

Setting PEEP in ALI/ARDS

Compared to a low tidal volume/low PEEP strategy, a low tidal volume/fixed plateau pressure/higher PEEP strategy offers no mortality benefit but may be associated with reduced morbidity.

Level of evidence: 1⁺ (RCT with a low risk of bias)

Appraised by: Sue Griffiths, Chris Cairns

Citation: Mercat A, Richard JM, Vielle B *et al.* Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA* 2008; 299: 646-55.

Lead author: Alain Mercat

Three-part clinical question:

Patients: Adults receiving mechanical ventilation for hypoxaemic respiratory failure caused by acute lung injury (ALI) or acute respiratory distress syndrome (ARDS).

Intervention: Comparison of a minimal distension strategy ie moderate PEEP (5-9 cm H₂O) against an increased recruitment strategy ie level of PEEP set to reach a plateau pressure of 28 to 30 cm H₂O. Tidal volume (Vt) of 6 mL/kg used in both groups.

Outcomes: Primary – 28-day mortality; Secondary – 60-day mortality, ventilator-free days, organ failure-free days at 28 days, incidence of pneumothorax during treatment

Search terms: ARDS; ALI; PEEP; ventilation; RCT; mortality

The study: Multi-centre, single-blinded, concealed randomised controlled trial with intention-to-treat analysis.

Study patients: From 37 ICUs in France over a three-year period. Age >18 years.

Exclusions: Pneumothorax, do-not-resuscitate order, chronic liver failure, lack of consent, expected duration of ventilation

<48 hours, participation in another trial, bone marrow transplant or chemotherapy-induced neutropaenia, long-term oxygen therapy, intracranial hypertension, morbid obesity.

Standard strategies: Volume-assist control mode used with targets of: Vt <6 mL/kg, plateau pressure limit <30 cm H₂O, respiratory rate (RR) <35, pH 7.30-7.45, PaO₂ 55-80 mm Hg, SpO₂ 88-95%. These oxygenation goals were achieved by adjusting the FiO₂. Recruitment manoeuvres were allowed but not recommended, adjunctive therapies ie inhaled NO, prone positioning, almitrine bismesylate were allowed when the oxygenation goal was not met despite an FiO₂ > 0.8 From day four onwards, if PaO₂:FiO₂ >150 mm Hg, a standardised PEEP weaning trial was performed and if tolerated, a standardised spontaneous breathing test undertaken. Based on this, the attending physician decided whether to extubate the patient or not.

Control group – minimal distension group: (n = 383; 382 analysed): Standard strategies plus: PEEP and inspiratory plateau pressure were kept as low as possible while achieving oxygenation targets. External PEEP was set to achieve a total PEEP 5-9 cmH₂O.

Experimental group – increased recruitment group: (n = 385; 385 analysed): Standard strategies plus: PEEP was adjusted based on airway pressure and kept as high as possible without increasing maximal inspiratory pressure above 28-30 cmH₂O regardless of oxygenation.

The evidence:

Outcome	Time to outcome	CER	EER	RRR	ARR	NNT
Mortality	28 days	0.311	0.278	11%	0.033	NS
	95% confidence intervals:			-10% to 31%	-0.031 to 0.097	NS
Mortality	60 days	0.394	0.358	9%	0.036	NS
	95% confidence intervals:			-8% to 27%	-0.032 to 0.104	NS
Pneumothorax	28 days	0.057	0.067	-18%	-0.010	NS
	95% confidence intervals:			-77% to 42%	-0.044 to 0.024	NS

Non-event outcomes	Time to outcome/s	Control group	Experimental group	P-value
Ventilator-free days	28 days	3 days	7 days	0.04
Organ failure-free days	28 days	2 days	6 days	0.04
Number of patients requiring adjunctive therapies to maintain oxygenation goals	7 days	132 patients	72 patients	< 0.001

Key CER: control event rate EER: experimental event rate RRR: relative risk reduction ARR: absolute risk reduction NNT: number needed to treat CI: confidence interval

Sub-group analysis: In patients with ARDS, the increased distension protocol was associated with earlier extubation and a trend towards improved mortality. The opposite was observed with patients with ALI but not ARDS.

EBM questions:

1. *Do the methods allow adequate testing of the hypothesis?* **Yes.** However, the study is potentially underpowered. The study was stopped early after the 18th scheduled interim analysis by the monitoring board, due to failure to demonstrate a 10% absolute reduction in mortality. (Target recruitment was 400 patients in each arm assuming 40% mortality in the control group.) The sub-group analysis of ARDS vs non-ARDS ALI relies on very small patient numbers.
2. *Do the statistical tests correctly test the results to allow differentiation of statistically significant results?* **Yes.**
3. *Are the conclusions valid in light of results?* **Perhaps.** The distension protocol was associated with less ventilation time and less need for adjunctive therapies.
4. *Did results get omitted and why?* **Yes.** One patient was lost to follow-up. However, this patient was included in the intention-to-treat analysis.
5. *Did they suggest areas of further research?* **Yes.** They suggested further studies to determine the ideal balance between lower plateau pressures and higher PEEP.
6. *Did they make recommendations and are these appropriate?* The authors make no general recommendations about what level of PEEP to use. Based on subgroup analysis they do suggest a strategy of high level of PEEP and low tidal volume should be used in caution in ALI.
7. *Is this study relevant to my clinical practice?* **No.** This study did look at similar patients with regard to age, sex and severity of illness as present to general ICUs in the UK. However, the study really used two non-standard ventilation strategies when considering current practice.

One could argue that the gold standard for the control arm of any ARDS study should be the interventional strategy used in the ARDSNet study.

There are two main concerns with the study protocol:

- The minimal distension group used significantly lower PEEP levels compared with conventional current ventilatory management.
 - The PEEP in the recruitment arm is really determined by lung compliance, in that, once the inspiratory pressure has been set to achieve 6 mL/kg tidal volume, the remainder of the 30 cm H₂O plateau pressure will be used for PEEP. In relatively compliant lungs, this could lead to unnecessarily high PEEP levels which could be detrimental. This may account for the trends towards poorer outcome in ALI-only patients and the greater need for fluid bolus in this group. In other words many of these patients may not require such a plateau pressure.
8. *What level of evidence does this represent?* **1⁺**
 9. *What grade of recommendation can I make on this alone?* **B**
 10. *What grade of recommendation can I make when this study is considered along with other available evidence?* No other studies compare these ventilation strategies. However, most recent studies agree that low tidal volume/plateau pressure strategies should be employed.
 11. *Should I change my practice in light of this study?* If you currently use ARDSNet ventilation strategies then there is little evidence here to change your practice.
 12. *Should I audit my current practice because of these results?* **Yes.**

Appraised by:

Sue Griffiths, SpR Anaesthetics, Royal Liverpool University Hospital, suegriff99@mac.com

Chris Cairns, Consultant, Intensive care, Stirling Royal Infirmary. Chris.Cairns2@nhs.net