**Critical Review Form**
**Therapy**

PGY-3

Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. Crit Care. 2010;14(1):R1.

**Objectives:** **"to determine whether mechanical ventilation with conventional or lower tidal volume would be associated with different cytokine patterns in the lungs and the plasma of critically ill patients without ALI [acute lung injury] at onset of mechanical ventilation." (p. 2)**

**Methods:** **Patients were enrolled from two intensive care units (ICUs), one in an academic center and one in regional teaching hospital, in the Netherlands from January 2005 to December 2007. Patients who did not meet criteria for ALI or acute respiratory distress syndrome (ARDS), who required ventilation for an anticipated 72 hours or more, and who could be randomized within 36 hours of the onset of mechanical ventilation were considered eligible. Exclusion criteria included age < 18 years, enrollment in another clinical trial, pregnancy, uncontrolled elevated intracranial pressure, COPD, restrictive lung disease, use of immunosuppressive agents, pulmonary embolism, prior pneumonectomy or lobectomy, or previous randomization in the study. Block randomization by site and by blocks of 50 patients was conducted using sealed, opaque envelopes.**

**All subjects were ventilated using volume-control. Patients in the conventional group were ventilated with a tidal volume ($V_T$) of 10 mL/kg of predicted body weight, while those in the intervention group were ventilated with a $V_T$ of 6 mL/kg of predicted body weight. For the intervention group, physicians were allowed to increase the $V_T$ to 7-8 mL/kg for severe dyspnea (defined as increased respiratory rate to 35-40 breaths per minute with increasing levels of discomfort). All ventilators were switched to pressure support 3 times per day, and if the patient tolerated this mode, pressure support was continued for further ventilation. Pressure support was adjusted to target $V_T$, but if the applied $V_T$ exceeded the target due to high levels of pressure support, this was accepted and such patients were analyzed according to their assigned randomization group (intention to treat analysis). If ALI was diagnosed in either group at any time, $V_T$ was set to 6 mL/kg in pressure-support mode for the remainder of the ventilation period.**

**Bronchoalveolar lavage was performed in blinded fashion on the day of enrollment and on each second day. The primary outcome measures were lavage fluid and plasma cytokine levels. Secondary outcomes included development of ALI or ARDS, duration of ventilation, and mortality. Two independent physicians blinded to clinical parameters and randomization group reviewed all chest radiographs. Radiographs with new or worsening abnormalities were selected for further review,**

**at which time the two physicians were given access clinical information required to diagnose ALI/ARDS.**

**The study was stopped early after recruiting 150 patients, as significantly more patients in the conventional $V_T$ group had developed ALI compared to the low $V_T$ group. The groups were similar with respect to gender, initial $V_T$ prior to randomization, APACHE II score, SOFA score, $PaO_2/FiO_2$ ratio, and x-ray abnormalities. Patients in the low $V_T$ group were older than those in the conventional $V_T$ group (mean age 63 vs. 58) and had higher rates of smoking (76% vs. 61%). Twelve patients developed ALI/ARDS by criteria after 1.9 ± 1.1 days.**

| Guide | | Comments |
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| **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. "Randomization was performed by using sealed opaque envelopes in blocks of 50 patients. Each study center had its own randomization block." (p. 2) |
| 2. | Was randomization concealed (blinded)? | Yes. Sealed, opaque envelopes were used. We are not told how the randomization sequence was generated. |
| 3. | Were patients analyzed in the groups to which they were randomized? | Yes. The authors explicitly state that for cases in which "the attending physician preferred pressure-support ventilation in a patient randomized to the lower-tidal-volume group, and the applied tidal volume exceeded the target tidal volume because of high levels of pressure support, then this was accepted. **Such patients were kept in their original randomization group in the statistical analyses**." (p. 3) An intention to treat analysis was therefore used. |

<table>
<tr><td>4.</td><td>Were patients in the treatment and control groups similar with respect to known prognostic factors?</td><td>Table 1. Baseline risk factors<table><tr><th>Risk factor</th><th>Conventional $V_T$ (n=74)</th><th>Low $V_T$ (n=76)</th><th>p-value</th></tr><tr><td>Age (mean)</td><td>58</td><td>63</td><td>0.06</td></tr><tr><td>Male sex (%)</td><td>68</td><td>64</td><td>0.69</td></tr><tr><td>APACHE II (mean)</td><td>20</td><td>21</td><td>0.93</td></tr><tr><td>SOFA (mean)</td><td>8</td><td>7</td><td>0.19</td></tr><tr><td>$PaO_2/FiO_2 > 40$ and normal CXR</td><td>17</td><td>17</td><td></td></tr><tr><td>$PaO_2/FiO_2 > 40$ and abnormal CXR</td><td>6</td><td>6</td><td></td></tr><tr><td>$PaO_2/FiO_2 < 40$ and normal CXR</td><td>33</td><td>34</td><td></td></tr><tr><td>$PaO_2/FiO_2 < 40$ and abnormal CXR</td><td>18</td><td>19</td><td></td></tr></table>The groups were similar with respect to gender, APACHE II score, SOFA score, $PaO_2/FiO_2$ ratio, and x-ray abnormalities. Patients in the low $V_T$ group were older than those in the conventional $V_T$ group and had higher rates of smoking.<br><br>Other key information was not reported for the groups, including vital signs, fluids, vasopressor use, antibiotics, and blood product transfusion. These factors may have influenced the ARDS rates for the groups.</td></tr>
<tr><td>B.</td><td>Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were patients aware of group allocation?</td><td>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 outcomes.</td></tr>
<tr><td>2.</td><td>Were clinicians aware of group allocation?</td><td>Yes. Clinicians were not blinded to group allocation, 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>Yes. The authors specifically mention that bronchoalveolar lavage was performed blindly, and that chest radiographs were reviewed for signs of ALI/ARDS by physicians blinded to clinical data and group allocation. In case of abnormal chest radiograph interpretation, the physicians were given enough clinical information to determine if criteria for ALI/ARDS was present.</td></tr>
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| 4. | Was follow-up complete? | No. Only one patient in the conventional $V_T$ group was lost to follow-up due to being transferred to another hospital. The remaining patients were followed through their hospital stay, during which time the developing of ALI/ARDS could be evaluated adequately. |
| **II.** | **What are the results (answer the questions posed below)?** | |
| 1. | How large was the treatment effect? | <u>Cytokine levels:</u><br>Baseline lavage-fluid levels of TNF-α and IL-1β were similar in both groups, while baseline IL-6 levels were higher in the conventional $V_T$ group compared to the low $V_T$ group (384 pg/mL vs. 112 pg/mL, p = 0.07). Lavage fluid levels remained similar in both groups over time.<br><br>Baseline plasma IL-6 levels were comparable between the two groups. Plasma IL-6 levels decreased more in the conventional $V_T$ group compared to the low $V_T$ group after 4 days (21 ng/mL vs. 11 ng/mL, p = 0.01).<br><br>Patients in whom ALI developed had higher baseline lavage-fluid levels of IL-6 (593 pg/mL vs. 226 pg/mL, p = 0.04). While baseline plasma IL-6 levels were similar between those who did and did not develop ALI, levels increased more after 4 days in those in whom ALI did develop (p = 0.01).<br><br><u>ALI/ARDS</u><br>In the conventional $V_T$ group, 10 (14%) developed ALI/ARDS compared to 2 (3%) in the low $V_T$ group (p = 0.01) for a RR of 5.1 (95% CI 1.2-22.6).<br><br>The median number of ventilator free days at 28-days was similar in the conventional and low $V_T$ groups (24.0 vs. 24.0, p = 0.88). Mortality at 28 days was also similar between the groups (31% vs. 32%, p = 0.94).<br><br>Multivariate analysis revealed that the randomization group (p = 0.007) and PEEP level (p = 0.001) were independent predictors for the development of ALI/ARDS). |
| 2. | How precise was the estimate of the treatment effect? | See above. |
| **III.** | **How can I apply the results to patient care (answer the questions** | |

| | posed below)? | |
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| 1. | Were the study patients similar to my patient? | No. These were patients admitted to the ICU, randomized within 36 hours of initiation of mechanical ventilation. While these results suggest that use of a low $V_T$ strategy reduces the risk of developing ALI or ARDS, it is unclear if initiation of such a strategy earlier in the clinical course (within a few hours of intubation) will reduce this risk, or if such a decision can be delayed to ICU admission. |
| 2. | Were all clinically important outcomes considered? | No. The primary outcome involved the levels of lavage and plasma cytokines, which is a surrogate marker of disease, and does not necessarily correlate with clinically important outcomes. The authors did assess patients for the development of ALI/ARDS, which is more clinically relevant, as well as the number of ventilator-free days and mortality at 28 days. Long-term mortality and quality of life were not assessed in this study. |
| 3. | Are the likely treatment benefits worth the potential harm and costs? | Yes. There is very little risk associated low $V_T$ ventilation (primarily atelectesis and $CO_2$ retention). Given the higher risk of developing ALI/ARDS with conventional ventilation, and the known association between ALI/ARDS and mortality, it seems reasonable to recommend lower $V_T$ ventilation for intubated patients. It remains to be seen whether this strategy is necessary in all intubated patients, or if certain subgroups are likely to see benefit, while others are not. |

**Limitations:**

1. **The authors do not provide information regarding sequence generation.**
2. **Plateau pressures were not measured/monitored.**
3. **There was incomplete blinding. While blinding of patients would likely not affect outcomes, and blinding of clinicians may not have been feasible, some degree of performance bias is possible.**
4. **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.**
5. **The primary outcome was change in lavage fluid and plasma cytokine levels. Such a surrogate marker may not correlate with patient-centered outcomes. The reduced risk of ALI was therefore a secondary outcome, and its statistical significance remains uncertain.**

**Bottom Line:**

**This methodologically sound, randomized controlled trial, demonstrated a larger decrease in plasma IL-6 levels in the conventional $V_T$ group compared to the low $V_T$ group. Patients in whom ALI developed had higher baseline lavage-fluid levels of IL-6, and larger increases in plasma IL-6 levels. The study also demonstrated a reduced risk of developing ALI when lung-protective (low $V_T$) ventilation was employed (ARR = 11%, NNT = 9). Unfortunately, this was a secondary outcome. Further studies should address the use of lung-protective ventilation using patient-important primary outcomes.**