Left Atrial Voltage during Sinus Rhythm in Paroxysmal and Persistent Atrial Fibrillation Patients without Structural Heart Disease

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Background: The mechanisms underlying self-perpetuation of persistent atrial fibrillation (AF) are not well understood. To gain insight into these mechanisms, we compared biatrial electroanatomic maps, obtained during sinus rhythm, in patients with paroxysmal AF, patients with persistent AF, and patients without AF (control patients).

Methods: The study involved 12 patients with paroxysmal AF (9 men, 3 women; 62 ± 11 years of age), 6 patients (5 men, 1 woman; 62 ± 6 years of age) with persistent AF treated unsuccessfully by direct-current cardioversion, and 6 patients (1 man, 5 women; 53 ± 16 years of age) with a left-sided accessory pathway but no AF (control patients). Biatrial voltage mapping was performed during sinus rhythm using the CARTO system. The clinical and electroanatomic characteristics of the 3 groups of patients were evaluated and analyzed statistically.

Results: The proportions of normal and low voltage areas in the right and left atria were not different between the control and paroxysmal AF groups. The proportion of the right atrial (RA) low voltage (< 0.5 mV) area did not differ between the 3 groups; however, the RA and left atrial (LA) normal voltage (≥ 1.5 mV) areas were significantly smaller in the persistent AF group. The LA low voltage area was significantly larger in patients with persistent AF.

Conclusion: The relatively large RA normal voltage and LA low voltage areas that we observed in patients with persistent AF may play a crucial role in the self-perpetuation of AF.

Key words: atrial fibrillation, remodeling, right atrial voltage, left atrial voltage, electroanatomic mapping


Introduction

It is widely accepted that atrial fibrillation (AF) involves complex relationships between triggers and the atrial substrate. Indeed, this paradigm appears to be relevant to both paroxysmal and persistent AF. However, the atrial substrate in patients with AF, persistent AF in particular, is not well characterized. Prior studies in patients with structural heart disease have revealed extensive right atrial (RA) substrate changes known to predispose to AF. A recent mapping study revealed left atrial (LA) substrate abnormalities in patients with paroxysmal AF. We aimed to characterize the extent of LA electroanatomic remodeling in patients with persistent AF and compare these characteristics with those in age-matched paroxysmal AF patients and in age-matched patients without AF. We hypothesized that patients with persistent AF would show more extensive remodeling than that in patients with paroxysmal AF and that in patients without AF.

Patients and Methods

The study involved 14 patients undergoing radiofrequency ablation (RFA) for drug-refractory paroxysmal AF, 5 age-matched patients undergoing RFA for persistent drug-refractory AF, and 6 age-matched control patients with no prior history of AF but undergoing RFA for a left-sided accessory pathway. We excluded patients with structural heart disease and valvular heart disease to avoid its potential influence on atrial remodeling. No patient who had undergone a prior AF-ablation procedure was included in the study. In addition, no patient with left ventricular dysfunction (ejection fraction [EF] < 50%), coronary artery disease, severe obstructive apnea, or poorly controlled hypertension associated with significant echocardiographically determined left ventricular hypertrophy (myocardial wall thickness > 1.1 cm) was included. AF was defined as paroxysmal when episodes lasted < 7 days and self-terminated and as persistent when episodes lasted > 7 days. In the paroxysmal AF group, the most recent episodes of AF had not occurred within 48 hours prior to RFA. The

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Electrophysiologic study

All patients underwent anticoagulation for at least 1 month before the ablation procedure, with a target international normalized ratio (INR) of 2.0–3.0. Antiarrhythmic medications were stopped for at least half-lives before the procedure. All AF patients underwent transesophageal echocardiography 1 day before the procedure to rule out the possibility of LA thrombus. Electrophysiologic study and ablation were performed under conscious sedation with propofol and fentanyl. Surface electrocardiograms (ECGs) and endocardial electrograms were monitored and stored on a digital electrophysiology recording system (BARD LabSystem Pro, Murray Hill, NJ, USA). Intracardiac electrograms were filtered at 30–250 Hz and measured at a sweep speed of 100–200 mm/sec. The left atrium was accessed by transseptal puncture, and a heparin bolus was administered to achieve a target activated clotting time (ACT) of >300 seconds.

Electroanatomic mapping

Electroanatomic maps of the right and left atria were acquired during sinus rhythm with the use of a CARTO mapping system (Biosense Webster, Diamond Bar, CA, USA) and a 4-mm-tip catheter (Navistar, Biosense Webster) before delivery of RF energy. For those patients in AF, external direct-current cardioversion was performed 15 minutes before the mapping procedure for conversion to sinus rhythm. If AF recurred during the mapping procedure, cardioversion was again performed. If cardioversion did not restore the sinus rhythm for even a few beats, the patient was excluded from the study. Three patients with persistent AF who showed immediate recurrence of AF after cardioversion were excluded from the study. The electroanatomic mapping system has been described in detail, accuracy of the sensor position has been previously validated and is within 0.8 mm and 5°. In brief, the system records the surface ECG and bipolar electrograms filtered at 30–400 Hz from the mapping and reference catheters. Endocardial contact during point acquisition was confirmed by electrogram stability, fluoroscopy, and the catheter icon on the CARTO system. Points were acquired in the auto-freeze mode if the stability criteria (≤6 mm) and local activation time (≤5 ms) were met. Mapping was performed with an equal distribution of points by using a fill-threshold of 15 mm. More than 150 electroanatomic data points were acquired per patient in the right and left atria. Editing of points was done offline. Voltage was measured peak-to-peak from the bipolar signal. Points not conforming to the 12-lead ECG P wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded.

Voltage analysis

Consistent with previous studies involving atrial mapping performed with the CARTO system, <0.5 mV² was deemed to represent areas of abnormally low voltage²,³, and ≥1.5 mV⁹ was deemed to represent normal atrial myocardium. Areas of low voltage were confirmed with serial catheter manipulations. The proportions of low-voltages areas (points) were calculated by the CARTO software.

Statistical analyses

Continuous variables, including patients’ clinical characteristics, are shown as mean ± SD values, and categorical variables are shown as proportions. Between-group differences in continuous variables were analyzed by Mann-Whitney U test, and between-group differences in categorical variables were analyzed by Fischer’s exact probability test. All statistical analyses were performed with the use of StatView 5.0 software (SAS Institute, Cary, NC, USA), and P values of <0.05 were considered significant.

Results

Patients’ clinical characteristics

Patients’ clinical characteristics are summarized in Table 1. There was no significant difference in age or left ventricular ejection fraction measured from transthoracic echocardiography by Simpson’s method among the 3 groups. The percentage of male patients was significantly greater in the paroxysmal AF group than in the control group, and it was greater in the persistent AF group than in the control group, although this difference was not significant. Hypertension was significantly more prevalent in the persistent AF group than in the control group and more prevalent, but not significantly so, in the paroxysmal AF group than in the control group. The left atrium measured from transthoracic echocardiography by parasternal long axis view at end systole increased in size stepwise from the control group to the persistent AF group to the paroxysmal AF group.

Areas of low and normal voltage

The mean RA low voltage (<0.5 mV) area did not differ between the 3 groups (Table 2). The mean RA normal voltage (>1.5 mV) area was significantly smaller in the persistent AF group than in the other 2 groups (Table 2). There was no significant
difference in the RA normal voltage area between the paroxysmal AF group and the control group (Table 2). The mean proportion of LA low voltage areas was significantly greater in the persistent AF group than that in paroxysmal AF and control groups (Table 2). There was no significant difference in the proportion of LA low voltage areas between the paroxysmal AF and control groups (Table 2). The mean proportion of LA normal voltage areas was significantly smaller in the persistent AF group than in the paroxysmal AF and control groups (Table 2). There was no significant difference in the LA normal voltage area between paroxysmal AF and control patients (Table 2). Representative electroanatomic maps are shown in Fig. 1.

Table 1 Patient characteristics per study group

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n = 12)</th>
<th>Persistent AF (n = 6)</th>
<th>Control (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.1 ± 10.8</td>
<td>62.0 ± 5.6</td>
<td>53.3 ± 16.3</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>75.0 †</td>
<td>83.3</td>
<td>16.6</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>48.5 ± 40.6</td>
<td>34.0 ± 36.2</td>
<td>0</td>
</tr>
<tr>
<td>LA size (mm)</td>
<td>36.5 ± 5.4 ‡</td>
<td>48.3 ± 5.1 * ‡</td>
<td>31.6 ± 4.8</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>62.4 ± 5.4</td>
<td>63.2 ± 6.7</td>
<td>66.8 ± 6.8</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>41.7</td>
<td>66.7 †</td>
<td>0</td>
</tr>
</tbody>
</table>

†P = 0.035 vs. Control, ‡P = 0.001 vs. Paroxysmal AF, *P = 0.004 vs. Control, §P = 0.030 vs. Control

AF: atrial fibrillation, LA: left atrium, LV: left ventricle

Table 2 Right (RA) atrial and left atrial (LA) high and low voltage areas per study group

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n = 12)</th>
<th>Persistent AF (n = 6)</th>
<th>Control (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA voltage &lt; 0.5 mV (%)</td>
<td>5.3 ± 2.4</td>
<td>7.0 ± 5.5</td>
<td>3.2 ± 2.1</td>
</tr>
<tr>
<td>RA voltage &gt; 1.5 mV (%)</td>
<td>85.2 ± 7.2</td>
<td>61.0 ± 27.2†</td>
<td>86.5 ± 9.5</td>
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<tr>
<td>LA voltage &lt; 0.5 mV (%)</td>
<td>5.0 ± 2.2</td>
<td>15.3 ± 19.1 ‡ *</td>
<td>3.3 ± 1.6</td>
</tr>
<tr>
<td>LA voltage &gt; 1.5 mV (%)</td>
<td>85.3 ± 6.7</td>
<td>56.2 ± 21.8 †</td>
<td>85.5 ± 11.5</td>
</tr>
</tbody>
</table>

†P = 0.039 vs. Paroxysmal AF, ‡P = 0.028 vs. Paroxysmal AF, *P = 0.002 vs. Paroxysmal AF, §P = 0.013 vs. Control, †P = 0.016 vs. Control

AF: atrial fibrillation

Fig. 1 Representative CARTO maps, one obtained from a patient with persistent atrial fibrillation (left panel) and one from a patient with paroxysmal atrial fibrillation (right panel). The left atrium is shown in the posterior-anterior projection. The color scale is identical in both images, with red representing voltage < 0.1 mV and purple representing voltage > 1.5 mV. Note that patient with persistent atrial fibrillation has a larger low voltage area.
Discussion

The main study findings can be summarized as follows: Compared to control patients, paroxysmal AF patients exhibited LA dilatation, but global mean RA and LA low voltage and normal voltage areas did not differ from those of control patients. In comparing global mean RA and LA voltages and LA diameter between patients with paroxysmal and patients with persistent AF who were otherwise comparable in terms of clinical characteristics, we found that persistent AF patients had a significantly smaller RA normal voltage area, larger LA low voltage area, smaller LA normal voltage area, and significant LA dilatation.

Previously reported studies

Previous studies of atrial voltage in patients with paroxysmal AF vs. reference patients without AF revealed substantially low voltage in both atria (right atrium: $1.7 \pm 0.7$ mV vs. $2.9 \pm 0.4$ mV, respectively; left atrium: $1.7 \pm 0.7$ mV vs. $3.3 \pm 0.7$ mV, respectively) in the patients with paroxysmal AF. Patients with persistent AF, in comparison to patients with paroxysmal AF, showed significantly lower LA voltage during AF, and patients with AF, in comparison to control patients, had lower LA regional voltage during atrial pacing. This change was shown to be more pronounced in the persistent AF patients. However, no previous studies compared RA and LA voltage during sinus rhythm between patients with paroxysmal AF, patients with persistent AF, and patients without AF. In our study, the low RA voltage areas did not differ between our 3 patient groups, but the RA normal voltage area was significantly smaller in the persistent AF group than in the paroxysmal AF and control groups. Furthermore, the low voltage area was considerably larger in the left atrium than in the right atrium in the persistent AF group (15.3% vs. 7.0%). Chang et al. reported that the LA voltage was lower than the RA voltage and that persistent AF patients, in comparison to paroxysmal AF patients, had lower atrial voltage and more extensive scarring.

Study limitations

Our study data must be interpreted cautiously in light of the study limitations. The study groups, particularly the persistent AF group and the control group, were small, and the statistical differences should be interpreted accordingly. In addition, the patients with persistent AF underwent direct-current cardioversion 15 minutes before the electroanatomic mapping; thus, it is possible that delivery of the electrical current affected the electrophysiologic properties of the atria. Further, other electrophysiologic variables such as intra-atrial conduction time and effective refractory period were not assessed in our study. The development of clinical AF is complex and depends not only on the substrate but also on such factors as triggers and perpetuators that were not addressed in the study.

Conclusion

We found in our comparative study that the RA and LA normal and low voltage areas did not differ between patients with paroxysmal AF and control patients. The RA and LA normal voltage areas were smaller in patients with persistent AF than in those with paroxysmal AF, and the LA low voltage area was larger than the RA low voltage area in patients with persistent AF. These substrate abnormalities, beyond the pulmonary veins, may be implicated in the mechanisms underlying AF maintenance and may be clinically important for successful catheter ablation.

References


