Mapping of Complex Fractionated Atrial Electrograms (CFAE) as Target Sites for AF Ablation

The myriad pathologies leading to and resulting from atrial fibrillation (AF) have led to many theories regarding how substrate should be defined and how to reconcile substrate ablation with trigger ablation. The identification of spatiotemporally stable areas of very low amplitude short cycle length CFAE, in a sea of otherwise discrete normal amplitude and relatively longer cycle length electrograms, led to ablate the CFAE as a marker of abnormal substrate. This pure substrate-based ablation strategy has resulted in remarkable success with great benefits, which include stroke and mortality reduction in high-risk patients with very long standing persistent AF. In this review, we discuss the prevailing mechanisms underlying CFAE, how to map and ablate CFAE sites, correlation of CFAE areas to those of ganglionic plexi, clinical outcomes of the approach, and the controversy surrounding targeting CFAE as substrate sites for AF ablation.

I. Characteristics of atrial electrograms during atrial fibrillation

Over the past decade, several important observations were made during mapping studies in human AF. First, atrial electrograms during sustained AF have three distinct patterns: single potential, double potential, and complex fractionated potential (CFAE).

Second, during AF, these atrial electrograms tend to localize in specific areas of the atria and do not meander, exhibiting surprisingly remarkable temporal and spatial stability. Third, the CFAE areas represent the AF substrate sites, which have become important target sites for AF ablation. By ablating such areas that have a persistent CFAE recording, one eliminates AF and usually renders AF non-inducible. Thus, CFAE mapping has become a novel approach for guiding a successful ablation of AF substrate, yielding excellent long-term outcomes. CFAEs are defined as low voltage atrial electrograms (ranging from 0.04 - 0.25 mV), that have fractionated electrograms composed of two deflections or more, and/or have a perturbation of the baseline with continuous deflection of a prolonged activation complex. CFAE have a very short cycle length (< 120 ms) with or without multiple potentials (Figure 1: 4th tracing, RIPV antrum); however, when compared to the rest of the atria, this site has the shortest cycle length.

II. Electrophysiologic mechanisms underlying CFAEs

The underlying etiology of CFAE has not yet been elucidated, but several theories are being investigated. During intraoperative studies in patients with WPW syndrome, Konings et al. identified mechanisms of propagation of the above three types of electrograms during AF:
Figure 1: Various examples of CFAE that were recorded from the ablation catheter (ABL d) from different sites. Four trace panels show CFAE recorded from CS ostium (CS os), LA septum, LIPV antrum and RIPV antrum. Each panel also shows recordings from reference site in the proximal CS (CS-7, 8 and CS-9, 10 [CSp]). The most highly fractionated electrograms can be seen in this example to exist on the LA septal wall, LIPV antrum and at the RSPV antrum.

CS = coronary sinus   LA = left atrium
LIPV = left anterior pulmonary vein   RSPV = right superior pulmonary vein

- **Type I** that exhibits discrete complexes separated by an isoelectric baseline free of perturbation. These electrograms were caused by single broad-wave fronts propagating without significant conduction delay, exhibiting only short arcs of conduction block or small areas of slow conduction not disturbing the main course of propagation.

- **Type II** that exhibits discrete complexes, but with perturbations of the baseline between complexes. These electrograms were recorded during activation patterns characterized either by single waves associated with a considerable amount of conduction block and/or slow conduction or the presence of two wavelets.

- **Type III** that exhibits CFAE. Konings and colleagues found that CFAE represented the presence of three or more wavelets associated with areas of slow conduction (10 cm/s) and multiple arcs of conduction block.

Waves propagating from these areas were found to break and change direction recurrently at a boundary zone, and demonstrate fractionation of local electrograms. Their findings suggested that one of the possible electrophysiologic mechanisms, by which fractionation occurred during AF, was due to high-frequency reentry at the boundary zones of the dominant frequency areas.

On the other hand, Kalifa et al. identified a key relationship between areas of dominant frequency and areas of fractionation in sheep. The investigators were able to localize areas with regular, fast, spatiotemporally organized activity and map the regions around them.

The most prominent theory underlying the occurrence of CFAE involves the complex interplay of the intrinsic cardiac nervous system on atrial tissues. The cardiac ganglionic plexi (GP) are a collection of autonomic nervous tissues with afferent and efferent sympathetic and parasympathetic fibers. Six major GPs (Figure 2) that may exert influence on the atria are: (1) Superior LA; (2) Posterolateral LA; (3) Posteromedial LA; (4) Anterior descending LA; (5) Posterior RA; (6) Superior RA. In animal models, the stimulation of parasympathetic fibers within the GP has been shown to decrease atrial effective refractory periods and allow AF to perpetuate. Simultaneously, stimulation of sympathetic fibers may occur in similar areas, which can initiate PV ectopy. Unfortunately, mapping and ablating the GP is time consuming and difficult.
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Figure 2: Six cardiac ganglionic plexi (GP) are located on or near the left and right atria and have been shown to exhibit influence on the initiation and perpetuation of AF: superior left atrial GP, posterolateral left atrial GP, posteromedial left atrial GP, left anterior descending GP, posterior right atrial GP, and superior right atrial GP.

AP = anteroposterior  PA = posterior-anterior  LAA = left atrial appendage
RAA = right atrial appendage  CS = coronary sinus  LOM = ligament of Marshall
SVC = superior vena cava  LSPV = left superior pulmonary vein
LIPV = left inferior pulmonary vein  RSPV = right superior pulmonary vein
RIPV = right inferior pulmonary vein

Ongoing research has identified a close relationship between the location of CFAE and the GP in animal models. CFAE-targeted ablation may provide a surrogate for modification of the GP if this relationship can be confirmed in humans. Certainly, ablation in areas that have resulted in a vagal response has shown excellent results in the treatment of AF.

III. Regional distributions of CFAE

Each individual has temporal and special stability of CFAE, which facilitates accurate mapping. These regions are not symmetrically located within the atria, but can be predictably sought in certain places during mapping. The following key areas have demonstrated a predominance of CFAE within our cohort: (1) the proximal coronary sinus; (2) superior vena cava-RA junction; (3) septal wall anterior to the right superior and inferior PVs; (4) anterior wall medial to the LA appendage; (5) area between the LA appendage and left superior PV; and (6) posterosuperior wall medial to the left superior PV (Figure 3). Typically, patients with persistent or long-lasting AF have greater numbers and locations of sites with CFAE than those with paroxysmal AF.

The distribution of CFAEs in the right and left atria is vastly different from one area to another. Despite regional differences in the distribution of these atrial electrograms, CFAEs are surprisingly stationary, exhibiting relatively spatial and temporal stability. Thus, one can perform point-to-point mapping of these CFAE areas and associate them into an electroanatomical map.
IV. CFAE Mapping to guide substrate ablation

Mapping is always performed during AF by point-to-point mapping, although detailed mapping of the LA, coronary sinus, and occasionally RA is also required. The spatial and temporal stability of CFAE allows the precise localization of these electrograms.

A map with a minimum of 100 data points is usually created, especially in high-density areas commonly known to have CFAE. Additionally, we usually create a detailed map of the proximal coronary sinus, and occasionally the RA. We identify locations with stable electrograms, and these are “tagged” to create targets for ablation. Areas with fleeting CFAE are not sought as a primary target. A highly reliable map allows for minimal use of fluoroscopy. We routinely use less than 10 minutes during average procedure duration of 113-27 minutes.

A customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA, USA) was produced. The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-second recording window and interprets it according to two variables: (1) shortest complex interval (SCL) minus the shortest interval found (in milliseconds), out of all intervals identified between consecutive CFAE complexes; and (2) interval confidence level (ICL) minus the number of intervals identified between consecutive complexes identified as CFAE, where the assumption is that the more complex intervals that are recorded - that is, the more repetitions in a given time duration - the more confident the categorization of CFAE. Information from these variables is projected on a three dimensional electroanatomic shell according to a color coded scale. This allows targeting and retargeting of areas of significant CFAE.

V. Evidence that CFAE areas represent AF substrates

Our recent study results support the hypothesis that CFAE areas are critical in perpetuating AF and RF ablations over these areas, resulting in the termination of AF and rendering the atria no longer able to sustain AF. The findings are summarized as follows.

The study population included 121 patients (29 females; mean age, 63 years) with refractory AF (57 paroxysmal, 64 chronic). All patients underwent non-fluoroscopic electroanatomic mapping (CARTO) during AF. Using CARTO, the bi-atrial replica, displayed in a 3-D color-coded voltage map, was created during AF, and areas associated with CFAEs were identified.
RF ablation of the area with CFAEs was performed to the closest anatomic barrier. We found CFAE in seven different regions, but mainly confined to the interatrial septum, PVs, roof of LA, and left posteroseptal mitral annulus and coronary sinus ostium. Ablations of the areas associated with CFAEs resulted in termination of AF without external cardioversion in 115 of the 121 patients (95%); 32 (28%) required concomitant ibutilide treatment. At 1-year follow up, 110 (91%) patients were free of arrhythmia and symptoms, 92 after one ablation (76%), and 18 after two.

In virtually all patients, after RF applications over the CFAE areas, most atrial electrograms either disappeared or were reduced drastically in amplitude, resulting in complete elimination of CFAEs, often associated with organization of atrial electrograms in the areas adjacent to the ablated ones. The elimination of CFAEs always uniformly increased tachycardia cycle lengths before AF termination, even though the cycle lengths were measured from the electrical reference of the area remote from the ablation sites. The overall tachycardia cycle length increased from 172 ± 26 ms at baseline to 237 ± 42 ms (p < 0.05).

Clearly, the preceding findings suggest that CFAE areas are indeed the substrates that perpetuate AF. Furthermore, we followed the above initial study with a larger study2 that included 674 high-risk AF patients (mean age 67 years). This study confirmed that our ablation approach is very effective and yields excellent long-term outcomes. More importantly, sinus rhythm after our ablative procedure is associated with a lower mortality rate and stroke risk.

VI. Other studies and Controversy

Our introduction of CFAE mapping to guide AF ablation as an alternative to anatomical approach of PVI spurred other investigators to follow our approach. However, our results were not fully reproduced by others.10,11 While it is unclear what exactly are the factors underlying the differences in both acute and long-term outcomes between our studies and others, it seems more likely that one or more of the following key variables may help explain the differences between these studies4:

1) Right atrial ablation. Other investigators often did not map and ablate the right atrium. We found that 15% of our patients required right atrial ablation; the common sites are right posteroseptum, Cavo-tricuspid isthmus, tricuspid annulus, and rarely posterior wall of the right atrium and SVC-right atrial junction.

2) Power and duration of RF energy applications. Our power of RF applications was significantly higher than those of others: we used RF power up to 50 watts over the anterior and septal wall and 30-40 watts in the posterior wall that is not close to the esophagus but titrated down to about 20-30 watts in the areas close to the esophagus.

3) Ablation endpoint. Perhaps this variable is the most significant factor influencing the differences among these studies. CFAE are low voltage atrial signals usually ranging from 0.05-0.25 mV and the areas with the very low voltage signals (between 0.05-0.1 mV) are often the most desirable. By contrast, other investigators defined successful lesion creation as a voltage reduction to < 0.1 mV or by decreased by ≤ 80% reduction. This single factor may explain why the investigators did not have a high success rate of acute termination. In our experience, the ablation sites where AF terminated are often the sites that we had applied RF before and often the voltage of atrial signals at these successful sites were in the range of 0.5-0.8 mV.

4) Procedure endpoint. The procedure endpoint in our study was sinus rhythm and/or complete elimination of CFAE target sites, we deliberately attempted to ablate all “new” arrhythmias, including pleomorphic forms of atrial tachyarrhythmias, whereas others often did not and elected to just merely perform cardioversion to revert the arrhythmias to sinus rhythm.

5) Comprehensive mapping. Lastly, the electroanatomic map for CFAE should have a high density of evenly spread mapping points. It was unclear whether other investigators were committed to a detailed mapping of the CFAE. There is, however, no question that the key to the success of AF ablation guided by CFAE is exploring all areas of the atria and coronary sinus.

VII. Future Development

Signal processing of low amplitude CFAE needs further improvement; many recording systems have great difficulty in separating such signals and noises. That poses an even greater difficulty for the software to accurately measure electrogram intervals, which are crucial for evaluating cycle lengths of CFAE and/or for dominant frequency analysis. Since excellent CFAE targets have distinct morphologies and electrogram patterns, one should have programmed pattern recognition built into the software package for an automated display of CFAE target sites.
Clearly more research studies need to be done to find the best algorithm with which to differentiate between CFAE sites that represent AF substrate that perpetuate the arrhythmia and those that are just merely passive bystanders. Finally, new tools such as robotic navigation of catheters, which are being introduced at an impressive pace, will undoubtedly help improving the efficacy and lowering the risks of AF ablation.

VIII. Conclusions

Substrate ablation guided by CFAE mapping is effective in both acute termination of AF and maintaining sinus rhythm. This highlights the fact that CFAE probably does represent the AF substrate that perpetuates the arrhythmias. Controversy remains as to what are the underlying electrophysiologic mechanisms of CFAE; however, several prevailing proposed mechanisms suggest that CFAE are either arrhythmogenic sites or hyperactive ganglionic plexi, both of which play a significant role in AF genesis. More clinical studies need to be performed to delineate the values and limitations of CFAE mapping in guiding ablation and resolve debates over its usefulness. Advances in technologies and development to improve signal processing and to incorporate CFAE pattern recognition are necessary to help electrophysiologists to be more proficient in performing the technique of CFAE mapping. Similarly, it is imperative that the AF ablation procedures be done in centers that are well equipped with an advanced electrophysiology mapping system and ancillary equipment, along with an experienced team, to ensure the best possible patient outcomes.

References