Effects of Sevoflurane on Autonomic Nerve Activities Controlling Cardiovascular Functions in Rats

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Effects of different inspiratory concentrations of sevoflurane (fluorometyl-1,1,1,3,3,3,-hexafluoro-2-propylether) on blood pressure, heart rate and efferent activities of cardiac sympathetic, cardiac parasympathetic and renal sympathetic nerves were examined using rats either under the resting condition or during noxious mechanical stimulation of a hindpaw. Under the resting condition, an increase in the inspiratory concentration of sevoflurane from 2.1% to 4.2% gradually caused a decrease in blood pressure and heart rate. With the increase in the sevoflurane concentration, cardiac sympathetic nerve activity decreased, whereas renal sympathetic nerve and cardiac parasympathetic nerve activities did not change significantly. When noxious mechanical stimulation was applied to a hindpaw by pinching, blood pressure and heart rate, renal sympathetic and cardiac sympathetic nerve activities all increased at the 2.1% concentration of sevoflurane. The responses of these parameters were attenuated at the 3.1% concentration of sevoflurane and almost disappeared at the 4.2% concentration. Cardiac parasympathetic nerve activity did not change significantly during the pinching stimulation throughout the 2.1–4.2% concentration increase. (Key words: sevoflurane; cardiac sympathetic and parasympathetic nerve; renal sympathetic nerve; blood pressure; heart rate; noxious somatic stimulation)

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Sevoflurane (fluoromethyl-1,1,1,3,3,3,-he-

Sevoflurane (fluoromethyl-1,1,1,3,3,3,-hexafluoro-2-propylether, $(CF_3)_2CHOCH_2F$), a recently developed anesthetic, has characteristically rapid anesthetic induction as well as rapid recovery due to its low blood-gas partition coefficient of 0.6[1]. It has also been reported that sevoflurane depresses blood pressure[2–4], cardiac output[4] and the cardiac index[3] dose-dependently, although sevoflurane has shown no significant effect on the heart rate in humans[2], dogs[3] and pigs[4]. Sevoflurane has already been reported to be a general depressant for these cardiovascular parameters at the level of the effector organs, however, there have been no reports as to whether it depresses the autonomic nerve activity involved in these cardiovascular parameters.

Therefore, the first purpose of the present experiments was to examine the effects of various concentrations of sevoflurane on autonomic neural mechanisms involved in car-

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diovascular functions under resting conditions. For this purpose, cardiac sympathetic and parasympathetic efferent nerve activities were recorded as indicators for autonomic neural regulations of the cardiac function while renal sympathetic efferent nerve activity was recorded as an indicator for autonomic neural regulation of vascular function. The effects of various concentrations of sevoflurane on heart rate and systemic blood pressure were examined under two different conditions: with or without administration of a muscle relaxant, gallamine, because administration of a muscle relaxant was necessary for recordings of autonomic nerve activity.

The second purpose of the present experiments was to examine autonomic neural mechanisms of cardiovascular reflex responses to noxious mechanical stimulation (pinching) of a hindpaw at various concentrations of sevoflurane. The mechanisms were analyzed by monitoring systemic blood pressure, heart rate and efferent activities of cardiac sympathetic, cardiac parasympathetic and renal sympathetic nerves.

Materials and Methods

The experiments were performed on 30 Wistar rats. The animals were first anesthetized by placing them in a box ($12 \times 22 \times 15$ cm^3) filled with 4.2% sevoflurane (Maruishi Pharmaceutical Co.) in oxygen gas. Tracheotomies were then performed for the insertion of a tracheal cannula for the maintenance of artificial ventilation using a respirator (Model 680, Harvard Apparatus Co.). End-tidal CO_2 was adjusted to $5.0 \pm 0.5\%$ by changing the stroke volume and frequency of the respirator using a gas monitor (Respina 1H26; Nippondenki San-ei Co.). A venous catheter was inserted into the right jugular vein through which 5% glucose in Ringer's solution was continuously infused at a rate of 1–2 ml/h. Rectal temperature was maintained at 37.0–38.0°C by means of a heating pad and an infrared lamp. When a muscle relaxant was necessary, gallamine triethiodide (10–20 mg/kg, Sigma) was administered intravenously.

Systemic arterial blood pressure was monitored through a catheter in the right carotid artery by a pressure transducer (TP-200T, Nihon Kohden). The heart rate was continuously recorded using a tachometer (AT-601G, Nihon Kohden) from pulse waves of systemic arterial blood pressure.

In order to record ongoing (or spontaneous) efferent nerve activities from cardiac sympathetic, cardiac parasympathetic or renal sympathetic nerves, the animals were placed in a spine position. For dissection of a cardiac sympathetic nerve branch on the right side, the second costal bone on the right hand side of the chest was partially removed taking care not to damage the underlying pleural membranes. About one-cm length of a cardiac postganglionic sympathetic nerve emerging from the right stellate ganglion was dissected from its surrounding tissues and severed near the heart. In this case, bilateral vagi were severed at the cervical level to eliminate the possibility of any input of their activity during the recording of cardiac sympathetic nerve activity. In order to record cardiac parasympathetic nerve activity, a cardiac parasympathetic nerve emerging from the right vagal main trunk was dissected from the surrounding tissues in a manner similar to that described above, and severed just before its entrance to the heart. A right stellate ganglion was crushed by the forceps to eliminate any possibility of sympathetic nerve activity during recording of cardiac parasympathetic nerve activity. A renal nerve branch was dissected after the mid-section of the abdomen and severed just before reaching the kidney.

Ongoing activities of these autonomic efferent nerves were recorded from the central severed section of these nerves through bipolar platinum iridium wire electrodes. The electrical activities of these nerves were first amplified (S-0476, Nihon Kohden), by setting the time constant at 0.01 s, and then counted every 5 s using a data processor (ATAC 450, Nihon-Kohden). Recordings from each of these three different autonomic nerves were obtained from different animals.

Three different concentrations of sevoflurane were employed in the present experi-

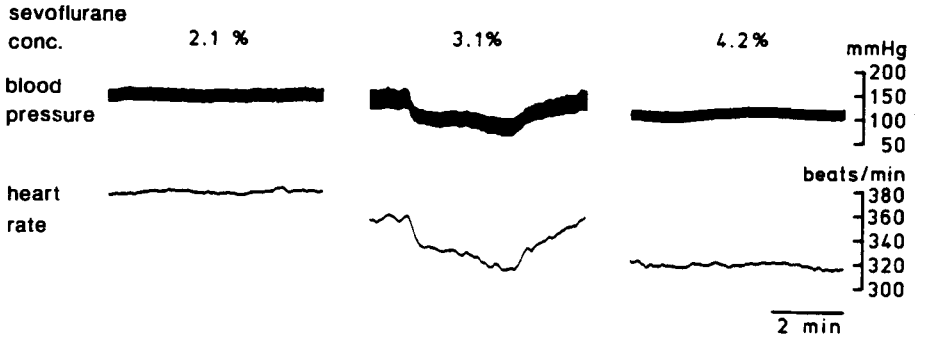

Fig. 1. Recordings of blood pressure (upper trace) and heart rate (lower trace) at different inspiratory concentrations of sevoflurane: 2.1% (left), 3.1% (middle) and 4.2% (right) in the same rat.

ments. In order to discuss the concentrations of sevoflurane, the minimum alveolar concentration (MAC) was used for the expression of the depth of sevoflurane. One MAC of sevoflurane in rats has been reported to be 2.0–2.2%[5]. In the present experiments, we used 3 different concentrations of sevoflurane: 2.1% (1MAC), 3.1% (1.5 MAC), and 4.2% (2MAC). The anesthetic was administered via a vaporizer (Maruishi Pharmaceutical Co.). A 30-minute delay between the two different concentrations of sevoflurane administrations was used in order to obtain stable cardiovascular conditions at each level. Once stability was reached, we measured the above-mentioned parameters: blood pressure, heart rate and efferent activities of renal sympathetic, cardiac sympathetic and cardiac parasympathetic nerves. After obtaining the data for these parameters under resting conditions without stimulation, we applied a noxious mechanical stimulation to the animal's hindpaw by pinching using a surgical clamp (3–5 kg force, 1 cm^2 area) and recorded the reflex responses of these parameters elicited by the pinching stimulation. We examined the reflex responses at 3 different concentrations of sevoflurane (2.1%, 3.1% and 4.1%).

All results were expressed as the mean ± S.E.

Results

1. *Cardiovascular functions under resting conditions*

(a) Blood pressure and heart rate

The effect of sevoflurane on systemic arterial blood pressure and heart rates was examined in artificially ventilated rats in which the muscle relaxant, gallamine, had not been administered. Figure 1 demonstrates that the systemic arterial blood pressure and heart rate gradually decrease with increases in the concentration of sevoflurane from 2.1% to 3.1% and, to 4.2% in the same rat. Both parameters, blood pressure and heart rate, were usually stable at the 2.1 and 4.2% concentrations of sevoflurane, but they sometimes fluctuated at 3.1%, as demonstrated in figure 1. These fluctuations were observed in 3 out of 6 rats tested. Figure 2 summarizes systolic, mean and diastolic blood pressures (in A) and heart rate (in B) at the 3 different concentrations (2.1, 3.1 and 4.2%) of sevoflurane in 6 rats tested. When these parameters fluctuated at the 3.1% concentration, mid-values of the fluctuation were employed. All these parameters showed a tendency to decrease in a dose-dependent manner. Blood pressure (systolic, mean and diastolic) at the 4.2% concentration was significantly lower than that at 2.1% and 3.1%. Heart rate was significantly decreased dose-dependently between 2.1% and 4.2%.

The effects of sevoflurane on blood pressure and heart rate were also examined in immobilized animals (n=6) using a muscle relaxant, gallamine. Administration of a muscle relaxant is necessary when obtaining recordings of autonomic nerve activity.

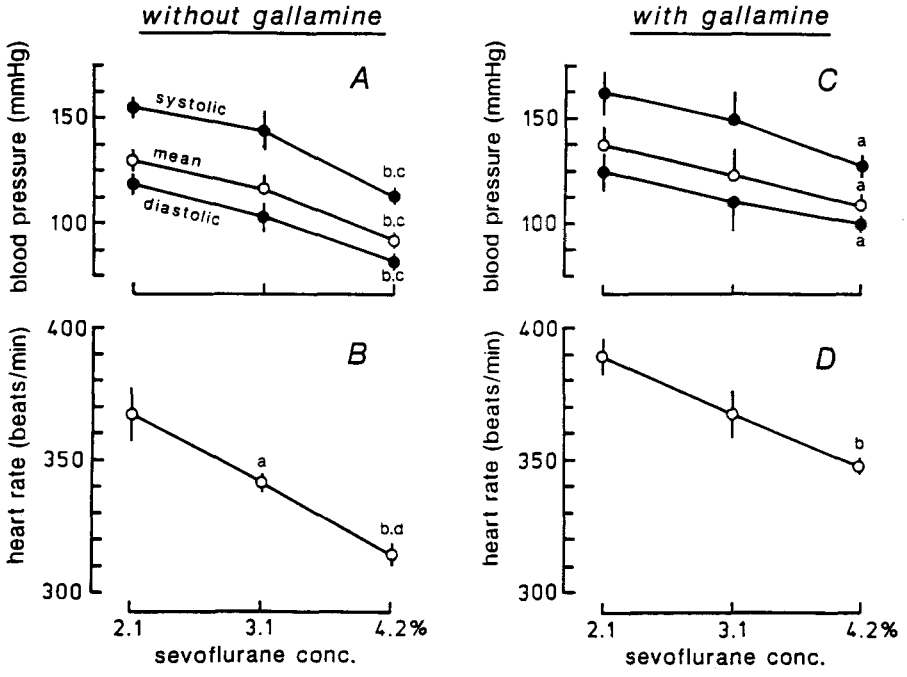

Fig. 2. Effect of different inspiratory concentrations of sevoflurane (2.1, 3.1 and 4.2%) on blood pressure (A and C), and heart rate (B and D). A and B: without gallamine, in 6 animals. C and D: with gallamine, in 6 animals. In A and C, systolic, mean and diastolic blood pressures were plotted. In B and D, heart rates are plotted. Circles and vertical bars show the mean ± S.E. Significance was determined by comparison with the values of 2.1% (a,b) and 3.1% (c,d) using the paired t-test. a,c: $P < 0.05$, b,d: $P < 0.01$.

As shown in figures 2C and D, both blood pressure and heart rate gradually decreased dose-dependently with increases in sevoflurane concentrations, although their absolute values were slightly higher than those in the non-gallaminized animals. Both blood pressure and heart rate at the 4.2% concentration were significantly lower than those at the 2.1% concentration, however, those at 3.1% did not differ significantly from those at 2.1%.

(b) Ongoing efferent activities of autonomic nerves.

It was impossible to compare, in absolute numbers of the ongoing efferent activities of autonomic efferent nerves between animals because of the different nerve preparatory conditions and different contacts between the nerves and recording electrodes. Therefore, ongoing activities of these nerves at different concentrations of sevoflurane were expressed by percentages of the number of the activity at the 2.1% concentration of sevoflurane in each animal.

The ongoing activities of the renal sympathetic nerve at 3.1% and 4.2% concentrations sevoflurane were 95 ± 6% and 105 ± 8% of the activity at 2.1%, respectively, as shown in figure 3A. No significant differences were seen at the 3 different concentrations of sevoflurane.

The cardiac sympathetic nerve activities at the 3.1 and 4.2% concentrations of sevoflurane were 92 ± 2% and 86 ± 4%, respectively, of the activity at the 2.1% concentration, as shown in figure 3B. The nerve activity decreased sevoflurane dose-dependently. The cardiac parasympathetic (vagal) nerve activities showed a tendency to increase (insignificant) with increases in sevoflurane concentrations, as shown in figure 3C.

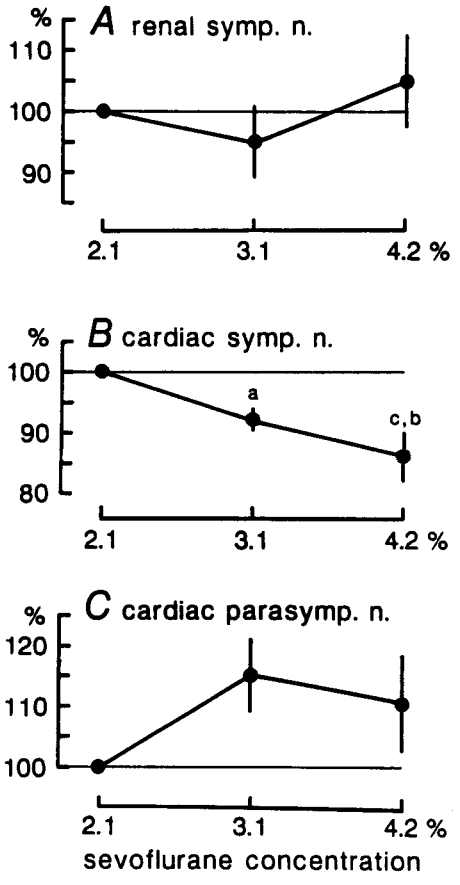

Fig. 3. Effects of different inspiratory concentrations of sevoflurane (2.1, 3.1 and 4.2%) on renal sympathetic nerve activity (A), cardiac sympathetic nerve activity (B) and cardiac parasympathetic nerve activity (C). Circles and vertical bars indicate the mean ± S.E. All three parameters were summarized from 6 rats. Significance was determined by comparison with the values of 2.1% (a,b) and 3.1% (c) using the paired t-test. a,c: $P < 0.05$, b: $P < 0.01$.

2. Cardiovascular responses to noxious stimulation of a hindpaw

Noxious stimulation of a hindpaw (pinching) for a period of 20 s usually produced a variety of responses from blood pressure (A), heart rate (B), renal sympathetic nerve (C), cardiac sympathetic nerve (D) and cardiac parasympathetic (vagal) nerve (E) at the 3 different concentrations of sevoflurane as demonstrated in figure 4.

(a) Responses of blood pressure to pinching of a hindpaw

Figure 5A summarizes the responses of blood pressure following the pinching stimulation of a hindpaw for 20 s under the 3 different concentrations of sevoflurane, e.g., at 2.1% (open circles), 3.1% (triangles), and 4.2% (closed circles). Systolic blood pressures were measured just before the stimulation (zero) and 5, 10, 20, 30 and 60 s after the onset of stimulation; these pressures were expressed as increments or decrements from the control pressure at time zero just before the stimulation. At 2.1% sevoflurane, blood pressure increased approximately 55 mmHg 5 s after the onset of stimulation and then gradually started to decline, however, it remained at an increase value, about 20 mmHg, even 40 s after cessation of the stimulation. At 3.1% sevoflurane, blood pressure increased more moderately for the first 10 s and reached a maximal increace, which was similar to the increase effected by the 2.1% concentration, following cessation of 20 s of stimulation. At 4.2% sevoflurane, the blood pressure did not respond significantly during the pinching period, but a slight decrease was noted 40 s after the end of stimulation.

(b) Responses of renal sympathetic nerve activity to pinching of a hindpaw

Figure 5B summarizes the responses of the renal sympathetic nerve activity following noxious stimulation (pinching) of a hindpaw for 20 s under the 3 different concentrations of sevoflurane (2.1%, 3.1% and 4.2%). The nerve responses to the pinching stimulation were expressed as percentages of the control activity for a period of 5 s just before the onset of stimulation. The nerve activity was measured every 5 s. At 2.1% sevoflurane (open circles), 5 s after the stimulation, ongoing efferent activity of the renal sympathetic nerve increased to approximately 220% of the control activity; this increase returned to the control level 10 s later. The nerve activity showed a marginal decrease 10 s after the end of stimulation. At 3.1% sevoflurane (triangles), the nerve activity increased only slightly (to about 120% of the control) for the first 10 s after the beginning of the stimulation. At 4.2% sevoflurane (closed circles), the nerve activity did not

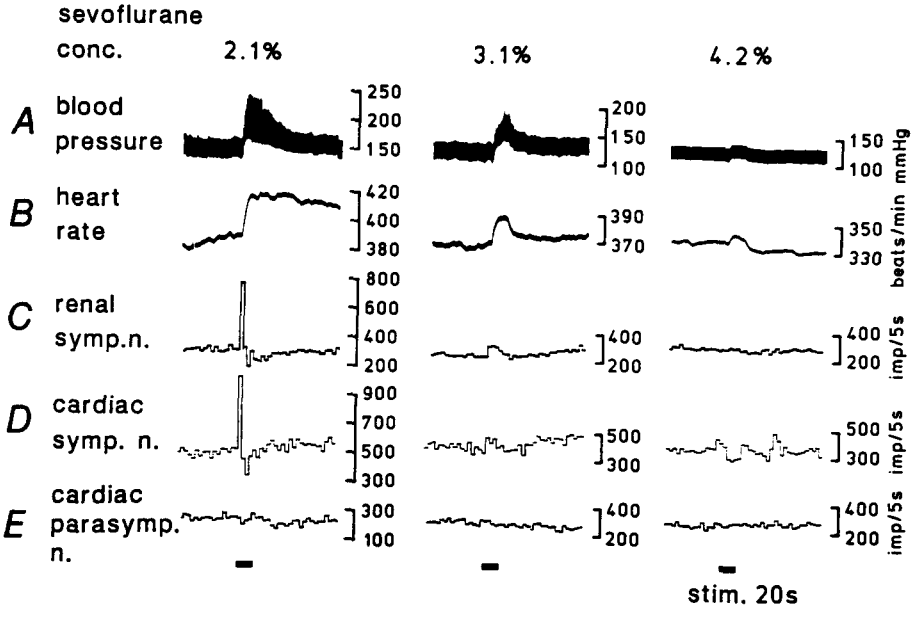

Fig. 4. Recordings of blood pressure (A), heart rate (B), renal sympathetic nerve activity (C), cardiac sympathetic nerve activity (D) and cardiac parasympathetic nerve activity (E) at different inspiratory concentrations of sevoflurane (2.1%, 3.1% and 4.2%). Recordings of each parameter (A-E) were taken from different animals. Underbars indicate the 20 s stimulation period of a hindpaw by pinching.

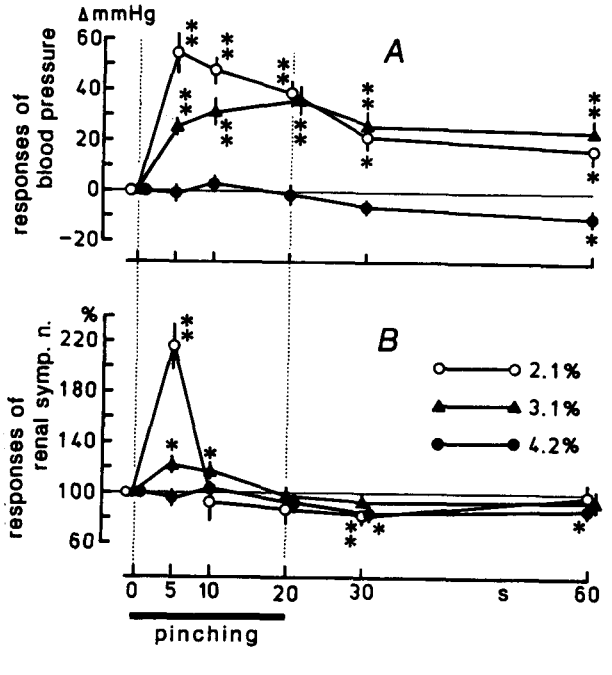

Fig. 5. Effects of pinching stimulation of a hindpaw for 20 s on blood pressure (A), renal sympathetic nerve activity (B) under various inspiratory concentrations of sevoflurane at 2.1% (open circles), 3.1% (triangles) and 4.2% (closed circles). The data of blood pressure and renal sympathetic nerve activity were summarized from 6 rats. Each point and each vertical bar indicate the mean ± S.E. The animals were immobilized with gallamine. Responses of blood pressure were expressed as the changes (increment or decrement) in the control value immediately prior to stimulation, indicated as 0 on the abscissa. Responses of renal sympathetic nerve activity were expressed as percentages of the control nerve activities for a period of 5 s prior to the onset of stimulation, indicated as 0 on the abscissa. The responses of blood pressure and renal sympathetic nerve activities were compared with the absolute values immediately before the stimulation by paired t-test. $^{*}P < 0.05$, $^{**}P < 0.01$.

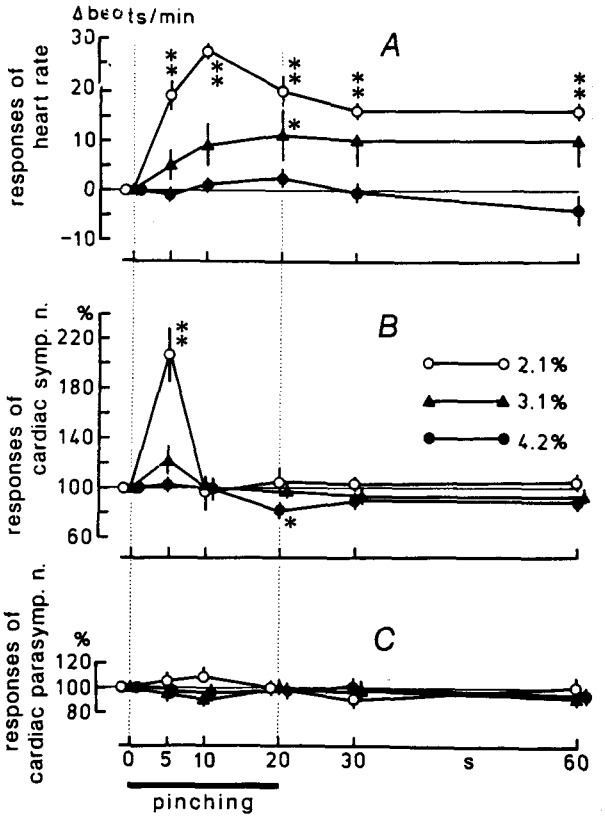

Fig. 6. Effects of pinching stimulation of a hindpaw for 20 s on heart rate (A), cardiac sympathetic nerve activity (B) and cardiac parasympathetic nerve activity (C) under various inspiratory concentrations of sevoflurane at 2.1% (open circles), 3.1% (triangles) and 4.2% (closed circles). The data of heart rate, cardiac sympathetic nerve activity and cardiac parasympathetic nerve activity were summarized from 6 rats. Each point and vertical bar indicates the mean ± S.E. The animals were immobilized using gallamine. Responses of heart rate were expressed as percentages of the control nerve in the control value immediately prior to stimulation onset, indicated as 0 on the abscissa. Responses of cardiac sympathetic and parasympathetic nerve activities were expressed as percentages of the control nerve activities for a 5 s period immediately prior to the stimulation onset, indicated as 0 on the abscissa. The responses of heart rate and cardiac sympathetic and parasympathetic nerve activities were compared with the absolute values obtained just before the stimulation by paired t-test. $*P < 0.05$. $**P < 0.01$.

change during the stimulus (pinching) period, although it decreased only marginally 10 s and 40 s after the end of stimulation.

(c) Responses of heart rate to pinching of a hindpaw

At 2.1% sevoflurane (open circles, fig. 6A), the heart rate was increased following pinching stimulation of a hindpaw for a duration of 20 s, and the increased response remained even 40 s after the cessation of the stimulation. The maximum increase in heart rate was about 28 beats/min at 2.1% sevoflurane. At 3.1% sevoflurane (triangles, fig. 6A), a significant but small increase (10 beats/min) in the heart rate was elicited at the cessation of stimulation. At 4.2% sevoflurane (closed circles, fig. 6A), the heart rate did not change significantly following the stimulation.

(d) Responses of cardiac sympathetic nerve activity to pinching of a hindpaw

At 2.1% sevoflurane (open circles, fig. 6B) at 5 s after the onset of stimulation, the nerve activity of the cardiac sympathetic nerve was increased to approximately 200% of the control level. This increased activity returned to the control level 10 s after the onset of stimulation. At 3.1% sevoflurane (triangles, fig. 6B), cardiac sympathetic nerve activity did not respond significantly to the pinching. However, at 4.2% sevoflurane (closed circles, fig. 6B), it decreased slightly (to about 80% of the control activity) towards the end of the stimulation.

(e) Responses of cardiac parasympathetic nerve activity to pinching of a hindpaw

Cardiac parasympathetic (vagal) nerve activity did not respond significantly to the pinching stimulation at any of the 3 different concentrations of sevoflurane, as shown in figure 6C.

Discussion

1. *Effects of sevoflurane on cardiovascular*

functions and their neural mechanisms under resting conditions

The present results demonstrate that blood pressure and heart rate decrease in a dose-dependent manner by increasing inspiratory concentrations of sevoflurane in rats. The evidence that ongoing activity of the renal sympathetic nerve (selected as a representative nerve of the sympathetic vasoconstrictors) did not change with increases in concentrations of sevoflurane, suggests that the sympathetic vasoconstrictor system is not a major contributor to the depressor responses induced by sevoflurane inhalation. These sevoflurane-induced depressor responses appear to depend on sevoflurane-induced decreases in various cardiovascular functions, such as cardiac output[4], vascular muscle tone and secretion of catecholamines from the adrenal medulla.

It was demonstrated in the present experiments that sevoflurane decreases cardiac sympathetic efferent nerve activities dose-dependently. Therefore, the sevoflurane-induced bradycardia seems to result either from the decrease in cardiac sympathetic nerve activity or a direct inhibitory action of sevoflurane on the cardiac pacemaker cells. The sevoflurane-induced bradycardia is considered to produce a decrease in cardiac output.

The present insignificant responses of cardiac parasympathetic (vagal) nerve activity to sevoflurane demonstrate that there are two different responses of cardiac sympathetic and parasympathetic nerves to the sevoflurane. Sympathetic nerve activity was depressed while parasympathetic nerve activity did not change. Cardiac parasympathetic nerves appear to play only a minor role in the sevoflurane-induced bradycardia. This assumption can be supported also by the evidence that extent of the sevoflurane-induced bradycardia was similar in both non-gallaminized and gallaminized animals, since vago-cardiac synaptic transmissions are blocked by gallamine triethiodide[6].

Furthermore, the present result showing the existence of sevoflurane-induced bradycardia is contradictory to other reports for the effect on heart rate in humans[2], dogs[3], and pigs[4]. In these studies, the heart rate was found to remain stable in response to various concentrations of sevoflurane. Thus, it appears that sevoflurane-induced bradycardia is specific to rats.

It is noted that sevoflurane produced two different responses for cardiac and renal sympathetic nerves with increases in concentrations of sevoflurane, i.e., cardiac sympathetic nerve activity decreased while renal sympathetic nerve activity did not change significantly. Sevoflurane may depress the renal sympathetic nerve activity, however, the sevoflurane-induced hypotension seems to release the arterial baroreceptor inhibitory system. It appears that the release of the baroreceptor inhibitory system results in activation of the renal sympathetic efferent nerve activity which in turn causes the nerve activity to adjust instead of decrease. The present finding concerning the stability of renal sympathetic nerve activity at different concentrations of sevoflurane agrees with that concerning the stability of renal blood flow at different concentrations of sevoflurane reported by Manohar and Parks (1984)[4]. On the contrary, cardiac sympathetic nerve activity appears to be imbalanced by the release of the baroreceptor inhibitory reflex mechanism during sevoflurane-induced hypotension, and therefore results in the decrease in the nerve activity.

2. *Effects of sevoflurane on cardiovascular responses to noxious cutaneous stimulation*

The present experiments using sevoflurane-anesthetized rats demonstrated that both blood pressure and heart rate were increased by pinching of a hindpaw for 20 s at 2.1% and 3.1% concentrations of sevoflurane, and that these increased reflex responses were gradually attenuated with an increase in the concentrations of sevoflurane from 2.1%, to 3.1% and finally to 4.2%. Further, the results demonstrated that both the renal (the representative nerve of the sympathetic vasoconstrictors) and cadiac sympathetic nerve activities were increased by pinching of a hindpaw, and that these

increases in activities attenuated with increases in the concentration of sevoflurane. These results suggest that the sympathetic vasoconstrictor and cardiac nerve responses to the pinching result in the increases in blood pressure and heart rate. It is noted that cardiac parasympathetic activity did not show any significant changes to the same pinching stimulation under the increasing concentrations of sevoflurane. Therefore, it can be concluded that the cardiac parasympathetic nerve is not reponsible for the heart rate responses to the pinching stimulation. Previous studies using urethane-chloralose-anesthetized cats and rats have also reported that cutaneous noxious pinching stimulation produced an increase in the heart rate via the cardiac sympathetic nerve[7,8].

There is other important evidence that both renal and cardiac sympathetic nerve responses to the pinching at 2.1% sevoflurane were observed only at the early stage (i.e., for about 5 s) of 20 s stimulus duration, while both responses of blood pressure and heart rate lasted longer (i.e., for more than 60 s). The short lasting responses of renal and cardiac sympathetic nerve to pinching may be elicited by baroreceptor reflexes. The initial sympathetic nerve responses to the pinching seem to initiate the increased responses of blood pressure and heart rate at the early stage (first several seconds). The second or subsequent responses of blood pressure and heart rate may depend on the inertia of the cardiovascular effector organs. Another possibility is that some vasoconstrictive hormones, such as the catecholamines, vasopressin and renin-angiotensin, are secreted in response to the noxious stimulation and cause the long-lasting responses of blood pressure and heart rate. In particular, prolonged responses of catecholamine secretion from the adrenal medulla to pinching under a different anesthesic (urethane and chloralose) have been demonstrated in this laboratory[9]. Sympathoadrenal medullary functions concerning catecholamine secretion during sevoflurane anesthesia is now under investigation in our laboratory.

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