ATRIAL FIBRILLATION

RESEARCH ARTICLE

Substrate-Based Atrial Fibrillation Ablation Guided by Voltage Gradient Mapping: A New Approach for Atrial Fibrillation Ablation

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ABSTRACT. Introduction: Understanding the mechanisms for maintenance and propagation of atrial fibrillation (AF) are critical to the development of successful ablation strategies. In the present study we test the hypothesis that voltage gradient mapping may be used to define atrial substrate, target ablation sites, and have successful outcomes. Methods and results: 54 consecutive patients, 28 paroxysmal AF (PAF); 26 persistent and permanent AF (PPAF), had contact voltage mapping with three-dimensional electroanatomic reconstruction of the left atrium (LA) and right atrium, pulmonary veins (PVs), superior vena cava, and inferior vena cava. Voltage levels were adjusted until low-voltage connections between higher-voltage regions were revealed. Ablation of low-voltage bridges was performed until no low-voltage connections were observed within the left atrium, including the PVs. Success was defined by 1) the absence of AF (primary endpoint); 2) freedom from sustained atrial tachycardia (secondary endpoint) documented by 30-day event monitors. Median follow-up was 765 days (PAF), 831 days (PPAF). The primary endpoint was achieved in 86% PAF and 79% PPAF patients. The secondary endpoint was achieved in 89% PAF and 58% PPAF patients. Conclusions: Voltage gradient mapping of atrial substrate is an effective tool for guiding ablation therapy. By targeting critical endocardial linkages, this methodology provides a high procedural success in both PAF and PPAF patients, and offers insight into the substrate necessary to maintain AF.

KEYWORDS. atrial fibrillation, catheter ablation, cardiac mapping.

Introduction

The underlying mechanisms involved in the propagation and maintenance of atrial fibrillation (AF) have remained largely unknown. Histology studies have demonstrated the presence of progressive fibrosis and loss of intercellular connections due to gap junction regression. These changes become more pronounced as the AF changes from paroxysmal AF (PAF) to persistent and permanent (PPAF) forms. In 1959, Moe proposed that AF is maintained by wavelets that are in constant collision within the atrium. AF can be maintained as long as there is sufficient tissue mass to maintain multiple wavelets.

Initial curative treatment pioneered by Cox demonstrated that division of atrial tissue into segments via a “MAZE” procedure prevented AF and offered long-term cures. More recently, electrophysiologists have focused...
on eliminating triggering foci residing within the left atrium (LA) or around the pulmonary veins (PVs). Others have mapped either high-frequency (CFAE) or targeted autonomie ganglia found in the left atrial epicardium. Both have been used as adjunctive therapy, but their utility is uncertain.\textsuperscript{6,7} Regardless of the technology used, ablation therapy is largely empiric and anatomic based. Most reports suggest that patients with PAF have better outcomes than patients with persistent or permanent forms of AF.\textsuperscript{8–10} Given the chaotic nature of AF, surface activation mapping is not useful. While high-density patch mapping of AF has indicated that chaos theory may be applicable,\textsuperscript{11} no clear methodology for atrial substrate mapping has been described. If it were possible to map atrial substrate, the fundamental structures necessary to maintain and propagate AF might become apparent. Such a model would have implications for the mechanism of AF progression from PAF to PPAF, which would be quantifiable, measurable in any rhythm, and be able to define targets for ablation therapy.

We have previously reported the use of voltage gradient mapping for the visualization of the slow pathway in AV nodal re-entry tachycardia.\textsuperscript{12} Using this methodology we have demonstrated that underlying endocardial substrate may be evaluated. This technique compares regional variations in endocardial voltage derived from contact electroanatomic mapping.

By using voltage gradient mapping (VGM) within the left and right atrium, we have observed high-voltage regions (HVRs) that are connected by low-voltage bridges (LVBs). We hypothesize that these LVBs represent abnormal atrial substrate caused by atrial fibrosis and loss of gap junctions seen in the atrium of AF patients. Targeting these LVBs by ablation would eliminate the endocardial fragmentation associated with AF and allow a methodology for successful ablation therapy. To test this hypothesis, 54 patients undergoing AF ablation had voltage gradient mapping performed with radiofrequency ablation targeted to the LVBs.

The LVBs were targeted for ablation via radiofrequency ablation (Safire TX 8mm, SJM or EPT Blazer 8mm, BS) set at 60W/60 degrees until a decrease of endocardial voltage was observed from the distal ablation electrode. For this reason, ablation lesions were focally applied, and therefore, linear ablation lines were not created. (See supplemental Video 2 for a video of the LVB ablation and supplemental Figure 7 for a sample of lesion placement). PV isolation was performed by focal ablation of the LVBs traveling from the LA to the PV until there was a loss of voltage and activation within the PV. The effect of LVB ablation was assessed with repeated VGMs as needed. Ablation endpoints were defined as

1. Termination of AF in patients with PPAF or inducible sustained AF
2. Completion of the substrate guided ablation until there was an absence of LVBs connecting HVRs (absent endocardial linking)
3. PV isolation via LVB ablation (defined by the absence of PV voltage and activation)
4. Non-inducibility of AF or atrial tachycardia (AT) despite aggressive atrial burst pacing (right atrium (RA) and coronary sinus (CS) at 10mA at 10V down to loss of capture).

The primary endpoint for the study was the absence of AF >30s as detected by the 30-event monitor. The secondary endpoint was defined by the absence of AT >30s on the event monitor. VGM, activation, and entrainment mapping were used for ablation of ATs. If a second procedure was required, the same methodology was used as noted above.

All patients had routine clinical follow-up including ECGs, holters, or event monitors as clinically indicated for symptoms. A 30-day event monitor was obtained 4 months and yearly following final ablation. Statistical analysis of the voltages settings was compared via $t$ testing. Clinical outcomes were expressed as a percentage of the group population and compared via ANOVA.

### Methods

Following informed consent, 54 consecutive patients undergoing AF ablation had high-density contact mapping with three-dimensional (3D) electroanatomic reconstruction using Navx (ESI-SJM), a standard quadrupolar ablation catheter, and a Reflexion HD circular 20 polar catheter (SJM). Voltage maps were obtained in either sinus rhythm (SR) or, if sustained, in AF. Maps were also generated from individual patients in both SR and AF whenever possible. The high- and low-voltage levels were adjusted to reveal the presence of LVBs connecting high- and low-voltage regions. Clinically relevant LVBs were defined by the presence of a low-voltage gradient (color variation yellow to red) within the LVB, and a connection to a HVR. The methodology for this technique may be found in Bailin et al. (see Video 1 supplemental video of VGM build).

### Results

Demographic data and ablation summaries are provided in Table 1. LVBs were observed in all patients and were seen connecting venous structures including the PVs, CS, and superior vena cava (SVC). LVB connections were seen throughout the atrium, anterior, posterior, septal, lateral walls, and along the left atrial roof. The location of the LVBs varied greatly and was not consistent in both patient populations.

The average number of voltage points collected was 1755 (888–3188) for the LA and PVs and 1699 (242–5280) in the RA, SVC, and IVC. An average of four LA maps and two RA maps were created. Total procedure time, measured from the time the patient entered the room to the time the patient exited the room was 305min (180–455): 293min for PAF and 318 minutes for PPAF (NS).
Figure 1a shows a characteristic image of LVB seen in patients with PAF, which, compared with patients with PPAF (Figure 1b), shows the overall voltage is higher and fewer LVBs are observed.

Ablation Mapping of the atrium and veins was performed in SR or in AF. The high- and low-voltage levels were recorded at baseline and following achievement of the ablation endpoints. The voltage settings at baseline were significantly different from those obtained during the last VGM in the LA when comparing the starting high-voltage cut-off between PAF and PPAF, 1.4mV versus 1.3mV (p<0.003), but was otherwise not significantly different comparing groups, including the final high-voltage setting (Table 2). Additionally, the total number of pulses delivered was higher in patients with PPAF than in patients with PAF 167 versus 135 (p<0.04). This number reflects both left and right atrial pulses. The number of pulses used to terminate AF in both groups ranged from 40 to 90. Additional ablation pulses were delivered for inducible atrial tachycardia and cavitricuspid isthmus ablation. Fluoroscopy time was also longer for PPAF compared with PAF patients, 91 versus 67min (p<0.007).

The average lesion time was 18s. Targeted LVB ablation resulted in extensive changes in endocardial voltage (Figure 2). Figure 3 demonstrates a VGM before and after LVB-targeted ablation. The initial VGM is shown in Figure 3a and the final VGM is shown in Figure 3b.

Ablation endpoints

Sustained AF was present or induced in 46 patients. LVB ablation resulted in conversion to SR in 43/46 patients (93%). Patients with PPAF (n=26) converted to SR 23/26 (88%) with LVB ablation. All patients organized to AT, but three patients required cardioversion of AT not converted with ablation, or had persistent right atrial AF.

AF was not inducible in 52/54 (95%) at the end of the study using the pacing protocol described in the methodology. The absence of inducible AF and ATs correlated with the absence of endocardial linking via LVB.

The PVs were successfully isolated in all patients by ablating the LVB connecting the PV to the atrium (Figure 4). Isolation was confirmed by the absence of

Table 1: Demographics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>PAF</th>
<th>PPAF</th>
<th>p-Value</th>
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<td>Number</td>
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<td>28</td>
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<td>58.1</td>
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<tr>
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<tr>
<td>Time*</td>
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*Time room entrance to time room exit.
LA: left atrium; LVEF: left ventricular ejection fraction; PAF: paroxysmal atrial fibrillation; PPAF: persistent and permanent atrial fibrillation.

Table 2: High- and low-voltage set points: first and final voltage maps

<table>
<thead>
<tr>
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<th>LVLA post</th>
<th>HVLA base</th>
<th>HVLA post</th>
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<tr>
<td>p-Value</td>
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<td>NS</td>
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<td>NS</td>
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<td>PPAF</td>
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<td>0.150.08</td>
<td>0.990.4</td>
<td>0.230.19</td>
</tr>
<tr>
<td>p-Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>LVRA base</th>
<th>LVRA post</th>
<th>HVRA base</th>
<th>HVRA post</th>
</tr>
</thead>
<tbody>
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<td>PAF</td>
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<td>0.210.14</td>
<td>1.300.8</td>
<td>1.300.41</td>
</tr>
<tr>
<td>p-Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PPAF</td>
<td>0.230.2</td>
<td>0.180.15</td>
<td>1.170.35</td>
<td>1.200.09</td>
</tr>
<tr>
<td>p-Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>

PAF: paroxysmal atrial fibrillation; PPAF: persistent and permanent atrial fibrillation.
recordable voltage or activation within the PV. Voltage measurements were confirmed via repeated LA mapping and at the end of LA ablation.

**Outcomes**

The median follow-up time from the EP procedure was 765.5 (+/− 240 SD) SD days in PAF patients; 831 (+/− 145 SD) SD days in PPAF patients. Two patients were lost to follow-up 6 months post procedure and were not included in the long-term follow-up data. Comparison of PAF and PPAF follow-up time was not significant (p=0.06). Procedure success was determined by 30-day monitoring at least 4 months and yearly following the last procedure.

**Table 3** displays the long-term outcome in 52 patients. The primary endpoint (absence of AF >30s) was achieved in the majority of patients and was not significantly different between patients with PAF or PPAF. Patients with PPAF were significantly less likely to achieve the secondary endpoint (absence of AT>seconds) than patients with PAF. Use of antiarrhythmic drugs was similar in both groups and was only used for symptomatic recurrence, not for suppression.

**Figure 2**: The ablation of low-voltage bridges (LVBs) results in dramatic changes in endocardial voltage. As seen in the figure, LVBs are observed along the anterior septum. Ablation targeted to these few LVBs resulted in a significant collapse of voltage on the anterior atrial wall.
Figure 5 demonstrates the percentage results of first and second procedures for patients opting for a second procedure. Patients with MART or AT fared better than patients presenting with recurrent AF. Of note, some patients with PPAF converted to PAF following the first ablation.

The impact of AF ablation upon P-wave duration has been previously reported. Most studies demonstrated that P-wave duration is shorter post ablation than baseline. There was a significant decrease in P-wave duration in patients with PAF from 134.520.3ms pre-ablation to 113.326.4ms post ablation (p \(<\) 0.03). Following ablation and conversion to SR, PPAF patients had an average P-wave duration of 118ms.

Complications

Complications were uncommon in these patients. Two patients had tamponade (3%). Pleuritic chest pain requiring extended non-steroidal anti-inflammatory therapy was observed in five patients (7.5%).

Discussion

Single-procedure success varies greatly in the literature. A meta-analysis, Calkins et al, found the single-procedure success was 57%, and with multiple procedures the success increases to 71%. In patients with PPAF the single-procedure results range from 40% to 50%. While these results are encouraging, we hypothesize that by using VGM and LVB ablation targeting, a more consistent and individually tailored approach may help create a strategy for ablation that is based upon the underlying substrate necessary for sustaining AF.

Recent magnetic resonance imaging data from patients with PAF and PPAF demonstrate progressive fibrosis that correlates with ablation outcomes and disease state. A true measurement of atrial substrate should also demonstrate such progression. Indeed, in the present study, we observed that there is increased endocardial fragmentation, increased number of LVBs, and lower measured voltages, which correlate to the severity and chronicity of AF.

Voltage as substrate

Global measurements of atrial voltage and conduction velocity are reduced in both PAF and PPAF. By mapping small-scale voltage variations, the nature of the
interactions between normal and diseased tissues offers insight into the mechanisms for AF propagation. The relationship between LVBs and HVRs may create a syncytium of atrial tissue that acts as regional wavelet reservoirs. The present study tested the hypothesis that ablation of the LVB connections disrupts wavelet propagation, terminates AF acutely, and may provide improved outcomes in patients with both PAF and PPAF.

Evidence supporting the hypothesis

1. If VGM represents an accurate depiction of endocardial substrate, then the resulting voltage map should be similar whether it is obtained in SR or during AF
If minute variations in atrial endocardial voltage truly reflect underlying atrial substrate, then the relative values of voltage recorded should be consistent whether obtained in SR or in AF. If this were not the case, then one could correctly argue that the recorded voltages represent a combination of activation and substrate. Since VGM recorded from patients in whom both a SR and an AF map correlate very well, VGM does reflect substrate as exemplified by figure 6. As can be seen, remarkable similarities are observed, and would allow accurate ablation of LVB in either AF or SR.

2. LVBs are markers for activation inputs to venous structures, including the pulmonary veins
LVBs that connect venous structures, such as the PVs, are ablated and result in electrical isolation (Figure 4). Following LVB ablation, there is no voltage or activation within the PVs. Therefore, focal inputs can be targeted without requiring circumferential ablation in order to isolate the PVs.

![Figure 5](image)

**Figure 5**: The graph displays the acute results of first and second procedures in the original 54 patients that underwent a second procedure. The percentage of patients with mitral annular re-entry tachycardia (MART), atrial tachycardia (AT), paroxysmal atrial fibrillation (PAF), and persistent and permanent atrial fibrillation (PPAF) are displayed for each group following the first procedure depicted in blue. The results of the second ablation are depicted in red. The results reflect the outcomes of 30-day monitoring an average of 6–8 months following the last procedure. The majority of patients benefit from repeat ablation when an AT is present compared with patients presenting with AF recurrence.

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PPAF</th>
<th>p-Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (days)</td>
<td>765.5 ± 240</td>
<td>831 ± 145</td>
<td>0.06 (NS)</td>
</tr>
<tr>
<td>Primary endpoint (AF)</td>
<td>24/28 (86%)</td>
<td>19/24 (79%)</td>
<td>0.5 (NS)</td>
</tr>
<tr>
<td>Secondary endpoint (AT)</td>
<td>25/28 (89%)</td>
<td>14/24 (58%)</td>
<td>0.01</td>
</tr>
<tr>
<td>No antiarrhythmic drugs</td>
<td>23/28 (82%)</td>
<td>18/24 (75%)</td>
<td>0.5 (NS)</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; AT: atrial tachycardia; PAF: paroxysmal atrial fibrillation; PPAF: persistent and permanent atrial fibrillation.

Table 3: Endpoint results in long-term follow-up. There was no significant difference between paroxysmal atrial fibrillation (PAF) and persistent and permanent atrial fibrillation (PPAF) patients with regard to the primary endpoint (absence of AF) or the number of patients on antiarrhythmic drugs, or duration of follow-up. There was a significant difference in achievement of the secondary endpoint (absence of atrial tachycardia) between the PAF group compared with the PPAF group.
3. LVBs activate atrial endocardium selectively and ablation of the low-voltage bridge results in a regional loss of voltage within the atrium

This is observed in Figure 2, where, despite focal ablation as shown, the ablation of the LVB creates a remarkable collapse of atrial voltage distant to the lesion. It appears that a disproportionally large area of atrial voltage is lost when the LVB serving that region is ablated. This finding suggests that atrial endocardial activation is not homogenous and multidirectional; rather endocardial activation has focal inputs identifiable by an adjacent LVB.

Termination of AF and inability to induce tachycardia was associated with the absence of LVB

In patients with PPAF or inducible sustained AF, conversion to AF was successful in 43/46 (93%) of patients with ablation alone. AF termination is less frequently observed using other techniques (53% with PV isolation+linear ablation, +CFAE ablation). This finding supports the hypothesis that endocardial fragmentation is critical for propagation of AF or ATs. Loss of endocardial fragmentation correlated with the inability to induce AF or ATs. When an AT was induced, the circuits were always associated with a residual endocar-
particularly important when assessing the consistency of the collected data.

Additionally, remapping with subsequent adjustment of the voltage values is required to exclude residual low-voltage connections. Therefore, voltage settings were decreased following each ablation session during the remap (Table 3). Despite this, late occurring residual atrial circuits are observed around the mitral valve or atrial septum sometimes requiring a second ablation. These ATs were observed within 3 months following ablation.

Some patients will have refractory AT despite successful substrate modification. Epicardial circuits cannot be assessed by the present technique, and cannot be excluded as a mechanism for refractory tachycardia. In addition, right atrial disease, particularly when the right atrial appendage is large, may be a source of continued arrhythmia despite successful left atrial substrate ablation.

In the present study, treatment of arrhythmia was symptom driven. As such, patients with AT who did not have clinical symptoms did not undergo a second ablation procedure. Thus, the overall results reflect occurrence of rhythms >30s duration, but does not reflect clinical success defined by patient perceptions, nor the real outcomes had recurrent ATs been treated by a second ablation.

Finally, the present study reports ablation outcomes based upon using VGM for selective targeting of critical endocardial sites in patients with AF compared with historical outcomes through meta-analysis and review of specific papers. Therefore, VGM in this study should serve as a proof of concept, rather than a proof of superiority compared with standard ablation techniques. A randomized trial will be required to confirm the relative merits of this approach to standard ablation procedures.

Conclusions

VGM appears to be a successful method to evaluate critical regions within the atrial substrate of patients with AF. By targeting LVB, the atrial endocardium is significantly modified, such that the mechanism of propagation and maintenance of AF is successfully interrupted. By reliably identifying regions for targeted ablation, patients receive tailored therapy. It also provides the ability to define an objective clinical endpoint by demonstration of not only PV isolation, but also the absence of endocardial fragmentation. This methodology provides a means to assess the underlying atrial substrate such that elimination of LVBs creates a measurable endpoint for successful AF ablation.

The present study offers an alternative model for AF ablation based on LVB targeting. The results herein presented represent a proof of concept that should stimulate further investigation.

References