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Anesthetics and Automaticity of Dominant and Latent Pacemakers in Chronically Instrumented Dogs

II. Effects of Enflurane and Isoflurane during Exposure to Epinephrine with and without Muscarinic Blockade

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Background: **Atrial dysrhythmias precede ventricular dysrhythmias during epinephrine-anesthetic sensitization, and may be caused by an altered relationship between automaticity of primary and subsidiary pacemakers. The following hypotheses were tested: (1) epinephrine-induced pacemaker shifts with enflurane or isoflurane require intact vagal reflexes and (2) these anesthetics sensitize the atrial myocardium to epinephrine-induced dysrhythmias.**

Methods: **Eight dogs were instrumented for chronic electrophysiologic investigation, including electrodes at the SA node, atrial appendages, right ventricle, and His bundle, and along the sulcus terminalis. After conscious-state testing, dogs were anesthetized with isoflurane or enflurane and exposed to epinephrine, with or without atropine methylnitrate. Eight-channel ECG recordings were analyzed before and during epinephrine infusions. Atrial pacemakers were assigned values 1–6 with increasing distance from the SA node, normalized and expressed as the site of earliest activation value (SEA).**

Results: **Epinephrine increased SEA values during enflurane or isoflurane anesthesia. Atropine enhanced this increase during enflurane anesthesia, but abolished the increase during isoflurane anesthesia. Enflurane increased SEA values only when combined with atropine. Isoflurane did not increase SEA values under any test conditions.**

Conclusions: **With enflurane, epinephrine-induced atrial pacemaker shifts in chronically instrumented dogs are caused by direct depression of SA node automaticity or a relative increase of automaticity in subsidiary atrial pacemakers. With isoflurane, pacemaker shifts are caused by reflex-induced vagal suppression of SA node automaticity and escape of latent pacemakers. Enflurane sensitizes the atrial myocardium to dysrhythmias when combined with muscarinic blockade; isoflurane does not sensitize the atrium. (Key words: Anesthetics: enflurane; isoflurane. Animal: dog, anesthetized. Heart: autonomic regulation; dysrhythmias; sinoatrial node; subsidiary atrial pacemakers. Hormones: epinephrine. Neurotransmitter: acetylcholine.)**

ANESTHETIC-EPINEPHRINE interactions are well known to result in ventricular dysrhythmias. In studies of anesthetic-catecholamine interactions, Atlee *et al.* reported that atrial dysrhythmias preceded ventricular dysrhythmias during ventricular sensitization with halothane,[1] enflurane, and isoflurane.[2] A variety of manifestations resulted, including wandering atrial pacemaker, atrial ectopy, and atrioventricular block with atrioventricular dissociation. Because cardiac dysrhythmias can be identified in the majority of patients when continuous methods are used for detection,[3] and because some patients may have hemodynamic compromise from these dysrhythmias, the understanding and prevention of dysrhythmias in the intraoperative setting remains clinically important. We have previously demonstrated that enhanced vagal tone caused by epinephrine-induced hypertension results in shifts in the site of earliest activation from the sinoatrial (SA) node to subsidiary atrial pacemakers, both in the conscious dog and during halothane anesthesia.[4] Halothane facilitated these atrial pacemaker shifts, thus "sensitizing" the atrial myocardium to supraventricular dysrhythmias.[4] In current practice, enflurane or isoflurane are used more frequently than halothane in adult patients, and are considered to be less sensitizing to the ventricular myocardium than halothane in humans[5] or in animals.[6,7] However, no *in vivo* studies have fo-

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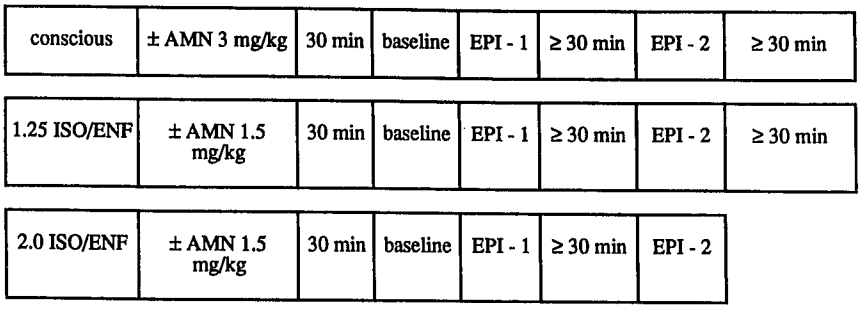

Fig. 1. Experimental protocol for testing with isoflurane (ISO) or enflurane (ENF) 1.25 and 2 MAC, epinephrine 1 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (EPI-1 and EPI-2, respectively), with (+) and without (−) atropine methylnitrate (AMN).

cused on their ability to promote atrial dysrhythmias. Evidence from *in vitro* studies from our laboratory shows that the atrial myocardium is sensitized to dysrhythmias by halothane[8] or isoflurane.[9] Atrial dysrhythmias with epinephrine and enflurane or isoflurane *in vivo* might be caused by enhanced automaticity in subsidiary atrial pacemakers relative to the SA node. Such an increase in automaticity could be explained by direct enhancement of automaticity in latent pacemakers relative to the SA node (independent of the vagus), or indirect enhancement (vagal suppression of the SA node) with escape of latent pacemakers. The following hypotheses were tested in a chronically instrumented dog model: (1) epinephrine produces atrial pacemaker shifts with enflurane or isoflurane anesthesia, (2) reflex-enhanced vagal tone secondary to epinephrine-induced hypertension with suppression of SA node automaticity would be the predominant mechanism if muscarinic blockade abolished these pacemaker shifts, and (3) enflurane or isoflurane exacerbate atrial pacemaker shifts observed with epinephrine alone *in vivo,* and, therefore, "sensitize" the atrial myocardium to supraventricular dysrhythmias.

Materials and Methods

The methodology is identical to that previously used by Woehlck *et al.*[4] Briefly, with approval of our Institutional Animal Care Committee, eight mongrel dogs (18–22 kg) were prepared for chronic electrophysiologic investigation by implanting epicardial electrodes and an indwelling aortic catheter. Through a right thoracotomy, electrode pairs were sutured to the atrial appendages and the ventricular apex. Five electrode pairs were sutured to the right atrium along the sulcus terminalis (ST), extending from near the SA node to the inferior vena cava.[10] A bipolar needle electrode was placed into the interventricular septum to record the His bundle electrogram.[11] The catheter and all leads were tunneled subcutaneously, exiting between the scapulae. Electrical signals were preamplified and filtered, and signal strength was individually adjusted. Lead II of the surface ECG and electrograms of the SA node, ST, left atrial appendage, and His bundle were recorded on a chart recorder. Systolic blood pressure (SBP) was continuously measured together with the heart rate (HR). A stimulator was used for cardiac pacing. Drugs were given in 0.9% saline solution, and epinephrine was administered with an infusion pump.

At weekly intervals, after completing conscious-state testing, anesthesia was induced *via* mask with inhalation of enflurane or isoflurane in oxygen, followed by tracheal intubation. End-tidal concentration of the anesthetics and P_{CO_2} were monitored by a mass spectrometer, and depth of anesthesia was maintained at the equivalent of 1.25 and 2 MAC.[12] Ventilation was controlled to keep end-tidal P_{CO_2} between 35 and 40 mmHg. Lactated Ringer's solution provided fluid requirements (3–5 $ml \cdot kg^{-1} \cdot h^{-1}$). After a 30-min equilibration, eight-channel paper recordings were obtained together with measurements of HR and SBP. As an indicator of automaticity, sinus node recovery time (SNRT) was determined by pacing the right atrial appendage (30 s at 200 and 250 beats/min, 2 msec pulse duration, 20 mA). Sinus node recovery time was measured from the last pacing spike to the first spontaneous atrial activity on the His bundle electrogram, after cessation of pacing. Epinephrine was infused at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min *via* a forelimb vein. Heart rate, SBP, and site of activation were allowed to return to baseline (>30 min) before infusing epinephrine at 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Data were recorded for 5 s at 15-s intervals during the second and third minute of the infusions. Atropine methylnitrate (AMN, 3 mg/kg) was administered for complete peripheral muscarinic blockade before conscious-state testing, and 1.5 mg/kg AMN was given 30 min before studies at 1.25 MAC,

and again before studies at 2 MAC (fig. 1). Anesthetized dogs were placed in the lateral decubitus position to avoid venous pooling.

Each heart beat occurring during the recording period was evaluated and assigned a score, corresponding to the earliest identifiable atrial origin, as follows: Score 1 = SA node; score 2 = high rostral sulcus terminalis (ST); score 3 = midrostral ST; score 4 = midcaudal ST; score 5 = low caudal ST; and score 6 = remote atrial. Some beats were of nonatrial origin (*i.e.*, His bundle or ventricular), and their incidence is presented as the percentage of all beats per condition (table 1). The fractions of beats from each atrial origin were multiplied by the corresponding scores (1–6). Products were summed and divided by the percentage of all beats of atrial origin. Thus, the resulting site of earliest activation value (SEA value, range 1–6) was independent of the number of nonatrial beats. Normal distribution was confirmed for baseline of SEA values, SNRT, SBP, and HR. The Kolmogorov-Smirnov test was used to identify differences in the distribution of SEA values. The incidence of nonatrial foci was compared by Friedman's test. Other variables were compared by paired Student's *t* test. Significance was identified at $P \leq 0.05$. Data are expressed as mean ± SEM.

Results

Effects of epinephrine and muscarinic blockade on SEA values are presented in figure 2, and the same data are arranged in a different way in figure 3 to present effects of the anesthetics.

Effects of Epinephrine

Epinephrine increased SEA values during enflurane anesthesia, but, during isoflurane anesthesia, epinephrine increased the SEA value only in the absence of atropine (fig. 2). At 2 MAC enflurane with muscarinic blockade, 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine caused the greatest increase in SEA value (fig. 2). Epinephrine increased the SBP under all test conditions (table 1). With muscarinic blockade, epinephrine increased the HR, but, in the absence of muscarinic blockade, epinephrine tended to decrease the HR during isoflurane anesthesia, and had little effect on HR during enflurane anesthesia (table 1). No ventricular beats occurred without exposure to epinephrine.

Effects of Anesthetics

Anesthetics Alone. Enflurane and isoflurane at 1.25 MAC both decreased the SEA value compared with control (conscious state, no epinephrine or atropine; table 1), and abolished the respiratory variability in HR and pacemaker origin present in the conscious state. Neither enflurane nor isoflurane altered HR or SNRT compared with control, but both anesthetics reduced SBP compared with the conscious state (table 1).

Anesthetics and Muscarinic Blockade. With muscarinic blockade present, neither anesthetic affected SEA values, although both agents reduced HR and SBP and prolonged SNRT (table 1). With isoflurane and muscarinic blockade, the HR decreased only at 2 MAC (table 1).

Anesthetics and Epinephrine, With and Without Muscarinic Blockade. With 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine and intact vagal reflexes, 1.25 MAC enflurane decreased the SEA value below the conscious state value (fig. 3). However, when vagal reflexes were blocked and epinephrine was infused, enflurane tended to increase the SEA value (fig. 3). Isoflurane had no effect on SEA values (fig. 3). With muscarinic blockade and 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ epinephrine, the SEA value was significantly less with isoflurane than with enflurane (fig. 4). In the absence of muscarinic blockade, the reduction in HR during exposure to epinephrine was less with enflurane than with isoflurane (table 1). However, with muscarinic blockade and exposure to epinephrine, enflurane decreased the HR more than isoflurane (table 1). Isoflurane tended to reduce the HR during exposure to epinephrine (table 1). With atropine and epinephrine, 2 MAC enflurane decreased the SBP compared with the conscious state (table 1). At 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with atropine and 1.25 MAC, enflurane (table 1) caused the least depression of SBP, but, in general, isoflurane caused the least depression of SBP response to epinephrine (table 1).

Dogs anesthetized with enflurane frequently exhibited AV block and ventricular escape beats at the beginning of epinephrine infusions, but mostly ventricular ectopic beats or bigeminy at the end of the infusions. During enflurane with atropine, all epinephrine-induced ventricular beats were premature ectopic beats. During epinephrine infusions, the atrial rate with 1.25 MAC isoflurane was often slowed to less than 40 beats/min, followed by ventricular escape beats with minimal ventricular aberration (fig. 5). No such escape beats were observed with isoflurane at 2 MAC or with isoflurane and muscarinic blockade. No His bundle beats occurred in the absence of epinephrine (table 1). With epinephrine, His bundle beats occurred more frequently with isoflurane at 1.25 MAC (fig. 5) than

Table 1. Sinoatrial Node Automaticity, Blood Pressure, and Nonatrial Beats Related to Epinephrine, Muscarinic Blockade, and Isoflurane or Enflurane

	Sinus Node Recovery Time (ms)							
	200 beats · min^{-1}	250 beats · min^{-1}	Epinephrine (μg · kg^{-1} · min^{-1})	SEA Value (range 1–6)	Systolic Blood Pressure (mmHg)	Heart Rate (beats · min^{-1})	His Bundle Beats (%)	Ventricular Beats (%)
Conscious Dogs	629 ± 49	639 ± 60	0	1.336 ± 0.125	145 ± 6	113 ± 6	0	0
			1	1.728 ± 0.197	191 ± 7*	114 ± 6	0.7	0
			2	1.919 ± 0.228	225 ± 8*	94 ± 7*	0.2	2.9
With AMN	401 ± 16†	405 ± 16†	0	1.16 ± 0.125	125 ± 3†	201 ± 7†	0	0
			1	1.356 ± 0.202	207 ± 13*†	210 ± 9†	0	0
			2	1.375 ± 0.249	236 ± 14*	232 ± 8*†	0	0.2
1.25 MAC enflurane	570 ± 40	502 ± 35	0	1.25 ± 0.164	95 ± 2‡	120 ± 5	0	0
			1	1.94 ± 0.37	206 ± 12*	109 ± 8	0	2.9
			2	1.74 ± 0.31	240 ± 11*	102 ± 5*	4.1	7.8
With AMN	808 ± 82†‡	615 ± 70†‡	0	1.47 ± 0.18	86 ± 4†‡	94 ± 5†‡	0	0
			1	1.896 ± 0.31	197 ± 12*	136 ± 10*‡	0	3
			2	1.58 ± 0.31	207 ± 9*	157 ± 13*†‡	1.8	9.5
2.0 MAC enflurane	676 ± 18	709 ± 28	0	1.375 ± 0.183	86 ± 4‡	104 ± 3	0	0
			1	2.16 ± 0.39	186 ± 12*	105 ± 3	0	1.8
			2	1.74 ± 0.3	210 ± 12*	122 ± 15	0	2.3
With AMN	926 ± 54†‡	898 ± 55†‡	0	1.483 ± 0.183	71 ± 4†‡	80 ± 4†‡	0	0
			1	2.74 ± 0.35	174 ± 11*‡	111 ± 7*‡	0	0.2
			2	1.9 ± 0.26	184 ± 12*†‡	126 ± 8*‡	0	6.9
1.25 MAC isoflurane	613 ± 58	583 ± 43	0	1.25 ± 0.164	93 ± 2‡	124 ± 5	0	0
			1	2.091 ± 0.421	200 ± 8*	75 ± 7*‡	10.1	4.3
			2	2.395 ± 0.354	230 ± 17*	74 ± 9*	8.6	11
With AMN	656 ± 40‡	679 ± 37‡	0	1.25 ± 0.164	93 ± 4‡	111 ± 4‡	0	0
			1	1.375 ± 0.262	222 ± 12*†‡	148 ± 5†‡	6.1	0
			2	1.313 ± 0.249	250 ± 10*	174 ± 8†‡	1.1	0
2.0 MAC isoflurane	674 ± 45	709 ± 64	0	1.375 ± 0.183	87 ± 5‡	106 ± 3	0	0
			1	2.16 ± 0.32	189 ± 9*	89 ± 7*‡	0	1
			2	1.99 ± 0.2	221 ± 14*	88 ± 12	0.3	0
With AMN	855 ± 38†‡	796 ± 69‡	0	1.375 ± 0.183	72 ± 5‡	85 ± 3†‡	0	0
			1	1.5 ± 0.247	191 ± 13*	114 ± 7*†‡	0	0
			2	1.58 ± 0.243	224 ± 14*	142 ± 9*†‡	6.1	0.1

Data shown mean ± SEM; n = 8. Data from the conscious state[4] are shown for purpose of comparison. Nonatrial beats are expressed as percentage of all beats per condition.

SEA = site of earliest activation; AMN = atropine methylnitrate; MAC = minimum alveolar concentration.

* $P < 0.05$ *versus* same condition without epinephrine.

† $P < 0.05$ *versus* same condition without AMN.

‡ $P < 0.05$ *versus* same condition without anesthesia.

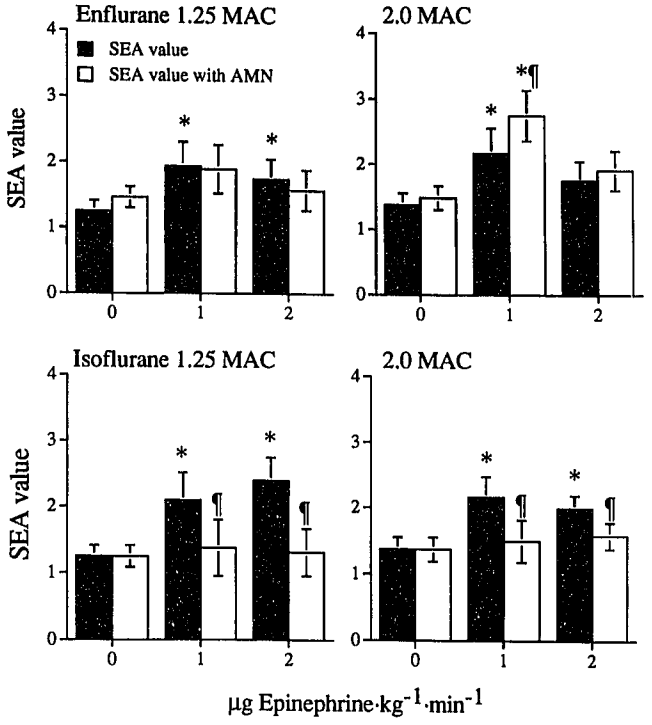

Fig. 2. Bar graphs depict effects of epinephrine on the site of earliest activation (SEA) value in enflurane or isoflurane anesthetized, chronically instrumented dogs and effects of muscarinic blockade by atropine methylnitrate (AMN). n = 8. Data are mean ± SEM. * *Versus* no epinephrine; ¶ *versus* no AMN.

with enflurane. Because only a subset of dogs (n = 3 of 8) was susceptible to developing this dysrhythmia, a statistically significant increase of His bundle beats beyond the conscious state was not achieved.

Effects of Muscarinic Blockade

With 1 μg epinephrine · kg^{-1} · min^{-1} and 2 MAC enflurane, muscarinic blockade increased the SEA value (fig. 2). Muscarinic blockade prevented the increase in SEA value observed with epinephrine and isoflurane (fig. 2). Without epinephrine, muscarinic blockade prolonged SNRT under both anesthetic agents and decreased HR and SBP under enflurane anesthesia. In contrast, during epinephrine infusions, muscarinic blockade generally increased HR and had variable effect on SBP (table 1).

Discussion

The first aim of this study was to evaluate the mechanisms for epinephrine-induced atrial pacemaker shifts under isoflurane and enflurane anesthesia. The second was to test these anesthetic agents for their ability to potentiate epinephrine-induced atrial dysrhythmias. Previously reported results for halothane anesthesia[4] were derived from the same group of dogs, and the order of halothane, enflurane, and isoflurane anesthesia was randomized for each dog. Thereby, increased comparability of data makes it more likely to identify differences in dysrhythmogenic potential of the three agents.

Atlee *et al.* found that, compared with halothane anesthesia,[1] enflurane and isoflurane[2] required more epinephrine to produce atrial ectopy, with isoflurane requiring the largest amount. Furthermore, Atlee *et al.*[1,2] reported that roughly similar doses of epinephrine were required to produce the onset of wandering atrial pacemaker, regardless of the inhalational agent. Enhancement of wandering atrial pacemaker or atrial ectopy by the anesthetics (*i.e.*, atrial sensitization)

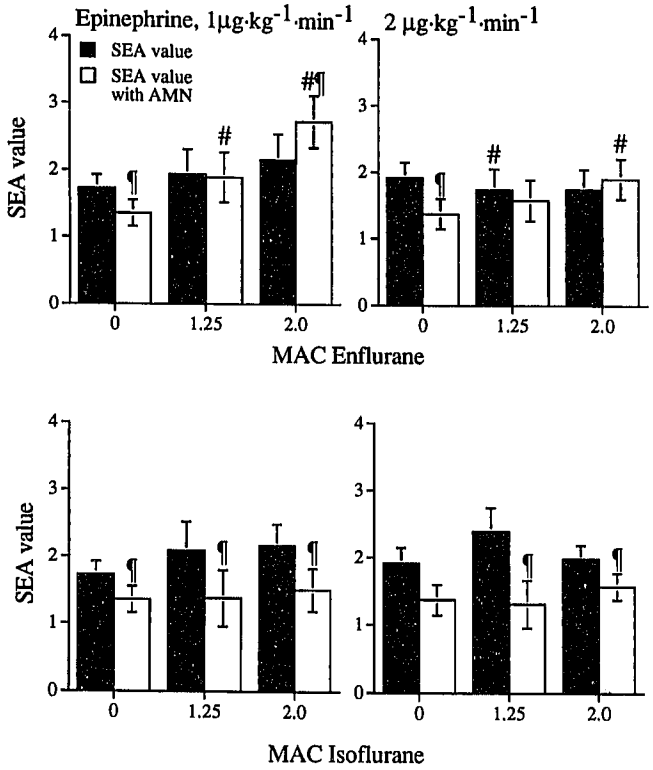

Fig. 3. Bar graphs depict effects of enflurane (*top*) or isoflurane anesthesia (*bottom*) on the site of earliest activation (SEA) values in chronically instrumented dogs and effects of muscarinic blockade by atropine methylnitrate (AMN). n = 8. Data are mean ± SEM. # *Versus* no enflurane/isoflurane; ¶ *versus* no AMN.

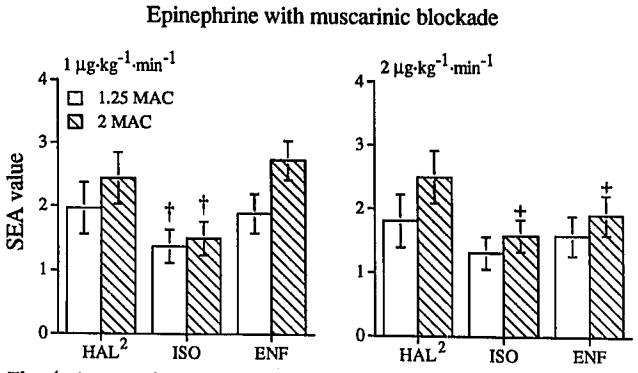

Fig. 4. Comparison of the site of earliest activation (SEA) values during anesthesia with halothane[4] (HAL, previously published data), isoflurane (ISO), and enflurane (ENF) in chronically instrumented dogs with muscarinic blockade, exposed to 1 and 2 μg epinephrine · kg^{-1} · min^{-1}. n = 8. Data are mean ± SEM. + *Versus* halothane; † *versus* halothane and enflurane.

could not be investigated in those studies, because of the lack of conscious-state data for comparison. Furthermore, none of these studies quantified the severity of atrial pacemaker shifts or the incidence of His bundle beats.

In the current study, epinephrine produced hypertension and bradycardia in isoflurane-anesthetized dogs, indicating a functioning baroreceptor reflex arc. As in the conscious state or with halothane,[4] this was accompanied by shifts from the SA node to increasingly remote pacemaker locations. Atropine prevented bradycardia and pacemaker shifts despite epinephrine-induced hypertension. This indicates that, as in the conscious state or with halothane,[4] atrial pacemaker shifts during isoflurane anesthesia can be attributed to epinephrine-induced hypertension and baroreflex-mediated suppression of SA node automaticity. We also conclude that, under isoflurane anesthesia and muscarinic blockade, no direct (nonvagally mediated) enhancement of automaticity in subsidiary atrial pacemakers relative to the SA node occurred, although epinephrine enhanced the spontaneous automaticity of the SA node. Vagal innervation is greater in the SA node region than in locations of subsidiary atrial pacemakers.[13,14] This implies that vagal activity may preferentially inhibit the SA node, allowing subsidiary pacemakers to escape and become dominant. Compared with the conscious state, isoflurane did not facilitate epinephrine-induced atrial pacemaker shifts under any test conditions. Thus, isoflurane did not sensitize the myocardium to epinephrine-induced atrial dysrhythmias *in vivo*.

Current findings for isoflurane differ considerably from *in vitro* results. Boban *et al.*[9] recently investigated effects of isoflurane and epinephrine (and norepinephrine) on the isolated, canine right atrium. They demonstrated that, without isoflurane, only 5 μg epinephrine/l (as well as norepinephrine) resulted in significant pacemaker shifts, but the addition of isoflurane potentiated pacemaker shifts with 2 and 5 μg epinephrine/l (and norepinephrine). Furthermore, epinephrine increased the atrial rate, although subsidiary pacemaker activation preceded that of the SA node.[9] It was concluded that enhanced automaticity in subsidiary atrial pacemakers could account for atrial dysrhythmias during isoflurane-epinephrine interaction.[9] Plasma levels during infusions of 1 and 2 μg epinephrine · kg^{-1} · min^{-1} *in vivo* (50–100 μg/l free fraction, confirmed in current experiments by random sampling)

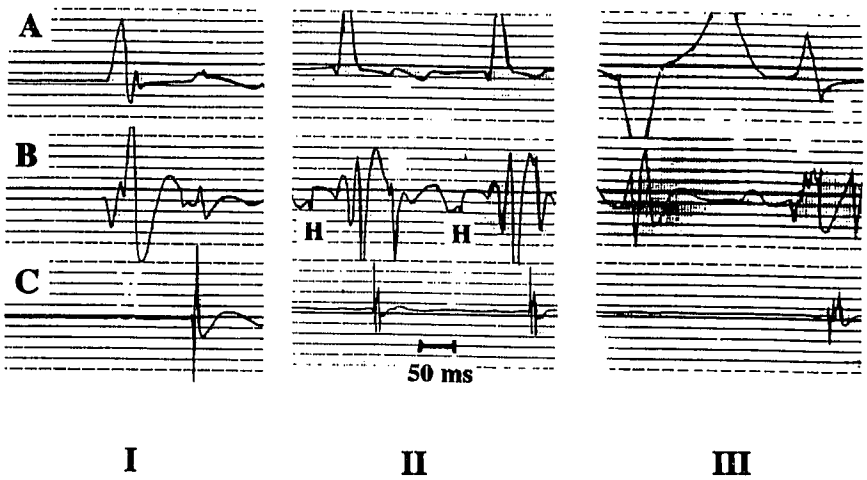

Fig. 5. Ventricular escape beat (I) at 1.25 MAC isoflurane and 2 μg epinephrine · kg^{-1} · min^{-1} as opposed to His bundle (H) beats (II) and polymorphic ventricular ectopic beats (III). Note that the signal of the H on panel I in *B* is missing. The QRS morphology on panel I in *A* is only slightly altered. *A* is a tracing from the surface electrocardiogram (lead II), *B* from the His bundle electrodes, and *C* from the SA node electrodes. Simultaneous recordings; paper speed = 200 mm/s.

exceed those used *in vitro* (2 and 5 μg/l perfusate) by a factor of 5–20. This is evidence that the *in vitro* canine right atrial preparation is more sensitive to epinephrine-isoflurane atrial dysrhythmias than the intact animal, possibly because of the lack of neurohumoral regulatory mechanisms *in vitro*.

Results under enflurane anesthesia appeared to be similar to those with isoflurane. Dogs anesthetized with 1.25 MAC enflurane developed epinephrine-induced hypertension, increase in pacemaker shifts, and a baroreceptor-mediated decrease in HR. In the presence of atropine, epinephrine caused equal hypertension, but resulted in a HR increase. We conclude, again, that vagal influences were blocked. However, the pacemaker shifts occurred independently from muscarinic transmission because, unlike with isoflurane or in the conscious state and with halothane,[4] atropine did not prevent them. This indicates that, during enflurane anesthesia, changes in vagal tone are not the predominant mechanism for epinephrine-induced atrial pacemaker shifts. Furthermore, these results invite the speculation that enflurane directly enhances subsidiary atrial pacemaker automaticity relative to SA nodal automaticity, rather than decreasing vagal tone, and, therefore, enhancing the automaticity of atrial pacemakers. As evidenced by changes in SNRT, enflurane caused the greatest direct (nonvagally mediated) depression of SA node automaticity. Preferential suppression of SA nodal automaticity is consistent with the marked prolongation of SNRT produced by enflurane with muscarinic blockade, but we cannot exclude that enflurane causes an absolute increase in subsidiary atrial pacemaker automaticity. Enflurane at 2 MAC reduced the SBP response to epinephrine; thus; it reduced the baroreflex-stimulus, which, in turn, can explain the lesser reduction of HR. However, enflurane also appeared to directly attenuate the baroreceptor reflex response, possibly with actions at various sites.[15,16,¶] Muscarinic blockade would be expected to have little effect on HR under these conditions. In contrast to results from conscious dogs and halothane[4] or isoflurane anesthesia, pacemaker shifts with 2 MAC enflurane and 1 μg epinephrine · kg^{-1} · min^{-1} were exacerbated by the addition of muscarinic blockade. This condition resulted also in the lowest HR and greatest SNRT of any test conditions with atropine. Direct depression of SA node automaticity by enflurane could be responsible for these effects.[17,18] As with 1.25 MAC, enhanced normal automaticity of subsidiary pacemakers relative to the SA node, or even an absolute increase in automaticity of subsidiary atrial pacemakers by enflurane, could account for our findings. Sensitization of atrial myocardium by enflurane without atropine was not verified in the current study, because pacemaker shifts during exposure to epinephrine were not facilitated by enflurane. In contrast, 1.25 MAC enflurane decreased pacemaker shifts at 2 μg epinephrine, which could be interpreted as desensitization or protection. However, when combined with muscarinic blockade, enflurane did increase epinephrine-induced pacemaker shifts. These results indicate a synergistic effect of muscarinic blockade and enflurane to sensitize atrial myocardium.

Johnston *et al.*[5] suggested that isoflurane and enflurane sensitize the human heart less to epinephrine-induced ventricular dysrhythmias than halothane. Joas and Stevens[6] and Sumikawa *et al.*[7] found equivalent tendencies for these agents to produce ventricular dysrhythmias in dogs. The authors have previously demonstrated that enhanced vagal tone caused by epinephrine-induced hypertension is the predominant mechanism for pacemaker shifts from the SA node to latent pacemakers in conscious dogs and during halothane anesthesia.[4] Comparing the current findings with previously reported results from halothane anesthesia,[4] we notice that, with muscarinic blockade and 1 μg epinephrine · kg^{-1} · min^{-1}, the SEA value was significantly less with isoflurane than with enflurane or halothane[4] (fig. 4). The SEA value with atropine and 2 μg epinephrine · kg^{-1} · min^{-1} was less with 2 MAC isoflurane or enflurane than with 2 MAC halothane[4] (fig. 4). We conclude that differences between halothane, enflurane, and isoflurane in sensitization of atrial myocardium exist, but are only significant in the absence of vagal influences on the heart. Under the latter condition, isoflurane appears to exert the least, enflurane an intermediate, and halothane the greatest atrial sensitization. Furthermore, in the presence of atropine, enflurane generally caused the greatest prolongation of SNRT and the lowest HR during exposure to epinephrine. Thus, enflurane caused the greatest direct, nonvagally mediated depression of SA node automaticity of all three agents. Enflurane and isoflurane depressed SBP during exposure to epinephrine less than halothane.[4] Assuming that a greater increase in SBP is followed by greater baroreceptor-mediated suppression of SA node automaticity, one would expect more severe

¶ Schmeling WT, Bosnjak ZJ, Kampine JP: Anesthesia and the autonomic nervous system. Seminars in Anesthesia IX 4:223–231, 1990.

atrial pacemaker shifts with enflurane or isoflurane than with halothane, adding further evidence that halothane exacerbates pacemaker shifts more than the other agents, because of a greater potential for sensitization. Consistent with our knowledge of ventricular sensitization, and in contrast to halothane[4] for which observed ventricular beats were overwhelmingly premature ectopic beats (abnormal automaticity), enflurane presented both ventricular escape (altered normal automaticity) and premature ectopic beats. With isoflurane, only ventricular escape, but no premature ectopic beats, were observed, probably because of isoflurane's lesser potential to sensitize the ventricles. As expected, ventricular escape occurred only with epinephrine-induced increase in SBP, and was completely abolished by atropine, regardless of the anesthetic, because it represents the ultimate response of sinoatrial pacemakers to increased vagal tone; *i.e.*, sinoatrial standstill. Beats during which P-waves dissociated from the QRS complex, but a His bundle signal preceded the QRS complex, were scored as His bundle beats. Although they occurred only in statistically insignificant numbers and in a subset of dogs, it is apparent that the overall incidence is somewhat less with enflurane than with isoflurane, which, in turn, is less than with halothane anesthesia.

In summary, the authors conclude the following. First, in chronically instrumented dogs anesthetized with enflurane or isoflurane, exposure to epinephrine causes shifts in site of earliest activation away from the SA node to latent pacemakers. Second, unlike in the conscious state,[4] or during isoflurane or halothane anesthesia,[4] vagal suppression of SA node automaticity in response to increased blood pressure with epinephrine does not appear to be the predominant mechanism for atrial pacemaker shifts during enflurane anesthesia. Instead, direct, selective depression of SA node automaticity and enhanced automaticity of subsidiary atrial pacemakers by enflurane are suggested as the mechanism. Third, enflurane sensitizes the atrial myocardium only with muscarinic blockade, whereas isoflurane does not sensitize to atrial dysrhythmias under any test condition. And, fourth, in contrast to halothane,[4] ventricular escape beats frequently emerge with isoflurane and epinephrine. With enflurane and epinephrine, both ventricular ectopic beats and ventricular escape beats occur.

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