

## Supraventricular Excitability in Dogs during Anesthesia with Halothane and Enflurane

John L. Atlee, III, M.D.,\* Ben F. Rusy, M.D.,† John F. Kreul, M.D.,\* Thomas Eby, B.S.‡

Spontaneous premature atrial systolic beats provoked by test stimulation of the atria were examined in groups of dogs anesthetized with 1.0, 1.5 and 2.0 MAC halothane or enflurane. Data for halothane effects on the atrial and AV nodal refractory periods and the AV nodal conduction time of premature atrial test beats are provided and compared with corresponding data previously obtained by the authors for enflurane. The results indicate that the probability of spontaneous premature atrial beats occurring in response to test atrial stimulation was: significantly increased in the dogs anesthetized with halothane as opposed to enflurane; significantly decreased by increasing MAC level of either halothane or enflurane; significantly altered by the basic paced atrial rate with halothane but not with enflurane. Increasing the depth of anesthesia with enflurane, but not with halothane, prolonged the atrial effective refractory period. Increases of both agents prolonged the AV nodal functional refractory period. AV nodal fatigue was similarly affected by both agents. Increasing the concentration of enflurane, but not halothane, prolonged AV nodal minimum conduction time. Increased anesthetic depth with both agents, but significantly more so with halothane, prolonged AV nodal interval-related conductivity. Changes in basic atrial paced rate with halothane, but not with enflurane, altered AV nodal interval-related conductivity. Critical alterations in atrial and AV nodal conduction are believed necessary for supraventricular arrhythmias due to atrial or AV nodal re-entry. The different effects of halothane and enflurane on supraventricular conduction may in part explain the authors' observation that an experimental atrial arrhythmia occurred more frequently with halothane than with enflurane. (Key words: Heart: arrhythmias; atria; AV node; conduction, His bundle; electrocardiography. Anesthetics, volatile: enflurane; halothane.)

CLINICAL STUDIES utilizing continuous cardiac monitoring have demonstrated that atrial fibrillation and other atrial arrhythmias are often preceded by premature atrial beats.<sup>1,2</sup> Furthermore, atrial premature beats that are followed by arrhythmias have shorter coupling intervals between them and their preceding normal beats.<sup>1,2</sup> Experimentally, critically timed stimulated premature atrial systolic beats are known to provoke atrial arrhythmias.<sup>3-6</sup> Controversy,

however, exists regarding the mechanism for the production of these arrhythmias. Montgomery and Dresel concluded from their study of experimental atrial arrhythmias that re-entry of excitation best explained their observations.<sup>3</sup> Conditions necessary for re-entry include: 1) block of conduction at some site within the normal conduction pathways, 2) slow conduction over an alternate pathway, 3) delayed activation of tissue distal to the site of block, and 4) re-excitation of tissue proximal to the site of block.<sup>7</sup> Montgomery and Dresel, however, were unable to demonstrate changes in the conduction times of stimulated premature atrial systolic beats that could be related causally to the production of arrhythmias.<sup>3</sup>

In this study, we report on the occurrence of experimentally induced atrial arrhythmias in two separate groups of dogs that underwent programmed stimulation of the atria for the determination of anesthetic effects on supraventricular conduction. We observed that the dogs anesthetized with halothane, in contrast to enflurane, were more likely to manifest arrhythmias in response to appropriately timed premature atrial stimuli. While data describing the effects on the conduction times of the atrial test beats used to provoke these arrhythmias have previously been reported for enflurane,<sup>8</sup> comparable data for halothane have not. Conduction data for halothane are, therefore, included here along with data for arrhythmias. Anesthetic effects on conduction times of test beats appeared to be related to the occurrence of experimental arrhythmias and, moreover, support our belief that re-entry of excitation is the mechanism underlying their production.

### Methods

Our methods for testing anesthetic effects on supraventricular refractory periods and AV nodal conductivity indices in dogs, *i.e.*, programmed premature atrial stimulation, have been described.<sup>8</sup> Sufficiently premature stimulated (test) atrial beats will, under favorable circumstances, result in spontaneous, premature, atrial activations. The taped records (FM recording tape) of ten experiments in which the effects of enflurane on supraventricular conduction were examined utilizing programmed stimulation<sup>8</sup> were re-examined for incidence of experimental arrhythmias. Another group of ten dogs was subse-

\* Assistant Professor of Anesthesiology.

† Professor of Anesthesiology.

‡ Medical student.

Received from the Department of Anesthesiology, University of Wisconsin Medical School, Madison, Wisconsin 53706. Accepted for publication March 20, 1978. Supported in part by Grant # 135 4433 funded from the University of Wisconsin Graduate School, the Wisconsin Heart Association (Grant-in-Aid), and the H. G. Barsumian, M.D., Memorial Fund. Presented in part at the Annual Meeting of the Federation of American Societies for Experimental Biology, Chicago, April 1977 and the Annual Meeting of the American Society of Anesthesiologists, New Orleans, October 1977.

Address reprint requests to Dr. Atlee.

TABLE 1. Effects of Halothane on Minimum AV Nodal Conduction Time at Basic Cycle Lengths of 500 and 300 Msec (Mean  $\pm$  1 SD, Ten Dogs)

	MAC		
	1.0	1.5	2.0
Minimum AV nodal conduction time (msec)			
At basic cycle length 500 msec	67.3 $\pm$ 9.2	68.6 $\pm$ 9.4	70.4 $\pm$ 7.4
At basic cycle length 300 msec	72.8* $\pm$ 9.0	72.1 $\pm$ 8.1	79.8*† $\pm$ 9.4

\*  $P < 0.05$  compared with value for basic cycle length 500 msec, same MAC level.

†  $P < 0.05$  compared with value for 1.5 MAC, same basic cycle length.

quently tested (programmed stimulation) at levels of anesthesia with halothane comparable to those previously evaluated with enflurane.<sup>8</sup> The relationship between anesthetic-induced alterations in conduction and the production of experimental atrial arrhythmias in the two experimental groups was then examined.

In this and the previous study,<sup>8</sup> animals were anesthetized on a single occasion. End-tidal anesthetic concentrations were maintained within  $\pm 10$  per cent of the desired levels equivalent to 1.0, 1.5 and 2.0 MAC in dogs<sup>9</sup> for 10 min prior to and for the duration of all experiments. Animals were kept normocarbic (controlled ventilation) and normothermic. Arterial blood pH was adjusted to  $7.40 \pm .03$  with sodium bicarbonate, given intravenously as needed. Mean arterial blood pressures for animals anesthetized with halothane at each MAC (1.0,  $97 \pm 8$ ; 1.5,  $83 \pm 11$ ; 2.0,  $61 \pm 11$  torr) did not significantly differ from those previously reported for enflurane.<sup>8</sup>

AV nodal conductivity indices (*i.e.*, minimum AV nodal conduction time, fatigue, interval-related conductivity) and supraventricular refractory periods (*i.e.*, functional refractory period, AV node; effective refractory period, atrium) measured in this study for halothane were defined previously.<sup>8</sup> For both halothane and enflurane groups, experimental atrial arrhythmias were observed during premature (test) stimulation of the atria at basic paced atrial cycle lengths of 500 (120 beats/min) and 300 msec (200 beats/min). Test beat cycle lengths were decreased by 5-msec increments beginning with a cycle length of 250 msec. Progressively premature test stimuli were delivered (basic cycle length held constant) until effective refractoriness of the atria was encountered. Following the test beat stimulus, 1,500 msec elapsed before the next series of basic paced atrial beats was initiated. The coupling interval between low atrial activity of the test beat (A') and similar activity of

the first unpaced or escape beat (A<sup>2'</sup>) was recorded. Also recorded were the atrial coupling intervals between consecutive low atrial complexes prior to the next series of basic beats, *i.e.*, A<sup>2'</sup>-A<sup>3'</sup>, A<sup>3'</sup>-A<sup>4'</sup> and so forth. Unpaced atrial complexes (A<sup>2'</sup>, A<sup>3'</sup> . . .) were considered to be of sinus origin when the atrial coupling interval between them and the preceding beat was approximately equal to or exceeded the unpaced (sinus) cycle length for a given experimental condition. Mean unpaced cycle lengths prior to stimulation for halothane were: 1.0 MAC,  $545 \pm 34$  msec; 1.5 MAC,  $556 \pm 40$  msec; 2.0 MAC,  $540 \pm 36$  msec. For enflurane they were: 1.0 MAC,  $550 \pm 44$  msec; 1.5 MAC,  $566 \pm 38$  msec; 2.0 MAC,  $571 \pm 28$  msec. A'-A<sup>2'</sup> or successive atrial coupling intervals less than 400 msec were considered premature (non-sinus-origin) atrial beats. The number of premature atrial beats following A<sup>2'</sup> (when it was premature) and their respective coupling intervals (A<sup>2'</sup>-A<sup>3'</sup>, etc.) were also recorded.

Paired *t* tests and multiple linear regression<sup>8</sup> were used to determine halothane effects (increased MAC level) on indices of conductivity and refractory periods. An unpaired *t* test<sup>10</sup> was used to compare means for these variables in the halothane and enflurane<sup>8</sup> groups. The ten animals in this study that underwent programmed atrial stimulation for arrhythmia production were compared with the ten animals that underwent similar stimulation in the enflurane study.<sup>8</sup> An analysis of variance of the proportion of dogs in each anesthetic group manifesting premature atrial beats was performed (fixed effects model: angular

TABLE 2. Effects of Halothane on the Effective Refractory Period of the Atrium and Functional Refractory Period of the AV Node at Basic Cycle Lengths of 500 and 300 Msec (Mean  $\pm$  1 SD, Ten Dogs)

	MAC		
	1.0	1.5	2.0
Effective refractory period of atrium (msec)			
At basic cycle length 500 msec	137.8 $\pm$ 31.9	131.4 $\pm$ 29.0	131.3 $\pm$ 27.5
At basic cycle length 300 msec	141.3 $\pm$ 34.6	120.2 $\pm$ 29.7	115.2 $\pm$ 27.4*†
Functional refractory period of AV node (msec)			
At basic cycle length 500 msec	262.7 $\pm$ 20.3	269.2 $\pm$ 19.3	277.0 $\pm$ 20.9
At basic cycle length 300 msec	247.2 $\pm$ 17.1*	252.3 $\pm$ 16.5*	261.5 $\pm$ 19.1*†

\*  $P < 0.05$  compared with value for basic cycle length 500 msec, same MAC level.

†  $P < 0.05$  compared with value for 1.0 MAC, same basic cycle length.

transformation of proportions<sup>11</sup>). An additional analysis of variance (fixed effects model: untransformed zero-one dependent variable to indicate absence or presence of premature beat<sup>12</sup>) was carried out to determine the relationship between the probability of occurrence of a premature beat and the experimental factors: namely, individual dog, anesthetic, MAC, basic rate, and test beat cycle length.

### Results

Minimum AV nodal conduction time was not altered by halothane except that the value for this variable measured at a basic cycle length of 300 msec for 2.0 MAC was prolonged over that for 1.5 MAC (table 1). The amount of fatigue, *i.e.*, the difference between minimum conduction times measured at basic cycle lengths of 300 and 500 msec, was not altered by increasing the concentration of halothane (table 1).

The atrial effective refractory period was not prolonged by halothane; in fact, at a basic cycle length of 300 msec it was shortened by increased depth of anesthesia (table 2). The functional refractory period of the AV node was not changed significantly by halothane except at 2.0 MAC, basic cycle length 300 msec, where it was prolonged (table 2). The AV nodal functional refractory period shortened when basic cycle length was decreased from 500 to 300 msec at each MAC level. Halothane increased interval-related conductivity ( $\Delta CT$ ) for atrial coupling intervals between 200 and 400 msec as its concentration was increased (fig. 1). In addition, there was a significant effect of basic cycle length on the slope of the relationship between  $\log_{10} \Delta CT$  and atrial coupling interval.

In some, but not all, dogs anesthetized with halothane or enflurane, a decrease in test beat cycle length (TCL) provoked spontaneous, premature atrial beats. This phenomenon is illustrated for one halothane experiment in figures 2-5. At a TCL of 200 msec (fig. 2) the atrial coupling interval of the escape beat ( $A'-A''$ ) was 544 msec. This escape beat ( $A''$ ) was probably of sinus origin. At a TCL of 145 msec (fig. 3),  $A'-A''$  was 162 msec and  $A''-A'''$  660 msec.  $A''$  was clearly a premature atrial beat;  $A'''$  was probably of sinus origin. Figure 2, therefore, is an example of a single premature atrial beat provoked by an appropriately timed premature atrial stimulus. At a TCL of 125 msec (fig. 4) multiple premature atrial beats were observed. We consider this to be an example of supraventricular tachycardia. While not shown, at TCL values of 100 and 95 msec it was possible to initiate atrial fibrillation. Atrial fibrillation was terminated by the next series of basic driven beats (cycle length = 500 msec). This was the only animal in either the enflurane or halothane groups in which atrial

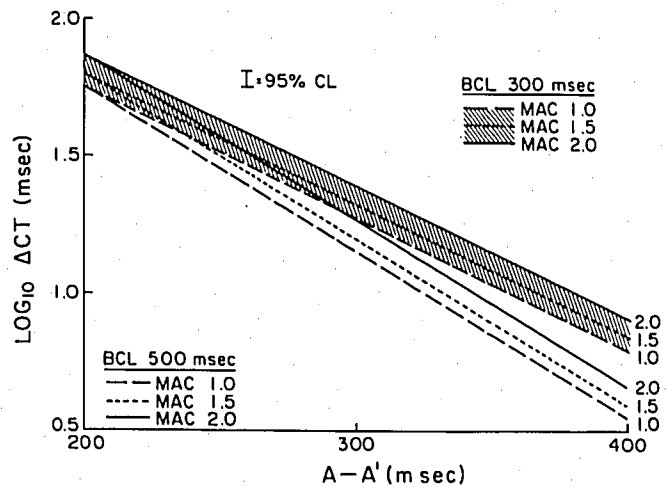


FIG. 1. Interval-related conductivity ( $\Delta CT$ ): Predicted\* effect of halothane on the relationship between  $\log_{10} \Delta CT$  and prematurity of the test beat ( $A-A'$  interval). Data from ten experiments. Correlation coefficient = 0.948.

\* See NAPS Document No. 03350 for 7 pages of supplementary materials that describe the model used for determining halothane and basic cycle length effects on interval-related conductivity ( $\Delta CT$ ). Predicted slope and intercept coefficients for the model for halothane are given along with those for enflurane. Order from NAPS: Microfiche Publications, P. O. Box 3513, Grand Central Station, New York, New York 10017. Remit in advance for each NAPS accession number. Institutions and organizations may use purchase orders when ordering; however, there is a billing charge of \$5.00 for this service. Make checks payable to Microfiche Publications. Photocopies are \$5.00. Microfiche are \$3.00 each. Outside the United States and Canada, postage is \$3.00 for a photocopy and \$1.00 for a fiche.

fibrillation could be provoked under the conditions of our experiments. The relationship that existed between all values of TCL tested and  $A'-A''$  for the dog described above at each halothane level and a basic paced cycle length of 500 msec (fig. 5) demonstrates that premature atrial beats occurred over a greater range of TCL values at 1.0 MAC; that is, an increase in anesthetic level decreased the production of premature atrial beats in response to short TCL values.

Analysis of our data (table 3) for the occurrence of spontaneous premature atrial beats during enflurane and halothane anesthesia indicates that: the probability that a premature atrial beat could be elicited at any MAC was significantly greater in the halothane group than in the enflurane group; increasing the MAC level decreased significantly the probability of occurrence of a premature atrial beat; basic paced cycle length significantly altered the likelihood of occurrence of premature atrial beats in the halothane group but not the enflurane group. Anesthetic, MAC and basic cycle length did not influence the range of TCL values over which premature atrial beats could be observed or the occurrence of multiple premature beats (two or more). In most dogs manifesting premature atrial beats, they occurred at TCL values less than 200 msec, although in one animal (halothane, 1.0 MAC, basic cycle length 500 msec) they

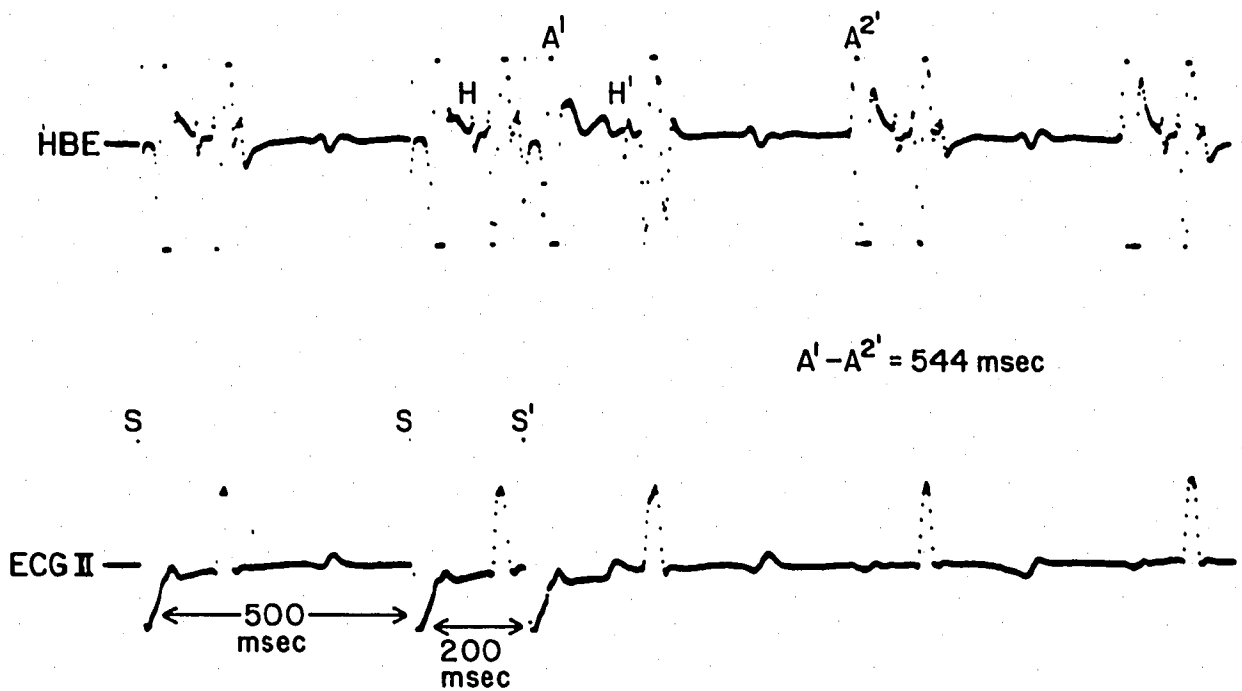


FIG. 2. Record from one experiment (Dog 13), basic paced cycle length (BCL) = 500 msec, test beat cycle length (TCL) = 200 msec. Atrial escape beat of probable sinus origin. The upper recording is the His bundle electrocardiogram (HBE). The lower recording is Lead II of the surface ECG recorded simultaneously with the HBE. S and S' denote the stimulus of the basic (S) and test (S') beats. A and H denote atrial and His bundle activity of the basic beat. A' and H' denote similar activity of the test beat. A<sup>2'</sup> is atrial activity of the first spontaneous or escape beat. The atrial coupling interval of the escape beat (A' - A<sup>2'</sup>) was 544 msec. A<sup>2'</sup> was probably of sinus origin, for reasons given in Methods.

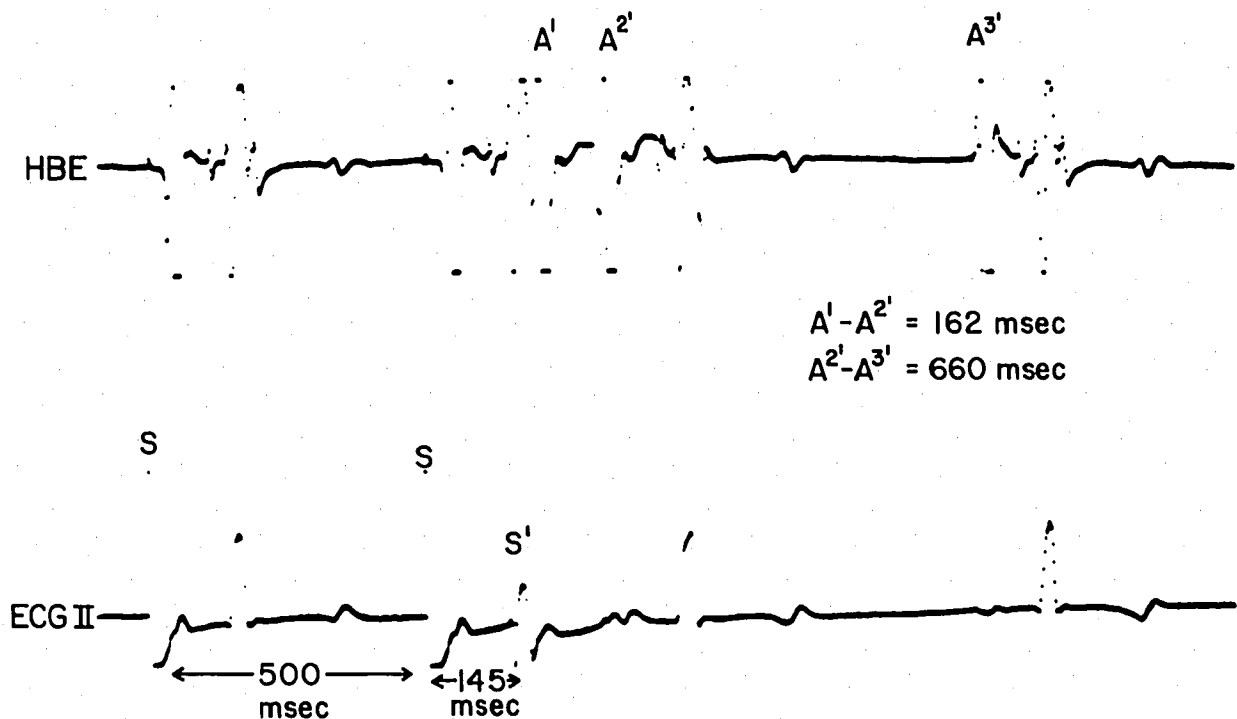


FIG. 3. Record from the experiment depicted in figure 2 (Dog 13), TCL = 145 msec. Example of spontaneous, premature atrial beat (PAB). Notice that the PAB denoted A<sup>2'</sup> occurred 162 msec after atrial activity of the test beat (A'). Atrial activity following A<sup>2'</sup>, i.e., the A<sup>3'</sup> complex, was probably of sinus origin (A<sup>2'</sup> - A<sup>3'</sup> = 660 msec).

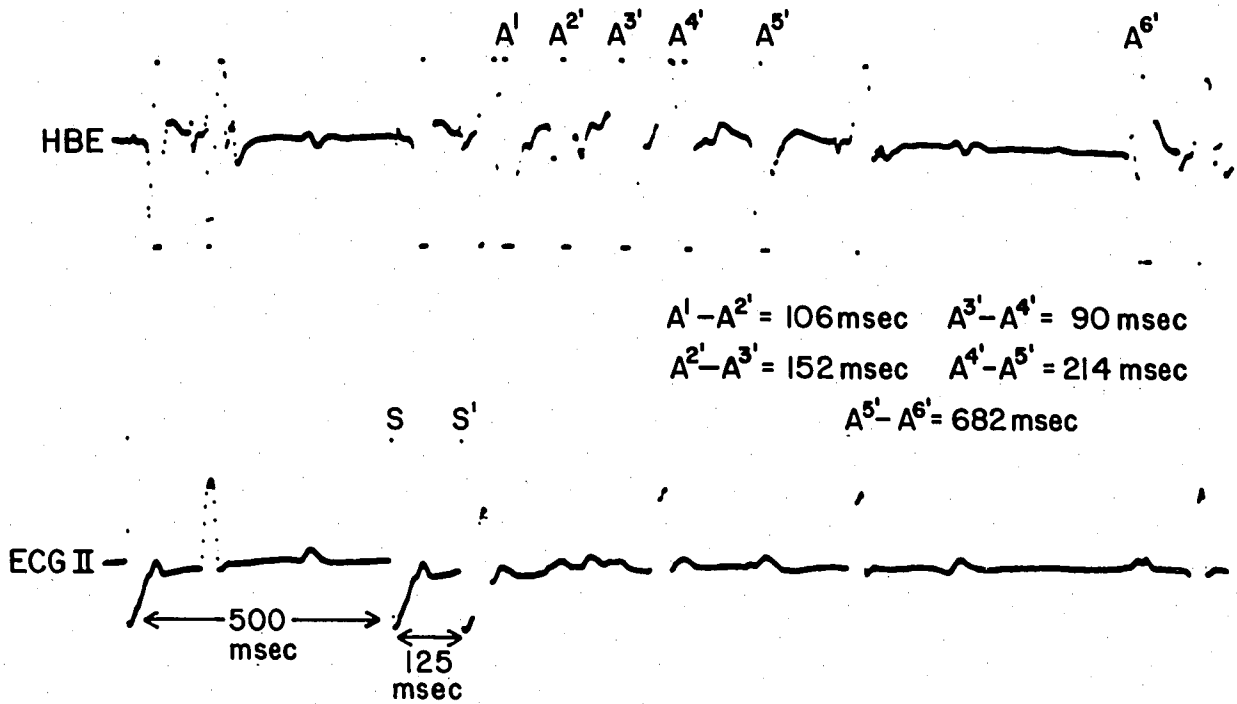


FIG. 4. Record from the experiment depicted in figures 2 and 3 (Dog 13), TCL = 125 msec. Example of multiple premature atrial beats (PAB's).  $A^2$ ,  $A^3$ ,  $A^4$ , and  $A^5$  are clearly PAB's with variable atrial coupling intervals between them and preceding atrial beats.  $A^6$  was probably of sinus origin ( $A^6 - A^5 = 682$  msec).

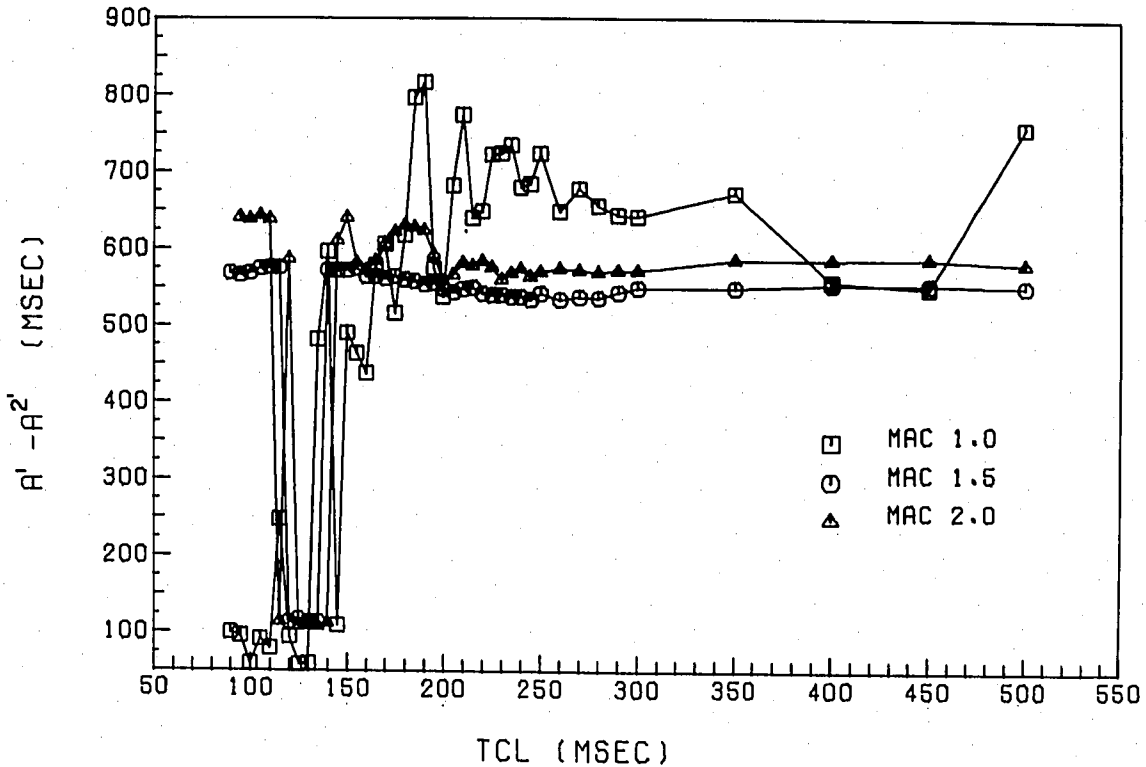


FIG. 5. Atrial escape beat coupling intervals ( $A^1 - A^2$ , ordinate) as a function of reduction in test beat cycle length (TCL, abscissa). Same animal as in figures 2, 3 and 4 (Dog 13). Depicted are  $A^1 - A^2$  intervals observed at all TCL's for three halothane MAC levels, basic cycle length (BCL) = 500 msec. See text for additional discussion.

TABLE 3. Effects of Halothane (Ten Dogs) and Enflurane (Ten Dogs) on the Occurrence of Atrial Premature Beats

	MAC		
	1.0	1.5	2.0
Enflurane			
At a basic cycle length of 500 msec	4/10	2/10	2/10
At a basic cycle length of 300 msec	5/10	2/10	2/10
Halothane			
At a basic cycle length of 500 msec	9/10	7/10	7/10
At a basic cycle length of 300 msec	7/10	5/10	3/10

were first observed at a TCL of 235 msec. The width of the range of TCL values for premature atrial beats varied between 10 and 135 msec. Within this range not all TCL values necessarily resulted in such beats. Multiple premature atrial beats occurred most often at TCL values less than 150 msec, but in one animal anesthetized with enflurane (1.0 MAC, basic cycle length 300 msec) they occurred for all TCL values between 215 and 110 msec.

Due to absence of awake measurements, we cannot state that the effect of halothane or enflurane on the occurrence of arrhythmias was statistically significant. For this reason, and the fact that the same animal was not anesthetized with both agents, we cannot say with certainty that our present findings extend to a general population of dogs. The computed probability (*F* test<sup>14</sup>) was 0.64 that in future experiments similar to these the anesthetic effect on proportions of dogs manifesting arrhythmias would be as large as or larger than the effect observed here.

### Discussion

Our present findings for effects of halothane on minimum conduction time, fatigue and the functional refractory of the AV node are in general agreement with those previously reported for 1.25, 2.0 and 2.75 MAC.<sup>15</sup> We have not previously determined the effects of halothane on the effective refractory period of the atrium or interval-related conductivity (AV node).

The hypothesis that conduction alterations are necessary for the production of arrhythmias prompted us to look for differences between the effects of halothane (reported here) and enflurane<sup>8</sup> on the conduction characteristics of the test beats used to provoke the experimental atrial arrhythmias used in this study. At comparable MAC levels and basic paced cycle lengths, effects of the two agents on AV nodal fatigue and the functional refractory period the AV node were similar. Enflurane prolonged minimum AV nodal conduction time as its concentration was increased, halothane did not. Mean values for the two

experimental groups for this variable were similar at 1.0 MAC, but different at 1.5 and 2.0 MAC.

Differences existed between the two agents for their effects on interval-related conductivity (AV node) and the atrial effective refractory period. For comparable experimental conditions, *i.e.*, MAC level and basic cycle length, halothane caused a greater increase in interval-related conductivity as the atrial coupling interval was decreased than did enflurane. Differences between agents were most pronounced at the shortest atrial coupling interval (200 msec) examined. Furthermore, with halothane a change in basic paced cycle length affected the steepness of the interval-related conductivity curves (fig. 1); with enflurane it did not.<sup>8</sup> Increasing the concentration of halothane did not prolong the atrial effective refractory period; increasing enflurane did.<sup>8</sup> Differences between halothane and enflurane for 1.5 and 2.0 MAC at both basic cycle lengths were significant.

Apparent differences between the effects of halothane and enflurane on supraventricular conduction support our belief that re-entry of excitation must seriously be considered as the mechanism underlying the production of experimental arrhythmias described in this study. Other possible mechanisms include automaticity and triggered activity.<sup>16</sup> We consider automaticity to be unlikely because fixed-rate atrial pacing, through the mechanism of overdrive suppression, would have effectively suppressed subsidiary atrial pacemaker foci, as those within the sinus node were suppressed.<sup>17</sup> We cannot exclude triggered activity as a possible mechanism for arrhythmias produced under our experimental conditions. Triggered arrhythmias are suspected clinically when their onset is characterized by a brief period of acceleration followed by a stable period of tachycardia.<sup>16</sup> The variation in coupling intervals between the atrial complexes of short bursts of tachycardia observed in this study (*e.g.*, fig. 4), may be evidence against triggered activity as the mechanism for these arrhythmias. Single, premature, unstimulated, atrial beats, however, quite possibly originated in atrial foci that were triggered.

Possible re-entry sites for experimental atrial arrhythmias observed in this study include the atria and AV node. Multiple recording electrode sites would have been necessary to determine where the re-entry actually occurred. We feel that it is necessary to consider both sites, however, for the range of test beat cycle lengths over which arrhythmias were observed by us was much greater than the range previously found by Montgomery and Dresel<sup>3</sup> in their study of arrhythmias confined to the atria.

Interval-related conductivity is the measure of additional delay encountered at the AV node of a prema-

ture (test) atrial systole.<sup>13</sup> A *critical* amount of delay, associated with a properly timed premature atrial systole, could allow a re-entrant impulse from above to gain access to distal, non-refractory, conduction pathways before the arrival of the next normal sinus impulse. Too little delay within the AV node would cause the re-entrant impulse to enter distal pathways while they were still refractory. Too much delay would cause the potentially re-entrant impulse to block within the AV node. The effects of halothane and enflurane on interval-related conductivity are different, as described above. We can only speculate at this time that these different effects are related causally to the more frequent occurrence of experimental arrhythmias during halothane anesthesia via the aforementioned mechanism.

Concerning arrhythmias of an atrial re-entrant origin, the atrial effective refractory period must be within a critical, albeit yet undefined, range for their production. Montgomery and Dresel found that acetylcholine shortened the atrial effective refractory period and at the same time increased the likelihood of atrial arrhythmias in their preparation.<sup>3</sup> We observed that the atrial effective refractory period was prolonged by increasing the concentration of enflurane, but remained relatively unaltered by increasing halothane. This prolongation by enflurane may be associated with the lesser probability of experimental atrial arrhythmias (*i.e.*, those due to atrial re-entry) with this agent.

Our data indicate that an experimental atrial arrhythmia can be produced in dogs during anesthesia with enflurane and halothane. The apparent relationship that exists between alterations in conduction and arrhythmias produced under conditions of this experiment provides new evidence that arrhythmias during anesthesia may be caused in part by anesthetic effects on conduction as opposed to automaticity.

The authors thank Dr. Peter Dresel, Chairman of the Department of Pharmacology and Therapeutics, Dalhousie University, Halifax, Nova Scotia, Canada, for his valuable advice and encouragement in carrying out these experiments. They thank Drs.

Jess Frank, Brian Joiner, and Warren Lamboy, of the University of Wisconsin Statistical Consulting Laboratory, for their professional assistance. They extend appreciation to Carol Malkinson for technical assistance, Ohio Medical Products for supplying enflurane (Éthrane), and Ayerst Laboratories, Inc., for supplying halothane (Fluothane).

## References

1. Killip T, Gault JH: Mode of onset of atrial fibrillation in man. *Am Heart J* 70:172-178, 1965
2. Bennett MA, Pentecost BL: The pattern of onset and spontaneous cessation of atrial fibrillation in man. *Circulation* 41:981-988, 1970
3. Montgomery PR, Dresel PE: Conduction defects in experimental atrial arrhythmia. *Am Heart J* 88:191-197, 1974
4. Orias O, Bilbert JL, Siebens AA, et al: Effectiveness of single rectangular electrical pulses of known duration and strength in evoking auricular fibrillation. *Am J Physiol* 162:219-225, 1950
5. Hoff HE, Geddes LA: Cholinergic factor in auricular fibrillation. *J Appl Physiol* 8:177-192, 1955
6. Sano T, Scher AM: Multiple recording during electrically induced atrial fibrillation. *Circ Res* 14:117-125, 1964
7. Moe GK: Evidence for re-entry as a mechanism of cardiac arrhythmias. *Rev Physiol Biochem Pharmacol* 72:55-81, 1975
8. Atlee JL, Rusy BF: Atrioventricular conduction times and atrioventricular nodal conductivity during enflurane anesthesia in dogs. *ANESTHESIOLOGY* 47:498-503, 1977
9. Eger EI: *Anesthetic Uptake and Action*. Baltimore, Williams and Wilkins, 1974, p 5
10. Brownlee KA: *Statistical Theory and Methodology in Science and Engineering*. Second edition. New York, John Wiley and Sons, 1965, pp 299-303
11. Snedecor G, Cochran W: *Statistical Methods*. Sixth Edition. Ames, Iowa State University Press, 1967, pp 327-329
12. Scheffé H: *Analysis of Variance*. New York, John Wiley and Sons, 1959, pp 90-146
13. Ferrier GR, Dresel PE: Relationship of the functional refractory period to conduction in the atrioventricular node. *Circ Res* 35:204-214, 1974
14. Scheffé H: *Analysis of Variance*. New York, John Wiley and Sons, 1959, pp 261-290
15. Atlee JL, Alexander SC: Halothane effects on conductivity of the AV node and His-Purkinje system in the dog. *Anesth Analg (Cleve)* 56:378-386, 1977
16. Cranefield PF: Action potentials, after potentials and arrhythmias. *Circ Res* 41:415-423, 1977
17. Vassalle M: The relationship among cardiac pacemakers. *Circ Res* 41:269-277, 1977