Impact of corrected sinus node recovery time in predicting recurrence in patients with paroxysmal atrial fibrillation

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Abstract
Objective: Atrial fibrillation (AF) and sinus node dysfunction (SND) have common underlying pathophysiological mechanisms. As an index of SND, corrected sinus node recovery time (CSNRT) may also reflect atrial function. The aim of the present study was to determine whether CSNRT predicts AF recurrence in patients undergoing AF ablation.
Methods: Consecutive patients with paroxysmal atrial fibrillation (PAF) who underwent radiofrequency catheter ablation between January 2017 and December 2018 were enrolled. Clinical data, CSNRT, and other electrophysiology indices were collected and analysed between patients with or without AF recurrence.
Results: A total of 159 patients with PAF who underwent the same radiofrequency catheter ablation procedure were enrolled, including 25 patients with SND. During the one-year follow-up period, 22 patients experienced AF recurrence. Patients with recurrence had a significantly longer CSNRT and a larger left atrial volume index (LAVI) than patients without AF recurrence. SND (CSNRT > 550 ms) and a larger LAVI were independently associated with AF recurrence after ablation. A statistically significant CSNRT cut-off value of 550 ms predicted AF recurrence with 73% sensitivity and 85% specificity.
Conclusion: CSNRT and LAVI are independent predictors of PAF recurrence following ablation.

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Introduction

Radiofrequency catheter ablation is the first-line therapy for paroxysmal atrial fibrillation (PAF). The primary limitation of radiofrequency catheter ablation is PAF recurrence, and the one-year recurrence rate of PAF following radiofrequency catheter ablation is reported to range between 10 and 20%.[1–3] Several clinical indices have been used to predict recurrence risk, such as left atrium (LA) diameter and PAF duration,[4,5] but they all lack specificity.

Approximately 10–30% of patients with PAF also have sinus node dysfunction (SND),[6,7] and structural and electrophysiological remodelling of the sinus node and atrium might be a shared mechanism of AF and SND.[8] The corrected sinus node recovery time (CSNRT) is used to evaluate sinus node function, and it might also reflect the severity of LA remodelling. SND is defined as $CSNRT > 550\,ms$.[9,10] Therefore, the present retrospective comparative study was conducted to investigate the predictive value of CSNRT for AF recurrence following radiofrequency catheter ablation in patients with PAF.

Patients and methods

Study population

The present retrospective comparative study complied with National Institutes of Health guidelines and was approved by the Clinical Research Ethics Committee of Tongji Hospital Affiliated to Tongji University (Ethical permit number: 2016-LC-008). All participants provided written informed consent for study inclusion. Consecutive patients with PAF who were referred to Tongji Hospital Affiliated to Tongji University for radiofrequency catheter ablation between January 2017 and December 2018 were enrolled. Existing databases were then searched for patients who met the following criteria for study inclusion: (1) symptomatic PAF that failed to respond to medication; (2) aged between 18 and 80 years; and (3) received radiofrequency catheter ablation therapy. All anti-arrhythmic drugs were stopped for a period of at least five half-lives before the procedure. The exclusion criteria were as follows: (1) thrombosis in the LA or LA appendage; (2) moderate to severe rheumatic mitral stenosis; (3) mechanical mitral valve; (4) severe bloodstream infection; (5) severe heart failure with New York Heart Association clinical classification stage III–IV; (6) severe hepatic or renal insufficiency; (7) advanced stage cancer; or (8) pregnancy.

Data collection

Detailed demographic and clinical data were extracted for each patient, including sex, age, PAF duration, concomitant diseases and medication use. The CHA_2DS_2-VASc score for AF (for evaluating ischemic stroke risk in patients with AF),[11] and HAS-BLED score for risk of major bleeding in patients receiving anticoagulation therapy for AF,[12] were determined. A standard 12-lead electrocardiogram (ECG) was analysed in all patients. The maximal P wave duration, maximal P wave amplitude, and PR interval were measured by two specialists (HMS and WJX). Prior to ablation, all patients underwent transthoracic echocardiography using a Vivid q echocardiography system (GE Healthcare, Chalfont St Giles, UK). LA diameter, LA volume, right atrial (RA) diameter, and left ventricular ejection fraction (LVEF) were measured. LA volume was normalized to the body surface area and presented as the LA volume index (LAVI) using the biplane Simpson's method.[13]

Measurement of electrophysiology indices

Electrophysiology indices were measured as follows: (1) CSNRT. The electrode catheter

was placed in the high right atrium area and S1S1 stimulations were released with different frequencies (600 ms, 500 ms, and 400 ms, for 60 s each). Sinus node recovery time (SNRT) was measured as the interval from the last paced impulse to the first sinus impulse, with CSNRT calculated as SNRT minus the sinus rhythm cycle length (Figure 1a and b); (2) Atrial effective refractory period (A-ERP). S1S2 stimulations were released from the high right atrium, beginning at 600/500 ms. S2 was decreased in a step-wise manner (10 ms at each frequency), until S2 could not capture the atrium. A-ERP was measured as the last S2 beat that captured the atrium; (3) Right atrial conduction time (RACT). While pacing in the high right atrium area, RACT was measured as the interval from the paced impulse to the A wave in the proximal coronary sinus electrode; and (4) LA conduction time (LACT). While pacing at the proximal coronary sinus, LACT was measured as the interval from the paced impulse to the A wave in the distal coronary sinus electrode.

Ablation procedure

All patients had undergone circumferential pulmonary vein isolation (CPVI) using the CARTO® 3 System (Biosense Webster, Irvine, CA, USA; Figure 1c). Under local anaesthesia, double transseptal punctures were created using a Brockenbrough needle, and two SL1 sheaths were introduced into the LA via the septum. A 100 U/kg dose of heparin was administered intravenously, with a target activated clotting-time value of 300–400 s. The catheters were placed in the LA through SL1 sheaths, and electroanatomical mapping was performed with a Pentaray NAV catheter (Biosense Webster). Ablation was performed using a THERMOCOOL SMARTTOUCH® catheter (Biosense Webster). The endpoint of the CPVI procedure was the achievement of a complete entrance and exit block. Following confirmation of PVI, a 20-min waiting period from the last radiofrequency application was required, with adenosine challenge to rule out dormant reduction.
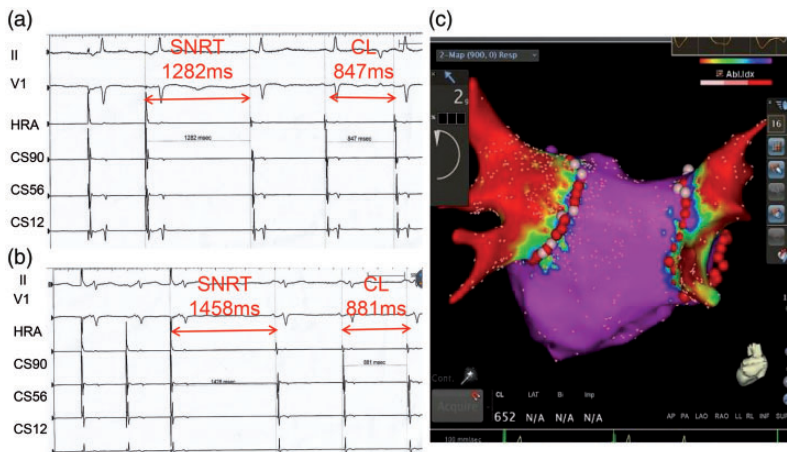
Figure 1. Representative images showing: (a) calculation of CSNRT in a patient without sinus node dysfunction, where CSNRT = SNRT − CL = 435 ms; (b) calculation of CSNRT in a patient with sinus node dysfunction, where CSNRT = SNRT − CL = 577 ms. The stimulations were released from the HRA; and (c) circumferential pulmonary vein isolation using the CARTO® 3 System (Biosense Webster, Irvine, CA, USA). SNRT, sinus node recovery time; CSNRT, corrected SNRT; CL, cycle length; HRA, high right atrium.

Perioperative medication

All antiarrhythmic drugs (AADs) were stopped for at least 5 half-lives before the procedure. Long half-life drugs, such as amiodarone, were avoided. Drugs with a short half-life, such as esmolol and metoprolol tartrate, were used if the patients had a rapid heart rate and high blood pressure. Anticoagulant drugs, including warfarin, rivaroxaban or dabigatran, were administered for at least 3 months after the procedure. Antiarrhythmic drugs were administered for 1–3 months depending on the basic heart rate after ablation. All AADs were stopped at 3 months following ablation.

Follow-up

All patients were followed for 12 months after ablation. The post-ablation blanking period was 3 months, and patients received an outpatient follow-up every 3 months. A standard ECG and 24-h Holter recording were scheduled at every visit. An ECG event recorder was used whenever a patient had cardiac symptoms. Recurrence of AF was defined as AF lasting for more than 30 s on the standard ECG, the ECG event monitor, or 24-h Holter recording, occurring after the 3-month postablation blanking period.

Statistical analyses

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean $\pm$ SD. Categorical variables were compared using χ^2-test, the CHA_2DS_2-VASc and HAS-BLED scores were compared using Mann–Whitney U-test, and Student's t-test was used to analyse the differences in continuous variables between patients with and without AF recurrence. Clinical factors associated with AF recurrence were determined by logistic regression. Age, sex and variables with a P-value < 0.1 in the univariate models were included in the multivariate analysis. Receiver operating characteristic (ROC) curves were constructed based on the CSNRT, and the area under the curve (AUC) was determined. AF recurrence-free survival after ablation was analysed by the Kaplan–Meier method. A P-value < 0.05 was considered to be statistically significant and all statistical analyses were performed with SPSS software, version 22.0 (IBM, Armonk, NY, USA).

Results

Baseline clinical characteristics

A total of 159 consecutive patients were enrolled (Table 1). The mean age of the total sample was 65.1 ± 8.2 years, and the patients were predominantly women (54.1%). The mean course of PAF was 4.8 ± 3.8 years. The mean CHA_2DS_2-VASc and HAS-BLED scores were 1.6 ± 1.1 and 1.1 ± 0.8, respectively, and mean RA and LA diameters were 44.5 ± 3.8 and 45.0 ± 7.0, respectively.

All patients reached the endpoint of PVI, and there were no severe complications, including cardiac tamponade or stroke. AF recurred in 22 patients (13.8%) during the 1-year follow-up period, and no patients required pacemaker implantation for SND. Patients with AF recurrence had a significantly longer CSNRT (532.7 ± 74.2 versus 474.5 ± 67.7 ms, $P < 0.001$) and a larger LAVI (36.4 ± 3.8 versus 32.7 ± 3.1, $P < 0.001$) than patients without AF recurrence. There were no statistically significant differences in age, sex, course, CHA_2DS_2-VASc score, A-ERP, RACT, LACT, or RA diameter (all $P > 0.05$).

Logistic regression analysis

Univariate logistic regression analysis revealed that SND (CSNRT > 550) (odds ratio [OR] 11.446, 95% confidence interval

Table 1. Baseline characteristics of patients with PAF prior to treatment with radiofrequency catheter ablation.

| Characteristic | Total ($n = 159$) | Study sub-group | | Statistical significance |
		No AF recurrence ($n = 137$)	AF recurrence ($n = 22$)	
Age, years	65.1 ± 8.2	65.1 ± 7.5	64.7 ± 12.0	NS
Female	86 (54.1)	71 (51.8)	15 (68.1)	NS
PAF duration, years	4.8 ± 3.8	4.9 ± 3.9	4.3 ± 3.0	NS
Hypertension	70 (44.0)	63 (45.9)	7 (31.8)	NS
Diabetes	24 (15.1)	23 (16.8)	1 (4.5)	NS
CAD	26 (16.4)	24 (17.5)	2 (9.1)	NS
CHA_2DS_2-VASc score	1.6 ± 1.1	1.6 ± 1.1	1.2 ± 1.1	NS
HAS-BLED score	1.1 ± 0.8	1.2 ± 0.8	1.1 ± 1.0	NS
Maximal P wave duration, ms	97.9 ± 11.4	98.0 ± 11.1	98.0 ± 13.0	NS
Maximal P wave amplitude, mV	20.5 ± 4.2	20.6 ± 4.3	20.2 ± 3.9	NS
PR interval, ms	159.0 ± 39.8	156.4 ± 21.3	175.5 ± 93.0	NS
CSNRT, ms	482.6 ± 71.3	474.5 ± 67.7	532.7 ± 74.2	$P < 0.001$
SND (CSNRT > 550 ms)	25 (15.7)	13 (9.5)	12 (54.5)	$P < 0.001$
A-ERP, ms	213.4 ± 19.5	214.0 ± 20.0	210.7 ± 17.3	NS
RACT, ms	48.0 ± 5.6	47.9 ± 5.5	48.8 ± 6.1	NS
LACT, ms	49.0 ± 6.9	49.1 ± 6.9	48.3 ± 7.2	NS
RA diameter, mm	44.5 ± 3.8	44.3 ± 3.8	45.5 ± 4.1	NS
LA diameter, mm	45.0 ± 7.0	43.0 ± 3.6	47.2 ± 4.7*	$P < 0.001$
LAVI, ml/mm^2	33.2 ± 3.4	32.7 ± 3.1	36.4 ± 3.8*	$P < 0.001$
LVEF, %	65.7 ± 5.1	65.5 ± 5.0	67.1 ± 5.5	NS
Medication				
Anticoagulant	127 (79.9)	110 (80.3)	17 (77.3)	NS
Beta-blockers	121 (76.1)	104 (75.9)	17 (77.3)	NS
Class I AADs	31 (19.5)	25 (18.2)	6 (27.3)	NS
Class III AADs	26 (16.4)	13 (9.5)	3 (13.6)	NS
Class IV AADs	34 (21.4)	31 (22.6)	3 (13.6)	NS

Data presented as n (%) prevalence or mean $\pm$ SD.

AF, atrial fibrillation; PAF, paroxysmal AF; CAD, coronary artery disease; CSNRT, corrected sinus node recovery time; SND, sinus node dysfunction; A-ERP, atrial effective refractory period; RACT, right atrial conduction time; LACT, left atrial conduction time; RA, right atrium; LA, left atrium; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; AADs, antiarrhytdmic drugs.

*$P < 0.05$, no recurrence versus recurrence group.

NS, no statistically significant differences between no recurrence and recurrence group ($P > 0.05$).

[CI] 4.147, 31.592; $P < 0.001$) and LAVI (OR 1.407, 95% CI 1.195, 1.657; $P < 0.001$) were independently associated with AF recurrence after ablation. Multivariate logistic regression analysis revealed that a cut-off value of 550 ms for CSNRT to predict an AF recurrence was statistically significant (OR 10.577, 95% CI 1.530, 73.116; $P = 0.017$) after adjustment for age, sex and other variables with $P < 0.1$, identified in the univariate model (Table 2).

ROC curve and Kaplan–Meier analysis of CSNRT

The ROC curve showed that CSNRT predicted AF recurrence with an AUC of 0.752. The sensitivity of the 550 ms

Table 2. Logistic regression analyses of characteristics associated with AF recurrence following radiofrequency catheter ablation.

Clinical characteristic	Univariate logistic regression			Multivariate logistic regression		
	Statistical significance	OR	95% CI	Statistical significance	OR	95% CI
Female	NS	0.502	0.193, 1.308	NS	0.747	0.227, 2.461
Age	NS	0.994	0.941, 1.050	NS	1.024	0.932, 1.124
PAF duration	NS	0.955	0.841, 1.086			
Hypertension	NS	0.548	0.210, 1.429			
Diabetes	NS	0.236	0.030, 1.844			
CAD	NS	0.471	0.103, 2.150			
CHA_2DS_2-VASc score	$P = 0.063$	0.652	0.415, 1.023	NS	0.537	0.262, 1.100
HAS-BLED score	NS	0.804	0.473, 1.369			
Maximal P wave duration	NS	1.001	0.962, 1.041			
Maximal P wave amplitude	NS	0.976	0.874, 1.090			
PR interval	NS	1.008	0.998, 1.019			
CSNRT	$P = 0.001$	1.012	1.005, 1.019	NS	0.996	0.985, 1.008
SND (CSNRT > 550)	$P < 0.001$	11.446	4.147, 31.592	$P = 0.017$	10.577	1.530, 73.116
A-ERP	NS	0.991	0.969, 1.015			
RACT	NS	1.028	0.951, 1.110			
LACT	NS	0.984	0.921, 1.052			
RA diameter	NS	1.089	0.961, 1.235			
LA diameter	$P < 0.001$	1.411	1.180, 1.688	NS	1.079	0.784, 1.487
LAVI	$P < 0.001$	1.407	1.195, 1.657	NS	1.243	0.872, 1.774
LVEF	NS	1.067	0.973, 1.169			
Medication						
Anticoagulant	NS	1.198	0.406, 3.537			
Beta-blockers	NS	1.079	0.370, 3.149			
Class I AADs	NS	1.680	0.598, 4.723			
Class III AADs	NS	0.576	0.212, 1.565			
Class IV AADs	NS	0.535	0.148, 1.927			

AF, atrial fibrillation; PAF, paroxysmal AF; CAD, coronary artery disease; CSNRT, corrected sinus node recovery time; SND, sinus node dysfunction; A-ERP, atrial effective refractory period; RACT, right atrial conduction time; LACT, left atrial conduction time; RA, right atrium; LA, left atrium; LAVI, left atrium volume index; LVEF, left ventricular ejection fraction; AADs, antiarrhythmic drugs; OR, odds ratio; CI, confidence interval.
NS, no statistically significant association with AF recurrence ($P > 0.05$).

CSNRT cut-off value to predict AF recurrence was 73%, and the specificity was 85%. Kaplan–Meier analysis revealed a significantly higher rate of AF recurrence in patients with CSNRT > 550 ms than in those with CSNRT ≤ 550 ms ($P = 0.01$ by log-rank test; Figure 2).

Discussion

The main findings of the present study were that CSNRT and LAVI are independent predictors of PAF recurrence. The course of PAF, concomitant disease, CHA_2DS_2-VASc score and HAS-BLED score were not significantly related to PAF recurrence; nor were the atrial remodelling indices, such as A-ERP, RACT, and LACT.

Circumferential pulmonary vein isolation remains the standard procedure for treating PAF, with reported success rates at 1 year of 80–90%.[1–3] In agreement with previous studies, the 1-year success rate in the present study was 86.2%.

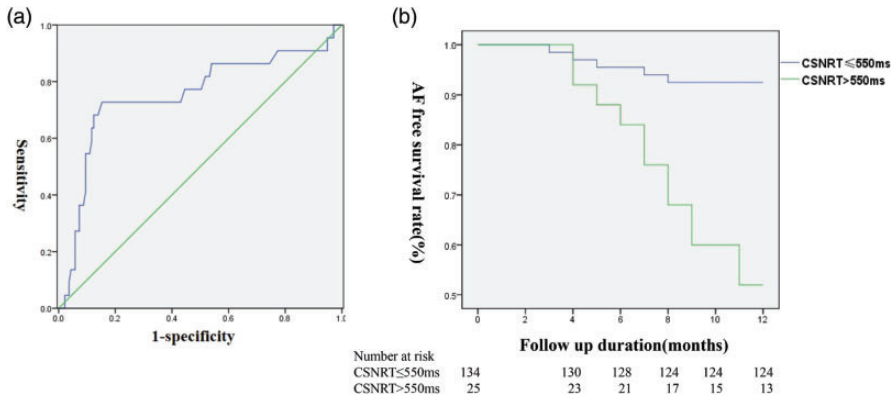Atrial tachyarrhythmia and SND are often seen in the same patient, with

Figure 2. Association between CSNRT and AF recurrence in patients with paroxysmal AF who underwent radiofrequency catheter ablation: (a) receiver operating characteristic curve of CSNRT to predict AF recurrence; and (b) Kaplan–Meier analysis of AF recurrence according to CSNRT > 550 ms and ≤550 ms. AF, atrial fibrillation; CSNRT, corrected sinus node recovery time.

atrial arrhythmias found to be present in 40–70% of patients at the time of SND diagnosis.[14–16] AF has been suggested as a cause of SND. Hadian *et al.*[17] selected 10 patients without organic heart disease, and with no history of atrial arrhythmia or autonomic nerve dysfunction. All patients received intracardiac electrophysiologic assessment and short-term atrial pacing, and the pacing rate exceeded 20–30 beats per min (bpm) of the basic heart rate. After pacing for 15 minutes, CSNRT was measured and found to be increased from 423 ms to 491 ms, and the increase was statistically significant. Another study investigated a dog model of AF, in which all 15 dogs received atrioventricular node ablation, and a VVI pacemaker was implanted.[18] Eleven dogs were implanted with an atrial pacemaker electrode, and to induce atrial fibrillation, the pacing rate of the atrial pacemaker electrode was set to 500 bpm. After pacing for 2–6 weeks, the intrinsic heart rate, maximal heart rate, and CSNRT were measured. The results suggested that CSNRT was obviously prolonged, the intrinsic heart rate and maximal heart rate were slowed, and the differences were statistically significant. These

studies suggest that AF and SND have a causal relationship.

Sinus node dysfunction and AF are considered to be interconnected.[19] As a particular RA tissue, the sinus node has a common pathological basis with the LA.[20] In patients with structural heart disease, progressive biatrial fibrosis is the pathological basis of AF and SND, however, patients with PAF without structural heart disease may have a different pathophysiology. SND associated with this latter condition is likely to primarily result from electrical remodelling and is potentially reversible.[21]

The CSNRT is an important index of sinus node function, and may also reflect the degree of structural and electrical remodelling. Substrate abnormalities in the RA have been shown in patients with SND, characterized by structural changes, altered conduction properties, and increased atrial refractoriness.[20] A study that used late gadolinium-enhanced magnetic resonance imaging to evaluate atrial fibrosis found that significant LA fibrosis was associated with clinically significant SND that required pacemaker

implantation.[22] Furthermore, an investigation of 51 long-standing persistent patients who all underwent their first ablation, reported a recurrence rate of 69% during a 28.4-month follow-up period;[23] in this study, a longer SNRT and a larger LA volume were shown to be independent predictors of AF recurrence.

The present study found that CSNRT and LAVI were independent risk factors for PAF recurrence. LAVI is a useful marker of LA structural remodelling and is reported to be significantly correlated with AF recurrence after ablation. However, some patients with PAF who have a standard LA diameter also have a high recurrence rate following ablation.[24–26] Electrical remodelling may play a significant role in these patients. The present authors believe that CSNRT is a marker for both electrical and structural remodelling of the atrium, and is an important supplement to LAVI for predicting AF recurrence. In addition, CSNRT may be a better index than RACT, LACT and RA to reflect atrial remodelling, since the latter indices lack specificity.

The results of the present study may be limited by several factors. First, the study was a retrospective, small-sized single-centre observational study. Secondly, the follow-up duration was only one year. Thirdly, follow-up monitoring for the detection of AF recurrence was mainly performed via 24-h Holter and electrocardiograms. More effective methods, such as loop recorders and 7-day Holter monitoring, should be used in future studies and follow-up assessments to improve AF detection rates. Follow-up will continue in the present patient group.

Conclusion

In the present study, 15.7% of patients with PAF had SND. CSNRT and LAVI were found to be independent predictors of PAF recurrence following radiofrequency ablation.

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