Review

Catheter ablation of atrial fibrillation guided by complex fractionated atrial electrogram mapping of atrial fibrillation substrate

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Summary Cardiologists and physicians have witnessed a significant change in the management of atrial fibrillation (AF): antiarrhythmic agents are no longer considered more effective than just merely using compounds that control ventricular response of the arrhythmia with anticoagulation in high-risk patients. Catheter ablation has grown into wider acceptance as an important therapeutic modality in treating tachyarrhythmias. And over the past decade, several studies have clearly established that catheter ablation of atrial fibrillation is safe and effective and is an important alternative therapeutic option to the pharmacological approach.

In general, there are two approaches to AF ablation: The anatomical approach, the most popular one, relies on isolation of electrical connections of all four pulmonary veins to the left atrium with or without adjuvant ablations, i.e. additional linear ablations. The second approach is the electrogram-guided approach by mapping and targeting areas of complex fractionated atrial electrograms (CFAE) which is the main topic of this review.

The myriad pathologies leading to and resulting from 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, including mortality benefit, even in high-risk patients with very long standing persistent AF. In this review, we discuss in detail 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 role of CFAE in the hybrid approach of AF ablation using a combination of pulmonary vein isolation and targeting CFAE areas.

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Introduction

It has been just about 15-year anniversary of the first serious attempt to perform catheter ablation to cure atrial fibrillation (AF) [1]. Shortly after Swartz et al. introduced the catheter-based Maze procedure [1], Haissaguerre and colleagues published a landmark paper revealing that the pulmonary veins (PVs) are an important source of triggering foci for paroxysmal AF [2]. This discovery caused electrophysiologists to focus on PVs as important target sites for AF ablation, marking a new era in the treatment of AF.

Antiarrhythmic drugs were the mainstay of AF management for a long time—until two key studies, AFFIRM [3] and RAFT [4], demonstrated that the strategy of maintaining sinus rhythm with antiarrhythmics was not better than that of rate control by a β-blocker or calcium-channel blocker in conjunction with anticoagulation. This observation inevitably disappointed clinicians and prompted researchers to look for an alternative way to treat AF patients. Thus, the development of catheter ablation emerged at an auspicious time.

Catheter ablation for AF is constantly evolving even today. The initial ablative approach was to focally ablate the culprit PV identified as the triggering site initiating AF [2,5]. This approach was quickly abandoned because it was time consuming and had a relatively low success rate. Electrophysiologists then began to isolate the electrical connections of all four veins from the left atrial (LA) muscle.

Various techniques were utilized to achieve electrical isolation of the PVs (PVI) including: (1) segmental isolation introduced by Haissaguerre and colleagues [6]; (2) PVI at the antrum of the PVs at the atrium—venous junction using intracardiac ultrasound guidance [7] or electroanatomical mapping; and (3) circumferential PV ablation popularized by Pappone et al. [8]. To avoid PV stenosis, more investigators now perform PVI further away from the PV ostia, making wider areas of ablation in the LA.

Current approaches for atrial fibrillation ablation techniques

A recent consensus of world-renowned experts in AF ablation states that PVI is a cornerstone of catheter ablation of the AF, and most laboratories perform PVI as the primary approach for patients with paroxysmal AF [9]. Its success rate in the paroxysmal AF subset ranges from 38 to 70% after a single procedure and 65 to 90% after repeated procedures.

However, PVI alone is not effective for treating patients with persistent AF [9]. As a result, there is a strong trend to add ablation lines in the LA and ablate in the coronary sinus and the right atrium (RA) over and above traditional PVI. These developments demonstrate the importance of AF substrate ablations, which should be an integral part of successful ablation strategies.

Logically, the best approach to identify target sites of AF ablation would be to find substrates that perpetuate the arrhythmia. In the past, it was believed that AF substrates cannot be mapped because reentrant circuits underlying the substrate are random and not amendable for point-to-point or endocardial mapping. However, our recent observational studies have demonstrated that substrates serving as “AF perpetuators” can be identified by searching for areas that have complex fractionated atrial electrograms (CFAEs) [10]. During sustained AF, CFAEs are often recorded in specific areas of the atria, and exhibit temporal and spatial stability [10—12]. By ablating areas that have persistent CFAE recording, our studies showed that AF was terminated in over 85% of patients, and more importantly, the procedure yielded a very good long-term outcome in both paroxysmal and chronic AF patients [10,13].

Hence, current ablation techniques include the following two approaches: (1) the anatomical approach with PVI; or (2) the electrogram (CFAE)-guided approach. At present, the anatomical approach is most commonly employed worldwide, whereas the electrogram-guided approach is confined to a few laboratories. Since there have been numerous excellent reviews of catheter ablation of AF using the
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 (CFAEs) [13–15]. 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 [11,12,16]. Third, the CFAE areas represent the AF substrate sites, which have become important target sites for AF ablation [10,17,18]. 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 to 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 ($\leq 120$ ms) with or without multiple potentials; however, when compared to the rest of the atria, this site has the shortest cycle length (Fig. 1).

Electrophysiologic mechanisms underlying CFAEs

The underlying etiology of CFAE has not yet been elucidated, but several theories are being investigated. Pioneering work by Wells et al. [15] identified four types of atrial electrograms that may be present in AF:

- Type I: Discrete complexes separated by an isoelectric baseline free of perturbation.
- Type II: Discrete complexes, but with perturbations of the baseline between complexes.
- Type III: Fractionated electrograms that fail to demonstrate either discrete complexes or isoelectric intervals.
- Type IV: Electrograms of Type III alternating with periods characteristic of Type I and/or Type II electrograms.

Konings et al. [14] applied this knowledge during intraoperative studies and identified three types of AF based on their mechanism of propagation:

- Type I: 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: 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: Presence of three or more wavelets associated with areas of slow conduction (10 cm/s) and multiple arcs of conduction block.

Kalifa et al. [19] 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. 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 for AF relating to the hypothesis that high-frequency reentry at the boundary zones is responsible for the fractionation.
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. 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 (adapted from [20,21]).

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 [20—23]. Six major GPs that may exert influence on the atria (Fig. 2) are:

1. Superior LA.
2. Posterolateral LA.
3. Posteromedial LA.
4. Anterior descending.
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 [24]. Simultaneously, stimulation of sympathetic fibers may occur in similar areas, which can initiate PV ectopy [25]. Unfortunately, mapping and ablating the GP is time consuming and difficult.

Ongoing research has identified a close relationship between the location of CFAE and the GP in animal models [24—26]. 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 [26].

**Regional distribution 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 [10,23,27]. 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 (Fig. 3). Typically, patients with persistent or long-lasting AF have greater numbers and locations of sites with CFAE than those with paroxysmal AF [10].

The distribution of CFAE 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
The most common locations of complex fractionated atrial electrograms are identified (darkest shading) on a grid representing the regions of the right and left atria. LA, left atrium; LAA, left atrial appendage; RA, right atrium; CS, coronary sinus; FO, fossa ovalis; LSPV, left superior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein. The ablation catheter (ABL d) is used to map and ablate the CFAE. The most highly fractionated electrograms can be seen in this example to exist on the LA septal wall, although they still exist in the CS ostia and LIPV antrum. The local electrograms at the RSPV antrum are less fractionated, but have a very short cycle length, and this may represent a “driver.” relatively spatial and temporal stability. Thus, one can perform point-to-point mapping of these CFAE areas and associate them into an electroanatomical map.

### CFAE mapping

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

In our institution, we usually create a map with a minimum of 100 data points, 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 min during an average procedure duration of 113–27 min.

Recently, we developed and tested a customized software package to assist in the process of mapping (CFAE software module, CARTO, Biosense-Webster, Diamond Bar, CA, USA) [11]. The software analyzes data on atrial electrograms collected from the ablation catheter over a 2.5-s 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.

### Procedural details

A decapolar catheter is placed in the coronary sinus for reference and pacing. A single transseptal puncture under hemodynamic and fluoroscopic guidance is used to access the LA. Patients who are not in AF at the onset of the procedure undergo an aggressive induction protocol utilizing burst pacing in the coronary sinus and atria at a lower limit of 1:1 capture or cycle length of 170 ms with additional intravenous isoproterenol (1–3 mcg/min) as required. AF is considered stable for mapping if it can be sustained for more than 60 s.

We use an open-irrigation 3.5-mm-tip ablation catheter with a large or extra-large curve (Thermacool F or J, Biosense-Webster) irrigating at 30 ml/min during lesion creation. Power settings are 35–50 W throughout the atria except for the posterior wall (15–30 W) and coronary sinus (10–25 W). Careful power titration is required during
Figure 4  (A) An example of electroanatomical maps from a patient (PO) who had chronic persistent atrial fibrillation (AF) with severe left ventricular dysfunction and chronic heart failure. The patient also had a previous atrioventricular nodal ablation and implantation of a cardioverter defibrillator. The map shows the 2 views (LAO and PA) [LAO = left anterior oblique; PA = posteroanterior] of mesh-voltage maps of both atria and the coronary sinus. The maps display ablation points (red dots) over the antrum of the left superior pulmonary vein (LSPV), the right superior and inferior pulmonary veins (RSPV and RIPV), septum, lateral aspect of mitral
Catheter ablation of atrial fibrillation

The atria no longer able to sustain AF (10). The findings are critical in perpetuating AF and RF ablations over these areas, resulting in the termination of AF and rendering areas indeed the substrates that perpetuate AF. These findings also demonstrate that our ablation approach is very effective and yields excellent long-term outcomes; thus, by elimination of CFAE areas, the substrate is also removed and the atria can no longer fibrillate.

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 (10). 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 3D 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 $172 \pm 26$ ms at baseline to $237 \pm 42$ ms ($p < 0.05$).

Clearly, the preceding findings suggest that CFAE areas are indeed the substrates that perpetuate AF. These findings also demonstrate that our ablation approach is very effective and yields excellent long-term outcomes; thus, by elimination of CFAE areas, the substrate is also removed and the atria can no longer fibrillate.

Long-term clinical outcomes

We recently expanded the preceding findings by studying 540 high-risk patients with both paroxysmal and chronic AF, who underwent catheter ablations for AF. Twenty-six patients were lost to follow-up [18].

After the follow-up period of 839 ± 493 days, 445 of the 514 patients remained in normal sinus rhythm (NSR) (87%); the remaining 69 patients continued to have AF (paroxysmal AF in 17, persistent AF in 34, and atypical atrial flutter in 2 patients). AF ablations were significantly more effective in maintaining sinus rhythm in patients with paroxysmal AF (93%; 208 of 224 patients) and persistent AF (87%; 99 of 114 patients) compared to those with permanent AF (78%; 138 of 176 patients). Of these 445 patients who remained in sinus rhythm, only 59 patients (11%) were taking antiarrhythmic agents: 43 oral amiodarone and 16 sotalol.

Effects of maintaining sinus rhythm on mortality

As shown in Fig. 5, maintaining sinus rhythm was associated with a much better survival rate compared to those whose AF ablation failed to restore sinus rhythm ($p < 0.0001$). There were 20 deaths; 11 of the 445 patients (2.5%; 3 cardiac and 8

radiofrequency (RF) to ensure complete lesion creation. RF duration is usually 10–60 s and is halted because of patient discomfort or elimination of CFAE. Because of occasional noise on the ablation catheter during RF, multiple short (15–30-s) applications may be used.

One of the most important aspects of CFAE ablation (and one of the most common challenges early in the learning curve of this technique) is to revisit areas that were initially ablated to ensure that there has been no recovery of electrical activity. If the patient remains in AF despite elimination of all visible CFAE, intravenous ibutilide (1 mg over 10 min; may repeat once to a maximum of 2 mg) is used to increase the cycle length of the arrhythmia in “non-driver” atrial tissue and thus highlight the remaining areas of greatest significance (e.g. CFAE associated with perpetuating AF).

Alternatively, an intravenous dose of procainamide at 1000 mg given as 20 mg/min may be used. Often during CFAE-targeted AF ablation, the arrhythmia evolves into an atrial tachyarrhythmia (AT). Using the CS catheter as a reference, the AT is subsequently mapped and ablated. Most often the sites of origin of the AT are at the same locations as the CFAE, which were targeted during the initial part of the procedure. The endpoints employed are either: (1) termination of AF (and if the presenting rhythm was paroxysmal AF, it must not be re-inducible); or (2) elimination of all CFAE.

Occasionally, a patient will remain in AF or AT after an extensive ablation eliminating all CFAE, and despite the use of ibutilide. In this small group of patients, an external cardioversion is required. Fig. 4 shows examples of our map from a patient who had persistent AF and severe LV dysfunction; the patient had previous atrioventricular (AV) nodal ablation with an implantable cardioverter defibrillator. After the ablation, atrial fibrillation burden was reduced to zero percent as shown in Fig. 4C; maintaining SR in this patient improved ejection fraction from 21% before the ablation to 54%.

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RF ablation of the area with CFAEs was performed to the closest anatomic barrier. We found CFAE in seven different

annulus and the coronary sinus OS; cavo-tricuspid isthmus was also ablated. Ablation over these areas terminated AF (B). Insets show representative electrograms over the areas pointed by the arrows. Note that atrial electrograms over the left the antrum of the pulmonary veins were low voltage complex fractionated atrial electrograms. Cavo-tricuspid isthmus areas of the right atrium also showed fast atrial electrograms (<120 ms) compared to the rest of the right atrium. The patient had been AF free for a couple of years as shown in (C). (C) A cardiac compass of AF burden from the patient of Fig. 1. After the ablation, the patient had no recurrent AF. (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)
Figure 5  Kaplan—Meier curve demonstrating improved survival in patients who remained in normal sinus rhythm (NSR) from all-cause mortality compared with patients who remained in atrial fibrillation (AF).

noncardiac deaths) who remained in NSR died compared to 9 of the 69 patients (13%; most were cardiac deaths) whose ablation failed to restore sinus rhythm during the follow-up period.

Multivariate analysis showed that sinus rhythm was an independent factor for survival (hazard ratio 0.085; \( p < 0.0001 \)), whereas AF was a dependent risk of death (hazard ratio 11.8; \( p < 0.0001 \)).

History of congestive heart failure, but not EF, was also an independent risk of death (hazard ratio 6.3; \( p = 0.0004 \)).

Effects of maintaining sinus rhythm on EF

There were 124 patients who had a depressed EF (\( \leq 40\% \)), of these 124 patients, 101 patients were in NSR. EF significantly improved after 6 months of being in NSR in a significant number of patients (Fig. 6); the EF increased from 31 ± 6% to 41 ± 12% (\( p < 0.001 \)). In contrast, there were no changes in EF in the 23 patients who failed to respond to AF ablation and remained in AF (pre-ablation EF was 24 ± 8% and post-ablation EF was 23 ± 8%).

Fig. 7 shows the Kaplan—Meier survival curves comparing four strata: Patients in sinus rhythm with an EF \( \leq 40\% \); patients in sinus rhythm with EF > 40%; patients in AF with EF \( \leq 40\% \); and patients in AF with EF > 40%. Clearly, patients with an EF \( > 40\% \) have the worst prognosis. Interestingly, patients with an EF \( > 40\% \), but who remained in AF had a lower survival rate compared to patients in sinus rhythm regardless of the EF.

Figure 6  Comparison of individual changes in ejection fraction before and after ablation: normal sinus rhythm patients after ablation vs. atrial fibrillation patients after ablation. Pre = pre-ablation and Post = 6—12 months post-ablation.

Figure 7  Multiple overlay Kaplan—Meier survival curves among 4 strata of patients: (1) patients with ejection fraction (EF) > 40% and normal sinus rhythm (orange), (2) patients with EF < 40% and normal sinus rhythm (green), (3) patients with EF > 40% and atrial fibrillation (purple), and (4) patients with EF < 40% and atrial fibrillation (blue). (For interpretation of the references to color in the figure caption, the reader is referred to the web version of the article.)
Relation between discontinuation of anticoagulation therapy and bleeding, stroke, and embolic incidence

Anticoagulation (AC) therapy was discontinued in 392 patients (76%). Seven patients experienced a major stroke or transient ischemic attack (TIA); 3 patients whose AC therapy was stopped developed a serious stroke and 1 patient had a TIA (1%) compared to 3 patients (2.7%) in the group with continued AC treatment; 2 were ischemic strokes and 1 involved central nervous system bleeding leading to patient death.

Thus, the AC group had a higher rate of events (death, bleeding, stroke) compared to the no-AC group, largely due to the higher death rate in the AC group since the majority of the anticoagulated patients continued to have AF.

Procedure complications

Five patients suffered from a cerebrovascular accident (CVA) (0.9%); incidentally, in 2 of the 5 patients, CVA occurred 24–48 h after the procedure. Hemopericardium occurred in 7 patients (1.4%), 1 of which required cardiovascular surgical repair of the perforation of the LA at the ablation site; the remaining 6 patients were treated successfully with pericardiocentesis. Nine patients developed major vascular complications at the groin sites (7 pseudoaneurysm; 2 AV fistula). Two patients developed AV block and required permanent pacemaker implantation. Three patients had transient pulmonary edema after the procedure. There were no procedure-related deaths. However, two patients died within 30 days of the procedures. One of the preceding patients who developed a serious stroke 2 days after the procedure died from a stroke 3 weeks later, and the other patient died from respiratory failure from her chronic obstructive pulmonary disease complicated with infection.

Other studies

Our introduction of CFAE mapping to guide AF ablation, as an alternative to anatomical approach of PVI, either alone for PAF or with linear lesions for chronic AF, spurred other investigators to follow our approach. Unfortunately, our results were not fully reproduced by others [28,29]. Oral et al. mapped CFAE as target sites for AF substrate in patients with chronic AF [28]. Of the 100 patients in this study, only 12 (12%) patients had AF converted to sinus rhythm during the ablation and 4 (4%) converted to atrial flutter. After ibutilide treatment, 27 more patients converted to sinus rhythm and 13 to atrial flutter. There were 44 patients (44%) who remained in AF and were converted to SR by external cardioversion. The low acute AF termination rate in the Oral et al. study also rendered a high rate of AF or atrial tachyarrhythmia recurrences: only 33% of their patients were in SR without any antiarrhythmic drug after single procedure (mean follow-up of 14 ± 7 months) and 57% of the patients were in SR after the second procedure. However, our subsequent experience in 410 persistent AF who underwent AF ablation guided by CFAE mapping confirmed our initial observation and in contrast with Oral’s study [18,30,34]. We were able to terminate atrial fibrillation in 80% of the patients (including using ibutilide). Of the 410 high-risk patients in our study, 81% were in SR without any antiarrhythmic drug including the second procedure.

While it is unclear what exactly are the factors underlying the differences in both acute and long-term outcomes between the two studies, it seems more likely that one or more of the following key variables may help explain the differences between the 2 studies [30]: (1) Right atrial ablation: Oral and co-workers, in the above study, did not map and ablate the right atrium. We found that 15% of our patients required right atrial ablation; the common sites are right postero-septum, 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 is significantly higher than those of Oral et al. (3) Ablation endpoint: perhaps this variable is the most significant factor influencing the differences in the two studies. We believe that 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 and 0.1 mV) are often the most desirable. By contrast, Oral and co-workers 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 the Oral study and our study is also different. After elimination of CFAE site ablations, we deliberately attempt to ablate all "new" arrhythmias including pleomorphic forms of atrial tachyarrhythmias whereas Oral and colleagues did not. Furthermore, we did not use ibutilide solely for converting the arrhythmias to sinus rhythm but rather as an aid to assist in mapping the tachycardia after CFAE ablations. My colleagues and I share the same experiences as Oral et al. in that ibutilide rarely converts the arrhythmias to SR. However, the drug is invaluable in helping identify sites that continue to be the source of tachyarrhythmias by further lengthening the tachycardia cycle length and removing the pleomorphic form of the tachycardia or making the tachycardia more stable. Again, often after ibutilide, we found that we had to go back to the areas that we had previously ablated and had to reapply RF applications to terminate tachycardia. CFAE mapping in the left atrium requires a deliberate and painstaking effort to explore all areas of the atria. (5) Comprehensive mapping: lastly, the electroanatomic map for CFAE should have high density of evenly spread mapping points. It was unclear whether other investigators committed to detailed mapping of the CFAE; but there is no question that the key to the success of AF ablation guided by CFAE must have all areas of the atria and coronary sinus explored.

Ablation of CFAE as an adjuvant to PVI and linear ablations

Recently, ablation of CFAE areas during AF has been adopted as part of a hybrid approach for AF ablation, espe-
Table 1
Comparisons of outcomes of different ablation approaches that incorporated complex fractionated atrial electrogram ablation in patients with atrial fibrillation.

<table>
<thead>
<tr>
<th>Investigators and ablation technique</th>
<th># of patients</th>
<th>Age (yr)</th>
<th>Procedure/time (min)</th>
<th>RF time (min)</th>
<th>Long-term success (1—2 ablations)</th>
<th>Acute AF termination</th>
<th>Types of AF success for persistent after 1 ablations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verma et al. [31]</td>
<td>40</td>
<td>56 ± 9</td>
<td>188 min/84 min</td>
<td>57 ± 12</td>
<td>82%</td>
<td>Persistent</td>
<td>Persistent 57% ± 12, Persistent 87% NA</td>
</tr>
<tr>
<td>Haissaguerre et al. [32]</td>
<td>60</td>
<td>53 ± 9</td>
<td>264 min/84 min</td>
<td>NA</td>
<td>264 min/84 min</td>
<td>Persistent/long lasting</td>
<td>Persistent 54 ± 19, Persistent 3% (with ibutilide)</td>
</tr>
<tr>
<td>Oral et al. [33]</td>
<td>50</td>
<td>62 ± 8</td>
<td>254 min/59 min</td>
<td>54 ± 19</td>
<td>34% (with ibutilide)</td>
<td>Paroxysmal (n = 42)</td>
<td>Paroxysmal 88% for PAF, 20% for Persistent (n = 25)</td>
</tr>
<tr>
<td>Porter et al. [17]</td>
<td>67</td>
<td>59 ± 10</td>
<td>197 min/33 min</td>
<td>50 ± 13</td>
<td>88% for PAF, 20% for Persistent</td>
<td>Paroxysmal</td>
<td>Paroxysmal 90% success for Persistent after 1 ablations</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; APVI = antrum pulmonary vein isolation; CFAE = complex fractionated atrial electrogram; PVI = pulmonary vein isolation; RF = radiofrequency.

Average fluoroscopic and RF times are given as mean values.

Table 1 summarizes the results of the recent published data which revealed that the long-term success rate after a hybrid approach of combining PVI plus CFAE ablation and linear lesions at some institutions yielded a better success rate than PVI alone in patients with persistent AF.

For patients with PAF, Porter et al. performed ablation initially targeting CFAE and resulting in AF termination in 88% of the patients and the investigators then proceeded to perform PVI yielding 90% long-term success in these PAF patients after a single procedure [17]. These results are quite impressive and clearly suggest further evaluations of the role of a combined PVI and CFAE ablations in treating AF patients.

### Conclusions

In conclusion, data from the technique of substrate ablation guided by CFAE mapping, in contrast with previous studies in AF ablation that included largely a young paroxysmal AF population, show greater benefits to the elderly and high-risk populations with structural heart disease. Clearly, more studies are needed before recommending catheter ablation as the first-line therapy for all high-risk AF patients. In the meantime, our research demonstrates that the catheter-based ablative approach is a promising modality for many symptomatic AF patients, and has great potential to become the mainstay for AF treatment.

Finally, one must recognize that AF ablation, regardless of the technique used, is a challenging task that requires operator skills in manipulating catheters in the atrial chambers, understanding all facets of clinical electrophysiology, early recognition, and treating procedure-related complications. Many of these skills can be achieved with proper training and hands-on experience after exposure to an adequate number of the procedures.

Advances in technologies and development of new tools such as robotic navigation of catheters, which are being introduced at an impressive pace, will undoubtedly help electrophysiologists to become more proficient to the task. 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.

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References


