Atrial fibrillation (AF) is the most common human arrhythmia and is associated with increased risk for ischemic stroke and cardiovascular mortality. The pulmonary veins (PV) are important trigger sites of paroxysmal AF, and their electric isolation from the left atrium (LA) is associated with a high rate of freedom from AF in patients without comorbidities. In persistent AF, however, additional arrhythmogenic atrial sites are responsible for AF maintenance and pulmonary vein isolation (PVI) is much less successful with reported 5-year AF freedom rate of 20% after a single and 45% after multiple procedures. Additional ablation strategies have been developed to improve outcomes including linear lesions and ablation of complex-fractionated atrial electrograms (CFAE) in the left and right atrium (RA), both as a stand-alone approach or in addition to PV isolation. Albeit improving the rate of AF-free survival in some studies, these ablation strategies are inconsistent because of the variable definition and significance of CFAE and require prolonged radiofrequency delivery times. Moreover, the recent multicenter trial, Substrate and Trigger Ablation for Reduction of Atrial Fibrillation 2 (STAR AF 2), did not reveal significant differences in rate of arrhythmia freedom between PVI only versus PVI+CFAE ablation versus PVI+linear ablation: all the 3 strategies resulted in a 1-year arrhythmia freedom of about 50%. Recent clinical and experimental studies have identified more specific electrograms in a discrete point or within a region suggestive of a localized reentry during ongoing AF and have been associated with higher ablation impact on AF.

**Background**—Complex-fractionated atrial electrograms and atrial fibrosis are associated with maintenance of persistent atrial fibrillation (AF). We hypothesized that pulmonary vein isolation (PVI) plus ablation of selective atrial low-voltage sites may be more successful than PVI only.

**Methods and Results**—A total of 85 consecutive patients with persistent AF underwent high-density atrial voltage mapping, PVI, and ablation at low-voltage areas (LVA < 0.5 mV in AF) associated with electric activity lasting > 70% of AF cycle length on a single electrode (fractionated activity) or multiple electrodes around the circumferential mapping catheter (rotational activity) or discrete rapid local activity (group I). The procedural end point was AF termination. Arrhythmia freedom was compared with a control group (66 patients) undergoing PVI only (group II). PVI alone was performed in 23 of 85 (27%) patients of group I with low amount (< 10% of left atrial surface area) of atrial low voltage. Selective atrial ablation in addition to PVI was performed in 62 patients with termination of AF in 45 (73%) after 11 ± 9 minutes radiofrequency delivery. AF-termination sites colocalized within LVA in 80% and at border zones in 20%. Single-procedural arrhythmia freedom at 13 months median follow-up was achieved in 59 of 85 (69%) patients in group I, which was significantly higher than the matched control group (31/66 [47%], P < 0.001). There was no significant difference in the success rate of patients in group I with a low amount of low voltage undergoing PVI only and patients requiring PVI+selective low-voltage ablation (P = 0.42).

**Conclusions**—Ablation of sites with distinct activation characteristics within/at borderzones of LVA in addition to PVI is more effective than conventional PVI-only strategy for persistent AF. PVI only seems to be sufficient to treat patients with left atrial low voltage < 10%.

**Key Words:** AF sources • atrial fibrillation • catheter ablation • fibrosis • low voltage • rotational activity
WHAT IS KNOWN

- Success in ablation therapy for persistent atrial fibrillation (AF) lags behind compared with paroxysmal AF. After a single procedure, the success rate of pulmonary vein isolation (PVI) is about 50% in patients with persistent AF versus 80% with paroxysmal AF. Moreover, previous substrate-based ablation strategies targeting complex-fractionated atrial electrograms guided by complex-fractionated atrial electrograms detection algorithms currently available on 3-dimensional navigation systems have not shown a beneficial effect on arrhythmia-free outcome.

- In contrast to paroxysmal AF, an important proportion of patients with persistent AF presents regional increase in atrial fibrosis (detectable as low-voltage areas on mapping), that is associated with reduced arrhythmia freedom rates in this group.

WHAT THE STUDY ADDS

- Patients with persistent AF who maintained sinus rhythm ≤2 months after electric cardioversion did not display left atrial low voltage at invasive mapping and had a high rate of arrhythmia freedom (78%) at 1 year after a PVI-only approach.

- PVI followed by ablation of atrial low-voltage areas (<0.5 mV) in AF that display fractionation (>70% of AF cycle length), repetitive rotational activity on circumferential catheter or rapid activity was associated with a high-procedural AF-termination rate.

- The novel ablation strategy (PVI and selective ablation of atrial low-voltage sites) ameliorated the rate of single-procedural arrhythmia freedom (69%) at 1 year, compared with a PVI-only approach (47%) in patients with persistent AF. This study establishes a mechanistic link between atrial low-voltage areas in AF and AF driver sites maintaining persistent AF.

Furthermore, atrial fibrosis and its border zones were identified as an important substrate of focal and reentrant activity involved in persistence of AF.14-17 Such areas identified on magnetic resonance imaging correlate to sites of bipolar low-voltage electrograms (<0.5 mV).15,16,18 In this study, we evaluated the effects of ablating regions harboring selective regional electrogram characteristics within or bordering low-voltage areas after PVI. This approach was compared with a control group of 66 patients treated with conventional PVI-only approach for persistent AF.

Methods

We prospectively enrolled 85 consecutive patients for ablation of persistent AF. The local institutional review board approved the study and each patient provided written informed consent. Inclusion criteria was the presence of symptomatic persistent AF (lasting >7 days and <12 months). Exclusion criteria were contraindications for AF ablation: presence of atrial thrombi on preprocedural transesophageal echocardiography, major bleeding under oral anticoagulant therapy. Patients underwent electric cardioversion 10 weeks before ablation therapy in an attempt to favor atrial remodeling in sinus rhythm (SR).19

Electrophysiological High-Density Atrial Mapping

Patients in SR were induced by atrial burst pacing from distal or mid-coronary sinus (CS) at a cycle of 250 to 180 ms. If repeat atrial burst stimulation up to 180 ms did not induce AF, sustaining for >6 minutes, patients were considered as noninducible for AF and underwent LA voltage mapping in SR or CS-paced rhythm (at 800 ms pacing cycle length (CL)). LA low voltage in sinus or CS-paced rhythm was defined as areas with bipolar voltage <1.0 mV20,21 Patients in (spontaneous or induced) AF underwent initial mapping in the LA and CS, whereas mapping in the RA was performed only after unsuccessful LA ablation to reduce procedure length and radiation exposure to patients. Low-voltage areas in AF were considered as sites displaying <0.5 mV peak-to-peak bipolar voltage.

Surface ECG and intracardiac ECGs were recorded using a surface digital amplifier/record system (Labsystem Pro, Bard Electrophysiology). ECGs were recorded with 0.05 to 100 Hz (high- and low-pass filter), intracardiac bipolar recordings at 30 to 250 Hz without additional filtering and intracardiac unipolar recordings at 0.05 to 500 Hz with the internal reference electrode within the inferior vena cava without additional noise filtering. Intracardiac bipolar electrograms were amplified to 0.1 to 0.2 mV/cm to display low-voltage electric activity.

The following catheters were introduced via the right femoral vein: (1) a steerable decapolar catheter was positioned in the CS; (2) an irrigated-tip quadripolar catheter with a distal 3.5-mm tip and three 1-mm proximal electrodes separated by interelectrode distance of 2, 5, and 2 mm (Thermocool Navistar [Biosense Webster, Diamond Bar, CA] or Thermocool SmartTouch Navistar [Biosense Webster] or TacrilCath [St. Jude Medical, St. Paul, MN]) were used for ablation; and (3) a 20-pole steerable mapping catheter able to cover an area of 2-cm diameter (=3.2 cm²) was used to map the left or right atrium (LA or RA) in addition to providing atrial geometry: a double-loop 20-pole catheter AFocus II HD (1-mm electrodes with 4-mm spacing, St. Jude Medical) with Ensite Velocity-V3 electroanatomic mapping system (St. Jude Medical) or a 20-pole variable Lasso-Nav catheter (1-mm electrodes with 2.5-2 mm spacing, Biosense Webster) in combination with the CARTO-V3 (Biosense Webster) system. To ensure highest accuracy of electrogram criteria, a minimal number of points >800 were acquired per chamber; and only mapping sites that were within a distance of 5 mm from the acquired atrial geometry contributed to the voltage map. Therefore, on the Ensite Velocity system the interior projection distance was set to 5 mm and on the CARTO-V3 system the map filtering was set to 5 mm. To ensure highest accuracy of the acquired atrial geometry by the 3D-mapping system, respiratory gating was performed on both systems and atrial geometry was acquired at high adjustment settings: 17 on Carto3 (BW) and 12 on Ensite Velocity (St. Jude Medical). Presence and accuracy of low-voltage areas were reconfirmed by contact-sensing enabled catheters (CF=4 g).

Electrogram Criteria Defining Target Areas for Ablation

Electrogram criteria defining target areas were established during AF. First, low-voltage areas were delineated based on bipolar voltage of <0.5 mV during AF (determined as the maximum bipolar voltage of 2 consecutive AF beats with exclusion of QRS complexes from the window of interest).15,16,20,21 High-mapping density (2–3 acquisitions per site) allowed integration of voltage variations that occur in AF into the map. Low-voltage border zones were strictly identified as the 1-cm tissue surrounding low-voltage areas. During
atrial mapping, the circumferential catheter was kept in the same position for at least 6 to 8 s to assess consistency of electrogram patterns (Figure 1A–1D; Movie 1 and Figure I in the Data Supplement). Within low voltage and border zone areas, electrogram patterns showing repetitively (1) the presence of electric activity covering >70% of AFCL at a site (prolonged fractionated activity on single bipolar, Figure II in the Data Supplement) or within the mapping area (mapping field of 3.2 cm² on the circumferential mapping catheter, Figure 1C and 1D; Movie I in the Data Supplement) potentially corresponding to an AF driver site 10–13 or (2) electrograms with discrete rapid activity (displaying a local CL >10 ms shorter than the concomitant AFCL in the left atrial appendage or CS) were annotated on atrial geometry for later ablation. Repeated sequential activation around the circumferential mapping catheter exceeded 8 adjacent electrodes (corresponding to >250° pivoting), and displayed >70% of AFCL was considered as intermittent repeated rotational activity (Figure 1A–1C; Figure I, Movies I and II in the Data Supplement) potentially corresponding to a AF driver site 10–13 or (2) electrograms with discrete rapid activity (displaying a local CL >10 ms shorter than the concomitant AFCL in the left atrial appendage or CS) were annotated on atrial geometry for later ablation.

**Ablation Method**

All the procedure was performed under heparin anticoagulation with a targeted ACT value of 300 to 350 s after transseptal access. The procedural end point of ablation was AF termination. PVI was the initial part of ablation in all patients and was achieved by circumferential ablation around PV ostia. Selective atrial ablation (outside the venous antra) was only performed in patients with AF persisting despite completion of PVI. Irrigated-tip catheter ablation was performed using with 20- to 25-W power at the posterior LA and within the CS and 28 to 35 W at other areas. When target areas (with electrogram voltage <0.5 mV and electric activity >70% of AFCL on a single or multiple electrodes of the circumferential catheter [corresponding to rotational activity] or discrete rapid activity) were present at several LA regions, the sequence of ablation was anterior LA (from septum to left appendage base/ridge), LA anterior roof region, then inferior LA (facing CS region) and finally within the CS. Radiofrequency (RF) energy was delivered at each low-voltage site displaying above-mentioned electrogram patterns for 20 to 40 s. Then the adjacent site within low-voltage region was mapped by the ablation catheter and targeted, if the mentioned electrogram characteristics were present. If AF terminated, the site of AF termination was annotated on the map. Remaining fractionated low-voltage potentials were eliminated during SR at the site of AF termination, to eliminate the slow conduction substrate responsible for the AF driver at that site.
When LA ablation could not terminate AF, the CLs with the right atrial appendage and left atrial appendage were compared. If both chambers had similar CLs, electrical cardioversion was performed to SR and patients were considered as nonterminated by ablation. If RA CL was shorter by >10 ms, a high-density map of the right atrium was created to target sites using the same criteria. If AF persisted despite biatrial ablation, patients were electrically cardioverted to SR and considered as nonterminated by ablation.

In case of AF termination to atrial tachycardia (AT), the AT was targeted using the combination of activation and entrainment mapping with the goal of SR restoration.

Control Group

To evaluate the benefit of PVI+selective ablation versus conventional PVI only for persistent AF, we compared 1-year clinical outcome against a control group of patients treated with conventional ablation strategy (PVI only). All consecutive persistent AF patients who presented AF during the ablation procedure were chosen from a database of 400 patients treated between 2010 and 2012 with the same circumferential PVI technique and by the same experienced operators. We found 42 persistent AF patients presenting AF during the PVI-only procedure. To achieve a control group consisting of 21% persistent AF patients with SR maintenance until ablation after cardioversion 10 weeks earlier, consecutive persistent AF patients from the same 400 patient cohort with SR during procedure were added to form a control group consisting of 66 patients: 42 patients with AF and 14 patients with SR during the ablation procedure. The baseline characteristics of this control group (66 patients) were compared with those of the total treatment group (85 patients, 21% in SR during the ablation procedure, Table 1).

End Points

We defined as primary study end point freedom of any atrial arrhythmia at 1-year follow-up without antiarrhythmic drug treatment after a single ablation procedure and as secondary end points procedure time, fluoroscopy time, and complications.

Follow-Up

Antiarrhythmic medications were continued during a blanking period of 3 months after the ablation procedure, during which arrhythmia recurrences were not judged as ablation failure. Patients underwent ambulatory medical control visits at 6 and at median follow-up of 13 (Q1–Q3: 11–15) months after the ablation procedure. At each time point, a 12-lead ECG and 24-hour holter ECG were recorded. If patients presented symptoms earlier (before 6 or 12 months follow-up dates), they underwent additional 12-lead ECG and 24-hour holter recordings. The follow-up was assessed in the same way in the control group.

Statistical Analysis

Statistical analysis was performed using commercially available software (IBM SPSS Statistics 20, IBM Corporation, Armonk, NY). Data were checked for normal distribution by visual assessment of histograms and q–q plots. Normally distributed data are presented as means±SD. Non-normally distributed variables (LA surface area, low-voltage area, and relative extent of low-voltage area) are presented as median with the 25th (Q1) and 75th (Q3) percentiles. Categorical variables were compared using Fisher exact test for 2-by-2 tables; otherwise the χ² test was applied.

Event-free survival was demonstrated using Kaplan–Meier survival curves for patients undergoing PVI+selective ablation of low-voltage sites (treatment group) or PVI-only approach (control group). Comparison of survival probabilities was carried out using the logrank test. Likewise, subgroups of interest were analyzed using this methodology. All tests were performed as 2-sided tests with α=0.05.

Cox regression analysis was performed on the ablation strategy and on data, which are known to be clinically significant for outcome (SR maintenance until day of procedure after cardioversion 10 weeks earlier, amiodarone treatment, arterial hypertension, sex, age, LA diameter >45 mm, and structural heart disease). In addition, cox...
analyses were carried out with manually omitting the variables that were not significant at \( \alpha = 0.1 \).

The proportional hazards assumption was assessed visually using log-minus-log survival plots and by creating time-dependent covariates. The proportionality assumption was rated as valid if the log-minus-log survival curves were parallel and did not cross, and if the interaction term had a hazard ratio (HR) near 1.0 and statistically not significant.24 The linearity assumption of interval-independent variables was visually tested by plotting the residuals against the independent variable.

### Results

The clinical characteristics of patients are summarized in Table 1. All 85 patients underwent electric cardioversion to restore SR 10 weeks before the ablation procedure and 26 maintained SR until their scheduled ablation date. In 18 of 26 patients in SR, sustained AF (lasting >6 minutes) was not inducible and a PVI-only ablation approach was performed (Figure 3). In 8 of 26 patients with SR sustained AF was induced. The remaining 59 patients presented in AF at the beginning of the procedure. Thus, the ablation procedure was performed in a total of 67 patients during sustained (spontaneous/induced) AF. Baseline AFCL was 168±27 ms. The number of points recorded in the LA was 1082±124 sites per voltage map.

PVI resulted in restoration of SR in 5 of 67 (7%) patients using 28±5 minutes of RF (Figure 3). In the 62 patients with maintenance of AF after completed PVI, additional selective atrial ablation was successful in terminating AF in another 45 patients with 11±9 minutes of RF delivery to low-voltage sites, resulting in an overall termination rate of AF of 75\% (50/67, Figure 3).

The distribution of all termination sites is illustrated in Figure 4. The termination sites were localized in the anterior LA or septum in 32 of 45 patients, in the RA in 7 of 45 patients, and CS in 6 of 45 patients (Figure 4). The termination sites were located within low-voltage areas in 80\% and within border zones in 20\% and displayed prolonged regional electric activity spanning >70\% of AFCL in 42 of 45 (93\%) and discrete rapid activity in 3 of 45 (7\%). Figure 1, Figures I and II in the Data Supplement show 3 distinct examples with recorded signals at sites of AF termination.

### Table 1. Comparison of Clinical Characteristics Between Patients Undergoing the Novel Voltage–Guided Ablation Strategy for Persistent AF (Treatment Group) vs Control Group Undergoing PVI-Only Strategy Followed by Electric Cardioversion to Sinus Rhythm After Completed PVI

<table>
<thead>
<tr>
<th></th>
<th>Low-Voltage–Based Ablation in Patients With Persistent AF ( \text{ }(n=85) )</th>
<th>Control Group Treated by PVI-Only Approach ( \text{ }(n=66) )</th>
<th>( P ) Value (Low-Voltage–Based Ablation ( \text{ }(n=85) ) vs Control Group ( \text{ }(n=66) ) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±8</td>
<td>59±10</td>
<td>0.227</td>
</tr>
<tr>
<td>Sex (male, female)</td>
<td>55, 28</td>
<td>49, 17</td>
<td>0.374</td>
</tr>
<tr>
<td>Sinus rhythm during procedure</td>
<td>18 (21%)</td>
<td>14 (21%)</td>
<td>1.000</td>
</tr>
<tr>
<td>AF during procedure</td>
<td>67 (79%)</td>
<td>52 (79%)</td>
<td>1.000</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53±9</td>
<td>55±9</td>
<td>0.683</td>
</tr>
<tr>
<td>Total left atrial surface area ( (cm^2) ), median ( \text{(Q1–Q3)} )</td>
<td>120 (108–134)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Extent of atrial low voltage ( (cm^2) ), median ( \text{(Q1–Q3)} )</td>
<td>32 (16–64)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Relative extent Atrial low voltage ( (%) ), median ( \text{(Q1–Q3)} )</td>
<td>25 (10–50)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>LAA baseline AFCL, ms</td>
<td>168±27</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Left ventricular dysfunction ( (LVEF&lt;50%) ) ( (n) )</td>
<td>13</td>
<td>10</td>
<td>1.000</td>
</tr>
<tr>
<td>LVEDD</td>
<td>55±3</td>
<td>54±3</td>
<td>0.724</td>
</tr>
<tr>
<td>IVSDD</td>
<td>11±2</td>
<td>11±1</td>
<td>0.672</td>
</tr>
<tr>
<td>LAD, mm</td>
<td>44±5</td>
<td>46±5</td>
<td>0.744</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>14</td>
<td>6</td>
<td>0.230</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>6</td>
<td>2</td>
<td>0.467</td>
</tr>
<tr>
<td>Hypertension</td>
<td>52</td>
<td>38</td>
<td>0.739</td>
</tr>
<tr>
<td>No. of failed AAD</td>
<td>2.3±1</td>
<td>2.5±1</td>
<td>0.962</td>
</tr>
<tr>
<td>No. of DCCV</td>
<td>2.0±0.8</td>
<td>2.2±0.7</td>
<td>0.924</td>
</tr>
<tr>
<td>Previous PV isolation</td>
<td>19 (22%)</td>
<td>14 (21%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Patients in the control group were matched to the treatment group with regard to rhythm at presentation: 21\% of patients were in sinus rhythm after electrical cardioversion 10 weeks earlier. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AFCL, AF cycle length; DCCV, electrical cardioversion; IVSDD, interventricular septum diastolic diameter; LAA, left atrial appendage; LAD, left atrial diameter (antero-posterior); LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; NA, not applicable; and PVI, pulmonary vein isolation.
Supplement illustrate an example of repetitive rotational activity during ongoing AF within the mapping field of the circumferential catheter at low-voltage area, where local RF delivery terminated persistent AF.

Ablation terminated AF directly into SR in 14 of 45 (31%) and into AT in 31 of 45 (69%) patients. The underlying mechanism of AT was localized reentry AT in 18, focal AT in 6, and macro-reentry in 7 patients. AT ablation was successful to restore SR in 29 of 31 patients (94%).

The procedure time was shorter in patients from the control group undergoing the PVI-only approach versus patients undergoing PVI+selective atrial ablation of low-voltage sites: 152±34 minutes versus 189±51 minutes, respectively (*P* <0.001). The total RF time was 44±19 minutes for PVI+atrial ablation. Isolation of all PVs was achieved after a mean of 28±11 minutes. Selective atrial ablation terminated persistent AF after 11±9 minutes (range: 1–18 minutes) of RF application. Ablation of AT required 12±9 minutes resulting in total atrial RF delivery of 23±11 minutes. In the total study group, 1 patient developed cardiac tamponade (because of steam pop during linear ablation for cavotricuspidian isthmus–dependent flutter), necessitating pericardiocentesis. No other adverse events were noted during and after the ablation procedure. Mean procedural x-ray time and dose were 20±12 minutes and 957±571 uGy*m², respectively for the total study group. X-ray time was shorter in patients in control group (undergoing PVI-only approach) versus patients undergoing PVI plus voltage-guided selective ablation: 14±8 minutes versus 22±12 minutes, respectively (P=0.023); however, there was no significant difference in x-ray dose between both groups: 860±836 uGy*m² versus 1010±566 uGy*m² (P=0.244).

**Extent of Atrial Low Voltage and Ablation Strategy**

High-density mapping of the LA revealed variable extent of low-voltage area between the patients (Table 1) ranging from...
from 2% to 77% of the total LA surface area (Figure 2A–2D; Table 1). Patients noninducible for AF at procedure beginning (18 patients) had low extent (median: 5%, Q1–Q3: 2%–11%) of left atrial low voltage during regular rhythm (defined as areas <1.0 mV in SR or CS pacing). Similarly, 5 patients in whom PVI alone terminated AF, had a limited extent of left atrial low voltage during AF (median: 8%, Q1–Q3: 7%–17% of LA surface <0.5 mV in AF). In contrast, patients requiring further atrial ablation after PVI (with AF persistence despite completed PVI) had significantly higher extent of LA low voltage <0.5 mV in AF (median: 31%, Q1–Q3: 18%–50% versus median: 8%, Q1–Q3: 7%–17%, \( P = 0.009 \)).

In the latter group, the extent of left atrial low-voltage areas in AF did not differ between patients without AF termination and those with successful termination (median: 32%, Q1–Q3: 19%–51% versus median: 30%, Q1–Q3: 16%–49%, \( P = 0.74 \)).

Clinical Outcome After PVI Plus Selective Voltage–Guided Ablation in Comparison With a Control Group Undergoing PVI-Only Approach

The single-procedural arrhythmia-free outcome (free from AF and AT) after a median follow-up (FU) of 13 months (Q1–Q3: 11–15) was significantly higher in the selective ablation approach (59/85 [69%]), compared with the control group undergoing PVI only (31/66 [47%]; log rank \( P<0.001 \), Figure 5A). Similarly, the rate of AF freedom was higher in the selective ablation approach (68/85 [80%]), compared with the control group undergoing PVI only (35/66 [53%]; \( P<0.001 \), Figure 5B).

Arrhythmia freedom was significantly ameliorated in the subgroup of patients with AF during the procedure and presence of LA low-voltage areas when the combined PVI and selective ablation of low-voltage approach was applied, compared with a PVI-only approach in the corresponding subgroup of control group (Figure 6A and 6B, \( P<0.001 \)). Importantly, arrhythmia freedom was high with a PVI-only approach in the subgroup of patients presenting in SR and absence of atrial low voltage (Figure 6C and 6D).

Clinical Factors Determining Arrhythmia Freedom After Ablation for Persistent AF

The results of cox regression analysis are reported in Table 2. Cox regression analysis including rhythm at procedure day (SR maintenance after electric cardioversion 10 weeks earlier), amiodarone treatment, arterial hypertension, sex, age, LA diameter >45 mm, structural heart disease revealed a statistically significant contribution of the applied ablation strategy and the rhythm at procedure (prior to ablation) to the outcome.

The age of patients was marginally significant (Table 2). After reanalyses with omitting the variables which were not significant at \( \alpha = 0.1 \), 4 variables remained in the model: (1) ablation strategy, (2) rhythm at procedure, (3) age, and (4) arterial hypertension. The novel ablation strategy PVI+selective ablation of low voltage versus PVI only for all patients reduced the risk of arrhythmia development by 74%: (HR, 0.26; 95% confidence interval, 0.14–0.47; \( P<0.001 \)). Maintenance of SR after previous cardioversion was associated with a 77% reduction of the risk of arrhythmia development (HR, 0.23; 95% confidence interval, 0.098–0.554; \( P=0.001 \)). In contrast, age (HR, 1.037; 95% confidence interval, 1.006–1.070; \( P=0.021 \)) and hypertension (HR, 0.60; 95% confidence interval, 0.36–1.08; \( P=0.091 \)) were no more significant contributors to clinical outcome.

Discussion

This study shows that ablation of sites harboring distinct regional electrogram characteristics suggesting rotational or rapid activity within/in the vicinity of low-voltage areas in addition to PVI is more effective than conventional PVI-only strategy for persistent AF as it produces high-procedural success rate with reduced RF delivery and favorable clinical outcome.
Previous Ablation Strategies for Persistent AF

Success in ablation therapy for persistent AF lagged behind compared with paroxysmal AF. In 2004, Nademanee et al\textsuperscript{5} demonstrated that focal ablation of CFAE can terminate persistent AF, but required large atrial ablation and long RF delivery times. Moreover, wide atrial ablation frequently leads to development of recurrent AF with necessity for repeat procedures.\textsuperscript{7}

The variable efficiency of CFAE ablation with regard to arrhythmia-free outcome lies in the ubiquitous presence of CFAE and their multiple significance. CFAE signals may be caused by electrogram filtering methods or farfield potentials.\textsuperscript{25} Relative to AF dynamics, they depend on rate and activation wavefront and may be because of passive phenomena as wave collisions, pivot points, or slow/anisotropic conduction, but also may be linked to AF perpetuation in meandering rotors.\textsuperscript{25-30} In previous studies, ablation of continuous CFAE sites was associated with the highest impact on AF, producing AF slowing or termination at 50% of ablated continuous CFAE sites.\textsuperscript{11,12} In addition, localized reentrant sources in which regional electrograms spanned all AFCL have been demonstrated to drive AF with prolonged fractionated electrograms acting as small isthmus or pivot point.\textsuperscript{10,13}
However, the recent randomized multicenter trial STAR AF 2 did not reveal significant differences in 1-year clinical outcome (arrhythmia freedom), when comparing a PVI only to PVI+CFAE and PVI+linear ablation approach.8,9 One possible explanation for the lack of efficiency of additional CFAE ablation, is related to the CFAE detection algorithm in the STAR AF 2 study on NavX mapping system, which does not take into account voltage criteria and underdetects CFAE sites within low-voltage areas. Figure 7A and 7B illustrates this discrepancy between the CFEmean map and low-voltage map and relationship to the targeted sites within low-voltage areas and the successful AF-termination site in a patient with persistent AF in this study. This inverse relationship of CFAE sites as displayed by CFEmean maps to low-voltage areas was reported previously.26 Our current study suggests a mechanistic role of low-voltage areas for maintenance of persistent AF.

### Identification of Fibrosis as the Arrhythmia Substrate of Persistent AF

Experimental and computer simulation models previously suggested an important role of myocardial fibrosis in maintenance of persistent AF.31,32 Patients with persistent AF have larger amount of atrial fibrosis than patients with paroxysmal AF.14 In addition, the AF recurrence rate after PVI-only ablation approach was correlated to the amount of LA fibrosis visualized by high-resolution magnetic resonance imaging.15,33

Using this imaging technique, we recently reported that most CFAE were found at apparently normal atrial tissue, 19% of sites with rapid/continuous CFAE sites were found within and at borderzones of atrial fibrosis with evidence for regional slow conduction and reentrant activity during AF.16,17 Further studies have confirmed the correlation between delayed enhanced atrial sites at magnetic resonance imaging and reduced bipolar voltage during AF16 as well as during SR more recently.15,16,20,21,34

### Atrial Low Voltage as a Novel Ablation Target

The current method of substrate identification to guide ablation is based on both bipolar voltage criteria and regional activation patterns during ongoing AF using simultaneous multielectrode mapping, in contrast to previous strategies based on local electrogram fractionation on a single bipolar recording. Target regions for ablation were restricted to low-voltage areas and their boundaries combined with local (Figure II in the Data Supplement) or sequential activation of the circumferential mapping catheter covering >70% of AFCL suggestive of repetitive rotational activity (Figure 1A–1C; Figure I, Movies I and II in the Data Supplement) or rapid focal activity. Mechanistically, the phenomenon of repetitive rotational activity (repetitive sequential activation around the circumferential catheter taking >8 adjacent electrodes and lasting for >70% of AFCL) may be because of a localized reentry source driving AF, that depends on a slow conduction isthmus displaying

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**Table 2. Impact of Ablation and Clinical Factors on Arrhythmia-Free Outcome (Cox Regression Analysis)**

<table>
<thead>
<tr>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ablation strategy (PVI+selective ablation of low-voltage vs PVI-only approach)</td>
<td>0.27 (0.15–0.50)</td>
</tr>
<tr>
<td>Sinus rhythm before ablation (yes vs no)</td>
<td>0.27 (0.11–0.64)</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.032 (1.000–1.065)</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>0.84 (0.45–1.59)</td>
</tr>
<tr>
<td>Amiodarone treatment (yes vs no)</td>
<td>1.35 (0.77–2.39)</td>
</tr>
<tr>
<td>Arterial hypertension (yes vs no)</td>
<td>0.56 (0.31–1.03)</td>
</tr>
<tr>
<td>LA diameter &gt;45 mm (yes vs no)</td>
<td>1.39 (0.75–2.59)</td>
</tr>
<tr>
<td>Structural heart disease (yes vs no)</td>
<td>0.56 (0.30–1.05)</td>
</tr>
</tbody>
</table>

Two factors affect the hazard of atrial arrhythmia development after ablation: (1) the novel ablation strategy and (2) maintenance of sinus rhythm until procedure after cardioversion 10 weeks earlier. CI indicates confidence interval; LA, left atrial; and PVI, pulmonary vein isolation.

**Figure 7.** A and B. Distribution of low-voltage areas (<0.5 mV) in atrial fibrillation (AF) vs areas of complex-fractionated atrial electrograms (CFAE) as determined by the CFEmean map with CFEmean<120 ms. An inverse correlation is noted between low-voltage areas (<0.5 mV) and the CFAE (CFEmean<120 ms) sites that are classically being ablated in patients with persistent AF. Notably, the RF application (black dots in A) within low-voltage area resulted in AF termination after 6 minutes of RF delivery at the anterior LA septum (red dot), which is not highlighted by the CFEmean map. A, Low voltage in AF (<0.5 mV). B, CFAE map in AF (CFEmean<120 ms).
low voltage. Alternatively, changes in the local tissue architecture and fiber orientations may favor pivoting of AF wavefronts at that site, which may lead to repetitive alternating pivoting in one or another direction. Both potential mechanisms seem to be important for maintenance of persistent AF in patients presenting low-voltage areas: PVI followed by ablation at such sites terminated AF in 75% of patients with persistent AF and was associated with an important reduction in the amount of RF delivery to atrial tissue when compared with previously reported ablation strategies targeting all CFAE sites.\(^{3,36}\) Clinical outcome after median 13 months was favorable in 69% of patients maintaining SR after a single procedure without antiarrhythmic drug treatment. The high-termination rate of AF by targeting these regions suggests that mechanically atrial low-voltage sites and their bordering zones harbor important sources of AF.

**Correlation Between Extent of Atrial Fibrosis (Low Voltage <0.5 mV) and Ablation Success**

In this study, patients who only required PVI (either noninducible or AF terminated by PVI) had limited amount of LA low voltage, whether voltage was assessed in SR or AF. In contrast, patients who required atrial ablation to terminate AF had high extent of LA low voltage at baseline. These findings strongly suggest a causal relationship between increased atrial tissue abnormality (presumably increased fibrosis and fatty replacement),\(^{14}\) resulting in proarrhythmic atrial sites. Pending confirmation by further studies, absence of atrial low voltage may identify patients in whom PVI alone is likely to be sufficient, whereas the presence of atrial low voltage may indicate a potential for atrial sources related to slow conducting substrate. This hypothesis was supported by favorable clinical follow-up similar for both the groups: PVI-only approach was effective to maintain SR in 78% of patients with atrial low-voltage areas <10% of LA surface area. Additional selective atrial ablation at low-voltage sites was associated with arrhythmia freedom in 66% of patients, a significantly better outcome than the control group undergoing conventional PVI-only approach for all patients resulting in 47% arrhythmia freedom after 1 year.

**Optimal Ablation Technique in Persistent AF**

In recent studies using simultaneous panoramic atrial mapping techniques during AF, focal sources and reentrant sources have been mapped using basket-based (64-pole) contact mapping\(^{3,37}\) or noninvasive (252 electrode) body-surface mapping.\(^{3,37}\) Ablation of these AF drivers has shown promising results with regard to procedural AF-termination rate and short- to midterm AF freedom on follow-up.\(^{3,36}\) Future studies should evaluate the spatial relationship of those AF drivers to the patient-specific distribution of low-voltage areas to improve our understanding of persistent AF and further optimize existing ablation strategies.

In this study, we used voltage mapping during ongoing AF combined with regional activation criteria to identify ablation targets with the end point of AF termination, which resulted in improved outcomes. A recent study used low-voltage sites in SR to identify the structural substrate in persistent AF, and linear ablation through these low-voltage sites was associated with improved clinical outcome.\(^{38}\) Future multicenter randomized studies should evaluate the value of each of these substrate-based ablation strategies for ablative treatment of persistent AF (low-voltage mapping in SR versus selective low voltage-guided ablation in AF to terminate AF and following ATs).

**Limitations**

Bipolar voltage of <0.5 mV during AF was selected because this value showed the best correlation with atrial regions with fibrosis detected by magnetic resonance imaging.\(^{16,17}\) However, the bipolar voltage in the mapping systems is measured in a single window as the maximum peak-to-peak voltage of 2–3 consecutive AF beats, subject to temporal variation as well as quality of contact. The same limitations applied to measurement in SR. The high density of atrial voltage maps (>800 mapped sites per LA, resulting in 5×2 mapped sites/cm²) may have compensated these phenomena.

Clinical follow-up for rhythm documentation was assessed by 24-hour Holter recordings at 6 and median follow-up of 13 months and additionally, if patients were symptomatic.

**Conclusions**

This study identifies low-voltage areas in AF with selective regional activation patterns as important contributors of persistent AF. A substrate-based ablation of those proarrhythmogenic atrial sites represents a promising new treatment strategy for persistent AF. PVI only seems to be sufficient to treat patients with little extent (<10%) of LA low voltage.

**Disclosures**

None.

**References**


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Ablation of Persistent Atrial Fibrillation Targeting Low-Voltage Areas With Selective Activation Characteristics


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The authors apologize for these errors.

These corrections have been made to the current version of the article, which is available at http://circep.ahajournals.org/content/9/3/e002962.full.

The surname of author Claudia Herrera-Siklody was misspelled as Claudia Herrera-Sidloky.

Figure 1C was missing identifying numbers on the right-hand color key.
In Figure 2C, Important LA Scar indicated 30–45% and in Figure 2D, Extensive LA Scar indicated >45%. These have been corrected to read 30–50% and >50%, respectively.
Figure S1. Identification of repetitive rotational activity (sequential activation of consecutive electrodes 19-20 to 13-14 on the circumferential catheter) with electrical activity spanning >70% of AF cycle length within bipolar low voltage site, where RF delivery terminates AF.
Figure S2. Example of another patient with repetitive activity > 70% of AF cycle length (white arrows) with prolonged fractionation on a single bipole (distal ablation electrodes (Abl 1-2) within low voltage area (<0,5mV) at base of LA appendage - RF application at that site terminated AF to sinus rhythm after 40 seconds. Note the initial activation gradient between distal and proximal bipoles of ablation catheter (blue arrows).

Movie 1 (corresponding to fig 1A-D) with audio comments:
Illustrates how during voltage mapping using the circumferential mapping catheter, repetitive rotational activity lasting over 70% of AF cycle length was recognized and annotated on the 3D-geometry for later ablation, if PVI did not terminate AF.

Movie 2 (corresponding to fig 1A-D):
Regional activation of a single AF beat at atrial site with repetitive rotational activity during ongoing persistent AF. Ablation at reentry core resulted in termination of AF within 35 seconds of RF application.