

Anesthetics and Automaticity in Latent Pacemaker Fibers

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

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Knowledge of anesthetic effects on the automaticity of dominant and subsidiary cardiac pacemakers is fundamental to an understanding of mechanisms of arrhythmia during anesthesia, as well as to the management of patients with sinus node dysfunction or atrioventricular (AV) conduction block. Among potential pacemakers of the heart are subsidiary atrial pacemakers (SAP), which are located outside the classic sinoatrial (SA) node region but still within the right atrium. SAP have a higher inherent rate of automaticity than AV junctional pacemakers, may contribute to a multicentric atrial pacemaker complex, and can control the rhythm of the heart when the SA node is absent or inhibited. How halothane, epinephrine (E), or norepinephrine (NE), alone or in combination, would affect the relation between the automaticity of the SA node and SAP was tested using an isolated, perfused canine right atrial preparation ($n = 78$). This preparation was perfused *via* the SA node artery with Krebs' solution ($36.0 \pm 0.5^\circ \text{C}$) equilibrated with 97% oxygen-3% carbon dioxide. Delivered concentrations of halothane of 1 or 2% corresponded to measured perfusate concentrations of 0.50 ± 0.02 or 0.80 ± 0.04 mM in experiments with E ($n = 24$) and 0.45 ± 0.02 or 0.75 ± 0.04 mM in experiments with NE ($n = 54$). E or NE perfusate concentrations were 1, 2, and 5 $\mu\text{g/l}$ or 2, 5, and 10 $\mu\text{g/l}$, respectively. To determine the site of earliest activation (SEA), 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. For control (absence of drugs), SEA was always the SA node. Alone, 1 or 2% halothane did not produce a significant number of pacemaker shifts to SAP sites. Without halothane, increasing concentrations of E or NE did produce shifts in SEA to SAP sites ($P < 0.05$). The magnitude of shifts to increasingly distal sites (1, 2, or 3) was normalized per number of experiments to produce a normalized magnitude score. The effect of increasing E or NE to increase normalized magnitude scores was not affected by exposure to 1 or 2% halothane. It is concluded that E or NE augment the automaticity of SAP more than that of the SA node, with or without halothane. Further, ectopic atrial rhythms with halothane require E or augmented adrenergic tone (NE). (Key words: Anesthetics, volatile: halothane. Animal: dog. Heart: arrhythmias; electrophysiology; normal automaticity; sinus node; subsidiary atrial pacemakers. Hormones: epinephrine; norepinephrine.)

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IT IS WIDELY BELIEVED that pacemakers within the atrioventricular (AV) junctional region are most likely to control the heart's rhythm in the absence of a functioning sinoatrial (SA) node. This notion is supported by experiments of James *et al.*,¹ Urthaler *et al.*,² and others³⁻⁷ in which nutrient arteries supplying the SA node or AV junctional region were selectively perfused with negative or positive chronotropic substances.¹⁻⁷ Selective perfusion of the SA node artery by negative chronotropic substances to permit emergence of secondary pacemakers located within the AV junctional region, however, assumes exclusive SA node distribution of the negative chronotrope.⁸ This is probably not the case, since injection of contrast medium,⁹ radioactive microspheres,¹⁰ and vitally staining dyes¹¹ into the SA node artery demonstrates distribution of blood *via* this artery to other potential pacemaker sites—namely, the subsidiary atrial pacemakers (SAP)—located along the sulcus (crista) terminalis and in the inferior right atrium at its junction with the inferior vena cava.⁸

Several groups of investigators have shown that after removal of the SA node, pacemaker activity still resides within the right atrium.¹²⁻²² Electrophysiologic mapping experiments by Boineau *et al.*²³⁻²⁵ and others support the existence of SAPs and are consistent with the idea that primary pacemaker function is provided by a pacemaker network including the SA node and SAPs—a multicentric atrial pacemaker complex.²³⁻²⁶ The cellular electrophysiology of SAPs, including pacemaker mechanisms, autonomic regulation, and electrotonic influences, as well as the possible role of SAPs in atrial electrical dysfunction, have recently been reviewed in depth elsewhere.²⁷

An alteration in the function of primary and secondary atrial pacemakers might be involved in the genesis of arrhythmias during anesthesia and surgery,²⁸ as suggested by the appearance of ectopic atrial arrhythmias prior to the development of ventricular arrhythmias during epinephrine-anesthetic sensitization.^{29,30} The current experiments were performed to determine the effects of halothane, epinephrine (E), or norepinephrine (NE), alone or in combination, on the rate and location of pacemaker activity in a perfused canine right atrial preparation. This preparation included primary and secondary pacemakers within the distribution of the SA node artery.²¹ In particular, we wished to determine the site of earliest activation (SEA) during perfusion with increasing concentrations of NE (as a model for increased adrenergic neural

input) or E (as a model for anesthetic sensitization). Halothane was the anesthetic selected for testing since it is known to decrease SA node automaticity³¹ as well as to facilitate E arrhythmias.²⁹ We believed that this approach would further our knowledge of mechanisms of arrhythmias, especially such common disturbances as atrial ectopic and AV junctional rhythms,³² during anesthesia and surgery.

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 ($n = 78$) 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% oxygen–3% carbon dioxide) Krebs solution. The Krebs' solution in all experiments contained the following components (in millimolar concentration units): NaCl = 137, KCl = 3.8, NaHCO₃ = 11.9, NaH₂PO₄ = 0.33, CaCl₂ = 1.8, MgCl₂ = 1.05, mannitol = 16, glucose = 11, and EDTA = 0.05; the pH was 7.4 units.

The SA node artery was cannulated with saline-filled polyethylene size-50 tubing, and the distribution of blood flow to the SA node and suspected subsidiary atrial pacemaker (SAP) regions was confirmed by inspection of the distribution of 0.1 ml indocyanine green dye. If this was satisfactory, dissection according to the method of Woods *et al.*³³ and Rozanski *et al.*²¹ was carried out during SA node artery perfusion with oxygenated Krebs solution at 2–4 ml/min. Ventricular tissue was removed by a cut 1–2 cm below the AV groove. The right atrium was then opened by an incision along the tricuspid valve and up along the superior vena cava. The AV node, coronary sinus, and all left atrial tissue up to the interatrial septum then was removed. The remaining tissue consisted of the anterior free wall of the atrium, including the atrial appendage, a portion of the interatrial septum, and a small rim of right ventricular tissue containing the isolated right coronary artery.

This right atrial preparation was then transferred to a 150-ml chamber and pinned to the silastic 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% oxygen–3% carbon dioxide. Perfusion pressure

was maintained at 100 mmHg and flow rates at 4–5 ml/min throughout the experiments. The preparation was also superfused with the same, warm, oxygenated Krebs' solution at 20 ml/min.

Four bipolar, extracellular recording electrodes (silver wire) were used to record the SEA, which could be the SA node or one of three increasingly remote sites of SAP (approximately 1, 2, and 3 cm distal from the SA node) along the sulcus terminalis (fig. 1). Electrodes were placed on the endocardial surface and coupled by silver–silver chloride wire to individual preamplifiers. Electrograms were recorded on frequency-modulation (FM) tape (AR Vetter Co., Rebersburg, PA) for later analysis of spontaneous rate and the SEA. If the SEA was not the SA node but rather one of the SAP sites after exposure to E, NE, or halothane, then such pacemaker shifts were scored 1, 2, or 3, depending on the SEA (for instance, a shift to remote site 1 would receive a score of 1). For preparations exhibiting pacemaker shifts with any of the experimental interventions (E, NE, or halothane), the magnitude of shifts was calculated by adding the score (1, 2, or 3) for all preparations with pacemaker shifts from the SA node; the result was the magnitude score. In turn, each magnitude score was normalized by dividing its value by the total number of preparations evaluated for a particular experimental condition.

Preparations were exposed to 1 or 2% halothane from a calibrated vaporizer. These concentrations were equivalent to measured perfusate concentrations of 0.50 ± 0.02 or 0.80 ± 0.04 mM, respectively, in experiments with E

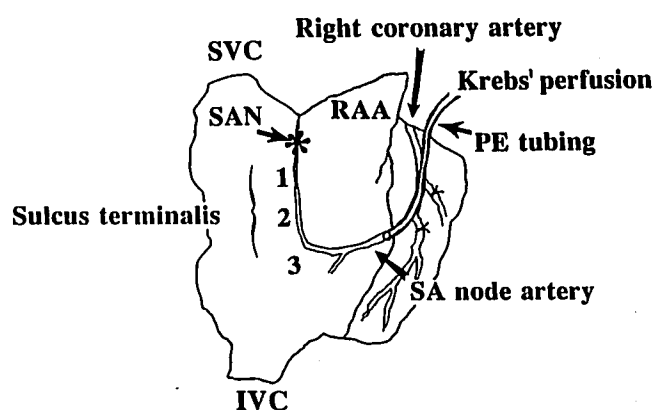


FIG. 1. Isolated, perfused, canine right atrial preparation with bipolar, extracellular recording electrode sites indicated. The perfusion cannula (PE tubing) is introduced via the right coronary artery and is passed through to the SA node artery. The region indicated by the asterisk is the normal site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

** Public Health Services, National Institutes of Health: Guide for Care and Use of Laboratory Animals. NIH Publication no. 85-23, revised 1985.

($n = 24$). For experiments with NE ($n = 54$), measured superfusate concentrations for halothane (1 and 2%) were 0.45 ± 0.02 and 0.75 ± 0.04 mM, respectively. E perfusate concentrations were 1, 2, and 5 $\mu\text{g/l}$, and those for NE were 2, 5 and 10 $\mu\text{g/l}$. These concentrations of E and NE in pilot experiments had produced comparable increases in spontaneous rate. In addition, higher E or NE perfusate concentrations produced no further increase in pacemaker shifts, magnitude scores, or normalized magnitude scores based on the results of pilot experiments. The sequence of the protocol for E is outlined in table 1; the same sequence was used for NE.

Experiments with E or NE lasted as long as 2 h, during which time preparations were exposed to 1 or 2% halothane, alone or with any of the three concentrations of E or NE. Heart rate data are provided as means \pm standard errors of the means, and statistical analysis was performed by analysis of variance and paired or unpaired t tests, as appropriate. Statistical significance was assigned at $P < 0.05$.

Results

SPONTANEOUS HEART RATE

Results for the effect of E or NE, alone or with 1 or 2% halothane, on spontaneous heart rate are summarized in figures 2 (for E) and 3 (for NE). In the absence of halothane (control), all concentrations of E (1, 2, and 5 $\mu\text{g/l}$) and NE (2, 5, and 10 $\mu\text{g/l}$) increased heart rate, irrespective of the SEA. Similarly, heart rate was increased in the presence of 1 or 2% halothane by all concentrations of E or NE. In the absence of E or NE, heart rate was decreased by 1 or 2% halothane. With E present (fig. 2), heart rate was decreased only by 2% halothane. In experiments with NE (fig. 3), heart rate was decreased only by 2% halothane for the lower NE concentration and by both 1 and 2% halothane for the two higher NE concentrations. The numbers of preparations used to generate each data point for heart rate (figs. 2 or 3) can be obtained from tabulated data for pacemaker shifts and severity scores (below).

PACEMAKER SHIFTS AND MAGNITUDE SCORES

Pacemaker shifts from the SA node to SAP sites are tabulated for experiments with E in table 2 and for experiments with NE in table 3. Tables 2 and 3 provide the number of preparations exhibiting shifts per number of preparations tested for each experimental condition, as well as the summed magnitude scores (sum of shifts to sites 1, 2, or 3) and normalized magnitude scores (magnitude scores divided by number of preparations tested). In figure 4, the effects of E (fig. 4A) and NE (fig. 4B), alone or with 1 or 2% halothane, on normalized magnitude scores are compared. Figure 5 illustrates the effects of halothane and NE on sites of pacemaker activity in one preparation, based on which electrode site was the SEA for each test condition. Under control conditions, SEA was always in the SA node region. Exposure to increasing concentrations of E (table 2) or NE (table 3) produced a dose-dependent increase in the number of pacemaker shifts to more distal electrode sites, the reported location of SAPs.^{11,14,15,18-21} This increase in pacemaker shifts with E or NE was also reflected by increased magnitude scores and normalized magnitude scores (tables 2 and 3; fig. 4). Halothane alone produced a small number of pacemaker shifts, but normalized magnitude scores for such shifts were not significantly different from control. In addition, halothane had little effect on the likelihood of pacemaker shifts with E (table 2) or NE (table 3) or on magnitude scores or normalized magnitude scores with E or NE (tables 2 and 3; fig. 4).

Discussion

Our results suggest that E or NE augments automaticity more in the SAP than in the SA node. This is based on our observation of pacemaker shifts, in response to increasing concentrations of E or NE, from the SA node to reported SAP sites along the sulcus terminalis.^{11,14,15,18-21} The addition of 1 or 2% halothane, which alone had little effect to alter the relation between automaticity of the SA node and SAP, neither significantly opposed nor facilitated the effects of E or NE to produce atrial pacemaker shifts.

TABLE 1. Protocol for Experiments with Epinephrine, with or without Halothane

Time	C ₁ 15	1% H 15	C ₂ 15	1 $\mu\text{g/l}$ E 5	2 $\mu\text{g/l}$ E 5	5 $\mu\text{g/l}$ E 5
Time	1% H + 1 $\mu\text{g/l}$ E 5	1% H + 2 $\mu\text{g/l}$ E 5	1% H + 5 $\mu\text{g/l}$ E 5	C ₃ 15		
Time	2% H 15	2% H + 1 $\mu\text{g/l}$ E 5	2% H + 2 $\mu\text{g/l}$ E 5	2% H + 5 $\mu\text{g/l}$ E 5	C ₃ 15	

Epinephrine concentrations were 1, 2, or 5 $\mu\text{g/l}$, with or without 1 or 2% halothane (H). C₁, C₂, and C₃ refer to the times used for control

measurements, after washout of drugs.
H = halothane; E = epinephrine.

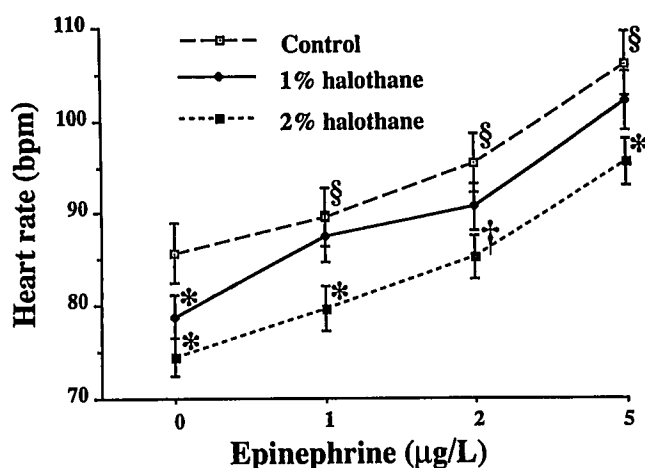


FIG. 2. Effect of epinephrine, alone (control) or with 1 or 2% halothane, on spontaneous heart rate. Comparisons with halothane are against control and the same concentration of epinephrine. Data points are shown with their respective standard errors. * $P < 0.001$ versus control or 1% halothane; † $P < 0.005$ versus control or 1% halothane; § $P < 0.001$ versus 0 $\mu\text{g/l}$ epinephrine. $n = 15-20$ (see table 2).

Rozanski and co-workers have reported, in contrast to our current findings, that NE augments automaticity of the SA node more than that of SAP.²¹ Their preparation was similar to ours except that automaticity of the SAP in response to NE was evaluated after exclusion of pacemakers within the SA node region. Exclusion of these pacemakers was produced by ligation of the portion of the SA node artery or its branches supplying the SA node region. Thus, changes in automaticity of the SA node or SAP in response to chronotropic interventions (including

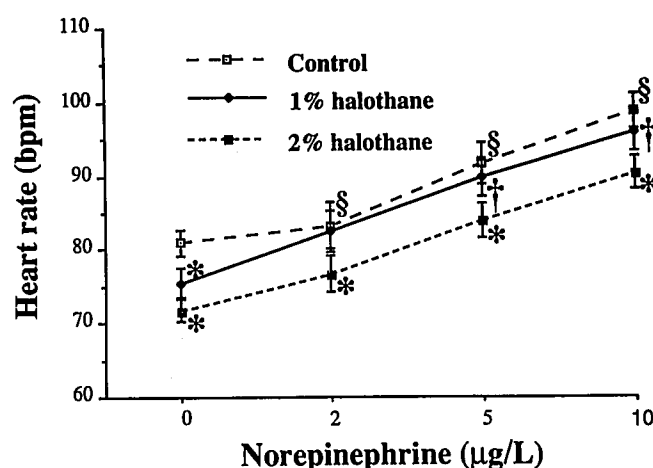


FIG. 3. Effect of norepinephrine, alone (control) or with 1 or 2% halothane, on spontaneous heart rate. Comparisons with halothane are against control and the same concentration of norepinephrine. Data points are shown with their respective standard errors. * $P < 0.001$ versus control; † $P < 0.05$ versus control; § $P < 0.001$ versus 0 $\mu\text{g/l}$ norepinephrine. $n = 22-44$ (see table 3).

TABLE 2. Pacemaker Shifts per Number of SA Node Preparations

E ($\mu\text{g/l}$)	Shifts/SA Nodes (Magnitude Score)			Normalized Score		
	E	1% H	2% H	E	1% H	2% H
0	0	1/24 (2)	3/24 (6)	0	0.08	0.25
1	0/15 (0)	1/17 (3)	3/19 (6)	0	0.17	0.31
2	4/17 (7)	4/20 (7)	7/22 (12)	0.41*	0.35*	0.54*
5	6/19 (11)	4/22 (7)	5/24 (9)	0.57*	0.31*	0.37*

Shown are magnitude scores (parentheses) and normalized magnitude scores for experiments with epinephrine (EPI), with or without 1 or 2% halothane (H).

* $P < 0.05$ versus 0% H and 0 $\mu\text{g/l}$ E.

acetylcholine)²¹ were not in concert, as they were in our preparation. Consequently, the results of the two experiments cannot be strictly compared, and we are left with the impression that when both groups of pacemakers (SA node and SAP) are present and viable, increased adrenergic neural input—NE or E—produces equivalent or augmented increases in the automaticity of SAP compared to that of the SA node.

Furthermore, based on our current findings, clinically useful concentrations of halothane should not be expected to alter the effect of NE or E to produce a preferential increase in the automaticity of SAP. Our current experiments, however, did not include testing for possible effects of other chronotropic interventions (e.g., acetylcholine, adenosine, calcium channel, or β -adrenergic blockers) on the relation between automaticity of the SA node and SAP. Data of Rozanski *et al.*²¹ suggest, as for NE, that SAP are more suppressed by acetylcholine than the SA node; again, however, SAP responses to acetylcholine were tested in the absence of a functioning SA node.²¹

TABLE 3. Pacemaker Shifts per Number of SA Node Preparations

NE ($\mu\text{g/l}$)	Shifts/SA nodes (magnitude score)			Normalized Score		
	NE	1% H	2% H	NE	1% H	2% H
0	0	0/22 (0)	3/38 (3)	0	0	0.12
2	1/22 (2)	0/22 (0)	4/22 (5)	0.09	0	0.22
5	8/27 (16)	9/27 (18)	11/27 (13)	0.59†	0.66†	0.48†
10	19/44 (39)	11/24 (19)	17/39 (29)	0.89*	0.88*	0.74*

Shown are magnitude scores (parentheses) and normalized magnitude scores for experiments with norepinephrine (NE), with or without 1 or 2% halothane (H).

* $P < 0.001$ versus 0 $\mu\text{g/l}$ NE.

† $P < 0.005$ versus 0 $\mu\text{g/l}$ NE.

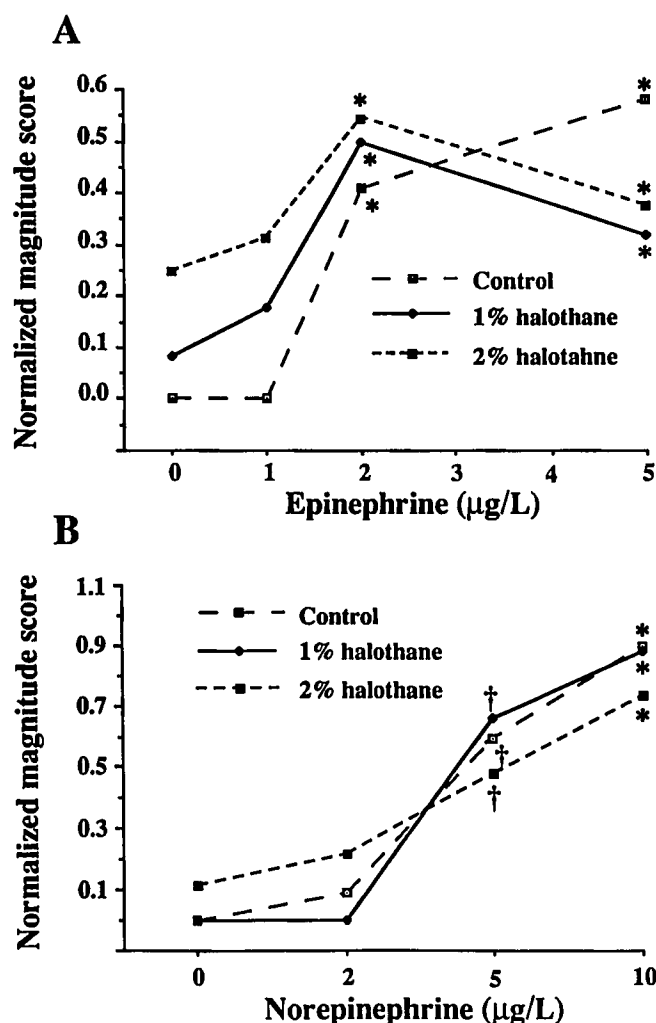


FIG. 4. Effects of epinephrine (A) and norepinephrine (B), alone or with 1 or 2% halothane, on normalized magnitude scores. A: * $P < 0.05$ versus 0% halothane and 0 µg/l epinephrine. B: * $P < 0.001$ versus 0 µg/l; † $P < 0.005$ versus 0 µg/l.

The adrenergic mediators tested in our experiments were chosen to model the effects of increased adrenergic neural input (*i.e.*, NE) to the SA node and SAP or to model the possible involvement of changes in automaticity of primary and secondary atrial pacemakers in the genesis of atrial rhythm disorders during the course of halothane- E sensitization. Based on spectrofluorometric analysis, the right atrium and SA node contain similar amounts of NE, the quantity of which presumably reflects the distribution of adrenergic nerve fibers.³⁴ It is reasonable to assume that such fibers do influence the rate of SAP similarly to the SA node, as results of experiments by Randall *et al.* in chronically instrumented dogs with excised SA nodes suggest.¹⁵ While our *in vitro* results suggest that SAP may be more responsive to increased adrenergic input than the SA node, this may not be so *in vivo*. To determine

whether or not it is, it will be necessary to test SA node and SAP chronotropic responses to direct sympathetic stimulation using *in vivo* or *in vitro* preparations with intact sympathetic innervation.

It is possible that a change in the SEA from the SA node to extranodal SAP sites could be the result of rate changes produced by catecholamines in our studies. Atrial isothermal activation sequence maps were used by Boineau *et al.* to examine P-wave changes with changing heart rate in dogs.^{23,24} Vagal stimulation or propranolol was used to decrease and isoproterenol or atropine to increase heart rate. Results of these two investigations indicated that the atrial pacemaker has a multicentric as opposed to a unifocal origin, that is, that its origin is three to five points spanning a distance three to four times that of the classic SA node region.²⁶ Each of these pacemaker points appeared functionally differentiated to generate a specific range of heart rates, confirmed in subsequent work by the same group of investigators.²⁵ Further, pacing from multicentric SEAs, both with and without chronotropic interventions, demonstrated similar activation sequences for paced and spontaneous rhythms.^{23,24} It was concluded that the site of pacemaker origin, and not changes in conduction properties brought about by drugs or pacing, accounted for changes in P-wave morphology with different SEA.^{23,24} Moreover, SEAs appear to be rate-dependent,²³ so that rate changes produced by catecholamines may ac-

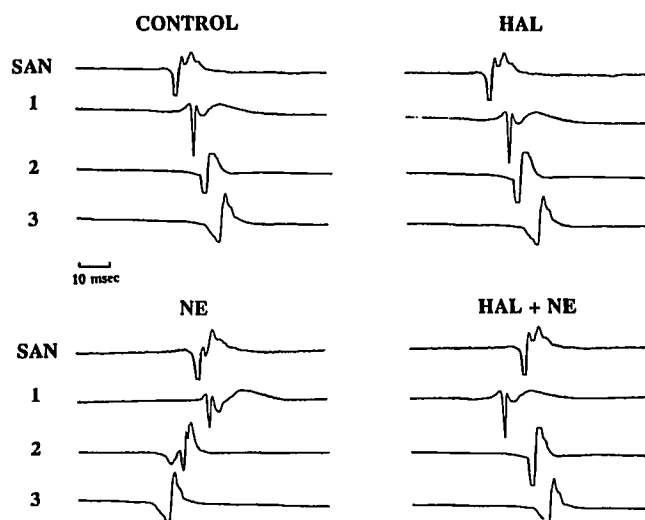


FIG. 5. The effects of 1% halothane (HAL) and 5 µg/l norepinephrine (NE) on sites of pacemaker activity in one preparation. Under control conditions, the site of earliest activation (SEA) is the electrode in the SA node region (SAN), with activation proceeding caudal along the sulcus terminalis to sites 1, 2, and 3, in that order. During exposure to halothane, the SEA is still the SAN, and activation of sites 1–3 remains as for control. With norepinephrine, the nonlinear activation sequence has shifted from SAN to electrode site 3. The magnitude score for this shift would be 3. Finally, with norepinephrine and halothane, the SEA has shifted to electrode site 1.

count at least in part for shifts in SEA away from the SA node to SAP sites.

It has been demonstrated both with halothane²⁹ and enflurane or isoflurane³⁰ that atrial rhythm disorders, including wandering atrial pacemaker and ectopic beats, occur at lower doses of E during the course of anesthetic sensitization. If our current findings apply *in vivo*, then it is possible that enhanced automaticity of SAP relative to the SA node may account in part for the genesis of ectopic atrial rhythm disorders early in the course of anesthetic sensitization. However, we studied only the response to E of SAP located along the sulcus terminalis. Other possible sites of SAP activity include the coronary sinus,³⁵ Bachmann's bundle,^{14,18,36} atrial plateau fibers,^{37,38} and the AV valve leaflets.³⁹ Additionally, wandering atrial pacemaker and atrial ectopic beats were diagnosed in the above-cited studies of anesthetic-E arrhythmias^{29,30} by changes in P-wave morphology in conventional (surface) ECG recordings. As noted by Waldo *et al.*, changes in P-wave polarity and morphology may be poor indicators of the site of origin of atrial activation.^{40,41} Clearly, detailed electrophysiologic mapping studies are required to establish that SAPs located along the sulcus terminalis or other potential sites^{14,18,35-39} are those responsible for impulse initiation with atrial rhythm disorders occasioned by anesthetic-E sensitization. Nevertheless, results of the current study do demonstrate that pacemakers outside the classic SA node region²⁶ can control the rhythm of the heart in response to increased catecholamines, despite an intact SA node. Thus, enhanced automaticity of SAP may account for some anesthetic-E arrhythmias.

Results of experiments such as ours may have relevance for the management of patients with intrinsic sinus node dysfunction, but they must be extrapolated cautiously because of possible species differences and the limitations of the *in vitro* preparation. If applicable to humans, our results suggest that in the presence (or absence) of clinically relevant concentrations of halothane, chronotropic responses of SAP to E or NE are preserved, and SAP can function as the pacemaker for the atrium. If so, enhanced automaticity of SAP may account for some ectopic atrial arrhythmias in patients with sinus node dysfunction and anesthetized with halothane. Nevertheless, conclusions regarding the clinical significance of these results for the genesis of clinical dysrhythmias must be made with caution: our results do not account for the possible role of several factors, including acetylcholine either at background or enhanced levels, as they might influence the genesis of dysrhythmias. Furthermore, anesthetic and chronotropic drug effects on SAP should be tested in chronic dogs with surgically excised or otherwise-damaged SA nodes.^{15,19,42} Finally, intracellular electrophysiologic methods⁴³ also should be used to test the effects of anesthetic and chronotropic drugs on SAP function.

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