Complex Fractionated Atrial Electrograms in Catheter Ablation of Atrial Fibrillation
Dead and Buried?

Aman Chugh, MD

_Are you gonna curse the darkness or light a candle?_

—Terry Hayes, _I Am Pilgrim: A Thriller_¹

Since the early days of atrial fibrillation (AF) ablation, it has been clear that patients with the persistent form respond poorly with pulmonary vein (PV) isolation.² Despite increasing experience with PV isolation and improvement in technology, the long-term efficacy of a PV-only approach in patients with long-standing arrhythmia is only ≈24%.³ Patients with persistent AF are afflicted with a greater degree of structural and electric remodeling than those with the paroxysmal form.⁴ Further, the structural changes are diffuse, which may help explain the multitude of target sites (left atrial [LA] appendage, coronary sinus, right atrium, among others) that may be involved in perpetuating the arrhythmia. Given a wide array of possible sources that vary from patient to patient, electrophysiologists have sought to identify electrograms that may be important in maintaining AF, irrespective of the location. The assumption is that complex, fractionated atrial electrograms (CFAE) may be markers of driver sites.⁵ The results have been mixed, with some studies concluding that CFAE ablation is incremental and others reporting no benefit. A prior meta-analysis concluded that CFAE ablation was associated with an improvement in outcomes in patients with persistent AF.⁶

In this issue of the _Circulation: Arrhythmia and Electrophysiology_, Providência et al present another meta-analysis that examines the impact of CFAE ablation in patients with both persistent and paroxysmal AF.⁷ A total of 13 studies were included, 9 of which were randomized controlled trials. Among the 1415 patients (number of participants per study, 35–318), 815 underwent PV+CFAE ablation and 600 underwent PV isolation only. CFAEs were defined by an automated algorithm in 6 studies and on the basis of visual inspection in the remaining.

Pooled data failed to reveal any benefit of CFAE ablation. CFAE ablation failed to improve outcomes in patients with paroxysmal (n=398, 28%), persistent, and long-standing persistent AF. Only 2 of the 13 studies suggested benefit, and the remainder were neutral. Nonrandomized studies were more likely to report a positive outcome. There was a trend toward better outcomes in the PV+CFAE group if the patients underwent linear ablation. CFAE ablation also seemed to benefit patients with a longer history of AF. Serious complications occurred in 1% to 1.5% of patients and were not related to more extensive ablation in the PV+CFAE group.

Why did not adjunctive ablation of complex electrograms result in better outcomes? We know that additional effort and radiofrequency energy were expended. But what is not reported in some of the studies is the actual impact of substrate ablation. In other words, did additional ablation slow or terminate AF? If not, it may be argued that the critical targets were not identified with the mapping protocol. Further, in some of the studies, patients randomized to CFAE ablation did not receive PV isolation, which may be considered heretical by today’s standards. In others, not all resultant organized atrial tachycardias were mapped and ablated; the operator had the option of performing transthoracic cardioversion instead.

Recall that there is no universal definition of CFAE and that multiple algorithms and visual methods were used in the studies included in the meta-analysis. It is unlikely that the investigators were targeting the same type fibrillatory electrogram, which may help explain the disparate findings. Also, fragmented atrial signals during AF are frequently generated by nonlocal activation.⁸ Targeting an electrogram that is rendered complex only on the basis of far-field activation (pseudo CFAE) is unlikely to affect AF. Furthermore, CFAEs may be generated by variety of processes, including conduction slowing/block, wave collision, oscillations in AF cycle length, autonomic influence, meandering of the source, and others. It may be difficult to decipher whether a given fragmented electrogram is being inscribed by active or passive phenomena.

The negative results of this meta-analysis perhaps should not be surprising because we do not even know what we are looking for when mapping for AF sources outside the PVs. Are AF sources maintained by small⁹ or large areas¹⁰ of reentry or focal activity? What do electrograms at the source look like? Are they discrete and rapid, and are they surrounded by fractionation because of an inability of adjacent areas to be activated in a one-to-one fashion? Are insights into such critical mechanistic questions only available through high-resolution optical mapping, which is not possible in intact human hearts? In the absence of such basic information, one may rightly question the assumptions that spawned some of the automated algorithms and their routine use. A recent study,
which compared various algorithms found that they demonstrated poor correlation with each other and with other methods used to characterize the atrial substrate.\textsuperscript{15}

Paroxysmal AF may be eliminated in \textasciitilde90\% of patients with PV isolation alone, and thus, routine extraneous ablation, in the form of CFAE or linear ablation, should be avoided in this setting. Patients with persistent AF should also receive PV isolation, but it as a sole strategy is unlikely to eliminate AF in the majority of patients. Although this study and the recently published STAR AF II trial (which was included in the meta-analysis) suggest a lack of benefit of extra-PV ablation,\textsuperscript{12} their results are nonetheless unsettling. In the latter, freedom from atrial arrhythmias was only achieved in 41\% of patients randomized to PV isolation after one procedure.

Fortunately, we do have some direction in an attempt to improve outcomes in patients with persistent AF. After PV isolation, both atria and the coronary sinus should be mapped for high-yield electrograms, that is, target sites whose ablation is likely to slow or terminate AF. Such sites are characterized by continuous activity, electrogram offset between the distal and proximal mapping electrode (signifying rotational activity), and short cycle length activity. Ablation of these sites has been shown to have a favorable effect in slowing or terminating AF.\textsuperscript{15} An elegant study showed that ablation of such sites indeed slows AF, whereas ablation of sites without continuous activity has a negligible effect.\textsuperscript{14} These data rule out a debulking effect of electrogram-based ablation and confirm that such sites are critical in maintaining AF. The advantage of this approach is that it does not require specific software or technology, only one’s eyes.

It must be acknowledged that AF often persists after ablation of such sites. It seems likely that not all AF sources are characterized by fractionation. For example, if a source is maintained by a large circuit, one may identify relatively discrete electrograms along the reentrant path. It is possible that we are oblivious to some sources because of our assumption that fractionation is the sine qua non of AF drivers. It is also possible that conventional mapping is unable to identify some sources because of suboptimal resolution of current mapping tools or on an epicardial location.

If AF persists after PV isolation and CFAE ablation, one may consider linear LA ablation.\textsuperscript{15} Even after such extensive ablation, AF usually does not give way to sinus rhythm, but to atrial tachycardia(s) instead. These circuits are often complex and contribute to an already lengthy procedure. However, one can expect a successful midterm outcome in \textasciitilde85\% of patients (with repeat procedures; without antiarrhythmic medications) with an extensive ablation strategy.\textsuperscript{16,17}

Apart from this strategy, there are number of other approaches that have been proposed in patients with persistent AF. These include isolation of the LA appendage,\textsuperscript{18} mapping and ablation of AF triggers,\textsuperscript{19} posterior LA isolation, and ablation of ganglionated plexi. Whatever method one chooses, it is imperative that the operator demonstrates an impact of the ablation protocol, for example, by comparing the pre- and post-ablation cycle length of the appendages.

The authors have made a forceful argument against CFAE ablation as it is performed today. In doing so, they have made us pause and reflect on how we are executing substrate ablation. The elephant test as it applies to CFAEs ("I don’t know how to describe a CFAE but I’ll know it when I see it”) is no longer sufficient. The current iteration of automated software designed to identify impactful fibrillatory electrograms has also been shown to be lacking. Yes, we all would welcome real-time AF mapping that would readily point us toward the source, but we are not completely rudderless until then. For example, we should focus on those relatively unambiguous electrograms, which have rigorously been shown to be critical in maintaining AF. For those patients who remain with AF after elimination of such electrograms in the LA, linear ablation and right atrium ablation may be helpful. This approach is difficult, but does offer the patient with persistent AF a reasonable chance of success.


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