Critical Review Form
Therapy

Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301-8.

Objectives: **"to determine whether the use of a lower tidal volume with mechanical ventilation would improve important clinical outcomes in such patients." (p. 1302)**

Methods: **This study was conducted at 10 hospitals in the Acute Respiratory Distress Syndrome Network, from March 1996 to March 1999. Patients were eligible if they were intubated, receiving mechanical ventilation, had an acute drop in the ratio of PaO_2 to FiO_2 ratio to ≤ 300 mmHg, had pulmonary edema on chest x-ray, and had no evidence of left atrial hypertension or a pulmonary-capillary wedge pressure of ≤ 18 mmHg. Exclusion criteria included intubation and development of ALI/ARDS ≥ 36 hours prior, age < 18 years, pregnancy, increased intracranial pressure, neuromuscular disease that would impair spontaneous breathing, sickle cell disease, severe chronic respiratory disease, a weight more than 1 kg per cm of height, burns over ≥ 30 body surface area, prior bone marrow or lung transplantation, chronic liver disease, refusal of the attending physician to use full life support, or any condition with a 6-month expected mortality of > 50%.**

Patients were randomly assigned to either traditional tidal volume (V_T) or lower tidal volume through the use of a centralized, interactive voice system. Traditional V_T involved initiating ventilation at 12 mL/kg of ideal body weight; V_T was then titrated by 1 mL/kg to maintain a plateau pressure between 45-50 cm H_2O, with a lower V_T limit of 4 mL/kg. In the lower V_T group, the V_T was reduced to 6 mL/kg within 4 hours of randomization, with titration by 1 mL/kg to maintain a plateau pressure of 25-30 cm H_2O, with a lower V_T limit of 4 mL/kg and an upper limit of 6 mL/kg. Volume-assist-control mode was used in all patients until the patient was weaned from the ventilator, or for 28 days following randomization.

Patients were assessed daily for signs of organ failure for 28 days, defined as:

1. **Systolic blood pressure ≤ 90 mm Hg, or need for vasopressors (circulatory failure)**
2. **Platelet count ≤ 80,000/mm^3 (coagulation failure)**
3. **Serum bilirubin ≥ 2 mg/dL (hepatic failure)**
4. **Serum creatinine of ≥ 2 mg/dL (renal failure)**

The primary outcome was death (prior to discharge home and breathing without assistance). The secondary outcomes were the number of ventilator-free days in the first 28 days, the number of days without organ/system failure, and the occurrence of

barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele).

The trial was stopped early (due to benefit) with 861 patients enrolled: 432 in the low V_T group, 429 in the traditional V_T group. Patients were similar with respect to age, gender, APACHE III score, PaO_2:FiO_2 ratio, initial tidal volume, and the presence of lung inury. The low V_T group had slightly higher initial minute ventilation compared to the traditional V_T group (13.4 L/min vs. 12.7 L/min, p = 0.01).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes. "A centralized interactive voice system was used for randomization." (p. 1302) The authors provide no details about how the randomization sequence was generated.
2.	Was randomization concealed (blinded)?	Uncertain. The authors do not provide any information regarding how the randomization sequence was generated, or how randomization was concealed.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. The authors do not mention any patients randomized to one group, but subsequently treated as if in the other group. While not specifically mentioned, an intention to treat analysis appears to have been used.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly yes. Patients in the low V_T and traditional V_T group were similar with respeact to mean age (51 vs. 52), % female (40% vs. 41%), APACHE III score (81 vs. 84), PaO_2:FiO_2 ratio (138 vs. 134), initial V_T (676 mL vs. 665 mL), and the number of organ or system failures at baseline (1.8 vs. 1.8). Patients in the low V_T group had slightly higher initial minute ventilation (13.4 vs. 12.7 mL/min, p = 0.01).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No mention of blinding is made, however all patients were intubated during the treatment period and were likely unaware of group allocation. Performance bias would be unlikely to affect the

<table>
<tr><td></td><td></td><td>outcomes.</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>Yes. The authors do not mention blinding of the clinicians, and this would be difficult to do given the nature of the intervention. This could potentially lead to performance bias.</td></tr>
<tr><td>3.</td><td>Were outcome assessors aware of group allocation?</td><td>Uncertain. There is no mention of blinding of outcome assessors (either during data collection or data analysis). There is therefore, a risk of observer bias.</td></tr>
<tr><td>4.</td><td>Was follow-up complete?</td><td>Yes. “Patients were followed until day 180 or until they were breathing on their own at home.” (p. 1303)</td></tr>
<tr><td>II.</td><td>What are the results (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>Mortality was 39.8% in the low V_T group and 31.0% in the traditional V_T group (p = 0.007; ARR = 8.8%, 95% CI 2.4-15.3%). NNT = 11 (95% CI 6.6-40.4).

Table. Main Outcome Variables
<table>
<tr><th>Variable</th><th>Low V_T</th><th>Trad. V_T</th><th>p-value</th></tr>
<tr><td>Death before D/C home and breathing w/o assistance</td><td>31.0</td><td>39.8</td><td>0.007</td></tr>
<tr><td>Breathing w/o assistance by day 28</td><td>65.7</td><td>55.0</td><td><0.001</td></tr>
<tr><td># of vent-free days for days 1-28</td><td>12±11</td><td>10±11</td><td>0.007</td></tr>
<tr><td>Barotrauma</td><td>10</td><td>11</td><td>0.43</td></tr>
<tr><td># of days w/o organ/system failure for days 1-28</td><td>15±11</td><td>12±11</td><td>0.006</td></tr>
</table></td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>Yes and no. These were previously intubated ICU patients who had developed acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). If a patient in the ED develops ALI/ARDS, the physiology of such a patient would be similar to the ICU patients in this study.</td></tr>
</table>

		However, few patients develop ALI or ARDS while still in the ED. While this study proves that low V_T strategies will reduce mortality and increase the number of ventilator-free days in patients who have developed ALI/ARDS, it is unclear from this study if such strategies will prevent the development of ALI or ARDS.
2.	Were all clinically important outcomes considered?	Yes, mostly. The authors did not assess quality of life, neurologically intact survival, pulmonary function, or healthcare costs.
3.	Are the likely treatment benefits worth the potential harm and costs?	Yes. There are no apparent costs associated with a low V_T strategy compared to traditional V_T. The associated harms involved increased FiO_2 and respiratory rate, however patient-important outcomes were not deleteriously affected, but rather showed significant improvements. Given the significant reduction in mortality (8.8%, NNT = 11) with low V_T in patients with ALI/ARDS, it seems reasonable to recommend this in all such patients without reasonable contra-indications.

Limitations:

1. **The authors do not provide information regarding sequence generation or detail the methods of allocation concealment.**

2. **There was incomplete blinding. While blinding of patients would likely not affect outcomes and blinding of clinicians may not have been feasible, the authors do not mention blinding of outcome assessors (data collectors or analysts). This would have been feasible and would reduce the risk of observer bias.**

3. **The authors do not provide a power analysis to justify their planned sample size (and do not in fact inform us of their planned sample size).**

4. **There is no flow-chart of patients screened, patients excluded, and patients enrolled.**

5. **The initial V_T used in the traditional group was 12 mL/kg of ideal body weight. This is higher than traditional V_T typically used, and may have resulted in an exaggerated effect size.**

6. **The trial was stopped early, due to perceived benefit. This practice has been called into question, and the results may have been different had the study been completed.**

7. **While this study proves that low V_T strategies will reduce mortality and increase the number of ventilator-free days in patients who have developed ALI/ARDS, it is unclear from this study if such strategies will prevent the development of ALI or ARDS.**

8. **Failure to discuss trial limitations.**

Bottom Line:

This randomized controlled trial of traditional versus low V_T ventilation in patients with ALI or ARDS demonstrated a significant reduction in 28 day mortality (ARR 8.8%, NNT = 11), with an increase in both ventilator-free days and days without organ or system failure. While this data suggests that lower tidal volumes should be employed in such patients, it does not prove that such strategies can prevent the development of ALI or ARDS. Further research will need to establish whether low tidal volume ventilation, initiate early following intubation, can reduce the risk of lung injury in select patients.