Unipolar R:S Development in Chronic Atrial Fibrillation

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Abstract

Past studies have examined the differences between R and S waves of unipolar atrial signals in patients with atrial fibrillation (AF) and have shown a difference in the R to S ratio (R:S) in certain regions of the atria compared to a healthy population. This work indicates a potential use of R:S as a marker for AF. In this study, we further examine these claims and investigate temporal changes in R:S over AF development in animals.

Four canines underwent AF development protocols and endocardial sinus rhythm maps were recorded as AF progressed. Unipolar signals gathered from mapping were used to calculate R:S within the left atrium of each animal. Calculations were performed at time points: before AF initiation, 3-4 months of chronic AF, and 6 months of chronic AF. From our analysis, we observed an increase in R-dominant signals within the left atrium once AF is induced. Temporal results show that R dominance may be an indicator for chronic AF patients and may be associated with the presence of arrhythmogenic substrate. With the addition of regional information, this unipolar signal analysis could guide therapeutic strategies.

1. Introduction

Atrial fibrillation (AF) is a disease of electrical dysfunction in the heart that affects over 5 million Americans annually and is projected to affect over 10 million Americans by 2050 [1-3]. AF is characterized by rapid and disorganized atrial activity. It is also associated with an increased risk of embolic stroke and heart failure [4]. Studying the electrical activity of the atria, especially that of the left atrium, is critical to understand how AF is propagating in cardiac tissue and how it can be treated.

Clinically, AF patients undergo electro-anatomical mapping with catheters that measure atrial signals along the endocardium. These measurements are often bipolar, which measures signal between two near points and provide local recordings with minimized influence of far-field signal. Unipolar measurements are less commonly used and contain far-field ventricular signals when measured in the atria but provide greater information on wavefront propagation [5].

Standard methods of analyzing AF include inquiries into low-voltage areas, dominant frequencies, and conduction velocities [6-8]. These methods fail to analyze the morphology of the atrial signal, which has been shown to hold information on atrial conduction properties critical in the development of AF in unipolar measurements [5]. Mathijs et al. further explored the value of unipolar atrial EGM morphology analysis and developed a classification technique to characterize these signals in sinus rhythm [9]. These studies have shown that waveform abnormalities persist in AF patients even in sinus rhythm, indicating that morphology is tied with the presence of arrhythmogenic substrate and that morphological analysis may be useful in guiding ablative treatment [9]. This work is limited and does not provide information on temporal changes in unipolar morphology from the onset of AF. In this study, we sought to classify the morphologies of atrial signals in sinus rhythm throughout the development of chronic AF in a canine model.

2. Methods

2.1 Electrophysiology Study

A rapid atrial-paced canine model (n=4) was used [10]. Pacemakers were implanted and programmed to induce AF by stimulating at 50Hz every other second. Pacemakers were turned off every week to check for sustained AF. Once AF is sustained, pacemakers were set to stimulate 1s every minute to reinitiate AF in case the animal spontaneously reverts to sinus rhythm. Periodic mapping studies were performed throughout AF development from baseline to chronic AF conditions. All

animals had mappings performed before the start of the pacing protocol, 3-4 months of sustained AF, and 6-7 months of sustained AF

During mapping, a 64-electrode Orion basket catheter with the Rhythmia Cardiac mapping System (Boston Scientific) was used to measure electrical activity on the endocardium of the left atrium (Boston Scientific). If animals were in AF, cardioversion via defibrillation was performed to return electrical activity to sinus rhythm. At each stage of AF development, sinus maps of the left atrium were collected. Sinus voltage maps were continuously recorded at 1kHz as the catheter navigated the LA. In addition to voltage maps, atrial geometries were generated as the Orion catheter traversed the atrial wall.

2.1 Analysis

These collected signals were analyzed in MATLAB utilizing signal processing and statistical toolboxes. The raw signal from the Orion catheter includes unwanted measurements due to the movement of the catheter and/or distance of a given electrode to the atrial wall. Position-based criteria were applied to the data to extract a signal with a minimized presence of unwanted noise. For each vertex on the atrial geometry, the signal collected by electrodes within 3mm of the vertex and whose position changes at a rate less than 0.1 mm/s on all Cartesian axes was selected and assigned to the relative vertex for further analysis. Atrial points where no collected signal met position-based criteria were not considered.

The collective unipolar EGM signals present at each atrial location were then analyzed with a peak finding algorithm to identify atrial R and S peaks. Firstly, the ventricular signal is removed by standard subtraction methods referencing surface ECG recordings. Peaks of the QRS complex were then identified via methods outlined by Park et al. This method applies discrete wavelet transformations and Shannon entropy envelope calculations to select waveform features of interest and is effective for this application in patients with AF [11].

The R to S ratio of each identified beat was calculated and classified following the definition by Mathijs et al (equation 1) where the relative differences in R and S wave amplitudes are scaled from -1 to 1 [9]. Classification values closer to -1 indicate R dominant waves and higher classification closer to +1 indicates S dominant waves. Figure 1 describes the general change in morphology of atrial signals that we classified when observing the R and S waves of each beat. The statistical skewness of the total distribution of R:S calculations was determined using native MATLAB functions at each atrial point. Skewness provides a single metric capable of quantifying the R:S distribution at any atrial point. More positive skewness relates to R-dominant distributions whereas more negative skewness describes S-dominant distributions. Outliers were defined as elements more than three scaled median absolute deviations from the median and were removed as likely artifacts of incorrect peak detection.

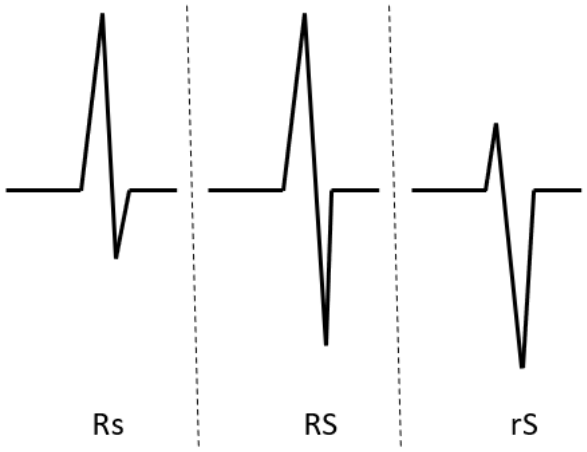

Figure 1. Generalized R:S classification of R and S wave amplitudes of an atrial signal.

$$RS = \begin{cases} 1 - RS(n) & for\ RS(n) \leq 1 \\ \frac{1}{RS(n)} - 1 & for\ RS(n) > 1 \end{cases} \quad (1)$$

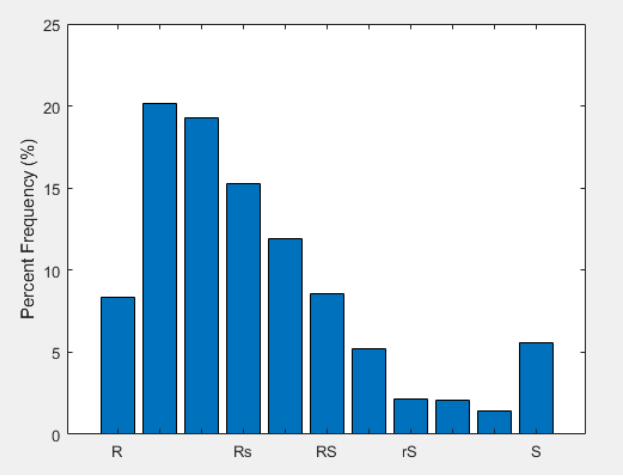

Figure 2. Distribution of R:S at a single atrial point. Skewness values would describe this distribution as more positive and signals at this point to be R-dominant.

This process was repeated for each animal at each mapping timepoint. Unpaired, two-tailed Student's T-tests were performed with Holm-Bonferroni corrections for multiple comparisons assuming unequal variance. Cohen's effect size was also calculated for all comparisons to investigate changes in the distribution.

3. Results

The results from skewness calculations are summarized in table 1, reporting the mean, standard deviation, variance, and total data points at each time point, inclusive of all animals. Differences in total data points used are the result of differences in atrial geometries and the number of vertices available for calculation. Statistical analysis showed significant differences ($p < 0.01$) were found when comparing baseline pre-AF skewness values to either the 3-4 month or 6–7-month chronic AF conditions. Between AF time points, we observed no significant difference ($p = 0.374$). From our calculation of Cohen's effect size, baseline values compared to both AF conditions were found to have a large effect size greater than 0.8 (3mo:0.976, 6-7mo;1.023). Comparisons between 3-4mo and 6-7mo found a small effect size of less than 0.10 (0.033). Figure 3 presents how the skewness of R:S distributions changed over time and increased from baseline. Positive skewness in this plot describes an R-dominant distribution of R:S in the LA.

Average skewness for each animal was also determined, and the results are plotted in figure 4. Here we see a trend indicating a similar relationship comparing AF conditions to baseline but potentially differing results between AF timepoints. Chronic AF of 6-7 months seems to show increased R-dominance from both baseline and 3–4-month timepoints. No significance is found between timepoint comparisons of this data, but the addition of more animals to the study could lead to a more conclusive analysis of the development of R:S from early AF to late AF.

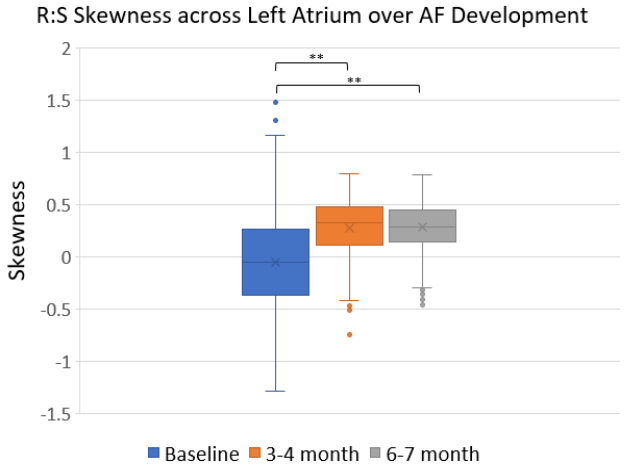

Figure 3. R:S skewness values over development of AF. Positive values describe R-dominant signals. ** indicates $p < 0.001$.

Table 1. Statistical summary of R:S skewness calculations.

Timepoint	n	μ	σ	σ^2
Baseline	1472	-0.057	0.405	0.164
3 Month	1052	0.274	0.258	0.067
6 Month	2051	0.282	0.238	0.057

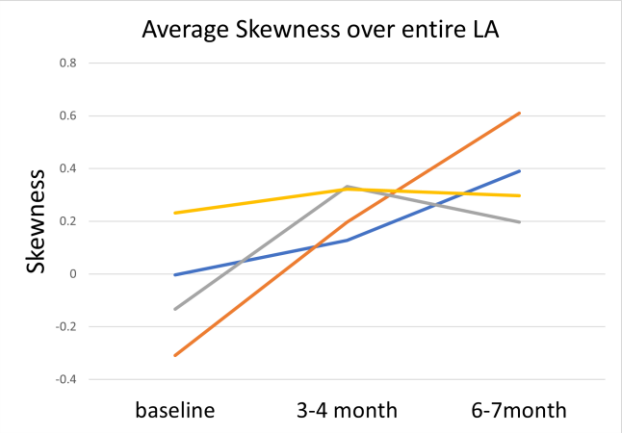

Figure 4. Average R:S skewness within each animal over time. No statistical significance found between timepoints ($p > 0.01$, $n = 4$).

3. Discussion

From our results, we see an overall increase in R-dominance in the LA from baseline to persistent AF conditions. Changes in waveforms of cardiac muscle are attributed to changes in the distribution of intracellular currents [12, 13]. Thus, the observed morphological change toward R-dominance may provide information on cellular changes in the myocardium as a result of AF. Additionally, the observed increase in R-dominant signals may be due to an increase in areas of fibrosis or electrical block within the left atrium. Measurements taken at or near fibrotic regions may have less signal exiting a unipolar measurement site leading to a minimization of negative deflections. Temporal analysis showed that these changes in R:S are recognizable at the onset (3-4 months of AF) of AF and that R:S may be a useful indicator of persistent AF. Additionally, we saw no significant changes in R:S between the onset of AF (3-4 months of AF) and long-term sustained AF (6-7 months of AF), suggesting that unipolar morphologies of the generalized LA during AF are stable.

Further analysis regionalizing the distribution of R:S in specific areas of the left atrium should be performed to see if stability is observed regionally or if R dominant signals dynamically change their position over time in AF

conditions. With regional information, further comparisons could be made relating R:S to driver sites of AF, areas of slow conduction velocities, and fibrotic regions. Combined temporal and regional analysis is critical for a comparison to driver sites as these sites are known to move across the endocardium over time and may be attributing to waveform changes.

Further histological analysis and corroboration with MRI scans at each time point could provide information on whether the presence of fibrotic regions drives the observed change. Additionally, improvements to the algorithm selecting positive and negative deflections could be made. Only sinus beats with clear R and S waves were considered for analysis. The inclusion of fractionated signals in analysis may be more informative in heterogeneous substrates.

In this study, we have shown that R:S is tied to the onset of arrhythmogenic activity within the left atrium. Future work involving the regionalized analysis of this marker over time could have clinical implications and may provide more information than low-voltage areas for targeting tissue for ablative therapy.

Acknowledgments

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