Sevoflurane has No Inhibitory Effect on Hypoxic Pulmonary Vasoconstriction (HPV) in Dogs

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There is no general agreement on the effect of inhalation anesthetics on hypoxic pulmonary vasoconstriction (HPV). We have examined the effect of sevoflurane upon the pulmonary vascular response to a left lower lobe (LLL) hypoxia in dogs by continuously measuring the fractional distribution to the LLL of total pulmonary blood flow (Q_{LLL}/Q_T) employing an ultrasonic transit time rheometer with flow probes attached to the LLL artery and the main pulmonary artery.

During regional hypoxia without sevoflurane, blood flow distribution to the LLL as a mean was 48.2% of that determined under hyperoxic conditions. When sevoflurane was administered at concentrations of 2% and 4%, the LLL blood flow distributions during hypoxia were as a mean 40.2% and 47.0%, respectively, of the values obtained during the first hyperoxic periods. No change occurred in the pulmonary vascular resistance of the LLL(PVR_{LLL}) and the shunt ratio(Qs/Qt) between the concentrations used.

Thus there was no significant effect of sevoflurane upon HPV whatever concentration used. (Key words: dog, hypoxic pulmonary vasoconstriction (HPV), pulmonary circulation, sevoflurane, ultrasonic doppler rheometer)

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Hypoxic pulmonary vasoconstriction (HPV) is a mechanism which counteracts arterial hypoxemia by diversion of pulmonary blood flow from poorly to more properly oxygenated areas of the lungs[1]. Although many reports have appeared in the last few years on the effect of inhalation anesthetics on HPV employing either isolated lungs[2–5] or lungs in situ[6,7], none of them have dealt with sevoflurane.

In a previous study in mongrel dogs, we rendered the left lower lobe (LLL) atelectatic and observed the pulmonary vascular resistance and shunt ratio while administering sevoflurane via the rest lung. We found no change caused by sevoflurane and assumed that at clinically assigned doses, sevoflurane would not influence HPV[8]. In the present study, we wanted to investigate, more in-depth, the effect of sevoflurane on HPV by measuring the percentage distribution of pulmonary blood flow to the left lower lobe using a pulse doppler rheometer.

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Materials and Methods

a) *Anesthesia and Operation*

Nine female mongrel dogs (7.6 ± 2.2 kg) were anesthetized with 30 $mg \cdot kg^{-1}$ of sodium pentobarbital (supplemented with 25–50 mg when blood pressure or heart rate increased) and 0.2 $mg \cdot kg^{-1}$ of pancuronium (supplemented with 0.5 mg when spontaneous respiration appeared). A tube

of 9.5 mm inner diameter was inserted into the trachea and the lungs were ventilated with 100% oxygen. A 20G plastic needle was put into the femoral artery to be used for sampling arterial blood and monitoring of arterial pressure. A 7 Fr Swan-Ganz catheter was inserted into the internal jugular vein and used for sampling mixed venous blood and pulmonary arterial pressure monitoring. A 18G central venous catheter was also inserted into the internal jugular vein (same side) for measurement of the right atrial pressure. Then, a leftsided thoracotomy was performed at the fourth intercostal space and the left auriue was cannulated through the left atriclm for measurement of the left atrial pressure. Pressures were recorded with a Hawlett Packard monitoring system (HP78342A Monitor with HP1290A quartz pressure transducer) by adjusting the reading at the mid-cardiac level to zero by in vitro calibration. Blood flow was determined by means of an ultrasonic transit time rheometer (Transonic T101, ADVANCE CO., LTD.), which was attached to the main pulmonary artery (mPA), and to the left lower lobe (LLL) artery employing flow probes of an internal diameter of 12 and 3 mm, respectively. Blood flow in the mPA was regarded as equal to the cardiac output (Q_T), and the blood flow distribution to the LLL was expressed as a fraction of cardiac output (Q_{LLL}/Q_T). A 14 Fr tube was inserted into the bronchus of the LLL and fixed there with the central end of the bronchus completely ligated. The residual lung (RL) was ventilated (Harvard NSH-34RH) with pure oxygen for the whole experimental period with 5 cmH_2O PEEP. The LLL was not ventilated with pure oxygen as was the residual lung. 2 $l \cdot min^{-1}$ flow (Igarashi precision membrane flow meter F-1) with 100% oxygen or anoxic mixed gas ($95\%N_2+5\%CO_2$) was applied to LLL under 5 cmH_2O CPAP with a water seal. A change in the gas composition of the LLL was preceded by 20 ventilations (tidal volume is about 200 ml) to provide a homogeneous gas mixing prior to each sequence. The LLL end-tidal concentration of sevoflurane was continuously measured. The RL end-tidal concentration of sevoflurane was intermittently measured. RL ventilation was started under conditions of 300 $ml \cdot kg^{-1} \cdot min^{-1}$, and was controlled later so that end-tidal CO_2(DATEX CD300 CO_2 ANALIZER) was kept between 35 mmHg and 45 mmHg.

Physiologic saline was continuously infused at a rate of 50–100 $ml \cdot hr^{-1}$. Sodium bicarbonate was infused i.v. to correct any metabolic acidosis. Blood temperature was monitored and maintained at 37 ± 2°C with the use of blankets and table lamps.

b) Experimental Protocol

Prior to the investigational period, LLL was exposed to three hypoxic challenges, each lasting 15 min interrupted by 15 min of 100% oxygen administration to achieve the maximum HPV.

After that, the effects on LLL hemodynamics of sevoflurane randomly administered at concentrations of 0, 2 or 4% were studied. Each experiment consisted of three sequences, a control period of LLL O_2 administration lasting one hour, a period of LLL anoxic mixed gas administration and a second period of LLL O_2 administration, each lasting 30 min. Sevoflurane was given throughout the entire period of the experiment. After each sequence, blood flow in the mPA and in the LLL artery were determined as well as heart rate, systemic blood pressure, pulmonary artery pressure, central venous pressure and left atrial pressure.

A sevoflurane vaporizer (ACOMA CO.) was used. The concentration of sevoflurane was measured with an inhalation anesthetic gas analyzer (RIKENEIKL RI-507M) calibrated by means of gas chromatography (SHIMAZU GC-9A). In order to minimize the possibility of fluctuations in the general circulatory condition, sevoflurane was given only to the LLL. Arterial and mixed venous oxygen and carbon-dioxide tensions, and pH, were measured with established techniques (ABL-2 analyzer, Radiometer Co). Hemoglobin concentration and oxygen saturation of blood were measured by spectrophotometry (OSM-2, Radiometer Co).

The electrodes were calibrated with known gases and buffer solutions before each determination. The shunt ratio was calculated by Hill's equation[9].

To confirm the reproducibility of the results, three sequences in the 4th experiment were performed in 6 of the 9 dogs. Sevoflurane was administered in the same concentration as in the first experiment.

c) Statistics and Calculations

Analysis of variance (ANOVA) was employed in a statistical comparison between the concentration of sevoflurane, while paired t-test was used in statistical comparison between each phase, and between the first and fourth administrations at the same concentration; the differences being labeled as significant at $P < 0.05$ invariably.

Results

No significant difference was observed in pH, Pa_{CO_2}, Q_T, heart rate, mean arterial pressure, right atrial pressure, left atrial pressure, systemic vascular resistance, or pulmonary vascular resistance of the residual lung; between each of the 1st O_2-administration phase, anoxic gas administration phase, and the 2nd O_2-administration phase, or between each concentration of sevoflurane (table 1).

a) Effects of Sevoflurane on Pulmonary Circulation

Changes in Q_{LLL}/Q_T, PVR_{LLL} and the mean pulmonary artery pressure (PAP) are shown in table 2 and figure 1–3.

No significant difference was observed between 0, 2 and 4% sevoflurane.

b) Effects of Sevoflurane on Pulmonary Gas Exchange

Changes in Pa_{O_2}, Pv_{O_2} and Qs/Qt are shown in table 2.

c) LLL and RL End-Tidal Concentration of Sevoflurane

When the vaporizer was set to give a sevoflurane concentration of 2%, LLL end-tidal values from 1.89 ± 0.21% (maximum %, Mean ± SD) to 1.81 ± 0.16% (minimum %, Mean ± SD) were noted on cessation of the initial ventilation period. The concentration at the end of each sequence or 30 min later was from 1.84 ± 0.15% to 1.62 ± 0.17%. When the vaporizer was set at a sevoflurane concentration of 4%, LLL end-tidal values from 4.65 ± 0.36% to 4.39 ± 0.41% were noted. The concentration at the end of each sequence or 30 min later was from 4.45 ± 0.31% to 3.94 ± 0.36%. The concentration of sevoflurane supplied into the LLL 30 min after 20 ventilations was 95.0 ± 16.3(%) at maximum and 88.4 ± 16.4% at minimum of the given concentration.

RL end-tidal sevoflurane was not detected throughout the experiment.

d) Comparison Between 1st Sevoflurane Concentration Trial and 4th Sevoflurane Concentration Trial

No difference was observed between the first and fourth experiment of sevoflurane administration at the same concentration with respect to changes in respiratory or circulatory condition caused by the hypoxic challenge.

Discussion

It is of interest that LLL perfusion decreased and LLL pulmonary vascular resistance (PVR_{LLL}) increased during exposure of the LLL to the anoxic gas mixture. Furthermore, since no significant difference was observed in these changes between concentrations of administered sevoflurane (0%, 2%, and 4%), it is considered that administration of sevoflurane does not influence these changes in the experiments.

In according to previous animal studies, a fundamental property of inhalational anesthetics is to decrease HPV. However, in intact animal preparations some biologic or physiologic property seems to remove or greatly lessen the inhibitory effect of anesthetic drugs on HPV. Sykes et al.[10] reported the pulmonary vasoconstrictor response to alveolar hypoxia was preserved during the administration of halothane to in vivo-intact dogs. Saidman et al.[11] reported isoflurane did not inhibit hypoxic pulmonary vasoconstriction in vivo-intact dogs. Hypoxic pulmonary vasoconstriction during the administration of other inhalational anesthetics was

Table 1. No changed paremeters by

	Sevoflurane 0%		
	C1 phase	H phase	C2 phase
pH	7.268±0.056	7.267±0.057	7.256±0.063
Pa_{CO_2} (mmHg)	38.5±4.2	37.7±4.0	38.7±4.7
Q_T ($l \cdot min^{-1}$)	0.71±0.37	0.70±0.34	0.71±0.37
HR ($beats \cdot min^{-1}$)	166±28	166±28	162±30
MAP (mmHg)	91±18	91±19	91±20
LAP (mmHg)	7±3	6±3	7±3
RAP (mmHg)	6±4	6±4	6±4
SVR ($dyne \cdot cm \cdot sec^{-5}$)	11817±4672	11338±4112	11264±3970
PVR_{RL} ($dyne \cdot cm \cdot sec^{-5}$)	1963±979	1939±853	1904±853

Abbreviations: Q_T = cardiac output, blood flow of main pulmonary artery; HR = heart rate; MAP = mean arterial pressure; LAP = left atrial pressure; RAP = right atrial pressure; SVR

Table 2. Changed parameters by

	Sevoflurane 0%		
	C1 phase	H phase	C2 phase
Pa_{O_2} (mmHg)	470.3±31.1	317.3±96.9**	466.4±37.2***
Pv_{O_2} (mmHg)	65.4±8.8	58.6±11.2**	65.2±9.9
Qs/Qt (%)	12.9±1.8	19.3±5.6**	13.0±3.4***
Q_{LLL}/Q_T (%)	16.6±4.9	8.6±5.6**	17.0±5.3***
PAP (mmHg)	18.4±4.2	19.4±4.5	18.5±4.5***
PVR_{LLL} ($dyne \cdot cm \cdot sec^{-5}$)	9852±4212	28748±19617**	9445±4181***

Abbreviations: Qs/Qt=shunt ratio; Q_{LLL}/Q_T=blood flow of left lower lobe as per cent of total lung flow; PVR_{LLL}=pulmonary vascular resistance of left lower lobe.

not studied with the same model, so sevoflurane and other inhalational anesthetics were not compared. However, the effect of sevoflurane on HPV may be subtle and it has a number of desirable properties which permit a high concentration of oxygen during anesthesia and a rapid emergence from anesthesia, so the inhalational anesthetic is a useful for the thoracic surgery which requires one-lung ventilation.

In our experiment we repeated, intermittently, hypoxic challenges to the LLL. Chen et al.[12] concluded that in the absence of surgical trauma the initial response to hypoxia was maximal and was not potentiated by repeated hypoxic stimulation. On the contrary, Unger et al.[13] and Marshall[14] reported that potentiation by repeated challenge seemed to be more pronounced, to some extent, the more extensive the surgical preparation of the lungs had been. So hypoxic challenges for the LLL were needed.

In the present study, the LLL was not ventilated and was kept under CPAP. However, the LLL end-tidal sevoflurane concentration was insignificantly changed through

hypoxic gas challenge in blood gas analysis and hemodynamic dates

Sevoflurane 2%			Sevoflurane 4%		
C1 phase	H phase	C2 phase	C1 phase	H phase	C2 phase
7.264±0.057	7.270±0.050	7.264±0.061	7.272±0.053	7.266±0.055	7.247±0.041
41.4±2.9	40.3±3.0	40.4±4.8	37.3±3.2#	36.5±3.3	38.6±3.1
0.62±0.18	0.61±0.19	0.60±0.22	0.58±0.21	0.58±0.25	0.56±0.25
159±17	161±17	158±17	159±22	161±23	158±20
96±23	96±27	94±24	87±21	85±23	82±19
7±2	7±2	7±2	7±3	7±3	8±3
6±4	6±3	6±3	5±4	5±4	6±4
12133±4051	12970±5737	13214±6209	12507±5335	12535±6095	12401±5035
1734±730	1882±861	1974±975	1988±1105	2027±1147	2288±1418

= systemic vascular resistance; PVR_{RL} = pulmonary vascular resistance of residual lung. Values are mean ± SD.

# $P < 0.05$ significant difference between 2% and 4%

hypoxic gas challenge in blood gas analysis and hemodynamic dates

Sevoflurane 2%			Sevoflurane 4%		
C1 phase	H phase	C2 phase	C1 phase	H phase	C2 phase
477.3±32.3	362.3±85.3**	451.3±26.8***	471.2±33.5	346.3±65.6**	466.0±34.4***
65.1±13.3	58.5±5.9	62.0±7.8***	65.8±10.9	62.7±10.4**	67.4±12.1***
11.6±1.4	17.2±5.8**	13.0±3.3***	13.4±3.7	20.4±7.2**	13.8±3.9***
15.7±3.6	6.7±4.6**	16.7±4.9***	20.1±6.5	10.0±6.5**	21.3±6.8***
17.5±4.4*	19.0±4.5**	18.0±4.6***	17.0±3.8*	18.5±3.8**	18.0±3.8
9265±3228	42780±33787**	9900±4208***	7690±2855	25031±16322**	8179±3889***

Values are mean ± SD.

*$P < 0.05$ significance between C1 and C2, **$P < 0.05$ significance between C1 and H, ***$P < 0.05$ significance between H and C2

each experiment.

One problem for no ventilation is the different end-tidal P_{CO_2}-values in two separated parts of the lung or the difference in ventilation mechanics. In other words, LLL P_{CO_2} will be higher than RL P_{CO_2} because the mixed venous/alveolar P_{CO_2} gradient will be less in LLL than in RL. Regional PVR will increase with an increase in end-tidal P_{CO_2} and that may increase the response of HPV. But this will not make it impossible to compare HPV responses among different sevoflurane concentrations.

In terms of circulatory stability, it was desirable that the cardiac output was measured directly by attaching the probes to the main pulmonary artery instead of using the thermodilution method with a Swan-Ganz catheter.

An electromagnetic flowmeter has often been used for the measurement of blood flow. However, there have been problems in preparation for experiments with this device; a flow probe must be chosen precisely depending on the diameter of blood vessels to be examined, and measurement values

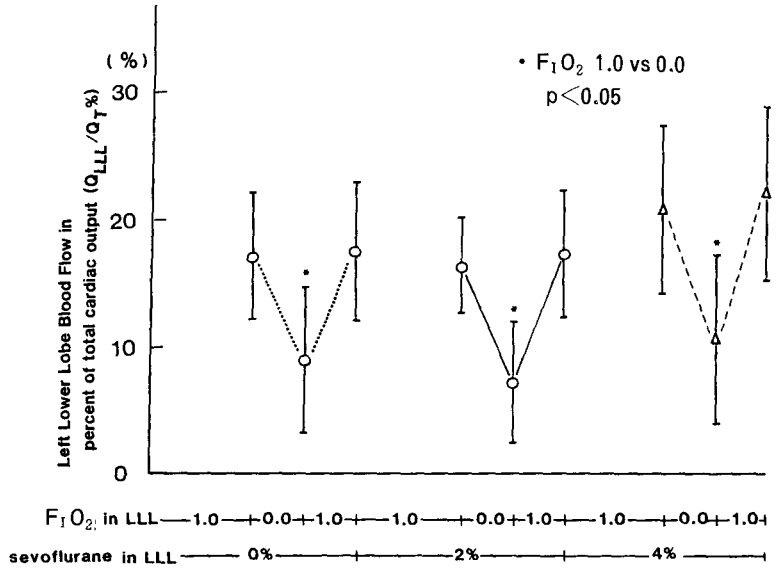

Fig. 1. LLL blood flow in percent of total cardiac output (Q_{LLL}/Q_T%).

This Q_{LLL}/Q_T significantly changed in period of anoxic gas administration (FI_{O_2} = 0.0) and returned to the values of the 1st O_2-administration phase (FI_{O_2} = 1.0) in the 2nd O_2-administration phase (FI_{O_2} = 1.0). No significant difference was observed between concentrations of sevoflurane.

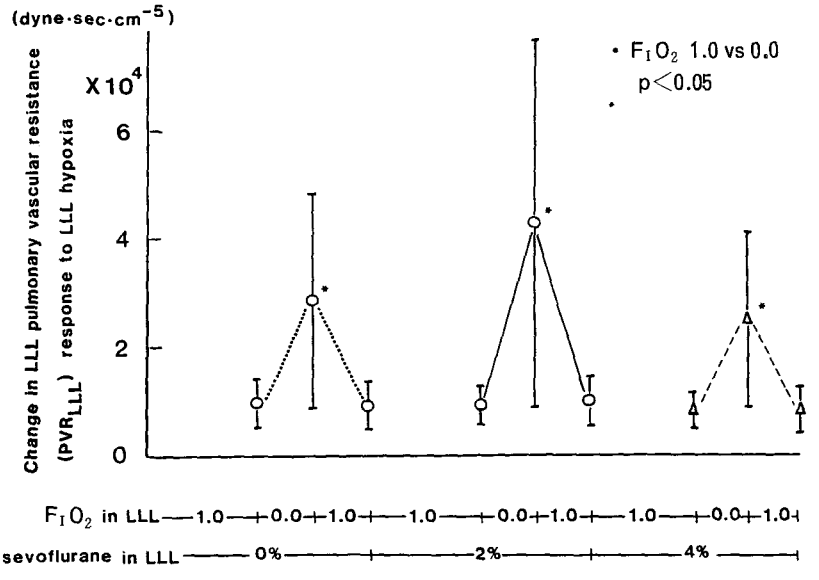

Fig. 2. Change in LLL pulmonary vascular resistance (PVR_{LLL}) response to LLL hypoxia.

PVR_{LLL} significantly changed in period of anoxic gas administration (FI_{O_2} = 0.0) and returned to the values of the 1st O_2-administration phase (FI_{O_2} = 1.0) in the 2nd O_2-administration phase (FI_{O_2} = 1.0). No significant difference was observed between concentrations of sevoflurane.

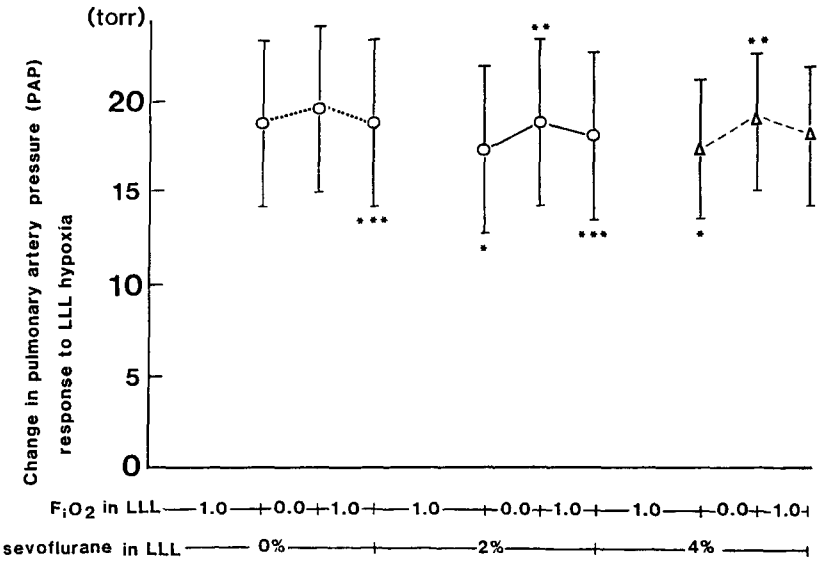

Fig. 3. Change in pulmonary artery pressure (PAP) response to LLL hypoxia.

The mean pulmonary artery pressure increased significantly in the period of anoxic gas administration ($FI_{O_2} = 0.0$) (**$P < 0.05$) at the concentration of 2% and 4% but not without sevoflurane. In experiments the pressures were significantly lower in the period of the 2nd O_2-administration ($FI_{O_2} = 1.0$) than in the period of anoxic gas administration ($FI_{O_2} = 0.0$) (***$P < 0.05$) without sevoflurane and at the concentrations of 2%, while during the period of the 2nd O_2-administration ($FI_{O_2} = 1.0$) the pressures remained higher than during the 1st O_2-administration ($FI_{O_2} = 1.0$) (*$P < 0.05$) at the concentration of 2% and 4%.

could vary depending on the extent to which the vessel is detached from connective tissue surrounding it. Therefore, we used an ultrasonic transit time rheometer for blood flow measurement in this experiment.

This type of rheometer enabled us to measure the flow rate directly regardless of the diameter of blood vessel. And it is important whether the measurement is based upon a continuous and stable determination of the transsectional area of the vessels. The flow probe has advantages in that it can correct aberrations in attachment angles by 2 return-samplings and that an adoption of free bracket has resolved the problem of deviation caused by pressure.

In conclusion, we have found that a local administration of sevoflurane has no inhibitory effect on HPV at the clinically assigned dose on the assumption that inhibition of HPV is dependent on the concentration of inhalation anesthetic in alveoli. Taking the results of our previous study on HPV in atelectasis into consideration, we believe that sevoflurane can be used safely even in cases in which HPV plays an important part, such as a lung operation.

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