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A Time-domain Approach for the Identification of Atrial Fibrillation Drivers

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Abstract— **The localization of atrial fibrillation (AF) driver sources, characterized by rapid and regular electrical activity, is crucial for an effective ablation treatment. This work proposes a double-criteria approach for the identification of AF drivers based on a time-domain evaluation of atrial rate and AF organization. These two features are quantified by the measurement of atrial cycle length (ACL) and wave-similarity (WS). Based on ACL/WS formalism, AF drivers can be operatively defined as sites displaying electrical activity with high-rate and high-similarity (HR AND HS). The capability of ACL/WS analysis to identify AF driver sites and distinguish them from non-critical areas is shown in representative examples. The double-criteria evaluation for the identification of AF drivers, provided by our time-domain approach, might open new perspectives for the development of electrogram-guided ablation strategies in the single patient.**

I. Introduction

Since the seminal work by Haïssaguerre and co-workers [1], catheter ablation of arrhythmic triggers has become an increasingly popular technique for the treatment of atrial fibrillation (AF). Nevertheless, while the ablative treatment in patients with paroxysmal forms of AF has been largely standardized, leading to a high success rate of the procedure, the optimal approach for patients with chronic forms remains unknown, mostly due to an incomplete understanding of the mechanisms sustaining the arrhythmia.

Experimental and clinical evidence based on high-density mapping studies has demonstrated the crucial role of regions displaying rapid and regular activation in the maintenance of AF [2;3]. Complementarily to organized sources, sites displaying complex electrogram morphology have been suggested as indicative of the substrate necessary for AF maintenance [4;5]. The ability to localize driver sources as well as critical substrates in patients prior to ablation may greatly simplify catheter ablation and improve its success rate, by directing the procedure to specific regions and sparing non-critical areas.

The development of electrogram-guided ablation strategies is conditioned by the implementation of suitable signal analysis techniques, performing a quick and objective identification of target sites, based on the quantification of the specific properties of atrial electrograms. In this perspective, a spectral approach based on the estimation of the electrogram dominant frequency has been proposed for the localization of high-frequency sites [3], while criteria and algorithms for complex fractionated atrial electrogram detection have been suggested to locate substrate regions [4]. Nevertheless, the sensitivity and specificity of these techniques in identifying and actually distinguish critical regions remain debated.

This work proposes a time-domain approach for the identification of AF drivers from atrial electrograms, based on the combined analysis of atrial cycle length (ACL) and waveform similarity (WS). WS analysis has been previously proposed by our group as a reliable technique to quantify AF organization [6;7]. In the present study the integration of WS index with a measure of atrial rate is used to operatively define AF drivers and obtain specific, quantitative criteria for the identification of these critical sites.

II. Time-Domain Approach for Driver Identification

Studies in animal models have shown AF to be sustained by the rapid and organized activity of rotor-like reentries, located in the posterior left atrium near the pulmonary veins, which results in a consistent left-to-right frequency and organization gradient [2].

Since driver electrical activity is characterized by peculiar rate and organization properties, our identification strategy is based on a distinct time-domain quantification of these features from atrial bipolar electrograms (Fig.1d). Atrial rates are accurately measured in the time-domain as atrial cycle lengths (Fig.1e) by applying an automatic procedure based on signal filtering and waveform barycenter estimation. The regularity of the signal is defined in terms of its morphological properties and quantified by wave-similarity analysis, which evaluates the repetitiveness over time of activation wave morphology (Fig.1f). The ACL/WS formalism is used to provide an operative definition of drivers, thus setting quantitative criteria for their identification.

A. Time-domain Determination of AF Rate

Experimental and clinical studies, mapping the activation rate through the atria, evidenced the existence of activation gradients between different atrial regions and suggested sites with higher activation rate as critical areas for the maintenance of AF [3]. In most of these studies, atrial rate was estimated by spectral analysis as the frequency containing the maximum spectral power (i.e., dominant frequency (DF)). As previously shown [8], this technique provides a consistent measure of atrial rate in presence of

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regular signal morphologies, while it may fail when applied to complex electrograms, characterized by amplitude and frequency variations, waveform fragmentation, and/or far field ventricular interference. Since these factors are more easily identifiable and treatable in the time-domain, in this study the estimation of atrial rate was performed through an atrial cycle length measure.

Schematically, activation times for ACL estimation were determined by: 1. preprocessing of bipolar electrograms by template matching and subtraction of ventricular artifact; 2. detection of activation waves by signal filtering and adaptive threshold crossing; 3. setting of activation times by calculation of the waveform barycenter [6]. These steps guaranteed: efficacy in ventricular interference removal and preservation of atrial waveform features, reliability in activation wave detection in presence of signal amplitude changes and accuracy in activation time determination in presence of fragmented waveforms.

In details, ventricular far-field effects were removed from atrial recordings by matching and subtraction of an adaptive template [9]. This was obtained by averaging ten 100 ms windows of atrial signal synchronized with ventricular activation times (detected on the R-waves of a surface ECG), and updated at each detected R-wave. A remainder atrial signal was generated by subtracting from the original atrial signal the average template aligned to ventricular activations [6]. After ventricular artifact removal, atrial activation times were automatically determined as schematized in Fig.1. The preprocessed atrial signal *s(t)* (panel a) was band-pass filtered (40–250 Hz, order-40, Kaiser window) to remove baseline shifts and high-frequency noise, rectified introducing low-frequency components related to the amplitude of the high-frequency oscillations of the original signal, and further low-pass filtered (finite impulse response, cutoff at 20 Hz, order-40, Kaiser window) to extract a waveform $s_w(t)$ proportional to the amplitude of the components of *s(t)* occurring at 40–250 Hz (panel b) [6;10]. Atrial activation waves were detected by threshold crossing of an adaptive threshold (dashed line in panel b). The threshold accounted for the variability in waveform amplitude, since it was defined as the weighted average of the amplitude of the last ten detected peaks of $s_w(t)$. Based on the refractory properties of the atrial tissue, a blanking period of 55 ms was imposed to avoid multiple detection of single activation waves. Following wave recognition, atrial activation times were estimated by calculating the barycenter of the waveform, i.e., the time that divided in two equal parts the local area of the modulus of the signal (black dots in panel c) [6;11]. Since the calculation of the barycenter involved the whole morphology of the activation waveform, the point resulted less sensitive to short modifications of the waveform, which consented reliable estimation of activation times even in presence of fragmented potentials and complex wave morphology [11]. Detected activation times were displayed on a computer screen for visual inspection and successive editing. Beat-to-beat atrial cycle lengths were finally determined as the difference between consecutive activation times (panel d), and the median of ACL distribution (panel e) was assumed as a measure of atrial rate.

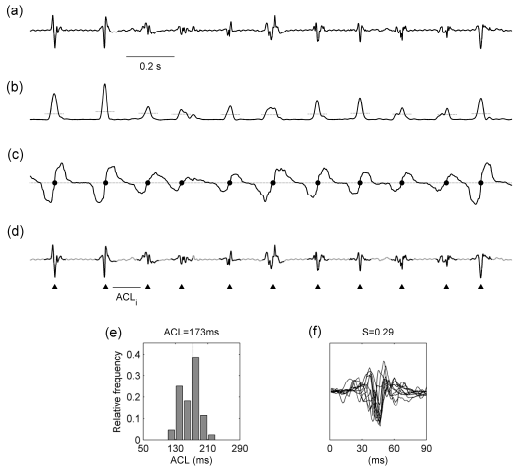

Fig. 1. Decomposition of atrial electrogram information in rate and morphological features. After ventricular interference removal, the atrial electrogram (a) was band-pass filtered, rectified and low-pass filtered (b) to detect activation waves by adaptive threshold crossing (dashed lines). The waveform barycenters (c, black dots) determined atrial activation times (triangle series in d), which were used for the calculation of atrial cycle length (ACL) distribution (e) and the extraction of local activation waves (d, in black) for similarity index (S) computation (f).

B. Determination of AF Organization by Wave-Similarity

Sites displaying high-frequency electrical activity may be characterized by different levels of organization. Indeed, AF high-frequency sites may show either spatio-temporal organization as in the case of driver sources, or highly irregular and fragmented activity as in presence of complex propagation patterns. The evaluation of the degree of organization of AF electrical activity is thus crucial for an effective identification of driver sources.

Since "organization" is not univocally defined in AF analysis, several methods have been proposed to quantify this concept in both time and frequency-domains [12]. Based on activation time series analysis, AF organization has been defined in terms of the rhythmic properties of interval series [13] and synchronization between activation times [14]. Alternatively, organization has been quantified from the whole signal in terms of electrogram dynamical complexity by linear and nonlinear indexes [13;15], or signal spectral and cross-spectral properties [16;17].

In previous studies we proposed a morphology-based approach for the quantification of signal organization, which was focused on the analysis of the shape of atrial activation waves [6;7]. The morphology of the signal during activation may indeed contain relevant information about the underlying propagation process. In fact, regular activation

patterns present activation waves with similar shapes, while complex propagation patterns, such as slow conduction, wave collisions or conduction blocks, determine complex wave morphologies [5]. Methods directly focused on the quantification of signal morphology can thus be helpful for supporting the investigation of the electrophysiological mechanisms underlying AF and its clinical treatment [18;19].

In details, wave-similarity analysis quantified the regularity of a single atrial bipolar electrogram, through the evaluation of the degree of repetitiveness over time of its activation waveforms. This was estimated by a quantitative comparison of the morphologies of all possible pairs of atrial activation waves extracted from the recording (Fig.1d and f). In order to calculate their similarity, local activation waves (LAWs) were defined as signal windows of p samples centered on the estimated atrial activation times (see previous paragraph), and extracted from atrial electrograms (Fig.1d, in black). The parameter p was set to 90 being the sampling period equal to 1 ms. To avoid that changes in electrode contact affected the similarity measure, each LAW was normalized before comparison. The morphological similarity between two LAWs was evaluated by computing their distance by the standard metric of the p-dimensional sphere:

$$d\left(y_i, y_j\right) = \arccos\left(y_i \cdot y_j\right) \qquad (1)$$

where y_i and y_j represented the i^{th} and j^{th} normalized LAW and $\cdot$ denoted the scalar product.

The similarity index (S) was finally defined by calculating the relative number of waveform pairs lying at distance lower than ε, i.e.:

$$S = \frac{2}{N(N-1)} \sum_{i=1}^{N} \sum_{j=i+1}^{N} \Theta\left(\varepsilon - d\left(y_i, y_j\right)\right) \qquad (2)$$

where Θ was the Heaviside function, N was the number of activation waves in the atrial electrogram, and ε was the similarity threshold. According to previous studies [6], the parameter ε was set to $\pi/3$ in order to guarantee maximal similarity (S=1) for highly repetitive and regular signals.

C. Combined ACL/WS Analysis for Driver Identification

Based on ACL/WS formalism, a double criteria, comprising rate and organization aspects, was defined for the identification of AF drivers. These were operatively defined as sites displaying electrical activity with high-rate (HR, ACL < ACL of the surrounding tissue) AND high-similarity (HS, S>0.5).

Fig.2 displays an exemplifying application of the combined ACL/WS analysis in a patient with permanent AF, in which 120 bipolar electrograms were recorded from the left and right atria, pulmonary veins (PVs) and superior caval vein by an electroanatomic mapping system.

As shown in the example, ACL/WS analysis was able to quantify peculiar rate and morphological properties of atrial

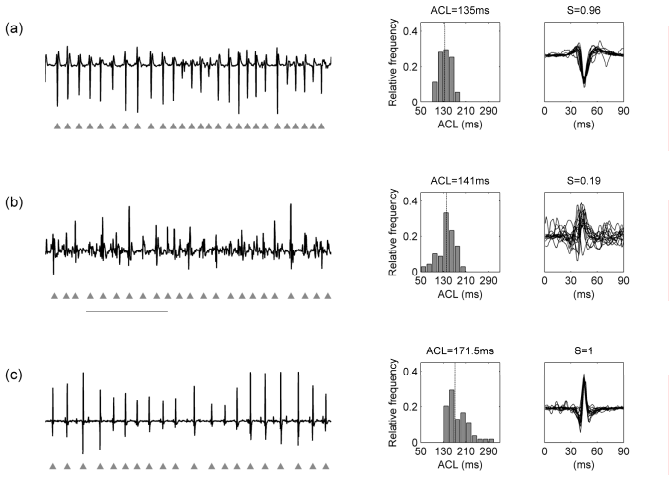

Fig. 2. Application of the time-domain approach for the identification of AF drivers in a representative patient. Atrial electrograms (left) recorded in different atrial sites (left inferior pulmonary vein (a), left atrial posterior wall (b) and superior caval vein (c)) are displayed with corresponding ACL distributions (central) and waveform similarity plots (right). A driver site was identified in (a), where the electrical activity displayed both high-rate and high-similarity (HR AND HS). Differently, the high-rate of electrogram (b) was accompanied by a low-similarity value, indicative of a complex propagation pattern. Finally, electrogram (c) displayed high-similarity but low-rate, suggesting the presence of a passive activation region.

electrograms, suggesting the differential role of different atrial regions in AF maintenance. The electrogram recorded at the left inferior PV (panel a) displayed high-rate (ACL=135ms) and regular morphology as testified by the high level of waveform superimposition (S=0.96). The fulfillment of both HR AND HS criteria suggested that the site might harbor an AF driver. A high-rate of activation (ACL=141ms) was observed also in the posterior wall of the left atrium (panel b), fulfilling the HR criterion. Nevertheless the electrical activity at this site was characterized by irregular and complex wave morphology, which resulted in a low-similarity value (S=0.19). The high fragmentation and low-similarity of the electrogram suggested the presence of a complex propagation pattern. Finally, the electrogram recorded in the superior caval vein region (panel c) displayed high-similarity (S=1, HS site), indicative of a regular underlying mechanism, but slow activation rate (ACL=171.5ms). Due to its low-rate this site might be a passively activated region or harbor a secondary source of activation. The spatial extension of the combined time-domain analysis in this representative patient revealed the presence of potential driver sites in the left PVs, which displayed both high-rate (ACL=139.1±2.7ms) and high-similarity (S=0.52±0.09) activity. Low-similarity sites (S<0.25), indicative of potential substrates, were instead located in the left atrial posterior wall and in the left and right septal regions (S=0.21±0.03).

III. Discussion and conclusions

In this study we introduced a novel time-domain approach for the identification of AF drivers, based on the combined use of ACL and WS indexes.

The time-domain representation favored the decomposition of signal information in rate and morphological aspects with respect to power spectra representation, where different signal properties may result entangled. The application of ACL and WS analysis provided reliable and specific measures of the two signal properties. Indeed, the time-domain determination of atrial cycle length yielded an accurate measure of atrial rate and displayed robustness against the effects of variations in wave amplitude and waveform fragmentation [11]. WS analysis complemented the rate information with a specific measure of organization based on signal morphology, which was able to distinguish areas displaying highly regular signals from regions showing complex and fragmented atrial electrograms (CFAE regions).

On the basis of the combined ACL/WS representation, we were able to provide an operative and quantitative definition of AF drivers (i.e., sites displaying HR AND HS electrical activity), and set strict rules for their identification. The representative example of Fig.2 suggests the capability of the ACL/WS descriptor to distinguish potential driver sites from substrate or passive activation regions, which may favor the inference of the differential role of different atrial regions in AF.

Finally, the presented approach, integrated with detailed anatomical reconstructions [20], may lead to the precise localization of critical arrhythmic sites, thus playing a crucial role in the development of stepwise, electrogram-guided ablation strategies in the single patient.

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