Myocardial Sensitization by Thiopental to Arrhythmogenic Action of Epinephrine in Dogs

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This study examined the interaction between thiopental and epinephrine in inducing ventricular arrhythmias in dogs. The arrhythmogenic threshold of epinephrine was determined during anesthesia with either halothane alone, thiopental alone, etomidate plus different doses of thiopental, or halothane plus different doses of thiopental. The arrhythmogenic dose and the corresponding plasma concentration of epinephrine during thiopental anesthesia (plasma thiopental concentration: 46–57 μg/ml) were 0.77 ± 0.04 μg·kg⁻¹·min⁻¹ and 10.7 ± 1.5 ng/ml, respectively. During halothane anesthesia (end-tidal: 1.3 MAC) they were 2.59 ± 0.49 μg·kg⁻¹·min⁻¹ and 45.3 ± 9.2 ng/ml, respectively. The dose-effect relationship for the thiopental action was examined during etomidate plus thiopental and halothane plus thiopental anesthesia. The arrhythmogenic plasma concentration of epinephrine was inversely proportional to the plasma thiopental concentration during both anesthetics. During etomidate plus thiopental anesthesia, at plasma thiopental concentrations of 0, 11.2 ± 0.88, 20.1 ± 1.34, and 33.2 ± 1.85 μg/ml, the corresponding epinephrine concentrations were 201.3 ± 34.3, 142 ± 19.5, 69.1 ± 21.3, and 22.7 ± 4.5 ng/ml. During halothane plus thiopental anesthesia, at plasma thiopental concentrations of 0, 10 ± 0.86, 18.3 ± 0.87, and 31.8 ± 1.05 μg/ml, the corresponding epinephrine concentrations were 45.3 ± 9.2, 34.6 ± 8.9, 16.2 ± 1.74, and 15.1 ± 1.32 μg/ml, respectively. These results suggest that thiopental sensitizes the heart to epinephrine in a dose-dependent manner. This sensitizing action of thiopental would in part explain the thiopental potentiation of hydrocarbon anesthetic-epinephrine arrhythmias. (Key words: Anesthetics, intravenous: thiopental. Heart: arrhythmia. Sympathetic nervous system: epinephrine.)

THIOPENTAL is known to potentiate cyclopropane-epinephrine-induced ventricular arrhythmias. Recently, this potentiation has also been demonstrated to occur in cases where myocardial sensitization is induced by hydrocarbon anesthetics, such as halothane, enfurane, isoflurane, and sevoflurane. The mechanism of this potentiation is as yet unknown. Thiopental itself has been shown to have a character similar to class 1 and class 3 antiarrhythmic agents, i.e., it has Na⁺ channel blocking properties and prolongs action potential duration and refractoriness, and it has been considered not to sensitized the heart to epinephrine. On the other hand, it has been reported that, in contrast with pentobarbital, thiopental when injected intravenously in anesthetic doses readily produces arrhythmias in dogs. Regarding epinephrine arrhythmias,Rolff and Campbello found that iv-administered epinephrine tended to induce arrhythmias more readily in dogs anesthetized with thiobarbiturate than in awake dogs.

The present study was designed to clarify whether or not thiopental alone sensitizes the heart to epinephrine, and if so, to analyze quantitatively the dose-effect relationship of this action.

Materials and Methods

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

Seventy-five adult mongrel dogs of either sex, weighing 9–12 kg were used. The dogs were anesthetized with either thiopental (eight dogs), halothane (ten dogs), etomidate plus thiopental (38 dogs), or halothane plus thiopental (19 dogs). A different dog was used for each experiment. Thus, only one arrhythmogenic dose was administered in any individual dog. The trachea of each animal was intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated (Aika® R60). The end-tidal CO₂ concentration was continuously monitored with an expired gas monitor (Minato® 1H 21A) and maintained at a level of 35–40 mmHg. A heating lamp and circulating water blanket were used to maintain esophageal temperature between 37–38.5°C.

For thiopental anesthesia, anesthesia was induced and maintained with thiopental alone as follows. An initial dose of 20 mg/kg was given iv, followed by continuous administration to maintain sufficient depth of anesthesia, i.e., to prevent spontaneous movement and coughing. The infusion dose of thiopental was started at 1 mg·kg⁻¹·min⁻¹ and gradually decreased to 0.25 mg·kg⁻¹·min⁻¹ to maintain a constant plasma concentration. This dose was based upon results from preliminary experiments. The time course of the thiopental dose and the corresponding plasma concentration are shown in fig-

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mEq/l by infusing K at a rate of 1–10 mEq/h. Arterial
pH, PaO₂, and serum Na were maintained within the range
of 7.35–7.45, 85–100 mmHg, and 135–150 mEq/l, re-
spectively.

**Determination of Arrhythmogenic Dose**

For all experiments, the arrhythmias were defined as
four or more premature ventricular contractions occurring
within 15 s.³⁺ The arrhythmogenic dose (AD) of epine-
phrine was defined as the lowest dose that produced arrhythmias. Using the method of Pace et al.,¹¹ the AD
of epinephrine was determined for each dog during stan-
dardized logarithmically spaced infusions of epinephrine
lasting 3 min (Terumo® STC-502) (0.67, 0.82, 1.00, 1.22,
etc., μg·kg⁻¹·min⁻¹). During thiopental anesthesia, epine-
phrine infusion was begun about 30 min after the be-
ginning of thiopental infusion. The first infusion rate was
also 0.67 μg·kg⁻¹·min⁻¹, and when the arrhythmias were
observed at this rate, still lower doses (0.45 and 0.55
μg·kg⁻¹·min⁻¹) were examined. Epinephrine infusion
continued for 3 min at each rate with at least a 10-min
(10–30 min) recovery period until AD was reached. A 4-
ml arterial blood sample was collected to allow measure-
ment of concentrations of plasma epinephrine and thiio-
pental at the time when the criterion for the AD had been
satisfied.

**Analysis of Plasma Concentration of
Epinephrine and Thiopental**

Blood samples were withdrawn into precooled plastic
tubes containing 40 μl of 0.2 M EDTA-2Na and 0.2 M
Na₂SO₄. These were then 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 addition
of 0.5 ml of 2.5% perchloric acid to precipitate protein.
The samples were stored at −40° C until analyzed within
7 days. Epinephrine and norepinephrine in deproteinized
plasma were determined by an automated double-column
HPLC system¹² (Model CA825®, Tosoh Co., Ltd., Tokyo,
Japan). This assay system is based on the trihydroxyindole
reaction, and has a limit of sensitivity of 5 pg/ml for epi-
nephrine and the inter and intraassay variations are less
than 8%.

Plasma concentrations of thiopental were measured by
a modified version of the method described by Toner et
al.¹³ using either extraction and HPLC. Each 0.5-ml
plasma sample was mixed with 1 ml of 0.1 M potassium
phosphate buffer pH 6.5, 1 ml of saturated potassium
chloride, 10 μl of 0.2% thiamylal that was used as an in-
ternal standard for the correction of assay recovery, and
2 ml of diethyl ether. The mixture was shaken vigorously
and then centrifuged at 4,000 rpm for 5 min. The ether
layer is removed and evaporated to dryness under nitro-
gen, followed by reconstitution with 100 μl of a 70:30

![Graph](image_url)

**Figure 1.** The time course of the dose and the plasma concentration of thiopental during thiopental anesthesia. An initial dose of 20 mg/kg was administered iv followed by continuous infusion at the doses indicated (mean ± SEM; n = 5).

For experiments with halothane, anesthesia was
induced with halothane alone and maintained at an end-
tidal concentration of 1.3 MAC (1.1%), which was con-
tinuously measured by an anesthetic gas analyzer (Datex®
AA-102-30-00). The end-tidal concentration was kept
constant for at least 15 min before the beginning of epi-
nephrine infusion. For dogs anesthetized with etomidate plus thiopental, anesthesia was induced with etomidate
2.0 mg/kg iv and maintained with continuous infusion of
etomidate at 0.15 mg·kg⁻¹·min⁻¹. Thiopental was added at various doses of 0, 0.1, 0.3, or 0.5
mg·kg⁻¹·min⁻¹. In these dogs, alcuronium (0.2 mg/kg)
was used to prevent involuntary muscle movements in-
duced by etomidate¹⁰ and to achieve complete muscular
immobilization. In addition, some dogs were anesthetized
without alcuronium to rule out any influence of alcu-
nonium. For dogs anesthetized with halothane and thiop-
tal, anesthesia was induced with halothane alone and
maintained at an end-tidal concentration of 1.3 MAC
(1.1%); then thiopental was added at various doses of 0,
0.1, 0.3, or 0.5 mg·kg⁻¹·min⁻¹. During anesthesia with
etomidate plus thiopental or halothane plus thiopental,
epinephrine infusion was begun exactly 15 min after the
beginning of thiopental infusion.

Lead II of the electrocardiogram was monitored con-
tinuously. A femoral artery catheter was inserted for both
pressure monitoring and blood gas and electrolyte sam-
ping. A right femoral vein was cannulated for the ad-
ministration of both drugs and a solution of 3% dextrose
in 0.5% NaCl. The latter was infused at a rate of 10
ml·kg⁻¹·h⁻¹. Serum K was maintained between 3.5–4.5

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mixture of methanol and 0.1 M sodium acetate buffer (pH 5.0) mixture. Five microliters of the sample was injected into a reversed phase ODS column (TSKgel ODS-80TM, 4 mm ID × 150 mm, Tosoh), and the column was eluted with a 70:30 mixture of methanol and 0.1 M sodium acetate buffer, pH 5.0, at a rate of 1 ml/min. The absorbance at 280 nm of the column eluate was monitored with a UV detector (Model UV-8000, Tosoh) equipped with a data processor (Model C-R6A, Shimadzu Co., Kyoto). The limit of sensitivity was 10 ng/ml and the inter and intra-assay variations are less than 5%.

STATISTICAL ANALYSIS

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

Results

Figure 1 shows the time course of thiopental dose and plasma concentrations during the thiopental anesthesia. The concentration of thiopental was maintained close to 50 µg/ml (46–57 µg/ml) for 90 min, and during this period no dog moved spontaneously. Table 1 shows the basal plasma concentrations of endogenous catecholamines during each type of anesthesia. The plasma concentration of endogenous epinephrine during thiopental, etomidate, and etomidate plus thiopental anesthesia was significantly less than that during halothane anesthesia. The plasma catecholamines during etomidate anesthesia were not significantly affected by additional thiopental administration.

As shown in table 2, the AD of epinephrine during thiopental anesthesia was significantly less than that during halothane or etomidate anesthesia. There was no significant difference between the hemodynamic data during halothane or thiopental anesthesia (table 3). Figure 2 shows the ADs of epinephrine during etomidate plus thiopental anesthesia. The AD of epinephrine decreased significantly as the dose of thiopental increased. Similarly, the plasma concentration of thiopental and the arrhythmogenic plasma concentration of epinephrine were inversely proportional (fig. 3). Hemodynamic data at the time of arrhythmias for varying doses of thiopental with etomidate are shown in figure 4. The systolic arterial pressure at induction of arrhythmias decreased with increasing dose of thiopental. However, both diastolic arterial pressure and heart rate did not vary significantly with varying doses of thiopental.

The effect of alcuronium on the AD of epinephrine during etomidate plus thiopental anesthesia is shown in table 4. The presence or absence of alcuronium had no significant effect on the AD of epinephrine or the blood pressure or the heart rate.

Figure 5 shows the ADs of epinephrine and figure 6 shows the plasma concentrations of epinephrine during halothane plus thiopental anesthesia. The AD of epinephrine and the plasma concentration of epinephrine decreased significantly as the dose of thiopental increased. Hemodynamic data at the time of arrhythmias for varying doses of thiopental with halothane anesthesia are shown in figure 7. The systolic and diastolic arterial pressure at induction of arrhythmias decreased with increasing dose of thiopental.

Discussion

In order to determine whether or not thiopental alone sensitizes the heart to epinephrine, the arrhythmogenic threshold of epinephrine during thiopental anesthesia was

<table>
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<tr>
<th>Table 2. Arrhythmogenic Threshold of Epinephrine during Thiopental, Halothane, or Etomidate Anesthesia (Mean ± SEM)</th>
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<td>Anesthesia</td>
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<tr>
<td></td>
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<tr>
<td>Halothane</td>
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<td>Thiopental</td>
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<td>Etomidate</td>
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Statistical significance: *P < 0.01 compared with halothane value.

<table>
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<tr>
<th>Table 1. Basal Plasma Concentrations of Endogenous Epinephrine and Norepinephrine during Each Type of Anesthesia (Mean ± SEM)</th>
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<td>Anesthesia</td>
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<tr>
<td>Halothane</td>
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<tr>
<td>Thiopental</td>
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<td>Etomidate</td>
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<tr>
<td>Etomidate plus Thiopental 0.5 mg·kg⁻¹·min⁻¹</td>
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Statistical significance: *P < 0.05 and †P < 0.01 compared with halothane value.

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<tr>
<th>Table 3. Blood Pressure and Heart Rate at the Time of Arrhythmias (Mean ± SEM)</th>
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<td>Anesthesia</td>
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</tr>
<tr>
<td>Halothane</td>
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<tr>
<td>Thiopental</td>
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<td>Etomidate</td>
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SAP = systolic arterial pressure. DAP = diastolic arterial pressure. HR = heart rate.
Statistical significance: *P < 0.01 compared with halothane value.
FIG. 2. The arrhythmogenic dose (AD) of epinephrine during etomidate plus varying doses of thiopental (mean ± SEM; number of observations is shown in parentheses). The dogs were anesthetized with etomidate, 2 mg/kg iv, followed by an infusion 0.13 μg·kg⁻¹·min⁻¹ and alcuronium 0.2 mg/kg, and then thiopental was given at varying doses as indicated. *P < 0.05, **P < 0.01 compared with control.

FIG. 3. The relationship between the plasma concentration of thiopental and the arrhythmogenic plasma concentration of epinephrine during etomidate plus varying doses of thiopental (mean ± SEM, number is shown in parentheses). The experimental condition is the same as figure 2, except for the point of the highest thiopental concentration, which was obtained in the experimental condition described in figure 1. *P < 0.01 compared with control.

FIG. 4. The hemodynamic data at the time of arrhythmias during etomidate plus varying doses of thiopental. The experimental condition is the same as figure 2 (mean ± SEM; number is shown in parentheses). SAP = systolic arterial pressure. DAP = diastolic arterial pressure. HR = heart rate. *P < 0.05 compared with control.

compared with that during halothane and during etomidate anesthesia. The results clearly show that epinephrine induces arrhythmias at a significantly lower dose during thiopental anesthesia than during halothane or etomidate anesthesia (table 2). This indicates that thiopental sensitizes the heart to epinephrine to a greater extent than that caused by halothane. In contrast to halothane, the effect of which on AD of epinephrine is not dose-dependent between 0.5–2.0% end-tidal concentration, the plasma concentration of thiopental is an important factor determining the degree of myocardial sensitization (figs.

TABLE 4. The Effect of Alcuronium on Arrhythmogenic Threshold of Epinephrine and the Blood Pressure and Heart Rate at the Time of Arrhythmias during Etomidate plus Thiopental (0.5 mg·kg⁻¹·min⁻¹) Anesthesia (Mean ± SEM)

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<th>Alcuronium (+)</th>
<th>Alcuronium (−)</th>
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<tr>
<td><strong>n</strong></td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td><strong>Arrhythmogenic dose of epinephrine (μg·kg⁻¹·min⁻¹)</strong></td>
<td>1.49 ± 0.28</td>
<td>1.60 ± 0.25</td>
</tr>
<tr>
<td><strong>Plasma concentration of epinephrine (ng/ml)</strong></td>
<td>22.7 ± 4.46</td>
<td>23.2 ± 4.73</td>
</tr>
<tr>
<td><strong>Systolic arterial pressure (mmHg)</strong></td>
<td>252 ± 9.14</td>
<td>262 ± 21.8</td>
</tr>
<tr>
<td><strong>Diastolic arterial pressure (mmHg)</strong></td>
<td>143 ± 6.4</td>
<td>140 ± 7.1</td>
</tr>
<tr>
<td><strong>Heart rate (bpm)</strong></td>
<td>145 ± 14.6</td>
<td>146 ± 4.3</td>
</tr>
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There are no significant differences between the two groups.
Fig. 5. The arrhythmogenic dose of epinephrine during halothane plus varying doses of thiopental. The dogs were anesthetized with halothane, 1.3 MAC end-tidal concentration, and the thiopental was given at varying doses as indicated. *P < 0.05 compared with control.

Fig. 6. The relationship between the plasma concentration of thiopental and the arrhythmogenic plasma concentration of epinephrine during halothane plus varying doses of thiopental (mean ± SEM, number is shown in parentheses). The experimental condition is the same as figure 5. *P < 0.05 compared with control.

Fig. 7. The hemodynamic data at the time of arrhythmias during halothane plus varying doses of thiopental (mean ± SEM; number is shown in parentheses). SAP = systolic arterial pressure. DAP = diastolic arterial pressure. HR = heart rate. *P < 0.05 **P < 0.01 compared with control.

2 and 3). Sensitization by thiopental appears at a plasma concentration of about 10 μg/ml. When the plasma concentration of thiopental exceeds 30 μg/ml, epinephrine induces arrhythmias more readily than during halothane anesthesia.

It is difficult to compare IV anesthetics with inhalational anesthetics in terms of their equipotency. The adequacy of the depth of thiopental anesthesia in the present study is based on the following. It has been reported that in humans, anesthesia produced by thiopental at plasma concentrations of 39–42 μg/ml was equivalent to that by 1 MAC of inhalational agents. The MAC of halothane for dogs is 0.87%, approximately 17% higher than that for humans (0.74%). Drummond has reported that the within-species ratios of MAC values for any pairing of volatile anesthetics is very similar. Applying this rule to thiopental, plasma level of 46–49 μg/ml would be equivalent to 1 MAC of halothane in dogs. In the present study, thiopental anesthesia was maintained at a plasma concentration of 46–57 μg/ml. At this level of anesthesia, no dog moved spontaneously and the basal concentration of plasma catecholamines was sufficiently low, indicating that the level of anesthesia was appropriate.

In the present study, there was a difference in the basal concentration of endogenous epinephrine among three types of anesthesia. Increased endogenous epinephrine might influence the AD of epinephrine resulting from
decreased sensitivity of heart-to-exogenous epinephrine. However, it is unlikely that this difference of basal epinephrine could influence the results of AD of epinephrine, because any of these values of basal epinephrine were less than 1% of the arrhythmogenic plasma concentration.

The hemodynamic data at the time of arrhythmias can be compared among the three types of anesthesia. The mean value of heart rate × arterial pressure (a rough determinant of myocardial oxygen demand) are approximately similar between halothane and thiopental groups. Although diastolic arterial pressure is 17% lower in thiopental group than halothane group, both values were within the range in which coronary autoregulation is preserved. Furthermore, in the etomidate group, arrhythmias were not observed until the blood pressure and heart rate reached far higher levels than in the halothane and thiopental group. These findings indicate that the differences in the AD of epinephrine among the groups could be related not to inadequacy of myocardial oxygen supply but to the degree of myocardial sensitizing effect of each anesthetic.

In the experiment to examine the dose-effect relationship of sensitizing action of thiopental, we used etomidate and alcuronium for basal anesthesia. Unlike nitrous oxide, which potentiates halothane-epinephrine arrhythmias, etomidate has been reported to have no effect of the arrhythmogenic threshold of epinephrine during halothane anesthesia. Furthermore, etomidate itself has little sensitizing action (figs. 2 and 3). Thus, etomidate was used as an appropriate supplemental agent. The dose of etomidate we used was twice the dose used in the previous studies by Metz et al.,14 and Lambalgen et al.20 In preliminary experiments, we used a similar dose of etomidate, i.e., 1 mg/kg iv followed by 0.067 mg·kg⁻¹·min⁻¹. The plasma concentration of epinephrine 20 min after starting anesthesia was 939 ± 187 pg/ml (n = 5), and systolic blood pressure was 183 ± 8.3 mmHg, indicating the presence of sympathoadrenal excitation. When the dose of etomidate was doubled, the plasma concentration of epinephrine was 178 ± 22 pg/ml (n = 7) and the systolic blood pressure was 152 ± 3.2 mmHg, indicating an appropriate level of anesthesia. The latter dose was therefore used in this series of experiments. In the previous studies,14,20 the smaller dose of etomidate would be effective in maintaining a sufficient depth of anesthesia because of simultaneous inhalation of nitrous oxide and halothane. Although the plasma etomidate concentration was not measured in the present study, it is probable on the basis of the previous study that it would be constant during the experiment.14

It has been shown that certain muscle relaxants, including succinylcholine and d-tubocurarine, affect halothane-epinephrine arrhythmias.21 In the present study, it was confirmed that alcuronium did not significantly affect the induction of thiopental-epinephrine arrhythmias and hemodynamic data at the time of arrhythmias (table 4). We therefore used alcuronium during anesthesia with etomidate plus thiopental to achieve complete muscular immobilization.

Mechanisms involved in the myocardial sensitization to epinephrine by thiopental are still not clear. It was reported that thiopental, when injected intravenously in anesthetic doses, readily produces arrhythmias in dogs,7 and may facilitate epinephrine arrhythmias by itself,6,8 or with cyclopropane,1 or the potent inhalation anesthetics.5,3,4 Hypoxia due to respiratory depression or endogenous epinephrine released from the adrenal medulla22 have been considered factors contributing to thiobarbiturate-related arrhythmias. In the present study, however, these factors could be excluded, because arterial blood gases were within normal range, and the plasma concentration of endogenous catecholamines was maintained at a low level. Thiopental has been shown to decrease the dose of digitalis and ouabain, which trigger fatal arrhythmias in dogs.24 Pentobarbital, however, did not have this action.24 Gruber and Lonergan25 suggested that the sulfur in the thiopental molecule would increase the irritability of the ventricle. This mechanism might be involved in the thiopental-epinephrine interaction. In fact, pentobarbital, the oxybarbiturate corresponding to thiopental, failed to significantly sensitize the heart to epinephrine,20 and thiamylal, which also has sulfur in the molecule (C₉ position), reduces the epinephrine arrhythmic dose with halothane.27 Finally, two reports suggest that thiopental may produce delayed afterdepolarizations.28,29 Additionally, exogenous catecholamines may also produce delayed afterdepolarizations and triggered activity.30 These two observations might underlie a possible cellular electrophysiologic mechanism of thiopental-epinephrine arrhythmia.

The present study has also demonstrated that during halothane-thiopental anesthesia, thiopental potentiates epinephrine-induced arrhythmias in a dose-dependent manner at the dose range approximately same as that present during etomidate-thiopental anesthesia. It is likely that the site of thiopental action in the heart is different from the site of halothane because the sensitizing action of halothane is not dose-dependent at the range of 0.5–2.0%.14 In other words, halothane-epinephrine arrhythmias are not potentiated by increasing halothane concentration from 0.5–2.0%. Therefore, if thiopental affected the heart in the same manner as halothane, thiopental must have failed to potentiate the halothane-epinephrine arrhythmias at the plasma thiopental concentration of 20 µg/ml or less, at which the sensitizing action of thiopental was less than that of 0.5–2.0% halothane.
In conclusion, thiopental alone sensitizes the heart to the arrhythmogenic action of epinephrine. This action of thiopental is dose-dependent in the presence of background etomidate with the arrhythmogenic plasma concentration of epinephrine inversely proportional to the plasma concentration of thiopental within the range of 0–50 μg/ml. Halothane-epinephrine arrhythmias are also potentiated by thiopental in a dose-dependent manner. These findings would explain the thiopental potentiation of hydrocarbon anesthetic-epinephrine arrhythmias.

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