Linear and Nonlinear Correlations Between Surface and Invasive Atrial Activation Features in Catheter Ablation of Paroxysmal Atrial Fibrillation

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Abstract

P-waves are vastly used to assess the outcome of catheter ablation (CA) of atrial fibrillation (AF). It remains unknown, however, if coronary sinus (CS), the key reference structure in CA procedures, follows similar patterns. This study's objective is to detect any correlations between the behavior of P-waves and CS local activation waves (LAWs) with regard to CA procedure. Duration, amplitude, area and slope rate were studied in P-waves and LAWs of five-minute recordings from 29 patients undergoing paroxysmal AF CA. Normalization ($\mathbf{N}$) due to heart rate (HR) fluctuations was performed. Pearson's correlation (PC) between CA-induced variations ($\boldsymbol{\Delta}$) of P-waves and LAWs was calculated. Linear correlations between each P-wave/LAW were studied with PC and linear regression with $10-$fold cross-validation. Cross-quadratic sample entropy (CQSE) assessed nonlinear correlations. PC ($\Delta:\ \rho < 52.27\%,\ p = 0.015$, P-wave/LAW: $\rho < 40.37\%,\ p = 0.001$) and linear regression analysis ($R^2-adj < 16.02\%,\ p = 0.015$) showed low/mediocre linear correlations. CQSE ($0.8-1.3$) also suggested weak nonlinear relationships. P-waves and LAWs are poorly correlated and do not describe to the same degree the substrate modification after CA. It is possible that P-waves reflect the cumulative CA-induced modifications of various atrial sites, with CS being one of them but not the dominant.

1. Introduction

Catheter ablation (CA) of pulmonary veins (PVs) is still the star treatment of atrial fibrillation (AF), the most common cardiac arrhythmia in the western world [1, 2]. So far, outcome prediction of CA of PVs during sinus rhytm (SR) is performed almost exclusively from P-waves, which are thought to provide crucial information on the atrial substrate condition before and after the procedure. P-waves analysis includes the study of the electrical characteristics of P-waves, with an attenuation trend being connected to the elimination of fibrotic phenomena, which in turn cause longer and more variable P-waves [3–5].

During CA, non-PV triggers are detected via catheters that move throughout the atria, localizing the site with the earliest activation before the AF outbreak [6]. Although CA of PVs does not involve the elimination of non-PV triggers, catheterization of atrial sites still takes place likewise. Therefore, observing how CA modifies the electrical characteristics of these atrial sites with respect to P-wave alterations would be of high interest for a more detailed perspective of the atrial substrate as well as of the CA procedure itself. Notwithstanding, constant movements of the mapping catheter do not allow the acquisition of electrograms (EGMs) from a stable observation point.

A standard yet significant part of the mapping process is the catheterization of certain sites that are used as references, with a stable catheter placed and hence constantly recording [6]. Due to its location between right and left atrium, coronary sinus (CS) is a highly employed reference [6–8]. CS recordings are therefore candidates for the inspection of the possible relationships between CS local activation waves (LAWs) and P-waves behavior. The objective of the present study is to clarify this assumption, by analyzing simultaneously P-waves and CS LAWs before and after CA of PVs and studying their correlations.

2. Materials and Methods

Surface and bipolar CS recordings of 29 paroxysmal AF patients undergoing radiofrequency CA of PVs for the first time were employed. Recordings were acquired for five minutes before and after the CA procedure with a sampling frequency of 1 kHz. For surface recordings, lead

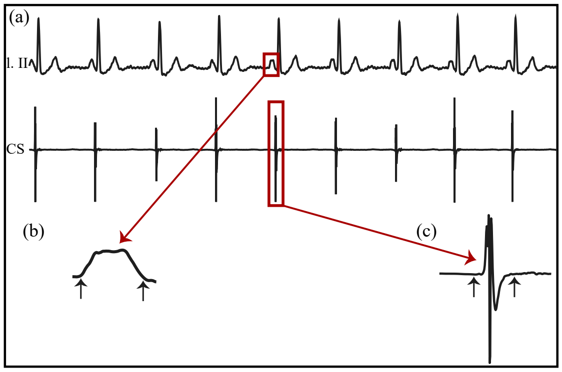

Figure 1. (a) Lead II (top) and CS (bottom) recordings. (b) P-wave and (c) CS LAW. Arrows show the fiducial points of the activations.

II was employed for the analysis. For CS recordings, the channel used for the analysis was customly selected for each patient upon inspection, with high amplitude and clear baseline being the only criteria. Pre- and postablative CS recordings of the same patient always consisted of the same CS channel, so that the analysis would be reliable and the tracking on CS evolution consistent.

Preprocessing consisted of denoising and mean removal for both surface and CS recordings [9, 10]. Invasive recordings were additionally subject to ventricular cancellation [11]. Presence of ectopic beats was less than 4% of total beats for the surface recordings and were corrected via linear interpolation. P-waves and CS local activation waves (LAWs) were detected and delineated [12–15], as can be seen in Figure 1. Delineations were afterwards inspected by two electrophysiologists.

For each P-wave and CS LAW, duration, amplitude and area were calculated as described elsewhere [15]. As CS LAWs have both negative and positive part, their amplitude corresponded in the present study to peak-to-peak (PP) amplitude. Slope rate expresses the rhythm of amplitude incrementation in specific time intervals and was calculated from the following equation:

$$S_{20}^{n} = \frac{A(t_{20}) - A(t_{onset})}{t_{20} - t_{onset}}, \quad (1)$$

where S_{20}^{n} is the slope rate of the $n-th$ activation at the sample point that corresponds to 20% of the activation length, $A(t_{onset})$ and $A(t_{20})$ is the amplitude at the onset and 20% of the activation, respectively. Finally, t_{onset} and t_{20} are the sample points corresponding to the $A(t_{onset})$ and $A(t_{20})$.

The effect of heart rate (HR) fluctuations was mitigated for duration, area and slope rate, which were normalized by a factor (**N**) as follows:

$$\boldsymbol{N}_n = \frac{1000}{R_n - R_{n-1}}, \quad (2)$$

where $n = 1, 2, \cdots, M$ with M- the number of activations of each recording and R_n, R_{n-1} are the R-peaks for the $n-th$ and the $(n-1)-th$ activations, respectively. Duration and area were multiplied by the normalization factor, while slope rate was divided by the normalization factor. Both standard and normalized values of these features were included in the analysis.

Pearson's correlation (PC) was recruited for the study of the effect of CA on each feature in P-waves with respect to the same effect on CS LAWs. For this purpose, a percentage reflecting the variation of each feature ($\Delta_{Post/Pre-1}$) was calculated. PC was additionally employed for the correlation between each activation of surface and CS recordings for each feature. Linear regression was utilized for the same purpose, additionally performing 10-fold cross-validation. Cross-quadratic sample entropy (CQSE) with $m = 1$ and $r = 0.35$ was finally applied for the evaluation of any nonlinear correlations between each activation of surface and CS recordings [16].

3. Results

Table 1 shows the correlation results for the PC analysis (variations of each feature due to CA in the first column, activation-to-activation analysis in second and third columns) and linear regression analysis. For PC analysis, when the correlations of the variations due to CA were investigated, only $\mathbf{N}(dur)$ seemed to show a moderate correlation ($\rho = 52.27\%$, $p = 0.015$). For the activation-to-activation analysis, amplitude and area showed negligent positive or negative statistically significant correlations (-0.92% to 3.17%, $p < 0.025$), while $\mathbf{N}(dur)$ showed a low to moderate correlation (40.37%, $p = 0.010$ for post-ablative recordings). The rest of the features did not show significant correlations ($p > 0.05$).

As only one predictor is involved in simple linear regression, statistical power is the same as in PC analysis. Regarding correlations, results were preserved in a similar direction after linear regression with $10-$fold cross-validation, showing noticeably lower correlations (maximum $R^2 - adj = 16.02\%$, $p = 0.010$). This variation in PC and linear regression results comes as a consequence of the cross-validation implementation in the case of linear regression, which yields more robust and reliable results. Figure 2 shows the effect of cross-validation in duration and amplitude, where linear regression results are mostly concentrated in a much smaller area (shaded area) than PC results. The rest of the features follow the same trend, but are not shown due to lack of space.

Results of CQSE analysis are shown in figure 3. Values span from 0.2 to 1.8 and are mostly concentrated in

Table 1. Correlations (%) and p-values for PC and linear regression. Statistically significant results are shown in **bold**.

Features	**PC**			**Linear regression**	
	Δ	**pre-CA**	**post-CA**	**pre-CA**	**post-CA**
	ρ [%] (p)	ρ [%] (p)	ρ [%] (p)	$R^2 - adj.$[%] (p)	$R^2 - adj.$[%] (p)
Duration	-5.69 (0.806)	4.38 (0.076)	-2.89 (0.216)	0.9 1(0.076)	0.20 (0.216)
PP amp.	5.91 (0.799)	**3.17 (0.007)**	**−0.92 (0.004)**	**2.66 (0.007)**	**3.06 (0.004)**
Area	− 30.76 (0.175)	-0.44 (0.122)	**0.34 (0.025)**	0.48 (0.122)	**1.20 (0.025)**
S_{20}	10.19 (0.660)	-2.97 (0.619)	-1.00 (0.499)	0.31 (0.619)	0.75 (0.499)
N(dur)	**52.27 (0.015)**	40.41 (0.072)	**40.37 (0.010)**	16.00 (0.072)	**16.02 (0.010)**
N$(area)$	-19.12 (0.406)	10.42 (0.080)	6.57 (0.766)	1.64 (0.080)	0.951 (0.766)
N(S_{20})	13.07 (0.572)	-5.06 (0.512)	1.40 (0.512)	0.37 (0.512)	1.09 (0.512)

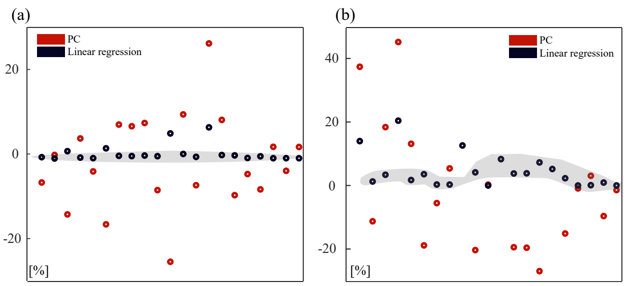

Figure 2. PC (red) and linear regression (blue) analysis for (a) duration after CA and (b) amplitude after CA. Shaded areas show the concentration of linear regression results, which are notably less disperse than PC results.

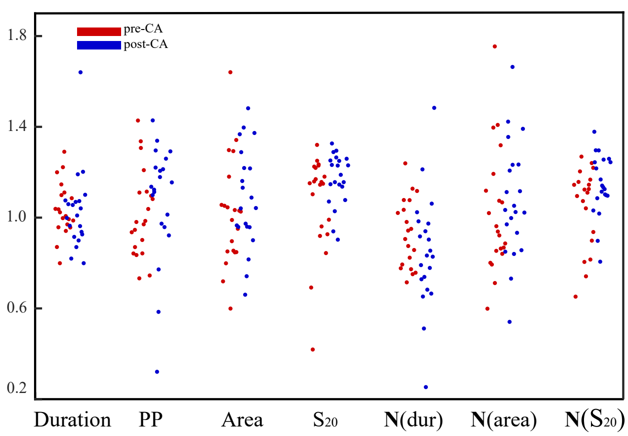

Figure 3. Scatterplot for CQSE values for the features before (red) and after (blue) CA.

the area between 0.8 and 1.3. As these values are far from 0, which is the optimal case of absolute concordance for CQSE, nonlinear correlations are not considered strong. In contrast with linear correlations, normalization did not have a significant effect in nonlinear correlations, as can be observed. Correlation in **N**(dur) is slightly improved with respect to duration, but stil remains quite weak.

4. Discussion

Analysis of CS recordings during CA is a fundamental step not only for the deeper understanding of the effect of CA on atrial structures but also for the exploration of the relationships between CS LAWs, as a key part of CA procedure and P-waves, as the dominant outcome prediction indices. Previous studies employing right atrium (RA) electrograms (EGMs) have reported linear correlations between long P-wave duration and fibrotic areas in EGMs as well as nonlinear correlations between chaotic features of lead II and V1 recordings and EGMs [17, 18].

Although the aforementioned studies are of great importance for the understanding of the correlations between RA fibrotic areas and surface recordings, some points should be highlighted. Firslty, employed analysis did not include LAWs. Instead linear or nonlinear indices, across longer periods of EGMs, implying fibrotic areas were used. Recordings were not obtained during CA of PVs, which is the baseline of the present study due to its significance in the AF treatment. Moreover, database population in one of these studies studies showed additional pathologies. Finally, the reported results are limited to RA, whereas the ignorance on left atrial sites remains. While CS role in AF initiation and perpetuation has been investigated, little is known about CS electrical characteristics during CA and how they evolve with respect to P-waves.

The present analysis showed a different effect of CA in CS LAWs than in P-waves, as can be concluded from the low correlations that the variations of the features showed. Mitigation of HR fluctuations significantly improved the way that duration in CS LAWs and P-waves was affected by CA, converting it from very low to moderate and from statistically non-important to important. Normalization showed the same effect in analysis from activation-to-activation, which also showed low correlations. Nonlinear analysis results additionally revealed weak nonlinear relationships. Overall, CS behavior is not clearly reflected by P-waves, which possibly express the total of the atrial sites and are mostly affected by areas other than CS.

5. Conclusions

No clear correlations between CS LAWs and P-waves are found. P-waves are the superstition of multiple atrial sites, while CS LAWs describe very local activities. Hence, the detection of other atrial sites that are more coherent with P-waves should be prioritized in order for them to be employed as references in CA of PVs.

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