Original Article

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

Shivshankar Thanigaimani, PhD[a], Anthony G. Brooks, PhD[a], Pawel Kuklik, PhD[a], Darragh J. Twomey, MBBS[a], Samantha Franklin, BVSc, PhD[b], Erik Noschka, DVM, PhD[b], Darius Chapman, BSc[a], Rajeev K. Pathak, MBBS[a], Rajiv Mahajan, MD, PhD[a], Prashanthan Sanders, MBBS, PhD[a], Dennis H. Lau, MBBS, PhD[a,*]

[a] Centre for Heart Rhythm Disorders, South Australian Health and Medical Research Institute, University of Adelaide and Royal Adelaide Hospital, Adelaide, SA 5000, Australia
[b] School of Animal & Veterinary Sciences, University of Adelaide, Roseworthy, South Australia, Australia

## 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

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 $\geq 2$ 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:

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

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 $p < 0.05$.
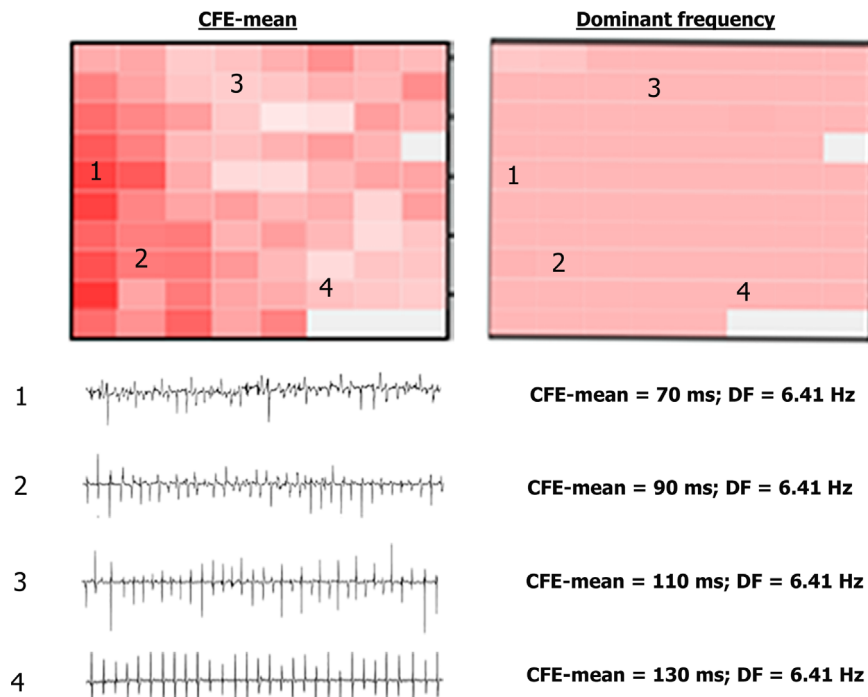
**Fig. 1.** Color intensity maps of CFE-m and DF in a 4-s epoch. A color intensity map is used to illustrate the degree of AF electrogram complexity in a 4-s epoch with higher fractionation (lower CFE-m) shown in darker shades of red (left). In this example, the corresponding DF color intensity map (right) shows uniform spatial distribution. Note that data from 4 bipolar electrodes were excluded from analysis because of poor contact (white).
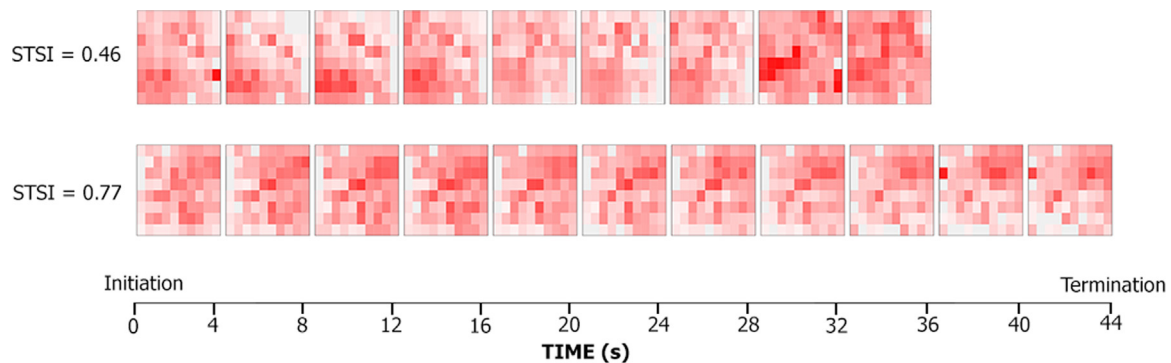


**Fig. 2.** STSI of CFE-m in self-terminating episodes. Two episodes of self-terminating AF episodes are shown. The upper example demonstrates higher spatiotemporal variability of CFE-m, with an STSI of only 0.46, as opposed to the lower example, in which the STSI is higher at 0.77.

## 3. Results

A total of 18 male merino cross sheep ($57 \pm 6$ kg) with induced hypertension ($162 \pm 7$ mmHg) of $12 \pm 2$ weeks' duration were used for this study. Mean interventricular septum and left atrial size were $18 \pm 1$ mm and $48 \pm 8$ mm respectively, consistent with hypertensive heart disease. A total of 42 self-terminating (mean duration: $60 \pm 23$ s, range: 28–100 s) and 6 longstanding sustained AF episodes ($> 15$ min; 6 sheep) were recorded. Following manual verification to ensure the correct annotation of electrograms and removal of data points with poor contact, a total of 67,733 4-s epochs from the 48 AF episodes were used for analysis.

### 3.1. Spatiotemporal stability during AF initiation: self-terminating versus sustained AF

Electrograms from the first 16 s (4 epochs) were used to study the spatiotemporal pattern of AF during the initiation of self-terminating versus sustained AF episodes (Fig. 3). During AF initiation, self-terminating AF episodes demonstrated a higher

CFE-m ($91 \pm 22$ vs. $73 \pm 7$ ms; $p=0.06$), although this did not reach statistical significance, and significantly lower median DF ($8.0 \pm 1.5$ vs. $10.4 \pm 0.9$ Hz; $p=0.001$) as compared to sustained AF episodes. On the other hand, neither the STSI of CFE-m ($0.60 \pm 0.19$ vs. $0.57 \pm 0.21$; $p=0.73$) nor that of DF ($0.21 \pm 0.28$ vs. $0.33 \pm 0.20$; $p=0.32$) differed between the initial phases of self-terminating and sustained AF episodes.

### 3.2. Spatiotemporal stability with sustained AF

The spatiotemporal pattern of AF electrograms with AF sustenance was examined by comparing the first and last 2 min of the 15-min sustained episodes. Both CFE-m ($73 \pm 7$ vs. $72 \pm 7$ ms; $p=0.5$) and median DF ($10.8 \pm 0.9$ vs. $10.3 \pm 0.8$ Hz; $p=0.07$) were unchanged during AF sustenance (Fig. 4, top row). By contrast, the STSI of CFE-m increased significantly between the two time points (from $0.59 \pm 0.19$ to $0.76 \pm 0.09$; $p=0.02$), although the STSI of DF remained unchanged ($0.27 \pm 0.14$ vs. $0.36 \pm 0.17$; $p=0.48$) (Fig. 4, bottom row). Fig. 5 shows the CFE-m color intensity maps during the first and last 2 min of the 15-min sustained AF episodes. The
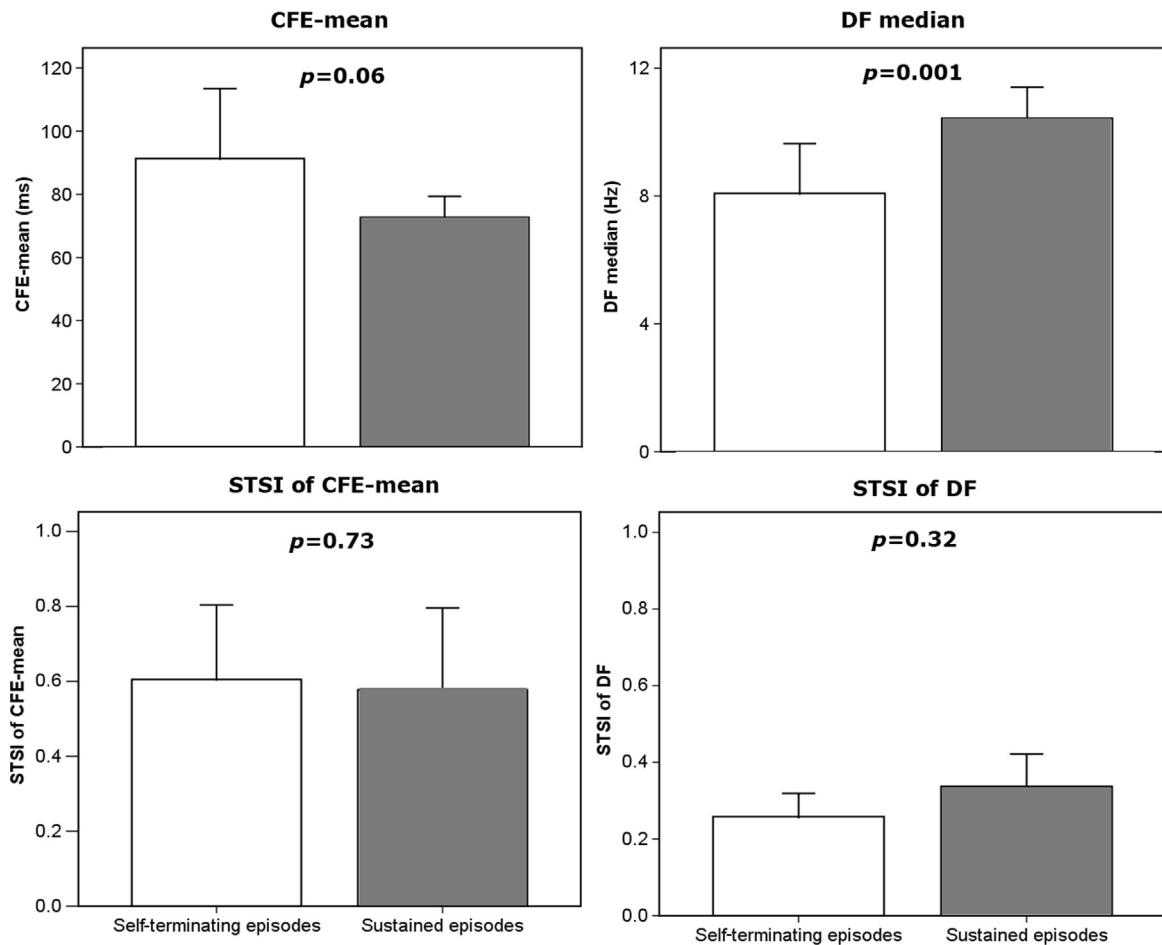
**Fig. 3.** Differences in electrogram characteristics between self-terminating and sustained AF episodes during AF initiation. The comparisons between self-terminating and sustained AF episodes were made using the first 16 s (4 epochs) of AF initiation.

color intensity of the heat maps remained quite consistent between these two time periods within each episode, consistent with the non-significant changes in mean CFE-m. However, spatiotemporal stability was higher during the 13th to 15th min as compared to the first 2 min in each sustained AF episode. This is most easily appreciated in episodes 4 and 5, with no differences seen in episode 6.

### 3.3. Spatiotemporal stability prior to AF termination

Mean CFE-m (last epoch vs. penultimate epoch vs. all remaining epochs: $96 \pm 20$ vs. $92 \pm 20$ vs. $92 \pm 22$ ms; $p=0.14$) was similar, but median DF ($7.7 \pm 1.0$ vs. $8.1 \pm 1.2$ vs. $8.0 \pm 1.3$ Hz, respectively; $p=0.006$) was lower prior to AF termination (Fig. 6A). Comparatively, the STSI of CFE-m increased significantly after removal of the penultimate and last 2 epochs (Fig. 6B, left: $0.49 \pm 0.18$ vs. $0.54 \pm 0.18$ vs. $0.56 \pm 0.18$; overall $p < 0.001$), indicating an increase in the spatiotemporal variability of CFE-m prior to AF termination. This pattern was not seen with the STSI of DF (Fig. 6B, right: $0.19 \pm 0.17$ vs. $0.21 \pm 0.19$ vs. $0.20 \pm 0.18$ Hz; overall $p=0.06$).

## 4. Discussion

In this study, a novel and more sophisticated measure of spatiotemporal stability (STSI) was compared to conventional sequential sampling of CFE-m and DF in an ovine hypertensive model for the detection of changes in the dynamics of AF from its

onset to stabilization and termination. The principal findings are as follows (Fig. 7).

First, the only parameter that mirrored the changing AF dynamics closely was the spatiotemporal stability of CFAE: the STSI of CFE-m increased with the stabilization of AF and decreased just prior to spontaneous AF termination. The same pattern was not seen with the STSI of DF or sequentially sampled mean CFE-m. Second, median DF trended lower with AF stabilization and was only significantly lower just prior to AF termination. However, the absolute change in both scenarios was physiologically non-significant, given that its magnitude was not more than 0.5 Hz. Third, the STSI of both CFE-m and DF were low (approximately 0.2–0.6) during both self-terminating and sustained AF episodes, indicating poor spatiotemporal stability. Last, during the first 16 s of AF initiation, sustained AF episodes demonstrated a significantly higher median DF than did those that terminated spontaneously. Taken together, the novel STSI of CFE-m is more representative of AF dynamics than the STSI of DF, or the sequential mean CFE-m or median DF.

### 4.1. Do CFAE and DF sites represent substrates for AF?

Konings et al. elegantly illustrated changes in fibrillatory pattern and varying degrees of CFAE during human AF that correlated with pivoting waves, wave collisions, lines of conduction block, and areas of slow conduction [18]. In addition, CFAE have been associated with conduction slowing or block around fibrous tissue [19–21]. In human AF, ablation at sites with high DF activity has been shown to prolong the AF cycle length and terminate the
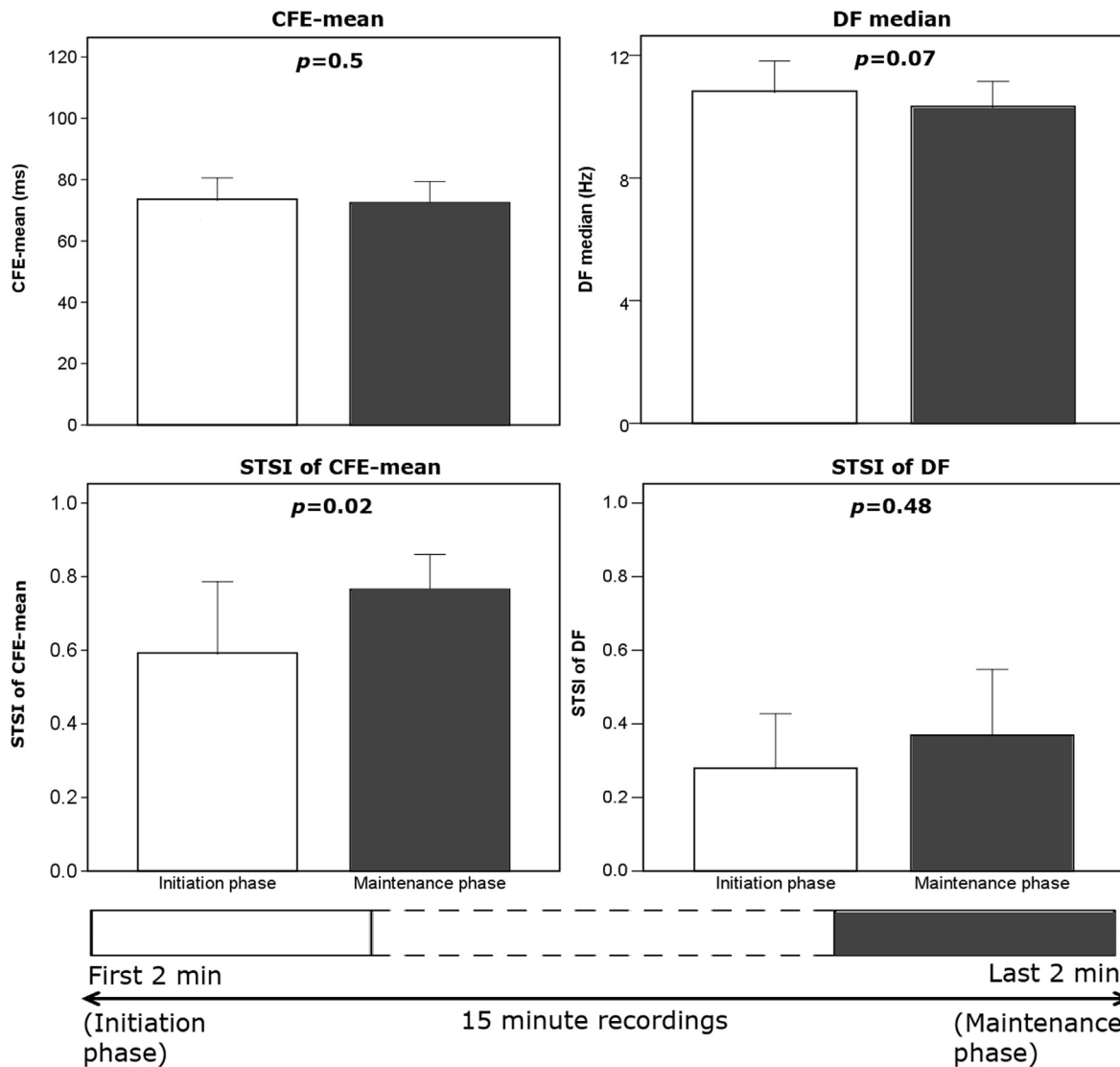
**Fig. 4.** Differences in electrogram characteristics with AF sustenance. The comparisons were made between the first and last 2 min of the 15-min recordings of sustained AF episodes.

arrhythmia [5]. Such high-frequency sites are thought to be drivers of AF that have a role in maintaining the arrhythmia [22–24]. Further, sites with CFAE have been shown to be in close proximity to high DF areas [25,26]. However, CFAE based ablation has only achieved comparable results to other contemporary techniques in patients with longstanding persistent AF [9,27]. Although prospective DF-guided catheter ablation in addition to pulmonary vein isolation did not improve the rate of AF termination or sinus rhythm maintenance, CFAE ablation adjunctive to pulmonary vein isolation was found to be beneficial in those with non-paroxysmal AF [8,10,28].

Given the lack of clear-cut advantages from these ablation studies, it is therefore uncertain whether areas with CFAE and high DF always represent substrate sites relevant to AF. Indeed, areas with CFAE during AF do not always represent an abnormal underlying atrial substrate, since these sites may also demonstrate normal electrophysiological characteristics during sinus rhythm [29]. More recently, activation mapping with monophasic action potential recordings has suggested that a majority of CFAE sites represent non-local activations, with only a minority of CFAE sites attributable to high activation rates in human AF [30]. In addition, the limitations of current techniques for the real-time mapping of

DF/CFAE and the diverse ways in which CFAE are defined may also contribute to the underwhelming ablation results [11,31,32].

In the present study, our novel method of assessing AF electrogram characteristics using STSI circumvented the inherent technical and algorithmic limitations, providing a true assessment of their spatiotemporal stability. We demonstrated that the STSI of CFE-m correlated well with changes in AF dynamics, despite the absence of any difference between self-terminating and persistent AF episodes in the STSI during the first 16 s of AF initiation. This phenomenon, where STSI increases with AF stabilization and decreases just prior to AF termination, implies that CFAE are physiologic. Further work is needed to demonstrate whether a site with a highly stable STSI of CFE-m may be a more useful ablation target, and whether monitoring of this index during an ablation procedure may help determine when the procedure is progressing towards AF termination. In contrast, the frequency domain component of fibrillatory signals showed a distinct lack of changes in either DF or its STSI that might have mirrored AF dynamics.

### 4.2. Poor spatiotemporal stability of AF electrograms

Clinical studies of CFAE have reported that they were stable and reproducible using sequential mapping data [33–35]. In contrast,
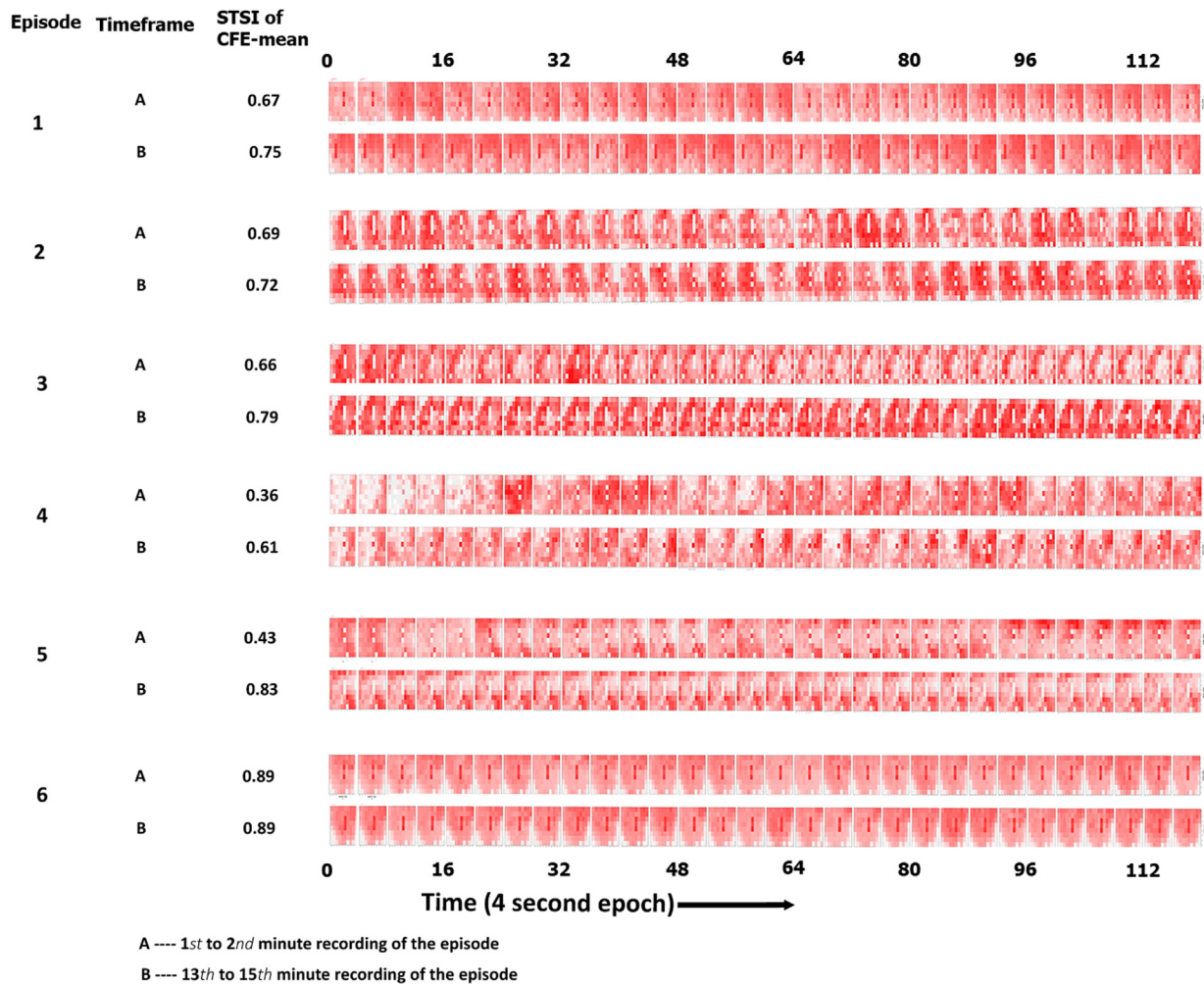
**Fig. 5.** Color intensity maps of CFE-m during the first and last 2 min of sustained AF episodes. The first 2 min of each of the 6 sustained episodes are labeled as A and the corresponding last 2 min are labeled as B. The spatiotemporal variability of CFE-m was reduced in all episodes (especially for episodes 4 and 5), with an increased STSI except for episode 6.

Habel et al. reported variability in the spatiotemporal characteristics of CFAE when the analysis was performed with continuously recorded signals over a 5-min period [12]. A recent systematic review of CFAE stability showed a moderate *r*-value of only 0.67 for the correlation between CFAE values from sequential mapping [11]. In the same review, CFAE sites remained fractionated from sequential and continuous recordings between 75% and 81% of the time [11]. Here, our assessment of AF electrogram stability took into account both spatial and temporal aspects by utilizing the STSI. The mean STSI of all self-terminating AF episodes was low for both CFE-m (Fig. 8) and DF ($0.59 \pm 0.18$ and $0.25 \pm 0.21$, respectively). Likewise, the mean STSI of CFE-m and DF from the first 2 min and the 13th–15th min of the sustained AF episodes were also low (CFE-m: $0.59 \pm 19$ and $0.76 \pm 0.09$; DF: $0.27 \pm 14$ and $0.36 \pm 0.17$, respectively). Taken together, the poor stability of fibrillatory electrograms in both time and frequency domains is consistent with the dynamic nature of AF and with previous studies showing that the sources sustaining AF are non-repetitive, unrestricted to any atrial sites, disorganized, and unstable [36–38]. Therefore, if a better tool such as the spatiotemporal stability of CFAE is available for detecting changes in AF dynamics, it may prove useful in guiding ablation.

### 4.3. Study limitations

The ovine data used for this analysis may not reflect human AF. The arbitrary segmentation of AF into 4-s epochs could have been modified to gain finer temporal information; however, it is well established that a reasonable signal sample is needed to estimate CFAE in a reliable fashion [39]. Phase analysis was not performed in this dataset, as the exact algorithm of phase analysis remains undisclosed. Electrogram fractionation analysis was performed using the CFE-m algorithm only. Further work is needed to evaluate the usefulness of this novel marker for guiding catheter ablation to treat AF.

### 5. Conclusions

AF electrogram characteristics demonstrate poor spatiotemporal stability consistent with the dynamic nature of the arrhythmia. The novel STSI, as an index of the spatiotemporal stability of CFAE, is a robust measure whose stabilization favors AF sustenance and whose destabilization heralds spontaneous termination.
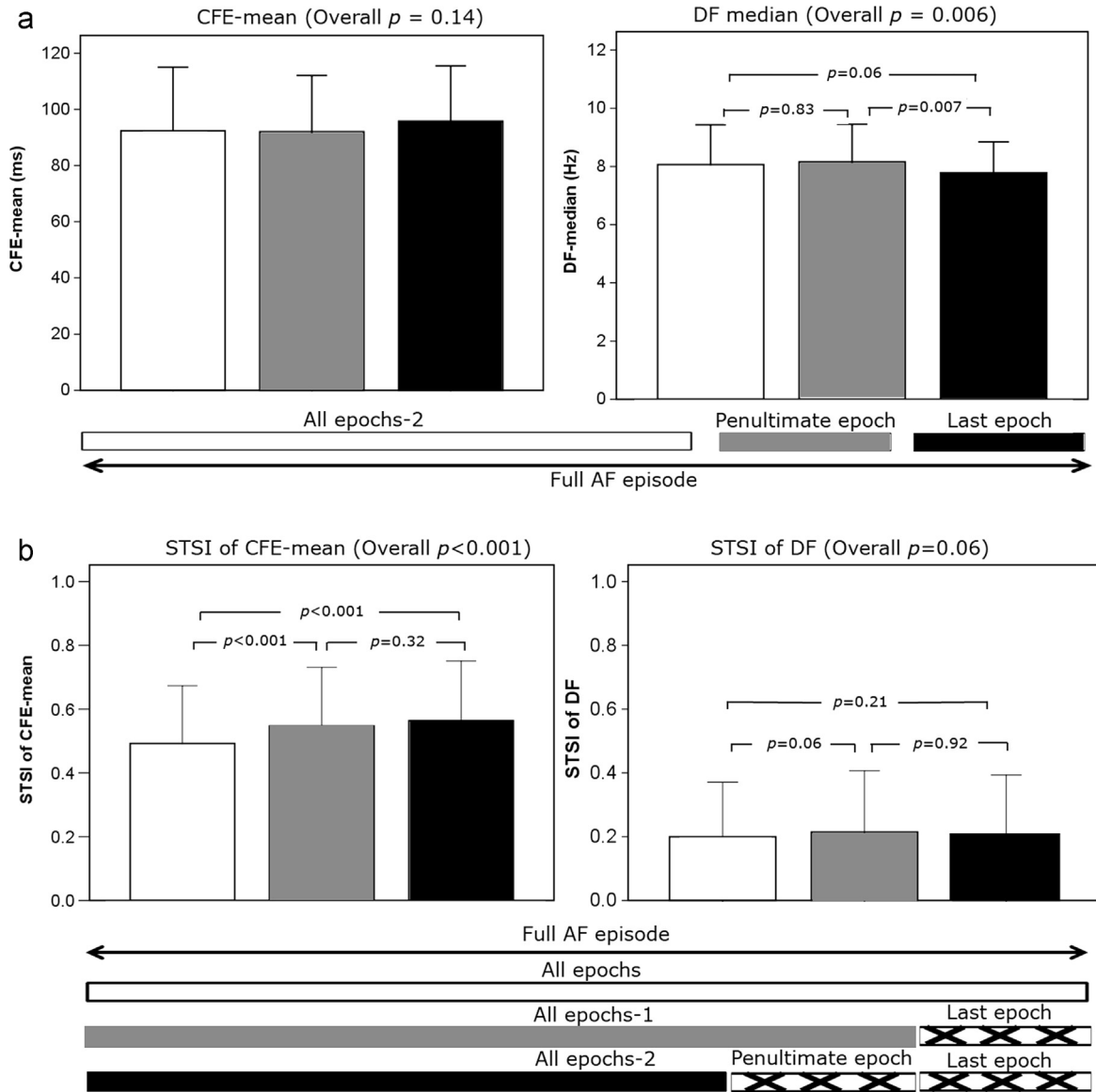
**Fig. 6.** Electrogram characteristics prior to AF termination. (A) CFE-m and median DF: The comparisons were made between the last epoch (black), the penultimate epoch (grey) and all remaining epochs (white). (B) STSI of CFE-m and DF: As the STSI is derived by calculating intraclass correlations between consecutive epochs, the changes prior to AF termination were determined by comparing the STSI for the whole self-terminating AF episode (white) to that of the whole episode minus the last epoch (grey), and that of the whole episode minus the last 2 epochs (black).
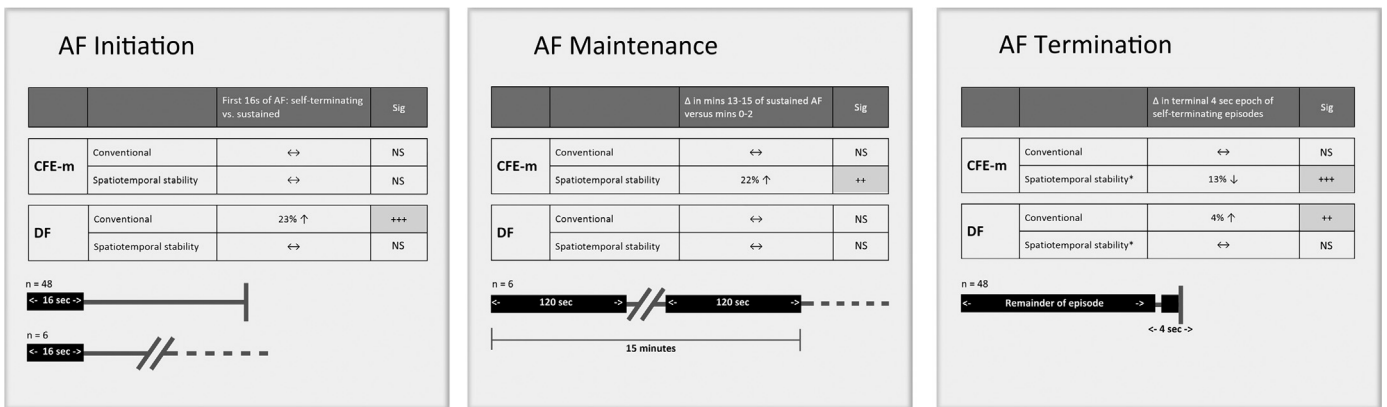


**Fig. 7.** Electrogram characteristics during different phases of AF. Only the STSI of CFE-m mirrored AF dynamics closely. "Conventional" denotes sequential mean/median of CFE-m and DF respectively; "NS" denotes non-significant; "++" denotes $p < 0.05$; "+++" denotes $p \leq 0.001$; ↔ denotes equivalent; ↓ denotes lower; ↑ denotes higher. *As it is not possible to calculate STSI based on a single epoch, the effect of the removal of the last epoch upon the overall episode STSI was examined. An elevation in STSI upon removal of the last epoch (13% in CFE-m) indicates that destabilization of AF dynamics preceded termination.
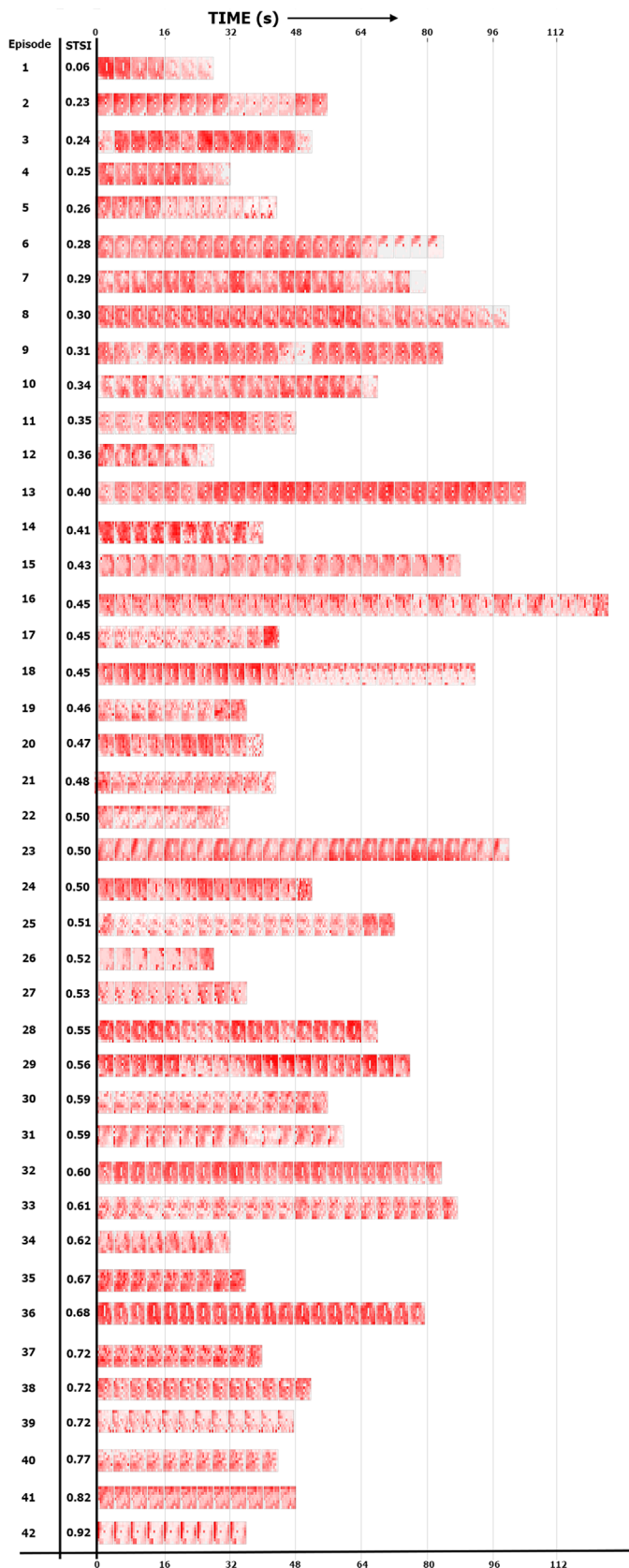
**Fig. 8.** Color intensity maps and STSI of CFE-m in self-terminating AF episodes. The color intensity maps of CFE-m of all 42 self-terminating AF episodes are shown. Note that the STSI ranges from 0.06 to 0.92 with a mean of only 0.59, indicating poor overall spatiotemporal stability of CFE-mean.

## Disclosures

## Funding Sources

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