Atrial Fibrillation Spatiotemporal Complexity Is Affected by Pulmonary Vein Isolation

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Abstract

Introduction *Pulmonary vein isolation (PVI) is the cornerstone of atrial fibrillation (AF) ablation. However, it is still unclear how AF complexity observed on body surface is affected by this intervention. This study aims to evaluate whether PVI has an impact on AF complexity as measured through principal component analysis (PCA) of body surface potential maps (BSPMs).* **Methods** *BSPMs were acquired with a* 252*-lead vest in* 22 *persistent AF patients (*20 *male,* 62 ± 11 *years, maximum AF duration:* 10 ± 18 *months) before and after PVI. The atrial fibrillatory wave signal (*9 ± 6 *s) was divided in* 0.5*-s segments, and AF complexity was assessed by the normalized amplitude norm* $d_{\boldsymbol{\epsilon}}$ *and the cosine similarity* $\cos(\alpha_{\boldsymbol{\epsilon}})$ *of the multilead error* $\boldsymbol{\epsilon}$ *between the input signal at the frame* (s) *and its PCA projection onto a 3D subspace computed in the previous segment* $(s-1)$*. AF organization was also quantified by the nondipolar component index (NDI), i.e., the amount of energy non-preserved by the 3D dipolar approximation of cardiac activity in the frame* (s)*.* **Results** *A significant reduction in AF complexity was measured by all markers after PVI (*$d_{\boldsymbol{\epsilon}}$ *and* $\cos(\alpha_{\boldsymbol{\epsilon}})$*:* $p<0.01$*; NDI:* $p<0.0001$*).* **Conclusions** *AF complexity can be reliably measured by the proposed BSPM features and reflect the impact of PVI.*

1. Introduction

Pulmonary veins (PVs) have been demonstrated to often play a critical role in the pathogenesis of atrial fibrillation (AF) [1]. Currently, PV isolation (PVI) is the cornerstone for catheter ablation (CA) of paroxysmal AF. While the effectiveness of PVI alone for persistent AF treatment is still under debate [2, 3], none of the alternative ablation protocols so far proposed [4–6] has convincingly contributed to improve its outcome [7, 8], and PVI is still a first-line strategy for AF ablation, either alone or in combination with additional lesions [9]. Multiple studies have demonstrated that the electrophysiological and anatomical properties of PVs create a proarrhythmogenic substrate [10], including larger size, thicker myocardial tissue, shorter refractory periods and slower conduction velocity [11]. Electrical isolation of PVs can help neutralizing arrhythmogenic sources, either focal or reentrant, and preventing their propagation to other atrial regions [12, 13]. PVI significantly affects atrial substrate, whose activity appears less fractionated and slower than at baseline [14]. Changes in the dominant frequency are also detectable on the standard electrocardiogram in response to PVI [15], although with some variability across the leads. More generally, AF complexity quantified by principal component analysis (PCA) of body surface potential maps (BSPMs) correlates with CA duration and strategy and is predictive of its outcome [16]. This study aims to investigate to which extent PVI affects AF organization measured from BSPMs. Variations in signal features determined by PCA as in [16, 17] were linked to changes in AF complexity occurring during PVI. Our approach provides deeper insights into the efficacy and the relevance of this intervention to persistent AF treatment.

2. Methods

2.1. AF electrophysiology study and CA protocol

We enrolled 22 persistent AF patients (20 male, 62 ± 11 years old, maximum AF duration: 10 ± 18 months) referred for CA. Biatrial electroanatomical mapping was performed with a multipolar catheter (Pentaray or Lasso, Biosense Webster), and atrial electrograms were continuously recorded through a computer-based digital amplifier/recorder system (Labsystem Pro, Bard Electrophysiol-

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ogy). Cycle length (CL) was measured in the left atrial appendage (LAA) at baseline and monitored during the procedure to assess local CA impact in the LA. All patients first underwent circumferential PVI. If AF was not terminated by PVI, extra-PV regions identified through noninvasive phase mapping were targeted [6]. The procedural endpoint was AF termination, i.e., organization to atrial tachycardia (AT) or sinus rhythm (SR). Electrical cardioversion was performed if CA failed to terminate AF.

2.2. BSPM data format and preprocessing

BSPMs were acquired with a 252-lead vest (ECVUE, Cardioinsight Technologies) at 1 kHz before and after PVI. The multilead atrial fibrillatory wave (f-wave) signal (9 ± 6 s) was processed as in [16], yielding a $L \times N$ matrix $\mathbf{Y} = [\mathbf{y}(1) \dots \mathbf{y}(N)] \in \Re^{L \times N}$, where $L = 252$ is the number of BSPM leads, and N is the number of samples. An example is shown in Figure 1.

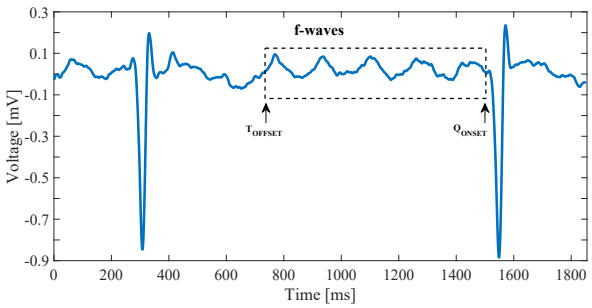

Figure 1. An example of f-wave signal segmented between the offset to the T wave ($\mathrm{T_{OFFSET}}$) and the onset of the following Q wave ($\mathrm{Q_{ONSET}}$) from a BSPM during AF.

2.3. AF complexity features from BSPMs

Multivariate measures of AF complexity were computed by PCA as in [17]. Body surface heart electrical activity can be modeled as a 3D dipole [18], and most of its energy can be well approximated by the 3 dominant PCA eigenvectors [19]. Accordingly, the input atrial signal $\mathbf{Y}$ was divided in 0.5-s frames, each projected on the 3D subspace $\mathbf{M}^{(s)}$ determined by PCA in the previous segment:

$$\hat{\mathbf{Y}}^{(s+1)} = \mathbf{M}^{(s)}(\mathbf{M}^{(s)})^{\#}\mathbf{Y}^{(s+1)} \tag{1}$$

where $(\cdot)^{\#}$ is the MoorePenrose pseudoinverse operator. AF spatiotemporal organization was described in terms of the ability of the PCA components determined in the frame (s) of the f-wave signal to be retrieved in $(s+1)$: the lower their repetitiveness, the higher signal complexity. Thus, we assumed that the instantaneous PCA estimation error $\boldsymbol{\epsilon}(t)$ between the input signal $\mathbf{y}^{(s+1)}(t)$ at the frame $(s+1)$ and its PCA estimation $\hat{\mathbf{y}}^{(s+1)}(t)$ was linked to AF complexity and expressed in terms of the normalized magnitude norm:

$$d_{\boldsymbol{\epsilon}}(t) = \frac{\|\hat{\mathbf{y}}^{(s+1)}(t) - \mathbf{y}^{(s+1)}(t)\|}{\|\mathbf{y}^{(s+1)}(t)\|}, \tag{2}$$

with higher $d_{\boldsymbol{\epsilon}}$ values describing more disorganized AF, and cosine similarity, ranging from 0 to 1 (from low to high AF complexity):

$$\cos(\boldsymbol{\epsilon})(t) = \frac{\langle \hat{\mathbf{y}}^{(s+1)}(t), \mathbf{y}^{(s+1)}(t) \rangle}{\|\hat{\mathbf{y}}^{(s+1)}(t)\| \|\mathbf{y}^{(s+1)}(t)\|}, \tag{3}$$

For the statistical analysis, the temporal average of these indices over each frame was considered. AF organization was also measured by the nondipolar component index (NDI), i.e., the energy retained by the PCA eigenvalues σ_ℓ, $\ell = 4, \dots, L$ outside the subspace $\mathbf{M}^{(s)}$ at the frame (s):

$$\mathrm{NDI} = 1 - \frac{\sum_{\ell=1}^{3} \sigma_\ell}{\sum_{\ell=1}^{\mathrm{L}} \sigma_\ell} \tag{4}$$

with low NDI values associated with more organized AF patterns, which were accurately reconstructed by PCA.

2.4. Statistical analysis

The impact of PVI on body surface cardiac activity was assessed in terms of intraprocedural variations in the PCA markers of AF organization in the whole dataset. The same analysis was then performed in two subgroups of AF patients, i.e., those who were free from AF at the end of the entire procedure ("Termination") and those who did not experience AF termination by CA ("No termination"). To evaluate whether atrial substrate could be affected by PVI even in patients with more advanced AF forms, AF organization was also assessed before and after PVI both in persistent and long-lasting AF patients. Finally, we verified whether the location of the AF termination site in the left or the right atrium (LA vs RA) could be related to PVI efficacy as measured by PCA features.

Lilliefors test for normality was applied to all indices. A one-sample t-test was used to verify whether CL variations were significantly different from zero. Intergroup comparisons between BSPM features computed at a specific moment of the procedure (i.e., "Before PVI" or "After PVI") were made with an unpaired t-test for normally distributed data, or with a Mann Whytney test otherwise. Differences between pre- and post-PVI parameters were also tested for each group. Significance was taken for p-value≤ 0.05.

3. Results

3.1. AF mapping and ablation

As in [16], patients with AF duration of $<$12 months were assigned to the persistent AF group (n=18), whereas

3 patients were diagnosed with long-lasting AF ($\geq$12 months). AF duration was unknown in one patient. Baseline AF CL was 179 ± 36 ms. Mean ablation time was 61 ± 25 min and 5 ± 3 atrial regions were targeted to terminate AF. AF was terminated in the PVs in 4 patients, in other LA sites in 2 patients, in the RA in 4 patients. AF was organized to AT in 4 patients, to SR in 6 patients.

3.2. PVI and body surface AF complexity

A significant reduction in AF complexity was measured by all PCA features after PVI (Figure 2). This evidence was corroborated by a significant prolongation of the initial AF CL (ΔCL: 10 ± 12 ms, p=0.002).

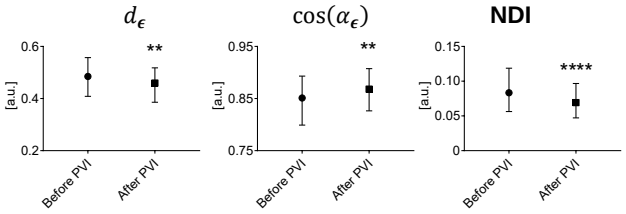

Figure 2. AF complexity and PVI (n=22).

In persistent AF patients higher organization was measured by all indices after PVI, whereas in more severe cases changes in the atrial substrate due to this intervention could not significantly reflect on body surface (Figure 3). Surprisingly, BSPM complexity at baseline was higher in persistent rather than long-lasting AF patients, whereas it was comparable in both groups after PVI.

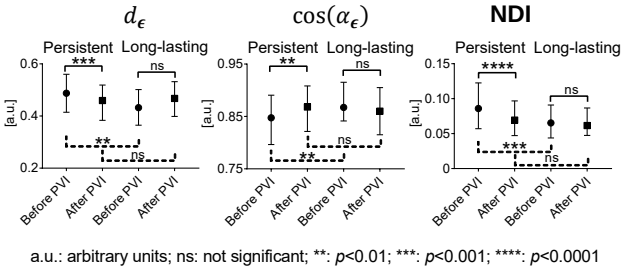

Figure 3. AF complexity in persistent (n=18) and long-lasting (n=3) patients before and after PVI.

AF complexity from BSPMs was lower after PVI regardless of CA outcome (Figure 4), with slower AF CL both in patients with (ΔCL: 14 ± 16 ms, p=0.04) and without AF termination (ΔCL: 8 ± 9 ms, p=0.02), and comparable in both groups (p=0.3). Higher AF organization at baseline predicted AF termination by CA, whereas there were no intergroup differences after PVI.

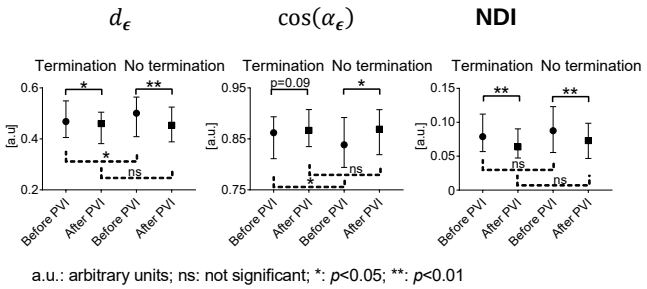

Figure 4. AF complexity for effective (n=10) and failed (n=12) CA procedures before and after PVI.

There were no changes in BSPM complexity in patients with AF termination in the LA, whereas AF was more organized after PVI when the termination site was located in the RA (Figure 5). While all indices measured lower baseline AF complexity when the CA endpoint was achieved in the LA, after PVI they underlined higher AF organization in patients who were free from AF after RA ablation.

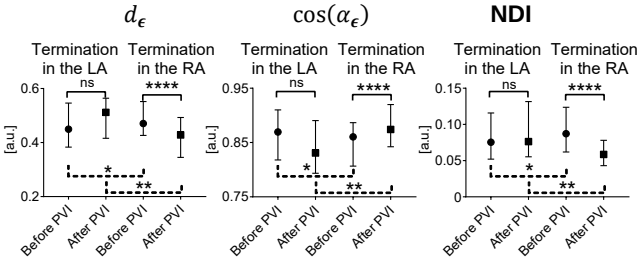

Figure 5. AF complexity for patients with AF termination in the LA (n=6) and the RA (n=4) before and after PVI.

4. Discussion

PVI significantly alters the atrial electrophysiology. Such modifications reflect on body surface as well, and they were effectively assessed by our PCA approach.

Electrical isolation of PVs substantially altered the atrial substrate in persistent AF patients, but not in the long-lasting ones, thus suggesting the presence of other drivers [20], which may be located at extra-PV sites and require a more extensive ablation [16].

As in [15, 16], more organized AF forms were more likely to be successfully treated by CA. Importantly, our method underlined how PVI contributed to modify the atrial substrate and simplify arrhythmia mechanisms, even when CA endpoint was not reached. These findings suggest that in some patients PVs may not only trigger AF, but also provide a substrate for its maintenance [21].

Our approach underlined higher disorganization at base-

line in patients with AF termination in the RA, which hints at the implication of other drivers from this anatomical structure in AF maintenance [6]. In those subjects lower post-PVI BSPM complexity was measured, thus proving the major role of PVs in AF initiation and perpetuation. Albeit PVI contributed to organize LA activity (as confirmed by the prolongation of the LAA CL: ΔCL: 26 ± 11 ms), AF was still ongoing, partly due to other drivers in the RA, whose suppression was more crucial to reach the CA endpoint. By contrast, CL variations were more moderate when AF was organized in the LA (ΔCL: 6 ± 14 ms) rather than in the RA (p=0.04), thus confirming that PVs were less critical to treat AF than other LA sites.

5. Conclusions

This study showed that our PCA approach can quantify AF complexity and assess the impact of PVI, which plays a crucial role in AF ablation. However, our results confirm that sometimes PVI alone may not be sufficient to terminate AF, and the underlying mechanisms should be clarified and validated by further intracardiac measures.

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