Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation

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Background—The high incidence of postprocedural atrial tachycardia reduces the absolute arrhythmia-free success rate of extensive ablation strategies to treat nonparoxysmal atrial fibrillation (NPAF). We hypothesized that a strategy of targeting low-voltage zones and sites with abnormal electrograms during sinus rhythm (SR-AEs) in the left atrium after circumferential pulmonary vein isolation and cavotricuspid isthmus ablation in patients with NPAF is superior.

Methods and Results—A total of 86 consecutive patients with NPAF were enrolled in study group. After circumferential pulmonary vein isolation, cavotricuspid isthmus ablation and cardioversion to SR, high-density mapping of left atrium was performed. Areas with low-voltage zone and SR-AE were targeted for further homogenization and elimination, respectively; 78 consecutive sex- and age-matched patients with NPAF who were treated with the stepwise approach served as the historical control group. In the study group, 92% (79/86) were successfully cardioverted after circumferential pulmonary vein isolation and cavotricuspid isthmus ablation. Among the patients converted to SR, 70% (55/79) had low-voltage zone and SR-AE and received additional ablation, whereas in 30% (24/79) without SR-AE or low-voltage zone, no further ablation was performed. During a follow-up period of >30 months, the Kaplan–Meier estimated probability to maintain SR at 24 months was 69.8% versus 51.3%. And after a single procedure, 3.5% (3/86) developed postprocedural atrial tachycardia in study group, compared with 30% (24/78) in control group (P=0.0003).

Conclusions—A strategy of selective electrophysiologically guided atrial substrate modification in SR after circumferential pulmonary vein isolation and cavotricuspid isthmus ablation is clinically more effective than the stepwise approach for NPAF ablation.

Clinical Trial Registration—URL: http://clinicaltrials.gov. Unique identifier: NCT01716143.

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Key Words: atrial fibrillation ■ atrial tachycardia ■ catheter ablation ■ fibrosis

Because the initial discovery that paroxysmal atrial fibrillation (AF) was triggered by ectopic foci from the pulmonary veins,1 circumferential pulmonary vein isolation (CPVI) with electric isolation of all PVs as the end point is established as the cornerstone of catheter ablation of AF.2 However, success rates of CPVI alone for nonparoxysmal (persistent or long-standing persistent) AF (NPAF) is associated with a significantly lower success rate.3,4 Therefore, more aggressive ablation strategies were developed, targeting extensive areas of the atria harboring sites perceived to be necessary for AF perpetuation.5–7 However, selection criteria of these targets such as complex-fractionated atrial electrograms were often empirical and subjective. Increased efficacy in preventing AF recurrence with extensive atrial ablation was achieved at the expense of greater occurrence of probably iatrogenic postablation atrial tachycardia (AT); hence decreasing the overall arrhythmia-free success rate.8–11 A large, prospective, multicenter, randomized controlled study reaffirms this notion that additional atrial ablation in the form of lines or complex-fractionated atrial electrogram ablations does not improve the success rate of NPAF ablation.14 Furthermore, the long-term impact of extensive atrial ablation on atrial transport function remains unclear.15

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Low-voltage regions consistent with localized fibrosis result in structural discontinuities and can perpetuate AF by either facilitating re-entry or acting as boundaries critical to anchor rotors.16 Patients with greater extent of left atrial (LA) scarring are...
WHAT IS KNOWN

- Long-term follow-up studies of persistent atrial fibrillation (AF) ablation demonstrated that the success rate was surprisingly low, and other studies revealed that the final success rate of persistent AF ablation depended on the extent of atrial fibrosis.
- Atrial fibrosis plays an important role in maintenance of AF, and this is even more pronounced in persistent AF. However, studies on how to ablate the fibrotic areas are very few.

WHAT THE STUDY ADDS

- The fibrotic areas can be indirectly translated into abnormal electrograms during sinus rhythm, either voltage diminishing or electrogram complex, and different extent of atrial fibrosis (slight, moderate, and profound) can be depicted by 3-D map.
- Sinus rhythm substrate correlates well with the electrophysiological basis, which promotes AF and atrial tachycardia (AT).
- Substrate modification after circumferential pulmonary vein isolation during sinus rhythm, which covers homogenization of the low voltage zones, elimination of abnormal complex electrograms in the transitional areas, and dechanneling, is both a curative (AF) and preventive (AT) ablation strategy in patients with persistent AF.

Methods

Study Subjects

Consecutive patients with drug refractory NPAF undergoing index AF ablation between March 2010 and December 2012 were enrolled. NPAF was defined as continuous AF of >7 days, and included long-standing persistent AF, which lasted >1 year. Patients were excluded if they met ≥1 of the following criteria: left ventricular dysfunction (ejection fraction <50%), presence of significant valvular disease, LA diameter ≥55 mm, thrombus in LA appendage, chronic obstructive pulmonary disease, or hyperthyroidism. Oral anticoagulation therapy was used before ablation and uninterrupted during the procedure, targeting an international normalized ratio between 2 and 3. All patients signed an informed written consent to the study protocol, which was approved by the Human Research Ethics Committee of the hospital.

Electrophysiological Studies and Ablation

Procedures were performed in fasted state and under conscious sedation using intravenous fentanyl. After double transseptal punctures, a deflectable decapolar circular mapping catheter (1-mm ring electrode with 3-mm interelectrode spacing, A-Focus catheter; IBI, St. Jude Medical, Inc, Minneapolis, MN) and a quadripolar open irrigated catheter (IBI, St. Jude Medical, Inc.) were advanced into the LA for mapping and ablation. Three-dimensional electroanatomical geometries of the LA and PVs were reconstructed using the circular catheter in conjunction with EnSite-NavX mapping system (St. Jude Medical Inc).

Ablation Protocol in Study Group

Ablation was performed with a maximal power of 35 W, temperature of 43°C and flow rate of 17 to 30 mL/min. CPVI was performed with ipsilateral PV isolation in pairs, with entrance and exit block as the electrophysiological endpoint.

Stepwise Approach in Historical Control Group

Once SR was restored by cardioversion, high-density bipolar voltage mapping of LA was performed using A-Focus catheter to identify the LVZ and transitional zone (TZ). The definitions of LVZ (bipolar voltage range: 0.1–0.4 mV) and TZ (bipolar voltage range: 0.4–1.3 mV) are chosen according to our previous published findings.

In our previous study, we mapped the normal LA in 13 patients undergoing ablation of left-sided accessory pathways without any cardiovascular risk factors and found that 95% of the points had bipolar voltage >0.38 mV. Therefore, we defined the upper limit cutoff value of the LVZ to be 0.4 mV (Figure 1A, top). SR-AE was defined as any multiphasic electrogram with ≥3 positive or negative distinct peaks and electrogram duration ≥50 ms, features suggestive of local conduction delay. When analyzing the distribution of SR-AE in the LA body in patients with NPAF, 95% of the SR-AEs were distributed in the areas with the bipolar voltage <1.32 mV. As such, we defined transitional zone (TZ) as sites with bipolar voltages between 0.4 and 1.3 mV to facilitate the search for SR-AEs (Figure 1A, bottom). At least 300 surface points evenly distributed in LA of each patient were acquired. To minimize the points that do not have good contact, the interior and exterior projection distances were set at 5 mm of the LA geometric surface.

The substrate-modification strategy during SR was represented in Figure 2. All the electrograms in LVZ were ablated to achieve an absolute bipolar electrogram of <0.1 mV, which we arbitrarily defined as electric silence, as monitored by real-time voltage caliper of the NavX system (Figure 3A). If SR-AEs were identified in TZ, ablation targeting SR-AE was performed to achieve electric silence or elimination of SR-AE (Figures 1B, top and 3B). Additional short linear lesions were placed to transverse potential conducting channels for re-entrant activity between isolation lines or anatomic conduction barriers and LVZs (Figure 3B). Arbitrarily, linear ablation was avoided across channels wider than 1.5 mm and contained local electrograms with amplitudes >1.3 V. No additional ablation would be performed if neither LVZ nor SR-AEs in TZ was identified (Figure 1 in the Data Supplement). For all linear lesions, confirmation of bidirectional conduction block was achieved by differential pacing and activation mapping with the NavX system (Figure 1B, bottom).

Clinical outcomes of the novel ablation strategy described above were compared with a historical cohort of age- and sex-matched patients who underwent NPAF ablation using a stepwise approach at
our institution from October 2008 to June 2010. Our institutional protocol for stepwise ablation is consistent with the approach pioneered by the Bordeaux group. Briefly, if AF persisted after CPVI, linear ablation at the LA roof, the posterior mitral, coronary sinus roof, and CTI followed by ablation of complex-fractionated electrograms (CFEs) were sequentially performed as deemed necessary by the operator to achieve termination of AF. If AF persisted, direct current cardioversion was performed to restore SR. PV isolation and bidirectional block across all linear lesions were confirmed at the end of the procedure during SR.

**Postoperative Treatment and Follow-Up**

Oral anticoagulation therapy was continued for at least 3 months in all patients. Thereafter, indication for anticoagulation therapy was based on the patient’s CHADS2 score. Antiarrhythmic drug (AAD)
was discontinued 3 months after procedure. In the first year, all patients were followed up with clinic visits and 24-hour Holter recordings at 1, 3 (considered beyond the blanking period), and 6 months; and 7-day Holter recordings at 12 months. In subsequent years, clinic visits and 24-hour Holters were conducted 6 monthly.

The primary end point of the study was defined as freedom from AT/AF off AADs after a single-ablation procedure. AF or AT occurring within the first 3 months after the ablation (blanking period) were censored as recommended by the recent AF guidelines.22 Any symptomatic or asymptomatic AT/AF episode that lasted for >30 s was categorized as a recurrence.

Evaluation of the Relationship Between SR LVZ/TZ and AT/AF

To further validate the relationship between the LVZ and ongoing AT/AF, another group of 15 patients undergoing clinically indicated ablation of NPAF was recruited from October 2014 to February 2015 for detailed mechanistic studies. After CPVI, CFE mapping was performed during AF using proprietary software embedded in EnSite-NavX system to find continuous slow conduction areas or rotational activation areas. The roving catheter, with a diameter of 15 mm and surface area of 1.8 cm² over the catheter was set to record unipolar and bipolar electrograms. (PP sensitivity, 0.1 mV; width value, 15 ms; refractory value, 35 ms; interpolation value, 5 mm, and interior and exterior projection, 5 mm) Once the rotational activation or slow conduction was noticed, the area of interest was marked by shadowing the position of the circular catheter on the map. Direct current cardioversion was performed to restore SR before high-density mapping of LA was undertaken. Programmed stimulation was performed in patients with LA substrates to induce AT. If ATs were induced, activation mapping using A-Focus circular catheter and entrainment mapping were performed to identify the mechanism of ATs.

Statistical Analysis

Continuous variables were expressed as the mean±SD or the median (range) if indicated. The comparison of the 2 groups was made by 2-sample t-test or Mann–Whitney test. The categorical data were analyzed with χ² test or Fisher exact test when expected cell sizes were <5. The 3 subgroups were summarized and compared on demographics and clinical characteristics using the 1-way ANOVA, Kruskal–Wallis test, χ² test, or Fisher exact test. Event-free survival was calculated by the Kaplan–Meier method and compared by the log-rank test. Statistical analysis was performed using SPSS software version 19.0.

Results

Patient Characteristics

A total of 86 and 78 consecutive patients were included in the study group and control group, respectively. There were no significant differences in baseline characteristics between both the groups (Table 1).

Acute Procedural Outcomes

In study group, AF did not terminate after CPVI and CTI ablation in all patients (Figure 4A); 79 patients were restored to SR by direct current cardioversion and underwent high-density mapping of the LA substrate (628±212 LA surface points). High-density mapping did not identify any LVZ or SR-AE in 30% (24/79) of these patients and no further ablation was performed; 70% (55/79) of patients had pathological TZ or LVZ and received electrophysiological substrate-guided ablation (Figure 4A; Table 1). A total of 71 regions of TZ and LVZ were ablated in the LA, and they were distributed in the anterior wall (33%), posterior wall (25%), roof (30%), septum (10%), and lateral wall (1%). Of note, TZ and LVZ were not seen in the LA appendage of any patient.

Seven patients who remained in AF despite direct current cardioversion underwent stepwise ablation, but AF termination was not achieved in any of them despite CFE ablation and linear ablation across the mitral isthmus and roof. However, additional ablation allowed for successful cardioversion to
Table 1. Clinical, Ablation, and Outcome Characteristics Between Study Group and Historical Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Group (n=86)</th>
<th>Control Group (n=78)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±10</td>
<td>55±10</td>
<td>0.091</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>66 (76.7)</td>
<td>60 (76.9)</td>
<td>0.857</td>
</tr>
<tr>
<td>AF duration, mo*</td>
<td>15 (1-12)</td>
<td>12 (1-12)</td>
<td>0.500</td>
</tr>
<tr>
<td>Long-standing PeAF, n (%)</td>
<td>50 (58.1)</td>
<td>44 (51.6)</td>
<td>0.444</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>45 (52.3)</td>
<td>50 (58.1)</td>
<td>0.540</td>
</tr>
<tr>
<td>SHD, n (%)</td>
<td>8 (9.3)</td>
<td>5 (6.8)</td>
<td>0.566</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>41.2±6.0</td>
<td>42.6±3.8</td>
<td>0.102</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.1±8.6</td>
<td>62.8±4.8</td>
<td>0.313</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>0.9±0.8</td>
<td>1.0±0.6</td>
<td>0.576</td>
</tr>
<tr>
<td>Procedure duration, min</td>
<td>182±35.7</td>
<td>211±34.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroscopy duration, min</td>
<td>22.6±9.8</td>
<td>30.8±8.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td>3 (3.5)</td>
<td>7 (9.1)</td>
<td>0.195</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>30±8</td>
<td>33±10</td>
<td>0.850</td>
</tr>
<tr>
<td>Sinus rhythm, n (%)</td>
<td>57 (66)</td>
<td>29 (37)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CTI cavotricuspid isthmus; LA, left atrium; LVEF, left ventricular ejection fraction; PeAF, persistent AF; and SHD structural heart disease. *Median (range), compared with Mann–Whitney test.

SR. These 7 patients were kept in the study group using an intention-to-treat analysis. In study group, the whole average procedural duration was 182.3±35.7 minutes (136.8±30.7 minutes for patients without LA substrate, 186.8±42.0 minutes for patients with LA substrate, and 211.0±41.1 minute for patients requiring stepwise ablation) and the mean fluoroscopy time was 22.6±9.8 minutes (17.0±7.1 minutes, 28.0±7.8 minutes, and 30.8±8.8 minutes in above 3 subgroups, respectively; Tables 1 and 2).

In the historical control group, all the 78 patients remained in AF after CPVI. During stepwise ablation, AF transitioned to AT in 6 of 78 (8%) patients and terminated directly to SR in another 8 (10%) patients. The remaining patients (64 of 78% or 82%) required cardioversion to restore SR (Figure 4B).

Complications
No major complications occurred in study group. Two (2.4%) of 86 patients developed femoral hematomas and 1 (1.1%) had pseudoaneurysm in the groin area that were managed by conservative therapy. In historical control group, cardiac tamponade occurred in 1 patient (1.2%), pericardial effusion in 2 patients (2.4%), and femoral hematomas in 4 patients (4.8%).

Follow-Up Outcomes
During a median follow-up of 30 (22–60) months, based on intention-to-treat analysis, freedom from AT/AF after a single procedure off antiarrhythmic medications was 66% (57/86) in the study group compared with 37% (29/78) in control group. With the Kaplan–Meier analysis, the estimated probability to maintain SR at 24 months of follow-up was 69.8% versus 51.3%, respectively (Figure 5A). In the study group, AF recurred in 26 of 86 (30%) patients and AT occurred in 3 (3.5%) patients, with 19 of 29 arrhythmia recurrences occurring within the first year of ablation. In the control group, AF recurrence was in 25 of 78 (32%) patients, and AT incidence was 30% (24/78). The latter was significantly higher than that in the study group (P=0.0003).

Per on treatment analysis, 70% (55 of 79) patients were free from AT/AF with a single procedure, without AAD, if they could be successfully cardioverted to SR after CPVI and CTI ablation to complete the substrate-guided ablation strategy. Subgroup analysis showed that patients without LA substrates (24/79, no LVZ or SR-AE found) had slightly higher success rates than the patients with abnormal LA substrates (55/79, LVZ and SR-AEs found). In the 7 patients who did not respond to cardioversion and received stepwise ablation, the overall success rate was only 29% (2/7). With the Kaplan–Meier analysis, the estimated probability to maintain SR at 24 months of follow-up was 79.1%, 72.7%, and 28.6%, respectively (Figure 5B).

When we further divided the whole study population based on AF duration into the subgroups of short persistent (<1 year), moderate persistent (1–3 years), and long persistent (>3 years), the estimated probability to maintain SR at 24 months of follow-up was 80.6%, 75%, and 50%, respectively (Figure 5C).

Relationship Between LVZ/SR-AEs and AT/AF
In the additional mechanistic study, 10 of 15 (67%) patients were found to have LA substrate characterized by the presence of LVZ or SRAE.

All the LVZ/TZs depicted slow conduction (covers 50% of the mapped cycle) or rotational activation (covers 90% of the mapped cycle) in the circular catheter recording during AF (Figure 6). Such electric behavior within LVZ/TZ has similarities with electrophysiological characteristics of rotors that are thought to be important in perpetuation of persistent AF. Three ATs (2 macroreentrant ATs and 1 microreentrant AT) were induced in 2 patients in whom SR-LVZs were localized on the anterior wall or anterior septal region (Figure 7A). The slow conduction area of the induced ATs colocalized to the LVZ/TZs mapped during SR (Figure 7B) and AT termination was achieved by focal ablation within the LVZ/TZ.

Discussion
In patients with NPAF, a novel strategy of LVZ and SR-AE-guided ablation after CPVI and CTI ablation, achieved long-standing SR after a single procedure without the need for AAD in 66% of patients after a mean follow-up period of 30±8 months. During a similar time period, the single procedural freedom from all atrial arrhythmias was significantly higher compared with a historical control group that underwent stepwise ablation (37%), largely achieved by minimizing the incidence of postprocedural AT (3.5% versus 30%).
Procedural, fluoroscopy time, and complications were also reduced with the novel strategy.

**AT Postempirical Linear Ablation and Extensive Defragmentation Ablation**

It is well known to all that CPVI alone is insufficient to eliminate the AF substrates, accounting for its low success rate after a single procedure. This spurred the adoption of stepwise or sequential ablation strategy (incorporating PV isolation, linear lesions, and defragmentations), especially in patients with NPAF. However, the incidence of postprocedural AT of such strategy is increased and decreases overall arrhythmia-free success. Previous trials have clearly shown that adjuvant linear ablation has its advantage, but it is difficult to achieve complete

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**Table 2. Subgroup Analysis of Baseline Characteristics and Procedural Results in Study Group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Without LA Substrate (n=24)</th>
<th>With LA Substrate (n=55)</th>
<th>Failure to Cardioversion (n=7)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>51.2±11.6</td>
<td>54.9±8.8</td>
<td>54.1±5.7</td>
<td>0.234</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>18 (90.0)</td>
<td>43 (89.6)</td>
<td>5 (71.4)</td>
<td>0.898</td>
</tr>
<tr>
<td>AF duration, mo*</td>
<td>9 (1–72)</td>
<td>13.5 (1–120)</td>
<td>72 (4–132)</td>
<td>0.020</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>9 (45.0)</td>
<td>32 (66.7)</td>
<td>4 (57.1)</td>
<td>0.230</td>
</tr>
<tr>
<td>SHD, n (%)</td>
<td>1 (5.0)</td>
<td>6 (6.9)</td>
<td>1 (14.3)</td>
<td>0.570</td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>39.5±5.3</td>
<td>42.1±3.6</td>
<td>42.4±3.5</td>
<td>0.671</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>62.3±5.6</td>
<td>64.3±5.2</td>
<td>61.5±5.3</td>
<td>0.659</td>
</tr>
<tr>
<td>CHADS2 score</td>
<td>0.8±0.7</td>
<td>1.1±0.8</td>
<td>0.9±0.9</td>
<td>0.690</td>
</tr>
<tr>
<td>Total procedural duration, min</td>
<td>136.8±30.7</td>
<td>186.8±42.0</td>
<td>211±41.1</td>
<td>0.994</td>
</tr>
<tr>
<td>Total fluoroscopy time, min</td>
<td>17.0±7.1</td>
<td>28.0±7.8</td>
<td>30.8±8.8</td>
<td>0.535</td>
</tr>
<tr>
<td>SR, n (%)</td>
<td>19 (79)</td>
<td>36 (65)</td>
<td>2 (29)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

LA indicates left atrium; LVEF, left ventricular ejection fraction; SHD, structural heart disease; and SR, sinus rhythm.

*Median (range).
linear block. Furthermore, conduction block across LA lines are difficult to achieve or maintain. Complete linear block could be achieved in only 72% of mitral lines and 44% of roof lines in 1 study, and the recurrence of conduction across previous ablation lines would predispose to ATs. These proarrhythmic effects make the empirical linear ablation a controversial strategy for patients with NPAF, especially placed during AF without further checking its conduction block after SR restoration.

The CFE during AF was thought to represent an important substrate for the maintenance of AF. However, definitions of CFEs are highly variable and subjective. There are discrepancies in reports examining the spatial relationship between CFE distribution during AF and LVZ distribution during SR. Although early investigators have reported excellent clinical outcomes in patients with AF undergoing CFE ablation, subsequent studies have failed to reproduce these results. The RASTA (Randomized Ablation Strategies for the Treatment of Persistent Atrial Fibrillation) study showed that CPVI plus CFE ablation was worse in terms of the freedom from AF and AT after 1 procedure compared with PVI and targeted ablation of atrial tachycardia; and CV, cardioversion.
non-PVI triggers. Similarly, the advantage of adjunctive CFE ablation was not yielded by recent STAR AF II (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation Trial) trial either. Our previous studies also found CFE ablation within the whole LA would create the zones of slow conduction, which predispose the development of post ablation AT. Therefore, although AF termination or likelihood of successful electric cardioversion is increased acutely by supplementing CPVI with empirical linear ablation and extensive CFE ablation, any short-term gains are attenuated by the long-term proarrhythmic effects of such extra-PV ablation.

Histological Substrate of Patients With AF and Its Correlation With Abnormal Electrophysiological Substrate

Atrial fibrosis plays an important role in the pathophysiology of patients with AF. Imaging techniques such as delay enhancement MRI could detect the extent of atrial fibrosis. Electrophysiologically, fibrosis of the atria produces lower-amplitude electrograms, electrogram fractionation, and inhomogeneity of local conduction. Such features could lead to conduction block, intra-atrial reentry, and AF. These abnormal electrophysiological properties could be identified by electroanatomic mapping during SR. Our previous study has demonstrated such findings in patients with AF, and it was used to develop the cutoff values for LVZ (0.1–0.4 mV) and TZ (0.4–1.3 mV), which were sensitive and specific for identification of SR-AEs. Interestingly, 95% of the SR-AEs were distributed within LVZ and TZ. These findings lead to our hypothesis: in patients with drug refractory NPAF undergoing catheter ablation, after achieving CPVI and CTI, homogenization of the LVZ and modification of sites with AEs during SR will directly target the potentially arrhythmogenic moderate or severe fibrotic areas perpetuating AF or AT. It should be noted that direct correlation between histological fibrosis and sites with low voltages and complex electrograms has not been clearly proven in human studies. Nonetheless, a few studies have explored targeting fibrosis as part of the AF ablation strategy.

CPVI Plus SR Defragmentation and LVZ Homogenization

In this single-center study, the overall single procedure success rate of the intention-to-treat (66%) and the substrate ablation group (70%) after a mean follow-up of 30 months is much higher than that in the control group (37%) during the similar follow-up period. Significantly, the incidence of postablation AT is much lower. This low incidence of postprocedural AT (3.5%) in the SR substrate modification group improves the overall success rate of our study subjects. It can be concluded that electrophysiological substrate-guided
ablation during SR after CPVI not only suppress AF but is less arrhythmogenic. Homogenization of LVZ, modification of SR-AEs, and removal of potential conducting channels are ablation strategies analogous to what has been done in ventricular tachycardia ablation for the past few decades. A similar study conducted by Rolf et al also yielded good results. In their approach, LVZ of <0.5 mV were targeted after CPVI. In a nonrandomized comparison, among AF patients with such LVZ, 70% of those who underwent LVZ modification were free from AT/AF at 12 months compared with only 27% who did not undergo LVZ modification.

There were methodological differences with our protocol. Given that atrial fibrosis is heterogeneous, apart from targeting the LVZs (0.1–0.4 mV), electrograms suggestive of slowed local conduction (SR-AEs) usually found in the TZs (0.4–1.3 mV) were also eliminated, resulting in a more substantial modification of the AF substrate.

It is clear that there is a wide variation in the composition of atrial substrate among patients undergoing AF ablation. In fact, ≈30% of the patients had healthy LA. Such patients only required CPVI and CTI ablation (79.2% success rate after a single procedure without AADs), and the extensive empirical ablation should be avoided to preserve LA contractility and minimize the risk of iatrogenic ATs. For the majority of the persistent AF patients, LVZ homogenization and SR-AE elimination during SR, after CPVI and CTI ablation, allows for a selective, individualized approach for further substrate modification. These results are in line with STAR AF II study in which for some of NPAF patients CPVI alone could achieve good clinical outcomes after short-term follow-up. Additional linear lesions and unfocused CFE ablation is arrhythmogenic, and did not produce additive effect. The improved success rate of this strategy could be attributable to several factors. First, defining the abnormal atrial substrate during SR is highly reproducible and objective. LVZs, capable of sustaining localized rotational activation or slow conduction and serving as critical sites for perpetuation of atrial arrhythmias as seen in our mechanistic study, can be easily targeted for ablation with the greatest benefit:risk ratio. As shown, this conservative strategy is less proarrhythmogenic without compromising on AF recurrence. The second is that doing a CTI minimizes the risk of patients needing to return for typical flutter ablation and helps to increase single procedural success rates. The third is while doing CTI ablation and LA substrate mapping, ≤1 hour observation time to assure more durable PV isolation. The last one is that AF termination is an overaggressive end point for AF ablation. Although patients with AF termination do better, AF termination may be because of the patient having a more normal substrate rather than a direct effect from ablation.

Study Limitations
This is a nonrandomized comparative study conducted at a single high volume center. Its efficacy will be further validated.
with a prospective randomized clinical trial, which is ongoing.
(STABLE-SR, clinicaltrials.gov number NCT01761188). The use of a historical cohort could introduce selection bias although by the time stepwise ablation was being performed on the control group, each operator in our institution had performed >300 AF ablation individually. Furthermore, the duration of follow-up was similar in both groups. CTI ablation was performed empirically in all patients, often without electrocardiographic evidence of CTI-dependent atrial flutter. CTI-dependent atrial flutter coexists in ~5% to 9% of patients with AF.39 As such, to prevent postablation typical atrial flutter and minimize the need for repeat procedures, CTI ablation with bidirectional conduction block as the end point was felt to be necessary during the index ablation, although this is contrary to current international guidelines. High-density mapping and substrate modification was limited to the LA. The right atrium and coronary sinus may play a role in the maintenance of AF, but were not targeted during the tested ablation strategy.40 These sites should be considered for additional ablation in future studies to evaluate its role in improving single procedural success rate. Atrial substrate modification was performed in all patients with LVZ and SR-AEs, and therefore the additive effect of such ablation above CPVI and CTI was not assessed. The proportion of patients who could be cardioverted to SR might be a small confounder factor. The use of 24-hour Holter recordings during follow-up may overestimate the success rate in both groups. However, because the method and frequency of follow-up was identical in both groups, the observed difference remained significant. Finally, the projection distance set at 5 mm in this study might not be enough to rule out insufficient endocardial wall contact. However, more points were acquired at areas of interest, to some extent, to avoid potential issues with poor contact. Any low-voltage areas targeted were further verified by analysis of the electrograms recorded by the ablation catheter.

Conclusions
For nonparoxysmal AF, electrophysiological substrate-guided LA ablation during SR in addition to CPVI, and CTI significantly improves single procedural success rates (freedom from AT/AF off all antiarrhythmic after a single procedure) compared with the widely practiced stepwise approach. This highly individualized ablation strategy avoids excessive atrial ablation, minimizes the risk of postprocedural AT, while reducing procedural times and complications.

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Disclosures
None.

References


Catheter Ablation of Nonparoxysmal Atrial Fibrillation Using Electrophysiologically Guided Substrate Modification During Sinus Rhythm After Pulmonary Vein Isolation

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SUPPLEMENTAL MATERIAL
• **Supplemental Figure 1.** Another example case of electrophysiologically substrate modification. Only local patches of LVZ were found and None of SR-AEs could be identified in TZ. So only LVZ homogenization was performed. Abbreviations are the same as in Figure 1.