Characterization of Fractionated Atrial Electrograms Critical for Maintenance of Atrial Fibrillation

A Randomized, Controlled Trial of Ablation Strategies (The CFAE AF Trial)

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**Background**—Whether ablation of complex fractionated atrial electrograms (CFAE) modifies atrial fibrillation (AF) by eliminating drivers or atrial debulking remains unknown. This randomized study aimed to determine the effect of ablating different CFAE morphologies compared with normal electrograms (ie, debulking normal tissue) on the cycle length of persistent AF (AFCL).

**Methods and Results**—After pulmonary vein isolation left and right atrial CFAE were targeted, until termination of AF or abolition of CFAE before DC cardioversion. Ten-second electrograms were classified according to a validated scale, with grade 1 being most fractionated and grade 5 normal. Patients were randomly assigned to have CFAE grades eliminated sequentially, from grade 1 to 5 (group 1) or grade 5 to 1 (group 2). An increase in AFCL (mean of left and right atrial appendage) \( > 5 \text{ ms} \) after a lesion was regarded as significant. CFAE (n=968) were targeted in 20 patients. AFCL increased after targeting 51% of grade 1 CFAE, 30% grade 2, 12% grade 3, 33% grade 4, and 8% grade 5 CFAE (\( P < 0.01 \) for grades 1, 2, and 4 versus 5; 3 versus 5, not significant). The proportion of lesions causing AFCL prolongation was unaffected by the order in which CFAE were targeted.

**Conclusions**—Targeting CFAE is not simply atrial debulking. Ablating certain grades of CFAE increases AFCL, suggesting they are more important in maintaining AF.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00894400.

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**Key Words:** atrial fibrillation ■ catheter ablation ■ fractionated electrogram ■ CFAE

Although Nademanee demonstrated that complex fractionated atrial electrogram (CFAE) ablation could eliminate atrial fibrillation (AF), there has been difficulty reproducing this success using CFAE ablation alone.\(^2\) Incremental benefit of CFAE ablation in addition to pulmonary vein isolation (PVI) has been demonstrated,\(^4\) although not consistently.\(^9\)\(^,\)\(^10\)

The variable definition of CFAE may partly explain these disparate results.\(^1\)\(^,\)\(^2\)\(^,\)\(^11\)\(^,\)\(^12\) It is uncertain what the various CFAE morphologies represent, and few studies have examined the importance of different electrogram characteristics of CFAE.\(^13\)\(^,\)\(^14\) It therefore remains unclear whether CFAE are sites critical to the maintenance of AF or whether the slowing or termination of persistent AF is the inadvertent result of debulking electrically active atrial tissue.

We hypothesized that certain CFAE morphologies are more likely to represent drivers of AF. To prove this, we sought to determine the impact of targeting different CFAE morphologies on AF cycle length (AFCL) in persistent AF through a randomized, controlled trial.

**Methods**

**Study Population and Random Assignment Procedure**

The study population comprised 20 patients who underwent catheter ablation of persistent AF at a single institution. Random assignment involved a random-number generator, with sealed envelopes opened on the day of the procedure. Although patients and physicians performing clinical follow-up were blinded, the nature of the study did not allow blinding of the operator. All patients gave written informed consent. The study was approved by East London and The City Research Ethics Committee and was prospectively registered on NIH clinicaltrials.gov (NCT00894400).

**Study Protocol**

Patients underwent transesophageal echocardiography before the procedure and were anticoagulated as described previously.\(^6\) Anti-arrhythmic drugs were not stopped before the procedure. Under local
anesthetic (Lidocaine) and conscious sedation (midazolam and diamorphine), a decapolar catheter (Viking, Bard EP, Lowell, MA) was inserted into the coronary sinus and a hexapolar catheter (Supreme, St Jude Medical, St Paul, MN) placed in the right atrial appendage. After double transseptal puncture, a 14-pole deflectable pulmonary vein mapping catheter (Orbiter PV, Bard EP, MA) and a 3.5-mm irrigated ablation catheter (Thermo-Cool Celsius, Biosense Webster, Diamond Bar, CA) were introduced to the left atrium. All electrograms targeted for CFAE ablation were recorded using the 3.5-mm ablation catheter with a 2–5–2 mm electrode configuration. Unclipped bipolar electrograms were examined on a computer-based digital amplifier/recording system (Labsystem pro, Bard EP, MA). Recordings were filtered at 30–250 Hz and displayed at 100 mm/s.

Mapping

Right and left atrial geometries were created using a 3D mapping system (Ensite NavX, St Jude, CA). The pulmonary vein mapping catheter (0.75—5–0.75 configuration) was used to record 10-second electrograms at evenly spaced points that were graded according to our previously validated classification.\(^{15}\) Electrograms were assigned a number on a scale from 1 to 6, with 1 being most fractionated and 5 being a normal electrogram (scar being nominally designated grade 6) and a letter “a” or “b” for high or low amplitude, respectively (the definition of each grade and the suffix for amplitude are shown in Table 1, with examples of each shown in Figure 1).\(^{15}\) Initially, grade 5 had been divided into normal electrograms that were rapid (cycle length \(\leq 120\) ms) or slow (cycle length \(>120\) ms), as a cycle length of 70 to 120 ms has generally been included as criteria for identifying CFAE.\(^1\) However, this distinction was found to be redundant and was abandoned because when the cycle length was \(<120\) ms, the deflections would often fall within 70 ms of the last and hence were classified as continuous fractionation (grade 1, 2, or 3, depending on the proportion of the sample fractionated).\(^{15}\)

Electrograms were located using 22- and 16-segment models of the left and right atria (Figure 2). For each map, at least 1 set of electrograms

<table>
<thead>
<tr>
<th>Grade</th>
<th>Electrogram Criteria</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Uninterrupted fractionated activity</td>
</tr>
<tr>
<td></td>
<td>Fractionated activity (defined as continuous deflections without pause at the isoelectric line for (\geq 70) ms) occupying (\geq 70)% of sample, and at least 1 uninterrupted episode of fractionated activity lasting (\geq 1) second</td>
</tr>
<tr>
<td>2</td>
<td>Interrupted fractionated activity</td>
</tr>
<tr>
<td></td>
<td>Fractionated activity occupying (\geq 70)% of sample</td>
</tr>
<tr>
<td>3</td>
<td>Intermittent fractionated activity</td>
</tr>
<tr>
<td></td>
<td>Fractionated activity occupying 30–70% of sample</td>
</tr>
<tr>
<td>4</td>
<td>Complex electrograms</td>
</tr>
<tr>
<td></td>
<td>Discrete electrograms (&lt;70 ms) and complex ((\geq 5) direction changes), with any fractionated activity occupying &lt;30% of sample (otherwise grade 3)</td>
</tr>
<tr>
<td>5</td>
<td>Normal electrogram</td>
</tr>
<tr>
<td></td>
<td>Discrete electrograms (&lt;70 ms) and simple ((\leq 4) direction changes)</td>
</tr>
<tr>
<td>6</td>
<td>Scar</td>
</tr>
<tr>
<td></td>
<td>No discernible deflections</td>
</tr>
</tbody>
</table>

In addition to the numerical grade, a suffix was added to reflect signal amplitude, with “a” denoting a peak to peak deflection of \(\geq 0.5\) mV in greater than half of all 500-ms intervals during the recording and “b” denoting signals not meeting this criterion.

Figure 1. Classification of complex fractionated atrial electrograms (CFAE). Examples of electrograms are from the classification of CFAE (as shown in Table 1).
was recorded using the pulmonary vein mapping catheter for each segment, and the most fractionated grade was recorded.

After PVI, a further left atrial CFAE map was acquired and used to guide subsequent CFAE ablation. The pre-PVI map of the right atrium was used to guide ablation because no ablation had yet been performed there. During CFAE ablation, electrogram grade was rechecked in each segment before ablation there. The effect of PVI on left atrial CFAE distribution was determined by comparing pre- and post-PVI maps. The stability during CFAE ablation was assessed by comparing the maps used to guide ablation with the grade found in each segment during CFAE ablation.

Ablation
PVI was by wide-area circumferential ablation (WACA), with electric isolation confirmed using the pulmonary vein mapping catheter. Irrigation of ablation catheters and power settings have been described previously.6

Targeting of CFAE
Patients were randomly assigned to targeting of CFAE starting with the most fractionated grade first (ie, grades 1–5) in group 1 or starting with the least fractionated first (ie, grades 5–1) in group 2. Because grade 5 electrograms were considered normal and served as control lesions, only 5 were ablated per patient. These were placed in locations that could later be incorporated into linear lesions. Once all left atrial CFAE were abolished and 5 grade 5 electrograms were targeted, the process was repeated in the right atrium. Targeting of CFAE continued until atrial tachycardia or sinus rhythm ensued or all atrial CFAE were abolished. Radiofrequency energy was delivered until electrogram amplitude was reduced by ≥80% or 60 seconds of energy was delivered.

If AF persisted after abolition of CFAE, linear lesions were added at the mitral isthmus and the roof. A cavotricuspid isthmus line was added only in patients with a history of typical right atrial flutter. If at any point AF organized into atrial tachycardia, this was mapped and ablated. If sinus rhythm was not restored after these lesions, the patient was cardioverted with a DC shock. PVI was then reconfirmed, and, if necessary, veins were reisolated.

AFCL is thought to reflect the number of drivers supporting AF.16 It lengthens progressively during ablation until termination of AF, with prolongation reflecting clinical outcome.17 AFCL has been used by others to quantify response to ablation, and an increase of ≥5 to 6 ms has been regarded as significant.13,14,18 Mean AFCL was determined manually over 30 cycles from bipolar electrograms recorded at the apex of the left and right atrial appendages (where electrograms are high amplitude and AFCL is unambiguous) before and after each CFAE lesion.

We analyzed baseline AFCL variability and considered a change greater than or equal to mean±2 SD as significant. The cycle length of fractionated electrograms (grades 1–3) was ambiguous and was therefore not quantified. The cycle length of complex electrograms (grade 4) was measured manually over the 10 second sample, with segments of continuous fractionation discarded (<30% of sample as per definition of grade 4).

The randomized strategy was used (1) to control for any cumulative effect of ablation on AFCL; (2) to examine whether elimination of highly fractionated electrograms first reduces the number of less fractionated electrograms remaining; and (3) to assess whether the order in which CFAE were targeted affects the amount of ablation required to abolish CFAE/terminate AF.
Interoperator Variability

All CFAE targeted were classified in real time by visual inspection. Electrograms were later graded off-line with the benefit of on-screen calipers by a second operator blinded to the earlier grade, and the 2 grades were compared. AFCL was also remeasured by a second operator blinded to the earlier grade, and the 2 grades were compared.

Statistics

Continuous variables are reported as mean±SD or median (range) if not normally distributed. Continuous data were compared by Student t test if normally distributed or Wilcoxon 2-sample test if not normally distributed. Categorical data were compared by $\chi^2$ test.

Because this study was completely novel, there were no pilot data available for sample size estimation. After 20 patients, interim analysis was conducted to clarify sample size but showed that the primary end point had been met.

To assess the primary end point, which was a comparison of the response to ablation of each CFAE grade, the mean percentages of lesions causing AFCL prolongation for each grade were compared, using repeated-measures ANOVA. To assess the impact of the order of ablation, group was included as an independent variable (repeated-measures MANOVA).

The number of CFAE per patient did not permit inclusion of further dependent variables in addition to CFAE grade in the repeated-measures MANOVA design. Therefore, response to ablation was assessed across all lesions using binary logistic regression, including grade, order of ablation, amplitude (categorized as high or low), and location (in the left or right atrium) as covariates. However, it is recognized that this approach did not account for the variable responses to ablation between patients.

The effect of the order of ablation on the mean number of lesions per patient for each grade was compared using repeated-measures MANOVA. Although comparison of the number of lesions between grades from MANOVA was not thought meaningful, comparison within each grade between groups was done using the Student t test. Agreement between observers for determination of CFAE grade was tested with the Cohen $\kappa$ coefficient.

Results

Patients and Procedures

The characteristics of the 20 patients randomly assigned are shown in Table 2. All patients had persistent AF, and 90% of these were long-lasting persistent AF (ie, ≥1 year). Although the patients were older in group 2, the other baseline characteristics were well matched between groups. Procedural characteristics are shown in Table 3. There was no difference between groups in procedure time or fluoroscopy time (Table 3). The only procedural complication was 1 groin hematoma, which did not require intervention.
Similarly, during right atrial CFAE ablation, there was an increase in grade from $3.6 \pm 1.3$ to $3.9 \pm 1.4$ ($P=0.002$).

**Impact of Targeting Different CFAE Grades on AFCL**

There was a significant overall effect of CFAE grade on the mean proportion of lesions causing AFCL prolongation ($P<0.001$; Figure 3A). The mean proportion of lesions that caused a significant increase in AFCL was significantly greater for grades 1, 2, and 4 CFAE compared with grade 5 ($P<0.01$ for each). There was no difference between grades 3 and 5 in the proportion of lesions affecting AFCL, with prolongation occurring no more often than during baseline variability testing (ie, during no ablation). There was no effect of the order of ablation on the proportion of lesions causing AFCL prolongation ($P=0.371$) and no interaction between grade and the order of ablation ($P=0.449$; Figure 3B).

Analysis of the proportion of lesions causing AFCL prolongation pooled across all CFAE showed a similar pattern of response to ablation across grades (Figure 4A and 4B). Binary logistic regression confirmed the effect of grade on the proportion of lesions causing AFCL prolongation ($P<0.001$) but showed no effect of group ($P=0.320$), amplitude ($P=0.717$; Figure 4A), or location in the left or right atrium ($P=0.987$; Figure 4B).

The CL of grade 4 CFAE was greater than the appendage CL of the atria in which it was located in $77\%$ of cases, and this did not affect the proportion of lesions causing AFCL prolongation ($31\%$ when CL was shorter and $34\%$ when CL was longer than the appendage CL, $P=0.683$).

**Location of CFAE Targeted**

No CFAE were targeted inside the PVs (because they were electrically silent after WACA) or the vena cavae. Otherwise, pooling CFAE lesions from all patients, the proportion of lesions per region (divided as shown in Figure 2) was normally distributed, with $3.0 \pm 2.2\%$ of lesions per region. The most targeted regions in the left atrium were the border of the left

![Figure 3](https://example.com/figure3.png)

**Figure 3.** Mean percentage of lesions causing atrial fibrillation cycle length (AFCL) prolongation are shown by grade (A) for all patients and (B) divided for groups 1 and 2. Bars show 95% confidence intervals.

![Figure 4](https://example.com/figure4.png)

**Figure 4.** Proportion of complex fractionated atrial electrograms (CFAE) lesions causing atrial fibrillation cycle length (AFCL) prolongation. Shown are percentages of all lesions causing AFCL prolongation by grade, divided according to amplitude (either high, “a,” or low, “b”): A and location in the left or right atrium (B).
atrial appendage (7.3% of all lesions), the mid anterior wall (7.2%), the roof (7.1%), the lateral wall bordering the left atrial appendage (6.9%), the ridge between the left atrial appendage and the left pulmonary veins (6.0%), and the mid septum (5.9%). The most targeted regions in the right atrium were the high and mid lateral wall (5.7% and 3.3% of all lesions, respectively), the high septum (5.1%), the roof bordering the superior vena cava (3.6%), and the right atrial appendage (2.6%). The proportion of lesions that prolonged AFCL was also normally distributed between regions (30±11% of lesions). The number of lesions per region was insufficient to allow meaningful comparison of these small regional differences.

Impact of Order of Ablation on the Number of CFAE Encountered

There was a significant overall effect of the order of ablation on the mean number of CFAE targeted per patient for each grade (P<0.01; Figure 5). Fewer grade 3 and 4 CFAE were encountered per patient in group 1 than in group 2 (both P<0.05; Figure 5) suggesting that elimination of the most fractionated electrograms (grade 1 and 2) changed the degree of fractionation of electrograms at other sites. This translated to a lower total number of lesions per patient in group 1 (P<0.01; Figure 5). There was no difference between groups in the number of grade 1 or 2 CFAE ablated or the number of grade 5 lesions created.

Impact of Order of CFAE Ablation on Outcome

Three patients were ablated to sinus rhythm in each group (2 via atrial tachycardia in each group). In group 1, this occurred once during PVI, once during CFAE ablation, and once during linear lesions. In group 2, this occurred once during PVI and twice during CFAE ablation. The number free from AF after a single procedure at 12 months off antiarrhythmic drugs and the proportion of recurrence due to AF/atrial tachycardia did not differ between groups (Table 3).

Discussion

This study is the first to prospectively compare the effect of targeting different CFAE morphologies in persistent AF. The grading of CFAE using our classification system was easily applied, accurate, and reproducible and enabled distinction between CFAE subtypes that produce a differential effect on AFCL when ablated. Importantly, targeting normal electrograms had no significant effect. PVI had an organizing effect on electrograms in all locations. Ablation of highly fractionated electrograms first resulted in a reduction in the number of grades 3 and 4 CFAE encountered subsequently, and, consequently, a reduction in the total number of lesions delivered.

Mapping studies have shown that targeting areas with concentric activation or slow conduction prolong AFCL, although these mechanisms may be difficult to infer from an ablation catheter electrogram. Takahashi et al analyzed electrogram characteristics associated with AFCL prolongation during CFAE ablation. Although dominant frequency and electrogram amplitude had no effect, fractionated activity for ≥70% of the recording was associated with AFCL prolongation. Our study has confirmed this first, by prospectively targeting CFAE with this characteristic, and second, by varying the order of CFAE ablation to ensure this effect was not a result of targeting this characteristic first or last.

Lin et al demonstrated improved outcomes after PVI with selective targeting of CFAE that were “consistent,” defined using an automated algorithm over a 1-minute recording. Sites with uninterrupted fractionated activity ≥1 second have been proposed as targets for ablation, based on the observation that they are more prevalent and more diffuse in patients with persistent AF than paroxysmal AF. The current study has demonstrated the incremental importance of these sites over those with interrupted fractionation.

Fractionated activity may represent areas within a few millimeters of focal drivers, whether they are rotors or rapidly discharging foci. Ibutilide has been shown to limit reentry in an animal model of AF, using high-density mapping, but did not affect focal sources. Similarly, procainamide has been shown to organize electrograms with either multiple deflections or limited fractionation in an animal model of AF but had little effect on more fractionated signals. These authors concluded that continuous fractionated activity (perhaps analogous to grades 1 and 2 in the present study) may represent focal mechanisms, whereas less fractionated signals (more like grades 3 and 4) are more likely to represent reentry.

The results of the present study would be compatible with grades 1 and 2 CFAE representing such focal drivers. The increased efficacy when ablating areas with uninterrupted fractionated activity (grade 1 CFAE) may suggest greater proximity to these foci, or perhaps that the drivers are more stable spatially and temporally. We did not incorporate a grade for rapid regular electrograms because these were invariably interspersed with fractionated activity and hence met the criteria for grades 1 and 2. Therefore, more consistent CFAE (grade 1) may have had different organizational characteristics that were not visually discernable.

An interesting finding was that an apparently less fractionated electrogram (grade 4) had a greater effect than a more fractionated electrogram (grade 3). We postulate that grade 3 electrograms are produced by passive wave front phenomena or superimposition of far-field and local electrograms, which are not critical for maintenance of AF. Grade 4 electrograms were not rapid, and in particular were not usually faster than the AFCL of the atria in which they were located. Therefore, although grade 4 CFAE are unlikely to be rapid drivers, they...
may represent other phenomena that facilitate AF, such as zones of slow conduction, pivot points, or wave-break.24,25

The optimal amplitude of CFAE to target is controversial. Although some authors consider only low-amplitude signals (<0.5 mV) to be CFAE,1 others disregard amplitude.11 Our data suggest that electrogram amplitude does not predict response to ablation.

Ablation of right atrial CFAE is also controversial. Although a small trial showed that right atrial CFAE ablation in addition to PVI and left atrial CFAE did not improve outcome,26 another study demonstrated that in those with continuing AF, right atrial CFAE ablation prolonged AFCL and terminated AF in 55%.27 The present study suggests that targeting CFAE in the right atrium was equally efficacious as in the left.

The lesions that caused AFCL prolongation were evenly distributed. A previous study that targeted CFAE in a randomized order of locations found no effect of ablation location on AFCL.13 However, it remains possible that CFAE are surrogate markers for gangionated plexi because their anatomy is variable.

Impact of PVI and CFAE Ablation on Electrogram Organization

The reduction in left atrial CFAE burden after PVI has been demonstrated by others.28,29 This may simply reflect the removal of pulmonary vein drivers, although this would not fully account for (1) the impact at sites distant to the pulmonary vein ostia and (2) the impact on areas with continuous fractionation suggestive of focal drivers.

Injection of epicardial fat pads with acetylcholine has been shown to cause continuous fractionation or rapid regular “rotor-like” electrograms, both locally and at distant atrial sites, due to a wider activation of the cardiac neural network.30 Targeting of gangionated plexi eliminated these areas of continuous fractionation, both locally and at distant sites.22,30 Hence, PVI may impact on atrial CFAE by reducing gangionated plexi innervation.

Significantly fewer CFAE were targeted in group 1, powered by the reduction in grades 3 and 4 CFAE. To some extent, these grades may be epiphenomena, with a greater functional component supported by the highly fractionated grades 1 and 2 CFAE. The number of grades 1 and 2 CFAE were unaffected by prior ablation of grades 3 and 4, consistent with their proposed focal mechanisms.

Limitations

This mechanistic study was not designed to assess the impact of CFAE ablation on outcomes, nor was it intended or powered to demonstrate superiority of either targeting strategy in terms of clinical end points. Nevertheless, by studying the response to ablation of different CFAE morphologies, we have clarified many key issues in CFAE ablation. Although this information could not have been gleaned from conventional, randomized, controlled trials looking at clinical outcomes, we recognize that such studies remain essential for determining the optimal approach to CFAE ablation.

Although ablation to sinus rhythm is a hard end point, this was achieved in a minority, and it is recognized that the alternative of elimination of all CFAE is more subjective. However, this cohort consisted mostly of patients with dilated atria and long-lasting persistent AF; hence, although the proportion ablated to sinus rhythm and the proportion free of AF at 1 year were disappointing, this was in keeping with reports for comparable cohorts.9,31,32

Conclusion

The differential effect of targeting different CFAE morphologies provides strong support for the hypothesis that certain CFAE represent focal drivers of AF. Therefore, targeting of CFAE is not simply debulking the atria. These results support ablating certain CFAE morphologies whether in the left or right atria, regardless of their amplitude. A selective strategy targeting only certain CFAE (grades 1, 2, and 4) and starting with the most fractionated (grades 1 and 2) should minimize left atrial destruction and time spent targeting CFAE.

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Disclosures

Prof Schilling is a member of the scientific advisory board for Biosense Webster and Endocardial Solutions.

References

The significance of complex fractionated atrial electrograms (CFAE) recorded during atrial fibrillation (AF) is controversial. It is unclear whether ablation of CFAE areas eliminates drivers or simply debulks atrial tissue. We hypothesized that certain CFAE morphologies are more likely to represent areas critical for the maintenance of AF. In this study, the effect of CFAE site ablation on AF cycle length was assessed in 20 patients. CFAE morphologies were graded from 1 (most fractionated) to 5 (normal). The sequence of CFAE ablation was randomized to either from grade 1 to 5, or from grade 5 to 1. Ablation at sites with CFAE grades 1, 2, and 4 produced cycle length prolongation more often than at grade 5 sites. The proportion of lesions causing AF cycle length prolongation was unaffected by CFAE amplitude, location, or grade. Ablation at sites with CFAE grades 1, 2, and 4 produced cycle length prolongation more often than at grade 5 sites. The proportion of lesions causing AF cycle length prolongation was unaffected by CFAE amplitude, location, or grade.

**CLINICAL PERSPECTIVE**

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**Factors further studied to warrant if selective CFAE ablation can improve efficacy and efficiency of AF ablation.**
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