ORIGINAL ARTICLE

Effects of inhalational anaesthesia with low tidal volume ventilation on end-tidal sevoflurane and carbon dioxide concentrations: prospective randomized study


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Received 16 April 2013; accepted 4 June 2013
Available online 25 December 2013

Abstract
Objective: We investigated how ventilation with low tidal volumes affects the pharmacokinetics of sevoflurane uptake during the first minutes of inhaled anaesthesia.
Methods: Forty-eight patients scheduled for lung resection were randomly assigned to three groups. Patients in group 1, 2 and 3 received 3% sevoflurane for 3 min via face mask and controlled ventilation with a tidal volume of 2.2, 8 and 12 ml kg⁻¹, respectively (Phase 1). After tracheal intubation (Phase 2), 3% sevoflurane was supplied for 2 min using a tidal volume of 8 ml kg⁻¹ (Phase 3).
Results: End-tidal sevoflurane concentrations were significantly higher in group 1 at the end of phase 1 and lower at the end of phase 2 than in the other groups as follows: median of 2.5%, 2.2% and 2.3% in phase 1 for groups 1, 2 and 3, respectively (P < 0.001); and 1.7%, 2.1% and 2.0% in phase 2, respectively (P < 0.001). End-tidal carbon dioxide values in group 1 were significantly lower at the end of phase 1 and higher at the end of phase 2 than in the other groups as follows: median of 16.5, 31 and 29.5 mmHg in phase 1 for groups 1, 2 and 3, respectively (P < 0.001); and 46.2, 36 and 33.5 mmHg in phase 2, respectively (P < 0.001).
Conclusion: When sevoflurane is administered with tidal volume approximating the airway dead space volume, end-tidal sevoflurane and end-tidal carbon dioxide may not correctly reflect the concentration of these gases in the alveoli, leading to misinterpretation of expired gas data.

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Introduction

The induction of inhalational anaesthesia by means of a constant inspired inhaled anaesthetic concentration ($C_{IA}$) occurs by a gradual increase in the inhaled anaesthetic (IA) concentration in the alveoli ($C_{IAa}$) and a simultaneous increase in the arterial partial pressure ($P_{IAa}$) and brain partial pressure. This phase of inhaled anaesthesia is characterized by its non-stationary nature, and depends on: (1) the inspired IA concentration; (2) the effective alveolar ventilation; (3) an appropriate alveolar-capillary IA exchange; and (4) the IA uptake in each compartment, including the plasma.

For a constant $C_{IAa}$, alveolar ventilation is the only variable that the anaesthesiologist can control to set the desired supply rate of IA molecules to the target organ. $C_{IAa}$ monitoring is performed by measuring end-tidal IA concentration ($ET_{IA}$). Thus, the minimum alveolar concentration (MAC) (represented by $ET_{IA}$) is a widely accepted parameter for monitoring the clinical effect of the IA.

For $ET_{IA}$ values to correctly account for the MAC of the inhaled anaesthetic, the $ET_{IA}$ should accurately reflect IA concentration in the alveoli. We know that a portion of the tidal volume does not participate in gas exchange because it does not contact the pulmonary capillary blood flow and represents the physiological dead space or dead volume. $ET_{IA}$ values may not accurately represent the $CA_{IA}$ in situations where ventilation is inadequate and result in ventilation of the dead space rather than ventilation of the alveoli, such as when using very low tidal volumes, which eventually leads to ventilation of the airway dead space ($VD_{aw}$). In the context of inducing anaesthesia while maintaining spontaneous ventilation, the probability of inadequate alveolar ventilation is very high, due to the presence of periods of airway obstruction, apnea, bradypnea or reduced tidal volumes.

In this study we emulated, under controlled conditions, these potential scenarios of alveolar hypoventilation during the initial phase of anaesthesia, in order to show the extent to which ineffective ventilation (airway dead space ventilation) can lead to alveolar hypoventilation (with the consequent increase in the arterial partial pressure of CO$_2$ in arterial blood and an unreliable reading of alveolar sevoflu- ran concentration). We compared $ET_{SEVO}$ and $ET_{CO2}$ values in three groups of patients receiving controlled ventilation via facemasks with low, standard or high tidal volumes for a constant $C_{IAa}$. We registered $ET_{SEVO}$ and $ET_{CO2}$ values during facemask ventilation; after intubation and after con- trolled ventilation with a standard tidal volume (8 ml kg$^{-1}$). Low tidal volume group was ventilated using volume slightly higher of $VD_{aw}$.9

Methods

This was a prospective, randomized, cohort study approved by the ethical and research committee of our centre (Ethical Committee N° 2012PI/018), Hospital Universitario Virgen del Rocio, Seville, Spain – Chairperson Dr. J Bautista – Paloma – on 03 May 2012). We included 48 adult patients (aged ≥ 18 years) scheduled for lung resection (lobar or wedge resection) between 01 January and 31 October 2012. Informed consent was obtained from all patients.

Exclusion criteria were: ASA ≥ IV; BMI ≥ 40 kg/m$^2$; presence of major cardiovascular clinical risk factors (unstable
or severe angina, recent myocardial infarction, decompen-
sated heart failure, significant arrhythmias or severe
valvular disease; (GOLD classification grade ≥ 3); moderate
to severely impaired renal function (plasma creatinine
≥ 2 mg dl−1); previous lung resection surgery; carbon
monoxide diffusing capacity related to alveolar volume
(DLCO/V_{A}) ≤ 65% of the predicted value; and the presence
of predictors of difficult airway including: previous difficult
intubation; previous Cormack-Lehane grade ≥ 3; Mallampati
grade ≥ 3; oral opening ≤ 4 cm; retrognathia; neck circum-
fERENCE ≥ 40 cm; anatomic neck alterations or presence of
neck masses.

To calculate the sample size we used data from the first
10 patients randomly assigned to groups 1 and 2 (5 patients
per group); using the means of the variable ET_{sevo} stage
1–ET_{sevo} stage 2 in both groups. To achieve a 80% power
to detect differences in the contrast of the null hypothesis
H_{0}: μ_{1} = μ_{2}, through bilateral Student’s t test for two inde-
pendent samples, considering a significance level of 5%, and
assuming a reference group mean of 0.20 units, the mean
of the experimental group of 0.70 units and the standard devi-
ation of both groups of 0.50 units. We needed to include
16 patients in group 1 and 16 in group 2, adding a second
control group (group 3) of the same size.

Patients were randomized to one of the three groups
using a computer-generated random number sequence (Epi-
dat 4.0).

Patients in groups 1, 2 and 3 received controlled ven-
tilation during phase 1 with V_{T} of 2.2, 8 and 12 ml kg⁻¹
based on corrected weight. We used the actual weight for
patients with BMI < 25 kg/m² when calculating the corre-
sponding ml kg⁻¹ and the corrected weight for patients with
BMI ≥ 25 kg/m² (the weight at an ideal BMI of 25 kg/m²).
We collected patients’ demographic and anthropometric
data, history of toxic habits, and presence of comorbidities
(Table 1).

Study protocol

We divided the study into four phases (phases 0–3). All
patients received oral midazolam (0.07 mg kg⁻¹ corrected
body weight) 30 min before initiation of the procedure.

Phase 0: prior to anaesthesia induction

We used a Dräger Primus anaesthetic circuit (Dräger Medi-
cal, Lübeck, Germany) and a new and fresh CO₂ absorber
(CLIC Absorber 800+, Dräger Medical) for each case. The cir-
cuit was primed with 3% sevoflurane and 80% oxygen using
a fresh gas flow (FGF) of 6 L min⁻¹. We monitored inspired
and expired gas concentrations using the gas analyzer of
the anaesthesia workstation. Patients were monitored with 5-
lead ECG continuous monitoring of the ST segment (Infinity
Kappa XLT, Dräger Medical); SpO₂ (Nellcor MAXA, Covi-
dien Inc., Mansfield, MA, USA); non-invasive arterial blood
pressure; and bispectral index (BIS Quatro, Coviden Inc.,
Norwood, MA, USA). After peripheral vein cannulation, an
epidural or paravertebral catheter was placed with no bolus
administration. With the patient under local anaesthesia and
sedation with a remifentanil infusion adjusted for corrected
body weight (0.05–0.1 mcg kg⁻¹ min⁻¹ for BIS > 90), the radial
artery was cannulated and baseline arterial blood gases and
haemodynamic data were collected (Stage 0).

Phase 1: controlled ventilation via face mask
after induction

Prior to induction, patients were oxygenated for 2 min with
100% O₂ with spontaneous breathing via face-mask with a
Mapleson C system (Anaesthesia Breathing System, Maple-
son C 22F, 2L bag, Intersurgical, Berkshire, UK) connected
to an oxygen tank independent of the anaesthesia circuit
with an FGF of 10 L min⁻¹. Anaesthesia was induced using
propofol (1 mg kg⁻¹), remifentanil 0.05–0.1 mcg kg⁻¹ min⁻¹
and cisatracurium 0.15–0.2 mg kg⁻¹ (all dosages based on
corrected body weight). When the patient reached a BIS
level ≤ 65, an oropharyngeal airway was inserted (Guedel
airway). We then connected the Y-piece of the anaesthesia
circuit primed with 3% sevoflurane to the facemask and
adjusted the tidal volume to the corrected body weight
according to the study group. An independent observer
assessed the adequacy of ventilation. If adequate ventila-
tion was not achieved (i.e., the monitored expired tidal
volume showed gas leaks or insufficient ventilation, or the
anaesthesia circuit analyzer failed to detect expired gas),
the patient was excluded from the study. In all cases we used
a FGF of 6 L min⁻¹; a ventilatory rate of 12 breaths/min; an
I:E ratio of 1:2; an inspiratory pause of 30%; and a PEEP of
6 cm H₂O. Variables were recorded 3 min after ventilation
with the tidal volume assigned to each study group (Stage
1).

Phase 2: orotracheal intubation and resuming
ventilation with 8 ml kg⁻¹

Three minutes after controlled ventilation was initiated,
we undertook direct laryngoscopy and intubate the trachea
with an appropriately sized double lumen endotracheal tube
(Mallinckrodt-Covidien, Mansfield, MA, USA), setting the
anaesthesia circuit to standby mode with the Y-piece closed.
Sevoflurane was maintained at 3% throughout phases 0–3.
After intubation, V_{T} was reset to 8 ml kg⁻¹ in all patients; the
remainder of the ventilation parameters were not modified;
the circuit was connected to the endotracheal tube; and
controlled ventilation was resumed. We excluded patients
requiring > 90 s for intubation. Alveolar ventilation was con-
sidered adequate and data were recorded when the circuit
was connected to the endotracheal tube and the spirome-
teter of the anaesthesia circuit showed that the expired
V_{T} matched the fixed V_{T}. ET_{sevo} and ET_{CO₂} values were cal-
culated as the mean of the values obtained during the first
tree adequate ventilation cycles with a V_{T} of 8 ml kg⁻¹
(Stage 2).

Phase 3: controlled ventilation with a V_{T}
of 8 ml kg⁻¹

After 2 min of controlled ventilation, data were collected,
including arterial blood gas values (Stage 3).
In all phases, a reduction in systolic blood pressure (SBP) of >15% from baseline values was treated with boluses of ephedrine and/or phenylephrine, according to the clinical characteristics of the patients and the heart rate. On completion of the study, correct positioning of the orotracheal tube was confirmed with a fiberoptic bronchoscope. All patients were interviewed 24 hours after the procedures to determine if they had any memories of the intervention.

Statistical analysis

We used the SPSS software system, version 16.0 (SPSS Inc., Chicago, IL, USA) for data collection and analysis. The normality of quantitative data distribution was assessed using the Shapiro–Wilk test. The homogeneity of variances was estimated using Levene’s test, and the distribution of variables was analyzed using the analysis of asymmetry and kurtosis. When the variables studied showed normal distribution, we used the ANOVA and Chi-square tests to analyze the difference in the means, medians and proportions of quantitative and qualitative variables in relation to the intervention group. We used the Bonferroni method to perform a post hoc study of the difference in means obtained by ANOVA. We used a paired Student’s t-test for intra-group comparison of the following variables: ET\textsubscript{sevo}, ET\textsubscript{CO\textsubscript{2}}, blood pressure (BP), heart rate (HR), and BIS over time.

Results

A total of 57 patients were recruited and randomized. Nine patients were excluded. Seven patients did not achieve adequate manual ventilation and all but one of these patients was toothless. We excluded two patients due to orotracheal intubation time >90 s. The surgery was successfully performed in all cases. The flow diagram is shown in Fig. 1.

The distribution of anthropometric variables, the history of substance abuse and comorbidities were similar in the three groups, except for a higher incidence of ischaemic heart disease in group 2. No differences were observed in baseline BIS, blood pressure, heart rate and Pa\textsubscript{CO\textsubscript{2}} values in the three groups (Table 1). No significant differences were observed in the duration of intubation with a median time of 38 s, (range, 33–55 s); 42 s (31–50 s); and 45 s (range, 35–57 s) for groups 1, 2 and 3, respectively. We observed significant differences in the ET\textsubscript{sevo} values and in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Anthropometric data, comorbidities and basal measurements.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 (n = 16)</td>
</tr>
<tr>
<td>Volume 1 (min–max)</td>
<td>168 (120–220)*</td>
</tr>
<tr>
<td>Volume 2 (min–max)</td>
<td>640 (425–800)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>14</td>
</tr>
<tr>
<td>Age (years) (min–max)</td>
<td>64.5 (39–78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (62.5–84)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.65 (1.57–1.73)</td>
</tr>
<tr>
<td>BMI (kg m\textsuperscript{2})</td>
<td>28.33 (24.3–30)</td>
</tr>
<tr>
<td>Active smoking</td>
<td>5</td>
</tr>
<tr>
<td>Smoking habit (&gt;25 pack-year)</td>
<td>12</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
</tr>
<tr>
<td>1–2</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
</tr>
<tr>
<td>CAD</td>
<td>1</td>
</tr>
<tr>
<td>COPD</td>
<td>6</td>
</tr>
<tr>
<td>Restrictive pulmonary disease</td>
<td>3</td>
</tr>
<tr>
<td>OSAS</td>
<td>1</td>
</tr>
<tr>
<td>DLCO/V\textsubscript{A} ≤ 80% predicted</td>
<td>9</td>
</tr>
<tr>
<td>BIS basal</td>
<td>97 (95–98)</td>
</tr>
<tr>
<td>Basal systolic blood pressure (mmHg)</td>
<td>134.5 (124–149)</td>
</tr>
<tr>
<td>Basal diastolic blood pressure (mmHg)</td>
<td>70 (65–81)</td>
</tr>
<tr>
<td>Basal HR (beats per minute)</td>
<td>73 (66–84)</td>
</tr>
<tr>
<td>Basal Pa\textsubscript{CO\textsubscript{2}} (mmHg)</td>
<td>43.3 (41.3–48.2)</td>
</tr>
</tbody>
</table>

Volume 1: 2.7, 8 and 12 ml kg\textsuperscript{–1} for groups 1–3; volume 2: 8 ml kg\textsuperscript{–1} in all cases; ASA: American Society of Anesthesiologists physical status; CAD: stable coronary artery disease; COPD: chronic obstructive pulmonary disease if ≤3 GOLD classification; OSAS: obstructive sleep apnea syndrome; DLCO/V\textsubscript{A}: carbon monoxide diffusing capacity related to alveolar volume; HR: heart rate; NS: non statistical significance.

Values for quantitative variables represented as median with interquartile range within brackets or maximum and minimum values when specified. Values for qualitative variables represented as n.

* Significant differences between the three groups (ANOVA).
** Significant differences in Chi-square test.
the ET<sub>SEVO</sub>/Cl<sub>SEVO</sub> ratio in the three groups in stages 1, 2 and 3 (paired Student’s t-test) (Table 2 and Fig. 2). We also found significant differences in the ET<sub>SEVO</sub> between group 1 and the other groups in all stages. Group 1’s ET<sub>SEVO</sub>/Cl<sub>SEVO</sub> values were significantly higher than those of group 2 and 3 in stage 1, and significantly lower than those of group 2 and 3 in stage 2 (Table 2 and Fig. 2). The ET<sub>CO₂</sub> values were significantly lower in group 1 three minutes after initiation of controlled facemask ventilation (stage 1) and significantly greater in stages 2 and 3 than in the other groups. No significant differences were observed between group 2 and 3 in any stage (Table 2). The Pa<sub>CO₂</sub> values were significantly higher in group 1 in stage 3 than in the other groups. No significant differences were found in the Pa<sub>CO₂</sub> – ET<sub>CO₂</sub> gradient or the ET<sub>CO₂</sub>/Pa<sub>CO₂</sub> ratio in stage 3 in the three groups (Table 2).

Patients in group 3 showed lower systolic BP values than the other groups following phase 1. No significant differences were observed in BP or heart rate between the three groups in the other stages (Table 3). A significant BP decrease was observed in all groups after phase 1, followed by an increase after intubation in all groups and a significant decrease at two minutes of ventilation with standard tidal volume (paired Student’s t-test) (Table 3). We also found significant changes in heart rate for all phases in group 1, and a significant increase after intubation in all groups (Table 3). Patients in group 3 showed a significant difference compared with the other groups in the incidence of a decrease in BP > 20% over basal values.

Patients in group 1 required less vasoactive drug support than patients in groups 2 and 3 (7, 12 and 13 cases...
in groups 1, 2 and 3, respectively, \( P = 0.02 \), with a median dose of ephedrine and phenylephrine of 7.5 mg and 75 mcg; 7.5 mg and 100 mcg; 15 mg and 100 mcg in groups 1, 2 and 3, respectively. BIS values in stages 1 and 2 were also significantly higher in group 1 than in group 2. No differences were observed in BIS values in the three groups at 2 min in stage 3 (Table 3). No episodes of intraoperative awareness were registered in the 24-h interview.

### Table 2  Sevoflurane and CO₂ concentrations in stages 1–3.

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{ET}_{\text{SEVO}} ) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>2.5 (2.4–2.6)</td>
<td>1.7 (1.62–1.87)</td>
<td>2.1 (2.0–2.27)</td>
</tr>
<tr>
<td>Group 2</td>
<td>2.2 (2.2–2.4)</td>
<td>2.1 (1.96–2.23)</td>
<td>2.3 (2.2–2.4)</td>
</tr>
<tr>
<td>Group 3</td>
<td>2.3 (2.2–2.3)</td>
<td>2.0 (1.90–2.20)</td>
<td>2.3 (2.2–2.3)</td>
</tr>
<tr>
<td>( \text{ET}<em>{\text{SEVO}}/\text{CI}</em>{\text{SEVO}} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>0.82 (0.78–0.85)</td>
<td>0.56 (0.52–0.59)</td>
<td>0.69 (0.66–0.74)</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.73 (0.68–0.77)</td>
<td>0.68 (0.64–0.71)</td>
<td>0.74 (0.72–0.77)</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.78 (0.76–0.79)</td>
<td>0.68 (0.65–0.72)</td>
<td>0.74 (0.72–0.77)</td>
</tr>
<tr>
<td>( \text{ET}_{\text{CO}_2} ) (mmHg)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>16.5 (13–20)</td>
<td>46.2 (41–48)</td>
<td>41.5 (38–46)</td>
</tr>
<tr>
<td>Group 2</td>
<td>31 (27–36)</td>
<td>36 (35–38)</td>
<td>35.5 (33–38)</td>
</tr>
<tr>
<td>Group 3</td>
<td>29.5 (28–32)</td>
<td>33.5 (32–37)</td>
<td>36 (32–37)</td>
</tr>
<tr>
<td>( \text{Pa}_{\text{CO}_2} ) (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>51 (49–54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>44.9 (39–46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>45.2 (43–48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Pa}_{\text{CO}<em>2} - \text{ET}</em>{\text{CO}_2} ) (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>9.1 (7–11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>8.5 (6.4–11.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>10.3 (3.8–14.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{ET}_{\text{CO}<em>2}/\text{Pa}</em>{\text{CO}_2} )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>0.82 (0.77–0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>0.82 (0.75–0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>0.79 (0.71–0.91)</td>
<td></td>
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</tr>
</tbody>
</table>

\( \text{ET}_{\text{SEVO}} \): end-tidal sevoflurane concentration; \( \text{CI}_{\text{SEVO}} \): inspiratory sevoflurane concentration; \( \text{ET}_{\text{CO}_2} \): end-tidal CO₂ partial pressure; \( \text{Pa}_{\text{CO}_2} \): arterial CO₂ partial pressure.

Values represented as median and interquartile range.

\( ^\dagger \) Significant differences intra-groups between stage 1 and stage 2; stage 2 and stage 3 (paired Student’s \( t \)-test).

\( ^\star \) Significant differences between group 1 and group 3 (ANOVA).

\( ^\ddagger \) Significant differences between the three groups (ANOVA).

\( ^\# \) Significant differences between group 1 and the other groups (ANOVA).

Figure 2  Modification of end-tidal sevoflurane concentrations throughout phases 0–3.

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Table 3 Blood pressure, heart rate and BIS values in stages 1–3.

<table>
<thead>
<tr>
<th></th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP/DBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1’</td>
<td>115 (101–113)/57 (51–69)</td>
<td>165 (134–180)/82 (74–91)</td>
<td>123 (125–146)/66 (51–71)</td>
</tr>
<tr>
<td>Group 2’</td>
<td>124 (96–150)/65 (55–80)*</td>
<td>159 (120–167)/83 (70–95)</td>
<td>136 (114–150)/70 (56–80)</td>
</tr>
<tr>
<td>Group 3’</td>
<td>96 (86–107)/50 (46–61)*</td>
<td>139 (115–161)/73 (58–85)</td>
<td>126 (101–149)/64 (54–75)</td>
</tr>
<tr>
<td>HR (BPM)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1’</td>
<td>66 (61–76)</td>
<td>83 (65.75–100)</td>
<td>77 (71–91)</td>
</tr>
<tr>
<td>Group 2’</td>
<td>67 (51–98)</td>
<td>75 (72.0–94.5)**</td>
<td>71 (64–98.5)</td>
</tr>
<tr>
<td>Group 3’</td>
<td>65 (56–76)§</td>
<td>79 (68.0–85.6)**</td>
<td>77 (70–86)</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1’</td>
<td>46 (37–53.5)$</td>
<td>46 (40–56)$</td>
<td>42.5 (37–47)$</td>
</tr>
<tr>
<td>Group 2’</td>
<td>31 (24–41)$</td>
<td>33 (26–35.5)$</td>
<td>32 (25–46.5)</td>
</tr>
<tr>
<td>Group 3’</td>
<td>41 (30–49)</td>
<td>35 (28–52)</td>
<td>35 (30–47)</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; BPM: beats per minute; BIS: bispectral index values. Values expressed as median and interquartile range.

* Intra-group differences between stage 0 and stage 1, stage 1 and stage 2; and stage 2 and stage 3 (paired Student’s t-test).

*# Significant differences between groups 2 and 3 (ANOVA).

§ Significant differences between group 3 and others (ANOVA).

$ Intra-group significant differences between stage 0 and stage 1 (paired Student’s t-test).

** Intra-group significant differences between stage 1 and stage 2 (paired Student’s t-test).

§ Significant differences between groups 1 and 2 (ANOVA).

€ Intra-group significant differences between stage 2 and stage 3 (paired Student’s t-test).

Discussion

We observed that patients receiving controlled ventilation via a facemask with a tidal volume approximating the $\text{VD}_{\text{AW}}$ (Group 1) presented a greater $\text{ET}_{\text{SEVO}}$ gradient between phases 1 and 2 ($\text{ET}_{\text{SEVO}1} - \text{ET}_{\text{SEVO2}}$) than normal and hyperventilated patients. Similarly, the $\text{ET}_{\text{SEVO}}/\text{Cl}_{\text{SEVO}}$ ratio in group 1 was significantly higher after the face-mask ventilation phase (stage 1), and significantly lower after intubation (stage 2) than in the other two groups. Group 1 had significantly lower $\text{ETCO}_2$ values after stage 1 and significantly greater values after stage 2 than the other groups. The $\text{ETCO}_2 1 - \text{ETCO}_2 2$ gradient was greater in group 1 than in the other groups (Table 2). Group 1 showed greater expired $\text{CO}_2$ values than the other two groups two minutes following tidal ventilation with 8 ml kg$^{-1}$.

Our initial hypothesis was that ventilation with tidal volumes approximating the $\text{VD}_{\text{AW}}$ is poorly effective. In theory, exclusive ventilation of the $\text{VD}_{\text{AW}}$ would have the following effects on sevoflurane and $\text{CO}_2$: (1) In a theoretical setting of non-effective alveolar ventilation, the inspired sevoflurane would be ‘‘retained’’ in the $\text{VD}_{\text{AW}}$. It would not fill the alveolar volume nor be transferred to the plasma compartment. In this case, the expired sevoflurane reading would tend to match the inspired sevoflurane, since we would be analyzing a gas sample that has not been ‘‘contaminated’’ by alveolar gas. (2) Similarly, the $\text{CO}_2$ reading would near zero as our gas analyzer would not collect alveolar $\text{CO}_2$ samples because the alveoli are not being ventilated. In normal or effective alveolar ventilation, gas analysis at the end of expiration would approach the real gas concentration in the alveoli, which is directly correlated with gas concentration in plasma. Failure to consider the potential for non-effective ventilation may lead clinicians to misinterpret expired gas data.

Currently, it is widely accepted that a ventilation/perfusion ($\text{V/Q}$) mismatch in certain lung areas, caused by either the presence of atelectatic areas (decreased $\text{V/Q}$ ratio) or alveolar dead space areas (increased $\text{V/Q}$ ratio), induces an increase in the $\text{ET}_{\text{GAS}} - \text{Pa}_{\text{GAS}}$ gradient and may lead clinicians to misinterpret expired gas data. To reduce the risk of atelectasis during anaesthesia induction, we used a $\text{FiO}_2$ of 0.8 and a PEEP of 6 cm H$_2$O during controlled ventilation via a facemask. However, the use of different tidal volumes during phase 1 in our sample created a possible influence on the risk of atelectasis. Nevertheless, it was not the purpose of this study to measure the potential risk of atelectasis associated with the use of tidal volumes approximating the $\text{VD}_{\text{AW}}$. In this regard, we found no differences in the three groups in the $\text{ETCO}_2 - \text{Pa}_{\text{CO}_2}$ gradient and the $\text{ETCO}_2/Pa_{\text{CO}_2}$ ratio after two minutes of ventilation with a $\text{Vt}$ of 8 ml kg$^{-1}$ (stage 3). This finding does not agree with the results of previous studies that found differences according to the ventilation method. The reason may be that intubation during phase 1 required disconnection from the pressurized circuit (PEEP of 6 cm H$_2$O), which would have neutralized a protective effect of ventilation with higher tidal volumes on the $\text{V/Q}$ ratio in patients in groups 2 and 3. This factor, i.e. a derecruitment effect, together with the use of the same ventilation regimen in the three groups after intubation ($\text{Vt}$ of 8 ml kg$^{-1}$ and PEEP of 6 cm H$_2$O) might have compensated for potential differences in the $\text{V/Q}$ ratios generated during phase 1. Because we did not measure blood sevoflurane concentrations, we could not assess potential differences in the $\text{Pa}_{\text{SEVO}} - \text{ET}_{\text{SEVO}}$ gradient in the three groups. Enekvist et al. reported that the use of high tidal volumes (12 ml kg$^{-1}$) versus normal 5.7 ml kg$^{-1}$ reduces the $\text{Pa}_{\text{SEVO}} - \text{ET}_{\text{SEVO}}$ gradient. Other authors have suggested that increases in the $\text{Pa}_{\text{AW}} - \text{ET}_{\text{AW}}$ gradient could be induced by a shunt that could be partly countered by...
high tidal volumes, favouring alveolar recruitment. Pre-vi- ous results support our hypothesis that ventilation with poorly effective tidal volumes not only yields unreliable data on gas exchange and alveolar gas concentrations, but may also increase alveolar-arterial partial pressure gradients because of the shunt effect associated with alveolar collapse.

In our study, after excluding the hypoventilated patients (group 1), the mean ET<sub>SEVO</sub>/Cl<sub>SEVO</sub> value two minutes after intubation was 0.74 ± 0.04. These data are consistent with previous studies on sevoflurane pharmacokinetics in the initial stage of inhalational anaesthesia with ET<sub>SEVO</sub> values increasing quickly and the ET<sub>SEVO</sub>/Cl<sub>SEVO</sub> ratio reaching 0.8 only 10min after sevoflurane administration and remaining constant thereafter. Enkvist et al. reported an ET<sub>SEVO</sub>/Cl<sub>SEVO</sub> ratio of 0.75 at 5min of sevoflurane administration in patients on both normal ventilation (V<sub>T</sub> of 5.7 ml kg<sup>−1</sup>) and hyperventilation (V<sub>T</sub> of 12 ml kg<sup>−1</sup>).

Patients in group 1 showed greater BIS values than those in the other groups but the difference was significant only for groups 1 and 2 (Table 3). Although ET<sub>SEVO</sub> correlates with the clinical effect of the inhaled anaesthetic during the maintenance phase of anaesthesia, its correlation with plasma sevoflurane concentrations during the early stages of anaesthesia has a non-linear distribution. As other variables affect the final sevoflurane concentration in the target organ during the initial stage, we consider that ET<sub>SEVO</sub> may not be a good predictor of Pa<sub>SEVO</sub>, especially when alveolar ventilation is not properly controlled for as a variable.

Previous studies of the management of the airway in patients undergoing general anaesthesia with sevoflurane or other halogenated agents under spontaneous ventilation have not examined the influence of the volume of effective alveolar ventilation on monitoring of expired gases, or have not properly assessed the adequacy of spontaneous ventilation. The dangers of assuming that end tidal gas measurements are accurate reflections of alveolar concentrations under all circumstances are that patients might experience direct laryngoscopy while inadequately anesthetized and that hypoventilation might go unrecognized. There are several examples of clinical scenarios where the latter might be important. For a patient with a critically raised intracranial pressure, for example, prolonged hypercapnia could have deleterious effects on cerebral blood flow and result in brain injury. The results of this study could be applicable to situations where sevoflurane is used as a hypnotic agent for airway management in patients with spontaneous breathing. In this setting, the variable, alveolar ventilation, is not directly controlled by the anaesthesiologist, but instead, depends on the patient’s state of hypnosis. Pean et al. assessed the performance of fiberoptic intubation in a prospective randomized study with propofol versus sevoflurane in anaesthetized patients with spontaneous breathing. The authors reported BIS values >65 (medians, 66 (range, 53–85) and 77 (range, 62–96) for nasal and oral intubation, respectively) for ET<sub>SEVO</sub> values of 3.8 (range, 2.7–5.3). These authors also reported a significantly high incidence of explicit memories (13%). Pean et al. used an 8% inspired fraction of sevoflurane to reach a Ramsey score of 5 and maintain spontaneous breathing. Sepúlveda et al. demonstrated that ET<sub>SEVO</sub> is not a good predictor of the clinical effect of sevoflurane during inhaled anaesthesia induction at high concentrations (8%) in patients with assisted spontaneous breathing with tidal volume ventilation. Sepúlveda reported greater ET<sub>SEVO</sub> values when the blink reflex was suppressed (ET<sub>SEVO</sub> 5.7% (range, 2–8.6, median and interquartile range), compared with the moment when the evoked response was <40 (ET<sub>SEVO</sub> 3.8%; range, 2.6–6.5), indicating a potential inconsistency between ET<sub>SEVO</sub> and Pa<sub>CO<sub>2</sub></sub>. One of the reasons for this inconsistency might be that when these authors monitored ET<sub>SEVO</sub> values, they were actually monitoring V<sub>D</sub>aw rather than alveolar gas volume. This explains why apparently high partial pressures of sevoflurane do not provide adequate levels of hypnosis; potentially because reduced tidal volumes cause alveolar hyperventilation, which worsens as the patient loses consciousness during spontaneous breathing. As the authors did not measure Pa<sub>SEVO</sub>, Pa<sub>CO<sub>2</sub></sub> and tidal volume values during the procedure, our explanation is only an hypothesis.

One of the limitations of our study has been the lack of specific measure of cardiac output. Recent works have shown that changes in cardiac output up to 100% may be required to significantly affect the initial uptake of IA. As shown in Fig. 3, changes in BP and HR followed a parallel distribution in the three groups throughout stages 0–4. We observed that BP and HR values decreased significantly in the three groups in stage 1, but only group 3 showed significant BP reduction >20% over baseline values (Table 3 and Fig. 3). Tracheal intubation was accompanied by an increase in BP and HR in the three groups (stage 2) followed by a reduction in BP at 2min of normal ventilation (stage 3).

The greater reduction in systolic BP reached in group 3 in stage 1 is not exclusively attributable to a greater blood sevoflurane concentration, as ET<sub>SEVO</sub> in this group was equal to that of group 2. We hypothesize that ventilation with high tidal volumes would create a PEEP-like effect, accompanied by an increase in intrathoracic pressure potentially compromising the preload. On the other hand, patients in group 1 required less amines support than patients in groups 2 and 3, which may be a potential result of the lower blood sevoflurane concentrations and its effect on systemic vascular resistances.

We conclude that in cases of hyperventilation induced by the use of tidal volumes approximating the V<sub>D</sub>aw, the ET<sub>SEVO</sub> and ET<sub>CO<sub>2</sub></sub> fractions may not be effective for assessing sevoflurane and CO<sub>2</sub> concentrations in the alveoli.
and may lead to misinterpreted expired gas data. Further studies are required to define which tidal volume limits and which ventilation variables (inspiratory times, PEEP level, and recruitment manoeuvres) are associated with adequate and efficient alveolar ventilation during the early stages of inhalational anaesthesia.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

We would like to thank Mr. Juan Manuel Pranea, from the Unidad de Apoyo a la Investigación, Hospital Universitario Virgen del Rocío, for the statistical advice.

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