Critical Review Form
Meta-analysis

PGY-4a

Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. JAMA. 2012 Oct 24;308(16):1651-9.

Objectives: To determine whether "lower tidal volume ventilation is associated with a decrease in progression to ARDS [acute respiratory distress syndrome] in mechanically ventilated patients."

Methods: A systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines. A search of the literature from 1967 to 2011 was conducted using MEDLINE, EMBASE, CINAHL, and the Cochrane Library, with the assistance of a trained information professional. The reference lists of articles chosen for inclusion were also screened by two study authors. Abstracts from the Society of Critical Care Medicine, European Society of Critical Care Medicine, American Society of Anesthesiology, American Thoracic Society, CHEST, and the Society of Academic Emergency Medicine were also searched from 2008 to 2011. A search for registered trials was also conducted using ClinicalTrials.gov.

Studies eligible for inclusion were randomized controlled trials (RCT), observational studies (retrospective or prospective), cross-sectional trials, or before-and-after trials of adults (age > 17) undergoing invasive positive-pressure ventilation, without ARDS at initiation of mechanical ventilation, in which tidal volume (TV) was assessed as a predictor of outcomes. Study titles and abstracts were reviewed independently by two reviewers for exclusion. Full text articles and manuscripts were then reviewed by the same reviewers. In case of disagreement, a third reviewer assessed the study and a consensus was reached among the three reviewers. Clinical trial study quality was assessed using the Cochrane Collaboration's tool, which assesses random sequence generation, concealment of allocation, blinding, and selective outcome reporting. Observational trial quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Thirteen studies, published between 2004 and 2011, were included in the final analysis. Of these, only one was a RCT; the remainder were observational studies. The RCT was rated as high quality, while none of the observational trials reported adherence to the STROBE guidelines. Ten of the trials were conducted using

patients in Intensive Care Units (ICUs), while 3 were performed in the operating room. None of the studies evaluated patients in the Emergency Department (ED).

Guide	Question	Comments
I	***Are the results valid?***	
1.	Did the review explicitly address a sensible question?	Yes. The question addressed was whether lower tidal volume ventilation strategies decreased the risk of developing ARDS. This is an important question, as the association between ARDS and mortality is well-known, and a simple intervention to reduce the risk of its development could potentially save countless lives, assuming to adverse effect related to that intervention. Given the previously described benefits of low tidal volume ventilation in patients who have already developed ARDS, it seems reasonable to assess the use of such an intervention in its prevention.
2.	Was the search for relevant studies details and exhaustive?	Yes. A literature search was conducted with the assistance of a trained information professional (e.g. medical librarian) using the major databases of medical literature (MEDLINE, EMBASE, CINAHL, and the Cochrane Collaborative). Additionally, the reference lists of included studies, conference abstracts, and registered trials were searched.
3.	Were the primary studies of high methodological quality?	No. Only one of these studies was a RCT, though this study was of high quality (grade A for random sequence generation, concealment of allocation, and selective outcome reporting; grade C for blinding). None of the observational trials reported adhering to STROBE guidelines.
4.	Were the assessments of the included studies reproducible?	Yes. The quality of the single RCT was assessed using the Cochrane Collaboration's tool, while the quality of the observational trials was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. Both of these tools have been well-described and are easily reproducible.
II.	***What are the results?***	
1.	What are the overall results of the study?	The single RCT found an increased risk of ARDS with conventional TV (10 mL/kg predicted body weight [PBW]) compared with low TV (6 mL/kg PBW) strategies, with a 10.9% ARR (NNT = 9.2). 3 studies were conducted in the OR (n=58,419). The largest of these (n=53,910) demonstrated an association between TV and progression to ARDS, however the TV difference between the groups was not clinically

		significant (0.1 mL/kg PBW). The incidence of ARDS in these studies was low (0.2%-1.9%). 9 observational studies were conducted in ICUs, of which 6 showed TV to be an independent predictor for progression to ARDS. 5 studies demonstrated a dose-response relationship (higher TV being associated with increased risk of ARDS). The incidence of ARDS in these studies ranged from 6.2% to 44%. None of the studies reported adverse events associated with the use of low tidal volumes. Due to significant heterogeneity among these studies, a meta-analysis was not performed.
2.	How precise are the results?	N/A. No meta-analysis was performed.
3.	Were the results similar from study to study?	No. There was significant clinical and methodological heterogeneity between these studies, including randomization in only one trial, different patient settings (OR, ICU), and a wide range in the incidence of ARDS. The authors wisely chose not to perform a meta-analysis given this heterogeneity.
III.	***Will the results help me in caring for my patients?***	
1.	How can I best interpret the results to apply them to the care of my patients?	The systematic review identified a single randomized controlled trial and several observational studies assessing lung protective strategies to prevent ALI/ARDS. While there was significant clinical and methodological heterogeneity, and the majority of the studies were of poor methodological quality, the preponderance of the evidence suggests that low tidal volumes may prevent the development of ALI/ARDS. Given the few downsides associated with this modality (atelectesis, hypoventilation) intubated patients without contraindications should be ventilated using lower tidal volumes (6-8 mL/kg of ideal body weight).
2.	Were all patient important outcomes considered?	Yes. The various studies assessed the development of ALI/ARDS, mortality, ICU and hospital length of stay, ventilator-free days, and the development of organ failure.
3.	Are the benefits worth the costs and potential risks?	Yes. As noted above, there are few downsides to using low tidal volume ventilation in appropriate patients, while prevention of ALI and ARDS are significant benefits.

Limitations:

1. **The included studies were of mostly poor methodological quality.**
2. **None of the included studies involved patients recruited from the emergency department.**
3. **The single included randomized controlled trial was stopped early for benefit after an unplanned interim analysis.**
4. **There was significant methodological and clinical heterogeneity between the included studies, precluding meta-analysis of the data.**
5. **Assessment of the funnel plot suggests the presence of publication bias.**

Bottom Line:

The systematic review identified a single randomized controlled trial and several observational studies assessing lung protective strategies to prevent ALI/ARDS. While there was significant clinical and methodological heterogeneity, and the majority of the studies were of poor methodological quality, the preponderance of the evidence suggests that low tidal volumes may prevent the development of ALI/ARDS. Given the few downsides associated with this modality (atelectasis, hypoventilation) intubated patients without contraindications should be ventilated using lower tidal volumes (6-8 mL/kg of ideal body weight).