Journal of Arrhythmia ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Original Article

Spatiotemporal characteristics of atrial fibrillation electrograms: A novel marker for arrhythmia stability and termination

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ARTICLE INFO

Article history:
Received 23 February 2016
Received in revised form
26 May 2016
Accepted 27 May 2016

Keywords:
Atrial fibrillation
Mapping
Electrogram fractionation
Dominant frequency
Spatiotemporal stability

ABSTRACT

Background: Sequentially mapped complex fractionated atrial electrograms (CFAE) and dominant frequency (DF) sites have been targeted during catheter ablation for atrial fibrillation (AF). However, these strategies have yielded variable success and have not been shown to correlate consistently with AF dynamics. Here, we evaluated whether the spatiotemporal stability of CFAE and DF may be a better marker of AF sustenance and termination.

Methods: Eighteen sheep with 12 weeks of "one-kidney, one-clip" hypertension underwent open-chest studies. A total of 42 self-terminating (28–100 s) and 6 sustained (> 15 min) AF episodes were mapped using a custom epicardial plaque and analyzed in 4-s epochs for CFAE, using the NavX CFE-m algorithm, and DF, using a Fast Fourier Transform. The spatiotemporal stability index (STSI) was calculated using the intraclass correlation coefficient of consecutive AF epochs.

Results: A total of 67,733 AF epochs were analyzed. During AF initiation, mean CFE-m and the STSI of CFE-m/DF were similar between sustained and self-terminating episodes, although median DF was higher in sustained AF ($p=0.001$). During sustained AF, the STSI of CFE-m increased significantly ($p=0.02$), whereas mean CFE-m ($p=0.5$), median DF ($p=0.07$), and the STSI of DF remained unchanged ($p=0.5$). Prior to AF termination, the STSI of CFE-m was significantly lower ($p<0.001$), with a physiologically non-significant decrease in median DF (-0.3 Hz, $p=0.006$) and no significant changes in mean CFE-m ($p=0.14$) or the STSI of DF ($p=0.06$).

Conclusions: Spatiotemporal stabilization of CFAE favors AF sustenance and its destabilization heralds AF termination. The STSI of CFE-m is more representative of AF dynamics than are the STSI of DF, sequential mean CFE-m, or median DF.

1. Introduction

Over the last several decades, substantial research interest has been focused on characterizing the pathophysiological substrate underlying atrial fibrillation (AF) [1]. AF is a complex arrhythmia and has been shown to be temporally variable, so that AF duration and burden can vary significantly within the same patient "substrate" [2]. In general, it is widely accepted that an abnormal atrial structural substrate is more crucial for AF persistence than electrical remodeling alone [3]. However, it remains poorly understood how the same atrial "substrate" could exhibit both sustained and spontaneously terminating AF episodes.

Various investigators have utilized AF electrogram characteristics, such as complex fractionated atrial electrograms (CFAE) and dominant frequency (DF), to identify critical substrate sites for catheter ablation [4,5]. To date, these approaches have demonstrated highly variable success rates, possibly due to the limitations of using sequential point-by-point mapping for the chaotic atrial activations underlying a temporally unstable arrhythmia [6–12]. Nevertheless, studies have also identified AF regularization, with a cumulative increase in AF cycle length, prior to AF termination by the stepwise ablation approach [13], while a decreased CFAE burden/degree of fractionation and DF have been reported following pulmonary vein isolation [14]. Therefore, AF electrogram

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http://dx.doi.org/10.1016/j.joa.2016.05.009
1880-4276/

characteristics can be good markers for predicting its stability or termination.

In this study, we utilized a novel statistical methodology to determine the spatial and temporal variance of CFAE and DF by calculating the intraclass correlation coefficient (ICC) and deriving the spatiotemporal stability index (STSI). We hypothesized that the STSI of CFAE or DF may be more predictive of AF sustenance or termination than conventional comparisons of their respective sequential mean values. Both sustained and self-terminating AF episodes from sheep with induced hypertension were used for this study. In addition, we aimed to fully characterize the STSI of fibrillatory signal characteristics in self-terminating and sustained AF episodes, and during the different phases of an AF episode from its initiation to maintenance and termination.

2. Materials and methods

We analyzed AF episodes recorded using epicardial direct contact mapping in "one-kidney, one-clip" hypertensive sheep. This induced hypertension model has been described previously [15]. In brief, nephrectomy is performed on the right kidney followed by placement of a vascular occluder over the left renal artery. Systolic blood pressure increases consistently over the ensuing weeks in a timely and reliable fashion. The hypertensive atria have been shown to develop atrial electrical and structural remodeling leading to a substrate for AF [16,17]. This study was approved by the "University of Adelaide Animal Ethics Committee" and "SA Pathology Animal Ethics Committee", Adelaide, Australia (M2010-109, approved 01 September 2010).

2.1. Direct contact mapping

Direct contact mapping was performed with the animals under general anesthesia. Sodium thiopentone (10–15 mg/kg) was used for induction to facilitate endotracheal intubation and isoflurane (2–4% in 100% oxygen at 4 L/min) was used for maintenance throughout the procedure. Noninvasive blood pressure, heart rate, pulse oximetry, end-tidal CO_2, and temperature were continuously monitored during the study. A midline sternotomy was performed to facilitate the open chest electrophysiological study. Direct contact mapping was performed using a custom-made epicardial plaque (80 electrodes, 4 mm inter-electrode spacing), which was placed over the left atrium and connected to a computerized recording system (LabSystem Pro, Bard Electrophysiology, MA, USA). Continuous recording of the surface ECG and overlapping bipolar electrograms (notch filtered from 30 to 500 Hz) were stored for offline analysis.

2.2. Atrial fibrillation electrogram analysis

AF was defined as a rapid irregularly irregular A-A intervals lasting for ≥ 2 s. We excluded episodes lasting < 28 s to facilitate the STSI analysis. AF episodes that terminated spontaneously without any intervention were defined as self-terminating ($n=42$ from 18 sheep), while those that continued for more than 15 min were defined as sustained ($n=6$ from 6 sheep). Each self-terminating episode was analyzed in consecutive 4-s epochs from the beginning to the end of the recording; for each sustained episode we performed a similar analysis for the first and last 2 min of the recording. Time-domain analysis of AF electrograms was performed using custom-made software with settings analogous to the Ensite NavX system (St. Jude medical, MN, USA) for determining the complex fractionated electrogram mean (CFE-m). The algorithm calculated CFE-m as the average of time intervals between marked deflections on the fibrillatory signal, using a refractory period of 40 ms, peak-to-peak sensitivity of 0.05 mV, minimum electrogram duration of 10 ms, and a downstroke threshold of 0.03 V/s. These settings were optimized to avoid over-tagging of far-field signals or noise. Frequency domain analysis was performed using the Fast Fourier Transform after the electrograms had been rectified and filtered using Butterworth filters (1–20 Hz) and edge-tapered with a Hanning window. Dominant frequency (DF) was defined as the frequency between 3 and 15 Hz that contained the maximum power within the frequency domain. DF values were excluded if the regularity index was less than 0.2.

2.3. Spatiotemporal stability index

The STSI of CFE-m and DF was determined by calculating the ICC. As per standard statistical methodology, ICC is defined as a ratio of relative variance of data across the plaque (i.e., spatial variation) as compared with variance across time (i.e., temporal variation). We used the following equation to calculate ICC agreement in a two-way random mixed effects model for each episode, where electrode and epoch were modeled as random effects:

$$STSI = \sigma^2(b)/\left[\sigma^2(a)+\sigma^2(b)+\sigma^2(w)\right]$$

where $\sigma^2(a)$ is the variance of the measured parameter (CFE-m or DF) between epochs (time variance), $\sigma^2(b)$ is the variance between electrodes for each epoch (spatial variance), and $\sigma^2(w)$ is the residual variance in the model. STSI is sensitive to changes in spatial variance over time, as well as changes in signal characteristics even if spatial patterns are stable. For example, STSI would reduce if the overall electrogram complexity increased between epochs, despite maintaining the same spatial pattern across the plaque. STSI therefore provides a measure of spatial agreement across time, with values that reflect the level of spatiotemporal stability in the signal characteristics. Furthermore, the ICC is sample-size independent, so that episodes of any number of epochs can be compared without sample-size bias.

Fig. 1 shows a representative 4-s epoch, in which electrograms with higher fractionation (lower CFE-m) are shown in darker shades of red in the color intensity map (left). The corresponding DF color intensity map shows a uniform spatial distribution of DF at 6.41 Hz (right). Fig. 2 shows CFE-m color intensity maps from 2 self-terminating AF episodes. The first episode (top) demonstrates high spatial variance in CFE-m over time, which is reflected by a low STSI of 0.46. In contrast, the second episode (bottom) demonstrates a more stable pattern over the entire episode, with a higher STSI of 0.77.

2.4. Statistical analysis

Normally distributed data were expressed as mean $\pm$ standard deviation. The STSI of CFE-m and DF, as well as median DF and mean CFE-m, were compared using independent sample *t*-tests to determine differences between the initial phases of self-terminating and sustained episodes. A paired samples *t*-test was used to compare the same parameters between the first and last 2 min of sustained AF episodes. To assess the spatiotemporal stability prior to AF termination, the STSI of CFE-m and DF for the entire episode were compared to the STSI following removal of the last epoch and the STSI following removal of the last 2 epochs, using the paired samples *t*-test. For mean CFE-m and median DF, direct comparisons were made between the last epoch, the penultimate epoch, and the remainder of the entire episode, using the linear mixed effects model. All tests were performed using PASW (Version 20; IBM, New York, USA) with statistical significance set at $p < 0.05$.

Please cite this article as: Thanigaimani S, et al. Spatiotemporal characteristics of atrial fibrillation electrograms: A novel marker for arrhythmia stability and termination. J Arrhythmia (2016), http://dx.doi.org/10.1016/j.joa.2016.05.009