Anesthetic Potency and Cardiopulmonary Effects of Sevoflurane in Goats: Comparison with Isoflurane and Halothane

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ABSTRACT

The anesthetic potency and cardiopulmonary effects of sevoflurane were compared with those of isoflurane and halothane in goats. The (mean ± SD) minimal alveolar concentration (MAC) was 0.96 ± 0.12% for halothane, 1.29 ± 0.11% for isoflurane, and 2.33 ± 0.15% for sevoflurane. Cardiopulmonary effects of sevoflurane, halothane and isoflurane were examined at end-tidal concentrations equivalent to 1, 1.5 and 2 MAC during either spontaneous or controlled ventilation (SV or CV). During SV, there were no significant differences in respiration rate, tidal volume and minute ventilation between anesthetics. Dose-dependent decreases in both tidal volume and minute ventilation induced by halothane were greater than those by either sevoflurane or isoflurane. Hypercapnia and acidosis induced by sevoflurane were not significantly different from those by either isoflurane or halothane at 1 and 1.5 MAC, but were less than those by halothane at 2 MAC. There was no significant difference in heart rate between anesthetics during SV and CV. During SV, all anesthetics induced dose-dependent decreases in arterial pressure, rate pressure product, systemic vascular resistance, left ventricular minute work index and left ventricular stroke work index. Systemic vascular resistance with isoflurane at 2 MAC was lower than that with sevoflurane. During CV, sevoflurane induced dose-dependent circulatory depression (decreases in arterial pressure, cardiac index, rate pressure product, systemic vascular resistance, left ventricular minute work index and right ventricular minute work index), similar to isoflurane. Halothane did not significantly alter systemic vascular resistance from 1 to 2 MAC.

RÉSUMÉ

L'efficacité anesthésiante et les effets cardiorespiratoires du sevoflurane ont été comparés à ceux de l'isoflurane et de l'halotane chez des chèvres. La concentration alvéolaire minimale (CAM) (moyenne ± ET) était de 0,96 ± 0,12 % pour l'halotane, 1,29 ± 0,11 % pour l'isoflurane et de 2,33 ± 0,15 % pour le sevoflurane. Les effets cardiorespiratoire du sevoflurane, de l'halotane et de l'isoflurane à des concentrations en fin d'expiration équivalentes à 1, 1,5 et 2 fois la CAM ont été examinés lors de ventilation spontanée ou contrôlée (VS ou VC). Aucune différence significative ne fut observée entre les agents anesthésiants durant la VS quant au rythme respiratoire, au volume courant et à la ventilation minute. La diminution dose-dépendante du volume courant et de la ventilation minute induite par l'halotane était plus important que celles induites par le sevoflurane ou l'isoflurane. L'hypercapnie et l'acidose induites par le sevoflurane n'étaient pas significativement différentes de celles induites par l'isoflurane ou l'halotane à des valeurs de 1 et 1,5 fois la CAM, mais étaient plus petites que celles de l'halotane à 2 fois la CAM. Aucune différence significative du rythme cardiaque ne fut notée durant la VS et la VC entre les agents anesthésiants. Au cours de la VS, tous les agents anesthésiants ont induit une diminution dose-dépendante de la pression artérielle, du produit fréquence-pression, de la résistance vasculaire systémique, de l'index du travail ventriculaire gauche par minute et de l'index du travail d'éjection du ventricule gauche. La résistance vasculaire systémique avec l'isoflurane à 2 fois la CAM était plus basse que celle avec le sevoflurane. Au cours de la VC, le sevoflurane a induit une dépression circulatoire dose-dépendente (diminution de la pression artérielle, de l'index cardiaque, du produit fréquence-pression, de la résistance vasculaire systémique, de l'index du travail ventriculaire gauche par minute, et de l'index du travail ventriculaire droit par minute) semblable à celle produite par l'isoflurane. Des concentration d'halotane de 1 à 2 fois la CAM n'ont pas modifiées significativement la résistance vasculaire systémique.

(Traduit par docteur Serge Messier)

INTRODUCTION

A non-flammable, halogenated inhalant, sevoflurane, has a low blood/gas partition coefficient similar to nitrous oxide (1), and produces rapid induction of and recovery from anesthesia and rapid alteration of anesthetic depth (2–7). The arrhythmogenic dose of adrenaline for

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sevoflurane is higher than that for halothane and enflurane, and similar to that for isoflurane in dogs (8–10) and cats (11). Sevoflurane appears to be a new anesthetic showing promise.

The anesthetic potency and cardiopulmonary effects of halothane and isoflurane have been well described in goats (12) and other ruminants (13–17). Sevoflurane has been used as an effective anesthetic producing a rapid recovery in adult cattle (18) and horses (19). However, there is no information available on the cardiopulmonary effects of sevoflurane anesthesia in small ruminants. In this study, we compared the anesthetic potencies and cardiopulmonary effects of sevoflurane, isoflurane, and halothane anesthesia under spontaneous or controlled ventilation in goats.

MATERIALS AND METHODS

ANIMALS

Eighteen healthy Shiba goats (*Capra hircus*) of either sex, 1.5 to 7 y of age, weighing from 18 to 39 kg body weight (mean 24.6 ± 7.9 kg), were used in this investigation. Health status was evaluated on the base of history, physical examinations, complete blood counts, serum biochemical profiles, and electrocardiograms using standard methods. They were given a commercial ruminant concentrate, hay and water ad libitum. All goats were fasted for 12 h and were not medicated before anesthesia. Anesthesia was carried out in a room controlled at 21 to 24°C.

ANESTHETIC PROCEDURES

In the experiment for determination of the minimal alveolar concentration (MAC), 6 male goats were anesthetized repeatedly at 2-week intervals with sevoflurane, isoflurane or halothane in randomized order as follows: 2 goats were anesthetized with sevoflurane, isoflurane and halothane, in that order. Another 2 goats were anesthetized with isoflurane, halothane and sevoflurane, in that order. The remaining goats were anesthetized with halothane, sevoflurane and isoflurane, in that order. Each anesthetic was vaporised in an out-of-circuit vaporiser. Agent-specific precision vaporisers were used for halothane (Honey Matic M-3, Kimura Med., Tokyo) and sevoflurane (Mark II, Acoma Med., Tokyo), and isoflurane was vaporised from another halothane vaporiser substituted for isoflurane. Gas samples were drawn from the breathing circuit through a tube attached to an adapter positioned between the Y-piece connection and the oral end of the endotracheal tube. The end-tidal anesthetic concentrations were measured continuously using infrared gas analysers (halothane: RI-507M, Riken Keiki Fine Instrument Co., Tokyo, Japan; isoflurane and sevoflurane: Capnomac, Datex, Helsinki, Finland). Airway gas was continuously sampled at the rate of 200 mL/min and the gas was not returned to the circuit. Anesthesia was induced with 4% halothane (Hoechst Japan, Tokyo), 4% isoflurane (Forane, Dinabott, Osaka), or 5% sevoflurane (Sevofrane, Maruishi Pharmaceutical Co., Osaka) in oxygen, at a total gas flow rate of 1.5 L/min using a face mask attached to a circle anesthetic system (Beaver 20, Kimura Med., Tokyo). After induction of anesthesia, a cuffed endotracheal tube was inserted and the cuff was inflated. The goats were placed in right lateral recumbency and ventilated mechanically to maintain at an arterial carbon dioxide pressure level of 35 ± 5 mmHg. Blood samples for gas analysis were collected from a polyethylene 22-gauge catheter inserted into the auricular artery. After an end-tidal anesthetic concentration of approximately 1 MAC, based on dogs as available reference (3), was administered for 15 min, the tail was clamped with a Kocher's forcep for 45 s. The initial values were for 0.9% for halothane, 1.3% for isoflurane, and 2.3% for sevoflurane. A positive response to this painful stimulus was defined as gross purposeful muscular movement of the head or extremities. If the animal showed a positive response to the stimulus, the end-tidal concentration was increased by 10%; if the animal did not show a positive response, the concentration was decreased by 10%. The painful stimulus was repeated at 15-minute intervals until at least two cross-over pairs of positive/negative responses were obtained. The MAC was defined as the average of the end-tidal anesthetic concentrations of the positive/negative responses.

In the spontaneous ventilation (SV) experiment, 6 goats (5 males, 1 female) were an anesthetized repeatedly at 2-week intervals with halothane, isoflurane or sevoflurane in randomized order. In the controlled ventilation (CV) experiment, 6 male goats were also anesthetized repeatedly at 2-week intervals in randomized order. Pre-anesthetic values for heart rate (HR), respiration rate (RR) and arterial blood gases were obtained with the goat resting in a room 15 to 30 min before induction of anesthesia. In both experiments anesthesia was induced as described above. After a cuffed endotracheal tube was inserted, goats were placed in right lateral recumbency and maintained at a surgical plane of anesthesia while breathing spontaneously. For arterial pressure monitoring and blood gas sampling, a polyethylene 20-gauge catheter was inserted into the skin loop of left jugular artery prepared previously. Electrocardiogram (ECG) electrodes were placed at the Apex-Base. A Swan-Ganz catheter (7-French) was inserted through the jugular vein, passed into the right ventricle and advanced into the pulmonary artery. These preparations for cardiopulmonary measurements were completed 25–35 min after induction of anesthesia. Subsequently, the goats were kept at end-tidal concentrations equivalent to 1 MAC of each anesthetic as determined in the first phase of this study. Cardiopulmonary variables were recorded during either SV or CV after 15 min stabilization. The end-tidal anesthetic concentration was then increased from 1 to 1.5 MAC, and from 1.5 to 2 MAC. After 15 min at each anesthetic level, cardiopulmonary variables were recorded. During SV, each anesthesia was maintained at oxygen flow rate of 1.5 L/min using a circle anesthetic system.

CARDIOPULMONARY MEASUREMENTS

At each anesthetic level, systolic and diastolic arterial blood pressures (SAP and DAP) were measured through the arterial catheter. The mean arterial blood pressure (MAP) was calculated as DAP + 1/3 pulse pressure (SAP-DAP). Mean right atrial pressure (MRAP), mean pulmonary arterial pressure (MPAP), and pulmonary capillary wedge pressure

(PCWP) were measured through the Swan-Gantz catheter. These pressures were measured using pressure transducers placed at the heart level and a multi-channel polygraph (RM-6100, Nihon Koden, Japan). A lead Apex-Base ECG was recorded to monitor heart rate and heart rhythm. Cardiac output (CO) was determined by the thermodilution technique with an injection of 5% glucose solution (5 mL, 0°C) into the right atrium during the expiratory phase of ventilation. The cardiovascular variables calculated from above values were as follows: cardiac index (CI) = CO /body weight (kg); stroke volume index (SVI) = CI × 1000/HR; systemic vascular resistance (SVR) = (MAP-MRAP)/CI; rate pressure product (RPP) = HR × SAP; pulmonary vascular resistance (PVR) = (MPAP-PCWP)/CI; left ventricular minute work index (LVMWI) = CI × (MAP-PAWP) × 13.6; left ventricular stroke work index (LVSWI) = SVI × (MAP-PAWP) × 0.0136; right ventricular minute work index (RVMWI) = CI × (MPAP-MRAP) × 13.6; and right ventricular stroke work index (RVSWI) = SVI × (MPAP-MRAP) × 0.0136.

The RR was measured by counting movements of the thorax or the rebreathing bag. Respiratory tidal volume (TV) was measured using a respirometer (Ohmeda RM 121, Japan) placed between the breathing hose and the endotracheal tube and minute ventilation (MV) was calculated. Arterial blood samples were taken anaerobically into heparinized syringes. The volume of blood drawn for each blood gas analysis was 0.3 mL. Arterial oxygen and carbon dioxide partial pressures (PaO_2 and $PaCO_2$, respectively) and arterial pH (pHa) were measured with a blood gas analyser (Blood Gas System 278, Ciba Corning Diagnostic Corp., Tokyo) at 37°C and corrected for each goat's rectal temperature. The arterial bicarbonate ($[HCO_3^-]a$) and base excess (BEa) were derived using standard formulae (20). All measurements and arterial blood sampling were performed at the end of the 15-minute maintenance period at each anesthetic level. The $PaCO_2$ during CV was maintained between 30 and 40 mmHg by adjustment of respiratory frequency (10 to 15/min) at a constant tidal volume (15 mL/kg) using a ventilator (Model B2, Igarashi Ika Kogyo, Tokyo). In the CV experiment, additional arterial blood samples were also taken before beginning the 15-min maintenance at each anesthetic level. If the $PaCO_2$ was not within the limits of values described above, the ventilation was changed and, after 5 min, the measurement of $PaCO_2$ was repeated. Fluids were not administered to goats during the experiments.

TABLE I. Effect of sevoflurane, isoflurane, and halothane anesthesia on respiration rate (RR), respiratory tidal volume (TV), and minute ventilation (MV) during spontaneous ventilation in goats[a]

Variable	Anesthetic Group	Pre-anesthesia	MAC multiples[b] 1	1.5	2
RR (breaths/min)	Halothane	16 ± 4	22 ± 8[c]	24 ± 11[c]	23 ± 13
	Isoflurane	15 ± 3	27 ± 15[c]	27 ± 14[c]	23 ± 15
	Sevoflurane	16 ± 4	25 ± 5[c]	31 ± 4[c]	26 ± 10[c]
TV (mL)	Halothane	ND	231 ± 119	141 ± 60	123 ± 53[d]
	Isoflurane	ND	145 ± 72	129 ± 39	144 ± 74
	Sevoflurane	ND	161 ± 91	141 ± 73	147 ± 88
MV (L/min)	Halothane	ND	4.53 ± 1.46	3.00 ± 1.06[d]	2.38 ± 1.22[d]
	Isoflurane	ND	3.16 ± 1.24	3.10 ± 1.38	2.53 ± 1.19[d]
	Sevoflurane	ND	3.99 ± 1.90	4.21 ± 1.91	3.19 ± 1.35[d]

[a] Data are expressed as mean ± SD ($n = 6$)
[b] The MAC values were 0.96, 1.29 and 2.33% for halothane, isoflurane and sevoflurane. respectively
[c] Significantly different from pre-anesthesia ($P < 0.05$)
[d] Significantly different from 1.0 MAC ($P < 0.05$)
ND = not determined

TABLE II. Effect of sevoflurane, isoflurane, and halothane anesthesia on arterial blood gas and acid-base balance during spontaneous ventilation in goats[a]

Variable	Anesthetic Group	Pre-anesthesia	MAC multiples 1	1.5	2
pHa	Halothane	7.46 ± 0.04	7.34 ± 0.09[d]	7.27 ± 0.09[de]	7.19 ± 0.09[def]
	Isoflurane	7.48 ± 0.03	7.35 ± 0.09[d]	7.28 ± 0.10[de]	7.23 ± 0.10[def]
	Sevoflurane	7.47 ± 0.03	7.40 ± 0.04[d]	7.34 ± 0.03[de]	7.29 ± 0.05[def]
$PaCO_2$ (mmHg)	Halothane	36.1 ± 3.7	51.0 ± 11.2[d]	59.4 ± 13.4[de]	73.2 ± 15.6[def]
	Isoflurane	35.8 ± 3.7	51.7 ± 10.7[d]	62.4 ± 17.5[de]	71.5 ± 18.2[def]
	Sevoflurane	36.1 ± 4.0	44.5 ± 2.8[d]	49.2 ± 3.5[de]	58.4 ± 4.3[defg]
PaO_2 (mmHg)	Halothane	80 ± 12	295 ± 188[d]	278 ± 153[d]	266 ± 154[d]
	Isoflurane	80 ± 10	435 ± 193[d]	329 ± 190[d]	321 ± 166[d]
	Sevoflurane	79 ± 8	369 ± 199[d]	315 ± 176[d]	289 ± 190[d]
$[HCO_3^-]a$ (mmol/L)	Halothane	25.5 ± 2.8	27.2 ± 3.9	27.3 ± 3.0	28.2 ± 3.7
	Isoflurane	29.1 ± 1.7	28.3 ± 3.3	29.1 ± 4.5	29.7 ± 3.3
	Sevoflurane	26.0 ± 2.7	27.6 ± 2.7	26.7 ± 1.9	28.2 ± 2.1
BEa (mmol/L)	Halothane	2.1 ± 2.9	2.1 ± 4.5	1.4 ± 3.8	1.1 ± 4.5
	Isoflurane	3.3 ± 4.9	3.3 ± 4.7	2.3 ± 4.1	2.1 ± 2.9
	Sevoflurane	2.6 ± 2.7	3.5 ± 3.0	1.8 ± 2.1	3.7 ± 1.5

[a] Data are expressed as mean ± SD ($n = 7$)
[b] pHa = arterial pH; $PaCO_2$ = arterial carbon dioxide partial pressure; PaO_2 = arterial oxygen partial pressure; $[HCO_3^-]a$ = arterial bicarbonate; BEa = base excess
[c] The MAC values were 0.96, 1.29 and 2.33% for halothane, isoflurane and sevoflurane, respectively
[d] Significantly different from pre-anesthesia ($P < 0.05$)
[e] Significantly different from 1.0 MAC ($P < 0.05$)
[f] Significantly different from 1.5 MAC ($P < 0.05$)
[g] Significantly different from halothane group ($P < 0.05$)

STATISTICAL ANALYSES

For intergroup comparisons among sevoflurane, isoflurane and halothane groups at common MAC multiples during either SV or CV, the data were subjected to an analysis of variance. When the F value was not significant, the Student's *t*-test was used to determine significant differences between anesthetic groups at a common MAC multiple. When a significant F value was found, a Wilcoxon-Mann-Whitney test was used for the statistical evaluation. For intragroup comparisons grouped according to anesthetic agent at each mode of ventilation, the paired *t*-test was used to identify significant differences between MAC multiple levels. Differences were considered significant when $P < 0.05$.

TABLE III. Cardiovascular effects of sevoflurane, isoflurane, and halothane anesthesia during spontaneous ventilation in goats[a]

Variable[b]	Anesthetic Group	Pre-anesthesia	MAC multiples[c] 1	1.5	2
HR	Halothane	93 ± 14	109 ± 8	118 ± 13	115 ± 12
(beats/min)	Isoflurane	95 ± 21	118 ± 9	116 ± 13	109 ± 13
	Sevoflurane	86 ± 9	113 ± 11[d]	111 ± 17	104 ± 15
MAP	Halothane		101 ± 14	91 ± 15[e]	76 ± 10[ef]
(mmHg)	Isoflurane		98 ± 17	79 ± 24[e]	65 ± 13[e]
	Sevoflurane		104 ± 15	86 ± 16[e]	79 ± 17[e]
CI	Halothane		0.11 ± 0.03	0.12 ± 0.03	0.11 ± 0.03
(L/min/kg)	Isoflurane		0.15 ± 0.0	0.15 ± 0.04	0.13 ± 0.0
	Sevoflurane		0.12 ± 0.03	0.11 ± 0.03	0.10 ± 0.03
SVI	Halothane		1.04 ± 0.25	1.01 ± 0.26	0.97 ± 0.30
(mL/kg)	Isoflurane		1.26 ± 0.33	1.26 ± 0.39	1.16 ± 0.32
	Sevoflurane		1.07 ± 0.32	0.98 ± 0.33	0.95 ± 0.31
RPP	Halothane		13598 ± 2291	13987 ± 3822	12215 ± 3140[f]
(mmHg·beat/min)	Isoflurane		14546 ± 3397	12678 ± 4273	9983 ± 2887[ef]
	Sevoflurane		15046 ± 2972	12570 ± 3867[e]	11397 ± 3845[e]
MPAP	Halothane		14.4 ± 4.8	16.4 ± 2.7	15.4 ± 2.0
(mmHg)	Isoflurane		13.5 ± 3.6	13.8 ± 3.7	16.2 ± 6.0
	Sevoflurane		16.1 ± 6.8	15.8 ± 6.9	16.0 ± 7.9
SVR	Halothane		959 ± 384	824 ± 359	721 ± 277[e]
(mmHg·L/min/kg)	Isoflurane		682 ± 228	564 ± 224[e]	523 ± 154[e]
	Sevoflurane		902 ± 265	852 ± 331	820 ± 275[eh]
PVR	Halothane		89.7 ± 51.7	84.0 ± 31.7	80.7 ± 31.3
(mmHg·L/min/kg)	Isoflurane		58.3 ± 17.8	49.5 ± 17.0[g]	61.3 ± 24.9
	Sevoflurane		72.8 ± 57.6	82.0 ± 70.9	83.7 ± 78.8
LVMWI	Halothane		146 ± 44	133 ± 31	103 ± 34[ef]
(g·m/kg/min)	Isoflurane		194 ± 76	147 ± 67[e]	104 ± 52[ef]
	Sevoflurane		154 ± 46	111 ± 45[e]	97 ± 39[e]
LVSWI	Halothane		1.36 ± 0.34	1.14 ± 0.26	0.91 ± 0.29[e]
(g·m/kg)	Isoflurane		1.62 ± 0.59	1.23 ± 0.49[e]	0.95 ± 0.45[ef]
	Sevoflurane		1.37 ± 0.44	1.02 ± 0.41[e]	0.90 ± 0.31[e]
RVMWI	Halothane		17.0 ± 6.8	19.7 ± 4.9	18.0 ± 6.6
(g·m/kg/min)	Isoflurane		20.7 ± 7.8	19.2 ± 7.2	24.1 ± 18.8
	Sevoflurane		20.5 ± 6.3	17.4 ± 9.0	16.6 ± 8.4
RVSWI	Halothane		0.16 ± 0.07	0.17 ± 0.05	0.16 ± 0.06
(g·m/kg)	Isoflurane		0.18 ± 0.06	0.16 ± 0.05	0.21 ± 0.16
	Sevoflurane		0.18 ± 0.06	0.17 ± 0.10	0.16 ± 0.08

[a] Data are expressed as mean ± SD ($n = 6$)
[b] HR = heart rate; MAP = mean arterial blood pressure; CI = cardiac index; SVI = stroke volume index; RPP = rate pressure product; MPAP = mean pulmonary arterial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; LVMWI = left ventricular minute work index; LVSWI = left ventricular stroke work index; RVMWI = right ventricular minute work index; RVSWI = right ventricular stroke work index
[c] The MAC values were 0.96, 1.29 and 2.33% for halothane, isoflurane and sevoflurane, respectively
[d] Significantly different from pre-anesthesia ($P < 0.05$)
[e] Significantly different from 1.0 MAC ($P < 0.05$)
[f] Significantly different from 1.5 MAC ($P < 0.05$)
[g] Significantly different from halothane group ($P < 0.05$)
[h] Significantly different from isoflurane group ($P < 0.05$)

RESULTS

MAC OF SEVOFLURANE, ISOFLURANE, AND HALOTHANE

The MAC values (mean ± SD) were 0.96 ± 0.12% for halothane, 1.29 ± 0.11% for isoflurane, and 2.33 ± 0.15% for sevoflurane. There were significant differences between the groups in MAC values.

PULMONARY FINDINGS DURING SV

The RR, TV and MV values are shown in Table I. Sevoflurane, halothane and isoflurane at each MAC multiple caused a significant increased in RR when compared with pre-anesthesia values. The TV in the halothane group decreased significantly at 2 MAC multiple when compared with 1 MAC. The MV in halothane group decreased significantly with the increase in the anesthetic concentration. The MV in sevoflurane and isoflurane groups decreased significantly at 2 MAC multiple when compared with 1 MAC. However, there were no significant differences in RR, TV and MV among any of the groups at equipotent MAC multiples. Respiratory arrest did not occur in any goat.

Blood gases and acid-base variables are summarized in Table II. All anesthetics induced significant increases in $PaCO_2$ and significant decreases in pHa with increasing inhalant concentration. Both $PaCO_2$ and pHa levels in isoflurane group were very similar to those in halothane group at equipotent MAC multiples. The $PaCO_2$ at 2 MAC in sevoflurane group was significantly lower than that in halothane group.

The PaO_2 in all groups increased significantly at each MAC multiple when compared with pre-anesthesia values, but there was no significant difference in PaO_2 among any of the groups at each MAC multiple. Both $[HCO_3^-]$a and BEa at each MAC multiple in all groups did not significantly change from pre-anesthesia values. There was no significant difference in either $[HCO_3^-]$a or BEa among any of the groups at equipotent MAC multiples.

CARDIOVASCULAR FINDINGS DURING SV

The results are summarized in Table III. The HR in all groups tended to be higher at each MAC multiple when compared to pre-anesthetic values, but there was no significant difference in HR among any of the groups at equipotent MAC multiples. No arrhythmias were observed in any group.

The MAP, RPP, SVR, LVMWI and LVSWI in all groups decreased significantly with increasing anesthetic concentration. However, CI, SVI, PVR, MPAP, RVMWI and RVSWI in all groups did not significantly change with increasing anesthetic concentrations from 1 to 2 MAC multiples. The MAP, RPP, SVR, PVR, LVMWI and LVSWI at each MAC multiple of sevoflurane were very similar to those of halothane. The MAP in isoflurane group tended to be lower than that in other groups at 1.5 to 2 MAC multiples, but not significantly. The SVR in isoflurane group tended to be lower than that in other groups at each MAC multiple, and was significantly lower than that in sevoflurane group at 2 MAC multiple. There were no significant differences in CI, SVI, RPP, MPAP, LVMWI, LVSWI, RVMWI and RVSWI among any of the groups at equipotent MAC multiples.

CARDIOVASCULAR FINDINGS DURING CV

The results are summarized in Table IV. The HR in all groups was

significantly higher at 1 to 1.5 MAC multiples when compared to pre-anesthetic values, but there was no significant difference in HR among any of the groups at equipotent MAC multiples. No arrhythmias were observed in any group.

The MAP, CI, SVI, RPP, SVR, LVMWI, LVSWI, RVMWI and RVSWI in all groups decreased significantly with increasing anesthetic concentration from 1 to 2 MAC multiples, except that SVI in isoflurane group and SVR in halothane group did not significantly change with an increase in anesthetic concentration. Both MPAP and PVR in each group did not significantly change with an increase in anesthetic concentration from 1 to 2 MAC multiples. Both MAP and RPP at 1 to 2 MAC of isoflurane and 1.5 to 2 MAC of sevoflurane were significantly lower than those of halothane. The RPP at 2 MAC of sevoflurane was significantly higher than that of isoflurane. The MPAP at 1 MAC and SVR at 2 MAC of isoflurane were significantly lower than those of halothane. The LVMWI at 1.5 to 2 MAC of isoflurane and 1.5 MAC of sevoflurane was significantly lower than that of halothane. There were no significant differences in CI, SVI, PVR, RVMWI and RVSWI among any of the groups at equipotent MAC multiples. The MAP, MPAP, SVR, LVMWI, LVSWI, RVMWI and RVSWI at each MAC multiple of sevoflurane were more similar to those of isoflurane, rather than to those of halothane.

TABLE IV. Cardiovascular effects of sevoflurane, isoflurane, and halothane anesthesia during controlled ventilation in goats[a]

Variable[b]	Anesthetic Group	Pre-anesthesia	MAC multiples[c] 1	1.5	2
HR	Halothane	92 ± 17	111 ± 11[d]	122 ± 13[d]	112 ± 16
(beats/min)	Isoflurane	84 ± 9	112 ± 8[d]	111 ± 12[d]	103 ± 11
	Sevoflurane	82 ± 16	112 ± 20[d]	103 ± 17[de]	98 ± 14[e]
MAP	Halothane		106 ± 5	95 ± 11	73 ± 11[ef]
(mmHg)	Isoflurane		84 ± 12[g]	59 ± 10[eg]	47 ± 7[efg]
	Sevoflurane		94 ± 11	65 ± 13[eg]	54 ± 11[eg]
CI	Halothane		0.12 ± 0.04	0.12 ± 0.04	0.09 ± 0.04[ef]
(L/min/kg)	Isoflurane		0.12 ± 0.04	0.11 ± 0.03	0.08 ± 0.01[e]
	Sevoflurane		0.11 ± 0.02	0.10 ± 0.02[e]	0.08 ± 0.01[ef]
SVI	Halothane		1.12 ± 0.30	0.98 ± 0.24[e]	0.83 ± .025[e]
(mL/kg)	Isoflurane		1.11 ± 0.30	1.01 ± 0.26	0.90 ± 0.15
	Sevoflurane		1.01 ± 0.17	0.98 ± 0.20	0.85 ± 0.14[e]
RPP	Halothane		14 833 ± 2540	13 486 ± 1030	9916 ± 1811[ef]
(mmHg·beat/min)	Isoflurane		11 250 ± 1356[g]	8143 ± 1455[eg]	5883 ± 1071[efg]
	Sevoflurane		12 253 ± 2436	8420 ± 1106[eg]	7045 ± 374[efgh]
MPAP	Halothane		17.4 ± 4	16.9 ± 3.4	14.9 ± 1.6
(mmHg)	Isoflurane		14.1 ± 3.6[g]	14.2 ± 3.9	13.8 ± 3.0
	Sevoflurane		15.0 ± 4.6	15.0 ± 4.3	14.4 ± 3.7
SVR	Halothane		830 ± 171	780 ± 176	821 ± 370
(mmHg·L/min/kg)	Isoflurane		713 ± 247	543 ± 248[e]	492 ± 176[eg]
	Sevoflurane		833 ± 183	649 ± 261[e]	605 ± 191[e]
PVR	Halothane		84.2 ± 30.8	74.0 ± 21.1	84.8 ± 53.4
(mmHg·L/min/kg)	Isoflurane		77.7 ± 36.4	91.3 ± 40.2	83.0 ± 36.0
	Sevoflurane		61.0 ± 13.7	67.0 ± 17.0	68.2 ± 16.7
LVMWI	Halothane		173 ± 51	139 ± 35[e]	84 ± 33[ef]
(g·m/kg/min)	Isoflurane		129 ± 47	77 ± 31[eg]	46 ± 6[eg]
	Sevoflurane		134 ± 36	76 ± 14[eg]	53 ± 12[eg]
LVSWI	Halothane		1.49 ± 0.42	1.16 ± 0.34[e]	0.68 ± 0.39[e]
(g·m/kg)	Isoflurane		1.20 ± 0.48	0.75 ± 0.31[e]	0.50 ± 0.11[e]
	Sevoflurane		1.21 ± 0.33	0.78 ± 0.21[e]	0.58 ± 0.23[ef]
RVMWI	Halothane		22.0 ± 8.9	18.5 ± 5.6	13.3 ± 4.8[ef]
(g·m/kg/min)	Isoflurane		16.6 ± 4.1	16.1 ± 3.5	10.3 ± 2.6[f]
	Sevoflurane		15.7 ± 6.0	13.9 ± 2.0	9.3 ± 1.6[ef]
RVSWI	Halothane		0.20 ± 0.08	0.15 ± 0.05[e]	0.12 ± 0.04[e]
(g·m/kg)	Isoflurane		0.15 ± 0.03	0.15 ± 0.02	0.10 ± 0.03[ef]
	Sevoflurane		0.15 ± 0.04	0.14 ± 0.03	0.10 ± 0.03[ef]

[a] Data are expressed as mean ± SD ($n = 6$)
[b] HR = heart rate; MAP = mean arterial blood pressure; CI = cardiac index; SV = stroke volume index; RPP = rate pressure product; MPAP = mean pulmonary arterial pressure; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; LVMWI = left ventricular minute work index; LVSWI = left ventricular stroke work index; RVMWI = right ventricular minute work index; RVSWI = right ventricular stroke work index
[c] The MAC values were 0.96, 1.29 and 2.33% for halothane, isoflurane and sevoflurane, respectively
[d] Significantly different from pre-anesthesia ($P < 0.05$)
[e] Significantly different from 1.0 MAC ($P < 0.05$)
[f] Significantly different from 1.5 MAC ($P < 0.05$)
[g] Significantly different from halothane group ($P < 0.05$)
[h] Significantly different from isoflurane group ($P < 0.05$)

DISCUSSION

The MAC values for sevoflurane, isoflurane, and halothane determined in this study are similar to those in dogs (3,21,22) and newborn swine (23), but are lower than those in cats (24,25) and higher than those in humans (26–28). The MAC value for isoflurane is similar to that in goats determined previously (12). Although factors such as techniques, age and animal species may be involved in slight differences of MAC values, it has been suggested that the ratio of the potencies for any pairing of inhalant anesthetic agents is constant from species to species (25) and provides a means for assessing the validity of preexisting or newly determined MAC values (29). In fact, the sevoflurane/isoflurane (1.81) and sevoflurane/halothane (2.43) ratios in our study are very similar to those (1.78 and 2.69, respectively) in humans (30). On the other hand, it has been reported that methane in expired gases highly interferes with halothane measurement using the Capnomac at the low spectrum band width of 3.3 μm of infrared light, whereas the interference of methane with isoflurane measurement is slight because isoflurane absorption at 3.3 μm is approximately 7 times greater than halothane absorption (31). The specific instrument (RI-507M, Riken) used for halothane measurement in this study also measures halothane at spectrum band width of approximately 3.3 μm of infrared light. Although the degree of interference of methane with sevoflurane measurement is unknown, one should pay attention to the readings of sevoflurane and halothane on the Capnomac or RI-507M, especially when long-term low-flow or closed circuit anesthesia is used in ruminants.

Sevoflurane induces dose-dependent respiratory depression in dogs (32)

and humans (33). The RR in dogs at 1.5 to 2 MAC multiples with sevoflurane is reportedly lower than that with halothane (32). The present findings in goats revealed that sevoflurane, isoflurane and halothane increased RR at 1 to 2 MAC multiples when compared with pre-anesthesia during SV, but RR with sevoflurane does not differ from that with both halothane and isoflurane. The TV and MV with sevoflurane did not significantly differ from those with either halothane or isoflurane at each MAC multiple; however, a dose-dependent decrease in both TV and MV from 1 to 2 MAC multiples with halothane tended to be greater than that with either sevoflurane or isoflurane. This study also revealed that the 3 anesthetics produced a dose-dependent respiratory acidosis (increase in $PaCO_2$ and decrease in pHa), and that the degree of respiratory acidosis induced by sevoflurane did not differ from that induced by either isoflurane or halothane at 1 to 1.5 MAC multiples, but was less than that induced by halothane at 2 MAC multiples. Therefore, the present findings in goats indicate that sevoflurane induces respiratory depression which is less than that induced by halothane at higher concentrations. In dogs, the degree of hypercapnia induced by sevoflurane does not differ from that induced by halothane (32), whereas the hypercapnia with isoflurane at 1.5 MAC multiple is greater than that with halothane (34). However, previous studies in cats have shown that the degree of hypercapnia and acidosis with halothane is greater than with isoflurane (21,35). These findings in dogs and cats somewhat differ from those obtained in goats. In the present study, the $PaCO_2$ during SV with all anesthetics is higher than that reported previously in dogs (21,32), cats (35,36), and humans (33). In ruminants, distension of the rumen due to increasing ruminal gases impairs the ventilation (37), and positioning in lateral recumbency is associated with respiratory depression (38). These factors may be involved in profound hypercapnia during anesthesia in this study. Furthermore, the increased RR with all anesthetics in this study might be in part due to profound hypercapnia, because central and peripheral chemoreceptors responding to increases in $PaCO_2$ can cause an increase in RR.

As we studied in an order of an increasing MAC multiples, as opposed to randomizing the order, an order effect on cardiopulmonary measurements might have occurred, especially during SV. It was reported in dogs that respiratory function was little changed for as long as 7 h of constant 1.2 MAC halothane anesthesia, but that a time-related progressive rise in $PaCO_2$ occurred at constant 1.7 MAC halothane anesthesia (39). The time-related increase in $PaCO_2$ was also reported to occur during 5 h of constant 1.2 MAC halothane or isoflurane anesthesia in laterally recumbent, spontaneously breathing horses (40,41), although the $PaCO_2$ did not significantly change for as long as 1 h of constant-dose anesthesia. In humans, it was reported that respiratory depression remained unchanged for as long as 3 h of constant-depth halothane anesthesia and thereafter ventilation tended to be improved (42). In our study, therefore, the duration of anesthesia at 1.5 to 2.0 MAC multiple of each anesthetic might have somewhat influenced the rise in $PaCO_2$. In addition, the maintenance and replacement fluids were not administered intravenously during anesthesia in this study. This might have also influenced the cardiopulmonary data of this study, particularly at a high MAC multiple.

The HR is unchanged or decreased slightly as sevoflurane concentration increased in dogs (4,43) and pigs (2), however, it is also reported to increase in dogs (44,45). Isoflurane has been reported to induce a slight increase HR in dogs (44–46). Halothane does not significantly alter HR at 1 to 2 MAC multiples in dogs (45). On the other hand, halothane, isoflurane and sevoflurane decrease HR at 0.5 to 1.5 MAC multiples compared to the awake HR in newborn swine (23). The present findings revealed that the three anesthetics significantly increased or tended to increase HR at 1 to 1.5 MAC multiples when compared to pre-anesthetic values during both SV and CV, but there was no significant difference in HR among the three anesthetics at equipotent MAC multiples. Therefore, the present findings indicate that sevoflurane produces a stable HR similar to both isoflurane and halothane in goats.

Sevoflurane produces a dose-dependent decrease in arterial blood pressure (AP), cardiac output, left ventricular work and peripheral vascular resistance in dogs (4,43–45) and pigs (2). Halothane induces a dose-dependent decrease in AP and cardiac output, but has little effect on total peripheral resistance in dogs (21) and cats (35,47,48). In contrast, isoflurane causes a greater fall in peripheral vascular resistance with a decrease in AP and a smaller decrease in cardiac output in dogs and cats (21,22). In chronically instrumented dogs the haemodynamic properties of sevoflurane are almost identical to those of isoflurane, and the vasodilatory action of sevoflurane is more comparable to that of isoflurane than halothane (44,45). The present findings in goats revealed that the three anesthetics induced dose-dependent decreases in MAP, RPP, SVR, LVMWI and LVSWI during SV, and that these circulatory changes with sevoflurane were similar to those with halothane rather than isoflurane. The SVR at higher MAC multiples was lower in isoflurane than sevoflurane during SV. On the other hand, the present findings revealed that the three anesthetics induced dose-dependent decreases in MAP, CI, SVI, RPP, SVR, LVMWI, LVSWI, RVMWI and RVSWI during CV, except that SVI of isoflurane and SVR of halothane did not significantly change from 1 to 2 MAC multiples. Our results further revealed that circulatory depression during CV by sevoflurane was similar to those of isoflurane rather than halothane, and MAP and SVR at higher MAC multiples of either isoflurane or sevoflurane were significantly lower than those of halothane during CV. Therefore, during CV, hemodynamic properties of sevoflurane are almost identical to those of isoflurane, and the vasodilatory action of sevoflurane is more comparable to that of isoflurane than halothane in goats. Halothane induces circulatory depression without a significant effect on total peripheral resistance during CV in goats.

Some of the cardiovascular depression such as MAP, CI and LVMWI were greater under conditions of CV

than SV in this study. As artificial ventilation with positive pressure reduces venous return to the heart by raising intrathoracic pressure, resulting in decreases in mean arterial pressure and cardiac output (49,50), these effects may be involved in a great cardiovascular depression in the CV of this study. On the other hand, it may be possible that the difference between CV and SV found in our study is in part due to the effect of hypercapnia, because carbon dioxide is a direct cardiac depressant and vasodilator, but it causes indirect cardiovascular stimulation via the sympathetic nervous system (51). However, in this study, there was no significant difference in HR between SV and CV. The decrease in sympathetic activity such as depression of ganglionic transmission and central sympathetic depression occurs during halothane anesthesia (52,53). Therefore, indirect cardiovascular stimulation via the sympathetic nervous system by hypercapnia may not be responsible for the differences in cardiovascular responses between CV and SV in this study. Furthermore, in this study, SVR with halothane anesthesia did not significantly change from 1 to 2 MAC multiples during CV, whereas it decreased significantly at 2 MAC multiple compared to 1 MAC multiple during SV. Although the precise mechanism of this difference is unknown, combined effects of both the depression of sympathetic activity by halothane and the peripheral vasodilation by hypercapnia may be involved in the decrease in SVR induced by halothane at 2 MAC multiple during SV in this study.

In conclusion, the present findings indicate that respiratory depression induced by sevoflurane is less than that induced by halothane in goats. Furthermore, sevoflurane produces heart rate similar to both halothane and isoflurane, and it causes circulatory depression similar to isoflurane rather than halothane during CV.

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