

A Prospective Randomized Study Comparing Isolation of the Arrhythmogenic Vein Versus All Veins in Paroxysmal Atrial Fibrillation

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ABSTRACT

Background: Ablation procedures in patients with paroxysmal atrial fibrillation (PAF) includes isolation of all pulmonary veins (PVs). We hypothesized that an approach using an algorithm to detect arrhythmogenic PVs (aPVs) might lead to shorter procedure duration (PD) and fewer proarrhythmic effects (PE).

Hypothesis: Isolation of the aPVs only leads to a reduced PD, reduced PEs, and fewer adverse events, with a success rate comparable to the standard all-PV approach.

Methods: In this prospective trial, 207 patients with PAF were randomized to undergo isolation of the aPV (AG group, $n = 105$) or isolation of all PVs (VG group, $n = 102$). The aPV was identified by atrial fibrillation (AF) induction, focal discharge, or short local PV decremental conduction during PV pacing. Patients were followed with repetitive 7-day Holter electrocardiograms (ECGs) after 3, 6, and 12 months in our arrhythmia clinic.

Results: In 97% of patients, at least 1 aPV was identified (mean, 2.1). PD did not differ significantly (152.3 ± 57.1 minutes vs 162 ± 68 minutes, $P = 0.27$) between the groups, but the number of radiofrequency (RF) applications and fluoroscopy time (FT) and dose were significantly lower in the AG group than in the VG group. The occurrence of PE (new-onset atrial tachycardia) and adverse events (AE) did not differ between the 2 groups ($P = 0.1$). Sinus rhythm off antiarrhythmic medication (documented on 7-day Holter ECGs) 12 months after a single procedure was achieved in 53% in the AG group and 59% in the VG group ($P = 0.51$).

Conclusions: Isolation of the aPVs detected by a straightforward algorithm leads to similar success rates compared to a standard all-PV approach with regard to PD, AE, or PE and is associated with less RF and a shorter FT.

Introduction

In 1998, Haissaguerre et al. described triggering foci inside the pulmonary veins (PVs) as the main source for episodes of paroxysmal atrial fibrillation (PAF).¹ Since then, isolation of all PVs has become the routine approach for PAF. However, this all-PV approach for a problem supposed to be caused by a localized focal source might imply a rather extensive ablation with potentially proarrhythmic effects, long procedure duration, and an increased risk of adverse events.

Selective isolation of the arrhythmogenic PVs is an attractive concept, but has widely been abandoned due to time-consuming procedures to identify the arrhythmogenic PV. Jais et al.² showed that PVs of AF patients have a short local refractory period and a markedly decremental conduction to the left atrium (LA) at the PV ostium. AF was induced significantly more often pacing inside the PVs compared to pacing in the LA. Based on these findings,

we used a straightforward and easily applicable pacing algorithm to detect arrhythmogenic PVs by pacing with decremental extrastimuli in each PV.

We hypothesized that the isolation of the arrhythmogenic PVs only leads to a reduced procedure duration, reduced proarrhythmic effects, and less adverse events with a success rate comparable to the standard all-PV approach.

Methods

Patients

This prospective randomized trial was accepted by the local ethics committee (ClinicalTrials.gov, identifier: NCT00605748). All patients (207 patients, 60.2 ± 10.6 years old, 72% male) were randomized using randomization envelopes either in the group with isolation of all PVs (VG) or in the group with isolation of the arrhythmogenic PV (AG).

Procedure

Patients were kept on continuous oral anticoagulation with intraprocedural international normalized ratio levels of 2.0

The authors have no funding, financial relationships, or conflicts of interest to disclose.

to 2.7. Ablation procedures were performed using a 3-dimensional mapping system for anatomy and catheter visualization. pulmonary vein isolation (PVI) was performed as described earlier.³ In short, the LA was accessed by single or double transseptal puncture. Preablation and postablation angiograms of all PVs were performed. Heparin was given to maintain an activated clotting time at ≥ 270 seconds.

Isolation of All PVs (VG Group)

PVI was performed using a circular steerable mapping and an irrigated tip ablation catheter. A segmental approach isolating all PVs was used. After the pulmonary vein was entered, the circular mapping catheter was positioned as close to the pulmonary vein ostium as possible. Circular mapping was performed by obtaining 10 bipolar electrograms (1 to 2, 2 to 3, up to 10 to 1 electrode pairs) from the circularly arranged electrodes. Each vein was mapped circumferentially to document typical, sharp, local pulmonary vein potentials during steady state coronary sinus pacing (left pulmonary veins) or sinus rhythm (right pulmonary veins). Pulmonary vein isolation was performed by applying radiofrequency current at the ostial sites showing the earliest bipolar pulmonary vein potentials during sinus or paced rhythms, as previously described.⁴

Isolation of the Arrhythmogenic Vein (AG Group)

Prior to the above-described PVI, the circular mapping catheter was placed at the ostial part in one of the superior PVs right superior PV (RSPV) or left superior PV (LSPV), and the ablation catheter was placed at the ostium in the opposite superior PV (LSPV, RSPV). For each PV, programmed stimulation with S1 = 400 ms and 1 extrastimulus (S2) from inside the vein was performed, with reduction of the coupling interval of S2 until local capture loss (output 5 V and pulse width 1 ms). A PV was regarded as arrhythmogenic if spontaneous or pacing-induced electrical activity from distally inside the PV induced AF or atrial runs (Figure 1). If there was no induced AF or atrial runs from any PV, orciprenaline was administered, and the stimulation protocol was repeated with S1 = 300 ms.

If there was again no induced AF or atrial runs from any PV, pacing inside the PVs was used to determine the PV with the most pronounced decremental conduction properties at the PV-LA junction. For this, the programmed stimulation from inside the PV was used to measure the increase of the delay between PV to LA activation while shortening the coupling interval of S2. PV to LA was measured using the map or circumferential mapping catheter inside the PV to the distal signal in the coronary sinus catheter. Additionally, the effective refractory period of the PV was documented. The most decremental PV with the shortest effective refractory period with and without orciprenaline was regarded arrhythmogenic. These maneuvers were repeated for the inferior PVs. After identification of the arrhythmogenic vein(s), only these were isolated.

Follow-up After Ablation

Patients were scheduled for visits in the arrhythmia clinic at 3, 6, and 12 months after the ablation. At each visit, intensive

questioning for arrhythmia-related symptoms was done, and a 7-day Holter electrocardiogram was performed. Routinely, multislice computed tomography or magnetic resonance imaging of the PVs was obtained 3 months after the ablation procedure to screen for procedure related PV stenosis. If no AF recurrence was detected within the first 6 months, and the CHADS₂ score was ≤ 2 , oral anticoagulation was discontinued. No antiarrhythmic medication besides β -blockers was prescribed after the ablation procedure.

Statistical Analysis

All values are presented as mean \pm standard deviation. Student *t* test, Fisher exact test, Wilcoxon test, and χ^2 test were applied for comparisons. A probability value of $P < 0.05$ was considered statistically significant. To test for independent variables, a logistic regression analysis was performed.

Results

Baseline characteristics did not differ between the 2 groups (Table 1). Patients were 59.4 ± 12 years old in the AG group, and 60.9 ± 9 years old in the VG group. Seventy percent of patients were male. Paroxysmal AF had been present for 4.8 ± 3.8 years (AG) and 4.9 ± 5.5 years (VG), and the LA diameter was slightly enlarged by 43.5 ± 5.7 mm (AG) vs 44.3 ± 5.8 mm (VG).

Procedural Data

In the AG group, procedure time was 152.3 ± 57.1 minutes compared to 162 ± 68.9 minutes in the VG group ($P = 0.27$). Fluoroscopy time, dose, and radiofrequency (RF) applications were significantly lower in the AG group (27.7 ± 14.2 minutes vs 33.5 ± 19.5 minutes, $P = 0.016$; 2857 ± 2138 cGy/m² vs 3981 ± 3103 cGy*cm², $P = 0.003$; 33.9 ± 22.9 vs 47.6 ± 21.1 , $P = 0.001$, respectively) (Table 2).

Ablation in the All-PV Group

In all VG patients, all PVs were successfully isolated.

Identification of Arrhythmogenic PVs in the Arrhythmogenic PV Group

A total of 2.1 ± 1.0 arrhythmogenic PVs per patient were identified in the AG group, and these PVs were successfully isolated (Figure 2).

In 74 of 105 patients (71%), AF or a trigger arrhythmia from 1 or more PVs was provoked by pacing inside the PV without orciprenaline. In 12 patients (11%), AF or PV triggers were present with pacing and orciprenaline. The surrogate end point of markedly decremental conduction properties and the shortest refractory period was found as the sole marker of arrhythmogenicity in 16 patients (15%). In 3 patients (3%), no PV could be classified as arrhythmogenic. In these patients, all 4 PVs were isolated (Figure 3). The anatomic distribution of the arrhythmogenic PVs is displayed in Figure 2. The most frequently observed arrhythmogenic PV was the left superior PV (29.6%), followed by the left inferior PV (26.6%) and the right superior PV (24.5%), whereas the right inferior PV accounted for only 19.2% of all arrhythmogenic PVs.



Figure 1. Programmed stimulation in the left inferior pulmonary vein (LIPV) with S1 400 ms and 1 extra stimuli with 150 ms inducing atrial fibrillation (AF), with a cycle length (CL) of 156 ms in the LIPV and AF with a slower CL in the left atrium. Abbreviations: CS, signal of coronary sinus catheter; Map, signal of ablation catheter; Orb, signal of circular mapping catheter in the pulmonary veins; RIPV, right inferior pulmonary vein.

Table 1. Baseline Characteristics

Baseline	Arrhythmogenic Group	All-Vein Group	P
Age, y	59.4 ± 12	60.9 ± 9	0.34
Gender, male	70.4%	70.5%	1.0
Duration of AF, y	4.8 ± 3.8	4.9 ± 5.5	0.85
Left atrium, mm	43.5 ± 5.7	44.3 ± 5.8	0.34
Arterial hypertension	65.7%	56%	0.19
Hyperlipidemia	50.4%	40%	0.16
Coronary artery disease	10.4%	15%	0.4
Cerebrovascular event	15.2%	13%	0.7
Diabetes mellitus	6.6%	7%	1.0

Abbreviations: AF, atrial fibrillation.
Baseline characteristics in both groups did not differ significantly.

Patients with only 1 arrhythmogenic PV did not differ regarding the baseline characteristics and cardiovascular risk factors compared to patients with more than 1 arrhythmogenic PV, and the distribution of the arrhythmogenic PVs was similar showing no significant difference.

Success Rate After 12 Months

After a follow-up of 12 months, stable sinus rhythm off antiarrhythmic medication was reached with a single ablation procedure in 53% of AG group and 59% of VG group ($P = 0.51$).

In patients with only 1 arrhythmogenic PV, stable sinus rhythm was reached in 63% (19/30 patients). Patients in

Table 2. Procedural Data

Procedural Data	Arrhythmogenic Vein Group	All-Vein Group	P
Procedure duration, min	152.3 ± 57.1	162 ± 68.9	0.27
Fluoroscopy time, min	27.7 ± 14.2	33.5 ± 19.5	0.016
Fluoroscopy dose, cGy*cm ²	2857 ± 2138	3981 ± 3103	0.003
RF applications	33.9 ± 22.9	47.6 ± 21.1	<0.001

Abbreviations: RF, radiofrequency.
In the arrhythmogenic vein group, fluoroscopy time, dose, and number of RF applications were significantly less than in the all-vein group. Procedure duration did not differ significantly between the groups.

whom the arrhythmogenic PVs had been identified based on electrical activity had a similar outcome as patients in whom the arrhythmogenic PVs had been identified by decremental conduction properties and effective refractory period only (53% in sinus rhythms after 12 months, $P = 0.9$). The location of the arrhythmogenic PVs did not statistically influence the success rate after 12 months.

Proarrhythmia and Complications

A progression to persistent AF was noted in 6 patients in the VG group and 3 patients in the AG group. In the VG group, 4 patients developed a stable atrial tachycardia as opposed to 2 patients in the AG group ($P =$ non significant). Acute adverse events were seen in 2 patients in the AG group (PV stenosis of 50%, $n = 1$; stroke 3 days after the procedure, $n = 1$) ($P =$ non significant). No pericardial effusion, major bleeding, or death occurred.

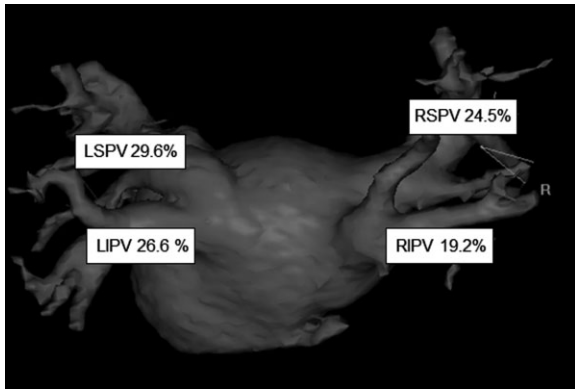


Figure 2. Anatomical distribution of all arrhythmogenic pulmonary veins (PVs) identified with our pacing algorithm. A total of 2.1 ± 1.0 arrhythmogenic PVs per patient were detected. Abbreviations: LIPV, left inferior PV; LSPV, left superior PV; RIPV right inferior PV; RSPV, right superior PV.

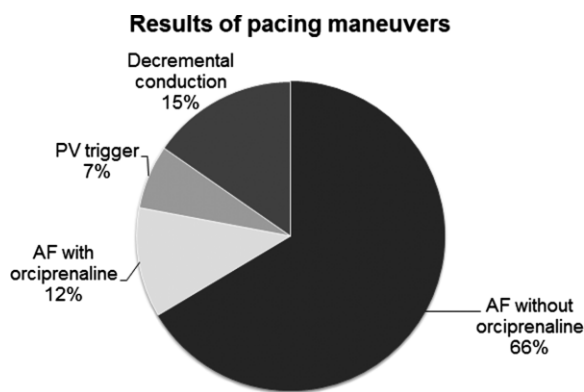


Figure 3. Results of pacing maneuvers. Atrial fibrillation (AF) induction and detection of pulmonary vein (PV) triggers were achieved with programmed stimulation inside the PVs in 71% of patients and after orciprenaline in 11% of patients. The arrhythmogenic PV was detected because of increased decremental conduction in 15% of patients, and in 3% of patients no arrhythmogenic PV was found.

Discussion

Main Findings

In this prospective randomized trial with 207 patients undergoing catheter ablation for paroxysmal AF, identification of arrhythmogenic PVs using an easily applicable pacing protocol was possible in 97% of patients. The success rate of the ablation of arrhythmogenic PVs vs all PVs after a single procedure was similar, suggesting that the pacing algorithm generated reliable results for the classification of arrhythmogenic PVs. Isolation of the arrhythmogenic PVs did not offer benefits compared to the standard all-PV approach with regard to procedure duration, safety, or proarrhythmic effects but was associated with fewer RF applications and a shorter fluoroscopy time.

How to Identify Arrhythmogenic PVs

The techniques to identify arrhythmogenic PVs differ substantially between published studies. In 2 reports from the University of Pennsylvania (Gerstenfeld et al.⁵ and Dixit

et al.⁶), provocation of PV focal activity was performed by isoproterenol administration. If no direct recording from a PV was available during an atrial premature complex (APC) or AF induction, a given PV was assumed to be arrhythmogenic if the activation pattern recorded in remote atrial localizations was consistent with a focal activity from this specific PV. In the study from Pak et al.,⁷ sustained AF was induced by isoproterenol administration and high-rate right atrial burst stimulation, and after internal cardioversion the reinitiating APC was mapped. A PV was assumed to be arrhythmogenic if reinitiation of AF from the same PV was observed 3 times. In the study by Hu et al.,⁸ spontaneous APCs were mapped and ablated.

The identification of arrhythmogenic PVs in these studies relied on the provocation of (spontaneous) electric activity from a given PV and on the chance that a recording catheter was placed in the right PV at the right moment. This approach is laborious, and large areas of both atria are not covered by mapping catheters.

The very early studies by Haissaguerre et al.⁹ pointed out the difficulty in provoking and localizing all PV foci during an electrophysiological study. In 2002, Jais et al.² showed in a study comparing patients with and without clinical AF episodes that the arrhythmogenic PV potential resulted not only from arrhythmogenic foci inside the PVs, but also from the very special conduction properties of the PV ostial tissue. In AF patients, this region showed marked decremental conduction patterns with frequent AF induction when pacing with extrastimuli inside the PV compared to pacing in the LA. Thus, decremental conduction properties at the PV ostium are essential features of the arrhythmogenicity of PVs.

We used these findings to create a simplified and straightforward pacing protocol to identify arrhythmogenic veins by measuring the venous effective refractory period and the degree of decremental conduction at the PV ostia and had a high percentage of AF induction when pacing inside the PV. Overall, we were able to identify 1 or multiple arrhythmogenic PVs in 97% of patients.

Efficacy of Arrhythmogenic PV Isolation

In our study, the long-term success rate after isolating the arrhythmogenic PVs only, was 53% comparable to isolating all PVs (59%) after a single procedure, which is also a hint that the algorithm used was quite reliable in detecting the arrhythmogenic PVs. Gerstenfeld et al.,⁵ who retrospectively studied 450 patients with isolation of arrhythmogenic PVs only, found almost identical success rates regarding stable sinus rhythm (58%) after a single procedure for the subgroup of patients with ≤ 2 arrhythmogenic PVs. In a study by Pak et al.,⁷ 35 patients who were found to have arrhythmogenic PVs by provocative maneuvers were randomized to arrhythmogenic PV isolation only and compared with 35 patients with empirical isolation of all PVs. There was no significant difference in outcome in both (61.4% vs 74.3%). Dixit et al.⁶ found in a randomized study in a smaller cohort (total of 107 patients, follow-up available for 95 patients) that isolation of arrhythmogenic PVs resulted in a comparable AF control (reduction of AF burden or elimination of AF with or without antiarrhythmic drugs) as compared to isolation of all PVs in 75% vs 71% of patients. A recent study by Hu et al.⁸ showed in 142

patients comparable success rates after isolation of selective ipsilateral PVs compared to bilateral PVI (63% vs 75%).

Number of Successful Arrhythmogenic PVs and Ablations

We were able to identify 2.1 ± 1.0 arrhythmogenic PVs per patient. Dixit et al.⁶ described 2.9 arrhythmogenic PVs/patient, and Pak et al.⁷ identified 1.4 veins per side (left or right). Furthermore, we found only 1 arrhythmogenic PV in 29% and 2 arrhythmogenic PVs in 45% of patients, whereas Dixit et al. found in 29% of patients up to 2 arrhythmogenic PVs, and 2/3 of patients had even >2 arrhythmogenic PVs. In our study, patients who had only 1 detectable arrhythmogenic PV showed even slightly better success rates (63%) compared to patients with isolation of all PVs (59%) ($P = 0.12$). This corroborates the impression that the pacing maneuvers used were reliable in detecting arrhythmogenic PVs, and that perhaps a subgroup of patients with only 1 arrhythmogenic vein might profit most from this approach.

Procedural Data, Proarrhythmic Effects, and Adverse Events

Procedure time did not differ significantly between both groups in this study. This is mainly due to the fact that the pacing maneuvers, which were necessary to identify the arrhythmogenic vein, still take some time. Similar results were seen by Dixit et al.⁶ In our cohort, fluoroscopy time, dose, and number of RF applications were significantly lower in the arrhythmogenic vein group, which can be explained by the lower number of targeted PVs. In the study by Dixit et al., a trend toward lower fluoroscopy time was seen; however, these differences were not significant.⁶ In the study by Pak et al.,⁷ procedure time, and fluoroscopy dose and time were significantly reduced in the arrhythmogenic vein group. In their protocol, however, all patients had undergone initial pacing maneuvers and were randomized thereafter.

No advantage of the limited arrhythmogenic PV isolation regarding proarrhythmia (atrial tachycardias, persistent AF) or adverse events was noted. This is in line with the other studies mentioned above, where no difference regarding adverse events between the isolation of all PVs vs arrhythmogenic PVs was reported.

Limitations

In 3 patients in the arrhythmogenic group, no arrhythmogenic PVs were identified, and therefore all PVs were

isolated. Possibly, the study with more than 200 patients is still too small to detect any meaningful differences.

Conclusion

Using an easily applicable pacing algorithm, an accurate and reliable identification of arrhythmogenic PVs seems possible in the vast majority of patients. After a follow-up of 12 months, patients with isolation of the arrhythmogenic PVs had a similar success rate regarding AF elimination as compared to the all-vein approach. Especially, patients with only 1 arrhythmogenic PV could benefit from isolating only this PV.

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