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

I. Methodology, Conscious State, and Halothane Anesthesia: Comparison with and without Muscarinic Blockade during Exposure to Epinephrine

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Background: **Supraventricular dysrhythmias are common during anesthesia, but have been incompletely investigated. Mechanisms may involve altered automaticity of subsidiary pacemakers and participation of vagal reflexes. The following hypotheses were tested: (1) shifts from the sinoatrial (SA) node to subsidiary pacemakers require intact vagal reflexes and (2) halothane sensitizes the heart to epinephrine-induced atrial pacemaker shifts.**

Methods: **Epicardial electrodes were implanted in eight dogs on both atrial appendages, the right ventricle, along the sulcus terminalis, and at the His bundle. Weekly testing awake (control), awake with atropine methylnitrate, with 1 and 2 μg epinephrine · kg^{-1} · min^{-1} (3 min-infusions), and under 1.25 and 2 MAC halothane was performed. Electrograms were analyzed for the site of earliest activation (SEA), which was scored 1–6 depending on the distance from the SA node, and expressed as the SEA value.**

Results: **In conscious dogs (control) and at 1.25 MAC halothane, epinephrine increased the SEA values (shifted activation from SA node) and blood pressure, and decreased heart rate; however, with atropine, SEA values were unaffected by epinephrine, although blood pressure and heart rate were elevated. At 2 MAC, atropine did not affect the epinephrine-induced increase in SEA values. Halothane increased SEA values when combined with 1 μg epinephrine · kg^{-1} · min^{-1}.**

Conclusions: **Pacemaker shifts account for atrial dysrhythmias in the conscious state and during 1.25 MAC halothane with epinephrine, and require vagal participation. Halothane sensitizes the heart to epinephrine-induced atrial dysrhythmias. Atropine and halothane facilitate His bundle beats during exposure to epinephrine. (Key words: Animal: dog, anesthetized; dog, conscious. Anesthetics, volatile: halothane. Heart: arrhythmias; autonomic regulation; sinoatrial node; subsidiary atrial pacemakers. Parasympathetic nervous system: acetylcholine. Sympathetic nervous system, catecholamines: epinephrine.)**

CARDIAC dysrhythmias may be detected in the majority of patients undergoing anesthesia and surgery when continuous monitoring is used.[1] Although some atrial and ventricular dysrhythmias may have minimal impact on cardiovascular function, others may cause significant hemodynamic compromise through bradycardia or impairment of diastolic ventricular filling. Adrenergic drugs may be administered to patients under general anesthesia,[2] and surgical stress or airway manipulation can elevate endogenous epinephrine levels and increase sympathetic activity.[3] Continuous infusions of epinephrine have been used *in vivo* to demonstrate interactions between epinephrine and anesthetics. Although these infusions do not mimic increased sympathetic nerve activity, they remain the most widely used animal model for demonstrating anesthetic-catecholamine interactions. The ability of an anesthetic to lower the dose of epinephrine required to provoke ventricular dysrhythmias is known as anesthetic-epinephrine sensitization,[4–6] but relatively little attention has been given to resulting atrial dysrhythmias. Some studies show that atrial rhythm disturbances precede ventricular dysrhythmias during epinephrine exposure ("arrhythmias of development").[4,5] Because of the high

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degree of autonomic innervation of the atrial myocardium, autonomic reflexes are expected to play an important role in the formation or suppression of atrial dysrhythmias.[3]

Therefore, we examined the potential of epinephrine, alone and with muscarinic blockade, to provoke atrial dysrhythmias in chronically instrumented dogs. At least for halothane, *in vitro* data indicate that enhanced automaticity of subsidiary atrial pacemakers may be responsible for arrhythmias of development.[6] Polic *et al.*[6] suggested that catecholamines alone augment the automaticity more in subsidiary atrial pacemakers than in the sinoatrial (SA) node *in vitro,* but that the addition of halothane caused little additional effect. Halothane alone was not sufficient to produce pacemaker shifts in their study. Later, Boban *et al.*[7] found that the combination of isoflurane with epinephrine produced a significant increase in incidence and severity of pacemaker shifts in a similar *in vitro* model. They concluded that isoflurane and catecholamines acted synergistically to increase the dysrhythmic potential in atrial tissue. Despite evidence from these studies, it is not clear whether the atrial myocardium and its pacemakers are sensitized to dysrhythmias *in vivo.* Halothane, which sensitizes the ventricle to dysrhythmias, may also act synergistically with catecholamines *in vivo* to augment atrial dysrhythmias.

We tested the following hypotheses under *in vivo* conditions: (1) epinephrine alone produces atrial pacemaker shifts; (2) pacemaker shifts with epinephrine require an intact vagus; and (3) halothane will further sensitize the atrial myocardium to epinephrine-induced dysrhythmias, as evidenced by enhanced automaticity of subsidiary atrial pacemakers relative to that of the SA node.

Materials and Methods

Surgical Preparation and Materials

All surgical and experimental procedures conformed to Institutional Animal Care Committee Guidelines. Eight healthy mongrel dogs of either sex, weighing 18–22 kg, were prepared for chronic electrophysiologic investigation by implantation of epicardial electrodes and an indwelling aortic catheter. A right thoracotomy was performed in the fifth intercostal space under anesthesia with 20 mg/kg thiopental and halothane. Electrode pairs were sutured to the epicardial surfaces of the right and left atrial appendages, and the right

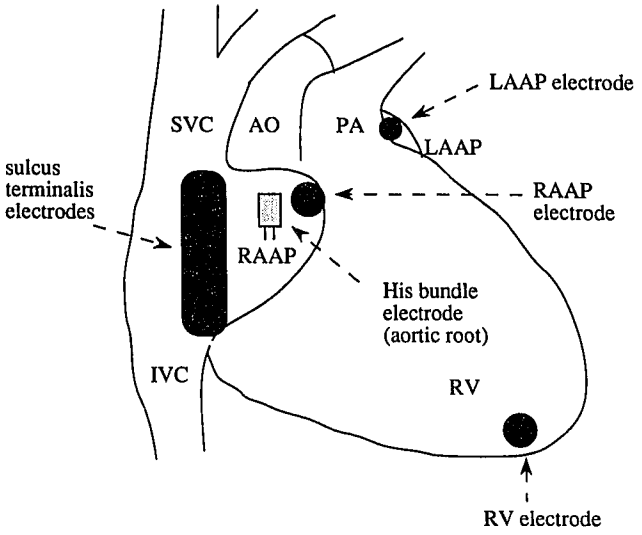

Fig. 1. Location of the electrode pairs sutured to the epicardial surface of the heart. AO = aorta; IVC = inferior vena cava; LAAP = left atrial appendage; PA = pulmonary artery; RAAP = right atrial appendage; RV = right ventricle; SVC = superior vena cava. The sulcus terminalis-patch electrode contains five evenly spaced electrode pairs. Bipolar needles of the His bundle electrode were advanced into the interventricular septum from the aortic root. Electrode lead wires are not shown. Only the RAAP electrode was used for pacing.

ventricular apex (fig. 1). A "patch electrode" of five linear, evenly spaced electrode pairs was sutured to the right atrium with the most rostral pair located at the junction of the right atrium and superior vena cava, closest to the anatomic region of the sinoatrial (SA) node. The most caudal pair was located near the junction of the right atrium and inferior vena cava.[8] This procedure placed the electrode pairs along the sulcus terminalis, in proximity to previously described subsidiary atrial pacemakers.[9–11] A bipolar needle electrode was advanced into the interventricular septum from the aortic root[12] to record the His bundle electrogram. An indwelling cannula was placed into the inferior aorta through a femoral artery after surgical exposure of the artery at the inner side of the hind limb. All leads and lines were tunneled subcutaneously, exiting between the scapulae. Incisions were closed in anatomic fashion, and dogs recovered for 2 weeks before testing. Standard postoperative methods of analgesia and antibiotics were used during the first week after surgery.

Electrograms, after amplification with custom-built preamplifiers (gain 1,000), were filtered with a separate, custom-built common mode rejection amplifier (bandpass of 10–1,000 Hz), individually adjusted for

signal strength (maximal gain 400), and instantaneously displayed on a programmable calculating oscilloscope (model NI3001; Norland, Fort Atkinson, WI). Paper records were made on a digital eight-channel recorder (MT 9500; Astromed, West Warwick, RI) with paper speeds of 200 mm/s, providing a resolution better than 3.0 ms. Lead II of the surface electrocardiogram (ECG) was amplified (78213 C; Hewlett Packard, Mountain View, CA), displayed, and recorded with seven other signals of interest (SA node, five subsidiary atrial pacemaker, and His bundle electrograms). Heart rate (HR) was continuously measured (peak detector). Right atrial pacing was performed with a programmable cardiac stimulator (model SEC3102; Nihon Kohden, Tokyo, Japan). Systolic (SBP) and diastolic blood pressures were measured using a pressure transducer (Baxter Uniflow, McGaw Park, IL) and amplifier (Hewlett-Packard, model HP 78205 D), with digital readout recorded. All drugs were given in 0.9% saline. Epinephrine infusions were administered with an infusion pump (model 5006100; Harvard Apparatus, Millis, MA).

Experimental Protocol

Surface ECG and HR were recorded before instrumentation, and the dogs were trained to stand quietly in a sling. Two weeks after instrumentation, when P-wave morphology, average HR, and cyclical variation in HR had returned to preinstrumentation levels, the animal was deemed suitable for testing. Dogs were observed to verify the absence of spontaneous dysrhythmias other than respiratory sinus dysrhythmia.

An overview of the experimental protocol is presented in figure 2. From the resting dog, two separate eight-channel paper recordings lasting 15 s were obtained. The paper speed was 200 mm/s. Recordings included surface ECG (lead II), electrograms from the His bundle, SA node region, four locations along the sulcus terminalis, and the left atrial appendage. In addition, measurements of heart rate (HR) and blood pressure were made. As an indicator of pacemaker automaticity, the response to overdrive suppression (sinus node recovery time (SNRT)) was determined by pacing the right atrial appendage at 200 and 250 beats/min for 30 s. Pulse duration was 2 ms and current was 10 mA. Sinus node recovery time was measured on the His bundle trace, from the last pacing spike to the first spontaneous sinus origin beat after cessation of pacing. Dogs were then given epinephrine infusions at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 3 min *via* a forelimb vein. Data were recorded for 5 s at 15-s intervals during the second and third minute of the epinephrine infusion, for a total of 45 s. The last 2 min were chosen because epinephrine plasma concentrations have been shown to reach a plateau during this time period.[5,13,14] Sinus node recovery time was not measured during exposure to epinephrine, because pacing would have interfered with the spontaneous development of pacemaker shifts. Because different protocols of epinephrine infusions affect the susceptibility to dysrhythmias,[13] site of pacemaker origin, HR, and blood pressure were allowed to return to baseline before continuing with the protocol (>30 min). Also, epinephrine plasma levels return to baseline values within this period.[15] This was verified by random sampling in some animals of the study. After return to baseline (above), data acquisition during infusion of 2 μg epinephrine $\cdot kg^{-1} \cdot min^{-1}$ was repeated.

Subsequently, anesthesia was induced by inhalation of halothane in oxygen, followed by tracheal intubation. Halothane was monitored (Marquette Gas Analyzer, model 1700 and Advantage 2000) and maintained at concentrations equivalent to 1.25 or 2 MAC end tidal.[16–18] Ventilation was controlled with a circle system (Foregger F 500 anesthesia machine; Puritan-Benett, Hauppauge, NY) to keep end-tidal P_{CO_2} between 35 and 40 mmHg. Esophageal temperature was mea-

conscious	± AMN 3 mg/kg	30 min	baseline	EPI - 1	≥ 30 min	EPI - 2	≥ 30 min
1.25 HAL	± AMN 1.5 mg/kg	30 min	baseline	EPI - 1	≥ 30 min	EPI - 2	≥ 30 min
2.0 HAL	± AMN 1.5 mg/kg	30 min	baseline	EPI - 1	≥ 30 min	EPI - 2	

Fig. 2. Experimental protocol for testing with epinephrine 1 (EPI-1) or 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (EPI-2), in the conscious state, and with halothane (HAL) 1.25 or 2.0 MAC. Testing was on two occasions separated by at least 1 week with (+) and without (−) atropine methylnitrate (AMN).

sured (YSI 43TE, Taylor thermometer; Yellow Springs, Yellow Springs, OH) and maintained at 36–38.5° C by radiant heating and heated humidifier (RCI, conchatherm III; Respiratory Care, Arlington Heights, IL). Lactated Ringer's solution maintained fluid requirements (3–5 $ml \cdot kg^{-1} \cdot h^{-1}$). Testing in anesthetized dogs was performed after a 30-min equilibration, and in the lateral decubitus position to avoid venous pooling. Epinephrine infusions and data acquisition during anesthesia were repeated according to the conscious-state protocol.

Experiments with atropine methylnitrate (AMN) as a peripheral muscarinic blocker were performed at least 1 week after experiments without muscarinic blockade. Atropine methylnitrate was used because of its lack of central nervous system toxicity and established dosage.[19] Three milligrams AMN/kg was administered intravenously 30 min before obtaining conscious state data. Atropine methylnitrate (1.5 mg/kg) was repeated 30 min before testing at 1.25 MAC, and again before testing at 2 MAC.

Data Evaluation

Each heartbeat occurring during the 45-s recording period was evaluated for the site of earliest myocardial activation (SEA). Each beat was assigned a score corresponding to the earliest identifiable activation. The site of earliest activation was determined from the bipolar electrograms obtained from electrodes sutured to the heart (fig. 1) and received a higher score (1–6) with increasing distance from the SA node, thus: score 1 = SA node (1st patch electrode); score 2 = high rostral sulcus terminalis (2nd patch electrode); score 3 = midrostral sulcus terminalis (3rd patch electrode); score 4 = midcaudal sulcus terminalis (4th patch electrode); score 5 = low caudal sulcus terminalis (5th patch electrode); and score 6 = remote atrial (left atrial appendage electrode). The fraction (expressed as a decimal) of beats from each origin (sites scored 1–6) was multiplied by their corresponding score. Resulting products were summed and then divided by the fraction of beats of atrial origin. Thus, the resulting normalized SEA value (range of possible values is 1–6) was independent of HR and nonatrial beats. Sometimes, His bundle or right ventricular electrograms preceded those from any atrial site. Beats arising from those nonatrial sites were counted separately. All mathematic and statistical procedures were performed using a desktop computer (Apple Macintosh SE/30, Cupertino, CA). To prove normal distribution and consistency in values for SEA, SNRT, SBP, and HR, we performed the one sample t test and the normality test. To detect similarities and possible differences in distribution of SEA values, including proof of individual consistency over time, the Kolmogorov-Smirnov test was used.[20] Data for SNRT, SBP, and HR were compared by means of paired Student's t test. Significance was identified at $P \leq 0.05$. Data are shown as mean ± SEM, except for HB and ventricular ectopic beats, which are presented as the percentage of all beats during the recording period.

Results

Conscious State

Values for SEA, SNRT, HR, and SBP in conscious dogs without atropine or epinephrine (control) did not change over the time period of study. Resting, conscious dogs without AMN or exposure to epinephrine (control state) had respirocyclic beat-to-beat variability in HR (respiratory sinus dysrhythmia) when breathing slowly, whereas panting eliminated cycle length variability. During respiratory sinus dysrhythmia, the site of earliest activation often changed between the first and second patch electrode pair, resulting in an SEA

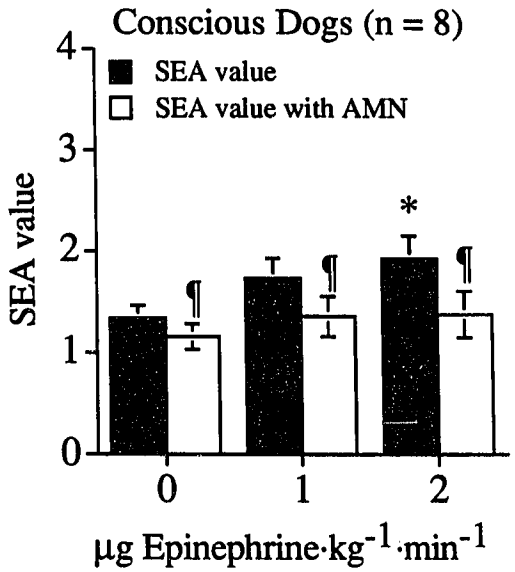

Fig. 3. Bar graphs depict effects of epinephrine on the site of earliest activation (SEA) values in conscious, chronically instrumented dogs with and without muscarinic blockade and effects of muscarinic blockade by atropine methylnitrate (AMN). Data are mean ± SEM. * *Versus* no epinephrine; ¶ *versus* no AMN.

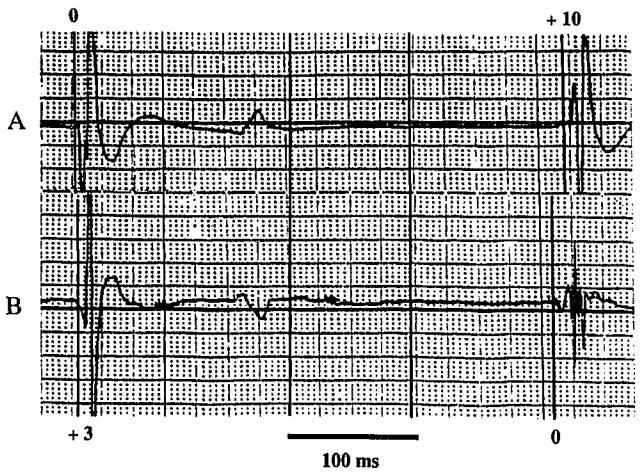

Fig. 4. Pacemaker shift from the SA node (first beat) to the high rostral subsidiary atrial pacemaker location (second beat). Simultaneous recordings. (*A*) SA node electrogram. (*B*) High rostral sulcus terminalis electrogram. Numbers on the top and bottom indicate the activation intervals between *A* and *B*. In addition to a shift in site of earliest activation, note changes in polarity, amplitude, and morphology of the atrial signals.

value of 1.34 ± 0.125 (fig. 3). These pacemaker shifts were accompanied by a remarkable variability in morphology, polarity, and amplitude of atrial electrograms from along the sulcus terminalis (figs. 4 and 5), indicating the changes in site of earliest activation (SEA) and conduction in the atrium. The administration of AMN increased HR, abolished the variability in cycle lengths, shortened SNRT, and decreased SBP (table 1). Atropine methylnitrate also decreased SEA values compared with control (fig. 3). Finally, with AMN, the variability in morphology, polarity, and amplitude of the atrial electrograms was no longer present.

Exposure to epinephrine increased SBP, with or without AMN. Dogs without AMN developed epinephrine-related reflex reductions in HR (table 1) and shifts in pacemaker location further from the SA node, evidenced by the significantly increased SEA value at 2 μg epinephrine $\cdot$ kg^{-1} $\cdot$ min^{-1} (figs. 3 and 6). Conversely, 2 μg epinephrine $\cdot$ kg^{-1} $\cdot$ min^{-1} with AMN increased HR compared with the absence of epinephrine (table 1), but left SEA values unchanged (fig. 3). Atropine methylnitrate increased SBP with 1 μg epinephrine $\cdot$ kg^{-1} $\cdot$ min^{-1} and increased HR with both doses of epinephrine (table 1). Finally, during exposure to epinephrine, AMN lowered the SEA value compared with the absence of AMN (fig. 3).

His bundle beats comprised less than 1% of total beats, and usually occurred after the onset of atrial pacemaker shifts and only without AMN. Furthermore, premature ventricular beats comprised less than 3% of total beats, and only with the highest level of epinephrine (table 1).

Halothane Anesthesia

Figure 7 shows the effect of epinephrine on pacemaker shifts in anesthetized dogs. Generally, epinephrine increased the SEA value during halothane anesthesia. Muscarinic blockade prevented this increase at 1.25 MAC halothane and 2 μg epinephrine $\cdot$ kg^{-1} $\cdot$ min^{-1}. Figure 8 shows the effect of halothane anesthesia on SEA values during exposure to epinephrine. Halothane at 1.25 MAC reduced the respiratory variability and the SEA value, and stabilized the

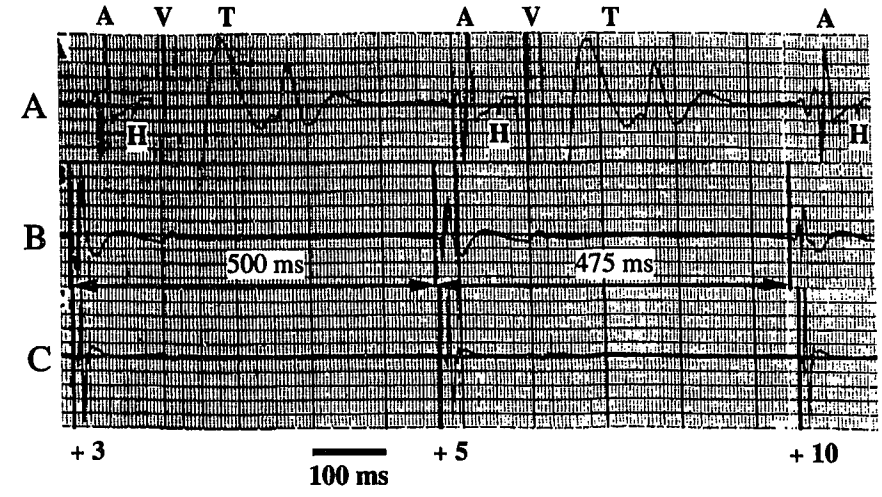

Fig. 5. Variability in morphology of three consecutive beats during respiratory sinus dysrhythmia (simultaneous recordings). (*A*) His bundle electrogram. (*B*) SA node electrogram. (*C*) High rostral sulcus terminalis electrogram. A = atrial; H = His bundle; T = repolarization; V = ventricular. Numbers on the bottom indicate the activation intervals between the electrical activation shown in *B* and *C*. The cycle length for beat 2 is 25 ms greater than for beat 3. Note changes in morphology and amplitude of atrial activity in *B*, without a pacemaker shift away from the SA node electrode.

Table 1. Sinoatrial Node Automaticity, Nonatrial Origin Beats, and Blood Pressure Related to Epinephrine, Halothane, and Muscarinic Blockade

	Sinus Node Recovery Time (ms)						
	200 beats · min^{-1}	250 beats · min^{-1}	Epinephrine (μg · kg^{-1} · min^{-1})	Systolic Blood Pressure (mmHg)	Heart Rate (beats · min^{-1})	His Bundle Beats (%)	Ventricular Beats (%)
Conscious dogs	629 ± 49	639 ± 60	0	145 ± 6	113 ± 6	0	0
			1	191 ± 7*	114 ± 6	0.7	0
			2	225 ± 8*	94 ± 7*	0.2	2.9
With AMN	401 ± 16†	405 ± 16†	0	125 ± 3†	201 ± 7†	0	0
			1	207 ± 13†	210 ± 9†	0	0
			2	236 ± 14*	232 ± 8*†	0	0.2
1.25 MAC halothane	500 ± 45‡	517 ± 45‡	0	100 ± 4‡	117 ± 6	0	0
			1	162 ± 6*‡	87 ± 7*‡	0	3.4
			2	193 ± 8*‡	77 ± 7*	1.3	7.5
With AMN	640 ± 20†‡	594 ± 32‡	0	89 ± 6‡	99 ± 6†‡	0	0
			1	172 ± 11*‡	138 ± 9*†‡	16	0
			2	173 ± 9*†‡	160 ± 21*†‡	13.2*†‡	25.2
2.0 MAC halothane	508 ± 38	596 ± 36	0	86 ± 5‡	113 ± 6	0	0
			1	154 ± 7*‡	102 ± 8	0	0.7
			2	155 ± 9*‡	85 ± 11*§	25.5*‡	2.4
With AMN	791 ± 62†‡	610 ± 73‡	0	80 ± 6‡	91 ± 4†‡	0	0
			1	149 ± 9*‡	115 ± 5*‡	8.5	0.6
			2	146 ± 15*‡	145 ± 18*†‡	22.2*‡	8.2

Data shown mean ± SEM; n = 8. His Bundle and ventricular beats are expressed as percentage of all beats per condition.

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 halothane.

§ n = 7, excluding a dog with ventricular tachycardia.

pacemaker location to the SA node. In contrast, stable shifts to the high rostral subsidiary pacemaker were present at 2 MAC. Furthermore, halothane tended to increase the SEA value when epinephrine was present.

Detailed data and comparisons for heart rate, sinus node recovery time, and systolic blood pressure during halothane anesthesia are presented in table 1. As in the control state, epinephrine decreased HR; however, with AMN, epinephrine increased HR. Surprisingly, AMN administered to dogs without epinephrine exposure reduced HR and prolonged SNRT compared with the corresponding test condition without AMN. As in the conscious state, AMN tended to elevate the HR during exposure to epinephrine. Generally, halothane reduced SBP and blunted the hypertension caused by epinephrine. In dogs without AMN or epinephrine, halothane abolished respiratory variability in HR. At 1.25 MAC, halothane shortened SNRT compared with control. With AMN, but without epinephrine, halothane reduced HR and prolonged SNRT compared with the conscious state. In the presence of 1 μg epinephrine · kg^{-1} · min^{-1}, 1.25 MAC of halothane reduced HR compared with the conscious state.

When the earliest electrical activity was observed on the His bundle electrogram (His bundle signal precedes all other signals), normal QRS morphology without visible or with inverted (retrograde) P-waves was present in the surface ECG (fig. 9). With the onset of His bundle beats, there was progressive shortening of the P-R interval, until P waves merged with the QRS complex. Table 1 shows the incidence of His bundle beats under each test condition. Increasing depth of anesthesia and increasing dose of epinephrine both increased the incidence of His bundle beats. Furthermore, His bundle beats tended to occur at the end of epinephrine infusions. Ventricular ectopic beats increased with increasing epinephrine dosage (table 1). Once ventricular ectopic beats were frequent, the site of earliest atrial pacemaker activity (dissociated from ventricular

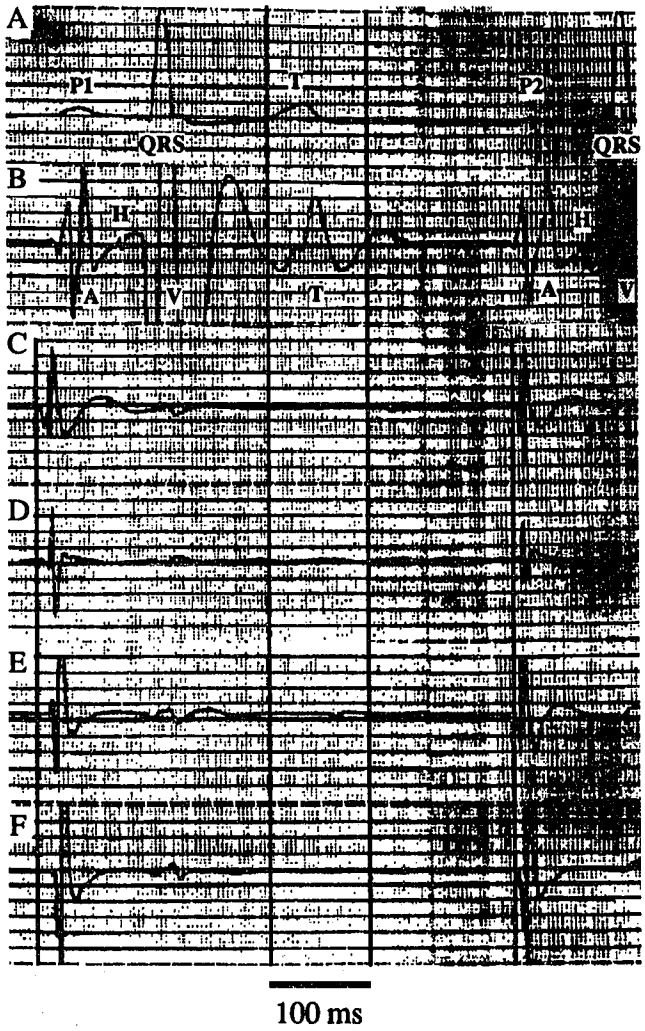

Fig. 6. Pacemaker shift from the SA node (first beat) to the midcaudal subsidiary atrial pacemaker region (second beat; simultaneous recordings). (*A*) Surface electrocardiogram (lead II). (*B*) His bundle electrogram. (*C*) SA node electrogram. (*D*) High rostral. (*E*) Midrostral. (*F*) Midcaudal sulcus terminalis electrogram. In *A*, P1 and P2 are atrial depolarizations, and QRS and T are ventricular depolarizations and repolarizations, respectively. A = atrial; H = His bundle; T = repolarization; V = ventricular. Note change in P wave morphology of beat 2 (slightly flattened) compared with beat 1 (more rounded contour).

activity) commonly shifted back to the SA node electrode (fig. 10).

Discussion

Using chronically instrumented, intact dogs, we tested whether epinephrine caused atrial pacemaker

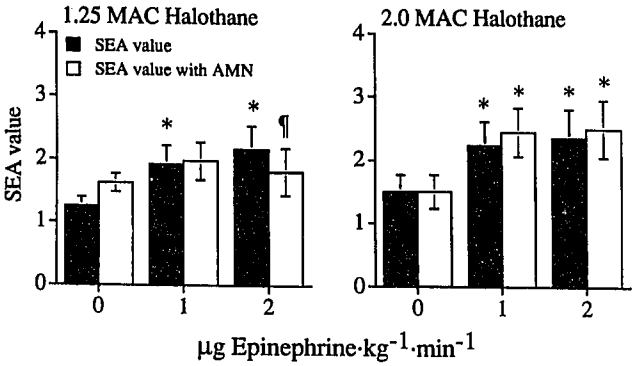

Fig. 7. Bar graphs depict effects of epinephrine on the site of earliest activation (SEA) values in halothane anesthetized, chronically instrumented dogs with and without muscarinic blockade and effects of muscarinic blockade by atropine methylnitrate (AMN). Data are mean ± SEM. * *Versus* no epinephrine; ¶ *versus* no AMN.

shifts (atrial dysrhythmias) in the conscious state or during halothane anesthesia. Second, we determined the influence of the baroreflex on the genesis of atrial dysrhythmias by testing with and without muscarinic blockade. Finally, whether halothane sensitized the atria to epinephrine was tested by comparing the incidence and severity of atrial pacemaker shifts in the conscious state with those during halothane anesthesia.

Conscious State

Atrial dysrhythmias may be explained by shifts to remote (subsidiary and latent) atrial pacemaker sites, which have different electrophysiologic properties than

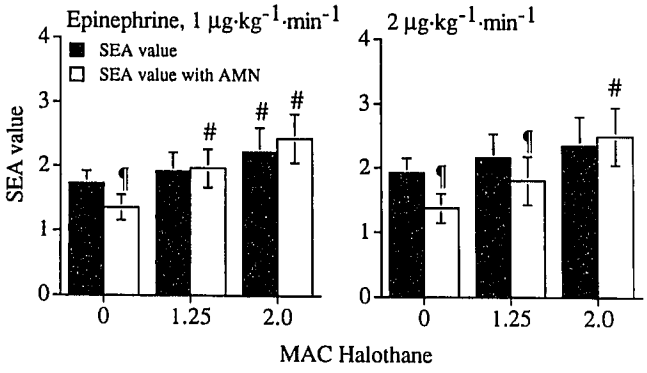

Fig. 8. Bar graphs depict effects of halothane anesthesia on the site of earliest activation (SEA) values in chronically instrumented dogs, with and without muscarinic blockade and effects of muscarinic blockade by atropine methylnitrate (AMN). Data are mean ± SEM. # *Versus* no halothane; ¶ *versus* no AMN.

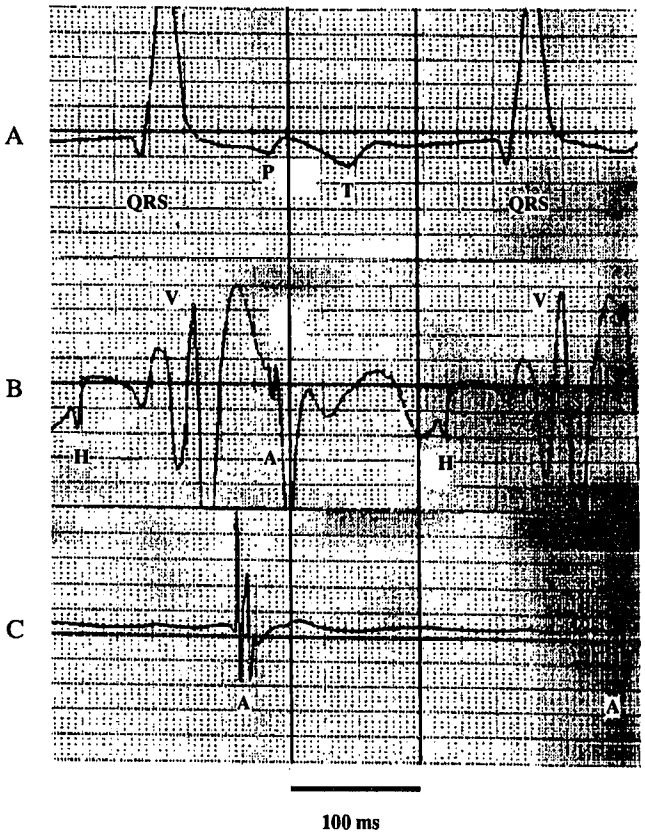

Fig. 9. Accelerated AV junctional rhythm (simultaneous recordings). (*A*) Surface electrocardiogram (lead II). (*B*) His bundle electrogram. (*C*) SA node electrogram. Note the His bundle (H) preceding the atrial (A) and ventricular (V) signal in *B*. Inverted (retrograde) P waves appear in the ST segment in *A*.

the SA node.[21–24] Gomes and Winters[25] suggested that the human SA node contained dominant and subsidiary foci, and that the subsidiary sites are escape pacemakers with longer cycle lengths. Polic *et al.*[6] and, later, Boban *et al.*[7] concluded that, in an isolated canine right atrial preparation, epinephrine augmented the automaticity of subsidiary atrial pacemakers more than that of the SA node. They found no pacemaker shifts without catecholamine stimulation. In the current study, pacemaker shifts during respiratory sinus dysrhythmia exemplify the concept of a "physiologic" pacemaker complex, confined to the rostral portions of the sulcus terminalis, including the SA node as described by Boineau *et al.* in the anesthetized dog.[26,27] Consistent with that concept, we did not observe pacemaker shifts to the caudal sulcus terminalis or more remote sites of atrial pacemakers in the control state. Even when the site of earliest activation was the SA node electrode, the morphology, polarity, and amplitude of the electrograms often changed, reflecting the widespread

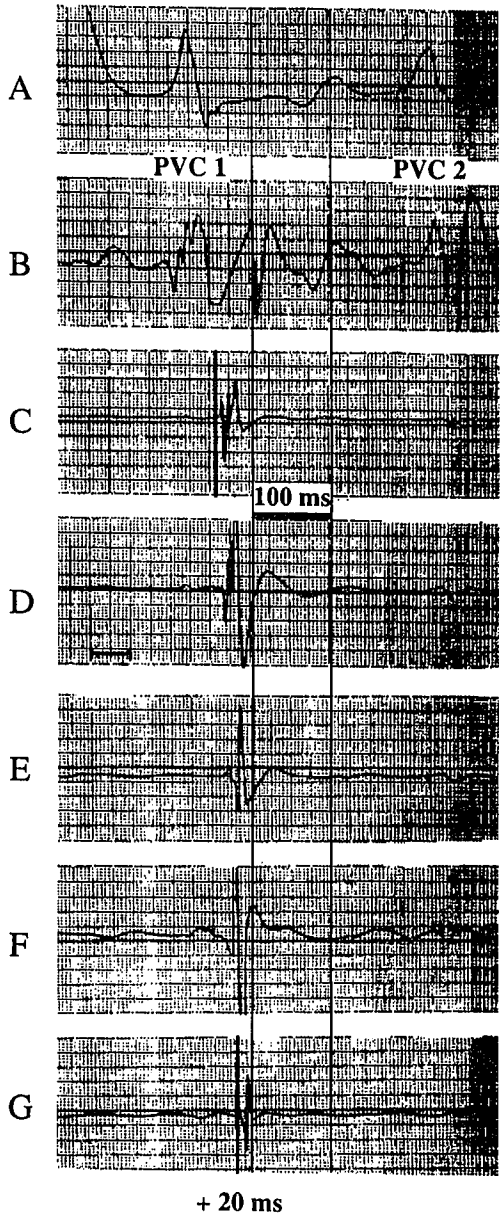

Fig. 10. Polymorphic ventricular ectopic beats (PVC 1, PVC 2; 1.25 MAC halothane, 2 μg epinephrine · kg^{-1} · min^{-1}; simultaneous recordings). (*A*) Surface electrocardiogram. (*B*) His bundle electrogram. (*C*) SA node electrogram. (*D*) High rostral. (*E*) Midrostral. (*F*) Midcaudal. (*G*) Low caudal subsidiary atrial pacemaker electrogram. The signal on the SA node electrode (*C*) precedes that of the low caudal sulcus terminalis (*G*) by 20 ms (bottom).

pacemaker activity within the anatomic region of the SA node.[28–30] Several mechanisms could yield an explanation for this observation. Competing pacemaker foci are possibly located rostral to or adjacent to the SA node electrode pair. Alternatively, pacemakers within the SA node region itself may be competing for dominance in the conscious state, because of differences in spontaneous automaticity and differences in vagal innervation and suppressibility. It is known that vagal innervation in the atria declines progressively from the SA node region to more remote locations along the sulcus terminalis and throughout the atrial muscle, making the SA node region potentially the most vagally inhibited pacemaker.[3,31] Furthermore, clinical reports indicate that distinct cases of SA node dysfunction are related to altered parasympathetic tone[32–34] and not to an organically diseased pacemaker. In our experiments, infused epinephrine caused arterial hypertension, which presumably activated the baroreceptor reflex. This caused HR to decline through enhanced vagal efferent tone.[35,36] In addition to the observed bradycardia, the site of earliest activation shifted to caudal sites along the sulcus terminalis, as reflected by increased SEA values, and also consistent with less potent inhibitory actions with increasing distance from the SA node.

Furthermore, our results support the concept that muscarinic blockade enhances SA node automaticity, as evidenced by increased HR and shortened SNRT, thus enabling overdrive suppression of subsidiary atrial and ventricular pacemakers.[37,38] Conversely, high vagal tone impairs this ability. The absence of variability in SA node and atrial electrograms with muscarinic blockade allows one to speculate that, even in a small area of physiologically activated pacemakers, not all cells have equal vagal inhibition. Stimulation with epinephrine in dogs with muscarinic blockade caused an additional increase in HR, instead of the dose-related decrease in HR observed without muscarinic blockade. No significant changes in SEA values occurred with muscarinic blockade, although the SBP was at least as high as without muscarinic blockade. Based on these observations, we suggest that a direct, nonmuscarinic receptor-mediated effect of SBP, such as myocardial stretch, is unlikely to be the predominant factor in shifts to subsidiary atrial pacemakers.[21,22] Furthermore, it is unlikely that an "intrinsic" potential of epinephrine to enhance automaticity of subsidiary atrial pacemakers relative to the SA node is the mechanism for pacemaker shifts with epinephrine in the conscious dog. However, Polic *et al.*[6] and Boban *et al.*[7] concluded that, in isolated canine hearts, epinephrine caused atrial dysrhythmias by enhancing automaticity of subsidiary atrial pacemakers relative to the SA node.

Joas and Stevens[39] performed conscious state testing for epinephrine-induced, ventricular dysrhythmias in dogs, but did not describe atrial dysrhythmias. During testing for ventricular sensitization in anesthetized dogs, Atlee *et al.*[4,5] observed that supraventricular dysrhythmias occurred at lower epinephrine doses, therefore preceding ventricular dysrhythmias during the course of sensitization. Because ventricular dysrhythmias became apparent at the highest epinephrine dose ($2\ \mu g \cdot kg^{-1} \cdot min^{-1}$), our experiments confirm that supraventricular dysrhythmias precede ventricular dysrhythmias in anesthetized, as well as conscious, dogs.[4,5]

Brunsting *et al.* and Schuil *et al.*[40–42] described the phenomenon of excess tachycardia, during which the HR resulting after pure muscarinic blockade is approximately 30–50 beats/min greater than the HR after vagotomy or muscarinic blockade preceded by ganglionic blockade. The heart rate resulting from the administration of atropine methylnitrate in the current study is consistent with the phenomenon of excess tachycardia. Although histamine H_1 blockers are shown to play an important role, the receptors and mediators for excess tachycardia are not yet clearly identified, and the influence on atrial dysrhythmias, if any, is unknown.[43,44] Because atropine without ganglionic blockade more closely resembles clinical situations, we omitted ganglionic blockade. Furthermore, blockade of muscarinic transmission alone served the purpose of identifying the predominant mechanism for atrial dysrhythmias in the current study.

The shape of the P-wave on lead II of the surface ECG did not change as long as the site of earliest activation projected to the SA node or high rostral sulcus terminalis electrodes. We suggest that only major atrial pacemaker shifts are recognized on the surface ECG. When the pacemaker shifted to more distal sites along the sulcus terminalis, slightly altered P-waves resulted (fig. 6). These P-waves were usually flattened. Also detected, however, were peaked, double-peaked, widened, biphasic, and negative P-waves, consistent with reports from observations in humans.[1] We suggest this as an explanation for the clinically observed phenomenon of "wandering atrial pacemaker."[45]

Halothane Anesthesia

Bosnjak and Kampine[46] suggested that SA node automaticity is both directly and indirectly decreased by

halothane. In this study, without atropine, halothane had no effect on SA node automaticity; however, with muscarinic blockade, direct depression of SA node automaticity caused by halothane was evidenced by decreased HR and increased SNRT. The failure of halothane to reduce HR in intact hearts may be caused by suppression of vagal tone.[47,¶]

As expected, muscarinic blockade enhanced automaticity of the SA node in the conscious state by suppressing the effect of high resting vagal tone.[48] In contrast, under halothane anesthesia, muscarinic blockade unexpectedly reduced SA node automaticity.[48] Seagard *et al.*[47] and Schmeling *et al.*¶ concur that halothane by itself reduces parasympathetic activity. If vagal tone was low during halothane anesthesia, the reduction of SA node automaticity in our study could represent direct depression of SA node automaticity by AMN. Because high doses of atropine have been shown to reduce ganglionic transmission,[49] and quaternary ammonium atropine derivatives have even greater ganglionic blocking properties than atropine,[50] the depressant effect of AMN on SA node automaticity may be indirect (*i.e.*, related to ganglionic blockade). Consistent with ganglionic blockade as opposed to direct depression, the HR response to epinephrine was not impaired in dogs with AMN. We suggest that a final decision on the mechanisms for these complex and opposing effects of AMN on the HR and the relation to excess tachycardia is beyond the scope of this paper. Yet, it seems important to clarify, in future investigations, if and how atropine compounds act synergistically with volatile anesthetics to depress SA node automaticity.

Seagard *et al.*[47] and others[51–54] reported that halothane attenuates baroreceptor reflex response. However, in our study, there was evidence that the baroreceptor reflex remained mostly intact at 1.25 MAC halothane, because an equivalent increase in SBP produced an equal or greater reduction in HR. In contrast, with 2 MAC halothane, the overall response was attenuated. With muscarinic blockade, epinephrine increased SBP and HR at both MAC values, from which we conclude that the baroreceptor reflex response was blocked. With epinephrine and muscarinic blockade, SBP and HR decreased with increasing halothane, consistent with expected direct myocardial depression by halothane.[55] The difference in HR between dogs with and without atropine diminished with halothane. Reduced baroreceptor reflex activity and impaired responsiveness to epinephrine with increased halothane could account for these differences.

During halothane anesthesia, epinephrine caused shifts to subsidiary atrial pacemakers. When muscarinic blockade interrupted the baroreceptor reflex, epinephrine did not induce pacemaker shifts at 1.25 MAC halothane. This supports the premise that epinephrine-induced atrial pacemaker shifts require intact muscarinic transmission. Halothane at 2 MAC appeared to attenuate the baroreceptor reflex, because hypertension was accompanied by little or no decrease in HR, and, in addition, it depressed SA node automaticity.[46]

Earliest myocardial activation from the His bundle region (His bundle activity preceded all other activity; fig. 9) often had the morphologic characteristics of accelerated AV junctional rhythm (nonparoxysmal AV junctional tachycardia) on the surface ECG.[1] It had a gradual onset and termination and a QRS complex of supraventricular origin, and was accompanied by AV dissociation or retrograde P-waves.[1] A subset of dogs appeared to have increased susceptibility to accelerated AV junctional rhythm. Although this dysrhythmia is common in anesthetized patients and is caused by accelerated automatic discharge at or near the His bundle,[1] treatment modalities are poorly defined, and not universally successful. The combination of AMN and epinephrine provoked accelerated AV junctional rhythm during halothane anesthesia in this study. A likely explanation is that atropine facilitates epinephrine-induced increase in AV node automaticity (muscarinic blockade) more than an increase in SA node automaticity (muscarinic blockade + direct depression or ganglionic blockade), with the anesthetic being the prerequisite for atropine's depressant property. Accelerated AV junctional rhythm was common only with the highest level of epinephrine, and tended to occur after pacemaker shifts to the more remote subsidiary atrial sites, indicating that subsidiary atrial and AV junctional pacemakers have similar physiologic requirements for emergence.[3,31] In contrast, with ventricular ectopy or tachycardia, the atria and ventricles were dissociated with the atrial pacemaker reverting back to the SA node region (fig. 10). This rostral shift of the atrial pacemaker with the onset of ventricular ectopy is an unexpected result, to the best of our knowledge not yet described by others, and indicates subtle interactions of the ventricle and the atrium.

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

Anesthetic-catecholamine sensitization is defined as the reduction in the dose of catecholamines required to produce ventricular dysrhythmias in the anesthetized, compared with the conscious, state. Our experiments support the concept of atrial sensitization as a more severe spectrum of atrial pacemaker shifts in the anesthetized, compared with the conscious, state during exposure to similar infusion levels of epinephrine. That halothane increased SEA values during epinephrine infusions provides evidence for atrial sensitization. Muscarinic blockade did not appear to enhance or reduce sensitization, because there were only small differences in SEA values with atropine, compared with the corresponding values without atropine.

In summary, we conclude, for chronically instrumented dogs, the following. First, the SA node is more suppressed by enhanced vagal tone than subsidiary atrial pacemakers. Second, subsidiary atrial pacemakers may assume control of the heart when not overdriven by the SA node. Third, during exposure to epinephrine, subsidiary atrial pacemakers become the site of earliest activation before His bundle and ventricular ectopic pacemakers. Four, atrial pacemaker shifts in response to epinephrine are predominantly mediated by enhanced vagal tone as a result of baroreceptor stimulation. However, direct enhancement of automaticity in subsidiary atrial pacemakers relative to the SA node by epinephrine at higher doses than tested here cannot be excluded. Fifth, halothane sensitizes the heart to epinephrine-induced atrial dysrhythmias. The process of atrial sensitization appears to be an effect of halothane-epinephrine interaction, and is not influenced by muscarinic blockade. Sixth, accelerated AV junctional rhythm is facilitated by halothane, muscarinic blockade, and higher infused doses of epinephrine. And, seventh, if results can be extrapolated to man, complex interactions between the vagus and catecholamines may explain wandering atrial pacemaker, commonly observed in healthy adults and trained athletes.[45]

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References

1. Atlee JL: Perioperative Cardiac Dysrhythmias. Chicago, Year Book Medical Publisher, 1990, pp 1–11, 380–381, 391–393

2. Stoelting RK: Sympathomimetics, Pharmacology and Physiology, Anesthetic Practice. Edited by Stoelting RK. Philadelphia, JB Lippincott, 1987, pp 251–268

3. Corr PB, Yamada KA, Witkowski FX: Mechanisms controlling cardiac autonomic function and their relation to arrhythmogenesis, The Heart and Cardiovascular System. 2nd edition. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven, 1986, pp 1343–1403

4. Atlee JL, Malkinson CE: Potentiation by thiopental of halothane-epinephrine-induced arrhythmias in dogs. ANESTHESIOLOGY 57:285–288, 1982

5. Atlee JL, Roberts FL: Thiopental and epinephrine-induced dysrhythmias in dogs anesthetized with enflurane or isoflurane. Anesth Analg 65:437–443, 1986

6. Polic S, Atlee JL, Laszlo A, Kampine JP, Bosnjak ZJ: 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. ANESTHESIOLOGY 75: 298–304, 1991

7. Boban M, Atlee JL, Vicenzi MN, Kampine JP, Bosnjak ZJ: Anesthetics and automaticity in latent pacemaker fibers: IV. Effects of isoflurane and epinephrine or norepinephrine on automaticity of dominant and subsidiary atrial pacemakers. ANESTHESIOLOGY 79:555–562, 1993

8. Randall WC, Rinkema LE, Jones SB, Moran JF, Brynjolfsson G: Functional characterization of atrial pacemaker activity. Am J Physiol 242:H98–H106, 1982

9. Jones SB, Euler DE, Hardie E, Randall WC, Brynjolfsson G: Comparison of SA nodal and subsidiary atrial pacemaker function and location in the dog. Am J Physiol 234:H471–H476, 1978

10. Jones SB, Euler DE, Randall WC, Brynjolfsson G, Hardie EL: Atrial ectopic foci in the canine heart: Hierarchy of pacemaker automaticity. Am J Physiol 238:H788–H793, 1980

11. Hardie EL, Jones SB, Euler DE, Fishman DL, Randall WC: Sinoatrial node artery distribution and its relation to hierarchy of cardiac automaticity. Am J Physiol 241:H45–H53, 1981

12. Atlee JL, Dayer AM, Houge JC: Chronic recording from the His bundle of the awake dog. Basic Res Cardiol 79:627–638, 1984

13. Woehlck HJ, Rusy BF, Atlee JL: Comparison of logdose and bracket protocols for determination of epinephrine arrhythmia thresholds in dogs anesthetized with thiopental-halothane. ANESTHESIOLOGY 75:884–892, 1991

14. Sumikawa K, Hirano H: Quantitative analysis of the contribution of pulmonary and hind limb circulation to the clearance of exogenous catecholamines. J Pharmacol Exp Ther 236:759–763, 1986

15. Metz S, Maze M: Halothane concentration does not alter the threshold for epinephrine-induced arrhythmias in dogs. ANESTHESIOLOGY 62:470–474, 1985

16. Eger EI, Lundgren C, Miller SL, Stevens WC: Anesthetic potencies of sulfur hexafluoride, carbon tetrafluoride, chloroform, and ethrane in dogs: Correlation with the hydrate and lipid theories of anesthetic action. ANESTHESIOLOGY 30:129, 1969

17. Eger EI, Saidman LJ, Brandstater B: Temperature dependence of halothane and cyclopropane anesthesia in dogs: Correlation with some theories of anesthetic actions. ANESTHESIOLOGY 26:764, 1965

18. Steffey EP, Howland DJ: Isoflurane potency in the dog and cat. Am J Vet Res 38:1833, 1977

19. Kenny D, Pelc LR, Brooks HL, Kampine JP, Schmeling WT, Warltier DC: Alterations of alpha 1 and alpha 2 adrenoceptor-mediated pressor responses by halothane and isoflurane anesthesia. ANESTHESIOLOGY 71:224–234, 1989

20. Conover WJ: Statistics of the Kolmogorov-Smirnov type, Practical Nonparametric Statistics. 2nd edition. Edited by Shewhart WA, Wilks SS. New York, John Wiley and Sons, 1971, pp 345–380

21. Vick RL: Effects of increased transmural pressures upon atrial and ventricular rhythms in the dog heart-lung preparation. Circ Res 13:39–47, 1963

22. Moe GK, Malton SD, Rennick BR, Freyburger WA: The role of arterial pressure in the induction of idioventricular rhythms under cyclopropane anesthesia. J Pharmacol Exp Ther 94:319–327, 1948

23. Rozanski GJ, Lipsius SL, Randall WC: Functional characteristics of sinoatrial and subsidiary pacemaker activity in the canine right atrium. Circulation 67:1378–1387, 1983

24. Rozanski GJ, Lipsius SL: Electrophysiology of functional subsidiary pacemakers in canine right atrium. Am J Physiol 249:H594–H603, 1985

25. Gomes JA, Winters SL: The origin of the sinus node pacemaker complex in man: Demonstration of the dominant and subsidiary foci. J Am Coll Cardiol 9:45–52, 1987

26. Boineau JP, Schuessler RB, Mooney CR, Wylds AC, Miller CB, Hudson RD, Borremans JM, Brockus CW: Multicentric origin of the atrial depolarization wave: The pacemaker complex. Relation to dynamics of atrial conduction, P-wave changes and heart rate control. Circulation 58:1036–1048, 1978

27. Boineau JP, Schuessler RB, Hackel DB, Miller CB, Brockus CW, Wylds AC: Widespread distribution and rate differentiation of the atrial pacemaker complex. Am J Physiol 239:H406–H415, 1980

28. Anderson RH, Ho SY, Becker AE: Gross anatomy and microscopy of the conducting system, Cardiac Arrhythmias. 2nd edition. Edited by Mandel JW. Philadelphia, JB Lippincott, 1987, pp 13–52

29. Anderson KR, Ho SY, Anderson RH: The location and vascular supply of the sinus node in the human heart. Br Heart J 41:28–32, 1979

30. James TN, Sherf L, Schlant RC, Silverman ME: Anatomy of the heart, The Heart. 5th edition. Edited by Hurst JW. New York, McGraw-Hill, 1982, pp 22–74

31. Randall WC, Talano J, Kaye MP, Euler DE, Jones SB, Brynjolfsson G: Cardiac pacemakers in absence of the SA node: Responses to exercise and autonomic blockade. Am J Physiol 234:H465–470, 1970

32. Kuga K, Yamaguchi I, Sugishita Y, Ito I: Assessment by autonomic blockade of age-related changes of the sinus node function and autonomic regulation in sick sinus syndrome. Am J Cardiol 61: 361–366, 1988

33. Kang PS, Gomes J, Kelen G, El-Sherif N: Role of autonomic regulatory mechanisms in sinoatrial conduction and sinus node automaticity in sick sinus syndrome. Circulation 64:832–838, 1981

34. Dresel PE, MacCannell KL, Nickerson M: Cardiac arrhythmias induced by minimal doses of epinephrine in cyclopropane-anesthetized dogs. Circ Res 3:948–955, 1960

35. Downing SE: Baroreceptor regulation of the heart, Handbook of Physiology. Edited by Berne RM. Bethesda, American Physiological Society, 1979, pp 621–652

36. Zipes DP: Specific arrhythmias, Diagnosis and Treatment in Heart Disease. 3rd edition. Edited by Braunwald E. Philadelphia, WB Saunders, 1988, p 667

37. Randall WC, Rinkema LE, Jones SB, Moran JF, Brynjolfsson G: Overdrive suppression of atrial pacemaker tissues in the alert, awake dog before and chronically after excision of the sinoatrial node. Am J Cardiol 49:1166–1175, 1982

38. Gilmour RF, Zipes DP: Abnormal automaticity and related phenomena, The Heart and Cardiovascular System. Edited by Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE. New York, Raven, 1986, pp 1239–1257

39. Joas TA, Stevens WC: Comparison of arrhythmic doses of epinephrine during forane, halothane, and fluroxene anesthesia in dogs. ANESTHESIOLOGY 35:48–53, 1971

40. Brunsting JR, Bennekers JH, Schuil HA, Zijlstra WG: Incomplete cardiac vagal blockade with atropine in the anesthetized dog. Pflugers Arch 381:293–295, 1979

41. Brunsting JR, Schuil HA, Zijlstra WG: Intrinsic heart rate in the dog determined by pharmacologic denervation. Am J Physiol 245: H592–H597, 1983

42. Schuil HA, Brunsting JR, van der Molen H, Zijlstra WG: Cardioacceleratory effect of muscarinic blocking agents in the dog. Eur J Pharmacol 69:229–233, 1981

43. Rigel DF, Lipson D, Katona PG: Excess tachycardia: Heart rate after antimuscarinic agents in conscious dogs. Am J Physiol 246: H168–H173, 1984

44. Rigel DF, Katona PG: Effects of antihistamines and local anesthetics on excess tachycardia in conscious dogs. J Pharmacol Exp Ther 238:367–371, 1986

45. Huston TP, Puffer JC, Rodney WM: The athletic heart syndrome. N Engl J Med 313:29–34, 1985

46. Bosnjak ZJ, Kampine JP: Effects of halothane, enflurane, and isoflurane on the SA node. ANESTHESIOLOGY 58:314–321, 1983

47. Seagard JL, Hopp FA, Donegan JH, Kalbfleisch JH, Kampine JP: Halothane and the carotid sinus reflex: Evidence for multiple sites of action. ANESTHESIOLOGY 57:191–202, 1982

48. Vicenzi MN, Woehlck HJ, Krolikowski JG, Bosnjak ZJ, Atlee JL: Halothane and epinephrine on the stability of atrial pacemakers (abstract). FASEB J 7:A97, 1993

49. Dujic Z, Roerig DL, Schedewie HK, Kampine JP, Bosnjak ZJ: Presynaptic modulation of ganglionic ACh release by muscarinic and nicotinic receptors. Am J Physiol 259:R288–R293, 1990

50. Heller Brown J: Atropine, scopolamine, and related antimuscarinic drugs, The Pharmacological Basis of Therapeutics, 8th ed. Edited by Goodman Gilman A, Rall TW, Nies AS, Taylor P. New York, Pergamon, 1990, p 159

51. Biscoe TJ, Miller RA: The effect of halothane on carotid sinus baroreceptor activity. J Physiol (Lond) 173:24–37, 1964

52. Cox RH, Bagshaw RJ: Effects of anesthesia on carotid sinus reflex control of arterial hemodynamics in the dog. Am J Physiol 239: H681–H691, 1980

53. Cox RH, Bagshaw RJ: Carotid sinus control of pulsatile hemodynamics in halothane-anesthetized dogs. Am J Physiol 238:H294–H299, 1980

54. Duke PC, Fownes D, Wade JG: Halothane depresses baroreceptor control of heart rate in man. ANESTHESIOLOGY 46:184–187, 1977

55. Pagel PS, Kampine JP, Schmeling WT, Warltier DC: Comparison of the systemic and coronary hemodynamic actions of desflurane, isoflurane, halothane, and enflurane in the chronically instrumented dog. ANESTHESIOLOGY 74:539–551, 1991