Work of Breathing During Lung-Protective Ventilation in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome: A Comparison Between Volume and Pressure-Regulated Breathing Modes

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BACKGROUND: Pressure-control ventilation (PCV) and pressure-regulated volume-control (PRVC) ventilation are used during lung-protective ventilation because the high, variable, peak inspiratory flow rate (V˙I) may reduce patient work of breathing (WOB) more than the fixed V˙I of volume-control ventilation (VCV). Patient-triggered breaths during PCV and PRVC may result in excessive tidal volume (VT) delivery unless the inspiratory pressure is reduced, which in turn may decrease the peak V˙I. We tested whether PCV and PRVC reduce WOB better than VCV with a high, fixed peak V˙I (75 L/min) while also maintaining a low VT target. METHODS: Fourteen nonconsecutive patients with acute lung injury or acute respiratory distress syndrome were studied prospectively, using a random presentation of ventilator modes in a crossover, repeated-measures design. A target VT of 6.4 ± 0.5 mL/kg was set during VCV and PRVC. During PCV the inspiratory pressure was set to achieve the same VT. WOB and other variables were measured with a pulmonary mechanics monitor (Bicore CP-100). RESULTS: There was a nonsignificant trend toward higher WOB (in J/L) during PCV (1.27 ± 0.58 J/L) and PRVC (1.35 ± 0.60 J/L), compared to VCV (1.09 ± 0.59 J/L). While mean VT was not statistically different between modes, in 40% of patients, VT markedly exceeded the lung-protective ventilation target during PRVC and PCV. CONCLUSIONS: During lung-protective ventilation, PCV and PRVC offer no advantage in reducing WOB, compared to VCV with a high flow rate, and in some patients did not allow control of VT to be as precise. Key words: acute lung injury, acute respiratory distress syndrome, asynchrony, lung-protective ventilation, mechanical ventilation, tidal volume, work of breathing. [Respir Care 2005;50(12):1623–1631. © 2005 Daedalus Enterprises]
WORK OF BREATHING DURING LUNG-PROTECTIVE VENTILATION

Table 1. Patient Demographics at Entrance Into Study

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Diagnosis</th>
<th>$C_{Ri}$ (mL/cm H$_2$O)</th>
<th>$C_{CW}$ (mL/cm H$_2$O)</th>
<th>PEEP (cm H$_2$O)</th>
<th>$P_{aO_2}/F_{I O_2}$ (mm Hg)</th>
<th>LIS</th>
<th>MIP (cm H$_2$O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>28</td>
<td>ARDS: necrotizing pancreatitis, ACS</td>
<td>26</td>
<td>98</td>
<td>8</td>
<td>290†</td>
<td>2.00</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>69</td>
<td>ALI: necrotizing pancreatitis, ascites, pleural effusions</td>
<td>41</td>
<td>102</td>
<td>5</td>
<td>276</td>
<td>1.75</td>
<td>50</td>
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<td>3</td>
<td>M</td>
<td>40</td>
<td>ARDS: necrotizing pancreatitis, ascites</td>
<td>29</td>
<td>67</td>
<td>10</td>
<td>184</td>
<td>2.75</td>
<td>57</td>
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<tr>
<td>4</td>
<td>M</td>
<td>24</td>
<td>ALI: necrotizing pancreatitis, ascites</td>
<td>24</td>
<td>66</td>
<td>8</td>
<td>229</td>
<td>2.25</td>
<td>92</td>
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<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>ARDS: Pneumocystis carinii pneumonia, pancreatitis</td>
<td>22</td>
<td>82</td>
<td>10</td>
<td>154</td>
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<td>6</td>
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<td>74</td>
<td>ARDS: burns</td>
<td>22</td>
<td>69</td>
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<td>161</td>
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<tr>
<td>7</td>
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<td>53</td>
<td>ALI: trauma, sepsis</td>
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<td>216</td>
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<td>8</td>
<td>F</td>
<td>36</td>
<td>ARDS: amniotic fluid embolism</td>
<td>37</td>
<td>146</td>
<td>5</td>
<td>185</td>
<td>2.25</td>
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<tr>
<td>9</td>
<td>M</td>
<td>39</td>
<td>ARDS: pneumonia, sepsis</td>
<td>14</td>
<td>200*</td>
<td>14</td>
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<td>3.75</td>
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<tr>
<td>10</td>
<td>F</td>
<td>41</td>
<td>ARDS: sepsis</td>
<td>25</td>
<td>93</td>
<td>5</td>
<td>297†</td>
<td>2.00</td>
<td>60</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>45</td>
<td>ARDS: multiple trauma, sepsis</td>
<td>20</td>
<td>73</td>
<td>5</td>
<td>250†</td>
<td>2.25</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
<td>65</td>
<td>ARDS: pancreatitis, ascites</td>
<td>23</td>
<td>99</td>
<td>10</td>
<td>156</td>
<td>2.75</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>72</td>
<td>ALI: multiple trauma</td>
<td>29</td>
<td>99</td>
<td>5</td>
<td>210</td>
<td>2.25</td>
<td>35</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>25</td>
<td>ARDS: trauma</td>
<td>15</td>
<td>112</td>
<td>10</td>
<td>158</td>
<td>3.25</td>
<td>27</td>
</tr>
</tbody>
</table>

Mean ± SD 46 ± 17  29 ± 16  102 ± 41  7.5 ± 2.9  209 ± 64  2.45 ± 0.64  50 ± 19

$C_{Ri}$ = respiratory system compliance. $C_{CW}$ = chest wall compliance. PEEP = positive end-expiratory pressure. $P_{aO_2}/F_{I O_2}$ = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen. LIS = lung injury score. MIP = maximum inspiratory pressure (esophageal). ARDS = acute respiratory distress syndrome. ACS = abdominal compartment syndrome. ALI = acute lung injury. *Normal $C_{CW}$ used as default; unable to achieve passive ventilation (mean ± SD of $C_{CW}$ excludes this patient’s data point). †$P_{aO_2}/F_{I O_2}$ is taken from reference arterial blood gas measurement on the day of study and does not reflect the fact that the patient originally met diagnostic criteria for ARDS (eg, $P_{aO_2}/F_{I O_2}$ < 200 mm Hg).

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During volume-control ventilation (VCV), increased patient WOB occurs when either the inspiratory flow rate ($V_{I}$) of the ventilator or the $V_{T}$ is below patient demand. In LPV this may be exacerbated by increased respiratory drive from acute hypercapnia. Pressure-regulated modes such as pressure-control ventilation (PCV),7 pressure-regulated volume-control (PRVC),8 and volume-assured pressure support9 ventilation are used to manage patients with ALI/ARDS. PCV and volume-assured pressure support utilize a high peak $V_{I}$ that varies with patient flow demand, and both modes reduce WOB in patients with ALI/ARDS ventilated at a $V_{T}$ of 10 mL/kg.7,9 During LPV with PCV, patient inspiratory efforts may result in excessive $V_{T}$ delivery4 unless the inspiratory pressure is reduced. This in turn may reduce the peak $V_{I}$, thus limiting the mode’s effectiveness in reducing patient WOB. Similarly, modeling of simulated patient-triggered ventilation with PRVC found that when $V_{T}$ delivery exceeded the preset $V_{T}$, both the airway pressure ($P_{aw}$) and peak $V_{I}$ subsequently decreased, resulting in increased simulated WOB.10 The effects of pressure-regulated modes on $V_{T}$ delivery, peak $V_{I}$, and WOB in patients undergoing LPV have not been investigated. Previous studies7,11,12 that used a conventional $V_{T}$ to compare WOB between pressure-regulated modes and VCV may have been biased because measurements were made at a constant $V_{T}$ and inspiratory time (TI) that resulted in an abnormally low peak $V_{I}$ during VCV (< 55 L/min). As an example, MacIntyre et al13 did not find a significant benefit in treating ventilator-patient asynchrony with a pressure-regulated mode, compared to VCV with the peak $V_{I}$ of approximately 75 L/min. In this study we inquired whether PCV and PRVC reduce patient WOB better than VCV with a fixed peak $V_{I}$ of 75 L/min while also maintaining $V_{T}$ close to an LPV target.

Methods

Subjects

Fourteen nonconsecutive patients on the general surgery, trauma surgery, and medical services were enrolled into the study (Table 1). Signed, informed consent was obtained from each patient’s relative. The study was approved by the Committee on Human Research of the University of California, San Francisco. Enrollment criteria
were to meet the North American-European Consensus Conference definition for ALI or ARDS,\textsuperscript{14} and clinical use of a $V_T \geq 8$ mL/kg predicted body weight. All patients were managed clinically with the National Institutes of Health ARDS Network\textsuperscript{15} low-$V_T$ protocol, and each patient had previously documented episodes of ventilator-patient asynchrony requiring an increased $V_T$ or increased sedation.

**Procedures**

Upon enrollment, a Smart Cath (Viasys Healthcare, Palm Springs, California) nasogastric tube with an esophageal balloon was placed in the lower third of the esophagus. The balloon position was manipulated while inspecting the synchrony of the peak esophageal pressure ($P_{eq}$) and $P_{aw}$ deflections. When cardiac artifact was minimized, an occlusion test was performed for position confirmation, using the method described by Baydur et al.\textsuperscript{16} All patients were studied in the semi-recumbent position. Peak inspiratory pressure ($P_{max}$) was measured using “Method 1” described by Marini et al.,\textsuperscript{17} whereby the airway was occluded at end-expiration, allowing no movement of air in either an inspiratory or expiratory direction.

Prior to data collection, relaxed chest-wall compliance curves were constructed using an analysis of 2–5 breaths during a brief period of controlled ventilation at the $V_T$ used clinically for LPV. This was achieved following additional sedation with propofol and transient hyperventilation to suppress spontaneous ventilatory activity. The curves were constructed from esophageal pressure-volume tracings with a counterclockwise movement, a narrow loop, and a rightward rotation of the axis.\textsuperscript{7} After patients recovered, central respiratory drive was monitored until the pre-sedation baseline had been achieved.

A Dräger Dura E-2 ventilator (Dräger Medical, Telford, Pennsylvania) was used for all studies. The target $V_T$ was that used clinically for LPV and was between 5.5 and 7.3 mL/kg predicted body weight, measured at the circuit Y adapter. For PCV the $P_{aw}$ change ($\Delta P_{aw}$) was set to achieve the target $V_T$ during VC while passive chest-wall compliance was measured. However, patient inspiratory efforts during PCV commonly caused the $V_T$ to exceed the target, so that the $\Delta P_{aw}$ then was decreased. The final $\Delta P_{aw}$ used was the *highest* pressure that at least *transiently* produced the target $V_T$, and this event marked the beginning of the stabilization period for PCV. The minimum $\Delta P_{aw}$ used was 10 cm H$_2$O above the positive end-expiratory pressure (PEEP) level, regardless of $V_T$ delivery. PEEP and fraction of inspired oxygen ($F_{O_2}$) were set according to the National Institutes of Health ARDS Network protocol.\textsuperscript{15}

Adjustments were made in each mode to achieve ventilator settings most favorable to reducing patient WOB while attempting to constrain $V_T$ delivery. During VC a square-wave flow pattern was used, with a peak $V_T$ of 75 L/min and a $T_I$ range of 0.50–0.80 s. This was done to minimize the end-inspiratory pause time on the Dräger E-2 ventilator, and also to limit intrinsic PEEP (PEEPi) at rapid respiratory frequencies ($f$).\textsuperscript{18} Likewise, the same $T_I$ range was used during PCV and PRVC to maximize peak $V_T$ (eg, by requiring a higher $P_{aw}$ to deliver the same $V_T$ within a shorter $T_I$). A nonbias flow trigger level of 3 L/min was used in all modes. In both PCV and PRVC the pressure-rise time feature was turned off so that the fastest inspiratory pressure-rise and highest possible peak $V_T$ could be achieved.\textsuperscript{19} The mandatory $f$ on each mode was set to produce the minute ventilation ($V_{E}$) used during clinical management.

**Protocol**

The study incorporated a random presentation of PCV, PRVC (Auto-Flow), and VC in a brief, time-series, cross-over design. A blind envelope pull was used to prevent presentation bias. Ten minutes were allowed for adaptation and stabilization of the breathing pattern, and data were collected over the following 10 min. Twenty breaths were used for analysis on each mode. After measurements had been completed on each mode, patients then were given a brief period (1–2 min) of breathing on continuous positive airway pressure (CPAP) at the same end-expiratory pressure used during mechanical ventilation, to measure each patient’s spontaneous $V_T$, peak $V_T$, and $T_I$. This was done to provide a gross estimation of ventilator-to-patient differences in $V_T$ ($\Delta V_{Tvent-pt}$), peak $V_T$ ($\Delta$ peak $V_T$vent-pt), and $T_I$ ($\Delta T_I$vent-pt) between modes, and to assess potential relationships to WOB and pressure-time product (PTP). Sedation during the study was controlled by the critical care team managing the patient. All patients received continuous infusions of sedatives and/or analgesics that produced a mean Ramsey score of 4.4 ± 0.7 during the study.\textsuperscript{20}

**Measurements**

Patient and ventilator variables were measured with a pulmonary mechanics monitor that incorporated Campbell diagram software (Bicore CP-100, Viasys Healthcare, Palm Springs, California). The precision and accuracy of this monitor has been previously validated.\textsuperscript{21,22} The monitor and transducers were calibrated prior to each study. The Var-Flex (Viasys Healthcare, Palm Springs, California) $P_{aw}$/flow transducer was placed at the circuit Y adapter so that reported $V_T$ excluded compressible circuit volume. End-tidal carbon dioxide partial pressure ($P_{ETCO_2}$) was measured at the circuit Y adapter, using a sidestream capnometer (Vital Cap, Oridion, Jerusalem, Israel).
Data collection included total f, inspired V_T, peak V_I, P_{ETCO2}, PEEP, the inspiratory change in P_es (ΔP_es), PTP, and T_I. Central respiratory drive was measured as the change in P_es at 100 ms (P_{0.1}) after the onset of inspiration. These variables were collected from two 40-breath printed reports, from which 20 randomly selected breaths were used for analysis. A separate 40-breath report was generated during the CPAP trial, from which 20 randomly selected breaths also were used for analysis. P_{ETCO2} was recorded at 1-min intervals. Campbell diagram software was used to measure patient WOB in J/L,\textsuperscript{21} and 20 consecutive breaths were analyzed. PEEP was measured dynamically as the difference in P_es between the end-expiratory plateau and were analyzed. PEEPi was measured dynamically as the change in P_es over T_I. During PCV, PRVC, and VCV, T_I were consistent with a normal distribution so that all data variables were collected from two 40-breath printed reports, from which 20 randomly selected breaths were used for analysis. A separate 40-breath report was generated during the CPAP trial, from which 20 randomly selected breaths also were used for analysis. P_{ETCO2} was recorded at 1-min intervals. Campbell diagram software was used to measure patient WOB in J/L,\textsuperscript{21} and 20 consecutive breaths were analyzed. PEEP was measured dynamically as the difference in P_es between the end-expiratory plateau and the pressure measured at the onset of inspiratory flow, minus the trigger sensitivity level measured at the airway (the lowest P_{aw} change from baseline at the onset of flow).\textsuperscript{2} \Delta P_{es} was measured as the change in P_es from the end-expiratory pressure to the most negative pressure achieved during inspiration. PTP was calculated using the method described by Sassoon et al,\textsuperscript{23} as the integral of the negative inspiratory flow during inspiration. PTP was calculated using the method of Murray et al.\textsuperscript{24}

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Table 2. Differences in Patient Work of Breathing and Other Variables During Lung-Protective Ventilation Using Volume-Regulated Modes and Pressure-Regulated Modes

<table>
<thead>
<tr>
<th>PRVC</th>
<th>PCV</th>
<th>VCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOB (J/L)</td>
<td>1.36 ± 0.60</td>
<td>1.27 ± 0.58</td>
</tr>
<tr>
<td>PTP (cm H_2O/s)</td>
<td>229 ± 116</td>
<td>195 ± 94</td>
</tr>
<tr>
<td>W (J/min)</td>
<td>16.4 ± 10.7</td>
<td>15.7 ± 9.0</td>
</tr>
<tr>
<td>P_{aw} (cm H_2O)</td>
<td>5.5 ± 3.1</td>
<td>4.4 ± 2.1</td>
</tr>
<tr>
<td>Δ P_{es} (cm H_2O)</td>
<td>17.0 ± 5.9</td>
<td>14.8 ± 4.1</td>
</tr>
<tr>
<td>V_e (mL)</td>
<td>418 ± 83</td>
<td>436 ± 106</td>
</tr>
<tr>
<td>V_T (mL/kg)</td>
<td>6.9 ± 1.1</td>
<td>7.2 ± 1.4</td>
</tr>
<tr>
<td>V_e (L/min)</td>
<td>57 ± 14*</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>V_T (L/min)</td>
<td>11.6 ± 3.3</td>
<td>12.3 ± 3.6</td>
</tr>
<tr>
<td>T_i (s)</td>
<td>0.63 ± 0.08</td>
<td>0.64 ± 0.09</td>
</tr>
<tr>
<td>f (breaths/min)</td>
<td>28 ± 7</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>P_{ETCO2} (mm Hg)</td>
<td>42 ± 6</td>
<td>41 ± 6</td>
</tr>
<tr>
<td>Peak P_{aw} (cm H_2O)</td>
<td>22 ± 9*</td>
<td>23 ± 8*</td>
</tr>
<tr>
<td>PEEP (cm H_2O)</td>
<td>7.7 ± 2.6</td>
<td>7.7 ± 2.9</td>
</tr>
<tr>
<td>PEEP (cm H_2O)</td>
<td>2.0 ± 1.4</td>
<td>1.6 ± 1.5</td>
</tr>
</tbody>
</table>

* p < 0.05, compared to VCV
†Includes an inspiratory flow time of 0.42 s and a pause time of 0.21 ± 0.06 s.
PRVC = pressure-regulated volume control
PCV = pressure-control ventilation
VCV = volume-control ventilation
WOB = work of breathing
PTP = pressure-time-product
W = power output of the inspiratory muscles
P_{aw} = esophageal pressure in the first 100 ms of inspiration
Δ P_{es} = tidal change in esophageal pressure
V_T = tidal volume
V_I = inspiratory flow rate
V_e = minute ventilation
T_i = inspiratory time
f = respiratory frequency
P_{ETCO2} = end-tidal carbon dioxide partial pressure
P_{aw} = airway pressure
PEEP = positive end-expiratory pressure
PEEPi = intrinsic positive end-expiratory pressure

**Results**

Patient WOB during LPV was markedly elevated, regardless of the ventilator mode. There was a nonsignificant trend toward increased WOB, PTP, and W with both PCV and PRVC, compared to VCV (Table 2). Among individual patients, WOB was lowest in 7 patients during VCV, in 5 patients during PCV, in 2 patients during PRVC (Fig. 1). Similarly, PTP was lowest in 7 patients during VCV, in 6 patients during PCV, and in 1 patient during PRVC (Fig. 2).
Overall, the inspired VT was not different between ventilator modes or with the target VT chosen for each patient (6.4 ± 0.5 mL/kg, p = 0.13). Yet in individual patients the inspired VT markedly exceeded the target VT (defined as > 0.5 mL/kg): 15 patients during PCV (average: 120 mL, 2.1 mL/kg), 6 patients during PRVC (80 mL, 1.5 mL/kg), and 3 patients during VCV (55 mL, 0.9 mL/kg) (Fig. 3). During VCV, sustained inspiratory effort by 3 patients was sufficient to open the high-pressure servo valve and augment their VT during the end-inspiratory pause by decreasing the circuit pressure 0.2 cm H2O below PEEP (Fig. 4) [personal communication, Draeger Medical]. A drop in P_{aw} below baseline was evident during the end-inspiratory pause on each breath (B), as was continued patient effort into the inspiratory pause (C). P_{es} = esophageal pressure.

During a brief trial of CPAP, the spontaneous breathing pattern was characterized by an f of 28.4 ± 6.4, an inspired VT of 279 ± 122 mL (4.6 ± 2.0 mL/kg), a peak VT of 38.4 ± 16 L/min, and a T_{I} of 0.79 ± 0.19 s. In general, the ventilator-delivered VT and peak VT during PCV, PRVC, and VCV exceeded what patients could generate during spontaneous breathing, whereas the ventilator T_{I} was 0.16 – 0.17 s less than each patient’s corresponding T_{I} during CPAP (Table 3). The ΔVT-vent-pt was significantly greater during PCV than VCV, whereas the Δ peak VT-vent-pt was significantly higher during VCV, compared to PCV or
Table 3. Ventilator-to-Patient Differences in Tidal Volume, Peak Inspiratory Flow Rate, and Inspiratory Time Between Modes

<table>
<thead>
<tr>
<th></th>
<th>PRVC</th>
<th>PCV</th>
<th>VCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta V_I\text{-vent-pt}$ (mL)</td>
<td>139 ± 91</td>
<td>156 ± 88*</td>
<td>119 ± 102</td>
</tr>
<tr>
<td>$\Delta V_I\text{-vent-pt}$ (mL/kg)</td>
<td>2.3 ± 1.5</td>
<td>2.5 ± 1.3*</td>
<td>1.9 ± 1.6</td>
</tr>
<tr>
<td>$\Delta$ peak $V_I$ vent-pt</td>
<td>19 ± 13†</td>
<td>22 ± 16‡</td>
<td>38 ± 15</td>
</tr>
<tr>
<td>$\Delta T_I$ vent-pt (s)</td>
<td>−0.17 ± 0.21</td>
<td>−0.16 ± 0.24</td>
<td>−0.16 ± 0.20</td>
</tr>
</tbody>
</table>

*p < 0.05 compared to VCV (Tukey-Kramer post-test)  
†p < 0.001 compared to VCV (Tukey-Kramer post-test)
PRVC = pressure-regulated volume control  
PCV = pressure-control ventilation  
VCV = volume-control ventilation  
$V_T$ = tidal volume  
vent-pt = ventilator-to-patient difference  
$V_I$ = peak inspiratory flow rate  
$T_I$ = inspiratory time

Table 4. Correlation Between Work Measurements in Each Mode and the Calculated Ventilator-to-Patient Difference in Tidal Volume and Peak Inspiratory Flow Rate Delivery

<table>
<thead>
<tr>
<th></th>
<th>PRVC</th>
<th>PCV</th>
<th>VCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta V_I\text{-vent-pt}$ vs WOB</td>
<td>−0.45</td>
<td>−0.08</td>
<td>−0.28</td>
</tr>
<tr>
<td>$\Delta V_I\text{-vent-pt}$ vs PTP</td>
<td>−0.37</td>
<td>−0.24</td>
<td>−0.31</td>
</tr>
<tr>
<td>$\Delta$ peak $V_I\text{-vent-pt}$ vs WOB</td>
<td>−0.44</td>
<td>0.03</td>
<td>−0.38</td>
</tr>
<tr>
<td>$\Delta$ peak $V_I$ vent-pt vs PTP</td>
<td>−0.35</td>
<td>−0.02</td>
<td>−0.37</td>
</tr>
</tbody>
</table>

*p > 0.05 for all correlations  
PRVC = pressure-regulated volume control  
PCV = pressure-control ventilation  
VCV = volume-control ventilation  
$V_T$ = tidal volume  
vent-pt = ventilator-to-patient difference  
WOB = work of breathing  
PTP = pressure-time product  
$V_I$ = peak inspiratory flow rate

Discussion

The main findings of this study are as follows. First, regardless of the ventilator mode used to achieve LPV, the average WOB was markedly elevated (> 1 J/L). Second, in sedated patients managed with LPV, PCV and PRVC offered no advantage in reducing WOB, compared to VCV with a high peak $V_I$. Third, peak $V_I$ during PCV did not achieve the high values previously reported in patients with ALI/ARDS ventilated at a traditional $V_T$. Fourth, PCV and PRVC often provided a reasonable $V_T$ for LPV, but $V_T$ was not adequately controlled in approximately 40% of patients, despite a reduction in $\Delta P_{aw}$ to low levels (10 cm H$_2$O).

During patient-triggered mechanical ventilation, patient WOB is believed to increase when the ventilator peak $V_I$ or the ventilator-delivered $V_T$ is less than the flow or volume demand of the patient.3–5 In this study, when the modes that caused the highest WOB and PTP were examined in individual patients, the ventilator peak $V_I$ and $V_T$ often exceeded what the patient could generate during spontaneous breathing. Furthermore, there was only a modest correlation between either the $\Delta V_I\text{-vent-pt}$ or the $\Delta V_I\text{-vent-pt}$ and WOB and PTP. The lack of a strong relationship between $V_I$, $V_T$, and WOB or PTP may be partially explained by the fact that we used measurements of $V_I$ and $V_T$ generated by patients during a brief trial of CPAP as a gross approximation of patient flow and volume demand during mechanical ventilation. This is a precarious assumption, as it is unknown whether the peak $V_I$ or $V_T$ generated during CPAP, under high work loads, reflects the peak $V_I$ or $V_T$ targeted by patients during mechanical ventilation, when the inspiratory muscles presumably would function under less stress.

Another reason why the ventilator peak $V_I$ and $V_T$ did not show a strong correlation to WOB and PTP was the peculiar effects of ventilator-patient asynchrony. Regardless of mode and despite adequate sedation, patients frequently exhibited asynchronous breathing during LPV that limited the effectiveness of traditional ventilator adjustments in peak $V_I$ or flow pattern in reducing WOB. Often this occurred in an unusual manner. In several cases, spontaneous breathing during VCV was stimulated by the ventilator, and patient effort commenced only toward the end of the mechanical breath, often negating the beneficial effects of a high $V_I$ (Fig. 5). This phenomenon was reported previously by Flick et al.,26 who observed that during controlled ventilation at a low $V_T$, electromyographic activity and reduced $P_{aw}$ were seen late in inspiration, particularly when the ventilator $V_T$ was close to the patient’s spontaneous $V_T$. This breathing pattern also was documented during the ARDS Network trial, in a patient whose $V_T$ was reduced to 5 mL/kg.27 In addition, the high mandatory $f$ needed to maintain a baseline $V_E$ may have
contributed to this particular type of asynchrony. In our experience, lowering the mandatory flow results in better synchrony in some patients, while in others it appears to have no effect.

Furthermore, during VCV, inspiratory effort sometimes continued during the end-inspiratory pause and likely contributed to the elevated WOB. In the Draeger ventilators, TI is set directly, while the portion dedicated to inspiratory flow is determined by the VT and the peak V˙I, so that any remaining TI after VT delivery is converted into an end-inspiratory pause. Acute alveolar edema was reported during LPV with a Draeger Evita 1 ventilator, when inspiratory efforts were sustained into the end-inspiratory pause. Unlike the Dura E-2 ventilator, the high-pressure servo valve of the Evita 1 did not open when the circuit pressure fell below the PEEP level, so that the imposed WOB was extraordinarily high. This situation presents something of a clinical quandary during LPV with VCV. If a high peak V˙I is used to alleviate increased WOB, the resulting brief TI (coupled with sustained inspiratory effort) may result in double-triggered breaths and a loss of lung-protection. Contrarily, increasing TI by using an end-inspiratory pause, a lower peak Vt, or a decreasing-ramp flow pattern may result in elevated WOB but likely would keep VT closer to the LPV target.

Of particular interest were the effects of asynchrony during PCV and PRVC. We noted that when patients stiffened their chest wall at the beginning of a time-triggered mechanical breath, the ventilator flow rapidly tapered off. Within the same breath, patients subsequently made inspiratory efforts that paradoxically caused the flow pattern to transform from a descending ramp into an ascending ramp, thus negating the beneficial effects of a decreasing-ramp flow pattern on WOB (Fig. 6). During PRVC we noted that when a patient’s effort resulted in a delivered VT above the pre-set target, typically there was a progressive decrease in peak Paw and peak V˙I over several breaths, with a corresponding increase in ΔPaw and WOB. This reflected the ventilator’s attempt to reduce VT toward the target while a greater proportion of the inspiratory work load was shifted onto the patient. Furthermore, we observed situations in which a patient exhibiting an asynchronous pattern would stiffen his/her chest wall on one breath, causing a decrease in VT, and then make a vigorous inspiratory effort on the subsequent breath, resulting in a large increase in VT. Because Paw is automatically titrated during PRVC to control VT, asynchrony often resulted in the VT, peak V˙I, and flow pattern being in constant flux (Fig. 7).
In this study the lower peak \( V_t \) found in PCV was caused by the need to reduce the inspiratory pressure level to constrain \( V_T \). This was accomplished during PRVC by the ventilator’s automated control of peak \( P_{aw} \) to maintain the \( V_T \) target. These results are contrary to our previous study, in which WOB was significantly lower during PCV, compared to VCV. In that study the target \( V_T \) was \( 10 \pm 2.5 \) mL/kg, so that a higher peak \( P_{aw} (33 \pm 6 \) cm H\(_2\)O) was required during PCV that resulted in a higher peak \( V_t \) \( (103 \pm 23 \) L/min), compared to the current study \( (23 \pm 8 \) cm H\(_2\)O and \( 61 \pm 16 \) L/min). Therefore, assumptions regarding the efficacy of pressure-regulated modes to reduce patient WOB based upon traditional \( V_T \) ventilation may not apply when these modes are used for LPV.

Another finding of this study is that patient-triggered, pressure-regulated ventilation frequently resulted in less precise control of \( V_T \), along with substantial negative swings in intrathoracic pressure. Ventilator-associated lung injury is caused by a high \( V_T \) that coincides with a large change in transpulmonary pressure. Animal studies have shown that lung injury can be induced by high-volume negative-pressure ventilation. Recommendations for LPV include the provision that tidal pressure changes should be \( \leq 20 \) cm H\(_2\)O. In theory, pressure-regulated modes can be used for LPV by adjusting the \( \Delta P_{aw} \) to \( \leq 20 \) cm H\(_2\)O to produce a \( V_T \) of 6 mL/kg. However, during patient-triggered, pressure-regulated ventilation the clinician must consider what happens to transpulmonary pressure. If the \( V_T \) substantially exceeds 6 mL/kg, then transpulmonary pressure also is increased and may exceed the recommended limits for LPV. We found the average \( \Delta P_{es} \), a surrogate for tidal pleural pressure change, was approximately \( 15-17 \) cm H\(_2\)O, while \( P_{aw} \) was regulated to levels \( > 20 \) cm H\(_2\)O. The substantial loss of \( V_T \) control that occurred in some patients suggests that occult high-pressure, high-\( V_T \) ventilation may persist during pressure-regulated LPV, despite an appropriately set \( \Delta P_{aw} \). It is interesting to note that when pressure-regulated modes were used in previous clinical trials of LPV, great care was taken to ensure that \( V_T \) did not exceed 6 mL/kg, by liberal use of sedation and, in some instances, the addition of small doses of neuromuscular blocking agents to weaken patient’s inspiratory efforts.

A limitation of this study is that only one type of ventilator was used, and any generalization of our results is restricted by how ventilators differ in mode design. For example, in the Dräger Dura E-2 version of PRVC (Auto-Flow), \( P_{aw} \) is titrated in increments of \( 1-3 \) cm H\(_2\)O per breath to achieve the \( V_T \) target. Auto-Flow also incorporates the “free breathing” feature used in airway-pressure-release ventilation, so that patients can actively inspire or expire at any point during the inspiratory cycle. Other versions of PRVC that use different inspiratory pressure titration algorithms or do not incorporate the “free-breathing” feature will respond somewhat differently than the Dräger E-2 ventilator during patient-triggered breaths. Therefore, caution should be used in generalizing our results to PRVC in other ventilators.

In addition, the study time periods used in our protocol may have been too brief for complete adaptation, and thus may not reflect how each mode affects WOB over time. To our knowledge, there are no studies describing the time course for how mechanically ventilated patients adapt their breathing pattern to sudden changes in inspiratory work load. In laboratory experiments, normal subjects begin to adapt to a sudden change in work load within one breath, and the adaptation is progressive. However, the breathing pattern typically returns to either baseline or a new equilibrium within 3–6 breaths. Therefore, the available data suggest that allowing 10 min for adaptation to each breathing mode is reasonable. Our interest was to make a preliminary assessment of WOB and \( V_T \) control during LPV, comparing the various modes used to manage patients with ALI/ARDS. Therefore, we were concerned that extending observations over a longer time period would increase the likelihood that later-occurring changes in WOB could be caused by changes in the patient’s condition (such as a sudden increase in pain or fever), rather than associated with the mode of ventilation.

Conclusions

During LPV in patients sedated to a Ramsey score of approximately 4, patient WOB was markedly elevated, regardless of ventilator mode. In addition, we found that PCV and PRVC provided no advantage in reducing WOB, compared to VCV with a high peak \( V_T \). We attributed this to the reduction in \( P_{aw} \) necessary to constrain \( V_T \) delivery within the LPV range, and in consequence resulted in a substantially reduced peak \( V_T \). Inadequate control of \( V_T \) coupled with substantial negative swings in pleural pressure may result in occult high-volume, high-pressure ventilation during PCV and PRVC, despite a relatively low \( P_{aw} \). Therefore, clinicians should be particularly vigilant in monitoring \( V_T \) stability when using PCV and PRVC for patient-triggered LPV.

REFERENCES

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