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Effects of halothane and enflurane on the peripheral vasoconstriction and shivering induced by internal body cooling in rabbits

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Abstract: General anesthetic agents have central and peripheral effects on body temperature regulation, and its alterations are related to the depth of anesthesia. To evaluate the effect of halothane and enflurane on thermoregulation, we investigated the threshold of body core temperatures to induce peripheral vasoconstriction and shivering in spontaneously breathing rabbits. Rabbits were anesthetized with halothane or enflurane at 0.0 (control), 0.2, and 0.4 MAC (minimum alveolar concentration). Internal whole body cooling was performed by perfusion with cold water (10°C) through a U-shaped intestinal thermode placed in the colon. Core (esophageal) and peripheral (ear skin) temperatures were measured with thermistor probes. The esophageal temperatures at the beginning of peripheral vasoconstriction and shivering induced by internal whole body cooling were determined. Core temperature threshold values for peripheral vasoconstriction were significantly higher than those for shivering in both groups. The incidence of peripheral vasoconstriction was not significantly affected by halothane or enflurane. However, the incidence of shivering decreased in a dose-dependent fashion with both anesthetic agents. At 0.2 MAC, the incidence of shivering in the enflurane group was significantly higher than that in the halothane group, suggesting that suppression of shivering by halothane is stronger than enflurane.

Key words: Enflurane, Halothane, Shivering, Thermoregulation, Vasoconstriction

Introduction

Anesthetized surgical patients frequently become hypothermic. During the recovery period, mild hypothermia prolongs the effect of some drugs and may trigger shivering [1–3] with a resulting increase in discomfort and metabolic stress. The factors responsible for these are related, not only to the patient, environment, or type and duration of surgery, but also to anesthetic regimen [4].

General anesthetic agents have central and peripheral effects on body temperature regulation, and the alterations are related to the depth of anesthesia [5,6]. In this study, to evaluate the effects of halothane and enflurane on thermoregulation, we investigated their effects on the threshold of body core temperatures at which peripheral vasoconstriction and shivering were induced in spontaneously breathing rabbits.

Materials and methods

With approval from the Yamanashi Medical University Committee on Animal Research, we used 34 male Japanese white rabbits, weighing 2.2~3.2 (mean 2.8 kg). The animals were anesthetized by inhalation of halothane or enflurane, in 67% nitrous oxide in oxygen, and were intubated with a 3.0-mm intratracheal tube following local anesthesia by 8% lidocaine spray. The animals were loosely fixed on the neck in an experimental chamber whose room temperature was maintained at 24°~26°C. The animals breathed spontaneously. Afterwards, nitrous oxide was discontinued and the concentration of halothane or enflurane was kept at 0.0 (control), 0.2, and 0.4 MAC (minimum alveolar concentration) at 37°C (body temperature) according to the method of Drummond [7]. Rabbits were given 8% lidocaine spray sufficiently to prevent bucking before the start of the experiment at 0.0 MAC. End-tidal halothane or enflurane concentration was quantified using an anesthetic agent monitor (NORMAC AA-102, Datex, Helsinki, Finland).

Esophageal and ear skin temperatures were measured with probes (MGA 3-219, Nihon Kohden, Tokyo,

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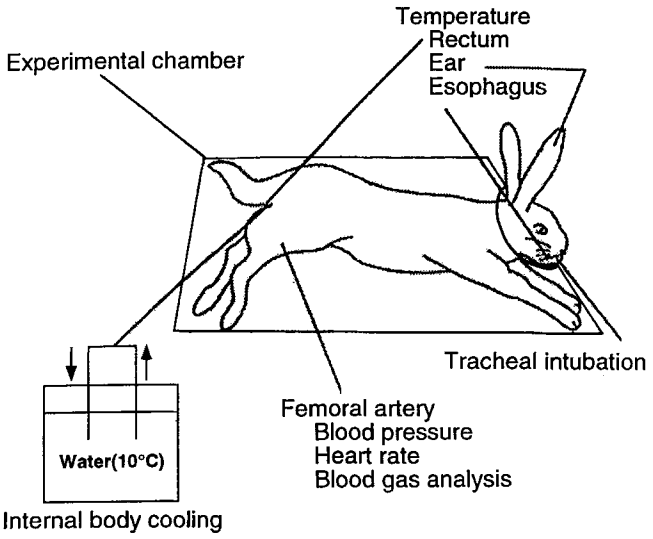

Fig. 1. Schema of experimental procedures. A rabbit was loosely fixed on the neck in an experimental chamber. Whole body cooling was done by means of heat extraction with a U-shaped intestinal polyethylene thermode, which was inserted about 25 cm deep into the colon and perfused with water at 10°C

Japan). The data were sampled once every minute with a personal computer (PC-9801, NEC, Tokyo, Japan) and these were expressed both in numbers and graphically.

Threshold core esophageal temperatures for cutaneous vasoconstriction (VT) and shivering (ST) were determined during whole body cooling by means of heat extraction with a U-shaped intestinal polyethylene thermode, which was inserted about 25 cm deep into the colon and perfused with water at 10°C [8,9] (Fig. 1). VT is the core temperature at which the ear skin vessels begin to constrict. ST is the core temperature at which shivering begins as determined by visual inspection. In addition, the differences between the core temperatures of VT (ΔVT) and ST (ΔST) were measured, respectively. Arterial blood gas analyses were made from the right femoral artery before internal body cooling and at the time when shivering began.

The data were analyzed for comparison of values obtained for both anesthetic agents at various MAC values. Two-way analysis of variance and Duncan multiple-range test, Student's paired *t*-test, and chi-square test were used. Differences were considered significant at $P < 0.05$. Data were expressed as the mean ± SD.

Results

The incidences of peripheral vasoconstriction and shivering are presented in Table 1. The incidences of peripheral vasoconstriction did not differ between anesthetic concentrations or between the halothane and enflurane groups, whereas the incidences of shivering decreased in a dose-dependent fashion with both anesthetic agents. The incidences of shivering in the both groups with 0.4 MAC were significantly ($P < 0.01$) lower than those with 0.0 MAC. At 0.2 MAC, the incidence of shivering in the enflurane group was significantly ($P < 0.05$) greater than that in the halothane group.

Core temperature threshold values for peripheral vasoconstriction (VT) at 0.0 and 0.2 MAC were significantly ($P < 0.05$) higher than those for shivering (ST) in both groups. Different core temperatures for peripheral vasoconstriction (ΔVT) at 0.0 and 0.2 MAC were significantly ($P < 0.05$) smaller than those for shivering (ΔST) in both groups. There were no significant differences in VT, ST, ΔVT, and ΔST at comparable MAC values between both groups (Fig. 2).

The results of various physiological parameters are given in Table 2. Mean arterial pressure before cooling (BC) and at the time of vasoconstriction (Vc) in the

Table 1. Incidences of peripheral vasoconstriction and shivering

		MAC					
		0.0 (control)		0.2		0.4	
		Hal (n = 10)	Enf (n = 10)	Hal (n = 10)	Enf (n = 11)	Hal (n = 9)	Enf (n = 9)
Vc	+	7	8	8	7	9	8
	−	1	0	2	1	0	0
	n.c.	2	2	0	3	0	1
Sh	+	9	9	5	11*	0	3
	−	0	0	4	0	9#	6+
	n.c.	1	1	1	0	0	0

MAC, minimum alveolar concentration; Hal, halothane; Enf, enflurane; Vc, vasoconstriction; Sh, shivering; n.c., not certain.
* Differs from halothane at 0.2 MAC ($P < 0.05$).
# 0.0 MAC *vs* 0.4 MAC in the halothane group ($P < 0.01$).
+ 0.0 MAC *vs* 0.4 MAC in the enflurane group ($P < 0.01$).

Table 2. Changes of various physiological parameters by body cooling

		MAC											
		0.0 (control)				0.2				0.4			
		Hal	(n)	Enf	(n)	Hal	(n)	Enf	(n)	Hal	(n)	Enf	(n)
MAP (mmHg)	BC	85.8 ± 9.2	(10)	86.0 ± 8.7	(10)	83.9 ± 14.7	(10)	79.9 ± 11.4	(11)	73.3 ± 7.3	(9)	62.8 ± 15.1*	(9)
	Vc	87.1 ± 10.2	(7)	82.8 ± 7.8	(8)	84.1 ± 14.3	(8)	80.5 ± 9.5	(7)	69.9 ± 5.5	(9)	57.7 ± 6.7*	(8)
	Sh	86.8 ± 8.9	(9)	83.9 ± 10.4	(9)	88.8 ± 10.2	(5)	77.4 ± 9.0	(11)				
HR (min^{-1})	BC	300.8 ± 26.8	(10)	281.3 ± 15.9	(10)	306.8 ± 20.4	(10)	302.8 ± 25.7	(11)	332.2 ± 31.8	(9)	303.5 ± 47.2	(9)
	Vc	293.4 ± 21.4	(7)	271.3 ± 17.2	(8)	298.4 ± 18.6^{+}	(8)	287.8 ± 22.7	(7)	316.2 ± 36.9^{++}	(9)	290.5 ± 71.4	(8)
	Sh	265.1 ± 22.2^{++}	(9)	251.9 ± 20.1^{++}	(9)	271.1 ± 39.9	(5)	255.0 ± 20.1^{++}	(11)				
RR (min^{-1})	BC	65.1 ± 14.3	(10)	71.3 ± 36.7	(10)	70.1 ± 13.0	(10)	54.9 ± 13.2°	(11)	69.4 ± 9.2	(9)	53.3 ± 10.6	(9)
	Vc	65.0 ± 6.9	(7)	62.4 ± 19.6	(8)	65.4 ± 12.2	(8)	51.5 ± 13.4	(7)	64.4 ± 10.2	(9)	46.4 ± 5.5°	(8)
	Sh	53.4 ± 13.8^{+}	(9)	52.0 ± 16.5^{+}	(9)	48.8 ± 9.9^{+}	(5)	44.7 ± 11.2^{++}	(11)				
BGA													
BC	pH	7.40 ± 0.04		7.42 ± 0.04		7.34 ± 0.06		7.38 ± 0.07		7.36 ± 0.04		7.42 ± 0.07	
	Pco_2	20.4 ± 2.5		20.8 ± 1.9		19.8 ± 3.0		22.4 ± 0.9		21.1 ± 4.7		21.1 ± 1.9	
	Po_2	432.4 ± 38.2	(10)	355.6 ± 62.1	(10)	427.2 ± 48.0	(10)	330.3 ± 146.8	(11)	347.3 ± 132.0	(9)	347.1 ± 86.4	(9)
	HCO_3^-	13.8 ± 1.4		13.5 ± 1.3		11.1 ± 1.9		13.6 ± 2.6		13.0 ± 2.4		13.9 ± 1.9	
	BE	−9.8 ± 2.4		−8.1 ± 1.6		−10.2 ± 2.6		−8.8 ± 3.8		−10.6 ± 1.8		−7.7 ± 3.0	
Sh	pH	7.36 ± 0.04		7.38 ± 0.05		7.32 ± 0.01		7.35 ± 0.08					
	Pco_2	22.5 ± 3.7^{++}		23.6 ± 2.4^{++}		26.2 ± 0.4^{++}		24.5 ± 2.3^{+}					
	Po_2	465.8 ± 38.2	(9)	404.4 ± 75.6	(9)	504.1 ± 59.4	(5)	320.7 ± 206.1	(11)				
	HCO_3^-	13.1 ± 2.6		14.1 ± 1.4		14.6 ± 0.6		13.6 ± 1.3					
	BE	−10.1 ± 3.1		−8.4 ± 2.0		−9.2 ± 0.5		−9.5 ± 2.8					

MAC, minimum alveolar concentration; Hal, halothane; Enf, enflurane; MAP, mean arterial pressure; HR, heart rate; RR, respiratory rate; BGA, arterial blood gas analysis; BC, before cooling; Vc, vasoconstriction; Sh, shivering.
* Differs from control value in the enflurane group ($P < 0.01$).
$^{+}$ Differs from the before cooling value ($P < 0.05$).
$^{++}$ Differs from the before cooling value ($P < 0.01$).
$^{\circ}$ Differs from halothane at comparable MAC values ($P < 0.05$).

enflurane group with 0.4 MAC were significantly lower than those with 0.0 MAC. Heart rate at Vc and at the start of shivering were significantly lower than those before cooling in the two groups. The respiratory rate at the start of shivering was lower than before cooling with 0.0 and 0.2 MAC in both groups. Respiratory rate in the enflurane group before cooling with 0.2 MAC and at Vc with 0.4 MAC were significantly lower than those in the halothane group with comparable MAC values. Pco_2 at the start of shivering were significantly higher than those before cooling in both groups with 0.0 and 0.2 MAC. Although hypocarbia and metabolic acidosis were found, pH values were within normal limits before cooling and at the start of shivering in both groups with each MAC.

Discussion

Intraoperative hypothermia is difficult to avoid, since firstly, cold exposure increases environmental heat loss; secondly, general anesthesia decreases metabolic heat production; and thirdly, anesthetic drugs inhibit thermoregulatory responses [3,6]. Hypothermia may produce a significant clinical risk during the early postoperative phase. For example, shivering in response to hypothermia increases tissue oxygen demand by as much as 400%–500% [10]. In addition, shivering involves risks to postoperative hypoxemia, wound dehiscence, dental damage, and disruption of delicate surgical repairs [1,11]. Therefore, anesthesiologists should prevent perioperative hypothermia and postanesthetic shivering.

It has been reported that postanesthetic shivering occurred with equal frequency in all anesthetic drugs [1]. However, Ramachandra et al. noted that the incidence of post-anesthetic shivering was greater in the halothane group than in the other (enflurane and isoflurane) groups [5]. Conversely, there is a report that shivering was observed more frequently following enflurane anesthesia than halothane anesthesia [12]. In this study, the incidence of shivering tended to decrease with both halothane and enflurane dose-dependently, and the incidence of shivering in the enflurane group with 0.2 MAC was significantly greater than that in the halothane group with the same MAC. Blockade of the thermoregulatory mechanism is thought to be profound at surgical concentration of anesthesia [13], but, presumably, the magnitude of blockade depends on both anesthetics and the dose administered [14]. Therefore, although there may be differences in the thermoregulatory mechanism between humans and rabbits, our results suggest that the protective effect of halothane against shivering may be stronger than enflurane. Two possible explanations regarding the cause of shivering in the recovery period have been reported: (1) shivering

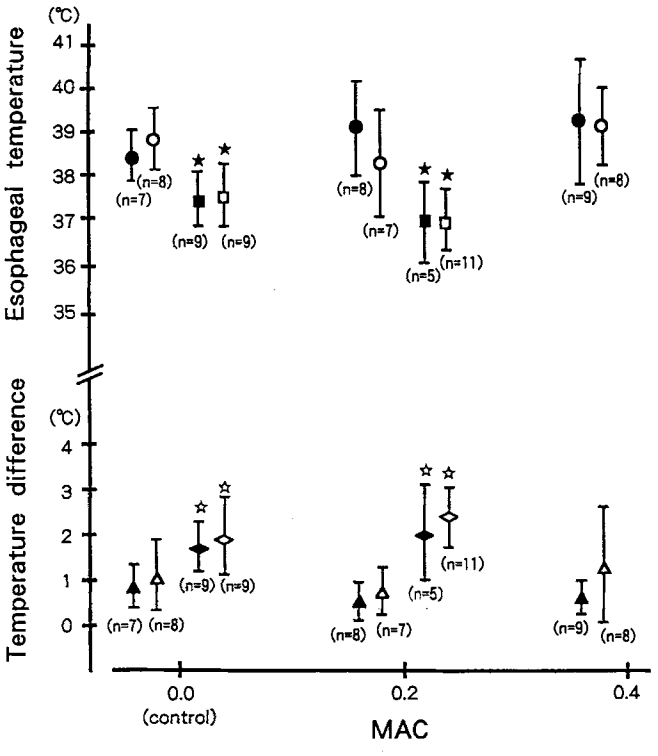

Fig. 2. Core temperature threshold values and difference values for peripheral vasoconstriction and shivering. *MAC*, minimum alveolar concentration; *VT*, threshold core temperature for vasoconstriction; *ST*, threshold core temperature for shivering; ΔVT, difference between the core temperature at which whole body cooling begins and VT; ΔST, difference between the core temperature at which whole body cooling begins and ST; *solid symbols*, halothane; *open symbols*, enflurane; * VT *vs* ST at comparable MAC values ($P < 0.05$); ☆ ΔVT *vs* ΔST at comparable MAC values ($P < 0.05$)

is related solely to hypothermia that occurs during anesthesia and operation [15], and (2) shivering is a manifestation of a generalized increase in CNS activity [16]. The results of our study support the concept that, although hypothermia may be a necessary condition for shivering, its appearance is also conditioned by the patient's state, which depends on both the anesthetics used and their doses [12].

The only thermoregulatory responses to hypothermia available to anesthetized patients are cutaneous vasoconstriction (decreased environmental heat loss) [17] and nonshivering thermogenesis (increased metabolic heat production) [18]. In humans, total digital skin blood flow is divided into nutritional (capillary) and thermoregulatory (arteriovenous shunt) components [19]. Similarly, rabbits also have two components of blood flow in their ear skins [20]. In our studies, core temperature threshold values for peripheral vasoconstriction (VT) were higher than those for shivering (ST), and difference values of core temperature for peripheral vasoconstriction (ΔVT) were smaller than those for shivering (ΔST). These results suggest that peripheral vasoconstriction appears to be the primary and most clinically important thermoregulatory response during anesthesia in humans [21].

Although peripheral vasoconstriction was not significantly affected by both halothane and enflurane, the incidence of shivering was decreased by halothane and enflurane dose-dependently in the present study. These results indicate a threshold dissociation of thermoregulatory effector responses during internal whole body cooling [9,22] and that thermoregulatory responses are evoked by the integration of thermal inputs from the periphery and core of the body [23].

In our study, enflurane depressed the respiratory system stronger than halothane in rabbits. This is consistent with the report that respiratory rates were depressed by enflurane to a greater extent than by halothane in rats [24]. To conserve heat, homeothermic animals and humans have developed a typical autonomic activity pattern to thermal stress. Central cooling enhances peripheral skin sympathetic activity resulting in vasoconstriction, while cooling depresses cardiovascular sympathetic activity [25]. In addition, with cooling, respiration becomes depressed to conserve heat loss from the airways [26]. Therefore, both heart rate and respiratory rate at the time of vasoconstriction and shivering might be decreased by such sympathetic reflexes.

There are no previous reports similar to our animal studies of thermoregulation under tracheal intubation and spontaneous breathing. We could evaluate the threshold core temperatures for peripheral vasoconstriction and shivering induced by internal whole body cooling in rabbits. Our experimental methods might be suitable for evaluating thermoregulatory responses under general anesthesia. Although the metabolic acidosis that might be caused by no fluid administration may influence peripheral vasoconstriction and shivering, all animals were studied under virtually identical conditions.

In conclusion, we studied the effects of halothane and enflurane on the peripheral vasoconstriction and shivering induced by internal body cooling in rabbits. Although both halothane and enflurane did not influence vasoconstriction, both produced dose-dependent suppression of the incidence of shivering. Additionally, the incidence of shivering in the enflurane group with 0.2 MAC was significantly greater than that in the halothane group at a comparable MAC value. Thus, the protective effect of halothane against shivering may be stronger than enflurane.

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References

1. Lipton JM, Giesecke AH (1988) Body temperature and shivering in the perioperative patient. Semin Anesth VII:3–10
2. Sessler DI, Rubinstein EH, Eger EI II (1987) Core temperature changes during N_2O fentanyl and halothane/O_2 anesthesia. Anesthesiology 67:137–139
3. Sessler DI, Moayeri A (1990) Skin-surface warming: heat flux and central temperature. Anesthesiology 73:218–224
4. Hall GM (1978) Body temperature and anaesthesia. Br J Anaesth 50:39–44
5. Ramachandra V, Moore C, Kaur N, et al. (1989) Effect of halothane, enflurane and isoflurane on body temperature during and after surgery. Br J Anaesth 62:409–414
6. Sessler DI, Olofsson CI, Rubinstein EH, et al. (1988) The thermoregulatory threshold in humans during halothane anesthesia. Anesthesiology 68:836–842
7. Drummond JC (1985) MAC for halothane, enflurane, and isoflurane in the New Zealand white rabbit: and a test for the validity of MAC determinations. Anesthesiology 62:336–338
8. Inomoto T, Mercer JB, Simon E (1982) Opposing effects of hypothalamic cooling on threshold and sensitivity of metabolic response to body cooling in rabbits. J Physiol 322:139–150
9. Iriki M, Hashimoto M, Riedel W (1984) Threshold dissociations of thermoregulatory effector responses in febrile rabbits in warm environment. In: Hales JRS (ed) Thermal physiology. Raven, New York, pp 535–537
10. Vaughan RW, Vaughan MS (1988) Temperature our most neglected perioperative monitor. Semin Anesth VII:38–46
11. Sessler DI, Israel D, Pozos RS, et al. (1988) Spontaneous postanesthetic tremor does not resemble thermoregulatory shivering. Anesthesiology 68:843–850
12. Rosenberg H, Clofine R, Bialik O (1981) Neurologic changes during awakening from anesthesia. Anesthesiology; 54:125–130
13. Flacke W (1963) Temperature regulation and anesthesia. Int Anesthesiol Clin 2:43–54
14. Jell RM, Gloor P (1972) Distribution of thermosensitive and nonthermosensitive preoptic and anterior hypothalamic neurons in unanesthetized cats, and effects of some anesthetics. Can J Physiol Pharmacol 50:890–901
15. Moir DD, Doyle PM (1963) Halothane and postoperative shivering. Anesth Analg 42:423–428
16. Solimon MG, Gillies DMM (1972) Muscular hyperactivity after general anesthesia. Can Anaesth Soc J 19:529–535
17. Benzinger TH, Pratt AW, Kitzinger C (1961) The thermostatic control of human metabolic heat production. Proc Natl Acad Sci USA 47:730–739
18. Jessen K (1980) An assessment of human regulatory nonshivering thermogenesis. Acta Anaesth Scand 24:138–143
19. Burton AC (1961) Special features of the circulation of the skin. In: Montagra W, Ellis RA (eds) Advances in biology of Skin, vol 2, blood vessels and circulation. Pergamon, New York, pp 117–122
20. Hales JRS, Iriki M, Tsuchiya K, et al. (1978) Thermally-induced cutaneous sympathetic activity related to blood flow through capillaries and arteriovenous anastomoses. Pfluegers Arch 375:17–24
21. Sessler DI, Olofsson CI, Rubinstein EH, et al. (1988) The thermoregulatory threshold in humans during halothane anesthesia. Anesthesiology 68:836–842
22. Iriki M, Hashimoto M, Saigusa T (1986) Threshold dissociation of thermoregulatory effector responses in febrile rabbits. Can J Physiol Pharmacol 65:1304–1311
23. Libert JP, Candas V, Vogt JJ, et al. (1982) Central and peripheral inputs in sweating regulation during thermal transients. J Appl Physiol 52:1147–1152
24. Dardai E, Heavner JE (1987) Respiratory and cardiovascular effects of halothane, isoflurane and enflurane delivered via a Jackson-Rees breathing system in temperature controlled and uncontrolled rats. Methods Find Exp Clin Pharmacol 9:717–720
25. Riedel W, Kozawa E, Iriki M (1982) Renal and cutaneous vasomotor and respiratory rate adjustments to peripheral cold and warm stimuli and to bacterial endotoxin in conscious rabbits. J Aut Nerv Syst 5:177–194
26. Holdcroft A (1980) Body temperature control in anaesthesia, surgery and intensive care. Bailliere Tindall, London, pp 18–27