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Original Articles

Abnormal Response of Superior Sinoatrial Node to Sympathetic Stimulation Is a Characteristic Finding in Patients With Atrial Fibrillation and Symptomatic Bradycardia

Boyoung Joung, MD, PhD; Hye Jin Hwang, MD; Hui-Nam Pak, MD, PhD;
Moon-Hyoung Lee, MD, PhD; Changyu Shen, PhD; Shien-Fong Lin, PhD; Peng-Sheng Chen, MD

Background—We hypothesized that unresponsiveness of superior sinoatrial node (SAN) to sympathetic stimulation is strongly associated with the development of symptomatic bradycardia in patients with atrial fibrillation (AF).

Methods and Results—We performed 3D endocardial mapping in healthy controls (group 1, n=10) and patients with AF without (group 2, n=57) or with (group 3, n=15) symptomatic bradycardia at baseline and during isoproterenol infusion. Corrected SAN recovery time was abnormal in 0%, 11%, and 36% of groups 1, 2, and 3, respectively ($P=0.02$). At baseline, 90%, 26%, and 7% ($P<0.001$) of the patients had multicentric SAN activation patterns. For groups 1, 2, and 3, the median distance from the superior vena cava-right atrial junction to the most cranial earliest activation site (EAS) was 5.0 (25–75 percentile range, 3.5–21.3), 10.0 (4–20), and 17.5 (12–34) mm at baseline ($P=0.01$), respectively, and 4.0 (0–5), 5.0 (1–10), and 15.0 (5.4–33.3) mm, respectively, during isoproterenol infusion ($P=0.01$), suggesting an upward shift of EAS during isoproterenol infusion. However, although the EAS during isoproterenol infusion was at the upper one third of the crista terminalis in 100% of group 1 and 78% of group 2 patients, only 20% of group 3 patients showed a move of the EAS to that region ($P<0.001$).

Conclusions—Superior SAN serves as the EAS during sympathetic stimulation in patients without AF and in most patients with AF without symptomatic bradycardia. In contrast, unresponsiveness of superior SAN to sympathetic stimulation is a characteristic finding in patients with AF and symptomatic bradycardia. (***Circ Arrhythm Electrophysiol.*** 2011;4:799-807.)

Key Words: sinoatrial node ■ nervous system sympathetic ■ atrial fibrillation ■ sick sinus syndrome ■ pacemakers

Sinoatrial node (SAN) automaticity is maintained by synergistic actions of a voltage clock mediated by voltage-sensitive membrane ionic currents, such as the hyperpolarization-activated pacemaker current,[1] and a Ca^{2+} clock mediated by rhythmic spontaneous sarcoplasmic reticulum Ca^{2+} release.[2] The Ca^{2+} clock in the superior SAN is primarily responsible for rate acceleration during sympathetic

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stimulation.[3] Unresponsiveness of the Ca^{2+} clock in the superior SAN to sympathetic stimulation is a characteristic finding in dogs with atrial fibrillation (AF) and heart failure.[4,5] AF in humans also is associated with significant SAN dysfunction and tachybradycardia syndrome or sick sinus syndrome.[6,7] If the findings in canine models are applicable to humans, then the superior SAN in patients without SAN dysfunction should respond to sympathetic stimulation by

serving as the earliest activation site (EAS). In contrast, failure of the superior SAN to serve as the EAS during isoproterenol infusion would be a characteristic finding in patients with SAN dysfunction. With the development of 3D endocardial electroanatomical mapping techniques, it is possible to define the activation patterns within the human atria to accurately locate the EAS.[8] The purpose of the present study was to use these mapping techniques to determine the EAS at baseline and during isoproterenol infusion in patients without AF (presumably normal SAN), in patients with AF without symptomatic bradycardia, and in patients with both AF and symptomatic bradycardia. The results were used (1) to ascertain whether superior (rostral, upward) shift of EAS is a normal response to isoproterenol infusion in patients without AF, (2) to test the hypothesis that unresponsiveness of the superior SAN to sympathetic stimulation (superior SAN dysfunction) is present in patients with AF, and (3) to test the

hypothesis that superior SAN dysfunction is a more frequent observation in patients with AF and symptomatic bradycardia than in patients with AF but without symptomatic bradycardia.

Methods

Study Population

This prospective study was approved by the Clinical Research and Ethics Committee of the Yonsei University Hospital, Seoul, South Korea, where all mapping studies were performed. Written informed consent was obtained from each patient. We excluded patients from the study if they had a recent (≤3 months) myocardial infarction, ongoing myocardial ischemia, heart failure, valvular heart disease, or ever been treated with amiodarone. All antiarrhythmic medications (including β-blockers and calcium blockers) were suspended >5 half-lives before the study. Group 1 (n=10; 6 men; mean±SD age, 40±12 years) included patients who underwent ablation for paroxysmal supraventricular tachycardia (AV-reciprocating tachycardia with 4 concealed and 3 manifested bypass tract, and 3 AV nodal reentrant tachycardia) but had no history of AF. Group 2 (n=57; 48 men; age, 54±12 years) and group 3 (n=15; 8 men; age, 61±7 years) included patients referred to electrophysiological study for the treatment of symptomatic AF. Group 2 patients had no evidence of symptomatic bradycardia, and group 3 patients had cardiac syncope, presyncope, or dizziness associated with either sinus bradycardia (<40 beats/min) (n=7) or prolonged sinus pauses (>3.0 s) (n=8). Although group 3 patients had indications for pacemaker implantation,[9] only 1 had a pacemaker implanted 3 years before the electrophysiological study. The remaining patients were referred for AF ablation partly because the patients or the referring physicians wanted to avoid pacemaker implantation through ablation-induced reverse remodeling of the SAN.[7]

Electrophysiological Study

Electrophysiological studies were performed in the postabsorptive state. The patients were sedated with midazolam and fentanyl. Multipolar catheters were positioned as follows: (1) 20-pole catheter with 2 to 5 2-mm interelectrode spacing in the coronary sinus with the proximal 10 electrodes positioned at the lateral right atrium (RA) and (2) 10-pole catheter with 2 to 7 2-mm interelectrode spacing along the lateral RA. Surface ECG and bipolar endocardial electrograms were monitored continuously and stored on a computer-based digital amplifier/recorder system with optical disk storage for off-line analysis. Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 400 mm/s.

Sinus node function was evaluated as follows. First, baseline sinus cycle length was determined over 10 consecutive sinus cycles. Second, SAN conduction time was determined after an 8-beat pacing train using the following formula: SAN conduction time=(return−basic cycle length)/2. The SAN conduction time was measured 3 times, and the averaged value was used for data analyses. Third, corrected SAN recovery time (CSNRT) was determined after a 30-s drive train at cycle lengths of 600, 500, and 400 ms, correcting for the baseline cycle length. At each cycle length, CSNRT was determined 3 times, and the average value was used for analyses. CSNRT ≤550 ms was considered normal.[10]

Atrial effective refractory periods (ERPs) were measured 3 times from the distal and proximal coronary sinus and from low and high lateral RA. The averaged values were used for analyses. Conduction time was assessed along the coronary sinus and the lateral RA. Methods for measuring ERP and atrial conduction are described in the online-only Data Supplement.

Electroanatomic Mapping

The 3D mapping was recorded before ablation in group 1 patients. In group 2 and group 3 patients, 3D mapping was performed after circumferential pulmonary vein isolation, linear ablation in the left atrium, or both. No ablation was performed in the RA or near the SAN.

Electroanatomic maps of the RA were created at baseline and during isoproterenol infusion using either Ensite NavX (n=79) or the CARTO mapping system (n=3). These systems record the 12-lead ECG and bipolar electrograms filtered at 30 to 200 Hz from the mapping catheter and the reference electrogram. Fluoroscopy, RA angiography, CT, and the Ensite NavX or CARTO merging were used to facilitate mapping of anatomic structures, particularly the crista terminalis and superior vena cava (SVC)-RA junction, and for ensuring endocardial contact when individual points were acquired. High-density mapping was performed along the crista terminalis, septal RA, and areas of low voltage. Points were acquired if the stability criteria in space (≤6 mm) and local activation time (≤5 ms) were met.[11,12] Editing of points was performed off-line. Local activation was manually annotated at the beginning of the first rapid deflection from the isoelectric line on bipolar electrograms. Points were excluded if they did not conform to the 12-lead ECG P-wave morphology or if they were <75% of the maximum voltage of the preceding electrogram. Low-voltage areas were defined as contiguous areas with a bipolar voltage amplitude of ≤0.5 mV.[11,12]

The crista terminalis was divided equally into 3 parts (lower, middle, and superior). The EAS was then assigned to 1 of the 3 locations based on the 3D maps. The linear distance from the SVC-RA junction to the most cranial EAS was used as a quantitative measure of EAS location. To evaluate the SAN activation patterns, the following definitions were assigned: (1) unicentric, where a single EAS spreads centrifugally to activate the atria, and (2) multicentric, where ≥2 origins of impulses around the SAN with activation time difference of ≤5 ms are separated by a distance of ≥10 mm.[13] Atrial activation patterns were qualitatively assessed and described using anatomically correct nomenclature. The mapping was performed both at baseline and during isoproterenol infusion. Isoproterenol infusion was started at a dose of 7 μg/min. The mapping during isoproterenol infusion was performed at a stable heart rate ≈5 minutes after the commencement of isoproterenol infusion.

Statistical Analysis

Continuous variables that are normally distributed are reported as mean±SD or 95% CI. ANOVA was used to compare the means of continuous variables that are approximately normally distributed among the 3 groups, and the SD estimate based on the ANOVA was used to construct the CIs of group means. Continuous variables that are not normally distributed (the distance from the SVC-RA junction to the most cranial EAS, CSNRT, and SAN conduction time (SANCT)) are reported as median (25th–75th percentile range) and compared using the Kruskal-Wallis test. Normality was determined using the Kolmogorov-Smirnov goodness-of-fit test. Categorical variables are reported as count (percentage) and compared using Fisher exact test. An exact 95% CI was calculated for percentage estimates discussed in the text. SPSS (SSPS Inc; Chicago, IL) software was used to perform all statistical evaluations. A $P \leq 0.05$ was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agreed to the manuscript as written.

Results

Patient Characteristics

The comparisons of basic characteristics among the 3 groups are presented in Table 1. There were more male patients in group 2 than in group 3. There was no significant difference in age, indications for electrophysiological study, left atrial dimension, and left ventricular ejection fraction between groups 2 and 3.

SAN Response to Sympathetic Stimulation

We analyzed a mean of 175±60 points per patient during sinus rhythm. There were no significant differences in the number of points analyzed among groups (P=0.71). At baseline, the EAS was multicentric in 9 of 10 (90%) group 1

Table 1. Clinical Characteristics

	Group 1 (n=10)	Group 2 (n=57)	Group 3 (n=15)	P
Male sex	6 (60)	48 (84)	8 (53)	0.02*
Age, y	40 (32–48)	54 (51–57)	61 (57–65)	<0.001
Type of AF				
PAF	0	44 (77)	9 (60)	<0.001
PeAF	0	13 (23)	6 (40)	<0.001
LA dimension, mm	38.5 (36.8–40.0)	40.4 (38.9–41.9)	43.0 (39.9–46.1)	0.14
LVEF, %	64.4 (60.0–68.4)	64.4 (62.7–66.1)	64.1 (61.3–66.6)	0.98
Underlying disease				
Heart failure	0	0	0	. . .
Hypertension	0	30 (53)	5 (33)	0.006
Age >75 y	0	2 (4)	0	0.64
Diabetes	0	2 (4)	0	0.74
Stroke	0	3 (6)	2 (13)	0.35
CHADS$_2$ score	0	0.6 (0.4–0.8)	0.3 (0.1–0.5)	0.01
ERP, ms				
High RA	223 (204–244)	217 (209–225)	235 (226–245)	0.11
Low RA	232 (216–248)	220 (214–227)	252 (238–266)	<0.001*
Proximal CS	234 (214–257)	236 (227–245)	262 (248–277)	0.03*
Distal CS	257 (245–268)	246 (232–262)	258 (246–269)	0.66
RA CV, m/s	1.29 (1.17–1.39)	0.88 (0.80–0.94)	0.64 (0.44–0.89)	<0.001*
LA CV, m/s	1.26 (1.17–1.33)	0.08 (1.02–1.13)	0.89 (0.82–0.97)	<0.001*

Data are presented as n (%) or as mean (95% CI). AF indicates atrial fibrillation; CHADS$_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or transient ischemic attack; CS, coronary sinus; CV, conduction velocity; ERP, effective refractory period; LA, left atrium; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; RA, right atrium.

*Significant between groups 2 and 3 at P<0.05.

patients and located at the superior to middle parts of the crista terminalis, with the median distances from the SVC-RA junction to the most cranial EAS of 5.0 mm (3.5–21.3 mm). During 7 to 10 μg/min of isoproterenol infusion, the EAS was at the superior part of crista terminalis in 10 (100%) group 1 patients. Figure 1A shows a multicentric EAS at baseline [Figure 1A (a)] within the SVC but not at the crista terminalis. The EAS moved to the superior crista terminalis during isoproterenol infusion [Figure 1A (b)]. The EAS was in the middle crista terminalis at baseline [Figure 1B (a)] and moved to the superior crista terminalis during isoproterenol infusion [Figure 1B (b)] in 1 group 2 patient. Figure 1C shows a typical example of unresponsiveness of the superior SAN to isoproterenol infusion in a patient from group 3. The EAS at baseline [Figure 1C (a)] was ectopic, located in the anterior free wall of the RA. During isoproterenol infusion of 7 μg/min, the EAS moved to the middle crista terminalis [Figure 1C (b)]. The superior SAN in this patient was always activated passively without and with isoproterenol infusion.

The EAS during isoproterenol infusion was at the upper third of the crista terminalis in 10 (100%) group 1 patients, with the median distances from the SVC-RA junction to the most cranial EAS of 4.0 mm (0–5 mm) (Table 2). Figure 2 summarizes the unicentric EAS in group 2 and group 3 patients at baseline (Figure 2A) and during isoproterenol infusion (Figure 2B). Among them, 43 (78%) group 2 patients showed the EAS at the superior margin of the crista

terminalis or SVC during isoproterenol infusion (Table 2). In contrast, only 3 (20%) group 3 patients had EAS in the superior part of the crista terminalis during isoproterenol infusion. The EAS was located significantly more superior (cranial) in group 2 than in group 3 (P<0001). The median distance from the SVC-RA junction to the most cranial EAS was 10.0 mm (4–20 mm) for group 2 and 17.5 mm (12–34 mm) for group 3 (P=0.03) (Figure 2C) at baseline. The distance shortened significantly to 5.0 mm (1–10 mm) in group 2 (P=0.006) and to 15.0 mm (5.4–33.3 mm) in group 3 (P=0.004) during isoproterenol infusion (Figure 2B). The distance from the SVC to the most cranial EAS was longer in group 3 than in group 2 during isoproterenol infusion (P=0.01).

Activation Rate in Sinus Rhythm

Baseline heart rate was 78 beats/min (95% CI, 68–86 beats/min) in group 1, 80 beats/min (95% CI, 76–83 beats/min) in group 2, and 62 beats/min (95% CI, 53–71 beats/min) in group 3 (P=0.001) patients. Group 3 patients had a significantly lower baseline heart rate than group 1 (P=0.02) and group 2 (P<0.001) patients. The mean maximum heart rate during isoproterenol infusion was 129 beats/min (95% CI, 121–137 beats/min) in group 1, 127 beats/min (95% CI, 123–131 beats/min) in group 2, and 106 beats/min (95% CI, 95–117 beats/min) in group 3 (P=0.001) (Table 2). Group 3 patients had a significantly lower heart rate than group 1 (P=0.02) and group
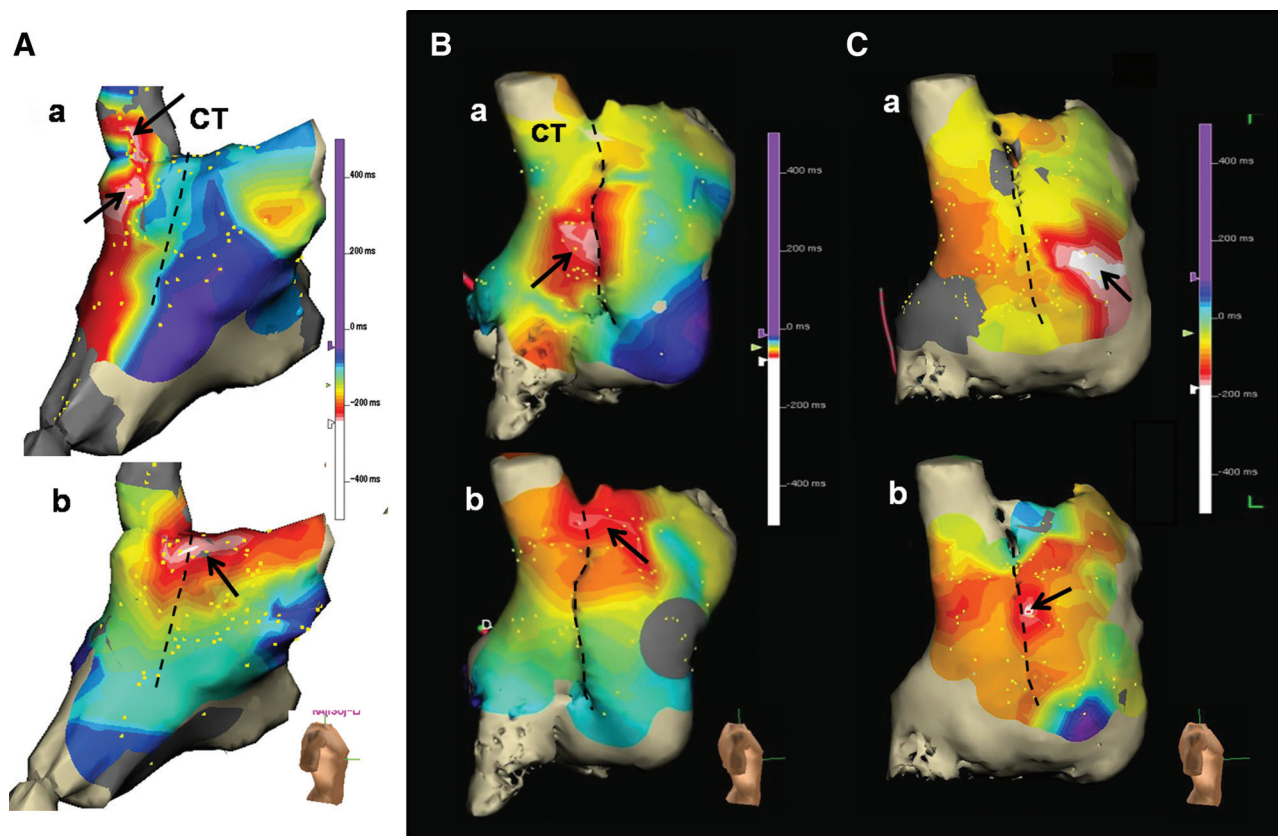
Figure 1. Effects of isoproterenol infusion on earliest activation site (EAS). **A,** From a group 1 patient, the most cranial EAS at baseline (a) was in the superior vena cava. The EAS during isoproterenol infusion (b) was at the superior third of the CT. **B,** Cranial shift of the EAS in a group 2 patient. The EAS at baseline (a) and during isoproterenol infusion (b) were at the middle and superior parts of CT, respectively. **C,** Impaired cranial shift of the EAS in a group 3 patient. The EAS at baseline (a) was ectopic (at the right atrial free wall). The EAS during isoproterenol infusion (b) was located at the middle third of CT. The superior sinoatrial node in this patient was inactive with or without isoproterenol. The dashed line marks the CT. CT indicates crista terminalis.

2 ($P<0.001$) patients during isoproterenol infusion. At baseline, a unicentric activation pattern (as shown in Figure 1A) was identified in 1 (10%; 95% CI, 0.3%–45%), 42 (74%; 95% CI, 60%–84%), and 13 (86%; 95% CI, 60%–98%) patients in groups 1, 2 and 3, respectively ($P<0.001$). After isoproterenol infusion, the unicentric activation patterns were observed in 8 (80%; 95% CI, 44%–97%), 52 (94%; 95% CI, 85%–99%), and 12 (80%; 95% CI, 52%–96%) patients in groups 1, 2, and 3, respectively ($P=0.13$).

The Multicentric Activation Pattern and Alternating EAS

The multicentric activation pattern was found in all patient groups (Table 2). Figure 3A shows an example of multicentric activation in a patient from group 2 at a heart rate of 60 beats/min before isoproterenol infusion. This patient had 4 origins of activation. The EASs were located in the anterior and posterior portion of the crista terminalis, anterior RA, and lower RA (arrows). Figure 3B (a) shows that the EAS (arrows) alternated between the superior and inferior parts of the crista terminalis in a patient from group 2 at a baseline heart rate of 90 beats/min. The distance between 2 EASs was 56 mm. During 10-μg/min isoproterenol infusion, the 2 EASs also were consistently observed at a heart rate of 180 beats/min, and the distance between them was reduced to 38 mm [Figure

3B (b)] because of the upward shift of the lower EAS. Alternating EASs was observed in 1 group 2 patient.

At baseline, multicentric activation patterns were observed in 9 (90%; 95% CI, 55%–99%), 15 (26%; 95% CI, 16%–40%), and 1 (7%; 95% CI, 0.2%–32%) patients in groups 1, 2, and 3, respectively ($P<0.001$). Group 2 ($P=0.008$) and group 3 ($P=0.005$) had a lower number of multicentric activation patterns than group 1. The number of early sites was 2.4 ± 0.7 separated by 20.4 ± 13.2 mm in group 3 compared with 3.5 ± 0.6 sites ($P=0.02$) separated by 27.5 ± 6.5 mm ($P=0.33$) in group 2. Because of frequent sinus arrests, we tried but failed to determine the exact EAS in 1 patient in group 3 (Table 2).

The SAN-RA Propagation

The propagation pattern during sinus rhythm was closely associated with the isoproterenol infusion and EAS location. When the EAS was located at the middle (n=38) and inferior (n=6) parts of the crista terminalis, the propagation pattern was slow across the crista terminalis (Figure 4A) or septum (Figure 4B). However, after the EAS located to the superior crista terminalis at baseline (n=30) and during isoproterenol infusion (n=54), the anterior and posterior conduction delay was not observed (Figure 4C), and the propagation across the crista terminalis showed no significant delays compared with propagation along the crista terminalis.

Table 2.   The Heart Rate and EAS at Baseline and During Isoproterenol Infusion

	Group 1 (n=10)	Group 2* (n=57)	Group 3 (n=15)	P
Baseline				
Heart rate, beats/min	78 (68–86)	80 (76–83)	62 (53–71)	0.001
EAS				
Unicentric	1 (10)	42 (74)	13 (86)	<0.001
Superior	0	28 (49)	2 (13)	
Middle	1 (10)	14 (25)	8 (53)	
Inferior†	0	0	3 (20)	
Multicentric	9 (90)	15 (26)	1 (7)	<0.001
Sinus pause	0	0	1 (7)	0.10
EAS location, mm†‡	5.0 (3.5–21.3)	10.0 (4–20)	17.5 (12–34)	0.01
Isoproterenol				
Heart rate, beats/min	129 (121–137)	127 (123–131)	106 (95–117)	0.001
EAS				
Unicentric	8 (80)	52 (94)	12 (80)	0.13
Superior†	8 (80)	43 (78)	3 (20)	
Middle	0	9 (16)	6 (40)	
Inferior	0	0	3 (20)	
Multicentric	2 (20)§	3 (6)	2 (13)	0.26
Sinus pause	0	0	1 (7)	0.11
EAS location, mm†‡	4.0 (0–5)	5.0 (1–10)	15.0 (5.4–33.3)	0.01

Data are presented as n (%) or mean (95% CI), unless otherwise indicated. EAS indicates earliest activation site.

*EAS was not evaluated in 2 patients in group 2 during isoproterenol infusion.

†P wave between groups 2 and 3.

‡EAS location means the median distance (25th–75th percentile range) from the superior vena cava and right atrial junction to the most cranial EAS.

§All multicentric sites were located at the upper third of the crista terminalis.

Normal Superior SAN Activity During Sympathetic Stimulation in a Patient With RA Scars

Although most of the patients in group 3 had an unresponsive superior SAN, 3 (20%) had responsive superior SAN. Figure 5 shows an example from a patient with long-standing persistent AF and symptomatic SAN dysfunction after cardioversion. In this patient, termination of AF during catheter ablation was followed by junctional rhythm at 40 beats/min [Figure 5A (a)]. There was no SAN activity to compete with the junctional rhythm. The slow junctional rhythm could have explained her symptoms; however, the heart rate increased to 110 beats/min during 10-μg/min isoproterenol infusion, and

the superior part of the crista terminalis came alive to serve as the EAS [Figure 5B (a) arrow]. Figure 5B (b) shows (in gray) that the low-voltage area (<0.5 mV) ranged from the middle to the lower part of the RA and crista terminalis, consistent with the presence of extensive scar formation.

Corrected SAN Recovery Time

The CSNRT was not different among the 3 groups at all pacing cycle lengths (online-only Data Supplement Table). Abnormal CSNRT (>550 ms) was found in 0 (0%; 95% CI, 0%–31%), 6 (11%; 95% CI, 4%–22%), and 5 (33%; 95% CI,
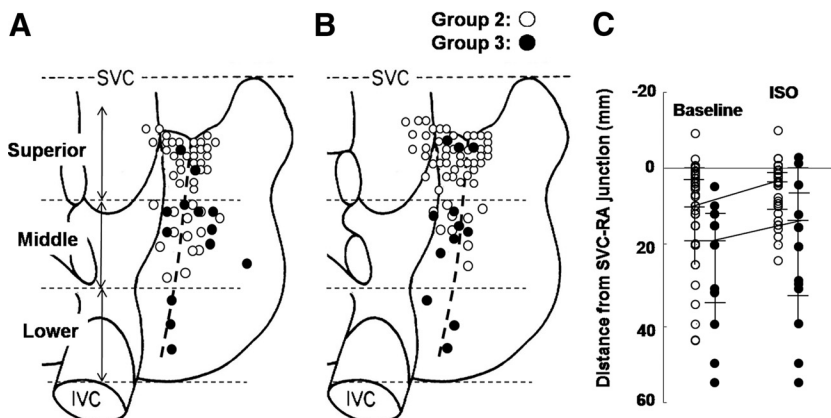

Figure 2. The distribution of the unicentric earliest activation site at baseline (A) and during isoproterenol infusion (B). C, The distance from the SVC-RA junction to the most cranial earliest activation site at baseline and during isoproterenol infusion. ISO indicates isoproterenol; IVC, inferior vena cava; RA, right atrial; SVC, superior vena cava.
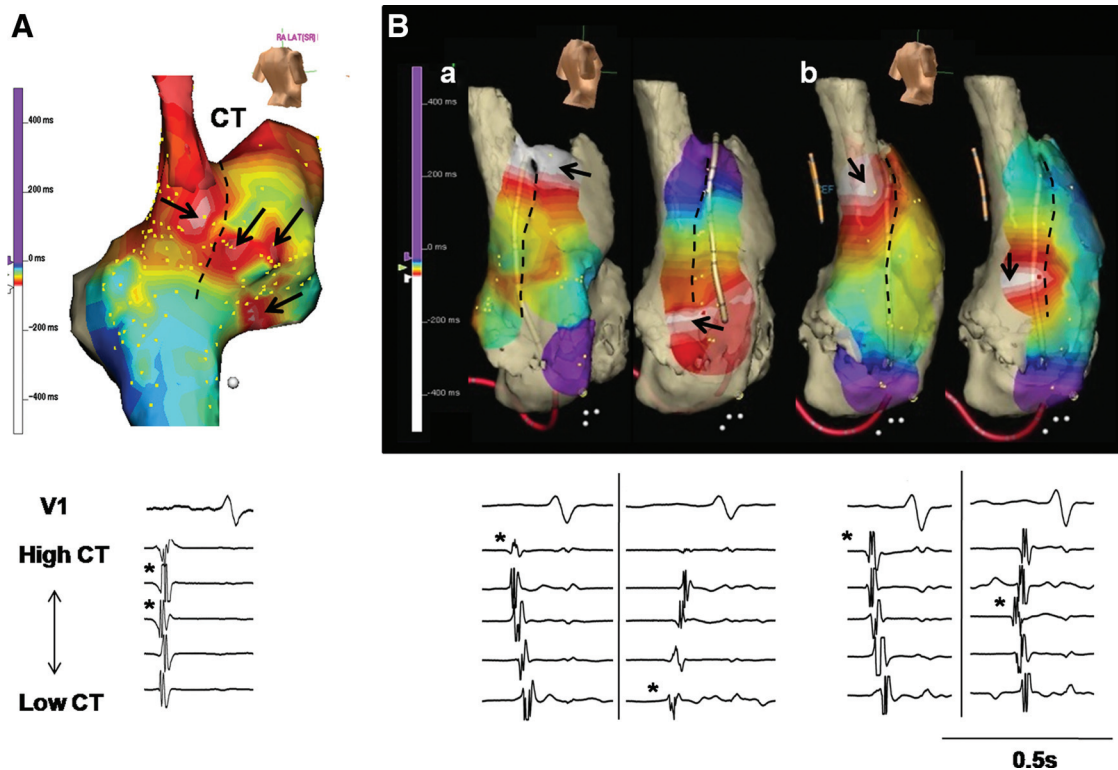
Figure 3. Examples of multicentric and alternating earliest activation sites (EASs). **A**, Multiple EASs were found in the anterior and posterior portion of CT, anterior right atrium, and lower right atrium (arrows). **B**, Alternating EAS at superior (left) to inferior (right) CT at baseline (a) and during isoproterenol infusion (b). Shown are the activation maps and electrograms. The asterisk marks the EAS of CT. The dashed line marks the CT. Abbreviation as in Figure 1.

12%–62%) patients in groups 1, 2, and 3, respectively, at the pacing cycle length of 400 ms ($P=0.02$).

Figure 6A and 6B show SAN response to rapid atrial pacing from group 2 and group 3 patients, respectively. Figure 6C presents the dot plots of the CSNRT from 2 groups, showing that there is a large overlap of CSNRT between the 2 groups.

Other Electrophysiological Differences Between Groups 2 and 3
The ERP and conduction velocity of the 3 groups are described in Table 1. ERPs were longer in group 3 than in group 2 at both high and low RA sites. Although the ERP of the proximal coronary sinus was longer in group 3 than in group 2, the distal coronary sinus showed no difference between group 3 and group 2. There was significant prolongation in the RA conduction velocity in group 3 compared with group 2. Left atrial conduction velocity along the coronary sinus catheter also was significantly longer in group 3 compared with group 2 at the pacing cycle length of 600 ms. RA low-voltage area was significantly larger in group 3 ($58\pm29\%$) than in group 2 ($38\pm30\%$, $P=0.01$).

Normalization of SAN Function After AF Ablation
After radiofrequency catheter ablation of AF, sinus rhythm was maintained in 13 of the 15 group 3 patients (87%; 95% CI, 60%–68%), including 4 (27%; 95% CI, 8%–55%) patients taking antiarrhythmic drugs during 10 months (25th–75th percentile range, 6–14 months) of follow-up. Excluding 1 patient with a previous pacemaker implantation and 2 patients with AF,

we compared the Holter monitoring before and after ablation of AF in 12 group 3 patients. Compared with that before baseline, maximum sinus pause shortened from 5.0 ± 3.1 to 2.0 ± 1.1 s ($P=0.03$), and minimum heart rate increased from 30.6 ± 8.4 to 47.4 ± 16.6 beats/min ($P=0.03$). Baseline symptoms of bradycardia (sinus pause >3 s) persisted in 2 patients with paroxysmal attacks of AF. There were no documented symptomatic bradycardia episodes in the other patients.

Comparative Efficacy of Testing for Symptomatic Bradycardia
We analyzed the comparative efficacy of CSNRT and 3D mapping in differentiating group 2 and group 3 patients. CSNRT >550 ms at 400 ms pacing cycle length is considered a positive CSNRT test. The failure of superior SAN to serve as the EAS during isoproterenol infusion is considered a positive 3D mapping test. The sensitivity, specificity, positive predicative efficacy, and negative predicative efficacy of the CSNRT test were 35%, 89%, 45%, and 84%, respectively, and of the 3D mapping test, 78%, 78%, 47%, and 93%, respectively. The 3D mapping test is twice as sensitive but slightly less specific than the CSNRT test in detecting patients with AF and symptomatic bradycardia. However, the predictive efficacies of these 2 tests are comparable.

Discussion
We found that the majority of EASs during sinus rhythm are located along the crista terminalis, but the exact location of an EAS is highly variable. The EAS at baseline can be found as
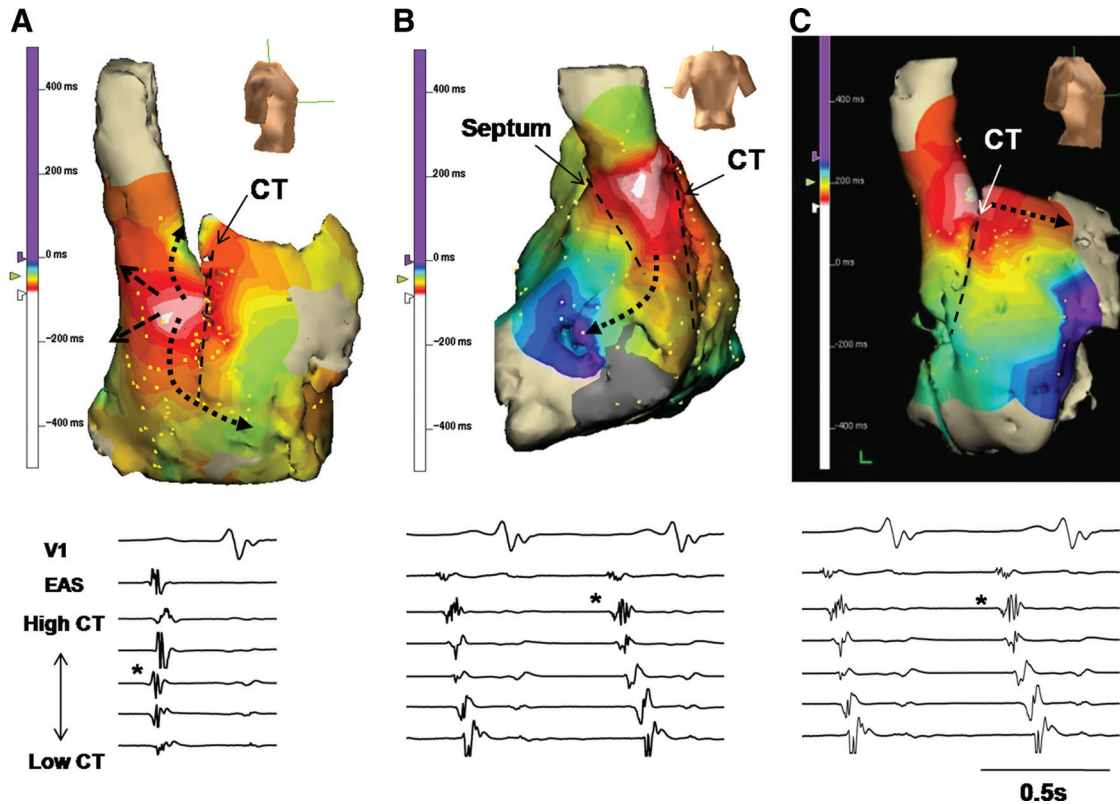
Figure 4. The EAS and propagation pattern. **A**, The EAS was located at the posterior side of the middle part of the CT. The anterior conduction was delayed at the CT. **B**, The posterior conduction was delayed at the septum. **C**, The EAS was located at the superior vena cava and right atrial junction, showing no delay in anterior conduction pathways. Activation maps and electrograms are shown. The asterisk marks the EAS of the CT. The dashed line indicates the location of the CT. EAS indicate earliest activation site. Other abbreviation as in Figure 1.

high as within the SVC and as low as 56 mm from the SVC-RA junction. In the majority of patients without AF and in approximately one half of the patients with AF but without symptomatic bradycardia, the EAS was located in the superior third of the SAN at baseline. During isoproterenol infusion, the superior SAN invariably served as the EAS in all patients without AF and in three fourths of patients with AF but without symptomatic bradycardia. On the other hand, in patients with both AF and symptomatic bradycardia, the EAS was usually located in the mid-SAN at baseline and rarely moved to the
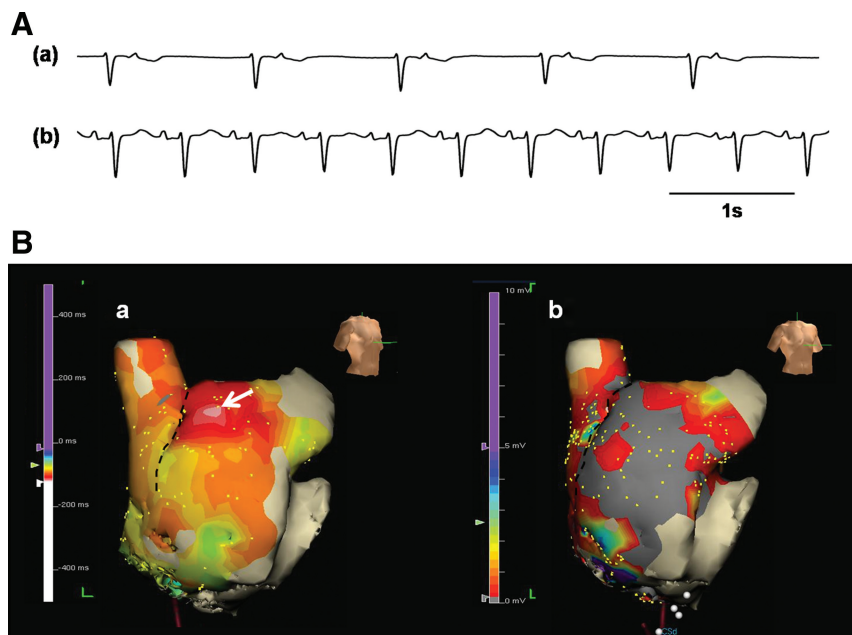

Figure 5. Responsive superior sinoatrial node during isoproterenol infusion in a 50-year-old woman with long-standing persistent atrial fibrillation and sinoatrial node dysfunction. **A**, Junctional rhythm of 40 beats/min after termination of AF (a). A sinus P wave appeared and the sinus rate increased to 110 beats/min during isoproterenol infusion of 10 μg/min (b). **B**, Right atrial activation map during isoproterenol infusion (a). The superior part of the crista terminalis is the earliest activation site (arrow) (a). The right atrial voltage map (b) shows low voltage in the middle and lower parts of the right atrium and crista terminalis, as indicated in gray (<0.5 mV). The dashed line indicates the location of the crista terminalis.
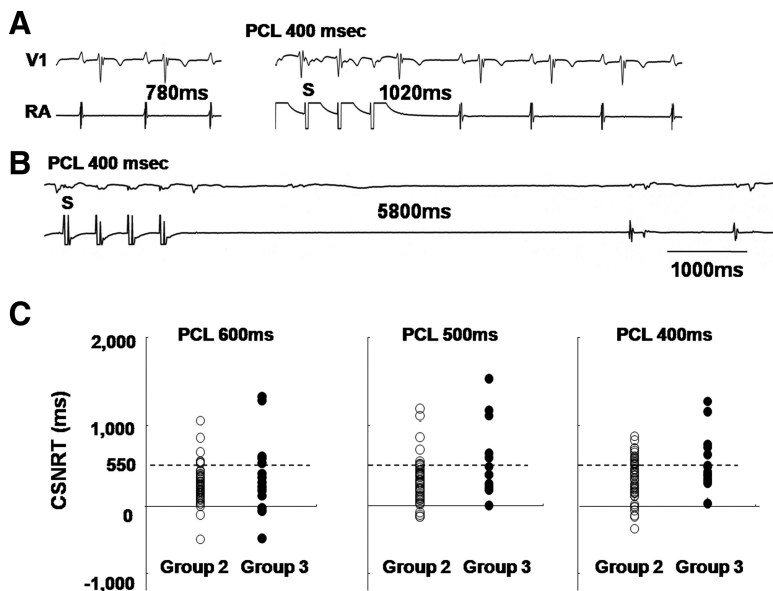
Figure 6. A, Normal CSNRT. The basic sinus cycle length and SNRT are 780 ms (left) and 1020 ms (right), respectively, resulting in a CSNRT of 240 ms. **B**, Abnormal CSNRT in a patient with tachy-bradycardia syndrome. The basic sinus cycle length and SNRT are 1000 ms (left) and 5800 ms (right), respectively, resulting in a CSNRT of 4800 ms. The upper and lower tracings are the V1 lead and RA electrogram, respectively. **C**, Dot plots of the CSNRT from group 2 and 3 at each PCL, showing large overlaps between the 2 groups. The dashed line shows the CSNRT of 550 ms. CSNRT indicates correct sinoatrial node recovery time; PCL, pacing cycle length. Other abbreviation as in Figure 2.

superior SAN during isoproterenol infusion. If a superior shift of the EAS during isoproterenol infusion is used as a test to identify patients with symptomatic bradycardia, then the test has a sensitivity of 78%. In comparison, sensitivity of CSNRT was only 35%. We conclude that a superior shift of EAS is a normal response to isoproterenol infusion in patients without AF and in a majority of patients with AF but no symptomatic bradycardia. In comparison, the unresponsiveness of superior SAN to serve as an EAS during sympathetic stimulation (superior SAN dysfunction) is a common finding among patients with both AF and symptomatic bradycardia.

EAS and Sympathetic Tone

Schuessler et al[14] reported that in a canine model, sympathetic stimulation in general tends to induce a cranial shift in the location of the pacemaker within the pacemaker complex. Although an upward shift of EAS has not been confirmed in humans by 3D mapping, the downward shift of EAS has been reported in patients after esmolol infusion.[8] Taken together, the canine and human studies show that superior SAN is primarily responsible for heart rate acceleration during sympathetic stimulation in patients with normal SAN function.

SAN Function in Patients With AF and Symptomatic Bradycardia

Sick sinus syndrome is an abnormality involving the generation of the action potential by the SAN and is characterized by an atrial rate inappropriate for the physiological requirements. AF is associated with significant electrophysiological and structural remodeling and often is associated with sick sinus syndrome.[6,7] In dogs, persistent (>2 weeks) rapid atrial pacing and chronic AF resulted in SAN dysfunction, as evidenced by prolongation of the SAN recovery time and a decrease in intrinsic heart rate.[15] SAN dysfunction has been reported in humans with AF[6,16] and may be reversible after successful AF ablation.[7] Consistent with that found in a canine model,[4] patients with AF in the present study had impaired heart rate acceleration and absence of upward shift of the EAS during isoproterenol stimulation. These findings

suggest that Ca^{2+} clock malfunction underlies these abnormal physiological responses to isoproterenol infusion.

Cranial Shift of the EAS and SAN-RA Propagation

An alternative mechanism for upward shift of the EAS is the change of the exit pathway between SAN and RA. Previous studies have shown that the impulse from the SAN propagates into the RA through an upper and a lower exit site.[17] It is possible that isoproterenol preferentially shifts the exit site to the upper portion of the SAN. Because the extracellular electrograms cannot be used to differentiate SAN activation and RA activation, the shifting of SAN exit sites and the shifting of the actual pacemaking sites may look the same on the 3D map. The data from the present study cannot be used to differentiate these 2 mechanisms, but we show that in 1 patient with extensive RA fibrosis and junctional rhythm at baseline, isoproterenol infusion reactivated the pacemaker in the superior SAN. In this patient, changing the SAN-RA exit pathway is not a mechanism of upward shift of the EAS. In other patients with an upward shift of EAS during isoproterenol infusion, the conduction between SAN and RA occurred at multiple directions without evidence of conduction delay along the crista terminalis or septum. Based on these findings and the mapping of the Ca^{2+} clock activity in canine models, we propose that the pacemaker hierarchy likely is created by differential responses of the Ca^{2+} clock to sympathetic tone at different portions of the SAN.

Unicentric Versus Multicentric Activation

Sanders et al[11] reported that multicentric activation is found both in healthy controls and in patients with heart failure. However, the EASs were more numerous in controls (average 4 sites) than in patients with heart failure (average 2.5 sites). They also reported that the SAN complex in patients with SAN dysfunction more often is unicentric, localized to the lower crista terminalis at the site of the largest residual voltage amplitude. Consistent with Sanders et al, we found in the present study that most group 1 patients had a multicentric

SAN activation pattern and that the number of EASs in group 2 and group 3 patients was lower than that in group 1 patients. A reduction of the EAS suggests that there are fewer back-up pacemaking sites to respond to sympathetic stimulation, which could be a sign of SAN dysfunction.

Conclusions

The superior SAN serves as the EAS during sympathetic stimulation in patients without AF and in most patients with AF but without symptomatic bradycardia. In contrast, unresponsiveness of the superior SAN to sympathetic stimulation is a characteristic finding in patients with AF and symptomatic bradycardia. Three-dimensional mapping is a more-sensitive test than CSNRT in identifying patients with AF and symptomatic bradycardia.

Disclosures
None.

References
1. Difrancesco D. The role of the funny current in pacemaker activity. *Circ Res*. 2010;106:434–446.
2. Lakatta EG, Maltsev VA, Vinogradova TM. A coupled system of intracellular Ca2+ clocks and surface membrane voltage clocks controls the timekeeping mechanism of the heart's pacemaker. *Circ Res*. 2010;106: 659–673.
3. Joung B, Tang L, Maruyama M, Han S, Chen Z, Stucky M, Jones LR, Fishbein MC, Weiss JN, Chen PS, Lin SF. Intracellular calcium dynamics and acceleration of sinus rhythm by beta-adrenergic stimulation. *Circulation*. 2009;119:788–796.
4. Joung B, Lin SF, Chen Z, Antoun PS, Maruyama M, Han S, Piccirillo G, Stucky M, Zipes DP, Chen PS, Das KM. Mechanisms of sinoatrial node dysfunction in a canine model of pacing-induced atrial fibrillation. *Heart Rhythm*. 2010;7:88–95.
5. Shinohara T, Park HW, Han S, Shen MJ, Maruyama M, Kim D, Chen PS, Lin SF. Ca2+ clock malfunction in a canine model of pacing-induced heart failure. *Am J Physiol Heart Circ Physiol*. 2010;299:H1805–H1811.
6. Gomes JA, Kang PS, Matheson M, Gough WB Jr, El Sherif N. Coexistence of sick sinus rhythm and atrial flutter-fibrillation. *Circulation*. 1981;63:80–86.
7. Hocini M, Sanders P, Deisenhofer I, Jaïs P, Hsu LF, Scavée C, Weerasoriya R, Raybaud F, Macle L, Shah DC, Garrigue S, Le MP, Clémenty J, Haïssaguerre M. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation*. 2003;108:1172–1175.
8. Marrouche NF, Beheiry S, Tomassoni G, Cole C, Bash D, Dresing T, Saliba W, Abdul-Karim A, Tchou P, Schweikert R, Leonelli F, Natale A. Three-dimensional nonfluoroscopic mapping and ablation of inappropriate sinus tachycardia. Procedural strategies and long-term outcome. *J Am Coll Cardiol*. 2002;39:1046–1054.
9. Epstein AE, Dimarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary. *Heart Rhythm*. 2008;5:934–955.
10. Josephson ME. *Clinical Cardiac Electrophysiology: Techniques and Interpretations*. 4th ed. Baltimore, MD: Lippincott, Williams and Wilkins; 2008.
11. Sanders P, Kistler PM, Morton JB, Spence SJ, Kalman JM. Remodeling of sinus node function in patients with congestive heart failure: reduction in sinus node reserve. *Circulation*. 2004;110:897–903.
12. Sanders P, Morton JB, Kistler PM, Spence SJ, Davidson NC, Hussin A, Vohra JK, Sparks PB, Kalman JM. Electrophysiological and electroanatomic characterization of the atria in sinus node disease: evidence of diffuse atrial remodeling. *Circulation*. 2004;109:1514–1522.
13. Boineau JP, Canavan TE, Schuessler RB, Cain ME, Corr PB, Cox JL. Demonstration of a widely distributed atrial pacemaker complex in the human heart. *Circulation*. 1988;77:1221–1237.
14. Schuessler RB, Boineau JP, Wylds AC, Hill DA, Miller CB, Roeske WR. Effect of canine cardiac nerves on heart rate, rhythm, and pacemaker location. *Am J Physiol*. 1986;250:H630–H644.
15. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs—electrophysiological remodeling. *Circulation*. 1996;94:2953–2960.
16. Van Den Berg MP, Van GI. Atrial fibrillation and sinus node dysfunction. *J Am Coll Cardiol*. 2001;38:1585–1586.
17. Fedorov VV, Schuessler RB, Hemphill M, Ambrosi CM, Chang R, Voloshina AS, Brown K, Hucker WJ, Efimov IR. Structural and functional evidence for discrete exit pathways that connect the canine sinoatrial node and atria. *Circ Res*. 2009;104:915–923.

CLINICAL PERSPECTIVE

Sinoatrial node (SAN) automaticity is maintained by synergistic actions of a voltage clock mediated by voltage-sensitive membrane ionic currents, such as the hyperpolarization activated pacemaker current, and a Ca^{2+} clock mediated by rhythmic spontaneous sarcoplasmic reticulum Ca^{2+} release. The Ca^{2+} clock in the superior SAN is primarily responsible for rate acceleration during sympathetic stimulation. In a canine model of atrial fibrillation (AF) and SAN dysfunction, the Ca^{2+} clock in the superior SAN was not responsive to sympathetic stimulation. However, the mechanism of SAN dysfunction in humans is not fully understood. Using 3D mapping techniques to determine the earliest activation site at baseline and during isoproterenol infusion, we found that the superior SAN serves as the earliest activation site during sympathetic stimulation in patients without AF and in most patients with AF without a history of symptomatic bradycardia. In contrast, unresponsiveness of the superior SAN to sympathetic stimulation was a characteristic finding in patients with AF with a history of symptomatic bradycardia. If a superior shift of the earliest activation site during isoproterenol infusion is used as a test to identify patients with symptomatic bradycardia, then the test has a sensitivity and specificity of 78% and 78%, respectively. The results suggest that the unresponsiveness of the superior SAN to serve as the earliest activation site during sympathetic stimulation (superior SAN dysfunction) is a mechanism of SAN dysfunction in patients with both AF and symptomatic bradycardia. The unresponsiveness of the superior SAN to sympathetic stimulation might be used as a test to detect patients with SAN dysfunction.

SUPPLEMENTAL MATERIAL

Supplementary Methods

Effective Refractory Period

Atrial effective refractory periods (ERPs) were evaluated with S_2 strength at twice diastolic threshold current (for a pacing threshold of <2 mA) after 8 S_1 paced beats at cycle lengths of 600, 500, and 400 ms. An incremental technique was used, starting with an S_1- S_2 coupling interval of 150 ms. The coupling interval was then increased with 5 ms increments until S_2 captured the atria. The ERP was defined as the longest coupling interval that failed to capture the atria. ERP was measured from the distal and proximal coronary sinus and from low and high lateral RA for 3 times. The averaged values were used for analyses.

Atrial Conduction

Conduction velocity was assessed along the coronary sinus by pacing from the distal bipole (1-2) of the coronary sinus catheter and measuring the activation time at the proximal bipole (9-10), and along the lateral RA by pacing from the distal bipole (1-2) of the lateral RA catheter and measuring time to activate bipoles 9-10. At both sites, conduction was measured at pacing cycle lengths of 600, 500, and 400 ms during stable capture. Conduction time was determined 10 times at each cycle length and the average value was used for analyses.

Supplementary Table. CSNRT, Number of patients with abnormal CSNRT (> 550ms), and SANCT.

	Group 1	Group 2	Group 3	P-value
CSNRT, ms, (median (25-75% percentile))				
PCL 600 ms	299 (215-364)	291 (210-402)	356 (138-621)	0.65
PCL 500 ms*	248 (183-314)	305 (140-405)	383 (224-736)	0.12
PCL 400 ms*	169 (151-313)	285 (98-440)	341 (220-723)	0.14
No. Patients with CSNRT > 550 ms, n				
PCL 600 ms*	0	7 (12)	5 (36)	0.03
PCL 500 ms*	0	4 (7)	5 (36)	0.005
PCL 400 ms*	0	6 (11)	5 (36)	0.02
SANCT, ms				
PCL 600 ms*	141 (56-189)	130 (78-173)	216 (126-258)	0.02
PCL 500 ms	133 (81-177)	135 (77-180)	116 (82-218)	0.97
PCL 400 ms	115 (84-151)	128 (70-155)	82 (32-135)	0.43

CSNRT, corrected sinus node recovery time; PCL, pacing cycle length; SANCT, sinoatrial node conduction time.

* P-value was significant between groups 2 and 3 (p<0.05).