Characterization of Fractionated Atrial Electrograms Critical for Maintenance of AF:

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

Running title: Hunter et al.; The CFAE AF trial.

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Abstract:

**Background** - Whether ablation of complex fractionated atrial electrograms (CFAE) modifies AF by eliminating drivers or atrial de-bulking remains unknown. This randomised study aimed to determine the effect of ablating different CFAE morphologies compared to normal electrograms (i.e. de-bulking 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 prior to DC cardioversion. 10s electrograms were classified according to a validated scale, with Grade 1 being most fractionated and grade 5 normal. Patients were randomised 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) $\geq 5$ ms following a lesion was regarded as significant. 968 CFAE were targeted in 20 patients. AFCL increased after targeting 51 ± 35% of grade 1 CFAE, 30 ± 15% grade 2, 12 ± 5% grade 3, 33 ± 12% grade 4, and 8 ± 15% 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.

**Conclusion** - Targeting CFAE is not simply atrial de-bulking. Ablating certain grades of CFAE increases AFCL, suggesting they are more important in maintaining AF.

**Clinical Trial Registration Information** - www.clinicaltrials.gov NCT00894400.

**Key words:** Atrial fibrillation, catheter ablation, fractionated electrogram, CFAE.
Introduction

Although Nademanee demonstrated that CFAE ablation could eliminate AF, there has been difficulty reproducing this success using CFAE ablation alone. Incremental benefit of CFAE ablation in addition to pulmonary vein isolation (PVI) has been demonstrated, although not consistently.

The variable definition of CFAE may partly explain these disparate results. It is uncertain what the various CFAE morphologies represent, and few studies have examined the importance of different electrogram characteristics of CFAE. 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 de-bulking electrically active atrial tissue.

We hypothesised 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 randomised controlled trial.

Methods

Study population and randomisation procedure

The study population was comprised of 20 patients who underwent catheter ablation of persistent AF at a single institution. Randomisation 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 trans-oesophageal echocardiography pre-procedure and were
anticoagulated as described previously. Antiarrhythmic drugs were not stopped pre-
procedure. Under local anaesthetic (lidocaine) and conscious sedation (midazolam and
diamorphine) a decapolar catheter (Viking, Bard EP, MA, USA) was inserted into the
coronary sinus and a hexapolar catheter (Supreme, St. Jude Medical, MN, USA) placed in the
right atrial appendage. After double trans-septal puncture a 14 pole deflectable pulmonary
vein mapping catheter (Orbiter PV, Bard EP, MA, USA) and a 3.5 mm irrigated ablation
catheter (Thermo-Cool Celsius, Biosense Webster, CA, USA) 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, USA). Recordings were filtered at 30 to 250 Hz and displayed at 100 mm/Second.

Mapping
Right and left atrial geometries were created using a 3D mapping system (Ensite NavX, St
Jude, CA, USA). The pulmonary vein mapping catheter (0.75 - 5 - 0.75 configuration) was
used to record 10 second electrograms at evenly spaced points which were graded according
to our previously validated classification. Electrograms were assigned a number on a scale
from 1-6, 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). Initially grade 5 had been divided into normal electrograms which were rapid (cycle length $\leq 120$ ms) or slow (cycle length $> 120$ ms), as a cycle length of 70-120ms has generally been included as criteria for identifying CFAE. However, this distinction was found to be redundant and abandoned, since when the cycle length was $< 120$ ms the deflections would often fall within 70ms of the last, and hence were classified as continuous fractionation (grade 1, 2 or 3 depending on the proportion of the sample fractionated).

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 was recorded using the pulmonary vein mapping catheter for each segment, and the most fractionated grade 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, since no ablation had yet been performed there. During CFAE ablation, electrogram grade was re-checked in each segment prior to 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 electrical isolation confirmed using the pulmonary vein mapping catheter. Irrigation of ablation catheters and power settings have been described previously.
Targeting of CFAE

Patients were randomised to targeting of CFAE starting with the most fractionated grade first (i.e. grades 1 to 5) in group 1, or starting with the least fractionated first (i.e. grades 5 to 1) in group 2. Since 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 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 60s of energy 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 organised into atrial tachycardia this was mapped and ablated. If sinus rhythm was not restored following these lesions the patient was cardioverted with a DC shock. PVI was then re-confirmed, and if necessary veins were re-isolated.

AFCL is thought to reflect the number of drivers supporting AF.\textsuperscript{16} It lengthens progressively during ablation until termination of AF, with prolongation reflecting clinical outcome.\textsuperscript{17} AFCL has been used by others to quantify response to ablation, and an increase of ≥ 5-6 ms has been regarded as significant.\textsuperscript{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 analysed baseline AFCL variability and considered a change $\geq$ mean + 2 standard deviations 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 randomised strategy was employed:

(i) To control for any cumulative effect of ablation on AFCL.

(ii) To examine whether elimination of highly fractionated electrograms first reduces the number of less fractionated electrograms remaining.

(iii) To assess whether the order in which CFAE were targeted affects the amount of ablation required to abolish CFAE/terminate AF.

Inter-operator variability

All CFAE targeted were classified in real time by visual inspection. Electrograms were later graded off-line with the benefit of on-screen callipers by a second operator blinded to the earlier grade, and the two grades compared. AFCL was also re-measured by a second operator before 5 lesions chosen at random in each patient to allow assessment of inter-operator variability.

Statistics

Continuous variables are reported as mean ± standard deviation, or median (range) if not normally distributed. Continuous data were compared by Student’s t-test if normally
distributed or Wilcoxon two-sample test if not normally distributed. Categorical data were compared by chi-squared test.

Since this study was completely novel there was 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 percentage of lesions causing AFCL prolongation for each grade were compared using repeated measures analysis of variance. 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 (categorised as high or low) and location (in the left or right atrium) as covariates. However, it is recognised that this approach did not account for the variable response 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 using Student’s t test.
Agreement between observers for determination of CFAE grade was tested with Cohen’s Kappa coefficient (κ).

Results

Patients and procedures

The characteristics of the 20 patients randomised are shown in Table 2. All patients had persistent AF, and 90% of these were long lasting persistent AF (i.e. ≥ 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 haematoma, which did not require any intervention.

Inter-operator variability

The CFAE grade determined by rapid visual inspection for the 968 electrograms targeted agreed with that at off-line manual measurement in 92.7%. The grade was in agreement within ± 1 grade in 99.0%. There was agreement in assessment of amplitude (i.e. ‘a’ or ‘b’) in 99.1%. There was agreement for both number and letter in 91.9% (κ = 0.91). Inter-operator variability for measurement of AFCL was 0.3 ± 0.2 ms.

Definition of AFCL prolongation

Baseline AFCL variability prior to any ablation over 10 successive cycles from each patient showed variation of 1.49 ± 1.74 ms. As mean ± 2 standard deviations was 4.97 ms, ≥ 5.0 ms was subsequently regarded as significant AFCL prolongation.
Distribution of CFAE

Mean CFAE grade pre-PVI was lower in the left atrium than the right atrium (2.4 ± 1.1 versus 3.7 ± 1.2, p < 0.001) reflecting decreased organisation in the left atrium. The most common sites for highly fractionated electrograms (grade 1-2 CFAE) in the left atrium were the pulmonary veins (55-75%), the LA appendage ridge (75%), the high and low left septum (80% and 70%), and the high and mid anterior wall (75% and 65%). The most common sites for highly fractionated electrograms in the RA were the mid and low right septum (both 38%), the roof/SVC (38%), and the high, mid and low lateral wall (31-38%).

Impact of PVI

All 40 PV pairs were successfully isolated by WACA, and 36 of 40 PV pairs contained at least 1 highly fractionated electrogram (grade 1-2 CFAE). AFCL prolongation occurred after isolation of 23 PV pairs. As 2 patients reverted to sinus rhythm during PVI and 1 during left atrial CFAE ablation, 18 patients had full maps of the left atrium pre-PVI, post-PVI, and during CFAE ablation, and 17 patients had maps of the right atrium pre-PVI and during CFAE ablation. Because all 4 pulmonary veins were electrically silent post-PVI, in effect 18 left atrial and 16 right atrial segments were available for comparison with baseline maps (324 left atrial segments and 272 right atrial segments in total for each stage). PVI caused an increase in the mean grade of left atrial segments (representing increased organisation of electrograms) from 2.4 ± 1.1 to 3.2 ± 1.4 (p < 0.0001). During left atrial CFAE ablation there was a further increase in mean grade from 3.2 ± 1.4 to 3.6 ± 1.5 (p < 0.0001). Similarly, during right atrial CFAE ablation there was an increase in grade from 3.6 ± 1.3 to 3.9 ± 1.4 (p = 0.002).
Impact of targeting different CFAE grades on AF cycle length

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 which caused a significant increase in AFCL was significantly greater for grade 1, 2 and 4 CFAE compared to grade 5 (p < 0.01 for each). There was no difference between grade 3 and 5 in the proportion of lesions affecting AFCL, with prolongation occurring no more often than during baseline variability testing (i.e. 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 (Figures 4A & B). 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 > 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 (since they were electrically silent post 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 ± 2.2% of lesions per region. The most targeted regions in the left atrium were the border of the left 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 SVC (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 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 (two via an 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 anti-arrhythmic drugs, and the proportion of recurrence due to AF/AT 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 which produce a differential effect on AFCL when ablated. Importantly, targeting normal electrograms had no significant effect. PVI had an organising effect on electrograms in all locations. Ablation of highly fractionated electrograms first resulted in a reduction in the number of grade 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.\(^{13, 18}\) Takahashi et al. analysed electrogram characteristics associated with AFCL prolongation during CFAE ablation.\(^ {13}\) Although dominant frequency and electrogram amplitude had no effect, fractionated activity for \(\geq 70\%\) of the recording was associated with AFCL prolongation. Our study has confirmed this firstly by prospectively targeting CFAE with this characteristic, and secondly 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 which were ‘consistent’, defined using an automated algorithm over a 1 minute recording.\(^ {8}\) Sites with uninterrupted fractionated activity \(\geq 1\) 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 millimetres of focal drivers, whether they are rotors or rapidly discharging foci. Ibutilide has been shown to limit re-entry in an animal model of AF using high density mapping, but did not affect focal sources. Similarly, procainamide has been shown to organise 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 re-entry.

The results of the present study would be compatible with grade 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 since 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 organisational characteristics which were not discernable by eye.

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, whilst grade 4 CFAE are unlikely to be rapid drivers, they may represent other phenomena which facilitate AF, such as zones of slow conduction, pivot points, or wave-break.\textsuperscript{24, 25}

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

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

The lesions which caused AFCL prolongation were evenly distributed. A previous study which targeted CFAE in a randomised order of locations found no effect of ablation location on AFCL.\textsuperscript{13} However, it remains possible that CFAE are surrogate markers for ganglionated plexi, since their anatomy is variable.

**The impact of PVI and CFAE ablation on electrogram organisation**

The reduction in left atrial CFAE burden after PVI has been demonstrated by others.\textsuperscript{28, 29} This may simply reflect the removal of pulmonary vein drivers, although this would not fully account for (a) the impact at sites distant to the pulmonary vein ostia, and (b) 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. Targeting of ganglionated plexi in eliminated these areas of continuous fractionation, both locally and at distant sites. Hence, PVI may impact on atrial CFAE by reducing ganglionated plexi innervation.

Significantly fewer CFAE were targeted in group 1, powered by the reduction in grade 3 and 4 CFAE. To some extent these grades may be epi-phenomena, with a greater functional component supported by the highly fractionated grade 1 and 2 CFAE. The number of grade 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 randomised controlled trials looking at clinical outcomes, we recognise 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 recognised 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, and
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 de-bulking the atria. These results support ablating certain CFAE morphologies whether in the left or right atria, and 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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Conflict of Interest Disclosures: Professor Schilling is a member of the scientific advisory board for Biosense Webster and Endocardial Solutions.

References:


### Table 1: Classification of CFAE

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.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Electrogram criteria</th>
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<tbody>
<tr>
<td>1</td>
<td><strong>Uninterrupted fractionated activity</strong></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, <em>and</em> at least 1 uninterrupted episode of fractionated activity lasting $\geq 1$s.</td>
</tr>
<tr>
<td>2</td>
<td><strong>Interrupted fractionated activity</strong></td>
</tr>
<tr>
<td></td>
<td>Fractionated activity occupying $\geq 70%$ of sample.</td>
</tr>
<tr>
<td>3</td>
<td><strong>Intermittent fractionated activity</strong></td>
</tr>
<tr>
<td></td>
<td>Fractionated activity occupying 30-70% of sample.</td>
</tr>
<tr>
<td>4</td>
<td><strong>Complex electrograms</strong></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><strong>Normal electrogram</strong></td>
</tr>
<tr>
<td></td>
<td>Discrete electrograms ($&lt;70$ms) and simple ($\leq 4$ direction changes).</td>
</tr>
<tr>
<td>6</td>
<td><strong>Scar</strong></td>
</tr>
<tr>
<td></td>
<td>No discernible deflections.</td>
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Table 2: Patient Characteristics. Data is presented as percentage of patients, or mean ± standard deviation.

<table>
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<tr>
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<th>Group 1 (grade order 1 to 5)</th>
<th>Group 2 (grade order 5 to 1)</th>
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<tr>
<td>Number</td>
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<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>90%</td>
<td>80%</td>
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<tr>
<td>Age</td>
<td>60 ± 7</td>
<td>66 ± 6</td>
<td>0.042</td>
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<tr>
<td>Months of continuous AF</td>
<td>25 ± 19</td>
<td>20 ± 9</td>
<td>0.424</td>
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<td>NYHA class</td>
<td>2.1 ± 0.6</td>
<td>2.3 ± 0.5</td>
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<td>Hypertension</td>
<td>50%</td>
<td>50%</td>
<td>1.000</td>
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<tr>
<td>Ischaemic heart disease</td>
<td>20%</td>
<td>40%</td>
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<tr>
<td>Left atrial diameter</td>
<td>4.5 ± 0.8</td>
<td>4.6 ± 0.8</td>
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<tr>
<td>Ejection fraction</td>
<td>51 ± 13</td>
<td>46 ± 15</td>
<td>0.379</td>
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</table>

Table 3: Procedural characteristics and success. Data is presented as percentage of patients, mean ± standard deviation, or median (range).

<table>
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<tr>
<th></th>
<th>Group 1 (grade order 1 to 5)</th>
<th>Group 2 (grade order 5 to 1)</th>
<th>p value</th>
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<tr>
<td>Procedure time (mins)</td>
<td>300</td>
<td>305 (300-450)</td>
<td>0.327</td>
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<tr>
<td>Time targeting CFAE (mins)</td>
<td>90 (0-143)</td>
<td>96 (0-148)</td>
<td>0.500</td>
</tr>
<tr>
<td>Fluoroscopy time (mins)</td>
<td>63 (35-114)</td>
<td>57.5 (28-78)</td>
<td>0.456</td>
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<tr>
<td>CFAE lesions per patient</td>
<td>43 ± 16</td>
<td>68 ± 18</td>
<td>0.007</td>
</tr>
<tr>
<td>Termination of AF by ablation</td>
<td>30%</td>
<td>30%</td>
<td>1.000</td>
</tr>
<tr>
<td>Single procedure success</td>
<td>40%</td>
<td>20%</td>
<td>0.629</td>
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<tr>
<td>Recurrence due to AT/AF</td>
<td>4/2</td>
<td>3/5</td>
<td>0.592</td>
</tr>
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Figure Legends:

**Figure 1:** Classification of CFAE. Examples of electrograms from the classification of CFAE as shown in Table 1.

**Figure 2:** Anatomical division of the left and right atrium. (A) Anterior and posterior views of the left atrium, showing the 22 segment model. (B) Right anterior oblique and left lateral views of the right atrium showing the 16 segment model.

**Figure 3:** Mean proportion CFAE lesions causing AF cycle length prolongation. The mean percentage of lesions causing AFCL prolongation (A) by grade for all patients; and (B) divided for groups 1 and 2. Bars show 95% confidence intervals.

**Figure 4:** Proportion of CFAE lesions causing AF cycle length prolongation. The percentage of all lesions causing AFCL prolongation by grade, divided according to (A) amplitude (either high ‘a’ or low ‘b’), and (B) location in the left or right atrium.

**Figure 5:** Impact of order of ablation on the number of CFAE subtypes. The mean percentage of lesions causing AFCL prolongation (A) by grade for all patients; and (B) divided for groups 1 and 2. Bars show 95% confidence intervals.
A. Left atrium 22 segment model

- RUPV
- LUPV
- RIPV
- LIPV
- Roof
- Posterior wall
- Anterior wall
- Inferior wall
- LAA
- Lateral wall
- Mitral Valve
- Septum
- Coronary sinus

Segments:
- High
- Mid
- Low
- Distal
- Mid
- Proximal
B. Right atrium 16 segment model

Right anterior oblique view

Left lateral view
A. Overall impact of CFAE grade.

![Graph showing the mean proportion of lesions causing CL prolongation across different grades]

- *p < 0.01 compared to grade 5
B. Impact of order of CFAE ablation.

Effect of group p = 0.371
A. Impact of CFAE amplitude.

Effect of amplitude 
\( p = 0.717 \)
B. Impact of CFAE location.

Effect of location

\[ p = 0.987 \]
* p < 0.05 for group 1 versus 2
Characterization of Fractionated Atrial Electrograms Critical for Maintenance of AF: A Randomized Controlled Trial of Ablation Strategies (The CFAE AF Trial)
Ross J. Hunter, Ihab Diab, Muzahir Tayebjee, Laura Richmond, Simon Sporton, Mark J. Earley and Richard J. Schilling

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