Pulmonary Vein Capture is a Predictor for Long-Term Success of Stand-Alone Pulmonary Vein Isolation with Cryoballoon Ablation in Patients with Persistent Atrial Fibrillation

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Abstract

Background: It is unknown whether cryoballoon technology for persistent atrial fibrillation (AF) is a reasonable initial strategy for patients with persistent AF (perAF). Methods: 390 consecutive procedures using cryoballoon for initial AF ablation were evaluated and divided first by clinical presentation: paroxysmal AF (PAF) or perAF, and then whether PV potentials associated PV pacing (PV capture) were identified after ablation. Patients were followed for recurrent AF (median 20 months). Results: PV capture was identified in patients with PAF and perAF (PAF: 20.3% vs. perAF: 14.6%; $p < 0.05$). No patient charactieristic differences were identified between those patients with or without PV capture. The presence of PV capture was not associated with different outcomes in patients with PAF. However, in patients with perAF, the presence of PV capture was associated with long-term outcomes similar to patients with PAF and significantly better than patients with perAF without PV capture ($p < 0.001$). In patients with perAF and PV capture, a strategy of reisolation of the PVs only for recurrent AF resulted in 20/23 (87%) patients in sinus rhythm off antiarrhythmic medications at study completion. In patients with PV capture, specific electrophysiologic properties of PV tissue did not have an impact on AF recurrence. Conclusion: PV capture (and not specific PV electrophysiologic characteristics) was associated with decreased recurrent AF in patients with perAF. PV capture may identify those patients with perAF in whom PV isolation alone is sufficient at initial ablation procedure and also as the primary ablation strategy for recurrent AF.

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Methods : 390 consecutive procedures using cryoballoon for initial AF ablation were evaluated and divided first by clinical presentation: paroxysmal AF (PAF) or perAF, and then whether PV potentials associated PV pacing (PV capture) were identified after ablation. Patients were followed for recurrent AF (median 20 months).

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Keywords: Atrial fibrillation, cryoballoon, pulmonary vein, ablation

Randomized controlled trials in patients with atrial fibrillation have demonstrated that catheter ablation is superior to pharmacological therapy with reduced likelihood of recurrent AF and improved quality of life measures, and may confer a survival benefit in patients with accompanying congestive heart failure.[1-3] Mechanisms underlying AF are complex and remain incompletely understood despite extensive research.[1] Despite relative efficacy of ablation, the risk of AF recurrence is still substantial, particularly in patients with persistent AF.[1] The central paradigm in ablation of persistent AF has been that atrial substrate modification in addition to pulmonary vein isolation (PVI) is necessary to achieve satisfactory success rates. However, several randomized trials demonstrated that adjunctive RF ablation strategies did not result in higher freedom from arrhythmia than a PVI-only strategy but were associated with higher fluoroscopy and procedure times.[4,5] Recently, several studies have suggested that cryoballoon ablation of the PVs may be moderately effective for the initial treatment of patients with persistent AF.[6-8]We evaluated whether electrophysiologic properties of PV properties (PV capture and PV cycle length) could predict which patients with persistent atrial fibrillation could be successfully treated with an initial cryoballoon approach.

METHODS

Patient Population and Follow-up: 390 consecutive initial PVI procedures using cryoballoon for symptomatic drug-refractory AF were evaluated. Patients with self-limited episodes shorter than 7 days duration

and no history of prior cardioversion (done for AF episodes ¿48 h duration) were defined as having paroxysmal AF, patients with AF who did not satisfy these criteria were defined as having persistent AF. Patients with atypical atrial flutter or prior ablation for atrial fibrillation were not included. Post-procedure follow up was performed at a routine cardiology clinic visits at 1 mo, 6 mo, 12 mo, and then annually or earlier as needed according to symptoms, including emergency department visits. Outcome analysis was started 3 months after the index ablation procedure. Antiarrhythmic medication was used based on the health provider's judgment during the first 3 months of blanking period but was stopped after the blanking period.

The primary clinical outcome was recurrence of arrhythmia identified as a symptomatic AF event [?] 3 months post ablation with the need for additional therapy such as cardioversion, re-ablation, or if recuurent arrhythmia was detected by rhythm monitoring data or symptoms reported by a patient during follow-up visit. There were no patients lost to follow-up.

Ablation Procedure: Patients underwent ablation using a 28 mm cryoballoon (Medtronic Inc., Minneapolis, Minnesota). Specific ablation techniques were left to operator disgression but generally ablation times of 150 to 240 seconds were used along with diaphragmatic pacing techniques for identifying phrenic nerve injury during ablation of the right-sided pulmonary veins. Additional ablation of the cavotricuspid isthmus was performed for previously clinically documented typical atrial flutter or if typical atrial flutter was induced or identified during the index procedure. Patients with inducible atypical atrial flutter underwent cardioversion or atrial pacing with no additional mapping or ablation for the atypical atrial flutter performed.

Evaluation of Electrophysiologic Properties of the PVs: After PV isolation a multipolar Lasso catheter or was placed in each PV and the presence of spontaneous PV activity was assessed. The PV was paced at multiple sites within the PV, beginning at a CL of 600 ms. PV capture was defined as a repetitive discrete EGM response within PV for ¿10 extrastimulus (10 mA) consecutively (Figure 1). The pacing cycle length was progressively decreased and electrogram behavior within the PV was recorded. When 2:1 PV capture was observed, the cycle length was increased to the point where 1:1 capture was reachieved and defined as the initial PV capture cycle length (PVCCL). After continuous pacing at a higher cycle length for 60 seconds, the pacing cycle length was was then progressively shortened and in most cases 1:1 capture was observed at cycle lengths that were previously associated with 2:1 block. The process was continued until no additional decrease in pacing cyle length with 1:1 capture was observed. The final PVCCL was defined as the minimum pacing cycle length in which 1:1 capture was observed. The ΔPVCCL was the difference between the initial PVCCL and final PVCCL.

Data Management and Statistical Analysis: The measured values were checked for distribution type by the Shapiro-Wilk test. Continuous variables with non-normal distribution are represented as *median [25th percentile, 75thpercentile]* , or as *mean [±standard deviation]* . Categorical variables were tested using Chi-square test. Arrhythmia recurrence was evaluated by the Kaplan-Meier method, differences in the freedom from arrhythmia were compared using the log-rank test. Hazard ratios were computed using a multivariable Cox proportional hazard regression model. Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, New York, USA) and two-tailed p-values <0.05 were deemed to be statistically significant.

RESULTS

Baseline characteristics . For purpose of our study patients undergoing AF ablation were divided into 4 groups depending on the type of AF ("persistent" vs "paroxysmal") and PV capture - whether discrete PV electrogram was identified during PV pacing or not ("PV capture" vs " Control" group). Figure 1 shows an example of PV capture.

The characteristics of the overall population evaluated were as following: age 67 [60.0;72.0] years, follow up period was 20 [9;36] mo, 72% of patients were males, 53.8% of the patients were taking class III antiarrhythmic and 60.8% were taking beta-blockers before the index procedure, arterial hypertension was comorbidity in 62.3% and DM in 23.8 % of cases. There were no significant differences between the groups studied besides the usage of class I antiarrhythmic drugs, which was significantly higher in patients with "paroxysmal AF and PV capture" vs. other groups (Tables 1 and 2).

Outcomes: PV capture was present in 52 of 256 (20.3%)of patients with paroxysmal AF and 23 of 134 (14.6%) of patients with persistent AF ($p < 0.05$). The development of recurrent atrial arrhythmias during follow-up was similar in patients with paroxysmal AF with or without PV capture (p = ns). However, the presence of PV capture in patients with persistent AF identified a group with ablation outcomes similar to patients with paroxysmal AF and significantly less likely to have recurrent atrial arrhythmias than patients with persistent AF and no PV capture ($p < 0.001$) (Figure 2).

Of the 23 patients with persistent AF and pulmonary vein capture, 8 underwent repeat ablation > 3 months after the index procedure. At repeat ablation, all patients had recurrent PV conduction and underwent reisolation of the pulmonary veins with no additional atrial lesions (Figure 3). At study completion, after a mean 16 month follow-up, 20 of the 23 patients were in sinus rhythm without antiarrhythmic medications.

PV electrophysiologic characteristics: For patients with pulmonary vein capture, the electrophysiologic characteristics of the pulmonary vein tissue were evaluated (Table 2). The minimal pulmonvary vein capture was dynamic. With initial pacing, 2:1 block would be identfied at the cycle length would vary from and with continued pacing the cycle length decreased. In several patients the pacing cycle length decreased to values [?]100 ms (Figure 1). In patients with PV capture CL [?] 150 ms, complex conduction patterns were also observed (Figure 4). The electrophysiologic properties of the PV did not differ between patients with paroxysmal or persistent AF were similar for the initial PVCCL and final PVCCL, although a more significant decrease in PVCCL during pacing was noted in patients with paroxysmal AF. The presence of spontaneous dissociated PV potentials was more commonly observed in patients with paroxysmal AF when compared to patients with persistent AF (paroxysmal AF: 9.6% vs. persistent AF 4.3%; $p < 0.001$). PV capture was usually observed in only one PV (in almost all cases, the left superior PV or right superior PV), though 3 patients with paroxysmal AF had PV capture identified in two PVs. No electrophysiologic characteristics of the pulmonary vein were identified that had an impact on clinical outcomes for the entire group with PV capture or in patients with paroxysmal or persistent AF.

DISCUSSION

The present study evaluated whether the characteristics of PV response on pacing during conventional ablation related to long-term AF-freedom. We found that excitability of PV (PV capture) after PVI was present in 19.5% of patients with paroxysmal AF and 14.6% of patients with persistent AF. The presence of PV capture did not have an effect on the clinical efficacy of PV isolation for paroxysmal AF, but did appear to identify a group of patients with persistent AF in whom PV isolation alone is an effective strategy and that a strategy targeting PV isolation isolation alone for these patients with persistent AF who later developed recurrent arrhythmias was associated with a high likelihood of maintaining sinus rhythm. In a prior study, the presence of dissociated PV potentials was identified in 19% of patients and their presence did not have an impact on outcomes.[9]However, this cohort was composed of mostly patients with paroxysmal atrial fibrillation who underwent alation using radiofrequency energy and our study too, found that the presence of PV capture in patients with paroxysmal AF had no impact on the likelihood of recurrent AF. Finally, though probably related, dissociated PV potentials were only observed in a small minority of patients with PV capture after cryoballoon ablation in the current study and dissociated spontaneous PV potentials and PV capture may have different implications particularly in the setting of different ablation enrgy sources.

The optimal lesion set for patients with persistent AF has not been established.[1] Prior studies using cryoablation have suggested moderate success rates in patients with persistent AF.[6-8] It is likely that persistent AF has multiple underlying electrophysiologic mechanisms and identifying the cause in an individual patient will be critical for designing a specific management or ablation strategy. The current study suggests that the presence of PV capture in patients with persistent AF identified a subset of patients in whom an initial approach of PV isolation is sufficient not only at initial ablation but also if subsequent ablation is required, even if atypical atrial flutter is induced with atrial pacing protocols. It may be that inducibility of atypical atrial flutter in specific situations, such as atypical atrial flutters that reproducibly use a region of slow or protected conduction within atrial scar, is important while other inducible atypical atrial flutters are less important and not clinically relevant.

In the current study, the simple presence of PV capture rather than specific electrophysiologic properties of PV tissue appears to be important. We found that the PVs have unique electrophysiologic properties such as very short paced PVCCL, in some cases < 100 ms that would develop after the progressive pacing protocols used in this study. PVs also displayed rapid rate dependence with significant shortening of the PVCCL even after very short periods of tachycardia (60 seconds). In addition, complex electrogram patterns suggestive of dynamic development of conduction block within different regions of the pulmonary vein that were dependent on direction of the depolarization wavefront were identified similar to what has been described at the PV-left atrial junction and left atrium, but at even shorter cycle lengths.[10,11] However, even though these electrophysiologic charactertistics from a mechanistic standpoint would appear to make AF more likely, similar to a previous study, in the current study the specific electrophysiologic characteristics of the PV did not have an identifiable impact on clinical outcomes in patients with paroxysmal or persistent AF.[12]

There are several limitations to the current study. The most important limitation is that the results are derived from a single center. However, this design also allowed this particular analysis to be performed, since the ablation strategies for management of patients with paroxysmal AF and persistent AF were consistent. In addition, there are likely many factors that lead to recurrent atrial fibrillation in persistent AF.[13] However, it is notable that a strategy only targeting pulmonary vein isolation at initial study and also for repeat ablation resulted in a high likelihood of freedom of maintaining sinus rhythm without antiarrhythmic medications in this selected group of patients with persistent AF.

Conclusion:

Currently there is no specific optimal approach for ablation of persistent AF and this likely represents the significant heterogeneity in underlying mechanisms in these patients. At this time we do not have any reliable intra-procedural electrophysiologic predictors of long-term success of AF ablation. However, the presence of PV capture appears to identify a group of patients in PV isolation using a cryoballoon approach is sufficient, and that if recurrent AF occurs and the patient is referred for repeat ablation, ablation should focus solely on reisolation of the PVs.

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Figure Legend

Figure 1: Electrograms demonstrating PV capture dissociated from atrial tissue. Pacing from electrode pair 1,2 at a cycle length of 100 ms results in 1:1 capture in PV tissue recorded by electrode pairs 17,18 and 15,16 and intermittent block in PV tissue recorded by electrode pairs 13,14 and 5,6. PV: Pulmonary vein; CS: Coronary sinus; p: proximal; d: distal.

Figure 2: Kaplan-Meier curves of the arrhythmia-free survival after initial ablation procedure.

Figure 3: Map from a repeat ablation procedure showing electrograms measured from different regions of the left atrium and PV in a patient with persistent AF and PV capture identified at the index procedure. Recurrent conduction to the right sided pulmonary veins was identified due to recurrent conduction in the septal and inferior regions of the right inferior pulmonary vein. Limited ablation with reisolation of the pulmonary veins (red circles) resulted in elimination of recurrent AF at follow-up. The apparent changes in voltages noted in the posterior LA in the post ablation maps is due to undercollection rather than new scar.

Figure 4: Complex conduction patterns within the PV observed with PV pacing. Pacing from electrode pair 11,12 in the PV results in 1:1 conduction that travels from electrode pairs 7,8 to 1,2 and 2:1 conduction in

electrode pair 17,18 (2:1). Progressive delay in conduction is observed that appears to travel from electrode pair 13,14 to 15,16 (arrows) which after block is replaced with rapid 1:1 conduction observed in electrode pair 15,16 but absent activation in electrode pair 13,14. PV: Pulmonary vein; CS: Coronary sinus; p: proximal; d: distal.

Table 1: Baseline characteristics

Characteristics	Overall across groups	Group 1 PV Capture (parox)	Group 2 Control (parox)	Group 3 PV capture (persist)	Group 4 Control (persist)	P-value
N	390	52	204	23	111	
Gender (M/F),	281/109	38/14	141/63	18/5	84/27	Ns
Age y [25^{th}-75^{th}]	67[60.0;72.0]	65[58.0;71.0]	67 [61.0;72.0]	67[60.0;73.0]	67[59.0;71.0]	Ns
BMI	30.2(5.1)	28.7(5.2)	29.7(5.5)	30.6(7.9)	31.9(7.5)	Ns
CHF, % (n)	11.3(44)	3.8(2)	11.3(23)	17.4(4)	13.5(15)	Ns
HTN, % (n)	62.3(243)	55.8(29)	65.2(133)	52.2(12)	62.2(69)	Ns
DM, % (n)	23.8(48)	31.6(6)	21.0(21)	37.5(3)	24.0(18)	Ns
Class 1 AA, % (n)	10.5(41)	26.9(14)*	9.8(20)	8.7(2)	4.5(5)	0.001
Class 3 AA, % (n)	53.8(210)	51.9(27)	48.0(98)	73.9(17)	61.3(68)	Ns
Diuretic, % (n)	21.8(85)	17.3(9)	20.1(41)	21.7(5)	27.0(30)	Ns
CCB, % (n)	22.6(88)	36.5(19)	17.6(36)	26.1(6)	24.3(27)	Ns
BB, % (n)	60.8(237)	59.6(31)	85.8(175)	65.2(15)	59.5(66)	Ns
ACEI, % (n)	42.1(164)	40.4(21)	39.7(81)	52.2(12)	45.0(50)	Ns

* Group significantly differs from each group. BMI: Body ass index; CHF: congestive heart failure; HTN: Hypertension; DM: Diabetes mellitus; AA: Antiarrhythmic medication; CCB: Calcium channel blocker; BB: Beta-blocker; ACEI: Angiotensin converting enzyme inhibitor

Table 2: PV electrophysiologic characteristics in patients based on arrhythmia type or whether or not recurrent AF was identified

	Paroxysmal AF	Persistent AF	Statistics	Recurrence	No Recurrence	Statistics
PVCCL initial (ms)	215 ± 50	218 ± 75	NS	216 ± 66	216 ± 56	NS
PVCCL final (ms)	160 ± 47	187 ± 54	NS	157 ± 54	177 ± 49	NS
ΔPVCCL (ms)	56 ± 33	34 ± 24	$p < 0.05$	56 ± 38	43 ± 27	NS

PVCCL: Pulmonary vein capture cycle length

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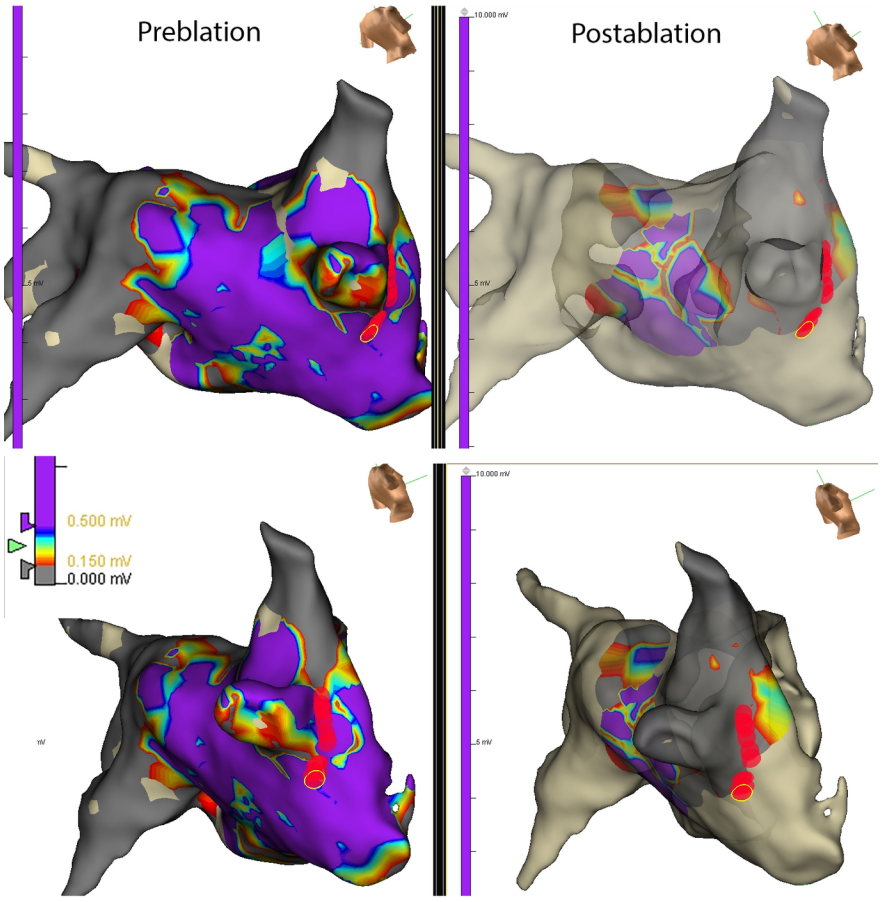
Figure 2: Kaplan-Meier curves of the arrhythmia-free survival after initial ablation procedure.



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