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Temporal and Spatial Indices of AF Regularization Predict Intraprocedural AF Termination and Outcome

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Introduction

Ablation has become a cornerstone of therapy for atrial fibrillation (AF), the most common arrhythmia in the Western world and an important cause of morbidity and mortality.[1] However, the optimal approach for ablation remains hotly debated, and this is particularly true for the selection of procedural endpoints. Since seminal studies by Haïssaguerre et al.[2] showed that ectopy from the pulmonary veins (PVs) may trigger paroxysms of AF, PV isolation has become central to most ablation approaches. However, PV isolation often fails to terminate AF, particularly in patients with persistent AF,[3] indicating AF sustaining mechanisms that lie outside the PVs. For this reason or to eliminate additional triggers, many approaches to ablate extra-PV tissue have been devised whose AF termination rates range from 58% [4] to 87%.[5] However, some constants remain. First, the event of AF termination is currently extremely difficult if not impossible to predict a priori. Second, AF termination by current ablative approaches is typically to atrial tachycardia, rather than to the sinus rhythm from which AF usually initiates. Finally, third, despite the intuitive advantages of AF termination, it remains disputed whether AF termination by current approaches is a desirable endpoint that improves long-term outcome. This brief review focuses on these facets of intra-procedural AF termination.

AF Regularization vis-à-vis AF Sustaining Mechanisms

The fashion in which AF regularizes en route to termination is fundamentally dependent upon the underlying sustaining mechanisms for AF. Two predominant hypotheses have been proposed. In the multiwavelet hypothesis,[6, 7] AF is caused by spatially distributed multiple reentrant wavelets that collide, extinguish and meander within the atria.[8, 9] Accordingly, AF should terminate if structural barriers are created to limit the mass of remaining patches of atrium below that required to sustain reentry[10] – the concept of the Maze procedure.[11] In this scenario, AF should regularize and terminate only after a substantial and possibly consistent proportion[11] of the atrium has been compartmentalized to limit the degrees of freedom of wavelet migration. As will be discussed, AF regularization and termination by ablation often does not follow this pattern. Conversely, the localized source hypothesis is based on data from animal models in which spiral waves (electrical rotors)[12, 13] or focal beats[14] activate rapidly to cause disorganized AF in surrounding tissue. In this model, regularization or termination of AF by ablation may occur whenever lesions approach critical sustaining sources, and thus should occur unpredictably at any time during the procedure including its initial, early or intermediate stages. In fact, this describes the patterns of AF termina-

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tion most often reported, such as during the elegant stepwise ablation approach of Bordeaux. [5]

Metrics of AF Organization and AF Regularization

The organization of AF can be measured temporally using its cycle length (CL), spectrally using measures of dominant frequency (DF), and spatially between regions of the atria.

Cycle Length

Quantifying the varying cycle lengths of AF for clinical purposes was first popularized by Haissaguerre et al., who showed that the CL of paroxysmal AF (averaged over multiple cycles) showed a stepwise prolongation during sequential isolation of the PVs[15] to the point of AF termination, that typically occurred when AF CL rose to 200 ms or longer. Subsequent studies have extended these results to show that longer baseline AF CL, measured from within the heart[5] or from the surface ECG,[16] is a multivariate predictor (along with factors such as a shorter duration of continuous AF) of the termination of longstanding persistent AF by ablation.

Several methods exist to measure CL. The simplest involves manually counting 10 or more consecutive atrial electrograms and taking their mean. This is typically easiest using left or right atrial appendage electrograms,[5] but can also be performed on electrograms from other locations.[17] In general, CL from fractionated or multicomponent waveforms must be interpreted with care, and such measurements remain controversial. Some commercially available electrophysiological recorders now provide automated measurements of AF CL.

One important issue pertains to technical reproducibility and spatial variability in AF CL measurement. Temporally, while it may be intuitively expected that AF CL should vary over time, several studies show that AF rate in any given patient is reproducible for hours[18] or even days.[19] Spatially, AF exhibits regional gradients in rate, that may also be consistent over hours,[20] emphasizing the need to examine AF CL over time at a constant location.

Spectral Dominant Frequency

Spectral dominant frequency has been applied to measure AF organization in many settings. Spectral analysis mathematically represents an electrogram by a large number of sine waves of differing frequency (=1/rate), amplitude and phase (i.e. relative timing) that, when summated algebraically, reconstitute the waveform shapes of this electrogram.[21] Several techniques exist to perform this "frequency-domain decomposition", including Fourier analysis and the wavelet transform. Although spectral analyses were initially performed using investigational software, several commercially available electrophysiological and electroanatomic mapping systems now provide online (near-instantaneous) spectral analyses of dominant frequency.

Seminal studies by Bollmann et al.[22] showed that spectral analysis can predict pharmacological termination of AF: in 61 AF patients, lower spectral DF peak (loosely, a lower rate) of AF on the ECG or intracardiac electrodes predicted AF termination within <5 minutes after ibutilide. Subsequently, Everett et al. showed in dogs with pace induced AF that electrical cardioversion[23] or burst pacing[24] to sinus rhythm were more effective when spectra revealed regularity in AF in the form of a narrow spectral DF peak – reflecting one predominant 'driver' frequency. More recent work showed that spectral DF of the ECG can quantify the spectrum of intra-atrial organization in patients with AF and other complex arrhythmias[25, 26] and, for a given AF patient, is reproducible over periods of many hours in the absence of an intervention.[19]

More recent studies of spectral analysis have shed light on AF mechanisms vis-à-vis contemporary ablation. A gradient in spectral DF frequency has been reported from the PVs to the left and then right atrium[20, 27] in paroxysmal AF but not persistent AF, that is eliminated by PV isolation.[28] Interestingly, the fact that AF may continue after PV isolation in these patients argues against a predominant role of the PVs or their DF gradient in AF maintenance, although both may contribute to the initiation and stabilization of AF.[29-31] Of note, spectral DF in these studies should be interpreted to indicate gradients in organization rather than rate, because DF may not accurately[21] measure AF rate from bipolar electrograms,[32] although it is more accurate when applied to monophasic action potentials[33] or unipolar electrograms.[34]

Most recently, spectral DF has been used to identify sites where ablation may acutely terminate AF. Sanders et al.[35] studied 32 AF patients (19 paroxysmal), in whom spectral DF was analyzed sequentially during AF at 126±13 points per patient. Ablation was performed blinded to DF maps, and sites of AF termination by ablation were compared to sites of high spectral DF. Ablation at sites of high DF terminated AF in 17/19 patients with paroxysmal AF, in whom high DF sites often lay in the PVs, but in none of the patients with persistent AF, in whom high DF sites lay throughout the atria but rarely in the PVs. In a more recent study, Atienza et al.[36] studied 50 AF patients (18 persistent) in whom DF was mapped during AF at 117±38 points per patient. Ablation at sites of maximum DF significantly reduced average atrial DF and eliminated frequency gradients, but did not acutely terminate AF. On follow-up, significant DF reduction with loss of the left-to-right gradient associated with a greater likelihood of AF elimination. By spatial analyzing spectral data, Krummen et al.[29] showed 'centrifugal' islands of regularized high spectral DF surrounded by regions of irregular and/or low spectral DF that identified successful AF ablation sites.

Most recently, spectral analyses have been used to predict AF termination intra-procedurally during the Bordeaux stepwise approach. Forclaz et al.[37] systematically evaluated a spectral index of regularity (temporal regularity index, TRI) in 75 patients with persistent AF after each ablation step. Of note, AF terminated during the first step (circumferential PV isolation) in 11 patients, and indeed prior to completion of PV isolation in some patients, more consistent with localized than spatially widespread AF sustaining mechanisms. In the remaining 64 patients in whom AF continued after PV isolation, TRI abruptly increased at the point of termination (in n=48 patients). Using receiver operating characteristic analyses, increased TRI after PVI predicted procedural AF termination with high specificity and positive predictive value (although a less impressive negative predictive value). On long-term followup, AF was more successfully eliminated in patients who exhibited post-PVI increases in TRI.

In summary, spectral DF provides a clinically relevant index of AF regularity. Although ablation at sites of high spectral DF has had mixed results, an increase in spectrally measured AF regularity by PV isolation predicts intra-procedural AF termination during the Bordeaux stepwise approach. Notably, AF terminated at any stage of the procedure including during the first step, and AF showed most regularization just before termination.

Spatial Indices of Organization

Several studies have quantified AF organization by the extent to which atrial regions activate synchronously ('in-phase') over time. Studies in this area have focused on the vector of surface ECG f-waves, and showed that the consistency of this vector over time (spatial phase) reflected AF organization.[26,38] Initial reports suggest that indices of spatial regularization can be an-

alyzed very rapidly but, at the current time, have only been conducted using custom-designed software in research laboratories.

Early intracardiac analyses showed organizational differences in the right atrium between persistent and paroxysmal AF, but did not relate this to AF termination or ablation outcome.[39] In a recent study, Forclaz et al.[37] tracked a novel intracardiac spectral regularity index (SRI) of cycle-to-cycle variations in the 3-dimensional AF activation vector between the right atrial appendage, proximal and distal coronary sinus. SRI remained reproducible over periods of minutes in the absence of an intervention. However, SRI dramatically increased after circumferential PV isolation in patients in whom AF later terminated during stepwise ablation. The dynamics of SRI during stepwise ablation paralleled those in the temporal regularity index above – after an initial SRI increase by PV isolation, minimal increases were then seen during continued ablation until just before AF termination.

Predictors of Acute Procedural Termination of AF

In patients with paroxysmal AF, prolongation of AF CL predicts AF termination during circumferential PV isolation. Interestingly, since AF may terminate before completion of wide encircling lesions,[5, 15] it is possible that ablation of atrial tissue within encircling lesions and/or adnexal structures such as ganglionic plexi[40] may contribute to termination. In patients with persistent AF, AF termination during stepwise ablation is predicted by longer baseline AF CL and, intraprocedurally, by AF regularization measured spatially or temporally (using spectral DF). Notably, the fact that AF may terminate at any procedural stage including the first step, and that AF regularization is sometimes subtle despite increasing cumulative ablation until just prior to termination, may support the localized source hypothesis for AF rather than spatially distributed mechanisms.

Until recently, there was little[41, 42] or no[9] evidence to support localized sources for human AF. However, the recently presented CONventional Ablation for AF with or without Focal Impulse and Rotor Modulation (CONFIRM) Trial detected rotors or focal beat sources for AF in nearly all (97%) patients using novel computational techniques that have recently become commercially available. Patients had 2.1±1.0 concurrent rotors or focal beats, that were detected for at least hundreds of cycles. Targeted ablation at these sources (FIRM) was able to acutely terminate or substantially slow AF within minutes prior to any conventional ablation, and improved long-term outcomes over conventional ablation alone using implanted continuous ECG monitors in 84% of patients to rigorously prove maintenance of sinus rhythm.[43]

There are several other unanswered questions with regards to AF termination by ablation. In particular, it is unclear why conventional ablation typically terminates AF to atrial tachycardia,[4, 5] despite the fact that AF usually initiates from sinus rhythm. Of interest, FIRM ablation at rotors and focal beat sources predominantly terminated AF to sinus rhythm in the CONFIRM trial. Further studies are required to define variations, if any, in the mechanisms of AF termination and their long-term implications between different approaches.

Do Intraprocedural Regularization or Termination of AF Predict Long-Term AF Elimination?

At present, the primary procedural endpoint for AF ablation is PV isolation.[6] Secondary procedural endpoints are less clear, and include confirmation of conduction block across linear lesions (when drawn), and elimination of CFAE (when targeted).[6] One major question is whether intraproce-

dural AF regularization or termination may be useful adjunctive endpoints for ablation. Although several small, predominantly single center studies show that AF regularization may identify patients who are less likely to experience recurrent AF,[27, 28, 37, 44] few if any studies have used these indices prospectively to guide ablation approach. Thus, additional prospective studies are required before any specific index of AF regularization can be recommended as an ablation endpoint.

More pressing is the question of whether acute AF termination should be used as a procedural endpoint. Several studies confirm that patients in whom AF terminates intraprocedurally have a higher long term freedom from AF than those in whom AF does not terminate.[45] Interestingly, some experienced groups have used precisely these data to argue the opposite case. Since the recurrence of any atrial tachyarrhythmia is similar whether AF does or does not terminate by ablation, AF termination may simply identify patients in whom recurrences are of atrial tachycardia (AF termination group) as opposed to AF (AF non-termination group) .[4, 45] The final outcome of that debate will be operator dependent, reflecting among other factors the preference to perform a repeat procedure for atrial tachycardia or AF. Although atrial tachycardia is often very symptomatic, it may be easier to eliminate definitively by ablation in many instances.

We feel that preliminary data from the CONFIRM trial are promising, in which rapid targeted ablation (FIRM) at rotors or focal beat sources was able to terminate AF to sinus rhythm within minutes, prior to PV isolation, with improved long-term outcome using continuous ECG monitors.[43] However, validation in additional centers is required before FIRM-guided ablation becomes a routine component of ablation.

Conclusions

Several quantitative indices may predict the acute procedural termination of AF. However, most have suboptimal predictive value and do not identify the stage at which AF will regularize or terminate during ablation. There continues to be lively debate on the value of procedural AF termination in improving long-term ablation outcomes. This debate may continue until such time as the precise mechanisms that sustain AF are identified and targeted directly for ablation, as we have now established for most other arrhythmias.

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