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Catheter Ablation Targeting Complex Fractionated Atrial Electrogram in Atrial Fibrillation

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Abstract

The relatively low success rates seen with pulmonary vein ablation in non-paroxysmal atrial fibrillation (AF) patients as compared to those with the paroxysmal form of the arrhythmia have prompted electrophysiologists to search for newer ablative strategies. A decade has passed since the initial description of complex fractionated atrial electrogram (CFAE) ablation aimed at targeting the electrophysiological substrate in atrial fibrillation. Despite intensive research, superiority of CFAE-based ablation over other contemporary approaches could not be demonstrated. Nevertheless, the technique has an adjunctive role to pulmonary vein ablation in non-paroxysmal AF patients. Perhaps our incomplete understanding of the complex AF pathophysiology and inadequate characterization or determination of CFAE has limited our success so far. This review aims to highlight the current challenges and future role of CFAE ablation.

Introduction

The foundation of catheter ablation for atrial fibrillation (AF) is based on the seminal finding of ectopic foci originating from the pulmonary veins initiating the arrhythmia.[1] However, in patients with long-lasting persistent AF, the current HRS/EHRA/ECAS expert consensus statement recommends more extensive ablation such as linear ablation or targeting of complex fractionated atrial electrograms (CFAE) since pulmonary vein ablation alone yielded much lower success rate than in those with paroxysmal AF.[2] The premise for CFAE ablation is built on the basis that CFAE sites may represent potential substrate sites that contribute to the maintenance of AF.[3] In 2004, Nademanee et al. reported on a novel CFAE ablation strategy with AF termination with or without concurrent anti-arrhythmic drugs in 91 or 63% of patients with persistent AF.[4] However, this high rate of acute procedural success has not been reproducible in other laboratories and CFAE ablation has not been shown to be superior to other contemporary ablation techniques in a recent systematic review.[5] Here, we explore the challenges inherent with characterization of CFAE as well as the current and future role of CFAE ablation in AF.

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None

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What is CFAE?

Depolarization of cardiomyocytes can be recorded as extracellular electrogram by an electrode placed in the vicinity. In principle, electrograms recorded from healthy normal myocardium show a simple morphology, but they can appear complex whenever electrical activation is dyssynchronous. Durrer et al. were first to describe broadening and fragmentation of electrogram using unipolar and bipolar recordings in the ischemic ventricular myocardium due to dyssynchronous activation.[6-10] Gardner et al. further extended this finding with demonstration of inhomogeneous activations and anatomical evidence of individual myocardial fiber separation in regions with CFAE.[3,11-13] More recent studies have identified other potential causes of such dyssynchronous activations: non-local activations from overlying or adjacent structures, tissue discontinuities or anisotropy, wave pivoting or collision, conduction block and endo-epicardial electrical dissociation; although measurement artifacts and electrogram filtering are also known to contribute to electrogram fractionation.[4,14-23]

While the electrical basis of CFAE is easily understood, its pathophysiology remains difficult to establish with diverse mechanisms being proposed to date. First, CFAE has been linked to high frequency AF drivers with several studies describing the proximity of CFAE to sites with high dominant frequency.[9,20,24-26] Likewise, the occurrence of CFAE had been associated with prior increase in atrial activation rate.[27,28] However, simultaneous activation mapping with monophasic action potentials recording showed that only a minority of CFAE sites were related to rapid AF drivers.[29]

More recently, panoramic contact mapping failed to demonstrate CFAE in the vicinity of stable AF rotors.[30] Similarly, only a weak correlation was seen between CFAE and highest Shannon entropy sites taken to represent pivot zones of AF drivers.[31] Second, several activation mapping studies have associated CFAE with the re-entrant mechanism of AF. Using a high-density multi-electrode catheter, Rostock et al. observed activation gradients in their mapping field covering the entire AF cycle length, indicative of local re-entry in regions with the broadest CFAE.[27] In the human posterior left atrium, Atienza et al. also related CFAE to re-entry around a line of functional block.[28] Furthermore, non-contact mapping studies have documented CFAE in the pivot zones and regions of wave break or collisions of meandering re-entrant waves, although CFAE determined with non-contact mapping may not equate to those recorded with direct contact mapping.[6,9,10] However, associations with such re-entrant activation patterns were encountered only in the minority of instances. Third, sites with CFAE are purported to reflect structural abnormalities that may maintain AF as demonstrated in: post-infarct myocardium with separation of myocardial fibers,[11] aging hearts with uncoupling of side-to-side connections between neighboring myocardial fibers,[17] normal porcine atria subjected to acetylcholine infusion and rapid pacing with increased fibrosis and reduced connexin 43 expression,[32] and simulated human heart failure atrial tissue model with heterogeneous fibroblast proliferation.[7] Koduri et al. provided further correlation of CFAE with heterogeneous distribution of fat and fibrosis in the posterior left atrium of canine with induced heart failure.[33] However, clinical studies have also reported that sites with CFAE during AF did not necessary demonstrate low voltage during sinus rhythm or pacing, suggestive of the absence of large structural abnormalities in most cases.[34,35] More recently, combined magnetic resonance imaging for atrial fibrosis and high-density CFAE mapping showed that most CFAE occurred at sites without delayed enhancement in patients with persistent AF.[36] In this study, sites with dense delayed enhancement demonstrated electrograms of lower voltage, less fractionation and longer cycle length than areas without delayed enhancement.[36] Fourth, CFAE have been associated with the autonomic nervous system in initiating and maintaining AF. Several groups have reported the occurrence of CFAE in the proximity of the ganglionated plexi and preceding the onset of AF[15,37] or with parasympathetic activation.[38] Moreover, abatement of CFAE has also been reported following ablation of the ganglionated plexi or with pharmacological autonomic blockade.[15,33,39-41]

Challenges with CFAE Determinations

Linking the phenomenon of asynchronous electrical activation underlying CFAE to pathophysiological causes has been highly challenging. Perhaps, the techniques used in the acquisition, interpretation and characterization of CFAE may in part contribute to the variable findings reported to date.[42] As seen in the published literature on CFAE, there are significant technical variations among investigators in how electrograms are acquired or processed for CFAE determinations. This can range from the type of catheter used (electrode size, inter-electrode spacing and electrode density), the filtering applied, electrogram configuration (bipolar or unipolar) and the CFAE algorithms employed (manual or semi-automated classifications).

Several reports have highlighted the effect of inter-electrode spacing on electrogram amplitude, morphology and fractionation.[43-45] In addition, amplification and filtering of electrograms are known to exacerbate artifacts caused by electrode motion that can resemble CFAE.[46] Bipolar electrode configuration has been the preferred recording technique in most electrophysiology laboratories with the advantage of capturing less far-field signal and compatibility with currently available semi-automated CFAE algorithms. However, it remains unknown whether the direction-dependent nature of bipolar electrograms has any significant impact on CFAE determinations although the impact of bipolar electrogram voltage on CFAE has previously been highlighted.[14,47] Furthermore, bipolar electrograms are not entirely immune from capturing non-local signals especially if these may be just millimeters away.[16] Even though unipolar electrograms are known to provide more precise determination of local activation, there remains a dearth of CFAE studies using unipolar electrode configuration.

The issue with current CFAE definitions has been highlighted recently. In Nademanee's initial report, CFAEs were defined as those with 'two or more deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex' or 'those with very short cycle length (≤120ms)' over a 10-second recording period.[4] Other investigators had defined CFAE with manual classifications that were slightly different to Nademanee's while a more complex grading system has also been proposed recently.[27,29,48,49] Over the last decade, different semi-automated algorithms (Figure 1) have also been investigated and became incorporated into the commonly used 3-D electroanatomic mapping systems (Ensite NavX, St Jude Medical, St Paul, MN, USA or CARTO, Biosense Webster, Diamond Bar, CA, USA).[50-53] However, consistency of semi-automated algorithms are known to be dependent on user-adjustable thresholds of electrogram amplitude, fractionated interval criteria and recording duration.[47,54] Not only are there differences in manual CFAE classifications that are subjected to additional inter-observer

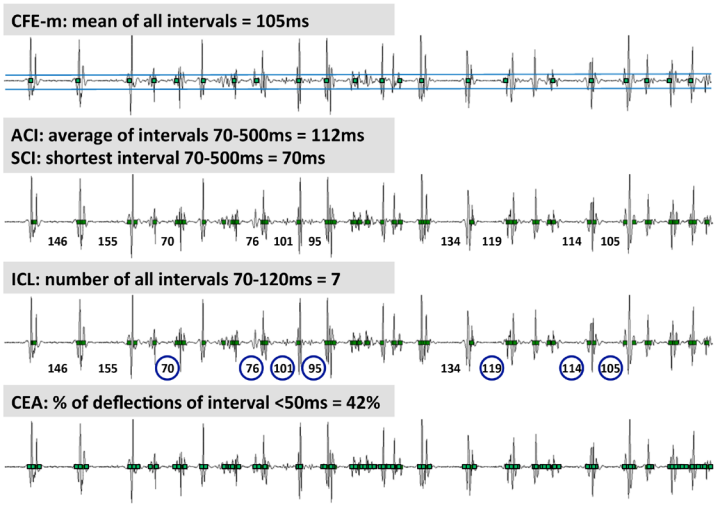

Figure 1: Semi-automated CFAE Algorithms

The 5 different semi-automated algorithms first tagged electrograms or deflections according to their specific amplitude and timing criteria adjusted to avoid noise or far-field detections. Based on the tagged deflections, each algorithm provides a quantitative measure of CFAE that is either interval or count based. In this example, the same 2.5s AF electrogram was subjected to the different algorithm. Complex fractionated electrogram mean (CFE-m) measures the mean of time intervals between all tagged deflections. Average complex interval (ACI) refers to the average interval of tagged deflections between 70 and 500ms. Shortest complex interval (SCI) denotes the shortest interval within the sample between 70 and 500ms. Interval confidence level (ICL) refers to the number of intervals between 70 and 120ms within a 2.5s sampling period. Continuous electrical activity (CEA) is defined by the presence of 2 or more successive tagged deflections with interval <50 ms and expressed as percentage of continuous activity.

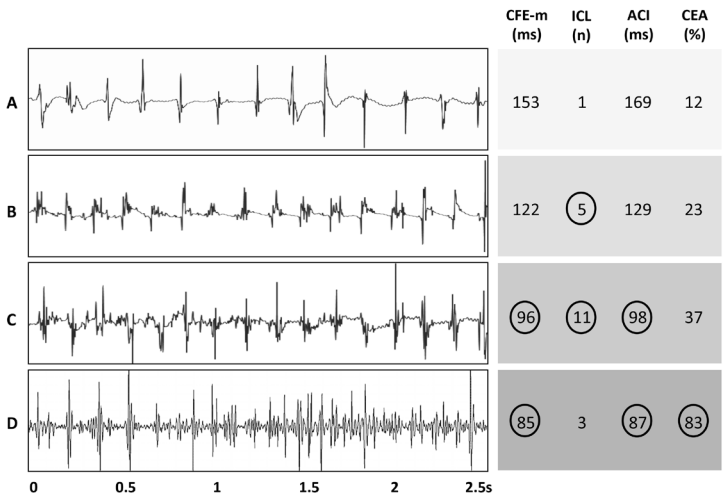

Figure 2: Variability in CFAE Determinations with Semi-automated Algorithms

Four of the five algorithms shown in Figure 1 were applied to four different 2.5s AF electrograms of increasing fractionation (sample A to D). CFAE was defined by complex fractionated electrogram mean (CFE-m) <120ms, interval confidence level (ICL) ≥5, average complex interval (ACI) ≤100ms and continuous electrical activity (CEA) ≥75%. The result is circled when the individual algorithm deemed the electrogram to be CFAE. Full agreement is seen with sample A only. This figure is adapted from Lau et al [Reference 41, Figure 2].

variability, semi-automated CFAE algorithms are also known to vary in CFAE determinations.[26,42,54,55] As shown in Figure 2, four 2.5 seconds bipolar fibrillation electrograms of increasing complexity (A to D) were graded by four different CFAE algorithms semi-automatically using published or default criteria. Non-congruent results were seen in three of the four AF electrograms, even with the most fractionated example in D.

Current mapping techniques in the electrophysiology laboratories utilize sequential acquisition of fibrillation electrograms aiming to cover most of the atrium. This technique provides multiple 'snapshots' of the arrhythmia ranging from 2.5 to 8 seconds in duration. The whole process can take between 10 to 15 minutes, depending on the density of mapping. Although studies have shown that a minimum of 5 seconds at each site is required to achieve good CFAE determinations, these comparisons were only made with the maximum allowable recordings of 8 seconds in the Ensite NavX system.[56,57] Similarly, 5 seconds recordings provided better consistency with CFAE detection as compared to 2.5 seconds using the CARTO mapping system.[54] Of course, the overriding limiting factor is that extensive sequential CFAE mapping will prolong the already lengthy AF ablation procedure. One may wonder whether a short recording segment at each site reflects the arrhythmia adequately. Although several investigators have reported that CFAE were stable and reproducible, Habel et al. was first to highlight the temporal variability in CFAE that constrains the validity of sequential mapping in human AF.[58] This is supported by a more recent systematic review where we reported that one out of four CFAE sites were no longer fractionated in a short time span of under two minutes.[42] Therefore, the inherent dynamic nature of CFAE presents further challenge for electrophysiologists in detecting and targeting them as substrate sites maintaining AF.

Sites with CFAE: Where to Ablate?

Due to our limited pathophysiological understanding and variable technical determinations of CFAE, it is plausible that not all CFAE sites are mechanistically important, while important CFAE sites may have been missed using sequential mapping technique. In general, CFAEs are more prevalent in patients with persistent than paroxysmal AF with higher fractionation, higher percentage area and greater proportion of mapped points with fractionated electrograms.[24,35,59] On the contrary, it has also been reported that greater degree of atrial remodeling, as gauged by larger left atrial dimension and lower atrial voltage, was associated with longer cycle length and smaller percentage area of CFAE.[60] This phenomenon can perhaps be explained by higher left atrial wall stress in those with greater left atrial volume, to account for lower atrial voltage and reduced CFAE.[61]

Nevertheless, numerous pre-clinical and human studies have indicated an association between CFAE and the underlying substrate complexity as a result of progressive atrial remodeling and senescence.[23,62,63] Ciaccio et al. further demonstrated significant differences in electrogram morphology in patients with paroxysmal and long-standing persistent AF independent of activation rate, with lower variability, greater repeatability and more uniform distribution seen at disparate left atrial sites in the latter.[64,65] CFAE are widely distributed in the human atria with preponderance to the left over right atrium and at specific atrial sites where there are abrupt changes in muscle fiber orientation. Early work by Centurion et al in the right atrium of patients with sick sinus syndrome showed a wider distribution of CFAE in those with AF than those without.[66]More recent high-density mapping studies have demonstrated longer CFAE maximum duration, higher fractionation and higher prevalence of CFAE in the left compared to the right atria of AF patients.[24,27,51,52] The sites where CFAE are encountered more frequently differ according to reports. These include the inter-atrial septum, pulmonary vein ostia, posterior left atrium, left atrial roof, left atria appendage, mitral annulus region and coronary sinus.[35,51-53,60,67-70] Specifically, CFAE have been noted to concentrate around the pulmonary veins in paroxysmal AF patients but more evenly distributed over all left atrial regions in those with persistent AF.[52]

The widespread nature of CFAE calls for means of differentiating sites with critical CFAE that maintain AF from non-critical or 'by-stander' sites. Several advantages can be gained by avoiding ablation of non-critical CFAE sites including: reduced procedural time, radiation exposure, risk of complications or collateral damage and longer-term sequelae of iatrogenic atrial tachycardia or 'stiff left atrial syndrome'.[71] Pre-clinical work examining pharmacologic cardioversion of persistent AF in the goats showed that cibenzoline (Class I anti-arrhythmic drug) resulted in AF slowing and organization while reducing electrogram fractionation.[72] Whether anti-arrhythmic drugs can help to distinguish critical CFAE sites and minimize unnecessary ablation of 'by-stander' sites were of interest subsequently. Kumagai and Toyama reported a reduction in CFAE sites following administration of nifekalant and pilsicainide in 60 AF patients undergoing catheter ablation. They were able to terminate AF in about 1 in 4 patients after targeting of the persistent CFAE sites following anti-arrhythmic drug administration.[73] The same investigators also reported higher AF termination rate, shorter procedural time and fewer radiofrequency ablation lesions in patients where adjuvant CFAE ablation was undertaken following CFAE localization with nifekalant than those without, to achieve similar success rates at 12 months.[74] Likewise, in a smaller study, intraprocedural administration of ibutilide has been used to organize AF activity and minimize the adjuvant CFAE ablation lesion set

without a clear reduction in longer-term success rates.[75] A larger prospective double-blinded multi-center study is now underway to further investigate whether ibutilide use can indeed improve current CFAE ablation strategy.[76] Other investigators have also shown that selective ablation of CFAE with certain morphologies led to greater prolongation in AF cycle length than others, indicating a likely usefulness of their CFAE classification system in minimizing ablation of non-critical sites.[49,77]

Current and Future Role of CFAE Ablation

The decade since the initial report by Nademanee has seen a significant number of studies examining the utility of CFAE ablation in AF patients. Pulmonary vein ablation remains the cornerstone for patients with paroxysmal AF and additional CFAE ablation in this patient cohort has not shown significant additional benefits.[78,79]Studies reporting CFAE ablation as a lone strategy in patients with persistent AF have not been able to demonstrate superior success over other established techniques such as pulmonary vein antrum isolation, box isolation or the stepwise ablation approach.[5] The largest of these studies by Oral et al. showed a single procedural drug-free success rate of 33% in 100 chronic AF patients at mean follow-up duration of 14 months.[80] However, recent meta-analyses have shown a beneficial role for adjunctive CFAE ablation following pulmonary vein ablation in patients with non-paroxysmal AF.[78,79]This is despite variability in the CFAE ablation endpoints used, which can range from elimination of fractionated potentials, transformation to discrete electrograms, organization of AF cycle length and termination into sinus rhythm or atrial tachycardia. Although termination of AF appears to confer superior longer-term success rates, this has not been consistently demonstrated, with alternative measures such as dominant frequency assessment having been proposed.[81-84]

At present, CFAE ablation remains as an adjunctive approach following pulmonary vein ablation in patients with non-paroxysmal AF. Its utility and success appear to be hampered by several factors as mentioned in this review: 1) CFAE can be due to a multitude of causes that can result in dyssynchronous activations with diverse pathophysiological mechanisms; 2) Current techniques in CFAE acquisition, interpretation and characterization remains suboptimal and challenging; 3) Difficulty in distinguishing critical from 'by-stander' CFAE sites that promote AF maintenance and risk of excessive or unnecessary ablation that may result in higher complications; 4) Lack of well-defined electrophysiological endpoints for CFAE ablation.

Conclusions:

This review highlights the many challenges with current CFAE-based ablation. Further work is necessary to improve the limitations with regard to our understanding and utility of CFAE targeting in catheter ablation for AF.

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