

Impact of AF Ablation Strategies on Autonomic Modulation Measured by Heart Rate Variability

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Abstract

Atrial fibrillation (AF) is associated with a more than 3.5-fold higher risk of all-cause death. Evidence suggests that the autonomic nervous system (ANS) plays a relevant role in the initiation and maintenance of AF. Catheter ablation is a cornerstone technique in AF treatment. Yet, the impact of different ablation modalities on cardiac autonomic modulation is not fully characterized. In this study, we compared the effects of cryoablation (CRYO) and pulsed field ablation (PFA) on heart rate variability (HRV), which serves as a surrogate for ANS function, using 10-minute ECG recordings obtained before and 3 months after ablation. HRV time-domain (SDNN and RMSSD) and frequency-domain ($\mathcal{P}_{LF}$, $\mathcal{P}_{HF}$, and $\mathcal{P}_{LF/HF}$ ratio) indices were computed. The CRYO group exhibited a significant ($p < 0.05$) reduction in HRV indices after ablation with median reductions of 10.5 ms for SDNN, 4.8 ms for RMSSD, 2.3×10^{-4} for $\mathcal{P}_{LF}$, and 1.0×10^{-4} for $\mathcal{P}_{HF}$. In contrast, the PFA group showed non-significant reductions of 1.6 ms for SDNN, 2.8 ms for RMSSD and 0.3×10^{-4} for $\mathcal{P}_{LF}$, and a significant but lower reduction of 0.5×10^{-4} for $\mathcal{P}_{HF}$. These findings reveal a significant effect of CRYO ablation on ANS control of heart rate compared to a minimal effect of PFA, underscoring the importance of further studies to elucidate the long-term clinical implications of these autonomic changes on AF recurrence.

1. Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia whose incidence is increasing progressively with time, driven by aging of the population, increasing prevalence of risk factors for AF among older people, and advances in arrhythmia detection strategies [1]. AF is associated with a more than 3.5-fold higher risk of all-cause death than the general population of the same age and sex, as well as a doubled

risk of heart failure (HF) and a 5-fold higher risk of stroke and systemic thromboembolism [2]. In addition, AF can substantially impair quality of life and exercise capacity due to its symptomatic nature.

To treat AF in persistent or paroxysmal symptomatic patients, catheter ablation has been shown to be superior to antiarrhythmic drugs in maintaining sinus rhythm and improving quality of life [3]. In 1998, Haïssaguerre et al. [4] identified ectopic electrical activity within the pulmonary veins (PVs) as the primary trigger of AF. This discovery led to the development of catheter ablation techniques that aimed to electrically isolate PVs from the left atrium. Pulmonary vein isolation (PVI) remains the cornerstone of contemporary AF ablation strategies.

Several cardiac ablation technologies have been developed over time. In addition to thermal strategies, such as radiofrequency (RF) and cryoablation (CRYO), a nonthermal procedure called pulsed field ablation (PFA) has recently been introduced [5]. Unlike the indiscriminate tissue damage characteristic of thermal ablative modalities, PFA is designed to be selective only for cardiomyocytes and therefore should not affect other surrounding tissues and structures, including nearby nervous complexes [5].

In fact, the heart is innervated by a network of adrenergic and cholinergic nerves: the cardiac autonomic nervous system (ANS). Structurally, the ANS is organized in clusters of ganglionated plexi (GPs), including parasympathetic and sympathetic neurons, located close to PVs [6]. Both systems, especially the parasympathetic one, appear to play a predominant role in the initiation and maintenance of AF [7].

Therefore, the purpose of this study is to investigate the effects of different ablation technologies on ANS and its modulation of heart rate during endocardial PVI. Heart Rate Variability (HRV) indices will be calculated from 12-lead ECG data and compared between patients treated with CRYO or PFA.

2. Methods

2.1. Data Set

Standard 12-lead ECGs of 54 AF patients (mean age 59 ± 10 years, 63% male) who underwent CRYO (39%, POLARx™, Boston Scientific Corporation) or PFA (61%, FARAPULSE™, Boston Scientific Corporation) procedures were collected before surgery and about 3 months after it, in the first follow-up control. The recordings, 10 minutes long, were acquired using the H12+™ Digital Holter Recorder (Hillrom, Baxter International Inc.) with an amplitude resolution of $2.5 \mu\text{V}$ and a sampling frequency of 1000 Hz.

2.2. ECG Processing

The initial and final 30 seconds of each ECG recording were excluded from the analysis to avoid the presence of artifacts attributed to the repositioning of the electrodes or the movement of the patient during preparation and the end of the procedure. The remaining 9 minutes of the recordings were bandpass-filtered between 0.4-30 Hz to reduce baseline wander and high-frequency noise. The R peaks of the QRS complexes were then identified for each k -th beat (sample $n_R(k)$) using a wavelet-based multilead delineator [8], and RR interval series were calculated as $d_{RR}(k) = n_R(k) - n_R(k-1)$.

2.3. Spectral Analysis

Starting from the beat-to-beat series $d_{RR}(k)$, normal-to-normal $d_{NN}(k)$ interval series was derived using the integral pulse frequency modulation (IPFM) model, also dealing with ectopic beat substitution and correction [9]. The series was then interpolated and resampled at 4Hz to generate $d_{HR}(n)$. Afterwards, this signal was lowpass-filtered with a cut-off frequency of 0.03Hz to remove the very low-frequency components, leading to $d_{MHR}(n)$, which was used in the correction of HRV by the mean heart rate to generate the HRV signal $m(n)$ [10]:

$$m(n) = \frac{d_{HR}(n) - d_{MHR}(n)}{d_{MHR}(n)}. \quad (1)$$

The dimensionless series $m(n)$ was subsequently decomposed using spectral analysis with the Welch method [11]. This procedure enabled the extraction of HRV frequency indices.

2.4. Extraction of HRV Indices

HRV refers to the variation in the time intervals between consecutive heartbeats. It serves as a key indicator of neurocardiac function and reflects dynamic processes of the

ANS [12]. To assess HRV, both time- and frequency-domain indices were calculated from the pre- and post-ablation recordings. In the time domain, linear HRV indices were extracted. Spectral analysis was performed to decompose the signals into their constituent frequency components, allowing the computation of HRV indices in the frequency domain.

2.4.1. Time-Domain Indices

Time-domain HRV indices were calculated to quantify the variability of normal-to-normal $d_{NN}(k)$ intervals. The calculated indices provide information on global and short-term fluctuations in heart rate. The following indices were evaluated:

- SDNN, expressed in ms, represents the standard deviation of $d_{NN}(k)$ intervals. It is computed as:

$$\text{SDNN} = \sqrt{\frac{1}{M-1} \sum_{k=1}^M (d_{NN}(k) - \bar{d}_{NN})^2}, \quad (2)$$

where M denotes the total number of $d_{NN}(k)$ intervals, and $\bar{d}_{NN}$ is their mean. SDNN reflects the overall HRV and is influenced by both sympathetic and parasympathetic activity [13].

- RMSSD, also expressed in ms, is the root mean square of successive differences between adjacent $d_{NN}(k)$ intervals, given by:

$$\text{RMSSD} = \sqrt{\frac{1}{M-1} \sum_{k=1}^{M-1} (d_{NN}(k+1) - d_{NN}(k))^2}. \quad (3)$$

RMSSD primarily reflects short-term HRV and is considered a reliable marker of parasympathetic (vagal) activity [13]. To quantify changes in HRV after ablation, the differences between post- and pre-ablation values (denoted Δ_I , $I \in \{\text{SDNN}, \text{RMSSD}\}$), were computed,

$$\Delta_I = I_{\text{post}} - I_{\text{pre}}. \quad (4)$$

2.4.2. Frequency-Domain Indices

Frequency-domain HRV indices were obtained from the power spectral density of $m(n)$. The power across predefined frequency bands [13] is characterized by the following indices:

- $\mathcal{P}_{\text{LF}}$, represents the total power within the low-frequency (LF) band (0.04–0.15 Hz). It is predominantly associated with sympathetic modulation, although it may also include parasympathetic contributions [13].

- $\mathcal{P}_{\text{HF}}$, denotes the total power within the high-frequency (HF) band (0.15–0.4 Hz). $\mathcal{P}_{\text{HF}}$ is primarily linked to parasympathetic activity, particularly vagal modulation of heart rate [13].
- $\mathcal{P}_{\text{LF/HF}}$ ratio, represents the ratio of LF to HF power. It is commonly used to assess the balance between sympathetic and parasympathetic influences on heart rate [13].

To evaluate the changes in autonomic modulation induced by ablation, similarly as with time-domain indexes, the Δ_I increments (4) were computed, with $I \in \{\mathcal{P}_{\text{LF}}, \mathcal{P}_{\text{HF}}, \mathcal{P}_{\text{LF/HF}}\}$.

2.5. Statistics

Following the Shapiro–Wilk test, the HRV data were determined to be non-normally distributed. Therefore, median and quartile values were used as a reference. The Wilcoxon Signed Rank test was used to compare metrics on HRV indices between pre- and post-ablation recordings. Mann-Whitney U tests were used to compare variables in patients treated with CRYO and PFA. The significance levels were set at 0.05.

3. Results

There were no significant differences in baseline demographics between the PFA (age = 59 ± 8) and CRYO (age = 57 ± 11) groups. In addition, no differences were found when comparing the baseline heart rate of the two populations before ablation ($p = 0.43$).

Analysis of HRV indices in the time domain did not reveal significant differences between the two groups before ablation. As illustrated in Fig. 1a, significantly greater reductions concerning both SDNN and RMSSD were exhibited in the CRYO group. Moreover, statistically significant differences were observed between pre- and post-ablation values in the CRYO population, in contrast with the non-significant ones in the PFA group. Table 1a summarizes the time-domain HRV indices measured before and after ablation.

A similar trend was observed in the frequency-domain analysis. Frequency-domain characteristics at baseline were comparable between the two groups (Table 1b). After ablation, the CRYO group showed a greater reduction in both low- and high-frequency power compared to the PFA group (Fig. 1b). The $\mathcal{P}_{\text{LF/HF}}$ ratio did not show any statistically significant changes after ablation in either group.

4. Discussion

This study compared the effects of CRYO and PFA on HRV indices to assess autonomic modulation of cardiac

electrical activity in patients undergoing AF ablation. Despite the fact that the baseline HRV indices presented similar values between the two groups, 3-month post-ablation analysis revealed differences in how the ANS modulation is affected by each ablation technology.

In the CRYO group, significant reductions in both time-domain (SDNN and RMSSD) and frequency-domain indices ($\mathcal{P}_{\text{LF}}$ and $\mathcal{P}_{\text{HF}}$) were observed, suggesting a marked attenuation of autonomic activity, possibly as a result of damage to the innervation of the GP to the SA node, which could contribute to a diminished likelihood of the generation of arrhythmogenic triggers in the post-ablation period. In contrast, the PFA group exhibited minimal changes in HRV indices, reflecting a preserved autonomic function: it might be beneficial, but, on the other hand, leaving the cardiac neural substrate active could predispose to the initiation of AF via GP activity.

These results are also in agreement with [14], in which lower time-domain HRV indices, including SDNN, were found in the thermal group compared to PFA; however, no baseline measurements or frequency-domain values were calculated in that study.

Interestingly, the $\mathcal{P}_{\text{LF/HF}}$ ratio remained stable in both groups, indicating that, while the overall autonomic tone decreased (particularly in the CRYO cohort), the balance between sympathetic and parasympathetic influences was largely preserved.

Future studies in a larger cohort of patients that involved the assessment of the long-term clinical implications of these differential autonomic effects, and specifically the correlation with AF recurrence, could be crucial in refining ablation techniques to optimize both procedural efficacy and long-term rhythm stability.

5. Conclusion

Cryoablation significantly reduced HRV indices, suggesting a marked alteration of autonomic structures, whereas pulsed field ablation preserved neural paths and GPs and led to minimal changes in HRV. Eventually, these metrics may play a role in stratifying the risk of AF recurrence.

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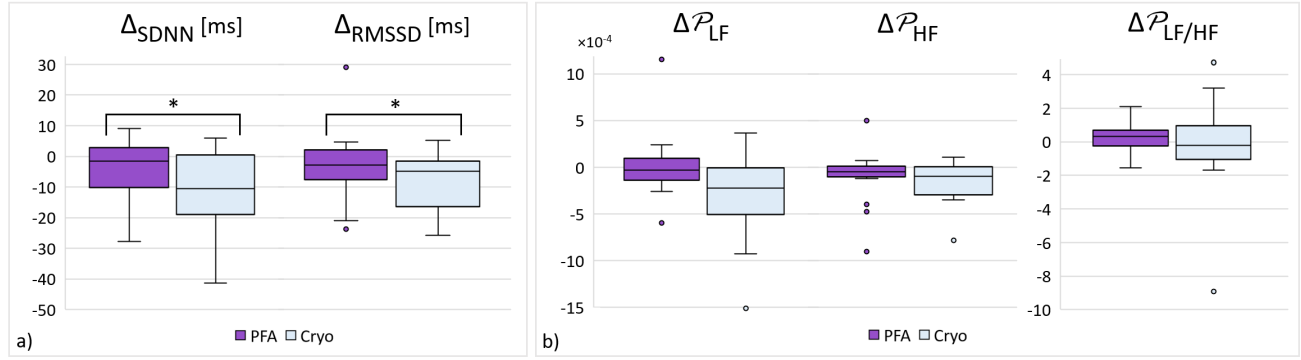


Figure 1. Boxplots of the Δ_{HRV} indices ($I_{post} - I_{pre}$ ablation). a) Time-domain indices Δ_{SDNN} and Δ_{RMSSD} . PFA vs CRYO: $*p < 0.05$. b) Frequency-domain indices $\Delta \mathcal{P}_{LF}$, $\Delta \mathcal{P}_{HF}$ and $\Delta \mathcal{P}_{LF/HF}$.

Table 1. Median[25th;75th] of time-domain (expressed in ms) and frequency-domain ($\mathcal{P}_{LF}$ and $\mathcal{P}_{HF}$ expressed in $\times 10^{-4}$) HRV indices in PFA vs CRYO populations. Before vs after ablation: $*p < 0.05$.

Ablation	$SDNN_{pre}$	$SDNN_{post}$	Δ_{SDNN}	$RMSSD_{pre}$	$RMSSD_{post}$	Δ_{RMSSD}
PFA	30.2[22.5;36.6]	24.4[18.2;32.7]	-1.6[-10.2;2.9]	20.1[12.9;33.3]	15.9[12.1;23.2]	-2.8[-7.6;2.2]
CRYO	30.3[18.0;44.2]	19.9[11.4;31.0]*	-10.5[-18.9;0.4]	18.8[13.5;28.2]	11.8[6.7;22.7]*	-4.8[-16.4;-1.5]

Ablation	$\mathcal{P}_{LF_{pre}}$	$\mathcal{P}_{LF_{post}}$	$\Delta \mathcal{P}_{LF}$	$\mathcal{P}_{HF_{pre}}$	$\mathcal{P}_{HF_{post}}$	$\Delta \mathcal{P}_{HF}$	$\mathcal{P}_{LF/HF_{pre}}$	$\mathcal{P}_{LF/HF_{post}}$	$\Delta \mathcal{P}_{LF/HF}$
PFA	2.3[1.1;4.8]	1.9[0.8;3.1]	-0.3[-1.4;0.4]	2.0[0.9;3.5]	1.3[0.7;2.0]*	-0.5[-1.1;0.0]	1.1[0.5;2.5]	1.1[0.8;2.5]	0.3[-0.3;0.7]
CRYO	2.4[0.9;9.6]	1.5[0.3;3.1]*	-2.3[-5.1;0.2]	1.6[1.1;4.1]	0.6[0.2;2.1]*	-1.0[-2.9;0.1]	1.7[0.9;2.8]	2.0[0.5;3.2]	-0.2[-1.0;1.0]

The calculations were performed using ICTS NANBIOSIS (HPC Unit at University of Zaragoza).

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