Tailored Atrial Substrate Modification Based On Low-Voltage Areas in Catheter Ablation of Atrial Fibrillation

Running title: Rolf et al.; Voltage-guided AF Ablation

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Journal Subject Code: [22] Ablation/ICD/surgery
Abstract:

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 (a) the incidence of LVAs in patients undergoing AF catheter ablation, (b) the distribution of LVAs within the LA, and (c) the impact 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 (<0.5mV) and inducible regular atrial tachycardias (AT). LVA 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-months AT/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 PVI irrespective of AF type. Application of this limited individualized approach may have the potential to compensate for the impaired 12-months outcome of patients with endocardial structural defects.

Key words: atrial fibrillation, catheter ablation, potentials, arrhythmia, fibrosis
Introduction

Catheter ablation has become an established treatment option for patients with atrial fibrillation (AF).\(^1\) 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.

Common strategies involve either application of empirical linear lesion sets similar to operative procedures,\(^2\) and/or ablation at sites with complex fractionated atrial electrograms (CFAEs) during AF considered crucial for AF perpetuation.\(^3\) 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. On the other hand, 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. LA scarring can be detected by late enhancement magnetic resonance imaging (MRI) and correlates well with reduced electrogram amplitudes as recorded by endocardial voltage maps.\(^4\) Pre-existence of low voltage areas (LVAs) as detected by LA voltage mapping has been shown to be a powerful predictor of arrhythmia recurrence post AF catheter ablation.\(^4\text{-}^6\)

Based on 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 (a) the proportion of patients with LVAs, (b) the distribution of LVAs within the left atrium, and (c) the impact of a personalized voltage-based substrate modification (VSM) on the long-term outcomes in a large patient cohort.

Methods

Study population

Patients 18 years or older 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 Tab.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, USA). After transseptal puncture, mapping and ablation were performed under the guidance of electroanatomical mapping systems (EAMS) (EnSite Velocity NavX, St. Jude Medical Inc., St. Paul, USA; or Carto, Biosense-Webster, Diamond Bar, USA), supplemented by 3D 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 steerable sheaths. 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 17-30 ml/min. Power delivery was reduced to 25W near the esophagus and further adapted based on esophageal temperature readings.

Following circumferential PV isolation (PVI), a detailed bipolar LA voltage map was acquired during sinus rhythm. Patients in 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 work-flow. 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 left atrium. 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 exactly delineate the extent of LVA, 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 to previous studies,5, 6, 8-10 peak-to-peak electrogram amplitude was defined as follows: >0.5 mV = healthy; 0.2-0.5 mV = diseased; <0.2 mV = likely scar tissue. LVAs were defined as sites of at least 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 left atrial appendage), inferior, and posterolateral.
Ablation line concept and procedural endpoints

In all patients, circumferential ablation around both ipsilateral PVs was performed at the atrial level of the PV antrum. Procedural endpoint was reached with bidirectional conduction block of the circumferential PV ablation lines. Gap detection and line verification was performed using the “Pace-and-Ablate” approach as described previously. 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 RF ablation. The endpoint for areal RF lesions was reached with a significant reduction in local electrograms, defractionation, as well as 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 (e.g. septal near the AV-node, or posterior close to the esophagus), or when extensive regional ablation might have created critical isthmus sites for potential macro-reentrant tachycardias (e.g. near the roof or anterior left atrium in order to prevent roof-dependent or perimital flutter).

These strategic linear lesions either connected non-conducting tissues with other non-conducting anatomic structures traversing target LVAs (e.g. septal line from the right superior PV to the anterior mitral annulus, or roof line between superior PVs), or encircled large LVAs to electrically isolate the diseased tissue from the rest of the healthy atrium (e.g. posterior box by roof line plus infero-posterior 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 endpoint for strategic lesion creation was reached with the confirmation of a complete block (e.g. 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/or analysis of activation sequence while stimulating near the linear lesion. Following circumferential PVI with or without VSM, burst pacing (10 V, 2 ms) from the proximal coronary sinus was conducted (10 sec periods, decreasing cycle lengths from 300 ms until refractoriness in 20 ms steps). Inducible regular atrial tachycardias (AT) were targeted for RF ablation with AT termination and non-reinducibility as the clinical endpoint. In case of AF inducibility, no further substrate modification was conducted.

**Post-procedural care and Follow-up**

Antiarrhythmic medication was discontinued after ablation and beta-blockers were administered. In case of symptomatic arrhythmia recurrences, anti-arrhythmic medication was administered per the investigator’s discretion. Follow-up contacts were scheduled, and serial 7-day-Holter ECGs (Lifecard CF, DelmarReynolds Medical Inc., Irvine, CA) were recorded at pre-discharge, 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 three months blanking period after the procedure. Documented AT/AF episodes within three months of the procedure were documented as early recurrences (Tab. 2).

**Comparison Group**

Before initiation of our VSM protocol, we started to routinely acquire voltage maps as described above in all our patients. In order 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 following 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 Tab.3.

**Data analysis**

Data were tested for normal (Gaussian) distribution by using the Kolmogoroff-Smirnov test. Normally distributed continuous variables are presented as mean ± SD. In the case of a non-Gaussian distribution, median (interquartile range) is given. Categorical variables are expressed as number and percentage of patients. Differences between two groups of continuous normally distributed data were tested for statistical significance using independent sample student’s t-test.

In the case of continuous data with a nongaussian 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 two groups were tested for statistical significance using Fisher’s exact test. Univariable and multivariable logistic regression analyses were performed to identify parameters associated with LVA. Multivariable stepwise logistic regression analysis (forward selection) was performed. The studied variables included all variables listed in Tab.1 significant at level α–0.1 in univariable analyses (age, gender, arterial hypertension, diabetes, structural heart disease, left atrial appendage flow velocity, AF type, history of AF, and medication with betablockers). 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, gender, AF type, LAA flow velocity) as potential confounders. A two-sided p-value < 0.05 was considered statistically significant. All analyses were performed using SPSS Statistics (IBM Corp., Armonk, NY, USA).
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 Tab.1.

Prevalence and distribution of Low Voltage Areas

LA voltage maps were created in all patients with 115±35 (54-158) mapping points per patient. Significant LVAs within the 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% (Fig.1). The posterolateral LA ("posterior mitral isthmus") was affected in 6%. 11% of the LVA patients exhibited either more than three large LVAs covering >50% of the LA surface or diffuse reduction of LA voltage. None of the patients showed single, isolated, small LVAs in an otherwise normal left atrium. Small islands (e.g. 3 adjacent low voltage points) of diseased tissue were usually associated with larger LVAs, or rarely part of a patchy distribution.

Comparison of patients with and without LVAs

Patient characteristics

Clinical comparison of patients with and without LVAs is listed in Tab.1. LVAs were found in 6 of 62 patients (10%) with paroxysmal AF, and 41 of 116 patients (35%) with persistent AF (Fig.1). Multivariable analysis showed that age (67±8 vs. 59±9 years, adjusted p=0.001), gender (male 53% vs. 73%, adjusted p=0.036), AF type (persistent AF 87% vs. 57%, adjusted p<0.001), and LA appendage flow velocity (0.35±0.14 vs. 0.56±0.20 m/sec, adjusted p=0.004, for those in sinus rhythm during echocardiographic assessment) were independently associated with LVAs.
Procedural data

Complete PV isolation with bidirectional conduction block was achieved in all 178 patients. Ablation lesions according to the observed LVAs – alone or in combination - were placed in 47 of 178 (26%) patients (see Fig.2 & Fig.3 for examples) as follows: superior septal line (24 of 47 patients, 51%), roof line combined with box line (24 patients, 51%), focal/areal septal lesions (15 patients, 32%), roof line alone (9 patients, 19%), inferior line from RIPV to inferior mitral annulus (7 patients, 15%), focal ablation below RIPV (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%). Due to inducibility of regular LA tachycardias, additional activation and/or entrainment mapping-guided ablation was performed in 10 of 47 (21%) patients with LVAs, and 4 of 131 (3%) patients without LVAs (p<0.001). Procedural parameters are listed in Tab.2.

Periprocedural complications

Procedure-related minor complications post-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, two groin pseudoaneurysms occurred. In the no-LVA group, one patient suffered from a transient ischemic event, one from gastroparesis, one from fluid overload with consecutive pulmonary edema, and another one from 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 Fig.4 for Kaplan-Meier plots). Success rate did not differ significantly in paroxysmal vs. persistent AF patients (69% vs. 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 vs. no-LVA patients (9% vs. 18%, p=0.11). In all 24 non-LVA patients, and in 2 of 4 LVA patients at least 1 pulmonary vein was reconnected (p<0.001). Reconduction 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 voltage-based substrate modification**

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 left atrial diameter 43±6 mm, and 17 of these patients had persistent AF (Tab.3). LVA patients with and without tailored substrate ablation post PVI differed in terms of AF type (87%, vs. 65% persistent AF, p= 0.036), fluoroscopy time (median 32 (quartiles 23,46) min vs. median 27 (quartiles 20,32) min, p=0.018), and freedom from AF/AT at 12 months (70% vs. 27%, p<0.001). Kaplan-Meier plots comparing both groups are shown in Fig.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 impact on rhythm outcome post AF catheter ablation.\(^4\,5\) In the study by Verma and colleagues,\(^6\) presence of LVAs was the strongest predictor of AF recurrence after PVI compared to 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\% vs. 81\%). Inspired by this elegant work,\(^6\) we adopted the protocol used, and identified LVAs in our patients. However, we did not just leave it at LVA diagnosis in order 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 compared to 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\%),\(^6\) or compared to our own comparison group (27\%). In our opinion, the results of our study allow the formulation of the hypothesis that tailored VSM in AF patients 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.
Low voltage areas and structural substrate in the atrium

LVAs detected by EAMS have been associated with structural atrial defects in congestive heart failure,9 advancing age,10 or atrial fibrillation.11 Oakes et al.5 have shown that LA fibrosis and scar tissue detected by delayed enhancement cardiac MRI correlates well with LVAs on voltage maps. We found significant LVAs within the LA in 47 patients (27% overall, and 35% in persistent AF patients). A similar proportion of scar areas (32% in persistent AF) was reported by others.12 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.5,11,13 In almost 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 electrical disturbances such as heterogeneities in atrial action potential duration, effective refractory period, and conduction velocity.14 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 due to microreentry or local automaticity.15 Successful substrate modification may then be achieved by homogenization of heterogeneousy scarred tissue (eliminating reentrant as well as focal sources), or blockage of typical pathways for left atrial 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 due to the relative absence of electrically-active tissue prior to ablation.

**Clinical parameters related to presence of low voltage areas**

We found LVAs in 10% of paroxysmal AF patients and in 35% of persistent AF patients. 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 like AF type. Similar to previous studies, clinical parameters like advanced age, female gender, 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 like a score may support procedure preparation, e.g. guiding the decision for or against single-shot devices like 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 LAA flow velocity as a surrogate parameter of left atrial transport function may be hypothesized.

**Consequences of a voltage–guided ablation strategy**

VSM resulted in RF lesion sets, which we had usually not applied and combined so far. 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 (Fig.2 and Fig.3). In some procedures, this lesion set was extended by an anterior mitral isthmus line (between left superior PV and anterior mitral valve annulus) in order to electrically isolate larger LVAs at the LA roof and anterior LA (see Fig.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 perimitral block.19

Apart from these qualitative differences compared to 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 like AF type, all persistent and probably no
paroxysmal AF patients would have undergone RF ablation of fractionated electrograms and/or
empirical linear lesions.1 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 proarrhythmic
potential of the approach. Randomized studies comparing our tailored strategy with established
approaches will clarify the potential of this strategy to prevent “overtreatment” in persistent AF
patients with structurally normal atrial myocardium and “undertreatment” in paroxysmal AF
patients with 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 voltage,23 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 bi-atrial ablation) affects AF tachycardia cycle
length, implying that exhaustive CFAE ablation may at least in part be unnecessary.

Limitations
This was a non-randomized observational study. However, due to the high AT/AF recurrence
rate in our comparison group of patients with untreated left atrial endocardial substrate, which is
also in congruence with previous publications,4-6 the similar 12-months outcome of patients with
additional personalized VSM compared to patients with healthy left atrial 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 further examine the role of
substrate- versus trigger-based AF.

We aimed to create homogeneous high-density voltage maps with an intended point
distance of less than 1 cm. It is possible, therefore, that very 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 very early in the mapping
process, if started at the preferential LVA sites (e.g. septum, roof, posterior wall). Moreover, it
has already been pointed out in previous publication that small, isolated LVAs (vs. larger scar
burden) may not have a significant impact on outcome.6 The reproducibility of voltage maps in
patients undergoing redo procedures suggests that under-detection of large LVAs (>1cm²) is
unlikely. In order to avoid false positive LVA results due to 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. 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 reconduction. We also 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 impact on clinical outcome. This aspect will be part of the above-mentioned randomized study.

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

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modest lecture honoraria from St. Jude Medical and Biotronik and is a member of the St. Jude Medical advisory board.

References:


Table 1: Baseline Characteristics

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<th>All patients (n=178)</th>
<th>LVA group (n=47)</th>
<th>No LVA group (n=131)</th>
<th>p-value</th>
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<tr>
<td>Age (years)</td>
<td>61 ± 10</td>
<td>67 ± 8</td>
<td>59 ± 9</td>
<td>&lt;0.001</td>
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<tr>
<td>Male</td>
<td>121 (68%)</td>
<td>25 (53%)</td>
<td>96 (73%)</td>
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<td>Arterial Hypertension</td>
<td>131 (74%)</td>
<td>40 (85%)</td>
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<td>Diabetes</td>
<td>29 (16%)</td>
<td>12 (26%)</td>
<td>17 (13%)</td>
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<td>Structural Heart Disease</td>
<td>41 (23%)</td>
<td>12 (26%)</td>
<td>29 (22%)</td>
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<td>Body Mass Index</td>
<td>29 ± 5</td>
<td>29 ± 5</td>
<td>29 ± 5</td>
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<td>Left atrial diameter (mm)</td>
<td>44 ± 7</td>
<td>45 ± 8</td>
<td>43 ± 6</td>
<td>0.26</td>
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<tr>
<td>LVEF (%)</td>
<td>60 (54,62)</td>
<td>60 (50,63)</td>
<td>60 (55,62)</td>
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<td>LAA flow velocity (m/sec)*</td>
<td>0.53 ± 0.20</td>
<td>0.35 ± 0.14</td>
<td>0.55 ± 0.20</td>
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<td>Persistent AF</td>
<td>116 (65%)</td>
<td>41 (87%)</td>
<td>75 (57%)</td>
<td>&lt;0.001</td>
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<td>History of AF (months)</td>
<td>49 (24,109)</td>
<td>35 (16,90)</td>
<td>66 (24,110)</td>
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Medication

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<th>No LVA group (n=131)</th>
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<tr>
<td>Betablockers</td>
<td>129 (73%)</td>
<td>36 (77%)</td>
<td>93 (71%)</td>
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<td>ACEI and/or ARB</td>
<td>105 (59%)</td>
<td>32 (68%)</td>
<td>17 (56%)</td>
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<td>Statins</td>
<td>21 (12%)</td>
<td>7 (15%)</td>
<td>14 (11%)</td>
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Independent predictors after multivariable testing in italics.
*for patients in sinus rhythm.
Table 2: Procedural parameters and Follow-up data

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<td></td>
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<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>Periproc. 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 months</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>

### Table 3: Comparison of LVA patients with and without voltage-based substrate modification

<table>
<thead>
<tr>
<th></th>
<th>LVA + SM group (n=47)</th>
<th>LVA w/o SM comparison group (n=26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>67 ± 8</td>
<td>67 ± 9</td>
<td>0.894</td>
</tr>
<tr>
<td>Male</td>
<td>25 (53%)</td>
<td>15 (58%)</td>
<td>0.808</td>
</tr>
<tr>
<td>Arterial Hypertension</td>
<td>40 (85%)</td>
<td>23 (89%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (26%)</td>
<td>4 (15%)</td>
<td>0.387</td>
</tr>
<tr>
<td>Structural Heart Disease</td>
<td>12 (26%)</td>
<td>12 (46%)</td>
<td>0.117</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>29 ± 5</td>
<td>28 ± 4</td>
<td>0.506</td>
</tr>
<tr>
<td>Left atrial diameter (mm)</td>
<td>45 ± 8</td>
<td>43 ± 6</td>
<td>0.551</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60 (50,63)</td>
<td>57 (45,65)</td>
<td>0.655</td>
</tr>
<tr>
<td>LAA flow velocity (m/sec)</td>
<td>0.37 ± 0.11</td>
<td>0.35 ± 0.10</td>
<td>0.354</td>
</tr>
<tr>
<td>Persistent AF</td>
<td>41 (87%)</td>
<td>17 (65%)</td>
<td>0.036</td>
</tr>
<tr>
<td>History of AF (months)</td>
<td>35 (16,90)</td>
<td>60 (33,84)</td>
<td>0.082</td>
</tr>
<tr>
<td><strong>Procedural data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy time (min)</td>
<td>32 (23,46)</td>
<td>27 (20,32)</td>
<td>0.018</td>
</tr>
<tr>
<td>Irradiation dose (Gycm²)</td>
<td>122 (83,164)</td>
<td>88 (53,118)</td>
<td>0.022</td>
</tr>
<tr>
<td>Procedural time (min)</td>
<td>160 (135,200)</td>
<td>150 (128,180)</td>
<td>0.125</td>
</tr>
<tr>
<td>RF time (min)</td>
<td>44 ± 16</td>
<td>39 ± 19</td>
<td>0.273</td>
</tr>
<tr>
<td>RF pulses</td>
<td>38 ± 18</td>
<td>31 ± 19</td>
<td>0.193</td>
</tr>
<tr>
<td>SR at procedure begin</td>
<td>13 (28%)</td>
<td>8 (31%)</td>
<td>0.793</td>
</tr>
<tr>
<td>Perproc. complications</td>
<td>2 (4.3%)</td>
<td>1 (3.8%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Clinical Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early Recurrences</td>
<td>24 (51%)</td>
<td>16 (62%)</td>
<td>0.465</td>
</tr>
<tr>
<td>Redo procedure</td>
<td>4 (9%)</td>
<td>6 (23%)</td>
<td>0.152</td>
</tr>
<tr>
<td>Freedom from AF/AT at 12 months</td>
<td>33 (70%)</td>
<td>7 (27%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AAD usage</td>
<td>2/33 (6%)</td>
<td>0/7 (0%)</td>
<td>1.00</td>
</tr>
<tr>
<td>AT recurrence only</td>
<td>3/14 (21%)</td>
<td>4/19 (21%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Figure Legends:**

**Figure 1:** The figure depicts left atrial distribution of low voltage areas (A) and shows examples of voltage maps of patients without (B) and with (C) low voltage areas. The upper maps (B,C) show modified antero-posterior views, and the lower maps show modified postero-anterior views of LA models post image registration. Color-coding is defined as follows: <0.2 mV = scar (grey), 0.2-0.5mV = diseased atrial tissue (red, yellow), >0.5mV = healthy atrial myocardium (pink). Note the different prevalence of low voltage areas in patients with paroxysmal atrial fibrillation (10%) and persistent (35%) atrial fibrillation. LVA: low voltage area, LA: left atrium, a.p.: antero-posterior view, p.a.: postero-anterior projection, AF: atrial fibrillation.

**Figure 2:** The figure depicts examples of low voltage distribution within the left atrium and the consecutive targeted radiofrequency lesion design. Color-coding as defined in Fig.1. A/B and C/D same patient. a.p.: antero-posterior view, p.a.: postero-anterior view, sup.: superior view.

**Figure 3:** The figure illustrates endpoints of individualized LVA-based substrate modification. A: Exitblock during high output pacing from all parts of the scar-encircling ablation lesion. B: Exitblock during high output sequential pacing from a circular mapping catheter within roof/box lesions. C: Verification of anterior mitral isthmus by pacing within LAA and interpretation of activation sequence in the CS as well as the right atrial septum. abl: ablation catheter, eso: esophageal temperature probe, cs: coronary sinus catheter, RF: radiofrequency, cmc: circular mapping catheter, laa: left atrial appendage, ra sept: right atrial septum.
**Figure 4:** Kaplan–Meier plots depicting the AT/AF free survival of the study population stratified by ‘substrate’ patients with LVA and targeted substrate modification (blue line) and ‘healthy’ patients without LVA following circumferential PV isolation only (green line).

**Figure 5:** Kaplan–Meier plots depicting the AT/AF free survival of the study ‘substrate’ patients with LVA following targeted substrate modification (blue line) and the comparison ‘substrate’ patients left without additional substrate modification after LVA identification (green line).
A LVA Distribution Within LA

B

„Healthy“ Left Atrium

<table>
<thead>
<tr>
<th>Paroxysmal AF</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF</td>
<td>65%</td>
</tr>
</tbody>
</table>

C Left Atrium With Substrate

<table>
<thead>
<tr>
<th>Paroxysmal AF</th>
<th>10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF</td>
<td>35%</td>
</tr>
</tbody>
</table>
Examples of Voltage Maps and Tailored Ablation
Loss of Local Pace Capture During Ablation

Verification of Conduction Block Of Strategic Linear Lesions

Absent Pace Capture in Areas Excluded by RF Ablation
unadjusted log rank p=0.30
adjusted p=0.09

**Circulation**
Arrhythmia and Electrophysiology

*Journal of the American Heart Association*

**Number at risk (pts.)**

<table>
<thead>
<tr>
<th>Group</th>
<th>47 (LVA)</th>
<th>36</th>
<th>36</th>
<th>2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>118</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Pts. with LVA and additional targeted ablation (LVA)**

**Pts. without LVA and PVI only (No LVA)**
log rank p<0.001

- Pts. with LVA and additional targeted ablation (LVA+)
- Pts. with LVA (PVI only, no substrate modification, LVA-)

Number at risk (pts.)

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LVA+</td>
<td>44</td>
<td>36</td>
<td>36</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>LVA-</td>
<td>22</td>
<td>13</td>
<td>9</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
Tailored Atrial Substrate Modification Based On Low-Voltage Areas in Catheter Ablation of Atrial Fibrillation

Sascha Rolf, Simon Kircher, Arash Arya, Charlotte Eitel, Philipp Sommer, Sergio Richter, Thomas Gaspar, Andreas Bollmann, David Altmann, Carlos Piedra, Gerhard Hindricks and Christopher Piorkowski

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