Response of Atrial Fibrillation to Pulmonary Vein Antrum Isolation Is Directly Related to Resumption and Delay of Pulmonary Vein Conduction

Atul Verma, MD; Fethi Kilicaslan, MD; Ennio Pisano, MD; Nassir F. Marrouche, MD; Raffaele Fanelli, MD; Johannes Brachmann, MD; Jens Geunther, MD; Domenico Potenza, MD; David O. Martin, MD, MPH; Jennifer Cummings, MD; J. David Burkhardt, MD; Walid Saliba, MD; Robert A. Schweikert, MD; Andrea Natale, MD

Background—The role of pulmonary vein (PV) isolation in ablative treatment of atrial fibrillation (AF) has been debated in conflicting reports. We sought to compare PV conduction in patients who had no AF recurrence (group I), patients who could maintain sinus rhythm on antiarrhythmic medication (group II), and patients who had recurrent AF despite antiarrhythmic medication (group III) after PV antrum isolation (PVAI).

Methods and Results—PV conduction was examined in consecutive patients undergoing second PVAI for AF recurrence. We also recruited some patients cured of AF to undergo a repeat, limited electrophysiological study at >3 months after PVAI. All patients underwent PVAI with an intracardiac echocardiography (ICE)–guided approach with complete isolation of all 4 PV antra (PVA). The number of PVs with recurrent conduction and the shortest atrial to PV (A-PV) conduction delay was measured with the use of consistent Lasso positions defined by ICE. Late AF recurrence was defined as AF >2 months after PVAI with the patient off medications. Patients in groups I (n=26), II (n=37), and III (n=44) did not differ at baseline (38% permanent AF; ejection fraction 53±6%). Recurrence of PV–left atrial (LA) conduction was seen in 1.7±0.8 and 2.2±0.8 PVAs for groups II and III but only in 0.2±0.4 for group I (P=0.02). In patients with recurrent PV-LA conduction, the A-PV delay increased from the first to second procedure by 69±47% for group III, 267±110% for group II, and 473±71% for group I (P<0.001). When pacing was at a faster rate, A-PV block developed in all 5 of the group I patients with recurrent PV-LA conduction.

Conclusions—The majority of patients with drug-free cure show no PV-LA conduction recurrence. Substantial A-PV delay is seen in patients able to maintain sinus rhythm on antiarrhythmic medication or cured of AF compared with patients who fail PVAI. (Circulation. 2005;112:627-635.)

Key Words: ablation ■ atrial fibrillation ■ pulmonary veins ■ recurrence

It is accepted that atrial fibrillation (AF) is frequently initiated by triggering foci located within the pulmonary vein (PV) antra (PVA).1 Techniques of ablating AF have therefore targeted radiofrequency lesions at the interface between the left atrium (LA) and the PVA.2 However, the pathophysiology of AF can be quite complex. Triggering foci for AF initiation may occur from non-PV locations in a minority of patients.3 Furthermore, formation of stable rotors at the interface between the PVA and the posterior LA wall may be critical to AF perpetuation.4 Therefore, whereas some approaches have emphasized the necessity of electrically isolating the PVs for procedural success,2-5,6 others have used an empirical anatomic approach targeting the “substrate” for AF maintenance without seeking to achieve PV isolation.7 Our group, in particular, has always targeted electric isolation of all 4 PVA using a technique guided by intracardiac echocardiography (ICE).8

The importance of PV isolation to procedural outcome is not well known, and reports published to date have had conflicting conclusions.9–13 However, if electric isolation of the PVA is not critical to procedural outcome, there should be no relationship between PV conduction and the status of the patient’s AF after ablation. In this study we examined PV conduction in patients who had previously undergone PV antrum isolation (PVAI) using an ICE-guided technique. We sought to characterize and compare PV conduction in patients who (1) had no AF recurrence, (2) could maintain sinus rhythm using antiarrhythmic medication ineffective before
ablation, and (3) had recurrent AF not controlled by antiarrhythmic medication.

Methods

Study Population
We examined all patients undergoing second PVAI procedures for AF recurrence from September 2003 until March 2004. All patients had undergone a first PVAI procedure within the preceding 6 months. Recurrence was defined as AF occurring beyond 2 months after PVAI. Patients were initially selected for PVAI because of symptomatic AF, which was paroxysmal, persistent, or permanent and refractory to ≥2 antiarrhythmic medications. Patients with preexisting extensive LA scar detected at their initial procedure were excluded from this study because of previous data showing the unique altered substrate in this small subset of patients (representing not more than 6% of our total AF ablation population). Extensive scarring was defined exactly according to the previously published criteria of absence of atrial electrogram seen in all 10 poles of a decapolar circular mapping catheter at in at least 3 distinct positions in the LA. Over this same time period, we recruited patients who were cured of AF after a first PVAI procedure to undergo a repeat, limited electrophysiological study to assess conduction within the PVA. These patients all underwent their repeat procedure at least 6 months after initial PVAI; again, patients with preexisting LA scar were excluded for the aforementioned reasons.

Patients were recruited from 3 participating institutions. Of the 107 patients studied, 65 were from the Cleveland Clinic, 25 from Casa Sollievo della Sofferenza (S. Giovanni Rotondo, Italy), and 17 from Klinikum Coburg (Coburg, Germany). Patients from all 3 institutions underwent the identical procedural protocol described below. All patients had to sign a written informed consent before undergoing both initial and repeat electrophysiological and ablation procedures. The collection of these data was performed in accordance with the ethical guidelines of each institution’s review board.

PVAI Procedure
All patients underwent PVAI with the use of an ICE-guided technique, which is summarized here but described in extensive detail elsewhere. After femoral venous access was obtained, a 10F 64-element phased-array ultrasound imaging catheter (Siemens AG) was positioned in the right atrium. A 14-pole recording catheter (TZ Medical) was placed in the coronary sinus via the right internal jugular access. Under ICE guidance, a decapolar circular (Lasso) mapping catheter and an 8-mm-tip ablation catheter (Biosense Webster) were advanced into the LA via 2 transseptal punctures. The patient was systematically anticoagulated with intravenous heparin to maintain an activated clotting time (ACT) of 350 to 400 seconds. Before the first transseptal puncture, a 140-IU/kg heparin bolus was given, and an infusion of 15 IU/kg/h was started. An additional 70 IU/kg bolus was given before the second transseptal puncture. The heparin infusion was then titrated to maintain the target ACT. ICE was used to define the PVA and guide sequential placement of the Lasso catheter in all positions surrounding (and outside of) each PV. Radiofrequency (RF) ablation was performed wherever PV potentials were recorded around the PVA. RF energy output was limited to a maximum of 70 W and 55 coulombs and was titrated according to microbubble formation detected by ICE. The end point of ablation was complete electric disconnection of the PVA from the LA. This was considered to be achieved when no PV potentials could be recorded along the antrum or inside the vein by the Lasso catheter during sinus rhythm or coronary sinus pacing. At the end of the procedure, all 4 PVA were extensively remapped with the Lasso catheter to check for any persisting PV potentials, and, if necessary, further ablation was performed to eliminate these. All 4 PVA and the superior vena cava (SVC) were isolated in every patient. The SVC was identified by placing the Lasso catheter at the SVC–right atrial junction defined by ICE. High-output pacing from the ablation catheter was used to localize the phrenic nerve to avoid phrenic injury during ablation. During the baseline ablation, we did not routinely look for non-PV foci apart from routinely isolating the SVC. No ablation lines between the mitral annulus and PVs were performed.

Repeat Electrophysiological Study
For patients cured of AF but agreeing to undergo repeat electrophysiological study, a limited procedure was performed compared with the original PVAI. As described for the PVAI procedure, the ICE imaging catheter was advanced via femoral venous access into the right atrium, and a 14-pole catheter was placed in the coronary sinus. A single transseptal puncture was performed under direct ICE visualization to minimize the risk of transseptal access (we have had no complications related to transseptal access in our last 1000 procedures). The patient was heparinized to maintain an ACT of 350 to 400 seconds. With the use of a single 8F sheath to cross the septum, a decapolar Lasso catheter was advanced into the LA and used to map all 4 PVA with and without pacing from the coronary sinus.

In all 3 groups, during the second ablation/electrophysiological procedure, intravenous isoproterenol infusion (up to 20 g/min) and boluses of adenosine were given to encourage PV or non-PV trigger firing and to assess whether they indeed led to AF initiation.

During both initial and repeat procedures, we determined the atrial to PV interval (A-PV). To ensure consistency in the A-PV measurement, we positioned the Lasso catheter at the end of the tubular segment of each PV as defined by ICE. Using this ICE definition, we could ensure that measurements of the A-PV interval were being performed at uniform locations. For the left and right-sided veins, A-PV was defined as the time interval from the onset of the local atrial potential to the earliest or latest PV potential recorded by any of the 10 Lasso catheter electrodes. For consistency, the shortest A-PV interval recorded by any of the 10 electrodes was taken as the A-PV interval for that particular vein.

If non-PV triggers for AF were identified during the study, 3-dimensional electroanatomic mapping with the use of the CARTO system (Biosense Webster) was used to assist in mapping and ablation of the focus. A subset of patients had complete voltage mapping of the LA performed at their repeat procedure with the use of CARTO as part of another study protocol. For these voltage maps, scar was defined as a bipolar voltage of <0.5 mV indistinguishable from noise. The CARTO system is able to measure the distance between any 2 points. With the assumption that a scarred segment of LA could be divided into multiple smaller rectangular or trapezoidal shapes, the area of the segment could be approximated by summing the areas of the smaller shapes. This segment was then expressed as a percentage of the total approximated LA surface area (assessed by the same technique) excluding the tubular portion of the PVs. A similar technique has been previously reported for mapping the left ventricle.

Follow-Up
After initial PVAI, patients continued anticoagulation with warfarin to maintain an international normalized ratio of 2.0 to 3.0 for a minimum of 4 months. In all patients, antiarrhythmic medications were continued for 2 months after ablation and were chosen from one of sotalol, propafenone, flecainide, or dofetilide. Amiodarone was not used after ablation and was discontinued 4 to 5 months before the initial ablation procedure. Antiarrhythmic medications were discontinued in all patients after 2 months. Patients had spiral CT scans 3 months after ablation to assess PV stenosis.

Late recurrence of AF was defined as AF occurring beyond 2 months after PVAI. Thus, success was defined as a lack of late AF recurrence with the patient off antiarrhythmic medication. If late AF recurrence occurred, antiarrhythmic medications were restarted to determine whether sinus rhythm could be maintained, but patients were still offered a second ablation procedure to achieve a true cure (sinus rhythm without the use of antiarrhythmic medication). To determine recurrence, all patients wore rhythm transmitters for a minimum of 3 months after PVAI, and this was extended by another 3 months for patients with early AF recurrences. Patients were asked to record events any time they experienced symptoms and to...
TABLE 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>26</td>
<td>37</td>
<td>44</td>
<td>NA</td>
</tr>
<tr>
<td>Age, y</td>
<td>55±9</td>
<td>54±13</td>
<td>58±7</td>
<td>0.32</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>19 (73)</td>
<td>25 (68)</td>
<td>31 (71)</td>
<td>0.48</td>
</tr>
<tr>
<td>AF frequency, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>11 (42)</td>
<td>16 (43)</td>
<td>15 (35)</td>
<td>0.11*</td>
</tr>
<tr>
<td>Persistent</td>
<td>6 (23)</td>
<td>8 (22)</td>
<td>10 (23)</td>
<td></td>
</tr>
<tr>
<td>Permanent</td>
<td>9 (35)</td>
<td>13 (33)</td>
<td>19 (43)</td>
<td></td>
</tr>
<tr>
<td>AF duration, y</td>
<td>7±7</td>
<td>7±7</td>
<td>9±7</td>
<td>0.18</td>
</tr>
<tr>
<td>No. failed AAM</td>
<td>2.4±0.8</td>
<td>2.6±0.9</td>
<td>3.1±0.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>6 (23)</td>
<td>10 (27)</td>
<td>13 (30)</td>
<td>0.09</td>
</tr>
<tr>
<td>LA size, cm</td>
<td>4.3±0.6</td>
<td>4.3±0.5</td>
<td>4.4±0.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>54±7</td>
<td>53±4</td>
<td>53±9</td>
<td>0.61</td>
</tr>
<tr>
<td>Initial procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total duration, min</td>
<td>166±40</td>
<td>170±42</td>
<td>169±48</td>
<td>0.35</td>
</tr>
<tr>
<td>RF time, min</td>
<td>45±25</td>
<td>46±25</td>
<td>45±28</td>
<td>0.69</td>
</tr>
</tbody>
</table>

AAM indicates antiarrhythmic medication; NA, not applicable.

*P represents comparison of distribution of AF frequency in each group.

Statistical Analysis

All data are reported as mean±SD for continuous variables and as percentage values for categorical variables unless otherwise indicated. Comparison of continuous variables among the 3 groups was made with the independent samples t test. Categorical variables were compared with χ² analysis. A-PV intervals are given for the individual PVs as well as the overall percent change in A-PV interval from the first to second procedure for all PVs. Overall percent change was compared between groups with ANOVA and t test analysis (as above). A probability cutoff of <0.05 was considered significant for all statistical determinations.

Results

Patient Characteristics

Baseline patient characteristics in each of groups I, II, and III are summarized in Table 1. There were no significant differences in patient characteristics among the 3 groups. The distribution of patients with paroxysmal, persistent, and permanent AF was similar in all 3 groups. Importantly, the total amount of RF delivery time at the initial PVAI procedure was similar in all 3 groups. Importantly, the distribution of patients with paroxysmal, persistent, and permanent AF was similar in all 3 groups. The proportions of patients with structural heart disease, LA size, and ejection fraction were also similar in all 3 groups.

Number of PVA With Recurrent Conduction

According to our technique, all 4 PVA were isolated for all patients during the initial ablation procedure. Recurrence of PV-LA conduction was seen in a larger number of PVA in patients who experienced AF recurrence after PVAI compared with patients who did not. Recurrence was seen in 1.7±0.8 PVA for group II patients and 2.2±0.8 PVA for group III patients. This was significantly higher than the 0.2±0.4 PVA showing recurrence in group I patients (P=0.021).

The number of patients experiencing 1, 2, 3, and 4 PVA recurrences is detailed in Table 2. In groups II and III, 95% and 100% of patients had recurrence of conduction seen in at least 1 PVA, respectively. Recurrence in only 1 culprit PVA was sufficient to cause AF recurrence in 12 of 37 patients (32%) in group II and 6 of 44 patients (14%) in group III. The majority of patients in group I (81%) did not show recurrence of PV-LA conduction in any of the PVA.

Two patients (5%) in group II did not show recurrent conduction in any of the PVs. In both of these cases, focal triggers for AF were found in non-PV sites within the LA. In 1 patient, the site was located in the anterior roof of the LA. Figure 1 is a CARTO activation map of this patient showing the anterior roof location of the premature atrial firing. Focal ablation at this site (2 RF lesions) was required to prevent AF initiation on isoproterenol despite the extensive scar on the posterior LA wall from the previous ablation. In the other patient, a focal non-PV trigger was mapped and successfully ablated along the LA septum (1 RF lesion). Again, this focal ablation prevented AF initiation despite extensive scarring from the previous ablation.

LA Voltage Mapping

At the time of the second study, voltage mapping of the LA was performed with the use of CARTO in 6 of 26 group I patients (23%), 14 of 37 group II patients (38%), and 18 of 44 group III patients (41%). The size of the low-voltage area created from the previous PVAI did not differ among the 3 groups. Low “scar” voltages occupied 38±8%, 40±12%, and...
41±10% of the estimated total LA surface area (Figure 2) in group I, II, and III patients, respectively (P=0.34).

A-PV Conduction Delay
A-PV intervals were significantly delayed from the first to second procedure in patients who could maintain sinus rhythm with/without antiarrhythmic medication compared with patients who failed PVAI. The A-PV intervals for each of the 4 PVs and the percent change from the first to second procedure are detailed in Table 3, except for the right superior PV and right inferior PV for group I. This is because none of the patients in group I had recurrence in the right superior PV and only 1 had recurrence in the right inferior PV, thereby preventing statistical analysis. The A-PV delay was significantly different among the 3 groups (P<0.001). For all PVs, the A-PV interval increased by 69±47% for group III patients from the first to second procedure. However, the delay in PV-LA conduction was much longer for group II patients, with an A-PV increase of 267±110%. In the minority of group I patients who demonstrated conduction recurrence in a single PVA, the delay in PV-LA conduction was longer still, with an overall A-PV increase of 473±71%.

In fact, when pacing occurred at a faster rate, A-PV block was observed in all 5 (100%) of the patients with recurrent PV-LA conduction in group I (Figure 3). A-PV block was not observed in any group II or III patients. Figures 4 and 5 demonstrate representative examples of A-PV delay recordings from patients in groups II and III.

Follow-Up
All of the patients in group II and III underwent repeat PVAI to reisolate those PVA that demonstrated recurrent conduction. Repeat ablation was not performed on those patients who were cured (group I). Repeat PVAI was performed in exactly the same manner as the initial ablation procedure. In all cases, only limited ablation in specific segments around the antral-LA interface was required for repeat isolation. Mean RF time was only 5.3±2.7 minutes for these repeat procedures. Median follow-up duration for the patients who underwent repeat PVAI was 8.3 months (range, 6 to 12 months) since the second procedure. Of the 37 patients in group II, 36 (97%) have remained free of AF while off antiarrhythmic medication since their second PVAI. In group III, 40 of 44 patients (91%) have remained free of AF while off antiarrhythmic medication since their second PVAI.

Figure 1. Three-dimensional electroanatomic CARTO maps of the LA (anterior view [left], posterior view [right]) showing the activation sequence of an ectopic atrial focus in a patient who had a previous PVAI procedure 5 months before. The gray areas represent regions of scar created by the initial PVAI procedure. In this case, the ablated regions represent 42% of the total LA surface area. This patient experienced AF recurrence after initial PVAI that was suppressed by antiarrhythmic medication. During this second procedure, no recurrent conduction between the pulmonary veins and the atrium was found. However, AF was initiated by an ectopic atrial focus firing from the LA roof (arrow), with red representing the earliest site of activation of the focus. Two RF lesions at this site successfully eliminated the ectopic trigger and prevented AF recurrence.

Figure 2. Three-dimensional electroanatomic CARTO maps of the LA (anterior view [right], posterior view [left]) showing the extent of scarring created by the first PVAI ablation procedure in a patient who had AF recurrence after the first procedure that was not controlled with antiarrhythmic medication (group III). The gray regions represent scar created by the first ablation as determined by absent or very low voltage amplitude. In this patient, the ablation scar represents 39% of the total LA surface area, which is typical of the scar area created by the ablation procedure. The size of scar seen at the time of the second procedure did not differ significantly between the 3 groups studied (see text for details). The colored tubes represent the tubular portions of the PVs.
TABLE 3. A-PV Interval for PVs by Patient Group

<table>
<thead>
<tr>
<th></th>
<th>Group I*</th>
<th>Group II*</th>
<th>Group III*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSPV First</td>
<td>39:5</td>
<td>41:11</td>
<td>39:14</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>230:34</td>
<td>146:37</td>
<td>58:14</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>500:40</td>
<td>268:102</td>
<td>47:22</td>
<td>0.002</td>
</tr>
<tr>
<td>LIPV First</td>
<td>39:4</td>
<td>32:10</td>
<td>31:15</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>210:57</td>
<td>119:26</td>
<td>50:13</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>430:22</td>
<td>284:121</td>
<td>59:34</td>
<td>0.007</td>
</tr>
<tr>
<td>RSPV First</td>
<td>...</td>
<td>29:7</td>
<td>30:9</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>...</td>
<td>99:17</td>
<td>60:19</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>...</td>
<td>256:90</td>
<td>97:31</td>
<td>0.001</td>
</tr>
<tr>
<td>RIPV First</td>
<td>...</td>
<td>25:7</td>
<td>27:10</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>...</td>
<td>93:21</td>
<td>43:10</td>
<td></td>
</tr>
<tr>
<td>procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>...</td>
<td>271:79</td>
<td>58:25</td>
<td>0.002</td>
</tr>
<tr>
<td>All PVs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>473:71</td>
<td>267:110</td>
<td>69:47</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Numbers in group columns represent mean shortest A-PV intervals in milliseconds. LSPV indicates left superior PV; LIPV, left inferior PV; RSPV, right superior PV; and RIPV, right inferior PV.

*All 4 PVs were assessed in all patients in each group.

Complications

During the initial ablation procedure, 1 patient experienced a large femoral hematoma that did not require transfusion. During the repeat procedure, no complications occurred. We did not have any cases of cardiac tamponade, stroke, or esophageal fistula. No complications occurred as a result of ICE-guided transseptal puncture. No PV stenosis was found on CT scan assessment after ablation.

Discussion

Main Findings

This study demonstrates the direct relationship between response of AF to PVAI and the resumption and delay in PV conduction. The majority of patients who have no episodes of AF after PVAI have no recurrent PV-LA conduction seen. In the few cured patients who had recurrent PV-LA conduction, this was limited to a single PV, and it was associated with substantial conduction delay between the PV and the LA and even A-PV block when pacing occurred at faster rates. In contrast, almost all patients with AF recurrence after PVAI showed recurrent PV-LA conduction in at least 1 PV. However, patients able to maintain sinus rhythm on antiarrhythmic medication demonstrated a significant conduction delay between recurrent PVS and the LA, whereas patients who did not respond to antiarrhythmic medication had only minimal conduction delay. Patients with AF recurrence who underwent repeat PVAI alone (without additional linear ablation) had excellent results, with >90% drug-free cure seen over a median follow-up of ~8 months. This is the first study that correlates long-term cure with isolation or significant PV-LA conduction delay. These findings may also explain why procedures not geared to achieving PVA isolation may be effective by creating significant conduction delay between the PVA and atrium.

PV Reconnection and AF Recurrence

Since the landmark study of Haissaguerre et al demonstrating that PV ectopy was the main trigger for AF initiation, isolation of the PVs has been considered important to curing AF. Our findings are consistent with other reports showing that recurrence of PV-LA conduction is almost universal in patients with recurrent AF after ablation. Cappato et al showed that PV-LA conduction in at least 1 PV occurred in all patients with AF recurrence. Callans et al also recently reported that reconnection of at least 1 PV was seen in 97% of patients with AF recurrence, and Nanthakumar et al reported that all 15 patients with AF recurrence in their series had reconnection seen in ≥2 PVs. Our findings not only show that reconnection occurred in almost all patients with AF recurrence but that more PVs tended to demonstrate reconnection in patients who failed PVAI compared with patients who were cured or maintained sinus rhythm on antiarrhythmic medication. Furthermore, it appears that AF recurrence from non-PV triggering sites is uncommon. The series of Callans et al and Nanthakumar et al identified non-PV triggers as the cause of recurrent AF in only 18% and 6% of patients, respectively. In our series, we found 2 cases of non-PV triggers, and we were able to achieve excellent cure rates in excess of 90% after performing a second PVAI procedure in which all 4 PVA were reisolated without the use of any further linear or extra-PVA ablation. Whether the remaining failures could have been cured by additional linear ablation or whether these represented AF secondary to unidentified non-PV triggers is not known from our data.

Our data are also consistent with the recently reported findings of Ouyang et al. As with our study, they found that almost all patients (>80%) with recurrent AF or atrial tachycardia after ablation had recurrent PV conduction at repeat study. In the few cases in which no recurrent PV conduction was found, non-PV ectopic foci were identified on the LA roof and anterior to the left-sided PVs. They also found that many of the patients with recurrent PV conduction also had a longer A-PV delay. However, they found that for their patients, pacing within the PV still resulted in rapid conduction into the LA, thus concluding that incomplete isolation with delayed activation will not prevent AF recurrence. Although this may seem inconsistent with our results, the average A-PV delay in their cohort was 121% and 61% for the right- and left-sided veins, respectively. This is similar to the delays we noted in group III patients, who all had recurrence, but much shorter than the delays we noted in groups I and II, in which patients either had no recurrence or were controlled on antiarrhythmic medication. Longer A-PV delays result in less rapid conduction from PV to LA (in some cases, Wenckebach conduction), which may make patients responsive to medication or unable to trigger AF altogether.

PV-LA Conduction Delay and AF Response

Interestingly, recurrence of PV-LA conduction may be seen in a minority of patients who are cured of AF. In our group I
patients, 19% demonstrated recurrence of PV-LA conduction in 1 PV. However, although conduction may have recurred, it was substantially delayed compared with the initial conduction time before ablation. Although triggering impulses may still conduct into the LA, the delay in conduction time may render the impulse incapable of initiating AF. Indeed, with faster pacing rates, A-PV block developed in all of these patients. Reconnection of 1 or more PVs has been reported in up to 32% of patients who achieve a drug-free cure from AF, but as with our findings, the conduction was significantly delayed compared with baseline.

Furthermore, PV-LA conduction delay seems to predict responsiveness to antiarrhythmic medication, and it was present even in some of the patients who had been cured. Patients who had AF recurrence but were able to maintain sinus rhythm on antiarrhythmic medication had significantly more PV-LA conduction delay than those patients with recurrence despite antiarrhythmic medication. Because of the already delayed conduction, antiarrhythmic medication may slow conduction even further, potentially causing exit block of the triggering impulses and preventing the development of AF.

At first glance, our study may appear inconsistent with other studies that have suggested that achieving PV isolation is not a prerequisite for procedural success of AF ablation. However, the main difference between our study and these other reports is in the definition of “cure.” We have used a lack of AF recurrence in patients off antiarrhythmic medication as our standard definition of cure. However, in the other series, many of the patients classified as having successful outcomes were on antiarrhythmic medication (40% to 63%), making the off-drug cure rates 30% to 38%. As we have shown, PV isolation is not required to be able to maintain sinus rhythm on antiarrhythmic medication after ablation; only a delay in PV-LA conduction seems to be needed for antiarrhythmic medication responsiveness. Thus, although these other reports describe full PV isolation in only 20% to 40% of their ablated patients, PV-LA conduction delay was likely present in most patients, explaining the good response to antiarrhythmic medication. Indeed, one of these reports used an empirical anatomic ablation approach guided by electroanatomic mapping and reduction of electrogram amplitude. Although complete PV isolation is achieved in only a minority of cases with the use of this technique, the technique results in substantial PV-LA conduction delay in almost all patients. Had complete PV isolation been achieved in these other series, it is possible that the cure rates

![Figure 3. Recording of both surface ECG and intracardiac electrograms during pacing from the coronary sinus (CS) os in a patient cured of AF by a PVAI procedure performed 7 months before. The Lasso catheter (Ls) is placed along the anterior segment of the left superior PV. There is considerable conduction delay between the far-field LA (A) potential (diagonal arrows) and the local high-frequency PV potential (*). During pacing from the CS os at 500 ms, there is Wenckebach conduction of the A-PV delay. The A-PV interval gradually lengthens from 340 to 380 ms until there is entrance block into the PV (Block). Gain on the intracardiac signals is 5000 with the use of the Prucka recording system (GE Prucka).](http://circ.ahajournals.org/content/circulation/112/7/632.full)
in patients off antiarrhythmic medication would have been higher.

Long-Term Success of PV Isolation–Based Procedures

Initial studies of segmental PV isolation for AF ablation showed variable, and often poor, success rates, suggesting that PV isolation was not adequate to achieve procedural success. However, many of these early approaches only targeted “arrhythmogenic” or easily accessible PVs instead of more modern approaches that empirically target all of the veins. It is often difficult to identify single, arrhythmogenic PVs, and even after a culprit vein is ablated, triggers from other PVs may become unmasked. Furthermore, many of these techniques ablated within the tubular portion of the PV, excluding the posterior, funnel-shaped extension of the PV, which we refer to as the antrum. Thus, large regions of the veins were not being isolated. Finally, out of concern for stenosis, power output was often limited to a very low wattage (<30 W), making recurrent PV conduction common place. Thanks to improved monitoring techniques, many operators now use higher power outputs and broader circumferential ablation, making isolation of the entire PVA more effective.

Some have suggested that ablation around the PVs prevents AF not by isolation of PV triggers but rather by modification of the atrial substrate, thereby preventing AF perpetuation. However, the strong relationship between PV-LA conduction and AF response to PVAI in this study would argue against this concept. Furthermore, in the 2 patients in whom AF recurred despite successful isolation of all of the PVA, AF still recurred despite extensive scarring and “modification” of the posterior LA wall. Focal non-PV triggers were responsible for the AF recurrence, and only ablating and removing these focal triggers prevented AF.

There was also no difference in the extent of RF ablation initially performed in patients who failed PVAI versus those who were cured or were responsive to antiarrhythmic medication. Initial PVAI RF time was the same for all groups, and the extent of scar created by the ablation was also the same in
the 3 groups. During repeat PVAIs, only limited, focused ablation was required (≤6 minutes of RF time) to produce lasting cure, which is unlikely to have “modified” the LA substrate any more than the initial ablation procedure.

Despite improved PVAI techniques, our 2-procedure success rate still falls short of 100%. Possible explanations for this include ongoing recurrence of PV-LA conduction or the presence of non–PV-related triggers for AF that are not identified during the initial procedures.

Conclusions
Resumption and delay of PV conduction is directly related to the response of AF to PVAI. The majority of patients with drug-free cure show no recurrence of PV-LA conduction, whereas all patients with recurrent AF show PV-LA reconnection. Substantial delay in PV-LA conduction is seen in patients able to maintain sinus rhythm on antiarrhythmic medication after ablation and in the minority of patients with drug-free cure who have recurrent PV-LA conduction in a single PV.

Acknowledgment
Dr Verma was supported by a fellowship award from the Heart and Stroke Foundation of Canada.

References
9. Callans DJ, Gerstenfeld EP, Dixit S, Zado E, Vanderhoff M, Ren JF, Marchlinski FE. Efficacy of repeat pulmonary vein isolation procedures...


Response of Atrial Fibrillation to Pulmonary Vein Antrum Isolation Is Directly Related to Resumption and Delay of Pulmonary Vein Conduction

Atul Verma, Fethi Kilicaslan, Ennio Pisano, Nassir F. Marrouche, Raffaele Fanelli, Johannes Brachmann, Jens Geunther, Domenico Potenza, David O. Martin, Jennifer Cummings, J. David Burkhardt, Walid Saliba, Robert A. Schweikert and Andrea Natale

_Circulation_. 2005;112:627-635
doi: 10.1161/CIRCULATIONAHA.104.533190

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/5/627

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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_ is online at:
http://circ.ahajournals.org/subscriptions/