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Reverse Remodeling of Sinus Node Function After Catheter Ablation of Atrial Fibrillation in Patients With Prolonged Sinus Pauses

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Background—Symptomatic prolonged sinus pauses on termination of atrial fibrillation (AF) are an indication for pacemaker implantation. We evaluated sinus node function and clinical outcome in patients with prolonged sinus pauses on termination of arrhythmia who underwent ablation of paroxysmal AF.

Methods and Results—Twenty patients with paroxysmal AF and prolonged sinus pauses (≥ 3 seconds) on termination of AF underwent ablation between May 1995 and November 2002. Patients with sinus pauses independent of episodes of AF were excluded from the analysis. The procedure included pulmonary vein and linear atrial ablation. After ablation, sinus node function was assessed during the first week and at 1, 3, and 6 months, by 24-hour ambulatory monitoring to determine the mean heart rate and heart rate range, and by exercise testing to determine the maximal heart rate. Corrected sinus node recovery time was determined at the completion of ablation and at 24.0 ± 11.3 months at 600 and 400 ms. After AF ablation, there was a significant improvement of sinus node function, with an increase in the mean heart rate ($P=0.001$), maximal heart rate ($P<0.0001$), and heart rate range ($P<0.0001$). The corrected sinus node recovery time decreased in all patients evaluated at 600 ms ($P=0.016$) and 400 ms ($P=0.019$). At 26.0 ± 17.6 months, 18 patients (85%) had no recurrence of AF (in the absence of medication), with no symptoms attributable to bradycardia or sinus pauses on ambulatory monitoring. Two patients had infrequent episodes of AF, 1 requiring pacemaker implantation.

Conclusion—Prolonged sinus pauses after paroxysms of AF may result from depression of sinus node function that can be eliminated by curative ablation of AF. This is accompanied by improvement in parameters of sinus node function, suggesting reverse remodeling of the sinus node. (*Circulation*. 2003;108:1172-1175.)

Key Words: ablation ■ atrium ■ arrhythmia ■ fibrillation ■ sinoatrial node

Sinus node disease (SND) is frequently associated with Atrial fibrillation (AF), forming the basis of the “tachycardia-bradycardia syndrome.”¹ Although the mechanisms of this association have not been fully elucidated, studies have implicated bradycardia-related heterogeneity of refractoriness in the development of AF in patients with SND.² In addition, atrial arrhythmias themselves may result in sinus node dysfunction.³⁻⁵

Prolonged sinus pauses on termination of AF are an accepted indication for pacemaker implantation. However, these frequently occur in patients on antiarrhythmic or rate-controlling drugs. In this prospective clinical study, we evaluate the recovery of sinus node function after ablation of AF in patients with prolonged sinus pauses on termination of

AF. We hypothesized that curative ablation of AF, with the cessation of associated pharmacotherapy, would obviate the need for pacing in a subset of patients.

Methods

Study Population

The study population consisted of all patients undergoing curative ablation of drug-refractory paroxysmal AF between May 1995 and November 2002 with documented, prolonged sinus pauses (≥ 3 seconds) on termination of AF. Patients were excluded if ambulatory monitoring revealed sinus pauses independent of episodes of AF. These patients had at least 1 episode of symptomatic AF every 10 days.

All patients gave written informed consent to the study, which was approved by the institutional Clinical Research and Ethics Committee.

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Electrophysiological Study

Electrophysiological study was performed in the postabsorptive state with sedation. All antiarrhythmics, including calcium channel and β -blockers, with the exception of amiodarone, were ceased ≥ 5 half-lives before ablation.

Surface ECG and bipolar endocardial electrograms were continuously monitored and recorded for offline analysis (Bard Electrophysiology). Intracardiac electrograms were filtered from 30 to 500 Hz and measured at a sweep speed of 100 mm/s.

Mapping and Ablation of AF

All patients had effective anticoagulation for ≥ 1 month and transesophageal echocardiography to exclude left atrial thrombus before ablation. The techniques used include ablation of pulmonary veins (PV), non-PV foci, and the addition of left atrial linear lesions. In all patients, the cavotricuspid isthmus was ablated.

Radiofrequency ablation was performed with continuous temperature feedback control by using a 4-mm-tip thermocouple-equipped or irrigated-tip ablation catheter (Biosense-Webster). PV ablation was performed with a target temperature of 50°C, a power limit of 30 W, and irrigation of 10 mL/min. For linear ablation, 40 to 50 W of power was delivered with irrigation of 30 to 50 mL/min.

Electrical Isolation of PVs

Ablation targeted regions of earliest PV activation or polarity reversal on circumferential mapping at the PV ostium to achieve electrical isolation of the PVs. The initial strategy was electrical isolation of the "arrhythmogenic PV"; however, because of recurrences of AF, the procedure was expanded to systematic isolation of all PVs.

Left Atrial Linear Ablation

Linear ablation was performed to join anatomic structures to prevent reentry. The extent of ablation performed was tailored to each individual. These included ablation of the left inferior PV to the lateral mitral annulus (mitral isthmus), joining the two superior PVs (roofline), or joining the roofline to the anterior mitral annulus (anterior line). The end point of these procedures was the demonstration of complete linear block with continuous wide double potentials with an activation detour that was confirmed using differential pacing techniques.

Sinus Node Function

Corrected Sinus Node Recovery Time

The sinus node recovery time (SNRT) was assessed at 600 and 400 ms after a 60-second pacing train at twice the diastolic threshold, and it was determined as the time from the stimulus artifact to the earliest atrial activity. The SNRT was repeated twice at each cycle length and averaged. The corrected SNRT was determined by correcting for the underlying sinus cycle length. In 9 patients, electrophysiological study was performed at >6 months after ablation to evaluate sinus node function.

Mean Heart Rate and Heart Rate Range

The mean heart rate was determined by 24-hour ambulatory monitoring during the first week and then 1, 3, and 6 months after ablation. Heart rate range was defined as the difference between maximum and minimum heart rates over the 24-hour period and was determined at the same time intervals.

Maximal Heart Rate

The maximal heart rate achieved by each patient was determined by a maximal exercise stress test performed during the first week and then at 1, 3, and 6 months after ablation.

Follow-Up

All patients were monitored in hospital for at least 3 days after ablation. Patients were clinically reevaluated at 1, 3, and 6 months after ablation, after which in the absence of AF or symptoms, the referring physician provided follow-up data. After ablation, all

antiarrhythmic drugs were ceased in the absence of concurrent indications. In the event of recurrent AF, patients were offered further ablation or trial of a previously ineffective drug therapy.

Statistical Analysis

All variables are reported as mean \pm SD. Sequential data measurements were analyzed by repeated-measures ANOVA followed by the Fisher's protected *t* tests for multiple comparisons. Comparison between groups was performed with the Student's *t* test. Statistical significance was established at $P < 0.05$.

Results

Patients' Characteristics

Twenty patients (14 men; age 56.0 ± 12.1 years) were included in this analysis. These patients had paroxysmal AF for 100 ± 80 months, with documented prolonged sinus pauses on termination of AF ranging from 3 to 10 seconds (4.8 ± 2.2 seconds). Sinus pauses were correlated with symptoms of syncope ($n=6$) or presyncope ($n=11$). These patients had failed therapy using 4.7 ± 1.7 antiarrhythmics and/or rate-controlling drugs (2 on amiodarone). Five patients had structural heart disease or hypertension, and 2 had prior implantation of a pacemaker.

Ablation of AF

A total of 33 ablation sessions were performed; 1 in 10 patients, 2 in 7 patients, and 3 in 3 patients. A total of 70 PVs were targeted. All 4 PVs were electrically disconnected in 13 patients, with 5.7 ± 0.9 minutes of radiofrequency energy delivered to each PV. Non-PV triggers of AF were ablated in 7 patients, at the posterior left atrium ($n=2$), the left atrial septum ($n=2$), left atrial roof ($n=1$), left-sided superior vena cava ($n=1$), and the ostium of the coronary sinus ($n=1$), with 7.5 ± 4.0 minutes of radiofrequency energy. Left atrial linear ablation was performed in 9 patients. This included mitral isthmus ablation ($n=6$), anterior line ($n=2$), and roofline ($n=1$). A mean of 6.0 ± 0.7 minutes of radiofrequency energy was delivered for each linear lesion.

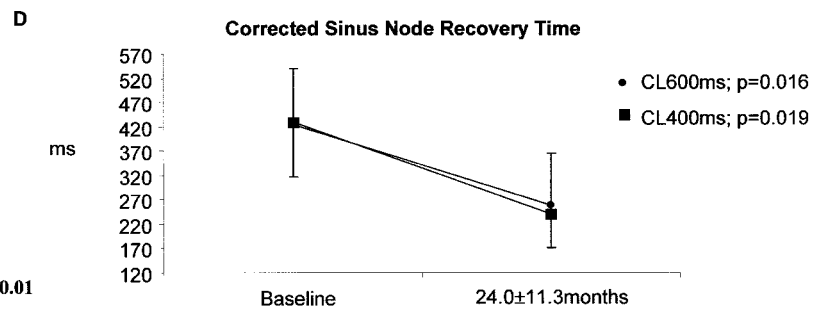
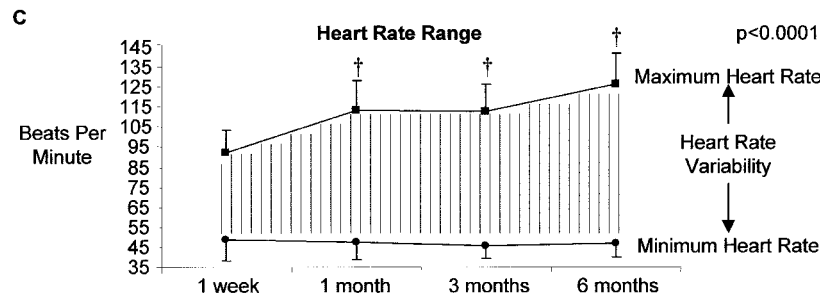
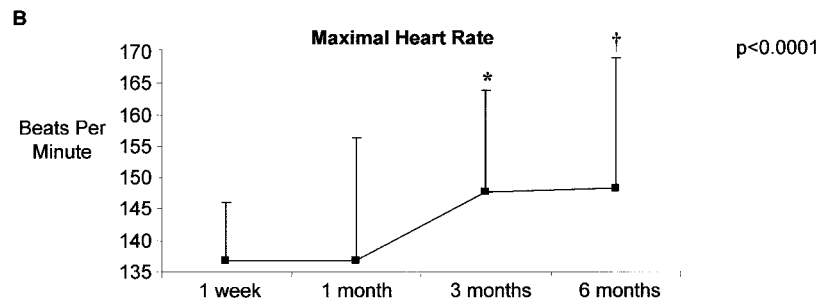
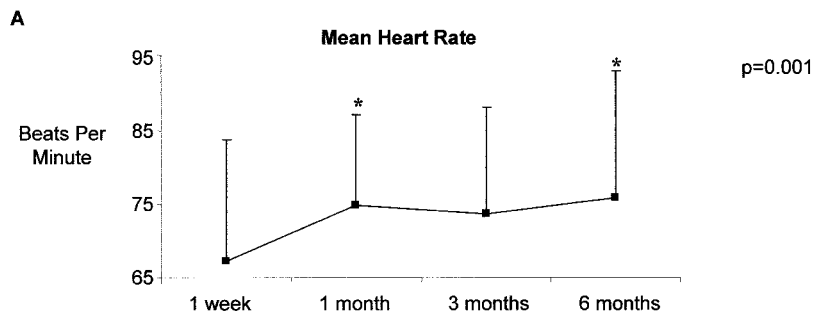
The mean fluoroscopy and procedural duration per session were 54 ± 28 and 165 ± 11 minutes, respectively. One patient developed a small postprocedural pericardial effusion that was managed medically. No patient had evidence of acute PV stenosis by angiography immediately after the procedure or at 12 months after ablation, according to CT angiography.

Clinical Outcome

At 26.0 ± 17.6 months after the last ablation session, 3 patients had recurrent episodes of AF. A previously ineffective antiarrhythmic drug was reinitiated resulting in the elimination of AF in 1 patient and a reduction in the frequency of AF in the remaining 2 patients. The third patient had ongoing symptomatic and persistent sinus pauses on termination of AF, which necessitated implantation of a pacemaker. Seventeen patients (85%) remained free of AF without the use of antiarrhythmic drugs. No patient developed symptoms attributable to SND.

Sinus Node Function

No sinus pauses ≥ 3 seconds were observed by ambulatory monitoring during the first week after ablation or at 1, 3, and 6 months in 19 patients.



A, Mean heart rate. B, Maximal heart rate. C, Heart rate range. D, Corrected SNRT. CL indicates cycle length.

Mean Heart Rate

A significant increase in the mean heart rate was observed with the maintenance of sinus rhythm after ablation ($P=0.001$). The mean heart rate increased from 67.2 ± 16.6 bpm after ablation to 75.9 ± 17.4 bpm at 6 months ($P<0.05$; Figure, A).

Maximal Heart Rate

A significant increase in the maximum heart rate achieved by exercise stress testing was observed with the maintenance of sinus rhythm after ablation ($P<0.0001$). The maximal heart rate achieved by exercise testing in the week after ablation was 136.8 ± 9.3 bpm and increased progressively to 148.3 ± 20.9 bpm at 6 months ($P<0.01$; Figure, B). There was no significant difference in the maximum exercise level achieved at each time point.

Heart Rate Range

Heart rate range was observed to significantly increase after ablation and the maintenance of sinus rhythm ($P<0.0001$), from 43.6 ± 8.9 bpm in the first week after ablation to 78.8 ± 14.4 bpm at 6 months ($P<0.01$; Figure, C).

Sinus Node Recovery Time

Immediately after ablation, 42% of patients had a corrected SNRT ≥ 500 ms. The corrected SNRT was 428.6 ± 111.3 and 425.0 ± 108.4 ms at 600 and 400 ms, respectively. At 24.0 ± 11.3 months after ablation, an abbreviation of the corrected SNRT was observed in all patients evaluated to 240.1 ± 124.4 ms (range 50 to 435 ms; $P=0.016$) and 259.1 ± 89.3 ms (range 100 to 330 ms; $P=0.019$) at 600 and 400 ms, respectively (Figure, D). The abbreviation in the corrected SNRT was observed to be independent of drug

therapy, with only 1 patient restudied being treated with amiodarone at the time of ablation.

Discussion

The present study demonstrates that prolonged sinus pauses on termination of AF may be eliminated by curative ablation and the cessation of antiarrhythmic or rate-controlling drugs. There is progressive improvement of sinus node function after elimination of AF, suggesting that these sinus pauses may be a manifestation of tachycardia-mediated remodeling of the sinus node.

The common association between SND and atrial tachyarrhythmias has long been recognized.¹ Although the development of AF in SND has been attributed to inhomogeneous refractoriness, whereby an atrial premature beat may fragment and induce repetitive activation to enhance the vulnerability of the atrium to AF,² evidence also supports the argument that AF leads to sinus node dysfunction.^{3,4}

Elvan and Zipes,³ in a chronic pacing-induced model of AF in dogs, initially recognized the occurrence of sinus node remodeling as a result of AF. In this model, there was prolongation of the corrected SNRT and P-wave duration and a decrease in the maximal and intrinsic heart rates. A prolonged corrected SNRT has been observed in humans after the cardioversion of chronic AF.⁴ Reverse remodeling of sinus node function has been demonstrated after the termination of chronic atrial flutter, suggesting that atrial flutter results in sinus node remodeling and that this process is reversible.⁵ Hadian et al⁶ have recently demonstrated sinus node remodeling even after brief durations (10 to 15 minutes) of rapid atrial pacing. Interestingly, patients with asynchronous ventricular pacing,⁷ atrial septal defects,⁸ or congestive heart failure⁹—conditions known to be associated with the development of AF—demonstrate evidence of sinus node remodeling.

In the present study, in patients with documented prolonged sinus pauses on termination of AF, ablation to cure AF together with the cessation of medical therapies resulted in significant reverse remodeling of sinus node function, characterized by an increase of the mean heart rate, maximal heart rate, and heart rate range and a decrease in the corrected SNRT. These findings were associated with the long-term

suppression of clinical and asymptomatic sinus pauses, with no patient developing features of SND after elimination of AF. These changes were observed to occur independently of the effect of antiarrhythmic drugs. Importantly, all patients in this cohort had sinus pauses only on termination of AF; therefore, the findings of this study may not be applicable to patients with SND with sinus pauses independent of episodes of AF.

Although the mechanisms resulting in the association between sinus node dysfunction and atrial arrhythmias remain unknown, the present study demonstrates that paroxysms of AF may produce depression of sinus node function resulting in prolonged sinus pauses. This phenomenon is reversible by curative ablation of AF, thus avoiding the need for pacemaker implantation.

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References

1. Ferrer MI. The sick sinus syndrome in atrial disease. *JAMA*. 1968;206:645–646.
2. Luck JC, Engel TR. Dispersion of atrial refractoriness in patients with sinus node dysfunction. *Circulation*. 1979;60:404–412.
3. Elvan A, Wylie K, Zipes DP. Pacing-induced chronic atrial fibrillation impairs sinus node function in dogs: electrophysiological remodeling. *Circulation*. 1996;94:2953–2960.
4. Kumagai K, Akimitsu S, Kawahira K, et al. Electrophysiological properties in chronic lone atrial fibrillation. *Circulation*. 1991;84:1662–1668.
5. Sparks PB, Jayaprakash S, Vohra JK, et al. Electrical remodeling of the atria associated with paroxysmal and chronic atrial flutter. *Circulation*. 2000;102:1807–1813.
6. Hadian D, Zipes DP, Olgin JE, et al. Short-term rapid atrial pacing produces electrical remodeling of sinus node function in humans. *J Cardiovasc Electrophysiol*. 2002;13:584–586.
7. Sparks PB, Mond HG, Vohra JK, et al. Electrical remodeling of the atria following loss of atrioventricular synchrony: a long-term study in humans. *Circulation*. 1999;100:1894–1900.
8. Morton JB, Sanders P, Vohra JK, et al. The effect of chronic atrial stretch on atrial electrical remodeling in patients with an atrial septal defect. *Circulation*. 2003;107:1775–1782.
9. Sanders P, Morton JB, Davidson NC, et al. Electrical remodeling of the atria in congestive heart failure: electrophysiological and electroanatomic mapping in humans. *Circulation*. In press.