Catheter ablation has become an established treatment option for patients with atrial fibrillation (AF). Trigger elimination by pulmonary vein (PV) isolation represents the cornerstone of ablation strategies. Further modification of AF maintaining atrial substrate seems necessary in at least some patients. However, selection of adequate candidates, as well as identification and treatment of atrial substrate, are not yet standardized.

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Common strategies involve either application of empirical linear lesion sets similar to operative procedures, and ablation at sites with complex fractionated atrial electrograms (CFAEs) during AF considered crucial for AF perpetuation. Patient selection for additional atrial substrate modification is usually based on their clinical presentation although the correlation between AF type and the extent of atrial structural disease remains unclear. Consequently, extended AF therapies may currently lead to overtreatment in the sense of unnecessarily increased procedure duration, complication rate, proarrhythmia, as well as x-ray exposure to the patient and staff. However, some patients with paroxysmal AF may be even undertreated with PV isolation alone.

Atrial structural remodeling involving atrial fibrosis and scarring is a well-recognized factor in AF pathogenesis. Left atrial (LA) scarring can be detected by late enhancement MRI and can be correlated well with reduced electrogram amplitudes as recorded by endocardial voltage maps. Pre-existence of low-voltage areas (LVAs) as detected by LA voltage mapping has been shown to be a powerful predictor of arrhythmia recurrence after AF catheter ablation.

On the basis of these reports, we consequently used voltage mapping as a tool to identify patient subgroups, which most likely benefit from additional substrate modification. In this pilot study, we aimed to assess (1) the proportion of patients with LVAs, (2) the distribution of LVAs within the LA, and (3) the effect of a personalized voltage-based substrate modification (VSM) on the long-term outcomes in a large patient cohort.

Background—Reduced electrogram amplitude has been shown to correlate with diseased myocardium. We describe a novel individualized approach for catheter ablation of atrial fibrillation (AF) based on low-voltage areas (LVAs) in the left atrium (LA). We sought to assess (1) the incidence of LVAs in patients undergoing AF catheter ablation, (2) the distribution of LVAs within the LA, and (3) the effect of an individualized ablation strategy on long-term rhythm outcomes.

Methods and Results—In 178 patients with paroxysmal or persistent AF, LA voltage maps were created during sinus rhythm after circumferential pulmonary vein isolation. Subsequent substrate modification was confined to the presence of LVA (<0.5 mV) and inducible regular atrial tachycardias. LVAs were identified in 35% and 10% of patients with persistent and paroxysmal AF, respectively. The LA roof and the anterior, septal, and posterior wall LA were most often affected. The 12-month atrial tachycardias/AF-free survival was 62% for patients without LVAs and 70% for patients with LVAs and tailored substrate modification (P=0.3). Success rate in a comparison group of 26 LVA patients without further substrate modification was 27%.

Conclusions—LVAs can be found at preferred sites in 10% of patients with paroxysmal AF and in 35% of patients with persistent AF. This is the first clinical report describing a consistent voltage-based approach for substrate modification in addition to circumferential pulmonary vein isolation irrespective of AF type. Application of this limited individualized approach may have the potential to compensate for the impaired 12-month outcome of patients with endocardial structural defects. (Circ Arrhythm Electrophysiol. 2014;7:825-833.)

Key Words: arrhythmias, cardiac ▪ atrial fibrillation ▪ catheter ablation ▪ fibrosis

Catheter ablation has become an established treatment option for patients with atrial fibrillation (AF). Trigger elimination by pulmonary vein (PV) isolation represents the cornerstone of ablation strategies. Further modification of AF maintaining atrial substrate seems necessary in at least some patients. However, selection of adequate candidates, as well as identification and treatment of atrial substrate, are not yet standardized.
Methods

Study Population

Patients ≥18 years who underwent catheter ablation for paroxysmal or persistent symptomatic drug-refractory AF between September 2010 and December 2011 were included in this pilot study. The type of AF was defined in accordance with current guidelines. Patients with previous catheter ablation or cardiac surgery and those participating in other clinical studies were excluded from the study. Patients provided written and verbal informed consent. Clinical characteristics of the study population are detailed in Table 1.

General Procedure Setup

Patients were studied under deep sedation. A temperature probe was introduced into the esophagus for continuous real-time monitoring of the intraluminal temperature (Sensitherm; St. Jude Medical, St. Paul, MN). After transseptal puncture, mapping and ablation were performed under the guidance of electroanatomical mapping systems (EnSite Velocity NavX; St. Jude Medical Inc or Carto; Biosense-Webster, Diamond Bar, CA), supplemented by 3-dimensional image integration as described previously.7

Voltage Mapping and Ablation Settings

Ablation was performed with 4-mm-tip irrigated-tip ablation catheters (Navistar Thermocool; Biosense-Webster or Therapy CoolPath; St. Jude Medical) facilitated by the use of sheath steerable. The standard ablation settings consisted of an upper temperature limit of 45°C, an radiofrequency power of 25 to 40 W, and a flow rate of 17 to 30 mL/min. Power delivery was reduced to 25 W near the esophagus and further adapted based on esophageal temperature readings.

After circumferential PV isolation (PVI), a detailed bipolar LA voltage map was acquired during sinus rhythm. Patients with AF at the beginning of the procedure were externally cardioverted before ablation allowing for a waiting period before voltage mapping. Subsequent substrate mapping usually followed a predetermined workflow. First, mapping points were systematically acquired with the decapolar circular catheter (Inquiry Optima or Reflexion Spiral; St. Jude Medical or Lasso; Biosense-Webster). Next, the ablation catheter was used to map sites not adequately accessible with the spiral catheter. An interpolation threshold of 10 mm was used for surface color projection. Filling all color gaps provided a minimal map density in all parts of the LA. Moreover, the ablation catheter was used to create high-density maps in all those areas where low-voltage potentials were found. On the one hand, this was necessary to delineate the extent of LVA exactly, and on the other hand, to rule out insufficient wall contact. In these areas, adequate tissue contact was double-checked using different ablation catheter angulations and looping maneuvers if necessary (especially for septal areas). Adequate endocardial contact was assessed by stable electrograms and consideration of the distance to geometry surface. Only true sinus beats were selected. Bipolar electrograms were filtered at 30 to 500 Hz. In accordance with previous studies,6,6,6 peak-to-peak electrogram amplitude was defined as follows: >0.5 mV=healthy; 0.2 to 0.5 mV=diseased; <0.2 mV=likely scar tissue. LVAs were defined as sites of ≥3 adjacent low-voltage points <0.5 mV. The LA was almost evenly categorized into 6 different areas, and the location of scar was classified accordingly as septal, roof, posterior, anterior (including LA appendage), inferior, and posterolateral.

Ablation Line Concept and Procedural End Points

In all patients, circumferential ablation around both ipsilateral PVs was performed at the atrial level of the PV antrum. Procedural end point was reached with bidirectional conduction block of the circumferential PV ablation lines. Gap detection and line verification were performed using the Pace-and-Ablate approach as described previously.10 Results were confirmed with circular mapping catheters in all patients. All patients with LVAs underwent additional ablation. Any LVA was considered as a possible target for substrate modification. Confined LVAs were targeted for regional ablation, which aimed to homogenize the diseased LA tissue by radiofrequency ablation. The end point for areal radiofrequency lesions was reached with a significant reduction in local electrograms, defractionation, and loss of capture, while stimulating with the ablation catheter with high output (10 V; 2 ms). Strategic linear lesions were performed, whenever ablative substrate homogenization could not be completed because of potential collateral damage (eg, septal near the AV-node or posterior close to the esophagus), or when extensive regional ablation might have created critical isthmus sites for potential macroreentrant tachycardias (eg, near the roof or anterior LA to prevent roof-dependent or perimital flutter). These strategic linear lesions either connected nonconducting tissues with other nonconducting anatomic structures traversing target LVAs (eg, septal line from the right superior PV to the anterior mitral annulus or roof line between superior PVs), or encircled large LVAs to isolate the diseased tissue from the rest of the healthy atrium electrically (eg, posterior box by roof line plus inferoposterior line connecting both inferior PVs or superior triangle by roof line plus septal line plus anterior mitral isthmus line from left superior PV to anterior mitral annulus). The end point for strategic lesion creation was reached with the confirmation of a complete block (eg, perimital conduction) as indicated by (1) reduction of local electrogram amplitude, (2) loss of local capture, (3) confirmation of double potentials on the line and analysis of activation sequence, while stimulating near the linear lesion. After circumferential PVI with or without VSM, burst pacing (10 V; 2 ms) from the proximal coronary sinus was conducted (10-s periods, decreasing cycle lengths from 300 ms until refractoriness in 20-ms steps). Inducible regular atrial tachycardias (AT) were targeted for radiofrequency ablation with AT termination and nonreinducibility as the clinical end point. In case of AF inducibility, no further substrate modification was conducted.

Postprocedural Care and Follow-Up

Antiarrhythmic medication was discontinued after ablation, and β-blockers were administered. In case of symptomatic arrhythmia recurrences, antiarrhythmic medication was administered per the investigator’s discretion. Follow-up contacts were scheduled, and serial 7-day-Holter ECGs (Lifecard CF; DelmarReynolds Medical

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N=178)</th>
<th>LVA Group (N=47)</th>
<th>No-LVA Group (N=131)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±10*</td>
<td>67±8*</td>
<td>59±9*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Men</td>
<td>121 (68%)*</td>
<td>25 (53%)*</td>
<td>96 (73%)*</td>
<td>0.017*</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>131 (74%)*</td>
<td>40 (85%)*</td>
<td>91 (70%)*</td>
<td>0.053</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (16%)*</td>
<td>12 (26%)*</td>
<td>17 (13%)*</td>
<td>0.064</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>41 (23%)*</td>
<td>12 (26%)*</td>
<td>29 (22%)*</td>
<td>0.69</td>
</tr>
<tr>
<td>Body mass index</td>
<td>29±5</td>
<td>29±5</td>
<td>29±5</td>
<td>0.90</td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>44±7</td>
<td>45±8</td>
<td>43±6</td>
<td>0.26</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>60 (54,62)</td>
<td>60 (50,63)</td>
<td>60 (55,62)</td>
<td>0.73</td>
</tr>
<tr>
<td>LAA flow velocity, m/s†</td>
<td>0.53±0.20*</td>
<td>0.35±0.14*</td>
<td>0.55±0.20*</td>
<td>0.002*</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>116 (65%)*</td>
<td>41 (87%)*</td>
<td>75 (57%)*</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>History of AF, mo</td>
<td>49 (24,109)</td>
<td>35 (16,90)</td>
<td>66 (24,110)</td>
<td>0.048</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>129 (73%)*</td>
<td>36 (77%)*</td>
<td>93 (71%)*</td>
<td>0.57</td>
</tr>
<tr>
<td>ACEI and ARB</td>
<td>105 (59%)*</td>
<td>32 (68%)*</td>
<td>17 (56%)*</td>
<td>0.17</td>
</tr>
<tr>
<td>Statins</td>
<td>21 (12%)</td>
<td>7 (15%)</td>
<td>14 (11%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

ACEI indicates angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; LA, left atrial appendage; LVA, low-voltage area; and LVEF, left ventricular ejection fraction. *Independent predictors after multivariable testing. †For patients in sinus rhythm.
Inc, Irvine, CA) were recorded at predischarge, 3, 6, and 12 months. Additional Holter or ECG monitoring was encouraged in case of symptoms. All patients included in this study were followed up for a minimum of 12 months. Recurrences were defined as documented AF/AT>30 s occurring beyond a 3-month blanking period after the procedure. Documented AT/AF episodes within 3 months of the procedure were documented as early recurrences (Table 2).

**Comparison Group**

Before initiation of our VSM protocol, we started to acquire voltage maps as described above in all our patients routinely. To provide a comparison group for the LVA patients with targeted ablation, we analyzed the natural course of 26 patients with identified LVA, but who were left untreated after PVI. Clinical characteristics, as well as procedural and outcome data, of these patients in comparison with the treated LVA patients on our study group are listed in Table 3.

**Data Analysis**

Data were tested for normal (Gaussian) distribution by using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as means±SD. In the case of a non-Gaussian distribution (left ventricular ejection fraction, history of AF, procedure time, fluoroscopy time, and irradiation dose), the Mann–Whitney U test was used. Differences of categorical data between 2 groups were tested for statistical significance using Fisher exact test. Univariable and multivariable logistic regression analyses were performed to identify parameters associated with LV A. Multivariable stepwise logistic regression analysis (forward selection) was performed. The studied variables included all variables listed in Table 1 significant at level α=0.1 in univariable analyses (age, sex, arterial hypertension, diabetes mellitus, structural heart disease, LA appendage flow velocity, AF type, history of AF, and medication with β-blockers). Survival curves were generated using Kaplan–Meier estimates, and time-to-event analyses were performed using the log-rank test. We calculated the adjusted the P value using cox regression survival analysis by including the covariates as identified by multivariable analysis (age, sex, AF type, LA appendage flow velocity) as potential confounders. A 2-sided P value <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics (IBM Corp, Armonk, NY).

**Results**

**Patient Characteristics**

A total of 178 patients, 121 men (68%), mean age 61±10 years with paroxysmal (35%) or persistent (65%) AF were included in the study. Patient demographics are shown in Table 1.

**Prevalence and Distribution of LVAs**

LA voltage maps were created in all patients with 115±35 (54–158) mapping points per patient. Significant LV As within the

### Table 2. Procedural Parameters and Follow-Up Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (N=178)</th>
<th>LVA Group (N=47)</th>
<th>No-LVA Group (N=131)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>25 (19,35)</td>
<td>32 (23,46)</td>
<td>24 (18,33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Irradiation dose, Gycm²</td>
<td>104 (70,156)</td>
<td>122 (83,164)</td>
<td>94 (65,152)</td>
<td>0.045</td>
</tr>
<tr>
<td>Procedural time, min</td>
<td>150 (120,180)</td>
<td>160 (135,200)</td>
<td>150 (120,180)</td>
<td>0.022</td>
</tr>
<tr>
<td>RF time, min</td>
<td>38±16</td>
<td>44±16</td>
<td>35±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RF pulses</td>
<td>28±15</td>
<td>38±18</td>
<td>25±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SR at procedure begin</td>
<td>81 (46%)</td>
<td>13 (28%)</td>
<td>68 (52%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Periprocedure complications</td>
<td>6 (3.4%)</td>
<td>2 (4.3%)</td>
<td>4 (3.1%)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Clinical outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early recurrences</td>
<td>84 (47%)</td>
<td>24 (51%)</td>
<td>60 (46%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Redo procedure</td>
<td>28 (16%)</td>
<td>4 (9%)</td>
<td>24 (18%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Freedom from AF/AT at 12 mo</td>
<td>114 (64%)</td>
<td>33 (70%)</td>
<td>81 (62%)</td>
<td>0.30</td>
</tr>
<tr>
<td>AAD usage</td>
<td>8/114 (7%)</td>
<td>2/33 (6%)</td>
<td>6/81 (7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>AT recurrence only</td>
<td>12/64 (19%)</td>
<td>3/14 (21%)</td>
<td>9/50 (18%)</td>
<td>0.715</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drug (flecainide, dronedarone, or amiodarone); AF, atrial fibrillation; AT, atrial tachycardia; LVA, low-voltage area; RF, radiofrequency; and SR, sinus rhythm.
LA were found in 47 patients (26%; 95% confidence interval, 20%–33%). Among these patients, the septum was involved in 72% of cases, the anterior LA in 60%, the posterior wall in 51%, the atrial roof in 49%, and the inferior LA in 30% (Figure 1). The posterolateral LA (posterior mitral isthmus) was affected in 6%. A total of 11% of the LV As patients exhibited either >3 large LV As covering >50% of the LA surface or diffuse reduction of LA voltage. None of the patients showed single, isolated, small LV As in an otherwise normal LA. Small islands (eg, 3 adjacent low-voltage points) of diseased tissue were usually associated with larger LV As or rarely part of a patchy distribution.

Comparison of Patients With and Without LV As

**Patient Characteristics**

Clinical comparison of patients with and without LV As is listed in Table 1. LV As were found in 6 of 62 patients (10%) with paroxysmal AF, and 41 of 116 patients (35%) with persistent AF (Figure 1). Multivariable analysis showed that age (67±8 versus 59±9 years; adjusted $P=0.001$), sex (men, 53% versus 73%; adjusted $P=0.036$), AF type (persistent AF, 87% versus 57%; adjusted $P<0.001$), and LA appendage flow velocity (0.35±0.14 versus 0.56±0.20 m/s; adjusted $P=0.004$, for those in sinus rhythm during echocardiographic assessment) were independently associated with LV As.

**Procedural Data**

Complete PV isolation with bidirectional conduction block was achieved in all 178 patients. Ablation lesions according to the observed LV As—alone or in combination—were placed in 47 of 178 (26%) patients (Figures 2 and 3) as follows: superior septal line (24 of 47 patients; 51%), roof line combined with box line (24 patients; 51%), focal/areal septal lesions (15 with paroxysmal AF, and 41 of 116 patients (35%) with persistent AF (Figure 1). Multivariable analysis showed that age (67±8 versus 59±9 years; adjusted $P=0.001$), sex (men, 53% versus 73%; adjusted $P=0.036$), AF type (persistent AF, 87% versus 57%; adjusted $P<0.001$), and LA appendage flow velocity (0.35±0.14 versus 0.56±0.20 m/s; adjusted $P=0.004$, for those in sinus rhythm during echocardiographic assessment) were independently associated with LV As.

**Procedural Data**

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patients; 32%), roof line alone (9 patients; 19%), inferior line from right inferior PV to inferior mitral annulus (7 patients; 15%), focal ablation below right inferior PV (4 patients; 9%), ablation of the posterior mitral isthmus (3 patients; 6%), ablation of the anterior mitral isthmus (2 patients; 4%), and ablation within the coronary sinus and adjacent mitral annulus (2 patients; 4%). Because of inducibility of regular LA tachycardias, additional activation and entrainment mapping-guided ablation was performed in 10 of 47 (21%) patients with LV As, and 4 of 131 (3%) patients without LV As (P<0.001). Procedural parameters are listed in Table 2.

Periprocedural Complications
Procedure-related minor complications after ablation were observed in 2 of 47 (4%) patients in the LVA group and in 4 of 131 (3%) LVA-free patients (P=0.7). In the LVA group, 2 groin pseudoaneurysms occurred. In the no-LVA group, 1 patient had a transient ischemic event, 1 had gastroparesis, 1 had fluid overload with consecutive pulmonary edema, and 1 had a groin pseudoaneurysm. All patients were conservatively treated without long-term sequelae.

Patient Follow-Up
All 178 patients completed 12 months of follow-up. Mean follow-up duration was 15±3 months. Single procedure success rate at 12 months was 64%, with 7% of these on antiarrhythmic drugs (8 of 114 patients). Success rate at 12 months was 70% in patients with LVAs, and 62% in patients without LVAs (unadjusted log rank P=0.30, adjusted P=0.09; see Figure 4 for Kaplan–Meier plots). Success rate did not differ significantly in paroxysmal versus patients with persistent AF (69% versus 61%; P=0.28). Recurrent arrhythmias were AF (38 patients), AT (12 patients), or both (14 patients).

Findings During Redo Procedures
Of 64 of 178 (36%) patients with recurrences, 28 patients underwent redo procedures within follow-up period, which followed the same protocol as the initial procedure. The proportion of redo procedures was not significantly different in LVA versus no-LVA patients (9% versus 18%; P=0.11). In all 24 non-LVA patients, and in 2 of 4 LVA patients, ≥1 PV was reconnected (P<0.001). Reconnection of median 3 veins was confirmed with circular catheters. In 18 of 28 (64%) patients, voltage mapping was repeated, which confirmed the previous voltage map result (plus applied radiofrequency lesions) in 16 of 18 (89%) patients. In 2 of 18 (11%) patients, the voltage map showed previously undetected LVAs.
Comparison of LVA Patients With and Without VSM

The comparison group consisted of 26 patients (15 men) with LVA identified by voltage mapping but left without VSM after PV isolation. Mean age in this group was 67±9 years, mean LA diameter 43±6 mm, and 17 of these patients had persistent AF (Table 3). LVA patients with and without tailored substrate ablation after PVI differed in terms of AF type (87% versus 65% persistent AF; P=0.036), fluoroscopy time (median 32 [quartiles 23,46] min versus median 27 [quartiles 20,32] min; P=0.018), and freedom from AF/AT at 12 months (70% versus 27%; P<0.001). Kaplan–Meier plots comparing both groups are shown in Figure 5.

Discussion

Main Findings of the Study

Our study is the first to describe the use of sinus rhythm voltage mapping as a tool to guide personalized AF substrate modification and reports on the correspondent clinical patient profiles, procedural observations, and clinical outcomes. Previous studies have already shown the correlation...
of LVAs with atrial fibrosis and scarring, as well as its significant negative effect on rhythm outcome after AF catheter ablation. In the study by Verma et al, presence of LVAs was the strongest predictor of AF recurrence after PVI when compared with other known risk factors, such as advanced age, persistent AF, low ejection fraction, or large LA size, and resulted in significantly decreased success rates (43% versus 81%). Inspired by this elegant work, we adopted the protocol used, and identified LVAs in our patients. However, we did not just leave it at LVA diagnosis to observe the natural course, but we actively used diseased tissue as ablation target irrespective of AF type. Ultimately, we have treated much less patients with additional substrate modification than projected by an approach based on AF type, yet we achieved similar single procedure long-term success rates in patients with treated substrate when compared with patients with apparently healthy LA tissue and PVI alone (70% and 62%; \( P = 0.3 \)). This success rate in patients with diseased atrial tissue was much higher than reported in the literature (43%) or compared with our own comparison group (27%). In our opinion, the results of our study allow the formulation of the hypothesis that tailored VSM in patients with AF may possess a considerable potential to compensate for the impaired outcome inherent with atrial structural defects. Therefore, this study serves as a hypothesis-generating pilot study encouraging direct randomized comparison with established strategies.

LVAs and Structural Substrate in the Atrium
LVAs detected by electroanatomical mapping systems have been associated with structural atrial defects in congestive heart failure, advancing age, or AF. Oakes et al have shown that LA fibrosis and scar tissue detected by delayed enhancement cardiac MRI correlate well with LVAs on voltage maps. We found significant LVAs within the LA in 47 patients (27% overall and 35% in patients with persistent AF). A similar proportion of scar areas (32% in persistent AF) was reported by others. Most often, the anterior LA (60%) and septum (71%), the posterior wall (51%), and the roof (47%) were involved in our study patients with substrate. This is also consistent with previous reports, which suggest a regional distribution of structural defects in AF patients—most often affecting the LAPW and septum. In \( \approx 90\% \) of our patients, voltage maps demonstrated reproducibility of LVAs. Previously undetected LVAs may indicate disease progression in the LVA group, whereas new LVAs were not detected in previously healthy atria.

Electrophysiological Effects of Atrial Remodeling and Fibrosis
Atrial remodeling is known to be associated with a variety of electric disturbances, such as heterogeneities in atrial action potential duration, effective refractory period, and conduction velocity. These phenomena can promote AF by a multitude of mechanisms. Altered conduction and dispersion of refractoriness may form the critical circuits for intra-atrial re-entry perpetuating AF or may increase general vulnerability to AF induction. Moreover, fibrosis may lead to rapid repetitive activity because of microreentry or local automaticity. Successful substrate modification may then be achieved by homogenization of heterogeneously scarred tissue (eliminating reentrant as well as focal sources) or blockage of typical pathways for LA macro-reentrant tachycardias. It may even be speculated that transmurality of radiofrequency lesions is generally easier to achieve in atria with diseased as opposed to healthy tissue because of the relative absence of electrically active tissue before ablation.

Clinical Parameters Related to the Presence of LVAs
We found LVAs in 10% of patients with paroxysmal AF and in 35% of patients with persistent AF. Patients with LVAs are identified with an 87% sensitivity and a 43% specificity using the clinical parameter of AF type. Thus, the results of voltage mapping challenge the general practice of selecting an AF ablation strategy primarily based on a rather soft clinical parameter, such as AF type. Similar to previous studies, clinical parameters, such as advanced age, female sex, reduced LA appendage flow velocity, and persistent AF type, were independently associated with atrial substrate. Risk stratification for the presence of LVAs using these simple clinical parameters, such as a score, may support procedure preparation (eg, guiding the decision for or against single-shot devices such as the cryo or laser balloon, which concentrate on PVI and leave the rest of the LA untreated). Moreover, a causal link between fibrosis-based LVAs and left atrial appendage flow velocity as a surrogate parameter of LA transport function may be hypothesized.

Consequences of a Voltage-Guided Ablation Strategy
VSM resulted in radiofrequency lesion sets, which we had usually not applied and combined to date. Given the regional distribution of LVAs concentrating around the LA posterior wall and septum, the most frequent substrate modification was the posterior box lesions and a modified septal line from the right superior PV to the anterior mitral isthmus, the latter resulting in an anterior mitral isthmus block (Figures 2 and 3). In some procedures, this lesion set was extended by an anterior mitral isthmus line (between left superior PV and anterior mitral valve annulus) to isolate larger LVAs at the LA roof and anterior LA electrically (Figure 3). Given the LVA distribution, the technically demanding posterior mitral isthmus line was infrequently applied, in favor of other linear lesions like the anterior mitral isthmus line. The latter has already been reported to be a safe and effective in achieving perimital block.

Apart from these qualitative differences when compared with established substrate modification approaches, also quantitative differences may be associated with the described personalized strategy. According to established protocols, which often preselect candidates for additional substrate modification using clinical parameters, such as AF type, all persistent and probably no paroxysmal AF patients would have undergone radiofrequency ablation of fractionated electrograms and empirical linear lesions. Extrapolated for our
study population, two thirds of patients would have undergone extended AF ablation. In contrast, the 26% proportion of patients with LVAs in our study implies a >50% overall reduction of additional substrate modifications. The relatively low rate of recurrent AT (7% AT only; 8% AF and AT) may also indicate a low proarhythmic potential of the approach.

Randomized studies comparing our tailored strategy with established approaches will clarify the potential of this strategy to prevent overtreatment in patients with persistent AF and structurally normal atrial myocardium and undertreatment in patients with paroxysmal AF and structural LA substrate.

Pathogenetic Difference of LVAs in Sinus Rhythm and CFAE Sites in AF

Theoretically, LVAs mapped in sinus rhythm may represent the same substrate as CFAE mapped in AF. CFAEs are also frequently found in septal and posterior areas. However, recent data showed no anatomic correlation between CFAE sites during AF and LVAs during paced or sinus rhythm,20–22 CFAE sites in AF displayed normal voltage23 and normal atrial myocardial characteristics during sinus rhythm,20,21 suggesting their functional or passive nature rather than diseased atrial tissue. Although the mechanisms of CFAE remain poorly understood and ablation outcomes are conflicting,24 this does not exclude the possibility that CFAE mark critical regions of AF perpetuation in a region of normal atrial myocardium unmasked during AF. However, not all CFAE ablation (often requiring extensive biatrial ablation) affects AF tachycardia cycle length, implying that exhaustive CFAE ablation may at least, in part, be unnecessary.

Limitations

This was a nonrandomized observational study. However, because of the high AT/AF recurrence rate in our comparison group of patients with untreated LA endocardial substrate, which is also in congruence with previous publications,4–6 the similar 12-month outcome of patients with additional personalized VSM compared with patients with healthy LA and PVI alone strongly supports the clinical potential of our approach. The strategy has already found its way into the clinical routine of our institution and led to the initiation of a randomized comparison of the tailored strategy with established linear strategies. More comparisons, including a treatment arm with targeted VSM in the absence of additional PVI should follow to examine the role of substrate- versus trigger-based AF further.

We aimed to create homogeneous high-density voltage maps with an intended point distance of <1 cm. It is possible, therefore, that small LVAs were not included in our voltage maps. However, we did not see any patients with single, isolated, small LVAs. Small LVAs were either part of a patchy LVA distribution or small islands in close proximity to larger LVAs. In most of the cases, a substrate patient could be identified early in the mapping process if started at the preferential LVA sites (eg, septum, roof, and posterior wall). Moreover, it has already been pointed out in previous publication that small, isolated LVAs (versus larger scar burden) may not have a significant effect on outcome.6 The reproducibility of voltage maps in patients undergoing redo procedures suggests that underdetection of large LVAs (>1 cm²) is unlikely. To avoid false-positive LVA results because of insufficient wall contact, the application of innovative contact technologies may be valuable.

LA voltage maps were created after PVI and as such, we cannot report on LVAs in the right atrium or native LA. Also, we did not precisely quantify the extent of diseased atrial tissue. Therefore, we cannot classify the patients according to the extent of atrial substrate and its effect on clinical outcome. This aspect will be a part of the above-mentioned randomized study. Patients with trigger-based AF might be distinguished from dominantly substrate-based AF from the start. The trend to better 1-year outcome and the fact that every second redo patient with LVA had persistent PV isolation leaves room for speculation that the outcome of patients with substrate-based AF may be less dependent on PV reconnection.

Conclusions

LVAs as a surrogate for structurally diseased atrial myocardium could be found in 27% of patients with AF undergoing AF catheter ablation, 10% in patients with paroxysmal AF, and 35% in patients with persistent AF. The LA roof as well as the posterior and antero-septal wall were affected most frequently. Tailored substrate-based radiofrequency catheter ablation in our study population resulted in (1) a relatively low proportion of patients with additional substrate modifications, (2) an individually adapted lesion design, and (3) similar rhythm outcomes in patients with atrial structural disease when compared with patients with healthy LA.

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Disclosures

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CLINICAL PERSPECTIVE

Although pulmonary vein isolation represents an accepted cornerstone of catheter ablation of atrial fibrillation, the role of additional substrate modification is less clear. Contemporary strategies involve either empirical linear lesions or elimination of fractionated electrograms identified during atrial fibrillation, both usually reserved for patients with chronic forms of atrial fibrillation. Identification of low-voltage areas in the left atrium during mapping in sinus rhythm has been correlated with atrial fibrosis and with reduced success rates after pulmonary vein isolation alone. Thus, we have systematically used sinus rhythm voltage mapping after pulmonary vein isolation in a series of patients. We found that low-voltage areas can be demonstrated in approximately every third patient with persistent atrial fibrillation and less often in patients with paradoxal atrial fibrillation, with preferred occurrence at the anterior, septal, and posterior left atrial walls. Our patients with low-voltage zones left untreated had reduced outcomes 1 year after pulmonary vein isolation. In a pilot study, we selectively treated those patients with low-voltage areas similar to a strategy known from ventricular tachycardia ablation: we aimed at preventing substrate-based initiation and perpetuation of arrhythmias by eliminating all reduced potentials of smaller areas or by applying strategic linear lesions through larger low-voltage zones. After this strategy, patients with additional voltage-based substrate modification had a similar outcome when compared with patients with normal voltages and pulmonary vein isolation alone. Application of this new individualized and targeted voltage-based approach may provide the potential to minimize over- and undertreatment in atrial fibrillation ablation.
Tailored Atrial Substrate Modification Based on Low-Voltage Areas in Catheter Ablation of Atrial Fibrillation

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