Automated Detection of Complex Fractionated Atrial Electrograms in Substrate-Based Atrial Fibrillation Ablation: Better Discrimination with a New Setting of CARTO® Algorithm

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Abstract
Background and purpose: Up until recently complex fractionated atrial electrogram (CFAE) ablation has been considered as time consuming and its achievement as challenging, especially for non experimented operators. Moreover, results of substrate ablation based on CFAE detection in atrial fibrillation (AF) are very disparate, mainly because of the operator’s subjective electrogram visual analysis and the difficult distinction between CFAEs really involved in AF perpetuation from other CFAE. Automatic detection provided by 3D mapping system (CARTO® algorithm) can be helpful but is not selective enough, drawing too wide CFAE areas. We sought to demonstrate a better selectivity of a new CFAE algorithm setting in order to better discriminate CFAEs really involved in AF perpetuation from other CFAE.

Methods and subjects: A population of 32 patients (60.4±12.7 years) with paroxysmal (n=3) AF (PAF), persistent (n=16) AF (PeAF) or long-standing persistent (n=13) AF (LSPeAF), and AF history =56±65 months, underwent CFAE ablation based on visual analysis. Before ablation, left atrium CFAE mapping was performed on CARTO® shortest complex interval (SCI) algorithm and reanalyzed after ablation with the two different settings: nominal (SCI 60-120ms/0.05-0.15mV) vs. customized setting (SCI 30-40ms/0.04-0.15mV). CFAE areas automatically detected by both settings (CFAE-CARTO® areas) were respectively measured. The decision to ablate CFAE was only based upon the operator’s electrogram visual analysis taken as reference because of high AF termination rate (93.7%) due to operator’s CFAE selection experience. These ablation points drawn reference-CFAE areas involved in AF perpetuation (ablation point=60mm2) allowing to compare the selectivity of the two previous automatic maps.

Results: With the customized CARTO® SCI setting, we observed a significant reduction of CFAE areas detected by CARTO® (CFAE-CARTO® areas) and of the ablated CFAE surface inside non-CFAE CARTO® areas, (30.6±20.5cm2 vs. 68.8±24.5cm2, p<0.0001, and 1.86±1.82% vs. 3±3%, p=0.003). Furthermore the proportion of ablated areas/detected CFAE-CARTO® areas were higher with customized setting (38.2±19.6% vs. 20.4±17.5%, p=0.008).

Conclusions: This new customized CFAE algorithm setting is significantly more selective than the nominal one and allows an automated detection of CFAE really involved in AF perpetuation truer to an efficient experienced operator’s electrogram visual analysis.

Key Words: Ablation-catheter; Atrial fibrillation; Substrate; Complex Fractionated Atrial Electrogram (CFAE); Electroanatomical 3D automated mapping

Introduction

Background
A new approach of substrate ablation in atrial fibrillation (AF) based on complex fractionated electrogram (CFAE) detection was first described by Nademanee et al.1 Though CFAE ablation in AF was described as efficient,1-2 the results (AF termination rate by ablation and long term outcomes) are heterogeneous1-3 partially because of the subjectivity of the CFAE detection method based on electrogram visual analysis known as the « gold standard ».

The identification of CFAE sites for ablation by visual analysis, based on distinction between “CFAEs really involved in AF perpetuation” from “other CFAE”, is subjective and depends on the experience of the operator in the field of substrate ablation.

A more objective approach, with the help of a selective algorithm,
substrate ablation was necessary, were eligible for inclusion. Exclusion criteria were: redo ablations and lone “focal” AF (PAF without structural heart disease or hypertension with short episode duration ≤ 24 hours, predicting a limited quantity of substrate).

Before ablation, for each patient included, left ventricular ejection fraction (LVEF) and antero-posterior left atrial (LA) diameter was measured by biplane transthoracic echocardiogram (TTE).

3D Electroanatomic Mappings and Ablation Techniques

All anti-arrhythmic medications were discontinued at least five half-lives prior to ablation, except for beta blockers and amiodarone in patients with non PAF. Patients were anticoagulated with warfarin for at least 3 weeks prior to the procedure (International Normalized Ratio 2–3). Warfarin was stopped 3 days prior to the procedure and anti-coagulation was maintained with low molecular weight heparin.

All procedures were performed under general anesthesia. The absence of LA appendage thrombus was confirmed by transesophageal echocardiogram before transeptal puncture. Surface electrocardiogram and bipolar endocardial electrograms (filtered from 30 to 500 Hz) were continuously monitored and stored on a computer-based digital amplifier/recorder system (GE Healthcare, Cardiolab, Milwaukee, Wisconsin, USA). The following catheters were introduced through the right femoral vein: a deflectable decapolar catheter (2–5–2 mm electrode spacing, Xtrem, ELA Medical, France) was able to detect CFAE but did not focus enough on CFAEs involved in AF perpetuation and finally chosen by operator (reference-CFAEs).

Rational objective

Our objective was to modify the CARTO® SCI maps settings to make it more discriminative (closer to our electrogram visual analysis taken as reference), helping non experienced operators to focus more rapidly on the area of interest and reducing the procedure time.

Material and Methods

Study Population

Between November 2009 and June 2010, all consecutive patients referred to our centers for symptomatic refractory AF in whom a substrate ablation was necessary, were eligible for inclusion. Exclusion criteria were: redo ablations and lone “focal” AF (PAF without structural heart disease or hypertension with short episode duration ≤ 24 hours, predicting a limited quantity of substrate).

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navigation and mapping system from Biosense Webster. Before starting ablation, an electroanatomic LA map using the SCI algorithm was drawn in AF with nominal setting. To allow correct local electrogram assessment, the mapping catheter was maintained in each location for 2.5 seconds minimum before points were acquired.

For patients in sinus rhythm (SR) at the beginning of the mapping (n=11), AF was induced by atrial pacing, using isoproterenol if necessary.

**Visual CFAE Selection and Ablation**

The primary targets of ablation were continuous and low voltage potentials (Figure 1). Only permanent CFAE over time were selected. CFAE ablation has a cumulative effect with progressive CL increase during ablation and an instantaneous effect in specific crucial areas with sudden CL increase of AF termination. The progressive CL increase during ablation may lead to the disappearance of CFAE not really involved in AF perpetuation.

Thus dynamic analysis of CFAE over time is still necessary, despite pre-selection by computer.

CFAE ablation was then performed with “point-by-point” applications (60 seconds). Ablation power control settings were parameterized at: 30 to 45W for the septum, 25W for Pulmonary Veins (PV) ostia, posterior wall of LA and CS, 35W for the other segments of LA and right atrium (RA) with an esophageal thermal monitoring. The endpoint was AF termination defined as conversion of AF to SR or regularization into stable Atrial Tachycardia (AT). In such cases, AT was mapped and ablated until SR was restored. AF “non-inducibility” was then tested using isoproterenol in PAF and PeAF. If the CFAE ablation approach failed to restore SR, no circumferential or anatomical linear ablations were carried out and external cardioversion was performed. After SR conversion, Lasso-guided PV isolation was performed as a final ablation step in all patients with PAF.

**Post Ablation Creation of Reference-CFAE maps (ablated areas taken as reference)**

The automatic CFAE maps created were not used during ablation. Only operator’s electrogram visual analysis was used to select CFAE eligible for ablation. Reference-CFAE mapping was obtained with the area drawn by all CFAE ablation points. RF applications performed during AT or PV isolation were excluded from the analysis as they do not correspond with CFAE ablation. Each ablation point covered a surface of 60 mm². This surface depends on the catheter movement and represents the mean area “brushed” by the ablation catheter in stable positions defined by 20 RF “point by point” applications (of 60 sec each measured in 10 patients).

Electro-anatomic points taken on preliminary maps were used to draw automatic CFAE maps with 2 different settings: nominal and customized.

Nominal setting of SCI CFAE maps were the following: CFAE was defined by the system based on the peak-to-peak (P-P) interval in millisecond (msec). Global CFAE parameters (for all CFAE points) and point CFAE parameters (for individual points) were set to standard values. In detail, minimal amplitude threshold and maximal amplitude threshold were set to 0.05 millivolt (mV) and 0.15 mV, and the minimal interval and maximal interval between two consecutive peaks were set to 60 msec and 120 msec.

For customized settings we empirically modified the CARTO® SCI maps settings to reduce the area of all automated detected CFAE and focus more on the detection of CFAE involved in AF perpetuation. Ablation points were considered as CFAE points of clinical value involved in AF perpetuation (Reference-CFAEs), because of high AF termination rate (93.7%). In the substrate-based ablation technique first described, the primary targeted electrograms involved in AF perpetuation, were low voltage (≤ 0.15mV) and continuous potential ones. Thus we changed the algorithm setting to reduce both voltage and cycle length (CL) of P-P interval limits, and narrowed the fractionation window (ms).

We proposed a new customized setting of CARTO® SCI mapping in this study (called “SCI 30-40”). The differences in the nominal setting (“SCI 60-120”) are the following:
- a shorter CL of P-P interval (30 ms vs. 60 ms)
- a narrower window for fractionation (30 to 40 ms vs. 60 to 120 ms)
- a wider window for non-fractionated potentials (40 to 120 ms)
- a lower voltage cut off at 0.04mV vs. 0.05mV (no change for upper voltage cut off: 0.15mV)

**Comparison**

We then compared the CARTO® maps of nominal “SCI 60-120” setting and customized “SCI 30-40” setting with reference-CFAE
maps of ablation points.

For each patient, CARTO® and reference-CFAE LA maps were analysed retrospectively (after ablation), and the following data was listed: number of electro-anatomic points (used to create CARTO® maps) in LA, number of ablation points, and LA map surface (cm²) as automatically computed by the CARTO® software.

On CFAE-CARTO® maps the colour grade scale for fractionation quantification is the following: red and yellow=highest degree of fractionation, green and blue=moderate degree of fractionation, and pink=no fractionation. Because the selection of electrograms for ablation is binary (to be ablated or not to be ablated), our selection of fractionated involved only the “red and yellow” areas.

For each setting, the following surfaces (cm²) were manually measured:
- the CFAE-CARTO® surface defined as the sum of all red and yellow areas detected by algorithm
- the total non-CFAE-CARTO® surface, defined as the sum of the remainder of LA areas
- the ablated surface localized inside the CFAE-CARTO® surface
- the ablated surface localized outside CFAE-CARTO® surface (or inside non-CFAE CARTO® surface).

For each setting, the number of patients, in whom ablation points leading to AF termination were located inside of CFAE-CARTO® areas, was specified.

We then compared the CFAE-CARTO® surface (in cm² and in % of total LA surface), the ablated surface inside CFAE-CARTO® surface (cm² and % of total CFAE surface), and the ablated surface outside CFAE-CARTO® surface (cm² and % of total non-CFAE-CARTO® surface).

Follow-Up

Patients were followed in the outpatient clinic 3, 6, 9 and 12 months post ablation. Twelve-lead ECG and 24-hour Holter recordings were obtained in all patients at each follow-up visit. Patients were asked to contact the investigator if symptoms suggestive of arrhythmia occurred. A 12-lead ECG was performed in case of reported symptoms between follow-up visits. Recurrences were based upon patient reporting, 24-hour Holter recordings, and/or ECG data.

Statistical Analysis

Statistical analysis was performed with the chi-square tests for categorical variables and Wilcoxon matched pairs signed rank-sum tests for numerical data. A two-tailed P value of < 0.05 was considered to indicate statistical significance. All statistical analyses were performed using STATA 9.2 software (Stata Corp., College Station, TX).

Results

Patients Characteristics

A population of thirty two patients (75% male, 60.4 ± 12.7 years), undergoing radiofrequency catheter ablation for paroxysmal (n=3) AF (PAF), persistent (n=16) AF (PeAF) or long-standing persistent (n=13) AF(LSPeAF), according to the ESC 2010 guidelines,11 was enrolled in this study.

All patients had experienced an AF recurrence whilst taking at least one antiarrhythmic drug (mean = 2.2). Included patients had a long history of AF (79±64 months with a mean sustained episode duration of non PAF=56 ± 65 months).

Mean LA dimension was 44.6±5.2 mm, and mean LVEF was 52.6±10.5 %. The clinical characteristics of the patients are shown in Table 1.

Ablation Results

AF was successfully terminated (converted to SR or stable AT) in 30 patients (93.7 %). Only 5 patients (all with LS-PeAF) needed electrical cardioversion: 2 for AF persistence, and 3 for stable AT . SR was restored in 27 patients (84.4%) without electrical cardioversion. Six were directly converted to SR (22.2%), and 21 regularized to AT
The mean CL of AF (measured in LA appendage) was 179.5 ± 25.6 ms. The mean procedure and fluoroscopy durations were 4.2±1.3 h and 31±17 min respectively. No serious adverse event related to the procedure occurred.

Electro Anatomic Maps
For automated CFAE-CARTO® maps the mean LA surface automatically measured on CARTO® maps was 174.4 ± 54.6 cm². The mean number of electro-anatomic points taken for SCI maps in LA was 294.2 ±138.4. A total of 9416 points acquired in the LA were analyzed. The mean mapping time was 18 ± 10 min. The mean density of electro-anatomic points was 1.53 ± 0.82 points/cm².

For reference-CFAE maps the mean number of 60 sec ablation points in LA for CFAE ablation was 63.3 ± 35.

Retrospective comparison of surfaces with nominal and customized settings (Figures 2 and 3):
The mean CFAE-CARTO® surfaces were significantly smaller in the customized vs nominal groups: 30.6 ± 20.5 cm² vs. 68.8 ± 24.5 cm², p < 0.0001. These areas represent a percentage of 17.5 ±37.5 % vs 39.5 ± 44.8 % of the total LA surface. The ablated surface inside or outside CFAE-CARTO® areas remains absolutely the same in both settings but the ablated proportion of CFAE-CARTO® areas was significantly higher in the customized setting group (38.2 ± 19.6 %, vs 20.4 ± 17.5 %, p = 0.008). However, the ablated area non-CFAE inside-CARTO® areas were smaller in this group (1.86 ± 1.82 %, vs 3.0 ± 3% p=0.003).

Furthermore, the % of patients, in whom ablation points leading to AF termination were located inside of CFAE-CARTO® areas, was significantly higher with custom setting (90% vs 83.3%, p=0.001).

Outcomes
During a mean follow-up of 12 ± 7 months after the last procedure, 25/32 patients (84.4%) were free from any arrhythmia (16 patients still under antiarrhythmic drug therapy, 1.6 ablation/patient). Redo procedures, using the same substrate based ablation technique, were performed in 16 patients (9 for AF, 9 for AT). A third procedure was necessary in 4 patients for AT recurrences.

Discussion
Main Findings
In this study, for the first time, a CFAE software program is compared to an efficient visual CFAE detection, validated by a high AF termination rate (93.7%). We demonstrated that our new simple customized setting (“30-40” SCI setting) is significantly more selective than the nominal one, and closer to the operator’s visual analysis.

With this new setting, the total CFAE-CARTO® area and ablated surface outside CFAE-CARTO® area were both significantly smaller. Furthermore ablated proportions of CFAE-CARTO® areas were larger than with nominal setting.

CFAE Definitions and Subjectivity of Target Electrograms
Many mechanisms have been suggested to explain the fractionation of electrograms during AF including: reentrant circuit pivot points, wave collision and slow conduction, anisotropic conduction or focal reentry, and wavebreaks at the periphery of high-frequency rotors. These mechanisms can play an active or a passive role in AF maintenance and multiple mechanisms may coexist in the same patient at different sites or times.16 This data suggests that all CFAEs...
may not be the same, and that ablation should primarily focus on 
CFAEs which play an active role in AF perpetuation.

The definitions of CFAEs, are large, blending together different 
types of electrograms.

To define the specific electroggram characteristics of different types 
of CFAE, Hunter et al. proposed a CFAE classification based on visual analysis. No information was provided regarding which type of 
CFAE should be ablated or not. Minimal data is available to differentiate the CFAEs issued from active drivers in AF or critical 
zones for AF maintenance, from other CFAE without clinical value, 
corresponding to passive epiphenomenon of fibrillary conduction. 
Takahashi et al. reported that only 17% of the CFAE areas were 
related to AF termination and described the specific characteristics of electrograms associated with the slowing or AF termination as 
continuous activity or a temporal activation gradient.

The “30–40” SCI Setting Focuses on Continuous and Low 
Voltage Potentials

Although this new SCI setting was created from empirical daily 
practice, we demonstrated its better selectivity for CFAE areas 
involved in AF perpetuation (low voltage, very fast and fractionated 
or continuous electrograms).

Decreasing the voltage cut off from 0.05 to 0.04 mV allowed 
us to unmask areas of very low voltage CFAE. In the substrate- 
based ablation technique first described, the primary targets 
were low voltage CFAE (≤ 0.15mV). These low voltage potentials 
may correspond to areas of remodelling or fibrosis that could participate in AF substrate. A very low level of interference (< 0.03 
mV) is needed for CFAE ablation and for the use of this setting.

Decreasing the SCI cut-off from 60 to 30 ms, and narrowing the 
SCI window to 30–40 ms seems to shift the focus to very fast or 
continuous potentials which are the primary target of ablation.

Calo et al. have previously shown that a specific setting of 
CFAE-CARTO® software is needed to improve its sensitivity 
and specificity. In their study, the best window of fractionation 
was “15–30 ms” which focused on very high frequency CFAEs. 
They also studied the “30–50 ms” window which was also a good 
setting with 74% of sensitivity and 87% specificity. These results are 
concordant with our findings, selecting very fast and fractionated 
potentials. In Calo’s study the CFAE-CARTO® was validated by 
two different electrophysiologists with good concordance, but results of the ablation of these fractionation potentials were not specified.

Regarding the validation of CFAE algorithms in other studies, 
ablation strategies did not target CFAEs or results of CFAE ablation 
were not specified. This is the main limitation of such studies regarding the debate toward CFAE ablation effectiveness and visual 
analysis subjectivity.

Focus on Electrograms Involved in AF Maintenance and 
Exclusion of CFAE Areas without Clinical Value

With the customized setting, the CFAE-CARTO® maps had 
smaller fractionated areas focusing in a more discriminating manner on the reference-CFAE ablated areas (with a high AF termination rate). This setting excludes fractionated potentials which have no important impact on AF and are not targeted in our ablation protocol.

This customized setting can help in guiding ablations, but because of color interpolation on CFAE maps and catheter movement, operator’s visual analysis remains necessary to validate electrograms before ablation within automated fractionated areas. Only very high density CFAE maps could standardize and automate this substrate- 
based ablation technique. A multi-electrode mapping tool could be very interesting with this setting.

Simple Use

Many algorithms are available to help physicians in CFAE ablation. 
Such an approach must be, in our opinion, as straightforward as possible, to simplify and standardize the technique. The 2.5 sec 
window of acquisition for each point appears to be a good compromise between mapping time and accuracy, taking into account the shortterm temporal stability of CFAEs. The time required for LA CFAE 
mapping in our study was 18 ± 10 min which is acceptable in daily 
practice. Only one kind of CFAE map with a simple setting is used in 
this study (no “complex” analysis or handling of CFAE maps are 
necessary); LA is divided into: CFAE-CARTO® areas (red to yellow areas) requiring visual validation before ablation; and non-CFAE- 
CARTO® areas excluded from ablation. This setting is very simple in daily practice even for physicians not currently using the CFAE 
approach and could help in standardizing the technique.

Acute and Long Term Results

Our acute and long term results on this 32 patient series might 
appear quite high especially for this population. Our EGM-based 
substrate ablation protocol was performed in complete accordance 
with the technique described in the first publication on this topic and 
include other targeted EGMs: temporal gradient of activation and 
rapid fires. The following differences from previous publications could explain differences in acute and long-term results: voltage of 
targeted potentials (often <0.1 mV in our protocol), point-by-point 
applications (60 seconds) without “dragging” (to confirm EGM elimination after RF applications), ablation in the CS and the RA, 
and dynamic power settings (15–45 W).

This technique is reproducible and can easily be taught and learned 
with a short leaning curve (less than 10 cases).

Study limitations

The greatest limitation of CFAE mapping is the density of 
acquisition points. In case of low-density LA maps, areas of 
fractionation may not be accurate because of point interpolation. The mean density of CFAE points in the present study is quite 
accurate (1.53 ± 0.82 points/cm2) but we must take account of the 
interpolation of points in the area measurement. The necessity to take 
as much CFAE points as possible is time consuming. High-density 
accurate maps, which would automate the technique, are the only way to reduce the importance of visual analysis. Further studies using 
this setting on high-density maps are necessary in the field of CFAE 
ablation automation.

Each RF application was considered on CARTO® maps as a 60 
mm2 diameter circle. This value could be criticized, but it is the result of 
measures on maps and reflects the natural and artificial movement of the catheter.

This study is based on the temporal stability hypothesis of the 
CFAE with a 2.5 sec window of acquisition. In the case of non- 
permanent fractionated potentials or if the tip movement is too fast 
during mapping, there is a risk of false positive and false negative
results (if points are taken too quickly).

Even though the right atrium is often ablated in our protocol, right atrium CFAE maps were not analyzed in this study. The “30-40” SCI setting was the most selective setting regarding a great majority of our patients. In “fast” (CL <150 ms) or “slow” AF (CL > 210 ms) cases this setting was less accurate. A dynamic setting based on the CL for these few cases could be discussed.

Despite the high AF termination rate in this study, some “passive” CFAEs, not playing any role in AF perpetuation, have probably been ablated needlessly. RF time may be reduced with a better understanding of both CFAE specific characteristics, and AF physiopathology. Nevertheless, the amount of ablation itself may also play an important role.  

This retrospective design of the study may be a weak point of the study.

To conclude on the benefits of such new Carto CAFEs discrimination algorithm, a prospective controlled study with multipoler mapping catheter could be interesting to conduct.

Conclusions

This new CFAE algorithm setting is significantly more selective than the nominal setting. As a result it focuses on visually targeted areas that lead to a high AF termination rate. These promising results may be less time consuming, and will simplify and improve the reproducibility of CFAE mapping in AF.

Multielectrode mapping could be proven as a very useful tool in this field.

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