Endocardial impedance mapping during circumferential pulmonary vein ablation of atrial fibrillation differentiates between atrial and venous tissue

Christopher C.E. Lang, MB, ChB, MD, Filippo Gugliotta, BEng, Vincenzo Santinelli, MD, Cézar Mesas, MD, Takeshi Tomita, MD, PhD, Gabriele Vicedomini, MD, Giuseppe Augello, MD, Simone Gulletta, MD, Patrizio Mazzone, MD, Francesco De Cobelli, MD, Alessandro Del Maschio, MD, Carlo Pappone, MD, PhD

aFrom the Division of Arrhythmology and Cardiac Electrophysiology, San Raffaele Hospital, Milan, Italy, and bDepartment of Diagnostic Radiology, San Raffaele Hospital, Milan, Italy.

BACKGROUND Circumferential pulmonary vein ablation (CPVA) is an effective treatment for atrial fibrillation (AF). Accurate left atrial (LA) mapping is essential for creating lesions at the LA–pulmonary vein (PV) junction, avoiding PV stenosis.

OBJECTIVES The purpose of this study was to establish whether endocardial impedance varies within the LA and PVs and whether it is a useful tool for mapping and ablation.

METHODS Pilot Phase: Three-dimensional LA maps were created using CARTO. Impedance (Z) was measured using a radiofrequency generator at multiple points in the LA, PV ostia (PVO), and deep PVs in 79 patients undergoing their first AF ablation (group 1) and 29 patients undergoing repeat CPVA (group 2). Prospective Phase: In an additional 20 patients, using pilot phase data, one operator defined catheter tip location as either LA or PVO based on CARTO and fluoroscopy. A second operator blinded to CARTO simultaneously did the same based on impedance at 15 points per patient.

RESULTS Group 1: $Z_{LA}$ was $99.4 \pm 9.0 \, \Omega$. $Z_{PVO}$ was higher ($109.2 \pm 8.5 \, \Omega$), rising further as the catheter advanced into deep PV ($137 \, \Omega \pm 18$). $Z_{PVO}$ differed from $Z_{LA}$ by $9 \pm 4 \, \Omega$. Group 2 had a lower $Z_{LA}$ and $Z_{PVO}$ compared with group 1 ($P < .05$). Impedance monitoring differentiated between LA and PVO, with 91% specificity and sensitivity, 96% positive predictive value, and 81% negative predictive value. At 3-month follow-up, no patients had evidence of PV stenosis on magnetic resonance imaging.

CONCLUSION Impedance mapping reliably identifies the LA–PV transitional zone, facilitating AF ablation, and its use is associated with a low incidence of PV stenosis.

KEYWORDS Ablation, Atrial fibrillation; Impedance; Mapping

Introduction

Circumferential pulmonary vein ablation (CPVA) is an effective treatment for atrial fibrillation (AF). The ability to understand and correctly reconstruct left atrial (LA) and pulmonary vein (PV) anatomy is essential to deploy continuous effective ablation lines around the target regions at the pulmonary vein ostium (PVO)–LA junction. In our experience, one of the advantages of CPVA over other techniques is the absence of PV stenosis. However, other centers have reported a high incidence of PV stenosis after AF ablation using an electroanatomic approach. To prevent this potentially serious complication, lesions must be deployed near the PVO–LA junction and not inside the vein.

We previously reported that the electrical impedance in the PVs is higher than in the LA, and we have been using endocardial impedance to assist in both mapping and abla-
Ablation technique has been described in detail elsewhere.2,3 In accordance with our institutional ethical guidelines. The informed written consent was obtained from all patients, and the study was conducted under the PVO; and to establish whether impedance was affected by the ablation procedure.

The predetermined goals of this study were to formally describe the variation in impedance in the LA, PVO, and PVs in order to facilitate the accurate identification of PVO-LA junction and suitable sites for placement of safe and effective linear lesions; to determine whether impedance can reliably determine the catheter position relative to the PVO; and to establish whether impedance was affected by the ablation procedure.

**Table 1** Baseline patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 79)</th>
<th>Group 2 (n = 29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>55.7 ± 9.3</td>
<td>59.1 ± 7.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>47/31</td>
<td>15/14</td>
<td>0.42*</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 8.1</td>
<td>78.7 ± 9</td>
<td>0.6</td>
</tr>
<tr>
<td>Left atrial volume (mL)</td>
<td>99.9 ± 37.4</td>
<td>89.5 ± 33.8</td>
<td>0.20</td>
</tr>
</tbody>
</table>

*Chi-square test.

**Impedance measurement circuit**

A Stockert 100-W RF generator (Biosense Webster Inc, Diamond Bar, CA) was used to perform real-time impedance mapping (RTIM) with a Navi-Star 8Fr F-curve 8-mm-tip catheter (Biosense-Webster). The generator is equipped with an independent electrical circuit for continuous real-time impedance monitoring that produces a sinusoidal current of 2 μA at a frequency of 50 kHz, which minimizes the complex polarization impedance at the electrode–tissue interface. Catheter–tissue contact was assessed using several criteria: local activation time (patients in sinus rhythm), electrogram morphology, electrogram dV/dt, location stability, and, if necessary, fluoroscopy before acquisition of endocardial points. Location stability was confirmed by CARTO and stability of the impedance reading. Impedance values at stable positions were noted to vary by ±2 Ω. The reference patch (Ref-Star, Biosense-Webster) was positioned on the patient’s back between T2–T6 to minimize the impact of electrode position on impedance.

**Atrial and PV mapping and impedance measurement**

Using the three-dimensional electroanatomic mapping system (CARTO, Biosense-Webster, Diamond Bar, CA, USA), the LA and PV anatomy was reconstructed, paying particular attention to the PVO regions. In each patient, impedance was monitored at a single point on the posterior wall of the LA for 30 seconds and was found to vary by ±2 Ω. Deep in the PV, impedance varied with respiration by ±10 Ω on average. Local impedance measurements (Z_{RTIM}) were taken in the LA at a minimum of 10 points on the posterior wall, septum, roof, and mitral valve region. No significant differences were found between these regions, and the LA impedance (Z_{LA}) was taken as the average of all points. The left atrial appendage (LAA) was distinguished by a higher-amplitude local electrogram (V_{LAA} >1.5 mV), organized activity in patients in AF, and the anterior position of the catheter as seen on CARTO in a left lateral view.

The atrial and PV anatomy was divided into three distinct zones based on anatomic location (defined by fluoroscopy and CARTO) and electrical characteristics: zone 1 (LA); zone 2—from the lip of the PVO (with detectable electrical signal 0.05 mV < V < 0.7 ± 0.2 mV) until the point where the vein became electrically silent; and zone 3—deep PV where no electrical signal is detected (V.
lesions (Figure 1). To determine the sensitivity and specificity of an impedance cutoff of \( (Z_{\text{LA}} + 4 \, \Omega) \), the impedance was recorded in an additional 20 patients at multiple points in the LA and PVO by an investigator blinded to the position of the ablation catheter. Based on impedance alone, one investigator would attempt to define whether the point was in the PVO (unsafe for RF application) or LA (safe for RF). A second investigator determined whether a location was safe or unsafe for RF application, based on the catheter’s anatomic position and local electrogram characteristics as seen on CARTO and/or fluoroscopy. A third operator who was responsible for the ablation procedure instructed the investigators when to take readings.

### Magnetic resonance imaging

At 3 ± 1 months after ablation, all 20 patients from the prospective phase underwent contrast-enhanced magnetic resonance angiography of the PVs using a 1.5-T superconducting magnet (Gyroscan Intera, release 9, Philips Medical Systems, Eindhoven, Netherlands).

### Statistical analysis

Statistical analysis was performed using SPSS10 (Chicago, Illinois) for Windows. Paired and unpaired t-tests were used to test the significance of differences in preablation and postablation impedance and between groups, respectively. The receiver operator characteristic (ROC) was determined comparing the local impedance at individual points \( (Z_{\text{RTIM}}) \) compared against the suitability (safe = 1, unsafe = 0) of each site for RF application as determined by electroanatomic mapping. Data are presented as mean ± SD.

### Results

### Patient characteristics

Baseline patient characteristics are given in Table 1. There was no correlation between patient characteristics and endocardial impedance. In particular, there was no relationship between patient weight and mean endocardial impedance. However, because data on patient height were not available, we cannot exclude a weak relationship between endocardial impedance and body mass index.

### Preablation impedance

Impedance data for each of the zones were normally distributed. In both groups, significant differences were detectable between the three predefined zones \( (P < .0001 \text{ for zone 2 of each PV vs LA in both groups}) \). Paired t-tests were used to compare the impedance in individual veins, but there was no significant difference between any of the veins. When all patients were grouped together the absolute values for each zone 2 were as follows: right upper PV 106.8 ± 10.5 \( \Omega \); right lower LPV 107.7 ± 12.8 \( \Omega \); left upper PV 106.0 ± 9.7 \( \Omega \); left lower PV 106.6 ± 10.3 \( \Omega \). Mean LA impedance \( (Z_{\text{LA}}) \) was 99.4 ± 9.0 \( \Omega \) and 95.9 ± 7 \( \Omega \) \( (P < .05) \) in groups 1 and 2, respectively. Upon entering zone 2, impedance rose beyond 90 \( \Omega \).
to 109.2 ± 8.5 Ω and 101.3 ± 9 Ω respectively (P < .005). Impedance continued to rise rapidly upon catheter advancement in zone 3, with mean impedances in these regions of 137 ± 18 Ω and 128 ± 17 Ω, respectively (P = .09). A small change in the depth of the catheter in zone 3 could result in a large difference in impedance. The gradient between LA and zone 2 was more marked in the CPVA-naive group in the left but not in the right PVOs. The mean impedance gradients between LA and zone 2 were 9.0 ± 4.1 Ω and 7.1 ± 3.9 Ω (P = NS) for groups 1 and 2, respectively. These data are summarized in Figure 2 and illustrated in Figure 3. The impedance in the LAA (ZLAA) was higher than the rest of the LA in groups 1 and 2 by 4.4 ± 3.3 Ω and 3.3 ± 3.2 Ω in both groups (P < .01).

**Postablation impedance**

Following CPVA, impedance reduced significantly in all regions in both groups, and the difference between preablation and postablation impedance values was highly statistically significant in all regions in both groups (P < .0001). The average absolute drop in LA impedance was 9.8 ± 4 Ω and 8 ± 5 Ω in groups 1 and 2, respectively, and between 9 and 15 Ω and between 9 and 12 Ω in zone 2 in groups 1 and 2, respectively, depending on the PV. The relative reduction in impedance was greatest in zone 2, thus reducing the gradient between LA and PVO. This phenomenon is illustrated in Figure 4.

**Impedance guided ablation and PV stenosis**

Using the impedance data from these populations, a decision algorithm was developed to help determine catheter position relative to the PV–LA junction (Figure 1). As the mean difference in impedance between the LA and zone 2 was 9 Ω, we assumed that a rise in impedance above ZLA represented the midpoint of the PV–LA transitional zone. As long as the impedance was ZLA = 4 Ω, we could expect to be on the atrial aspect of the transitional zone, and this value was used as an upper limit for lesion deployment. Using this algorithm, an additional 20 patients underwent mapping prior to CPVA. After standard impedance mapping to calculate ZLA, a mean of 15 ± 4 location points was collected per patient. For each point, one inves-
tigator blinded to catheter position on CARTO and fluoroscopy estimated whether the ablation catheter was in the LA (safe for ablation) or in the PVO/deep PV (unsafe) at each point using an impedance limit of (mean LA impedance + 4). A second investigator who was blinded to impedance readings determined whether the catheter was in the LA, PVO, or PV at these same points based on the local electrograms and catheter position relative to the PVO as seen on fluoroscopy and CARTO geometry. Of 324 points sampled, impedance alone correctly identified 212 (91%) of 232 points determined as safe based on CARTO data and 84 (91%) of 92 regarded as unsafe (PVO). Positive and negative predictive values were 96% and 81%, respectively. If the catheter was being dragged during RF application and a rise relative to the previous locus was observed, this was an indication to stop RF, check catheter position, and move to an adjacent area of lower impedance. It was possible to successfully perform the ablation using the impedance cutoff criteria in all patients without any significant adjustment of the lesion sets (i.e., no visible deviations from normal on the postablation maps). No patient had evidence of PV stenosis on contrast-enhanced magnetic resonance angiography at 3 months. Using the difference between local and mean LA impedance and the position data from CARTO, the ROC was constructed. The area under the curve was 0.916 (95% confidence limits 0.875–0.958, P < .001).

**Discussion**

Impedance monitoring is used often in the electrophysiology laboratory. Sudden rises in impedance during RF application often indicate carbonization on the catheter tip, and a drop in local impedance usually is seen after successful lesion creation. During mapping, higher endocardial impedance is seen when the catheter is in contact with or inserted into venous structures such as the coronary sinus or other cardiac veins. The LA–PV anatomy is complex,14 posing problems for operators attempting to isolate the PVs, whether a segmental or an anatomic approach is used. At our center, we have routinely used impedance as a guide for catheter positioning for several years, and we believe that this is one potential explanation for the absence of clinical PV stenosis in our large series of patients.

**Impedance variation and tissue type**

We have shown that, during baseline mapping, impedance rises significantly as the ablation catheter enters the PVO (zone 2) and that, when located deep inside the electrically silent portion of the vein, impedance is much higher. Several studies have shown that there is a gradual transition in histology from the muscular atrium to the venous tissue.15–17 The PVO tissue is complex, having myocardial fibers traveling in multiple directions. Previous studies have shown that both fiber direction18 and fibrosis19 are associated with higher tissue resistivities. The observed difference in impedance between LA and PVO may reflect these transitional tissue characteristics. Other investigators have described fractionated electrograms around the PVO20,21 and have targeted these electrograms for ablation with considerable success in the treatment of AF. We do not specifically target these fractionated areas, but they can be a useful guide to the proximity to the PV–LA junction and are frequently present at sites designated for RF application.

Case reports of PV stenosis or occlusion occurring with the circumferential approach to AF ablation are rare. However, the Johns Hopkins group describes a case of hemoptysis following circumferential AF ablation that was shown to be due to the occlusion of a small sub-branch of a right inferior PV.22 It is possible that when high impedance
values are detected, the catheter tip is in contact with the ostium of a small branch; therefore, we recommend that ablation not be performed at points where impedance is higher than expected or permitted by the algorithm. However, in our experience, routine use of impedance does not prohibit the completion of a successful lesion set; it merely forces a slight “detour” around the area of higher impedance.

Impedance mapping vs voltage mapping in the LA

Using impedance values collected from catheter locations ($Z_{\text{RTIM}}$), we created offline impedance maps of the LA. Close monitoring of impedance readings can guide mapping and ablation, and a combination of voltage and impedance data can be used to select suitable sites for ablation, although we rely more on impedance, particularly in patients with extensive low-voltage regions in the LA and PVO (Figure 5), or disorganized electrical activity as seen in patients in AF.

Acute and chronic reduction in atrial impedance

Endocardial impedance falls during CPVA at sites remote from lesions. This most likely is due to the creation of interstitial edema in response to injury. Other studies have shown that osmotically induced increases in the extracellular volume, modeling tissue edema, cause a decrease in myocardial tissue impedance. Magnetic resonance imaging performed a few days after CPVA shows extensive edema throughout the posterior wall, PVO, and interatrial septum (Figure 6). Our data also support a possible chronic reduction in impedance following CPVA, as group 2 patients had lower LA and overall zone 2 impedance preablation and a lower LA–PVO impedance gradient. It could be that the observed difference was related to measurement at sites of previous ablation, although this is unlikely as zone 2 points were taken inside the ostia, some distance from the perimetric external circumferential lines. Previous studies on animal models of myocardial infarction have shown that infarcted tissue has lower impedance. This may be due to a relatively greater proportion of extracellular matrix and fewer myocytes. Others have shown that fibrosis affects tissue impedance because of loss of cell-to-cell communication. Repeat evaluation of patients in this study would be required to determine whether the observed acute reduction in impedance is maintained in the long term.

Impedance and PV stenosis

This article represents the formal description of LA endocardial impedance mapping for assisting AF ablation. In this
study, we were able to detect suitable sites for ablation with high sensitivity, specificity, and positive predictive value using impedance alone. When used in combination with a three-dimensional map, impedance can become a valuable surrogate marker for the presence of transitional or venous tissue at the catheter location. It may be that sites that appeared to be safe according to anatomy but had a higher than expected impedance may represent regions where small venous branches are arising\cite{14,22} (Figure 7) and therefore were misclassified as safe by CARTO. Our findings are in keeping with a previous article study on impedance in the atrial, ostial, and deep venous region that can be found in different veins. In contrast, there is little variation in impedance between the corresponding areas in different veins (panel 1). LA = left atrium; MV = mitral valve; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

Conclusion

This study formally describes the impedance characteristics of the LA–PV complex in patients undergoing AF ablation. Impedance monitoring can be used to reliably distinguish between LA and PVO, increasing our ability to safely ablate within the LA. Impedance may prove to be more reliable than three-dimensional mapping alone for detecting the presence of minor veins, which also are at high risk for stenosis should RF energy be inadvertently delivered at their ostium\cite{22,25}. Use of impedance mapping may help reduce the incidence of PV stenosis following CPVA. RF energy should be delivered in the peristomial region only when the impedance value is comparable to that of the LA ($\leq 4 \Omega$ above LA mean) to avoid ablation within the PV and the associated risk of PV stenosis. The ability to create online impedance maps would enhance our ability to identify the LA–PV junction and perform LA ablations.

References


Figure 7 Panel 1: CARTO offline impedance map. Panel 2: Three-dimensional reconstruction from magnetic resonance imaging (3D MRI) of the same patient in the posteroanterior (PA) view. The three zones based on impedance are highlighted with dark lines. The similarity between the 3D CARTO map and the 3D MRI reconstruction is notable. Panels 3, 4: Electrogram insets illustrate the variation in amplitude and morphology in local electrograms in the atrial, ostial, and deep venous region that can be found in different veins. In contrast, there is little variation in impedance between the corresponding areas in different veins (panel 1). LA = left atrium; MV = mitral valve; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.


