Repeated Provocation of Time- and ATP-Induced Early Pulmonary Vein Reconnections After Pulmonary Vein Isolation

Eliminating Paroxysmal Atrial Fibrillation in a Single Procedure

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Background—Recurrence of atrial fibrillation (AF) after successful pulmonary vein isolation (PVI) occurs mainly due to the reconnection of the once isolated PV. Although provocation and elimination of the early pulmonary vein reconnection (EPVR) soon after PVI has been widely performed to improve the outcome, AF recurrence due to subsequent PV reconnections still occurs. In this study, we repeatedly provoked and eliminated the EPVR to determine the appropriate procedural end point.

Methods and Results—Seventy-five patients with paroxysmal AF underwent PVI. EPVR was provoked by both time and ATP induction every 30 minutes until 90 minutes after the individual isolation of all PVs. The number of reconnected atrio-PV gaps were evaluated and reablated at each provocation step. Although both time- and ATP-dependent EPVR was induced most frequently at 30 minutes after PVI (75 and 76 gaps, respectively), the prevalence of induced EPVR at 60 minutes was still high (64 and 36 gaps induced by time and ATP, respectively). Only a small number of EPVR appeared at 90 minutes after the elimination of all EPVR by 60 minutes (8 gaps, \( P < 0.01 \)). During the mean follow-up period of 370 days, 92% of cases were free from AF without antiarrhythmic drugs.

Conclusions—Provocation and elimination of time- and ATP-induced EPVR not only at 30 minutes but also at 60 minutes is recommended after PVI to improve its efficacy. (Circ Arrhythm Electrophysiol. 2011;4:601-608.)

Key Words: atrial fibrillation ■ pulmonary veins ■ catheter ablation ■ adenosine triphosphate ■ dormant conduction

The efficiency of catheter ablation targeting pulmonary veins (PVs) to cure paroxysmal atrial fibrillation (AF) is well established.1–5 However, recurrence of AF after a successful PV isolation (PVI) procedure is still an unresolved problem requiring multiple ablation procedures to suppress the occurrence of AF.5 Curing the majority of PAF cases by a single procedure, similar to the treatment of Wolff-Parkinson-White syndrome, is a prominent goal in the field of clinical arrhythmia.

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AF recurrences are predominantly due to the resumption of the electric conduction in isolated PVs to the left atrium (LA).6–8 Because reconduction occurs in insufficiently ablated tissue, their identification and complete ablation in the initial procedure will decrease the subsequent AF recurrence. Several modifications of the PV isolation procedures minimize the PV reconnection. Elimination of ATP-induced PV reconnection (dormant PV conduction) by additional radiofrequency (RF) application reduces the recurrence and increase the success rate.9,10 Prolonging the waiting time after the establishment of PVI is also useful to provoke the early PV reconnection (EPVR).11–14 However, AF recurrences due to PV reconnection are still not rare and further modification of the procedure is therefore necessary. This study investigated the affects of both repeated time- and ATP-induced provocations on the recovery of LA-PV conduction. In addition, the midterm outcome of the patients who underwent repeat provocation and elimination of early PV reconnection was evaluated.

Patient Population

This study included 75 consecutive patients who underwent PV mapping and ablation for drug-resistant paroxysmal AF and were
followed for at least 6 months. They included 69 men and 6 women with a mean age of 55.4 ± 1.0 years. Twenty-seven patients had evidence of cardiovascular disease: 20 had hypertension, 6 had coronary artery disease, 2 had dilated cardiomyopathy, and 3 had mitral valve regurgitation (mild to moderate degree). The mean AF history (duration from diagnosis) was 4.5 ± 0.4 years. The mean LA diameter was 39.9 ± 0.7 mm and the mean left ventricular ejection fraction was 65.5 ± 0.9%. All patients underwent the PVI procedure and subsequent observations in a single institution (Jikei University Hospital). Informed consent was obtained from each patient before the procedure according to the protocol approved by the Hospital Human Research Committee.

**Catheter Ablation Procedure**

PVI was performed as described previously. The procedures were performed 7 days after the withdrawal of antiarrhythmic drugs (no patient took amiodarone). The LA and PVs were explored through either a patent foramen ovale (11 patients) or transseptal catheterization and thereafter, intravenous heparin was administered continuously to maintain an activated clotting time between 300 and 350 seconds. The procedures were performed under the mild sedation by pentazocine, hydroxyzine pamoate, flunitrazepam, and so forth, which made patients drowsy, but not under general anesthesia. Direct visualization of all 4 PVs was performed using selective venography to show the venous anatomy and the location of the LA-PV junction.

The PV antrum was determined by selective venography and/or 3-dimensional mapping systems (CARTO Merge, Biosense-Webster, Diamond Bar, CA, or Ensite NavX, St Jude Medical, St Paul, MN). All 4 PVs were targeted to be electrically disconnected from the LA at their antrum using large Lasso catheters (large size, A). Radiofrequency currents were applied with the guide of 3D images at the earliest activation of each PV antrum (B through D).

The localization of EPVRs, defined by the location of RF application site eliminating EPVR, was considered fluoroscopically as the area of the PV antrum demonstrating the earliest activation of each PV (Figure 1A). RF current application was performed as proximal to the antrum of the PV as possible, regardless of the ongoing rhythm (sinus rhythm or AF, Figure 1B through 1D). In cases with sinus rhythm, the segments of the PV perimeter demonstrating the earliest activation with the electrogram polarity reversal were preferentially targeted, whereas in patients who underwent PVI during ongoing AF, the segments demonstrating either fractionated electrograms, or electrogram polarity reversal, or the earliest activation during the transient or sustained organization of the local potential activation, were preferentially targeted. RF energy was delivered at the distal electrode (8-mm tip or 4.5-mm irrigated-tip) of the thermocouple-equipped ablation catheter (target: 45–50°C) with a power limit of 25–35 W for 30 to 60 seconds at each site. A nasogastric tube was inserted to identify the course of the esophagus during all ablation procedures to avoid esophageal injury. The power and the target temperature of the RF energy was limited to 25 W and 45°C, respectively, for up to 30 seconds when the site of RF application was close to the esophagus.

The end point of ablation was the establishment of a bidirectional conduction block between the LA and PV. The elimination of PV muscle conduction distal to the ablation sites was confirmed by either the abolition or dissociation of PV potentials recorded by the Lasso catheter, and the absence of conduction from the PV to LA was also confirmed by circumferential pacing inside the PV by Lasso catheter during SR (pacing by 20-mA pulse of 2-ms duration from each of the 10 bipoles on Lasso catheter).

**Induction and Elimination of Early PV Reconnection**

After the initial isolation of all 4 PVs, the presence/absence of the EPVR was checked in each PV after waiting for 30 minutes after the final RF application in each vein (time 1 in Figure 2A). Any PV reconnection was eliminated by additional applications of RF. Thereafter, 20 mg of ATP was rapidly injected to induce the dormant PV conduction after isoproterenol injection (4–8 μg) during SR or the coronary sinus pacing (ATP 1, in Figure 2A). The presence/absence of EPVR conduction in the ipsilateral PVs was simultaneously evaluated using double Lasso catheters. Patients showing EPVR received additional RF energy, applied at the earliest transient PV activation site identified on the Lasso catheter to establish further PV disconnection. The elimination of ATP-induced EPVR was subsequently reconfirmed at each step by repeat ATP injections under isoproterenol injection. The successful RF application site for eliminating EPVR was regarded as the reconnected gap site. In some cases, multiple reconnected gaps appeared requiring stepwise ablations to target each gap-site. These procedures were stage I (as demonstrated in Figure 2A). The provocation and elimination of time- and ATP-induced EPVR was repeatedly performed at every 30 minutes until 90 minutes after the initial PV isolation (stage II at 60 minutes, and stage III at 90 minutes).

The localization of EPVRs, defined by the location of RF application site eliminating EPVR, were classified fluoroscopically into 4 segments around the antrum of each PV (top, bottom, anterior, and posterior, as shown in Figure 2B). The appearance of recon-
Statistical Analysis

A mixed-effects model was used either to compare the prevalence of reconnected gaps in the 4 PVs according to the progression of provocative stage or to compare the prevalence among the four segments of each vein. When significant interactions were detected, post hoc multiple comparisons were made with the use of the Bonferroni method. In the analysis of the prevalence of EPVR, only the newly appeared gaps were counted and no region in any PV was doubly counted. Statistical significance was accepted at the 5% level. Results are presented as mean±SEM. Data were analyzed with the use of the SPSS software version 11.5J for Windows (SPSS Inc, Chicago, IL).

Results

A total of 293 PVs were ablated and isolated from the LA in 75 patients. The left common pulmonary vein was seen in 7 cases, isolated at the common PV trunk and regarded (counted) as the left superior PV. The initial isolation required 6.5±0.4, 4.3±0.3, 7.8±0.5, and 4.2±0.4 RF applications for the left superior (LS), left inferior (LI), right superior (RS), and right inferior (RI) PVs, respectively. The unidirectional block revealed by PV pacing was observed in 62 PVs in 54 patients (mean: 0.83±0.08 PVs per patient).

EPVRs were induced during the stepwise provocation process as shown in Figure 3 and the Table. In total, 75 gaps were observed to reconnect in 53 PVs among 37 patients after a waiting time of at least 30 minutes (time 1). Each of these reconnected gaps was successfully disconnected with an average of 1.2±0.1 RF applications. Transient reconnection of 76 gaps were induced by a rapid ATP injection (ATP 1), and again successfully eliminated by an additional 1.1±0.1 RF applications. Seventy-one of these 76 gaps were newly reconnected while the remaining 5 gaps were the same that had been ablated at the beginning of this stage. Another 30 minutes later (stage II), 64 gaps were observed to reconnect (time 2), and 54 of these gaps were newly reconnected while 10 other gaps were the same that had been eliminated during stage I. Although all these 64 gaps were successfully eliminated by a mean of 1.1±0.1 applications of RF, rapid ATP injections again transiently induced 36 gaps (ATP 2, 28 newly appeared and 8 reconnected in spite of their elimination through the earlier procedures). All 36 gaps were successfully eliminated by 1.2±0.1 applications of RF.

Another 8 gaps were observed to reconnect to the LA at 90 minutes after the initial PVI in stage III (Table). Six of these 8 gaps newly appeared at this stage, whereas 2 gaps were considered to be the same with that had been eliminated during the past stages. Another 1.2±0.1 applications of RF were required to eliminate each of these gaps. A final attempt of inducing pharmacological PV reconnection by ATP injection failed to reveal dormant PV-conduction at the end of stage III in any of the patients. In total, 257 gaps reconnected in 179 PVs of 61 patients either time- or ATP-dependently. The number of reconnected gaps significantly decreased in line with the progression of the provocation stage.

Figure 4 (A and B) demonstrates the mean number of reconnected gaps in all 75 patients according to the progression of provocative stage. In both superior PVs, the number of reconnected gaps was significantly smaller at the ATP 2, time 3, and ATP 3 compared with that of time 1, whereas no significant difference was observed in both inferior PVs in the number of gaps among the provocative stages. When the mean number of reconnected gaps were compared among the 4 PVs at each step, both superior PVs (especially RSPV) showed significantly larger number of...
reconnected gaps compared with the inferior PVs at time 1 and ATP 1 (Figure 5A and 5B), whereas no significant difference was detected among the four PVs at time 2 and ATP 2 (Figure 5C and 5D).

As for each vein, the mean number of reconnected gaps was significantly larger in the top and bottom segments of the RSPV (Figure 6A) and also in the bottom and posterior segments of the RIPV (Figure 6B). In contrast to the right veins, they distributed more evenly among the 4 segments in the left veins (Figure 6C and 6D).

The operation time (for the mapping and ablation) required for the initial PV isolation was about 1.5 hours (96.7 ± 1.8 minutes). The total procedure time (from the femoral puncture to the sheath removal) was around 3 hours (190.7 ± 2.4 minutes), including repeat EPVR inductions until 90 minutes after the initial PV isolation. Non-PV firing foci appeared in 8 patients during the procedure, including 4 foci in the superior vena cava, 3 at the LA roof, and 1 at elsewhere in the LA. All 4 arrhythmogenic superior vena cavae were electrically isolated from the RA and 2 foci at the roof were successfully ablated, whereas the other 2 non-PV foci remained nonablated. There were no life-threatening complications in this study population, including cerebral infarction, esophageal injury, and PV stenosis. Left atrial flutter, which newly appeared after the procedure, was observed in 2 patients during the follow-up period.

During the mean follow-up period of 370 ± 9 days, 6 cases (8%) showed recurrence of AF an average of 111 ± 6 days after the procedure, whereas the other 69 cases (92%) were free from AF without antiarrhythmic drug treatment. Two cases with remained non-PV foci did not show AF-recurrence. Three cases with AF-recurrence underwent a second procedure, which revealed the reconnection in 2.7 ± 0.3 previously isolated PVs (2–3 PVs).

![Figure 3. Typical example of repeat appearance of pulmonary vein (PV) reconnection. A, Both the superior and inferior right PVs were mapped simultaneously with the Lasso catheters. The circumferentially recorded PV potentials were initially eliminated (post-PVI). PV potentials reappeared in both PVs 30 minutes later (marked by a black star) and were eliminated by additional radiofrequency applications. Although no PV potentials could be observed at 60 minutes after the initial PVI (stage II), rapid ATP injection induced transient PV reconnection in both PVs. After elimination of these dormant conductions, another PV potential reappeared in the right inferior PV 90 minutes after the initial PVI. No further reconnection could be induced by the third ATP injection at the end of stage III. B, Example of left PVs in another case. Early PV reconnections were induced in stage I (both time and ATP dependently) and in stage II (only ATP dependently). Both superior and inferior PVs simultaneously reconnected in this case.](http://circep.ahajournals.org/)

<table>
<thead>
<tr>
<th>Table. Number of Reconnected Gaps at Each Provocation Step</th>
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<tr>
<td>Time 1</td>
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<tr>
<td>Total No. of reconnected gaps</td>
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<tr>
<td>No. of newly appeared gaps</td>
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<td>No. of RFs required to eliminate gaps</td>
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RFs indicates radiofrequency energy applications.
the observation time after the completion of the initial PV isolation, and the other is the rapid ATP-injection to reveal the dormant PV conductions. The prevalence of time-dependent EPVR ranges from 50–64% of PVs in 24–30% of all patients examined. Cheema et al. demonstrated a higher incidence of time-dependent EPVR (50% of PVs among 93% of patients). Their study applied a 60 minutes waiting time that revealed the first reconnection at 30 minutes in 33% of PVs, whereas 17% of the PVs showed the first recurrence at 60 minutes.

Pharmacological provocation of EPVR was first described by Arentz et al and Tritto et al by rapid injections of ATP, demonstrating that ATP-induced transient reconnection (dormant conduction) occurred in 13–43% of isolated superior PVs and 22% of inferior PVs. The elimination of these ATP-induced dormant conductions by additional RF applications increases the AF-free rate from 60% to 73–80% in the initial ablation procedure. The equivalence/difference of the time- and ATP-dependent EPVR has been demonstrated to be moderate (κ value=0.50) by Jiang et al. Ninomiya et al also demonstrated that 40% of all reconnection (8 of 20 PVs) was detected with the use of ATP, while the remaining 60% appeared time dependently.

The mechanism by which ATP reveals the insufficiently ablated tissues was recently described by Datino et al. They showed that ATP-induced hyperpolarization (through the increase of $I_{KAdo}$) restores excitability of PV muscle by removing voltage-dependent $I_{Na}$ inactivation.

**Combination of Time- and ATP-Dependent Provocation of EPVR**

Approximately 20% of patients demonstrate AF-recurrence during the postprocedure observation period, even with the elimination of ATP-induced EPVR. Ninomiya et al found 12 and 8 PVs reconducted among a total of 81PVs with the combination of time- and ATP-induced provocation. Although their study revealed a difference between the two methods of provoking PV reconnection, the end point to minimize the AF recurrence after the procedure remains unclear. This study attempted to induce EPVR repeatedly by the combination of time- and ATP-dependent provocation in order to establish a practical end point to minimize AF-recurrence after the PV isolation procedure. Observation and ATP induction only at 30 minutes are not sufficient to eliminate the reconductable gaps since the repeat provocation at 60 minutes revealed a substantial number of EPVR. A waiting time of 90 minutes may be unnecessary because the incidence of provoked EPVR at this stage was rare and might be negligible. The midterm outcome of this procedure (AF recurrence <10%) was marginally satisfactory.
site among 4r segments in the right superior and inferior PVs. The mean number of reconnected gaps was significantly larger in the top and bottom segments of the RSPV antrum, whereas the bottom and posterior segments of RIPV showed larger numbers of reconnected gaps compared with the anterior segment. On the other hand, they distributed more evenly in the left veins. These results are similar to previous reports, which evaluated the preferential site of reconnection either by observation time\textsuperscript{14} or a single trial of ATP-injection,\textsuperscript{21} demonstrating the higher prevalence at the carina region of both left and right PVs, top of RSPV, bottom of RIPV, and the PV–left atrial appendage ridge. This similarity suggests that although repeat provocation would reveal a larger number of EPVRs than a single provocation method, the preferential sites of reconnection are similar in each trial.

**Lasso-Guided PV Isolation for the Elimination of EPVR**

Several different methods to ablate PV have been developed so far, including segmental PV ostial/antral isolation guided by a

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**Figure 5.** Comparison of the mean number of reconnected gaps among the 4 pulmonary veins (PVs) at each provocative stage. In time 1 (A), the mean number of reconnected gaps was significantly lower in the left inferior PV compared with both superior PVs (0.07±0.03 in the LIPV versus 0.39±0.08 and 0.36±0.07 in the RSPV and LSPV, respectively, *P*<0.01, as shown by *). In ATP 1, the mean number of reconnected gaps was significantly larger in the right superior PV compared with both inferior PVs (0.37±0.07 in RSPV versus 0.16±0.05 and 0.16±0.05 in the RIPV and LIPV, respectively, *P*<0.01, as shown by *). There was no significant difference among the four PVs in time 2 and ATP 2 (shown by ◆ and ♦ in C and D). RS indicates right superior PV; RI, right inferior PV; LS, left superior PV; and LI, left inferior PV.

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**Figure 6.** Comparison of the mean number of reconnected gaps among the 4 segments in each pulmonary vein (PV). In RSPV (A), the mean number of gaps was significantly larger in the bottom segment (segment c) compared with the anterior or posterior segments (segments b and d) (0.010±0.014 in segment c versus 0.040±0.009 and 0.031±0.008 in segments b and d, respectively, *P*<0.01). The number of gaps was also significantly larger in the top segment (segment a) compared with that of posterior segment (segment d) (0.073±0.012 versus 0.031±0.008, *P*<0.01). In RIPV (B), the number of reconnected gaps was significantly smaller in the anterior segment (segment f) compared with that of bottom and posterior segment (segments g and h) (0.004±0.003 in segment f versus 0.053±0.011 and 0.036±0.009 in segments g and h, respectively, *P*<0.01). In the left PVs (C and D), no significant difference was observed in the mean number of reconnected gaps among the 4 segments.
Lasso catheter, circumferential PV isolation, and anatomic guide PV ablation by using a 3-dimensional mapping system.\textsuperscript{1–8} Although all methods of PV ablation were effective for AF patients, Lasso-guided mapping and ablation has advantage for the identification of the LA-PV gaps (especially for the temporal gap induced by ATP). The current study used the double large-Lasso technique at the antrum of ipsilateral PVS,\textsuperscript{9,11} which allowed easy identification of the location of the provoked reconnected gaps, resulting in successful elimination of EPVR with minimal RF applications (1.1–1.2 in average).

**Limitations**

There are some limitations in this study. The waiting time after the initial PV isolation, which was reported as 30, 60, and 90 minutes, was the approximate time that we intended to wait. Because all 4 PVs cannot be treated all at once, the waiting time differed, depending on the PVS; however, we tried to minimize the difference of the waiting time among the 4 PVS as small as possible. Although the results indicated that the elimination of EPVR until 60 minutes is sufficient because further EPVR at 90 minutes was rare, the overall AF-free rate shown in the present study was the results of eliminating EPVR until 90 minutes. Ignorance of the EPVR at 90 minutes may be detrimental in some cases. Requirements of double Lasso catheters may be a major limitation to the widespread use of this technique from the view of medical costs. Although the current study demonstrated the high efficiency of AF suppression by a single ablation procedure, a randomized, controlled study is necessary to verify the efficiency of repeat provocation and elimination of time- and ATP-induced PV-reconnection.

**Conclusions**

Repeat provocation of EPVR revealed considerable numbers of reconnected gaps, not only at 30 minutes but 60 or 90 minutes after the initial completion of PV isolation. Repeat elimination of repetitively provoked EPVR decreased the recurrence rate to less than 10% with a single ablation procedure in paroxysmal AF patients.

**Acknowledgments**

We thank to Dr Mitsuyosi Urashima (Division of Molecular Epidemiology, the Jikei University School of Medicine) and Dr Nobuo Shirahashi (Clinical Epidemiology, Osaka City University Graduate School) for their advice regarding statistical analysis and Dr Brian Quinn (Department of Linguistic Environment, Kyushu University) for linguistic comments on the manuscript.

**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

The efficiency of catheter ablation targeting pulmonary veins (PVs) to cure paroxysmal atrial fibrillation (AF) is well established. However, recurrence of AF after a successful PV isolation (PVI) procedure is still an unresolved problem requiring multiple ablation procedures to suppress the occurrence of AF. AF recurrences are predominantly due to the resumption of the electric conduction in isolated PVs to the left atrium. Because reconduction occurs in insufficiently ablated tissue, their identification and complete ablation in the initial procedure will decrease the subsequent AF recurrence. Several modifications of the PV isolation procedures have been proposed to minimize the PV reconnection, such as the elimination of ATP-induced PV reconnection by additional radiofrequency application, and prolonging the waiting time after the establishment of PVI to provoke the early PV reconnection (EPVR). However, AF recurrences due to PV reconnection are still not rare. This study investigated the affects of repeat both time- and ATP-induced provocations on the recovery of LA-PV conduction. In 75 patients with paroxysmal AF who underwent PVI, EPVR was provoked both time and ATP dependently every 30 minutes until 90 minutes after completion of PVI. Although both time- and ATP-dependent EPVR was induced most frequently at 30 minutes after PVI (75 and 76 gaps, respectively), their prevalence at 60 minutes was still high (64 and 36 gaps, respectively). On the other hand, only a small number of EPVR appeared at 90 minutes after PVI (8 gaps). During the mean follow-up period of 370 days, 92% of cases were free from AF without antiarrhythmic drugs.
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Circ Arrhythm Electrophysiolog. 2011;4:601-608; originally published online August 13, 2011; doi: 10.1161/CIRCEP.110.960138

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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