Trials and Travails of Electrogram-Guided Ablation of Chronic Atrial Fibrillation

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Catheter-based ablation has revolutionized arrhythmia management by offering the most definitive treatment for virtually all types of tachyarrhythmias. The reasons behind the success of ablation are many, but chief among them is the ability of the electrophysiologist to identify underlying mechanisms and to precisely localize and eliminate the tachycardia foci or circuits. Armed with many new tools to map and ablate these arrhythmias, electrophysiologists gain experience and become more proficient in the procedure, resulting in a shortened procedure time, increased rates of success, and decreased rates of complications. As a result, catheter ablation is gradually but inexorably replacing pharmacological approach as the first-line therapy for just about all supraventricular tachyarrhythmias except atrial fibrillation (AF).

Unlike ablation for other types of supraventricular tachyarrhythmias, ablation of AF generally is not based on mapping of target sites for ablation; rather, it relies largely on an approach that aims to electrically isolate the pulmonary veins, especially for paroxysmal AF.1–4 The rational behind this anatomic approach is 2-fold: that the pulmonary veins are the primary sites responsible for AF initiation and perpetuation in most patients and that human AF is too complex to map and the responsible reentrant wavelets are too capricious for point-to-point mapping. However, although pulmonary vein isolation is very successful in treating paroxysmal AF, it alone is not effective in treating chronic AF. Often, supplement linear ablations are added to the pulmonary vein isolation with a significantly improved success rate.1 It has become clear that to successfully ablate chronic AF, more extensive ablations are essential, but it remains unclear why and how this combined approach works.

It is possible that the multiple linear lesions (ie, a mitral isthmus line, roofline) in addition to pulmonary vein isolation effectively modify AF substrate akin to a surgical Maze procedure. However, treating all chronic AF patients with an identical approach has 1 glaring weakness: Not all chronic AF patients are the same. Subjecting every patient to the same ablation set is not logical and likely results in many unnecessary lesions. The search for a new approach to identify target areas for AF ablation resulted in 2 new strategies: mapping of “high-dominant-frequency areas” and mapping of areas with stable complex fractionated atrial electrograms (CFAEs).

Unfortunately, mapping of high-dominant-frequency areas has been shown not to be effective in chronic AF patients.5 On the other hand, mapping of CFAE as target sites for AF ablation has shown great promise.6 This approach is based on observations of several recent mapping studies in human AF. During sustained AF, CFAEs often are recorded in specific areas of the atria and exhibit surprisingly remarkable temporal and spatial stability.6,7 CFAEs usually are low-voltage electrograms (0.05 to 0.25 mV) with highly fractionated potential or with a very short cycle length (≤120 ms). What causes CFAEs in human AF? Although there is not a clear answer to this question, the following represent prevailing ideas of possible mechanisms. First, CFAEs are found mostly in the areas of slow conduction and/or pivot points where the wavelets turn around the end of the arch of the functional block.8 Second, local vagal stimulation in the atrial myocardium could markedly shorten local refractory periods, resulting in high-frequency CFAEs.9 Third, CFAEs could represent an area of focal reentry using pathological or functional anisotropic propagation; this phenomenon is commonly observed in ischemic myocardium or around the border zone of the scarred myocardium. Fourth, mapping of sustained AF in sheep models has demonstrated that CFAEs are found in the boundaries of high-frequency excitation (mother rotors), suggesting that CFAE areas may not be the main driving source that perpetuates AF but are in a location that abuts the driver.10 It is possible that some or all of the above electrophysiological changes are the underlying causes of CFAE. However, regardless of the mechanism underlying CFAEs, it is compelling to hypothesize that CFAE areas represent AF substrate and should serve as good target sites for AF ablation, especially for chronic AF patients.

Indeed, my colleagues and I found that by targeting CFAE sites in both paroxysmal and chronic AF, we were able to lengthen tachycardia cycle length, organize AF into atrial tachycardia or flutter, and then terminate it in most patients.6 Our findings support the above hypothesis that CFAE sites represent AF substrate. If this observation is confirmed by studies from other investigators with a larger number of patients, mapping CFAE sites for AF ablation would lead the electrophysiologist back to mapping arrhythmogenic areas for a successful AF ablation and perhaps provide an alternative approach to the current anatomic approach.
Unfortunately, the observation by Oral et al.\textsuperscript{11} from their study published in this issue of \textit{Circulation} douses any fiery enthusiasm of mapping CFAEs as target sites for AF substrate. Of the 100 patients with chronic AF in this study, only 12 patients (12\%) 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. Forty-four patients (44\%) remained in AF and were converted to sinus rhythm by external cardioversion. The above findings raise doubt as to whether CFAE is a good surrogate for key AF substrate and challenge our initial observation. However, our subsequent experiences with 290 high-risk chronic AF patients (114 persistent AF, 176 permanent AF) confirmed our initial observation and are in contrast to the study by Oral et al. Of these 290 high-risk patients, we were able to terminate AF by targeting CFAEs alone in 181 patients (62\%) to sinus rhythm during ablation (using an 8-mm-tip Navistar catheter) of CFAE target sites and in 65 additional patients (22\%) whose ablation was augmented by ibutilide treatment. Forty-four patients required external cardioversion to restore sinus rhythm. Of the 44, only 6 were in AF before cardioversion (all also had ibutilide infusion), and the remaining 48 had organized flutter that could not be converted by ablation.

Not surprisingly, the low acute AF termination rate in the Oral et al study also renders a high rate of AF or atrial tachyarrhythmia recurrences; only 33\% of their patients were in sinus rhythm without any antiarrhythmic drug after a single procedure (mean follow-up, 14±7 months), and 57\% were in sinus rhythm after the second procedure. In contrast, 175 of the 290 patients (60\%) in our study were in sinus rhythm without any antiarrhythmic drug after a single procedure (mean follow-up, 28±16 months), and a total of 229 patients (79\%) maintained sinus rhythm after the second procedure.

How then does one reconcile the differences in both acute and long-term outcomes between the 2 studies? Although one cannot exclude the possibility of differences in patient population, this is unlikely to be the key factor. It seems more likely that ±1 of the following variables may help explain the differences between the 2 studies.

\textbf{Right Atrial Ablation}

Ooral and coworkers did not map and ablate the right atrium. My colleagues and I found that 15\% of our patients required right atrial ablation; the common sites are right posterosuperior, cavo-tricuspid isthmus, tricuspid annulus, and rarely posterior wall of the right atrium and superior vena cava–right atrial junction.

\textbf{Power and Duration of Radiofrequency Energy Applications}

We set our maximum temperature at 60°C (maximum power, 70 W) along the septum and anterior wall compared with 50°C in the study by Oral et al. At the pulmonary vein ostia, we set the maximum temperature at 50°C with the maximal power at 60 W compared with 35 W in the Oral et al study.

\textbf{Ablation End Point}

Perhaps this variable is the most significant factor influencing the differences in the 2 studies. We believe that CFAEs are low-voltage atrial signals usually ranging from 0.05 to 0.25 mV, and the areas with the very low-voltage signals (between 0.05 and 0.1 mV) are often the most desirable. In contrast, Oral and coworkers defined successful lesion creation as a voltage reduction to <0.1 mV or a decrease by ≥80\% of preablation voltage. 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 is terminated are often the sites where we had applied radiofrequency before, and the voltage of atrial signals at these successful sites often ranged from 0.5 to 0.8 mV.

\textbf{Procedure End Point}

The procedure end point between the Oral et al study and our study also is different. After elimination of CFAE sites, we deliberately attempted to ablate all “new” arrhythmias, including pleomorphic forms of atrial tachyarrhythmias, whereas Oral and colleagues did not. Furthermore, we did not use ibutilide solely to convert the arrhythmias to sinus rhythm but rather as an aid 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 sinus rhythm. However, the drug is invaluable in helping to 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 return to the areas that we had previously ablated and reapply radiofrequency applications to terminate tachycardia.

\textbf{Comprehensive Mapping}

CFAE mapping in the left atrium requires a deliberate and painstaking effort to explore all areas of the atria. The electroanatomic map for CFAE should have a high density of evenly spread mapping points. Interestingly, an example of the electroanatomic map shown in Figure 2 of the Oral et al study appears not to have enough points over the mid septum, roof, and posterior aspect of the right superior pulmonary vein.

It is not unusual to miss some CFAE areas very close to the areas where previously mapping has been done. Although Oral and his colleagues are very experienced AF ablators, they may have missed some important CFAE areas, especially if they contain very low-voltage signals <0.1 mV.

Whether the above confounding variables govern the success or failure to acute AF termination during the procedure remains unclear. One may also argue that AF termination does not bear a relationship to the long-term outcomes as shown by Oral et al. However, the number of patients who converted to sinus rhythm acutely was very small, making it difficult to draw any firm conclusions. In essence, more lesions may be needed for many of the patients of Oral et al to increase rates of AF termination, to reduce the number of repeated procedures, and to deliver a better long-term outcome.
The Oral et al study is important because it draws our attention to the odyssey of mapping AF substrate in humans and using it to guide a successful AF ablation, particularly in chronic AF patients. Further studies are needed before we can either accept or reject the concept of AF substrate ablation by targeting CFAE sites. The results from future studies addressing the controversy will undoubtedly settle the debate between the anatomic approach and the target approach or support a hybrid procedure combining both the anatomic and the electrogram-guided approaches. Meanwhile, I will continue to target CFAE sites because it not only has produced excellent long-term outcomes thus far but also follows the logical path of targeting arrhythmogenic areas in an approach similar to the highly effective ablation therapy for other cardiac tachyarrhythmias. Choosing to be on this path that is less traveled will eventually help settle all the differences between our ablation approaches.

Disclosures
Dr Nademanee has received a research grant and honoraria from and has served as a consultant or on the advisory board for Biosense Webster.

References

Key Words: Editorials □ ablation □ atrial fibrillation □ arrhythmia □ catheter ablation □ electrophysiology □ fibrillation
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Circulation. 2007;115:2592-2594
doi: 10.1161/CIRCULATIONAHA.107.700187
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/115/20/2592

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