Inhalation Anesthesia Increases V/Q Regional Heterogeneity during Spontaneous Breathing in Healthy Subjects

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ABSTRACT

Background: The underlying mechanism for the increased alveolar-arterial oxygen tension difference resulting from almost all forms of general anesthesia is unknown. We hypothesized that inhalation anesthesia influences the intrapulmonary distribution of ventilation (V) and perfusion (Q), leading to less advantageous V/Q matching.

Methods: Ten healthy volunteers were studied in supine position on two separate occasions, once awake and once during mild anesthesia (sevoflurane inhalation) with maintained spontaneous breathing. On both occasions, the distribution of V and Q were simultaneously imaged using single photon emission computed tomography. V was tagged with $^{[99mTc]}$-labeled carbon particle aerosol and Q with $^{[113mIn]}$-labeled macroaggregates of human albumin. Atelectasis formation during anesthesia was prevented using low concentrations of oxygen in inhaled air.

Results: Mean V and Q distributions in the ventral-to-dorsal direction, measured in 20 equally spaced volumes of interest and in three regions of interest of equal volume, did not differ between conditions. Anesthesia, when compared with the awake state, significantly decreased the total heterogeneity of the Q distribution ($P=0.002$, effect size 1.16) but did not alter V ($P=0.37$, effect size 0.41). The corresponding V/Q total heterogeneity was higher under anesthesia ($P=0.002$, effect size 2.64). Compared to the awake state, the V/Q frequency distribution under anesthesia became wider ($P=0.009$, 1.76 effect size) with a tendency toward low V/Q ratios.

Conclusion: Inhalation anesthesia alone affects Q but not V, suggesting that anesthesia has a direct effect on the active regulatory mechanism coordinating Q with V, leading to less favorable V/Q matching.

What We Already Know about This Topic

- Anesthesia is associated with deterioration in pulmonary gas exchange. The underlying mechanism is not fully understood.

What This Article Tells Us That Is New

- In healthy volunteers, inhalation anesthesia affects lung perfusion (Q) but not ventilation (V), increasing intrapulmonary heterogeneity in V/Q distribution.

Almost all forms of general anesthesia, including inhalation anesthesia, are associated with deterioration in pulmonary gas exchange. Maintained coordination of regional lung perfusion (Q) and ventilation (V) is crucial for optimal blood oxygenation. The underlying mechanism of this function is still not fully understood. Several determinants of regional Q have been reported in animal studies, among them, lung vascular structure, differences in vessel conductance between lung regions, gravity and hypoxic...
pulmonary vasoconstriction. In addition, human studies have shown that selective nitric oxide synthesis also seem to influence Q with a more uniform distribution in the ventral-to-dorsal direction in prone versus supine position. This effect was also observed in healthy volunteers under general anesthesia with mechanical ventilation. The regional distribution of V is more likely regulated by passive mechanisms, such as variations of alveolar compliance in different parts of the lungs, inspiration rate, and regional pleural pressure.

During inhalation anesthesia with spontaneous breathing, there is increased passage of mixed venous blood through the lungs that is believed to be, at least partly, related to formation of atelectasis. Atelectasis formation is a known phenomenon currently considered an effect of a decreased functional residual capacity and high oxygen concentration in the inhaled gas during anesthesia induction. In addition, a recent report has also shown a vasoconstrictive effect from halothane and other volatile anesthetics. However, researchers have also shown that inhalation anesthetics inhibit hypoxic pulmonary vasoconstriction in humans and animals. These results suggest that the overall effect of inhalation anesthesia on pulmonary circulation is limited and with no apparent regional effects. On the other hand, the underlying mechanisms for increased dead space and impaired oxygenation during anesthesia are still unclear. The direct effect of inhalation anesthesia on the regional distribution of the V and Q studied in vivo has, to our knowledge, not been studied in humans. This combination of factors may contribute to the resulting passage of mixed venous blood through the lungs. Furthermore, in acute respiratory distress syndrome, where increased shunt and dead space result in an abnormal V/Q ratio distribution, the addition of inhalation anesthetics could be detrimental. In the current investigation, we hypothesized that facial mask mild inhalation anesthesia would lead to a change in the distribution of V/Q ratios within the lung.

We previously developed a quantitative scintigraphic method using single photon emission computed tomography (SPECT) that simultaneously measures regional V and Q. In the current study, we used this method to compare regional V and Q in healthy subjects breathing spontaneously while awake and during inhalation anesthesia.

Materials and Methods

Subjects

Ten healthy, nonsmoking volunteers (5 men, 5 women; mean age 25 yr, range 20–34 yr) were studied. All were of normal weight (mean 68 kg, range 58–81 kg) and height (mean 1.73 m, range 1.58–1.81 m). The study was approved by the local ethics and radiation protection committees. Informed, written consent was obtained from all participants.

Radio pharmaceuticals

Approximately 50 MBq of [113mIn]-labeled macroaggregates of human albumin (Technescan LyoMAA, Mallinckrodt Medica, Petten, The Netherlands) was used as tracer for Q. Simultaneously, approximately 50 MBq of [99mTc]-labeled Technegas (Tetley Manufacturing Ltd., Sydney, Australia) was used as tracer for V.

Anesthesia

To avoid excessive saliva secretion, 0.1 mg glycopyrron was injected. Standard monitoring equipment for electrocardiography and pulse oximetry was applied. Inhaled oxygen fractions, end-tidal concentration of carbon dioxide, pulse oximetry, tidal volume, minute ventilation, respiratory rate, and expired concentration of the anesthetic agent were monitored continuously in accordance with clinical practice.

Anesthesia was induced by inhalation of sevoflurane through a tight fitting facemask. In each subject, anesthesia was continued under spontaneous breathing for approximately 20 min with sufficient sevoflurane to reach a minimum alveolar concentration value of approximately 1. Age correction was performed so that slightly different end-tidal concentration of sevoflurane between subjects was obtained (average 2.9 ± 1.4%). During anesthesia, a maximum of 500 ml of a balanced acetate solution were infused intravenously while inhaled and exhaled gases were analyzed continuously (DATEX AS/3; Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland).

Because the major focus of this investigation was to isolate the effect of anesthetics alone on the V and Q distribution, atelectasis formation during anesthesia was prevented by keeping low concentrations of oxygen in inhaled air (0.3).

Experimental Design

Volunteers fasted for 6 h before examinations. Each subject was examined on two different days using SPECT, once awake and once during inhalation mask anesthesia and spontaneous breathing. The order of the investigations was randomized by lottery. Five subjects were investigated first awake and then anesthetized and the other five in the reverse order. At least 3 days (mean 9 days) elapsed between examinations. The subject was, on both occasions, examined in the supine posture. The steady state during anesthesia was reached at approximately 20 min after induction (range 18–25 min). Technegas was administered via facial mask while LyoMAA was administered intravenously. After administration of the radiotracers, sevoflurane delivery was terminated and anesthesia ended. The mean duration of anesthesia was 33 min (range 25–44 min). SPECT image acquisition started as soon as the patient regained complete consciousness. At completion of the scan, the subject was kept a few hours for recovery before hospital discharge. The procedure during the awake state mimicked that during anesthesia except for the administration of the anesthetic drug.
**SPECT Scan**

Image acquisition using SPECT scans was performed using a three-headed Triad XLT y camera (Trionix, Twinsburg, OH) with middle energy collimators. Emission data were collected in 72 projections during a 360° rotation with a total acquisition time of 25 min. A matrix size of 128×128 and a voxel size of 3.6 mm³ were used. Photon emission data were registered simultaneously in four energy windows, two primary windows centered at 140 keV (for V) and 392 keV (for Q) and two secondary windows placed beneath each primary window for scatter corrections. After registration of emission images, a 15-min transmission scan was made with a [99mTc]-filled line source. These images were used for attenuation correction of the emission images and as anatomical reference. Filtered back projection was used for image reconstruction.

**Data Analysis**

After image reconstruction, SPECT data for each isotope were corrected for scattering, attenuation, activity decay, and organ outline. In addition, the root-mean-square noise component was calculated and subtracted from each dataset. For each subject, corrected and noise-free images were pixel-wise normalized to the total activity within the lungs for V and Q, respectively. V/Q ratios were obtained as the quotient between the fraction of V and the fraction of Q in each pixel.

In each individual, the regional V, Q and V/Q ratio distribution were first analyzed in three compartments of equal volume in the anterio-posterior direction. They were then analyzed in 20 isogravitational planes along the ventral-to-dorsal axis. A two-tailed, paired Student t test with Bonferroni correction was used for significance testing of the regional distribution of the V, Q, and V/Q between awake and anesthetized conditions (Microsoft Office Excel 2003; Microsoft Corporation, Redmond, WA). A P value less than 0.016 was considered statistically significant.

The frequency distribution of V/Q ratios was compared between awake and anesthetized conditions. A Gaussian function was fitted using a least-squares method to the V/Q ratio distribution for both the awake and anesthetized states and the full width at half maximum calculated. Differences in full width at half maximum of V/Q ratio distributions between awake and anesthetized states were pair-wise analyzed using a two-tailed, paired Student t test with a significance level set at 0.05.

The heterogeneities of the regional distribution of the V, Q, and V/Q ratios were estimated using a variance analysis. The global lung heterogeneity (SS_total) was obtained as the sum of squares of the pixel-wise differences from the entire lung average value respectively for V, Q, and V/Q ratio. Thereafter, the average pixel value within each isogravitational plane in the ventral-to-dorsal direction was calculated. The sums of squares of the pixel-wise deviations from mean in each plane were added (SS_residual), respectively, for V, Q, and V/Q ratio. Finally, the heterogeneity of V, Q, and V/Q ratio explained by the vertical direction (SS_vertical) was respectively calculated by subtracting SS_residual from SS_total. A two-tailed Student t test was used to compare SS_total and SS_vertical between awake and anesthetized states, respectively, for V, Q, and V/Q. A P value less than 0.05 was considered statistically significant.

**Results**

**Physiologic Variables**

Physiologic variables recorded during anesthesia are shown in table 1. During the awake state, mean ± SD systolic blood pressure was 115 ± 8 mmHg, higher than during anesthesia (P = 0.002). Diastolic blood pressure was 69 ± 6 mmHg and did not differ between states (P = 0.191). Heart rate during the awake condition was 61 ± 6 min⁻¹, lower than that observed during anesthesia (P = 0.016).

**Regional Distribution of V, Q, and V/Q**

The regional distribution of V and Q did not show any significant difference along the ventral-to-dorsal direction between the anesthetized and awake states when comparing equal lung volumes of interest, as shown in table 2. This finding was also observed in the 20 isogravitational planes.

**Table 1. Subject Variables during Mild Anesthesia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial blood pressure, mmHg</td>
<td>—</td>
</tr>
<tr>
<td>Systolic</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>Diastolic</td>
<td>67 ± 8</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>74 ± 12</td>
</tr>
<tr>
<td>Fraction of inhaled oxygen, %</td>
<td>35 ± 2</td>
</tr>
<tr>
<td>End-tidal carbon dioxide, %</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Saturation of carbon oxide</td>
<td>97 ± 1</td>
</tr>
</tbody>
</table>

Mild anesthesia (sevoﬂurane inhalation) with maintained spontaneous breathing was used.

SS_remaining from SS_total. A two-tailed Student t test was used to compare SS_total and SS_vertical between awake and anesthetized states, respectively, for V, Q, and V/Q. A P value less than 0.05 was considered statistically significant.

**Table 2. Regional Mean ± SD Distribution of Lung Ventilation vs. Perfusion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Location within Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventral 1/3</td>
</tr>
<tr>
<td>V, %</td>
<td>—</td>
</tr>
<tr>
<td>Awake</td>
<td>24.7 ± 2.5</td>
</tr>
<tr>
<td>P value</td>
<td>0.18</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>23.5 ± 4.6</td>
</tr>
<tr>
<td>Q, %</td>
<td>—</td>
</tr>
<tr>
<td>Awake</td>
<td>26.4 ± 2.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.08</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>25.3 ± 2.0</td>
</tr>
</tbody>
</table>

Mild anesthesia (sevoﬂurane inhalation) with maintained spontaneous breathing was used. All physical examinations were made with the subject in supine position. P values refer to awake vs. anesthetized state.

Q = perfusion; V = ventilation.
illustrated in figure 1, which shows a dependent V and Q distribution in anesthetized and awake states. The width of the lung frequency distribution of V/Q ratios, expressed as full width at half maximum, was significantly larger during anesthetized versus awake states, 0.77 ± 0.12 and 0.57 ± 0.12, respectively (P = 0.009). The V/Q ratio frequency distribution under awake conditions was symmetric at V/Q = 1.0 (fig. 2). However, under inhalation anesthesia, there is a clear broadening of the V/Q ratio frequency distribution toward lower ratio values with maximum at V/Q = 0.9 (fig. 2).

**Variance Analysis of the Regional Distribution of V, Q, and V/Q**

The total and vertical variances (SS_total, SS_vertical) in ventilation distribution were not altered between awake versus anesthetized states (table 3). However, the variances (SS_total, SS_vertical) in the perfusion distributions decreased during anesthesia when compared to the awake state (table 3). This, however, resulted in increased variance of V/Q (SS_total, SS_vertical) during anesthesia.

**Discussion**

As related to healthy individuals, the main findings of this study are that the V and Q relative distribution along the ventral-to-dorsal direction is not significantly altered between awake and inhalation anesthesia conditions. In addition, regional heterogeneity of the V distribution is unaltered between conditions whereas it decreases with inhalation anesthesia for the Q distribution. Finally, inhalation anesthesia increases V/Q ratio regional heterogeneity and causes a widening in the frequency distribution with a tendency toward smaller ratios.

Because we did not observe any change in V distribution in either the regional deposition nor in the heterogeneity of the distribution, it is more likely that the observed widening and increased heterogeneity of the V/Q ratio distribution are

<table>
<thead>
<tr>
<th>Variable</th>
<th>Consciousness State</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS_total</td>
<td>Awake</td>
<td>Anesthetized</td>
</tr>
<tr>
<td>V</td>
<td>0.57 ± 0.15</td>
<td>0.48 ± 0.29</td>
</tr>
<tr>
<td>Q</td>
<td>0.37 ± 0.09</td>
<td>0.24 ± 0.14</td>
</tr>
<tr>
<td>V/Q</td>
<td>0.08 ± 0.02</td>
<td>0.13 ± 0.02</td>
</tr>
<tr>
<td>SS_vertical</td>
<td>0.16 ± 0.08</td>
<td>0.11 ± 0.07</td>
</tr>
<tr>
<td>Q</td>
<td>0.09 ± 0.04</td>
<td>0.06 ± 0.06</td>
</tr>
<tr>
<td>V/Q</td>
<td>0.008 ± 0.003</td>
<td>0.03 ± 0.03</td>
</tr>
</tbody>
</table>

Mild anesthesia (sevoflurane inhalation) with maintained spontaneous breathing was used. P values refer to awake vs. anesthetized state.

Q = perfusion; SS_total = global lung heterogeneity; SS_vertical = vertical (ventral-to-dorsal) lung heterogeneity; V = ventilation.
the result of observed changes in Q between conditions. A feasible explanation is that Q is actively directed to follow the inherent natural inhomogeneities of V when awake and spontaneous breathing so that well-ventilated lung regions receive more blood flow whereas poorly ventilated areas receive less. However, during anesthesia, this regulatory mechanism is apparently affected so that the distribution of Q is less selective. This finding is reflected in the observed decrease in total variance of the Q regional distribution. As saturation remained within normal limits during anesthesia, this effect seems to be of limited importance in healthy volunteers. It may, however, be of greater importance among patients with compromised lung function.

A recent study observed that mild hypoxia has no effect on the heterogeneity of Q, which makes it unlikely that pulmonary hypoxic vasoconstriction is actively affecting Q distribution under normal and mild hypoxic conditions. In addition, the influence from atelectasis formation during anesthesia was minimized during this study. Therefore, we hypothesized that the observed increase in V/Q heterogeneity during inhalation anesthesia was a direct effect of the inhaled anesthetic substance.

The limitations of our study deserve discussion. All findings in this work are based on the assumption that the radiotracer distributions observed accurately reflect V and Q distributions. Likewise, we assumed that the acquired images accurately represented tracer distribution. The deposition of both Technegas and LyoMAA has been shown to be proportional to the distribution of air and blood flow, respectively.29–31 Phantom and physiologic studies using the same imaging technique and correction algorithms as demonstrated in this work have shown that corrected images are reliable estimates of the real distribution of radiotracers in the lungs.26,27 Furthermore, anatomical positioning of the subjects during image registration was identical during anesthetized and awake states, and the time span between examination days was too short to be considered a confounding factor in these healthy volunteers. The SPECT scan corresponding to the anesthetized condition was always performed after reversing anesthesia and with the subject fully returned to consciousness to guarantee similar anatomy when compared to the awake condition. However, radiotracer distribution within the lungs at the time of the SPECT scan reflects the radiotracer distribution at the time of administration regardless of state. Therefore, our results are most likely caused by the anesthetic. Furthermore, no significant differences were observed between study groups by protocol sequence, i.e., awake-anesthetized versus anesthetized-awake.

Measurements of cardiac output required invasive procedures, a requirement that could have influenced pulmonary estimates of V and Q, our primary focus. However, pulse oximetry under anesthesia was performed (table 1).

Another limitation of our study is that respiratory parameters were not measured during awake administration of radiotracers. We have demonstrated, however, small differences in regional ventilation (tables 2 and 3). These data suggest that any difference in tidal volume or respiratory rate had little effect on ventilation distribution.

Observed high respiratory frequencies during inhalation anesthesia could influence measured end-tidal concentrations because of the limited response time of the Datex AS/3. This limitation could result in varying sevoflurane concentration values. Indeed, alveolar sevoflurane concentration values could be greater than in end-tidal samples.

In a recent study,10 our group focused on the effect of posture on V, Q, and V/Q matching in healthy volunteers during mechanical ventilation. In that investigation, V distribution in the supine position was similar to that observed in the current study. However, results for Q distribution differed from those found in the current study by being more gravity dependent during mechanical ventilation. Although a balanced anesthetic technique was used in the previous study,10 as compared to inhalation anesthesia in the current study, we believe that the major difference was mode of respiration, which may be an important factor for determining Q distribution. Indeed, mechanical ventilation through an endotracheal tube alters the anatomical dead space,32 modifies total lung capacity, and bypasses the addition of nitric oxide in the paranasal sinuses.33 Furthermore, mechanical ventilation induces positive airway pressure. Therefore, our results indicate that anesthesia with spontaneous breathing through a facial mask is more beneficial for V/Q matching. Inspiratory flow patterns differ between spontaneous breathing and mechanical ventilation, which may result in different regional ventilation, even with identical tidal volume. In addition, dead space will also be different between facial mask ventilation and endotracheal tube.

To our knowledge, no previous imaging study has been done on the distributions of V and Q during inhalation anesthesia in spontaneously breathing humans. Previous investigations have been made with awake or paralyzed and mechanically ventilated subjects.14,34–36 A multiple inert gas–elimination technique study17 done using spontaneously breathing subjects showed a widening V/Q distribution that was similar to that described for the current study.

In conclusion, we have shown evidence for increased regional V/Q heterogeneity during inhalation anesthesia and spontaneous breathing, which may contribute to a less effective pulmonary gas exchange. However, this impairment is less pronounced than that observed in anesthetized patients using mechanical ventilation in supine posture.17

The authors thank Anette Ebberyd, R.N., Technicin, Department of Anesthesiology and Intensive Care, Karolinska University Hospital, Solna, Stockholm, Sweden, for her excellent help with the experiments.

References
