Difference Between Dormant Conduction Sites Revealed by Adenosine Triphosphate Provocation and Unipolar Pace-Capture Sites Along the Ablation Line After Pulmonary Vein Isolation

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Summary

Dormant pulmonary vein (PV) conduction revealed by adenosine/adenosine triphosphate (ATP) provocation test and exit block to the left atrium by pacing from the PV side of the ablation line (“pace and ablate” method) are used to ensure durable pulmonary vein isolation (PVI). However, the mechanistic relation between ATP-provoked PV reconnection and the unexcitable gap along the ablation line is unclear.

Forty-five patients with atrial fibrillation (AF) (paroxysmal: 31 patients, persistent: 14 patients; age: 61.1 ± 9.7 years) underwent extensive encircling PVI (EEPVI, 179 PVs). After completion of EEPVI, an ATP provocation test (30 mg, bolus injection) and unipolar pacing (output, 10 mA; pulse width, 2 ms) were performed along the previous EEPVI ablation line to identify excitable gaps. Dormant conduction was revealed in 29 (34 sites) of 179 PVs (16.2%) after EEPVI (22/45 patients). Pace capture was revealed in 59 (89 sites) of 179 PVs (33.0%) after EEPVI (39/45 patients), and overlapping sites, ie, sites showing both dormant conduction and pace capture, were observed in 22 of 179 (12.3%) PVs (17/45 patients).

Some of the ATP-provoked dormant PV reconnection sites were identical to the sites with excitable gaps revealed by pace capture, but most of the PV sites were differently distributed, suggesting that the main underlying mechanism differs between these two forms of reconnection. These findings also suggest that performance of the ATP provocation test followed by the “pace and ablate” method can reduce the occurrence of chronic PV reconnections. (Int Heart J 2016; 57: 000-000)

Key words: Atrial fibrillation, Durable pulmonary vein isolation, Recurrence

Atrial fibrillation (AF), the most sustained cardiac arrhythmia encountered in clinical practice, is associated with reductions in quality of life, functional status, cardiac performance, and overall survival.1,2) Radiofrequency (RF) catheter ablation centered on electrical isolation of triggering foci within the pulmonary veins (PVs) by creation of circumferential lesions around the PV ostia (PV isolation [PVI]) and elimination of the arrhythmic substrate have been shown to be a highly effective option for both paroxysmal AF (PAF) and persistent AF (PerAF).3,4) Unfortunately, despite initial procedural success, ± 20% to 40% of patients will require a second intervention for arrhythmia recurrence, which is most often attributable to recovery of conduction between the PVs and the left atrium (LA).5,6,7)

Two procedural techniques aimed at identifying regions of incomplete ablation and residual gaps within the ablation line have been postulated to reduce PV reconnection. One such technique is the use of intravenous adenosine/adenosine triphosphate (ATP) to differentiate permanent PV-antral block from dormant conduction (ie, viable but latently non-conducting tissue). Thereafter, further ablation targeting sites of dormant conduction can be performed with the goal of eliminating the sites of acute, adenosine/ATP-provoked reconnection.11-15) The alternative strategy is an approach guided by pace capture, whereby after completion of PVI, the antral ablation line encircling the ipsilateral PVs is mapped during pacing from the ablation catheter distal electrode pair.16,17) Where local LA capture is identified, additional ablation can be performed with the goal of closure of the residual gaps. However, no full comparison of the sites of dormant conduction and pace-capture in the same patients has been conducted. Therefore, we conducted a study to compare the sites of incomplete ablation and residual gaps identified by these two methods in patients with AF undergoing PVI. The goal of the study was to determine the efficacy of the two methods for the detection of dormant PV conduction.

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METHODS

Study patients: Consecutive patients with AF referred for catheter ablation between April 2013 and September 2013 were prospectively enrolled in the study. Each of the patients underwent clinical evaluation and cardiac imaging (echocardiography, computed tomography, and magnetic resonance imaging). The study was approved by the Institutional Review Board of Nihon University Itabashi Hospital, and written informed consent was obtained from each participant.

PVI procedure: Effective anticoagulation with warfarin (international normalized ratio, 2-3) or dabigatran for ≥ 1 month and ruling out of LA thrombus on a recent transesophageal echocardiogram were carried out before ablation. Antiarrhythmic drugs were discontinued before the procedure, allowing a washout period of 5 half-lives (no patient was taking amiodarone). Ablation was performed under sedation with an intravenous infusion of dexmedetomidine, propofol, and fentanyl as previously described. In brief, after vascular access was obtained, a single transseptal puncture was performed and then intravenous heparin was administered to maintain an activated clotting time of > 300 seconds. After 3 long sheaths (two SRO and one SL1 sheath; St. Jude Medical, St. Paul, MN, USA) were inserted into the LA via the transseptal puncture, two decapolar circular mapping catheters (Lasso®; Biosense Webster, Diamond Bar, CA, USA) and an irrigated 3.5-mm-tip mapping and ablation catheter (Thermocool®; Biosense Webster) were advanced into the LA. Extended encircling ipsilateral PVI was performed, guided by double Lasso catheters and a 3-dimensional electroanatomical mapping system (CARTO®; Biosense Webster). Targeting ipsilateral PVs in pairs, we placed RF catheter ablation lesions at a minimum of 1 cm outside of the PV ostia. Ablation was allowed within 1 cm of the ostium of the left superior PV (LSPV) because of the narrow ridge of tissue between its anterior aspect and the LA appendage. RF energy was delivered at a power of 20 to 35 W and irrigation flow rate of 17 to 30 mL/min. The upper temperature limit was set to 41°C. On the posterior wall, the RF power was reduced to 25 W with a flow rate of 17 mL/min. Patients remaining in AF at the end of the procedure were electrically cardioverted back to sinus rhythm. Remapping of all PVs' postablation lesions was performed to confirm PVI. The procedure was considered complete when spontaneous associated PV potentials were no longer recorded by the circular mapping catheter (entrance block), and PV to LA dissociation was noted either spontaneously or with PV pacing (exit block). A waiting time of ≥ 20 minutes after the index isolation was used to monitor for early reconnection, and if spontaneous reconnection occurred, reconnected PVs were reisolated. No induction testing (via burst pacing or isoproterenol infusion), prophylactic linear ablation lesions, or ablation of complex fractionated atrial electrograms was performed.

ATP-induced dormant conduction: After confirmation of PVI, provocative testing with 30 mg of intravenous ATP was performed to evaluate the presence of dormant conduction. ATP was administered during atrio-ventricular sequential pacing with an AV delay of 200 ms at a cycle length of 600 ms. Sites of dormant conduction, which were defined as the reappearance of PV activity recorded for ≥ 1 beat on two circular catheters appropriately positioned at the ipsilateral PVs, were tagged on the electroanatomic map.

Pace capture on the ablation line: After performance of ATP provocation, high-output bipolar pacing (output, 10 mA; pulse width, 2 ms) was performed from the distal electrode of the ablation catheter (with the indifferent electrode placed in the inferior vena cava) while moving the catheter slowly along the inner aspect of the entire circumference of the ablation line surrounding the ipsilateral veins. The presence or absence of local LA capture on the ablation line was monitored on the basis of the atrial signal of the coronary sinus catheter and the PV signals on the circular mapping catheter. Lack of local LA capture was considered to represent a site of efficacious ablation.

After tagging the dormant conduction site(s) and pace-capture site(s) on the 3-dimensional electroanatomical mapping system, supplementary RF energy was delivered at the site(s) of dormant conduction and pace capture. The procedure endpoint was confirmation of bidirectional block in all PVs despite repeat ATP provocation and loss of pace capture along the entire circumference of the ablation line.

Post-ablation follow-up: All patients were discharged 2 days after the procedure. The patients continued anticoagulation with dabigatran or warfarin (to maintain an international normalized ratio of 2-3) for a minimum of 2 months. Antiarrhythmic medications were continued for a maximum of 3 months after ablation and then discontinued.

Statistical analysis: Continuous variables are expressed as the mean ± SD. Categorical variables are expressed as percentages and differences were analyzed by Fisher’s exact probability test. P < 0.05 was considered statistically significant. All statistical analyses were performed with JMP 8 software (SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics: The study group consisted of 45 patients (male/female ratio, 36/9; age, 61.1 ± 9.7 years) undergoing first circumferential PVI for symptomatic drug-refractory PAF (n = 31) or PerAF. Mean LA size was 39.2 ± 5.4 mm, and left ventricular ejection fraction was 66.0 ± 5.8%. Structural heart disease, as assessed by clinical evaluation and cardiac imaging, was not present in any patient.

Dormant PV conduction: Dormant conduction was revealed in 29 (34 sites) of 179 PVs (16.2%) after PVI (22/45 patients). The distribution of the dormant PV conduction sites is illustrated in Figure 1. Dormant conduction occurred at 2 sites in the LSPV roof, 2 in the anterior LSPV, 3 in the posterior LSPV, 3 in the anterior left PV (LPV) carina, 2 in the posterior LPV carina, 1 in the anterior left inferior PV (LIPV), 1 in the posterior LIPV, 1 in the LIPV floor, 3 in the right superior PV (RSPV) roof, 1 in the anterior RSPV, 4 in the posterior RSPV, 3 in the anterior right PV (RVP) carina, 4 in the posterior RVP carina, 2 in the anterior right inferior PV (RIPV), and 2 in the RIPV floor.

Pace capture along the ablation line: Pace capture was revealed in 59 (89 sites) of 179 PVs (33.0%) after PVI (39/45 patients): Distribution of the dormant PV conduction sites is illustrated in Figure 2. Dormant conduction occurred at 3 sites in the LSPV roof, 5 in the anterior LSPV, 5 in the posterior LSPV, 11 in the anterior LPV carina, 13 in the posterior LPV carina, 2 in the anterior LIPV, 2 in the posterior LIPV, 3 in the LIPV floor, 2 in the RSPV roof, 4 in the anterior RSPV, 3 in

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Comparison of dormant conduction sites and pace-capture sites:
Overlapping sites, ie, sites showing both dormant conduction and pace capture, were observed in 22 of 179 (12.3%) PVs (17/45 patients): Distribution of the dormant PV conduction and pace-capture sites is illustrated in Figure 3. Both dormant conduction and pace capture occurred at 1 site in the anterior LSPV, 3 in the posterior LSPV, 3 in the anterior LPV carina, 2 in the posterior LPV carina, 1 in the anterior RIPV, 1 in the posterior LIPV, 1 in the LIPV floor, 2 in the posterior RSPV, 2 in the anterior RVP carina, 3 in the posterior RPV carina, 1 in the anterior RIPV, and 2 in the RIPV floor.

Regional distributions of the dormant conduction and pace-capture sites were compared. Dormant conduction was observed at 12 carina sites and 22 other sites, whereas pace-capture was observed at 46 carina sites and 43 other sites. Pace-capture sites were somewhat more prevalent than dormant conduction sites in the carina region ($P = 0.076$).

Comparison of the prevalence of dormant conduction and pace capture between PAF and PerAF: Dormant conduction was observed in 20 of 31 (64.5%) patients with PAF and in 2 of 14 (14.3%) patients with PerAF ($P = 0.0018$). Pace capture was observed in 2 of the 31 patients with PAF (64.5%) and in 12 of the 14 (85.7%) patients with PerAF ($P = 0.0018$). Overlapping sites were observed in 15 of the 31 (48.4%) patients with PAF and in 2 of the 14 (14.3%) patients with PerAF ($P = 0.0289$).

**DISCUSSION**

**Major findings:** In patients with drug-refractory PAF and PerAF undergoing PVI, 1) high-output pacing (PV-LA conduction) unmasked residual conduction along the ablation line at a higher rate than did ATP provocation; 2) the incidence of dormant conduction was significantly higher in relation to PAF than in relation to PerAF; but the incidence of pace capture was similar between the two arrhythmia types; and 3) a higher incidence of overlap between dormant conduction sites and pace-capture sites was observed in PAF than in PerAF.

**Dormant LA-PV Reconduction by ATP:** Although wide circumferential PVI is an established treatment for patients with AF, a significant minority (approximately 30%) of patients will require a second intervention attributable to arrhythmia recurrence. Although the persistence of non-PV foci and AF-maintaining rotors have been proposed as potential pathogenic factors for AF recurrence, the majority of arrhythmia recurrences reflect recovery of electric conduction between PVs and the LA after successful initial isolation. In other words, the failure to achieve durable PV-LA conduction block at the index ablation procedure, because of 1) intra-atrial variability in tissue depth, tissue contact force, and catheter stability, 2) edema formation, and 3) operator competency. Unfortunately, the accepted procedural endpoints of PVI (ie, entrance and exit conduction block) do not always represent the index creation of later contiguous transmural scar. Innovative intraprocedural techniques, such as the use of adenosine/ATP and the use of...
high-output pacing along the ablation line, represent means to accurately differentiate permanent PVI from reversible dormant conduction.\(^{11,17}\) It is postulated that delivering additional ablation targeting these regions of residual myocardial viability may improve the durability of the index lesion set, and in turn optimizing longer term patient outcomes. We have previously shown that the incidence of ATP-provoked PV connection is significantly reduced by adding the “pace and ablate” method after electrical PVI compared to electrical PVI alone.\(^{20}\) However, Anter, et al reported that the identification of acute PV reconnection by isoproterenol and/or adenosine, even when successfully targeted, is a strong predictor of arrhythmia recurrence following PVI.\(^{31}\) Furthermore, Lin, et al found that when additional ablation is performed to eliminate adenosine-induced PV reconnection after PVI, dormant conduction is not a significant predictor of recurrent AF and that although PVs with dormant conduction at the initial procedure may develop chronic reconnections, the majority of PVs showing conduction recovery at repeat ablation occur in non-dormant PVs.\(^{7,20}\)

The incidence of ATP-provoked PV reconnection was significantly higher in our patients with PAF than in those with PerAF. We previously showed that PV-LA junction wall thickness is significantly greater in patients with AF than in control patients, and also the PV-LA wall is significantly thicker in patients with ATP-induced dormant PV reconnection.\(^{21}\) Therefore, we postulated that the thickened PV-LA junction in patients with PAF may be composed of degenerated but surviving tissue, whereas that in patients with PerAF may be composed mainly of scar tissue. PV-LA Reconnection by PV Pace: Conversely, pace-capture-guided ablation, is based on the principle that an effective ablation lesion will result in the generation of local nonexitability. In addition, the effective use of high-output pacing is dependent on operator experience, because loss of capture of adequate tissue contact during pacing may be misconstrued as an effective ablation site and thus compromise procedure efficacy. In addition, atrial far-field capture may be misinterpreted as an area of viable myocardium leading to unnecessary RF delivery. Therefore, we used unipolar pacing in the present study. Similarly, it is important to limit pacing output in anatomically susceptible locations such as the ridge between the LSPV and the LA appendage. Moreover, the use of this technique is associated with longer procedure and fluoroscopy times.\(^{20}\)

Comparison of Dormant LA-PV and PV-LA Reconnection by PV Pace: Overlapping of ATP-provoked dormant conduction sites and pace-capture sites was observed in only 17 of the 45 (37.7%) patients, and the overlap characterized 22 of the 179 (12.3%) sites. Pace-capture sites were somewhat more prevalent than dormant conduction sites in the carina region. A previous study reported that PV mapping with the double-Lasso technique misses the non-isolation of the PV carina after successful PVI, which is an independent predictor of AF recurrence after extended encircling PVI (EEPVI). Therefore, pacing from the PV carina may be required to confirm the electrical isolation of the PV carina after EEPVI with the double-Lasso technique.\(^{25}\) Another study showed that there was no significant difference in the prevalence of dormant PV conduction among patients with PAF, PerAF, and long-lasting AF (62%, 66%, and 48%, respectively; \(P = 0.13\)).\(^{26}\) The incidence of dormant conduction in our patients with PAF (64.5%) was similar to that reported previously,\(^{26}\) but the incidence of dormant conduction in the patients with PerAF (14.3%) was lower than that of the same study.\(^{21}\) These different findings may relate to differences in the ablation method. Previous studies have shown that patients with PerAF, in comparison to patients with PAF, have lower regional voltage, an increased proportion of low voltage, slowed conduction, and an increased proportion of complex signals.\(^{7,28}\) We speculate that the lower incidence of dormant conduction in our patients with PerAF is related to the increased structural remodeling occurring at the PV antrum in these patients. Andrade, et al reported that the use of post-PVI pace capture without ablation of dormant conduction results in long-term freedom from AF recurrence comparable to that achieved with adenosine-guided ablation.\(^{20}\) Therefore, ablation based on the combined use of pace-capture and ATP-induced dormant conduction findings might be a useful method to better ensure freedom from AF recurrence.

**Study limitations:** The number of patients, and especially patients with PerAF, was small. Further, the study did not document the rates of AF recurrence during follow-up of the patients who underwent EEPVI alone, EEPVI plus additional ablation of the dormant conduction site(s), EEPVI plus additional ablation of the pace-capture site(s), or EEPVI plus additional ablation of sites of dormant conduction and pace capture overlap.

**Conclusions:** The sites of ATP-provoked dormant PV reconnection and the sites with excitatory gaps located by pacing were differently distributed, suggesting that the main underlying mechanism differs between these two forms of reconnection. Therefore, the ATP provocation test followed by the “pace and ablate” method might be useful in reducing chronic PV reconnections.

**DISCLOSURES**

We have no financial conflicts of interest to disclose.

**REFERENCES**