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Are Coronary Sinus Features Reflecting the Effect of Catheter Ablation of Atrial Fibrillation as P-waves Do?

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***Abstract*—Atrial substrate alteration due to catheter ablation (CA) of atrial fibrillation (AF) is primarily assessed from P-waves . Nonetheless, how CA affects critical structures is ignored. The aim of the current study is to investigate if CA effect on CS, the principal CA reference, is related to that observed from P-waves analysis. Five-minute lead II and bipolar CS recordings of 29 paroxysmal AF patients were obtained before, during and after CA. Duration, amplitude, area and heart-rate (HR) variability (HRV) features were calculated for P-waves and local activation waves (LAWs). Normalization mitigated the effect of HR fluctuations. Linear correlations between each P-wave and LAW were tested with linear regression (LR) and Pearson correlation (PC) and nonlinear correlations with cross-quadratic sample entropy (CQSE). Correlation between the CA effect on P-waves and LAWs was investigated with PC. Negligent statistical correlations were found by PC and LR for amplitude and area ($-3.30\% < corr < +18.36\%$, $p < 0.0142$). After normalization, correlation in duration increased from non-significant to significant and from low to moderate (up to 47.25%, $p < 0.0001$). CQSE values were from 0.6 to 1.2. The effect of CA on P-waves and LAWs duration showed a moderate/high concordance after normalization (from 50% to 89%, $p < 0.0210$) and a highly tuned HRV ($> 90\%$, $p < 0.0297$). Apart from HRV, no significant correlations between CS LAWs and P-waves have been found. HR fluctuations mask any possible tuning and normalization should be applied prior to the analysis.**

***Keywords*—Atrial fibrillation; pulmonary vein isolation; coronary sinus; correlation; local activation waves.**

I. INTRODUCTION

Atrial fibrillation (AF) is considered the most common cardiac arrhythmia, accompanied with significant health and economic impact [1]. As pulmonary veins (PVs) are the principal AF trigger, their catheter ablation (CA) is currently considered the main AF treatment [2]. Despite the fact that CA of PVs involves the isolation of the main AF activity source, fibrosis found in the atria may sustain AF, causing AF recurrencies [3]. Considering the afore, the study of substrate alteration due to CA of PVs is of high importance in order to evaluate the CA outcome and plan the follow-up treatment.

For this purpose, many studies are focused on the observation of the P-waves or heart rate variability (HRV) alterations. P-wave shrinking is probably the most popular phenomenon observed after CA by multiple studies, predicting a favorable outcome attributed to the elimination of fibrosis and isolation of arrhythmogenic sources [4]–[6]. Temporal HRV reduction is observed after CA sessions due to radiofrequency (RF) energy affecting the autonomous nervous system, being another favorable index regarding the CA outcome [7], [8].

The analysis of the aforementioned techniques offers information exclusively about the alterations of the entire atria. However, how CA affects local atrial structures which contribute by any means to the AF phenomenon is yet to be explored. Coronary sinus (CS) is a key structure not only for the AF perpetuation but also for the CA procedure [9]–[11]. CS catheterization is a solid CA step, assisting in AF mapping. Due to this fact, stationary recordings obtained from the CS catheter are available and could be recruited to help in understanding further the AF mechanisms.

As spherical knowledge on the AF mechanisms is the key to the successful AF elimination, the main objective of the present study is to offer a deeper perspective of the CA effect on the function of CS. For this purpose, any kind of correlations between the alterations of the CS electrical features and the P-waves features as a function of the CA procedure will be analyzed.

II. MATERIALS

Twenty-nine paroxysmal AF patients undergoing first time ever RF CA formed the database of the study. Five-minute lead II and bipolar CS recordings were obtained during sinus

TABLE I

CORRELATIONS (%) AND p VALUES FOR PC AND LR, COMPARISON OF EACH AND EVERY ACTIVATION. STATISTICALLY SIGNIFICANT RESULTS ARE SHOWN IN BOLD. LR RESULTS EXPRESS THE R^2-ADJUSTED PARAMETER.

		pre-CA			**LPVI**			**RPVI**	
Feature	PC [%]	LR [%]	p value	PC [%]	LR [%]	p value	PC [%]	LR [%]	p value
Duration	-2.19	0.56	0.1291	-3.08	0.69	0.1040	4.53	0.22	0.2221
Amplitude	$\mathbf{-1.98}$	$\mathbf{2.12}$	$\mathbf{0.0090}$	$\mathbf{15.19}$	$\mathbf{2.34}$	$\mathbf{0.0033}$	$\mathbf{7.26}$	$\mathbf{3.49}$	$\mathbf{0.0016}$
RMS	$\mathbf{0.38}$	$\mathbf{5.33}$	$\mathbf{0.0019}$	$\mathbf{18.36}$	$\mathbf{3.60}$	$\mathbf{0.0017}$	$\mathbf{5.46}$	$\mathbf{4.12}$	$\mathbf{0.0142}$
Area	$\mathbf{-3.30}$	$\mathbf{2.94}$	$\mathbf{0.0032}$	$\mathbf{16.18}$	$\mathbf{3.24}$	$\mathbf{0.0015}$	$\mathbf{0.99}$	$\mathbf{1.40}$	$\mathbf{0.0142}$
S_{20}	0.61	2.38	0.0839	0.97	0.09	0.3927	-0.64	0.38	0.1426
$\mathbf{N}(Duration)$	$\mathbf{45.25}$	$\mathbf{20.32}$	$\mathbf{< 0.0001}$	$\mathbf{69.91}$	$\mathbf{47.25}$	$\mathbf{< 0.0001}$	$\mathbf{43.82}$	$\mathbf{18.97}$	$\mathbf{< 0.0001}$
$\mathbf{N}(PosAr)$	$\mathbf{10.00}$	$\mathbf{1.90}$	$\mathbf{0.0142}$	$\mathbf{35.40}$	$\mathbf{12.22}$	$\mathbf{< 0.0001}$	$\mathbf{10.66}$	$\mathbf{1.03}$	$\mathbf{0.0425}$
$\mathbf{N}(S_{20})$	-2.78	0.47	0.1431	0.60	0.78	0.0843	-0.44	0.47	0.1187

rhythm (SR) before the beginning (R.0), after LPVs isolation (LPVI) (R.1) and after right PVs isolation (RPVI) (R.2) with a sampling frequency of 1 kHz. A unique channel for all ablation steps (R.0, R.1 and R.2) was chosen for each patient based on high signal amplitude and low presence of noise for CA recordings, inspected by two electrophysiologists.

III. METHODS

Preprocessing started with denoising and mean removal for both lead II and CS recordings. The latter were additionally subject to ventricular cancellation in case that ventricular activity was present [12]–[14]. Presence of ectopic beats was observed in lead II recordings with a prevalence of $< 4\%$ of the total beats. Linear interpolation was applied for the correction of the ectopic beats [15]. Detection and delineation of P-waves for lead II and local activation waves (LAWs) for CS recordings was the final preprocessing step, details of which are described elsewhere [16]–[19].

Main analysis consisted of activation-based and recording-based features. Activation-based features were calculated at each P-wave and CS LAW and then averaged for each recording. Duration, amplitude, area and slope rate at 20% of the activation duration were calculated [19]. The following equation was used to calculate slope rate of the n activation at 20% of its duration

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

being $A(t_{20,\ onset})$ the amplitude at 20% of duration and the beginning of the activation, respectively and $t_{20,\ onset}$ the respective sample points.

The aforementioned features, apart from amplitude, are subject to heart rate (HR) fluctuations and were additionally normalized by

$$\mathbf{N}(x_i) = \frac{1000}{RR_i}, \tag{2}$$

where x_i is the value of x = duration, area or slope rate of the i-th activation and RR_i is the corresponding R-R interval. Duration and area were multiplied by $\mathbf{N}(x_i)$, while slope rate was divided by $\mathbf{N}(x_i)$.

Recording-based features were calculated across each recording, providing a unique value describing the recruited indices. For this purpose, time-domain HRV indices (SDNN, VARNN, RMSSD) [20] were utilized by considering **NN** as the atrial interbeat intervals of lead II and CS recordings.

Linear correlations between each P-wave and CS LAW were investigated by linear regression (LR) with $10-$fold cross-validation and Pearson correlation (PC). The latter was also used in order to compare the variation that each CA transition caused to the features of the P-waves with respect to that of the CS LAWs. Nonlinear correlations at each P-wave/CS LAW were tested with cross-quadratic sample entropy (CQSE) with $m = 1$ and $r = 0.35$ [21].

IV. RESULTS

Table I shows the results of linear correlations between P-wave and CS features, measured at each and every activation. As LR is performed using only one independent variable, statistical power is the same as in Pearson analysis. Hence, p value is only shown once and corresponding to both analyses. LR results revealed weaker correlations than PC analysis due to cross-validation, which adds robustness to the test as database is relatively small. Amplitude, RMS and area showed low statistically significant correlations, which yielded higher concordance in measurements right after LPVI.

Altthough no similar patterns in the duration of CS LAWs and P-waves were found, normalization of duration revealed statistically significant moderate correlations between LAWs and P-waves. Normalization did increase the correlation of area as well, although to a lesser extent. The effect of normalization in correlation for duration feature is shown in figure 1, where the results of a patient are shown as an example. It can be observed there how patterns become much more similar indicating higher correlation after normalization.

Figure 2 shows the results for PC analysis, when the effect of each CA transition on P-waves and LAWs features is investigated. For activation-based features before normalization, only RMS values after RPVI showed a significant yet moderate concordance between P-waves and CS LAWs. In this case as well, normalization boosted significantly the correlation between the alteration of duration in P-waves and LAWs after each CA step, which were once more converted to statistically significant, additionally showing moderate to high values.

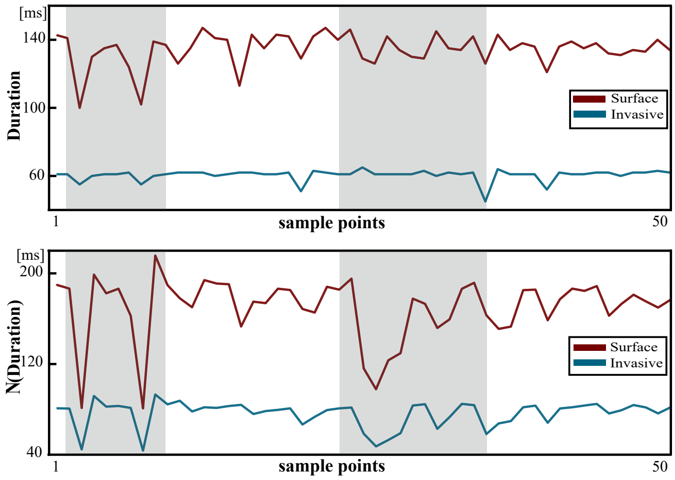

Fig. 1. Correlation results for duration (top) and **N**(duration) (bottom) for the same patient across the same 50 sample points. Normalization caused a notable incrementation of correlation between surface and invasive results. Gray areas show patterns that were especially corroborated after normalization.

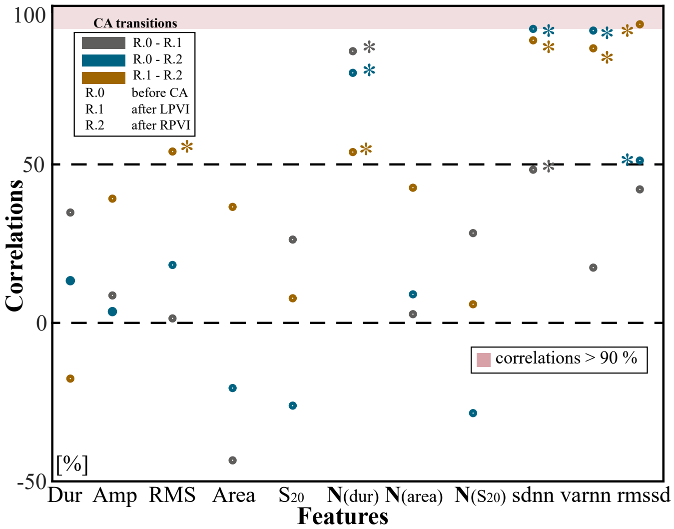

Fig. 2. PC analysis for the variation that each CA step has caused to the P-wave/LAWs features. Top line of the figure (in red shadow) shows very high correlations. Statistically significant results are shown in (∗).

How HRV feature varied after each CA step in CS recordings was in line with the way that lead II HRV values were modified, showing very high correlations. Finally, nonlinear correlation analysis is shown in figure 3. As a value closer to 0 would reveal a perfect concordance, values between 0.6 to 1.2 that the present analysis revealed do not imply the existence of even nonlinear patterns between P-wave and LAWs features. In contrast with the linear correlation analysis, normalization did not have a significant effect in nonlinear correlation study. Despite the fact that **N**(Duration) showed the lowest CQSE values and hence the highest nonlinear correlations, they remained nonsignificant.

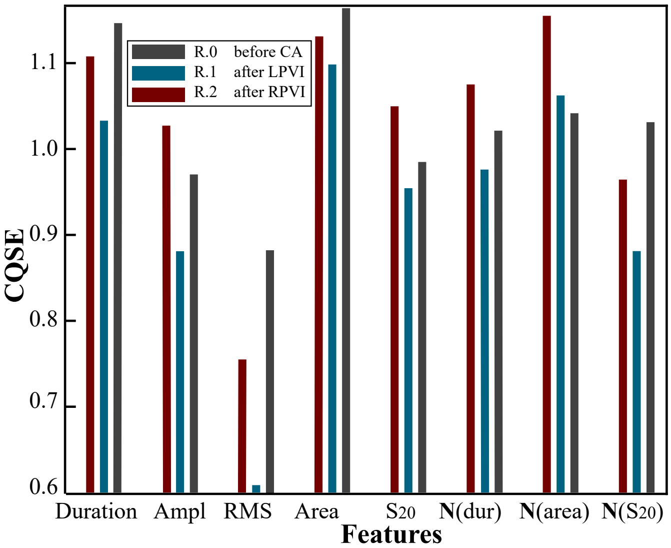

Fig. 3. CQSE results for each ablation step. Values do not indicate significant nonlinear correlations.

V. DISCUSSION

CS is a critical structure both for the AF perpetuation and for the most important AF therapy, the CA [9]–[11]. So far, its behavior with regard to the CA procedure has been remaining in the dark. The purpose of the present study was to enlighten this very issue. The most popular methods for the assessment of the CA outcome have been recruited for this reason and recordings acquired after crucial CA steps have been analyzed.

Previous studies investigating correlations between surface and invasive signals report the existence of linear or nonlinear relationships between characteristics of right atrium and surface recordings [22]–[24]. Although the results of the present study do not report the same outcomes, many differences exist between the baseline of the present and that of past studies. The latter utilize signals recorded during AF, a medley of patients with additional pathologies and right atrial recordings.

In the present study, correlations between P-waves and CS LAWs were, for the most part, negligible or moderate, not revealing a CS behavior similar to that observed when the atria are analyzed as an entity. Before normalization, correlation was higher when amplitude and area were measured. Notwithstanding, amplitude depends on the lead and CS channel under analysis. This work made use of lead II surface recordings, where P-wave shows the highest amplitude [25] and selected CS channels with high amplitude as a criterion. High correlation was only observed when the alterations of time-domain HRV features were investigated, possibly due to RF energy applications as reported from past studies [26].

When features were normalized, correlation was significantly amplified both in terms of statistical power and in terms of magnitude. After this normalization, a moderate correlation was found between duration of P-waves and CS LAWs and a moderate to high correlation between the alteration of duration in lead II and CS recordings for each CA transition. Given the high importance of P-wave duration to the prediction of the CA outcome [4]–[6], normalization is considered a crucial step for the comparison between surface and invasive recordings. Without this step, linear correlations of duration would have been masked. Normalization has not been observed to have the same effect on nonlinear correlation analysis, where no significant patterns have been reported either.

VI. CONCLUSIONS

Atrial substrate alteration is not performed uniformly. CS function is not affected by CA in the same way than the entire atria, lacking significant linear or nonlinear correlations. Moreover, HR fluctuations mask any possible correlations between surface and invasive electrical features. For a more detailed perspective on the AF mechanisms, the adoption of a strategy that includes the study of separate atrial sites in addition to the P-waves analysis and the normalization of the features dependent on HR fluctuations are highly recommended.

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REFERENCES

[1] G. Hindricks, T. Potpara, N. Dagres, E. Arbelo, J. J. Bax *et al.*, "2020 esc guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the european association of cardio-thoracic surgery (eacts)," *European heart journal*, 2020.

[2] M. Haissaguerre, P. Jaïs, D. C. Shah, A. Takahashi, M. Hocini, G. Quiniou, S. Garrigue, A. Le Mouroux, P. Le Métayer, and J. Clémenty, "Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins," *New England Journal of Medicine*, vol. 339, no. 10, pp. 659–666, 1998.

[3] W.-H. Cheng, L.-W. Lo, Y.-J. Lin, S.-L. Chang, Y.-F. Hu, Y. Hung, F.-P. Chung, J.-N. Liao, T.-C. Tuan, T.-F. Chao *et al.*, "Ten-year ablation outcomes of patients with paroxysmal atrial fibrillation undergoing pulmonary vein isolation," *Heart rhythm*, vol. 16, no. 9, pp. 1327–1333, 2019.

[4] K. Van Beeumen, R. Houben, R. Tavernier, S. Ketels, and M. Duytschaever, "Changes in p-wave area and p-wave duration after circumferential pulmonary vein isolation." *EP Europace*, vol. 12, pp. 798–804, Jun. 2010.

[5] A. Maan, M. Mansour, J. N. Ruskin, and E. K. Heist, "Impact of catheter ablation on p-wave parameters on 12-lead electrocardiogram in patients with atrial fibrillation." *Journal of electrocardiology*, vol. 47, pp. 725–733, 2014.

[6] Q. Chen, S. Mohanty, C. Trivedi, C. Gianni, D. G. Della Rocca, U. Canpolat, J. D. Burkhardt, J. E. Sanchez, P. Hranitzky, G. J. Gallinghouse, A. Al-Ahmad, R. Horton, L. Di Biase, and A. Natale, "Association between prolonged p wave duration and left atrial scarring in patients with paroxysmal atrial fibrillation." *Journal of cardiovascular electrophysiology*, vol. 30, pp. 1811–1818, Oct. 2019.

[7] M. H. Hsieh, C. W. Chiou, Z. C. Wen, C. H. Wu, C. T. Tai, C. F. Tsai, Y. A. Ding, M. S. Chang, and S. A. Chen, "Alterations of heart rate variability after radiofrequency catheter ablation of focal atrial fibrillation originating from pulmonary veins." *Circulation*, vol. 100, pp. 2237–2243, Nov. 1999.

[8] Z. Zhu, W. Wang, Y. Cheng, X. Wang, and J. Sun, "The predictive value of heart rate variability indices tested in early period after radiofrequency catheter ablation for the recurrence of atrial fibrillation." *Journal of cardiovascular electrophysiology*, vol. 31, pp. 1350–1355, Jun. 2020.

[9] M. Antz, K. Otomo, M. Arruda, B. J. Scherlag, J. Pitha, C. Tondo, R. Lazzara, and W. M. Jackman, "Electrical conduction between the right atrium and the left atrium via the musculature of the coronary sinus." *Circulation*, vol. 98, pp. 1790–1795, Oct. 1998.

[10] U. Boles, E. E. Gul, A. Enriquez, N. Starr, S. Haseeb, H. Abdollah, C. Simpson, A. Baranchuk, D. Redfearn, K. Michael *et al.*, "Coronary sinus electrograms may predict new-onset atrial fibrillation after typical atrial flutter radiofrequency ablation (cse-af)," *Journal of atrial fibrillation*, vol. 11, no. 1, 2018.

[11] I. Razeghian-Jahromi, A. Natale, and M. H. Nikoo, "Coronary sinus diverticulum: Importance, function, and treatment." *Pacing and clinical electrophysiology : PACE*, vol. 43, pp. 1582–1587, Dec. 2020.

[12] M. García, M. Martínez-Iniesta, J. Ródenas, J. J. Rieta, and R. Alcaraz, "A novel wavelet-based filtering strategy to remove powerline interference from electrocardiograms with atrial fibrillation." *Physiological measurement*, vol. 39, p. 115006, Nov. 2018.

[13] M. Martínez-Iniesta, J. Ródenas, J. J. Rieta, and R. Alcaraz, "The stationary wavelet transform as an efficient reductor of powerline interference for atrial bipolar electrograms in cardiac electrophysiology." *Physiological measurement*, vol. 40, p. 075003, Jul. 2019.

[14] R. Alcaraz and J. J. Rieta, "Adaptive singular value cancelation of ventricular activity in single-lead atrial fibrillation electrocardiograms." *Physiological measurement*, vol. 29, pp. 1351–1369, Dec. 2008.

[15] A. Martínez, R. Alcaraz, and J. J. Rieta, "Detection and removal of ventricular ectopic beats in atrial fibrillation recordings via principal component analysis." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society.*, vol. 2011, pp. 4693–4696, 2011.

[16] A. Martinez, R. Alcaraz, and J. J. Rieta, "A new method for automatic delineation of ecg fiducial points based on the phasor transform." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society.*, vol. 2010, pp. 4586–4589, 2010.

[17] F. González, R. Alcaraz, and J. J. Rieta, "Electrocardiographic p-wave delineation based on adaptive slope gaussian detection," in *2017 Computing in Cardiology (CinC)*, 2017, pp. 1–4.

[18] D. Osorio, R. Alcaraz, and J. J. Rieta, "A fractionation-based local activation wave detector for atrial electrograms of atrial fibrillation," in *2017 Computing in Cardiology (CinC)*, 2017, pp. 1–4.

[19] A. Vraka, V. Bertomeu-González, J. Osca, F. Ravelli, R. Alcaraz, and J. J. Rieta, "Study on how catheter ablation affects atrial structures in patients with paroxysmal atrial fibrillation: The case of the coronary sinus," in *2020 International Conference on e-Health and Bioengineering (EHB)*. IEEE, 2020, pp. 1–4.

[20] "Heart rate variability: standards of measurement, physiological interpretation and clinical use. task force of the european society of cardiology and the north american society of pacing and electrophysiology." *Circulation*, vol. 93, pp. 1043–1065, Mar. 1996.

[21] R. Alcaraz and J. J. Rieta, "Nonlinear synchronization assessment between atrial and ventricular activations series from the surface ecg in atrial fibrillation," *Biomedical Signal Processing and Control*, vol. 8, no. 6, pp. 1000–1007, 2013.

[22] Z. Liu, M. Hayano, T. Hirata, K. Tsukahara, Y. Quin, K. Nakao, M. Nonaka, T. Ishimatsu, C. Ueyama, and K. Yano, "Abnormalities of electrocardiographic p wave morphology and their relation to electrophysiological parameters of the atrium in patients with sick sinus syndrome." *Pacing and clinical electrophysiology : PACE*, vol. 21, pp. 79–86, Jan. 1998.

[23] S. Yahyazadeh, S. Firoozabadi, M. Haghjoo, and S. Parvaneh, "Quantitative relation between chaotic features of surface electrocardiogram and intracardiac electrogram," in *2010 Computing in Cardiology*, Sep. 2010, pp. 593–596.

[24] R. Alcaraz, F. Hornero, and J. J. Rieta, "Validation of surface atrial fibrillation organization indicators through invasive recordings," in *2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 2011, pp. 5519–5522.

[25] S. Meek and F. Morris, "Introduction. ii–basic terminology." *BMJ (Clinical research ed.)*, vol. 324, pp. 470–473, Feb. 2002.

[26] J. Misek, M. Veternik, I. Tonhajzerova, V. Jakusova, L. Janousek, and J. Jakus, "Radiofrequency electromagnetic field affects heart rate variability in rabbits." *Physiological Research*, vol. 69, no. 4, 2020.