Left Pulmonary Veins Isolation: The Cornerstone in Noninvasive Evaluation of Substrate Modification After Catheter Ablation of Paroxysmal Atrial Fibrillation

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Abstract

While pulmonary vein isolation (PVI) is the cornerstone of the paroxysmal atrial fibrillation (pAF) treatment, whether left (LPVI) and right PVI (RPVI) provoke equal atrial substrate modifications (ASMs), vastly assessed by P-waves, remains unexplored. Five-minute recordings from 40 pAF patients undergoing first-time PVI were extracted before PVI (B), after LPVI (L) and RPVI (R) at 1 kHz sampling rate. Signal-averaged P-wave features of duration, amplitude and area were calculated. Heart-rate fluctuations (HRF) were mitigated for duration and area ($\mathbf{HR_{Dur,area}}$*). Results were compared between each transition (B-L: LPVI, L-R: RPVI) and between variations in values due to transitions with non-parametric tests. Duration (* $\Delta_{B-L} : -13.3\%$, $p = 0.001$, $\Delta_{L-R} : +2.40\%$, $p = 0.558$*) and amplitude* $\Delta_{B-L} : -17.29\%$, $p = 0.055$, $\Delta_{L-R} : +5.65\%$, $p = 0.319$*) got decreased after LPVI and slightly increased after RPVI. HRF mitigation mostly preserved these trends but lost statistical power (*$\mathbf{HR_{Dur}}$*:* $\Delta_{B-L} : -10.54\%$, $p = 0.141$, $\Delta_{L-R} : -5.52\%$, $p = 0.740$*). LPVI showed a significantly higher effect on duration than RPVI (*$p < 0.0001$*). Variations observed in P-wave features after PVI stem principally from LPVI, which contributes significantly to the ASM. Studies focusing on ASM observation should implement and prioritize the analysis of LPVI recordings.*

1. Introduction

Atrial fibrillation is the most common cardiac arrhythmia, with a rapidly growing incidence and signfiicant impact in the quality of life of the AF individuals [1]. Pulmonary vein (PV) isolation (PVI) is the first and foremost AF treatment, performed by isolating electrically the PVs, which are considered the principal AF foci [1, 2]. Due to concentration of AF triggers in PVs, paroxysmal AF (pAF) patients are especially benefited from PVI [3]. Nonetheless, variability of AF sources throughout the atria as well as altered anatomy or electrical function due to high AF burden, often observed in persistent AF patients, may complicate the procedure and require the ablation of additional areas [1, 4, 5].

Even in cases of anatomical or electrical alterations, PVI alone can have a significant impact on impeding the AF development and restoring the proper cardiac function, known as atrial substrate modification (ASM) [6]. In fact, ASM in terms of electrical function restoration has been reported soon after PVI conduction [6, 7]. The advantages of following the ASMs from the very first moment after PVI include the prediction of the PVI outcome and the befitting design of a tailor-made follow-up as well as the consideration of additional non-PVI applications.

P-waves analysis is a widespread technique in order to observe the ASM right after PVI or during follow-up [8–11]. The most critical P-wave feature highly associated with ASM is the P-wave duration (PWD), which offers information on the electrical function of the atria [12]. ASM cannot only be assessed by atrial but also by ventricular parameters. Heart-rate (HR) variability (HRV) is a measure of ventricular response [6]. Regulated by autonomous nervous system, which plays a significant role in AF, HRV evolution is studied after PVI in order to predict the AF outcome [13, 14].

Despite the importance of PVI in hindering the degenerative process of the AF mechanisms, little is known in the particular impact of left (LPVI) and right (RPVI) PVI on the ASM. In fact, P-waves and HRV analysis are both

performed comparing the atrial condition before with respect to after PVI. At the same time, PVI procedure is usually performed by completely isolating the left PVs (LPVI) before proceding to RPVI, facilitating the conduction of separate analyses to define the role of each PV side to the ASM, offering new insights into the AF mechanisms during PVI.

2. Materials and Methods

Electrocardiogram (ECG) recordings of 40 paroxysmal AF patients undergoing PVI for the first time were acquired at three time instances: before PVI (B), after LPVI (L) and after RPVI (R). For each patient, the same protocol was followed: firstly, circumferential radiofrequency (RF) PVI was performed at left PVs (LPVI-B), followed by RF PVI at right PVs (RPVI-R). All patients were in sinus rhythm (SR) during the procedure. Each recording had a five minute duration and was obtained with a sampling frequency of 1 kHz. Only lead II was utilized, due to its capacity to show P-waves of higher amplitude [15].

Powerline interference and muscle noise removal were the first preprocessing steps, followed by baseline wander removal [16, 17]. Finally, if present, ectopic beats were detected and removed [18]. Only recordings with ectopic beats $\leq 4\%$ of total beats were allowed.

P-waves were detected and delineated [19,20]. For each P-wave, the following characteristcs were calculated: duration, amplitude and area. In order to remove any bias related with variable HR, duration and area were adjusted by the following factor:

$$\mathbf{HR_x} = \frac{\mathbf{1000}}{\mathbf{IBI_i}}, \tag{1}$$

where IBI_i is the interbeat interval between the i^{th} and the $(i-1)^{th}$ activations and x = duration\area.

In addition to the features calculated at each P-wave, the following features were calculated across the entire recording: morphology variability (MV), dispersion, standard deviation (SDNN) and variance of normal-to-normal beat intervals (VARNN) and root mean square of successive interbeat differences (RMSSD). MV was calculated as the percentage of signals with lower similarity than 95% of the reference signal, calculated by the 20 most similar P-waves. Dispersion was the 25^{th}–75^{th} percentile difference of the sorted P-wave durations of each recording. SDNN, VARNN and RMSSD are time-domain HRV indices. Although the aforementioned indices are traditionally calculated at R-R intervals, this analysis implements the P-wave to P-wave intervals, hence converting the HRV to a study of the atrial function, which will be henceforth called atrial rate variability (ARV).

Statistical analysis was performed with Kruskal-Wallis (KW) and Mann-Whitney U-test (MWU) with Bonferroni correction in order to compare the values of each feature between two steps or among all steps, respectively. Median values and variations [%] were performed at each step and between two steps, respectively. Variations in each feature as a product of two successive steps (B-L and L-R) were compared with MWU. For a more detailed perspective, HR was additionally measured at each step and compared with KW among all steps.

3. Results

Table 1 shows the median HR at each step. HR is comparable between each step and no significant difference is found when all steps are compared. Table 2 shows the comparison between steps (B, L and R). Multistep comparison indicates only duration to vary statistically between steps. Difference in steps B-R ($p = 0.009$) shows a statistical alteration of the P-wave duration after the end of the PVI. When the analysis is performed in pairs of two sucessive steps (B-L and L-R), it can be observed that the difference stems from the B-L comparison, which suggests LPVI to be the principal source of P-wave duration alteration. Analysis of the remaining features shows insignificant alterations, with amplitude showing a trend both in multistep comparison and in the comparison between ablation steps. Finally, all three ARV features show a trend for statistically significant alteration of their values between L-R steps, while area and RMSSD show a trend for variation after LPVI (B-L).

Figure 1 shows the median values of each feature at each of the three ablation steps. In gray textbox can be observed how the value of each feature varies after each successive transition. Comparing these results with the results from table 2, it can be concluded that LPVI provokes a significant P-wave shortening (-13.30%) which is actually the 100% of the shortening of the P-wave throughout the PVI procedure. After adjsutment of the P-wave to mitigate the HR variation, LPVI continued to be the principal source of P-wave shortening, although lacking statistical significance. RPVI in this case provoked a lower level P-wave shortening.

Although all activation-based features showed a decreasing trend after LPVI and an increasing trend after LPVI, features measured at each recording, besides dispersion, revealed the opposite effect, with their values being increased after LPVI and decreased after RPVI. These fea-

Table 1. Median: HR at each step (B: before PVI, L: after LPVI, R: after RPVI). KW: comparison among all steps

	B	**L**	**R**
Median [bpm]	57.2	55.0	58.6
KW		0.7713	

Table 2. Statistical comparison (p values) among all steps (KW) and between each pair of two steps (MWU). Statistically significant results are shown in ($*$). Due to Bonferroni correction, threshold for MWU is $\alpha = 0.0167$.

	KW	MWU		
Features		**B-L**	**B-R**	**L-R**
duration	0.003$*$	0.001$*$	0.009$*$	0.558
amplitude	0.084	0.055	0.097	0.319
area	0.141	0.103	0.103	0.438
$\mathbf{HR_{Duration}}$	0.159	0.141	0.079	0.740
$\mathbf{HR_{area}}$	0.144	0.085	0.110	0.716
MV	0.476	0.189	0.624	0.646
dispersion	0.310	0.208	0.176	0.949
SDNN	0.136	0.133	0.862	0.060
VARNN	0.136	0.133	0.862	0.060
RMSSD	0.136	0.052	0.962	0.069

tures describe variability of the atrial rate and morphology, hence being connected with atrial response. Considering the fact that step B (LPVI) is the only step that applies analysis during RF application, the augmentation of ARV and MV during LPVI might be a byproduct of the autonomous nervous system endings in the atria being directly affected from the RF energy. The slight but not statistical decrease of HR during this step corroborates this hypothesis.

4. Discussion

The purpose of this study was to clarify whether ASM reported by various studies performing P-wave and HRV analysis is provoked to the same degree by LPVI and RPVI. By sheding light on this simple yet important question, the AF mechanisms and their interaction with PVI can be better understood and the AF treatment can be more carefully designed. In the first place, the findings of this study were in line with previous studies, reporting an overall and statistical shortening of the P-wave duration as well as the nonstatistical decrease of the remaining P-wave features [8–11]. Moreover, ARV was found to decrease after PVI, in coherence with previous studies reporting temporal HRV withdrawal after PVI [14].

Interestingly enough, LPVI was the one and only source of P-wave shortening, achieving the 100% of overall P-wave shortening throughout the procedure without HR adjustment and the 81.4% of shortening with adjustment (B: 119.5 ms, L: 106.9ms, R: 101 ms). Therefore, emphasizing LPVI both during analysis and during the procedure may lead to better PVI results and more precise assessment of the ASM, which in turn might improve the follow-up therapy. While the major objective of the current work was the investigation of the role of each side of PVI, an interesting fact has been observed. Despite the general decreasing tendency of ARV after PVI, these features showed a notable, although statistically insignificant, augmentation after LPVI. According to previous studies, RF application may slow HR and intensify HRV [21]. Indeed, HR after LPVI was found to be slightly decreased.

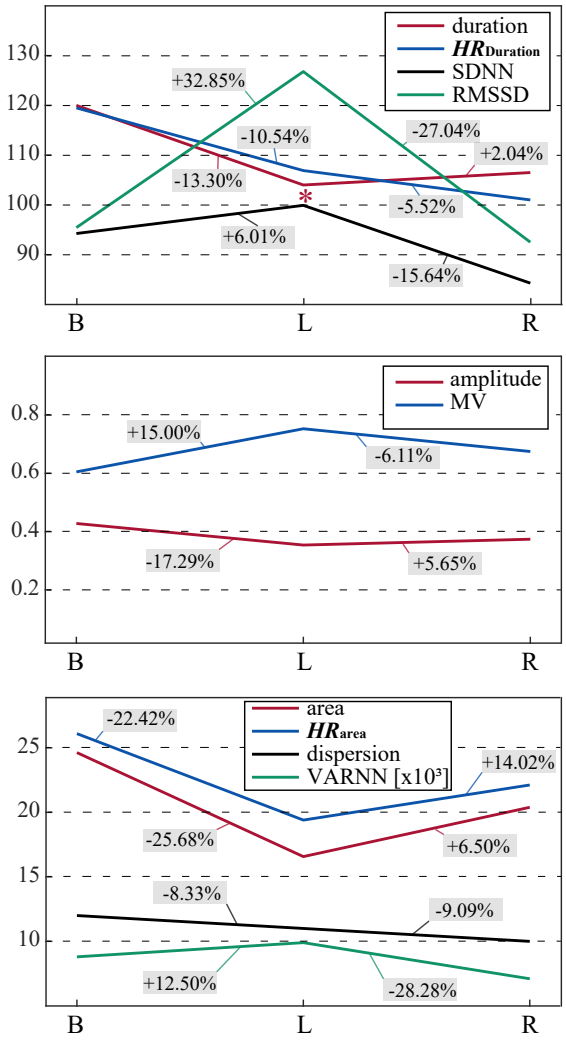

Figure 1. Median values of features measured before PVI (B) after LPVI (L) and after RPVI (R) and variations in values after each transition (percentage numbers). Asterisk shows statistical difference between variations in feature values of B-L and L-R.

5. Conclusions

LPVI is critical in observing and evaluating ASM and is worth of more careful analysis and applications. Recruiting recordings during PVI is a costless analysis step which can increase the understanding of the AF mechanisms during PVI and reveal interesting phenomena related with the effect of autonomous nervous system on the atria.

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