Desflurane Inhibits Hypoxic Pulmonary Vasoconstriction in Isolated Rabbit Lungs

Stephan A. Loer, M.D.,* Thomas W. L. Scheeren, M.D.,* Jörg Tarnow, M.D., F.R.C.A.†

Background: Inhalational anesthetics inhibit hypoxic pulmonary vasoconstriction (HPV) in vitro and in vivo with a half-maximum inhibiting effect (ED₅₀) within concentrations applied for general anesthesia. Because it is unknown whether desflurane acts likewise, we studied its effect on HPV in isolated blood-perfused rabbit lungs and compared its ED₅₀ with that of halothane.

Methods: Isolated blood-perfused rabbit lungs were randomly allocated to treatment with either desflurane (n = 6) or halothane (n = 6). HPV, defined as an increase in pulmonary arterial pressure (PAP) at constant flow, was elicited by decreasing inspiratory oxygen concentration from 20% to 3% for 4 min. This effect was determined without (control HPV) and with increasing concentrations of the anesthetics (fraction of inspired carbon dioxide kept constant at 4.8 ± 0.2%, perfusate temperature at 37°C, and blood flow at 100 ml·min⁻¹).

Results: Before exposure to the anesthetics, PAP increased by 8.6 ± 1.9 cmH₂O for all lungs within 4 min of hypoxia (control PAP for all lungs 19.6 ± 2.5 cmH₂O). Desflurane decreased this effect in a concentration-dependent fashion with an ED₅₀ of 14.5%, compared with that of halothane, with an ED₅₀ of 1.7%.

Conclusions: Assuming that 1 minimum alveolar concentration (MAC) values of desflurane and halothane for rabbits are 8.9% and 1.3%, respectively, this study yields ED₅₀ values for the inhibition of HPV of approximately 1.6 MAC for desflurane and 1.2 MAC for halothane (P not statistically significant).

(Key words: Anesthetics, volatile: desflurane, halothane. Lung hypoxic pulmonary vasoconstriction; isolated rabbit lung.)

INHALATIONAL anesthetics inhibit hypoxic pulmonary vasoconstriction (HPV) in vitro in animal experiments in a concentration-dependent fashion.¹,² Whether desflurane, a new volatile agent acts likewise is unknown. Because most other inhalational anesthetics have a half-maximum inhibiting effect (ED₅₀) of HPV within the therapeutic range it is of interest to study whether this applies also to desflurane. We therefore elicited HPV in blood-perfused isolated rabbit lungs ventilated with increasing concentrations of desflurane and halothane.

Materials and Methods

Isolated Lung Preparation

With approval of the Institutional Animal Care and Use Committee adult New Zealand White rabbits (body weight 3.4 ± 0.3 kg, mean ± SD) of either sex were anesthetized with 30 mg·kg⁻¹ pentobarbital sodium intravenously and randomly allocated to the desflurane or halothane group. After tracheostomy, the animals' lungs were ventilated with air at a tidal volume of 10 ml·kg⁻¹ and a rate of 30 min⁻¹ (respirator 683, Harvard, South Natick, MA). Heparin (1,000 IU·kg⁻¹) was injected 3 min before the rabbits were rapidly exsanguinated through the carotid artery. After midline sternotomy, the trachea, heart, and lungs were removed en bloc and perfusion cannulas were tied into the pulmonary artery and the left atrium via the left ventricle, with meticulous care taken to avoid pulmonary air embolism during preparation. The rabbit's autologous blood was used to fill the extracorporeal circulation circuit, and perfusion was instituted at a constant flow of 100 ml·min⁻¹, about 30 ml·min⁻¹·kg⁻¹ body weight (calibrated roller pump 16670, American Optical, Bedford, MA). The perfusate temperature was maintained at 37°C with a water bath, and pH was maintained between 7.35 and 7.45 by the addition of sodium bicarbonate, if necessary. The time from the start of exsanguination to the start of ex situ perfusion was less than 12 min.

After removal of the lungs from the chest they were inflated for a short period with positive pressures to 15 cmH₂O until any visible atelectasis had resolved. Thereafter they were ventilated with 5% carbon dioxide in air and a positive end-expiratory pressure of 3 cmH₂O maintained by a water seal in the expiratory

INHIBITION OF HPV BY DESFLURANE

In preliminary studies we used inspiratory variations of 0.2% around 20% during HPV. Observations of 3% during hypoxia had not clearly defined HPV, because variations within these ranges in inspired oxygen content and 5% oxygen in nitrogen gases did not alter HPV. We therefore varied the inspired oxygen content and 3% during hypoxia and determined HPV. All gases were supplied by Messer (Hanau, Germany), desflurane by Mead Johnson (Milton Keynes, United Kingdom), and 5% oxygen in nitrogen by Becht AG (Frankfurt am Main, Germany) vaporizers were used with desflurane and halothane, respectively.

Measurements

Pulmonary arterial pressure (PAP), pulmonary arterial oxygen saturation (PAo₂), and airway pressures were measured with a micromanometers (P23 ID, Statham, Oxnard, CA). The zero reference level for PAP was chosen at the top of the lung and PAP was calculated on the catheter. Perfusion oxygen saturation, pH (CMS 3Mk2, Radiometer, Copenhagen), and hematocrit (HemoCue, HemoCue, Hedge, Germany) were determined. Total lung weight was measured with a balance (Sartorius, Göttingen, Germany). Oxygen concentrations were measured in an anesthetic gas monitor (PM 890, Grass Instruments, Quincy, Mass.).

Experiments

The perfused lungs were initially kept at room temperature to establish an isogravimetric state. The perfusion pressure was then increased to 20 cmH₂O, and the lungs were gently inflated to a constant tidal volume of 10 ml·kg⁻¹ with air for 3 breaths. The lungs were then allowed to settle at a steady state of perfusion for another 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was decreased to 0 cmH₂O and perfused for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths. The perfusion pressure was then decreased to 0 cmH₂O for 3 breaths. The airway pressure was increased to 20 cmH₂O for 2 breaths.

Table 1. Effects of Desflurane and Halothane

<table>
<thead>
<tr>
<th>Agent</th>
<th>Preo₂</th>
<th>PAP (cmH₂O)</th>
<th>PAo₂ (%)</th>
<th>Hct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>19.0 ± 2.1</td>
<td>8.7 ± 1.2</td>
<td>20.2 ± 1.2</td>
<td>8.6 ± 2.1</td>
</tr>
<tr>
<td>Halothane</td>
<td>19.0 ± 2.1</td>
<td>8.7 ± 1.2</td>
<td>20.2 ± 1.2</td>
<td>8.6 ± 2.1</td>
</tr>
</tbody>
</table>

Desflurane was administered as a single positive end-expiratory pressure of 3 cmH₂O maintained by a water seal in the expiratory

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Inhibition of HPV by Desflurane

In preliminary studies we found that carbon dioxide variations of 0.2% around 4.8% and oxygen variations of 2% around 20% during normoxia and 0.1% around 3% during hypoxia had no measurable effects on HPV, so variations within these ranges were allowed. Premixed gases (5% carbon dioxide in air, 5% carbon dioxide and 3% oxygen in nitrogen) were used with flow meter-controlled addition of oxygen or carbon dioxide or both during ventilation with high concentrations of desflurane until the measured gas concentrations were again within the tolerated ranges.

All gases were supplied by Messer Griesheim GmbH (Duisburg, Germany), desflurane by Kabi Pharmacia (Milton Keynes, United Kingdom), and halothane by Hoechst AG (Frankfurt am Main, Germany). Dräger (Lübeck, Germany) vaporizers were used to deliver desflurane and halothane, respectively.

Measurements

Pulmonary arterial pressure (PAP), left atrial pressure, and airway pressures were measured continuously with electromagnetic transducers (P23 ID, Statham, Gould, Oxnard, CA). The zero reference level for these pressures was chosen at the top of the lung and balanced to atmospheric pressure. Perfuse oxygen and carbon dioxide tensions, pH (CMS 3MK2, Radiometer, Copenhagen, Denmark) and hematocrit (Haematokrit-Zentrifuge, Hettich, Germany) were determined intermittently. Total lung weight was measured by a force transducer (FT 03, Grass Instruments, Quincy, MA). Inspiratory gas concentrations were measured continuously with an anesthetic gas monitor (PM 8050, Dräger).

Experiments

The perfused lungs were initially observed for 20 min to establish an isogravimetric state with a PAP of approximately 20 cmH₂O. If an isogravimetric state could not be attained experimental results were not used in this study. Left atrial pressure was adjusted above airway pressure (5 cmH₂O) at the beginning of the experiments by the height of the venous reservoir to attain zone 3 flow conditions excluding most likely vascular recruitment during increases of PAP.

HPV was elicited by a reduction of inspiratory oxygen concentration from 20% to 5% for 4 min during ventilation without (control HPV) and with randomized concentrations of desflurane (+5, 9.0, 13.5, and 18.0%) and halothane (1.0, 2.0, and 3.0%). At every

![Fig. 1. Time course of the increase in pulmonary arterial pressure (ΔPAP) in response to 4 min of hypoxia without (open circles) and with increasing concentrations of desflurane (filled circles, diamonds, squares, asterisks) in one representative example (baseline pulmonary arterial pressure [PAP] 17 cmH₂O, perfusion rate 100 ml·min⁻¹). With increasing concentrations of desflurane, PAP response declined, and pressure plateaus were achieved later but within 4 min. PAP returned to baseline within 4 min of normoxia (fraction of inspired oxygen 0.20).](image)

### Table 1. Effects of Desflurane and Halothane on Pulmonary Artery Pressure and Hypoxic Pressor Response

<table>
<thead>
<tr>
<th></th>
<th>Preanesthetic 0%</th>
<th>4.5%</th>
<th>9.0%</th>
<th>13.5%</th>
<th>18%</th>
<th>Postanesthetic 0%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline PAP (cmH₂O)</strong></td>
<td>19.0 ± 3.1</td>
<td>18.7 ± 3.2</td>
<td>18.5 ± 2.6</td>
<td>19.0 ± 2.4</td>
<td>17.9 ± 2.2</td>
<td>19.6 ± 1.9</td>
</tr>
<tr>
<td>ΔPAP (cmH₂O)</td>
<td>8.7 ± 1.9</td>
<td>8.5 ± 2.1</td>
<td>6.6 ± 3.0*</td>
<td>4.7 ± 2.6*</td>
<td>3.6 ± 2.3*</td>
<td>9.2 ± 2.2</td>
</tr>
<tr>
<td><strong>Halothane 0%</strong></td>
<td>0%</td>
<td>1.0%</td>
<td>2.0%</td>
<td>3.0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline PAP (cmH₂O)</strong></td>
<td>20.2 ± 1.8</td>
<td>20.0 ± 1.9</td>
<td>19.2 ± 1.3</td>
<td>18.7 ± 1.4</td>
<td>19.1 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>ΔPAP (cmH₂O)</td>
<td>8.6 ± 2.0</td>
<td>7.2 ± 2.4</td>
<td>2.9 ± 1.6*</td>
<td>0.9 ± 0.6*</td>
<td>9.2 ± 1.7</td>
<td></td>
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</tbody>
</table>

Values are mean ± SD (n = 6).

ΔPAP = increase in pulmonary artery pressure with hypoxic ventilation.

* Significant difference (P < 0.05) versus preanesthetic period within the group.
new inspiratory concentration of the anesthetics, 10 min was allowed for equilibration. Inspiratory carbon dioxide concentration was kept constant.

ED50 values for desflurane and halothane on pulmonary artery pressure increases during hypoxia were determined as the anesthetic concentrations at which 50% of the maximum pressure response to hypoxia during control HPV (absence of anesthetics) occurred.

To evaluate unspecific effects of a time factor, control HPV was introduced before and after exposure to the anesthetics so that each lung served as its own control.

Statistics
All data are presented as mean ± SD, unless otherwise indicated. Within both groups, HPV during increasing anesthetics concentrations was compared with control HPV and analyzed by Wilcoxon's signed-rank test. HPV, expressed as a percentage of control HPV, was used to assess ED50 values of the dose-response relations in both groups after linear interpolation. Between both groups differences between means of control HPV and ED50 values (after linear interpolation for each lung) were analyzed by Wilcoxon's signed-rank test. A P value of less than 0.05 was considered to be statistically significant.

Results
HPV was studied in 12 rabbit lungs, allocated randomly to treatment with desflurane or halothane and perfused with autologous blood (hematocrit 33 ± 1%, pH 7.38 ± 0.02). There were no statistically significant differences between the groups in baseline PAP or the increase in PAP during hypoxia before (pranesthetic) and after administration of the anesthetics (postanesthetic) (table 1). Furthermore, within the groups, neither of these variables differed between the pre- and postanesthetic periods, so nonspecific time effects can most likely be excluded.

With the institution of hypoxia, PAP increased promptly in both groups and attained a plateau within the hypoxic period of 4 min. One typical time course of the hypoxic response in the absence and presence of increasing concentrations of desflurane is shown in

**Fig. 2.** Concentration-effect relations for desflurane (filled circles) and halothane (open circles). Maximum pressure increases in the pulmonary artery (ΔPAP) of the individual lungs were determined during hypoxia (fraction of inspired oxygen 0.03) for increasing concentrations of the anesthetics. Pulmonary arterial pressure (PAP) under baseline conditions was 19.6 ± 2.5 cmH2O for all lungs. With increasing concentrations of desflurane and halothane ΔPAP decreased.

**Fig. 3.** Concentration-effect relations for desflurane (filled circles) and halothane (open circles): effect expressed as a percentage of control hypoxic pulmonary vasoconstriction (HPV) (means ± SEM, n = 6). Significant difference from control HPV, P < 0.05. The half-maximum inhibiting effect (ED50) values were 14.5% for desflurane and 1.6% for halothane. Both are within the range of 1 and 2 MAC, assuming 1 MAC in rabbits to be 8.9% for desflurane and 1.39% for halothane.

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INHIBITION OF HPV BY DESFLURANE

In the absence of desflurane (control HPV), PaP attained a maximum within 2 min and remained constant during hypoxia. With subsequent normoxia, this effect faded within 2–4 min. With increasing concentrations of desflurane the maximum effect decreased, but a plateau was reached within 4 min of hypoxya. The same pattern was observed in all experiments. Therefore, it appeared justified to use the plateau values to determine the concentration–effect relations for both anesthetics in the individual lungs (fig. 2). With increasing concentrations of desflurane (from 0–18%) and halothane (from 1–3%), HPV decreased. The means of the effects as percentages of control HPV were used to estimate ED_{50} values (fig. 3). Desflurane attenuated HPV in a concentration-dependent fashion, with an ED_{50} of 14.5%. In the halothane group the inhibition of control HPV was observed with an ED_{50} of 1.7%. To compare the two groups, 1 minimum alveolar concentration (MAC) in rabbits was assumed to be 8.9% for desflurane and 1.39% for halothane. This approach revealed ED_{50} values of 1.6 MAC for desflurane and 1.2 MAC for halothane. This difference was not statistically significant.

Discussion

HPV is important for regional ventilation–perfusion distribution, diverting pulmonary blood flow from hypoxic to normoxic alveolar regions. Several studies have provided evidence that volatile anesthetics attenuate this local vascular control mechanism. We have shown that desflurane acts likewise in isolated rabbit lungs. Our experimental design allowed us to examine the direct effects of desflurane and halothane on HPV and to control secondary influences such as pH, carbon dioxide tension in perfusate, and pulmonary blood flow, which have been shown to influence HPV. To ensure that perfusate and thus oxygen tension in the pulmonary artery had little effect on alveolar oxygen tension during HPV, lungs were ventilated at about ten times the rate at which they were perfused. Because red blood cells play a crucial role in maintaining vascular reactivity to hypoxia, we perfused the lungs with autologous blood at normal hematocrit (33%) for rabbits.

Desflurane as well as halothane inhibited HPV in a concentration–dependent manner. We found ED_{50} values of 14.5% for desflurane and 1.7% for halothane. Assuming the rabbit’s MAC of desflurane to be 8.9% and 1.39% for halothane, this reveals similar ED_{50} values for desflurane and halothane of 1.6 and 1.2 MAC, respectively, both ED_{50} values being within the clinical range of 1–2 MAC.

Marshall et al. investigated the effects of anesthetics on HPV in isolated rat lungs and found ED_{50} values of 0.47 MAC for halothane, 0.60 MAC for isoflurane, and 0.56 MAC for enfurane. These authors concluded that halogenated volatile anesthetics inhibit HPV with almost the same potency. The lower ED_{50} value for halothane compared with that in our study may be due to differences in species (rats vs. rabbits), perfusate (heterologous vs. autologous blood), hematocrit (18.5 vs. 33%), and lung perfusion (zone II vs. zone III).

Another study in isolated rabbit lungs (Japanese white) found ED_{50} values of 0.85 MAC for isoflurane and 1.0 MAC for sevoflurane with perfusion under zone II conditions using autologous blood (hematocrit 10%). An in vivo study in dogs revealed an ED_{50} value for isoflurane of 2.4%. Apparently, in addition to the investigated anesthetic and the species, study conditions (in vivo vs. isolated lung; hematocrit; and lung perfusion conditions) play a crucial role when HPV is investigated.

In summary, we have shown that desflurane inhibits HPV in blood-perfused rabbit lungs in a dose-dependent fashion, with 50% inhibition occurring at a concentration of 14.5%, representing about 1.6 MAC.

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