Respiratory effects of low versus high tidal volume with or without positive end-expiratory pressure in anesthetized dogs with healthy lungs

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Received March 6, 2017.
Accepted August 9, 2017.

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ABBREVIATIONS

Cstat
Static compliance of the lungs
CstatRS
Static compliance of the respiratory system
CstatTW
Static compliance of the thoracic wall
EELV
End-expiratory lung volume
EILV
End-inspiratory lung volume
FiO2
Inspired oxygen fraction
HU
Hounsfield unit
PAO
Airways opening pressure
PAOpeak
Airways peak pressure
PAOplat
Airways plateau pressure
PAO2
Alveolar oxygen tension
PcO2
Pulmonary end-capillary partial pressure of oxygen
PEEP
Positive end-expiratory pressure
PEEPtotRS
Total positive end-expiratory pressure of the respiratory system
PEEPtotTW
Total positive end-expiratory pressure of the thoracic system
PES
Esophageal pressure
PESpeak
Esophageal peak pressure
PESplat
Esophageal plateau pressure
PETCO2
End-tidal partial pressure of carbon dioxide
PTP
Transpulmonary pressure
RR
Respiratory rate
TV
Tidal volume

OBJECTIVE
To evaluate the impact of 2 tidal volumes (TV) with or without positive end-expiratory pressure (PEEP) on lung mechanics, aeration, and gas exchange in healthy anesthetized dogs.

ANIMALS
40 mixed-breed dogs with healthy lungs.

PROCEDURES
Anesthetized dogs were randomly assigned to 4 groups (n = 10/group) with different ventilatory settings: TV of 8 mL/kg and PEEP of 0 cm H2O (low TV group), TV of 8 mL/kg and PEEP of 5 cm H2O (low TV plus PEEP group), TV of 15 mL/kg and PEEP of 0 cm H2O (high TV group), or TV of 15 mL/kg and PEEP of 5 cm H2O (high TV plus PEEP group). Expired CO2 and respiratory rate were titrated on the basis of a predetermined stepwise protocol. Gas exchange, respiratory mechanics, and pulmonary aeration were evaluated by means of CT 30 minutes after starting mechanical ventilation at the assigned setting.

RESULTS
Partial pressures of arterial and expired CO2 were higher in the low TV and low TV plus PEEP groups than in the high TV and high TV plus PEEP groups. Peak and plateau airway pressures were higher in the PEEP group than in the other groups. Static lung compliance was higher in the high TV plus PEEP group than in the low TV group. Relative percentages of atelectatic and poorly aerated lung were lower in the high TV plus PEEP group than in the other groups. Oxygenation was similar among groups.

CONCLUSIONS AND CLINICAL RELEVANCE
Differences in TV and PEEP application during mechanical ventilation may affect respiratory function in anesthetized dogs with healthy lungs. Ventilation with a TV of 15 mL/kg and PEEP of 5 cm H2O significantly improved lung compliance and reduced the amount of atelectatic and poorly aerated lung.


General anesthesia in dogs and cats often requires controlled mechanical ventilation to improve lung function and anesthetic uptake. Mandatory indications for such ventilation during anesthesia include apnea, hypercapnia (hypoventilation), use of neuromuscular blocking drugs, and intrathoracic surgery. However, anesthetized patients in other circumstances could benefit from controlled mechanical ventilation as well, such as those with impairment of oxygenation, diseases that increase the work of breathing, or unusual characteristics or those undergoing certain surgical procedures.1,2 Various strategies for controlled mechanical ventilation are available, including controlled or assisted modes, pressure or volume cycling, and application of PEEP.1,2

Positive pressure has been used for many years in veterinary practice to ventilate the lungs, suggesting this technique is safe and feasible. Nevertheless, positive pressure ventilation can be considered a nonphysiologic condition for the respiratory system, which functions primarily at negative pressures. An
inappropriate ventilator setting can result in serious intraoperative complications and pulmonary damage and may aggravate a preexisting lung injury.\textsuperscript{2,3}

Tidal volume is an important variable to adjust during mechanical ventilation because it can affect several intrapulmonary and extrapulmonary functions. Indeed, considerable evidence from experimental and observational studies\textsuperscript{4,5} indicates that high $T_v$'s can cause alveolar overstretching, initiate ventilator-induced lung injury, and contribute to extrapulmonary organ dysfunction through systemic release of inflammatory mediators. High $T_v$'s contribute to and worsen acute respiratory distress syndrome in human intensive care patients after hours or days of ventilation.\textsuperscript{6}

Traditionally, atelectasis and hypoxemia associated with anesthesia have been treated in humans through ventilation with a $T_v$ between 10 and 15 mL/kg of predicted body weight.\textsuperscript{7} Nevertheless, over the past decade, in view of experimental and clinical evidence of the benefits of the use of a low $T_v$ (6 mL/kg) for humans with acute respiratory distress syndrome, many health-care providers have also begun to reduce $T_v$ (6 to 8 mL/kg) in anesthetized patients with healthy lungs.\textsuperscript{8,9} Lung-protective ventilation refers to a ventilatory strategy aimed at the use of a low $T_v$ and PEEP in combination with recruitment maneuvers (periodic hyperinflation of the lungs).\textsuperscript{10} However, the possibility of exploiting lung-protective ventilation and its benefits in the human surgical setting remains to be explored.\textsuperscript{11,12}

Positive end-expiratory pressure is an adjunctive treatment that can be combined with all forms of mechanical ventilation. In patients with pulmonary atelectasis, PEEP can improve arterial oxygenation\textsuperscript{13-15} by increasing functional residual capacity,\textsuperscript{14,16} reducing venous admixture,\textsuperscript{17} shifting the $T_v$ to a more compliant portion of the pressure-volume curve,\textsuperscript{18} preventing loss of compliance during mechanical ventilation,\textsuperscript{19} reducing intratidal alveolar opening and closing,\textsuperscript{20} and reducing the work of breathing.\textsuperscript{21}

Nowadays, mechanical ventilation is commonly used for anesthetized dogs owing to advancement in anesthetic techniques and an increase in the number of critical care patients undergoing general anesthesia. Textbooks and review articles\textsuperscript{1,22-23} suggest an approximate $T_v$ of between 10 and 20 mL/kg for dogs undergoing general anesthesia. These values are mainly based on physiologic data derived from research involving awake and spontaneously breathing dogs.\textsuperscript{24} Moreover, despite evidence from prospective controlled clinical studies\textsuperscript{24-26} of the therapeutic effects of PEEP in dogs for resolution of pulmonary atelectasis, a global evaluation is lacking of the effect of PEEP and $T_v$ in dogs.

The purpose of the study reported here was to evaluate the impact of 2 $T_v$'s (8 mL/kg [low] vs 15 mL/kg [high]) with or without PEEP (5 cm H$_2$O) on lung mechanics, ventilation, and gas exchange in dogs with healthy lungs undergoing general anesthesia. Our hypothesis was that, in such conditions, low $T_v$ ventilation with PEEP could be beneficial, compared with high $T_v$ ventilation.

**Materials and Methods**

**Animals**

Fifty-two adult female mixed-breed dogs with mammary gland tumors that required a thoracic CT examination to assess the presence of pulmonary metastases were initially considered for enrollment in the study with owner consent. All dogs received a complete physical examination and standard radiographic examination of the thorax before the experimental procedures began. Dogs with evidence of pulmonary disease or metastasis (n = 12) were excluded from the study, leaving 40 dogs for inclusion. The study was conducted in compliance with the Italian Animal Welfare Guidelines concerning use of client-owned animals in clinical investigations, and the study protocol was approved by the Ethical Committee of the Department of Emergency and Organ Transplantation of the University of Bari.

**Anesthesia protocol**

Each dog was premedicated with acepromazine maleate\textsuperscript{3} (0.02 mg/kg) and morphine sulfate\textsuperscript{3} (0.3 mg/kg) administered IM. When an adequate degree of sedation was achieved, a cephalic vein was aseptically catheterized and lactated Ringer solution (5 mL/kg/h) was administered. General anesthesia was induced via administration of propofol\textsuperscript{4} (4 to 6 mg/kg, IV) and maintained with isoflurane\textsuperscript{d} vaporized in oxygen and delivered via orotracheal tube. All dogs were connected to a mechanical pulmonary ventilator\textsuperscript{c} equipped with a dedicated vaporizer\textsuperscript{c} and a standard nonrebreathing circuit. After administration of vecuronium bromide\textsuperscript{e} (0.1 mg/kg, IV), lungs were ventilated in a volume-controlled mode on the basis of group assignment, as indicated by the study protocol. After an adequate depth of anesthesia was obtained, dogs were positioned in dorsal recumbency for the instrumentation and execution of a helical CT scan of the thorax.

Heart rate; RR; $\text{PETCO}_2$; invasively measured (at the level of the metatarsal artery) systolic, diastolic, and mean arterial blood pressure; arterial oxygen saturation; and PAO$\text{peak}$ were continuously monitored.\textsuperscript{h}

Moreover, for the specific requirements of the study, dogs were instrumented with a pneumotachograph\textsuperscript{i} and esophageal balloon (catheter). The FiO\textsubscript{2} was maintained at > 0.8, and end-tidal concentration of isoflurane was maintained between 1.3% and 1.5%, depending on the specific requirements of each dog. Neuromuscular function was monitored (peroneal nerve) with a peripheral nerve stimulator\textsuperscript{i} operating in train-of-4 stimulation mode. During each experiment, a profound neuromuscular blockade (no twitch present) was maintained and additional doses of vecuronium (0.03 mg/kg, IV) were administered.

\textsuperscript{1,2,4-6,8,9,11-13,16,17,19,21,24,26,28-30}
to each dog when the first twitch in response to the train-of-4 stimulation reappeared. Vecuronium administration was discontinued at the end of the anesthetic session, and atropine8 (0.02 mg/kg, IV) was administered, followed by neostigmine9 (0.05 mg/kg, IV) to reverse the neuromuscular blockade when at least 2 twitches were present.

Study protocol

The study was designed as a randomized controlled clinical trial. After induction of anesthesia, dogs were randomly (computer-generated randomization sequence) allocated to 4 groups (n = 10/group), each of which were mechanically ventilated with a different ventilatory setting per the study protocol: TV of 8 mL/kg and PEEP of 0 cm H2O (low TV group), TV of 8 mL/kg and PEEP of 5 cm H2O (low TV plus PEEP group), TV of 15 mL/kg and PEEP of 0 cm H2O (high TV group), or TV of 15 mL/kg and PEEP of 5 cm H2O (high TV plus PEEP group). The FiO2 (> 0.8) and inspiration-to-expiration ratio (1:2) were the same in all protocols. Respiratory rate was adjusted on the basis of a predetermined stepwise protocol targeting precise PETCO2 intervals, depending on the individual response of the dog to the ventilator setting. In particular, the primary target range was to maintain PETCO2 between 40 and 45 mm Hg, if this required an RR of > 20 breaths/min, a higher target range was considered (45 to 55 mm Hg); if the new target required an RR of > 30 breaths/min, a new target range was considered (55 to 60 mm Hg) up to an RR limit of 40 breaths/min. If the dog required an RR > 40 breaths/min to maintain the target PETCO2 value, the dog was excluded from the study and the anesthesiologist in charge decided on the best treatment from clinical judgment and personal experience. Gas exchange, respiratory mechanics, and pulmonary aeration were assessed 30 minutes after the beginning of mechanical ventilation at the predetermined setting.

Gas exchange assessment

For gas exchange assessment, an arterial blood sample (1 mL) was anaerobically collected from a metatarsal artery at the beginning of the study protocol, after stable ventilator settings were established (0 minutes; baseline) and at 30 minutes. Baseline measurements were used to assess respiratory function to confirm whether dogs had healthy lungs and were therefore eligible for inclusion in the study. Arterial blood samples were collected before measurement of respiratory mechanics and lung aeration to avoid any interference of those procedures with blood gas measurements. Collected blood samples were immediately analyzed. Arterial blood pH, PaO2, and PaCO2 were measured and corrected for the esophageal temperature of the dog at the time of sample collection. Arterial O2 saturation was calculated by the analyzer.

The ratio of PaO2 to FiO2 was calculated as an index of arterial blood oxygenation. The estimate of intrapulmonary blood shunt percentage (Fshunt) was calculated as follows:

\[
F_{\text{shunt}} = \left( \frac{[C_c'O_2 - C_a'O_2]}{[C_c'O_2 - C_a'O_2 + 3.5 \text{ mL/dL}]} \right) \times 100
\]

where Cc'O2 is the pulmonary end-capillary oxygen content, Cao2 is the arterial oxygen content, and 3.5 mL/dL is an approximate fixed value of the arterial-to-mixed venous oxygen content difference. Values for Cc'O2 and Cao2 were calculated as follows:

\[
C_{c'O_2} = ([Hb \times 1.31 X Sc'O_2] + 0.0031) \times Pc'O_2
\]

\[
C_{a'O_2} = ([Hb \times 1.31 X Sa'o_2] + 0.003) \times Pa'o_2
\]

where Hb is hemoglobin concentration as measured by the blood gas analyzer, 1.31 is the oxygen-carrying capacity of hemoglobin (mL/g), Sc'O2 is the pulmonary end-capillary oxygen saturation, and 0.003 is the solubility coefficient of oxygen in dog plasma. The Pc'O2 was assumed to be equal to PaO2. For PaO2 > 100 mm Hg, Pc'O2 was assumed to be 100% (ie, 1); for PaO2 ≤ 100 mm Hg, Pc'O2 was calculated from the actual PaO2 via the same method.

Respiratory system mechanics assessment

For each dog, gas flow was measured with a heated pneumotachograph connected to a differential pressure transducer placed between the Y-piece of the ventilator circuit and the endotracheal tube. The pneumotachogram was linear over the experimental range of gas flows. Volume was obtained by numerical integration of the flow signal. Values of PAO were measured proximally to the endotracheal tube with a pressure transducer. Changes in intrathoracic pressure were evaluated by assessment of PES as measured with a thin latex balloon-tipped catheter system, which was connected to a pressure transducer. An esophageal balloon (volume, 10 mL) was introduced through the dog’s mouth and advanced within the distal third of the esophagus. The balloon was then filled with 1 mL of air, and its correct position was confirmed by observation of cardiac oscillations and performance of positive pressure occlusion testing to confirm changes in PES during tidal ventilation. The position of the catheter was further confirmed via CT.

To estimate the static mechanical properties of the respiratory system, end-inspiration and end-expiration automatic airway occlusion (4-second duration each) was performed at each assessment point (at the end of any ventilatory protocol) by applying the ventilator controls to close both the inspiratory and the expiratory branches of the circuit system at the end of an inspiration and expiration, respectively.

The PEEPtotRS was measured as the plateau pressure in PAO during the end-expiratory occlusion. The PEEPtotTW was measured as the plateau pressure of PES during the end-expiratory occlusion. The total PEEP applied to the lungs (PEEPtotl) was calculated
as PEEP<sub>totRS</sub> minus PEEP<sub>totTW</sub>. The Cstat<sub>RS</sub> (adjusted for body weight) was calculated as follows:

\[
C_{\text{statRS}} = \frac{T_i}{[\text{PAOplat} - \text{PEEP<sub>totRS</sub>}/\text{body weight}
\]

where PAOplat is the value of PAO during the 4-second-long end-inspiratory occlusion. The Cstat<sub>TW</sub> (adjusted for body weight) was calculated as follows:

\[
C_{\text{statTW}} = \frac{T_i}{[\text{PESplat} - \text{PEEP<sub>totTW</sub>}/\text{body weight}
\]

where PESplat is the value of PES during the end-inspiratory occlusion, with its value at the elastic equilibrium point of the respiratory system used as a reference value. The Cstat<sub>i</sub> (adjusted for the dog’s body weight) was calculated as follows:

\[
C_{\text{stat}i} = 1/(1/C_{\text{statRS}} - 1/C_{\text{statTW}}).
\]

The PTP was calculated as follows:

\[
\text{PTP} = (\text{PAOplat} - \text{PEEP<sub>totRS</sub>}) - (\text{PESplat} - \text{PEEP<sub>totTW</sub>})
\]

For each dog, measurements of respiratory mechanics were performed after profound neuromuscular blockade had been confirmed. For further data analysis, values of the aforementioned variables were displayed and collected on a personal computer through a 12-bit analog-to-digital converter board at a sample rate of 200 Hz. Two-point calibration of the pneumotachograph and the transducers used to measure flow and pressures (airway and esophageal) was performed before the beginning of each anesthetic session.

**CT scanning and lung aeration assessment**

For each dog, a frontal topogram and helical CT images of the thorax were obtained with a third-generation spiral CT<sup>3</sup> at the 30-minute assessment point during both an end-expiration and end-inspiratory apnea, with the dog positioned in the scanner in dorsal recumbency with the forelimbs extended cranially. To maintain a constant volume of gas during the CT scan, the endotracheal tube was clamped cranially. To maintain a constant volume of gas during the end-expiratory phase immediately before the scan commenced. All images were obtained at a setting of 120 kVp and 160 mA by use of a lung algorithm; the matrix size was 512 X 512, field of view was 35 cm, and pitch was 1.5. Images (slice thickness, 10 mm) were reconstructed.

The CT images were analyzed as described elsewhere<sup>4,15</sup> by means of a computer program<sup>7</sup> by an operator who was unaware of the dog’s treatment allocation. Briefly, both right and left lungs were chosen as regions of interest for analysis; in the CT images, the outer boundary of each of these regions was traced along the inner aspect of the ribs and the inner boundary of each region was traced along the mediastinal organs. The portion of the pulmonary hilum containing the trachea, main bronchi, and hilar blood vessels was excluded from each region of interest.

In accordance with previous studies, the aeration status of regions (or compartments) within the lung was classified as hyperinflated (ie, composed of pixels with density values of -1,000 to -901 HU), normoaerated (ie, composed of pixels with density values of -900 to -501 HU), poorly aerated (ie, composed of pixels with density values of -500 to -101 HU), or nonaerated (ie, composed of pixels with density values of -100 to 100 HU, indicative of complete atelectasis). The volume of each compartment in each CT image was calculated by use of the following formula<sup>31</sup>:

\[
\text{Gas volume} = \text{density value}/(-1.000) \times \text{voxel volume}
\]

where each voxel is a pixel with a square base of 0.59 mm on each side and a height corresponding to the CT slice thickness (10 mm).

For each dog, the data acquired from each CT image were then added together to yield the total volume that each compartment (ie, hyperinflated, normoaerated, poorly aerated, or nonaerated) occupied within both lungs. The volumes of each compartment were expressed as a percentage of the total lung volume. The EELV and the EILV were computed by including pixels with density values of -1,000 to 100 HU during the end-expiration and the end-inspiration apnea, respectively. Lung strain was calculated as the ratio of EILV to EELV.<sup>32</sup>

**Statistical analysis**

For all recorded numeric variables, mean ± SD values were reported. Data were tested for normality of distribution with the Shapiro-Wilk test. Ventilator setting groups were compared<sup>14,15</sup> with respect to dog age and body weight, time between anesthetic induction and first CT scan, and duration of CT scanning via 1-way ANOVA followed by the Tukey test. Data regarding gas exchange, respiratory mechanics, lung aeration, and cardiovascular function were compared<sup>16</sup> among ventilator setting groups via 1-way ANOVA followed by the Dunnett procedure for multiple comparisons. A value of P < 0.05 was considered significant.

**Results**

All 40 dogs completed the study protocol with no complications. No significant differences were identified among the 4 ventilator setting groups in terms of age, body weight, interval between anesthetic induction and CT scanning, and scan duration (Table 1). Mean PaCO<sub>2</sub> and PetCO<sub>2</sub> as measured 30 minutes after mechanical ventilation began were significantly (P < 0.001) higher in the low T<sub>i</sub> and low T<sub>V</sub> plus PEEP groups than in the high T<sub>i</sub> and high T<sub>V</sub> plus PEEP groups (Table 2). Mean arterial blood pH was significantly (P < 0.05) lower in the low T<sub>V</sub> plus PEEP group than in the other 3 groups. No other physiologic variables differed among ventilator setting groups.

Mean PAOpeak and PAOplat as measured 30 minutes after mechanical ventilation were significantly (P < 0.001) higher in the high T<sub>V</sub> plus PEEP group
than in the other ventilator setting groups (Table 3). Mean PAOpeak and PAOplat in the low T\(_V\) group and the high T\(_V\) group were significantly (P < 0.05) higher than in the low T\(_V\) group. Mean PESpeak and PESplat were significantly (P < 0.001) higher in the high T\(_V\) plus PEEP group than in the other groups. Mean Cstat\(_L\) was significantly (P < 0.001) higher in the high T\(_V\) plus PEEP group than in the low T\(_V\) group. Mean PTP was significantly (P < 0.001) higher in the high T\(_V\) and high T\(_V\) plus PEEP groups than in the low T\(_V\) and low T\(_V\) plus PEEP groups. Mean RR was significantly (P < 0.001) lower in the high T\(_V\) and high T\(_V\) plus PEEP groups than in the low T\(_V\) and low T\(_V\) plus PEEP groups. No other respiratory system mechanics values differed among the groups. All measured hemodynamic values were similar among groups (Table 4).

Relative percentages of hyperinflated, normoaerated, poorly aerated, and nonaerated (or atelectatic areas) lung regions as measured via CT 30 minutes after mechanical ventilation began were summarized (Figure 1). Analysis of lung aeration in the end-expiratory phase revealed significantly (P < 0.01) lower percentages of atelectatic and poorly aerated lung and a significantly (P < 0.01) higher percentage of normoaerated lung in the high T\(_V\) plus PEEP group than in the other ventilator setting groups. Relative percentages of atelectatic and poorly aerated regions of lung in dogs in the high T\(_V\) group were significantly (P < 0.01) higher in the end-expiratory phase than in the end-inspiratory phase. No other differences related to pulmonary aeration were identified.

Mean EELV in the low T\(_V\) plus PEEP (0.82 ± 0.24 L) and high T\(_V\) plus PEEP (0.85 ± 0.23 L) groups was higher (P < 0.001) than in the low T\(_V\) (0.75 ± 0.19 L) and high T\(_V\) (0.70 ± 0.19 L) groups. Mean EILV as measured 30 minutes after mechanical ventilation was significantly (P < 0.001) higher in the high T\(_V\) plus PEEP group (mean ± SD, 1.17 ± 0.29 L) than in the low T\(_V\) (0.95 ± 0.24 L), low T\(_V\) plus PEEP (1.01 ±

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**Table 1**—Mean ± SD age, body weight, interval between anesthetic induction and CT scanning, and CT scan duration for 40 anesthetized dogs with healthy lungs ventilated with 1 of 4 settings (n = 10/group): T\(_V\), of 8 mL/kg and PEEP of 0 cm H\(_2\)O (low T\(_V\) group), T\(_V\), of 8 mL/kg and PEEP of 0 cm H\(_2\)O (low T\(_V\) plus PEEP group), T\(_V\), of 15 mL/kg and PEEP of 0 cm H\(_2\)O (high T\(_V\) group), or T\(_V\), of 15 mL/kg and PEEP of 5 cm H\(_2\)O (high T\(_V\) plus PEEP group).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low T(_V)</th>
<th>Low T(_V) plus PEEP</th>
<th>High T(_V)</th>
<th>High T(_V) plus PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>67 ± 12</td>
<td>64 ± 11</td>
<td>63 ± 3</td>
<td>60 ± 10</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>28 ± 5</td>
<td>35 ± 12</td>
<td>31 ± 12</td>
<td>29 ± 14</td>
</tr>
<tr>
<td>Interval to scanning (min)</td>
<td>55 ± 7</td>
<td>58 ± 9</td>
<td>51 ± 7</td>
<td>57 ± 6</td>
</tr>
<tr>
<td>Scan duration (s)</td>
<td>48 ± 5</td>
<td>49 ± 8</td>
<td>43 ± 6</td>
<td>47 ± 9</td>
</tr>
</tbody>
</table>

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**Table 2**—Mean ± SD values of blood gas variables and oxygenation indices measured 30 minutes after mechanical ventilation began for the dogs in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low T(_V)</th>
<th>Low T(_V) plus PEEP</th>
<th>High T(_V)</th>
<th>High T(_V) plus PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pa(_O_2) (mm Hg)</td>
<td>469.4 ± 88.8</td>
<td>484.7 ± 62.7</td>
<td>499.9 ± 51.7</td>
<td>499.5 ± 67.7</td>
</tr>
<tr>
<td>Pa(_CO_2) (mm Hg)</td>
<td>54.4 ± 6.5</td>
<td>61.4 ± 12.7</td>
<td>44.9 ± 4.1</td>
<td>46.8 ± 5.0</td>
</tr>
<tr>
<td>Pet(_CO_2) (mm Hg)</td>
<td>50.7 ± 8.6</td>
<td>54.9 ± 12.1</td>
<td>40.3 ± 3.8</td>
<td>42.9 ± 4.8</td>
</tr>
<tr>
<td>Sa(_O_2) (%)</td>
<td>100.0 ± 0.0</td>
<td>100.0 ± 0.0</td>
<td>100.0 ± 0.0</td>
<td>100.0 ± 0.0</td>
</tr>
<tr>
<td>pH</td>
<td>7.24 ± 0.05</td>
<td>7.21 ± 0.07</td>
<td>7.30 ± 0.05</td>
<td>7.29 ± 0.04</td>
</tr>
<tr>
<td>Paco(_2)/Fi(_O_2)</td>
<td>469.4 ± 88.8</td>
<td>484.7 ± 62.7</td>
<td>499.9 ± 51.7</td>
<td>499.5 ± 67.7</td>
</tr>
<tr>
<td>F(_shunt) (%)</td>
<td>13.0 ± 5.1</td>
<td>11.7 ± 3.6</td>
<td>11.8 ± 3.0</td>
<td>11.6 ± 4.3</td>
</tr>
</tbody>
</table>

\(F_{shunt} = \text{Estimate of intrapulmonary blood shunt percentage. PaO}_2/\text{FiO}_2 = \text{Ratio of PaO}_2/\text{FiO}_2, \text{SaO}_2 = \text{Arterial oxygen saturation.}\)

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**Table 3**—Mean ± SD values of respiratory mechanics variables measured 30 minutes after mechanical ventilation began for the dogs in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low T(_V)</th>
<th>Low T(_V) plus PEEP</th>
<th>High T(_V)</th>
<th>High T(_V) plus PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAOpeak (cm H(_2)O)</td>
<td>10.4 ± 0.7</td>
<td>13.2 ± 0.5</td>
<td>14.2 ± 1.6</td>
<td>17.0 ± 1.1</td>
</tr>
<tr>
<td>PAOplat (cm H(_2)O)</td>
<td>8.7 ± 0.4</td>
<td>11.3 ± 0.4</td>
<td>12.4 ± 1.5</td>
<td>15.2 ± 0.8</td>
</tr>
<tr>
<td>PESpeak (cm H(_2)O)</td>
<td>7.3 ± 0.9</td>
<td>8.6 ± 1.2</td>
<td>8.6 ± 1.4</td>
<td>9.5 ± 1.1</td>
</tr>
<tr>
<td>PESplat (cm H(_2)O)</td>
<td>6.2 ± 1.0</td>
<td>7.4 ± 1.0</td>
<td>7.4 ± 1.3</td>
<td>8.2 ± 1.0</td>
</tr>
<tr>
<td>Cstat(_L) (mL/cm H(_2)O/kg)</td>
<td>3.5 ± 1.1</td>
<td>4.1 ± 1.6</td>
<td>4.4 ± 1.4</td>
<td>5.0 ± 1.8</td>
</tr>
<tr>
<td>Cstat(_L) (mL/cm H(_2)O/kg)</td>
<td>1.7 ± 0.5</td>
<td>1.9 ± 0.6</td>
<td>1.9 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>PTP (cm H(_2)O)</td>
<td>2.7 ± 0.3</td>
<td>2.7 ± 0.5</td>
<td>5.0 ± 0.6</td>
<td>5.7 ± 0.9</td>
</tr>
<tr>
<td>RR (breaths/min)</td>
<td>38.8 ± 7.1</td>
<td>38.3 ± 7.2</td>
<td>38.0 ± 3.9</td>
<td>12.6 ± 5.6</td>
</tr>
</tbody>
</table>

\(c\)Within a variable, values with different superscript letters differ significantly (P < 0.05).

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[Figure 1](#).

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AJVR • Vol 79 • No. 5 • May 2018
Discussion

Results of the study reported here indicated that in the range of settings evaluated, differences in \( T_V \) and PEEP significantly affected lung compliance and alveolar ventilation, but not oxygenation, in mechanically ventilated, anesthetized dogs with healthy lungs. A \( T_V \) of 8 mL/kg resulted in more atelectasis and alveolar hypoaeration as well as a higher Pa\( \text{CO}_2 \) despite the use of a higher RR, independent from the application of PEEP. On the contrary, a \( T_V \) of 15 mL/kg and PEEP of 5 cm H\( \text{O} \) was the ventilator setting that ensured the best lung aeration and respiratory system mechanics. Oxygenation was adequate regardless of the \( T_V \) and PEEP setting.

Use of mechanical ventilation with a \( T_V \) setting < 10 mL/kg for anesthetized patients with healthy lungs is increasing in human medicine because this practice reduces the duration of postoperative mechanical ventilation, improves hemodynamic instability, and reduces the incidence of renal failure. Predictable effects of mechanical ventilation with a low \( T_V \) include \( \text{CO}_2 \) retention with subsequent respiratory acidosis. In the present study involving dogs with healthy lungs, administration of a \( T_V \) as low as 8 mL/kg caused notable hypercapnia and acidosis despite the use of an RR > 30 breaths/min. The Pa\( \text{CO}_2 \) values obtained at 30 minutes of mechanical ventilation were considerably greater than those reported for humans in similar conditions (healthy lungs), who better tolerate a \( T_V \) as low as 6 mL/kg.

These differences between humans and dogs may be due to physiologic differences. In particular, dogs have a greater amount of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low ( T_V )</th>
<th>Low ( T_V ) plus PEEP</th>
<th>High ( T_V )</th>
<th>High ( T_V ) plus PEEP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>113.9 ± 24.1</td>
<td>112.9 ± 24.1</td>
<td>111.3 ± 22.5</td>
<td>104.9 ± 26.4</td>
</tr>
<tr>
<td>SAP (mm Hg)</td>
<td>117.0 ± 15.8</td>
<td>112.8 ± 17.7</td>
<td>119.0 ± 18.3</td>
<td>114.4 ± 21.4</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>79.5 ± 11.1</td>
<td>76.5 ± 10.8</td>
<td>88.1 ± 16.6</td>
<td>82.2 ± 14.9</td>
</tr>
<tr>
<td>DAP (mm Hg)</td>
<td>57.9 ± 5.8</td>
<td>53.8 ± 5.11</td>
<td>67.8 ± 13.9</td>
<td>63.3 ± 12.8</td>
</tr>
</tbody>
</table>

DAP = Diastolic arterial blood pressure. MAP = Mean arterial blood pressure. SAP = Systolic arterial blood pressure.

Figure 1—Volumes of 4 lung regions (according to aeration status) at end-inspiration (A) and end-expiration (B) expressed as a percentage of the total lung volume for 40 anesthetized dogs with healthy lungs ventilated with 1 of 4 settings (n = 10/group): \( T_V \) of 8 mL/kg and PEEP of 0 cm H\( \text{O} \) (low \( T_V \) group), \( T_V \) of 8 mL/kg and PEEP of 5 cm H\( \text{O} \) (low \( T_V \) plus PEEP group), \( T_V \) of 15 mL/kg and PEEP of 0 cm H\( \text{O} \) (high \( T_V \) group), or \( T_V \) of 15 mL/kg and PEEP of 5 cm H\( \text{O} \) (high \( T_V \) plus PEEP group). Aeration status as determined via CT 30 minutes after mechanical ventilation began was classified as hyperinflated (ie, composed of pixels with densities of –1,000 to –901 HU; black portion of bars), normoaerated (ie, composed of pixels with densities of –900 to –501 HU; dark gray portion of bars), poorly aerated (ie, composed of pixels with densities of –500 to –101 HU; light gray portion of bars), or nonaerated (ie, composed of pixels with pixel densities of –100 to 100 HU, indicative of complete atelectasis; white portion of bars). *Indicated value differs significantly (\( P < 0.05 \)) from that for all other groups. †Indicated value differs significantly (\( P < 0.05 \)) between inspiration and expiration within the same group.
physiologic dead space than humans. 32–35 Moreover, the basal metabolism of dogs is greater than that of humans, which may account for a higher metabolic production of CO2 at rest as well as during general anesthesia. 33 The results of the present study were confirmed in a similar study34 in which the effects of T V s of 10, 12, and 15 mL/kg with PEEP at 4 cm H2O were evaluated in healthy dogs undergoing general anesthesia. In that study,34 investigators used volumetric capnography to assess dead space and lung mechanics. A T V of 15 mL/kg (with a PEEP of 4 cm H2O) resulted in better ventilatory efficiency than the other 2 T V s.34 In light of this finding, and given that our results indicated that a T V ≤ 8 mL/kg, with or without 5 cm H2O of PEEP, caused hypercapnia and respiratory acidosis, its application in clinical situations should be avoided, except for situations involving dogs with lung abnormalities that would benefit from the use of a low T V. Human and experimental research has shown that hypercapnia may be tolerated (permissive hypercapnia) in patients with lung disease, in whom a large T V may be associated with a higher risk of lung injury. 40

Relative percentages of atelectatic and poorly aerated lung at end-expiration were greater in dogs ventilated with a low T V than in those ventilated with a high T V, regardless of whether PEEP was applied. The use of a high FiO2 may have promoted lung collapse, as demonstrated in previous studies involving dogs, and thus less atelectasis should be expected with the use of a lower FiO2. Moreover, the similar amounts of atelectatic and poorly aerated lung between end-expiration and end-inspiration in the low T V and low T V plus PEEP groups indicated the absence of T V and PEEP-induced alveolar recruitment. In other words, in those dogs, the PTPs developed during T V were not high enough to reach the opening pressure of the collapsed alveoli, 29 even with the application of PEEP at 5 cm H2O. Conversely, in the high T V and high T V plus PEEP groups, the higher PTP promoted lung recruitment as suggested by the lower amount of atelectatic and poorly aerated lung. The significant difference in the amount of atelectasis between inspiration and expiration in the high T V group, a condition that suggested the presence of tidal recruitment, was noteworthy. The PTP attained in the high T V group exceeded the opening pressure of the alveoli, recruiting the lung parenchyma and improving lung aeration (ie, a greater amount of normally aerated lung). At the end of expiration, PAO returned to atmospheric pressure (0 cm H2O), inducing derecruitment of the lung parenchyma.

Opening and closing of alveoli during controlled mechanical ventilation (so-called tidal recruitment) is an established mechanism of lung injury (atelectrauma) that can be prevented by the application of PEEP. 38 Within the high T V plus PEEP group, the lack of a significant difference in the amount of atelectasis between end-expiration and end-inspiration was likely the result of the stabilizing effect of PEEP, which prevents the derecruitment of the alveoli. This possibility may have accounted for the larger EELV and Cstat, in dogs ventilated with the high T V plus PEEP.

The higher PAO and PES obtained with the high T V and high T V plus PEEP setting (vs the other ventilator settings) in the study reported here were the result of the higher T V. A possible adverse effect of the use of a high T V during mechanical ventilation is hyperinflation, a condition that can promote direct lung damage (ie, barotrauma or volutrauma) and may trigger ventilator-induced lung injury. Use of a T V of 15 mL/kg did not significantly increase the amount of hyperinflated lung in the present study.

Nevertheless, another key mechanism for the development of ventilator-induced lung injury is the straining (deformation of the alveoli relative to its initial volume) of the lung tissue beyond a certain limit (ie, total lung capacity), resulting in a degree of lung stress that causes the release of inflammatory cytokines (mechanotransduction). 39 Research involving healthy pigs has shown that ventilator-induced lung injury develops only when a strain > 1.5 or 2 is reached or exceeded, 40 which is a threshold that was never exceeded with any ventilator setting in the present study. The high T V group had the highest degree of strain per breath, which was then reduced by the application of PEEP, further suggesting the potential harmful condition created by application of a T V of 15 mL/kg without PEEP. As previously reported, 40 these data confirmed that a given T V will result in different degrees of strain, depending on the resting end-expiratory lung volume and thus the level of PEEP.

Arterial oxygen saturation was similar among ventilator setting groups in the present study, although the mean value was lower (albeit nonsignificantly) in the low T V group. The limited small number of dogs per group might have weakened the statistical power to detect differences among groups in terms of oxygenation. Future clinical studies involving a larger number of dogs are required to clarify the observed discrepancies between alveolar aeration and oxygenation and to determine whether different T V values may also affect oxygenation.

Another potential adverse effect of the use of a high T V is the development of high intrathoracic pressures that may cause hemodynamic impairment because of the reduction of venous return. Values of the basic cardiovascular variables measured in the present study indicated no significant differences among ventilator settings in terms of mean arterial blood pressure and heart rate. However, included dogs were healthy and cardiovascularly stable, and no conclusions could be drawn regarding the effect of high T V on the cardiovascular system in dogs with cardiac disease or hemodynamic compromise. Additional studies are required to identify any possible adverse effects of high T V and PEEP on cardiac output and oxygen delivery.

The results obtained in the present study failed to support our hypothesis that low T V ventilation
with PEEP would be beneficial, compared with high TV ventilation, and instead indicated that the use of a TV of 15 mL/kg and PEEP of 5 cm H2O was safe in anesthetized dogs with healthy lungs undergoing mechanical ventilation. Use of PEEP is important to stabilize the alveoli and avoid atelectrauma and mechanical ventilation. Use of PEEP is important to stabilize the alveoli and avoid atelectrauma and mechanical ventilation.

Footnotes

References


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34. Bumbacher S, Schramel JP, Mosing M. Evaluation of three tidal volumes (10, 12 and 15·mL kg⁻¹) in dogs for controlled mechanical ventilation assessed by volumetric capnography: a randomized clinical trial. *Vet Anaesth Analg* 2017;44:775–784.


