Electroanatomic Remodeling of the Left Atrium in Patients Undergoing Repeat Pulmonary Vein Ablation: Mechanistic Insights and Implications for Ablation

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Left Atrium Remodeling in Repeat AF Ablation. Introduction: There is limited information describing late changes in the electroanatomic characteristics of the left atrium (LA) associated with recurrence after an anatomical circumferential pulmonary vein ablation (CPVA) for atrial fibrillation (AF).

Methods and Results: Forty-seven patients (57 ± 8 years) undergoing a repeat ablation after CPVA were included. Using an electroanatomic mapping system, we measured the bipolar voltage by averaging points in the pulmonary vein (PV)-LA junction and four other LA sites. Conduction velocity and AF cycle length (AFCL) were also measured and the results are compared with the first procedure. After an initial decrease observed at the end of the first procedure, voltage and conduction velocity returned to intermediate values in all LA sites, with lower voltage at the LIPV antrum ($P = 0.004$), and lower conduction velocity across the LIPV and RSPV ($P < 0.001$). Conduction gaps were more prevalent at the septal aspect of the right PV encircling lines (85%), between the left atrial appendage (LAA) and the LSPV (70%) and lines at the posterior wall (71%). There was a nonsignificant increase in AFCL, with a more widespread distribution of organized electrograms (32.4% vs 46.6%).

Conclusion: Recurrence after CPVA is associated with a reverse process of voltage and conduction velocity increase across ablated areas, especially the PV-LA junction, and is related to the presence of conduction gaps, which are distributed mostly at the septal aspect of the lines encircling the right PVs and at the LAA-LSPV area. Organization of atrial electrograms seen during AF ablation is maintained at a repeat procedure. (J Cardiovasc Electrophysiol, Vol. 17, pp. 1279-1285, December 2006)

atrial fibrillation, ablation, recurrence, remodeling

Introduction

Although it has been demonstrated that atrial fibrillation (AF) can be successfully treated by either a segmental ablation strategy aimed at electrically isolating the pulmonary veins (PVs)\textsuperscript{1,2} or by an anatomically guided circumferential pulmonary vein ablation (CPVA),\textsuperscript{2,3} recurrence of atrial tachyarrhythmia is still prevalent. Several studies have demonstrated recovery of conduction across previously isolated PVs as a major determinant of AF recurrence following the segmental ablation approach.\textsuperscript{4-6} CPVA, however, has several possible mechanisms of action, including some degree of PV isolation, elimination of anchor points or rotors near the left atrium (LA)-PV junction, LA compartmentalization, and PV denervation.\textsuperscript{7,8}

Recent studies have shown multiple gaps at the encircling lines, recovery of potentials inside the ablated area, and LA scars in patients undergoing a repeat procedure for recurrent tachyarrhythmia following an anatomical approach.\textsuperscript{9,10} However, there is a relative paucity of data regarding the incidence and distribution of these phenomena. Furthermore, changes in AF cycle length (AFCL), intra-atrial conduction velocity (IACV), and complex fractionated atrial electrograms (CFAEs), which are considered markers of substrate modification during AF ablation,\textsuperscript{11-13} have not been evaluated in patients undergoing a repeat ablation.

In the present study, we investigate the correlation between acute electroanatomic remodeling caused by CPVA and its chronic maintenance at a repeat electrophysiological study in patients with recurrent atrial tachyarrhythmia.

Methods

Study Population

Between October 2003 and April 2004, 595 consecutive patients without prior LA interventions were submitted to CPVA for the treatment of either paroxysmal or persistent, symptomatic AF. Forty-eight patients were excluded due to use of a different mapping system or incomplete data availability. Of the remaining 547 patients, 52 (9.5%) had recurrence of atrial tachyarrhythmias after 4.2 ± 1 months and were offered a second procedure, which was performed in 47 patients after a mean of 9 months (ranging from 1 to
Baseline characteristics of the study group are presented in Table 1. At the first ablation, 28 patients were in sinus rhythm and 19 were in AF (59.6% and 40.4%, respectively). At the second procedure, 14 (50%) of patients previously in sinus rhythm and 9 (47%) of those in AF were in the same rhythm as the index ablation. Ten (21.3%) patients were in incessant atrial tachycardia (AT). Written informed consent was obtained from all patients and the study was conducted in accordance with our institutional ethical guidelines.

**Initial Ablation Procedure**

All antiarrhythmic drugs, except amiodarone, were interrupted ≥5 half-lives prior to ablation. After transseptal catheterization, patients were heparinized, and the activated clotting time maintained constantly above 280 seconds. Electroanatomic mapping and ablation was performed with the CARTO System (Biosense-Webster, Diamond Bar, CA, USA), as previously described. Both bipolar and unipolar electrograms were recorded by the electroanatomic mapping system (filtered at 30–400 Hz and 1–240 Hz, respectively). If the patient was in stable sinus rhythm, maps were created during constant pacing from the distal coronary sinus (CS) at a cycle length of 600 msec. If AF or AT terminated at the beginning of ablation, further mapping was performed during CS pacing. Measurements were taken off-line after completion of LA mapping and after ablation. The following were determined using the electroanatomic mapping system:

1. **Atrial bipolar voltage**: bipolar peak-to-peak voltage was analyzed as the mean of at least three representative points of each of the following LA sites: LA-PV junction area (antrum), around each of the PVs, posterior wall, mitral isthmus, inter-atrial septum, roof and left atrial appendage (LAA). Electrically silent areas were defined as no detectable activity or amplitude <0.05 mV.
2. **Regional conduction velocity**: for patients in sinus rhythm, conduction velocity was calculated by expressing the linear distance between two points as a function of the difference in the local activation time, using 3-msec intervals to construct isochronal maps (Fig. 1). The values were calculated as the mean of conduction velocity between at least three pairs of points along the wavefront propagation through regions of least isochronal crowding at the same LA sites. All maps were created during distal CS pacing, and the segments used to measure conduction velocity were chosen considering their orthogonal orientation with the ablation lines.

![Figure 1. A: Observed changes of conduction velocity after acute ablation and at subsequent repeat procedure (in mm/ms). B: Postero-anterior view of an activation map constructed during distal coronary sinus pacing (white arrows) from a patient undergoing a repeat procedure. Earliest activity is displayed in red and latest in violet. A significant delay can be seen at the left inferior and right inferior pulmonary veins (RIPV). A wide conduction gap is seen on the previous line encircling the right superior PV (RSPV) at the posterior wall (black arrows). LAA = left atrial appendage; MA = mitral annulus.](image_url)
3. Atrial fibrillation cycle length: AFCL was determined for each point in a 3-second window by averaging consecutive cycles manually corrected off-line with electronic calipers at a paper speed of 100 mm/sec. Interelectrogram intervals of <120 msec and continuous electrical activity were counted as a single interval and excluded from analysis.\(^1\)

For each LA site, AFCL was determined as the mean of at least three representative locations. AFCL dispersion was taken as the difference between the longest and the shortest mean value at each site and between sites. A coefficient of variation (COV) was calculated (COV AFCL = SD/mean × 100%).

4. Complex fractionated atrial electrograms: CFAEs were defined as electrograms with two or more deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex. Atrial electrograms with a very short cycle (≤120 msec) were also included.\(^1\)

In order to validate all ablation lines, postablation remap was performed acquiring new points on both sides of the lines during distal CS and right atrial pacing. Measurements of conduction velocity were performed using only points in line with the direction of the wavefront propagation, taken from the surrounding atrial tissue and the PV antra, across the ablation lines.

**Second Procedure**

Of 47 patients undergoing the second procedure, 24 (51.1%) had only AF, 8 (17%) had AT, and the remaining 15 (31.9%) had both AF and AT documented during follow-up.

At the beginning of the electrophysiological study, previous ablation lines were evaluated for the presence of gaps, defined as breakthroughs in an ablated area identified as sites with a single potential and by activation mapping. Successful reduction in bipolar voltage and conduction velocity of reconducting PVs with a few RF applications at these sites further confirmed the presence of gaps. The location of conduction gaps was arbitrarily defined as septal or PW for the right PVs, lateral or PW for the left PVs, LAA-LSPV area, mitral isthmus, and PW intervenous areas (Fig. 2). Atrial bipolar voltage, regional conduction velocity, AFCL, and CFAEs were analyzed in the same sites for retrospective correlation with the first procedure. For most patients, a 3.5-mm irrigated-tip catheter (Navi-Star Thermo-Cool, Biosense Webster) was used at the second procedure. Gaps were closed with focal or linear RF applications, and the same acute endpoints were used for patients in AF or sinus rhythm. In patients with AT, ablation was directed to the critical isthmus in macroreentrant AT or at sites of earliest activation in focal AT.

**Follow-Up**

Patients were discharged on warfarin and a previously ineffective antiarrhythmic drug, which was discontinued at 3 months if the patient remained free of atrial tachyarrhythmia. Follow-up was scheduled at 1, 3, 6, and 12 months, when Holter monitoring was performed. Patients were given a transtelephonic ECG recording device (Sorin Life Watch, Segrate, Lombardy, Italy), and were instructed to send a recording to the central monitoring center every working day or in the event of symptoms.

**Statistical Analysis**

Continuous variables are expressed as mean ± SD, unless otherwise specified. Discrete variables are presented as a percentage and compared by Chi-square analysis or with Fisher’s exact test. Sequential data were analyzed by the repeated measures ANOVA model. A value of P < 0.05 was considered significant. To assess intra and interobserver variation in 12 randomly selected patients, measurements were made by two independent investigators. Intra and interobserver agreement was accessed with the kappa statistics or with the intraclass correlation coefficient, for categorical or continuous variables, respectively. Statistical analysis was performed using the SAS software, version 8.01, and the SPSS for Windows, version 12.0.1 software.

**Results**

Fluoroscopy time was similar for both procedures (22.6 ± 13 vs 22.3 ± 16 minutes, P = 0.90). LA volume decreased significantly from the first to the second procedure (96.7 ± 25 vs 82.4 ± 30 mL, P = 0.001). Prevalence of gaps on the ablation lines is shown on (Fig. 2). Single or multiple gaps were present in all but five patients, with a higher prevalence at the septum (85%), between the LAA and the LSPV (70%), and at the lines bridging the PVs at the posterior wall (71%). Such gaps were responsible for most macroreentrant circuits in those patients with LA tachycardia as the presenting arrhythmia upon recurrence. Intra and interobserver agreement was considered excellent or good for all variables analyzed.

**Atrial Bipolar Voltage**

During the initial procedure, no significant difference was found in atrial voltage between areas surrounding the four PVs. After the ablation, the acute endpoint of voltage abatement was present in 81.9% of the target veins. Although there was no significant difference between LA sites regarding voltage at this point, LIPV was more likely to achieve adequate voltage reduction (87.2%), whereas the RIPV was responsible for most cases of failure, with 74.5% of success.

At the repeat procedure, recovery of bipolar voltage above the initial ablation target occurred in 143 (76.1%) of the PVs, with the acute result maintained in 18 (38.3%) of the LIPVs, 12 (25.5%) of the LSPVs, 8 (17%), and 7 (14.9%) of the

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**Figure 2.** A: Occurrence of gaps at different locations on previous ablation lines observed at the repeat procedure. The diagram (B) displays the definition of gap locations. PW RPG = lines encircling the right PVs at the posterior wall; Lateral LPVs = lateral aspect of the lines encircling the left PVs; PW RLVs = lines encircling the left PVs at the posterior wall.
Figure 3. Comparison of bipolar voltage measured at the PV antra before and after the first ablation, and at the repeat procedure. *P = 0.004. NS = non significant.

RSPVs and RIPVs, respectively. Figure 3 illustrates that although voltage was lower than that observed at the index procedure in all PV territories, the mean voltage was significantly lower in the LIPV area, as compared with other PVs (P = 0.004). The increase in mean voltage values after ablation was significant only for the RSPV and RIPV (P = 0.034 and 0.002, respectively). The LA posterior wall and mitral isthmus had lower voltages compared with the first procedure (0.91 ± 0.12 vs 0.46 ± 0.12 mV and 1.16 ± 0.14 vs 0.54 ± 0.09 mV, respectively; P < 0.001), whereas no difference was found between the two procedures at the roof, septum, and LA appendage. As a whole, the acute endpoint of voltage abatement was preserved in all four veins in five (10.6%) of the patients at the repeat procedure.

Conduction Velocity

Ablation caused a significant reduction in conduction velocity across all PV lines, except around the LSPV, which did not achieve significance (P = 0.085). Acute reduction in conduction velocity was more pronounced across the lines circumscribing the LIPV and the RIPV. In a subset of 14 patients whose maps were constructed in sinus rhythm also at the repeat procedure, mean conduction velocity increased to intermediate values in all LA sites (Fig. 1). Compared with the baseline map of the index ablation, conduction velocity was significantly lower across areas surrounding the LIPV and RSPV (1.49 ± 0.17 vs 0.86 ± 0.09 mm/ms and 1.24 ± 0.09 vs 0.89 ± 0.09 mm/ms, respectively; P < 0.001). Recovery of conduction velocity was not significant at other LA sites, including the posterior wall.

AFCL Behavior and CFAEs Distribution

Of the 19 patients in AF at the beginning of the index ablation, four (21%) patients were converted to sinus rhythm after an increase in mean local CL of 50 ± 10.7 msec. Comparisons between AFCL behavior and CFAEs distribution were performed in a subset of nine patients in which AF was present at both procedures. Although we observed an increase in mean AFCL at the second ablation compared to the index procedure, this did not reach statistical significance (P value ranging from 0.145 to 0.73). There was no difference between the coefficient of variance values of both procedures (9.6 ± 1.9 vs 9.4 ± 1.0, P = 0.93). AFCL gradient also did not change significantly (36.9 ± 10.7 msec vs 44.8 ± 8.8 msec, P = 0.61). However, we observed a more widespread distribution of organized electrograms and a reduction in the number of CFAEs at the repeat procedure (Fig. 4), with 32.4% of the electrograms evaluated showing stable, organized characteristics at the beginning of the first procedure versus 46.6% at the repeat study (P < 0.001). Results of the electrophysiological variables are summarized in Table 2.

Clinical Outcome

All patients included in the present study had atrial tachyarrhythmia recurrence after the first ablation. Twenty-four (51.1%) had only AF, while the remainder had either AF plus AT or only left AT. Following the second procedure, after a follow-up of 12.7 ± 3.7 months, 27 (58%) patients were arrhythmia-free off all antiarrhythmic drugs, while 9 (19%) patients maintained sinus rhythm on a previously ineffective drug. Of 11 (23%) patients with recurrent arrhythmia, one had an unsuccessful ablation for an incessant AT, whereas another one developed persistent AF after a successful ablation of a macroreentrant left AT. Nine patients developed recurrent AF (5 paroxysmal and 4 persistent). None of the variables analyzed were predictors of recurrence in this patient sample. No significant complications occurred.
Discussion

This study presents new, detailed information on the electroanatomic remodeling of the LA both acutely and late after circumferential PV ablation for the treatment of AF.

Reversal of the Electroanatomic Remodeling

Previous studies addressing recurrence after a circumferential, anatomical approach have focused on the maintenance of complete electrical isolation of the PVs and on the features of LA tachycardia and its clinical significance.\textsuperscript{6,9,13,15} These reports demonstrated recovered conduction in previously isolated PVs in 80–100\% of patients after an anatomical approach. One study found that after CPV A, only 45\% of the target PVs were electrically isolated, as demonstrated by circumferential mapping, after which complete PV isolation was performed in all veins.\textsuperscript{15} Since all patients with recurrence had recovered conduction in at least one PV, the authors concluded that such recovery was probably implicated in the initiation of AF. On the other hand, Lemola and coworkers\textsuperscript{16} demonstrated that incomplete electrical isolation in one or more PVs could still be associated with a successful outcome. Another report showed that delay of PV-LA conduction, and not only resumption of conduction, is directly related to the response of AF to PV ablation.\textsuperscript{13} The present study demonstrates that in almost 90\% of patients with atrial tachyarrhythmia recurrence after CPVA, the ablated areas surrounding the PVs shows a reversal of the initial electroanatomic remodeling endpoint, with recovery of atrial voltage and regional conduction velocity. Although the prevalence of these changes in asymptomatic patients remains unknown, we believe that, regardless of complete electrical PV isolation, such reversal contributes to the recurrence of atrial tachyarrhythmias.

Distribution of Conduction Gaps

We have previously reported a preferential distribution of gaps and AT foci in patients with LA tachycardia following CPVA.\textsuperscript{10} The present study confirms those findings in a larger group of patients. While Ouyang and colleagues\textsuperscript{6} found no predilection in the distribution of conduction gaps after a hybrid anatomical/electrophysiological approach, Gerstenfeld et al.\textsuperscript{17} described a clear predilection of focal reentrant AT to

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Comparison Between Electrophysiological Variables Seen at the Beginning of the First and Second Procedures*</th>
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<tbody>
<tr>
<td>Variable</td>
<td>1st procedure ++</td>
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<tr>
<td>Mean bipolar voltage (mV)</td>
<td></td>
</tr>
<tr>
<td>LSPV</td>
<td>0.64 ± 0.08</td>
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<tr>
<td>LIPV</td>
<td>0.64 ± 0.08</td>
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<tr>
<td>RSPV</td>
<td>0.75 ± 0.1</td>
</tr>
<tr>
<td>RIPV</td>
<td>0.63 ± 0.07</td>
</tr>
<tr>
<td>Mean conduction velocity (mm/ms)</td>
<td></td>
</tr>
<tr>
<td>LSPV</td>
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<tr>
<td>RSPV</td>
<td>1.24 ± 0.09</td>
</tr>
<tr>
<td>RIPV</td>
<td>1.51 ± 0.13</td>
</tr>
<tr>
<td>PW</td>
<td>1.49 ± 0.15</td>
</tr>
<tr>
<td>Mitral isthmus</td>
<td>1.6 ± 0.8</td>
</tr>
<tr>
<td>AFCL gradient (msec)</td>
<td>36.9 ± 10.7</td>
</tr>
<tr>
<td>COV AFCL</td>
<td>9.6 ± 1.9</td>
</tr>
</tbody>
</table>

LSPV = left superior PV; LIPV = left inferior PV; RSPV = right superior PV; RIPV = right inferior PV; PW = posterior wall; AFCL = atrial fibrillation cycle length; COV = coefficient of variance.

*Variables expressed as mean ± standard error of mean (SEM).

++Comparison of voltage between PV sites was non significant (P = 0.36).

+++LIPV voltage was lower comparing with other PV sites (P = 0.004).
occur at the septal aspect of the right PVs. Possible reasons to explain such distribution include structural and technical factors. Contiguous lesions are easier to achieve when ablating the LA posterior wall. This is often not the case when ablating septally and between the LAA and the LSPV. The anatomy of the LAA-LSPV ridge is difficult to define with standard electroanatomic mapping. Frequently, there is only a narrow rim of tissue, which makes stable catheter positioning difficult to obtain.

The LA chamber is inhomogeneous. Muscle bundles deeply located in the epicardial fat at the posterior interatrial septum and atrioventricular groove may be spared by RF ablation, giving origin to breakthroughs on the septal lines due to nontransmurality. Similarly, the presence of dense, pectinate muscle in the LAA, contiguous with the normal atrial wall, renders the creation of transmural lesions more difficult.

**Behavior of AFCL and CFAEs**

Recent studies of RF ablation targeting CFAEs to modify the substrate for AF have shown a progressive organization of atrial electrograms often precedes conversion to sinus rhythm or to a stable, organized tachycardia. This could be expected to occur during CPVA, as many sites associated with fractionated electrograms underlie the standard lesion set of CPVAs. In a recent report, Sanders et al. showed that regions of high-frequency activity, sometimes manifest as CFAEs, could be identified by spectral analysis, and that frequency mapping could be used to guide ablation at sites of dominant frequencies perpetuating AF. Sequential ablation of these sites progressively decreases the frequency gradient, ultimately leading to AF termination. In the present work, CFAEs were less commonly observed at the repeat procedure, and organized activity was more prevalent throughout the LA areas. This suggests that in patients with AF recurrence, many of the CFAEs eliminated during CPVA may have been passively activated sites caused by fibrillatory conduction or by local autonomic influences rather than focal driving sources perpetuating AF. Alternatively, eliminated CFAEs may correspond to nondominant sites that could become dominant if the critical primary sources of activity maintaining AF have been ablated.

**Clinical Implications**

Our study suggests that recurrence following CPVA is mainly due to recovery of conduction across previous ablation lines, leading to a reverse process of voltage and conduction velocity recovery at the ablated areas. These phenomena have a characteristic regional distribution, which should be taken into account when planning the ablation strategy. Different energy settings and catheter designs may be necessary for each LA area. The LA posterior wall, especially at the LIPV antrum, requires lower power settings, with permanent effective lines being readily achieved with standard ablation catheters and imaging techniques. Lower energy use at the PW is desirable, as thermal injury can be associated with atrioesophageal fistula. Effective ablation at the interatrial septum and LAA-LSPV ridge may require alternative tools. Better anatomic definition could be obtained with integration of computed tomography into electroanatomic maps. Different catheter designs like irrigated-tip catheter or cryocatheter may safely improve the quality of lesions at these sites. Man-

**Study Limitations**

The present study has several limitations. We included patients with different arrhythmia presentation at each procedure, limiting the number of subjects suitable for analysis of variables like conduction velocity and AFCL.

We did not perform differential pacing maneuvers to exclude far-field potentials contributing to the mean voltage at each LA area, although no significant difference in voltage was observed between PV antra and other sites at the beginning of the first ablation. Nevertheless, repeated measures and the coefficient of variance differed significantly between the first and the second procedure. An average of three time windows of 3 seconds could be considered too short to allow accurate estimation of AFCL. Previous studies used considerably longer time windows or electrograms counts. However, most of them included only a few fixed sites.

We did not perform extensive mapping in search for CFAEs, as they were not considered specific targets for ablation. The present study did not aim to evaluate the impact of incidental true PV isolation occurring during CPVA, and the late effect of circumferential ablation in asymptomatic patients remains unknown.

The absence of a control group consisting of patients who had undergone CPVA but had not had recurrences of atrial arrhythmias limits our ability to implicate the recovery of atrial electrophysiological parameters in the recurrence of arrhythmias.

**Conclusion**

Recurrence of atrial tachyarrhythmia after CPVA is associated with a reverse process of regional voltage and conduction velocity increase across ablated areas, especially at the PV-LA junction. This is mainly related to the presence of conduction gaps observed at the repeat procedure, which are distributed mostly at the septal aspect of the lines encircling the right PVs and between the LAA and the LSPV. These observations stress the importance of ensuring adequate mapping and delivering permanent, transmural ablation lines at these particular sites. Incorporating new mapping and ablation technologies may be necessary. Organization of atrial
electrograms with elimination of complex activity seen during AF ablation is usually maintained at a repeat procedure, suggesting a secondary role for many of the CFAEs initially observed.

**References**