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Atrial activation time and pattern of linear triple-site vs. single-site atrial pacing after cardioversion in patients with atrial fibrillation

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Aims Multisite atrial pacing has been suggested to be effective in suppressing atrial fibrillation (AF), however, the effect of linear triple-site atrial pacing (LTSP) in humans has not been evaluated. We compared the effects of LTSP to single-site atrial pacing (SSP) on the atrial activation and wavefront propagation pattern in patients with persistent AF.

Methods and results In 10 patients with persistent AF, the effects of LTSP and SSP were evaluated by left atrial (LA) endocardial non-contact multielectrode array mapping and multipolar catheters. LTSP and SSP were delivered from the high right atrium (HRA), the distal coronary sinus (CS), and within the LA at the site showing maximal overlay of low-voltage zones during sinus rhythm and pacing at HRA and CS. Atrial activation time and pattern, P wave duration, and the prevention of AF induced by burst pacing were assessed with these pacing interventions. Compared with SSP, LTSP at the HRA, CS, and LA shortened atrial activation times (183 ± 24 vs. 174 ± 24 ms, 186 ± 29 vs. 166 ± 28 ms, and 171 ± 40 vs. 163 ± 39 ms; $P < 0.05$, respectively). P wave duration was shorter with LTSP than SSP at all three sites (141.7 ± 35.1 vs. 146.9 ± 38.5 ms, 138.1 ± 34.6 vs. 145.7 ± 33.7 ms, and 142.7 ± 33.4 vs. 151.3 ± 35.1 ms; $P < 0.05$, respectively). LTSP initially depolarized a larger area than SSP, and produced more uniform and planar wavefront propagation. LTSP prevented the burst-induction of AF during LA pacing in 3 of 10 patients, while SSP was never successful.

Conclusion In patients with persistent AF, LTSP provided more rapid and uniform activation of the atria compared with SSP, which was associated with prevention of burst-induction of AF in some patients. Further study is required to determine whether LTSP can modify the substrate of chronic AF, leading to frank AF suppression.

Keywords Atrial fibrillation • Multisite pacing • Three-dimensional mapping • Activation • Prevention

Introduction

Current therapeutic interventions for atrial fibrillation (AF) include various antiarrhythmic drug (AAD) therapies, and catheter-based ablative and surgical procedures. Unfortunately, these therapies have demonstrated only limited efficacy in treating AF, especially in preventing recurrent AF. Also, these interventions carry potential significant adverse effects. One experimental study demonstrated that right atrial (RA)-based linear triple-site pacing (LTSP) significantly reduced the RA and biatrial activation times compared with single-site pacing (SSP).[1] Furthermore, it has been suggested that shortening of atrial activation time and multidirectional excitation by triple-site pacing contribute to AF suppression.[2] However, the underlying electrophysiological mechanisms responsible for AF suppression by atrial pacing remain unclear, and LTSP pacing has not been investigated in humans. Therefore, we hypothesized that LTSP would reduce atrial activation time and provide for more uniform wavefront propagation over the atria compared with SSP in patients with persistent AF, subsequently resulting in improved prevention of burst-induction of AF. The purpose of

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this study is to compare the effects of LTSP to SSP on atrial activation and AF inducibility in substrate-dominant chronic AF.

Methods

Patient selection

The investigational institution (Korea University Medical Center, Seoul, Korea) attempted to recruit consecutive subjects who met the inclusion criteria for study enrolment. A signed statement of informed consent, approved by the institutional review board, was obtained from each subject prior to subject enrolment. Criteria for inclusion included the following: persistent AF ($\geq$30 days event duration), a clinical indication for electrophysiological (EP) testing with left atrial (LA) mapping, and more than 18 years of age. The patients who did not show re-initiation of AF after direct current (DC) shock were included in this study. Exclusion criteria included LA thrombus or mass, history of Maze surgery, previous AF ablation attempt(s), acute decompensated congestive heart failure within 1 month of enrolment, a left ventricular ejection fraction (LVEF) of $<$30%, currently participating in a clinical investigation that includes an acute treatment arm, and a life expectancy of $<$12 months.

Pre-electrophysiological study procedures

All AADs were stopped before the procedure in order to exclude the effect of AAD(s) during the study. Class Ic drugs were discontinued for a period corresponding to at least five half-lives, and amiodarone was discontinued for at least 4 weeks. There was no patient who complained of symptoms related to rapid ventricular response, such as palpitation or chest discomfort during that period. Warfarin for anticoagulation was orally administered (target INR: 2–3) for at least 1 month before the procedure. To exclude the presence of atrial thrombus, transoesophageal echocardiography was performed within 48 h before the procedure.

Electrophysiological study procedure

A decapolar catheter was positioned in the high right atrium (HRA), and a duo-decapolar catheter was inserted via a femoral vein and positioned inside the coronary sinus (CS) and along the low right atrium (LRA, *Figure 1*). A quadripolar catheter was placed along the His bundle recording region. Intracardiac electrograms were recorded using a Prucka CardioLab™ Electrophysiology system (GE Medical Systems Inc., Milwaukee, WI, USA). Before the procedure, spiral computerized tomography (CT) scans of the heart with a three-dimensional reconstruction were performed in order to accurately define the LA anatomy. DC shocks (mean energy: 5 J) were delivered using decapolar catheters positioned at the RA and CS, respectively, and we confirmed the stability of the recording catheters after each shock.[3]

Non-contact endocardial mapping and electroanatomical mapping procedure

The non-contact endocardial mapping (NCM) balloon with multielectrode array (MEA; St Jude Medical Inc., St Paul, MN, USA) was positioned in the LA, with stability ensured with a 0.035 inch guide-wire passing through the transseptal puncture positioned in the left superior pulmonary veins (LSPV; *Figure 1*). After the double transseptal punctures, anticoagulation was begun with heparin, maintaining an activated clotting time between 350 and 400 s. The NCM mapping technique has been described elsewhere.[4–8] A three-dimensional geometry of the LA was attained by sampling location points with the steerable catheters in the LA, PVs, and sampling location points under the guidance of fluoroscopy, angiography, CT, and the electrograms. LA voltage and activation maps were created by the MEA catheter. Concurrently, multiple multipolar EP catheters were placed in the RA and the CS for electrical mapping. After electrical cardioversion of AF, a low-voltage zone (LVZ) within the LA was determined by dynamic substrate mapping (DSM).[6] We interactively placed virtual electrodes on the coloured map contours to analyse the corresponding non-contact unipolar electrograms. The LVZ was defined as the area with $<$30% amplitude of non-contact unipolar electrogram peak negative potential.[6] The LVZ areas attained for each sinus rhythm (SR) and pacing at the HRA and CS were then overlaid, and the convergence of these multiple areas correlating with a more fixed, rather than functional, substrate condition, was used as the test pacing site within the LA.[9]

Validation of non-contact endocardial mapping

Besides the NCM, we also performed three-dimensional electroanatomical mapping using contact bipolar electrode catheter (NavX, St Jude Medical Inc., Minnetonka, MN, USA), and the overlay LVZs of the two mapping methods were compared. A representative example resulting from the two different methods in the same patient is shown in *Figure 2*. The multiple overlay sites in NCM were in agreement with the low-voltage areas in contact mapping, which located at the LA septum and LA posterior wall (*Figure 2*).

Pacing protocol

Pacing study at each site was first performed before AF induction test to minimize the cumulative effects of DC shocks. SSP and LTSP with cycle lengths (CLs) of 500 ms or 600 ms at twice the diastolic voltage threshold were performed at the HRA, the distal CS, and the LA at the sites showing maximal overlay of LVZs during SR. LA pacing was performed with a 7-Fr steerable, decapolar catheter (Polaris, Boston Scientific Corp., Natick, MA, USA). Before mapping, at least 1 min of stable continuous capture at each pacing site with each pacing configuration was performed to achieve steady-state conditions. After the pace-mapping portion of the pacing protocol, SR was maintained for more than 5 min in preparation for the prevention of burst-induction of AF portion of the pacing protocol. Burst-pacing (10 mA, 50 ms pacing CL) for 5 s was delivered to the RA while maintaining, in turn, SSP and LTSP (500 ms or 600 ms) at each of the HRA, CS, and LA. This AF inducibility test was conducted twice in each patient to assess its reproducibility.

Data analysis

Atrial activation times were measured during SR and during each pacing configuration from each test pacing site. RA activation times were estimated as the duration between the earliest and the latest RA catheter intracardiac electrograms. LA activation times were measured for each pacing configuration from each test pacing site were assessed similarly (earliest to latest activations) from the MEA virtual electrograms. Biatrial activation times were estimated similarly as earliest to latest activations, but taking into account the MEA and contact electrograms. Each atrial activation time was calculated as averaged over three to four consecutive beats. The pacing scheme that elicited the shortest biatrial activation times was identified. P-wave duration during SR and each pacing site and configuration was measured in leads II and III at a paper speed of 50 mm/s. P wave duration was taken as the time interval between the earliest onset of the

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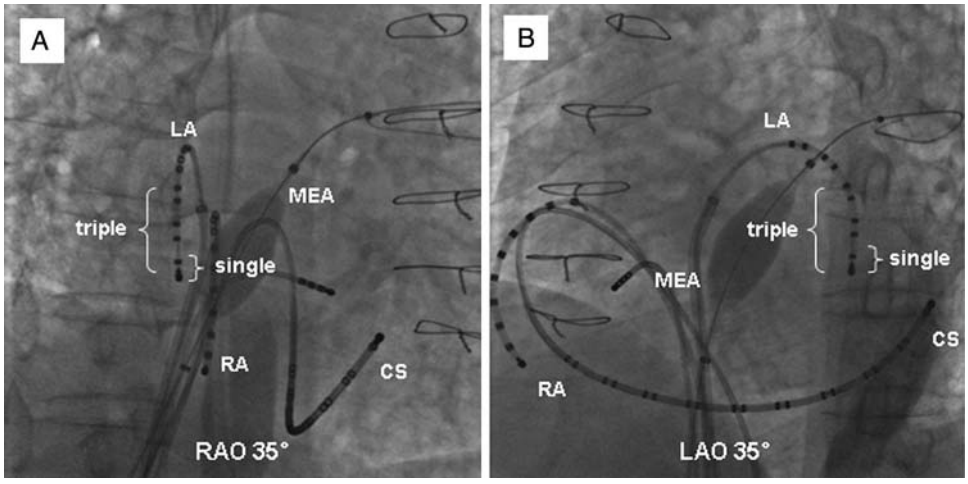

Figure 1 Fluoroscopic images show the positions of the electrodes and the multiple electrode array catheter. (*A*) Right anterior oblique (RAO) 35° view. (*B*) Left anterior oblique (LAO) 35° view. Single- and triple-site pacing were performed by one pair and three pairs of the bipolar electrode, respectively.

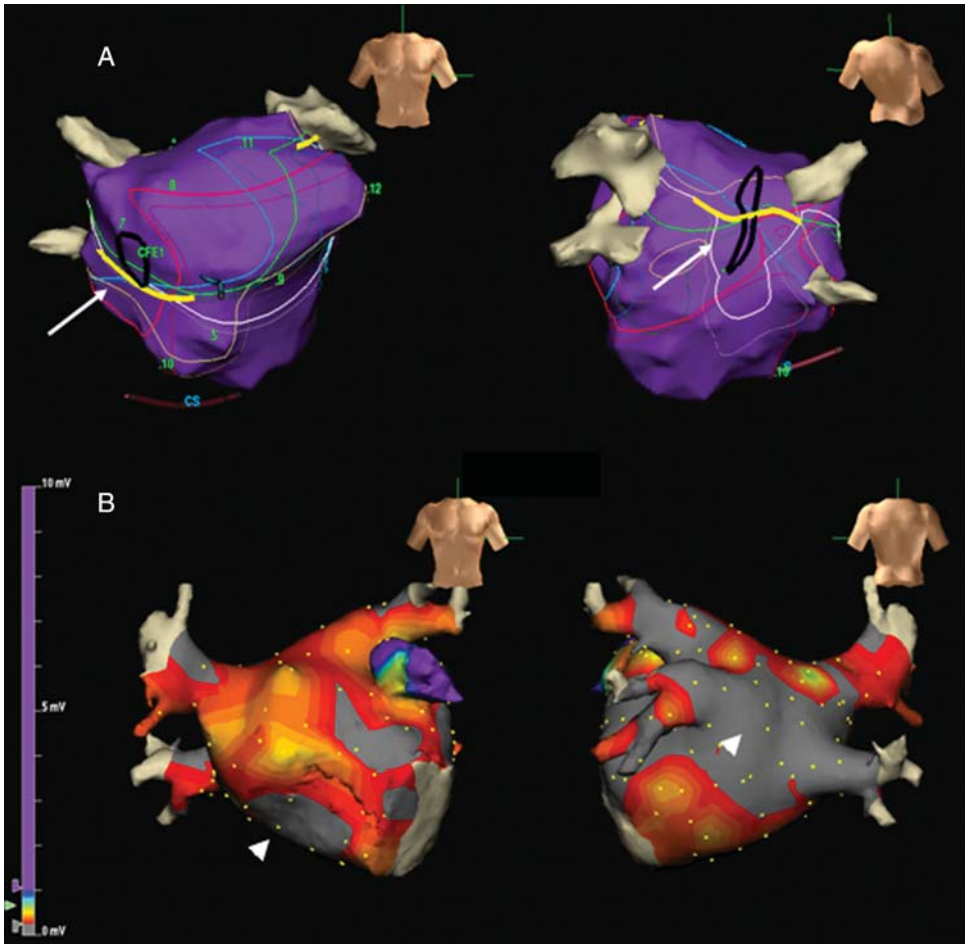

Figure 2 A representative example of simultaneous mapping with non-contact and contact electrode catheter in the same patient. (*A*) In NCM system, multiple overlay of LVZ (arrows) located in the left septum and posterior wall of left atrium. (*B*) The area of LVZ (arrowheads) recorded by contact bipolar electrode catheter was identified in the sites showing multiple overlay of LVZs obtained by NCM.

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P wave and the latest offset in the same lead. We analysed how the LVZs were affected by SSP and LTSP.

Statistical analysis

All values are expressed as mean ± standard deviation. Differences between groups were examined by means of paired *t*-test, Student's *t*-test or Mann–Whitney *U* test, and Spearman's correlation coefficient. A value of $P < 0.05$ was considered statistically significant. Data were analysed using SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The patient characteristics are shown in *Table 1*. Mean age was 55.2 ± 12.7 years, and 8 of 10 patients were male. Mean AF duration was 76.9 ± 71.9 months. The mean LA diameter on echocardiographic measurement was 52.0 ± 10.9 mm and the mean LVEF was 56.0 ± 5.3%. As for associated cardiovascular disease, hypertension was present in six patients, coronary artery disease in two, and diabetes mellitus in one. One patient had a history of myomectomy of the interventricular septum owing to hypertrophic cardiomyopathy, and one patient had a history of cerebral embolism. The number of previously used AADs for AF averaged 2.2 ± 0.9 agents. Antiarrhythmic agents used in these patients before the study included flecainide, propafenone, or amiodarone. A β-blocker had been used in combination with AADs (class Ic or III) in five patients.

Multiple overlay sites on dynamic substrate mapping

SSP and LTSP at the LA were performed at the sites showing maximal overlay of LVZs during SR. The multiple overlay sites by DSM were identified in all patients, which was found at the septum in five patients, the junction between LSPV and the roof in four patients, lateral ridge between left atrial appendage (LAA) and left PVs in four patients, roof in four patients, left inferior pulmonary vein (LIPV) in one patient, and posterior wall in one patient (*Table 1*). The multiple overlay sites in the LA were multiple in seven patients (two in three patients and three in four patients).

Atrial activation time

The mean twice-diastolic threshold at each test pacing site were HRA: 1.8 ± 1.5 mV; distal CS: 3.1 ± 2.7 mV; and LA: 2.2 ± 1.3 mV. The activation times obtained at each pacing site are shown in *Table 2*. The LA, RA, and biatrial activation times by LTSP elicited from the HRA and LA were all significantly shorter than those by SSP, respectively. LA and biatrial activation times from the CS were only significantly shorter during LTSP compared with SSP. In order to analyse the relation with the LA size and the biatrial activation time, we analysed using Spearman's correlation coefficient. There are a trend with positive correlations between biatrial activation times and LA size (with biatrial AT in SSP: $r = 0.552$, $P = 0.098$; with biatrial AT in triple-site pacing: $r = 0.588$, $P = 0.074$). In patients with large LA (numbers 1 and 7), atrial

Table 1 Patients' characteristics

Patient no.	Age (year)/ Gender	Clinical diagnosis	Previous drugs used	Underlying disease	LA diameters (mm)	LVEF (%)	AF duration (month)	NYHA class	Multiple overlay site on DSM
1	55/M	PeAF	AMD, BB, DIG	HCMP	71.7	62.5	120	2	LIPV Post/right roof/septum
2	37/M	PeAF	PRF, BB, FLC	HTN	39.2	57.5	13	1	Ant septum/Post roof
3	49/M	PeAF	AMD, BB, FLC	DM	43.7	52.5	108	1	Septum/Post roof/LAA junction
4	61/F	PeAF	FLC, BB, PRF	CVA, HTN	44.9	57.5	12	1	LSPV-ant roof/LAA junction
5	76/M	PeAF	AMD, DTZ	CAD, HTN	47.0	62.5	120	3	LSPV Post
6	47/F	PeAF	FLC, PRF, AMD	HTN	44.7	57.5	12	1	LSPV ant
7	69/M	PeAF	AMD	HTN	66.3	44.5	48	2	Ant septum/Ant roof
8	52/M	PeAF	DIG	None	53.5	57.5	240	2	LSPV-roof
9	40/M	PeAF	AMD, BB	CAD	47.3	55.5	36	2	LSPV–LAA junction
10	66/M	PeAF	AMD, DIG	HTN	62.0	52.5	60	2	Ant septum/Post wall/LAA junction

LVEF, left ventricular ejection fraction; AF, atrial fibrillation; PeAF, persistent AF; PAF, paroxysmal AF; AMD, amiodarone; PRF, propafenone; FLC, flecainide; BB, β-blocker; DIG, digoxin; DTZ, diltiazem; HCMP, hypertrophic cardiomyopathy; HTN, hypertension; DM, diabetes mellitus; CVA, cerebrovascular accident; CAD, coronary artery disease; DSM, dynamic substrate map; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; Ant, anterior; Post, posterior; LAA, left atrial appendage.

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Table 2 RA, LA, and biatrial activation time after triple-site vs. single-site pacing

Pacing site	RA activation time			LA activation time			Biatrial activation time		
	Single	Triple	*P*-value	Single	Triple	*P*-value	Single	Triple	*P*-value
Sinus rhythm (ms)	68.6 ± 14.8		–	75.4 ± 16.6		–	117.8 ± 24.2		–
HRA (ms)	109 ± 30	97 ± 33	0.004	81 ± 14	76 ± 14	0.009	183 ± 24	174 ± 24	0.001
CS (ms)	88 ± 27	88 ± 28	0.472	130 ± 21	119 ± 20	0.002	186 ± 29	166 ± 28	0.000
LA (ms)	71 ± 16	69 ± 16	0.013	101 ± 34	94 ± 33	0.001	171 ± 40	163 ± 39	0.002

RA, right atrial; LA, left atrial; HRA, high right atrium; CS, coronary sinus; LA, left atrium; LAA, left atrial appendage; *P*-value, SSP vs. LTSP.

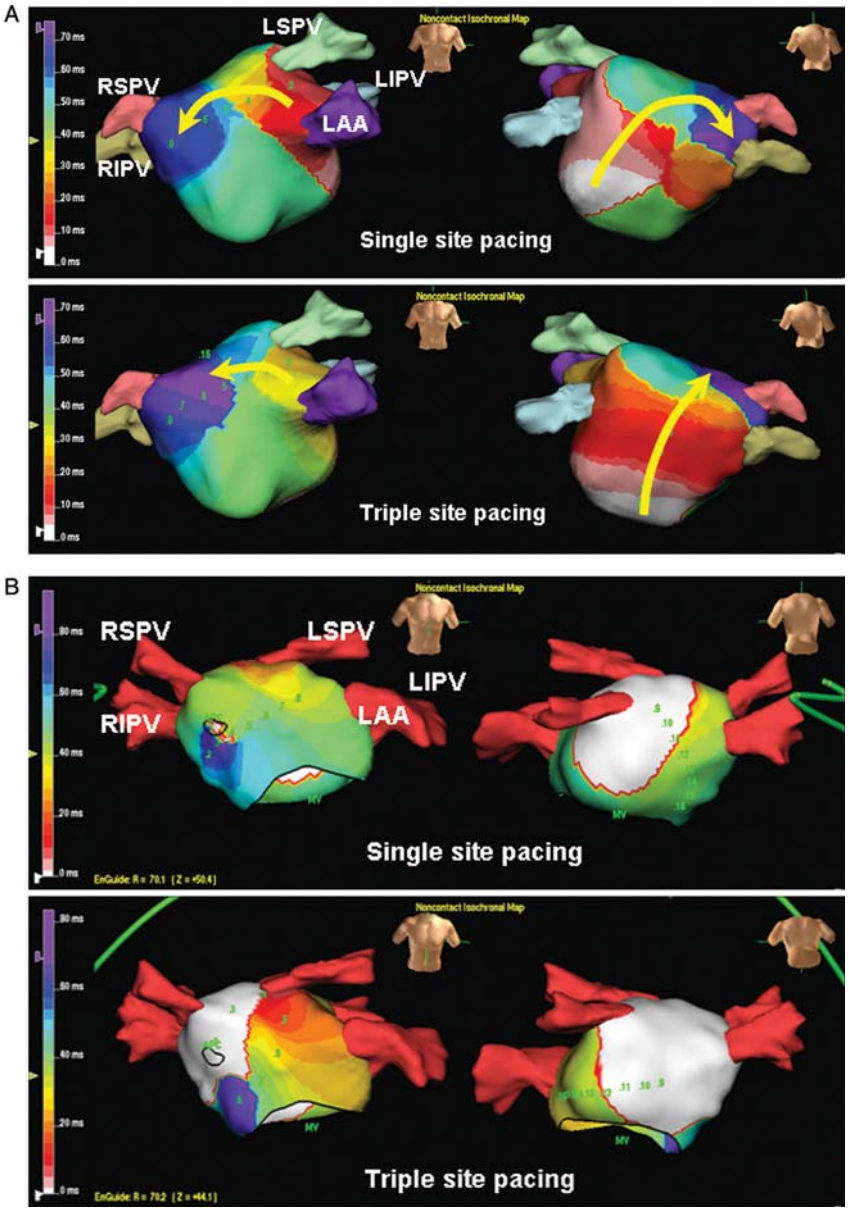

Figure 3 Representative examples of activation map during pacing. (*A*). During distal CS pacing, LTSP produced more uniform and linear wave-front propagation than SSP (arrows indicated activation pattern during each pacing at distal CS). (*B*) Larger area was depolarized by LTSP than by SSP.

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activation times during the LA pacing are much longer than other patients.

Atrial activation patterns

LTSP manifested more linear and uniform wave-front propagation compared with SSP at all test sites. LTSP also depolarized larger areas of the LA immediately upon stimulation than SSP. Representative examples are shown in *Figure 3*.

P wave duration

The P wave duration was significantly shorter during LTSP than SSP when pacing from the HRA (141.7 ± 35.1 vs. 146.9 ± 38.5 ms; $P = 0.045$), distal CS (138.1 ± 34.6 vs. 145.7 ± 33.7 ms; $P = 0.016$), and the LA (142.7 ± 33.4 vs. 151.3 ± 35.1 ms; $P = 0.014$; *Table 3*).

Effects of pacing on atrial fibrillation inducibility

Sustained LTSP delivered from the LA prevented AF induction in 3 out of 10 patients (*Figure 4*). This effect was reproducibly confirmed in each patient with a repetitive trial within 3 min, however, sustained LTSP delivered from the HRA and CS did not prevent AF induction in any patient. Sustained SSP from any test pacing site did not affect AF inducibility in all patients.

Activation time in patients with atrial fibrillation prevention

In the three patients (numbers 1, 2, and 9) who showed prevention of AF induction during LTSP at the LA, the pacing sites are posterior wall of LIPV, posterior roof, and junction between LSPV and LAA, respectively. Biatrial activation times during TSP in these three patients was significantly shorter than during SSP (153.0 ± 47.6 vs. 161.0 ± 54.5 ms; $P = 0.038$). There were trends toward shortening of activation time in LA, with paradoxically its prolonging in RA, by TSP at the LA compared with those by SSP (LA activation time: 92.3 ± 48.1 vs. 99.3 ± 53.0 ms; $P = 0.079$; RA activation time: 77.0 ± 19.7 vs. 77.7 ± 17.2 ms; $P = 0.084$).

Discussion

The main findings of this study are as follows: First, LTSP provided for decreased biatrial and LA activation time compared with SSP; this was confirmed by both endocardial mapping as well as P wave duration. Second, LTSP depolarized a larger area of atrial tissue than SSP, and produced more uniform and linear wave-front propagation over the atria, Finally, LTSP delivered from the LA showed some efficacy in preventing burst-induction of AF, while SSP did not.

Table 3 P wave duration during sinus rhythm and atrial pacing: single- vs. triple-site pacing

Pacing site	Single-site pacing	Triple-site pacing	*P*-value
Sinus rhythm (ms)	125.4 ± 22.4		–
HRA (ms)	146.9 ± 38.5	141.7 ± 35.1	0.045
Distal CS (ms)	145.7 ± 33.7	138.1 ± 34.6	0.016
LA (ms)	151.3 ± 35.1	142.7 ± 33.4	0.014

HRA, high right atrium; CS, coronary sinus; LA, left atrium; *P*-value, SSP vs. LTSP.

Effects of linear triple-site atrial pacing

Hemels *et al.*[10,11] reported that SSP in combination with AADs may be effective for reducing AF burden and prevention of AF in patients without bradyarrhythmias. Ryu *et al.*[1] investigated that comparative effects of SSP and LTSP at the RA in a canine model using a pacing electrode configuration comprising three closely spaced electrodes arranged in a line and epicardial mapping. They reported that LTSP created more uniform excitation propagation over the atria compared with SSP. Furthermore, conduction abnormalities, such as conduction block and slow conduction, induced by diseased myocardium, were also reduced or eliminated by TSP, and RA-based LTSP significantly reduced the RA and biatrial activation time compared with SSP.[1] Our study is the first study to investigate the utility of LTSP in humans, and serves to extend the previous preclinical findings, maintaining the potential implications. It has been demonstrated that atrial pacing has the benefit of attenuating the burden of AF and incidence of thrombo-embolic events compared with the accumulation of ventricular pacing.[12,13] Several studies have reported that dual-site biatrial pacing decreases the recurrence and inducibility of AF.[14–18] Becker *et al.*[2,19] showed that multisite pacing is effective for AF suppression in an animal model by producing less functional conduction block with multidirectional excitation and a reduction in total activation time. However, these studies used multisite pacing in two or more locations far from one another, with each location working as effectively as SSP. As suggested by Becker *et al.*, shortening of activation time and multidirectional excitation may contribute to the effectiveness of multi-site pacing in AF suppression. In the present human study, reduction of atrial activation times, shortening of P wave duration, and more uniform propagation were noted with LTSP compared with SSP. These findings further support the feasibility of LTSP for AF suppression.

Linear triple-site atrial pacing at the area of multiple overlay of low-voltage zones

The properties of the LA substrate and electroanatomical remodelling have been known to be important in the maintenance of AF.[20,21] The development of AF sustenance may result from increased tissue anisotrophy owing to fibrosis,[21] and long-standing AF itself may promote a progressive increase in the fibrosis of the LA.[22,23] Propagation wave break may occur in the area of scar or LVZ which, in the setting of prolonged activation time, may result in reentry.[24] Such conduction disturbance may also increase the dispersion of refractoriness and the heterogeneity of recovering tissue, which may contribute to the induction and maintenance of AF.[24] In addition, the LA scarring has been reported to be a strong predictor of procedural failure in patients undergoing radiofrequency catheter ablation for AF.[25] The non-contact unipolar electrograms in the LVZ in this study were wide, low-amplitude,

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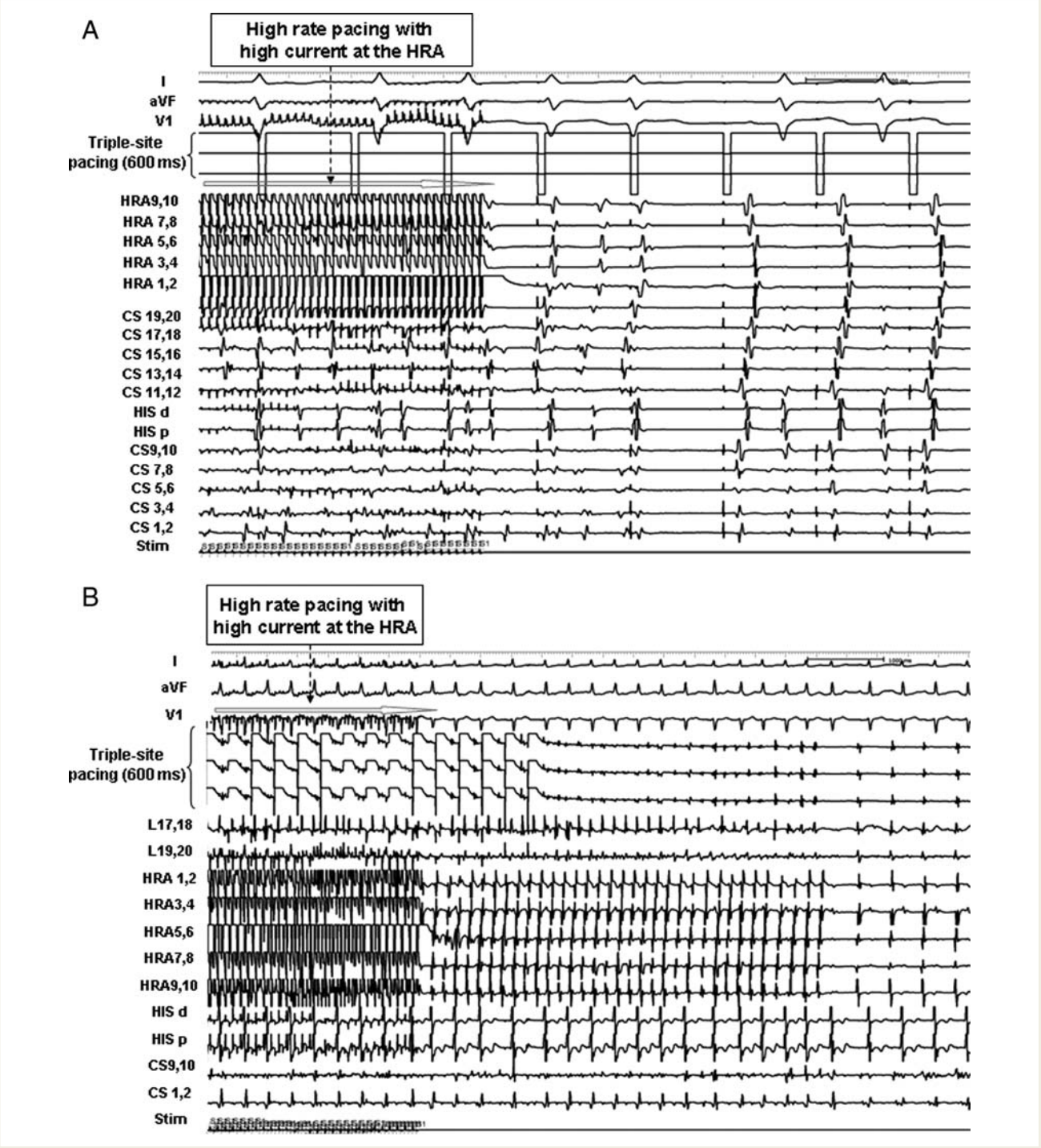

Figure 4 Examples showing non-inducible AF while maintaining triple-site pacing at the zone of multiple overlay of the LA. (*A*) AF was non-inducible during continuous triple-site pacing at the LA. (*B*) Induced AF was non-sustained while maintained triple-site pacing at the multiple overlay of LVZs.

and fractionated, suggesting delayed and non-uniform anisotropic conduction through the diseased atrium, which may be associated with atrial fibrosis.[26] The overlay and convergence of multiple areas of LVZs correlated with a more fixed rather than functional substrate.[9] This study showed that LTSP, delivered at the multiple overlay sites of LVZs, shortened atrial activation time by attenuation of non-uniform anisotropic conduction, which may suppress AF. While several mechanisms underlying AF suppression by LTSP at the LVZs may be postulated, we propose that a key may be to prevent propagation wave break-up or perturbation of reentry by reducing slow conduction and multidirectional, non-uniform propagation. In our study, the pacing sites of the LA

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were selected by maximal overlay of LVZs obtained by pacing at different sites (DSM), which presumed as atrial scarring with in-homogenecity, however, DSM was not performed at the CS for the selection of pacing sites, just empirically from distal to proximal bipoles. Furthermore, the multiple overlay sites of the LA were mostly noted at the septum, roof, lateral ridge, etc., not at the posterior wall or near CS. Therefore, pacing at the CS might result in different activation pattern when compared with pacing at the LA, and preventive LTSP in the CS did not show the same or better results than LA LTSP in patients with posterior 'atrial scarring' in view of the shorter distance and better organization of the induced atrial activation.

Study limitations

First, the effect of LTSP in patients with paroxysmal AF was not assessed in this study. There may be differences between paroxysmal and persistent AF according to the level of remodelling or the modification of substrate which may affect conduction time or activation pattern. Second, the acute effect of LTSP in patients with substrate-dominant AF was evaluated within a relatively short time period. Third, even though non-contact mapping is known to be useful and applicable in clinical fields, it is not exactly the same as the contact electrode. Therefore, differences between contact and non-contact electrograms may have existed, which might have misguided the activation time and precise identification of suitable pacing sites. Fourth, we cannot completely rule out the possibility that DC shocks change electrophysiological parameters during the study. Another limitation was the small sample size and follow-up period for only short duration.

Clinical implications

Atrial pacing from the traditional RA appendage or from within the CS, if implemented with multisite pacing, may improve AF suppression.[27] There is no consistent data that support the use of alternative SSP, multisite RA pacing, biatrial pacing, therefore, at present, permanent pacing to prevent AF is not indicated.[28] Our study is the first to investigate the usefulness of linear multisite pacing in human, and the result of this study is expected to be helpful in clarifying the potential role of linear multisite pacing for AF.

However, it still remains to be determined whether chronic LA pacing is available in our practice. Several candidate sites for LA pacing, such as vein of Marshall, one of the tributaries of the cardiac veins, or direct endocardial LA, might be considered, but further study is required. DSM, in conjunction with dynamic activation display, is useful in revealing underlying the substrate properties and their relationship with wave dynamics, and the assessment of pacing effect at these sites may be helpful in distinguishing LVZ or scar as an effective target from bystander fibrillatory conduction which could guide effective substrate modification. Therefore, LTSP at these locations may be expected to provide an effective therapeutic modality in AF suppression and prevention through these novel pacing modalities.

Conclusions

Compared with SSP, LTSP at the HRA, CS, or LVZ of the LA-reduced atrial activation times and P wave duration, produced more uniform and linear wavefront propagation, and depolarized a larger area. LTSP showed some efficacy in preventing burst-induction of AF, and may offer an effective means of AF suppression. These results warrant further clinical investigation with larger numbers of the patients.

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