

Arrhythmogenic Plasma Levels of Epinephrine during Halothane, Enflurane, and Pentobarbital Anesthesia in the Dog

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Plasma levels of epinephrine which correspond to the arrhythmogenic doses were determined during halothane, enflurane, and pentobarbital anesthesia in the dog. The arrhythmogenic dose was established by a series of 3-min infusion of epinephrine at 10-min intervals. The mean values of the arrhythmogenic doses and the corresponding plasma levels of epinephrine were: 2.18 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 38.7 ng/ml during halothane; 11.43 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 206.3 ng/ml during enflurane; and 15.27 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 296.5 ng/ml during pentobarbital anesthesia. The arrhythmogenic plasma levels of norepinephrine during halothane anesthesia was nearly the same as that of epinephrine. (Key words: Anesthetics, volatile: halothane; enflurane. Anesthetics, intravenous: pentobarbital. Heart: arrhythmia. Sympathetic nervous system: catecholamines; epinephrine; norepinephrine.)

THE USE OF EPINEPHRINE has significant clinical relevance in anesthesia because of the sensitization of the myocardium by halothane and other anesthetics to the adrenergic drug.¹ The arrhythmogenic doses of epinephrine during various types of anesthesia have been reported,²⁻⁴ and many influencing factors have been examined.⁵⁻⁸ However, circulating levels of epinephrine, which correspond to the arrhythmic threshold, have not been reported. Therefore, this study was carried out to determine the plasma levels of epinephrine that correspond to the arrhythmogenic doses during halothane, enflurane, and pentobarbital anesthesia in the dog. In addition, the arrhythmogenic plasma level of norepinephrine was determined during halothane anesthesia.

Materials and Methods

Thirty-one mongrel dogs of either sex, weighing 10.5 \pm 0.4 kg (mean \pm SE) (range, 8.2–12.5 kg) were anesthetized initially with 20 mg/kg thiopental, iv. The animals were intubated with a cuffed endotracheal tube and mechanically ventilated with a respirator (Aika® R60) at a tidal volume of 15 ml/kg. End-tidal CO₂ concentration was measured continuously with an infrared CO₂ analyzer (Cavitron® PM-20N) and maintained at

levels of 37 to 40 mmHg by adjusting the respiratory rate. An infrared heating lamp and a circulating water blanket were used to maintain the esophageal temperature between 37.0–38.5°C. Anesthesia was maintained with an inspired concentration of 1.1% halothane or 2.75% enflurane in oxygen or with 100% oxygen plus 30 mg/kg pentobarbital sodium, iv. (Equivalent MAC values for the dog are 0.87% for halothane,⁹ and 2.2% for enflurane.¹⁰) The inspired anesthetic concentration was measured in each dog by gas chromatography (Shimadzu® GC-7A). A 100-min equilibration period was allowed for halothane and enflurane anesthesia and a 15-min period was allowed for pentobarbital anesthesia.

A femoral vein was cannulated for administration of drugs and salt and dextrose solutions. A femoral arterial catheter was placed for arterial blood sampling and intraarterial pressure monitoring. Lead II of the electrocardiogram also was monitored continuously. Arterial blood-gas analysis and measurement of serum electrolytes were carried out frequently to maintain a pH 7.35–7.40, serum Na of 135–145 mEq/l, and serum K of 3.8–4.8 mEq/l.

After the equilibrium period, the arrhythmogenic dose of epinephrine and norepinephrine (halothane only) was determined by the method of Pace *et al.*⁷ The catecholamines were freshly diluted in 0.9% saline to concentrations of 30 $\mu\text{g}/\text{ml}$ for lower doses and 60 $\mu\text{g}/\text{ml}$ for higher doses and administered intravenously by a constant volume infusion pump (Terumo® STC-502) at standardized logarithmically spaced increasing rates (0.67, 0.82, 1.00, 1.22, etc., $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). The infusion was continued for 3 min at each rate with a 10-min recovery period until the arrhythmogenic threshold was reached. The arrhythmogenic threshold is the dose that produced four or more premature ventricular contractions within 15 s.⁷ The arrhythmogenic threshold was expressed by three terms, *i.e.*, infusion rate, dose, and plasma level of epinephrine. The dose was calculated as a function of both infusion rate and time. A different dog was used for each anesthesia experiment, *i.e.*, only one arrhythmogenic dose was determined in individual dogs. The dog was killed after the experiment to isolate the cerebral artery for another experiment.

In order to examine the relationship between infusion time and plasma level of epinephrine, a 3-ml arterial blood sample was collected at 30-s intervals during

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infusion of epinephrine at the rates of 1.0 to 2.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ under pentobarbital anesthesia. A blood sample also was collected at the end of each 3-min infusion period during halothane and pentobarbital anesthesia and at the time when the criteria for the arrhythmogenic dose was satisfied for all three anesthetics. The blood sample was withdrawn into a precooled glass tube containing 3 mg of ethylene-diamine-tetra-acetic acid-2Na (EDTA-2Na) and was centrifuged at 4,000 rpm for 3 min at 2°C. The plasma then was separated, immediately frozen, and stored at -20° C until analyzed within five days. On the day of the analysis, 1 ml of the thawed plasma was acidified by addition of 44 μl of 60% perchloric acid to precipitate protein. After purification on alumina, the catecholamines were measured by semi-automated fluorimetric analysis based on the trihydroxyindole reaction,¹¹ which was combined with high-performance liquid chromatography¹² (Shimadzu catecholamine analysis system), determining epinephrine and norepinephrine differentially. This assay method has a limit of sensitivity of 20 pg for each catecholamine. All reported values are based on standards that were carried through the entire extraction procedure. Recoveries of standards are $86 \pm 4\%$ for norepinephrine, and $79 \pm 3\%$ for epinephrine. The interassay and intraassay variations are less than 5%.

Student's *t* test for unpaired data was used for statistical comparison. *P* values of less than 0.05 were con-

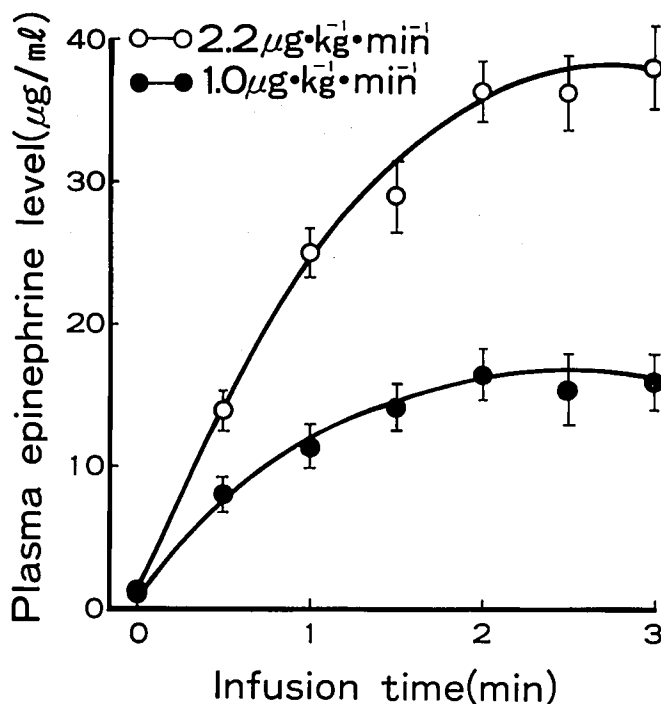


FIG. 1. The time course of the plasma epinephrine level during infusion of epinephrine (mean \pm SE, $n = 4$ for each value). Anesthesia was maintained with 100% oxygen plus 30 mg/kg pentobarbital. Epinephrine was administered at 1.0 and 2.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

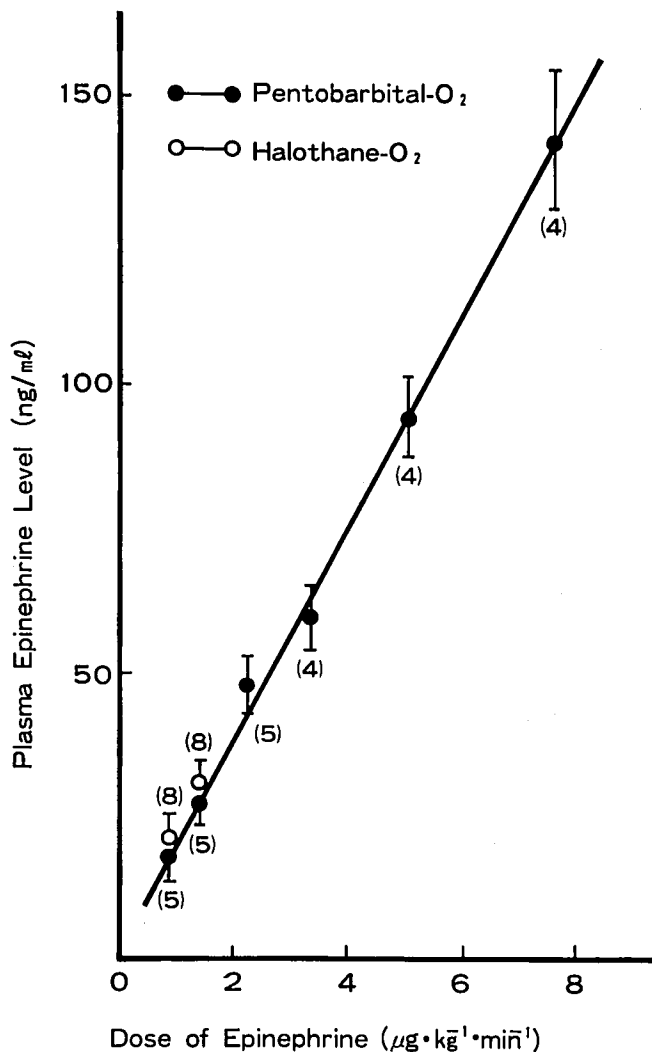


FIG. 2. Plasma epinephrine levels at the end of the 3-min infusion period at the various rates of administration (mean \pm SE). Anesthesia was maintained with 1.1% halothane in oxygen or with 100% oxygen plus 30 mg/kg pentobarbital. The number of experiments is indicated by the figures in parentheses. The regression line was obtained by the method of least-squares. ($y = 18.4x + 1.44$, $r = 0.98$; $P < 0.01$)

sidered significant. The relationship between the dose and plasma level of epinephrine was analyzed with linear regression by the least-squares method.

Results

The time course of the plasma epinephrine level during infusion of epinephrine was obtained as shown in figure 1. At the rates of 1.0 and 2.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the plasma epinephrine level reached a maximum after 2 min and maintained a constant level until the end of the infusion. Plasma levels of epinephrine at the end of the 3-min infusion periods during pentobarbital and halothane anesthesia were combined (fig. 2). A positive correlation was present between the dose and plasma

TABLE 1. Plasma Levels of Epinephrine and Norepinephrine that Correspond to the Arrhythmogenic Threshold during Pentobarbital, Enflurane, and Halothane Anesthesia

Anesthesia	Epinephrine Threshold			
	n	Infusion Rate ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	Dose \S ($\mu\text{g}/\text{kg}$)	Plasma Level (ng/ml)
Pentobarbital 30 mg/kg	6	15.27 \pm 2.83	34.73 \pm 4.26	296.5 \pm 30.1
Enflurane 2.7%	6	11.43 \pm 1.44	20.91 \pm 3.5	206.3 \pm 17.9*
Halothane 1.1%	10	2.18 \pm 0.17	4.18 \pm 0.85	38.7 \pm 2.5 \ddagger
Norepinephrine Threshold				
Halothane 1.1%	5	2.41 \pm 0.22	4.62 \pm 0.72	42.3 \pm 3.9

* $P < 0.05$, $\ddagger P < 0.01$ compared with pentobarbital value. $\ddagger P < 0.01$ compared with enflurane value. \S The dose was calculated as a function of both infusion rate and time.

level of epinephrine. Comparing halothane and pentobarbital anesthesia at infusion rates of epinephrine of 1.0 and 1.49 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, the plasma epinephrine levels tended to be higher during halothane anesthesia than pentobarbital anesthesia. However, there was no significant difference between the two types of anesthesia.

The mean plasma levels of epinephrine that correspond to the arrhythmogenic thresholds during halothane, enflurane, and pentobarbital anesthesia are tabulated (table 1). Epinephrine produced arrhythmias at significantly lower plasma levels during halothane and enflurane than pentobarbital anesthesia. Arrhythmia was induced by the lowest concentration of plasma epinephrine during halothane anesthesia. Norepinephrine exerted an arrhythmogenic effect at nearly the same plasma level as epinephrine during halothane anesthesia (table 1).

Discussion

We determined the concentrations of plasma epinephrine that correspond to the arrhythmogenic doses in the dog during halothane, enflurane, and pentobarbital anesthesia. The arrhythmogenic dose was established by a series of 3-min infusions of epinephrine at 10-min intervals according to the method of Pace *et al.*⁷ The results of time-course experiments demonstrate that 3 min is adequate for one infusion period, because the plasma epinephrine level reached a maximum after 2 min. The arrhythmogenic doses of epinephrine during halothane and enflurane anesthesia are similar to previous reports. Pace *et al.*⁷ and Kapur *et al.*⁸ determined the arrhythmogenic dose by the same method as ours and reported that they were 2.07 and 2.58 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, during halothane anesthesia. The lower value of the arrhythmogenic dose determined by Pace *et al.*⁷ might be due to the fact that they used fasted dogs, since it has been shown that fasting

reduces the arrhythmogenic dose of epinephrine.⁶ In their experiments as well as in ours, thiopental was administered prior to halothane anesthesia. Atlee *et al.*¹³ has reported that 20 mg/kg of thiopental altered the arrhythmogenic response to epinephrine for as long as 5–6 h, and the arrhythmogenic dose of epinephrine during halothane anesthesia was reduced to about 60% of control. It is possible that an effect of thiopental was also present in these experiments.

Arrhythmogenic doses of epinephrine during halothane anesthesia without prior administration of thiopental have been determined by other investigators. Tucker *et al.*¹⁴ administered epinephrine at a rate of 2.5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and reported that the arrhythmogenic dose was 4.15 $\mu\text{g}/\text{kg}$, which was calculated as a function of time. Munson *et al.*³ determined the dose by the same method as Tucker *et al.*¹⁴ and reported that the epinephrine dosage for halothane was 4.6 $\mu\text{g}/\text{kg}$ and the corresponding value for enflurane was 17.1 $\mu\text{g}/\text{kg}$. Chapin *et al.*¹⁵ determined the arrhythmogenic dose with the administration of epinephrine at 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and calculated it as 4.66 $\mu\text{g}/\text{kg}$. Joas *et al.*² determined the corresponding doses by administering a predetermined dose of epinephrine over a 60-s period and reported them as 5 $\mu\text{g}/\text{kg}$ for halothane and 36 $\mu\text{g}/\text{kg}$ for awake dogs.

Our epinephrine dosages are almost equivalent to these reports. The somewhat lower value we obtained during halothane anesthesia might be due to the combined use of thiopental. The arrhythmogenic dose for pentobarbital seems to correspond to that in awake dogs determined by Joas *et al.*,² and this suggests that the epinephrine dosage of 20.91 $\mu\text{g}/\text{kg}$ during enflurane anesthesia represents at least a slight sensitizing effect of this anesthetic on the myocardium.

The arrhythmogenic response to epinephrine is probably dependent, at least in part, on catecholamine-terminating mechanisms.⁵ However, halothane seems to have no significant effect on the elimination of circu-

lating epinephrine because the plasma levels of epinephrine at the end of the 3-min infusion period during halothane anesthesia were not significantly different from that during pentobarbital anesthesia.

The present results have shown that norepinephrine is as arrhythmogenic as epinephrine during halothane anesthesia. This result agrees with the findings of Deterling *et al.*,¹⁶ who have demonstrated the arrhythmogenicity of norepinephrine during cyclopropane anesthesia.

It is possible that there might be a species differences in the arrhythmogenic dose of epinephrine. Miletich *et al.*⁶ reported that the arrhythmic threshold for epinephrine during halothane anesthesia was 10.9 $\mu\text{g}/\text{kg}$ in non-fasted rats and 5.5 $\mu\text{g}/\text{kg}$ in 12-hour fasted rats. These thresholds seem to be higher than those in dogs. On the other hand, the arrhythmogenic dose of epinephrine in humans seems to be lower than in dogs. Johnston *et al.*⁴ reported that the arrhythmic threshold in humans with submucosal injections of epinephrine was 2.1 $\mu\text{g}/\text{kg}$ for halothane and 10.9 $\mu\text{g}/\text{kg}$ for enflurane, although the dose was that necessary to produce a positive response in 50% of the patients (ED_{50}).

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