Hypoxic Ventilatory Response in Cats Lightly Anesthetized with Ketamine: Effects of Halothane and Sevoflurane in Low Concentrations

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The effect of low concentration sevoflurane and halothane on the ventilatory response to isocapnic hypoxia was studied in sixteen cats. The cats were divided into two groups, sevoflurane group and halothane group, of eight subjects each. As parameters of the hypoxic ventilatory response, A value [the slope of the hyperbolic curve, $\dot{V}_E = \dot{V}_0 + A/(Pa_{O_2}-32)$] and ratio of $\dot{V}_{50}$ (the minute volume obtained from the hyperbolic equation when $Pa_{O_2} = 50$ mmHg) to $\dot{V}_0$ were studied. These two parameters were examined at three states, sedative state with ketamine as the control, ketamine plus 0.1 MAC inhalation anesthetic, and ketamine plus 0.5 MAC inhalation anesthetic.

In the sevoflurane group, the A values were 4789 ± 1518, 2187 ± 1214, 1730 ± 880 (mean ± SE. ml·min^{-1}·mmHg) at the control state, 0.1 MAC and 0.5 MAC, respectively. In the halothane group, the A values were 6411 ± 2368, 2529 ± 842 and 2372 ± 545, respectively. The ratios of $\dot{V}_{50}$ to $\dot{V}_0$ were 1.32 ± 0.09, 1.22 ± 0.09, 1.25 ± 0.08 in the sevoflurane group, 1.47 ± 0.18, 1.32 ± 0.11, 1.54 ± 0.18 in the halothane group, respectively. The A value at 0.1 MAC of the halothane group was less than the control value significantly. This proved that even low concentration halothane depressed the hypoxic ventilatory responses. The depression of hypoxic ventilatory response could cause postanesthetic hypoventilation. On the other hand, we could not find significant depression on the hypoxic ventilatory response in the sevoflurane group, but we should notice that variances of the hypoxic ventilatory response were large. (Key words: hypoxic ventilatory response, sevoflurane, halothane)

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For inhalation anesthetics, depressive effects on hypoxic ventilatory response at anesthetic concentrations are fairly important. However, at subanesthetic concentrations the depressive effects are much more important because in these conditions patients are usually extubated and do not receive respiratory supports. When an inhalation anesthetic used strongly depresses the hypoxic ventilatory drive at low concentrations, the patient could develop postanesthetic hypoxemia and hypercapnia at recovery rooms or wards. Knill et al. reported that a subanesthetic concentration of halothane, which had no impact on the ventilatory response to carbon dioxide, reduced the reactions to hypoxemia[1]. However, the effects of sevoflurane on the hypoxic ventilatory responses

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Table 1. Characteristics of the groups

	Sevoflurane	Halothane
Number of subjects	8	8
Sex (female/male)	4/4	3/5
Weight (kg)	3.01 ± 0.66	3.14 ± 0.99

mean ± SD.

have not been studied. Thus we studied the effect of sevoflurane and halothane on the hypoxic ventilatory response in cats, using low concentrations (0.1 MAC and 0.5 MAC) of each agent.

Methods

Sixteen mongrel cats were divided into two groups of eight subjects each. One group was anesthetized with sevoflurane and the other with halothane. There were no significant differences in weight and sex between two groups (table 1). Ketamine was administered intramuscularly of 30 $mg \cdot kg^{-1}$. The trachea was intubated with a 5.0 mm ID cuffed endotracheal tube without using any muscle relaxant. Just after cannulation into the femoral vein, ketamine was infused continuously at a rate of 0.2 $mg \cdot kg^{-1} \cdot hr^{-1}$ to maintain constant plasma ketamine concentration. The endotracheal tube was attached to a non-rebreathing Rudolph valve (Collins Co., Ltd.) (fig. 1). The study was performed under condition of spontaneous breathing in supine position and no less than 90 min following an intramuscular injection of ketamine. Arterial blood pressure, heart rate, esophageal temperature and end-tidal carbon dioxide tension were monitored throughout the study. The arterial blood pressure was measured through a catheter cannulated into the femoral artery. The esophageal temperature was controlled at 37.5–38.5°C using infrared heat lamps.

The cats breathed an oxygen enriched gas mixture to which nitrogen was stepwise added such that the Pa_{O_2} was gradually lowered to approximately 40 mmHg and carbon dioxide was added to control arterial carbon dioxide partial pressure at 50 mmHg. Samples for monitoring blood gases were obtained from the femoral artery catheter. Expired gas volume was measured using a bellows-driven potentiometer[2] (Anima, Japan). Measurements were made following no less than 3 min after a change in inspired oxygen concentration[3]. The data were analyzed by the method of least-square regression, using equation 1 (fig. 2).

$$\dot{V}_E = \dot{V}_0 + A/(Pa_{O_2}-32) \quad \text{equation 1}$$

$\dot{V}_E$: minute volume

$\dot{V}_O$: asymptote for ventilation obtained by extrapolation

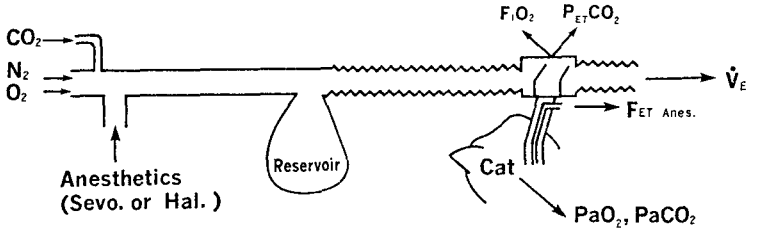

Fig. 1. Outline of method used to induce isocapnic hypoxia.
Nitrogen and CO_2 are added to inspired gas. Pa_{CO_2} is controlled at 50 mmHg. The end-tidal anesthetic concentration is measured by a gas chromatograph.
Sevo. sevoflurane
Hal. halothane
$F_{I_{O_2}}$ fraction of inspiratory O_2
$P_{ET_{CO_2}}$ pressure of end-tidal CO_2
$F_{ETAnes.}$ fraction of end-tidal anesthetics
$\dot{V}_E$ minute volume

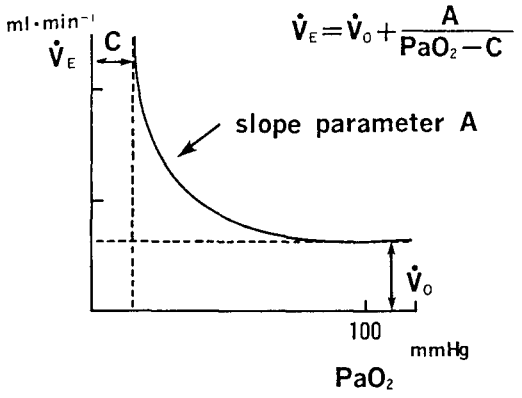

Fig. 2. The curve resulting from a least squares fit to the equation 1. The parameter $\dot{V}_0$ is the value for ventilation extrapolated to an infinitely great Pa_{O_2}while the parameter A describes curve shape. We adopted the method which fixed the C value (32 mmHg).

A: coefficient for the hyperbolic equation

Pa_{O_2}: arterial oxygen partial pressure

Measurements were made at three states, the sedative state with ketamine as the control and following addition of each volatile agent of 0.1 MAC and 0.5 MAC (at random). The end-tidal anesthetic concentration was measured by a gas chromatograph (GC-9A, Shimadzu Co., Ltd., Japan). The A value and the ratio of $\dot{V}_{50}$ (the minute volume obtained from the hyperbolic equation when Pa_{O_2} = 50 mmHg) to $\dot{V}_0$ were compared with the control values and each other by Wilcoxon t-test. The level of statistical significance used was 0.05 throughout.

Results

The results of the studies of the ventilatory response to hypoxia as measured by the shape parameter A are presented in table 2. Only the value in 0.1 MAC of the halothane group was less than the control significantly. The ratios of $\dot{V}_{50}$ to $\dot{V}_0$ are presented in table 3. There were no significant differences compared with each other in both the groups. The arterial pressures and the heart rates under hyperoxic conditions are presented in table 4. Compared to the control, significant decreases in the arterial systolic pressure were observed at 0.1 MAC, 0.5 MAC in the halothane group and at 0.5 MAC in the sevoflurane group, respectively. Similar trends were also noted in the arterial diastolic pressure. On the other hand, no marked change was observed in the heart rate, except the decrease from 185 ± 23 at 0.1 MAC to 168 ± 20 beats·min^{-1} at 0.5 MAC in the sevoflurane group.

Table 2. Hypoxic ventilatory response (A)

	Sevoflurane	Halothane
Control	4789 ± 1518	6411 ± 2368
0.1 MAC	2187 ± 1214	2529 ± 842*
0.5 MAC	1730 ± 880	2372 ± 545

Values represent mean ± SE. (ml·min^{-1}·mmHg)
*$P < 0.05$ vs Control

Table 3. $\dot{V}_{50}/\dot{V}_0$

	Sevoflurane	Halothane
Control	1.32 ± 0.09	1.47 ± 0.18
0.1 MAC	1.22 ± 0.09	1.32 ± 0.11
0.5 MAC	1.25 ± 0.08	1.54 ± 0.18

Values represent mean ± SE.
Intergroup differences are not significant.

Discussion

There are some problems when we discuss the results of the studies.

First, ketamine was injected throughout the study. Therefore, the control state was not awake one. Ketamine has been reported not to further depress canine ventilation in the presence of hypoxia[4]. Hongo et al. have reported that satisfactory anesthesia of cats was obtained from an intravenous dose of 8–10 mg·kg^{-1} and an intramuscular dose of 25–30 mg·kg^{-1} [5]. And they presented duration of anesthesia ranged from 13′56″ to 25′49″ by intravenous injection and from 49′30″ to 86′05″ by intramuscular injection. In our study, ketamine was administered intramusculary of 30 mg·kg^{-1} and infused continuously at a rate of 0.2 mg·kg^{-1}·hr^{-1}. Measurements were made following no less than 90 min after an intramuscular injection.

Table 4. Arterial pressure and heart rate

		Sevoflurane	Halothane
Arterial systolic pressure (mmHg)	Control	150.3 ± 16.3	150.9 ± 20.4
	0.1 MAC	139.6 ± 22.8	137.3 ± 26.8*
	0.5 MAC	123.9 ± 29.7*§	117.8 ± 32.2*
Arterial diastolic pressure (mmHg)	Control	102.3 ± 14.7	105.1 ± 9.2
	0.1 MAC	89.0 ± 24.8	91.8 ± 18.4*
	0.5 MAC	81.5 ± 27.9*	75.5 ± 26.0*
Heart rate (bpm)	Control	180.5 ± 33.6	205.5 ± 21.2
	0.1 MAC	184.6 ± 22.8	198.6 ± 25.8
	0.5 MAC	167.6 ± 19.6§	188.8 ± 28.3

Values represent mean ± SD.
* $P < 0.05$ vs Control, § $P < 0.05$ vs 0.1 MAC

The sedative state with ketamine seemed light. However, ketamine and the inhalation anesthetics might interact each other.

Second, the arterial carbon dioxide tension was controlled fairly high. In study of the ventilatory response to isocapnic hypoxia, arterial carbon dioxide tension should be kept unchanged. We chose 50 mmHg in this study. Because the ventilation was spontaneous throughout the study period and was depressed especially with 0.5 MAC by the interactions of ketamine and the inhalation anesthetics, 50 mmHg was minimal to be settled. Considering that most of patients in recovery rooms present respiratory depressions and remain hypercapnic, 50 mmHg is appropriate to simulate the postanesthetic state.

Concerning the method of analysis, some investigators have regarded the hypoxic ventilatory response curve as variant functions, for example, a logarithmic function[6]. However, it is most commonly accepted to approximate it to the hyperbola advocated by Lloyd et al.[7]. And Weil[8] has presented the expression as follows:

$\dot{V}_E = \dot{V}_0 + A/(P_{A_{O_2}} - C)$

$\dot{V}_E$: minute volume

$\dot{V}_0$: asymptote for ventilation obtained by extrapolation

A: coefficient for the hyperbolic equation

$P_{A_{O_2}}$: alveolar oxygen partial pressure

Weil fixed the C value (32 mmHg). But there were some arguments to the effect that the C value fixed at 32 had no physiological foundation. Some reports requested the C value in every test as a variable number. Nishimura reported that the method which fixed the C value proved to be more reliable[9]. Therefore we adopted the fixed method. Concerning A, coefficient for the hyperbolic equation, Hirshman et al.[4] have compared the A values evaluated by fitting the $\dot{V}_E$-Pa_{O_2} data points to the equation, $\dot{V}_E = \dot{V}_0 + A/(Pa_{O_2} - C)$, with those obtained by end-tidal p_{O_2} sampling by the paired t-test. They reported that no significant difference was found. Thus we used equation 1 instead of Weil's equation.

We evaluated the ventilatory response using minute volume. However, it is doubtful if minute volume was the best parameter or not. It is necessary to study the ventilation from all viewpoints, $P_{0.1}$[10], integrated phrenic nerve activity[11], for example.

It had been suspected that inhalation anesthetics would depress the hypoxic ventilatory response in dose-dependent manner. However, the A value at 0.5 MAC was not significantly different from the control either in the groups respectively. The inhalation anesthetics of 0.5 MAC proved rather strong depressants on respiration than we had expected especially under the hyperoxic condition. Therefore, the A value was calculated higher.

Because tidal volume in cats was small, it was difficult to obtain accurate end-tidal anesthetic concentration and end-tidal oxygen partial pressure for the isocapnic progressive hypoxic method. We, therefore, adopted the steady state method. In the steady state method, however, there were demerits. Since measurements were troublesome, we could not get many points especially at 0.5 MAC and the accuracy of the A values could decreased.

At 0.1 MAC, the results from two groups were different. The A value at 0.1 MAC halothane was less than the control value significantly. This proved that even low concentration halothane depressed the hypoxic ventilatory response. On one hand, in the sevoflurane group, the A value at 0.1 MAC was not significantly different from the control value. But variances of the A value were large. We need to augment the number of subjects and add detailed investigation whether sevoflurane causes less suppression than halothane or not. And we have to examine the way how ventilatory patterns change quantitatively, for example, study thoraco-abdominal motion using a respiratory inductive plethysmograph[12]. In addition, it is necessary to reconsider the mechanism of hypoxic ventilatory response. Hypoxia causes to stimulate ventilation through activation of the peripheral chemoreceptor, on one hand, depresses the center[13]. Therefore, the parameter of hypoxic ventilatory response contains both the factors. The peripheral chemoreceptor denervation may be useful to separate the central suppression from the peripheral stimulation.

In conclusion, we observed that the A value was less in the halothane group with 0.1 MAC compared with that in the control group. This indicated that hypoxic ventilatory response could be depressed during inhalation of halothane of subanesthetic concentration and reserved an attention that postanesthetic hypoventilation would be continued for a considerably long period. On the other hand, no significant difference was noted in the A value between the sevoflurane group and the control.

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