

Inducibility of atrial tachyarrhythmias after circumferential pulmonary vein isolation in patients with paroxysmal atrial fibrillation: clinical predictor and outcome during follow-up

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KEYWORDS

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Aims We investigated the presence and clinical outcome of inducibility of atrial tachyarrhythmias after circumferential pulmonary vein isolation (CPVI) in patients with paroxysmal atrial fibrillation (PAF).

Methods and results Sixty patients with symptomatic PAF underwent CPVI guided by 3D mapping and double Lasso technique. After achievement of CPVI, the induction was performed. The left atrium (LA) volume and the isolated LA area around the right and left-sided pulmonary veins were measured by the 3D mapping system. Sustained atrial tachyarrhythmias (>10 min) were induced after CPVI in 17 of 60 patients (28%). Patients with inducible atrial tachyarrhythmias had significantly smaller isolated areas when compared with the group with non-inducible tachyarrhythmias (16.7 ± 2.3 vs. $18.8 \pm 2.9\%$, $P < 0.05$). After the initial procedure, recurrence occurred in 18 of 43 (42%) patients in the non-inducible group and in 7 of 17 (41%) in the inducible group during follow-up. A repeat procedure was performed in all 25 patients with recurrence. Five patients had a recurrence after the repeat procedure during 20.8 ± 7.5 months, and there was no difference between the two groups.

Conclusion Inducibility of atrial tachyarrhythmias is associated with proportionally smaller isolated area and does not predict the clinical efficacy of CPVI in patients with PAF.

Introduction

Previous studies have demonstrated that atrial fibrillation (AF) could be initiated by spontaneous focal discharges originating from the pulmonary veins (PVs).¹ This important finding has led to the development of a smaller segmental PV isolation (PVI) and a larger circumferential PVI (CPVI) using continuous circular lesions (CCLs) around the ipsilateral PVs.^{2,3} The ablation approach has shifted from segmental PVI to CPVI in clinical practice because CPVI is more effective than segmental PVI in patients with

paroxysmal AF (PAF).^{4,5} However, recurrence after the initial procedure is still a major concern, and recent studies have demonstrated that recovered PV conduction after the initial PVI is a dominant factor of recurrent atrial tachyarrhythmias in patients with PAF.^{3,6} Furthermore, induction of AF after the PVI calls for aggressive ablation with either additional linear lesions or ablation of fractionated electrograms in the left atrium (LA) to reduce clinical recurrence in patients with PAF,^{7–10} but inducible atrial tachyarrhythmias do not clinically recur in many patients with inducibility after PVI.⁸ There are still limited data about inducibility after CPVI using our approach in patients with PAF. This study prospectively investigated the inducibility of atrial tachyarrhythmias

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and the relationship between inducibility and clinical outcome after CPVI in patients with PAF.

Methods

Patients

This prospective study included 60 consecutive patients (45 males; 58.3 ± 10.4 years) with highly symptomatic PAF. Paroxysmal atrial fibrillation was defined as AF lasting <7 days and demonstrating spontaneous termination and followed by sinus rhythm (SR) confirmed by ECG in 3 months before the catheter ablation. In the initial procedure, all patients underwent only CPVI consisting of two CCLs around the ipsilateral PVs guided by 3D electroanatomical mapping and two Lasso catheters within the PVs.

Electrophysiological study

All patients provided written informed consent. All anti-arrhythmic agents, except amiodarone ($n = 10$), were stopped at least five drug half-lives before the study. Oral anticoagulation was administered (international normalized ratio 2–3 times) for at least 1 month, and transoesophageal echocardiography was performed prior to the procedure to exclude LA thrombus.

Inducibility was evaluated using 10 s burst pacing from the coronary sinus (CS) at a maximum current output (20 mA: UHS20, Biotronik Inc., Germany) starting at a cycle length of 250 ms decreasing down to refractoriness.⁸ Induction was tested five times before and after the PVI. Sustained AF was defined as AF lasting more than 10 min.⁸ Atrial flutter (AFL) was confirmed by the entrainment study at the isthmus, including the cavotricuspid AFL (right AFL) or left AFL involving the left isthmus between the mitral annulus and the left inferior PV. Other regular tachycardia with a stable cycle length recorded in the CS catheter and a constant P-wave morphology was defined as the atrial tachycardia (AT).

Left atrium mapping

The method of 3D electroanatomical mapping in the LA has been described previously in detail.^{2,11} Electrical and pharmacological cardioversion were not attempted before complete isolation. Mapping was performed with a 3.5 mm-tip catheter (ThermoCool Navi-Star, Biosense Webster Inc., Diamond Bar, CA, USA) during SR or AF using the CARTO mapping system (Biosense-Webster Inc., Diamond Bar, CA, USA). Mapping was complete when all regions of the LA had been systematically sampled and when a sufficient density of points had been acquired to determine the LA chamber. After reconstruction of the LA, each PV ostium identified by selective venography was tagged on the electroanatomical map. All points inside PV were deleted. The volume of the LA chamber and the LA surface area were automatically analysed by the CARTO system. The isolated areas surrounding the left-sided and right-sided PVs within CCLs (isolated area) were also measured by the CARTO system. These measurements were performed by experienced cardiologists independent of this study. The proportionally isolated area was defined as the value of both isolated area divided by the whole LA area (proportionally isolated area = isolated area/LA area \times 100) (Figure 1).

Catheter ablation

Two decapolar Lasso catheters (Biosense Webster Inc., Diamond Bar, CA, USA) were placed within the ipsilateral superior and inferior PVs or within the superior and inferior branches of a common PV before radiofrequency (RF) delivery. Irrigated RF energy was delivered as described previously with a target temperature of 45°C, a maximal power of 30–40 W, and an infusion rate of 17 mL/min.² In all patients, maximal power of 30 W was delivered to the posterior wall to avoid a potential risk of LA-oesophageal fistula. Radiofrequency ablation was initially performed to create the right-sided

CCLs and subsequently on the left-sided CCLs. These CCLs were performed in the posterior wall ≈ 1 cm and in the anterior wall ≈ 5 mm from the angiographically defined PV ostia (Figure 1).

The endpoint of the CCLs was defined as an absence of all PV spikes documented with the two Lasso catheters within the ipsilateral PVs at least 30 min after isolation. No linear lesions were created, such as block of right cavo-tricuspid annulus or left mitral isthmus.

Post-ablation care and follow-up

After the procedure, intravenous heparin was administered for 3 days in all patients, followed by warfarin for at least 3 months. All patients were kept on the previously ineffective anti-arrhythmic drugs for 1 month after ablation. Surface ECG, transthoracic echocardiography, and 24 h Holter recording were performed 1 day after the procedure and repeated after 1, 3, 6, 12, 18, and 24 months by the referring physician or the ablation centre. Recurrent tachycardias included all tachycardia after the first procedure without any blanking period. The diagnosis of tachyarrhythmias was defined by 12 ECG or 24 h Holter recording.

Statistical analysis

All measured data are shown as the mean \pm standard deviation. The unpaired *t*-test was used for comparisons between the two groups corrected using the Tukey–Kramer analysis. Categorical variables were compared by the χ^2 analysis or with Fisher exact test when appropriate. To determine the predictors of AF inducibility, variables entered into a multivariate logistic regression analysis. The Kaplan–Meier analysis was used for the examination of the event-free rate. Differences in arrhythmic event-free rate were assessed by the log-rank test. A two-sided $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using JMP Release 5.0 statistical software package (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

The clinical characteristics are shown in Table 1. Atrial fibrillation was first diagnosed 62 ± 56 months before referral and had been ineffectively treated by a mean of 2.0 ± 1.0 anti-arrhythmic drugs (ranged 1–5), including amiodarone in 10 patients (16.7%). Structural heart diseases had been diagnosed in nine (15%) patients. There were five patients with coronary heart disease, two patients with dilated cardiomyopathy, one patient with mitral valve replacement, and one patient after atrial septal defect repair. A dual-chamber pacemaker had been implanted in one patient. Primary hypertension had been documented in 20 patients (33%). The mean of the LA diameter was 43.0 ± 5.6 mm.

Procedure outcome

The complete electrical isolation of all PVs was achieved in all 60 patients. Mean procedure time was 198 ± 57 min, RF duration 42 ± 8 min, and fluoroscopy exposure time 21 ± 9 min. No complication occurred during and after the ablation procedure.

Before ablation, AF spontaneously occurred or was induced by the manipulation of the Lasso catheter or the mapping catheter in the LA in 30 patients and was induced by burst pacing after 3D mapping in 23 patients (non-sustained AF in 12 and sustained AF in 11 patients). Spontaneous or induced AF was terminated before ablation in

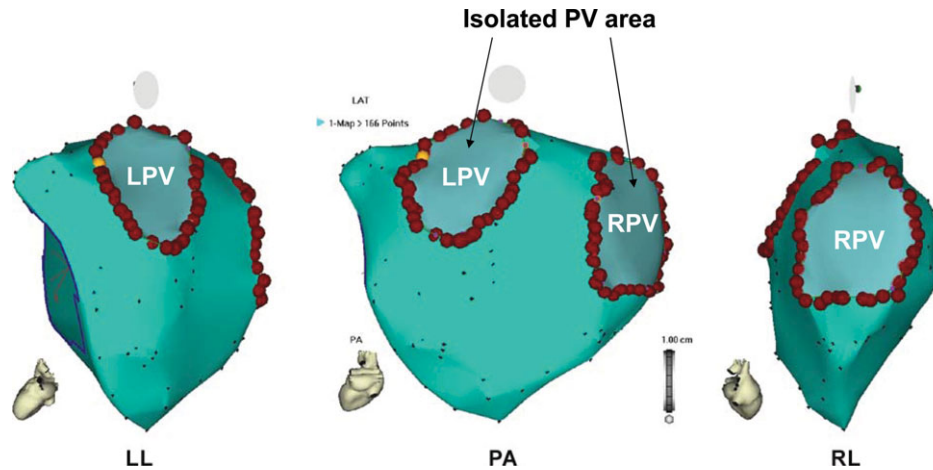


Figure 1 Three-dimensional anatomic map of the left atrium in the left lateral (LL; left panel), posteroanterior (PA; middle panel), and the right lateral view (RL; right panel). Right and left continuous circular lesions are marked by multiple red dots around the pulmonary veins, and the two sites with brown dots located in the right superior circular linear lesions and in the left anterior circular linear lesions indicate simultaneous isolation of the ipsilateral pulmonary vein when both circular linear lesions are complete. The bilateral blue areas surrounded by circular lesions are the isolated pulmonary vein area. PV, pulmonary vein; LPV, left-sided PV; RPV, right-sided PV.

Table 1 Patients characteristics

Gender (male/female)	45/15
Age (year)	58.3 ± 10.4
History of AF duration (m)	61.9 ± 55.7
LAD (mm)	43.0 ± 5.6
Structural heart diseases, n(%)	9 (15%)
History of HT, n(%)	20 (33.3%)
Amiodarone, n(%)	10 (16.7%)

AF, atrial fibrillation; LAD, left atrial dimension; HT, hypertension.

35 patients. Therefore, ablation was performed during SR in 42 patients, including 7 patients without inducible AF and 35 patients with AF termination before ablation. In the remaining 18 patients with long-lasting AF >30 min (13 patients with spontaneous AF and 5 with induced AF), ablation was performed during AF. In 9 out of these 18 patients (50%), AF terminated before 2 CCLs in 7 patients and after 2 CCLs in 2 patients. In 6 of these 18 patients (33.3%), AF converted to cavo-tricuspid AFL in 3 patients and left atrial AFL in 3 patients. Atrial fibrillation remained after complete PVI and required electrical cardioversion in three patients (16.7%).

Relationship between the inducibility test and left atrium substrate

In 42 patients with ablation during SR, sustained AF was inducible in 10 patients (23.8%) after complete PVI; whereas AF was induced in 7 out of 18 patients (38.9%) with ablation during AF ($P=0.23$). Surprisingly, sustained AF was not inducible in two out of three patients in whom electrical cardioversion was required to terminate AF after CPVI.

After PVI, sustained atrial tachyarrhythmias were non-inducible in 43 (71.7%, group I) patients and inducible in 17 patients (28.3%, group II). In group II, only AF was induced in eight patients (13.3%); in the remaining nine patients (15%), the induced tachyarrhythmias were

Table 2 Comparison of clinical and electrophysiological characteristics between inducible and non-inducible patients

	Non-inducible <i>n</i> = 43	Inducible <i>n</i> = 17	<i>P</i> -value
Age (year)	57.7 ± 10.4	59.8 ± 10.8	0.4933
Gender (male/female)	32/11	13/4	0.8686
History of HT (%)	13 (32.5%)	7 (41.2%)	0.657
LAD (mm)	42.1 ± 4.7	44.9 ± 6.8	0.1188
Use of amiodarone (%)	5 (11.6)	5 (29.4)	0.0958
History of AF duration (m)	59.9 ± 68.4	48.4 ± 40.8	0.5499
Structural heart diseases (%)	6 (13.4%)	3 (17.7%)	0.7181
LA volume (mL)	91.3 ± 21.9	106.6 ± 26.1	0.0282
LA area (mm ²)	114.4 ± 18.1	125.1 ± 19.9	0.0590
Isolated PV area, absolute (mm ²)	21.5 ± 4.5	21.2 ± 5.1	0.3287
Isolated LA area, proportion (%)	18.8 ± 2.9	16.9 ± 2.3	0.0173

HT, hypertension; AF, atrial fibrillation; LAD, left atrial dimension; LA, left atrium; PV, pulmonary vein.

common-type AFL in six patients and left macro-re-entrant AT in three patients.

Clinical characteristics of both groups of patients are shown in Table 2. The age, gender, structural heart diseases, the history of AF duration, LA dimension, administration of amiodarone, and history of hypertension and structural heart diseases showed no significant difference between the two groups. In contrast, patients from group II had a significantly larger LA volume and a relatively larger LA area than that of group I (106.6 ± 26.1 vs. 91.3 ± 21.9 mL; $P < 0.05$; 125.1 ± 19.9 vs. 114.4 ± 18.1 mm²; $P = 0.059$). Also, the proportionally isolated areas around the right and left ipsilateral PV were significantly smaller in group II than in group I after complete PVI (16.7 ± 2.3 vs. 18.8 ± 2.9%; $P < 0.05$). On the basis of regression logistic analysis, the proportionally isolated area is the only predictor for

non-inducibility of atrial tachyarrhythmias after complete PVI (HR, 0.437; 95% CI, 0.212–0.898; $P = 0.0243$).

Compared with nine patients with inducible AT or AFL, eight patients with inducible AF had larger LA volume (120 ± 28 vs. 94 ± 17 mL; $P < 0.05$) and LA surface area (135 ± 21 vs. 114 ± 11 mm²; $P < 0.05$).

Clinical outcome during follow-up

After the initial procedure, 18 of 43 patients (42%) from group I and 7 of 17 patients (41%) from group II had recurrences at mean follow-up of 16.1 ± 8.2 months. In 18 patients from group I, the clinical atrial tachyarrhythmias were recurrent AF in 13 patients and new occurrence of AT in 5 patients; whereas in 7 patients from group II, the clinical atrial tachyarrhythmias after the PVI were recurrent AF in 2 patients and new occurrence of regular AT in 5 patients. Statistically, there seemed to be no difference in recurrence after complete PVI between both groups by the Kaplan-Meier analysis.

Repeat procedure after circumferential pulmonary vein isolation

All of 25 patients with recurrent atrial tachyarrhythmias after the initial PVI underwent a second ablation procedure. In all of 25 patients, the recovered PV conduction was found. All conduction gaps on the CCLs were easily identified by using two Lasso catheters within the ipsilateral PVs and were successfully closed with a few irrigated RF applications in all 25 patients. All Macro-ATs were successfully ablated with a linear lesion across the isthmus in four patients.

After the second procedure, AF occurred in 5 out of 25 patients (4 patients from group I and 1 from group II). Stable SR was maintained in 55 patients during 20.8 ± 7.5 months. The success rate was not significantly different between the two groups after the second ablation procedure (91% in group I and 94% in group II) (Figure 2).

Discussion

Major findings

This report demonstrates that (i) inducibility of atrial tachyarrhythmias after CPVI is associated only with the size of proportionally isolated LA area and (ii) it is most likely that inducibility after CPVI cannot predict clinical atrial tachyarrhythmias recurrence during follow-up in patients with PAF and nearly normal hearts.

Previous studies on atrial fibrillation inducibility after pulmonary vein isolation

Previous studies have demonstrated that non-inducibility of sustained AF after PVI associated with lower recurrence rates and a better clinical outcome.^{7–9,12,13} Additional linear lesions in the LA isthmus or LA roof line after PVI can reduce inducibility⁸ and improve success rate in the follow-up after PVI.^{14,15} A 'step-wise approach' was associated with a significantly lower recurrence rate of 13 vs. 38% in patients with sustained or persisting AF during long-term follow-up.⁸ Oral *et al.* described an ablation approach based on non-inducibility of AF in patients with circumferential PV ablation and linear lesions in the posterior and lateral LA. After the first lesion, this study randomized the patients

to no further ablation or electrogram-guided ablation in the LA targeting non-inducibility. After a 6-month follow-up, 33% of the patients with inducible AF and no additional ablation and 14% of the patients who were rendered non-inducible had recurrent arrhythmia.⁹

Several studies have shown that inducibility of AF could be preferred as an endpoint for ablation of PAF. However, each study was based on a different protocol for the induction test, such as the type of stimulation and the definition of AF. Also some different ablation strategies were used; segmental PVI, CPVI including atrial tissue, or modification of the atrial substrate required maintaining AF regardless of PVI. Importantly, recent observations have shown that the arrhythmic substrate in PAF is localized in the PV or the atrial tissue around the PV, so-called 'PV antrum' in PAF.¹² This can give a strong support why CPVI have a better outcome in PAF.

Inducibility after circumferential pulmonary vein isolation

In the present study, we showed that (i) inducibility of AF or other AT after CPVI was frequent in patients with larger LA volume and proportionally smaller isolated areas surrounding PV and (ii) the induction of atrial tachyarrhythmias after CPVI resulted in a relative lower incidence (28%) when compared with the previous studies (43–60%). The CCLs surrounding the PV in our procedure are larger than the lesions of segmental PVI and include the atrial tissue around the PV. The endpoint of our procedure is complete isolation of the PV. This may result in the elimination of some random re-entry outside the PV ostium that drives AF. The larger circumferential lesion may contribute to the lower incidence of inducibility in our study. A recent study described a better prognosis after PVI with CCLs with larger isolated area than segmental ostial ablation in patients with AF, and this outcome supports our results.⁵

Atrial fibrillation inducibility and clinical outcome after circumferential pulmonary vein isolation

There are few reports to show that the inducibility is not associated with the recurrence in patients with PAF. In our report, all 25 patients who received the second procedure for recurrent tachycardia showed recovered PV conduction. After the closure of the conduction gap and ablation of AT circuits, 91% of the patients from group I and 94% from group II maintained SR, and the recurrence rate showed no significant difference between the inducible and the non-inducible group after the second procedure in this study. Recovered conduction across previously disconnected PVs has been observed as one of the dominant factors in patients undergoing repeat ablation for recurrent AF.^{2,3,6,16,17} These observations suggest that the substrate of AF consisting of trigger and maintenance is localized in the PV and/or the LA tissue surrounding the PV in most patients with PAF. The most critical issue in PVI is that recovered conduction across CCLs was not possible to predict at the initial ablation procedure.

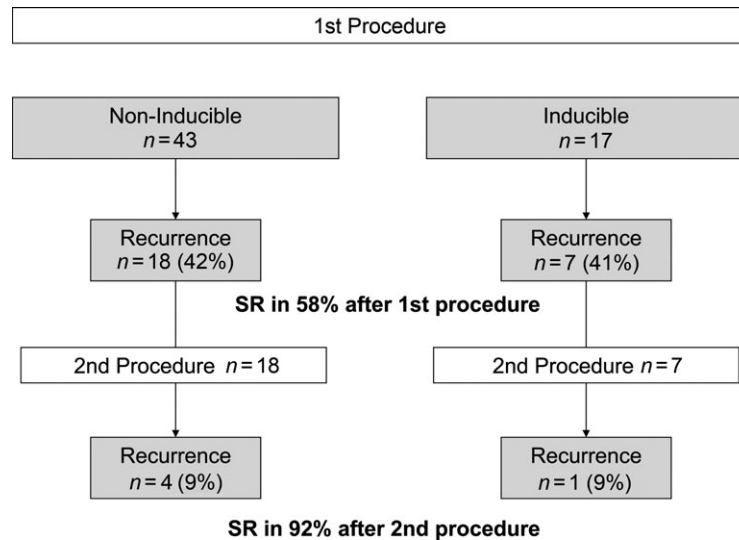


Figure 2 Diagram showing the outcome of the first ablation and the outcome of the second ablation. SR, sinus rhythm.

Inducibility of atrial fibrillation and atrial tachycardia/atrial flutter

Interestingly, inducibility of regular tachycardias (AT or AFL) after CPVI also did not correlate with recurrence of AT/AFL. The positive and negative predictive values were 33.3 and 88.3% of the induction test for AT/AFL recurrence. The negative predictive value for recurrence of AF was 69.8%. Left atrium volume and LA area were significantly larger in patients with inducible AF, compared with patients with inducible AT or AFL and non-inducible patients. These data suggested that (i) non-inducibility of AT/AFL might be a better predictor for no recurrence of AT/AFL than that of AF and (ii) more diseased atrium might contribute to the inducibility of AF. However, our previous observation also showed that even regular AT developed with the recovered conduction of PV, as a role of trigger of tachycardia.³ In clinical practice, it is very difficult to create conduction block over the left isthmus.¹⁸ An incomplete linear lesion is a potential risk factor for the recurrence of AT/AFL.¹⁹ The permanent disconnection of PVs can achieve long-term success in patients with PAF regardless of the inducibility of AF, and it remains associated with AF cure in patients treated with PVI.^{3,6} On the basis of our observations, additional linear ablation in the LA may be unnecessary except in patients with clinically suggested LA macro-re-entrant tachycardia.

Study limitations

There were several limitations in the study. First, induced AF was manipulated by the Lasso or mapping catheter within the PVs in 30 patients before ablation. Electrophysiologically, it may be different from that of burst pacing. Also, it was almost impossible to induce AF from the PV after ablation. Secondly, in this study, sustained atrial tachyarrhythmias were defined more than 10 min before ablation. This may result in a different incidence of inducibility after CPVI if the sustained AF definition was used as <10 min. Thirdly, no computed tomography or magnetic resonance image was used before ablation. Therefore, the CARTO-based calculation of LA area and isolated areas may be

inappropriate due to different PV size in the isolated areas. Fourthly, routine surface ECG and multiple 24 h Holter ECG were used to identify asymptomatic recurrence of AF, it might have been clinically missed. Finally, the study population was relatively small. Further evaluation with increasing number of patients may be required.

Conclusions

The patients with inducible atrial tachyarrhythmias have a proportionally smaller isolated area after CPVI for PAF. Importantly, inducibility after CPVI cannot predict the clinical outcome in patients with PAF and nearly normal hearts. These data provide new clinical information that additional ablation with linear lesions or ablation of fractionated potentials in the LA may be unnecessary in patients with inducible atrial tachyarrhythmias after CPVI.

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Conflict of interest: none declared.

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