Effects of Halothane on Carotid Occlusion in Rabbits

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Effects of halothane on the carotid sinus baroreflex control of circulation were stuied in chronically instrumented rabbits. The carotid sinus baroreflex was evaluated by the hemodynamic responses to bilateral carotid occlusion (BCO). Either 0.5 or 1.0 MAC of halothane inhalation did not alter mean arterial pressure (MAP) or total peripheral resistance (TPR), but significantly increased heart rate (HR). Carotid occlusion produced a significant increase in MAP and HR, and both responses were attenuated dose-dependently by halothane. Halothane depressed the reflex gain of arterial pressure from 3.5 ± 0.3 at conscious state to 1.3 ± 0.2 at 1.0 MAC halothane. Response of cardiac output (CO) to BCO was attenuated significantly only at 1.0 MAC compared with those responses at conscious state and at 0.5 MAC. Response of TPR was attenuated at both 0.5 and 1.0 MAC halothane as compared with at conscious state but no significant defference existed between the two concentrations of halothane. These data suggested that halothane could attenuate the carotid occulusion responses to various degrees in the involved effector componets. 0.5 MAC halothane attenuated MAP response to BCO predominantly by attenuating reflex peripheral vasoconstriction. The reduced CO response was mainly responsible for further attenuation of MAP response at 1.0 MAC halothane. (Key words: halothane, carotid sinus baroreflex, reflex control of circulation)

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Acute homeostatic conrol of arterial pressure is mediated by the arterial baroreflex, which operates through alterations in heart rate, cardiac output, and peripheral vascular resistance. Anesthetic drugs, which were reported to affect these effector components, modulate tha arterial baroreflex control of circulation[1–8]. In previous studies[1,2], we examined the influence of fentanyl or diazepam on arterial baroreflex control of circulation and found dissociated effects of the drugs on arterial baroreflex control of circulation in rabbits. These data indicated that influences of anesthesia on the reflex control of circula-

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tion reflected action of the anesthetics on each effector component. Halothane is one of volatile anesthetics and effects of halothane on baroreflec control have been widely studied[3–6]. However, these experiments on halothane were performed with superimposed anesthesia and/or premedication, which may possibly affect arterial baroreflex system. Furthermore, these earlier studies do not answer an important question: What extent is modulatory effect of halothane involved in each effector componet?

In the present study, we tried to quantify effects of halothane on the carotid sinus baroreflex system by a reflex gain. To avoid influences of superimposed anesthesia and acute surgical procedures, we used conscious rabbits which were chronically instrumented. Carotid sinus baroreflex function was assessed by bilateral carotid occlusion (BCO). In order to give a similar magnitude of input stimulus to the carotid sinus baroreceptors, carotid sinus pressure was continuously monitored and reduced to a predetermined level by BCO. The second aim of this study was to examine influences of halothane on carotid sinus baroreflex control of hemodynamic variables and analyze on which effector component halothane exerts greater effects in modulation of the reflex control of arterial pressure. To examine effects of halothane on the carotid sinus baroreflex control of each effector, we measured heart rate, cardiac output and total peripheral resistance along with arterial pressure.

Materials and Methods

Surgical procedure

Fourteen rabbits, weighing 2.8–3.8 kg, were used for the main experiments. All surgery was performed under sterile condition and general anesthesia. Anestheisa was induced with 30 $mg \cdot kg^{-1}$, IV of sodium pentobarbital and the level of anesthesia was maintained with supplemental doses of pentobarbital. Surgical intervention was divided into two stages to minimize surgical stress on the animals.

In the first stage, common carotid arteries were separated from surrounding tissue through a mid-cervical incision and an occlusion cuff was placed around each of them 1–2 cm caudal from the carotid sinus for occlusion of bilateral common carotid arteries. Tubing to each occluder was routed subcutaneously to the dorsal side of the neck and fixed to the skin at the exit point. Bilateral aortic nerves were separated and transected at the mid cervix to interrupt afferent pathways from the aortic baroreceptors. In eight of the fourteen rabbits, under tracheal intubation and mechanical ventilation, the ascending aorta was accessed through a right second intercostal space, and an electromagnetic flow probe (FC-060TS, Nihon-Kohden) was placed around the root of the ascending aorta for measurement of cardiac output. The probe wire was exteriorized at the back through a subcutaneous tunnel. Prophylactic antibiotics were given subcutaneously for a few days after the operation. The animals were allowed 2 weeks to recover from surgical stress.

In the second surgery, an arterial catheter was inserted in the iliac artery through the femoral artery for measurement of arterial pressure. Another cathter was inserted in the left external carotid artery near the carotid sinus through the mandibular artery. The cathter was passed subcutaneously and fixed in the neck at the exit point. Each arterial catheter was flushed daily with heparin solution (1,000 u).

Experimental protocols

Experiments were conducted in conscious rabbits a few days after the second surgery. The animals were placed

Table 1. Influence of halotane on arterial blood gases

	Conscious State	Halothane 0.5 MAC	Halothane 1.0 MAC
Pa_{O_2} (mmHg)	236.8 ± 25.6	217.8 ± 14.5	217.2 ± 14.3
Pa_{CO_2} (mmHg)	33.7 ± 1.2	35.1 ± 1.8	37.2 ± 3.4
pH	7.37 ± 0.02	7.36 ± 0.03	7.35 ± 0.03

Values are means ± SEM. Pa_{O_2}; arterial P_{O_2}, Pa_{CO_2}; arterial P_{CO_2}

Table 2. Baseline hemodnyamic values before Bilateral Carotid Occlusion

	Conscious State	Halothane 0.5 MAC	Halothane 1.0 MAC
MAP (mmHg)	80 ± 2	79 ± 3	77 ± 3
HR (beats·min^{-1})	227 ± 8	263 ± 7*	291 ± 8***
CO (ml·min^{-1})	520 ± 26	510 ± 28	460 ± 28**
TPR (mmHg·min·ml^{-1})	0.157 ± 0.012	0.154 ± 0.011	0.166 ± 0.013

Values are mean ± SEM. MAP; mean arterial pressure (n=14), HR; Heart rate (n=14), CO; Cardiac output (n=8), TPR; Total peripheral resistance (n=8)

*$P < 0.05$ compared with at conscious state

**$P < 0.05$ compared with at 0.5 MAC halothane

in a small sealed plexiglass box which loosely restricted their movement. The box was ventilated at 5 l·min^{-1} of oxygen and air mixture gas ($F_{I_{O_2}}$=0.5) and the rabbits breathed spontaneously in the box. One hour was allowed for stabilization of their hemodynamics after the animal was placed in the box. After baseline recordings were obtained, BCO was done at conscious state to examine carotid sinus baroreflex function. Then, 0.5 MAC of halothane (0.7%) was added to the ventilating gas mixture with the calibrated vaporizer (Fluotec Mark 2) for one hour and then the concentration of halothane was increased to 1.0 MAC (1.4%)[9]. In one hour of inhalation at each halothane level, baseline hemodynamic variables were obtained and the responses to BCO were examined. To confirm that the end tidal halothane concentrations reached the inspired gas levels in one hour inhalation, a preliminary experiment was done in the same condition as the main experiment. End tidal gas was sampled in rabbit's nose cavity and halothane concentration was measured with Capnomac (Datex, Finland). The end tidal halothane concentrations almost reached each inspired halothane concentration within one hour.

In BCO procedure, bilateral common carotid arteries were occluded simultaneously for one minute. Inflation of the balloon occluders was controlled to reduce mean carotid sinus pressure by 15–20 mmHg and hold at the level for one minute. Instantaneous and mean arterial pressure (MAP), instantaneous carotid sinus pressure, and heart rate (HR) were continuously recorded before and during BCO. Steady-state hemodynamic responses to BCO were obtained 30–60 sec after initiation of BCO. We tried to evaluate carotid sinus barore-

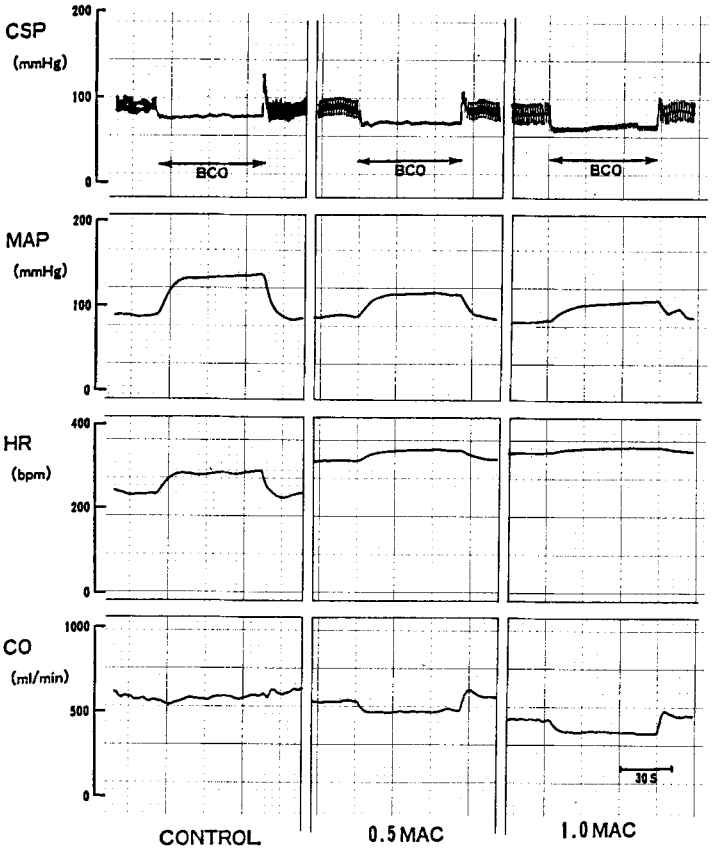

Fig. 1. Tracings from an original record of hemodynamic variables during bilateral carotid occlusion (BCO) at conscious state and during 0.5 MAC and 1.0 MAC halothane inhalation. MAP; mean arterial pressure, HR; heart rate, CO; cardiac output, CSP; carotid sinus pressure.

flex function by quantifying a reflex gain, which was estimated by a ratio of the corresponding increase in MAP to a reduction of carotid sinus pressure (CSP) during BCO (Δ MAP/Δ CSP). In the eight rabbits with the implanted aortic flow probe, cardiac output (CO) was also measured and total peripheral resistance (TPR) was calculated as a ratio of mean arterial pressure to cardiac output. To evaluate the hemodynamic response to BCO, the change in each hemodynamic variable to the value before BCO was obtained.

Arterial pressure was measured with a Statham P23 ID transducer from the implanted arterial catheters. Cardiac output was derived continuously with an electromagnetic flowmeter (MFV-2100, Nihon-Kohden). The level of late diastole of instantaneous aortic flow was assumed to be zero during the period of measurement. Heart rate was counted using a cardiotachometer (Nihon-Denki Sanei, 1321) triggered by the ascending aortic flow wave or by the systemic arterial pressure wave.

Statistical analysis

The values are reported as mean $\pm$ SEM. One-way analysis of variance (ANOVA) with repeated measures and post hoc Tukey's test were applied to analyze effects of halothane on the responses to BCO. A $P < 0.05$ was considered statistically significant.

Results

In one hour inhalation of 0.5 MAC halothane, the rabbits became quiet. They lay on the floor of the box with their eyes closed. At 1.0 MAC, they lost voluntary movement completely. Although respiratory rate was decreased by inhalation of halothane, arterial P_{O_2} and P_{CO_2} were not af-

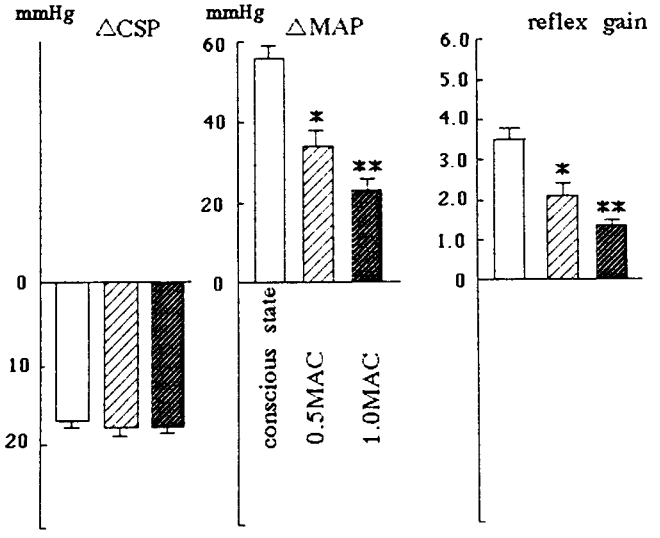

Fig. 2. Influence of halothane on the carotid sinus baroreflex gain.
△ CSP; reduction in carotid sinus pressure during bilateral carotid occlusion (BCO), △ MAP; mean systemic arterial pressure resnponse to BCO. The reflex gain was calculated by the ratio of an increase in MAP to decrease in CSP.
*$P < 0.05$ compared with at conscious state
**$P < 0.05$ compared with at 0.5 MAC halothane

fected significantly (table 1). Table 2 shows control hemodyanamic values before BCO at conscious state, and at the two concentrations of halothane. Halothane did not affect MAP or TPR significantly at either concentration. However, HR was significantly increased with increment in halothane concentration. CO was decreased significantly only at 1.0 MAC halothane.

Figure 1 shows a representative record of hemodynamic responses to BCO. BCO caused prominent increase in MAP, HR and TPR at conscious state, and during halothane anesthesia. During BCO, carotid sinus pressure was reduced constantly by 17 ± 1 at conscious state, and 18 ± 1 and 17 ± 1 mmHg at 0.5 and 1.0 MAC halothane, respectively. There were no significant differences between the values. Figure 2 shows reduction in CSP, the response of MAP to BCO and the reflex gain at conscious state and each halothane inhalation in 14 aminals. The MAP response fell dose-dependently with increasing halothane levels. The reflex gain was decreased significantly from 3.5 ± 0.3 to 2.1 ± 0.3 (at 0.5 MAC) and 1.3 ± 0.2 (at 1.0 MAC).

Figure 3 presents changes in HR, TPR and CO responses to BCO at conscious state and at the halothane inhalation. The HR response fell dose-dependently. The CO response did not change significantly either at the conscious state or 0.5 MAC halothane. However, at 1.0 MAC, BCO decreased the CO response significantly. 0.5 MAC of halothane attenuated the TPR response significantly as compared with at the conscious state. However, the increment in halothane concentration did not attenuate TPR response further. Figure 4 shows percent changes in MAP, TPR and CO from each pre-occlusion value at conscious state and during the halothane inhalations to compare changes in hemodynamic responses. Attenuation of the MAP response by halothane was not parallel with attenuation of responses of TPR or CO.

Discussion

The present study showed that the halothane inhalation dose-dependently attenuated the reflex gain, and the both responses of arterial pressure and heart rate to carotid occlusion. The CO response was decreased significantly at

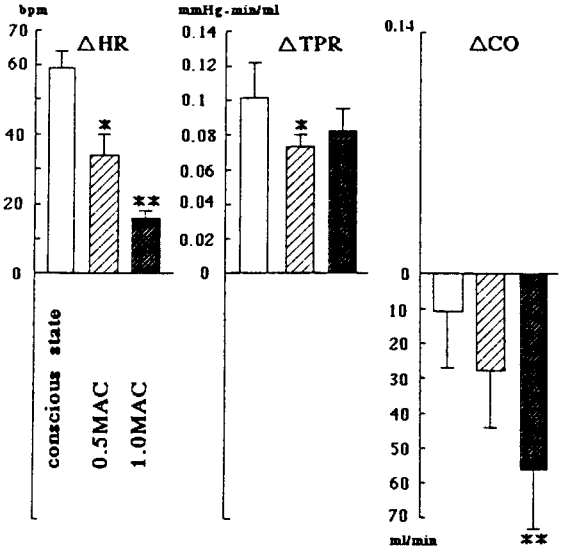

Fig. 3. Hemodynamic responses to bilateral carotid occlusion (BCO) at conscious state and during 0.5 MAC and 1.0 MAC halothane inhalation.
△ HR; Heart rate response to BCO, △ TPR; total peripheral responses to BCO, △ CO; cardiac output response to BCO
*$P < 0.05$ compared with at conscious state
**$P < 0.05$ compared with at 0.5 MAC halothane

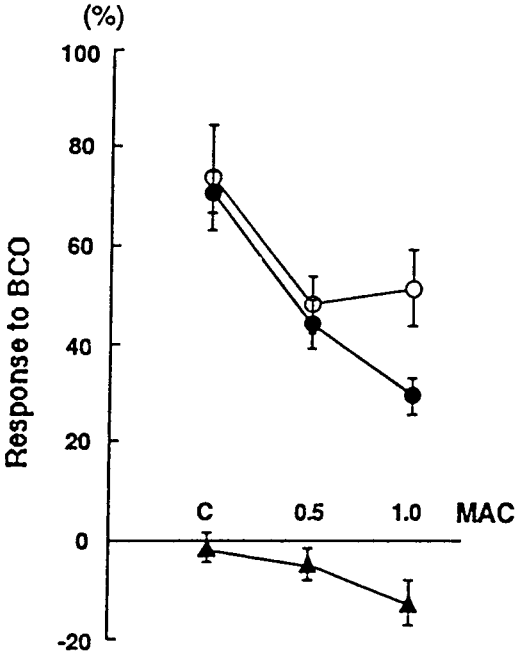

Fig. 4. Comparison of attenuation of each hemodynamic response to bilateral carotid occlusion by the halothane inhalation. Open circles; total peripheral resistance responses, Closed circles; arterial pressure responses, Triangles; changes in cardiac output responses.

1.0 MAC compared with those responses at conscious state and 0.5 MAC. The TPR response was decreased significantly both at 0.5 MAC and 1.0 MAC as compared with at conscious state, but there was no significant difference between those at the two halothane concentrations.

Bilateral carotid occlusion technique has been frequently used to examine carotid sinus baroreflex function in conscious animals. However, in these earlier studies, it was not possible to compute a true open loop reflex gain, since the carotid sinus was not completely isolated from the systemic circulation and the reduction in CSP tended to recover due to blood flow through anastomotic channels[16]. We monitored CSP and controlled the inflation of the occlusion cuffs to reduce and hold CSP at a predetermined level for 60 sec. The constantly reduced CSP separated from the influence of the reflexly elevated systemic arterial pressure during BCO enabled us to compute an static reflex gain in the open loop condition. In anesthetized rabbits with vascularly isolated carotid sinus, Stinnett et al.[10] showed that changs in MAP were linear and inversely correlated to changes in carotid sinus pressure when the carotid sinus

pressure was altered within −15 to +15 mmHg from its baseline. Under the linear assumption, our data indicated that halothane depressed the reflex gain of arterial pressure in a dose-dependent manner.

Bagshow and Cox[3] observed in acute experiments using vagotomized dogs that carotid sinus baroreflex gain was decreased exponentially by increasing halothane levels. However, they did not compare the effect of halothane on carotid sinus reflex gain with an awake control. We obtained the similar results as Bagshaw's and showed that halothane attenuated carotid sinus reflex gain to 60% at 0.5 MAC and 37% at 1.0 MAC as compared with the awake control in rabbits. During BCO, pressure in carotid sinuses became non-pulsatile in the present study (fig. 1, 4th panel), whereas pulsatile carotid sinus perfusion pressure was maintained during the carotid isolation in Bagshow's experiment. The depulsatile effect of carotid occlusion may also cause an increase in arterial pressure. However, an earlier study demonstrated that a variation of pulse pressure had less of a pressor effect than variation of the mean carotid sinus pressure within the physiological range[12].

Magnitude of the arterial pressure response, which directly reflects magnutude of the reflex gain, is determined by the reflex changes in CO and TPR. At 0.5 MAC, the TPR response was decreased significantly but the CO response was not altered. Attenuation of the MAP response at 0.5 MAC was predominantly due to depression of TPR response (the reflex vasoconstriction). At 1.0 MAC, compared with 0.5 MAC, the reflex vasoconstriction was not attenuated further, but the CO response decreased significantly. Our data indicated that the further attenuation of the MAP response at 1.0 MAC was explained by the decrease in the CO response.

The reflex induced vasoconstriction is mainly regulated by sympathetic neurons. It was reported that halothane dose-dependently depresses reflex augmentation of sympathetic nerve activity in acute hypotension[6]. TPR response to BCO was attenuated in inhalation of halothane but it was not in a dose-dependent fashion in the present study. The discrepancy between these results may be explained by the contribution of humoral factors. Millar et al.[13] found that a competitive inhibitor of angiotensin II further reduced arterial pressure during halothane anesthesia and demonstrated a significant role of angiotensin II for the maintenance of arterial pressure during halothane anesthesia. Furthermore, halothane anesthesia could increase other vasopressor substances such as vasopressin or norepinephrine[14,15]. The alternations in humoral environment might prevent further depression of TPR response in the higher concentration of halothane in spite of a dose relate inhibitory effect of halothane on sympathetic nerve activity.

The prominent dose-dependent depression of the HR response to BCO was shown during the halothane inhalations. Seagard et al.[6] showed that 1.5% halotane attenuated HR response to efferent sympathetic nerve stimulation. Their data suggested that attenuation of the chronotropic response with halothane might be due to its effects on the autonomic neuroeffector transmission as well as depressd cardiac sympathetic nerve activity. Alternatively, depressed HR response can be explained by considering the sigmoid nature of input-output relationship of arterial baroreflex[11]. Inhalation of halothane increased baseline HR from 220 to 280 beats·min^{-1}. It means that carotid sinus pressure-HR relationship curve could shift towards up-

per saturated plateau level. Therefore, the carotid occlusion with the similar magnitude of reduction in carotid sinus pressure can depress the reflex increase in heart rate.

In summary, we examined the function of the carotid sinus baroreflex during inhalation of halothane. Halothane depressed the carotid sinus baroreflex gain in a dose-dependent fashion. We suggested that the dose-dependent attenuation of MAP response could be involved in both changes in TPR and CO. Inhalation of halothane at 0.5 MAC attenuated MAP response to BCO predominantly by reducing peripheral vasoconstriction. The inhibition in components of cardiac output was mainly responsible for the further attenuation of arterial pressure response at 1.0 MAC halothane.

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