Repeated Provocation of Time- & ATP-induced Early Pulmonary Vein Reconnections after Pulmonary Vein Isolation: Eliminating Paroxysmal Atrial Fibrillation in a Single Procedure

Running title: Yamane et al.; Repeat elimination of PV-reconnections

Teiichi Yamane, MD1; Seiichiro Matsuo, MD1; Taro Date, MD1; Nicolas Lellouche, MD2; Mika Hioki, MD1; Ryosuke Narui, MD1; Keiichi Ito, MD1; Shin-ichi Tanigawa, MD1; Seigo Yamashita, MD1; Michifumi Tokuda, MD1; Hiroshi Yoshida, MD1; Ken-ichi Inada, MD1; Kenri Shibayama, MD1; Satoru Miyanaga, MD1; Hidekazu Miyazaki, MD1; Kunihiko Abe, MD1; Ken-ichi Sugimoto, MD1; Michihiro Yoshimura, MD1

* Division of Cardiology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; 2Fédération de Cardiologie, Henri Mondor Hospital, Créteil, France

Address for correspondence:
Teiichi Yamane, MD
Division of Cardiology, Department of Internal Medicine
The Jikei University School of Medicine
3-25-8, Nishi-shinbashi, Minato-ku, Tokyo, 105-8461, JAPAN
Phone: 81-3-3433-1111 (ext. 3261)
Fax: 81-3-3459-6043
E-mail address: yamanet1@aol.com

Abstract:

**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 endpoint.

**Methods and Results** - Seventy-five patients with paroxysmal atrial fibrillation (AF) underwent PVI. EPVR was provoked by both time- and ATP-induction every 30 min until 90 min after the individual isolation of all PVs. The number of re-connected atrio-PV gaps were evaluated and re-ablated at each provocation step. Although both time- and ATP-dependent EPVR was induced most frequently at 30 min after PVI (75 and 76 gaps, respectively), the prevalence of induced EPVR at 60 min was still high (64 and 36 gaps induced by time and ATP (respectively). Only a small number of EPVR appeared at 90 min after the elimination of all EPVR by 60 min, (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 min but also at 60 min is recommended after PVI to improve its efficacy.

**Key words**: atrial fibrillation, pulmonary veins, catheter ablation, adenosine triphosphate, dormant conduction
Introduction

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 WPW syndrome, is a prominent goal in the field of clinical arrhythmia.

AF-recurrences are predominantly due to the resumption of the electrical conduction in isolated PVs to the left atrium (LA).\(^6\)\(^-\)\(^8\) Since re-conduction 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 mid-term outcome of the patients who underwent repeat provocation and elimination of early PV reconnection was evaluated.

Methods

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 males and 6 females with a mean age of 55.4±1.0 years old. 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.\textsuperscript{9,11} 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, etc, which
made patients drowsy, but not under the 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 three-dimensional
mapping systems (CARTO Merge, Biosense-Webster, Diamond Bar, California, or Ensite
NavX, St Jude Medical, St. Paul, Minnesota). All four PVs were targeted to be electrically
disconnected from the LA at their antrum using large Lasso catheters\textsuperscript{11} (25 or 30 mm for the
superior PVs, 20 or 25 mm for the inferior PVs; Biosense Webster, Diammond Bar, CA, USA).
Double Lasso catheters were placed at the antrum of ipsilateral superior and inferior PVs\textsuperscript{11}
(Figure 1A). RF current ablation was performed as proximal to the antrum of the PV as
possible, regardless of the ongoing rhythm (sinus rhythm or AF, Figure 1B–D). In cases with
sinus rhythm, the segments of the PV perimeter demonstrating the earliest activation with the electrogram polarity reversal were preferentially targeted, while 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.11) 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 to 50°C) with a power limit of 25 to 35 W for 30 to 60 seconds at each site. A naso-gastric 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 25W 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 ten bipoles on Lasso catheter).

**Induction and Elimination of Early PV-reconnection**

After the initial isolation of all four PVs, the presence/absence of the EPVR was checked in each PV after waiting for 30 minutes following the final RF application in each vein (Time-1, in Figure 2A). Any PV re-connection was eliminated by additional applications of RF. Thereafter, 20 mg of ATP was rapidly injected to induce the dormant PV conduction following isoproterenol (ISP) injection (4-8 μg) during SR or the coronary sinus (CS) 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 ISP injection. The successful RF application site for eliminating EPVR was regarded as the re-conducted gap site. In some cases, multiple re-conducted 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 following 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 four segments around the antrum of each PV (top, bottom, anterior, and posterior, as shown in Figure 2B). The appearance of re-conducted gaps during the advanced stages (stages II or III) was observed to determine whether they were identical to those previously eliminated in the past provocation step (re-reconduction) or newly re-conducted at the present step. The re-conducted gaps located in the same quadrant of segment were defined as the same gap to simplify the evaluation.

In cases with non-PV firing foci, which were revealed either baseline state or during the provocation of EPVR, additional RF ablations were performed to eliminate these remaining foci if necessary.

**Patient Follow-up after Ablation**

All patients remained hospitalized for at least 4 days after the PVI procedure, under continuous ECG monitoring. The patients underwent careful observation (2 weeks after discharge, then every month) at the cardiology clinic, without taking any antiarrhythmic agents. The outcome of PVI was evaluated by the patient symptoms, ECG at periodical follow-ups, and also by periodically conducted 24-hour ambulatory monitoring (at 1 day, 1, 3, 6, 9, and 12
months after the procedure). A cardiac event recorder was used to define the cause of symptoms suggestive of tachycardia. Patients were discharged on warfarin anticoagulation but without antiarrhythmic drugs.

AF recurrence was defined as the appearance of sustained AF (lasting more than 30 seconds). AF recurrence within the first month after ablation was not included in the analysis and those who did not have any evidence of tachycardia later than one month during the follow-up (F/U) period were considered to be successful cases. On the other hand, the appearance of AF later than one month was considered to be true AF recurrence and repeat ablation (2nd procedure) was thus recommended.

Statistical Analysis

A mixed effects model was used either to compare the prevalence of reconnected gaps in the four 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 means ± SEMs. 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, 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 Table-1. In total, 75 gaps were observed to re-connect in 53 PVs among 37 patients after a waiting time of at least 30 min (Time-1). Each of these re-connected gaps was successfully disconnected with an average of 1.2 ± 0.1 RF applications. Transient re-conductions 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 min 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 re-connected 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 re-conduct to the LA at 90 minutes after the initial PVI in Stage-III (Table 1). Six of these 8 gaps newly appeared at this stage while 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. Totally, 257 gaps re-conducted in 179 PVs of 61 patients either time- or ATP-dependently. The number of re-conducted gaps significantly decreased in line with the progression of the provocation stage.

**Figure 4 (A, 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 to 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 four PVs at each step, both superior PVs (especially RSPV) showed significantly larger number of reconnected gaps compared to the inferior PVs at Time-1 and ATP-1 (Figure 5A, B), while no significant difference was detected among the four PVs at Time-2 and ATP-2 (Figure 5C, D).

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 four segments in the left veins (Figure 6C&D).

The operation time (for the mapping and ablation) required for the initial PV isolation was about 1.5 hours (96.7±1.8 min). The total procedure time (from the femoral puncture to the sheath removal) was around 3 hours (190.7 ± 2.4 min) including repeat EPVR inductions until 90 min after the initial PV isolation. Non-PV firing foci appeared in 8 patients during the procedure, including 4 foci in SVC, 3 at the LA roof, and 1 at elsewhere in the LA. All 4 arrhythmogenic SVCs were electrically isolated from the RA and 2 foci at the roof were successfully ablated, while the other 2 non-PV foci remained non-ablated. 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 pts 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, while the other 69 cases (92%) were free from AF without antiarrhythmic drug treatment. Two cases with remained non-PV foci did not show AF-recurrences. Three cases with AF-recurrence underwent a 2nd procedure, which revealed the reconnection in 2.7 ± 0.3 previously isolated PVs (2~3 PVs).
Discussion

Major findings

The present study demonstrated the characteristics of early PV reconnection during the initial catheter ablation procedure for patients with PAF. EPVR was frequently induced not only ATP-dependently but also time-dependently until 60 min after the completion of the initial PV isolation. Further provocation at 90 min rarely revealed another re-conduction of isolated PVs. The AF-recurrence rate after the initial procedure was less than 10% with repeat provocation and elimination of EPVR in this study, without the administration of antiarrhythmic drugs.

Previous studies for EPVR

Several reports showed that the major cause of AF-recurrence after the ablation of paroxysmal AF is reconnection of the isolated PV, indicating that re-connectable tissue can remain after the establishment of a complete electrical conduction block between the LA and PV. Two methods of inducing EPVR are useful to identify the re-connectable tissue at the PV ostium/antrum during the initial ablation procedure. One is 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 to 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 min waiting time that revealed the first reconnection at 30 min in 33% of PVs, whereas 17% of the PVs showed the first recurrence at 60 min.

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 re-connection (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.\textsuperscript{9,10} The equivalence/difference of the time- and ATP-dependent EPVR has been demonstrated to be moderate (kappa value = 0.50) by Jiang et al.\textsuperscript{18} Ninomiya et al. also demonstrated that 40% of all reconduction (8 of 20 PVs) was detected with the use of ATP, while the remaining 60% appeared time-dependently.\textsuperscript{19}

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 $I_{K_{Avo}}$) restores excitability of PV muscle by removing voltage-dependent $I_{Na}$ inactivation.\textsuperscript{20}

**Combination of time- & ATP-dependent provocation of EPVR**

Approximately 20\% of patients demonstrate AF-recurrence during the post-procedure observation period, even with the elimination of ATP-induced EPVR.\textsuperscript{9,10} Ninomiya et al. found 12 and 8 PVs re-conducted among a total of 81PVs with the combination of time- and ATP-induced provocation.\textsuperscript{19} Although their study revealed a difference between the two methods of provoking PV reconnection, the endpoint 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 endpoint to minimize AF-recurrence after the PV isolation procedure. Observation and ATP-induction only at 30 minutes are not sufficient to eliminate the re-conductable gaps since the repeat provocation at 60 minutes revealed a substantial number of EPVR. A waiting time of 90 minutes may be unnecessary since the incidence of provoked EPVR at this stage was rare and might be negligible. The mid-term outcome of this procedure (AF-recurrence < 10\%) was marginally satisfactory.

**Region of reconnected gaps**

The current study observed that superior PVs were more likely to reconnect than
inferior PVs during stage-I (at 30 min), while the reconnected gaps evenly distributed among the four PVs during stage-II (at 60 min), suggesting that repeat provocations and eliminations of EPVRs later than 60 min are important in all four PVs. As for each vein, there was a significant difference in the prevalence of the EPVR-site among four 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, while the bottom and posterior segments of RIPV showed larger numbers of reconnected gaps compared to 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-guide 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 Lasso catheter, circumferential PV isolation and anatomical guide PV ablation by using a three-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. Since all four PVs can not 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 four PVs as small as possible. Although the results indicated that the elimination of EPVR until 60 min is sufficient since further EPVR at 90 min was rare, the overall AF-free rate shown in the present study was the results of eliminating EPVR until 90 min. Ignorance of the EPVR at 90 min 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 control 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 re-conductable gaps, not only at 30 min but 60 or 90 min after the initial completion of PV isolation. Repeat elimination of repetitively provoked EPRV decreased the recurrence rate to less than 10% with a single ablation procedure in paroxysmal AF patients.

Acknowledgements: The authors 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, Dr. Brian Quinn (Department of Linguistic Environment, Kyushu University) for linguistic comments on the manuscript.

Conflict of Interest Disclosures: None.
References:


Table 1. Number of reconnected gaps at each provocation step

<table>
<thead>
<tr>
<th></th>
<th>Time-1</th>
<th>ATP-1</th>
<th>Time-2</th>
<th>ATP-2</th>
<th>Time-3</th>
<th>ATP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of reconnected Gaps</td>
<td>75</td>
<td>76</td>
<td>64</td>
<td>36</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>No. of newly appeared Gaps</td>
<td>75</td>
<td>71</td>
<td>54</td>
<td>28</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>No. of RFs required to eliminate Gaps</td>
<td>1.2 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

RFs: radiofrequency energy applications

Figure Legends:

Figure 1: Demonstration of the method of PV antrum isolation by fluoroscopic and three-dimensional view obtained during the procedure. All four PVs were individually targeted to be electrically isolated from the LA at their antrum using double Lasso catheters (large-size, panel A). RF currents were applied with the guide of 3D images at the earliest activation of each PV antrum (panel B–D).
Figure 2: Method of provocation of PV reconnection. The presence/absence of time- and ATP-induced PV reconnection was checked every 30 min until 90 min after the initial PVI (stage I–III). The identified PV reconnection gaps were eliminated at each provocation step.

Figure 3: Typical example of repeat appearance of 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 re-appeared in both PVs 30 min later (marked by a black star), and were eliminated by additional RF applications. Although no PV potentials could be observed at 60 min 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 re-appeared in the right inferior PV 90 min after the initial PVI. No further reconnection could be induced by the 3rd 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.

Figure 4: The demonstration of the mean number of reconnection gaps at each provocation step (Panel A: right superior and right inferior PV, Panel B: left superior and left inferior PV). As shown in panel A, the mean number of reconnected gaps was largest in Time-I and decreased according to the progression of provocative stage in the right superior PV (●), while no significant difference was observed among the provocative stages in the right inferior PV (○). Panel B: Similar to the right veins, the mean number of reconnected gaps decreased according to the progression of provocative stage in the left superior PV (●), while no significant difference was observed among the stages in the left inferior PV (○). In both the right and left
superior PVs, the number of reconnected gaps was significantly smaller at the ATP-1, Time-3
and ATP-3 compared to that of Time-1 (labeled by *, p<0.01).

Figure 5: The comparison of the mean number of reconnected gaps among the four PVs at each
provocative stage. In Time-1 (panel A), the mean number of reconnected gaps was
significantly lower in the left inferior PV compared to both superior PVs (0.07±0.03 in the
LIPV vs. 0.39±0.08 and 0.36±0.07 in the RSPV and LSPV, respectively, p<0.01). In ATP-1,
the mean number of reconnected gaps was significantly larger in the right superior PV
compared to both inferior PVs (0.37±0.07 in RSPV vs. 0.16±0.05 and 0.16±0.05 in the RIPV
and LIPV, respectively, p<0.01). There was no significant difference among the four PVs in
Time-2 and ATP-2 (panel C&D). RS: right superior PV, RI: right inferior PV, LS: left
superior PV, LI: left inferior PV.

Figure 6: The comparison of the mean number of reconnected gaps among the four segments in
each PV. In RSPV (panel A), the mean number of gaps was significantly larger in the bottom
segment (segment-c) compared to the anterior or posterior segments (segment-b and d)
(0.010±0.014 in the segment-c vs. 0.040±0.009 and 0.031±0.008 in segment-b and d,
respectively, p<0.01). The number of gaps was also significantly larger in the top segment
(segment-a) compared to that of posterior segment (segment-d) (0.073±0.012 vs. 0.031±0.008,
p<0.01). In RIPV (panel B), the number of reconnected gaps was significantly smaller in the
anterior segment (segment-f) compared to those of bottom and posterior segment (segment-g
and h) (0.004±0.003 in the segment-f vs. 0.053±0.011 and 0.036±0.009 in the segments g and
h, respectively, p<0.01). In the left PVs (panel C and D), no significant difference was
observed in the mean number of reconnected gaps among the four segments.
(A) PVAI

Stage I (30 min)

Time-1

ATP-1

Stage II (60 min)

Time-2

ATP-2

Stage III (90 min)

Time-3

ATP-3

(B) RSPV

<table>
<thead>
<tr>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>e</td>
<td>f</td>
<td>g</td>
<td>h</td>
</tr>
</tbody>
</table>

LSPV

<table>
<thead>
<tr>
<th>i</th>
<th>j</th>
<th>k</th>
<th>l</th>
</tr>
</thead>
<tbody>
<tr>
<td>m</td>
<td>n</td>
<td>o</td>
<td>p</td>
</tr>
</tbody>
</table>

RIPV

LIPV
<table>
<thead>
<tr>
<th></th>
<th>Stage-I</th>
<th>Stage-II</th>
<th>Stage-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>Post-PVI</td>
<td>Time-1</td>
<td>ATP-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-2</td>
<td>ATP-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-3</td>
<td>ATP-3</td>
</tr>
</tbody>
</table>

(A) 

<table>
<thead>
<tr>
<th></th>
<th>Stage-I</th>
<th>Stage-II</th>
<th>Stage-III</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>Post-PVI</td>
<td>Time-1</td>
<td>ATP-1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-2</td>
<td>ATP-2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time-3</td>
<td>ATP-3</td>
</tr>
</tbody>
</table>

(B)
(A) Mean No. of Reconnected Gaps

<table>
<thead>
<tr>
<th>Time</th>
<th>ATP-1</th>
<th>Time-2</th>
<th>ATP-2</th>
<th>Time-3</th>
<th>ATP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-I (30min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage-II (60min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage-III (90min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(B) Mean No. of Reconnected Gaps

<table>
<thead>
<tr>
<th>Time</th>
<th>ATP-1</th>
<th>Time-2</th>
<th>ATP-2</th>
<th>Time-3</th>
<th>ATP-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage-I (30min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage-II (60min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage-III (90min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(A) Time-1

(B) ATP-1

(C) Time-2

(D) ATP-2

Mean No. of Reconnected Gaps

RS RI LS LI

RS RI LS LI

RS RI LS LI

RS RI LS LI

**RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS LI

* RS RI LS L
Repeated Provocation of Time- & ATP-induced Early Pulmonary Vein Reconnections after Pulmonary Vein Isolation: Eliminating Paroxysmal Atrial Fibrillation in a Single Procedure
Teiichi Yamane, Seiichiro Matsuo, Taro Date, Nicolas Lellouche, Mika Hioki, Ryosuke Narui, Keiichi Ito, Shin-ichi Tanigawa, Seigo Yamashita, Michifumi Tokuda, Hiroshi Yōshida, Keiichi Inada, Kenri Shibayama, Satoru Miyanaga, Hidekazu Miyazaki, Kunihiro Abe, Ken-ichi Sugimoto and Michihiro Yoshimura

Circ Arrhythm Electrophysiol. published online August 13, 2011;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circep.ahajournals.org/content/early/2011/08/13/CIRCEP.110.960138

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Arrhythmia and Electrophysiology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Arrhythmia and Electrophysiology is online at:
http://circep.ahajournals.org//subscriptions/