

Myocardial Epinephrine Sensitization with Subanesthetic Concentrations of Halothane in Dogs

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The authors investigated myocardial epinephrine sensitization by subanesthetic concentrations of halothane. The dose-response relationship for the action of halothane was examined with etomidate plus varying subanesthetic concentrations of halothane in dogs. The arrhythmogenic threshold of epinephrine was decreased in a dose-dependent manner at end-tidal concentrations of halothane between 0.1 and 0.3%. At end-tidal halothane is greater than 0.3%, and no further reduction of arrhythmogenic threshold of epinephrine occurred. The plasma concentrations of epinephrine producing four or more premature ventricular contractions in 15 s were 201.3 ± 34.3 , 98.1 ± 13.9 , 60.3 ± 8.63 , 57.9 ± 12.8 , 54.5 ± 8.61 , and 53.9 ± 4.86 ng/ml (mean \pm SEM), at 0, 0.1, 0.3, 0.5, 1.0, and 1.5% of halothane at end-tidal concentrations, respectively. The results suggest that in the presence of etomidate, halothane produces myocardial sensitization to epinephrine at subanesthetic concentrations as low as 0.1%. Increasing halothane to 0.3% produces a further reduction in the arrhythmogenic dose of epinephrine. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmia. Sympathetic nervous system: epinephrine.)

MANY REPORTS DESCRIBE myocardial epinephrine sensitization by halothane in both animal experiments and clinical studies.¹⁻¹³ In most of these reports, the halothane concentration was set at more than 1 MAC. Only one report¹ demonstrated myocardial sensitization by halothane at subanesthetic concentrations. According to this report, increasing the halothane concentration does not alter the threshold for epinephrine-induced arrhythmias between an end-tidal halothane concentrations of 0.5 and 2.0%. However, there is no information concerning the sensitizing effect of halothane at concentrations less than 0.5%. The current study was carried out to clarify the dose-response relationship of myocardial sensitization by

halothane at end-tidal concentrations between 0.1 and 0.5%.

Materials and Methods

The studies were conducted under guidelines approved by the Animal Care Committee of Osaka University Medical School.

Fifty-seven adult mongrel dogs of either sex and weighing 8-12 kg were used in this study. The dogs were anesthetized either with etomidate plus halothane or with halothane alone. A different dog was used for each experiment; thus, only one arrhythmogenic dose (AD) was determined in any individual dog. The trachea of each animal was intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated (Aika R60, Tokyo, Japan). The end-tidal CO₂ concentration was continuously monitored with an expired gas monitor (Minato 1H 21A, Osaka, Japan) and maintained at a level of 35-40 mmHg. A heating lamp and circulating water blanket were used to maintain the esophageal temperature between 37.0 and 38.5° C. For dogs anesthetized with etomidate plus halothane, anesthesia was induced with etomidate 2.0 mg/kg and maintained with a continuous infusion of etomidate ($0.13 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).¹⁴ Alcuronium (0.2 mg/kg) was administered to achieve complete paralysis. Halothane then was administered to maintain end-tidal concentrations of 0, 0.1, 0.3, 0.5, 1.0, and 1.5%, which were continuously monitored by an infrared anesthetic gas analyzer (Datex AA-102-30-00, Helsinki, Finland). In addition, in order to rule out any influence of etomidate and alcuronium, some dogs were anesthetized with either halothane alone at an end-tidal concentration of 1.3 MAC (1.1%) or halothane (end-tidal 1.1%) with etomidate and alcuronium, as described above.

Lead II of the electrocardiogram was monitored continuously. A femoral artery catheter was inserted for both pressure monitoring and blood sampling. A right femoral vein was cannulated for the administration of both epinephrine and a solution of lactated Ringer's solution, infused at a rate of $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Serum K⁺ was maintained between 3.5 and 4.5 mEq/l by infusion of K⁺ at a rate of 1-10 mEq/h. Arterial pH ranged between 7.35 and 7.45; PaO₂, between 85 and 100 mmHg; and serum Na⁺, between 135 and 150 mEq/l.

Arrhythmias were defined as four or more premature ventricular contractions occurring within 15 s.⁵ The AD

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of epinephrine was defined as the lowest dose that produced arrhythmias. According to the method of Pace *et al.*,⁵ the AD of epinephrine was determined in each dog with standardized logarithmically spaced infusions (Terumo STC-502, Tokyo, Japan) of epinephrine lasting 3 min with 10–30-min recovery periods between infusions. In this procedure, the infusion was started at the minimum dose of $0.67 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the dose was increased by $e^{0.4}$ ($e = 2.72$) (1.0, 1.49, 2.23, 3.32, 4.95, 7.39, 11.0, *etc.*, $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) until arrhythmias occurred. If arrhythmias did occur at one of these doses, a smaller arrhythmic dose, divided by $e^{0.2}$, was tested. For example, if there were arrhythmias at $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a dose of $0.82 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ($1.0/e^{0.2}$) was tested. Similarly, in cases of 1.49, 2.23, 3.32, 4.95, 7.39, and 11.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, a smaller dose of 1.22, 1.82, 2.72, 4.06, 6.05, or 9.03 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, respectively, was tested. Epinephrine infusions for AD testing were begun more than 30 min after the beginning of halothane inhalation. A 4-ml arterial blood sample was collected to allow measurement of arrhythmogenic plasma concentration (APC) of epinephrine at the time when the criterion for the AD had been satisfied.

Plasma epinephrine was measured by the method of Yamatodani and Wada,¹⁵ summarized as follows. Blood samples were withdrawn into precooled plastic tubes (2° C) containing 40 μl 0.2 M EDTA-Na₂ and 0.2 M Na₂S₂O₅. These were centrifuged at 4,000 rpm for 10 min at 2° C to separate the plasma. For analysis of epinephrine, 1 ml of the plasma was acidified by the addition of 0.5 ml 2.5% perchloric acid to precipitate protein. The samples were stored at -40° C until analyzed within 14 days. Epinephrine in deproteinized plasma was determined by an automated double-column high-performance liquid chromatography system (model CA825, Tosoh, Tokyo, Japan). This assay is based on the trihydroxyindole reaction; it has a limit of sensitivity of 5 pg/ml for epinephrine and inter- and intraassay variations of less than 3%.

TABLE 1. Basal Arterial Pressure and Heart Rate during Etomidate with Increasing Concentrations of Halothane

Concentration of Halothane (%)	n	SAP (mmHg)	DAP (mmHg)	HR (beats per min)
0	7	157 ± 3.64	83 ± 2.80	79 ± 6.38
0.1	7	153 ± 5.29	80 ± 4.85	86 ± 7.21
0.3	7	147 ± 2.66	76 ± 5.44	88 ± 8.71
0.5	7	134 ± 1.89*	68 ± 4.53	99 ± 6.83
1.0	7	116 ± 1.37†	59 ± 2.77*	101 ± 7.82
1.5	6	106 ± 6.95†	57 ± 5.33*	112 ± 7.55

Mean ± SEM.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.

Statistical significance: * $P < 0.05$ and † $P < 0.01$ compared with control value (halothane 0%).

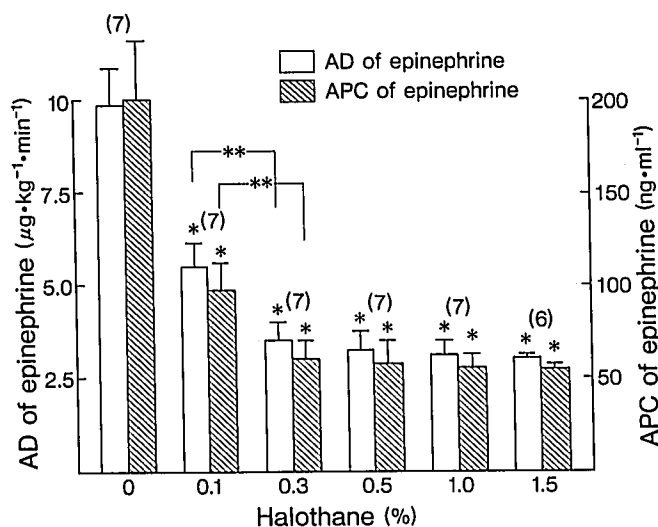


FIG. 1. The arrhythmogenic dose (AD) and arrhythmogenic plasma concentration (APC) of epinephrine during etomidate plus varying concentrations of halothane. The number of observations is shown in parentheses. * $P < 0.01$, compared to value with basal anesthesia but no halothane. ** $P < 0.05$, compared to each other.

Data are expressed as mean ± SEM. The results of multiple groups were analyzed by one-way analysis of variance, and comparison between groups was assessed by Scheffe's test. Comparison between two groups was assessed by Student's *t* test for unpaired data. $P < 0.05$ was considered statistically significant.

Results

Basal hemodynamic data at various end-tidal halothane concentrations are presented in table 1. Both systolic and diastolic arterial pressures decreased significantly as the halothane concentration increased. Heart rate tended to increase with increasing halothane concentration, but the increase was not significant. The AD and APC of epinephrine at various halothane concentrations are shown in figure 1. Halothane, even at 0.1%, decreased the arrhythmogenic threshold (AD or APC) to approximately 50% of the control value (halothane 0%) with a further dose-dependent decrease in AD or APC of epinephrine for halothane concentrations of up to 0.3%. On the other hand, increasing the halothane concentration to above 0.3% had no effect on the AD or APC of epinephrine. Figure 2 shows hemodynamic data at the time of AD or APC with varying concentrations of halothane. Both systolic and diastolic arterial pressure at AD or APC decreased significantly with increasing concentrations of halothane, whereas the heart rate at AD or APC did not vary significantly for the various concentrations of halothane.

The hemodynamic data obtained at the arrhythmogenic threshold of epinephrine during halothane anes-

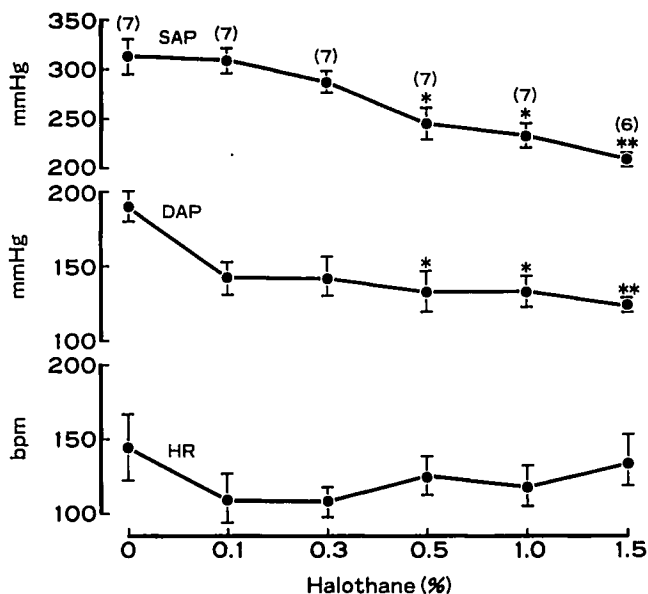


FIG. 2. Hemodynamic data at the time of arrhythmias were observed with basal anesthesia and varying concentrations of halothane. SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate. * $P < 0.05$, ** $P < 0.01$ compared with no halothane.

thetia are shown in table 2. There were no significant differences in AD or APC of epinephrine, blood pressure, or heart rate between dogs receiving halothane alone and those receiving halothane with etomidate and alcuronium.

Discussion

It is well known that halothane at anesthetic concentrations exerts a potent myocardial-sensitizing action to epinephrine.¹⁻¹³ However, it is not known whether halothane exerts this effect at subanesthetic concentrations. Metz and Maze¹ reported that halothane concentrations at or above 0.5% do not alter the arrhythmogenic threshold of epinephrine. The current results clearly demonstrate that halothane exerts a myocardial-sensitizing action even at concentrations as low as 0.1%, a concentration at which it lowers the arrhythmogenic threshold of epinephrine to approximately 50% of the value with basal etomidate anesthesia (control).

Halothane itself is known to reduce blood pressure in a dose-dependent manner.¹⁶ In the current study, both systolic and diastolic arterial pressure at the time of the arrhythmias decreased with increasing concentration of halothane. The decrease in systolic pressure would be expected to oppose halothane-epinephrine arrhythmias: systolic pressure elevation has been considered an important factor in the genesis of halothane-epinephrine ventricular arrhythmias^{8,9} and especially ventricular bigeminy in dogs with severed vagi.¹⁰ However, the arrhythmogenic threshold was not further reduced by halothane at end-

tidal concentrations above 0.3%, although when arrhythmias occurred the systolic pressure tended to decrease further. The decrease in diastolic pressure, however, might potentiate halothane-epinephrine arrhythmias because of the decrease in coronary blood supply. This mechanism might be involved in the sensitization by halothane at 0.1% end-tidal concentration. Actually, at 0.1% halothane, the diastolic pressure had decreased but the systolic pressure had not changed, compared with control (figure 2).

With regard to heart rate, we demonstrated in our previous report⁸ that the increase in heart rate was not an important factor in the intact dog preparation. Moreover, changes in heart rate in this study were not significant. Therefore, heart rate probably are not an important factor in the genesis of halothane-epinephrine arrhythmias.

If anesthesia is maintained with subanesthetic concentrations of halothane alone, sympathoadrenal excitation due to inadequate anesthesia would be expected to affect the dose of epinephrine for ventricular arrhythmias with halothane. Therefore, an appropriate supplemental basal anesthesia would be required. In this study, we used etomidate and alcuronium for basal anesthesia because these agents have been shown not to affect myocardial sensitization by thiopental.¹⁴ Etomidate, in contrast to thiopental¹¹ and nitrous oxide,¹² has been reported not to affect the AD of epinephrine during halothane anesthesia¹ and to have little myocardial-sensitizing action.¹⁴ Some muscle relaxants, such as succinylcholine and *d*-tubocurarine, have been shown to affect the dose of epinephrine for ventricular arrhythmias with halothane.¹³ Alcuronium, at least with etomidate, does not affect the arrhythmia thresholds with 1.1% end-tidal halothane. Although we did not test this possibility, we see no reason why this lack of effect would not extend to higher or subanesthetic halothane concentrations. Additionally, as noted earlier, the accurate assessment of AD of epineph-

TABLE 2. The Effect of Alcuronium and Etomidate at the Time of Arrhythmias during Halothane Anesthesia

	Halothane Alone (n = 9)	Alcuronium and Etomidate plus Halothane (n = 7)
Arrhythmogenic dosage of epinephrine ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	2.69 \pm 0.47	3.03 \pm 0.36
Plasma concentration of epinephrine ($\text{ng} \cdot \text{ml}^{-1}$)	47.7 \pm 9.74	53.7 \pm 12.5
Systolic arterial pressure (mmHg)	223 \pm 12.4	222 \pm 11.0
Diastolic arterial pressure (mmHg)	127 \pm 6.08	132 \pm 7.3
Heart rate (beats per min)	148 \pm 12.3	121 \pm 18.9

Mean \pm SEM.

Halothane: 1.1% end-tidal.

There were no significant differences between the two groups.

rine with subanesthetic halothane concentrations without appropriate supplemental anesthesia may be unreliable because of high plasma concentrations of endogenous catecholamines.

The current results, if applicable to humans, may have clinical relevance. Halothane may potentiate epinephrine-induced ventricular arrhythmias during anesthetic induction or recovery or during inhalation of low concentrations of the agent when used as an anesthetic supplement.

In conclusion, subanesthetic concentrations of halothane in dogs exert a myocardial-sensitizing action to epinephrine. This action is dose-dependent at end-tidal halothane concentrations between 0.1 and 0.3%.

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