Aims

The purpose of our study was to determine the acute effects of complex fractionated electrograms (CFAE) ablation guided by automated detection on dominant frequency (DF) and regulatory index (RI) for the fibrillatory process.

Methods and results

The study included 41 patients (21 paroxysmal and 20 persistent) referred for catheter ablation of atrial fibrillation (AF). Our ablation strategy included pulmonary vein isolation (PVI) as first step, CFAE ablation as second step, roof line ablation as next, and mitral isthmus ablation as last step. On the CFAE map, we were targeting only points outside the previous PVI lines. Simultaneously, we evaluated DF and RI changes in the coronary sinus after each step of ablation. The termination rate by CFAE ablation was low (12.5% in paroxysmal and 10% in persistent AF). Changes in DF and RI after CFAE ablation were not significant (<0.25 Hz and max. 0.02 increase for RI) compared with other ablation steps. Pulmonary vein isolation, roof line, and mitral isthmus ablation resulted in significant changes in DF and RI.

Conclusion

On the basis of our results, CFAE ablation guided by a dedicated software algorithm and performed after standard PVI without CFAE remapping does not influence the fibrillatory process significantly. Application of a modified algorithm with different settings warrants further investigations.

Keywords

Fibrillation • Electrogram • Dominant frequency • Atrium • Ablation

Introduction

Pulmonary vein isolation (PVI) is a well-established ablation strategy with remarkable long-term success rates in paroxysmal atrial fibrillation (AF). Patients with persistent AF and a subset of patients with paroxysmal AF require further ablation which modifies the substrate and increases the success rates. A relatively new method for substrate modification is targeting the areas of complex fractionated electrograms (CFAEs) which can be used alone or as an adjunctive strategy. The acute and long-term results with CFAE ablations are inconsistent until now.

There are several proposed mechanisms in which CFAEs contribute to the maintenance of AF: focal re-entry or anisotropic conduction, pivotal points of re-entrant waves, wave fractionation at boundaries of high frequency rotors, and autonomic mechanisms related to ganglionic plexi.

A limitation of CFAE ablation is subjective visual assessment of local electrograms to determine CFAE points during AF leading to both high intra- and inter-observer variability in the interpretation of electrograms and low reproducibility of the results. To overcome this obstacle, new automated mapping algorithms have been introduced to supplement 3D mapping systems and provide a basis for the quantitative analysis of electrograms.

The purpose of our study was to determine the acute effects of CFAE ablation on dominant frequency (DF) and regulatory index (RI) for the fibrillatory process. Moreover, we compared this effect with the impact on DF and RI made by additional ablation steps during ongoing AF.

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Methods

Study population
In this prospective single-centre study, 41 consecutive patients with symptomatic paroxysmal (n = 21) or persistent (n = 20) AF were referred for catheter ablation. All patients had AF which was refractory to at least one antiarrhythmic drug. Paroxysmal and persistent AF were defined according to the classification proposed in the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.17

Patients referred for a second procedure were excluded. The baseline characteristics of the study population are presented in Table 1. The mean duration of AF in a group of patients with persistent AF was 6.7 months (in a range from 1 week up to 11.8 months). There was no patient with longstanding persistent AF included in the study. All patients provided written informed consent for the study protocol.

Electrophysiological study
All antiarrhythmic drugs except amiodarone were discontinued at least five half-life periods before the study. In patients receiving amiodarone, the drug was withdrawn at least 1 month prior to the procedure. A 10-pole catheter (Lasso, Biosense Webster, Diamond Bar, CA, USA) was sequentially positioned in each PV. An irrigated 3.5 mm tip ablation catheter (Thermocool Navistar™, Biosense Webster) was used for mapping and ablation.

If the patient was not already in AF at the start of 3D mapping, AF was induced by rapid atrial pacing using a maximum current output (20 mA) at the shortest 1:1 atrial capture rate for up to 10 s.

We performed induction from the mid-coronary sinus (CS) and the left atrial appendage (LAA) for three times at each site. Atrial fibrillation was considered inducible if it persisted for ≥ 1 min. A 3D reconstruction of the LA was performed by an electroanatomical mapping system (CARTO™, Biosense Webster). The electroanatomical map was merged with the CT anatomy (CARTO Merge™, Biosense Webster).

Signal processing and frequency domain analysis
For offline measurements of DF and RI, we used a dedicated software implemented in the electrophysiological recording system (Dual Lab, Bard Electrophysiology). Analysis was performed on bipolar electrograms recorded from the proximal CS bipoles which showed minimal ventricular far-field potentials (<10% of atrial signal amplitude). We also performed measurements on distal CS and found statistically non-significant differences between results derived from proximal and distal CS with only one exception: in the group with persistent AF after mitral isthmus ablation, the RI was significantly higher and DF significantly lower than it was measured on proximal bipoles of the CS. Nevertheless, this finding had no influence on basic trends and the main conclusion. The recording time was 32 s for each step of measurement. After signal preprocessing, a fast Fourier transform (FFT) was performed with a spectral resolution of 4096 (0.24 Hz) over a sliding 4 s window. All recordings and FFTs were visualized to prevent defining a harmonics as DF in the cases of fractionated, split, or double potentials.18

The largest peak in the resulting magnitude spectrum was defined as DF. The RI is defined as a ratio between the computed area below the DF (and its harmonics) and the total power, and it was calculated as a mean value. Only mean values >0.20 were used.19 For measuring the DF of PVs, we used electrograms recorded from each Lasso bipole, defining the highest DF as a DF of the given pulmonary vein. To prevent potential miscalculations, we controlled every result manually (time domain analysis) determining the atrial fibrillation cycle length (AFCL) on CS (or Lasso) bipoles with online callipers at a paper speed of 100 mm/s by averaging 30 consecutive cycles. Because of the possible transitional CL variations, we measured the AFCL 10 cycles before termination and 1 min after the onset of AF. If the inter-electrogram distance was <100 ms between two consecutive electrograms, they were counted as one signal.

Complex fractionated atrial electrogram mapping
Reconstruction of the LA geometry was performed during ongoing AF with a recording time of 2.5 s for each mapping point. The recorded electrograms were analysed by a programmable software (CFAE Software Module, Biosense Webster) which provided online automated identification and electroanatomical display of CFAEs. The density of mapping was identical in every patient, as we acquired 80 points in the LA equally distributed in the following sequence: 15 points on the posterior wall (including posterior parts of PVs, region 1), 15 points on the anterior wall (including the mitral annulus, region 2), 15 points in paraseptal left atrium (including anterior parts of right PVs, region 3), 15 points on the anterior parts of the left PVs (including LAA, region 4), 10 points on the LA roof (region 5), and 10 points in the inferior LA (including the endocardial aspect of the CS, region 6). Our division of the LA into six areas is comparable with partitions used in previous studies.6,16,20

For the reconstruction of CFAE maps, we applied the following settings: voltage threshold within 0.05–0.15 mV (before displaying the CFAE map, the level of noise was reconfirmed to stay below the level of 0.05 mV) and electrograms with short cycle lengths (duration) between 50 and 120 ms were counted. Our settings were similar to the settings used by other investigators.9,16 We applied the interval confidence level (ICL) to define the level of repetitiveness of the CFAE signals. We classified points according to their ICL into points with very high (>15), medium (10–15), and low ICL (5–10). Detailed definitions for CFAEs, ICL and software settings have been described previously.16,21

Study protocol
We designed the study to assess the effects of subsequent ablation steps on the fibrillatory process. The ablation endpoint for patients with paroxysmal AF was non-inducibility with pacing manoeuvres described previously. We performed re-induction if PVI, CFAE, or roof line ablation resulted in conversion to sinus rhythm. For the

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal (n = 21)</th>
<th>Persistent (n = 20)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56 ± 8</td>
<td>55 ± 9</td>
<td>ns</td>
</tr>
<tr>
<td>Male</td>
<td>20 (95)</td>
<td>18 (90)</td>
<td>ns</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>5 (24)</td>
<td>7 (35)</td>
<td>ns</td>
</tr>
<tr>
<td>LA diameter (mm)*</td>
<td>40 ± 3</td>
<td>42 ± 6</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 (61)</td>
<td>10 (50)</td>
<td>ns</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>52 ± 3</td>
<td>50 ± 7</td>
<td>ns</td>
</tr>
</tbody>
</table>

Values are given as n (%) or as mean ± SD.

*Parasternal left atrial diameter.
patients with persistent AF, the endpoint for ablation was termination of AF which is defined as conversion to sinus rhythm or regularization to atrial tachycardia/flutter with the cycle length variations of < 30 ms measured in the CS.22,23 In this group of patients, we did not performed re-induction.

After detailed 3D mapping (during ongoing AF), a standard wide area circumferential PVI was performed in every patient as described elsewhere.23 The endpoint for PVI was total elimination or dissociation of the PV potentials. For this first ablation step, information available on the CFAE map were not used. The second ablation step was targeting all the CFAE points outside of the circular lines from previous PVI starting with the points presenting highest ICL towards the points with smaller ICLs. The endpoint for CFAE ablation was termination and/or non-inducibility of AF or elimination of all CFAE clusters with local electrogram diminution < 0.05 mV. The third and fourth ablation steps consisted of creating a roof and a mitral isthmus line with a technique described elsewhere.3,4

For both lines, we performed differential pacing manoeuvres in sinus rhythm to confirm block on the line. Patients without termination of AF after completing the mitral isthmus line were electrically cardioverted.

**Radiofrequency ablation**

We applied radiofrequency energy with a maximum temperature of 43 °C and a maximum power of 30 W in anterior LA positions and with a maximum power of 25 W along the posterior LA and in the coronary sinus. Radiofrequency energy was applied for 20–60 s at each site.

**Statistical analysis**

Continuous variables were reported as mean ± SD and median. We compared them using independent-samples t-test. Categorical variables were expressed as frequency (%) and compared by the use of Fisher’s exact test. Comparison between groups was performed with the Wilcoxon rank-sum or sign-exact test. Statistical significance was established at P < 0.05. All statistical analyses were performed using SPSS 12.0 statistical software (Chicago, IL, USA).

**Results**

**Anatomical distribution of complex fractionated atrial electrograms**

Only CFAE points with ICL > 5 and outside the circumferential line from previous PVI were included (Figure 1). Sites at a distance of ≥ 10 mm were defined as different. The mean number of all CFAE sites per patient was 10 ± 6 in paroxysmal AF with mean of 5 ± 2 sites/patient exhibiting low, 3 ± 3 sites/patient presenting medium, and 2 ± 1 sites/patient presenting high fractionation with an ICL level of > 15, respectively.

The mean number of all CFAE sites per patient was 19 ± 7 in persistent AF with a mean of 9 ± 2 sites/patient exhibiting low, 6 ± 4 sites/patient presenting medium, and 4 ± 1 sites/patient presenting high fractionation. The mean number of all CFAE sites per patient was significantly higher in patients with persistent AF (19 ± 7 vs. 10 ± 6), and this was true for all sites independent of their level of fractionation.

In the paroxysmal AF group, the percentages of patients presenting CFAEs in different regions were 10, 85, 80, 65, 42, and 28% for regions 1–6, respectively. In the persistent AF group, the respective number of patients with CFAEs in different regions was 40, 80, 90, 25, 32, and 70% in regions 1–6, respectively.

Consequently, a high clustering of CFAE points with medium and high level of fractionation was found in regions 2 and 3, which is in accordance to results reported in the literature.6,7,9,16

**Amount of energies in different steps of ablation**

In the paroxysmal group, the mean value of radiofrequency energy applied for PVI was 22 404 Ws, for CFAE ablation we used 8300 Ws and for the creation of the roof line 6500 Ws. In the persistent group, we applied 19 808 Ws for PVI, 14 560 Ws for CFAE ablation, 5900 Ws for the roof line, and 13 770 Ws for completion of the mitral line.

**Termination and non-inducibility**

Out of 21 patients with paroxysmal AF termination was reached by PVI in 19 (90%) and non-inducibility in 13 (62%). In the remaining eight patients, CFAE ablation was performed as described previously. With this step of ablation, termination was reached in one patient (13%) who was also rendered non-inducible after completion of CFAE ablation. In the remaining seven patients, we performed roof line ablation and reached termination and subsequent non-inducibility in all seven patients (100%). Because of latter, there was no need for mitral isthmus ablation in paroxysmal
group of patients. Using differential pacing manoeuvres in sinus rhythm, we confirmed bidirectional block along roof line in every patient.

Non-inducibility was tested after each step of ablation, i.e. after PVI, after CFAE ablation, and after completion of the roof line. The overall rate of non-inducibility in the paroxysmal group was 100% using the ablation steps described above.

Pulmonary vein isolation in combination with CFAE ablation resulted in 67% of non-inducibility in this group of patients.

In 20 patients with persistent AF, not a single termination was reached with PVI, in 2 patients (10%) termination occurred during CFAE ablation. In the remaining 18 patients, we reached termination of AF with completion of the roof line in 7 patients (39%), and in the remaining 11 patients, mitral isthmus ablation was performed. We reached conduction block along roof line in every patient. In 7 out of the 11 (64%) patients undergoing mitral isthmus ablation, we completed the line using epicardial ablation from the distal CS but reached complete conduction block only in 5 out of the 11 patients (45%). Termination occurred during mitral isthmus ablation in four patients (36%). In the remaining seven patients, electrical cardioversion was performed.

Therefore, the overall termination rate in a group of patients with persistent AF was 65% with the set of ablations described above.

## Acute effects of different ablation steps on dominant frequency and regulatory index for the fibrillatory process

In a study conducted by Haissaguerre et al.,23 serial measurements of CL in CS have been used as a quantitative tool for monitoring substrate changes during ablation of ongoing AF. In addition, previous studies24 emphasized that CS provides the longest cycle length with least fragmentation, which permits univocal measurement of atrial activity. Because of the well-known strong inverse correlation between AFCL and DF, we presented these AFCL changes as changes in the DF after each different step of ablation.22

We defined changes in the DF as significant when the level of change was ≥0.25 Hz (which corresponds to ~10 ms cycle length change in the time domain for a DF of 5.0 Hz) and change in RI >0.025 was considered statistically significant.19,22,23

Before ablation, we determined the mean DF and RI of the PVs and a mean DF and RI in the CS. The latter reflects the DF and level of organization of the fibrillatory process in LA. In the paroxysmal AF group, the mean DF in the PVs was 6.41 ± 1.0 Hz and the mean RI in the PVs was found to be 0.30 ± 0.04. In patients with persistent AF, the mean DF of the PVs was 6.49 ± 0.8 Hz and the RI 0.28 ± 0.06. Values of DF and RI measured in CS before ablation (in both groups) are presented in Table 2.

The frequency gradient between PVs and CS was 0.94 ± 0.97 Hz in paroxysmal and only 0.12 ± 0.58 Hz in persistent group of patients.

After PVI, the DF in the CS decreased and RI increased significantly in the paroxysmal AF group. After CFAE ablation in this group of patients, we found a non-significant decrease in DF and a small increase in RI. After (or during) completion of the roof line in paroxysmal AF patients, we recorded a further significant decrease in DF and a notable rise in a level of RI before termination of AF.

The changes in DF and RI in patients with paroxysmal AF after different steps of ablation are presented in Figures 2 and 3 and summarized in Table 2.

In the persistent AF group, PVI led to a non-significant decrease in DF of the CS and to a remarkable increase in RI. After CFAE ablation, there was no significant change in DF and RI but after completion of the roof line DF decreased and RI increased significantly in the persistent AF group. With the accomplishment of mitral line, there was further significant decrease in DF and increase in RI.

The changes in DF and RI in patients with persistent AF after different steps of ablation are shown in Figures 4 and 5 and summarized in Table 2.

## Discussion

In previous animal and human studies, a high level of spatial and temporal stability of CFAEs was verified.20,25,26 We hypothesized that CFAE sites acquired during 3D mapping before ablation are stable without any shifting after PVI, and this would be applicable also for CFAE points outside the PVI antrum without need for a further and time-consuming CFAE remap. We targeted only the latter points in the LA considering CFAE points in PV–LA junction regions already excluded from the fibrillatory process by previous PVI.

The substantial reason for standard PVI was the fact that PVs are electrically not isolated after CFAE ablations.7,9–11 This was convincingly shown in a study by Oral et al.10

### Table 2 Overview of changes in dominant frequency and regulatory index measured in CS after different steps of ablation

<table>
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<tr>
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<th>Paroxysmal AF</th>
<th>Persistent AF</th>
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<tbody>
<tr>
<td></td>
<td>DF (Hz)</td>
<td>RI</td>
</tr>
<tr>
<td>Before ablation</td>
<td>5.46 ± 0.70</td>
<td>0.24 ± 0.03</td>
</tr>
<tr>
<td>After PVI</td>
<td>4.96 ± 0.31</td>
<td>0.32 ± 0.05</td>
</tr>
<tr>
<td>After PVI + CFAE abl.</td>
<td>4.83 ± 0.29</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>After PVI + CFAE + RL abl.</td>
<td>3.93 ± 0.45</td>
<td>0.44 ± 0.05</td>
</tr>
<tr>
<td>After PVI + CFAE + RL + MI abl.</td>
<td>3.60 ± 0.92</td>
<td>0.53 ± 0.07</td>
</tr>
</tbody>
</table>
With our sequence of ablation in which targeting of CFAEs always followed PVI, we found a low rate of termination (10–13%) and a negligible impact of CFAE ablation on the fibrillatory process reflected by insignificant changes in DF and RI compared with changes that were achieved by other ablation steps. This finding is not surprising knowing that there is a high clustering of CFAE points in PV–LA junction regions which sites were already excluded from fibrillatory process by PVI. We found a small effect of CFAE ablation on the fibrillatory process despite the fact that energy used for CFAE ablation was higher than energy spent for creation of the roof line in both the paroxysmal and persistent group of patients (8300 vs. 6500 Ws and 14 560 vs. 5900 Ws). Also the mean energy used for CFAE ablation in the persistent group was higher than the mean value of energy spent for the creation of the mitral line (14 560 vs. 13 770 Ws). The mean time spent for CFAE ablation was 34 min (in a range from 15 to 58 min).

Success rates of CFAE ablations reported in the literature are inconsistent. In a recent study by Porter et al., the acute termination rate with CFAE ablation guided by automated detection was 88% in paroxysmal and 20% in persistent AF. In a study by Verma et al., termination occurred in 54% of cases during CFAE ablation. In both studies, the first step was ablation of CFAEs (including CFAE points adjacent to PVs) and the second was standard PVI. On the basis of our results, the reasons for this low rate of termination in our study are the following.

(i) In studies described above, there was a high clustering of CFAE points in PV–LA junction regions (64–83%) and the acute termination of AF was achieved targeting CFAE points adjacent to PVs in ≈50% of patients with paroxysmal AF. In a study by Schmitt et al., the most common sites for termination of AF during CFAE ablation were the regions of the PV ostia.

(ii) With PVI as a first step, we already covered these sites and reached termination in 90% and non-inducibility in 62% of patients with paroxysmal AF. Adding CFAE ablation to PVI, the termination rate increased just by 5% from 90 to 95% and non-inducibility from 62 to 67%.

(iii) In a study conducted by Porter et al., mapping of the LA was performed with a mean density of 143 sites/patient which is doubling the mapping density in comparison with our mapping technique of 80 points/patient. As a result, they found a mean of 28 ± 18 sites/patient with ICL > 7, and we observed a mean of 14.5 ± 6.5 sites per patient with ICL > 5.

(iv) We did not perform mapping in the right atrium and in the CS epicardially which may also contribute to a low termination rate. By virtue of latter observations, there is a possibility that the success rates of CFAE ablations simply correlates with the amount of tissue destroyed by ablation which is in
sharp contrast to the aim of targeting selective CFAE sites to preserve left atrial myocardium as much as possible.

The significantly higher frequency gradient between PVs and CS in paroxysmal vs. persistent AF patients (0.94 ± 0.97 vs. 0.12 ± 0.58 Hz) is in accordance with the results of a study by Sanders et al.27 Also the mean DF in the CS was found to be significantly higher in the persistent vs. the paroxysmal AF group (6.37 ± 0.7 vs. 5.46 ± 0.7).

In contrast, we could not confirm a significant difference between the mean DF of PVs in paroxysmal vs. persistent AF (6.41 ± 1.0 vs. 6.49 ± 0.8) which was found in the same study.

The non-significant decrease in DF of the CS after PVI (together with the significant increase of the RI) in the persistent AF group corresponds with the results from a study conducted by Razavi et al.28

**Study limitations**

The major study limitation is relatively low mapping density which subsequently resulted in a lower diagnostic accuracy of CFAE maps. Our recording time for each point during the mapping procedure was 2.5 s. However, in a recent study by Lin et al.,29 the highest consistency of CFAE mapping was achieved by ≥ 5 s recording time.

We were using the 50–120 ms setting for electrogram cycle length (duration), which might be improved by a different setting as recently reported by Caló et al.,30 where a higher diagnostic accuracy could be obtained by a setting of 15–30 ms.

In our paroxysmal AF patients, inducibility was assessed with pacing manoeuvres and not by isoproterenol infusion which has a higher specificity and sensitivity.

We did not perform a CFAE remapping after PVI, so we cannot state that the CFAE points were absolutely the same (in same location with the same level of fractionation) before and after PVI. This issue was recently clarified by Roux et al.31 at least for the patients with persistent AF. They demonstrated that the CFAE burden is significantly reduced after PVI, not just in the vicinity of the PVs but also in LA regions remote from the PVs.

Our study only describes the acute effects of CFAE ablation, whereas Porter et al.9 reported a notable long-term success rates with CFAE ablation followed by PVI.

**Conclusions**

Complex fractionated electrogram ablation guided by a dedicated software algorithm and performed after PVI in the LA regions outside of the circular PVI lines without a CFAE remapping after isolation of veins had no significant impact on the fibrillatory process and plays a minor role in achieving higher rates of termination and non-inducibility in AF. This is observed for both paroxysmal and persistent AF. In contrast, both PVI and linear lesions are effective in changing the fibrillatory substrate. Implicitly we concluded that CFAE mapping and ablation should be performed always after pulmonary vein isolation.

**Conflict of interest:** none declared.
Acute effects of CFAE ablation

Funding

G.B. is a fellow of the European Heart Rhythm Association (EHRA) and receives support for the 1 year fellowship (Advanced Program) in Electrophysiology.

References