Rapid Inhalation Induction of Anesthesia by Halothane, Enflurane, Isoflurane and Sevoflurane and Their Cardiopulmonary Effects in Dogs

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ABSTRACT. The rapid inhalation induction of anesthesia (RII) by mask inhalation of halothane, enflurane, isoflurane and sevoflurane at an equianesthetic concentration (2.5 MAC) was evaluated in 24 beagle dogs. The differences in movements, induction and intubation time between anesthetics were mainly associated with the differences in each blood/gas solubility. The most rapid and smoothest induction was observed by sevoflurane inhalation (209.0 ± 44.2 sec), followed by isoflurane inhalation (285.8 ± 34.1 sec). Halothane inhalation took the longest induction time (790.3 ± 75.7 sec). Movements during RII were minimal in sevoflurane group comparing to the other groups. Heart rate, cardiac output and rate pressure product significantly increased after the beginning of inhalation in all the dogs except for those of halothane group. These changes exceeded the physiological level just after the beginning of inhalation, however, rapidly reversed to the maintenance level (1.5 MAC) approximately 10 min after intubation. Consequently, sevoflurane seemed to be the best inhalational anesthetic for RII in dogs without significant problems in respiratory and/or cardiac functions. Isoflurane also induced rapid induction with some degree of the movements. — KEY WORDS: anesthesia (rapid inhalation induction), canine, cardiopulmonary effect, isoflurane, sevoflurane.

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Ideal drugs for induction of anesthesia in small animals must be rapid and smooth onset and safe without any undesired side effects. Various kinds of intravenous anesthetics including barbiturates and ketamine have been used for this purpose in small animals, among which ultrashort barbiturates such as thiopental sodium are the most common drug. It induces anesthesia in 30 to 60 sec after administration, but the over-dosed or rapid administration sometimes causes apnea, cardiac arrhythmia, respiratory depression and hypotension [11, 18, 29]. These side effects often continue as the "hangover" effect, which makes it difficult to shift to the following maintenance of inhalation anesthesia [1, 5]. Ketamine rapidly induces anesthesia without cardiovascular depression. But inadequate muscle relaxation, considerable salivation and sometimes seizure are seen when not combined with anticholinergic agents, sedatives or tranquilizers [8].

Other injectable agents such as opioid agonists or sedatives cannot induce anesthesia when used alone, though most of them do not cause cardiac depression. If they are used in combination, induction may be obtained without undesired side effects, however, it is difficult to produce rapid and smooth induction compared with other intravenous anesthetics [2, 21].

Inhalation induction is another choice for induction of anesthesia. Inhalation induction can be smoothly shifted to maintenance anesthesia by using the same anesthetic apparatus. Recovery from inhalation anesthesia induced by mask inhalation is quite rapid because there is no prolonged effect of intravenous anesthetics. Thus the method is suitable for poor risk patients or the patients receiving examinations such as CT-scan or minor surgery that needs rapid recovery after the end of these procedures. However, it is still not an alternative induction technique over intravenous induction for its prolonged onset of anesthesia [7, 16].

The major factor that determines the speed of inhalation induction is the blood/gas solubility of anesthetics. Halothane, enflurane and isoflurane are the most common and widely available inhalational anesthetics. Among them, isoflurane has been most frequently used because of its cardiovascular stability and rapid recovery from anesthesia. The blood/gas solubility of isoflurane is 1.40 at 37°C, which is lower than that of halothane (2.30) or enflurane (1.90) [8]. Recently, sevoflurane, a new inhalational anesthetic, has been developed in our country. Sevoflurane has the lower blood/gas solubility (0.63 at 37°C) than isoflurane and has the similar cardiovascular stabilizing effect to isoflurane [22]. With the recent application of these highly volatile and safer anesthetics, the usefulness of inhalation induction technique is also reconsidered.

There are two approaches for inhalation induction [1, 5]. The conventional technique is a slow inhalation induction, which induces anesthesia by an gradual increase in inhalated anesthetic concentration at intervals of 30 to 60 sec. Although this technique aims for the patients to accustom to the pungency of anesthetic gas because inhalational anesthetics generally have an irritation on airways, it is impossible to avoid excitement while passing through light level of anesthesia during induction [7, 16]. Another relatively new induction technique is rapid inhalation induction (RII). In RII patients inspire anesthetic gas at a higher concentration by the patient's vital capacity. RII was first described by Ruffe *et al.* [1, 5] and has been widely

accepted in human medicine in the patients to whom an intravenous induction is not desired [31–34].

Though the volatile anesthetics are thought as safer and easily adjustable agents, RII has some practical problems. Body movement under restraint may reduce the gross volume of inhalated anesthetics, which will cause prolonged induction time. It is very difficult to force animals to inspire at the animal's vital capacity. The dog sometimes hates to inspire the gas with strong smell and resists to mask inhalation. Spontaneous ventilation also causes prolonged induction compared with the voluntary deep inspiration. In addition, mask inhalation may cause the strong excitement of dogs which may affect the cardiopulmonary function.

The purpose of the present study is to evaluate the practical usefulness and the influences of RII on cardiopulmonary functions in dogs.

MATERIALS AND METHODS

Animals: Twenty-four healthy beagle dogs (12 females and 12 males) were used in this study. Their mean age was 13.4 months old (ranging from 10 to 19 month) and mean body weight was 9.2 kg (ranging from 7.9 to 10.8 kg). The animals were randomly assigned to the following 4 anesthetic groups of 6 dogs each. Food was withheld at least 12 hr before the experiments.

Animal preparation: At least 7 days before the experiment, a 14G heparin-coated polyvinyl chloride catheter (Anthron, Toray Medical Co., Japan) was implanted into the left common carotid artery under isoflurane anesthesia. Approximately 2 hr before the experiment, a 6-French 10 cm introducer (SI-5600, Arrow International Inc., U.S.A.) was implanted percutaneously into the right jugular vein under local anesthesia with 1 m*l* of 2% lidocaine.

Drugs: In this study, the following anesthetics were used: halothane (Halothane®, Hoechst Japan Co., Japan), enflurane (Ethrane®, Dainabot Co., Japan), isoflurane (Forane®, Dainabot Co., Japan) and sevoflurane (Sevofrane®, Maruishi Medical Co., Japan). The MAC values of each anesthetic are 0.87% in halothane, 2.06% in enflurane, 1.28% in isoflurane, and 2.36% in sevoflurane, respectively [3, 12, 17].

Anesthetic condition: An anesthetic machine used in this study was a unit (Model KA-3020, Kimura Medical. Co., Japan) with an out-of-circle vaporizer, which was the specific type for each anesthetic. The maximum concentrations of each anesthetic agent was 5.0 vol.%. RII with enflurane and sevoflurane, two vaporizers were connected and placed in the anesthetic circuit to obtain 2.5 MAC of concentration.

The rapid inhalation induction technique: Before inhalation of each anesthetic, oxygen at a flow rate of 3 *l*/min was delivered via the face mask. The anesthetic circuit was primed with each vapor at the desired concentration measured by the infrared gas analyzer (AGM-103 Capnomac, Datex, Finland), where the gas sample was collected from the connector attached to the face mask at a sternal position with their fore and hind limbs tying together. Then the face mask was fitted over the muzzle of the dog by one person and the inhalation of anesthesia was started. The inhalation of each anesthetic was continued keeping the dogs on the restrainting table until laryngeal reflex disappeared, then the dog was placed on the surgical table and intubated with a cuffed endotracheal tube keeping the animal in lateral recumbency.

Experimental design: In sternal recumbency without anesthesia, a 5-French Swan-Ganz catheter (Model 93–132–5F, Baxter Healthcare Co., U.S.A.) was inserted through the placed introducer and advanced into the pulmonary artery for monitoring the intravascular pressures. The Swan-Ganz catheter was then positioned with the proximal portion in the atrium. After the dog's condition was stabilized, all cardiopulmonary measurements were obtained as base-line values. Following the measurements in the conscious state (base-line), the dogs were induced to anesthesia as described above. Dogs were intubated after induction of anesthesia at 2.5 MAC with a flow rate of 3 *l*/min oxygen, then maintained anesthesia under spontaneous ventilation using the same anesthetics at 1.5 MAC of end-tidal anesthetic concentration for 30 min.

Cardiovascular measurements were repeated every minute during the induction period until intubation. In addition, the durations from the beginning of inhalation to onset of movements, end of movements, loss of laryngeal reflex and intubation were recorded. The duration from onset of movements to end of movements was defined as movement time. Induction time represented the time from the inhalation to disappearance of the laryngeal reflex. Intubation time represented the time requiring for the completion of endotracheal intubation. After intubation, all cardiopulmonary measurements were repeated every 10 min. During maintenance anesthesia, pulmonary arterial temperature was kept at approximately 37.0 to 38.0°C by using a warming mat.

Determination of cardiopulmonary measurements: Heart rate (HR) was recorded on a multi-function cardiograph (CMO-104 Cardiocap, Datex, Finland). Systolic, mean and diastolic arterial blood pressures (APs, APm, and APd) were measured through the arterial catheter. Right atrial pressure (RAP) was measured through the Swan-Gantz catheter using a calibrated pressure transducers (PR-AS123S, Terumo Co., Ltd., Japan) connected to a multi-channel polygraph (BSM-8300 Life Scope 9, Nihon Kohden, Japan). Cardiac output (CO) was determined by the thermo-dilution technique by an injection of 3 m*l* of 0°C saline solution into the right atrium during end-expiration. Arterial blood was collected into heparinized glass syringes and stored on ice for the measurements of arterial pH (pHa), PO_2 (PaO_2) and PCO_2 ($PaCO_2$) by blood gas analyzer (IL-1303, Instrumentation Laboratory Ltd., U.S.A.). Blood gas and pH values were corrected according to the dog's body temperature. Respiratory rate (RR), end-tidal anesthetic concentration (F_A) and inspiratory anesthetic concentration (F_I) were monitored by the infrared gas analyzer.

From above values, following cardiovascular parameters were calculated: cardiac index (CI) = CO/body weight,

systemic vascular resistance (SVR) = (APm – RAP)/CO, and rate pressure product (RPP) = APs · HR.

Statistical analysis: To compare the cardiopulmonary parameters within each inhalational anesthetic group, analysis of variance (ANOVA) with a two-way repeated measure and a Scheffe's multiple paired *t*-test were used. Comparison between anesthetic groups was made on the movements, induction and intubation time, which were analyzed by a one-way ANOVA of repeated measures and a Scheffe's multiple paired *t*-test. P values less than 0.05 were considered as significant.

RESULTS

Induction with 2.5 MAC inhalation anesthetics: Induction time, intubation time and movements during RII were summarized in Table 1. Among the anesthetics, induction time and intubation time by sevoflurane were the shortest. Those by isoflurane inhalation were slightly longer than by sevoflurane inhalation, however there was no significant difference between the two. Induction time and intubation time in these two anesthetic inhalation groups were significantly shorter than those in the other anesthetic inhalation groups.

Movements during the inhalation procedure were similar in the anesthetics except for sevoflurane. Movements started at approximately 2 min after the beginning of enflurane or isoflurane inhalation, then continued for approximated 2 min in enflurane inhalating dogs and for 1.3 min in isoflurane inhalating dogs, respectively. In halothane inhalation group, however, movements started at approximately 3.5 min and continued for 4 min, which was significantly longer than in enflurane or isoflurane inhalation groups. In sevoflurane inhalation group, there were almost no movements in 5 of 6 dogs, and they were rapidly and smoothly induced to deep anesthesia.

In all anesthetic inhalation groups, complications such as coughing, laryngospasm, breath-holding and salivary secretion were not observed.

Changes in cardiovascular parameters: Changes in cardiovascular parameters in RII were summarized in Table 2. There were no significant differences in conscious base-line values among inhalation groups. Since the time until intubation was various in each inhalation group, the duration for recording of cardiovascular parameters was different in each group.

Heart rate rapidly and significantly rose after the beginning of inhalation and reached to the maximum level in approximately 2 to 3 min. Then it rapidly declined in enflurane, isoflurane, and sevoflurane inhalation groups while at that moment a slight but not significant increase was seen in halothane inhalation group. Mean arterial blood pressure mildly but not significantly increased just after the beginning of inhalation. Then it mildly decreased in halothane, enflurane, and sevoflurane inhalation groups, whereas slight but not significant increases were observed in isoflurane group until 3 min after inhalation.

Systemic vascular resistance tended to decrease in the inhalation groups after the beginning of inhalation, but any significances were not observed. The changing patterns of CI and RPP were similar to that of HR. Significant increases from the base-line values in RPP were observed in all anesthetic inhalation groups except for halothane inhalation group.

Changes in these parameters during maintenance anesthesia after RII were shown in Table 3. During maintenance anesthesia, significant increases in HR compared with the base-line values were observed at intubation in enflurane inhalation group and at 10 min after intubation in isoflurane and sevoflurane inhalation groups, respectively. Mean arterial blood pressure and SVR significantly decreased compared with the base-line values after intubation in all inhalation groups. Cardiac index showed little changes throughout this period in any anesthetic inhalation groups. Rate pressure product mildly but not significantly increased at intubation, but declined to the base-line values thereafter.

Changes in respiratory parameters at and after intubation: Changes in respiratory parameters were summarized in Table 4. Respiratory rate significantly increased and maintained the level at and after intubation in halothane inhalation group. In sevoflurane inhalation group RR was also significantly higher at intubation compared with the base-line value, but reversed to the base-line value thereafter. On the contrary, RR in enflurane inhalation group decreased after intubation and showed significantly lower levels than the base-line value from 20 to 30 min of intubation. Respiratory rate did not change significantly in

Table 1. Comparison of induction time, intubation time, and movements during RII by inhalation of 2.5 MAC anesthetics in dogs[a)]

Measurements		Halothane (n=6)	Enflurane (n=6)	Isoflurane (n=6)	Sevoflurane (n=6)
Induction time	(sec)	790.3 ± 75.7*§¶	374.8 ± 36.0§¶	285.8 ± 34.1	209.0 ± 44.2
Intubation time	(sec)	821.3 ± 72.5*§¶	404.5 ± 32.4§¶	311.0 ± 44.3	237.8 ± 47.8
Onset of movements	(sec)	217.2 ± 38.5*§¶	125.5 ± 40.0	117.2 ± 25.0	48.0
End of movements	(sec)	457.5 ± 66.6*§¶	250.8 ± 47.4	197.7 ± 31.1	135.0
Movements time	(sec)	240.3 ± 95.6*§¶	125.3 ± 40.9	80.5 ± 35.0	87.0
Movements		6/6 (100%)	6/6 (100%)	6/6 (100%)	1/6 (16.7%)

a) All data were expressed as mean ± standard deviation. *: Signifiantly ($p<0.05$) different from enflurane group. §: Significant ($p<0.05$) different from isoflurane group. ¶: Significantly ($p<0.05$) different from sevoflurane group.

Table 2. Changes in cardiovascular parameters after inhalation of 2.5 MAC anesthetics during RII in dogs[a)]

Measurements		Base-line	Time (sec) after anesthetic inhalation						
			60	120	180	240	300	420	540
HR	Hal	97 ± 4	103 ± 16	114 ± 12	122 ± 7	127 ± 10	127 ± 12	124 ± 8	112 ± 12
(min^{-1})	Enf	95 ± 8	140 ± 23*	182 ± 25*	174 ± 20*	153 ± 13*	148 ± 10*	ND	ND
	Iso	95 ± 5	110 ± 15	159 ± 14*	178 ± 20*	161 ± 19*	ND[b)]	ND	ND
	Sevo	97 ± 13	149 ± 15*	171 ± 10*	158 ± 13*	ND	ND	ND	ND
APm	Hal	118 ± 12	131 ± 10	126 ± 12	122 ± 11	116 ± 13	114 ± 12	108 ± 12	95 ± 10
(mmHg)	Enf	119 ± 11	125 ± 23	119 ± 25	111 ± 27	91 ± 23	83 ± 22	ND	ND
	Iso	116 ± 9	129 ± 14	134 ± 13	132 ± 5	110 ± 13	ND	ND	ND
	Sevo	117 ± 5	121 ± 16	111 ± 18	101 ± 18	ND	ND	ND	ND
SVR	Hal	533 ± 96	569 ± 90	547 ± 79	480 ± 53	425 ± 57	401 ± 62	397 ± 77	398 ± 59
($mmHg \cdot min \cdot kg \cdot l^{-1}$)	Enf	539 ± 96	460 ± 88	414 ± 101	397 ± 86	368 ± 92	353 ± 61	ND	ND
	Iso	544 ± 85	542 ± 115	442 ± 30	444 ± 45	428 ± 67	ND	ND	ND
	Sevo	546 ± 54	449 ± 104	382 ± 81	419 ± 85	ND	ND	ND	ND
CI	Hal	219 ± 21	226 ± 22	225 ± 17	247 ± 24	264 ± 31	277 ± 31	246 ± 16	231 ± 13
($ml \cdot min^{-1} \cdot kg^{-1}$)	Enf	218 ± 25	263 ± 17*	279 ± 24*	269 ± 21*	239 ± 10*	221 ± 27	ND	ND
	Iso	212 ± 24	235 ± 29	294 ± 25*	292 ± 31*	250 ± 23	ND	ND	ND
	Sevo	211 ± 24	266 ± 29*	284 ± 20*	237 ± 25	ND	ND	ND	ND
RPP	Hal	15634 ± 1207	17465 ± 3901	18446 ± 3493	18779 ± 2426	18846 ± 2590	18271 ± 2555	16803 ± 1694	13354 ± 2007
($mmHg \cdot min^{-1}$)	Enf	14659 ± 1844	21969 ± 5512*	27220 ± 7145	24637 ± 6520	17985 ± 4927	17045 ± 3351	ND	ND
	Iso	14383 ± 901	18448 ± 4218*	26676 ± 4347*	29507 ± 4052	23539 ± 3168	ND	ND	ND
	Sevo	14884 ± 2556	23103 ± 3047*	23737 ± 4080	20064 ± 4158	ND	ND	ND	ND

a) Data were expressed as mean ± standard deviation. HR=heart rate, APm=mean arterial blood pressure, SVR=systemic vascular resistance, CI=cardiac index, and RPP=rate pressure product. Hal=halothane, Enf=enflurane, Iso=isoflurane, and Sevo=sevoflurane.
b) ND: Not done.
*: Significantly ($p<0.05$) different from the base-line value.

Table 3. Changes in cardiovascular parameters during maintenance anesthesia after RII by inhalation of 2.5 MAC anesthetics in dogs[a)]

Measurements		Base-line	Intubation	Time (min) after inhalation		
				10	20	30
HR	Hal	97 ± 4	118 ± 10	117 ± 12	114 ± 14	115 ± 13
(min^{-1})	Enf	95 ± 8	137 ± 16*	120 ± 11	117 ± 11	114 ± 11
	Iso	95 ± 5	142 ± 19*	133 ± 14*	133 ± 13*	128 ± 8*
	Sevo	97 ± 13	149 ± 8*	134 ± 15*	128 ± 17*	125 ± 17*
APm	Hal	118 ± 12	92 ± 7*	72 ± 7*	67 ± 9*	67 ± 7*
(mmHg)	Enf	119 ± 11	78 ± 20*	62 ± 9*	61 ± 10*	59 ± 11*
	Iso	116 ± 9	96 ± 13*	71 ± 8*	68 ± 7*§	66 ± 6*§
	Sevo	117 ± 5	94 ± 19*	73 ± 10*	67 ± 10*	65 ± 10*
SVR	Hal	533 ± 96	392 ± 44	332 ± 50*	324 ± 49*	325 ± 39*
($mmHg \cdot min \cdot kg \cdot l^{-1}$)	Enf	539 ± 103	341 ± 117	299 ± 49*§	291 ± 45*§	291 ± 48*§
	Iso	544 ± 85	433 ± 68	329 ± 47*	322 ± 37*	313 ± 30*
	Sevo	546 ± 54	419 ± 79	354 ± 54*	341 ± 73*	326 ± 54*
CI	Hal	219 ± 21	226 ± 19	206 ± 20	197 ± 16	196 ± 17
($ml \cdot min^{-1} \cdot kg^{-1}$)	Enf	218 ± 25	222 ± 36	198 ± 29	198 ± 37	189 ± 30
	Iso	212 ± 24	215 ± 22	205 ± 13	198 ± 16	198 ± 10
	Sevo	211 ± 24	216 ± 14	200 ± 16	191 ± 22	192 ± 22
RPP	Hal	15634 ± 1207	13524 ± 1600	11633 ± 1561	10784 ± 2106	10455 ± 1945
($mmHg \cdot min^{-1}$)	Enf	14659 ± 1844	14592 ± 2721	10370 ± 1862	9462 ± 1964	8982 ± 2203
	Iso	14383 ± 901	18204 ± 2584	12795 ± 549	12331 ± 869	11526 ± 1076
	Sevo	14884 ± 2556	17136 ± 3256	12602 ± 3088	11223 ± 3548	10461 ± 3243

a) Data were expressed as mean ± standard deviation. HR=heart rate, APm=mean arterial blood pressure, SVR=systemic vascular resistance, CI=cardiac index, and RPP=rate pressure product. Hal=halothane, Enf=enflurane, Iso=isoflurane, and Sevo=sevoflurane.
*: Significantly ($p<0.05$) different from the base-line value.
§: Significantly ($p<0.05$) different from the value at intubation.

Table 4. Changes in respiratory parameters at and after intubation under RII by inhalation of 2.5 MAC in dogs[a)]

Measurements		Base-line	Intubation	Time (min) after inhalation 10	20	30
RR (min^{-1})	Hal	13.7 ± 2.7	29.0 ± 5.7*	24.3 ± 3.7*	28.0 ± 3.6*	28.8 ± 3.1*
	Enf	13.3 ± 2.1	14.2 ± 2.5	8.7 ± 2.5	8.2 ± 2.6*	7.2 ± 1.8*
	Iso	15.0 ± 4.7	18.5 ± 4.8	15.3 ± 3.4	14.5 ± 2.9	14.5 ± 3.1
	Sevo	14.0 ± 2.2	25.8 ± 4.3*	15.0 ± 2.0§	15.8 ± 3.1§	14.5 ± 3.3§
PaO_2 (mmHg)	Hal	104 ± 13	496 ± 24*	491 ± 9*	488 ± 12*	500 ± 19*
	Enf	100 ± 11	460 ± 26*	472 ± 22*	473 ± 29*	465 ± 27*
	Iso	103 ± 8	484 ± 14*	496 ± 14*	496 ± 18*	500 ± 17*
	Sevo	108 ± 12	486 ± 23*	510 ± 12*	508 ± 12*	510 ± 16*
$PaCO_2$ (mmHg)	Hal	36.9 ± 4.7	42.2 ± 3.4	47.9 ± 4.9*	45.0 ± 5.5	45.2 ± 5.4
	Enf	37.4 ± 5.2	49.3 ± 4.7*	46.9 ± 7.9	54.5 ± 5.0*	53.5 ± 2.8*
	Iso	37.7 ± 3.5	46.2 ± 2.8*	49.2 ± 4.0*	49.7 ± 3.3*	48.9 ± 4.0*
	Sevo	39.9 ± 5.6	45.2 ± 5.4	52.3 ± 6.8*	49.1 ± 7.1*	51.3 ± 6.3*
pHa	Hal	7.30 ± 0.01	7.24 ± 0.01*	7.21 ± 0.02*	7.20 ± 0.02*	7.18 ± 0.03*
	Enf	7.28 ± 0.02	7.19 ± 0.05*	7.17 ± 0.03*	7.16 ± 0.04*	7.16 ± 0.03*
	Iso	7.29 ± 0.03	7.22 ± 0.02*	7.19 ± 0.03*	7.19 ± 0.02*	7.19 ± 0.03*
	Sevo	7.30 ± 0.03	7.24 ± 0.02*	7.19 ± 0.02*	7.20 ± 0.02*	7.20 ± 0.01*

a) Data were expressed as mean ± standard deviation. RR=respiratory rate. PaO_2, $PaCO_2$, and pHa=arterial blood PO_2, PCO_2, and pH. Hal=halothane, Enf=enflurane, Iso=isoflurane, and Sevo=sevoflurane.
*: Significantly ($p<0.05$) different from the base-line value.
§: Significantly ($p<0.05$) different from the value at intubation.

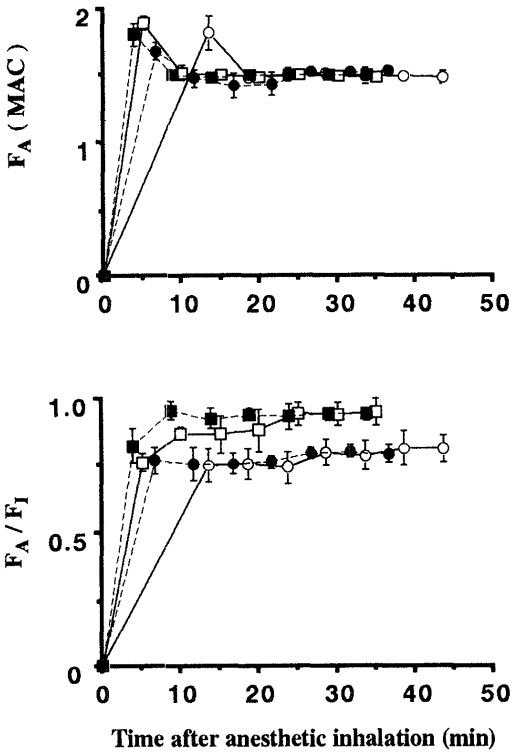

Fig. 1. F_A and F_A/F_I under RII with halothane (open circle and solid line), enflurane (closed circle and brolen line), isoflurane (open square and solid line), and sevoflurane (closed square and broken line). F_A=end-tidal anesthetic concentration. F_I=inspiratory anesthetic concentration. Values were expressed as mean standard ± deviation. First recording points after anesthetic inhalation indicate the intubation time.

isoflurane inhalation group.

PaO_2 increased during RII in all anesthetic inhalation groups and maintained considerably high levels during the maintenance period. $PaCO_2$ also increased during RII, and after intubation their levels were maintained the higher levels than the base-line value throughout maintenance period. In relation to the increased $PaCO_2$, pHa significantly decreased during RII.

Changes in anesthetic concentrations: Changes in end-tidal and inspiratory anesthetic concentrations during and after RII were showen in Fig. 1. In all inhalation groups, F_A rapidly increased after the beginning of inhalation, then reached to the expected anesthetic concentration (1.5 MAC) in 10 min after intubation. F_A/F_I was also rapidly increased after the beginning of inhalation, and reached to the plateau level in 10 min after intubation.

DISCUSSION

Sevoflurane induced the anesthetic stage for intubation most rapidly and smoothly among the anesthetics at an equianesthetic concentration (2.5 MAC). Isoflurane also induced anesthesia rapidly though the movements during RII were stronger than sevoflurane. Movements during RII seems to be related to the time for the increase in end-tidal anesthetic concentration. The most important factor for the rapid increase in end-tidal anesthetic concentration is blood/gas solubility of anesthetics. Sevoflurane is the lowest solubility among the anesthetics used in this study.

In addition, most of the dogs hate the smell of the anesthetic agents, thus the dogs were allowed spontaneous ventilation during RII in the present study, which caused

the shallow respiration during RII. This may cause a slower increase in end-tidal concentration and prolonged exposure to the light stage of anesthesia, which resulted in stronger and longer movements.

Cardiovascular changes during RII were remarkable in enflurane, isoflurane, and sevoflurane groups. Heart rate showed an approximately 85% increase after the beginning of the inhalation. Cardiac output also showed a rapid increase, which was mainly caused from the increased HR and partly from the mild decrease in afterload represented by SVR. Myocardial oxygen demand represented by RPP steeply increased, accompanied by the rapid increase in HR. Arterial blood pressures initially increased mildly along with the increase in CO, but tended to decrease, which might be caused by the decrease in SVR. These changes initially exceeded the physiological level just after inhalation, however, rapidly reversed to the normal level, thereafter. Thus, the RII by those anesthetics may be safe in the patients without significant cardiovascular diseases.

On the contrary, the degree of changes in cardiac parameters in halothane group was milder compared with other anesthetic groups. In this group, the increase in HR was mild and CO did not change significantly, suggesting changes in afterload in this group was minimal. The cause of differences in these cardiovascular parameters between halothane group and the other three groups are not clear. If these changes would be mainly caused by the central nervous activation associated with the light anesthetic condition [6], the dog in halothane group must show the most remarkable changes since the blood/gas solubility of halothane was the highest among the anesthetics used. Halothane is known to have less depressive effects on baroreceptor reflex function compared with other anesthetics [20, 27], which may be one of the causes of the less cardiovascular changes. Further study will be needed to clarify the mechanism.

In this study, any dogs did not show the signs of airway stimulation. In human, isoflurane and enflurane are not used for inhalation induction because of the strong irritation to the airway mucosa [4]. The irritation is caused by the chemical stimulation of inhalational anesthetics on the irritant receptors through the vagal afferent nerve. Nishino *et al.* reported that a large number of irritant receptors are activated by halothane, enflurane, and isoflurane in a dose-dependent manner in dogs [14], while Sant'Ambrogio *et al.* concluded that no stimulation on irritant receptors by halothane or isoflurane is recognized, even though they inspired the anesthetics at higher concentrations [19]. Our results supported the results reported by Sant'Ambrogio *et al.*

In spite of the dramatic changes in cardiovascular function during induction by inhalation of enflurane, isoflurane, or sevoflurane, the stabilization after intubation was fast in all anesthetics. The stable states in circulatory and respiratory system could be obtained in 10 min after intubation in all the dogs of any anesthetic groups. The adjustment of end-tidal anesthetic concentration was completed in 5 min, which suggests that alveolar and blood anesthetic concentration was stabilized in 5 min after intubation. These findings in dogs were similar to those in human [20]. The level of circulatory and respiratory measurements at 10 min after intubation corresponded to those at 1.5 MAC of each anesthetic previously reported [8, 13, 24, 25], which suggests any "hangover" [1] effect was not produced by RII.

Throughout the RII, dogs of any anesthetic groups did not lose spontaneous ventilation. This is a great advantage over the injectable anesthetics because rapid induction using ultrashort barbiturates such as thiobarbiturates often causes a certain period of apnea [11, 18, 29]. It is reported that the inhalational anesthetics hardly depress ventilation at the light (1 MAC) through middle (1.5 MAC) anesthetic level [9, 23–25]. These anesthetics may gradually depress ventilation when deeper anesthetic level (2 MAC) is maintained, however, most of surgeries may be performed at an end-tidal anesthetic concentration less than 2 MAC, thus the respiratory depression will not be a problem in this type of anesthetic method. The increase in respiratory rate at and after intubation was the highest in halothane as previously reported [9, 10, 15], which suggests that the depressant effect of halothane on the respiratory center was least among anesthetics used in this study.

In conclusion, sevoflurane seems to be the best inhalational anesthetic for RII in dogs. Isoflurane also induced rapid induction with more movements during induction, but higher concentrations may help the reduction of movements. Though there were a certain level of problems in cardiovascular functions, these two anesthetics can be used as a safer and useful induction agent in dogs without significant cardiac and/or respiratory diseases. Considering the longer movements and induction time, halothane may not be recommended for rapid inhalation induction. Advantages of cardiovascular stability can not compensate for these disadvantages.

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