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Pathogenesis of AF: Impact on intracardiac signals

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Abstract—**Atrial fibrillation (AF) is the most common cardiac arrhythmia, and is responsible for the highest number of rhythm-related disorders and cardioembolic strokes worldwide. Intracardiac signal analysis during the onset of paroxysmal AF led to the discovery of pulmonary vein as a triggering source of AF, which has led to the development of pulmonary vein ablation—an established curative therapy for drug-resistant AF. Complex, multicomponent and rapid electrical activity widely involving the atrial substrate characterizes persistent/permanent AF. Widespread nature of the problem and complexity of signals in persistent AF reduce the success rate of ablation therapy. Although signal processing applied to extraction of relevant features from these complex electrograms has helped to improve the efficacy of ablation therapy in persistent/permanent AF, improved understanding of complex signals should help to identify sources of AF and further increase the success rate of ablation therapy.**

I. Introduction

THE term "atria1 fibrillation" (AF) is applied both clinically and electrophysiologically to tachycardia so rapid that uniform atrial excitation does not occur. Different areas within the fibrillating biatrial chamber experience electrical activation not in tandem with each other. Because of out of phase intra- and interatrial electrical excitation several possible arrhythmogenic mechanisms could coexist. Scientists have perceived that atrial fibrillation could be produced by single or multiple rapidly firing focal source(s) within the atrium or rapidly circulating multiple wavelets – wandering or stable – in the atria. Although multiple wandering wavelet hypothesis predominated over the focal source mechanism in experimental studies during the late 20th century, atrial chambers remained at the center of the human and experimental studies that were undertaken to decipher the etiopathogenesis of this fibrillatory rhythm disorder [1], [2]. By the end of the century, the central pulmonary veins (PVs) were first recognized as important sources of spontaneous electrical activity that initiated AF [3], [4]. Subsequently, over last score of years, multiple studies have clearly established the role of pulmonary veins in the initiation of AF in general and the maintenance of paroxysmal AF in particular [5], [6].

We review the characteristics of intracardiac signals in patients with different clinical types of AF. We also discuss the impact of AF pathology on atrial signals based on the recent clinical data from intracardiac mapping and catheter ablation of AF.

II. Clinical classification of AF

When a patient has had 2 or more episodes of AF, it is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 days, AF is designated persistent. First-detected AF may be either paroxysmal or persistent AF. The category of persistent AF also includes cases of long-standing AF (e.g., greater than 1 year), usually leading to permanent AF, in which cardioversion has failed or has not been attempted [7].

III. Paroxysmal AF

A. Onset of Arrhythmia

In the classical paper [4] describing the arrhythmogenic role of human pulmonary veins, 45 patients with frequent episodes of AF (mean duration, 344±326 minutes per 24 hours) refractory to and off drug therapy were mapped. All patients had frequent isolated atrial ectopic beats, which were also responsible for the initiation of sustained AF lasting more than one minute in most of them.

Out of 69 foci detected to trigger AF in 45 patients, 65 were found to be arising from focal pulmonary venous source (see Fig.1 in [4]). During normal sinus rhythm, the potentials within the PVs are recorded slightly after the potential associated to the atria, but, this relationship between the far-field of the atrial electrogram and the local PV potential is reversed during the atrial ectopy. The persistence of reversed relationship is seen during the first few beats at the initiation of AF suggestive of triggering role of PV in the initiation of AF. The ablation of the PVs consists of electrically isolating the vein from the atria; to prevent the abnormal PV activity from triggering the AF. Acute elimination or dissociation of the venous potential (see Fig. 4 in [4]) was observed during focal ablation of the

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source in 38/45 patients.

Successful ablation of ectopic foci was associated with reduction in the daily frequency of ectopics recorded using a Holter monitor. AF disappeared in 36/38 patients acutely and was not found for a mean period of 8 months in 28/45 patients off drug therapy. In patients with late recurrence of AF, similar ectopic beats initiating AF as observed initially were documented. Ablation of the focus was unsuccessful in 7/45 patients all of whom also continued to experience recurrent AF.

The characteristic local PV signal preceding the initiation of AF by the ectopy which also continued to emanate from the PVs in an isolated manner provided proof of focal source arrhythmogenic concept for AF. It also defined distinct targets and end-points which paved a way for catheter-based ablation therapy for this arrhythmia.

Takahashi et al. [8] mapped the atrial substrate in paroxysmal AF to look for focal sources outside the PV using a specially designed multispline mapping catheter. However, AF was terminated without targeting these focal atrial sites by PV isolation and/or atrial substrate modification. This provided another evidence towards the role of PVs as primary trigger sites initiating AF and the passive or bystander role of atrial substrate in paroxysmal AF.

B. Maintenance of Arrhythmia

Sanders et al.[9] conducted a study to understand the role of PVs in the maintenance of AF. In 19 patients with ongoing paroxysmal AF, spectral analysis of the intracardiac signals recorded from several sites (126±13) in the left and the right atrial chambers and the coronary sinus for 5 seconds was performed. The intracardiac signal was windowed, rectified and band pass-filtered as a preprocessing step; and the power spectrum at each recording site was estimated using 4096-point fast Fourier transformation (spectral resolution, 0.24 Hz) [9]. In each spectrum, the frequency with the largest amplitude was assigned to be the dominant frequency (DF) at that site.

Among the 126±13 sites analyzed per paroxysmal patient, 5.1±1.9 sites exhibited a large value of the DF and the most likely locations was PV ostium region. Other regions in the left and the right atria and the coronary sinus were less likely to harbor large DF values (Fig. 1). Ablation at the maximal DF sites was associated with either significant prolongation of AF cycle length measured in the coronary sinus or termination of AF. The latter was achieved during ablation in 17/19 patients. AF terminated during or with isolation of the PV harboring DF in 13/17 patients suggestive of a vital role played by PV triggers in the maintenance of AF in the atrial chamber. In others, arrhythmia terminated during focal ablation elsewhere in the atria suggestive of infrequent role of non-PV triggers in the maintenance of paroxysmal AF.

Nademanee *et al.* [10] confirmed these findings in a large cohort of patients. PV-left atrial junction (ostial PV) region was one of the predominant sites where ablation of complex fractionated electrical activity resulted in successful termination of AF in 115/121 patients and 57 of them had paroxysmal AF. This study first introduced the concept of targeting the fractionated areas where fractionation was defined as: 1) electrograms composed of two or more deflections and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period; 2) electrograms with a very short cycle length ≤120 ms averaged over a 10-second recording period.

Thus, the role of PV triggers was established not only in the initiation but also in the maintenance of paroxysmal AF in the biatrial chamber.

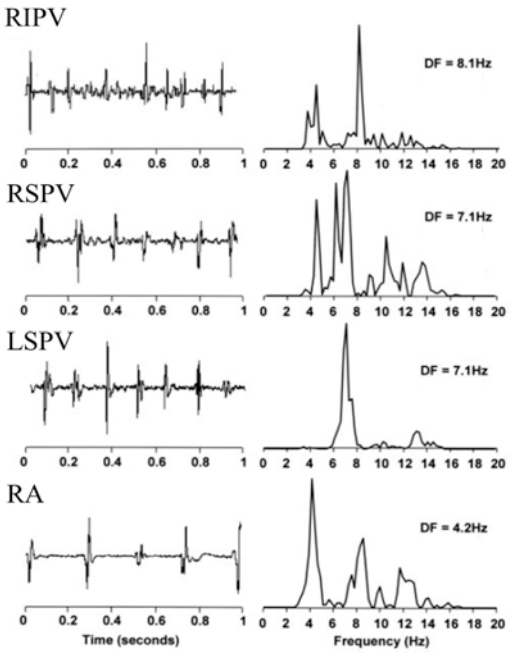

Figure 1: PVs harbor maximal DF and maintain paroxysmal AF in a given patient. The DF in right atrium (RA) is non-maximal; suggesting the triggering from the PVs. (RIPV stand for Right Inferior Pulmonary Vein, RSPV: Right Superior PV, LIPV: Left Inferior PV, LSPV: Left Superior)

IV. PERSISTENT/PERMANENT AF

Sanders et al. [9] performed spectral analysis of intracardiac signals from the sites, as described above, using 4096-point fast Fourier transformation to obtain the DF in 13 patients with permanent AF. Among the 126±13 sites acquired per permanent patient, the number of DF sites that exhibited large value of DF was similar to that observed in 19 patients with paroxysmal AF (5.3 ± 1.9 vs. 5.1 ± 1.9) but the sites were more concentrated in non-PV areas like the septum and the right and left appendages (see Fig. 5 in [9]). Compared with patients with paroxysmal AF, these patients had notable differences in the DF signal characteristics as shown in Table I. In persistent AF, the DF signal was more likely to be non-discrete and fractionated with higher absolute value of maximal DF. Global AF cycle length was also faster in persistent AF patients than their paroxysmal counterparts. And unlike the latter, ablation of sites with

prominent DF values did not result in AF termination. This effect was observed after targeting similar number of sites as in paroxysmal AF suggestive of presence of multiple other AF drivers over and above those targeted.

In the majority of paroxysmal AF patients, the drivers are limited in number and they are confined to the PVs but in persistent AF, it may be possible that there is a mixture of sites with fixed and dynamic drivers and targeting only the fixed ones may not be sufficient. Previous descriptions of wandering wavelets [1], [2] and stable microreentry [11] provide an evidence in favour of existence of these two types of drivers in AF. The power spectral analysis consolidated the concept that paroxysms of AF are initiated by discharges from one or only a few focal PV sources. Repetitive such discharges can produce progressive pathologic changes in the atrial substrate that may lead to the perpetuation of AF independent of the PV trigger sources [12]. Ablation is therefore, required in areas other than the PV trigger sites for successful termination of self-perpetuating or persistent AF [13].

In patients with persistent AF, Takahashi et al. [14] studied signal characteristics at the successfully targeted sites defined as the sites where ablation led to significant prolongation of AF cycle length (>5ms) or termination of AF. After isolation of the PVs, electrogram-based ablation was undertaken. Electrograms were acquired at several sites in each successfully targeted atrial region for 4 seconds prior to ablation. These sites included the anterior, inferior and posterior left atrial regions, the septum, the left atrial appendage and the coronary sinus. Electrograms were categorized into complex/continuous and discrete varieties. Continuous activity was considered to be present when interelectrogram interval was <50ms. Complex electrical activities were evaluated for: 1) total duration of continuous electrical activity during 4s (Fig. 2A); 2) maximal bipolar voltage during continuous activity (Fig. 2B); 3) determination of dominant frequency (DF) by a fast Fourier transform, and difference in this local DF compared with that in the left appendage; 4) determination of a fractionation index defined as the number of deflections with an absolute value of >0.05 mV from the baseline using specially designed computation (Fig. 2C); and 5) mean absolute value of derivatives of electrograms (dV/dt) (Fig. 2).

Discrete electrograms were assessed by: 1) mean local cycle length and difference between cycle length at the local site and the left appendage; and 2) presence of a temporal gradient of activation, defined as a temporal difference of ≥70 ms between the proximal and distal bipoles of the mapping catheter (Fig. 3).

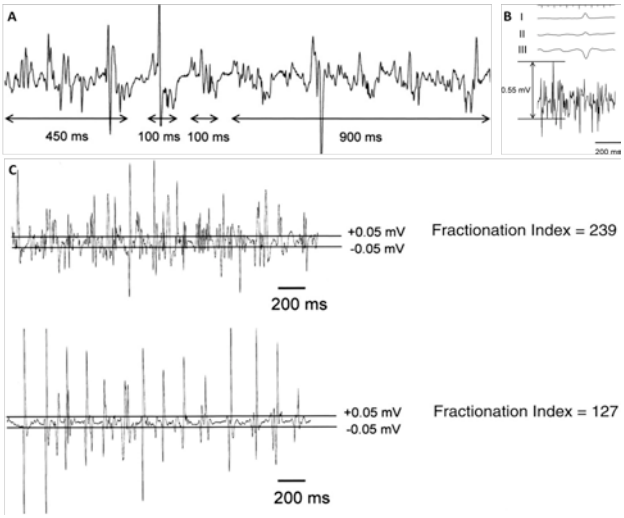

Figure 2: Panel A – Total duration of continuous activity in the given time window. Panel B – Measurement of bipolar voltage during continuous activity. Panel C – Computing fractionation Index at two sites.

Only two local-signal characteristics predicted successful prolongation of AF cycle length or AF termination during ablation of persistent AF. They included the presence of continuous activity (Fig. 2A) in complex electrograms and temporal activation gradient in discrete electrogram (Fig. 3), see Table II in [14].

Thus, targeting the sites within the atrial chamber where continuous electrical signals are recorded or substantial temporal gradient is recorded during discrete organized rhythm can yield success during persistent AF ablation. These studies highlight additional importance of non-PV sources in the maintenance of persistent AF.

V. Discussion

The dominant roles of PV triggers in paroxysmal AF and non-PV atrial drivers in persistent AF have been recognized electrophysiologically. Catheter-based ablation has paved way for understanding the complex pathophysiology of AF directly in the humans. These drivers often continue to fibrillate rapidly after having been completely isolated from their surroundings. These observations lend credence to the source-sink hypothesis in AF. The cellular mechanism

TABLE I
Characteristics of Power Spectrum in AF

Characteristic	Paroxysmal AF	Persistent/Permanent AF
Total number of acquired sites per patient	126 ± 13	
Total number of sites with maximal DF per patient	5.1 ± 1.9	5.3 ± 1.9
Distribution of sites	PVs>Atrial chamber	PVs<Atrial chamber
Signal at DF site	Discrete	Complex and fractionated
Number of bands/DF site	Single	Often, more than one
Most common location of max. DF site	PV-LA junction	Atrial chamber
Absolute value of maximal DF	Lower	Higher
Global AF frequency	Slower	Faster

behind such a fibrillatory transformation of PV and non-PV drivers remains speculative. Microreentry within the source or reentry spread over 2-3 cm^2 area locally is often believed to be responsible behind such transformation. Using current mapping catheters, localized reentry has been observed as a new clinical mechanism maintaining the arrhythmia which has been organized by previous ablation at the source [15]. This is in line with experimental description of stable rotor with a wavelength of 6-10mm.

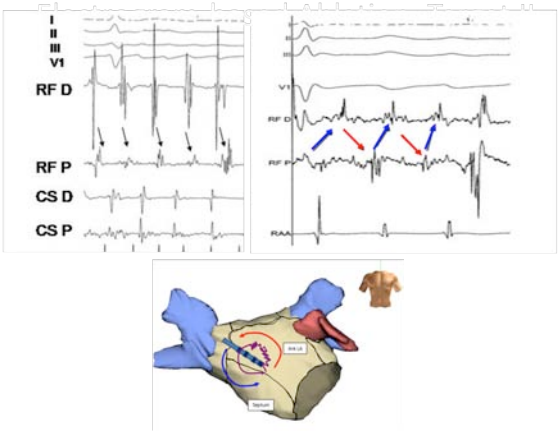

Figure 3: Temporal gradient between the proximal (P) and distal bipoles (D) of the mapping catheter (RF).

Further advancement in catheter design may help to identify smaller circuits than those currently detected using electrode with contemporary dimensions and interelectrode spacing. Improvement in spatial resolution of the mapped surface and simultaneous extension of mapping into the intramural layers together with new mapping catheters that record monophasic action potential [16, 17] might probably help in understanding the underlying processes of fibrillating tissues.

Up to now, the DF demonstrated its efficiency as a diagnostic tool especially in paroxysmal AF. But the prediction of target sites to terminate persistent/permanent AF remains a major challenge. To that end, many signal processing tools have been proposed including auto/inter-correlation based system [18] [19] and ad-hoc wavelet transform [20]; but all of them are mostly designed for non-fragmented (discrete) EGMs that are relatively sparse in persistent/permanent cases. Recently, techniques based on the quantification of the fragmentation of complex EGMs [10], [14], [21] have been reported in the literature. During the decade starting 2011, the focus will necessarily remain on the signal processing applied to extraction of relevant features from complex EGMS to improve the efficacy of ablation therapy in permanent/persistent AF.

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