Novel Assessment of Temporal Variation in Fractionated Electrograms Using Histogram Analysis of Local Fractionation Interval in Patients With Persistent Atrial Fibrillation

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Background—The characteristics of atrial electrograms associated with atrial fibrillation (AF) termination are controversial. We investigated the electrogram characteristics that indicate procedural AF termination during continuous complex fractionated electrogram ablation.

Methods and Results—Fifty-two consecutive patients with persistent AF (47 men; aged 54±9 years), who underwent electrogram-based catheter ablation in the left atrium and coronary sinus after pulmonary vein isolation, were enrolled. The intracardiac bipolar atrial electrogram recordings were characterized by (1) fractionation interval (FI) analysis (>6 seconds), (2) kurtosis (shape of the FI histogram), and (3) skewness (asymmetry of the FI histogram). Sites showing complex, fractionated electrograms (mean FI ≤60 ms) were targeted, and AF was terminated in 20 patients (38%) after the pulmonary vein isolation. The conventional complex fractionated electrogram sites (mean FI ≤120 ms) in patients with AF termination exhibited higher median kurtosis (2.69 [interquartile range, 2.03–3.46] versus 2.35 [interquartile range, 1.79–2.48]; P=0.024) and higher complex fractionated electrogram-mean interval (102.7±19.8 versus 87.7±15.0; P=0.008) than patients without AF termination. Furthermore, AF termination sites had higher median kurtosis than targeted sites without AF termination (5.13 [interquartile range, 3.51–6.47] versus 4.18 [interquartile range, 2.91–5.34]; P<0.01) in patients with procedural termination. In addition, patients with AF termination had a higher sinus rhythm maintenance rate after a single procedure than patients without AF termination (log-rank test, P=0.007).

Conclusions—A kurtosis analysis using the FI histogram may be a useful tool in identifying the critical substrate for persistent AF and potential responders to catheter ablation. (Circ Arrhythm Electrophysiol. 2012;5:949-956.)

Key Words: atrial fibrillation • catheter ablation • electrophysiology mapping • histogram • left atrium

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia encountered in clinical practice. Pulmonary vein isolation (PVI) is the mainstream catheter ablation technique for AF. For longer durations of AF, substrate modification with complex fractionated electrogram (CFE) ablation is necessary for patients who do not respond to PVI. The development of automated analysis algorithms for electrogram fractionation is important for a reproducible and objective assessment of this technique. However, most algorithms are based on the mean fractionation interval (FI) between the deflection of time-domain electrograms, such as the CFE-mean of the NavX system or shortest complex interval of the CARTO system. The variation in the FIs acquired by these modalities may be important for the algorithms of CFEs. Therefore, if the local FIs are not normally distributed, the mean FI has limited clinical applicability because of the

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temporal variation. We hypothesized that, in addition to the conventional FI algorithm, the temporal variation in the annotated FIs may provide important information for determining the features of critical CFEs. The purpose of this study was to evaluate a novel signal analysis concept based on the histogram of the FI values acquired by the CFE-mean algorithm, including the kurtosis (ie, shape of the FI distribution) and skewness (ie, asymmetry of the FI distribution).7

Methods

Patient Characteristics

Fifty-two consecutive patients with persistent AF who underwent radiofrequency ablation guided by a 3-dimensional anatomic mapping system (NavX, St. Jude Medical, St. Paul, MN) were studied retrospectively. Persistent AF (including long-standing persistent AF) was defined according to the consensus statement on catheter and surgical ablation of AF.5 At the beginning of the procedure, all patients presented with incessant AF. Patients with paroxysmal AF or persistent AF terminated by PVI were excluded.

Electrophysiological Study

After informed consent was obtained, each patient underwent an electrophysiological study and catheter ablation in a fasting state. All antiarrhythmic drugs except amiodarone were discontinued at least 5 half-lives before the procedure. The 3-dimensional electroanatomic mapping method was performed as described previously.5 Mapping was performed with an irrigated, 3.5-mm-tip, deflectable catheter (EPT, Boston Scientific Corporation, Natick, MA) inserted into the left atrium (LA) alongside the transeptal sheath without the need for an additional puncture site. The 3-dimensional geometry of the LA was then generated using the NavX system.

Catheter Ablation

The catheter ablation of AF involved the following steps.

Step 1: PVI

After a successful transseptal procedure, continuous circumferential lesions encircling the right and left pulmonary vein (PV) ostia guided by the NavX system were created using a 3.5-mm irrigated-tip ablation catheter (EPT, Boston Scientific Corporation), as described previously.9 Radiofrequency energy was applied continuously while repositioning the catheter tip every 40 seconds, with a target temperature of 35°C to 40°C and maximum power of 25 to 30 W in the power control mode. After the circumferential lesion set was completed, the ipsilateral superior and inferior PVs were mapped carefully by recording with a circular catheter (Spiral, AF Division, St. Jude Medical). Supplementary ablation applications were applied along the circumferential lines close to the earliest ipsilateral PV potentials.

Step 2: Continuous CFE Site Ablation

If AF did not stop after PVI, an additional CFE-guided substrate ablation was performed on the basis of the CFE maps after PVI. Because a prospective randomized study demonstrated that the empirical right atrial (RA) CFE ablation does not improve long-term AF-free survival,10 the CFE ablation was confined to the continuous CFEs (mean FI ≤60 ms) in the LA and proximal coronary sinus (CS).11,12 The RA CFEs were not targeted. The end points of the CFE site ablation were to obtain prolonged cycle length, eliminate the CFEs (mean FI >120 ms), or abolish the local fractionated potentials (bipolar voltage <0.05 mV). The end point of step 2 was the elimination of all continuous CFEs in the LA and CS. If AF terminated during the linear ablation through the CFE sites, a complete linear ablation to the mitral annulus was represented by the mean or whether they should be represented by the median and mode (Figure 1B). The higher the skewness, the larger the differences between the mean FIs and their medians and modes. In addition, positive or negative skewness means that the distribution, which indicates whether the FIs can be sufficiently represented by the mean or whether they should be represented by the median and mode (Figure 1A). Kurtosis indicates the relationship between each of the FIs to the mean; the higher the kurtosis, the less probability that FIs deviate from the mean. Meanwhile, skewness assesses the degree of asymmetry of the distribution, which indicates whether the FIs can be sufficiently represented by the mean or whether they should be represented by the median and mode (Figure 1B). The higher the skewness, the larger the differences between the mean FIs and their medians and modes.

Step 3: Non-PV Ectopies

After SR was restored from AF either by procedural AF termination or by electric cardioversion, mapping and ablation were only applied to spontaneously initiating focal atrial tachycardias and non-PV ectopies that initiated AF.13 First, we placed multiple catheters in the LA (ablation and spiral catheters), superior vena cava-RA (duodecapolar catheter), and CS to identify the location of the AF-initiating ectopy. Second, we used a mapping catheter to identify the earliest activation site of the ectopy. If any non-PV ectopy initiating AF from the superior vena cava was identified, the superior vena cava was isolated, guided by the circular catheter recordings from the superior vena cava-RA junction.

In this study, if the AF became organized during steps 1 or 2, electroanatomic mapping and ablation were performed to terminate the organized tachycardia. The AF termination was defined as AF restored to SR during the ablation in steps 1 or 2 without cardioversion. All patients underwent an RA cavotricuspid isthmus ablation with an 8-mm-tip ablation catheter. No AF inducibility tests using any β-agonists or pacing maneuvers were performed after the ablation procedure.

Signal Recording and Analysis

After acquiring the LA geometry, a 3.5-mm-tip catheter was selected as the roving catheter for sequential contact mapping, as described previously.9,14,15 Regarding the protocol for signal sampling in the LA and CS, we divided the LA into 10 parts, as follows: the high and low anteroseptal wall, high and low posterior wall, medial and lateral mitral isthmus, anterior and posterior roof, and right and left PV-atrial junction.14 At least 10 sites were determined in each region. The numbers of sites in each region were similar and nearly equally distributed. To avoid high-density mapping in the procedural termination sites, the distance of any paired adjacent mapping sites ≤5 mm was detected by the off-line software based on the 3-dimensional location.9 Therefore, we selected the nearest site to analyze the characteristics of the procedural termination sites.

Regarding fractionation mapping, the NavX mapping parameters were set to the CFE mean, which is an interval analysis algorithm that measures the average index of the fractionation at each site and produces a color map representative of the CFE distribution. The settings used have been described previously:5 a refractory period of 30 ms, peak-to-peak sensitivity from 0.05 to 0.1 mV, and duration of 10 ms. A CFE was defined as mean FI ≤120 ms, whereas non-CFEs were defined as FI >120 ms. Sites of continuous CFEs were the most fractionated sites with a local mean FI of ≤60 ms and recording duration of >6 seconds. The color annotation was set to a range of colors, with an FI of ≤60 ms shown in white to an FI of >120 ms shown in purple. The white areas in the NavX map represent the regions with continuous CFEs. Sites with shorter mean FIs indicated a high degree of spatial stability of the fractionated electrograms. The consistency of the fractionated electrograms over time was previously validated.15

The electrograms assessed for each patient were acquired and characterized by the FI analysis. Furthermore, the statistical properties of the FI, including the kurtosis and skewness of FI distribution during a 6-second window, were assessed. Briefly, kurtosis measures the shape of the distribution of the fractionated intervals within the window beyond simply using means and SD (Figure 1A). Kurtosis indicates the relationship between each of the FIs to the mean; the higher the kurtosis, the less probability that FIs deviate from the mean. Meanwhile, skewness assesses the degree of asymmetry of the distribution, which indicates whether the FIs can be sufficiently represented by the mean or whether they should be represented by the median and mode (Figure 1B). The higher the skewness, the larger the differences between the mean FIs and their medians and modes. In addition, positive or negative skewness means that the mode and median of the FIs are lower or higher than the mean of the FIs, respectively. These features of bipolar electrogram recordings in patients with and without procedural AF termination were analyzed and compared. In patients with AF termination, we selected the
**Results**

**Patient Characteristics and Catheter Ablation**

The clinical characteristics of the study population are shown in Table 1. Patients without AF termination had higher incidences of long-standing persistent AF and hypertension than those with AF termination ($P<0.01$). Patients without AF termination had a larger LA diameter and lower left ventricular ejection fraction on 2-dimensional echocardiography than patients with AF termination.

In the initial ablation step, PVI was performed successfully, and electric isolation was confirmed in all patients. However, PVI did not terminate the AF in all patients. In the next step, CFE ablation terminated the AF in 20 patients (38%); in the other 32 patients (62%), SR was restored by electric cardioversion. In the patients with AF termination, 6 patients (30% of the patients with AF termination) were restored to SR by CFE ablation around the CS. The residual PV potentials and non-PV triggers were subsequently eliminated in all patients. All patients successfully underwent a cavotricuspid isthmus ablation.

**Signal Characteristics at the Patient Level**

Table 2 shows the signal characteristics of all CFEs of the patients with and without AF termination at the patient level. There were no significant differences in the median FI or skewness between patients with and without AF termination ($P>0.05$). Patients with AF termination had higher median kurtosis (2.69 [2.03–3.46] versus 2.35 [1.79–2.48]; $P=0.024$) and longer mean FI (102.7±19.8 versus 87.7±15.0; $P=0.008$) than in the patients without AF termination.

**Signal Characteristics at Individual CFE Sites**

Table 3 summarizes the signal characteristics of the targeted continuous CFE sites (FI ≤60 ms) in patients with and without AF termination. According to the Shapiro-Wilk test, both patients with and without AF procedural termination had low incidences of normal distributions of FI histograms, not only in the conventional CFE sites (≤120 ms; 10±8% versus 14±14% per patient, respectively; $P=0.45$) but also in

<table>
<thead>
<tr>
<th>Variables</th>
<th>AF Termination (-) (n=32)</th>
<th>AF Termination (+) (n=20)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±7</td>
<td>55±11</td>
<td>0.70</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>30 (94)</td>
<td>17 (85)</td>
<td>0.28</td>
</tr>
<tr>
<td>Long-standing AF, n (%)</td>
<td>26 (81)</td>
<td>3 (15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Associated condition, n (%)</td>
<td>23 (72)</td>
<td>4 (20)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8 (25)</td>
<td>2 (10)</td>
<td>0.17</td>
</tr>
<tr>
<td>Echocardiographic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>46±6</td>
<td>41±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>52±12</td>
<td>59±7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
Table 2. Differences in the Signal Characteristics Between Patients With and Without AF Termination (Sites With Complex Fractionated Electrogram <120 ms)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patient Without AF Termination (n=32)</th>
<th>Patient With AF Termination (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean FI</td>
<td>87.7±15.0</td>
<td>102.7±19.8</td>
<td>0.008</td>
</tr>
<tr>
<td>Median FI (25%–75%), ms</td>
<td>72.7 (59.2–81.7)</td>
<td>82.5 (84.9–118.6)</td>
<td>0.053</td>
</tr>
<tr>
<td>Kurtosis (median, 25%–75%)</td>
<td>2.35 (1.79–2.48)</td>
<td>2.69 (2.03–3.46)</td>
<td>0.024</td>
</tr>
<tr>
<td>Skewness (median, 25%–75%)</td>
<td>1.50 (1.35–1.57)</td>
<td>1.52 (1.45–1.73)</td>
<td>0.306</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; FI fractionation interval.

Table 3. Summary of the Signal Characteristics in the Complex Fractionated Electrogram-Targeted Ablation Sites (<60 ms)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sites in Patients Without AF Termination (n=559)</th>
<th>Targeted Sites Without Immediate Termination (n=178)</th>
<th>Targeted Sites With Immediate Termination (n=20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fl (median, 25%–75%), ms</td>
<td>55.4 (50.3–59.8)</td>
<td>49.5 (46.5–59.1)</td>
<td>53.2 (44.2–58.1)</td>
<td>0.27</td>
</tr>
<tr>
<td>Kurtosis (median, 25%–75%)</td>
<td>3.72 (2.95–4.55)</td>
<td>4.18 (2.91–5.34)*</td>
<td>5.13 (3.51–6.47)*†</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Skewness (median, 25%–75%)</td>
<td>1.24 (0.94–1.54)</td>
<td>1.23 (0.81–1.58)</td>
<td>1.65 (1.09–2.06)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; Fl fractionation interval.

AF indicates atrial fibrillation; Fl fractionation interval.

*P<0.01 when compared with sites without termination in patients with non–AF-termination.
†P<0.01 when compared with sites without immediate termination patients with in termination.

Discussion

Main Findings

To the best of our knowledge, this is the first report addressing the novel concept of histogram analysis for substrate mapping in patients with persistent AF. The results of this study demonstrate that histogram analysis from annotated FI data provides information about temporal variations of the annotated FI in the fractionation analysis. The lower temporal variability of the continuous CFEs (FI <60 ms), evidenced by the high kurtosis associated with AF termination, indicates the reliability of the mean FI. Furthermore, the response to the continuous CFE ablation was higher. However, in sites with low kurtosis, conventional methods using the mean FI may be inappropriate for identifying critical sites with a low procedural AF termination rate. This study demonstrates the adjunctive role of histogram analysis in the conventional mean interval–based algorithm for prediction termination.

Predicting AF Termination During Catheter Ablation

Because PVI alone is ineffective for treating patients with persistent AF, it is necessary to perform additional substrate modification after complete PVI. Because several investigators report a correlation between procedural AF termination and better clinical outcomes in patients with AF, most laboratories define procedural AF termination as an end point in patients with persistent AF. However, achieving procedural AF
termination, especially in patients with persistent AF, may require more extensive procedures, including CFE modification and linear ablation.\textsuperscript{20–23} Although the results of the present study also revealed high SR maintenance rates in patients with AF termination, AF termination was achieved in only 38% of this population even though we targeted the continuous CFE sites after the complete isolation of all 4 PVs. A recent study by Elayi et al\textsuperscript{20} found that procedural AF termination may not be a good indicator of long-term outcomes. However, in that study, the incidence of AF termination directly to SR was low (2%). Despite converting to atrial tachycardia in 56% of their study population, most patients still required electric cardioversion after further extensive ablation. These results indicate that the current algorithm based on the CFE mean is not optimal. Thus, it could be difficult to differentiate the responsible CFEs from the unimportant ones.

Implications of the Novel Histogram Analysis Method

A recent clinical study (the CFAE AF trial [Characterization of Fractionated Atrial Electrograms Critical for Maintenance of Atrial Fibrillation: A Randomized, Controlled Trial of Ablation Strategies]) demonstrates that ablating certain grades of CFE increases AF cycle length, irrespective of the order of CFE ablation; this indicates that different grades of CFEs play different roles.\textsuperscript{24} The different roles of CFEs were also revealed by monophasic action potentials recordings, demonstrating the characteristics of the responsible sites,
which differ from nonlocal and far-field signals. At present, most automatic algorithms are based on the mean interval during AF. The present study is the first to use histogram analysis to evaluate the shape of the FI distribution within a 6-second window. For individual mapping sites, higher kurtosis indicates a lower probability that FIs deviate from the mean. Furthermore, because skewness assesses the degree of asymmetry of a distribution, it indicates whether FIs can be sufficiently represented by the mean or median or mode. The temporal variability of FIs can be used as an adjunctive tool for identifying the critical atrial substrate. At the patient level, the characteristics of continuous CFEs in patients with AF termination were different from those without AF termination. In patients with AF termination, high kurtosis in the maximal CFEs corresponded to the reliability of the mean FI values of these regions (Figure 2C and 2D). On the contrary, low kurtosis in the continuous CFEs indicated larger variations in the FIs, less accuracy of the mean FI values for detecting the CFEs, and a lower response to catheter ablation. These variations in the FIs and non-normally distributed data sets in the histogram analysis may limit the application of the cycle length–based automatic algorithms of CFEs for defining target sites. Low kurtosis of the CFE sites indicated the complexity of the fibrillation signals, as well as the difficulty in isolating the signals for precise analysis. Furthermore, the results of the present study demonstrate that the combination of kurtosis with the conventional CFE-mean can improve the predictive accuracy of procedural AF termination compared with the use of the CFE-mean value alone. Thus, in patients with persistent AF undergoing catheter ablation, histogram analysis may provide additional information regarding the reliability of the automatic algorithm of the FIs and predict the response to catheter ablation.

Study Limitations

The present study is limited because it was a single-center retrospective study with a relatively small number of patients. In addition, the priority of CFE ablation was not based on kurtosis. A further prospective study is warranted to confirm the role of these regions. The morphology of the discrete electrograms during AF may provide some useful information for AF ablation. However, we only investigated the variation in the intervals and not the electrogram morphology, which requires further study. We did not analyze the FI histograms before PVI. Therefore, our findings could be affected by the elimination of a critical area for AF maintenance along the PVI line, as reported previously. Finally, the atrial debulking effect may exist when targeting the next CFE site; this is the universal limitation faced when investigating the characteristics of CFE sites.
Conclusions
In persistent AF patients with AF termination, continuous CFEs (mean FI ≤60 ms) are characterized by a high stationarity status compared with patients without AF termination. A kurtosis analysis using the FI histogram may be a useful tool in identifying the critical substrate for persistent AF and potential responders to catheter ablation. Continuous CFEs with higher temporal stability between intervals are shown to be an important characteristic of ablation sites that cause procedural AF termination in patients with persistent AF. In patients without AF termination, low kurtosis in the continuous CFEs indicated larger variations in the FIs and less accuracy of the mean FI values for detecting the CFEs.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

Because pulmonary vein isolation may not be sufficient in patients with persistent atrial fibrillation (AF), substrate modification with a complex fractionated electrogram (CFE) ablation is considered to be necessary in patients who do not respond to pulmonary vein isolation. However, the rate of successful procedural AF termination by a CFE-targeted ablation in different laboratories is discrepant. We investigated the electrogram characteristics that indicated procedural AF termination during a continuous CFE (fractionation interval [FI] ≤60 ms) ablation by a novel histogram analysis of the local FI, including the kurtosis (ie, shape of the FI distribution) and skewness (ie, asymmetry of the FI distribution). We found that a histogram analysis from the annotated FI data provided additional information on the temporal variations in the annotated FI derived from the fractionation analysis. In patients with procedural AF termination, high kurtoses in the maximal CFEs corresponded to the reliability of the mean FI values. On the contrary, patients without procedural AF termination had a low incidence of a normal distribution of the FI histograms that corresponded to a larger variation in the FIs. These variations in the FIs and non-normally distributed data sets in the histogram analysis may limit the application of the cycle length–based automatic algorithms of CFEs for defining target sites. This study demonstrated the adjunctive role of a histogram analysis in the conventional interval-based algorithm to identify potential responders to AF ablation.
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