

## Effect of Sevoflurane on Hypoxic Pulmonary Vasoconstriction in the Perfused Rabbit Lung

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**Background:** *In vitro* studies have shown that isoflurane, enflurane, and halothane inhibit the hypoxic pulmonary vasoconstriction (HPV) with essentially the same potency. The aim of this study is to compare the effects of sevoflurane and isoflurane on HPV in constant-flow perfused rabbit lungs.

**Methods:** Constant-flow perfused lungs from Japanese white rabbits were tested. The lungs were divided into three groups: isoflurane alone ( $n = 6$ ), sevoflurane alone ( $n = 6$ ), and sevoflurane with ibuprofen pretreatment ( $n = 6$ ). Baseline HPV responses were measured as the pulmonary arterial pressure increased after changing inspired oxygen concentration from 95% for 15 min to 3% (with 5%  $\text{CO}_2$ ) for 5 min without anesthetic administration. Next, three different concentrations of anesthetics were added to the inspired gas for 15 min in random order. The HPV response in the presence of anesthetic was expressed as a percentage of the pressor response in the absence of anesthetics, and dose-response relationships were calculated using the nonlinear least-squares method.

**Results:** Isoflurane and sevoflurane both depressed the HPV response in a dose-related manner. The half-inhibition values ( $\text{ED}_{50}$ ) of HPV with isoflurane and sevoflurane were  $0.85 \pm 0.22$  MAC and  $1.00 \pm 0.12$  MAC (mean  $\pm$  SD), respectively, and were not statistically different. Ibuprofen pretreatment did

not alter  $\text{ED}_{50}$  and slope of dose-response curve, although the absolute value of pressor response in the sevoflurane group with ibuprofen pretreatment was greater than that in the sevoflurane alone group at every concentration of sevoflurane.

**Conclusions:** Sevoflurane inhibits the HPV response in a dose-related manner, and its potency is similar to that of isoflurane *in vitro*. Cyclooxygenase products do not mediate the inhibition of HPV by sevoflurane. (Key words: Anesthetics, volatile: isoflurane; sevoflurane. Cyclooxygenase inhibitor. Hypoxia. Lung: blood flow; vascular resistance.)

HYPOXIC pulmonary vasoconstriction (HPV) is a mechanism by which blood is diverted from poorly ventilated to better ventilated areas of the lung so that the arterial oxygen tension is maintained. Abolition of HPV by inhalational anesthetic agents has been suggested as one of the causes of hypoxemia during anesthesia.<sup>1</sup> Studies *in vitro*<sup>2</sup> have demonstrated that halothane, enflurane, and isoflurane equipotentially inhibit HPV. This inhibition of HPV often is obscured *in vivo* because secondary effects of anesthetics such as circulatory depression, sympathetic inactivation, and hormonal alteration modulate the HPV response.<sup>3-5</sup> Sevoflurane, a new inhalational anesthetic, was reported to not inhibit HPV in intact dogs,<sup>#</sup> although it was not compared with other agents in the same preparation. The present study was designed to investigate whether sevoflurane inhibits HPV *in vitro* as compared with the results of experiments with isoflurane. The contribution of cyclooxygenase products of arachidonic acid to HPV inhibition with sevoflurane also was examined.

### Materials and Methods

The protocol for this study was approved by the Kinki University Laboratory Animal Care Committee. A standard perfused rabbit lung preparation *in vitro*<sup>6</sup> was modified as described below.

#### Subjects and Preparation

Adult female Japanese white rabbits weighing  $2.2 \pm 0.1$  kg (mean  $\pm$  SE) were anesthetized with 20 mg/kg

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intravenous pentobarbital and 35 mg/kg intramuscular ketamine and anticoagulated with 300 IU/kg heparin. A tracheotomy was performed, and the lungs were mechanically ventilated with a Harvard ventilator (model 681, Harvard Apparatus, South Natick, MA) at a rate of 40 breaths/min and a tidal volume of 10 ml/kg with a hyperoxic gas mixture consisting of 95% O<sub>2</sub>, 5% CO<sub>2</sub>, and balance nitrogen and 2 cmH<sub>2</sub>O positive end-expiratory pressure. After sternotomy, the pulmonary artery and the left atrium were cannulated *via* right and left ventriculostomies, respectively. The pulmonary circulation was at first perfused in a nonrecirculating manner with 3% bovine serum albumin-physiologic salt solution until the effluent was clear, and then autologous blood was added to the physiologic salt solution and the lungs were perfused in a recirculating manner with a peristaltic pump (model 1215, Harvard Apparatus) at a flow rate of 30 ml · kg<sup>-1</sup> · min<sup>-1</sup> monitored with an electromagnetic blood flowmeter (MF-1200, Nihon Kohden, Tokyo, Japan). The perfusate reservoir temperature was maintained at 37.5° C with a heated water bath. The physiologic salt solution contained (mM) NaCl 119, KCl 4.7, MgSO<sub>4</sub> 1.17, NaHCO<sub>3</sub> 22.61, KH<sub>2</sub>PO<sub>4</sub> 1.18, CaCl<sub>2</sub> 3.2, and to each 100 ml of this stock solution, 100 mg dextrose, 20 IU of insulin, and 3 g of bovine serum albumin were added. The final perfusate contained 50 ml of physiologic salt solution and 20 ml of autologous blood, and its hematocrit was about 10%. Pulmonary arterial pressure (PAP), left atrial pressure, and airway pressure were measured continuously *via* side holes in the cannula with pressure transducers (Hewlett Packard, Andover, MA) and recorded on a four-channel recorder (model 7754A, Hewlett Packard). All pressures were referred to the level of the left atrium. The level of the drainage tube from the left atrium was adjusted to maintain left atrial pressure at 0 mmHg. The opened chest cavity of the rabbit was covered with a transparent vinyl wrapping material to maintain the humidity surrounding the lungs, and an infrared light and a rubber mat circulating hot water were applied to maintain the chest cavity temperature at 37.5° C.

#### Study Protocol

The 18 rabbit lung preparations were divided into three groups: group 1, isoflurane alone; group 2, sevoflurane alone; and group 3, sevoflurane with ibuprofen pretreatment. The rabbits in groups 1 and 2 received no pretreatment, whereas the rabbits in group 3 received 12.5 mg/kg ibuprofen, a cyclooxygenase path-

way inhibitor, into the ear vein after anesthesia, and additional ibuprofen (0.06 mg/ml of physiologic salt solution) was added into the reservoir before perfusion. Before and after inhalation of anesthetics, a hypoxic test stimulus with 5 min of hypoxic ventilation was imposed as pre- and postanesthetic controls. One minimum alveolar concentration for rabbit was assumed to be 3.7% for sevoflurane<sup>7</sup> and 2.05% for isoflurane,<sup>8</sup> and vaporizers (Tec 3, Ohmeda, Madison, WI) were used to deliver sevoflurane or isoflurane vapor. The end-tidal concentrations of anesthetics were measured continuously with an anesthetic gas monitor (Capnomac, Datex, Tewksburg, MA).

After 30 min of stabilization, 0.2 µg angiotensin II was injected into the pulmonary artery catheter, and this was repeated at the end of the study. This procedure was not performed in group 1. The precontrol value was obtained as the average of the two sequentially identical hypoxic pressor responses by switching the inspired gas from the hyperoxic to hypoxic gas mixture (3% O<sub>2</sub>, 5% CO<sub>2</sub>, balance nitrogen) for 5 min. This period of 5 min was determined as a sufficient time for maximum hypoxic pressure increase based on the results of our preliminary studies. Because our studies and others<sup>2</sup> demonstrated that the anesthetic concentration in the perfusate was equilibrated with that in the lungs within 10 min after changing the concentration, the lungs were ventilated for 15 min with each hyperoxic test gas mixture then for 5 min with hypoxic gas mixture containing the same concentration of anesthetics. Three concentrations of sevoflurane—0.4, 0.8, and 1.2 MAC (or isoflurane 0.5, 1.0, and 2.0 MAC)—were administered randomly to each perfused lung. Finally, a postanesthetic control value was obtained without anesthetic gas. The PAPs in both hyperoxic and hypoxic phases were observed at each of three MAC fractions of each anesthetic under constant flow conditions. The baseline PAP for each hypoxic phase was determined as the mean of PAP during normoxia immediately before and after the hypoxic test period. The hypoxic pressor response (ΔP) was calculated as the difference between this baseline pressure and the peak of PAP recording during hypoxia. The percent ΔPAP was calculated by dividing each ΔP by the ΔP measured during the pre-anesthetic control phase. At the end of study, immediately after completion of perfusion, the lungs were removed; and after weighing, whole lungs were placed in a microwave oven for desiccation by repeated low-energy heating for 60 min.<sup>9</sup> These samples were reweighed. The sim-

**Table 1. Effect of Isoflurane and Sevoflurane on Hypoxic Pressor Response**

Group	Parameter	Preanesthetic Control	Postanesthetic Control			
			0.5 MAC	1.0 MAC	2.0 MAC	
Isoflurane alone	Baseline PAP (mmHg)	9.10 ± 0.38	9.33 ± 0.45	9.48 ± 0.52	9.83 ± 0.64	9.33 ± 0.72
	ΔP (mmHg)	4.58 ± 0.39	3.40 ± 0.19	1.62 ± 0.27*	0.78 ± 0.18*	4.83 ± 0.88
	%ΔP (%)	100	75.47 ± 4.08	36.02 ± 6.08*	17.75 ± 4.28*	105.73 ± 13.42
Sevoflurane alone	Baseline PAP (mmHg)	8.65 ± 0.31	9.07 ± 0.53	9.27 ± 0.61	8.92 ± 0.35	10.62 ± 0.71
	ΔP (mmHg)	2.97 ± 0.23 <sup>a</sup>	2.67 ± 0.25 <sup>b</sup>	2.10 ± 0.25 <sup>a,c</sup>	0.97 ± 0.20 <sup>a,d</sup>	3.15 ± 0.35 <sup>e</sup>
	%ΔP (%)	100	90.62 ± 6.64	70.03 ± 4.28*	32.47 ± 6.07*	107.02 ± 9.99
Ibuprofen + sevoflurane	Baseline PAP (mmHg)	10.05 ± 1.12	9.68 ± 0.98	9.60 ± 0.86	9.60 ± 0.87	10.38 ± 1.05
	ΔP (mmHg)	6.37 ± 1.01 <sup>a</sup>	5.77 ± 1.19 <sup>b</sup>	3.43 ± 0.69 <sup>a,c</sup>	1.80 ± 0.47 <sup>a,d</sup>	6.52 ± 0.88 <sup>e</sup>
	%ΔP (%)	100	88.33 ± 5.85	52.40 ± 3.42*	26.08 ± 4.00*	104.42 ± 4.19

Values are mean ± SE (n = 6).

ΔP = increase in pulmonary artery pressure with hypoxic ventilation; %ΔP = percentage of ΔP supposing that preanesthetic control value is 100.

\* Significant difference ( $P < 0.05$ ) compared with both pre- and postanesthetic control phase within the group by analysis of variance.

<sup>a-e</sup> Significant difference between values marked with the same letter by unpaired *t* test.

ple, blood-inclusive, wet-to-dry lung weight ratio was then calculated using the formula: (wet - dry)/dry lung weight.

### Statistics

All data were presented as mean ± SE. Within each group, baseline pressure, ΔP and %ΔP were compared with one-way analysis of variance (ANOVA), and if a statistical difference was observed, a multiple-comparison test was performed by Tukey's *post hoc* test. To evaluate the effect of interaction between sevoflurane concentration and ibuprofen pretreatment on HPV, two-way ANOVA with repeated measures was employed to analyze the difference among ΔP measurements for each sevoflurane concentration in both groups with or without ibuprofen pretreatment. An unpaired *t* test determined significance between ΔP with or without ibuprofen in the same phase. Slope(s) and ED<sub>50</sub> of dose-response relationship in the three groups were compared with one-way ANOVA.  $P < 0.05$  was considered significant.

### Results

The general conditions of all lungs in group 1 (isoflurane group) did not differ throughout the experiment, and the average data are as follows: pH 7.448 ± 0.009, PaCO<sub>2</sub> 32 ± 0.6 mmHg, PaO<sub>2</sub> 476 ± 5.1 mmHg, BE -2 ± 0.4, perfusate hematocrit 13 ± 0.3%, and

leukocyte count  $6.1 \pm 0.4 \times 10^2/\mu\text{l}$ . The lung (wet - dry)/dry weight ratio was  $5.8 \pm 0.1$ . The general conditions of all lungs in groups 2 and 3 (sevoflurane group with or without ibuprofen) did not differ throughout the experiment, and the data therefore have been combined as follows: pH 7.446 ± 0.020, PaCO<sub>2</sub> 31 ± 0.5 mmHg, PaO<sub>2</sub> 467 ± 10.9 mmHg, BE 2 ± 0.4, perfusate hematocrit 11 ± 0.3%, and leukocyte count  $7.2 \pm 0.2 \times 10^2/\mu\text{l}$ . The lung (wet - dry)/dry weight ratio was  $6.8 \pm 0.39$  in group 2 and  $8.0 \pm 0.74$  ml/g in group 3, and though not statistically different, they were significantly greater than that in group 1. The lungs were zone II condition throughout the experiment in all three groups.

The pressor responses to 0.2 μg angiotensin II in the sevoflurane alone group were  $0.6 \pm 0.1$  and  $0.6 \pm 0.1$  mmHg, and in the sevoflurane with ibuprofen group,  $0.7 \pm 0.04$  and  $0.6 \pm 0.03$  mmHg, at the beginning and the end of the study, respectively. There were no statistical differences among these four values.

The hypoxic pressor responses in the three groups are summarized in the table 1. In group 1, the baseline PAP did not change within five experimental steps. The hypoxic PAP responses (ΔP) were maximal in pre- and postanesthetic control, and there was no statistical difference between pre- and postcontrol values. The ΔP and %ΔP at 1.0 and 2.0 MAC isoflurane were significantly less than those in both pre- and postanesthetic control phases. In the sevoflurane with or without ibu-

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profen groups, the baseline PAP did not change either between two groups or within the five steps of different sevoflurane concentrations. The  $\Delta P$  in two groups were maximal in the steps without sevoflurane, and no significant difference in  $\Delta P$  between pre- and postcontrol values was observed. Without regard to the pretreatment with ibuprofen, sevoflurane significantly depressed the hypoxic pressor response at both 0.8 and 1.2 MAC. In every step, the absolute  $\Delta P$  values in the ibuprofen pretreatment group were significantly greater than those in the sevoflurane alone group. However, there was no interaction of sevoflurane concentration and ibuprofen pretreatment on  $\Delta P$ .

The individual responses in the three groups were expressed as a percentage of the maximum ( $\%R_{\max}$ ), as shown in figure 1. The dose-response relationships were evaluated with the following equation<sup>10</sup>:  $R = R_{\max} \cdot C^s \cdot (Q^{-1} + C^s)^{-1}$ , using a nonlinear regression based on a least-squares method (Gauss-Newton's method). Values (mean  $\pm$  SD) for  $ED_{50}(Q^{-1/s})$  were  $0.85 \pm 0.22$ ,  $1.00 \pm 0.12$ , and  $0.82 \pm 0.12$  MAC, and for the slope(s) were  $2.14 \pm 0.56$ ,  $3.57 \pm 2.15$ , and  $2.83 \pm 0.78$  for isoflurane alone, sevoflurane alone, and sevoflurane with ibuprofen pretreatment, respectively. There were no statistical differences among the values for  $ED_{50}$  and the slope.

## Discussion

In the constant-flow perfusion rabbit lung model, sevoflurane and isoflurane inhibited HPV in a dose-related manner, and concentrations causing a 50% depression of the response were 1.00 MAC and 0.85 MAC for sevoflurane and isoflurane, respectively. These results agree with the previous report from Marshall *et al.*,<sup>2</sup> which showed that halogenated general anesthetics inhibited HPV with essentially the same potency, although the  $ED_{50}$ s of isoflurane and the other halogenated anesthetics were about 0.6 MAC in the rat lung, and the effects of sevoflurane were not examined in their study. These differences of  $ED_{50}$  between the two studies may be due to species differences (rabbits and rats) or the different sample sites at which the anesthetic concentration was measured (end-tidal gas and perfusate).

The sensitivity of the HPV response and the inhibitory effect of anesthetics on the HPV response to some extent depend on the experimental model used. A constant-flow preparation *in vitro* is suitable to examine the direct effect of anesthetics on the HPV response because

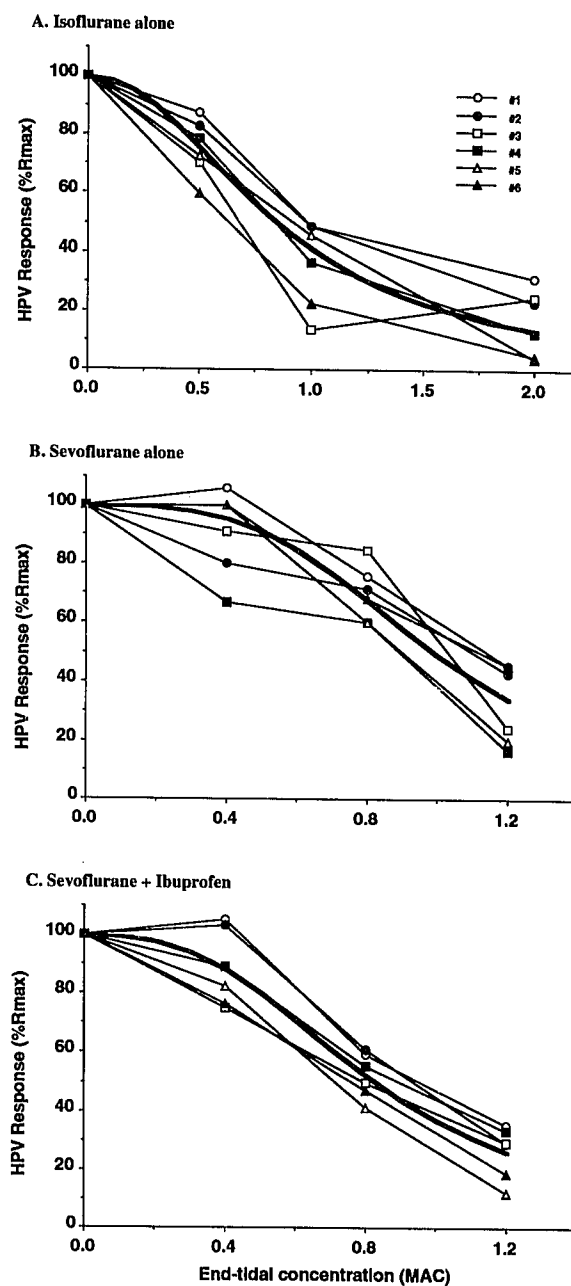


Fig. 1. Dose-response relationship for hypoxic pulmonary vasoconstriction (HPV) inhibition by (A) isoflurane alone, (B) sevoflurane alone, and (C) sevoflurane with ibuprofen pretreatment. From the six individual rabbit lungs, HPV response ( $\%$ ) of the maximum response ( $R_{\max}$ ) was plotted against MAC unit of end-tidal anesthetic concentration. The superimposed curve (solid line) in each panel was obtained by fitting data to the following equation<sup>10</sup>:  $R = R_{\max} \cdot C^s \cdot (Q^{-1} + C^s)^{-1}$ . See explanations in the text.

a high concentration of anesthetic may be administered without confounding effects related to circulatory depression. In addition, the constant-flow perfused lung preparation permits strict control of variables that may affect pulmonary vascular tone.<sup>11-13</sup> Models *in vivo* include a number of factors that can modify pulmonary vascular tone indirectly, and these preparations are useful to evaluate the net effects of the drugs on both pulmonary and systemic hemodynamics. We selected the constant-flow *in vitro* model in the present study to isolate the effects of sevoflurane and isoflurane on HPV.

In our model, baseline PAPs in three groups were similar and the responses to angiotensin II in groups 2 and 3 were identical at beginning and end of the study. These findings demonstrate that vascular response of the perfused lung was constant throughout the study. However, the lung water content in group 3 lungs treated with ibuprofen was larger than the normal value, although the lung (wet - dry)/dry weight ratio in group 3 did not significantly differ from that in group 2. It is unlikely that increased pulmonary vascular permeability or slightly high baseline pressure with ibuprofen was responsible for edema formation in our model because the changes were small. It is possible that higher PAP during hypoxic stimulation in group 3 was responsible for edema formation as a result of venoconstriction, but this was not tested here. However, previous reports<sup>14,15</sup> show that the HPV responses were not altered in the edematous lung, and therefore, this result seems unlikely to have influenced our conclusions.

Administration of ibuprofen did not alter the inhibitory effect of sevoflurane on HPV; ED<sub>50</sub> and the slope of the two dose-response curves of sevoflurane with or without pretreatment of ibuprofen were almost identical. Our choice of the ibuprofen dose 12.5 mg/kg was based on the manufacture's suggestion and extrapolation from the literature.<sup>16-18</sup> Our work therefore suggests that cyclooxygenase products do not mediate the inhibitory effect of sevoflurane on HPV in perfused rabbit lungs *in vitro*. This finding is consistent with another study<sup>19</sup> that reported indomethacin, another cyclooxygenase blocker, did not alter the inhibition of HPV by halothane in perfused dog lungs. Our study does not exclude a potential role for leukotrienes as mediators or modulators of the effect of sevoflurane on HPV. Other investigators<sup>20</sup> have demonstrated that leukotrienes are released during hypoxic exposure and that inhibition of leukotriene synthesis or release may

inhibit HPV in perfused lung. However, no report has demonstrated that leukotrienes mediate or modulate the inhibitory effect of inhalational anesthetics on HPV.

The absolute values of hypoxic pressor response in the group with ibuprofen pretreatment were significantly greater than that in the group not receiving ibuprofen, regardless of sevoflurane administration. Two explanations are proposed for this finding. First, the inhibition of cyclooxygenase by ibuprofen results in decreased production of the prostacyclin, which normally is released during hypoxic constriction<sup>21</sup> so that enhancement of HPV response occurs under these conditions. On the other hand, the inhibition of cyclooxygenase by ibuprofen may result in increased leukotrienes,<sup>22</sup> so that it is also possible that increased leukotrienes enhanced HPV response itself. Second, there is a high probability of increased basal vascular tone with cyclooxygenase pathway block, because our single-flow study was not sufficient to show that ibuprofen did not increase basal vascular tone, even though the baseline pressure did not change. Generally, increased basal tone of pulmonary artery may be followed by augmentation of HPV. A more complete analysis of the pressure-flow relationship is required to clarify this problem.

Though high doses of inhalational anesthetics usually inhibit HPV *in vivo*,<sup>1,3-5</sup> 4% sevoflurane has been reported to have no inhibitory effect on HPV in an *in vivo* nonintact dog model.<sup>#</sup> This discrepancy with our results may depend on the experimental method used. In the study of Okutomi and Ikeda,<sup>#</sup> the left lower lobe was not ventilated, and sevoflurane was given only to the rest of the lung. Sevoflurane concentration in the left lower lobe is likely to be less than the expected value, which may explain why sevoflurane did not inhibit HPV in their model. The secondary effect of decreased cardiac output,<sup>23</sup> pulmonary vascular pressure,<sup>23</sup> and arterial<sup>24</sup> and mixed venous oxygen tension<sup>25</sup> induced with sevoflurane administration also might change and influence the effects of inhibition of HPV by sevoflurane.

In summary, this study has demonstrated that sevoflurane directly inhibits pulmonary vascular response to alveolar hypoxia. The concentration at which 50% inhibition of HPV occurred was 1.0 MAC for sevoflurane. Cyclooxygenase products may not mediate the HPV inhibition by sevoflurane.

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