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Comparison of Logdose and Bracket Protocols for Determination of Epinephrine Arrhythmia Thresholds in Dogs Anesthetized with Thiopental–Halothane

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Previous studies in dogs of anesthetic–epinephrine arrhythmias have used logdose or bracketed epinephrine infusion protocols to determine the arrhythmic dose of epinephrine (ADE) or plasma level of epinephrine at arrhythmias (PCE). Reported logdose ADE values for halothane preceded by thiopental induction (thiopental–halothane) are twice those with the bracket protocol. There are no reported PCE data for the bracket protocol, and neither protocol has been directly compared in the same dogs. Therefore, direct comparisons were made of thiopental–halothane ADE and PCE in seven dogs (group 1). Dogs were induced with thiopental (20 mg/kg), followed by halothane inhalation at end-tidal concentrations equivalent to MAC 1.25. Epinephrine infusion protocols were compared on two weekly test occasions, with the sequence and order of protocol testing randomized. Logdose ADE for four or more ventricular beats within 15 s was 3.92 ± 0.60 μg/kg (mean ± standard error), higher than the bracket ADE (2.54 ± 0.34 μg/ml) ($P < 0.05$). PCE at ADE were similar for both protocols, but six separate infusions of epinephrine were required to establish ADE with the logdose compared to four with the bracket protocol ($P < 0.05$). These findings suggested enhanced epinephrine clearance with the logdose protocol. Therefore, five additional but similarly anesthetized dogs (group 2) were tested to determine if physiologic or hemodynamic conditions prior to epinephrine infusions ("initial conditions") were equivalent for both protocols. Protocols were modified to avoid provocation of ventricular arrhythmias. For initial conditions prior to epinephrine 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, values for cardiac output, central venous pressure, heart rate, and hemoglobin were higher, and systemic vascular resistance lower for the modified logdose compared to the bracket protocol ($P < 0.05$). With both protocols, however, plasma epinephrine concentrations were similar at 1, 2, and 3 min during epinephrine 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Thus, with the modified logdose protocol there was evidence for a residual epinephrine effect that could have enhanced its own clearance. This could explain higher ADE but similar PCE with the logdose protocol compared to the bracket protocol in group 1 experiments. It is concluded for thiopental–halothane that the bracket protocol, which reduces epinephrine exposure and requires sufficient time (variable) between epinephrine infusions for return to baseline hemodynamic conditions (*vs.* 10-min spacing with logdose), provides a more conservative ADE estimate. Nevertheless, since PCE were similar for both protocols, PCE at arrhythmias might be a better indicator of anesthetic–epinephrine compatibility, at least for thiopental–halothane. (Key words: Anesthetics, intravenous: thiopental. Anesthetics, volatile: halothane. Heart: arrhythmias. Sympathetic nervous system: epinephrine.)

TWO DIFFERENT epinephrine infusion protocols are commonly used to test compatibility of anesthetic drugs with catecholamines ("anesthetic sensitization") in dogs. The first uses logarithmically and closely spaced infused doses of epinephrine, each lasting 3 min with 10 min between infusions: this is a logdose protocol.[1] The second employs bracketed doses of epinephrine infused over 3 min, but with sufficient time (variable) between infusions for heart rate, heart rhythm, and blood pressure to return to baseline values, a bracket protocol.[2,3] With the same anesthetic test conditions, higher values for arrhythmic dose of epinephrine (ADE) have been reported with the logdose compared to bracket protocols. For example, Sumikawa *et al.* used the logdose protocol and reported an ADE of 20.9 μg/kg for enflurane preceded by thiopental induction (thiopental–enflurane),[4] four times the value found by Atlee and Roberts using the bracket protocol (5.0 ± 0.6 μg/kg).[3] For more sensitizing thiopental–halothane, ADE with the logdose protocol (4.18 ± 0.85 μg/kg[4]) was more than two times that with the bracket protocol (1.88 ± 0.41 μg/kg).[2]

These reported differences for ADE values are probably too large to be explained by test subject variability, minor differences in ventricular arrhythmia endpoint,§ or possible small differences in test conditions (*e.g.*, acid–base or electrolyte status). Perhaps more important could be nonequivalent physiologic or hemodynamic states for the two protocols that may have existed during testing of epinephrine infusions. Thus, while epinephrine tolerance[5] was suggested[3] to explain higher thiopental–enflurane ADE with the logdose compared to bracket protocols, enhanced epinephrine clearance with the former is also plausible. The latter could be the explanation if, for the

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§ The first appearance of premature ventricular beats *versus* three or four or more premature ventricular beats within 15 s.[1,4]

same anesthetic test condition, it can be shown that ADE are higher but plasma concentrations of epinephrine at arrhythmias (PCE) similar for the two epinephrine infusion protocols when tested in the same animal.

Therefore, this study was undertaken to compare ADE and PCE with the logdose[1] and bracket protocols[2,3] in the same dogs with the same anesthetic test conditions. The more sensitizing thiopental–halothane combination, compared to halothane alone,[2] was specifically chosen to minimize possible differences for ADE or PCE between the two epinephrine infusion protocols. Nevertheless, results of this testing confirmed higher ADE but similar PCE for the logdose compared to bracket protocols. Consequently, additional testing was carried out to determine if nonequivalent physiologic or hemodynamic states existed just prior to the epinephrine infusions used to determine ADE with the two protocols, which could explain the previously observed variance in ADE but not PCE.

Materials and Methods

This research conforms with standards set forth in the Guide for Care and Use of Laboratory Animals¶ and was approved by our institutional Animal Use Committee.

General Methods

Conditioned, unpremedicated mongrel dogs of either sex (n = 16) weighing 15–25 kg were studied after an overnight fast. Of these 16 dogs, 7 completed testing under group 1 protocols and 5 under group 2 protocols. Anesthesia was induced with intravenous thiopental (20 ml/kg) followed by tracheal intubation. Mechanical ventilation was instituted with halothane in oxygen (fractional inspired oxygen concentration = 1.0) to maintain end-tidal carbon dioxide pressure (Beckman LB-2, Fullerton, CA) between 33 and 38 mmHg and end-tidal halothane (Beckman LB-2) at 1.09% (± 5%), equivalent to 1.25 MAC for the dog.[6]

External jugular or femoral vein cannulation was performed for central venous access (epinephrine infusion, pulmonary artery catheter). A femoral arterial catheter was used for arterial sampling and blood pressure monitoring (Gould P23 ID pressure transducer, Cleveland, OH). Surface ECG lead II and blood pressure were continuously displayed (E for M/Honeywell VR-12, Denver, CO) or recorded (FM Recorder, A. R. Vetter, Rebersburg, PA) for later playback and analysis (Norland 3001 Digital oscilloscope, Fort Atkinson, WI). For hemodynamic studies (group 2), cardiac output measurements (performed in duplicate) were made with a thermistor-equipped pulmonary artery catheter (Baxter Healthcare, Santa Ana, CA).

¶ Public Health Services: NIH publication no. 85-23.

A peripheral vein was used for infusion of 0.9 N sodium chloride (3–5 $ml \cdot kg^{-1} \cdot min^{-1}$) and administration of sodium bicarbonate to correct base deficits greater than 3 mEq/l. A heating blanket was used to maintain esophageal temperature between 36.0 and 38.5° C. Acid–base (Corning 178 pH/Blood Gas Analyzer, Corning, NY), hemoglobin (OSM-2 Hemoximeter, Medtron Chicago, Rosemont, IL), glucose (Glucometer, Miles Laboratory Diagnostic Division, Elkhart, IN), and serum ionized potassium and calcium (NOVA, Newton Upper Falls, MA) determinations were made at times specified under the arrhythmia threshold (group 1) and hemodynamic (group 2) protocols.

Group 1: Arrhythmia Threshold

Epinephrine was infused into a central vein using either logdose or bracketed protocols (below) to determine the ADE and PCE in group 1 dogs (n = 10). Dogs were tested on two occasions at least 1 week apart. Due to exclusion criteria (below), data from only seven of these dogs are included in Results. On each occasion, each dog was tested with both epinephrine infusion protocols, the sequence and order of which were randomized for each dog and test occasion. Thus, after an initial 45- to 60-min period for stabilization and anesthetic equilibration, one or the other epinephrine infusion protocol was tested first. After this was completed, there was a 60-min period for stabilization (return to baseline hemodynamic conditions) before the second (other) protocol was begun. The reverse order of epinephrine infusion protocol testing was used on a second test occasion, at least 1 week later.

Logdose Protocol

With this protocol, logarithmically spaced doses of epinephrine were infused over 3 min, with 10 min between infusions.[1] Infusions began at 0.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and were increased by $e^{0.2}$ (e = 2.72) increments until ADE was reached.[1] ADE (μg/kg) was the product of infusion rate and time to the first occurrence of four or more continuous or intermittent premature ventricular beats within 15 s.[1] The PCE (below) at ADE was also established for the logdose protocol, as previously done by Sumikawa *et al.*[4]

Bracket Protocol

This protocol was similar to the logdose protocol except for the epinephrine dose schedule and time between successive infusions. With the bracket protocol, infusions began at 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and were doubled until arrhythmias occurred.[2,3] Under the present test conditions (including pilot studies), arrhythmias always occurred by the 4.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion level. Then, ADE was

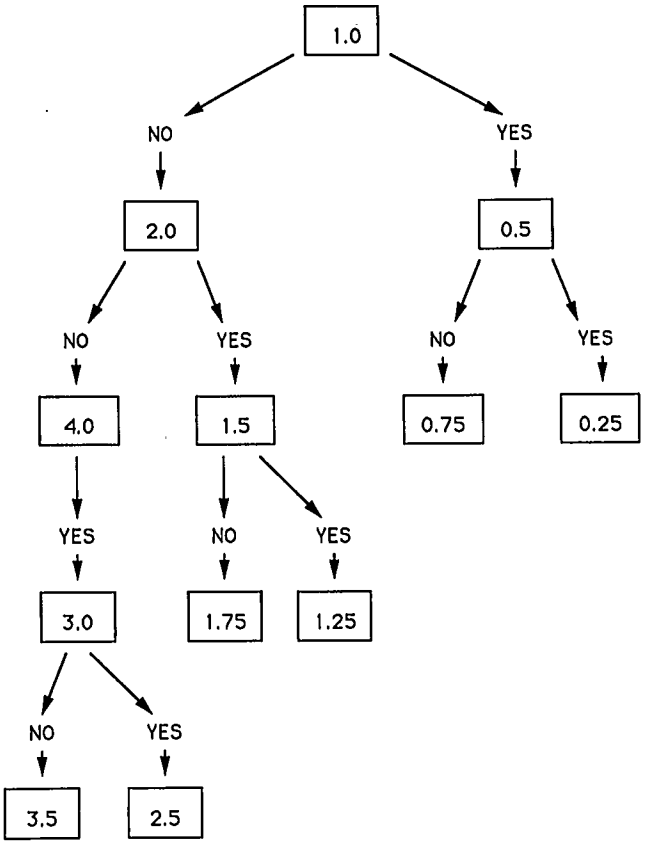

FIG. 1. Epinephrine infusion procedure with bracket protocol in group 1 dogs. Numbers refer to infused epinephrine dose (micrograms per kilogram per minute) and "yes" or "no" to whether ventricular arrhythmias (see text for definition) occurred at a particular infusion level.

bracketed by using successive infusion rates that were the arithmetic mean of the two previous infusion rates until ADE was established, as illustrated in figure 1. A maximum of five epinephrine infusions, each lasting 3 min (or less if arrhythmias occurred), could be tested with the bracket protocol (fig. 1). The goal with this protocol was to establish ADE and PCE with minimum exposure to epinephrine. Finally, with the bracket protocol, sufficient time (15–60 min) between infusions was allowed for heart rhythm, heart rate, and blood pressure to return to baseline values before beginning the next level of epinephrine infusion.

Epinephrine Plasma concentrations

Blood samples for "blank" or PCE determinations, performed in duplicate, were drawn into precooled plastic tubes containing an EDTA–metabisulfite solution. Blank determinations were samples taken prior to epinephrine exposure. Samples were centrifuged at 2° C until analyzed, within 14 days. High-performance liquid chromatography with an epinephrine sensitivity of greater than 10 pg/ml was used for analysis.[7,8]

Exclusion Criteria

Arterial blood gas, serum ionized potassium and calcium, and hemoglobin values were determined prior to beginning each epinephrine infusion for both protocols. Additional sampling was done during the longer rest periods between infusion protocols to permit adjustment of ventilation and to correct metabolic acidosis with sodium bicarbonate. If arterial carbon dioxide tension and base deficit values prior to subsequent protocol testing were found to exceed earlier mentioned tolerances, the day's data were discarded and the animal retested on another occasion. Hemoglobin and ionized calcium were allowed to vary. Low serum potassium values were not corrected, with the justification that a transient intracellular shift, not total body depletion, had occurred as the result of exposure to epinephrine.[9] One dog, later found pregnant, was excluded because of severe metabolic acidosis, which developed repeatedly during epinephrine exposure. Two group 1 dogs could not be resuscitated from ventricular fibrillation and were discarded due to incomplete data. Thus, seven dogs completed group 1 protocol testing.

GROUP 2: HEMODYNAMIC EXPERIMENTS

After analysis of group 1 data, additional experiments (group 2) were performed to determine why ADE were approximately 2-fold higher for the logdose compared to bracket protocols, despite similar PCE at ADE (Results). One possible explanation for this discrepancy was higher epinephrine clearance with the logdose compared to bracket protocols, possibly because of nonequivalent physiologic or hemodynamic states that could have existed prior to the epinephrine infusions used to establish ADE under the logdose protocol. It was our distinct impression from group 1 experiments that heart rate and blood pressure did not always return to baseline values during the 10 min between infusions with the logdose protocol but did return to baseline as a requirement for beginning the next level of infusion with the bracket protocol. Furthermore, there was laboratory evidence for an added effect of epinephrine just prior to infusions used to establish ADE with the logdose as compared to bracket protocol. Included were significant differences in values for ionized potassium, hemoglobin, and arterial carbon dioxide tension values obtained just prior to beginning epinephrine infusions used to establish ADE for either protocol (Results). This suggested, in dogs studied with the logdose protocol, an effect of residual epinephrine to enhance its own clearance.

Therefore, it was the purpose of group 2 experiments to determine whether hemodynamic and laboratory val-

ues had in fact returned to baseline just prior to beginning the epinephrine infusions used to establish ADE with the logdose or bracket protocols. To model such "initial conditions" with both protocols, modified logdose and bracket protocols were tested on weekly occasions (sequence and order of protocol testing randomized) in a separate group of dogs (n = 6). Three of these dogs had also completed testing under the group 1 protocol. In addition to determining whether initial conditions were equivalent, we were also interested in determining whether the plasma concentrations of epinephrine reached at 1, 2, and 3 min during infusion of the same epinephrine dose were similar with both modified protocols. Therefore, an upper epinephrine infusion rate of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was tested with both modified protocols to avoid provocation of ventricular arrhythmias. Ventricular arrhythmias could have affected cardiac output measurements or made it necessary to terminate infusions before 3 min.

With the *modified logdose protocol,* three successive infusion rates were used (0.67, 0.82, and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$), each lasting 3 min, with 10 min between infusions. Measurements for hemodynamic and laboratory variable values for initial conditions with the modified logdose protocol were made just prior to beginning the 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion. With the *modified bracket protocol,* only the 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine infusion rate was tested. However, measurements for hemodynamic and laboratory variable values at "initial conditions" were made at one of two times, depending on the sequence of protocol testing on a particular test occasion. If the modified logdose protocol was tested first, measurements were made just prior to beginning the 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion rate (the only infusion) under the modified bracket protocol. If the modified bracket protocol was tested first, measurements were made just prior to beginning the 0.67 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion under the modified logdose protocol. This procedure for epinephrine testing and initial condition measurement times is summarized in figure 2. It can be seen (fig. 2) that measurements for initial conditions with the modified bracket protocol corresponded to the same time period, namely the period immediately after the 60-min rest period, regardless of which modified protocol was tested first. Finally, values for hemodynamic and laboratory variables under initial conditions were compared to baseline (*i.e.*, before any epinephrine was infused) for each of the modified protocols.

For testing of both modified epinephrine protocols, anesthetic induction and maintenance were exactly as described above under General Methods, above. After thiopental induction, animals were equilibrated with halothane for 60 min, during which time hemodynamic monitoring was instituted and baseline measurements made. The latter included systemic arterial and central venous pressures, thermodilution cardiac output *via* a flow-directed pulmonary artery catheter, systemic vascular resistance,** serum ionized potassium, hemoglobin, and blood glucose measurements. Plasma epinephrine was measured at 1, 2, and 3 min during the infusion of 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of epinephrine under both modified protocols in group 2 dogs.

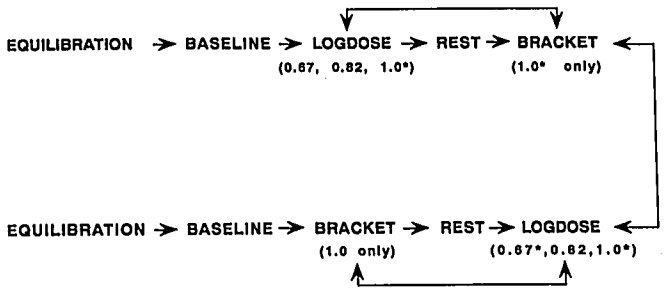

FIG. 2. Modified protocols for epinephrine testing with group II dogs. Joined arrows indicate randomization. With the modified logdose protocol, 0.67, 0.82, and 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine were infused. With the modified bracket protocol, only 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine was infused. Infusions lasted 3 min with both protocols, with 10 min between infusions (logdose only) and a 60-min rest period between protocols. Hemodynamic and other measurements for "initial conditions" were made during a 2-min period prior to infused dose levels, marked by an asterisk.

Except for one dog, no group 2 dogs developed ventricular arrhythmias during exposure to epinephrine. Data from this dog was discarded since arrhythmias likely affected cardiac output measurements and since complete testing with both modified infusion protocols could not be accomplished.

STATISTICAL ANALYSIS

All values shown are means ± standard error. In both group 1 and 2 dogs, each dog had two values for each experimental variable. These were obtained on two test occasions at least 1 week apart; the order and sequence for protocol testing was randomized. Data from each of these occasions were tested statistically (paired *t* test) and found were not different. Therefore, data for the two occasions were pooled and used to compute group means. In group 1 dogs, group mean data values for the logdose and bracket protocols were compared by a paired *t* test. In group 2 dogs, group means for hemodynamic and experimental variables for the modified logdose and bracket protocols were compared (paired *t* test) with means obtained under baseline conditions. Finally, in group 2 dogs, group mean values for plasma level of epinephrine

** Systemic vascular resistance (dyne · s · cm^{-5}) = 80 × (mean arterial pressure − central venous pressure) ÷ cardiac output.

TABLE 1. Arrhythmic Dose of Epinephrine and Plasma Concentration of Epinephrine at Arrhythmias

Dog	Order	ADE ($\mu g \cdot kg^{-1}$)		PCE ($pg \cdot ml^{-1}$)	
		L	B	L	B
2	LB, BL	3.52	2.33	24500	32000
5	LB, BL	6.21	3.99	53500	54000
7	BL, LB	2.84	1.72	16900	14250
8	BL, LB	3.13	2.45	14200	38500
9	BL, LB	5.33	2.15	54500	44500
10	LB, BL	1.63	1.63	13500	13850
11	LB, BL	4.78	3.55	55500	49000
Mean		3.92	2.54*	33229	35157
SEM		0.60	0.34	7643	6068

ADE = arrhythmic dose of epinephrine; PCE = plasma concentration of epinephrine. "Order" specifies the order of protocol testing on the first and second test occasions: L = logdose; B = bracket.
* $P = 0.013$ ADE (B) *versus* ADE (L).

reached at 1, 2, and 3 min were also compared between the two protocols using a paired t test. P values < 0.05 were considered statistically significant.

Results

GROUP 1: ARRHYTHMIA THRESHOLD

The ADE and corresponding PCE are compared in table 1 for seven dogs who completed two trials, at least 1 week apart, with both the logdose and bracket protocols. The order of protocol testing is specified in table 1 and pooled values for ADE and PCE provided, since values for the two trials were not significantly different from each other. Note that ADE was significantly greater with the logdose compared to bracket protocol, but that PCE was not different (table 1).

The mean number of epinephrine infusions required to establish ADE was greater ($P < 0.05$) with the logdose (mean = 6, range = 3–8) compared to the bracket protocol (mean = 4, range 3–4). However, the mean epinephrine infusion rate that provided ADE was not different between protocols (logdose = 1.79 ± 0.25, bracket = 1.45 ± 0.18 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Neither was the time to arrhythmia endpoint during the infusion which established ADE different between the two protocols (logdose = 2.04 ± 0.13, bracket = 1.73 ± 0.12 min).

Values for laboratory variables with the two protocols are listed in table 2. Measurements for these were made just prior to starting the epinephrine infusion level which established ADE and therefore represent initial conditions for both protocols. There were no measurements of blood glucose in group 1 dogs. Note (table 2) that serum ionized potassium and arterial carbon dioxide tension were less, and hemoglobin greater, with the logdose compared to bracket protocol ($P < 0.05$). Values for serum ionized calcium and pH were not different between the two protocols. Hemodynamic parameters (heart rate and blood pressure) were not recorded for initial conditions for both protocols in all dogs.

Values for systolic, diastolic, and mean arterial pressure, as well as increase in mean blood pressure over baseline at ADE for the logdose and bracket protocols, are provided in table 3. These data indicate that levels of blood pressure reached at ADE, as well as increase in mean blood pressure over baseline, were equivalent with the logdose and bracket protocols. Heart rate at ADE was not recorded, since this was quite variable due to ventricular arrhythmias. Neither were there measurements of cardiac output or other hemodynamic parameters in group 1 dogs.

GROUP 2: HEMODYNAMIC EXPERIMENTS

Of interest in these experiments was whether values for hemodynamic and laboratory variables obtained just prior to beginning the 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine

TABLE 2. Values for Laboratory Variables in Group 1 Dogs

Dog	K^+ (mEq/l)		Ca^{2+} (mEq/l)		Hemoglobin (g%)		Arterial pH		Pa_{CO_2} (mmHg)	
	L	B	L	B	HbL	HbB	L	B	L	B
2	3.0	3.6	2.3	2.5	17.0	15.3	7.39	7.39	37	41
5	2.8	3.5	2.2	2.4	17.0	13.3	7.42	7.39	36	38
7	3.1	3.9	2.3	2.5	14.6	13.6	7.40	7.40	36	42
8	3.2	5.5	2.4	2.4	15.0	13.4	7.40	7.41	39	39
9	2.9	4.1	2.3	2.4	17.0	13.1	7.35	7.38	36	37
10	2.8	3.7	2.6	2.3	14.3	13.9	7.40	7.41	34	43
11	3.0	3.8	2.5	2.4	16.0	12.1	7.38	7.39	33	35
Mean	3.0	4.0*	2.4	2.4	15.8	13.5†	7.39	7.39	36	39‡
SEM	0.1	0.3	0.1	0.0	0.5	0.4	0.01	0.01	1	1

Measurements were made just prior to the level of epinephrine infusion that established ADE under the logdose (L) or bracket (B) protocols. The order of testing was as shown in Table 1.
Pa_{CO_2} = arterial carbon dioxide tension.
* $P = 0.003$, K^+ (B) *versus* K^+ (L).
† $P = 0.006$, hemoglobin (B) *versus* hemoglobin (L).
‡ $P = 0.039$, Pa_{CO_2} (B) *versus* Pa_{CO_2} (L).

TABLE 3. Blood Pressure Values in Group 1 Dogs

Dog	SBP (mmHg)		DBP (mmHg)		MAP (mmHg)		MAP Increase (mmHg)	
	L	B	L	B	L	B	L	B
2	260	250	150	165	185	195	93	91
5	280	260	165	150	200	185	100	89
7	245	230	150	145	180	175	62	64
8	260	250	160	145	195	180	78	60
9	245	230	155	140	190	175	115	80
10	215	185	150	140	170	160	70	55
11	240	230	145	145	175	175	72	82
Mean	249	234	154	147	185	178	84	74
SEM	8	9	3	3	4	4	7	6

Values are shown for the logdose (L) and bracket (B) protocols. The order of testing was as shown in Table 1.

SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; MAP increase = increase in MAP over baseline values at the arrhythmic dose of epinephrine.

infusion (*i.e.*, initial conditions) under the modified logdose or bracket protocols were different from baseline or each other. Initial-condition values for systolic, diastolic, and mean arterial pressure with either protocol were not significantly different from baseline or each other. Baseline values for arterial pressure were 118 ± 12 (systolic), 76 ± 7 (diastolic), and 89 ± 8 mmHg (mean).

Values for cardiac output, central venous pressure, systemic vascular resistance, and heart rate under initial conditions for the modified logdose, but not modified bracket, protocol were significantly different from baseline (table 4). Furthermore, except for heart rate ($P = 0.062$), values for these parameters were significantly different between the two protocols (table 4). Initial condition values for hemoglobin with the modified logdose protocol (15.2 ± 0.6 g/100 ml) were also different from baseline (11.9 ± 0.6 g/100 ml) and compared to the modified bracket protocol (10.8 ± 0.6 g%), with $P = 0.001$ in both cases. The initial condition value for serum ionized potassium with the modified logdose protocol (3.4 ± 0.2 mEq/l) was nearly different compared to baseline (3.8 ± 0.2 mEq/l) ($P = 0.059$). The value for the modified bracket protocol (3.6 ± 0.1 mEq/l) was not different from baseline.

Blood glucose was measured at baseline and under initial conditions for both protocols in four group 2 dogs, but in each dog only on a single test occasion. Glucose values at baseline were 91 ± 22 mg/100 ml, compared to initial conditions (123 ± 8 and 92 ± 7 mg/100 ml) with the logdose and bracket protocols, respectively.

Finally, plasma concentrations of epinephrine measured at 1, 2, and 3 min during infusion of epinephrine in group 2 dogs were not different between the two protocols (table 5). Furthermore, epinephrine plasma concentrations under initial conditions for the two modified protocols were not different (logdose ≤ 100 and bracket ≤ 420 pg/ml).

Discussion

Epinephrine arrhythmia threshold infusion rates for four or more continuous or intermittent premature ventricular beats within 15 s have been determined before with the logdose infusion protocol for dogs anesthetized with *thiopental–halothane*—specifically, halothane inhalation preceded by an intravenous induction dose of thiopental (20 mg/kg). Pace *et al.* reported a mean infusion rate of 2.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (95% confidence interval = 1.73 − 2.48).[1] Sumikawa *et al.* reported 2.18 ± 0.17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (mean ± standard error).[4] Both values for infusion rate are similar to our present logdose value of 1.79 ± 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Pace *et al.* did not provide comparable values for the ADE (*i.e.*, ADE in $\mu g \cdot kg^{-1} \cdot min^{-1}$) or PCE.[1] Sumikawa *et al.* reported an ADE of 4.18 ± 0.85 μg/kg and PCE of 38,700 ± 2,500 pg/ml,[4] similar to our present logdose values of 3.92 ± 0.60 μg/kg and 33,229 ± 7,643 pg/ml for ADE and PCE, respectively. Finally, Pace *et al.* reported an increase in mean arterial pressure at ADE (*vs.* baseline value) of 87 ± 7 mmHg,[1] similar to our value of 92 ± 13 mmHg.

TABLE 4. Hemodynamics of "Initial Conditions" in Group 2 Dogs (n = 5)

Dog	Order	CO (l/min)			CVP (mmHg)			SVR (dyne·s·cm^{-5})			HR (beats per min)		
		BA	L	B	BA	L	B	BA	L	B	BA	L	B
2	BL, LB	2.3	3.1	2.2	6	7	5	2960	2040	2840	112	118	104
5	LB, BL	2.0	3.0	2.4	8	11	8	4360	2960	3720	89	111	91
7	LB, BL	2.3	3.1	2.6	3	6	3	2600	1800	2280	94	112	112
9	BL, LB	1.7	2.6	2.0	8	11	8	3200	2160	3040	102	103	97
11	LB, BL	2.4	2.8	2.3	7	10	8	2640	2320	2720	108	116	110
Mean		2.1	2.9*	2.3†	6	9*	6†	3152	2256*	2920†	101	112*	103
SEM		0.1	0.1	0.1	1	1	1	321	195	236	4	3	4

Comparison of values obtained just prior to beginning 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine under the modified logdose (L) or bracket (B) protocols with baseline (BA) values. Under order is specified the order of protocol testing on the first and second test occasions.

CO = cardiac output; CVP = central venous pressure; SVR = systemic vascular resistance; HR = heart rate.

* $P < 0.05$, L or B *versus* BA.

† $P < 0.05$, B *versus* L.

TABLE 5. Plasma Concentrations of Epinephrine

Dog	Order	1 min		2 min		3 min	
		L	B	L	B	L	B
2	BL, LB	14800	14950	18950	18200	20500	16200
5	LB, BL	19200	18200	24550	30250	23900	29000
7	LB, BL	15500	18000	22000	22500	18250	24500
9	BL, LB	20000	22500	28500	31500	24000	35000
11	LB, BL	12800	12550	14600	18250	18000	14750
Mean		16460	17240	21720	24140	20930	23890
SEM		1362	1679	2371	2865	1308	3825

Plasma concentrations of epinephrine (pg/ml) measured in group 2 dogs (n = 5) at 1, 2, and 3, min during infusion of 1.0 $\mu g \cdot min^{-1}$ epinephrine under the modified logdose (L) or bracket (B) protocols.

Sumikawa *et al.* did not report blood pressure increase at ADE.[4]

The present data for ADE in thiopental–halothane-anesthetized dogs with the bracket infusion protocol also compare well with existing data. Atlee and Malkinson reported ADE for three categories of ventricular rhythm disturbances: the first appearance of ventricular premature beats, ventricular bigeminy, or ventricular tachycardia. ADE for these disturbances were 1.88 ± 0.41, 1.47 ± 0.25 and 2.41 ± 0.62 μg/kg, respectively.[2] Even though not exactly the same ventricular arrhythmia endpoint, our present value for ADE under the bracket protocol (2.54 ± 0.34 μg/kg) is in favorable agreement with previous data from this laboratory for ADE values determined with the same protocol.[2] The range of values for increase in systolic arterial pressure (*vs.* baseline) for the various ventricular arrhythmia endpoints in the previous study from this laboratory was 124–140 mmHg, also in agreement with the comparable value (104 ± 9 mmHg, not in table 3) for the present study. Sumikawa *et al.* did not report blood pressure values at arrhythmias.[4]

Thus, the present and existing data[2,4] indicate that ADE for thiopental–halothane-anesthetized dogs are about two times greater with the logdose compared to the bracket epinephrine infusion protocol. Although this difference is relatively small for thiopental–halothane, a relatively sensitizing anesthetic combination,[2–4] the difference appears much larger with less sensitizing anesthetic combinations. For example, Sumikawa *et al.* reported an ADE of 20.9 ± 3.5 μg/kg for thiopental–enflurane (logdose),[4] and Atlee and Roberts reported 5.0 ± 0.6 μg/kg for the same anesthetic combination (bracket).[3] Also, as found in the present study, there might be a difference in number of epinephrine infusions required to establish ADE with the logdose as compared to bracket protocol. We calculate that as many as 13 infusions would have been required to establish ADE for thiopental–enflurane with the logdose protocol[4] compared to as many as 7 for the bracket protocol.[3] Therefore, as has been suggested,[5] epinephrine tolerance, which develops during repeated exposure to epinephrine,[5] might explain larger ADE with the logdose compared to bracket protocol.

Instead, the present results indicate the nonequivalent physiologic and hemodynamic states existed at initial conditions for the two protocols (*i.e.*, just prior to the epinephrine infusions used to determine ADE). Such nonequivalent states may have resulted from residual epinephrine at the tissue level, if 10 min between epinephrine infusions (logdose protocol) was not sufficient for tissue clearance of epinephrine. Thus, enhanced epinephrine clearance due to effects of residual epinephrine, not tolerance, appears to explain the higher ADE with the logdose protocol. Had tolerance been the explanation, both ADE and PCE should have been higher with the logdose compared to bracket protocol in this study. They were not: PCE at ADE were similar for both protocols. These findings provide evidence for increased epinephrine clearance from plasma with the logdose as compared to bracket protocols, although epinephrine clearance from plasma was not directly measured.

Increased epinephrine clearance, in turn, was likely caused by higher cardiac outputs for initial conditions (logdose) compared to baseline. Although cardiac output was not measured in group 1 experiments, cardiac output was higher than baseline for the logdose but not bracket protocols just prior to epinephrine 1.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during modified protocol testing (group 2). We speculated above that increased cardiac output and other changes from baseline values at initial conditions for hemodynamic and laboratory variables in group 1 or 2 dogs tested with the logdose or modified logdose protocols (*i.e.*, increased heart rate and central venous pressure, and reduced systemic vascular resistance, serum ionized potassium and hemoglobin) resulted from effects of residual epinephrine at the tissue level. If so, previously reported data indicate that effects of such residual epinephrine on ADE can be even greater with less sensitizing anesthetics, since a nearly 4-fold higher ADE was reported for thiopental–enflurane with the logdose[4] compared to bracket protocol.[3]

Nevertheless, additional studies are required that di-

rectly compare the logdose and bracket protocols in the same animals anesthetized with thiopental–enflurane. These studies should include hemodynamic and pharmacokinetic data and possibly also test with one or more other anesthetic agents or combinations with varying sensitizing ability (*e.g.*, halothane, enflurane, or thiopental–isoflurane). However, interpretation of findings for ADE and PCE in such studies could be confounded if pulmonary artery or other intracardiac catheters used for hemodynamic measurements themselves initiate ventricular arrhythmias due to mechanical stimulation of the endocardial surface of the heart. To avoid such artifacts, which could affect ADE and PCE values, pharmacokinetic testing should be performed separately from ADE and PCE experiments and in the same animals if possible. Further, infused doses of epinephrine for pharmacokinetic experiments should be somewhat below those that had previously established ADE and PCE. This would reduce the likelihood of ventricular arrhythmias, which could decrease cardiac output (and thereby possibly increase PCE values) or necessitate discontinuing infusions before the full 3-min time period. Finally, additional ADE–PCE or pharmacokinetic testing of a logdose protocol that provides sufficient time between epinephrine infusions for return to baseline hemodynamic conditions appears necessary. We suggest this because reduced epinephrine intervals (10 min)[1] may be just as or even more important than increased exposure to epinephrine for explaining higher apparent epinephrine clearance and measured ADE values with the logdose compared to bracket protocols.

For the present or previous[1–4] experiments, we do not exclude a possible effect of thiopental on ADE or PCE measurements with either the logdose or bracket protocols. Hayashi *et al.* have shown that increasing thiopental concentrations, with etomidate or halothane, produce dose-dependent reductions in ADE and PCE in dogs tested with a logdose epinephrine-infusion protocol.[10] However, in their study, thiopental was administered as a continuous infusion in doses required to maintain constant thiopental plasma concentrations. In contrast, in the present study, thiopental was administered in a single intravenous induction dose, a method previously shown by us to reduce ADE for up to 4 h with halothane[2] and enflurane or isoflurane.[3] While we lack measurements of thiopental plasma concentrations over time in this and our previous studies,[2,3] thiopental plasma concentrations should have declined substantially due to redistribution to tissues[11] by the time epinephrine infusions that established ADE and PCE with either protocol were administered (≥ 90 min after thiopental induction). Nevertheless, if significant amounts of thiopental were still present in plasma (even if decreasing with time) and perhaps more importantly at the tissue level, any effect thereof on ADE or PCE should have cancelled out since both epinephrine infusion protocols were tested in randomized order on two occasions in the same animal. In support of this contention, we note that ADE and PCE for either protocol were not statistically different from each other on either of the two test occasions—our justification for pooling data (see Results). Therefore, we believe that our ADE and PCE measurements were not greatly affected by possible time-related differences in thiopental plasma or tissue concentrations.

Finally, it is our impression that clinicians usually view anesthetic–epinephrine compatibility in terms of reported ADE, not necessarily PCE values. If so, the present data for thiopental–halothane indicate that the method for epinephrine infusion is an important determinant of results. Values in dogs for ADE determined with established logdose[1,4] or bracket[2,3] protocols could vary more with less sensitizing anesthetic agents or combinations. Therefore, based on this and previous studies, the bracket protocol should provide a more conservative estimate of ADE, at least for thiopental–halothane. Previous data suggest this also to be the case for thiopental–enflurane,[3,4] provided that thiopental administration precedes enflurane or halothane inhalation, as usually is the case in clinical settings. Nonetheless, since ADE values can vary substantially with established logdose and bracket epinephrine infusion protocols, PCE might be considered a better indicator of anesthetic—epinephrine compatibility. This could be so since PCE at ADE were similar with both the logdose and bracket protocols for thiopental–halothane. However, this conjecture concerning PCE should not at present be extended to other anesthetics. Reported values for PCE at ADE with thiopental–enflurane differ 3-fold. With the logdose method, PCE was 206,000 ± 18,000 μg/ml[4] compared to 63,000 ± 16,000 μg/ml with the bracket method.[3] This difference seems to be too large to be explained by interlaboratory variance. Hence, additional confirmation is required by direct comparison of both epinephrine infusion protocols in the same animal.

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