Effects of isoflurane on regional pulmonary blood flow during one-lung ventilation

J. Groh, G. E. H. Kuhnle, L. Ney, A. Sckell and A. E. Goetz

Summary
Isoflurane has been reported to inhibit hypoxic pulmonary vasoconstriction. However, the effects of one-lung ventilation and isoflurane on regional pulmonary blood flow (Qr) have not been investigated in detail. Therefore, using radionuclide labelled microspheres we measured Qr in rabbits (n = 8) in the left lateral decubitus position during two- and one-lung ventilation under i.v. baseline anaesthesia and during additional administration of 1.5% isoflurane. Macrohaemodynamic variables were recorded continuously. Isoflurane increased non-dependent lung blood flow during two-lung ventilation. One-lung ventilation caused a homogeneous decrease in Qr throughout the hypoxic lung, irrespective of isoflurane administration (P < 0.001). However, isoflurane significantly augmented Qr of the hypoxic lung during one-lung ventilation (P < 0.05). During all phases, Qr of the upper lobe was higher compared with that in the lower lobe in isogravitational slices of both lungs; a ventrodorsal perfusion gradient was found in the left upper lobe. We conclude that 1.5% isoflurane increased perfusion of the non-dependent lung, inhibited hypoxic pulmonary vasoconstriction-induced redistribution of pulmonary blood flow and did not influence isogravitational perfusion gradients. (Br. J. Anaesth. 1995; 74: 209–216)

Key words

Volatile halogenated anaesthetics are commonly used during one-lung ventilation for thoracic surgery, as they have a salutary effect on airway irritability and permit delivery of a high inspired oxygen concentration without loss of anaesthesia. However, all volatile agents, particularly isoflurane, have been suspected to inhibit the protective mechanism of hypoxic pulmonary vasoconstriction (HPV), thereby increasing venous admixture and lowering PaO2]1-3].

With the methods used so far to study the effects of one-lung ventilation and volatile anaesthetics on pulmonary blood flow distribution, such as flow probes [4], differential elimination of carbon dioxide or inert gases [3, 5, 6], perfusion scintigraphy [3] and calculation of venous admixture [1, 3], spatial resolution was restricted to the hypoxic segment as a whole.

Gravity is a major determinant of regional pulmonary blood flow distribution, which depends on the local relationship between pulmonary arterial, venous and airway pressures [7]. In the lateral decubitus position, regional blood flow has been shown to increase from the non-dependent to the dependent thoracic wall [8]. In addition, gravity-independent craniocaudal, ventrodorsal and radial gradients of regional perfusion have been reported [8-12]. The effects of one-lung ventilation on these intrapulmonary perfusion gradients and their modification by volatile anaesthetics, however, have not been quantified.

The present study was performed to investigate the effects of one-lung ventilation and isoflurane on regional blood flow distribution within the lungs using a high resolution technique.

Materials and methods
After approval by the institutional animal research review board, we studied eight White New Zealand rabbits (mean weight 2675 g). Anaesthesia was induced with thiopentone 10–20 mg/kg body weight, the animals were tracheotomized and the lungs ventilated mechanically (Sechrist Infant-Ventilator, Kontron, Eching, Germany) with an inspiratory oxygen fraction (FiO2) of 0.3 during preparation; peak inspiratory pressure was set at 12 cm H2O. A positive end-expiratory pressure of 2 cm H2O was maintained resulting in a mean airway pressure (Paw) of 7 cm H2O. Baseline anaesthesia was maintained with an i.v. infusion of α-chloralose 50 mg kg\(^{-1}\) over 30 min (Merck, Darmstadt, Germany) and piritramid 1.5 mg kg\(^{-1}\) i.v. (Dipidolor, Janssen GmbH, Neuss, Germany). Continuous haemodynamic monitoring did not reveal any need for additional anaesthetics throughout the experiments. Neuromuscular block was obtained with pancuronium 1 mg i.v. followed by a continuous infusion of 0.6 mg h\(^{-1}\). Body temperature was maintained at 38 °C by use of an automatic heating pad. Catheters were inserted for continuous measurement of systemic arterial (SAP), central venous (CVP), pulmonary arterial (PAP) and left atrial (LAP) pressures. Cardiac output (CO) was measured using an electromagnetic flow probe placed around the...
pulmonary artery. At the end of the surgical preparation $F_{PA}$ was increased to 1.0 and maintained at this level until the end of the experiment. The preparation was allowed to stabilize for 30 min, and thereafter baseline haemodynamics were measured, and arterial and mixed venous blood samples were obtained for blood-gas analyses (ABL 300, Radiometer, Copenhagen, Denmark) and calculation of venous admixture ($Qs/Qt$).

The technique used for one-lung ventilation in the rabbit has been described previously in detail [13]. Briefly, a 4-F bronchus blocker (AI-07121, Arrow International, Reading, PA, USA) was advanced through the ventilation tube into the right main bronchus and the blocker cuff was inflated precisely distal to the carina. The catheter lumen was connected to a pressure transducer for monitoring $Paw$. Ventilation of the dependent lung was continued during one-lung ventilation with the same pressure profile as during two-lung ventilation. In addition, mean $Paw$ of the right lung was maintained at the same level as during two-lung ventilation (7 cm H$_2$O) in order to minimize mechanical influences on regional blood flow distribution. For this purpose a polyethylene catheter ($Q$ 0.96 mm) was advanced with its tip 2–3 mm distal to the blocker tip and nitrogen was inflated through its lumen into the inflated lung. The correct position of the bronchus blocker was verified by fiberoptic bronchoscopy (BF-N20, Olympus, Tokyo, Japan) during each experimental phase. Fibreoptic demonstration of the adequate location of the inflation catheter was restricted to two-lung ventilation phases. During one-lung ventilation, free nitrogen flow was monitored by constant right lung $Paw$.

INJECTION OF RADIOACTIVE MICROSHERES

For measurements of regional pulmonary perfusion, $5 \times 10^5$ microspheres with a nominal diameter of 15 µm (NEN, Dupont GmbH, Dreieich, FRG) labelled with a radioactive isotope were suspended in normal saline in a 1-ml glass vial. Microspheres were mixed for 3 min by sonication and injected over 20 s encompassing 6–7 ventilatory cycles via the central venous catheter into the superior vena cava. Injection was accomplished by flushing the vial with 5 ml of saline followed by air until the vial and the connecting silicone tube (3 cm) were free of fluid. There was no measurable effect on haemodynamic variables when microspheres were injected. The position of the central venous catheter was verified by autopsy at the end of the experiment. Microsphere injections were repeated during four experimental phases using different radionuclides in random sequence for each injection ($^{141}$Ce, $^{46}$Sc, $^{85}$Sr, $^{95}$Nb).

MEASUREMENT OF REGIONAL LUNG PERFUSION

At the end of the experiments the animals were killed, the lungs were removed carefully and major vessels and extraparenchymal tissue were dissected. The lungs were then inflated to full capacity ($Paw$ 25 cm H$_2$O), dried in the inflated state over a 5-day period at room temperature and cut into 16 sagittal slices using an electric slicing machine. Slices R2–R7 and L2–L6 were dissected further into lobar components; peripheral and central parts of the right and left lower lobes were separated additionally into slices R2–R6 and L2–L7, respectively. Ventrodorsal differences in regional perfusion were analysed in isogravitational planes of the left upper lobe of slices L2–L6.

The lung specimens were weighed and spectral radioactivity for the various nuclides, which is assumed to be linearly proportional to the number of microspheres, was measured in each probe by an automatic counter (Auto Gamma 5650, United Technologies Packard, Downers Grove, IL, USA) and evaluated using the software program MIC III [14]. In order to limit measurement errors caused by small probe size [8], lung specimens weighing < 10 mg or containing less than 500 microspheres during any experimental phase were excluded from statistical evaluation. Fractional perfusion during each experimental phase was calculated as:

$$\%Q = \frac{n_p}{n} \times 100$$

$$\%m = \frac{m_p}{m} \times 100$$

where $%Q$ = fractional perfusion (percent) of total lung perfusion, $%m$ = fractional probe mass (percent) of total lung mass, $n_p$ = number of microspheres in the probe, $n$ = total number of microspheres in the lung, $m_p$ = probe mass (mg) and $m$ = total lung mass (mg).

Differences in regional perfusion along the gravitational axis were evaluated comparing relative perfusion in sagittal slices. Craniodorsal variation was analysed comparing isogravitational upper, middle and lower lobe relative perfusion. Because of the small dimensions of the rabbit lung, assessment of cranio-caudal, central–peripheral and ventrodorsal differences in regional perfusion in isogravitational planes were restricted to slices R2–R7/L2–L6, R2–R6/L2–L7 and L2–L6, respectively.

EXPERIMENTAL DESIGN

Haemodynamic measurements, blood-gas analyses and injections of isotope labelled microspheres were performed in the lateral decubitus position under four experimental conditions instituted in random order: two- and one-lung ventilation under baseline anaesthesia (2LV$_B$, 1LV$_B$) and during additional administration of 1.5% isoflurane (2LV$_I$, 1LV$_I$). Measurements and microsphere injections were accomplished 30 and 20 min after changing the anaesthetic (baseline/isoflurane) and ventilatory (2LV/1LV) regimens, respectively.

STATISTICAL EVALUATION

Statistical analysis of the differences between the four experimental phases and between upper, middle and lower lobe perfusion in isogravitational slices was performed using the Quade test followed by paired comparisons [15]. Central–peripheral and ventrodorsal differences in relative perfusion were assessed using the Wilcoxon matched pairs test.
Pulmonary blood flow during one-lung ventilation

Table 1 Haemodynamic and gas exchange variables (mean (SEM)) measured during one- and two-lung ventilation under baseline anaesthesia (1LV, 2LV) and during additional administration of 1.5% isoflurane (1LV*, 2LV†). LL = Left lung, RL = right lung. Significant differences (P < 0.05) compared with: *1LV vs 2LV, †1LV vs 2LV.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>2LV</th>
<th>1LV</th>
<th>2LV</th>
<th>1LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP (mm Hg)</td>
<td>78 (4)</td>
<td>83 (4)</td>
<td>60 (3)*</td>
<td>74 (2)</td>
<td>65 (3)†</td>
</tr>
<tr>
<td>PAP (mm Hg)</td>
<td>14 (2)</td>
<td>15 (2)</td>
<td>15 (2)</td>
<td>17 (2)*</td>
<td>17 (2)†</td>
</tr>
<tr>
<td>CVP (mm Hg)</td>
<td>5 (1)</td>
<td>5 (1)</td>
<td>6 (1)</td>
<td>7 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>LAP (mm Hg)</td>
<td>4 (1)</td>
<td>5 (1)</td>
<td>6 (1)</td>
<td>6 (1)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Paw LL (cm H₂O)</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Paw RL (cm H₂O)</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>CO (ml min⁻¹)</td>
<td>164 (6)</td>
<td>158 (9)</td>
<td>194 (15)*</td>
<td>114 (8)*</td>
<td>151 (14)††</td>
</tr>
<tr>
<td>HR (beat min⁻¹)</td>
<td>246 (12)</td>
<td>250 (10)</td>
<td>243 (8)</td>
<td>240 (14)</td>
<td>240 (12)</td>
</tr>
<tr>
<td>SVR (mm Hg min⁻¹ litre⁻¹)</td>
<td>46 (33)</td>
<td>516 (41)</td>
<td>365 (32)*</td>
<td>615 (30)</td>
<td>424 (57)††</td>
</tr>
<tr>
<td>PVR (mm Hg min⁻¹ litre⁻¹)</td>
<td>63 (10)</td>
<td>66 (14)</td>
<td>51 (9)*</td>
<td>109 (30)*</td>
<td>82 (20)††</td>
</tr>
<tr>
<td>pH</td>
<td>7.34 (0.02)</td>
<td>7.35 (0.02)</td>
<td>7.31 (0.03)</td>
<td>7.23 (0.02)*</td>
<td>7.21 (0.04)††</td>
</tr>
<tr>
<td>PaCO₂ (kPa)</td>
<td>4.9 (0.4)</td>
<td>4.9 (0.3)</td>
<td>5.9 (0.3)*</td>
<td>6.1 (0.4)*</td>
<td>7.0 (0.7)</td>
</tr>
<tr>
<td>PaO₂ (kPa)</td>
<td>62 (2.8)</td>
<td>63 (2.5)</td>
<td>59 (2.4)</td>
<td>27 (3.7)*</td>
<td>19 (2.9)††</td>
</tr>
<tr>
<td>Qs/Qt (%)</td>
<td>5 (1)</td>
<td>5 (2)</td>
<td>7 (2)</td>
<td>14 (2)*</td>
<td>21 (2)††</td>
</tr>
</tbody>
</table>

Values are given as mean (SEM) and the level of significance was P < 0.05 unless otherwise indicated.

Results

HAEMODYNAMICS AND PULMONARY GAS EXCHANGE

Table 1 summarizes the baseline haemodynamic and gas exchange variables recorded before surgical preparation and a stabilization period of 30 min, and data obtained during the experimental phases. Isoflurane reduced SAP, systemic (SVR) and pulmonary (PVR) vascular resistance and increased CO during both two- and one-lung ventilation. CO declined, whereas PAP, PVR and Qs/Qt increased during unilateral hypoxia compared with two-lung ventilation whether or not isoflurane was administered. Corresponding with the increase in Qs/Qt, there was a significant reduction in arterial oxygen tension (PaO₂) during 1LV and 1LV*. During 1LV, PaO₂ was significantly lower and Qs/Qt was significantly higher than during 1LV. Moderate respiratory acidosis developed during 1LV and 1LV*, as ventilation was restricted to the left lung during one-lung ventilation with the same airway pressure profile as during two-lung ventilation. Statistical analysis revealed no differences in heart rate (HR), CVP and LAP between the four experimental phases.

REGIONAL BLOOD FLOW

Right vs left (table 2)

During all experimental phases, relative blood flow to the right lung was lower than to the left lung (P < 0.001). One-lung ventilation induced a significant decrease in blood flow to the hypoxic right lung compared with the corresponding phases of two-lung ventilation (P < 0.05), whereas relative perfusion of the left lung increased during contralateral hypoxia (P < 0.05). Isoflurane caused an increase in right lung perfusion during two- and one-lung ventilation (P < 0.05 2LV vs 2LV†, P < 0.05 1LV vs 1LV* compared with i.v. baseline anaesthesia, corresponding to the increase in venous admixture calculated from blood-gas measurements.

Gravitational distribution

Measurement of relative blood flow in sagittal lung slices during two-lung ventilation yielded a gravitational gradient from the non-dependent to the dependent thoracic wall (fig. 1). During two-lung ventilation administration of isoflurane was followed by a slight increase in relative blood flow in the six uppermost slices of the non-dependent lung, which isoflurane was administered. Corresponding with the increase in Qs/Qt, there was a significant reduction in arterial oxygen tension (PaO₂) during 1LV and 1LV*. During 1LV, PaO₂ was significantly lower and Qs/Qt was significantly higher than during 1LV. Moderate respiratory acidosis developed during 1LV and 1LV*, as ventilation was restricted to the left lung during one-lung ventilation with the same airway pressure profile as during two-lung ventilation. Statistical analysis revealed no differences in heart rate (HR), CVP and LAP between the four experimental phases.

TABLE 2 Relative blood flow (mean (SEM)) to the right (RL) and left lung (LL) during one- and two-lung ventilation under baseline anaesthesia (1LV, 2LV) and during additional administration of 1.5% isoflurane (1LV*, 2LV†). Significant differences (P < 0.05) compared with: *2LV vs 1LV, †2LV vs 1LV*

<table>
<thead>
<tr>
<th>Phase</th>
<th>RL</th>
<th>LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>2LV</td>
<td>0.68 (0.04)</td>
<td>1.44 (0.06)</td>
</tr>
<tr>
<td>2LV*</td>
<td>0.72 (0.05)*</td>
<td>2.06 (0.06)</td>
</tr>
<tr>
<td>1LV</td>
<td>0.24 (0.05)</td>
<td>1.39 (0.06)*</td>
</tr>
<tr>
<td>1LV*</td>
<td>0.33 (0.04)††</td>
<td>1.94 (0.06)††</td>
</tr>
</tbody>
</table>

Figure 1 Mean relative blood flow (%Q/%m) in 16 sagittal right (R) or left (L) lung slices during one- (●) and two-lung (●) ventilation under baseline anaesthesia and during one- (●) and two-lung (●) ventilation after additional administration of 1.5% isoflurane. *P < 0.05, isoflurane vs baseline anaesthesia.
Table 3  Relative perfusion (% Q/\%m) (mean (SEM)) of lobar components of isogravitational slices during one- and two-lung ventilation under baseline anaesthesia (1LV\textsubscript{B}, 2LV\textsubscript{B}) and during additional administration of 1.5\% isoflurane (1LV\textsubscript{I}, 2LV\textsubscript{I}). RUL = Right upper lobe, ML = middle lobe, RLL = right lower lobe, LUL = left upper lobe, LLL = left lower lobe. *P < 0.05 compared with LUL; †P < 0.01 compared with RUL; ‡‡P < 0.001 compared with ML.

Table 4  Relative perfusion of ventral and dorsal regions of the left upper lobe (mean (SEM)) during one- and two-lung ventilation under baseline anaesthesia (1LV\textsubscript{B}, 2LV\textsubscript{B}) and during additional administration of 1.5\% isoflurane (1LV\textsubscript{I}, 2LV\textsubscript{I}).

Regional blood flow in isogravitational planes

The lower lobe was significantly more perfused than the upper lobe in isogravitational slices of both lungs at all experimental phases except 1LV\textsubscript{I} (table 3). Relative perfusion was lowest in the middle lobe throughout the experiment. A lower relative blood flow was found in ventral compared with dorsal regions of the left upper lobe in slices L3–L6 (P < 0.05, table 4). In isogravitational planes comparison of relative blood flow in central vs peripheral parts of the right and left lower lobe did not reveal significant differences during any experimental condition.

Discussion

The present study provides the first analysis of the effects of one-lung ventilation on regional pulmonary blood flow distribution in the lateral decubitus position and of the modification by exposure to 1.5\% isoflurane. The most important findings were that one-lung ventilation caused a uniform redistribution of blood flow in favour of the ventilated lung, which was inhibited significantly by isoflurane; isoflurane increased blood flow to the non-dependent lung during two- and one-lung ventilation; and neither one-lung ventilation nor isoflurane affected the gravitational gradients of regional blood flow within the lungs or the pattern of regional perfusion in isogravitational planes.

REGIONAL BLOOD FLOW

Blood flow distribution between the lungs (table 2)

According to the zonal model of regional pulmonary perfusion of West, Dollery and Naimark [16] and in agreement with previous studies on pulmonary blood flow distribution in the lateral decubitus position [8, 9, 17, 18], the dependent lung was markedly more perfused than the non-dependent lung during all experimental phases. One-lung ventilation caused a significant redistribution of regional blood flow from the hypoxic (non-dependent) to the ventilated (dependent) lung during baseline anaesthesia and during isoflurane administration. Relative blood flow to the non-dependent lung was increased significantly by administration of 1.5\% isoflurane during both two- and one-lung ventilation. These data suggest a vasodilator effect of isoflurane on the pulmonary vasculature, which counteracts the protective mechanism of HPV (see below).

Gravitational blood flow distribution (fig. 1)

Gravity is a major determinant of regional blood flow distribution within the lungs [19]. During two-lung ventilation with i.v. baseline anaesthesia, relative blood flow increased along the gravitational axis in both lungs from slice 1 to 6 (R1–R6, L1–L6), whereas a subsequent decline was found to the bottom of each lung (R7–R8, L7–L8). A similar pattern of blood flow distribution in the lateral decubitus position has been reported previously in dogs [8, 9]. According to the zonal model of regional lung perfusion of West, Dollery and Naimark [16], the increase in relative blood flow in the vertical direction in slices R1–R6 and L1–L6 was caused by decreasing vascular resistance in alveolar vessels caused by changes in the relationship of intravascular and alveolar pressures induced by gravity. Decreasing regional blood flow in the lowermost slices of each lung (R7–R8 and L7–L8) corresponds to data of Greenleaf and colleagues [8] and Hughes and colleagues [20] and may be explained by the revised zonal model of the lung [21], which includes a fourth zone. In contrast with the three upper zones, regional blood flow in zone 4 is determined mainly by...
increasing resistance to flow in extra-alveolar vessels because of declining regional lung expansion [17] and increasing interstitial pressure.

During two-lung ventilation, administration of isoflurane slightly increased the fraction of cardiac output perfusing the uppermost slices of the right lung, whereas relative blood flow decreased in contralateral slices L2–L7. In accordance with previous studies using indirect methods [22, 23], we have recently demonstrated a vasodilator effect of isoflurane on pulmonary arterioles by intravital microscopy [24]. If alveolar pressure is constant, dilatation of arteriolar resistance vessels leads to an increase in capillary inflow pressure thereby increasing capillary transmural pressure. In zone 3 pulmonary capillaries are open under baseline conditions [16, 25]; capillary distension and higher blood flow velocity are the only mechanisms to account for increased regional blood flow at higher perfusion pressure. In contrast, in zone 2 blood flow increases more strikingly with capillary transmural pressure, as capillary recruitment occurs in addition to vascular distension. Relative blood flow expressed as the fraction of cardiac output per fraction of lung mass is therefore expected to increase in zone 2, but to decrease in zone 3 during isoflurane administration. Zone 1 conditions are absent in the rabbit lung [26, 27]. Therefore, capillary recruitment in zone 2 leads to an increase in relative perfusion even in the uppermost slices of the non-dependent lung (fig. 1).

One-lung ventilation caused a marked and uniform reduction in relative blood flow in all slices of the non-dependent lung because of HPV whether or not isoflurane was administered; a corresponding increase was observed in the left lung. Thus 1.5% isoflurane did not abolish HPV. However, direct comparison of 1LV with 1LVb revealed higher relative blood flow in each slice of the right lung with isoflurane (P < 0.05). These findings indicate a significant inhibitory effect of isoflurane on HPV corresponding to higher venous admixture during 1LV compared with 1LVb (see table 1). Inhibition of HPV by isoflurane has been reported previously from experimental studies in vitro [22, 28, 29] and in vivo [3, 22], and from clinical studies [1]. The present study, however, is the first to demonstrate that the gravitational perfusion pattern within both single lungs is almost preserved during administration of isoflurane with a uniform increase in blood flow to all slices of the hypoxic lung and a corresponding decrease in the contralateral lung.

**Regional blood flow in isogravitational planes (tables 3, 4)**

There are consistent hints in the literature that factors other than gravity, lung expansion and the interrelationship of intravascular, alveolar and interstitial pressures may considerably influence intrapulmonary blood flow distribution. In particular, craniocaudal [8, 9], ventrodorsal [8, 10] and radial perfusion gradients [8, 11, 12] have been observed in isogravitational planes.

In isogravitational slices of both lungs, the upper lobes were consistently more perfused than the lower lobes (table 3) according to the assumption of a gravity-independent craniocaudal perfusion gradient [8, 9]. However, middle lobe perfusion was lowest in all animals. Reduced ventilation of the middle lobe could account for this finding. Thorough inspection of the lungs during removal at autopsy, however, did not reveal signs of middle lobe dys- or atelectasis. Furthermore, middle lobe perfusion was lowest throughout the experiments, including one-lung ventilation with deliberate hypoxia of the entire right lung. Therefore, regional hypoxia is unlikely to have caused this phenomenon and low middle lobe perfusion is most likely attributed to the specific anatomical properties of the rabbit lung. We cannot exclude, however, that regional perfusion of the middle lobe per gram lung tissue was slightly underestimated. One may speculate that, because of its central anatomical position near the hilum, the middle lobe may have contained a greater portion of bronchial and vascular components in isogravitational slices compared with slices from the upper and lower lobe.

Dorsal regions were consistently more perfused than ventral regions of the left upper lobe (table 4). Similar results have been obtained in dogs by scintiscanning of lung slices [8] and well counting of single probes after injection of microspheres [10]. The existence of a consistent gravity-independent ventrodorsal gradient is further supported by the fact that the increase in regional blood flow along the gravitational axis is much less pronounced in the prone compared with the supine position [8, 9].

Controversial results have been reported on central to peripheral gradients of regional perfusion. Hakim, Lisbona and Dean, using SPECT, reported a central to peripheral perfusion ratio of 3:1 to 10:1 in dogs and in humans [11, 30]. Scintiscanning of transversal lung slices yielded higher blood flow in the centre compared with the periphery of individual lobes [8]. However, others were unable to detect a radial gradient of regional blood flow in isogravitational slices by well counting of lung tissue probes after injection of radioactive labelled microspheres [10, 31, 32]. According to the latter results we were unable to detect any differences in relative perfusion between central and peripheral regions of both lower lobes. The discrepancies may be caused by methodological differences: SPECT is particularly advantageous if non-invasive measurement of regional perfusion is required. As the method is based on a computer reconstruction of planar projections, reliability of blood flow measurement in the periphery may be limited by geometric artefacts [12, 32]. A SD of 1 cm must be taken into account when interpreting measurements obtained by scintiscanning of the lung [8]. Injection of isotope labelled microspheres followed by well counting of tissue specimens provides the highest spatial resolution. The microsphere method is therefore accepted as the “gold standard” for quantification of regional organ perfusion [8]. However, we cannot exclude that, despite careful dissection, central lung regions may contain larger bronchi and vessels compared with the lung periphery, thereby reducing the number of alveoli per gram probe weight. The technique used
in our study may therefore slightly underestimate blood flow per alveolus near the hilum, whereas SPECT and γ-scanning rather indicate reduced blood flow to the periphery.

**PULMONARY GAS EXCHANGE**

During one-lung ventilation $Q_s/Q_t$ was higher and $P_{A_{O_2}}$ was lower when isoflurane was administered. These data demonstrate the functional significance of increased shunt perfusion of the hypoxic lung, which can be assumed to be the predominant factor accounting for this effect. Enhanced blood flow to hypoxic segments of the ventilated lung, however, may have contributed to the increase in venous admixture. As the airway pressure of the left lung was kept constant, the total tidal volume decreased during one-lung ventilation resulting in an increase of $P_{CO_2}$. Conflicting results have been reported on the effects of $pH$ and $P_{CO_2}$ on the pulmonary vascular response to hypoxia. Most authors have concluded, however, that respiratory acidosis does not significantly affect HPV [33–35] as the enhancing effect of low $pH$ on HPV is counteracted by carbon dioxide-induced vasodilatation.

**MACROHAEMODYNAMICS**

Macrohaemodynamic baseline values were comparable with those reported previously using the same animal model [27]. Our results confirm the known vasodilator effect of isoflurane in the systemic circulation. One-lung ventilation did not alter systemic arterial pressure. However, an increase in calculated SVR was found as a result of a decrease in cardiac output.

In the pulmonary circulation isoflurane caused vasodilatation during both two- and one-lung ventilation, as documented by constant pulmonary artery pressure despite enhanced cardiac output. A marked increase in pulmonary vascular resistance was observed during one-lung ventilation with and without isoflurane, which resulted in a significant increase in PAP despite lower cardiac output. The one-lung ventilation-induced reduction in cardiac output is in contrast with some data reported from other species [1, 4, 5, 36, 37]. Possible explanations for this discrepancy include reduced left ventricular preload caused by an increase in pulmonary vascular resistance induced by HPV or by increased airway pressure, and reduced functional reserve of the right ventricle. Left atrial pressure did not differ between one- and two-lung ventilation phases, and mean airway pressure was kept constant in both lungs throughout the experiments. Our results therefore suggest a reduced ability of White New Zealand rabbits to cope with increases in right ventricular afterload compared with other species.

**EXPERIMENTAL MODEL**

**Measurement of regional blood flow**

Counting tissue probe activity after injection of isotope labelled microspheres provides the highest spatial resolution compared with all other methods used for assessment of regional pulmonary blood flow [19, 38] and allows multiple independent sequential measurements [14]. The microsphere technique was therefore chosen to assess regional pulmonary blood flow. The number of microspheres injected during each experimental condition was calculated to avoid methodological errors, which may be caused by an insufficient number of microspheres being trapped in each tissue specimen [39]. Injection of microspheres did not elicit any measurable haemodynamic effects in the animals. In order to exclude transpulmonary shunting of microspheres, the radioactivity of the kidneys, which receive a significant part of the systemic perfusion, was measured routinely. Values did not differ significantly from background activity.

**Anaesthetic regimen**

I.V. baseline anaesthesia comprised the synthetic opioid compound piritramid and α-chloralose in order to ensure adequate anaesthesia and analgesia while avoiding the side effects on the pulmonary circulation. Several studies in vitro and in vivo investigating the effect of opioids on HPV did not reveal an inhibitory potency [1, 40–44]. α-Chloralose has been shown not to influence autonomic reflexes in animals [45] and is commonly considered an ideal anaesthetic for cardiovascular studies [46]. Thus α-chloralose has recently been recommended when prolonged anaesthesia is required for experimental studies of cardiovascular physiology [47].

**One-lung ventilation**

During one-lung ventilation the right main bronchus was occluded by a bronchus blocker and the lung was inflated with pure nitrogen. Mean airway pressure of the right lung was kept at the same level as during two-lung ventilation (7 cm H$_2$O) in order to minimize mechanical effects on the pulmonary circulation. Although this experimental setting differs from the methods of one-lung ventilation used clinically in humans, these methodological differences are unlikely to have significantly influenced the effects of isoflurane on regional pulmonary blood flow during one-lung ventilation.

In conclusion, the data obtained from the present study are consistent with the zonal model of pulmonary blood flow distribution and support the existence of gravity-independent craniocaudal and ventrodorsal gradients of regional blood flow. Besides a marked shift of regional blood flow toward the ventilated lung, one-lung ventilation did not essentially alter intrapulmonary blood flow distribution. Isoflurane increased non-dependent lung perfusion during two- and one-lung ventilation, but did not influence isogravitational perfusion gradients. The results demonstrate that 1.5% isoflurane increased the fraction of cardiac output perfusing the hypoxic lung during one-lung ventilation thereby counteracting the protective mechanism of HPV.

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