COMPONENTS OF THE INSPIRATORY-ARTERIAL ISOFLURANE PARTIAL PRESSURE DIFFERENCE

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SUMMARY
We have measured the partial pressure of isoflurane simultaneously in inspired gas (P\textsubscript{ISO}\textsubscript{ISO}), end-expired gas (P\textsubscript{ISO}\textsubscript{ISO}), mixed-expired gas (P\textsubscript{ISO}\textsubscript{ISO}), arterial (P\textsubscript{ISO}\textsubscript{ISO}) and mixed venous blood (P\textsubscript{ISO}\textsubscript{ISO}) in six patients (aged 57-79 yr) anaesthetized with nitrous oxide, oxygen and isoflurane before surgery and after P\textsubscript{ISO}\textsubscript{ISO} had been stable for at least 15 min. We related these changes to the various indices of pulmonary maldistribution to determine if they were sufficient to explain reported differences between P\textsubscript{ISO}\textsubscript{ISO} and P\textsubscript{ISO}\textsubscript{ISO}. Alveolar deadspace dilution of end-expired gas was calculated for carbon dioxide and this dilution factor used to calculate the "ideal" alveolar P\textsubscript{ISO} (P\textsubscript{ISO}) from the observed inspired and end-expired concentrations. Shunt fraction was measured for oxygen and then used to calculate the partial pressure of isoflurane in the pulmonary end-capillary blood (P\textsubscript{ISO}\textsubscript{ISO}) from the partial pressure in arterial and mixed venous blood. Mean (SE) values were: P\textsubscript{ISO}\textsubscript{ISO} 0.69 (0.05) kPa; P\textsubscript{ISO}\textsubscript{ISO} 0.52 (0.04) kPa; P\textsubscript{ISO}\textsubscript{ISO} 0.50 (0.04) kPa; P\textsubscript{ISO}\textsubscript{ISO} 0.38 (0.04) kPa; P\textsubscript{ISO}\textsubscript{ISO} 0.35 (0.03) kPa and P\textsubscript{ISO}\textsubscript{ISO} 0.22 (0.02) kPa; P\textsubscript{ISO}\textsubscript{ISO} 0.66 (0.02) kPa. The mean "ideal" alveolar to pulmonary end-capillary P\textsubscript{ISO} difference was 0.12 (0.01) kPa and highly significant (P < 0.001). P\textsubscript{ISO}\textsubscript{ISO} was substantially less than P\textsubscript{ISO}\textsubscript{ISO} but, for isoflurane, the difference was reasonably constant (range 0.14-0.22 kPa). The difference was attributable in part to the effects of shunt and deadspace, but also a failure of equilibration of isoflurane between the alveolar gas and pulmonary end-capillary blood. It is likely to be different for other anaesthetics. We conclude that, while P\textsubscript{ISO}\textsubscript{ISO} may adequately reflect P\textsubscript{ISO}\textsubscript{ISO} for isoflurane, it cannot be assumed that the relation between end-expiratory gas and arterial partial pressures is the same for all anaesthetics. (Br. J. Anaesth. 1993; 70: 605-611)

KEY WORDS

The relation between the end-expired and arterial partial pressures of inhaled anaesthetic agents is important for both theoretical and practical reasons. In formulating the concept of MAC, the assumption is made that "the alveolar partial pressure is transmitted without change to the arterial blood" [1] and anaesthetic machines have been developed in which the administration of the agent is controlled by continuous measurement of the end-expired partial pressure [2]. Crowell and colleagues [3], in a study on healthy volunteers breathing sub-anaesthetic concentrations of isoflurane, found no significant end-expiratory to arterial partial pressure difference. However, the recently published studies of Frei and colleagues [4] and Dwyer and colleagues [5] have shown an arterial to end-expiratory partial pressure ratio, after equilibration, ranging from 0.79 to 0.86. This ratio can be explained partly by the effects of venous admixture and alveolar deadspace, which are known to be increased in the anaesthetized patient. However, our own preliminary studies [unpublished] suggested that this explanation was insufficient to account for the whole of the arterial to end-expiratory partial pressure gradient for isoflurane. Eger [1] has suggested that anaesthetics of high molecular weight might fail to achieve uniform mixing within the alveoli, resulting in an "ideal" alveolar–pulmonary end-capillary partial pressure difference. To test this hypothesis, we have measured this difference for isoflurane in a group of patients in whom we simultaneously measured the shunt and physiological deadspace according to the three-compartment model (fig. 1). This enabled us to make an estimate of the likely effect of these factors on the end-expiratory–arterial partial pressure difference for isoflurane. In the course of these measurements, we have determined the mixed venous partial pressure of isoflurane, which has not been reported previously in man.

PATIENTS AND METHODS
With the approval of the Hospital Ethics Committee we studied six patients, aged between 57 and 79 yr, undergoing major elective vascular surgery, in whom placement of an arterial cannula and Swan–Ganz catheter was required for clinical reasons. Patients were premedicated and anaesthetized in a routine manner as dictated by the attending anaesthetist. Thiopentone 3–5 mg kg\textsuperscript{-1} was the induction agent
used in every case. Paralysis was with vecuronium
0.1 mg kg⁻¹ or alcuronium 0.25–0.3 mg kg⁻¹. A
cuffed tracheal tube was passed and a leak-proof seal
obtained. Anaesthesia was maintained with nitrous
oxide, 34–51 % oxygen and isoflurane. After in-
duction, over-pressure of isoflurane (not greater than
2 %) was maintained for not more than 5 min after
induction. The inspired concentration was then held
constant (range 0.5–0.8 %) until blood samples had
been taken (table I). Ventilation was with a Manley
MP3 ventilator using a minute volume of
approximately 6 litre.

Inspired oxygen percentage was measured con-
tinuously in the inspiratory limb of the circuit using
a Servomex OA 580 paramagnetic analyser. Inspired
and end-expired isoflurane percentages were
monitored using a Datex Capnomac (95 % re-
response time 900 ms) and end-expired carbon dioxide
percentage was measured using an Ohmeda 5200
CO₂ monitor (95 % response time 360 ms). The
sampling lines for isoflurane and carbon dioxide
analysis were attached to the catheter mount of the
tracheal tube, on the machine side of a Pall BB22–15
breathing system filter and the outputs recorded
continuously on a Kipp and Zonen BD9 twin-
channel chart recorder. The volume of the filter
(approximately 90 ml) was included in the deadspace
calculations.

Definitive measurements of end-expired carbon
dioxide and inspired and end-expired isoflurane
were taken from the chart recorder. A slow
ventilatory frequency (approximately 12 b.p.m. with
an inspired to expired ratio of 1:4) was deliberately
set to allow a plateau for both inspired and expired
gas to be recorded. The recorded end-tidal PO₂
bore the normal relation to the arterial PCO₂ and the
recorded inspired Piso agreed closely with a genuine
upstream inspired sample measured by gas
chromatography. Under these conditions, we are
confident that we had a valid end-expiratory sample.
Arterial and mixed venous blood samples were
taken after at least 25 min of anaesthesia at a constant
inspired isoflurane percentage, with the end-expired
isoflurane percentage changing by not more than
0.02 % for at least 15 min. Blood samples for arterial
and mixed venous pH, PO₂, PCO₂ and oxygen
saturation were obtained anaerobically in duplicate
2-ml, heparinized syringes, using three-way taps to
clear the deadspace from both the arterial and
pulmonary artery cannulae. Samples were stored on
crushed ice for a maximum of 15 min before analysis
using an IL 1302 blood-gas machine and an IL 282
Co-oximeter. Oxygen saturation of haemoglobin
(SO₂) was derived also from the virtual PO₂
(calculated for 37 °C) using the Severinghaus nomo-
gram [6]. In all cases the calculated saturation agreed
with the measured saturation to within 2 %
(corrected for carboxyhaemoglobin), the mean
difference being 0.1 %. Separate 5-ml blood samples
were also obtained to measure arterial and mixed
venous haemoglobin concentration and PCV (Coul-
ter Counter model S). Oxygen content of arterial,
mixed venous and pulmonary capillary blood was
then derived as:

$$[\text{Hb}] \times \frac{\text{SO}_2}{100} \times 1.31 + 0.0225 \times \text{PO}_2$$

where [Hb] = haemoglobin concentration corrected
for carboxyhaemoglobin; PO₂ was at 37 °C; 1.31 =
haemoglobin combining factor obtained by Gregory
[7]; 0.0225 = solubility coefficient of oxygen in
whole blood. The pulmonary end-capillary PO₂ was
assumed to equal the alveolar PO₂. This was derived
from the Filley equation [8] which allows for nitrous
oxide uptake.

Blood samples for measuring isoflurane partial
pressure were obtained in gas-tight, heparinized, 2-
ml all-glass syringes. Aliquots (0.5 ml) were then
injected immediately through a Teflon seal into 2-ml
glass vials with loosened screw caps; the caps were
tightened immediately after injection. This pro-
cedure allowed the blood-gas mixture in the vial to
remain at barometric pressure.

During the period of blood sampling, mixed
expired gas was collected from the expiratory port of
the patient ventilator into a Douglas bag for at least
3 min. After expired gas collection, two 20-ml and
two 100-ml samples of inspired gas were obtained
from the inspiratory limb of the patient ventilator,
and two 20-ml and two 100-ml samples of mixed
expired gas from the Douglas bag.

Barometric pressure, room temperature and the
patient’s tympanic membrane temperature
(Mallinckrodt Mon-A-Therm) were noted at the
time of sampling and the appropriate corrections
made in calculations.

Mixed expired gas samples (100 ml) were analysed
in duplicate for oxygen, carbon dioxide and
isoflurane by the same monitors used for inspired
and end-expired gas analysis. The 20-ml samples of
inspired and mixed expired gas were analysed for
isoflurane by gas chromatography to cross-check
measurements taken from the chart recorder. The
mean (SEM) difference was 0.011 (0.009) kPa. The
mean value was calculated and used for subsequent
calculations.

Isoflurane partial pressures in blood samples were
measured as described by Knill and colleagues [9]
using a Pye 104 gas chromatograph (GC) fitted with a 60-μl or 500-μl gas sampling loop and a flame ionization detector. The carrier gas was oxygen-free nitrogen. Oven temperature was 125 °C and detector temperature was 175 °C. The blood-gas samples were equilibrated at 37 °C in a thermostatically controlled chamber by gentle rotation in a vertical plane at 20 r.p.m. for 45 min. A portion of the gas was then flushed into the gas sampling loop of the GC to obtain an isoflurane partial pressure and the remaining gas expelled. The same volume of un-equilibrated humidified air was added to the vial and allowed to equilibrate as before. The procedure was repeated four times in total. The natural logarithms of the chromatogram peak heights from each of the four equilibrated gas phases were plotted against the serial number of the equilibration. Assuming that the partition coefficient of isoflurane is independent of absolute tension, these plots should fall on a straight line. The Y-intercept is proportional to the Isoflurane ratio.

### Table I. Patient characteristics and ventilatory variables

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<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>Mean</th>
<th>SEM</th>
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<td>Age (yr)/Sex</td>
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<td>57 F</td>
<td>76 M</td>
<td>79 M</td>
<td>70 M</td>
<td>68 M</td>
<td>69</td>
<td>—</td>
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<td>72.7</td>
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<td>79.5</td>
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<td>10.2</td>
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<td>0.42</td>
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<td>82.4</td>
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<td>13.0</td>
<td>13.7</td>
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<td>10.4</td>
<td>12.8</td>
<td>12.8</td>
<td>0.9</td>
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<td>5.9</td>
<td>4.8</td>
<td>6.1</td>
<td>6.3</td>
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<td>7.37</td>
<td>7.32</td>
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<td>0.17</td>
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<td>0.21</td>
<td>0.30</td>
<td>0.22</td>
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<td>Alveolar deadspace dilution factor</td>
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<td>7.32</td>
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<td>12.50</td>
<td>17.86</td>
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<td>0.58</td>
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<td>0.39</td>
<td>0.59</td>
<td>0.50</td>
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<td>37.23</td>
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<td>10.25</td>
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<td>0.49</td>
<td>0.21</td>
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<td>0.29</td>
<td>0.43</td>
<td>0.38</td>
<td>0.04</td>
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<td>0.70</td>
<td>0.81</td>
<td>0.70</td>
<td>0.78</td>
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<td>0.46</td>
<td>0.42</td>
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<td>0.47</td>
<td>0.52</td>
<td>0.50</td>
<td>0.02</td>
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<tr>
<td>Mixed venous : arterial</td>
<td>0.55</td>
<td>0.53</td>
<td>0.81</td>
<td>0.59</td>
<td>0.75</td>
<td>0.71</td>
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<tr>
<td>Arterial : end-expired</td>
<td>0.69</td>
<td>0.63</td>
<td>0.60</td>
<td>0.71</td>
<td>0.67</td>
<td>0.67</td>
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<td>0.02</td>
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<tr>
<td>Ideal alveolar : end-expired</td>
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<td>0.97</td>
<td>1.03</td>
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<td>Arterial : Pulm. end-cap.</td>
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<td>0.79</td>
<td>1.00</td>
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<td>Pulm. end-cap. : end-expired</td>
<td>0.74</td>
<td>0.80</td>
<td>0.60</td>
<td>0.75</td>
<td>0.71</td>
<td>0.68</td>
<td>0.71</td>
<td>0.03</td>
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<td>Mixed venous : arterial (kPa)</td>
<td>0.19</td>
<td>0.18</td>
<td>0.04</td>
<td>0.15</td>
<td>0.07</td>
<td>0.12</td>
<td>0.12</td>
<td>0.02</td>
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<tr>
<td>End-expired : arterial (kPa)</td>
<td>0.19</td>
<td>0.22</td>
<td>0.14</td>
<td>0.15</td>
<td>0.14</td>
<td>0.21</td>
<td>0.18</td>
<td>0.02</td>
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<tr>
<td>Ideal alveolar minus pulmonary end-capillary (kPa)</td>
<td>0.15</td>
<td>0.09</td>
<td>0.13</td>
<td>0.09</td>
<td>0.10</td>
<td>0.16</td>
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</table>
(Piso). The partial pressure in the samples was determined as described above. The mean (SEM) Piso in the gas phase was 0.241 (0.008) kPa and that in the blood samples 0.243 (0.008) kPa. The difference between paired analyses was not significant (t = 0.76).

Analytical equipment was calibrated before and after each study. The GC was calibrated using the same standard gas mixtures as those used for calibration of the Capnomac and the Ohmeda CO2 monitor was calibrated against the same standard as that used for blood-gas analysis. The Servomex OA 580 was calibrated with oxygen-free nitrogen and room air. The Datex Capnomac, the Ohmeda CO2 monitor, the Servomex paramagnetic analyser and GC were all checked for linearity before the study.

CALCULATIONS (fig. 1)

Dilution factor for end-expiratory gas

The inspired partial pressure of isoflurane, Piso, was calculated as follows:

\[ P_{iso} = F_{ins}(P_B - P_{N_2}) \]

where \( F_{ins} \) = fractional inspired concentration of isoflurane in dry gas; \( P_B \) = barometric pressure; \( P_{N_2} \) = saturated vapour pressure of water at body temperature.

On the assumption that the alveolar deadspace gas has the same composition as inspired gas, the dilution factor for end-expiratory gas is available. The inspired partial pressure of isoflurane, \( P_{iso} \), was calculated as follows:

\[ P_{iso} = F_{ins}(P_B - P_{N_2}) \]

where \( F_{ins} \) = fractional inspired concentration of isoflurane in dry gas; \( P_B \) = barometric pressure; \( P_{N_2} \) = saturated vapour pressure of water at body temperature.

The ideal alveolar partial pressure of isoflurane was then derived by subtracting the inspired partial pressure of isoflurane from the alveolar partial pressure of isoflurane.

Derived values

Applying the alveolar deadspace dilution factor to isoflurane, the calculated ideal alveolar Piso would be 0.69 (0.05) kPa and end-expiratory Piso was 0.69 (0.04) kPa, giving an end-expiratory: inspired ratio of 0.96 (0.03) kPa, with an arterial: end-expiratory ratio of 0.66 (0.02). Piso of the mixed venous blood was 0.22 (0.03) kPa.

At the time of the isoflurane measurements, the physiological deadspace (including apparatus deadspace) was 53.6 (3.1)%, and the arterial-end-expiratory \( P_{CO_2} \) difference 0.56 (0.16) kPa. Calculated for carbon dioxide, the dilution factor for alveolar gas by alveolar deadspace was 11.58 (3.39)%.

The shunt fraction was 14.8 (4.74)%, with an ideal alveolar to arterial \( P_{CO_2} \) gradient of 14.2 (2.21) kPa.

DISCUSSION

The presence of an end-expiratory to arterial anaesthetic partial pressure difference has been demonstrated for several volatile anaesthetic agents in healthy subjects. Our mean measured arterial: end-expiratory Piso ratio for isoflurane was 0.66 (0.02), which is less than the values obtained by Frei and colleagues [4] and Dwyer and colleagues [5], but we are in full agreement that a substantial difference exists. This gradient has been attributed hitherto to the increased alveolar deadspace and venous admixture (shunt) found in anaesthetized patients [10–14].

In the present study, the values for physiological
deadspace and the arterial--end-expiratory \( P_{\text{CO}_2} \) difference were typical for anaesthetized patients with tracheal tube and apparatus deadspace included [15]. The alveolar deadspace dilution factor of 11.6% can have little effect on the ideal alveolar--end-expiratory difference, partly because it is normally quite small during anaesthesia and partly because the alveolar deadspace gas would contain isoflurane approximating in composition to the inspired gas. Thus the ideal alveolar \( P_{\text{ISO}} \) is very little less than the measured end-expired value: only 0.02 kPa in the present study. Similar considerations would apply to ventilation of alveolar units of large (but not infinite) ventilation: perfusion ratio simulating a true alvolar deadspace.

The mean shunt in this study accords very closely with previous observations on anaesthetized patients in the age range 57--79 yr [12]. If the three-compartment model is applied to isoflurane, the pulmonary end-capillary \( P_{\text{ISO}} \) would be only 0.03 kPa greater than the arterial \( P_{\text{ISO}} \). This is to be expected because, in common with carbon dioxide, \( P_{\text{ISO}} \) bears a constant relation to content and the partial pressures in mixed venous and arterial blood are not greatly different. It is only because of its alinear dissociation curve that oxygen has so large an alveolar-arterial \( P_{\text{O}_2} \) difference in the presence of a shunt. Thus the corrections for shunt and deadspace together account for only 33% of the total end-expired to arterial \( P_{\text{ISO}} \) difference (fig. 2, table I).

Our analysis has followed the classical three-compartment model of the lung suggested by Riley and Courmand [16]. Although this approach treats relative maldistribution of ventilation and perfusion as though it contributed to alveolar deadspace and shunt, it gives values for these parameters which permit satisfactory prediction of arterial \( P_{\text{CO}_2} \) and \( P_{\text{O}_2} \) in a wide range of clinical situations. In this analysis some approximations are made, and it remains to consider how these effect the validity of our conclusions.

The Riley analysis assumes that the alveolar deadspace gas contains gas which has the same composition as inspired gas. In fact, a small quantity of end-expiratory gas from the anatomical deadspace must be re-inhaled into the alveolar deadspace. If, as seems likely, this effect were to increase the \( P_{\text{CO}_2} \) of the alveolar deadspace gas by 0.4 kPa, then the mean value for the alveolar deadspace dilution factor would be increased by about 0.9% (equation (1)). This would result in a reduction in the calculated ideal alveolar \( P_{\text{ISO}} \) of about 0.002 kPa (equation (2)). However, the Riley analysis also assumes that ideal alveolar \( P_{\text{CO}_2} \) equals arterial \( P_{\text{CO}_2} \). This is not so when there is an appreciable shunt, but the effect is usually very small because the mixed venous--arterial \( P_{\text{CO}_2} \) difference is normally only about 10% of the arterial--mixed venous \( P_{\text{O}_2} \) difference, and much less when the concentration of oxygen in the inspired gas is increased. A mean shunt of 14.8%, with our measured values for mean arterial and mixed venous \( P_{\text{CO}_2} \), would reduce the mean ideal alveolar \( P_{\text{CO}_2} \) from an assumed 4.9 kPa to 4.8 kPa. Substitution of the corrected value into equation (1) reduces the mean alveolar deadspace dilution factor by about 2%, increasing the calculated ideal alveolar \( P_{\text{ISO}} \) by about 0.004 kPa. This offsets the previous correction and the net result is a very small increase (0.002 kPa) in the calculated ideal alveolar \( P_{\text{ISO}} \).

Calculation of shunt in the Riley analysis depends on the value for ideal alveolar \( P_{\text{O}_2} \), which is derived from the ideal alveolar \( P_{\text{CO}_2} \), conventionally assumed to be equal to the arterial \( P_{\text{CO}_2} \). Applying the correction to the alveolar \( P_{\text{CO}_2} \) derived in the previous paragraph, the calculated shunt would be decreased by less than 0.1%. This would increase
the derived pulmonary end-capillary $P_{iso}$ by a negligible quantity—less than 0.0002 kPa. This would have no significant effect on the residual gradient.

Anaesthesia results in compression atelectasis of dependent lung zones, with a true shunt which relates to the amount of atelectasis observed by computed tomography [17]. However, during anaesthesia about 50% of the observed alveolar to arterial $P_{O_2}$ difference and the venous admixture (calculated from the shunt equation) is explained by an increased spread of ventilation:perfusion ratios and, in particular, as a result of perfusing alveolar units with ventilation:perfusion ratios in the range 0.005–0.1 [11, 12, 18]. This has a much greater effect on $P_{O_2}$ than on either $P_{CO_2}$ or $P_{iso}$ because of the upward convexity of the oxyhaemoglobin dissociation curve. However, this factor is considered in calculating the equivalent "shunt effect" of perfusion in areas of low ventilation:perfusion ratios.

Dueck and colleagues [19] have argued that the method of analysing $V_a/Q$ relations in the lungs used by Nunn, Bergman and Coleman [12] and in our present study has limitations because calculated shunt increases with smaller inspired oxygen concentration. However, the range of fractional inspired concentrations of oxygen used in our study was 0.34–0.50 and it is likely that most of the calculated venous admixture represents true shunt. Even if our calculations of shunt are underestimates, a large shunt, in the region of 50%, would be required to explain the observed end-expired–arterial $P_{iso}$ difference. In spite of the limitations of the three-compartment model, it seems improbable that abnormal distribution of ventilation:perfusion ratios, sufficient to cause the observed alveolar–arterial $P_{O_2}$ difference, could explain more than a small fraction of the observed end-expired–arterial $P_{iso}$ difference.

If there is indeed a finite ideal alveolar–pulmonary end-capillary $P_{iso}$ difference, there are two possible explanations: there could be resistance to transfer through the alveolar capillary membrane; or isoflurane may not achieve uniform distribution throughout the alveoli during the ventilatory cycle. It is difficult to say how the physical properties of isoflurane could influence its ease of passage through the alveolar–capillary membrane. There is no measurable impairment of oxygen or carbon dioxide, except under conditions of maximal exercise at decreased inspired $P_{O_2}$. For isoflurane, both water and lipid solubilities are greater than those of oxygen, which should favour its passage through the membrane. However, its molecular weight is much greater.

Gas mixing within the alveoli occurs predominantly by diffusion and the rate at which a gas diffuses is inversely proportional to the square root of its molecular weight. Under normal circumstances, incomplete mixing of gases such as oxygen and carbon dioxide is unlikely to occur. The average diameter of the human alveolus at functional residual capacity is about 200 μm and it is likely that mixing of gases of low molecular weight is almost instantaneous over the very small distance from the centre to the periphery [20]. However, this may not be the case for isoflurane or other anaesthetics of relatively high molecular weight. Georg and colleagues [21] studied diffusion differences in the gas phase of the lungs of normal and emphysematous subjects using three inert gases of widely different molecular weights and found that the ratio of heavier to lighter gas varied with the volume of expired gas. These differences were exaggerated in emphysematous subjects. Further evidence that the changes in ratio are the result of differing rates of gas diffusion comes from breath-holding experiments: when a breath is held for 30 s the ratios in the expired gas are independent of the volume expired [22]. Robertson, Whitehead and Hlastala [23] observed a difference in the retention of isoflurane (184.5 Da) and acetylene (26 Da) during its passage from blood to expired air. This could not be explained by differences in partition coefficients, and they concluded that it was consistent with a diffusion-related impairment of gas exchange. In support of this view, they cited several authors who had reported differences in anatomical deadspace as measured with gases of markedly different molecular weights.

This evidence suggests that some volatile anaesthetics may not be uniformly distributed throughout the alveolus and these inhomogeneities may make some contribution to the gradient between ideal alveolar gas and pulmonary end-capillary blood. It is likely that this gradient will differ for different anaesthetics. For nitrous oxide, Eger and colleagues [24] found a $P_a:Pe$ ratio of 0.98 after 8 min, implying that when deadspace and shunt have been accounted for, there is no residual gradient.

Our results and those of Frei and colleagues [4] and Dwyer and colleagues [5] show clearly that end-expiratory partial pressures of some volatile anaesthetics are greater than those in arterial blood, and must be greater than at the site of action in the brain. Thus MAC is related to values which differ significantly from those at the site of action. Nevertheless, it is not possible to measure partial pressures at the site of action, nor is it feasible to monitor arterial partial pressure in the present state of technology. It is therefore fortunate that the arterial:end-expiratory $P_{iso}$ ratio was found to be remarkably constant at 0.66 (0.02). Thus measuring end-expiratory partial pressures in relation to MAC values is a valid method to monitor the depth of anaesthesia. However, comparison of MAC values as an absolute measure of potency might be questioned if the arterial:end-expired ratios are significantly different, as seems to be the case at least for nitrous oxide and isoflurane.

To our knowledge, mixed venous concentrations of an anaesthetic have not been measured before in humans and on average they were 40% smaller than the arterial value. However, it can be predicted that, in humans, it would take several days of anaesthesia for the mixed venous concentration of isoflurane to equal that of arterial blood, when the inspired–end-expiratory–arterial gradient would disappear. The presence of this gradient for isoflurane is therefore likely to persist even during prolonged anaesthesia.
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In conclusion, we suggest that the effects of shunt and deadspace are small and the main reason for the end-expired to arterial partial pressure gradient for isoflurane observed by Frei and colleagues [4], Dwyer and colleagues [5] and ourselves may be the failure to achieve uniform distribution within the alveolus. This will impede changes in anaesthetic partial pressure in blood and therefore tissues, thus hindering the attainment and reversal of the anaesthetic state. Further studies on other volatile anaesthetics are needed.

REFERENCES