The Substrate Maintaining Persistent Atrial Fibrillation

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Complex fractionated atrial electrogram (CFAE) ablation is one successful approach for treating patients with persistent atrial fibrillation (AF), along with strategies that incorporate pulmonary vein isolation and linear lesions. In this issue of Circulation: Arrhythmia and Electrophysiology, Oral et al\(^1\) investigate the effect of right atrial CFAE focused ablation in patients with long-lasting persistent fibrillation. All patients had CFAE ablation in the left atrium and coronary sinus, and patients who did not convert to either sinus rhythm or atrial tachycardia were randomized to either additional right atrial CFAE ablation or to no further ablation. Patients were followed up for more than 1 year with similar outcomes in both groups, which suggests that right atrial CFAE ablation has no incremental benefit to targeting CFAE in the left atrium in persistent AF. Oral et al\(^1\) do acknowledge some limitations in their study design, which may have given a false-negative result.

Does CFAE Represent the Atrial Substrate?

The Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus document\(^2\) on catheter and surgical ablation of AF suggests that areas with CFAEs potentially represent AF substrate sites, ie, the atrial, venous, and ganglionic tissue that is critical in perpetuating or “driving” AF. Is this widely held assumption that CFAEs are related to the substrate correct? CFAEs are defined as electrograms displaying fractionation, and so far they also have not been helpful in differentiating between myocardial fibers sensed by the recording electrode, is supported by multiple prior studies, notably those by Spach and Allessie. Underlying myocardial fibers have poor electrical coupling and can be separated by fibrous tissue, causing activation to spread into a maze of micropathways. Fractionation is critically dependent on both the direction of wavefront progression and its cycle length.\(^3,6\) In animal experiments, Kalifa et al\(^8\) demonstrated that the fractionation was located at the boundary of high-frequency sources because of wavebreak related to local tissue architecture. In humans, high-density mapping during AF demonstrated that the formation of CFAE was preceded in 91% of mapped sites by shortening of the atrial cycle length, which further supports the key role that cycle length plays in the generation of CFAE.\(^9\) In practice, diffuse fractionation will accompany short AF cycle length (AFCL) (commonly \(\approx 150\) ms in persistent AF); more limited fractionation will occur in paroxysmal AF because of the longer AFCL (typically \(>170\) ms); and little fractionation is observed when AFCL is long.

Therefore, the mechanism by which CFAE ablation can prolong AFCL or terminate AF is unknown. On the basis of their physiopathology, we may hypothesize that some fractionated areas act like a reservoir of microreentrant activities, continually refueling the fibrillatory process.

In animal experiments, the AF substrate involves wandering wavelets, macroreentries, and focal sources. In humans, no study has demonstrated the feasibility of individually discriminating these mechanisms. Noncontact mapping, allowing simultaneous acquisition of beat-to-beat activity in the whole chamber, is theoretically the ideal tool to map AF; however, so far it has not proved practical in the clinical setting. Studies that use frequency domain analysis are limited by methodological issues, notably with regard to fractionation, and so far they also have not been helpful in persistent AF. Time domain analysis is difficult because of irregularity of cycle, definition of early versus late activation, and ambiguity in ascribing local activation during fractionated activity. In addition, a perpetuating source may act intermittently or may be rendered “invisible” when the surrounding tissue has been rendered refractory by other coexisting sources (see below).

Identification of AF sources has been reported to be feasible with high-density mapping during specific conditions, either peroperatively\(^10\) or during organized AF.\(^11\) These studies have demonstrated atrial activation spreading from focal point sources or from small areas harboring localized reentry, displaying fractionated or nonfractionated electrograms at the source location.

Indirectly, by evaluating the impact of CFAE on AFCL, we have learned that all anatomic areas are not equal in their contribution to maintenance of AF. Regions that have the greatest influence are the pulmonary veins, the base of the left atrium in persistent AF. Does the right atrium needs to be targeted as part of a catheter ablation strategy from those in whom the right atrium is unimportant?

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atrial appendage, and the inferior left atrium–coronary sinus interface. Interestingly, these regions have the common feature of being annexed to the main body of the left atrium by numerous connections. Their arrhythmogenic potential may be due to local structural discontinuity or to dynamic “ping-pong” interaction between the 2 structures that continuously refuel the AF process. In support of this hypothesis, it is striking that isolation of the pulmonary veins often leads to cessation of pulmonary vein tachycardia, distal to the isolation site, which suggests that the connection to the left atrium was necessary for the continuation of venous firing, and vice versa.

**Fibrillatory Cycle Length as a Marker of Substrate Burden**

It is well known that the extent of AF substrate correlates with the duration of AF and the volume of the left atrium. Furthermore, AFCL, a measurement of fibrillation rate, strongly correlates with acute termination of AF both by catheter ablation and pharmacological or electrical cardioversion and hence can be used as a marker of AF substrate burden. That AFCL is not simply a surrogate of the local refractory period is evidenced by the prolongation of AFCL at remote sites during ablation. Additional insights have been gained by computer modeling of AF. In a model based on the assumption that AF is due to multiple sources, AFCL progressively decreases with the addition of more focal sources, up to a threshold. In this computer simulation, although all sources are continually firing, not all of them can be “seen” at any given time, and thus several snapshots in time are necessary to be able to visualize and map all of the sources (Figure 1). Initially, AFCL changes only minimally, as another source can take over from the one that has been ablated. Then, as more sources are eliminated, the AF becomes more organized, and the AFCL prolongs to the point of conversion to either sinus rhythm or atrial tachycardia, when only 1 or 2 sources are present (Figure 2). This correlates well with what we have observed during catheter ablation of persistent AF. The shorter the baseline AFCL, the more ablation is required to prolong the AFCL and to reach the critical point at which conversion to either sinus rhythm or atrial tachycardia occurs, typically around 200 ms.

**Multiple Sources as a Major Mechanism in Human AF**

The evidence from catheter ablation supports the hypothesis that AF involves multiple sources. *Source* is used in a broad sense to indicate a localized origin of atrial wavefronts,

Figure 1. Computer simulation of AF. With the use of a multiple-source model of AF, with 8 active sources, the local activation is visualized. Transmembrane potential is color coded. Tissue in the resting state is coded blue and activated tissue in yellow/orange. The 8 sources have different periodicities, and at any one time only 3 sources are seen because of local tissue refractoriness, even though all are continually active. A, Anterior and posterior views of the right and left atrium, with the location of the sources marked. B through D, Different snapshots in time showing the different active sources at that instant.

Figure 2. Effect of extinguishing sources on AFCL. In the computer model, as the number of sources decreases, the AFCL progressively increases, which only becomes significant when fewer than 4 sources remain. As further sources are extinguished, the AF organizes into an atrial tachycardia.
without inferring the mechanism or size of the source. Work
in human electrophysiology has confirmed the dominance of
pulmonary vein sources in paroxysmal AF. In persistent AF,
the role of sources is less clear. Studies by Oral et al. and
others demonstrate that multiple-point ablation targeting
CFAE leads to AF termination. The latter finding is not
consistent with the wandering wavelet mechanism, given that
point ablation should increase the number of wavelets by
creating multiple anchoring points, thus worsening AF.

Finally, the critical AFCL at which conversion of AF
occurs is strikingly similar to the cycle of the subsequent
atrial tachycardia, mimicking a progressive extinction of
sources. In a few patients, however, AF cannot be organized
by ablation, which suggests incessantly changing activation
sequences that could be due to wandering wavelets.

The Role of the Right Atrium

Early work investigated the utility of right atrial linear
lesions, with or without additional left atrial linear lesions,
with only modest success in patients with either paroxysmal
or persistent AF. In the stepwise approach in which multiple
atrial structures are targeted, termination occurred in 84% of
patients during left atrial ablation. Notably, the order of
ablation targets (pulmonary veins, CFAE, coronary sinus, and
linear lesions) was shown to be irrelevant, which suggests
that all of the targets contributed to the maintenance of AF. In
most patients, the AFCL prolongation in the left atrium was
mirrored by a similar prolongation of AFCL in the right
atrium, which clearly indicates that the right atrium was
driven from the left atrium. In patients without termination in
the left atrium, AFCL was less prolonged in the right atrium,
resulting in a right-to-left frequency gradient and suggesting
that the right atrium harbored the driving activity. This
hypothesis was confirmed by the fact that right atrial ablation
resulted in termination in most of these patients, whereas it
was found that the right atrium was involved in 20% of all
cases of persistent AF (M. Hocini, unpublished observations).

An earlier study demonstrated that AF that originated
solely from the right atrium could be effectively ablated by
targeting the crista terminalis. The long-term success rate in
these patients was 85%, but they only constituted 3% of the
screened population. This relatively low prevalence of pa-
patients with right atrial drivers may explain why Oral et al.
were unable to demonstrate any benefit of right atrial ablation
because of a limited sample size, as the authors acknowledge.
Therefore, indiscriminate targeting of the right atrium is
apparently unnecessary, but in a specific subset of patients
and guided by AFCL monitoring in both chambers, targeting
of the right atrium is key to termination of AF.

The Future: Effective Cure of AF With
Minimal Ablation

The circuit in atrioventricular nodal reentrant tachycardia is still
not fully understood; nevertheless, we are able to effectively
treat this arrhythmia. The same is now true for AF. We may
ultimately fail in our quest to fully understand the mechanisms
underlying AF, but we are approaching the end of this journey,
with an effective cure of this complex arrhythmia.

AF ablation success rates with a number of different
strategies—pulmonary vein isolation, electrogram-based
ablation, and linear lesions—are continually improving. The
combination of these approaches has led to unprecedented
success in treating persistent AF, particularly when proce-
dural termination of AF is achieved. Such patients have better
outcomes than patients without termination, as observed in
the study by Oral et al. Intuitively, AF termination means that
all actively participating elements have been eliminated;
in our opinion, this represents the optimal end point. After
restoration of sinus rhythm, assessment and completion of
pulmonary vein isolation and linear block are necessary to
ensure long-term maintenance of sinus rhythm.

This extensive ablation approach is associated with signif-
icient alteration of atrial tissue, and although extensive scar-
ring and low-voltage areas result (~40% of left atrial sur-
faced), mechanical function is restored. In patients who had no
atrial function in AF, restoration of mechanical function is a
great improvement, and we can expect it to affect their
embolic risk, ventricular function, and quality of life. Never-
theless, we should do better. In addition to improving ablation
catheters, further effort should be directed to identifying the
sources or other mechanisms that are active in any particular
patient, either by refining the present mapping tools or by
developing new techniques. One challenge is to decipher
CFAEs and link them to the underlying substrate to obtain an
effective cure of AF with the minimum degree of ablation in
each individual patient.

Disclosures

None.

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