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Enhancement by Propofol of Epinephrine-induced Arrhythmias in Dogs

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Although propofol is a widely used intravenous anesthetic, its effect on epinephrine-induced arrhythmias remains unknown. This study examined the possible interaction between propofol and epinephrine that might affect the induction of ventricular arrhythmias in dogs. The arrhythmogenic threshold of epinephrine was determined during anesthesia with halothane alone, propofol alone, etomidate alone, or etomidate plus varying doses of propofol. The arrhythmogenic dose and the corresponding plasma concentration of epinephrine during propofol anesthesia (blood propofol concentration 18.0 ± 0.98 μg/ml) were 2.52 ± 0.43 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 23.6 ± 8.5 ng/ml, respectively. During halothane anesthesia (end-tidal 1.3 MAC), they were 2.66 ± 0.21 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 35.7 ± 1.9 ng/ml, respectively. During etomidate anesthesia, they were 9.67 ± 1.06 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 205 ± 27.5 ng/ml, respectively. The dose–effect relationship for propofol was examined during etomidate plus propofol anesthesia. Propofol reduced the arrhythmogenic plasma concentration of epinephrine in a concentration-dependent manner: at blood propofol concentrations of 2.33 ± 0.46, 5.46 ± 0.71, and 11.2 ± 0.81 μg/ml, the corresponding plasma epinephrine concentrations were 182.6 ± 52.5, 89.0 ± 28.8, and 26.6 ± 6.9 ng/ml, respectively. These results suggest that propofol enhances epinephrine-induced arrhythmias in a dose-dependent manner in dogs. (Key words: Anesthetics, intravenous: propofol. Heart: arrhythmia. Sympathetic nervous system, catecholamines: epinephrine.)

EPINEPHRINE-INDUCED ARRHYTHMIAS are known to be enhanced by halothane and some other hydrocarbon anesthetics.[1,2] It has been demonstrated that thiopental reduces the dose of epinephrine required for production of arrhythmias during halothane, enflurane, or isoflurane anesthesia.[3,4] Hayashi *et al.*[5] reported that thiopental alone enhanced epinephrine-induced arrhythmias to a greater extent than did halothane. Among intravenous anesthetics, etomidate and pentobarbital have been reported to have little effect on epinephrine-induced arrhythmias.[1,6]

Propofol is a relatively new intravenous anesthetic agent and is widely used not only as an induction agent but also as a sole anesthetic agent.[7] The effect of propofol on epinephrine-induced arrhythmias has not been reported. The present study was designed to clarify whether or not propofol alone enhances epinephrine-induced arrhythmias in dogs, and if so, to analyze quantitatively the dose–effect relationship of this action.

Materials and Methods

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

Sixty-two adult mongrel dogs of either sex and weighing 8–12 kg were used. The dogs were anesthetized with propofol, halothane, etomidate, or etomidate plus varying doses of propofol. Propofol was administered as a 1% (weight/volume) aqueous emulsion containing (in weight/volume percentages) 10% soya bean oil, 1.2% egg phosphatide, and 2.25% glycerol. A different dog was used for each experiment. The trachea of each animal was intubated with a cuffed endotracheal tube, and the lungs were mechanically ventilated (Aika R60, Tokyo, Japan). The end-tidal CO_2 concentration was continuously monitored with an expired gas monitor (Minato 1H21A, Osaka, Japan) and maintained at 35–40 mmHg. A heating lamp and circulating water blanket were used to maintain esophageal temperature at 37–38.5° C.

Propofol anesthesia (eight dogs) was induced and maintained using only propofol, as follows. An initial intravenous dose of 10 mg/kg was administered, followed by continuous infusion at 40 $mg \cdot kg^{-1} \cdot h^{-1}$ to maintain a depth of anesthesia sufficient to prevent spontaneous movement and coughing. Epinephrine infusion was commenced exactly 60 min after the start of continuous infusion of propofol. For experiments with halothane (eight dogs), anesthesia was induced with halothane alone and maintained at an end-tidal concentration of 1.3 MAC (1.1%), continuously measured by an anesthetic gas analyzer (Datex AA-102-30-00, Helsinki, Finland). The end-tidal concentration was kept constant for at least 15 min

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before the start of epinephrine infusion. For dogs anesthetized with etomidate (eight dogs), anesthesia was induced with intravenous (iv) etomidate 2.0 mg/kg and maintained with a continuous infusion of etomidate 8.0 $mg \cdot kg^{-1} \cdot h^{-1}$. In these dogs, alcuronium (0.2 mg/kg) was used to prevent involuntary muscle movements induced by etomidate[8] and to achieve complete muscular immobilization. Epinephrine infusion was commenced exactly 60 min after the start of etomidate infusion. In addition, to examine possible interaction between propofol and etomidate, seven dogs were induced with propofol (10 mg/kg iv) and maintained with a continuous infusion of propofol (40 $mg \cdot kg^{-1} \cdot h^{-1}$). An intravenous loading dose of etomidate, 2.0 mg/kg, was given and followed by a continuous infusion of 8.0 $mg \cdot kg^{-1} \cdot h^{-1}$. Epinephrine infusion was commenced exactly 60 min after the start of etomidate infusion.

To examine the dose–effect relationship for propofol, the effect of lower doses of propofol was examined. In this experiment, we used etomidate for supplementing anesthesia to prevent sympathoadrenal excitation that would result from inadequate anesthesia and that would be expected to affect the arrhythmogenic dose (AD) of epinephrine. Anesthesia was induced with etomidate 2.0 mg/kg iv and alcuronium 0.2 mg/kg iv and maintained with a continuous infusion of etomidate 8.0 $mg \cdot kg^{-1} \cdot h^{-1}$. Propofol was added at various doses of 5 (eight dogs), 10 (seven dogs), and 20 (seven dogs) $mg \cdot kg^{-1} \cdot h^{-1}$. Eight dogs were anesthetized without alcuronium to exclude any influence of alcuronium. In addition, eight dogs were anesthetized with etomidate and administered lipid emulsion (10% soya bean oil, 1.2% egg phosphatide, and 2.25% glycerol) at 2 $ml \cdot kg^{-1} \cdot h^{-1}$ to determine the influence of the lipid emulsion of the emulsion formulation of propofol. Epinephrine infusion was commenced exactly 60 min after the start of propofol or lipid emulsion infusion.

Lead II of the electrocardiogram was monitored continuously. A femoral artery catheter was inserted for both pressure monitoring and blood sampling. Arterial blood pressure was measured with a pressure transducer (Nihon Kohden AC-611G, Tokyo, Japan). The electrocardiogram and arterial blood pressure were recorded continuously with an thermal array recorder (Nihon Kohden WS-641G). A right femoral vein was cannulated for the administration of drugs and 3% dextrose solution in 0.5% NaCl, which was infused at 10 $ml \cdot kg^{-1} \cdot h^{-1}$. Serum K^+ was maintained at 3.5–4.5 mEq/l by infusing K^+ at a rate of 1–10 mEq/h. A solution of 5% dextrose or 0.9% NaCl was administered if necessary to maintain serum Na^+ at 135–150 mEq/l. Arterial *p*H and oxygen tension were maintained at 7.35–7.45 and 85–100 mmHg, respectively.

Determination of Arrhythmogenic Dose

For all experiments, arrhythmias were defined as four or more premature ventricular contractions occurring within 15 s.[9] The AD of epinephrine was defined as the smallest dose that produced arrhythmias. According to the method of Pace *et al.*,[9] the AD of epinephrine was determined for each dog using standardized logarithmically spaced infusions (Terumo STC-502, Tokyo, Japan) of epinephrine lasting 3 min with a recovery period of 10–30 min between infusions. With this procedure, the infusion was started at the minimum dose of 0.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the dose was increased by $e^{0.4}$ (1.0, 1.49, 2.23, 3.32, 4.95, 7.39, 11.0, *etc.* $\mu g \cdot kg^{-1} \cdot min^{-1}$) until arrhythmias occurred. If arrhythmias did occur at one of these doses, a smaller dose equal to the dose divided by $e^{0.2}$ was tested. A 7-ml arterial blood sample was collected to allow measurement of concentrations of plasma epinephrine and blood propofol at the time when the criterion for AD had been satisfied.

Analysis of Plasma Concentration of Epinephrine and Blood Concentration of Propofol

For measurement of plasma concentration of epineph rine, blood samples were added to precooled plastic tubes containing 40 μl 0.2 M EDTA-2Na and 0.2 M $Na_2S_2O_5$, which were then centrifuged at 4,000 rpm for 10 min at 2° C to separate the plasma. For analysis of epinephrine, 1 ml plasma was acidified by the addition of 0.5 ml 2.5% perchloric acid to precipitate protein. The samples were stored at −40° C for not longer than 7 days, until analysis. Epinephrine concentration in deproteinized plasma was determined by an automated double-column high performance liquid chromatography (HPLC) system[10] (model CA825, Tosoh, Tokyo, Japan). This assay system is based on the trihydroxyindole reaction, and its limit of sensitivity is 5 pg/ml for epinephrine, with inter- and intraassay variations of less than 3%.

Blood concentrations of propofol were measured by a modified method described by Plummer[11] using cyclohexane extraction and HPLC. A 1-ml blood sample was mixed with 1 ml 0.1 M sodium phosphate buffer, 20 μl methanol that contained thymol as an internal standard for the correction of assay recovery, and 5 ml cyclohexane. The mixture was shaken vigorously and then centrifuged at 1,500 rpm for 10 min. The cyclohexane layer (4.5 ml) was transferred to a tube containing 50 μl dilute tetramethylammonium hydroxide solution and evaporated to dryness under N_2, followed by reconstitution with 200 μl HPLC mobile phase (a 550:450:2 mixture of acetonitrile, distilled water, and phosphoric acid). A volume of 10 μl of the sample was injected into a reversed-phase column

(Hypersil C18, 4.6 mm ID × 100 mm, GL Science, Tokyo, Japan), and the column was eluted with the HPLC mobile phase at a rate of 1 ml/min. The fluorescence of the column eluate was monitored with a fluorescence detector (model F1000, Hitachi, Tokyo, Japan). The excitation and emission wavelengths were 276 and 310 nm, respectively. The limit of sensitivity was 2 ng/ml, and the inter- and intraassay variations were less than 6%.

Statistical Analysis

The data were expressed as means ± standard error of the means. The results of multiple groups were analyzed by one-way analysis of variance, and comparisons between groups were assessed by Scheffé's test. Comparison between two groups were assessed by Student's t test for unpaired data. Values of $P < 0.05$ were considered significant.

Results

The AD values of epinephrine during anesthesia with propofol alone, halothane alone, or etomidate alone are shown in table 1. The AD of epinephrine during anesthesia with propofol was significantly less than that during anesthesia with etomidate. There was no significant difference between the AD values of epinephrine during anesthesia with propofol and with halothane. Systolic arterial pressure at the time of arrhythmias during anesthesia with propofol or etomidate was significantly greater than that during anesthesia with halothane (table 2). Table 3 shows the effect of etomidate on the AD of epinephrine during propofol anesthesia. Etomidate infusion did not significantly affect the AD of epinephrine or hemodynamic data at the induction of arrhythmias during propofol anesthesia. Figure 1 shows the AD values of epinephrine during anesthesia with etomidate alone or etomidate plus propofol. The AD of epinephrine decreased significantly as the dose of propofol increased. At propofol doses of 5, 10, and 20 $mg \cdot kg^{-1} \cdot h^{-1}$, the corresponding blood concentrations of propofol were 2.33 ± 0.46, 5.46 ± 0.71, and 11.2 ± 0.81 μg/ml, respectively. Figure 2 shows the relationship between blood propofol concentration and arrhythmogenic plasma concentration of epinephrine. Propofol reduced the arrhythmogenic plasma concentration of epinephrine in a concentration-dependent manner. Hemodynamic data at the time of arrhythmias during anesthesia with etomidate alone or etomidate with varying doses of propofol are shown in figure 3. At propofol doses of 5 and 10 $mg \cdot kg^{-1} \cdot h^{-1}$, diastolic arterial pressure at the time of induction of arrhythmias was significantly lower than that without propofol. At the propofol dose of 20 $mg \cdot kg^{-1} \cdot h^{-1}$, heart rate was significantly higher than that without propofol, but systolic arterial pressure was not significantly different.

The effect of alcuronium on the AD of epinephrine during etomidate plus propofol anesthesia is shown in table 4. The presence or absence of alcuronium had no significant effect on the AD of epinephrine or on hemodynamic data at the induction of arrhythmias.

Table 5 shows the effect of lipid emulsion infusion on the AD of epinephrine during etomidate anesthesia. Lipid emulsion infusion did not significantly affect the AD of

TABLE 1. Arrhythmogenic Threshold of Epinephrine during Propofol, Halothane, or Etomidate Anesthesia (Mean ± SEM)

Anesthesia	n	Epinephrine Threshold: Arrhythmogenic Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	Epinephrine Threshold: Plasma Concentration (ng/ml)
Propofol	8	2.52 ± 0.43*	23.6 ± 8.5*
Halothane	8	2.66 ± 0.21*	35.7 ± 1.9*
Etomidate	8	9.67 ± 1.06	205 ± 27.5

Statistical significance: *$P < 0.01$ compared with etomidate value.

TABLE 2. Blood Pressure and Heart Rate Before Epinephrine Infusion (Basal) and at the Time of Arrhythmias (Epinephrine) (Mean ± SEM)

	Anesthesia	SAP (mmHg)	DAP (mmHg)	HR (beats per min)
Basal	Propofol	128 ± 4.2	69.5 ± 4.5	106 ± 7.7
	Halothane	122 ± 4.1	63.9 ± 2.4	106 ± 15
	Etomidate	137 ± 5.0	70.8 ± 4.2	80.0 ± 5.9
Epinephrine	Propofol	323 ± 13*	146 ± 8.2†	149 ± 23
	Halothane	218 ± 8.6	125 ± 8.2‡	151 ± 13†
	Etomidate	307 ± 15*	182 ± 11*	90.4 ± 8.4§

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.
* $P < 0.01$ compared with halothane value.
† $P < 0.05$ compared with etomidate value.
‡ $P < 0.01$ compared with etomidate value.
§ $P < 0.05$ compared with halothane value.

TABLE 3. The Effect of Etomidate on Arrhythmogenic Threshold of Epinephrine and Blood Pressure and Heart Rate at the Time of Arrhythmias during Propofol (40 $mg \cdot kg^{-1} \cdot h^{-1}$) Anesthesia (Mean ± SEM)

	Etomidate (+) (n = 7)	Etomidate (−) (n = 8)
Arrhythmogenic dose of epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	2.59 ± 0.34	2.52 ± 0.43
Plasma concentration of epinephrine (ng/ml)	26.2 ± 7.25	23.6 ± 8.54
Systolic arterial pressure (mmHg)	320 ± 13.8	323 ± 12.7
Diastolic arterial pressure (mmHg)	146 ± 9.2	146 ± 8.2
Heart rate (beats per min)	145 ± 9.11	149 ± 23.4

There are no significant differences between the two groups.

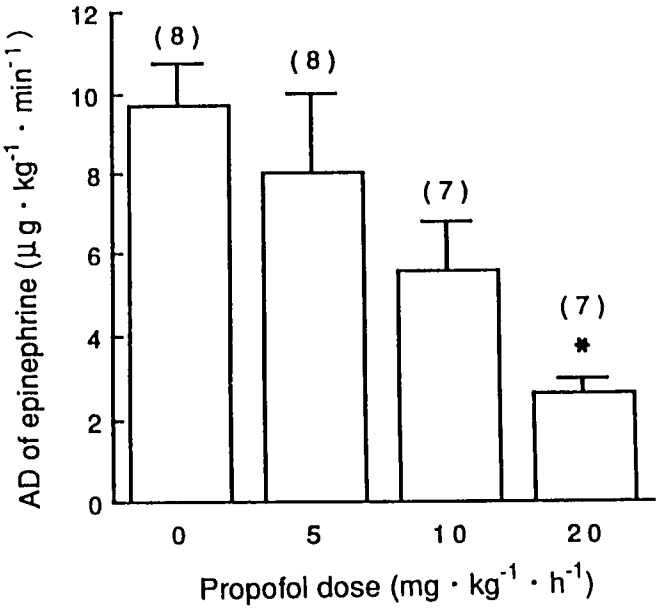

FIG. 1. The arrhythmogenic dose (AD) of epinephrine during anesthesia with etomidate plus varying doses of propofol (mean ± SEM; number of observations is shown in parentheses). The dogs were anesthetized with etomidate, 2 mg/kg iv, followed by an infusion 8 mg·kg^{-1}·h^{-1} and alcuronium 0.2 mg/kg, and then propofol was given at varying doses as indicated. *P <0.01 compared with control.

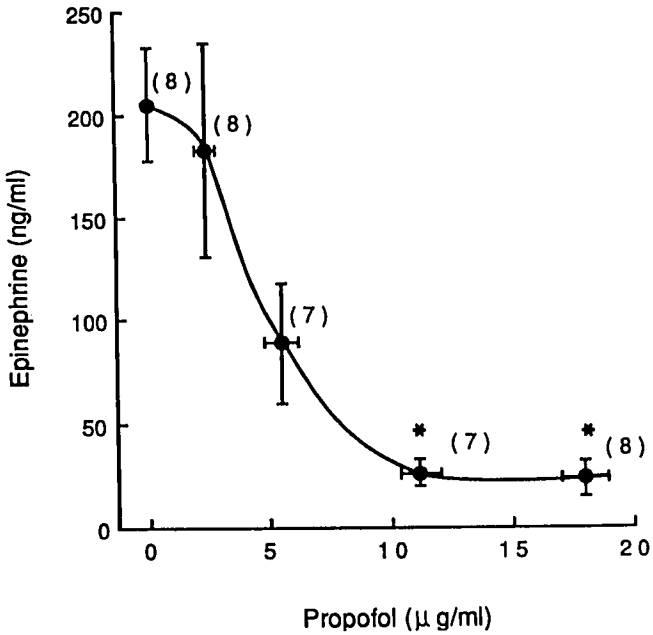

FIG. 2. Relationship between blood concentration of propofol and arrhythmogenic plasma concentration of epinephrine during anesthesia with etomidate plus varying doses of propofol (mean ± SEM; number of observations is shown in parentheses). Experimental conditions are the same as for figure 1, except for the point of the highest propofol concentration, which was obtained in the experimental condition without etomidate or alcuronium. *P < 0.01 compared with control.

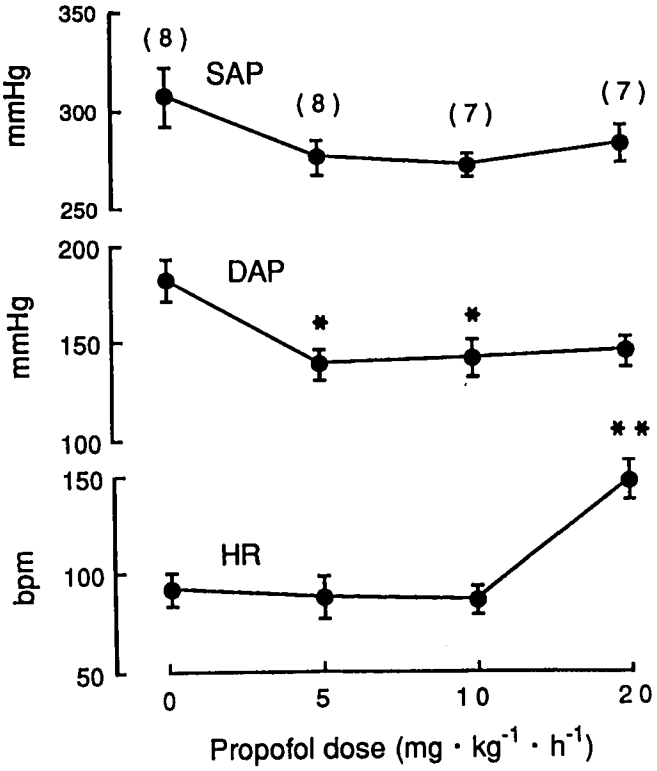

FIG. 3. Hemodynamic data at the time of arrhythmias during anesthesia with etomidate plus varying doses of propofol. Experimental conditions are the same as for figure 1 (mean ± SEM; number of observations is shown in parentheses). SAP = systolic arterial pressure, DAP = diastolic arterial pressure, HR = heart rate. *P <0.05 **P < 0.01 compared with control.

epinephrine or hemodynamic data at the induction of arrhythmias during etomidate anesthesia.

Discussion

To determine whether or not administration of propofol alone enhances epinephrine-induced arrhythmias, the arrhythmogenic threshold of epinephrine during anesthesia with propofol was compared with that during anesthesia with halothane and with etomidate. The results show that epinephrine induced arrhythmias at a significantly lower dose during anesthesia with propofol than during anesthesia with etomidate. Similar to that of thiopental, which has a concentration-dependent effect on AD of epinephrine,[5] the blood concentration of propofol is an important factor in determining the degree of enhancement of epinephrine-induced arrhythmias. Propofol reduces the arrhythmogenic plasma concentration of epinephrine in a concentration-dependent manner, and when the blood concentration of propofol exceeds 11 μg/ml, epinephrine induces arrhythmias at a plasma concentration comparable to that during halothane anesthesia.

In the clinical setting, some studies have examined blood propofol concentration during anesthesia with propofol supplemented with N_2O, opiates, or other agents.[12–15] However, no study to our knowledge has investigated the effective blood concentration of propofol when used as a sole anesthetic. Turtle *et al.*[13] reported that the blood concentration of propofol required to supplement 67% N_2O in O_2 to prevent movement at the time of skin incision in 95% of patients premedicated with lorazepam was 5.92 μg/ml. If propofol is used as a sole anesthetic, a higher blood concentration of propofol should be required to achieve sufficient depth of anesthesia. Therefore, the blood concentrations used in the present study are considered to be clinically relevant. The applicability of the present study to the clinical situation may be limited because of the animal model used here, but it might be prudent to avoid using propofol at high doses when potentiation of arrhythmias is of major concern. Instead, it is recommended that propofol is used with opioids or other supplemental agents to reduce the dose of propofol required to provide adequate anesthesia. Indeed, opioids markedly reduce the amount of propofol needed to achieve adequate clinical anesthesia.[12]

Hemodynamic data were obtained during each type of anesthesia (table 2). Systolic arterial pressure at the time of arrhythmias during propofol anesthesia was significantly higher than that during halothane anesthesia, although there were no significant differences in the AD values of epinephrine between propofol and halothane anesthesia. This may be explained by the observation that propofol does not affect pressure responses to catecholamines,[16] whereas halothane has an inhibitory effect on the pressor action of catecholamines.[17] The heart rate at the time of arrhythmias during anesthesia with propofol 20 $mg \cdot kg^{-1} \cdot h^{-1}$ was significantly higher than that during anesthesia with etomidate alone. Although the reason for this difference is not clear, propofol at a higher dose might enhance the chronotropic action of epinephrine.

TABLE 4. The Effect of Alcuronium on Arrhythmogenic Threshold of Epinephrine and Blood Pressure and Heart Rate at the Time of Arrhythmias during Etomidate plus Propofol (20 $mg \cdot kg^{-1} \cdot h^{-1}$) Anesthesia (Mean ± SEM)

	Alcuronium (+) (n = 7)	Alcuronium (−) (n = 8)
Arrhythmogenic dose of epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	2.60 ± 0.38	2.73 ± 0.36
Plasma concentration of epinephrine (ng/ml)	26.6 ± 6.95	28.1 ± 6.56
Systolic arterial pressure (mmHg)	282 ± 9.58	307 ± 13.9
Diastolic arterial pressure (mmHg)	144 ± 7.7	146 ± 8.1
Heart rate (beats per min)	144 ± 10.1	139 ± 11.1

There are no significant differences between the two groups.

TABLE 5. The Effect of Lipid Emulsion Infusion on Arrhythmogenic Threshold of Epinephrine and Blood Pressure and Heart Rate at the Time of Arrhythmias during Etomidate Anesthesia (Mean ± SEM)

	Lipid Emulsion (+) (n = 8)	Lipid Emulsion (−) (n = 8)
Arrhythmogenic dose of epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	9.75 ± 1.45	9.67 ± 1.06
Plasma concentration of epinephrine (ng/ml)	198 ± 45.1	205 ± 27.5
Systolic arterial pressure (mmHg)	299 ± 11.9	307 ± 14.6
Diastolic arterial pressure (mmHg)	175 ± 11.5	182 ± 11.3
Heart rate (beats per min)	91.0 ± 11.5	90.4 ± 8.4

There are not significant differences between the two groups.

In the experiment examining the dose–effect relationship of propofol on epinephrine-induced arrhythmias, we used etomidate and alcuronium for basal anesthesia. The dose of etomidate applied was based on a previous study[5] in which the dose of etomidate used maintained a sufficient depth of anesthesia without requiring supplementation. Etomidate has been shown not to affect the AD of epinephrine during anesthesia with halothane[6] or thiopental[5] and to have little effect on epinephrine-induced arrhythmias when administered alone.[5] In the present study, etomidate does not affect the AD of epinephrine during anesthesia with propofol at 40 $mg \cdot kg^{-1} \cdot h^{-1}$ (table 3). Thus, it is considered probable that etomidate would not potentiate propofol effects on epinephrine-induced arrhythmias also at lower doses of propofol.

It has been reported that alcuronium does not affect thiopental-epinephrine arrhythmias.[5] In the present study, it was confirmed that alcuronium did not significantly affect the induction of propofol–epinephrine arrhythmias or the hemodynamic data at the time of arrhythmias (table 4). We therefore used alcuronium during anesthesia with etomidate plus propofol to achieve complete muscular immobilization.

To determine the influence of lipid emulsion of the emulsion formulation of propofol on epinephrine-induced arrhythmias, the AD of epinephrine during etomidate anesthesia with lipid-emulsion infusion was compared with that without lipid-emulsion infusion (table 5). The results show that lipid-emulsion infusion does not significantly affect the AD of epinephrine or the hemodynamic data at the time of induction of arrhythmias during etomidate anesthesia, which indicates that enhancement of epinephrine-induced arrhythmias by the emulsion formulation of propofol is due not to the lipid emulsion but to the action of propofol itself.

In conclusion, propofol alone enhances epinephrine-induced arrhythmias in dogs. This action of propofol is dose-dependent in the presence of a background of etomidate.

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