

## Potential by Thiopental of Halothane-Epinephrine-induced Arrhythmias in Dogs

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Epinephrine-induced arrhythmias were studied in 14 dogs (Group 1) anesthetized with halothane alone (1.09% end-tidal), and on another occasion, at the same halothane concentration following intravenous thiopental (20 mg/kg). Surface (Lead II), catheter His bundle and high right atrial electrocardiograms, and airway and femoral arterial pressures were recorded. Graded doses of epinephrine (EPI-least dose  $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) were infused over five minutes, but terminated sooner if ventricular tachycardia occurred (maximal sensitization). Sensitizing EPI doses ( $\mu\text{g} \cdot \text{kg}^{-1}$ ) were calculated (dose  $\times$  time to arrhythmia) for: Shift in or wandering atrial pacemaker (SAP-WAP), atrial ectopy (At Ect), A-V dissociation (AVD), and ventricular ectopy, bigeminy, or tachycardia (V Ect, V Bigem, V Tach). With halothane alone, SAP-WAP occurred at the least dose of EPI followed by At Ect, AVD, V Ect, V Bigem, and V Tach in order of increasing EPI dose. Following thiopental, EPI doses for AVD, V Ect, V Bigem, and V Tach were reduced, as well as EPI dose differences for At Ect, AVD, V Ect, and V Bigem.

In an additional seven dogs (Group 2), anesthesia was induced with thiopental (20 mg/kg) followed by halothane (1.09% end-tidal). These animals were observed for arrhythmias during graded EPI infusions at 1-2 h and 3-4 h following thiopental. Sensitizing EPI doses for SAP-WAP and V Tach were similar at each time period.

The authors concluded that with halothane and increasing EPI dose, sensitization constitutes a spectrum of arrhythmias, beginning with atrial and progressing to severe ventricular arrhythmias. Thiopental reduces the EPI dose needed for AVD and ventricular, but not atrial, arrhythmias. It also reduces the EPI dose discrepancies for atrial and ventricular arrhythmias. (Key words: Anesthetics, intravenous: thiopental. Anesthetics, volatile: halothane. Heart: arrhythmias; electrocardiography. Sympathetic nervous system: catecholamines, epinephrine.)

THIOPENTAL has been shown in dogs to potentiate cyclopropane-epinephrine ventricular arrhythmias (sensitization).<sup>1</sup> Potentiation persists for three to five hours, far outlasting the expected duration of thiopental anesthetic action.<sup>1</sup> This interaction has not been documented for humans. Of course, thiopental is commonly used to facilitate the induction of anesthesia with halothane, an agent which resembles other hydrocarbon anesthetics in its ability to sensitize the heart to arrhythmogenic effects of epinephrine.<sup>2,3</sup>

The possibility of an interaction of thiopental with halothane to potentiate sensitization has not been investigated in any species. In the present study, we have examined both the thiopental effect and duration thereof on halothane-epinephrine sensitization in dogs. As it was our impression that atrial and A-V junctional arrhythmias often preceded ventricular arrhythmias in the course of clinical sensitization, we used graded infusions of epinephrine lasting five minutes to characterize all arrhythmias appearing prior to unifocal or multifocal ventricular tachycardia.

### Methods

#### GROUP 1

Fourteen unpremedicated mongrel dogs of either sex were anesthetized on two occasions, one week apart, with inspired concentrations of halothane in oxygen sufficient to produce a steady end-tidal concentration (Beckman® infrared analyzer, Model LB-2) of 1.09% equivalent to 1.25 MAC.<sup>4</sup> On one occasion, randomized dogs received 20 mg/kg thiopental intravenously prior to halothane. Ventilation was controlled (tidal volume = 20-25 ml; rate 6-8 breaths/min) to keep end-tidal CO<sub>2</sub> levels (Beckman infrared analyzer, Model LB-2) between 35 and 40 mmHg. Rectal temperatures ranged from 36.5° to 38.0° C, and experiments lasted no more than five hours.

The surface electrocardiogram (Lead II), catheter His bundle and high right atrial electrograms,<sup>5</sup> femoral arterial pressure (Statham® P23Db), and airway pressure were displayed simultaneously (Electronics for Medicine, VR-12 recorder) and FM tape-recorded (Tandberg Instrumentation Series 100, 4-channel recorder). Only arrhythmias occurring during the apneic phase of ventilation were evaluated, since in at least some dogs the presence of intracardiac catheters appeared to trigger arrhythmias during the inspiratory phase.

Graded intravenous epinephrine (EPI) infusions (Harvard® infusion pump) lasting five minutes were administered through a catheter in the external jugular vein. Arrhythmias appearing within this time period were characterized. The beginning EPI dose was  $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . This dose was increased logarithmically until unifocal or multifocal ventricular tachycardia was observed at some time during an infusion. At this time, the infusion was stopped. Ventricular tachycardia spon-

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TABLE 1. Thiopental Effect on Halothane-Epinephrine Arrhythmias of Development and Ventricular Tachycardia. Mean ( $\pm$ SE) Epinephrine Sensitizing Doses ( $\mu$ g/kg) for Six Categories of Arrhythmias. Results of Paired Comparisons in 14 Group 1 Dogs

CONDITION	SAP-WAP	AT ECT	AVD	V ECT	V BIGEM	V TACH
HALO	0.60 $\pm$ 0.15	1.43 $\pm$ 0.34	2.52 $\pm$ 0.46	3.82 $\pm$ 0.74	3.95 $\pm$ 0.96	5.49 $\pm$ 0.34
THIO	0.66 $\pm$ 0.20	1.34 $\pm$ 0.32	1.26 $\pm$ 0.22	1.88 $\pm$ 0.41	1.47 $\pm$ 0.25	2.41 $\pm$ 0.62
P	NS	NS	0.01	0.02	0.04	0.02
N	13	12	9	8	5	5

HALO = halothane only; THIO = THIO + HALO.

taneously reverted to sinus rhythm in all dogs. Doses along an exponential curve below that at which ventricular tachycardia was observed were subsequently examined. If, for example, ventricular tachycardia occurred during the 2.0  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> EPI infusion, a dose half-way between this dose and the previously examined dose (1.0  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) was administered, and continued until the least EPI infusion dose producing ventricular tachycardia was found. This was determined to the nearest 0.125 or 0.25  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> increment. Heart rate and arterial blood pressure were allowed to return to their respective control levels (at least 10 min) before beginning the next EPI infusion. Arterial blood was sampled for pH, PaO<sub>2</sub>, and PaCO<sub>2</sub> determinations before and after each EPI challenge. Serum electrolytes were not measured.

The sensitizing dose of EPI ( $\mu$ g  $\cdot$  kg<sup>-1</sup>) was determined as the product of time to appearance of a particular arrhythmia (min) and the lowest infusion level of EPI ( $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) producing that arrhythmia. EPI sensitizing doses were calculated only for arrhythmias appearing during the first 2.5-min period of infusion (see below). Arrhythmias were categorized as shift in or wandering atrial pacemaker (SAP-WAP), atrial ectopic beats (At Ect), atrioventricular dissociation (AVD), ventricular ectopic beats (V Ect), ventricular bigeminy (V Bigem), and ventricular tachycardia (V Tach). Arrhythmias other than V Tach we collectively term arrhythmias of development, since in all dogs they were observed at a lower dose of EPI than V Tach. SAP was a single atrial (other than sinus) or high A-V junctional pacemaker, and WAP was two or more competing atrial pacemakers. These arrhythmias were associated with synchronous atrial and ventricular contractions. AVD was low A-V junctional rhythm or unifocal ventricular rhythm (rate less than 120 beats/min) in which the atria and ventricles beat asynchronously. V Bigem was a sinus, atrial, or A-V junctional beat coupled with a ventricular ectopic beat. Ventricular tachycardia (uni- or multifocal) was ventricular rhythm with the rate greater than 120 beats/min.

EPI sensitizing doses were calculated for arrhythmias appearing during the first 2.5-min period of infusion for two reasons: 1) maximum increases in systolic blood pressure were seen in all dogs within the first 2.5 min of the 5.0-min infusion period; 2) some dogs which man-

ifested AVD, V Ect, V Bigem, or V Tach at or prior to the first 2.5 min of infusion reverted to less severe rhythm disturbances (*e.g.*, V Tach to AVD, V Bigem to V Ect., etc.) during the second 2.5 min of infusion. This suggested that the maximum EPI effect was present by 2.5 min, and that some animals developed tolerance to EPI after 2.5 min of infusion.

## GROUP 2

Anesthesia was induced with thiopental (20 mg/kg intravenously) in an additional seven dogs who were then equilibrated with halothane (1.09% end-tidal). Ventilation was controlled and rectal temperatures were the same as in Group 1 dogs. Intracardiac catheters were not placed (as in Group 1 dogs). The surface ECG (Lead II) and femoral arterial and airway pressure were displayed and recorded. EPI infusions (0.5–3.0  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>) lasting 2.5 min (in contrast to 5 min for Group 1 dogs) were administered through a catheter in the external jugular vein. This was done during two time periods following induction with thiopental: 1–2 h (EARLY) and 3–4 h (LATE). These time periods were chosen to determine whether EPI sensitizing doses for the various arrhythmia categories were similar at each of these time periods following thiopental induction. The same EPI infusion levels were tested both EARLY and LATE, and infusions were terminated upon the appearance of V Tach. EPI sensitizing doses were calculated as for Group 1 dogs.

## STATISTICAL METHODS

Paired and unpaired *t*, binomial, and chi-square tests were used for statistical comparisons.<sup>6</sup>

## Results

### ARTERIAL BLOOD-GAS VALUES AND HEMODYNAMIC EFFECTS

Arterial blood-gas values (pH, PaCO<sub>2</sub>, PaO<sub>2</sub>) were within normal limits for all animals and there were no differences among any groups. Epinephrine (EPI) had no significant effect on pH in any animals. For a given dog (Group 1) and test condition (halothane = HALO; HALO preceded by thiopental = THIO + HALO), the maximum systolic blood pressure increase irrespective

of EPI infusion level always occurred before 2.5 min. This increase (mean  $\pm$  SE) with HALO was  $134 \pm 9$  mmHg, and with THIO + HALO was  $122 \pm 6$  mmHg (not significantly different). The maximum increase in systolic blood pressure, however, was reached at lower EPI infusion levels with THIO + HALO than with HALO alone ( $P < 0.025$ , binomial test).

#### ARRHYTHMIAS (TABLES 1 AND 2)

Mean values ( $\pm$ SE) for EPI sensitizing doses ( $\mu\text{g} \cdot \text{kg}^{-1}$ ) for each of the five categories of arrhythmias of development and V Tach are listed in table 1 for Group 1 dogs. It was noticed that with HALO, EPI doses for each of the arrhythmia categories, except V Ect *vs.* V Bigem, could be distinguished from one another ( $P < 0.05$ ); with THIO + HALO, such distinction could not be made, except that SAP-WAP occurred at a lower and V TACH at a higher EPI dose than At Ect, AVD, V ECT, and V Bigem taken collectively ( $P < 0.05$ ). In particular, THIO had no potentiating effect on atrial sensitization (SAP, WAP, At Ect) but did have a potentiating effect on AVD and ventricular sensitization (V Ect, V Bigem, V Tach).

Additionally, the systolic blood pressure increase accompanying each category of rhythm disturbance potentiated by thiopental in Group 1 dogs (AVD, V Ect, V Bigem, and V Tach) is shown in table 2. The systolic blood pressure increase was the difference between the systolic pressure at the time of arrhythmia appeared and just before the EPI challenge. This was not necessarily the maximum pressure increase reached irrespective of EPI infusion level (see above). The data indicate that the systolic pressure increase for V Ect and V Bigem was greater for HALO compared with THIO + HALO ( $P < 0.05$ ).

#### DURATION OF THIOPENTAL EFFECT ON SENSITIZATION (TABLE 3)

SAP-WAP and V Tach were the only arrhythmias observed during both the EARLY and LATE test periods in all Group 2 dogs. Mean EPI doses for each category of arrhythmia are shown in table 3. The sensitizing doses for SAP-WAP and V TACH were not significantly different despite the passage of time. Also, they were not different from the sensitizing doses found for SAP-WAP and V TACH Group 1 dogs (table 1).

TABLE 2. Systolic Blood Pressure (mmHg) Increase (Mean  $\pm$  SEM) for Arrhythmias Potentiated by Thiopental. Results of Paired Comparisons in 13 Group 1 Dogs

CONDITION	AVD	V ECT	V BIGEM	V TACH
HALO	102 $\pm$ 10	124 $\pm$ 13	140 $\pm$ 10	125 $\pm$ 12
THIO	83 $\pm$ 13	90 $\pm$ 9	99 $\pm$ 18	104 $\pm$ 11
P	0.10	0.03	0.02	NS
N	8	7	4	4

HALO = halothane only; THIO = THIO + HALO.

With respect to At Ect, AVD, V Ect, and V Bigem, too few dogs exhibited these rhythm disturbances to make statistical comparisons of the EARLY *vs.* LATE effect, or of the EPI sensitizing doses (Group 1 *vs.* Group 2 dogs). These data, taken collectively, indicate that sensitization following thiopental is qualitatively the same up to four hours following induction.

#### Discussion

Our results indicate that thiopental potentiates the development of AVD and ventricular arrhythmias when epinephrine (EPI) is administered to halothane-anesthetized dogs. Atrial arrhythmias were not potentiated. Additionally, it was shown that the thiopental effect on sensitization (SAP-WAP, V TACH) persists well beyond its expected duration of anesthetic action. With halothane alone and increasing EPI dose, there was a distinct order to the appearance of arrhythmias before V Tach, the arrhythmia we chose as indicating maximal sensitization. Atrial arrhythmias (SAP-WAP, At Ect) were seen at the least dose of EPI, followed in turn by AVD and ventricular arrhythmias at higher doses (table 1). This sequence of arrhythmia development supports our clinical impression that when intravenous EPI is administered during halothane anesthesia, atrial and A-V junctional arrhythmias develop before ventricular arrhythmias. Accordingly, we term lesser arrhythmias than V Tach, arrhythmias of development. With thiopental preceding halothane, there was not such a distinct sequence to arrhythmias of development.

#### THIOPENTAL POTENTIATION OF HALOTHANE-EPINEPHRINE ARRHYTHMIAS

The potentiation by thiopental of EPI sensitization with halothane has not been reported previously. It has

TABLE 3. Duration of Thiopental Effect on Sensitization. Mean ( $\pm$ SE) Epinephrine Sensitizing Doses ( $\mu\text{g}/\text{kg}$ ) for Arrhythmias at 1-2 h (EARLY) and 3-4 h (LATE) Following Induction with Thiopental (Group 2 Dogs)

Time	SAP-WAP	AT ECT	AVD	V ECT	V BIGEM	V TACH
EARLY	0.79 $\pm$ 0.24	—	2.34 $\pm$ 1.17	1.74 $\pm$ 0.72	0.84 $\pm$ 0.19	2.15 $\pm$ 0.61
LATE	0.55 $\pm$ 0.08	—	1.38 $\pm$ 0.47	1.63 $\pm$ 0.90	2.01 $\pm$ 0.98	2.08 $\pm$ 0.54
N	7	0	2	3	2	7

N = number of dogs in which these arrhythmias occurred both EARLY and LATE.

been observed with cyclopropane-anesthetized dogs.<sup>1</sup> Furthermore, in that study<sup>1</sup> and this study, thiopental potentiation persists well beyond its expected anesthetic duration of action. The mechanism for this potentiation is not known. McCannell and Dresel, utilizing selective intracoronary injections of thiopental in cyclopropane-anesthetized dogs, localized the site of the thiopental effect on sensitization to the A-V node and His bundle.<sup>1</sup> A thiopental action at these sites is consistent with its effect to potentiate AVD and ventricular arrhythmias, as noted in this study (table 1).

Previous investigators have demonstrated that a critical level of arterial pressure<sup>3,7-9</sup> and, or more particularly, intraventricular end-systolic pressure<sup>10</sup> is important for the genesis of ventricular arrhythmias due to sensitization. We did not systematically investigate the role of pressure in this study. That pressure may be a factor in explaining thiopental potentiation of halothane-EPI sensitization is suggested by two of our observations. First, the maximum systolic pressure increase observed in a given animal in response to EPI was achieved at a lower level of EPI infusion with thiopental present (see Results, arterial blood-gas values and hemodynamic effects). Second, the systolic pressure increases necessary for V Ect and V Bigem were less with thiopental present (table 2).

#### ARRHYTHMIAS OF DEVELOPMENT

With the exception of a single study,<sup>11</sup> attempts have not been made by others to determine the dose of EPI required to produce atrial arrhythmias. Meek *et al.*, in a classic study of sensitization, recognized that atrial arrhythmias also occur during sensitization.<sup>12</sup> Tucker *et al.* studied arrhythmias produced by EPI injected into dogs anesthetized with halothane or isoflurane.<sup>13</sup> They noted the occurrence of junctional arrhythmias and AVD in some dogs, but did not determine the doses of EPI required to produce them. Puerto *et al.* observed that more EPI was required for ventricular than atrial arrhythmias during morphine-nitrous oxide anesthesia.<sup>11</sup> In the present study, atrial arrhythmias (SAP-WAP, At Ect) and AVD occurred at lower EPI doses than did ventricular arrhythmias (table 1). With thiopental present, this dose-discrepancy was reduced.

Our observations are of potential clinical importance for several reasons. First, they call attention to the fact that arrhythmias due to EPI sensitization originate in atrial as well as ventricular foci. Sensitization constitutes a spectrum of atrial and ventricular arrhythmias, as well as A-V dissociation. The present finding that atrial arrhythmias occur at lower EPI doses than ventricular arrhythmias during sensitization, however, may not be

transferable to humans. Second, certain atrial arrhythmias and A-V dissociation are not benign occurrences if they result in significant deterioration of cardiac output. Third, with thiopental present, there was little margin between the EPI dose producing atrial and ventricular arrhythmias. In fact, in Group 1 dogs pretreated with thiopental, AVD, V Ect, and V Bigem occurred at nearly the same dose of EPI as At Ect, and most importantly, at a dose not too far below that for V Tach (table 1). Again, these findings may not be transferable to humans. Finally, with thiopental present, hemodynamically adverse arrhythmias for patients with little myocardial reserve might occur at lower EPI levels.

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