Comparison of the Epinephrine-induced Arrhythmogenic Effect of Sevoflurane with Isoflurane and Halothane

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The effect of sevoflurane on cardiac arrhythmias induced by the infusion of epinephrine into dogs was compared with those of isoflurane and halothane. The arrhythmogenic doses of epinephrine determined in this comparative study were expressed by both infusion rates of epinephrine and the corresponding plasma levels obtained by a series of three-minute epinephrine infusions during sevoflurane, isoflurane, and halothane anesthesia at 1.25 MAC. The mean values of the arrythmogenic infusion rates of epinephrine and the corresponding plasma levels were 17.3 μg/kg/min and 275.7 ng/ml for sevoflurane, 6.7 μg/kg/min and 149.2 ng/ml for isoflurane and 1.9 μg/kg/min and 39.1 ng/ml for halothane, respectively. These results indicate that the arrythmogenic doses of epinephrine during sevoflurane and isoflurane anesthesia were significantly higher than those during halothane anesthesia.
(Key words: sevoflurane, isoflurane, halothane, arrhythmia, epinephrine)

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It is generally recognized that the use of an inhalation anesthetic which does not cause sensitization of the myocardium to epinephrine is significantly advantageous from a clinical viewpoint. As for the arrhythmogenicity of commonly used inhalation anesthetics with epinephrine, there are a number of reports.[1-7] Sevoflurane is a potent and nonexplosive inhalation anesthetic (fluoromethyl 2,2,2-trifluolo-1 [trifluolometyl] ethyl ether), which is on the point of being introduced into clinical situations.[8] This anesthetic is an inducer of halogenated ether, and is therefore expected to be free of the effect of sensitizing the myocardium to epinephrine. The objective of our present study was to determine both the infusion rate of epinephrine which would produce cardiac arrhythmia, and the corresponding plasma levels of epinephrine during sevoflurane anesthesia and to compare them with corresponding values obtained during isoflurane and halothane anesthesia. For determination of these values, we used an experimental method, based on that of Pace et al.[9], which we slightly modified in terms of infusion rates, since Pace et al. (as well as other investigators who have also used their method) have reported several quantitative evaluations of the arrhythmogenic doses of epinephrine during halothane anesthesia[7, 10, 11], which were thought to be quite useful for our comparative study.

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Materials and Methods

Throughout this study, 28 experiments were performed using a total of 13 mongrel dogs with a weight of 9.2 ± 0.1 kg (mean ± SE). Whenever different anesthetics were administered to the

same dog, there was at least a one-week interval between one experiment and the next. Each anesthetic was administered randomly. Prior to experiments, each dog was fasted and given no premedicants. Sevoflurane, isoflurane and halothane were administered with oxygen, respectively, to maintain anesthesia in each case. Tracheal intubation was performed with a cuffed endotracheal tube without muscle relaxants. Ventilation was controlled with a volume-limited ventilator (Harvard® Model 613) and endo-tidal carbon dioxide concentration was maintained at approximately 4% as determined with a capnograph (Datex® CD300). A forelimb vein was cannulated for infusion of both epinephrine and Ringer's lactate solution, and a femoral artery was also catheterized for blood sampling and intraarterial pressure monitoring. Femoral arterial pressure and lead II of the ECG were monitored continuously, and recorded on a polygraph (HP® 38304 AS, 7404 A). Esophageal temperature was measured, and a heating blanket was used to maintain the temperature between 36.5 and 38.5°C. Anesthesia was maintained at an end-tidal concentration of 1.25 MAC (equivalent MAC values for the dogs were 2.36% for sevoflurane, 1.39% for isoflurane, and 0.89% for halothane).[12] An anesthetic gas analyzer (Engström® EMMA) was used to monitor both inspired and expired end-tidal anesthetic gas concentrations. After achieving a stedy state for 45 min, control measurements for heart rate and arterial blood pressure were recorded. Blood was sampled for measurements of the controlled value of plasma epinephrine concentration.

Arrhythmogenic doses of epinephrine were determined using a modified method based on that of Pace et al.[9] as follows. The epinephrine was freshly diluted in 0.9% saline and administered intravenously at double-spaced increasing rates (0.50, 1.00, 2.00, 4.00, 8.00--- μg/kg/min) by a constant infusion pump (Atom® 201 B). The infusion was continued for three minutes at each rate until the arrhythmogenic threshold was reached. The arrhythmogenic threshold was the dose that produced within 15 seconds during three-minute continuous epinephrine infusion.[9] The time interval between epinephrine infusion was determined by the time required for the arterial blood pressure and the heart rate to return to approximately preinfusion levels. The arrhythmogenic doses determined were expressed as the infusion rates of epinephrine and the corresponding plasma levels.

When the arrhythmogenic threshold had been defined, blood was sampled, placed in a precooled test tube containing EDTA-2Na and centrifuged at 4,000 rpm for three minutes. Once the plasma had been separated, it was immediately frozen and stored at −20°C for several days until the day of analysis. The analysis was done by semiautomated fluorimetry based on the trihydroxyindole reaction which was combined with highperformance liquid chromatography (Hitachi® catecholamine analysis system).

Statistical comparison of the arrhythmogenic doses of epinephrine was performed using Student's unpaired t test. A value of $p<0.05$ was considered to be statistically significant. The correlations between the arrhythmogenic infusion rates of epinephrine, and the corresponding plasma concentrations were analyzed using linear regression by the least squares method.

Results

Arrhythmias were induced after more than two minutes had elapsed following the start of epinephrine administration at each arrhythmogenic infusion rate. The relation between arrhythmogenic infusion rate of epinephrine and the corresponding plasma concentration during each anesthesia are shown in fig. 1. There is a positive correlation between these values.

The mean values of arrhythmogenic doses of epinephrine and the corresponding plasma concentrations established during sevoflurane, isoflurane, and halothane anestheisa are shown in table 1, being 17.3 μg/kg/min and 275.7 ng/ml for sevoflurane, 6.7 μg/kg/min and 149.2 ng/ml for isoflurane and 1.9 μg/kg/min and 39.1 ng/ml for halothane. These values indicate that the arrhythmogenic doses of epinephrine during sevoflurane and isoflurane anesthesia were significantly higher ($p<0.05$) than that during halothane anesthesia. There was no significant difference between sevoflurane and isoflurane. Histogram of the arrhythmogenic dose of

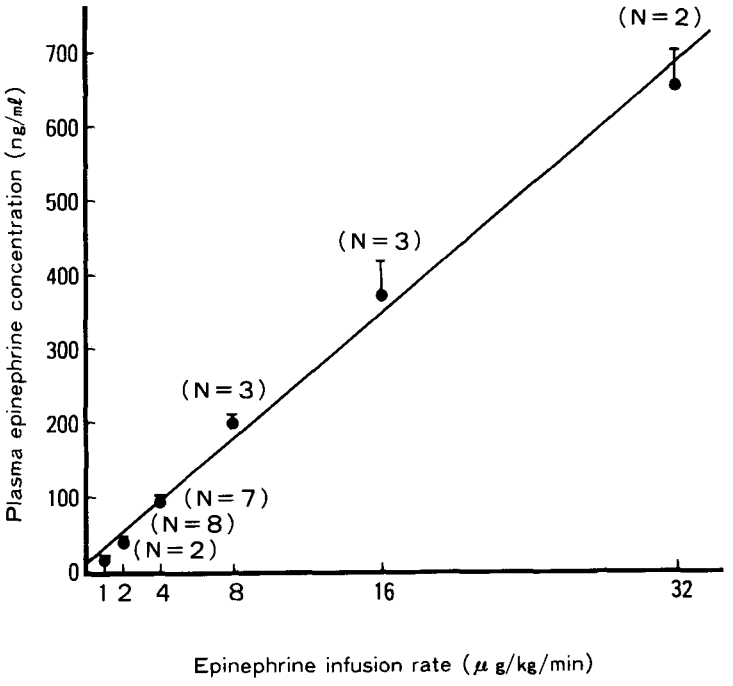

Fig. 1. The relation between infusion rates of epinephrine and the corresponding plasma concentrations upon attaining the arrhythmogenic threshold during each anesthesia. A linear regression line for these values was determined by means of the least squares method, showing the existence of a high correlation between the two. ($y = 20.9x + 12.45$, $r = 0.98$; $p<0.01$)

Table 1. Arrhythmogenic doses of epinephrine during halothane, sevoflurane and isoflurane anesthesia

ADE	Infusion Rate (μg/kg/min)	Plasma epinephrine concentration (ng/ml)	
		Control	Arrhythmogenic threshold
Halothane n=8	1.9± 0.1	0.6± 0.2	39.1± 4.3
Sevoflurane n=11	17.3± 5.7*	0.5± 0.1	275.7± 71.0* n=10**
Isoflurane n=9	6.7± 1.8*	0.4± 0.1	149.2± 54.9* n=7***

Mean± SE * $p< 0.05$ in comparison with halothane

** In one case (infusion rate was 64), plasma epinephrine concentration was not obtained for hemolysis.

*** In two cases (infusion rates were 4 and 16), plasma epinephrine concentration were not obtained for hemolysis.

epinephrine expressed infusion rate during each anesthesia are shown in fig. 2. During halothane anesthesia, in most cases, arrhythmogenic threshold are attained at 2 μg/kg/min. In comparing to halothane, sevoflurane and isoflurane have wide distribution of arrhythmogenic doses. Table 2 gives a comparison of the arrythmogenic doses of epinephrine in the same dog during both sevoflurane and isoflurane anesthesia, showing that in most cases sevoflurane had much higher

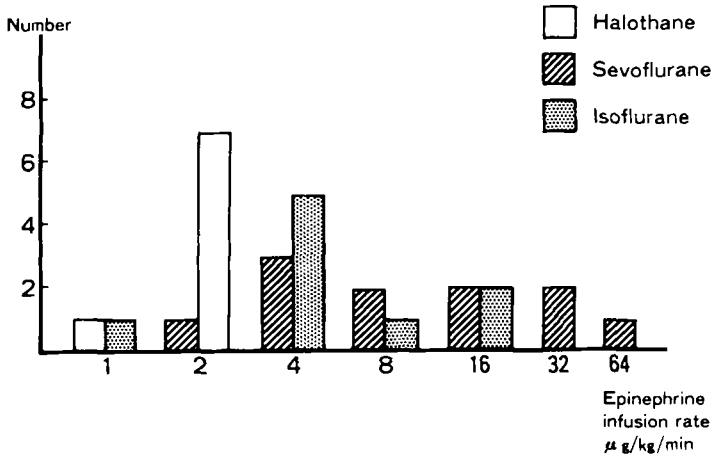

Fig. 2. Histogram of the arrhythmogenic dose of epinephrine expressed infusion rate during each anesthesia

values than isoflurane, although the differences were not significant.

The mean blood pressures during sevoflurane, isoflurane and halothane anesthesia which were measured both before and after epinephrine infusion are shown in fig. 3. The mean blood pressure before epinephrine infusion was significantly higher ($p<0.05$) during isoflurane anesthesia than during halothane anesthesia. The mean blood pressure at the time when arrhythmias were produced was significantly higher ($p<0.01$) during sevoflurane and isoflurane anesthesia than during halothane anesthesia. However, there was no significant difference in the blood pressure between sevoflurane and isoflurane anesthesia.

Table 2. Comparison of arrhythmogenic dose of epinephrine during sevoflurane and isoflurane anesthesia in the same dogs

NO	Sevoflurane	Isoflurane
1	8	4
2	2	16
3	32	4
4	4	1
5	16	4
6	8	4
7	32	8
8	4	4

These values represent the infusion rates of epinephrine expressed in μg/kg/min.

In most cases sevoflurane had much higher values than isoflurane, although the differences were not significant.

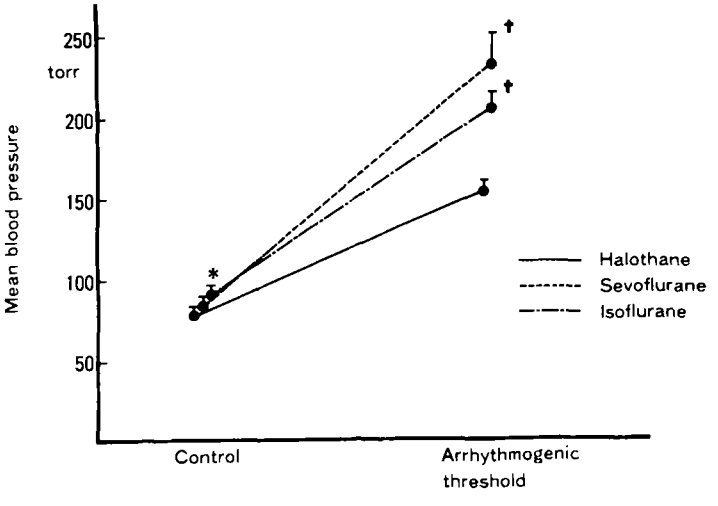

Fig. 3. Mean arterial pressures before epinephrine infusion and upon attaining the arrhythmogenic threshold during halothane, sevoflurane and isoflurane anesthesia

* Significant difference ($p<0.05$) with respect to halothane

† Significant difference ($p<0.01$) with respect to halothane upon arrhythmias

Discussion

In dogs during sevoflurane, isoflurane and halothane anesthesia, we established the arrhythmogenic doses of epinephrine which were expressed as the infusion rates of epinephrine and the corresponding plasma concentration. Throughout the experiment, three-minute continuous infusion of epinephrine was repeatedly performed at double-spaced increasing rates, starting from 0.5 μg/kg/min. Sumikawa et al.[7] measured the plasma concentrations of epinephrine in a series of three-minute infusions using the same method as that of Pace et al.[9] They reported that the plasma epinephrine concentration reached a maximum after two minutes and then maintained a constant level until the end of the infusion. Accordingly, they considered this three-minute infusion method to be reliable for measuring arrythmogenic doses. The results of our present study are similar to those of Sumikawa et al.[7], showing that during each episode of anesthesia, infusion of epinephrine led to the occurrence of premature ventricular contractions when slightly more than two minutes had elapsed after the start of infusion and that the infusion rates were highly correlated with the corresponding plasma concentration. This suggests that our infusion method could also be considered reasonable.

On the other hand, Pace et al.[9] injected epinephrine at the standardized logarithmically spaced increasing rates (0.67, 0.82, 1.00, 1.22, 1.49, 1.82, 2.23, 2.72, ----- μg/kg/min) at 10-minute intervals in order to determine the arrythmogenic threshold for halothane anesthesia. Other investigators have reported the arrythmogenic doses of epinephrine for halothane anesthesia using this method.[7, 10, 11] These reports related to halothane show that only a small dose of epinephrine is necessary for production of arrhythmias. In contrast to these results, our preliminary experiment required frequent infusion of highly concentrated epinephrine to produce arrhythmias during sevoflurane and isoflurane anesthesia, and there was also an unexpected tendency for the blood pressure after many epinephrine infusions to recover to its control level. Furthermore, because of this highly concentrated epinephrine administration, we observed occasionally that it took over 30 minutes the elevated blood pressure and also the elevated heart rate to recover to their control levels. In order to overcome this problem and reduce the number of overall infusions of epinephrine throughout the experiment, we decided to use double-spaced increasing rates.

Kapur et al.[10], Mervyn et al.[11], and Sumikawa et al.[7] have reported the arrythmogenic doses of epinephrine for halothane using the method of Pace et al.[9], and the results obtained were 2.58, 2.15 and 2.18 μg/kg/min, respectively, in comparison with the 2.07 μg/kg/min reported Pace et al.[9] In contrast to these values, our result was 1.90 μg/kg/min, which is a slightly lower value. There are two possible reasons for this lower value. One is that we used fasted dogs. Miletich et al.[13] speculated that fasting could increase the amount of free fatty acid secreted in plasma, thereby sensitizing the myocardium to epinephrine during halothane anesthesia. The other is that the double-spaced increasing rates (0.5, 1.0, 2.0, 4.0,----) were not fractionalized at as low infusion rate as many as the original method of Pace et al. (0.67, 0.82, 1.00, 1.22, 1.49, 1.82, 2.23, 2.72, 3.32,----). As a result, it is possible that the accuracy of the arrythmogenic doses determined by our present infusion rates might have been somewhat deviated for halothane anesthesia. Nevertheless, the arrythmogenic plasma concentration of epinephrine obtained by us was 39.1 ng/ml, which was nearly consistent with the 38.7 ng/ml obtained by Sumikawa et al.[7] This will therefore explain why the arrhythmogenic doses of epinephrine for halothane determined by us was substantially comparable to that determined by the above authors.[7, 10, 11]

With regard to isoflurane, Joas et al.[1] have reported that the arrhythmogenic doses of epinephrine determined during halothane and isoflurane anesthesia at 1.25 MAC by means of infusing precalculated doses of epinephrine for one minute were 5 μg/kg/min for halothane and 22 μg/kg/min for isoflurane. Tucker et al.[3] have also reported experimental results similar to those obtained by Joas et al.[1] that in dogs, isoflurane anesthesia required a dose of epineph-

rine four time as large as that required during halothane anesthesia in order to induce arrhythmias. Similarly, Johnston et al.[5] have reported that the arrhythmogenic dose which was needed to generate a positive response in 50% of patients using submucosal infusion of epinephrine was 2.1 μg/kg for halothane anesthesia and 6.7 μg/kg for isoflurane anesthesia. The infusion rates of epinephrine determined in our study were 1.9 μg/kg/min for halothane and 6.7 μg/kg/min for isoflurane, and the corresponding plasma concentrations were 39 ng/ml for halothane and 149 ng/ml for isoflurane. With regard to the infusion rates, the arrhythmogenic doses obtained by us were comparatively smaller than those obtained by Joas et al.[1] This presumably resulted from the fact that the infusion times of epinephrine performed by Joas et al.[1] were short (one minute) in comparison with that used by us (three minutes), and probably that the plasma concentration of epinephrine determined by them had not yet reached the maximum on that occasion. However, the ratio of the infusion rate of halothane to that of isoflurane observed by us was nearly equal to that obtained by the above authors.[1,3,5] Although there are no reports comparing halothane anesthesia with isoflurane anesthesia from the viewpoint of plasma epinephrine concentration, it is clear that in terms of the ratio of the infusion rate of halothane to that of isoflurane, the ratio of the plasma concentration of epinephrine measured by us was consistent with those ratios measured by the above authors. This leads us to consider that our results apparently substantiate all the aforementioned results to a large extent.

With regard to sevoflurane, Wallin et al.[8] have reported that they were able to establish cardiac sensitization scores for both sevoflurane and halothane anesthesia using a method similar to that adopted by Thompson,[3] obtaining figures of 9.8 for sevoflurane and 33 for halothane. This indicates that sevoflurane did not stimulate the sensitivity of the myocardium to epinephrine as much as halothane did. In our study, the infusion rate of epinephrine was 17.3 μg/kg/min and the plasma concentration of epinephrine 275.7 ng/ml during sevoflurane anesthesia, figures which were significantly higher than those during halothane anestheisa. However, comparing these values with those obtained during isoflurane anesthesia, there was no significant difference between them. Furthermore, comparison between sevoflurane and isoflurane in the same dog showed that sevoflurane tended to cause higher values, although the difference was not significant (table 2). Since sevoflurane showed larger variances in its arrhythmogenic doses. For example, sevoflurane did not produce arrhythmias until the infusion rate of epinephrine reached 64 μg/kg/min in one animal, whereas produced arrhythmias at an infusion rate of only 2 μg/kg/min in the other (fig. 2). Johnston et al.[5] determined the arrhythmogenic doses which were necessary in order to produce a response in 50% of patients during halothane, isoflurane and enflurane anesthesia and reported that although enflurane had a higher arrhythmogenic value than the other two, its dose-response curve was moderate, and not parallel with those of the others, so that it was difficult to compare its effects. Horrigan et al.[6] have also made a similar report, in which they have showen that only a small dose of epinephrine is enough to produce arrhythmia in some patient during enflurane anesthesia. Together with these reports, our present results suggest the possibility that the interaction of epinephrine with sevoflurane appears to be somewhat analogous to that of enflurane, and further details remain to be clarified in future studies.

Katz et al.[14] explained in their report that an increase in arterial pressure is one of the possible factors that can produce arrhythmias during anesthesia and also that the control of blood pressure during anesthesia is important for prevention of arrhythmias in surgery for pheochromocytoma. In our experiment; no arrhythmias were produced during sevoflurane and isoflurane anesthesia, even when the mean blood pressure exceeded 200 torr during epinephrine infusion, although it is quite easy to think that blood pressure elevated to high levels similar to this figure could lead to immediate induction of arrhythmias due to stretching of the myocardium. This result leads us to conclude that sevoflurane is not only superior anesthetics to halothane for use in epinephrine-involved anesthesia, but also have a clinical advantage in providing much better anesthesia like iso-

flurane,[5] particularly for pheochromocytoma surgery.

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