</td>
<td>15+/−11</td>
<td>24/58</td>
<td>N/A</td>
<td>2 vs 2 (no. of organs/patients)</td>
<td>0.3 vs 1.2 (no. of organ failure post-pre randomization)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation</td>
<td>N/A</td>
<td>8-10 both groups (median)</td>
<td>23+/−20 21+/−16 versus 11+/−2.2 vs 12+/−1.9</td>
<td>16.6+/−39 versus 9.7+/−10</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Total duration of mechanical support</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Total duration of stay in intensive care</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>20+/−39 versus 14+/−16</td>
<td>N/A</td>
</tr>
<tr>
<td>Total duration of stay in hospital</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>33+/−48 versus 27+/−26</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Table 3. Secondary outcomes considered for this review (Continued)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
<th>Study 4</th>
<th>Study 5</th>
<th>Study 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-term mortality</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Long-term health-related quality of life</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Long-term cognitive outcomes</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Costs</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Risk of bias in included studies**

All the studies found similarity of the two study groups at the time of randomization with respect to important determinants of outcome. All the studies reached a high level of quality. Most studies included complete follow up and intention-to-treat analysis. In the ARDS Network trial 31 patients (3.6%) were lost to follow up (ARDS Network 2000). Twenty-two of them were patients still hospitalized when the trial was stopped, and for nine patients the outcome was unknown (legend, Figure 1 in the original trial). See the 'Characteristics of included studies' for a more detailed description of individual trial quality. In one trial (Amato 1998) it was clearly stated that the study was not blind. No mention of blinding was found in all the other studies. Protocols for management of mechanical ventilation were found in all the studies, thus minimizing performance bias. A protocol for weaning was found only in the ARDS Network study (ARDS Network 2000).

In five studies (Amato 1998; ARDS Network 2000; Brochard 1998; Brower 1999; Villar 2006) sample size was calculated before the beginning of the study. With the exception of the Amato trial, which reached the target sample (53 patients), the other four studies were stopped early. Brochard 1998 based the calculation on 30 to 40% reduction of hospital mortality. They estimated a sample of 240 patients and the trial was stopped at 116 because protective ventilation was clearly detrimental (RR = 1.23). Brower 1999 used an estimation of treatment effect based on reversal of respiratory failure as the target outcome for calculation of sample size. The study was designed to detect a 30% reduction in respiratory failure. They estimated a sample of 130 patients, but the trial was stopped at 52 because the second interim analysis showed that it was unlikely that beneficial treatment effects on reversal of respiratory failure could be demonstrated if the trial were to continue. ARDS Network 2000, calculation of sample size was based on 10% reduction in cumulative mortality at day 180. The estimated sample consisted of 1000 patients and the trial was stopped after enrolling 861 patients because the interim analysis demonstrated that lower tidal volume ventilation was beneficial. The ARDS Network trial, in its design, tried to detect the smallest difference in mortality between groups. Villar 2006 calculated sample size on 20% reduction in absolute mortality. The trial was stopped after enrolling 103 patients due to benefits of low tidal volume ventilation. None of the trials reported a long-term follow up.

**Effects of interventions**

The ARDS Network trial coordinator and the corresponding author of the Brochard study were requested to supply further data on mortality at day 28. Unfortunately this information has not been made available. Therefore we extracted these numerical data from figure 1 and figure 5 as presented in the original publications (ARDS Network 2000; Brochard 1998). Total number of randomized patients was 1297. Globally, when considering mortality at the end of the follow-up period as reported by the trialists, the results from the trials clustered between a RR of 0.6 and 1.23, with overlapping CI (see Additional Table 4). Overall, the test for heterogeneity yielded a borderline result (P-value 0.10; 5 degrees of freedom). The I² was above the established threshold for combinability, but within the range of 'moderate heterogeneity', I² = 45.9%. Therefore, random-effects models were applied for calculating an overall estimate (see 'Comparisons and data' table).
### Table 4. Results of individual studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect Name</th>
<th>Treated</th>
<th>Control</th>
<th>Total</th>
<th>Effect</th>
<th>Lower 95%CI</th>
<th>Upper 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>Hospital mortality</td>
<td>13/29</td>
<td>17/24</td>
<td>53</td>
<td>0.63</td>
<td>0.39</td>
<td>1.02</td>
</tr>
<tr>
<td>Amato 1998</td>
<td>Mortality at day 28</td>
<td>11/29</td>
<td>17/24</td>
<td>53</td>
<td>0.54</td>
<td>0.31</td>
<td>0.91</td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>Mortality at day 180</td>
<td>133/432</td>
<td>170/429</td>
<td>861</td>
<td>0.78</td>
<td>0.65</td>
<td>0.93</td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>Mortality at day 60</td>
<td>27/58</td>
<td>22/58</td>
<td>116</td>
<td>1.23</td>
<td>0.80</td>
<td>1.89</td>
</tr>
<tr>
<td>Brower 1999</td>
<td>Hospital mortality</td>
<td>13/26</td>
<td>12/26</td>
<td>52</td>
<td>1.08</td>
<td>0.62</td>
<td>1.91</td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>Hospital mortality</td>
<td>30/60</td>
<td>28/60</td>
<td>120</td>
<td>1.07</td>
<td>0.74</td>
<td>1.55</td>
</tr>
<tr>
<td>Villar 2006</td>
<td>Hospital mortality</td>
<td>17/50</td>
<td>25/45</td>
<td>95</td>
<td>0.61</td>
<td>0.38</td>
<td>0.98</td>
</tr>
</tbody>
</table>

### Primary outcomes

Overall mortality at the end of the follow-up period for each trial showed a trend toward a reduction, but it did not reach a statistical significance. Using a random-effects model, the RR was 0.86 (95% CI 0.69 to 1.06), absolute risk difference -6% (95% CI -16% to 3%), $I^2$ 45.9% (see 'Comparison and data' 01). The different duration of follow up used in each trial for outcome assessment - one trial followed patients up to 180 days, one trial had 60 days follow up, one trial used 28 days and the remaining trials used 'in-hospital' mortality - should suggest caution when interpreting this overall estimate of effect. The legend to Figure 1 of the ARDS Network trial states that 31 patients were censored from the count. Assuming that the 31 patients were approximately evenly distributed, then the actual number of patients reported is Treatment: 416 (432 less 16) and Control: 414 (429 less 15). The calculated deaths are Treatment: 129 and Control: 165. Without further explanation from the authors, this is a conservative approach to getting an estimate of the counts actually used in their analysis. Comparison 11 and 12 show that the best/worse analysis does not show significant effect of the 31 censored patients on the overall results.

We stratified the trials based on comparable outcomes. Using hospital mortality (Amato 1998; ARDS Network 2000; Brower 1999; Stewart 1998; Villar 2006), 1181 patients, the point estimate was in favour of the low tidal volume ventilation with both the fixed- and random-effects model: RR 0.80 (95% CI 0.69 to 0.92), absolute risk difference -8% (95% CI -13% to -2%) and RR 0.81 (95% CI 0.66 to 0.98), absolute risk reduction -9% (95% CI -18% to 0.0%), respectively. $I^2$ was 30.8% (see 'Comparison and data' 03).

Mortality at day 28 (Amato 1998; ARDS Network 2000; Brochard 1998), 1030 patients, was significantly lower in patients with the lung-protective ventilation strategy (fixed-effect model: RR 0.74 (95% CI 0.61 to 0.88); the absolute risk difference was -10% (95% CI -15% to -4%). When applying a random-effects model the RR was largely unchanged: 0.73 (95% CI 0.61 to 0.87), but the upper limit of the 95% CI of risk difference approached unity: absolute risk difference -12% (95% CI -23% to 0%). The test for heterogeneity gave a P-value 0.22 (3 degrees of freedom), $I^2 = 31.8%$; and P-value 0.41 (2 degrees of freedom), $I^2 = 0%$ for hospital mortality and mortality at day 28, respectively; thus
confirming more homogeneous data (see 'Comparisons and data' 02).

Secondary outcomes

Amongst the secondary outcomes, there was only sufficient data to assess the association between lung-protective ventilation strategy and the duration of mechanical ventilation (see Additional Table 3). Three trials looked at this endpoint (Brochard 1998; Brower 1999; Stewart 1998), and enrolled a total of 288 patients. No additional data were requested from the authors. There was a trend toward a lower duration of mechanical ventilation in patients with the protective ventilation strategy, but this reduction was not statistically significant (fixed-effect model: WMD -0.83 (95% CI -1.92 to 0.27), (random-effects model: WMD 0.38 (95% CI -3.06 to 3.82). (test for heterogeneity: P-value 0.22, df= 3, I² = 33.1%).

Sub-group analyses

We found insufficient data in the trials to perform sub-group analyses assessing the effect of age, severity of disease, aetiology of ARDS/ALI. Similarly, the studies did not report enough data to perform a sub-group analysis based on concomitant treatments. Sub-group analysis based on severity of the disease also was not feasible because all the studies included patients with more severe impairment of lung function (PaO₂:FIO₂ between 200 and 300 mm Hg or less). ARDS Network 2000 included patients with less severe impairment (PaO₂:FIO₂ between 200 and 300 mm Hg), but these patients accounted only for 15 to 18% of the total sample. Finally, sub-group analysis based on the underlying risk factor was not practicable because each trial included ARDS/ALI from any cause, and in all the studies the authors reported only aggregate data. We performed sub-group analysis based on the delivery of interventions and comparing the overall estimate of effect of treatment, on all-cause mortality at the end of the follow-up period, between trials with 'low pressure' control group (mean plateau pressure 31 cm H₂O or less) (Brochard 1998; Brower 1999; Stewart 1998), 288 patients, with the effect of treatment in trials with 'high pressure' control group (plateau pressure greater than 31 cm H₂O, mean value) (Amato 1998; ARDS Network 2000; Villar 2006), 1009 patients. Overall mortality was significantly lower in the lung-protective ventilation group when a 'higher' plateau pressure in the control arm was applied (fixed-effect model: RR 0.74 (95% CI 0.63 to 0.87), absolute risk reduction -11% (95% CI -17% to -5%)) and not significantly different with a 'lower' plateau pressure in the control arm (fixed-effect model: RR 1.13 (95% CI 0.88 to 1.45), absolute risk reduction 6% (95% CI -6% to 17%)). The test for heterogeneity yielded I² = 0%, respectively, for 'low' and 'high' plateau pressure groups (see 'Comparisons and data' 05).

Publication bias

Although publication bias is not the only cause of an asymmetrical plot, the symmetrical shape of the funnel plot of precision by effect size showed that the overall effect of meta-analysis in this review was not affected by publication bias or biased inclusion criteria. However, the small numbers of trials included should suggest a cautious interpretation.

Sensitivity analysis

We excluded one trial that was clearly unblinded and that used a different method to deliver the intervention in the treatment group (Amato 1998), 53 patients. The test for heterogeneity changed slightly (P-value 0.13 (df = 3). Overall mortality at the end of follow-up periods was also changed slightly (fixed-effect model: RR 0.87 (95% CI 0.75 to 1.01); absolute risk difference -5% (95% CI -11% to 0%); random-effects model: RR 0.97 (95% CI 0.76 to 1.24), absolute risk difference -2% (95% CI -11% to 8%)). We evaluated the impact of the largest study (ARDS Network 2000), 861 patients, by excluding it from the analysis. The effect of lung-protective and conventional treatment strategies on all-cause mortality disappeared (fixed-effect model: RR 0.92 (95% CI 0.75 to 1.12); random-effects model: RR 0.90 (95% CI 0.67 to 1.15)).

The ARDS Network investigators reported that nine patients (hospital mortality unknown) and 22 additional patients (still hospitalized when the trial was stopped) were censored in the survival plot (Legend, Figure 1) (ARDS Network 2000). There was no later information about the eventual outcome of those patients. We performed a sensitivity analysis imputing values for the 31 dropouts according to 'best/worse' case analysis (see 'Comparisons and data' 11 and 12). For the best-case analysis, the 16 and 15 patients are added back and all added Control patients are assumed to have died with no additional deaths in the Treatment group. Thus the counts are Treatment: (129 plus 0)/(416 plus 16) = i.e. 129/432; and Control: (165 plus 15)/(414 plus 16) = i.e. 180/429. The test for heterogeneity was P-value 0.04, I² = 59.1%. Therefore, we applied the random-effects model: RR 0.89 (95% CI 0.68 to 1.16). For the worst-case analysis, the 16 and 15 patients are added back and all added Treatment patients are assumed to have died with no additional deaths in the Control group. Thus the counts are Treatment: (129 plus 16)/(416 plus 16) = i.e. 145/432 and Control: (165 plus 15)/(414 plus 15) = i.e. 165/429. The test for heterogeneity was P-value 0.25, I² = 25.7%. Therefore, we applied the fixed-effects model: RR 0.92 (95% CI 0.80 to 1.06). In both cases, the confidence intervals reached the no-difference line; the shift of events from one case to the other did not change the statistical significance.

Other secondary outcomes

Although there is evidence that the cause of death in ARDS is the development of organ failure (Monchi 1998), only three studies...
reported that outcome, each of them using different criteria to define organ failure, thus preventing from combining the results in a summary estimate. In only two studies (ARDS Network 2000; Villar 2006) the ventilatory strategy affected the development of organ failure, reduced in the protective arm, whereas in the ‘non-beneficial’ studies (Brochard 1998; Stewart 1998), the occurrence of MOF was similar in both groups.

Long-term cognitive outcome and costs were not assessed by the trials.

**DISCUSSION**

We found evidence that ventilation strategy using a tidal volume equal or less than 7 ml/kg of measured body weight and plateau pressure less than 31 mm H$_2$O reduced mortality at day 28. Evidence from a new study (Villar 2006) shows that it also reduces hospital mortality. In all the selected studies although the primary purpose of the investigators was to compare two different tidal volumes, other elements of ventilatory strategy were associated with it. The experimental intervention included permissive hypercapnia, variable levels of PEEP and low plateau airway pressure. The traditional intervention consisted of higher tidal volume, normocapnia, lower levels of PEEP and potentially higher plateau pressures. Some of these co-interventions were unavoidable and consequent to the nature of the main intervention. Therefore, the studies performed a comparison of two approaches rather than two single interventions, and caution is required in interpreting these results, especially when analyses have been inspired by looking at the available aggregate data, which makes it difficult to assess the respective importance of each factor. All patients where hypercapnia could be potentially associated with damage were excluded from the studies. The meta-analysis is dominated by the large ARDS Network trial (ARDS Network 2000). Interestingly, Amato 1998 included the youngest population but reported the highest mortality rate in the control group (70.8%), presumably reflecting the presence of severe prognostic factors at baseline. The overall estimate is of borderline statistical significance when using the fixed-effect model. The statistic I$^2$ (45.9%) showed that an important percentage of variability in point estimates is due to heterogeneity rather than sampling error. That value is sufficiently high to justify using a random-effects model. Although the point estimate is similar to that given by the fixed-effect model, the random-effects confidence intervals are wider, the treatment effect is non-significant and this result is more conservative. The discordant figures also reflect an unstable conclusion (Deeks 2001). Several hypotheses can explain and interpret these data

- There is a ‘hidden’ source of heterogeneity. Although statistical tests of heterogeneity were not significant, we showed that studies were clinically different in some points.

Furthermore, most of the trials did not report protocols of concomitant treatments and associated diseases (i.e. ventilator-associated pneumonia).

- There is a sub-group of patients that can be ventilated with lower tidal volumes or volumes in the conventional range, as long as plateau pressure is kept below 31 cm H$_2$O, without differences in mortality. Because alveolar recruitment occurs during tidal inflation (Gattinoni 1995), reduction of tidal volume may prove beneficial when it prevents hyperinflation and over-distention, but it could be harmful if it is unable to recruit previously collapsed or compressed alveoli. In this situation, the level of PEEP may play a critical role (Ranieri 1995) and individual titration of ventilation is crucial (Glasziou 1995).

- Low volumes are at best associated with lower mortality, and at worst, they are no better than higher volumes. However, higher volumes are at best as good as low volumes and in the worst case they are associated with an increased mortality.

Several differences in the choice of time of follow up for outcome assessment, and in the delivery of intervention in control groups raise concern when interpreting the results. When meta-analysis was repeated using a homogeneous outcome (mortality at day 28), it showed a relevant, stable benefit from the protective ventilatory approach (Relative Risk Reduction = 26%). The benefit from low tidal volume ventilation was maintained, although reduced, when considering hospital mortality as the endpoint. The effect of lower tidal volumes on the development of organ failure (main determinant of long-term outcome) is uncertain. Conversely, lower tidal volumes are effective on short-term endpoint, protecting aerated lung parenchyma, and leading to lung recovery.

Among the secondary outcomes only the duration of mechanical ventilation was reported in the studies. If mortality is not changed by the experimental intervention, a different duration of MV puts the patient at risk of developing major infectious lung diseases and affects lung recovery, ending up in pulmonary fibrosis and low quality of life (Davidson 1999). Reduction of duration of MV in the low tidal volume group was a common finding in all the trials except two (Brochard 1998; Stewart 1998). The quantitative summary estimate did not show a statistically significant effect of protective ventilation on duration of MV. The impact of this outcome could not be assessed properly because important long-term outcomes potentially affected by MV were missing. Although survival to hospital discharge may improve, surprisingly little is known about long term outcome. We know that impaired health-related quality of life is common following recovery from ARDS/ALI (Davidson 1999). The decreased health-related quality of life is related to physical rather than emotional or psychological complaints. Two studies reporting follow up at one to two years were unable to demonstrate that a limited ventilation strategy improves either long-term function or quality of life in survivors of ARDS/ALI (Cooper 1999; Orme 2003). Health-related quality
of life and long-term cognitive outcome were not considered in the trials selected for this review.

Can we attribute all the differences between the two groups to differences in the tidal volumes used?

This is a controversial issue. A recent study by the ARDS Network (Brower 1999) (so-called ALVEOLI study) reported no difference in outcome when ARDS patients were ventilated with low tidal volume and high or low PEEP. That means that PEEP is not as important as tidal volume in changing outcomes. Villar 2006 confirms this finding: when a high-low PEEP and large tidal volume difference was used between groups, the difference in outcomes appeared again. Therefore, the tidal volume difference clearly had an impact on mortality.

However, three studies (Amato 1998; ARDS Network 2000; Villar 2006) actually used a plateau pressure in the control groups that was higher than the other trials. In the study design, the ARDS Network investigators would have allowed plateau pressure to be raised to 45 mm H2O if necessary to deliver the target tidal volume of 12 ml/kg IBW. Interestingly, these studies were the only studies which showed benefit from low tidal volume ventilation. Meta-analysis performed stratifying trials according to 'high plateau pressure' and 'low plateau pressure' in control group confirmed that when delivery of conventional tidal volume was associated with plateau pressure of 31 cm H2O or less there was no evidence of decreased mortality from protective ventilation. The large difference in sample size of the two groups (288 versus 1009) calls for cautious interpretation. A previous meta-analysis (Eichacker 2002) investigated whether differences in treatment effect could be explained by differences in plateau pressure associated with either the control or low tidal volumes. The authors concluded that treatment in controls differed from current practice, in terms of too-high tidal volumes and plateau pressure, and this difference may have influenced outcomes in two trials (Amato 1998; ARDS Network 2000). Although the method applied in the work by Eichacker has been questioned (Petrucci 2003), his study suggests that as long as tidal volumes produce airway pressures considered safe (31 cmH2O or less), there is no benefit from using lower tidal volumes.

In addition, following the paper by Eichacker (Eichacker 2003), which raised some safety-related concerns about the ARDS Network trial, the Office for Human Research Protections (OHRP) started an investigation, which led to suspension of a major ARDS Network trial on fluid and catheter treatment in ALI or ARDS (Steinbrook 2003b). However, following the investigation, the OHRP declared that risks to subjects participating in the ARDS Network trial were minimal and reasonable in relation to anticipated benefits. The concerned studies were needed in the first place because many aspects of the care of ARDS patients were highly variable, with no standard of care (Steinbrook 2003a).

A possible interpretation of the discordant results, as proposed byGattinoni (Gattinoni 2002), could involve variations of trans-pulmonary pressure, which is the distending force of the lung, in the individual patient. The high volume might induce lung damage when the resulting trans-pulmonary pressure is high. Conversely, when trans-pulmonary and airway pressure are within the safe limits, high or intermediate tidal ventilation (8 to 10 ml/Kg) could be used, thus avoiding potentially deleterious effects of low tidal volume. Thus, when chest wall compliance is low, a higher plateau pressure may be necessary to reach the same trans-pulmonary pressure, without increase in tidal volume.

Some questions still remain open:

The treatment may be effective only in a sub-group of patients. The lower tidal volume ventilation may be clinically worthwhile only in the more severely ill patients.

- The issue of adverse effects of lower tidal volume was not tackled in the studies. Specifically, the impact of acidosis and hypercapnia on the development of organ failure was not clear.

- Ventilation with lower tidal volume can be very effective for short-term lung recovery, but its impact on the development of organ failure and long-term recovery is still uncertain or unknown;

AUTHORS’ CONCLUSIONS
Implications for practice

Overall, the relative risk of death at day 28 is reduced by using ventilation with lower tidal volume. Hospital mortality is also
beneficially affected, but there is insufficient evidence to draw any conclusions about morbidity and long-term outcomes. Ventilation with higher tidal volume and higher plateau pressure is associated with increased risk of death, but the independent contribution of higher tidal volume (over distension) and/or higher plateau pressure (barotrauma) cannot be identified. Lower tidal volume ventilation may be preferable when lung recovery is a priority.

**Implications for research**

Further data are required to assess long-term health-related quality of life, long-term cognitive outcomes and cost. Large, adequately designed trials with sub-group analysis would be able to determine whether an “intermediate” tidal volume of 8-10 ml/Kg IBW would be beneficial, too.

Alternatively, a systematic review that uses individual patient data (IPD) can achieve the ultimate aim to:

- Undertake survival and other time-to-event analyses. If individual survival times were available for each trial, heterogeneity of the considered outcomes (a major issue of this review) could be solved and the issue whether protective ventilation leads to a prolongation of long term survival or only to lung recovery could be investigated.

- Undertake sub-group analysis to assess differences in hypercapnia, actually administered tidal volumes, and other confounders.

- Ensure the appropriateness of analysis.

**ACKNOWLEDGEMENTS**

We would like to thank Prof. Marcus Müllner, Prof. Nathan Pace, Dr Asima Bokhari, Dr Mark Davies, Janet Wale, Nete Villebro and Kathie Godfrey for commenting on the original review (Petrucci 2004a), and Dr Harald Herkner, Prof. Nathan Pace, Dr Antonio Anzueto, Dr Jeffrey Man and Damon Scales for commenting on the updated review. We would also like to thank John Senior for his assistance in reviewing the manuscript of the original review, Karen Hovhannisyan for help in searching the literature, and Mario Mergoni for a constructive critique.

**REFERENCES**

**References to studies included in this review**

Amato 1998  *published data only*  

ARDS Network 2000  *published data only*  

Brochard 1998  *published data only*  

Brower 1999  *published data only*  

Stewart 1998  *published data only*  

Villar 2006  *published data only*  

**References to studies excluded from this review**

Brower 2004  *published data only*  

Esteban 2000  *published data only*  

Ranieri 1999  *published data only*  
Rappaport 1994 (published data only)

Additional references

ARDS Conference 1977

Artigas 1998

Ashbaugh 1967

Bernard 1994

Cooper 1999

Davidson 1999

Deeks 2001

Dowdy 2006

Dreyfuss 1994

Eichacker 2003

Feihl 1994

Frutos-Vivar 2004

Gattinoni 1995

Gattinoni 2002

Glasziou 1995

Hickling 1990

Hickling 1994

Higgins 2002

Knaut 1985

Knaut 1991

Lewandowski 1999

Marini 1990
Monchi 1998

Murray 1988

Orme 2003

Parker 1993

Petrucci 2003

Ranieri 1995

Ranieri 1997

Roupie 1995

Roupie 1999

Steinbrook 2003a

Steinbrook 2003b

Ware 2000

References to other published versions of this review

Petrucci 2004a

Petrucci 2004b

Petrucci 2004c

* Indicates the major publication for the study
### Characteristics of included studies  [ordered by study ID]

#### Amato 1998

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, multi-centre, controlled, RCT.</td>
</tr>
<tr>
<td>Concealment of treatment allocation: yes.</td>
</tr>
<tr>
<td>Generation of allocation sequences: sealed envelopes and a 1:1 assignment scheme.</td>
</tr>
<tr>
<td>Intent to treat: yes.</td>
</tr>
<tr>
<td>Blinding of treatment: no.</td>
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<tr>
<td>Blinding of outcome assessment: not stated.</td>
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</table>

<table>
<thead>
<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>53 adults &gt; 14 and &lt; 70 years old (2 centres).</td>
</tr>
<tr>
<td>Included: LISS $\geq 2.5$, PaO2:FiO2 &lt; 200, P wedge $&lt; 16$ mmHg.</td>
</tr>
<tr>
<td>Exclusion: Previous lung or neuromuscular disease, MV &gt; 1 week, terminal disease, previous barotrauma, previous lung biopsy or resection, intracranial hypertension, uncontrollable and progressive acidosis, documented coronary insufficiency.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume &lt; 6 ml/Kg (n=29) or tidal volume 12 ml/Kg (n=24).</td>
</tr>
<tr>
<td>Plateau pressure &lt; 20 mmHg (experimental arm) or unlimited (control arm).</td>
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<td>PEEP 2 cmH2O above LIP or titrated to best PaO2:FiO2.</td>
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<table>
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<tr>
<th>Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Primary: mortality at day 28, in-hospital mortality.</td>
</tr>
<tr>
<td>Secondary: development of MOF, barotrauma.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate if pH $&lt; 7.20$. Use of PV curve to set Vt and PEEP. PCV. NNT=4.</td>
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<tr>
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<tbody>
<tr>
<td>Item</td>
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<td>Allocation concealment?</td>
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</table>

#### ARDS Network 2000

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<tr>
<td>Concealment of treatment allocation: yes.</td>
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<td>Generation of allocation sequences: centralized interactive voice system. Each research coordinator had a unique PIN.</td>
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<td>Intent to treat: yes.</td>
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<td>Double blind: not stated.</td>
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<table>
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<tr>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>861 adults &gt; 18 years old (10 centres).</td>
</tr>
<tr>
<td>Included: AECCC, PaO2:FiO2 $&lt; 300$ mmHg, P wedge $&lt; 18$ mmHg.</td>
</tr>
<tr>
<td>Exclusion: Pregnancy, high intracranial pressure, sickle cell disease, COPD, weight $&gt; 1$ Kg/cm height, neuromuscular disease, burns over more than 30% BSA, bone marrow or lung transplantation, chronic liver disease.</td>
</tr>
</tbody>
</table>

Interventions
- Tidal volume 6 ml/Kg or 12 ml/Kg of IBW.
- Plateau pressure <= 30 mmHg or <= 50 mmHg.
- PEEP titrated to SaO2 88-95%.

Outcomes
- Primary: mortality before hospital discharge or at day 180.
- Secondary: development of MOF, duration of mechanical ventilation, ventilator-free days, barotrauma.

Notes
- Powered for 1000 patients. Stopped early because of statistically significant benefit in the experimental arm (fourth interim analysis).
- Increased ventilation if pH < 7.15. NNT=12.

Risk of bias

<table>
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<tr>
<th>Item</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>

Brochard 1998

Methods
- Prospective, multi-centre, controlled, RCT.
- Concealment of treatment allocation: yes.
- Generation of allocation sequences: sealed envelopes.
- Intent to treat: yes.
- Double blind: not stated.

Participants
- 116 patients <= 76 years old (25 centres).
- Inclusion: LISS >= 2.5, PaO2:FiO2 < 200 mmHg, Pwedge < 18.
- Exclusion: History of left heart failure, cardiogenic oedema, organ failure other than the lung, need for epinephrine > 1mg/hr or nor-epinephrine > 2 mg/hr, COPD or liver failure or renal failure, moribund state, intracranial hypertension, head injury, chest wall abnormalities.

Interventions
- Tidal volume 7 ml/Kg or 10 ml/Kg.
- Plateau pressure between 25-30 mmHg or peak pressure <= 60 mmHg.
- PEEP titrated to PaO2:FiO2 > 200 mmHg.

Outcomes
- Primary: mortality at day 60.
- Secondary: development of MOF, duration of mechanical ventilation, barotrauma.

Notes
- Use of nitric oxide allowed. Bicarbonate if pH < 7.05. NNH=12.
### Brochard 1998

| Allocation concealment? | Yes | A - Adequate |

### Brower 1999

#### Methods
- Prospective, multi-centre, controlled, RCT.
- Concealment of treatment allocation: yes.
- Generation of allocation sequences: yes, block design, method not stated.
- Intent to treat: yes.
- Double blind: not stated.

#### Participants
- 52 patients >= 18 years old.
- Included: AECCC, PaO2/FiO2 < 200 mmHg, Pwedge < 18 mmHg.
- Exclusion: Pregnancy, Acute neurologic disease, life expectancy < 3 months, COPD, sickle cell disease, lobectomy or pneumonectomy.
- Time period of study: not stated.

#### Interventions
- Tidal volume 8 ml/Kg or (10-12) mm/Kg of IBW.
- Plateau pressure <= 30 mmHg or <= (45-55) mmHg.
- PEEP titrated to SaO2 86-94%.

#### Outcomes
- Primary: in-hospital mortality.
- Secondary: duration of mechanical ventilation, reversal of respiratory failure, barotrauma.

#### Notes

#### Risk of bias

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<td>Unclear</td>
<td>B - Unclear</td>
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</table>

### Stewart 1998

#### Methods
- Prospective, multi-centre, controlled, RCT.
- Concealment of treatment allocation: yes.
- Generation of allocation sequences: block design, computer-generated random numbers tables.
- Intent to treat: yes.
- Double blind: not stated.

#### Participants
- 120 patients >= 18 years old (8 centres).
- Included: High risk for ARDS, PaO2/FiO2 < 250 mmHg.
- Exclusion: MV expected to be required for > 48 hrsPIP > 30 cmH2O for 2 hrs or more before randomization moribund state cardiogenic pulmonary oedema myocardial ischaemia; pregnancy; known intracranial abnormalities.
- Time period of study: not stated.
Stewart 1998  (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Tidal volume 8 ml/Kg or (10-15) ml/Kg of IBW. Peak pressure 30 mmHg or 50 mmHg. PEEP titrated to 89-93%.</th>
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<tbody>
<tr>
<td>Notes</td>
<td>Bicarbonate if pH &lt; 7.00, or increased ventilation if refractory acidosis. NNH=30.</td>
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**Risk of bias**

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Villar 2006

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<tr>
<td>Participants</td>
<td>103 patients &gt; 15 years old (8 centres). Included: AECCC, PaO2:FiO2 &lt; 200 mmHg, Pwedge &lt; 18 mmHg. Exclusion: Pregnancy, severe neurologic damage, cancer patients in terminal stage, high risk of mortality within 3 months. Time period of study: March 1999 - March 2001</td>
</tr>
<tr>
<td>Interventions</td>
<td>Tidal volume (5-8) ml/Kg (n=53) or tidal volume (9-11) ml/Kg (n=50). PEEP 2 cmH2O above LIP or &gt; 5 cmH2O, titrated to SaO2 &gt; 90%.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary: ICU mortality. Secondary: in-hospital mortality, ventilator-free days, nonpulmonary organ dysfunction, barotrauma.</td>
</tr>
<tr>
<td>Notes</td>
<td>Use of PV curve to set PEEP. Stopped early because of statistically significant benefit in the experimental arm. NNT=5</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Yes</td>
<td>A - Adequate</td>
</tr>
</tbody>
</table>


In the ARDS network trial 31 patients were lost to follow up and were censored from the count.

**Characteristics of excluded studies**  *ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brower 2004</td>
<td>This trial used low tidal volumes in both the study groups. Thus, it is not eligible for inclusion, because it did not compare different tidal volumes, but only different levels of PEEP</td>
</tr>
<tr>
<td>Esteban 2000</td>
<td>This RCT has not been designed to test MV with lower tidal volume in ARDS. Tidal volume and plateau pressure in the experimental arm overlap tidal volume and plateau pressure in the control group.</td>
</tr>
<tr>
<td>Ranieri 1999</td>
<td>This RCT tested the hypothesis that protective ventilation minimizes pulmonary and systemic cytokine response and was not specifically designed to assess the benefit on mortality of lower tidal volume ventilation. Although the context of interventions in both groups met the inclusion criteria for this review, the protocol was designed to be a 36-hour study, and 28-days mortality is reported as a post-hoc analysis. In addition, analysis was not conducted on an intention-to-treat basis. Loss to follow up was 14%.</td>
</tr>
<tr>
<td>Rappaport 1994</td>
<td>Prospective, non-blinded RCT. Analysis was not conducted to intention-to-treat basis (attrition bias). Tidal volumes overlap in both groups.</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial. ARDS: acute respiratory distress syndrome.
## DATA AND ANALYSES

### Comparison 1. protective versus conventional

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality at the end of the follow up period for each trial</td>
<td>6</td>
<td>1297</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.83 [0.72, 0.95]</td>
</tr>
<tr>
<td>2 Mortality at day 28</td>
<td>3</td>
<td>1030</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.74 [0.61, 0.88]</td>
</tr>
<tr>
<td>3 Hospital mortality</td>
<td>5</td>
<td>1181</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.80 [0.69, 0.92]</td>
</tr>
<tr>
<td>4 Duration of mechanical ventilation</td>
<td>3</td>
<td>288</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.83 [-1.92, 0.27]</td>
</tr>
<tr>
<td>5 Mortality at different plateau pressure in control groups</td>
<td>6</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>5.1 low-pressure control (&lt; or = 31 cm H2O)</td>
<td>3</td>
<td>288</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.13 [0.88, 1.45]</td>
</tr>
<tr>
<td>5.2 high-pressure control (&gt; 31 cm H2O)</td>
<td>3</td>
<td>1009</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.74 [0.63, 0.87]</td>
</tr>
<tr>
<td>6 Mortality at the end of the follow-up period for each trial - best case</td>
<td>6</td>
<td>1297</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.79 [0.69, 0.90]</td>
</tr>
<tr>
<td>7 Mortality at the end of the follow-up period for each trial - worst case</td>
<td>6</td>
<td>1297</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.89 [0.78, 1.02]</td>
</tr>
</tbody>
</table>
Analysis 1.1. Comparison 1 protective versus conventional, Outcome 1 Mortality at the end of the follow up period for each trial.

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 1 Mortality at the end of the follow up period for each trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Protective n/N</th>
<th>Conventional n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>13/29</td>
<td>17/24</td>
<td></td>
<td>6.7 %</td>
<td>0.63 [ 0.39, 1.02 ]</td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>27/58</td>
<td>22/58</td>
<td></td>
<td>7.9 %</td>
<td>1.23 [ 0.80, 1.89 ]</td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>30/60</td>
<td>28/60</td>
<td></td>
<td>10.1 %</td>
<td>1.07 [ 0.74, 1.55 ]</td>
</tr>
<tr>
<td>Broower 1999</td>
<td>13/26</td>
<td>12/26</td>
<td></td>
<td>4.3 %</td>
<td>1.08 [ 0.62, 1.91 ]</td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>133/432</td>
<td>170/429</td>
<td></td>
<td>61.5 %</td>
<td>0.78 [ 0.65, 0.93 ]</td>
</tr>
<tr>
<td>Villar 2006</td>
<td>17/50</td>
<td>25/45</td>
<td></td>
<td>9.5 %</td>
<td>0.61 [ 0.38, 0.98 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>655</strong></td>
<td><strong>642</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.83 [ 0.72, 0.95 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 233 (Protective), 274 (Conventional)

Heterogeneity: $\chi^2 = 9.24$, df = 5 ($P = 0.10$); $I^2 = 46$

Test for overall effect: $Z = 2.69$ ($P = 0.0072$)

Analysis 1.2. Comparison 1 protective versus conventional, Outcome 2 Mortality at day 28.

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 2 Mortality at day 28

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Protective n/N</th>
<th>Conventional n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>11/29</td>
<td>17/24</td>
<td></td>
<td>9.7 %</td>
<td>0.54 [ 0.31, 0.91 ]</td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>112/432</td>
<td>150/429</td>
<td></td>
<td>78.8 %</td>
<td>0.74 [ 0.60, 0.91 ]</td>
</tr>
<tr>
<td>Broower 1999</td>
<td>19/58</td>
<td>22/58</td>
<td></td>
<td>11.5 %</td>
<td>0.86 [ 0.53, 1.42 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>519</strong></td>
<td><strong>511</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.74 [ 0.61, 0.88 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 142 (Protective), 189 (Conventional)

Heterogeneity: $\chi^2 = 1.78$, df = 2 ($P = 0.41$); $I^2 = 0.0$

Test for overall effect: $Z = 3.36$ ($P = 0.00077$)
Analysis 1.3. Comparison 1 protective versus conventional, Outcome 3 Hospital mortality.

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 3 Hospital mortality

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Amato 1998</td>
<td>13/29</td>
<td>17/24</td>
<td>7.3 %</td>
<td>0.63 [0.39, 1.02]</td>
<td></td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>133/432</td>
<td>170/429</td>
<td>66.8 %</td>
<td>0.78 [0.65, 0.93]</td>
<td></td>
</tr>
<tr>
<td>Brower 1999</td>
<td>13/26</td>
<td>12/26</td>
<td>4.7 %</td>
<td>1.08 [0.62, 1.91]</td>
<td></td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>30/60</td>
<td>28/60</td>
<td>11.0 %</td>
<td>1.07 [0.74, 1.55]</td>
<td></td>
</tr>
<tr>
<td>Villar 2006</td>
<td>17/50</td>
<td>25/45</td>
<td>10.3 %</td>
<td>0.61 [0.38, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>597</td>
<td>584</td>
<td>100.0 %</td>
<td>0.80 [0.69, 0.92]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 206 (Treatment), 252 (Control)
Heterogeneity: Chi² = 5.78, df = 4 (P = 0.22); I² = 31%
Test for overall effect: Z = 3.12 (P = 0.0018)

Analysis 1.4. Comparison 1 protective versus conventional, Outcome 4 Duration of mechanical ventilation.

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 4 Duration of mechanical ventilation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>58</td>
<td>23 (20)</td>
<td>2.8 %</td>
<td>2.00 [-4.59, 8.59]</td>
<td></td>
</tr>
<tr>
<td>Brower 1999</td>
<td>26</td>
<td>11 (2.2)</td>
<td>96.1 %</td>
<td>-1.00 [-2.12, 0.12]</td>
<td></td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>60</td>
<td>16.6 (39.2)</td>
<td>1.1 %</td>
<td>6.90 [-3.34, 17.14]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>144</td>
<td>144</td>
<td>100.0 %</td>
<td>-0.83 [-1.92, 0.27]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.99, df = 2 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.48 (P = 0.14)
### Analysis 1.5. Comparison 1 protective versus conventional, Outcome 5 Mortality at different plateau pressure in control groups.

**Review:** Lung protective ventilation strategy for the acute respiratory distress syndrome

**Comparison:** 1 protective versus conventional

**Outcome:** 5 Mortality at different plateau pressure in control groups

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 low-pressure control (&lt; or = 31 cm H2O):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>27/58</td>
<td>22/58</td>
<td>35.5 % 1.23 [ 0.80, 1.89 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>30/60</td>
<td>28/60</td>
<td>45.2 % 1.07 [ 0.74, 1.55 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brower 1999</td>
<td>13/26</td>
<td>12/26</td>
<td>19.4 % 1.08 [ 0.62, 1.91 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>144</strong></td>
<td><strong>144</strong></td>
<td>100.0 % 1.13 [ 0.88, 1.45 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>70 (Treatment), 62 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 0.24, df = 2 (P = 0.89); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 0.95 (P = 0.34)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 high-pressure control (&gt; 31 cm H2O):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amato 1998</td>
<td>13/29</td>
<td>17/24</td>
<td>8.6 % 0.63 [ 0.39, 1.02 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>133/432</td>
<td>170/429</td>
<td>79.2 % 0.78 [ 0.65, 0.93 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villar 2006</td>
<td>17/50</td>
<td>25/45</td>
<td>12.2 % 0.61 [ 0.38, 0.98 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>511</strong></td>
<td><strong>498</strong></td>
<td>100.0 % 0.74 [ 0.63, 0.87 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>163 (Treatment), 212 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>Chi² = 1.33, df = 2 (P = 0.51); I² = 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 3.58 (P = 0.00034)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Favours treatment | Favours control
**Analysis 1.6. Comparison 1 protective versus conventional, Outcome 6 Mortality at the end of the follow-up period for each trial - best case.**

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 6 Mortality at the end of the follow-up period for each trial - best case

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Protective n/N</th>
<th>Conventional n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>13/29</td>
<td>17/24</td>
<td>0.63 [0.39, 1.02]</td>
<td>6.5%</td>
<td></td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>27/58</td>
<td>22/58</td>
<td>1.23 [0.80, 1.89]</td>
<td>7.7%</td>
<td></td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>30/60</td>
<td>28/60</td>
<td>1.07 [0.74, 1.55]</td>
<td>9.7%</td>
<td></td>
</tr>
<tr>
<td>Brower 1999</td>
<td>13/26</td>
<td>12/26</td>
<td>1.08 [0.62, 1.91]</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>129/432</td>
<td>180/429</td>
<td>0.71 [0.59, 0.85]</td>
<td>62.8%</td>
<td></td>
</tr>
<tr>
<td>Villar 2006</td>
<td>17/50</td>
<td>25/45</td>
<td>0.61 [0.38, 0.98]</td>
<td>9.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>655</strong></td>
<td><strong>642</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.79 [0.69, 0.90]</strong></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 1.7. Comparison 1 protective versus conventional, Outcome 7 Mortality at the end of the follow-up period for each trial - worst case.

Review: Lung protective ventilation strategy for the acute respiratory distress syndrome

Comparison: 1 protective versus conventional

Outcome: 7 Mortality at the end of the follow-up period for each trial - worst case

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Protective n/N</th>
<th>Conventional n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amato 1998</td>
<td>13/29</td>
<td>17/24</td>
<td>6.8 % 0.63 [ 0.39, 1.02 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brochard 1998</td>
<td>27/58</td>
<td>22/58</td>
<td>8.1 % 1.23 [ 0.80, 1.89 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stewart 1998</td>
<td>30/60</td>
<td>28/60</td>
<td>10.3 % 1.07 [ 0.74, 1.55 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brower 1999</td>
<td>13/26</td>
<td>12/26</td>
<td>4.4 % 1.08 [ 0.62, 1.91 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS Network 2000</td>
<td>145/432</td>
<td>165/429</td>
<td>60.8 % 0.87 [ 0.73, 1.04 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Villar 2006</td>
<td>17/50</td>
<td>25/45</td>
<td>9.7 % 0.61 [ 0.38, 0.98 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>655</strong></td>
<td><strong>642</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.89 [ 0.78, 1.02 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 245 (Protective), 269 (Conventional)
Heterogeneity: $\chi^2 = 8.05, df = 5 (P = 0.15)$; $I^2 = 38\%$
Test for overall effect: $Z = 1.72 (P = 0.086)$

**Appendices**

Appendix 1. CENTRAL and Cochrane Library - Search Strategy

**Search terms**

#1MeSH descriptor Respiratory Distress Syndrome, Adult explode all trees
#2 acute lung injury
#3 Adult Respiratory Distress Syndrome
#4 Acute Respiratory Distress Syndrome
#5 ARDS or ALI
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Tidal Volume explode all trees
#8 artificial near ventilation
#9 tidal volume
#10 protective near ventilation
#11 pressure-limited
#12 LPVS
Appendix 2. SilverPlatter MEDLINE - Search

<table>
<thead>
<tr>
<th>Search terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>#41 #14 and #40</td>
</tr>
<tr>
<td>#40 #23 or #39</td>
</tr>
<tr>
<td>#39 #38 not #23</td>
</tr>
<tr>
<td>#38 #36 not #37</td>
</tr>
<tr>
<td>#37 (TG=ANIMALS)not ((TG=HUMAN) and (TG=ANIMALS))</td>
</tr>
<tr>
<td>#36 #24 or #26 or #27 or #29 or #30 or #31 or #32 or #33 or #34 or #35</td>
</tr>
<tr>
<td>#35 RESEARCH-DESIGN</td>
</tr>
<tr>
<td>#34 random* in AB</td>
</tr>
<tr>
<td>#33 random* in TI</td>
</tr>
<tr>
<td>#32 placebo* in AB</td>
</tr>
<tr>
<td>#31 placebo* in TI</td>
</tr>
<tr>
<td>#30 PLACEBOS</td>
</tr>
<tr>
<td>#29 (#28 in TI) or (#28 in AB)</td>
</tr>
<tr>
<td>#28 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)</td>
</tr>
<tr>
<td>#27 (clin* near trial*) in AB</td>
</tr>
<tr>
<td>#26 (clin* near trial*) in TI</td>
</tr>
<tr>
<td>#25 explode CLINICAL-TRIALS / all subheadings</td>
</tr>
<tr>
<td>#24 CLINICAL-TRIAL in PT</td>
</tr>
<tr>
<td>#23 #21 not #22</td>
</tr>
<tr>
<td>#22 (TG=ANIMALS)not ((TG=HUMAN) and (TG=ANIMALS))</td>
</tr>
<tr>
<td>#21 #15 or #16 or #17 or #18 or #19 or #20</td>
</tr>
<tr>
<td>#20 SINGLE-BLIND-METHOD</td>
</tr>
<tr>
<td>#19 DOUBLE-BLIND-METHOD</td>
</tr>
<tr>
<td>#18 RANDOM-ALLOCATION</td>
</tr>
<tr>
<td>#17 RANDOMIZED-CONTROLLED-TRIALS</td>
</tr>
<tr>
<td>#16 CONTROLLED-CLINICAL-TRIAL in PT</td>
</tr>
<tr>
<td>#15 RANDOMIZED-CONTROLLED-TRIAL in PT</td>
</tr>
<tr>
<td>#14 #6 and #13</td>
</tr>
<tr>
<td>#13 #7 or #8 or #9 or #10 or #11 or #12</td>
</tr>
<tr>
<td>#12 LPVS</td>
</tr>
<tr>
<td>#11 pressure?limited</td>
</tr>
<tr>
<td>#10 protective near ventilation</td>
</tr>
<tr>
<td>#9 tidal volume</td>
</tr>
<tr>
<td>#8 explode respiration, artificial/all subheadings</td>
</tr>
<tr>
<td>#7 explode tidal volume/ all subheadings</td>
</tr>
<tr>
<td>#6 #1 or #2 or #3 or #4 or #5</td>
</tr>
<tr>
<td>#5 ARDS or ALI</td>
</tr>
<tr>
<td>#4 Acute Respiratory Distress Syndrome</td>
</tr>
</tbody>
</table>
Appendix 3. SilverPlatter EMBASE - Search

Search terms

#43 #17 and #42
#42 #37 not #41
#41 #39 not #40
#40 #38 and #39
#39 (animal or nonhuman) in DER
#38 (human) in DER
#37 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
#36 clinic* near trial*
#35 explode "comparative-study" / all SUBHEADINGS in DEM,DER,DRM,DRR(87715 records)
#34 research near design*
#33 prospective?stud*
#32 explode "prospective-study" / all SUBHEADINGS in DEM,DER,DRM,DRR(31366 records)
#31 evaluation stud*
#30 (follow?up near stud*) in TI, AB
#29 explode "follow-up" / all SUBHEADINGS in DEM,DER,DRM,DRR
#28 ((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in TLAB
#27 (RANDOM* or CROSS?OVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI, AB, TW
#26 explode phase-4-clinical-trial / all subheadings or explode double-blind-procedure / all subheadings or explode single-blind-procedure / all subheadings
#25 multi?cent*
#24 explode multicenter-study / all subheadings
#23 explode "clinical-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR
#22 randomi?ation
#21 explode "randomization-" / all SUBHEADINGS in DEM,DER,DRM,DRR
#20 random*
#19 (randomi?ed controlled trial*) in TI, AB
#18 explode "randomized-controlled-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR
#17 #9 and #16
#16 #10 or #11 or #12 or #13 or #14 or #15
#15 LPVS
#14 pressure?limited
#13 protective near ventilation
#12 tidal volume
#11 explode "artificial-ventilation" / all SUBHEADINGS in DEM,DER,DRM,DRR
#10 explode "tidal-volume" / all SUBHEADINGS in DEM,DER,DRM,DRR
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
Appendix 4. SilverPlatter CINAHL - Search

Search terms

#13 #6 and #12
#12 #7 or #8 or #9 or #10 or #11
#11 pressure?limited
#10 protective near ventilation
#9 tidal volume
#8 artificial near ventilation
#7 explode “Tidal-Volume” / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#6 #1 or #2 or #3 or #4 or #5
#5 ARDS or ALI
#4 Acute Respiratory Distress Syndrome
#3 adult Respiratory Distress Syndrome
#2 Acute Lung Injury
#1 (explode “Respiratory-Distress-Syndrome” / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) or (explode “Respiratory-Distress-Syndrome-Acute” / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE)

WHAT’S NEW

Last assessed as up-to-date: 14 November 2006.

18 February 2009  Amended  minor editing of text
This review has been updated in the following ways:

1. A new literature search was run covering trials published up to October 2006.
2. One new trial has been published since the previous version of the review.
3. This trial was included in the analysis. The results from this trial confirmed that low tidal volumes improve survival in acute respiratory distress syndrome (ARDS).
4. The title of the review has changed from “Ventilation with lower tidal volumes versus traditional tidal volumes in adults for acute lung injury and acute respiratory distress syndrome” to “Lung protective ventilation strategy for the acute respiratory distress syndrome”. This is because it emerged from the updating that additional (but subordinate) factors other than low tidal volume are involved. The favourable outcome depends on low volume AND low pressure. Positive end expiration pressure (PEEP) is not a determinant of outcome. Thus, as it is a strategy rather than a single intervention the title has been changed to a more general one.
CONTRIBUTIONS OF AUTHORS

Conceiving the review: Nicola Petrucci (NP)
Co-ordinating the review: NP
Undertaking manual searches: NP and Walter Iacovelli (WI)
Screening search results: NP
Organizing retrieval of papers: NP
Screening retrieved papers against inclusion criteria: NP
Appraising quality of papers: NP and WI
Abstracting data from papers: NP and WI
Writing to authors of papers for additional information: NP
Data management for the review: NP
Entering data into Review Manager (RevMan 4.2): NP
RevMan statistical data: NP
Double entry of data: (data entered by person one: NP; data entered by person two: WI)
Interpretation of data: NP and IW
Statistical inferences: NP
Writing the review: NP
Guarantor for the review (one author) NP

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Azienda Ospedaliera Desenzano, Desenzano del Garda, Italy.
External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)
Randomized Controlled Trials as Topic; Respiration, Artificial [* methods]; Respiratory Distress Syndrome, Adult [mortality; *therapy]; Tidal Volume

MeSH check words
Adult; Humans