Effects of Halothane and Isoflurane Anesthesia on Sympathetic Adrenal Nerve Responses to Carbon Dioxide Challenge in Rats

Sumio AMAGASA, Tatsuro TAKAHASHI, Seiji TAKAOKA and Hideo HORIKAWA

We studied the influence of two volatile anesthetics, halothane and isoflurane, on the circulatory and sympathetic nerve responses to carbon dioxide (9% CO_2) in rats.

Systolic blood pressure was depressed throughout the CO_2 challenge and after an initial reduction, a gradual increase was observed in heart rate. Sympathetic adrenal nerve action potentials (SANA) significantly increased in contrast to negative responses in the circulatory functions. SANA responses against time were trapezoid in shape. There were no significant differences in SANA responses between 1%(1 MAC) and 1.5%(1.5 MAC) halothane groups, nor between 1.4%(1 MAC) and 2%(1.5 MAC) isoflurane groups. Halothane and isoflurane, therefore, did not produce dose-dependent effects on sympathetic response to hypercapnia within these concentrations. The maximum changes in SANA from the baseline values were 110% and 40% for the halothane and isoflurane groups, respectively.

The sympathetic reflex response to hyperacapnia was retained at 1.5 MAC for both anesthetics, though isoflurane depressed these responses more markedly than halothane.

Our results suggest that halothane is a more preferable anesthetic than isoflurane when viewed from the standpoint of preservation of sympathetic nerve response in such undesirable situations as severe hypercapnia occurring during anesthesia. (Key words: sympathetic adrenal nerve action potentials, hypercapnia, halothane, isoflurane)

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Carbon dioxide (CO_2) activates the sympathetic nervous system, resulting in increased myocardial contractility and tachycardia. These circulatory responses to hypercapnia are less remarked during general anesthesia. The purpose of this study is to evaluate to what extent halothane and isoflurane modify the circulatory and sympathetic nerve responses to CO_2 in the rat. The central response of sympathetic nervous system was determined by directly measuring the sympathetic adrenal nerve action potentials (SANA).

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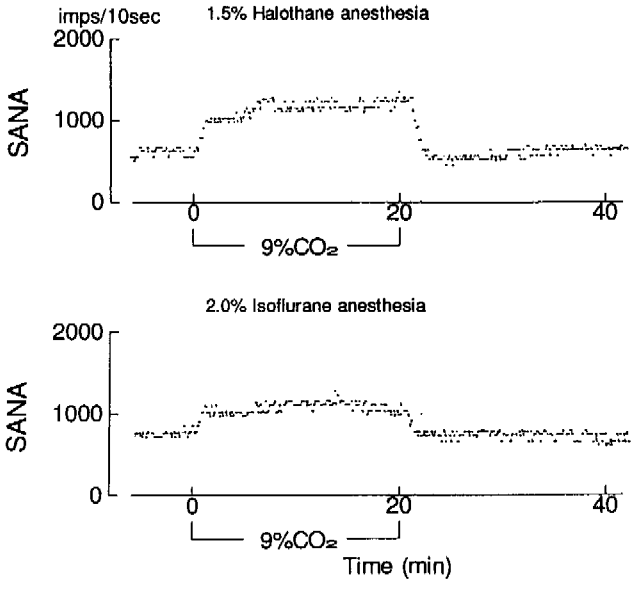

Fig. 1. Recording of SANA changes during CO_2 challenge.
SANA responses showed a trapezoid shape during CO_2 challenge.

Materials and Methods

Twenty-six male rats, 350–500g, were used for the experiment. They were fed ad libitum before the experiment. The animals were randomly allocated to four groups according to the inspired concentration of volatile anesthetics: 1% halothane (n=8), 1.5% halothane (n=6), 1.4% isoflurane (n=6) and 2% isoflurane (n=6).

The animals were anesthetized initially with intraperitoneal pentobarbital (50 $mg \cdot kg^{-1}$). The trachea was cannulated percutaneously and either halothane or isoflurane was given. The inspired concentrations of these anesthetics were adjusted to maintain systolic blood pressure (SBP) at reasonable levels (80–150 mmHg) during the surgical preparation. The lungs were ventilated mechanically with a tidal volume of 10 $ml \cdot kg^{-1}$, the respiratory rate being adjusted to maintain Pa_{CO_2} at 40 mmHg. The left external jugular vein was cannulated for continuous infusion of Ringer's solution (10 $ml \cdot kg^{-1} \cdot hr^{-1}$) and the administration of drugs. The left femoral artery was cannulated for measurements of the arterial blood pressure, heart rate (HR), and blood gas analysis. Pancuronium in a dose of 0.1 mg was given as required. The rectal temperature was maintained at 36.5–38°C by means of water mattress. Blood gases were measured (ABL300, Radiometer) and pH was corrected to 7.4 ± 0.05 with sodium bicarbonate.

The left adrenal gland was exposed via retroperitoneal approach and a few branches of splanchnic nerve inervating the adrenal gland were identified and cut as close as possible to the gland under a binocular microscope. The proximal ends of the cut nerve were placed on bipolar platinum-iridium electrodes in a pool of warm paraffin oil. The efferent mass discharges of sympathetic adrenal nerve (sympathetic adrenal nerve action potentials: SANA) were displayed on an oscilloscope (ATAC-350, Nihon Koden) through a preamplifier and an amplifier (VC-10, Nihon Koden). Discharges greater than the background noise were selected by program setting. SANA were counted every ten seconds to make a histogram (DAB-1100,

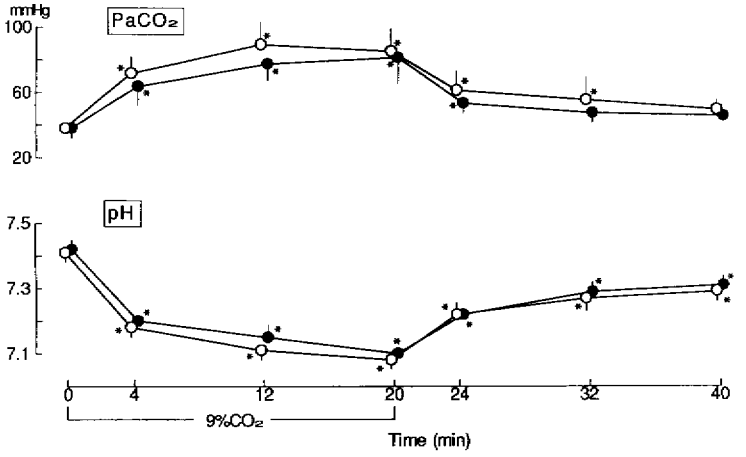

Fig. 2. Pa_{CO_2} and pH changes during CO_2 challenge in halothane anesthetized rats.
○—○ 1% halothane group
●—● 1.5% halothane group
* vs 0 min ($P < 0.05$)

Nihon Koden) and stored in a floppy disc (fig. 1).

The volatile anesthetics were set at designed concentrations at the end of the surgical preparation. The SBP, HR and SANA were allowed to stabilize after the surgical preparation. The CO_2 challenge was given for 20 min by introducing CO_2 into the inspired oxygen (CO_2 200 ml + O_2 21: 9% CO_2) without changing the respiratory rate or tidal volume. Circulatory and sympathetic nerve responses during the CO_2 challenge were recorded and blood samples were analyzed for pH and Pa_{CO_2}.

The minimum alveolar concentrations (MAC) for the rat were assumed to be 1.03% for halothane and 1.34% for isoflurane (1). The concentrations used in our study, therefore, were considered almost identical to 1 and 1.5 MAC of each anesthetic.

Statistics

Values were expressed as mean ± SD. Repeatedly measured data within each group were analyzed with ANOVA for repeated measures. Differences between the four groups at each time point were analyzed with one-way ANOVA. When these tests revealed a significant level, Tukey's multiple comparison test was used. $P < 0.05$ were defined as significant.

Results

1. *Pa_{CO_2} and pH changes during CO_2 challenge*

Pa_{CO_2} increased significantly from the baseline, reaching a maximum of 80 mmHg, and pH decreased to 7.10 during the 20 min CO_2 challenge. They gradually returned to the baseline after the end of the CO_2 challenge. These changes were of the same degree among the four groups studied. Figure 2 shows changes in Pa_{CO_2} and pH in the halothane groups. Changes in a similar fasion were also seen in the isoflurane groups.

2. *SBP and HR responses to CO_2 challenge*

As shown in figure 3 and 4, there were significant differences in the SBP and HR among the four groups prior to the CO_2 challenge. SBP was lower

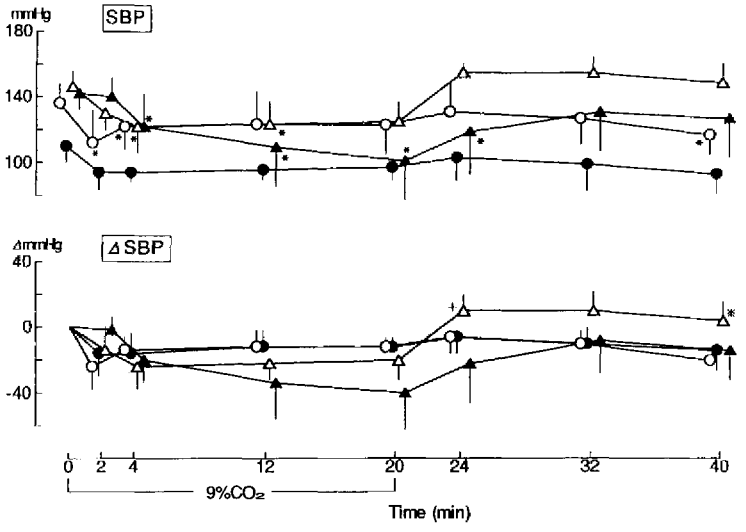

Fig. 3. Systolic blood pressure changes during CO_2 challenge.
○—○ 1% halothane group
●—● 1.5% halothane group
△—△ 1.4% isoflurane group
▲—▲ 2% isoflurane group
* vs 0 min ($P < 0.05$)
\+ 1.4% isoflurane group vs 2% isoflurane group ($P < 0.05$)
※ 1% halothane group vs 1.4% isoflurane group ($P < 0.05$)

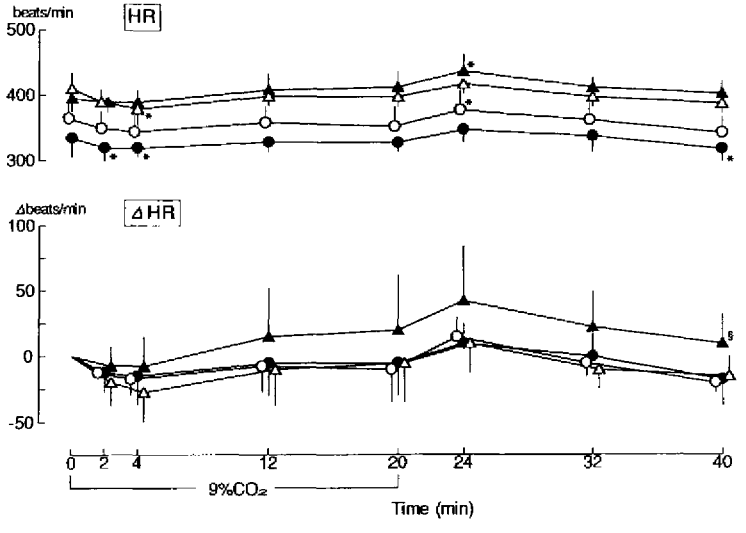

Fig. 4. Heart rate changes during CO_2 challenge.
○—○ 1% halothane group
●—● 1.5% halothane group
△—△ 1.4% isoflurane group
▲—▲ 2% isoflurane group
* vs 0 min ($P < 0.05$)
§ 1.5% halothane group vs 2% isoflurane grup ($P < 0.05$)

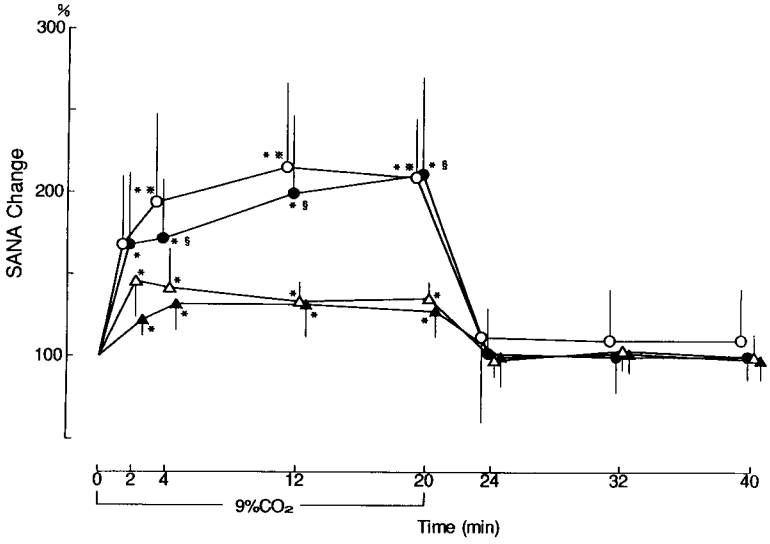

Fig. 5. SANA changes during CO_2 challenge.
○—○ 1% halothane group
●—● 1.5% halothane group
△—△ 1.4% isoflurane group
▲—▲ 2% isoflurane group
* vs 0 min ($P < 0.05$)
※ 1% halothane group vs 1.4% isoflurane group ($P < 0.05$)
§ 1.5% isoflurane group vs 2% isoflurane group ($P < 0.05$)

in the groups anesthetized with higher concentrations of either anesthetic. The SBP in the 1.5 MAC halothane group showed the lowest values. With respect to δSBP and δHR, which were the differences from the baseline values, the CO_2 challenge was associated with negative δSBP responses in all groups. This decline was the greatest in the 2% isoflurane group. After an initial decreases in δHR, a small and transient increase was noticed after the end of the CO_2 challenge. No significant differences in δSBP or δHR were observed during CO_2 challenge among the four groups.

3. *SANA responses to CO_2 challenge*

Figure 5 demonstrates the SANA responses to the CO_2 challenge which were expressed as percentage of the mean baseline values prior to the CO_2 challenge. SANA increased rapidly immediately after the start of the CO_2 challenge, reaching a plateau, and returned rapidly to the baseline after the end. There were no significant differences in SANA responses between the 1 MAC and 1.5 MAC groups of either anesthetic. The maximal activities in the halothane and isoflurane groups reached nearly 210% and 140% of the baseline values, respectively.

Differences in the SANA responses were large and significant between the halothane and isoflurane groups and intergroup difference was greater with halothane than with isoflurane during the CO_2 challenge.

Discussion

Noxious stimuli activate sympathoadrenomedullary and hypothalamo-pituitary-adreocortical reflexes with associated increases in some stress

hormones, such as catecholamines and cortisol[2]. Recently, electrophysiological methods have been used to directly observe the magnitude and duration of sympathetic nerve responses to surgical and other stimulation. Only a few reports, however, have dealt with the effects of volatile anesthetics on sympathetic reflex responses to nociceptive stimulation[3]. Kurosawa et al.[4] demonstrated that the increased cardiac and renal sympathetic nerve responses of the rat to hind paw pinching were attenuated by sevoflurane in a dose-dependent manner.

The innervation of the adrenal medulla contains only preganglionic sympathetic nerve fibers which pass through the splanchnic nerve. It is recognized that the adrenal medulla developed from the sympathetic ganglia and shares similar properties with the latter. It has been established that the adrenal catecholamine secretion rate is determined by the firing frequency of the sympathetic adrenal nerve[5,6]. It is, therefore, rational to measure SANA as a way to assess sympathetic outflow from the central nervous system in response to stresses of various nature.

In our study, to examine the effects of volatile anesthetics on sympathoadrenomedullary responses to the CO_2 challenge under as close to clinical circumstances as possible, the cervical vagus and carotid sinus nerves were left intact. They constitute the major afferent pathways for signals from the peripheral baroreceptor and chemoreceptor. Administration of excessive amounts of fluid and pressor agents to maintain blood pressure was also avoided.

Our results showed that the SBP and HR during halothane anesthesia were lower than during isoflurane anesthesia with equipotent doses of 1 and 1.5 MAC's. These findings are in accordance with previous reports[7]. The SBP and HR were reduced during the CO_2 challenge in all the four groups, but no significant intergroup differences in δSBP or δHR were observed, indicating that the magnitude of the suppressive effect of CO_2 was similar in these four groups.

CO_2 can rapidly pass the blood-brain barrier. Mild hypercapnia has excitatory effects on the cardiovascular and central nervous systems mediated through not only the central excitation of the sympathetic nerve cells in the brainstem and spinal cord[8] but also through the direct stimulation of adrenergic nerve endings and the adrenal medulla[9]. Severe hypercapnia has depressant effects mediated via the profound reduction of intra- and extracelluar pH. Volatile anesthetics modify these excitatory and inhibitory effects of CO_2. It is difficult to evaluate the effects of CO_2 alone by the changes in the SBP and HR. The depressant effects of CO_2 on these two parameters in our study were probably due to several mechanisms: firstly, intact vagus nerve; secondly, volatile anesthetics with potent cardiovascular depressant effect; and thirdly, a high concentration of inspiratory CO_2.

SANA increased immediately after the start of the CO_2 challenge and rapidly reached a plateau. This positive change in SANA against time was not in accordance with the direction and magnitude of negative changes in the SBP and HR in anesthetized rats.

It has been observed in the rat that hind paw pinching increased SANA significantly by 34.7% and 20.0% from the control values with 1% and 1.5% halothane, respectively[6]. In our study SANA responses to a CO_2 challenge were more marked than those to hind paw pinching, suggesting that CO_2 challenge is a more potent stimulation compared with hind paw pinching. In our study SANA responses to acute hypercapnia were investigated in the presence of 1.0 and 1.5 MAC

of halothane and isoflurane. These anesthetics did not affect SANA responses in a dose-dependent fasion. It seems that deeper anesthetic levels are needed to completely suppress SANA responses. The mean SANA responses to halothane at each time point were two to three times greater than those to isoflurane, suggesting that the depressant effect of isoflurane on the sympathetic nervous system is more potent than that of halothane.

Fukuda et al.[10] demonstrated in urethane-anesthetized rats that cardiac and renal sympathetic discharges reached 180% and 140%, respectively, of the control values at 10% end tidal CO_2. It has been known that sympathetic nerve responses to CO_2 differ from one organ to another. In contrast, Dohzaki et al.[3] showed that cervical sympathetic responses to acute hypoxia in the dog were depressed by halothane, enflurane, isoflurane and sevoflurane in a dose-dependent manner, but there was significant difference in these responses between equipotent doses of these anesthetics.

In guinea pig thalamic neurons halothane produced hyperpolarization activated by an increased conductance of K^+ ions resulting in a depression of spontaneous firing[11]. Recent studies revealed that volatile anesthetics affect ionic currents by modifying the kinetics of Na^+, K^+ or Cl^- channels in nerve cells[12,13]. However, the effects of volatile anesthetics on CO_2 action mediated by these ionic channel mechanisms is not yet entirely clear. Our results suggest the possibility that sympathetic reflex responses to hypercapnia may not provoke warning signs in SBP or HR during inhalation anesthesia.

In summary, in the present study it was shown that, in rats anesthetized with halothane and isoflurane, CO_2 challenge produced depression of the SBP and HR despite activated SANA. The SANA responses were of the same degree in the 1 and 1.5 MAC groups of each anesthetic. The average SANA responses were 110% and 40% of the control values with halothane and isoflurane, respectively.

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