

Comparison of Minimum Alveolar Concentration between Intravenous Isoflurane Lipid Emulsion and Inhaled Isoflurane in Dogs

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Background: As in inhaled isoflurane anesthesia, when isoflurane lipid emulsion (ILE; 8%, vol/vol) is intravenously administered, the primary elimination route is through the lungs. This study was designed to determine the minimum alveolar concentration (MAC) and the time course of washout of isoflurane for intravenously infused ILE by monitoring end-tidal isoflurane concentration.

Methods: Twelve healthy adult mongrel dogs were assigned randomly to an intravenous anesthesia group with 8% ILE or to an inhalation anesthesia group with isoflurane vapor. An up-and-down method and stimulation of tail clamping were used to determine MAC of 8% ILE by intravenous injection in the intravenous anesthesia group and MAC by the inhaled approach in the inhalation anesthesia group, respectively. Isoflurane concentration and partial pressure in end-tidal gas, femoral arterial blood, and jugular venous blood were measured simultaneously just before each tail clamping and during washout.

Results: The induction time in the intravenous anesthesia group (105 ± 24 s) was shorter than that in the inhalation anesthesia group (378 ± 102 s; $P < 0.01$). MAC of 8% ILE by intravenous injection ($1.12 \pm 0.18\%$) was significantly less than MAC by the inhaled approach ($1.38 \pm 0.16\%$; $P < 0.05$). No significant difference was found between the two groups in the time course of washout of isoflurane.

Conclusion: The MAC of intravenous anesthesia with 8% ILE was less than that of inhalation anesthesia with isoflurane vapor in dogs.

THE ED₅₀ and LD₅₀ of intravenous isoflurane lipid emulsion (ILE) in mice,¹ the anesthetic and physiologic effects of intravenous halothane lipid emulsion in swine,² and the hemodynamics effects of intravenous infusion of halothane lipid emulsion in dogs³ have been studied. However, the dog's minimum alveolar concentration (MAC_{iv}) with intravenous infusion of ILE (8%, vol/vol) has not been investigated. As with inhaled isoflurane

anesthesia, the primarily eliminative route of isoflurane by intravenous infusion of ILE is also through the lungs. Therefore, the MAC of 8% ILE by intravenous injection (MAC_{iv}-ILE8) could be determined by monitoring end-tidal isoflurane concentration. Musser *et al.*² demonstrated that the MAC_{iv} (0.78%) of intravenous emulsified halothane (5%, vol/vol) was smaller than the MAC by the inhaled approach (MAC_{inh}; 1.13%) of halothane vapor in swine. Because of the similar chemophysical properties of halothane and isoflurane, we hypothesized that the MAC_{iv} of isoflurane was smaller than its MAC_{inh}. The difference of anesthetic partial pressure between alveolar gas and arterial blood has been shown to be a positive value during maintaining or deepening anesthesia by inhaled volatile anesthetic⁴ and might be a negative value when emulsified anesthetics are infused intravenously. However, the arterial partial pressures (indicating the partial pressure in the central nervous system after equilibration) of isoflurane between the intravenous approach and inhalation should be the same, because isoflurane dissolved in Intralipid® (Huarui Pharmacy, Ltd., Wuxi, Jiangsu, China) produces anesthesia through the same mechanism as inhaled isoflurane when half of the animals are anesthetized. We designed this study to verify these predictions during intravenous and inhaled anesthesia approaches by simultaneously measuring isoflurane concentrations and partial pressures in the femoral arterial blood, jugular venous blood, and end-tidal gas.

Materials and Methods

Isoflurane was purchased from Abbott Laboratories (Queenborough, Kent, United Kingdom). Intralipid®, 30%, was provided by Huarui Pharmacy, Ltd. On the day before the experiment, using an aseptic technique, 18.4 ml Intralipid®, 30%, and 1.6 ml liquid isoflurane were transferred into a 20-ml glass ampoule using syringes, and the ampoule was sealed using an alcohol blowtorch. Then, the ampoule was vigorously shaken on a vibrator for 15 min to solubilize isoflurane into the lipid emulsion. Sixty ampoules of 8% ILE were prepared for the study using this procedure. The ampoule was opened just before use, and the residual ILE in the opened ampoule was not reused in this study. Before this experiment, the stability of 8% ILE was investigated; no change in isoflurane concentration and no lipid drop-

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lets were found during 6 months of storage at room temperature (20°–26°C). The measured concentration of isoflurane in this lipid emulsion at 15 min after the ampoule was opened was not different compared with the isoflurane concentration before the emulsion was transferred into the ampoules, which might be due to a high isoflurane lipid/gas partition coefficient (70/52 at 20°–25°C; unpublished data from our laboratory Xiao-Lin Yang, M.D., Han-Xiang Ma, M.B., Nan-Fu Luo, M.B., Wen-Sheng Zhang, M.D., and Jin Liu, M.D., June 2004).

After obtaining approval from the Institutional Animal Care and Use Committee of Sichuan University (Chengdu, Sichuan, China), 12 healthy mongrel dogs, aged 12–18 months and weighing 9.0–12.5 kg, were randomly assigned to the intravenous anesthesia group (G_{iv}) with 8% ILE or to the inhalation anesthesia group (G_{inh}) with isoflurane vapor. All dogs were allowed to socialize with people on daily basis before the study. Food, but not water, was withheld for 12 h before the start of each experiment.

After body weight had been measured, dogs were positioned in a sternal recumbency on a restraining table. Each dog was fitted for a special facemask connected to an anesthesia machine (Excel 210 SE; Datex-Ohmeda, Madison, WI) fitted with an isoflurane vaporizer; dogs initially breathed 100% oxygen before ILE or isoflurane vapor was administered. In G_{iv} , 8% ILE was administered into the right cephalic vein at a rate of 1 ml/s, and in G_{inh} , 5% isoflurane was inhaled with a fresh oxygen flow rate at 4 l/min through the facemask. The tidal volume and respiratory rate were monitored using the anesthesia machine. The dog's palpebral reflex was assessed by gently brushing the eyelashes of one eyelid with a finger every 5 s after isoflurane administration. After the palpebral reflex disappeared, an 8-French cuffed endotracheal tube was inserted. Ventilator settings were adjusted to maintain normal end-tidal carbon dioxide pressure at 35–40 mmHg. Heart rate, electrocardiograph, lingual pulse oxygen saturation, femoral arterial blood pressure, and esophageal temperature were monitored with use of a 150B3 monitor (Philips, Suzhou, China). The inspired and expiratory anesthetic concentrations and end-tidal carbon dioxide pressure were also monitored with this monitor through a sampling line placed in the tip of the cuffed endotracheal tube. The fresh oxygen flow rate was maintained between 3 and 3.5 l/min, which exceeded the minute ventilation volume to avoid isoflurane rebreathing. The left jugular vein was chosen for infusing lactated Ringer's solution (10 ml · kg⁻¹ · h⁻¹) and for collecting blood samples. The esophageal temperature was maintained at 36.5°–38.5°C by using heated blankets.

The up-and-down method and the tail clamping stimulation were used to determine MAC_{iv} -ILE8 and MAC_{inh} .^{5–7} In G_{iv} , the initial end-tidal isoflurane concentration for determining MAC_{iv} -ILE8 was maintained at

0.9% for at least 20 min by adjusting the rate of the microinfusion pump (TCI-I; Silugao High Technology Development Co., Ltd., Beijing, China). In G_{inh} , the initial end-tidal isoflurane concentration of 1.1% was maintained for 20 min by adjusting the isoflurane vaporizer. Before each tail clamping, 5 ml end-tidal gas, 4 ml femoral arterial blood, and 4 ml jugular venous blood were drawn simultaneously for determining isoflurane concentrations and partial pressures by using a gas chromatograph (described two paragraphs below). Then, a pair of forceps was clamped on the shaved tail approximately 5–10 centimeters from its base in intervals of three times every 15 s for 1 min. A positive response to the tail clamping was considered to be a gross purposeful muscular movement, usually of the head or other extremities. Only significant jerking or twisting motions were included, not head movements such as twitches or grimaces. Coughing, swallowing, or chewing was not considered to be a positive response.⁵ If the tail clamping response was positive or negative, the end-tidal isoflurane concentration was increased or decreased by 20% and maintained for 20 min before subsequent clamps. The process of assessing the response was continued until a crossover of a positive response with a negative response had occurred. The concentration or partial pressure in the arterial blood, the venous blood, or the end-tidal gas to a midway point between the highest (which allowed movements) and the lowest (which prevented movements) was defined as the value of minimum arterial concentration or partial pressure, minimum venous concentration or partial pressure, or minimum alveolar concentration (MAC_{iv} -ILE8 for G_{iv} and MAC_{inh} for G_{inh}) or partial pressure, respectively.

Administration of 8% ILE or isoflurane vapor was immediately stopped when the last tail clamping was finished. The anesthetic vapor analyzer continued to monitor the elimination of isoflurane from the lungs. The dog was considered awake when palpebral reflex recovered and the endotracheal tube could not be tolerated. Then, 2–4 mg midazolam, 0.05–0.1 mg fentanyl, and 10–15 mg atracurium were intravenously injected to keep the dog anesthetized and the ventilation controlled. The time from stopping administration of ILE or isoflurane vapor to just before intravenous injection of these anesthetics for the first time was defined as the awakening time. During the period from stopping intravenous ILE or inhaled isoflurane to the end-tidal isoflurane concentration on the screen reading zero, samples of end-tidal gas and femoral arterial and jugular venous blood were obtained simultaneously when the end-tidal isoflurane concentration decreased to 0.7%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, and 0%, respectively. Samples were also obtained at the awakening time. All dogs were observed daily for 2 weeks after experimentation for redness, swelling, or thrombophlebitis at the infusion site, and for death.

Isoflurane concentration was determined by using a gas chromatograph (Agilent 4890D; Tegment Technology Ltd., Shanghai, China) equipped with a 6-m-long stainless steel column (3.2-mm internal diameter) packed with Chromosorb-P 60/80 mesh maintained at 75°C. A 17-ml/min nitrogen carrier stream flow was delivered through the column to a flame ionization detector supplied by hydrogen at 40 ml/min and by air at 200 ml/min. The output from the gas chromatography was collected by an HP 3398 GC workstation (Tegment Technology Ltd.), and peak areas were automatically integrated. The isoflurane concentration in the blood (C) and the determined value of isoflurane blood/gas partition coefficient ($\lambda_{b/g}$) were measured by the two-stage headspace equilibration method.⁸⁻¹⁰ Isoflurane partial pressure in the blood (P) was calculated by the equation $P = (C/\lambda_{b/g}) \times 760$ mmHg, and the end-tidal isoflurane partial pressure was equal to its percent of concentration multiplied by 760 mmHg.

Data were reported as mean \pm SD. The Student *t* test was used for comparison between the two groups. One-way analysis of variance was applied to the comparisons among the isoflurane concentration or partial pressure in the arterial blood, venous blood, and end-tidal gas either in G_{iv} or in G_{inh} . $P < 0.05$ was accepted as statistical significance. Linear regression analysis was used to analyze the correlation between $\lambda_{b/g}$ and the volume of infused lipid emulsion. Combined data during the period of administration and washout were used for linear regression analysis to correlate isoflurane partial pressures between arterial blood and end-tidal gas at corresponding time points for both G_{iv} and G_{inh} . During washout, the rate constant of isoflurane elimination (β) was obtained by the slope of each linear regression equation between the logarithm of isoflurane concentration in the blood and its corresponding washout time.¹¹ The elimination half-life of isoflurane concentration in the blood ($t_{0.5}$) after stopping administration of the anesthetic agent was calculated by the equation $t_{0.5} = 0.693/\beta$. The time of isoflurane washout from the blood for 95% ($t_{0.95}$) or 99% ($t_{0.99}$) was calculated by the equation $t = \log(C_0/C)/\beta$, where C_0 was the isoflurane initial concentration in the blood at the beginning of the washout phrase, and the ratios of C_0/C should be 100/5 and 100/1 when isoflurane was washed out to 95% and 99%, respectively. The mean values of $t_{0.5}$, $t_{0.95}$, and $t_{0.99}$ were obtained for the two groups.

Results

In G_{iv} , the palpebral reflex was lost at 13 ± 2 s at an injection speed of 1 ml/s of ILE, and the consumed liquid isoflurane to successful intubation was 1.8 ± 0.5 ml on average (table 1). The whole course of induction and intubation took 105 ± 24 s, which was very smooth on

Table 1. Comparison of Parameters between the Two Groups during Induction

Parameter	G_{iv} (n = 6)	G_{inh} (n = 6)
Time to loss of palpebral reflex, s	13 ± 2	348 ± 90
Time to finish intubation, s	$105 \pm 24^*$	378 ± 102
Liquid isoflurane for induction, ml	$1.8 \pm 0.5^*$	9.8 ± 2.0
Respiratory rate before induction, breaths/min	26 ± 2	26 ± 3
Tidal volume before induction, ml	270 ± 20	270 ± 25
Respiratory rate at loss of palpebral reflex, breaths/min	$4 \pm 1^*$	8 ± 2
Tidal volume at loss of palpebral reflex, ml	$60 \pm 10^*$	90 ± 10

Data are presented as mean \pm SD.

* $P < 0.01$ vs. values of the isoflurane inhalation anesthesia group (G_{inh}).

G_{iv} = intravenous isoflurane lipid emulsion anesthesia group.

the first attempt in all dogs in this group. In G_{inh} , palpebral reflex was lost at 348 ± 90 s, and the consumed liquid isoflurane for successful intubation was 9.8 ± 2.0 ml. The whole induction and intubation course took a much longer time (378 ± 102 s) than that in G_{iv} , and some dogs displayed induction-related complications such as struggling, swallowing, vocalizing, excitement, or coughing, which made the induction course relatively difficult. Before induction, no significant differences were found either in respiratory rate or in tidal volume between the two groups. However, just when dogs lost palpebral reflex, the respiratory rate and tidal volume in G_{iv} had rapidly decreased to 4 ± 1 breaths/min and 60 ± 10 ml, respectively, which indicated significant respiratory depression compared with those in G_{inh} (8 ± 2 breaths/min and 90 ± 10 ml).

Table 2 indicates that the difference of minimum arterial concentration (4.77%) versus minimum venous concentration (4.44%) or minimum arterial partial pressure

Table 2. Comparison of Minimum Arterial, Venous, and Alveolar Concentrations or Partial Pressures between the Two Groups

Parameter	G_{iv} (n = 6)	G_{inh} (n = 6)
Minimum arterial concentration, % atm	$4.77 \pm 0.86^*$	1.60 ± 0.10
Minimum arterial partial pressure, mmHg	$10.53 \pm 0.66^\ddagger$	$9.01 \pm 0.87\text{§}$
Minimum venous concentration, % atm	$4.44 \pm 0.76^*$	1.46 ± 0.10
Minimum venous partial pressure, mmHg	$9.83 \pm 0.68^{**}$	$8.18 \pm 0.98\text{§}$
MAC, % atm	$1.12 \pm 0.18^\ddagger$	1.38 ± 0.16
Minimum alveolar partial pressure, mmHg	$8.51 \pm 1.35^\ddagger$	10.09 ± 0.53

Data are presented as mean \pm SD.

* $P < 0.01$ vs. values of the isoflurane inhalation anesthesia group (G_{inh}).

† $P < 0.01$ vs. minimum alveolar partial pressure of the intravenous isoflurane lipid emulsion anesthesia group (G_{iv}). ‡ $P < 0.05$ vs. values of G_{inh} . § $P < 0.01$ vs. minimum alveolar partial pressure of G_{inh} .

MAC = minimum alveolar concentration.

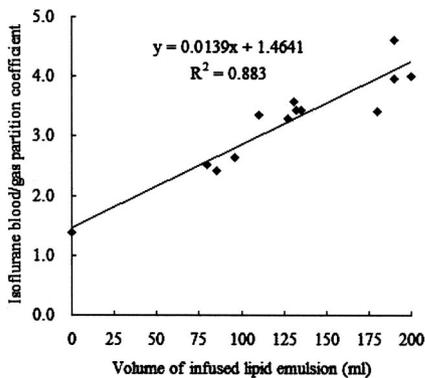


Fig. 1. Significant positive correlation between the infused volume of lipid emulsion and the determined value of isoflurane blood/gas partition coefficient ($R^2 = 0.883$).

(10.53%) versus minimum venous partial pressure (9.83%) was not significant in G_{iv} ($P > 0.05$), but both minimum arterial partial pressure and minimum venous partial pressure were remarkably higher than minimum alveolar partial pressure (8.51%; $P < 0.01$). Similarly, in G_{inh} , no significant differences were found either in minimum arterial concentration (1.6%) versus minimum venous concentration (1.46%) or in minimum arterial partial pressure (9.01%) versus minimum venous partial pressure (8.18%), but both minimum arterial partial pressure and minimum venous partial pressure were lower than minimum alveolar partial pressure (10.09%, $P < 0.01$). Although no significant difference in minimum arterial partial pressures or in minimum venous partial pressures between the two groups was found, $MAC_{iv-ILE8}$ was lower than MAC_{inh} . The infused volume of lipid emulsion (x) in G_{iv} had a remarkable impact on the isoflurane blood/gas partition coefficient ($\lambda_{b/g} = y$), and the regression equation was $y = 0.0139x + 1.4641$ ($R^2 = 0.883$; fig. 1). A positive linear correlation existed in the isoflurane partial pressures between the arterial blood and the end-tidal gas either in G_{iv} (fig. 2A) or in G_{inh} (fig. 2B). At the awakening time point, the isoflurane concentrations in both groups were in the same order—venous blood > arterial blood > end-tidal gas—and no significant difference in the arterial partial pressure, the venous partial pressure, or the end-tidal anesthetic partial pressure was found between the two

Fig. 2. Combined data during the period of administration and washout were used for a linear regression analysis to correlate isoflurane partial pressures between arterial blood and end-tidal gas for both the intravenous anesthesia and the inhalation anesthesia groups. **A** (in the inhalation anesthesia group) and **B** (in the intravenous anesthesia group) show a positive linear correlation of isoflurane partial pressure between end-tidal gas and arterial blood at corresponding time points when isoflurane was inhaled or administered intravenously, respectively.

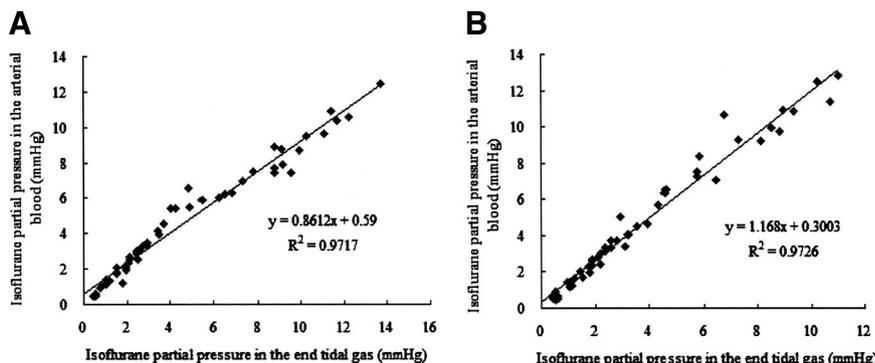


Table 3. Comparison of Parameters between the Two Groups at Awakening

Parameter	G_{iv} (n = 6)	G_{inh} (n = 6)
Awakening venous partial pressure, mmHg	4.67 ± 1.16*	3.76 ± 0.59†
Awakening venous concentration, % atm	2.21 ± 0.74‡	0.70 ± 0.12
Awakening arterial partial pressure, mmHg	3.81 ± 0.62*	3.28 ± 0.46†
Awakening arterial concentration, % atm	1.91 ± 0.67‡	0.55 ± 0.14
Awakening end-tidal partial pressure, mmHg	3.13 ± 0.78	2.57 ± 0.53
Awakening end-tidal concentration, % atm	0.41 ± 0.10	0.34 ± 0.07
Awakening time, s	511 ± 182	464 ± 192
Awakening blood/gas partition coefficient	3.58 ± 0.83‡	1.39 ± 0.10

Data are presented as mean ± SD.

* $P < 0.01$ vs. awakening end-tidal partial pressure of the intravenous isoflurane lipid emulsion anesthesia group (G_{iv}). † $P < 0.01$ vs. awakening end-tidal partial pressure of the isoflurane inhalation anesthesia group (G_{inh}). ‡ $P < 0.01$ vs. values of G_{inh} .

MAC = minimum alveolar concentration.

groups, respectively (table 3). Also, no significant difference was found in the awakening time between the two groups. Table 4 indicates that $t_{0.5}$, $t_{0.95}$, and $t_{0.99}$ were not significantly different between arterial blood and venous blood within each group or between the two groups, respectively. No fatalities occurred in the two groups during the 2-week observation after the MAC determination, and daily evaluations of the cephalic vein used for infusion showed no evidence of redness, swelling, or thrombophlebitis in G_{iv} .

Discussion

In this study, anesthesia with isoflurane administered intravenously in an emulsion was compared with an inhaled delivery of isoflurane in dogs. Compared with intravenous injection, the inhalation approach takes a longer time for a volatile agent to be delivered from the anesthetic vaporizer to alveoli, then dissolve into blood, and finally arrive in the central nervous system. Faster

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Table 4. Comparison of Isoflurane Washout Time between the Two Groups after Stopping Administration of Agents

	G_{iv} (n = 6)		G_{inh} (n = 6)	
	Arterial Blood	Venous Blood	Arterial Blood	Venous Blood
$t_{0.5}$	31.5 ± 14.4	30.8 ± 14.8	28.1 ± 7.4	29.4 ± 9.5
$t_{0.95}$	136.5 ± 62.2	133.7 ± 64.4	121.8 ± 32.4	127.0 ± 40.9
$t_{0.99}$	209.8 ± 95.6	205.0 ± 98.2	187.3 ± 49.8	195.2 ± 62.9

Data are presented as mean ± SD, in minutes.

$t_{0.5}$, $t_{0.95}$, and $t_{0.99}$ represent the times of isoflurane washout from arterial or venous blood for 50%, 95%, and 99%, respectively.

G_{iv} = intravenous isoflurane lipid emulsion anesthesia group; G_{inh} = isoflurane inhalation anesthesia group.

onset and less liquid isoflurane consumption were found in G_{iv} than those in G_{inh} during induction (table 1). This is mainly because the anesthetic agent can reach the site of action in the brain in one arm-brain circulation by intravenous administration and also partly because of the faster injection rate in this study, which imitated clinical intravenous induction. If the infusion rate for ILE were designed for mimicking the inhalation induction with isoflurane, the onset time might be longer, and liquid isoflurane consumption might be higher.

The elimination of isoflurane after intravenous infusion of ILE is mainly through the lungs, as when isoflurane vapor was inhaled. Therefore, intravenous ILE anesthesia has the characteristics of both intravenous anesthesia and inhalation anesthesia. The depth of anesthesia could be easily adjusted by changing the infusion rate of the ILE based on the monitoring of end-tidal isoflurane concentration. If low fresh gas flow is used, the eliminated isoflurane from the blood to the alveoli is reabsorbed. Then, the mode of isoflurane delivery will in part be inhalational, and the actual MAC_{iv} may be altered to a value between MAC_{iv} -ILE8 and MAC_{inh} obtained in this study. In addition, the consumed liquid isoflurane and the cost of anesthesia will be decreased.¹²⁻¹⁴ Similar to the results obtained by Musser *et al.*² showing that MAC_{iv} (0.78%) of emulsified halothane (5%, vol/vol) was lower than MAC_{inh} (1.13%) of halothane in swine, our current study indicated (table 2) that MAC_{iv} -ILE8 (1.12 ± 0.18%) was lower than MAC_{inh} (1.38 ± 0.16%), which corresponded with the prediction mentioned in the introduction. The difference between MAC_{iv} -ILE8 and MAC_{inh} might mainly relate to the following factors: First, because ILE was administered intravenously and the pulmonary system is not the organ of entry of isoflurane, expired isoflurane concentration at an anesthetizing blood level would be lower and the MAC_{iv} -ILE8 would not reflect MAC_{inh} in the traditional sense. Second, the equilibration time for isoflurane concentration (or partial pressure) between alveolar gas and arterial blood was also important.⁴ In this study, minimum alveolar partial pressure (8.51%) was lower than minimum arterial partial pressure (10.53%) in G_{iv} , but minimum

alveolar partial pressure (10.09%) was higher than minimum arterial partial pressure (9.01%) in G_{inh} , indicating that the partial pressures of isoflurane between alveolar gas and arterial blood had not achieved complete equilibration within 20 min. If the equilibration time were prolonged for both groups, the difference between MAC_{iv} -ILE8 and MAC_{inh} would be smaller. Third, the infused lipid emulsion increases the gradient of isoflurane partial pressure between blood and alveolar gas. Our results demonstrated that the infused volume of lipid emulsion remarkably impacted isoflurane $\lambda_{b/g}$, as figure 1 showed that approximately 1 ml Intralipid®, 30%, could increase isoflurane $\lambda_{b/g}$ by 0.0139 at 37°C. In G_{iv} , the mean infused lipid emulsion was 159.7 ± 33.9 ml, and the highest isoflurane $\lambda_{b/g}$ was 5.23 at 37°C, whereas the isoflurane $\lambda_{b/g}$ was constant at 1.4 ± 0.24 at 37°C in G_{inh} because no lipid emulsion was infused. The increased isoflurane $\lambda_{b/g}$ in G_{iv} made isoflurane much easier to be dissolved in the blood and not easier to be eliminated from the blood to the lungs. This has been demonstrated in this study by that the minimum arterial concentration and minimum venous concentration in G_{iv} were much higher than those in G_{inh} .

Although MAC_{iv} -ILE8 was less than MAC_{inh} , minimum arterial partial pressures between the two groups were similar, suggesting that an equal partial pressure for isoflurane in the central nervous system and the same depth of anesthesia existed in the two groups at respective MAC values. In this study, the venous blood was drawn from the jugular vein, and no difference was found between the minimum venous partial pressure and the minimum arterial partial pressure for both groups. This implies that the isoflurane partial pressure in both jugular vein blood and arterial blood can reflect the brain tissue partial pressure. In this study, a good positive linear correlation in isoflurane partial pressures between the arterial blood and the end-tidal gas during isoflurane inhalation in G_{inh} was shown again (fig. 2A).¹⁵ More important, a good positive linear correlation also existed in isoflurane partial pressures between the arterial blood (possibly the central neural system) and the end-tidal gas in G_{iv} (fig. 2B). This result indicates that the depth of anesthesia could be controlled by adjusting the infusion rate of ILE based on monitoring the end-tidal isoflurane concentration when ILE is administered intravenously in the clinic.

The awakening speed in both groups was very fast. The awakening times (approximately 8 min) were not significantly different between the two groups, and the awakening end-tidal isoflurane concentrations between the two groups exhibited no obvious differences. When the dogs awoke, the partial pressures in both groups were in the same order—venous partial pressure > arterial partial pressure > end-tidal partial pressure—which was reversed in relation to those during the MAC measurement in G_{inh} . The awakening isoflurane concen-

trations in both arterial blood and venous blood in G_{iv} were higher than those in G_{inh} , which might also be due to a greater isoflurane $\lambda_{b/g}$ in G_{iv} than that in G_{inh} . When concentrations were transferred into partial pressure, the above comparison showed no significant difference. Therefore, the isoflurane partial pressures in the central nervous system should be close in the two groups when dogs awaken. The same awakening time and awakening blood partial pressure in both groups suggest that the awakening course in dogs has not been affected by the different isoflurane administration approaches. In addition, the time for isoflurane elimination for 50% ($t_{0.5}$), 95% ($t_{0.95}$), and 99% ($t_{0.99}$) from the blood between the two groups had no remarkable differences, which indicates that the infused lipid emulsion had not remarkably impacted the time course for isoflurane elimination from the blood in this study.

Neither death nor local redness, swelling, or phlebitis at the infusion site occurred during 2 weeks' observation after MAC determination, which implies that intravenous anesthesia with 8% ILE for dogs is safe. However, attention should be paid to the possible drawbacks of 8% ILE. Because of the high volatility of isoflurane, 8% ILE should be kept in a container that is absolutely sealed until immediately before use and not be reused. Also, liquid isoflurane must be completely dissolved into lipid emulsion with no lipid droplets to be found for extended periods of time to enable the delivery of consistent isoflurane concentrations.

In conclusion, compared with inhaled isoflurane vapor, intravenous 8% ILE has a smaller MAC, has faster induction of anesthesia, and uses less isoflurane. The infused lipid emulsion increases the isoflurane blood/gas partition coefficient, but the awakening time courses of the dogs are not significantly different between G_{iv} and

G_{inh} . When 8% ILE was administered intravenously, end-tidal isoflurane concentration could be used for adjusting the infusion rate of 8% ILE, estimating the isoflurane partial pressure in arterial blood and further judging the depth of anesthesia. This conclusion indicates a good prospect for delivering 8% ILE intravenously in the clinical setting.

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