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Anesthetics and Automaticity in Latent Pacemaker Fibers

IV. Effects of Isoflurane and Epinephrine or Norepinephrine on Automaticity of Dominant and Subsidiary Atrial Pacemakers in the Canine Heart

Mladen Boban, M.D.,* John L. Atlee III, M.D.,† Martin Vicenzi, M.D.,‡
John P. Kampine, M.D., Ph.D.,§ Zeljko J. Bosnjak, Ph.D.¶

Background: Anesthesia and surgery may be associated with atrioventricular junctional or ventricular rhythm disturbances. These may be caused by alteration of automaticity of primary and subsidiary pacemakers.

Methods: The direct effects of isoflurane, alone or in combination with epinephrine (E) and norepinephrine (NE), as well as single effects of E and NE, were examined on automaticity of primary and subsidiary atrial pacemakers (SAP) using a perfused canine right atrial preparation (n = 29). Preparations were perfused with oxygenated Krebs' solution at a constant perfusion pressure of 87 mmHg and a temperature of 36.5 ± 0.5° C. Delivered concentrations of isoflurane of 1.4 and 2.8% corresponded to measured perfusate concentrations of 315 ± 7 and 617 ± 16 μM in experiments with E (n = 14), and 316 ± 10 and 610 ± 26 μM in experiments with NE (n = 15). Epinephrine or NE perfusate concentrations were 2 and 5 μg/l or 5 and 10 μg/l, respectively. To determine the site of earliest activation, extracellular recordings were made from the SA node region and distal sites (approximately 1, 2, and 3 cm) along the sulcus terminalis, the previously reported locations of SAP. Sites of earliest activation shifts from SA node to SAP were scored 1, 2, or 3 depending on the distance from the control pacemaker. The summed shift scores (magnitude score) were normalized by dividing by the total number of preparations for each experimental condition.

Results: Exposure to isoflurane, NE, or E alone did not produce a significant increase in the incidence of pacemaker shifts or normalized pacemaker shift scores. Only the high dose of E significantly increased the incidence of pacemaker shifts and normalized shift scores. Dysrhythmogenic potential of E and NE tended to be greater after earlier exposure to isoflurane. Every combination of isoflurane with E or NE produced a significant increase in the incidence of pacemaker shifts and normalized shift scores.

Conclusions: It was concluded that isoflurane with E or NE acts synergistically to increase dysrhythmic potential in the atrial tissue. (Key words: Anesthetics, volatile; isoflurane. Animal: dog. Heart: arrhythmias; electrophysiology; sinus node; subsidiary atrial pacemakers. Sympathetic nervous system: catecholamines.)

AFTER removal¹⁻⁶ or suppression⁷⁻⁹ of the SA node, subsidiary atrial pacemakers (SAP) may assume control of the heart. Electrophysiologic properties of SAPs, however, are significantly different than those of the SA node.^{8,10-12} Subsidiary atrial pacemaker rhythms may be unstable and respond unpredictably to standard physiologic or pharmacologic perturbations.^{1,7}

Anesthesia and surgery often result in disturbances of atrial rhythm.^{13,14} Furthermore, ectopic atrial dysrhythmias have been reported to precede rhythm disturbances of ventricular origin during anesthetic-epinephrine sensitization.^{15,16} Whether enhanced automaticity of SAP explains these dysrhythmias is not known, but earlier results with halothane and epinephrine indicate this possibility.¹⁷

In this study, we examined single and combined effects of isoflurane, norepinephrine, or epinephrine on the location and rate of pacemaker activity in isolated, perfused canine right atrium.⁸ This model, developed by Rozanski *et al.*,⁸ and subsequently tested in our laboratory,¹⁷ makes possible functional studies of primary

* Postdoctoral Fellow, Department of Anesthesiology. Current position: University of Zagreb, Medical School in Split, Department of Pharmacology, Republic of Croatia.

† Professor of Anesthesiology.

‡ Research Associate, Department of Anesthesiology.

§ Professor and Chairman, Department of Anesthesiology.

¶ Professor of Anesthesiology and Physiology.

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Address reprint requests to Dr. Bosnjak: Medical College of Wisconsin, Anesthesia Research, MFRC, Room A1000, Milwaukee, Wisconsin 53226.

and SAPs within the distribution of SA node artery under more controlled conditions compared with *in vivo*. For example, possible confounding effects of extrinsic autonomic control and more remote latent pacemakers are removed. Isoflurane was tested because it causes similar depression of SA node function compared with halothane,¹⁸ but appears less sensitizing than halothane or enflurane under *in vivo* conditions.^{15,19-21} Additionally, at least in North America, isoflurane is the most commonly used volatile anesthetic. Norepinephrine was tested as a model for increased adrenergic neural input, and epinephrine as a model for anesthetic sensitization.

Materials and Methods

This research was approved by the Medical College of Wisconsin Animal Care Committee and conformed with standards set forth in the National Institutes of Health Guide for Care and Use of Laboratory Animals.

Mongrel dogs of either sex ($n = 29$) weighing 10–22 kg were anesthetized with sodium pentobarbital (30 mg/kg, intravenously). The heart, with at least 2 cm of superior vena cava, was quickly excised and immersed in cold, oxygenated (97% O₂/3% CO₂) Krebs' solution. The composition in mm of Krebs' solution was: NaCl, 134; KCl, 3.9; NaHCO₃, 16; NaH₂PO₄, 0.85; CaCl₂, 1.8; MgCl₂, 0.51; mannitol, 16; glucose, 5.5; and EDTA, 0.05 (an antioxidant for better preservation of epinephrine).

The sinoatrial (SA) node artery was cannulated with fluid-filled PE 50 tubing and the distribution of the perfusate flow to the SA node and suspected subsidiary atrial pacemaker (SAP) regions along the sulcus terminalis confirmed by inspection of the distribution of 0.1 ml of indocyanine green dye. If this was satisfactory, dissection of the right atrium was carried out during SA node artery perfusion with oxygenated, cold Krebs' solution, as described earlier.^{8,17} After dissection, the right atrial preparation was transferred to a 150-ml chamber and pinned to the Sylgard floor with the epicardial side face up. The SA node artery perfusion cannula was then switched to a second pump, which delivered warmed ($36.5 \pm 0.5^\circ\text{C}$) Krebs' solution gassed with 97% O₂/3% CO₂. This solution was passed through an in-line filter (5 μm pore size; Astrodisc, Gelman Scientific, Ann Arbor, MI). All preparations were perfused at a constant pressure of 87 mmHg. The perfusate flow rate was measured using an electromagnetic flow probe (Biotronix BL610-2A with Series 2000C extracorporeal

transducer, 1.5 mm ID; Biotronix Laboratories, Kensington, MD) placed into the SA node artery inflow line. The flowmeter was calibrated daily by collecting timed samples into a volumetric cylinder over a flow range of 0–24 ml/min. Finally, preparations were also superfused with the same warm, oxygenated Krebs' solution at 20 ml/min.

Four bipolar, extracellular recording electrodes (silver wire) were placed on the epicardial surface of the right atrium to record the site of earliest activation (SEA), which could be the SA node or one of three increasingly remote sites of SAP (approximately 1, 2, or 3 cm distal from the SA node) along the sulcus terminalis (fig. 1). Recorded signals were amplified, filtered, and continuously displayed on an image-storing oscilloscope (Tektronix 5A26N, 5B12N; Tektronix, Beaverton, OR) for analysis of spontaneous rate and SEA. Signals were filtered by a dual-filter system, 100 Hz High Pass Filter and 1,000 Hz Low Pass Filter. All measured variables were recorded on a high-resolution, fast-writing, eight-channel recorder (Astro-Med MT9500; Astro-Med, West Warwick, RI). Pacemaker shifts from SA node to SAP after exposure to the drugs were scored 1, 2, or 3 depending on the distance from the control pacemaker (fig. 2). A group pacemaker shift score, termed "magnitude score,"¹⁷ was then calculated by

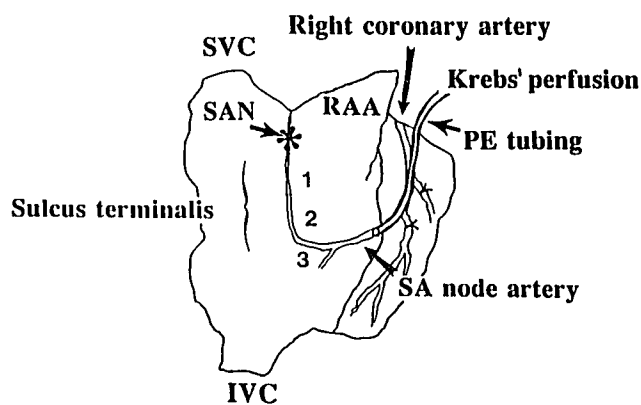


Fig. 1. Isolated, perfused, canine right atrial preparation with bipolar, extracellular recording electrode sites indicated. The perfusion cannula (PE tubing) is introduced *via* the right coronary artery and passed through to the SA node artery. The SA node (SAN) region, indicated by the asterisk, is normally the site of earliest activation (SEA). One electrode records from the SAN region. Three additional electrodes (1, 2, and 3) record from potential SAP sites approximately 1, 2 and, 3 cm distal to the SA node along the sulcus terminalis. These SAPs may become SEAs after exposure to drugs or other interventions. SVC = superior vena cava; IVC = inferior vena cava; and RAA = right atrial appendage.

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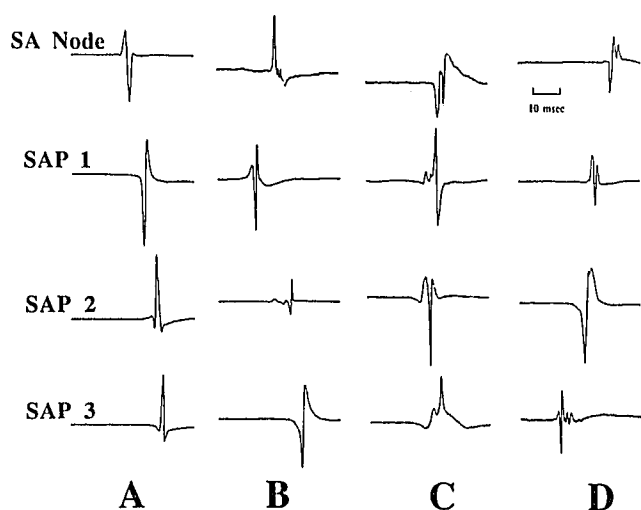


Fig. 2. Bipolar electrograms from the normal site of the earliest activation (SA node) and increasingly remote sites of SAPs (SAP 1, SAP 2, SAP 3; see fig. 1). (A) The SA node electrogram precedes all others, making the SA node the site of earliest activation (SEA) for that beat. (B) Subsidiary atrial pacemaker 1 is the SEA, with a pacemaker shift score of 1. (C) Subsidiary atrial pacemaker 2 is the SEA (shift score = 2). (D) Subsidiary atrial pacemaker 3 is the SEA (shift score = 3).

adding scores for all preparations exhibiting pacemaker shifts under each experimental condition. In turn, magnitude scores were normalized, termed "normalized score"¹⁷ by dividing the magnitude score by the total number of preparations evaluated for a particular experimental condition.

Isoflurane was delivered with the gas mixture, bubbled into perfusate, *via* a vaporizer. Superfusate did not contain isoflurane. At each experimental interval, 1 ml of the perfusate solution was collected at the inflow port of a cannulated artery into sealed, 2-ml vials for a head-space analysis of anesthetic concentration

by gas chromatography. Anesthetic was not measurable in perfusate, nor in superfusate, at the end of washout periods.

Protocol and Statistical Analysis

Preparations were exposed to 1.4 and 2.8% isoflurane, equivalent to 1 and 2 MAC for dogs.²² These concentrations produced measured isoflurane perfusate concentrations of 315 ± 7 and $617 \pm 16 \mu\text{M}$, respectively, in experiments with epinephrine (E) ($n = 14$). For experiments with norepinephrine (NE) ($n = 15$), measured isoflurane perfusate concentrations were 316 ± 10 and $610 \pm 26 \mu\text{M}$, respectively. Epinephrine perfusate concentrations were 2 and 5 $\mu\text{g/l}$, and those for NE were 5 and 10 $\mu\text{g/l}$. These concentrations of E and NE were shown, in pilot experiments, to produce comparable increases in spontaneous rate, irrespective of pacemaker location. Single and combined effects of isoflurane and E and NE were tested according to protocol sequence A or B (randomized) as shown in table 1. Preparations were randomized for order of initial exposure; *i.e.*, to isoflurane, or E or NE.

Heart rate data are provided as mean \pm SEM, and statistical differences for values obtained over the time course were determined by two-way analysis of variance (repeated measures). The incidence of pacemaker shifts was evaluated by Chi-square test. Differences in magnitude and normalized scores for each experimental condition were evaluated by two-way ANOVA and unpaired *t* test where appropriate. Changes were statistically significant when $P < 0.05$.

Results

Effects on Spontaneous Atrial Rate

Changes in atrial rate reported for any particular experimental condition do not take into account possible

Table 1. Study Protocol for Experiments with Epinephrine and Isoflurane

Protocol A	C1	2 $\mu\text{g/L}$ E	5 $\mu\text{g/L}$ E	C2	1.4% I	1.4% I 2 $\mu\text{g/L}$ E	1.4% I 5 $\mu\text{g/L}$ E	C3	2.8% I	2.8% I 2 $\mu\text{g/L}$ E	2.8% I 5 $\mu\text{g/L}$ E	C4	
Time (min)	15	5	5	15	15	5	5	15	15	5	5	15	
Protocol B	C1	1.4% I	C2	2 $\mu\text{g/L}$ E	5 $\mu\text{g/L}$ E	C3	1.4% I 2 $\mu\text{g/L}$ E	1.4% I 5 $\mu\text{g/L}$ E	C4	2.8% I	2.8% I 2 $\mu\text{g/L}$ E	2.8% I 5 $\mu\text{g/L}$ E	C5
Time (min)	15	15	15	5	5	15	5	5	15	15	5	5	15

A total of 2 or 5 mg/L epinephrine (E) and isoflurane (1.4% or 2.8% I) was given alone or in combination. Epinephrine was randomly given before (protocol A) or after (protocol B) exposure to isoflurane. C1-C5 represent control and washout intervals with no drug present in the perfusate. Similar randomization was used for experiments with norepinephrine (5 or 10 mg/L) and isoflurane.

differences in site of earliest activation (SEA). Initial values for spontaneous atrial rate were not different for preparations exposed to E or NE, regardless of protocol sequence (fig. 3). Both concentrations of E (2 and 5 $\mu\text{g/L}$) and NE (5 and 10 $\mu\text{g/L}$) produced a significant increase in atrial rate, whether alone or with isoflurane, as compared with 0 $\mu\text{g/L}$ E or NE, respectively. Increasing concentrations of isoflurane, alone or with E or NE, produced dose-dependent decreases in atrial rate.

Effects of Protocol Sequence on Pacemaker Shifts

Epinephrine and NE effects on magnitude and normalized pacemaker shift scores were minimal when these drugs were given before exposure to isoflurane; *i.e.*, protocol sequence A, table 1. Only two preparations exhibited pacemaker shifts (one out of seven from the E group, and one out of eight from the NE group), both to site 2 (shift score = 1), thus yielding a low normalized score value of 0.13 and 0.14, respectively (table 2). When E and NE were given after exposure to isoflurane, after 15 min of washout and return to the control value for atrial rate (protocol B, table 1), three out of seven preparations from the E and NE group exhibited pacemaker shifts with a normalized shift score of 0.57 (table 2).

Effects of Epinephrine, Norepinephrine, and Isoflurane on Magnitude and Normalized Pacemaker Shift Scores

Although there was a tendency of prior exposure to isoflurane to increase effects of catecholamines alone on magnitude and normalized shift scores (table 2), there was no significant difference between protocol sequences A and B on magnitude and normalized shift scores for any combination of isoflurane with epinephrine or norepinephrine. Therefore, results from the protocol sequences A and B were combined for the final data analyses.

Except for the highest concentration of E (5 $\mu\text{g/L}$), exposure to increasing concentrations of E or NE in the absence of isoflurane did not produce a significant increase in the incidence of pacemaker shifts or normalized pacemaker shift scores (table 3, fig. 4). Increasing concentrations of isoflurane without E or NE also did not affect the incidence of pacemaker shifts or normalized pacemaker shift scores. However, exposure to either concentration of isoflurane with E or NE caused a significant increase in the incidence of pacemaker shifts (table 3) and normalized pacemaker shift

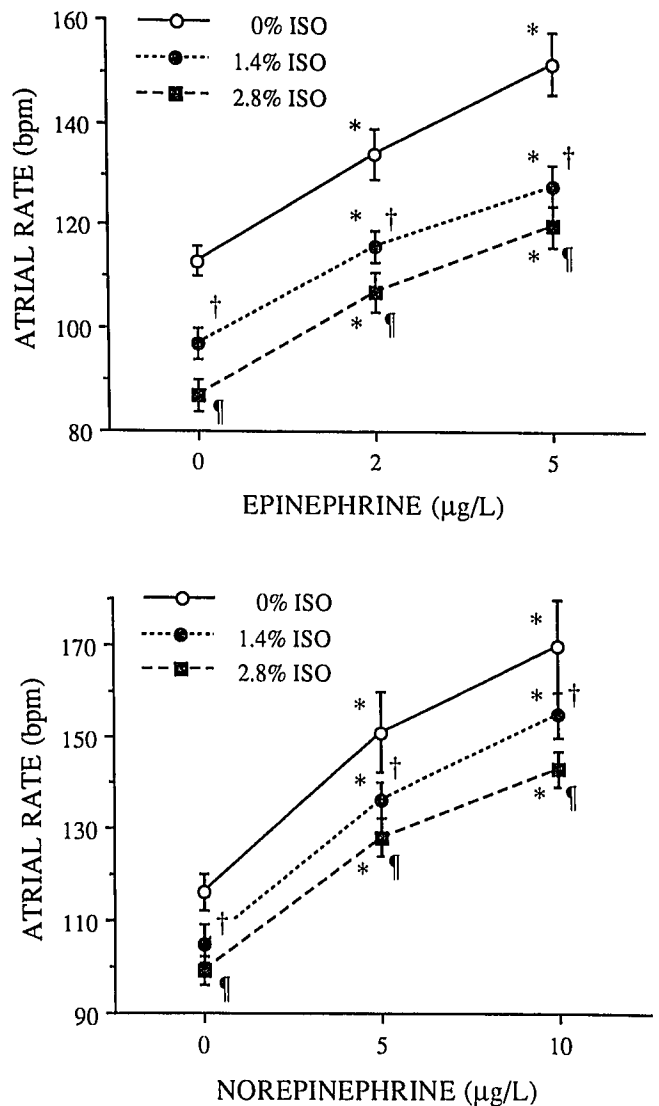


Fig. 3. Effects of epinephrine (top) and norepinephrine (bottom), alone or with 1.4 or 2.8% isoflurane (ISO) on spontaneous atrial rate, irrespective of pacemaker location. * $P < 0.05$ versus 0 $\mu\text{g/L}$ of epinephrine or norepinephrine; † $P < 0.05$ versus 0% of isoflurane; ‡ $P < 0.05$ versus 1.4% of isoflurane.

scores (fig. 4) compared with the absence of E or NE. Effects of E compared with NE on the incidence of pacemaker shifts and normalized pacemaker shift scores were not different during exposure to either concentration of isoflurane.

Discussion

The aim of these experiments was to determine the direct effects of isoflurane, E, and NE on relative au-

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Table 2. Incidence of Pacemaker Shifts and Summarized and Normalized Shift Scores Caused by Epinephrine and Norepinephrine When Given before or after Exposure to Isoflurane

	Norepinephrine				Epinephrine			
	Before Isoflurane (n = 8)		After Isoflurane (n = 7)		Before Isoflurane (n = 7)		After Isoflurane (n = 7)	
	5 µg	10 µg	5 µg	10 µg	2 µg	5 µg	2 µg	5 µg
Shift score	0	0	0	2	0	0	0	1
Shift score	0	0	2	0	0	0	1	1
Shift score	0	1	0	0	0	0	0	2
Shift score	0	0	2	2	1	1	0	0
Shift score	0	0	0	0	0	0	0	0
Shift score	0	0	0	0	0	0	0	0
Shift score	0	0	0	0	0	0	0	0
Shift score	0	0	—	—	—	—	—	—
Summarized shift score	0	1	4	4	1	1	1	4
Normalized shift score	0	0.125	0.57	0.57	0.14	0.14	0.14	0.57

automaticity of primary (SA node) or secondary pacemakers (SAPs along the sulcus terminalis) in a canine right atrial preparation. This was a model for determining electrophysiologic mechanisms for ectopic atrial rhythm disturbances occurring during epinephrine-anesthetic sensitization^{15,16} or for similar disturbances with sympathetic stimulation during anesthesia and surgery.^{13,14} This model excludes possible confounding effects of extrinsic autonomic and humoral control, as well as potential physiologic interference because of the enhanced discharge of lower (AV junctional, ventricular) pacemakers. Results indicate that isoflurane has only minimal potential to alter normal dominance of the SA node over SAP. Although E and NE had a tendency to produce pacemaker shifts, only higher doses of E induced a significant increase in incidence and normalized pacemaker shift score. Rozanski *et al.* also showed that NE increases automaticity of the SA node more than SAP.⁸ However, with isoflurane and either E or NE, SAP can assume dominance in many preparations, which may, in part, account for atrial ectopic rhythms with sensitization^{15,16} or with sympathetic stimulation during anesthesia and surgery.^{13,14}

Results of the current study are slightly different from those published previously in which halothane, E, and NE were tested in a perfused canine right atrial preparation.¹⁷ Namely, NE was also found to augment automaticity of SAP more than that of the SA node, and halothane neither opposed nor facilitated the ability of E or NE to cause pacemaker shifts to SAP. Variance between this and our earlier study¹⁷ may be caused by

procedural differences, aside from any differences caused by exposure to halothane or isoflurane, anesthetics known to differ in their sensitizing propensity.¹⁹⁻²¹ In this study, E and NE were administered before or after exposure to isoflurane (table 1). In our previous study with halothane,¹⁷ E and NE were given only after exposure to halothane. Normalized pacemaker shift scores in this study, in the absence of isoflurane, tended to be greater when E and NE were administered after earlier exposure to isoflurane (table 2). This indicates an effect of residual tissue isoflurane on atrial pacemaker automaticity (SA node *vs.* SAP), although the net atrial rate, *per se*, had returned to control levels after a 15-min washout period and there was no measurable anesthetic in the perfusate. Observed effects may simply be the result of incomplete washout of isoflurane, as well as a result of "aftereffects" of isoflurane on distinctive cellular mechanisms.

Table 3. Incidence of Pacemaker Shifts during Exposure to Isoflurane (I) and/or Epinephrine (E) and Norepinephrine (NE)

E (µg/L)	Preparations with Pacemaker Shift (n = 14)			NE (µg/L)	Preparations with Pacemaker (n = 15)		
	0% I	1.4% I	2.8% I		0% I	1.4% I	2.8% I
0	0	1	3	0	0	0	1
2	2	6*†	9*†	5	2	6*	7*†
5	4*	9*	12*†	10	3	6*	8*†

* $P < 0.05$ versus 0 µg/L NE or E.

† $P < 0.05$ versus 0% isoflurane.

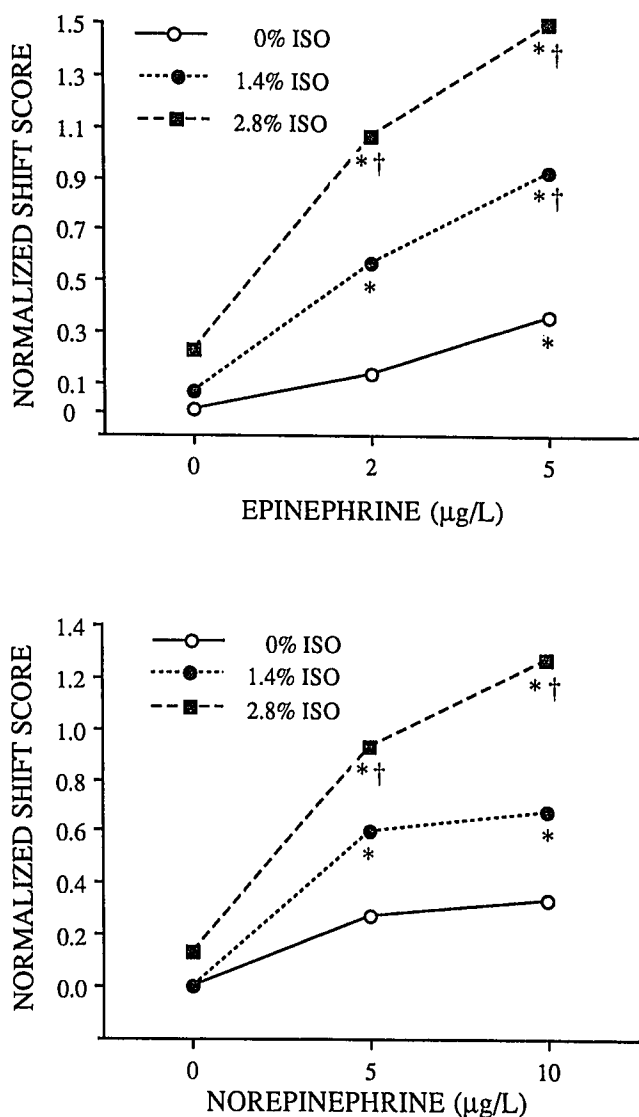


Fig. 4. Effects of epinephrine (top) and norepinephrine (bottom), alone or with 1.4 or 2.8% isoflurane (ISO), on normalized pacemaker shift scores. * $P < 0.05$ versus 0 µg/L of epinephrine or norepinephrine; † $P < 0.05$ versus 0% of isoflurane.

Similar observations of residual isoflurane and halothane effects have been reported in studies of vascular smooth muscle responsiveness, even after much longer washout periods than ours.^{23,24} Because the order of halothane and E or NE was not randomized in our previous work,¹⁷ it is possible that residual halothane could have skewed results in favor of E and NE to augment automaticity of SAP compared with SA node.

Another difference between this and the previous study¹⁷ that could account for different results concerns

the perfusion methods. In the current study, preparations were perfused at constant pressure; however, in the halothane study, constant flow (4–5 ml/min) was used. Measurements of the perfusate flow rate in this study revealed somewhat larger variability, ranging from 5–12 ml/min (data not shown), depending on the size of the preparation and the number of branches from the SA node artery. Variability in the flow rate was further increased when isoflurane, a known coronary vasodilator,^{25,26} was added. Thus, we speculate that perfusion in the constant flow mode, at the level of 4–5 ml/min, may not have provided stable and adequate perfusion of the SA node area required for the stable SA node activity in these preparations.⁸

Every combination of isoflurane with E or NE produced a significant increase in the incidence and severity (normalized magnitude score) of pacemaker shifts in these experiments (table 3, fig. 4), indicating a synergistic action of isoflurane and E or NE to increase dysrhythmic potential in the atrial tissue. These results would also indicate, if applicable *in vivo*, that SAP located along the sulcus terminalis may account, in part, for ectopic atrial rhythm disturbances with anesthetic sensitization and increased sympathetic activity. Although human¹⁹ and *in vivo* dog studies^{15,16,20,21} indicate that isoflurane is less sensitizing than halothane to epinephrine as far as ventricular dysrhythmic potential is concerned, atrial dysrhythmic potential (dogs, *in vivo*) appears to be nearly the same.^{15,16} It is unknown which cellular mechanisms are responsible for altered dominance of the SA node over SAP during exposure to isoflurane with E or NE. The most important ionic currents underlying automaticity in SA node²⁷ and SAP^{11,12} cells are Ca^{2+} current, K^+ outward current, and hyperpolarization-activated inward current. It is possible that the relationships between these currents, and, thereby, automaticity of the cardiac pacemaker cells, are intimately related to the intracellular Ca^{2+} handling.^{12,27} Because isoflurane is known to strongly interfere with the inward Ca^{2+} current²⁸ and Ca^{2+} transient²⁹ in ventricular muscle, we believe that investigation of isoflurane and catecholamine effects on Ca^{2+} current and transient in SA node and SAP cells are required to determine the mechanism for isoflurane-catecholamine-induced pacemaker shifts in the atria.

Another question concerning interpretation of current results is based on evidence presented by Boineau *et al.*^{30,31} Their data indicate that primary pacemaker activity has a multicentric, rather than unifocal (SA node), origin; namely, primary pacemaker activity ap-

pears to arise in at least three different, and widely separated, sites, encompassing an area three to four times that of the SA node. Furthermore, Boineau *et al.* have used electrophysiologic mapping techniques to show that the site of earliest activation (SEA) moves between these points, with the SEA related to the changes in heart rate. This leads to the question of whether observed SAP activity in this study is a part of a normal, multicentric pacemaker complex. If so, could changes in atrial rate alone be responsible for observed pacemaker shifts from the SA node to SAP? Although we have not used electrophysiologic mapping methods as elaborate as those used by Boineau *et al.*, our results do not support the contention that pacemaker shifts to SAP in our preparation were produced because of changes in heart rate alone. Namely, within the maximal range of observed changes in atrial rate caused by NE or isoflurane alone, we did not observe a significant number of pacemaker shifts. However, our results are compatible with a multicentric origin for the atrial pacemaker complex, because waveforms recorded at the SA node electrode (electrode No. 1) very often altered in their appearance with changes in atrial rate, although pacemaker shift toward distal electrodes did not occur. Therefore, we cannot exclude the notion that effective heart rate is determined by a group of potential pacemakers with the highest rate of discharge (automaticity) at a particular moment in time.

In summary, the results of this study indicate that, during exposure to epinephrine or norepinephrine in the presence of isoflurane, SAP located along crista terminalis may assume pacemaker control of the atria. If applicable to intact hearts and humans, this may explain some ectopic atrial rhythm disturbances observed during clinical anesthesia and surgery. Possible involvement of other areas with potential SAP activity, including the like coronary sinus,³² Bachmann's bundle,^{2,3} atrial plateau fibers³³ or the atrioventricular valve leaflets,³⁴ was not excluded by this study. Therefore, isoflurane cannot be expected to oppose disturbances of atrial rhythm caused by exogenous epinephrine or enhanced adrenergic tone. It is important to note that it appears that even residual isoflurane in myocardial tissue may potentiate dysrhythmogenic effects of catecholamines. Confirmatory studies in intact dogs would substantiate our belief that enhanced automaticity of SAP may be a plausible electrophysiologic mechanism for atrial ectopic rhythms during anesthesia and surgery.

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