Atelectasis formation can be reduced by positive end-expiratory pressure (PEEP), but resulting increases in intrathoracic pressure could affect circulation. We have earlier demonstrated that increased tidal volumes with larger apparatus dead space improves oxygenation and sevoflurane uptake. In the present study, we hypothesize that isocapnic ventilation with increased tidal volumes increases oxygen and sevoflurane uptake similar to ventilation with PEEP, but with less impact on cardiac output. Thirty patients, with ASA physical status 1 or 2, scheduled for elective open colon surgery were randomly assigned to be ventilated with either PEEP at 10 cm H2O (PEEP, 15 patients) or increased tidal volumes achieved with larger apparatus dead space with zero end-expiratory pressure (DS group, 15 patients).

Oxygen tension and arterial sevoflurane concentration were significantly higher in the DS group (P < .05). Cardiac output decreased significantly less in the DS group compared with the PEEP group (5% and 33%, respectively; P < .05). Consequently, isocapnic ventilation with increased tidal volumes using apparatus dead space increased oxygen and sevoflurane tensions in arterial blood and preserved cardiac output better than did PEEP.

**Keywords:** Cardiac output, pulmonary gas exchange, sevoflurane.

**Materials and Methods**

Ethical approval for this study according to the standards set in the Helsinki Declaration (Regional Ethics Committee, Dnr: 2009/529 with amendment Dnr: 2010/481) was provided by the Regional Ethics Committee, Lund, Sweden, in September 2009 and September 2010. The study was registered with ClinicalTrials.gov, identifier NCT01343017. Consent to participate in the study was received from each patient.

The investigation included 30 patients, with ASA physical status 1 or 2, scheduled for elective open abdominal colon surgery at Skåne University Hospital, Malmö, Sweden, from September 2010 to February 2011. Patients were considered for inclusion in the trial if they were older than 18 years and if the procedure was estimated to last more than 60 minutes. Patients with known pulmonary or cardiovascular disease were excluded. Patients were randomly assigned to 1 of 2 groups with
15 patients in each group via randomly mixed sealed-envelope assignment at the start of the procedure in the operating room.

The methods have previously been described in detail. After induction of anesthesia and insertion of an endotracheal (ET) tube, patients were ventilated at a respiratory rate of 15/min with a fraction of inspired oxygen (FiO₂) of 0.35 provided by an initial fresh gas flow of 5 L/min. The inspiratory-expiratory ratio was 1:2, including an inspiratory plateau of 10%. The Vₜ or apparatus dead space was adjusted as needed to achieve an end-tidal carbon dioxide (ETCO₂) measured at the end of the ET tube (PETCO₂) at 34 mm Hg throughout the study. Initially, no PEEP was applied. Propofol, 8 mg/kg/h, was infused until an arterial cannula had been inserted in the radial artery. Stroke volume and CO was assessed in 20 patients (10 in each group) with a cardiac sensor system (LiDCOrapid, LiDCO Ltd).

Transesophageal echocardiography (TEE) was used to assess CO in 6 patients (3 in each group; Philips CX50 TEE ultrasound with X7-2T transducer, Philips Ultrasound). After a 3-mL control (time zero) sample of arterial blood had been obtained, the ventilatory mode was altered as follows. In the experimental group with increased VT with apparatus dead space, initial plateau pressure was monitored, and then VT was increased until plateau pressure was 0.04 cm H₂O/kg over the arterial blood had been obtained, the ventilatory mode was altered as follows. In the experimental group with increased VT with apparatus dead space, initial plateau pressure was monitored, and then VT was increased until plateau pressure was 0.04 cm H₂O/kg over the

pressure was monitored, and then VT was increased until plateau pressure was 0.04 cm H₂O/kg over the arterial line into heparinized syringes at the start and at 1, 3, 5, 10, 15, 30, 45, and 60 minutes after the start of the sevoflurane administration (total, 27 mL). No recruitment maneuver was performed during the study. Static compliance of the respiratory system was calculated as Vₜ divided by the inspiratory plateau pressure minus PEEP. If mean arterial pressure decreased below 60 mm Hg, patients received 5 to 10 µg of norepinephrine intravenously. All patients received 3 to 5 mL/kg/h of 2.5% glucose solution with sodium (70 mmol/L), chloride (45 mmol/L), and acetate (25 mmol/L) intravenously. Arterial tension (Pa) of sevoflurane was measured using gas-liquid chromatography as previously described.

For cardiac output monitoring, the LiDCO system was used in the first 10 randomly assigned patients in each group. The system uses pulse waveform contour analysis via an arterial catheter. The device uses a proprietary algorithm to analyze the pulse contour, incorporating patient-specific data from the patient monitor. Linton and colleagues found good conformity between thermodilutions and LiDCO-measurements in 40 patients, with a linear regression value of 0.94.

To examine the reliability of the LiDCO system, the first 3 randomly assigned patients in each group were assessed using TEE for stroke volume, CO, and right ventricular function. Both 4- and 5-chamber transgastric views were obtained in all 6 patients. The velocity time integral at the left ventricular outflow tract (LVOT) was measured using pulsed-wave Doppler ultrasonography. The diameter of the aorta was measured using a midesophageal, long-axis view at the level of the aortic annulus. Measurement of stroke volume was made by multiplying the velocity time integral at the LVOT by the aortic diameter. CO was calculated by multiplying stroke volume with heart rate. All images were recorded in triplicate by the same operator, and measurements were made off-line in a blinded fashion.

- Statistical Analysis. All statistical analyses were performed with SPSS version 16.0 for Windows (SPSS Inc). An initial power analysis assuming a sevoflurane Pa concentration difference at 0.3% with a standard deviation (SD) of 0.2%, revealed that 15 patients in each group would be needed to achieve a power of 0.8 at P < .05. Fifteen patients in each group were enrolled. Descriptive variables, VT, airway pressures, and lung compliance are expressed as the median and interquartile range in square brackets and analyzed with a nonparametric method according to Mann-Whitney. The values of FiO₂, PaO₂, fraction of inspiratory (Fi) sevoflurane, expiratory tension (Pe) of sevoflurane, sevoflurane Pa, and PETCO₂ are presented as mean ± SD. The analysis was conducted with an independent 2-tailed t test. For change of values over time, a 2-way repeated-measures analysis of variance (ANOVA) was used. The ANOVA was followed by a Greenhouse-Geisser post hoc test when appropriate. The rationale for this test is to reduce the risk of getting significant differences by fortuity. A P value less than .05 was considered to indicate statistical significance.

Results

Patients’ characteristics are presented in Table 1. Patients in the 2 groups were comparable in sex distribution, age, and BMI. The median weight of the patients was somewhat larger in the experimental group. All measured values were similar between the 2 groups before the increased VT or the PEEP was applied (Tables 2-5). Mean arterial pressure and heart rate were similar in the 2 groups throughout the observation period. Blood
loss in all patients was lower than 50 mL during the study period. Surgery and postoperative care took place without adverse events.

After the change of ventilation mode, V_T values were significantly larger in the experimental group (see Table 2), whereas peak airway pressures were similar in the 2 groups. Plateau pressure and mean airway pressure were significantly lower in the experimental group compared with the PEEP group ($P < .05$, see Table 2). The patients in the experimental group required an additional median dead space of 2.8 mL/kg (interquartile range, 2.6 - 3.1 mL/kg) to maintain $P_{a\text{etco}_2}$ at 34 mm Hg. The total respiratory system compliance was similar in the 2 groups throughout the observation period (see Table 2).

Except at 1 and 3 minutes, when the mean $P_e$ of sevoflurane was higher in the PEEP group, there was no statistically significant difference between the 2 groups regarding $P_e$ of sevoflurane. At 1 and 3 minutes, mean sevoflurane Pa was similar in the 2 groups but then higher in the experimental group ($P < .05$, Table 3). The difference between the Pa and $P_e$ of sevoflurane was smaller in the experimental group compared with the PEEP group ($P < .05$, see Table 3).

In both groups, $F_{i\text{O}_2}$ was stable at 35%, but 5 minutes after change of ventilation mode and onward, arterial oxygen saturation ($S_a\text{O}_2$) and Pa$_o2$ were significantly higher in the experimental group ($P < .05$, Table 4). There were no statistically significant differences between the 2 groups concerning mean $ETCO_2$ values or Pa$_cO_2$ throughout the observation period (see Table 4). The difference between Pa$_cO_2$ and $P_{a\text{etco}_2}$ was, however, statistically significantly smaller in the experimental group compared with the PEEP group (see Table 4).

The baseline stroke volumes and CO calculated from the LiDCO measurements were similar in the 2 groups.
but 5 minutes after application of PEEP or increase in VT, the values were significantly higher in the experimental group compared with the PEEP group (P < .05, Table 5). Thus, stroke volume and CO decreased significantly less in the experimental group compared with the PEEP group (see Table 5). Furthermore, TEE performed in 6 patients (3 in the experimental group and 3 in the PEEP group) demonstrated that the stroke volume was unaffected in the 3 patients in the experimental group, whereas it decreased in all 3 patients in the PEEP group (mean, 12%).

## Discussion

In the present study, the Pa of sevoflurane was found to be higher in patients ventilated with increased VT (median, 8.6 mL/kg body weight) and dead space compared with patients ventilated with PEEP (median, 5.2 mL/kg body weight). The effect of VT on sevoflurane uptake is in line with previous results obtained from both normal-weight and overweight patients ventilated with increased VT using additional apparatus dead space to maintain isocapnia in the absence of PEEP.9,10

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### Table 3. Sevoflurane Measures in Both Groups

<table>
<thead>
<tr>
<th>Sevoflurane measure (%)</th>
<th>Group (n = 15 each)</th>
<th>5 min</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fi</td>
<td>Experimental</td>
<td>2.5 ± 0.17</td>
<td>2.2 ± 0.26</td>
<td>2.2 ± 0.14</td>
<td>2.2 ± 0.19</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>2.6 ± 0.21</td>
<td>2.0 ± 0.19</td>
<td>2.2 ± 0.20</td>
<td>2.2 ± 0.21</td>
</tr>
<tr>
<td>Pe</td>
<td>Experimental</td>
<td>1.8 ± 0.21</td>
<td>1.8 ± 0.24</td>
<td>1.8 ± 0.17</td>
<td>1.9 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>2.0 ± 0.18</td>
<td>1.6 ± 0.18</td>
<td>1.8 ± 0.21</td>
<td>1.8 ± 0.23</td>
</tr>
<tr>
<td>Pa</td>
<td>Experimental</td>
<td>1.4 ± 0.26b</td>
<td>1.6 ± 0.24b</td>
<td>1.7 ± 0.20b</td>
<td>1.7 ± 0.19b</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>1.2 ± 0.22</td>
<td>1.2 ± 0.23</td>
<td>1.3 ± 0.19</td>
<td>1.4 ± 0.21</td>
</tr>
<tr>
<td>Pe-Pa</td>
<td>Experimental</td>
<td>0.37 ± 0.18b</td>
<td>0.22 ± 0.13b</td>
<td>0.19 ± 0.10b</td>
<td>0.23 ± 0.16b</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>0.75 ± 0.28</td>
<td>0.42 ± 0.21</td>
<td>0.48 ± 0.24</td>
<td>0.49 ± 0.26</td>
</tr>
</tbody>
</table>

### Table 4. Inspiratory Oxygen Fraction, Arterial Oxygen Saturation and Tension, End-Tidal Carbon Dioxide Tension, Arterial Carbon Dioxide Tension PaCO2, and Difference in Arterial–End-Tidal Carbon Dioxide Tension (Pa-PetCO2) in Both Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group (n = 15 each)</th>
<th>Time zero</th>
<th>15 min</th>
<th>30 min</th>
<th>60 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>FiO2 (%)</td>
<td>Experimental</td>
<td>35 ± 1.0</td>
<td>35 ± 0.64</td>
<td>35 ± 0.83</td>
<td>35 ± 0.46</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>35 ± 0.83</td>
<td>35 ± 0.64</td>
<td>35 ± 0.83</td>
<td>35 ± 0.70</td>
</tr>
<tr>
<td>SaO2 (%)</td>
<td>Experimental</td>
<td>975 ± 1.32</td>
<td>98.8 ± 0.76b</td>
<td>98.9 ± 0.56b</td>
<td>98.9 ± 0.56b</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>976 ± 1.25</td>
<td>98.1 ± 0.53</td>
<td>98.0 ± 0.71</td>
<td>97.7 ± 1.41</td>
</tr>
<tr>
<td>PaO2 (mm Hg)</td>
<td>Experimental</td>
<td>104.3 ± 29.8</td>
<td>141.0 ± 30.3b</td>
<td>143.3 ± 26.7b</td>
<td>145.5 ± 24.6b</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>115.5 ± 36.2</td>
<td>114.8 ± 11.2</td>
<td>116.3 ± 16.3</td>
<td>113.3 ± 20.9</td>
</tr>
<tr>
<td>PetCO2 (mm Hg)</td>
<td>Experimental</td>
<td>33.8 ± 0.6</td>
<td>33.8 ± 0.45</td>
<td>33.8 ± 0.45</td>
<td>33.8 ± 0.53</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>33.0 ± 1.13</td>
<td>33.8 ± 0.83</td>
<td>33.8 ± 0.68</td>
<td>33.8 ± 0.60</td>
</tr>
<tr>
<td>PacO2 (mm Hg)</td>
<td>Experimental</td>
<td>40.5 ± 2.70</td>
<td>39.8 ± 3.68</td>
<td>39.8 ± 3.75</td>
<td>39.0 ± 4.20</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>413 ± 2.93</td>
<td>42.0 ± 2.85</td>
<td>42.0 ± 3.38</td>
<td>42.0 ± 3.75</td>
</tr>
<tr>
<td>Pa-PetCO2 (mm Hg)</td>
<td>Experimental</td>
<td>6.98 ± 3.60</td>
<td>5.63 ± 3.45b</td>
<td>5.85 ± 3.68b</td>
<td>5.03 ± 3.83b</td>
</tr>
<tr>
<td></td>
<td>PEEP</td>
<td>8.40 ± 3.38</td>
<td>8.40 ± 2.48</td>
<td>8.18 ± 3.45</td>
<td>8.10 ± 3.83</td>
</tr>
</tbody>
</table>
The present study, the vaporizer was fixed on 3% since Fi sevoflurane should not differ between the groups. Thus, differences in inspired concentrations could be ruled out as an explanation for the increased sevoflurane uptake in the dead space (DS) group. It is reasonable to assume that recruitment of lung tissue could be the reason for the increase in uptake of sevoflurane in this group.

In our study, the initial PaO₂ and SaO₂ were similar between the groups, but both PaO₂ and SaO₂ were higher in the DS group compared with the PEEP group 5 minutes after application of the different ventilator modes. Hedenstierna concluded that airway closure during anesthesia, and thereby ventilation to perfusion mismatch, can be reduced with increasing FRC with PEEP. However, Futier and colleagues recently showed that although PEEP improves the end-expiratory lung volume after anesthesia induction, PaO₂ remains unchanged. The effect of added PEEP alone in obese patients is, however, controversial, since several studies have demonstrated that a recruitment maneuver is needed before the application of PEEP. In our study it is reasonable to assume that recruitment of more ventilated lung tissue occurred in the DS group and that this ventilation mode was sufficient to keep the lungs open. In fact, the lower value of PaO₂ and Pa of sevoflurane in the PEEP group indicates more atelectasis of lung tissues in this group. A recruitment maneuver after intubation might, however, eliminate the differences between our 2 groups.

The patients in our PEEP group received an average V₉ corresponding to 6.6 mL/kg predicted weight, as compared with 10.9 mL/kg predicted weight in the DS group determined by the Lemmens formula for estimating ideal body weight. Despite the larger V₉ in the DS group, compliance increased to a similar extent in both groups, suggesting that recruitment of lung tissue took place in both groups.

In intensive care medicine, protective ventilation (ie, PEEP and small V₉) is an established concept. Recently, Sundar and colleagues demonstrated a potentially protective effect of small V₉ in cardiac surgery patients, at least in the first day after surgery. It may be debated, however, whether this can be applied to patients who are not undergoing cardiac surgery, because cardiopulmonary bypass per se has been identified as a risk factor for lung injury. Furthermore, Boussarsar and colleagues found that the risk of barotrauma increases with higher pulmonary plateau pressure and/or lower lung compliance in patients with acute respiratory distress syndrome, and they also found a weak correlation with V₉. The present method may be considered controversial insofar as increased V₉ without PEEP may increase the risk of “atelectrauma,” a factor of cyclic lung recruitment. However, we believe that our method corresponds well to different patients’ thoracic compliance. The adjustable dead space volumes in the DS group reflect the variation of the patients’ different body weights and BMI. The method used in our study, with a plateau pressure of 0.04 cm H₂O/kg over the initial plateau pressure, corresponded with a PEEP of 5 cm H₂O.

It is true that alveolar recruitment may occur and could increase the risk of atelectrauma. Several studies have addressed the influence of V₉ recruitments on pulmonary inflammatory response, but taken together the results are inconclusive. In the present study the patients in the DS group had lower pulmonary plateau pressures than in the PEEP group. It thus cannot be excluded that at least in our patients, who had no signs of pulmonary disease, a moderate increase in V₉, in fact, constitutes a lower risk of barotrauma than with 10 cm H₂O PEEP. However, further research must be done to describe the impact on atelectrauma with the used method.

To avoid excessive airway pressure in the DS group, we adjusted the V₉ to achieve an increase in plateau pressure corresponding to 0.04 cm H₂O/kg actual weight, instead of applying a predetermined volume. Pelosi and colleagues demonstrated that compliance decreases with increased BMI. Thus, in obese patients, the V₉ increase will be less if the pressure increase is determined by body length or predicted body weight. By using actual body weight, we compensated for the differences in compliance at different BMI values. This is supported by the narrow range of resulting V₉ (in milliliters per kilogram; Table 2). Despite similar median BMI in the 2 groups, the patients assigned to the DS group had a greater body

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group</th>
<th>Time zero</th>
<th>5 min</th>
<th>Difference</th>
<th>Percent change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume (mL/min)</td>
<td>Experimental</td>
<td>68.0 ± 11.0</td>
<td>63.0 ± 9.8b</td>
<td>4.8 ± 5.8b</td>
<td>7 ± 8b</td>
</tr>
<tr>
<td>PEEP</td>
<td>59.0 ± 6.6</td>
<td>47 ± 9.2</td>
<td>12.0 ± 8.0</td>
<td>21 ± 14</td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>Experimental</td>
<td>4.41 ± 0.85</td>
<td>4.14 ± 0.96b</td>
<td>0.27 ± 0.77b</td>
<td>5 ± 8b</td>
</tr>
<tr>
<td>PEEP</td>
<td>4.16 ± 0.92</td>
<td>2.76 ± 0.57</td>
<td>1.41 ± 0.56b</td>
<td>33 ± 9</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CO, cardiac output; PEEP, positive end-expiratory pressure.

Table 5. Stroke Volume and Cardiac Output in Both Groups

a Experimental group received increased tidal volume with apparatus dead space. Values for both groups were obtained before the increased tidal volume or PEEP was added (time zero) and 5 minutes after change of ventilation mode. Values are mean ± standard deviation.

b P < .05 with independent 2-tailed t test.
weight. To our knowledge, the relationship of gas exchange to body weight in persons with similar BMI has not been determined. It seems unlikely, however, that the greater body weight would explain the better gas exchange in the DS group.

The better maintained CO in the DS group compared with the PEEP group could benefit hypovolemic and non-

molvolemic patients. The fact that plateau pressure and mean airway pressure reflecting intrathoracic pressure, were greater in the PEEP group could, at least partly, explain the difference in circulatory parameters. It should be noted that to avoid unnecessary interventions, we did not calibrate the LiDCO using lithium injections. Thus, the absolute values of stroke volume and CO must be interpreted with caution. It seems unlikely, however, that this would have any major effect on the relative change of these values 5 minutes after the change in mode of ventilation. Furthermore, although only obtained in a limited number of patients, the data from the TEE measurements are in line with the LiDCO findings.

There are some other limitations of the present study. No baseline lung function tests were performed. Additionally, we only studied effects of VT during the first hour and did not investigate effects of, for instance, oxygenation in the postoperative period.

Conclusion
We have demonstrated that ventilation with increased VT, with increased apparatus dead space to maintain isocapnia, increases oxygen and sevoflurane concentrations in arterial blood and preserves CO better than does ventilation with 10 cm H₂O PEEP.

REFERENCES

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