Effects of pulsed field ablation on the parasympathetic nervous system: a mechanistic approach

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Abstract

Background: Pulsed field ablation (PFA) is a novel technique for pulmonary vein isolation in atrial fibrillation management. Notably, asystole episodes of varying durations have been observed during electroporation, but the underlying mechanisms remain unclear. **Objective:** This study hypothesizes that asystole during PFA is attributable to the activation of parasympathetic ganglia on the left atrium's surface. **Methods:** We conducted a study with 24 patients (67% male, 62.8 ± 11.0 years, BMI: 25.3 ± 5.6) suffering from paroxysmal atrial fibrillation. The order of pulmonary veins chosen for electroporation was randomized to avoid cumulative electroporation effects. PFA was performed and the duration of cardiac pauses post-electroporation was recorded for each application. To examine the impact of electroporation on the parasympathetic nervous system, transjugular vagal stimulation (TJVS) was performed from the right internal jugular before and after isolation of each vein, during sinus rhythm and atrial pacing. Continuous data were analyzed with Student's t-tests or Mann-Whitney U tests as appropriate; nominal data were evaluated using chi-square or Fisher exact tests. **Results:** Pre-PFA TJVS induced sinus pauses of 10.1 ± 2.74 seconds. A sinus block of over 3 seconds was present in 23 out of 24 patients. Post-PFA, the Right Superior Pulmonary Vein (RSPV) showed the highest decrease of TJVS-induced sinus pauses (RSPV: before 8.41 ± 4.53 vs after 3.27 ± 3.53 sec, $p<0.001$, RIPV: before 6.76 ± 4.54 sec vs. 6.89 ± 5.07 sec, $p=0.90$; LSPV: before 6.76 ± 5.25 sec vs. after 6.93 ± 4.29 sec, $p=0.61$; LIPV: before 7.80 ± 4.06 sec vs. after 7.88 ± 3.84 sec, $p=0.91$). Notably, sinus blocks over 3 seconds decreased significantly after RSPV ablation (19 before PFA, 10 after PFA, $p<0.01$), with less dramatic changes in other veins (RIPV: before 19, after 16, $p=0.33$; LSPV: before 14, after 19, $p=0.11$; LIPV: before 21, after 21, $p=1.00$). RSPV PFA also had the strongest impact on TJVS-induced AV block duration compared to the remaining veins (RSPV: before 6.49 ± 3.48 vs after 4.07 ± 3.27 sec, $p<0.01$, RIPV: before 6.00 ± 3.29 sec vs. 4.58 ± 3.99 sec, $p=0.08$; LSPV: before 5.15 ± 3.94 sec vs. after 5.14 ± 3.48 sec, $p=0.93$; LIPV: before 6.06 ± 3.98 sec vs. after 5.83 ± 3.44 sec, $p=0.38$). The incidence of AV blocks over 3 seconds was markedly reduced post-RSPV and post RIPV ablation (RSPV: before:19 vs. after: 14, $p=0.11$, RIPV: before:19 vs. after: 14, $p=0.11$), with minor changes in other veins (LSPV: before 14, after 16, $p=0.55$; LIPV: before 17, after 18, $p=0.77$). **Conclusions:** PFA applications during pulmonary vein isolation have acute effect on the autonomic nervous system, as evidenced by the decrease in TJVS-induced sinus and atrioventricular block at the level of the right superior pulmonary vein. PFA-induced pauses are more frequent during applications on the LSPV, and less frequent when prior isolation of the RSPV has been performed, suggesting a vagally-mediated mechanism involving the right superior and/or right posterior ganglionated plexi.

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Kowalewski, Parasympathetic activation by electroporation

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Conclusions: PFA applications during pulmonary vein isolation have acute effect on the autonomic nervous system, as evidenced by the decrease in TJVS-induced sinus and atrioventricular block at the level of the right superior pulmonary vein. PFA-induced pauses are more frequent during applications on the LSPV, and

less frequent when prior isolation of the RSPV has been performed, suggesting a vagally-mediated mechanism involving the right superior and/or right posterior ganglionated plexi.

Abbreviations:

AF Atrial fibrillation

GP Ganglionated plexus

LSPV Left superior pulmonary vein

LIPV Left inferior pulmonary vein

PFA Pulsed field ablation

PVI Pulmonary vein isolation

RSPV Right superior pulmonary vein

RIPV Right inferior pulmonary vein

TJVS Transjugular vagal stimulation

Introduction:

Atrial Fibrillation (AF), the most common sustained cardiac arrhythmia, presents a significant challenge in cardiac rhythm management[1,2]. Pulmonary vein isolation (PVI) stands as the cornerstone of AF ablation strategies, predominantly due to the pulmonary veins' role as a major source of ectopic beats initiating AF[3,4]. Catheter ablation is being increasingly performed as first line therapy or following antiarrhythmic drug failure. Different energies and techniques are available to perform PVI, however, the quest for an optimal ablation technique continues, particularly one that minimizes collateral damage while maximizing efficacy.

Pulsed Field Ablation (PFA) is a relatively novel approach in this landscape[5]. The technique utilizes electric fields to create electroporation of cell membranes, primarily affecting myocardial tissue while theoretically sparing adjacent structures such as nerves, blood vessels and the esophagus[6]. This selectivity offers a potential reduction in procedural complications commonly associated with thermal ablation techniques[7,8].

Clinical and pre-clinical data have begun to shed light on the neural implications of PFA[9-14]. Studies suggest that PFA, compared to traditional ablation techniques, results in less cardiac denervation[15]. This is evidenced by a lower degree of damage to neurons and axons, which in theory should translate to fewer autonomic complications post-ablation. However, recent clinical observations challenge this assumption. Reports of reversible and irreversible phrenic palsy, a complication associated with collateral nerve damage, indicate that PFA may not be entirely benign in its neural implications[16].

One of the intriguing phenomena observed following PFA applications is the occurrence of asystolic pauses. These episodes, while frequently transient, raise concerns about the direct stimulation of cardiac autonomic ganglia. The potential for PFA to activate parasympathetic ganglia adjacent to the left atrium's epicardial surface, thereby inducing asystole, is a hypothesis of significant clinical relevance. Understanding the mechanisms behind these asystolic pauses is crucial for refining PFA and mitigating its risks.

Methods:

Patient inclusion

We identified 24 patients with paroxysmal AF, as defined by the guidelines[17], that had not undergone ablation. Pulmonary vein isolation by PFA (Farapulse, Boston Scientific Inc., Marlborough, Massachusetts, USA) was scheduled at the CHU Haut Leveque (CHU Haut-Leveque, Avenue de Magellan, 33604 PESSAC CEDEX) between june 2023 and december 2023. The procedures were performed by two experienced operators (BB, FS). This study was approved by the institutional ethics committee. Written patient consent was collected prior to the procedure.

The order of pulmonary veins chosen for electroporation was randomized to avoid cumulative electroporation effects. With four veins in each patient (LSPV, LIPV, RSPV, RIPV), this resulted in 24 possible permutations, that were assigned to patients in randomized order.

Electrophysiological study and ablation

Left atrial (LA) thrombus was ruled out via pre-operative computed tomography scan. All procedures were performed under general anesthesia. Oral anticoagulation was uninterrupted and complemented during the procedure by intravenous heparin, administered to reach an ACT of over 300. A quadripolar catheter was positioned in the coronary sinus and used for atrial pacing. Pulmonary vein isolation was performed through transeptal access using a PFA ablation catheter (Farawave, Farapulse) with five splines, deployed in either a flower or a basket configuration. The catheter was advanced over a guidewire such that the splines achieved circumferential contact/proximity with the PV antra. Twelve applications were performed on the superior pulmonary veins (3 applications in 4 different positions), and eight at the inferior pulmonary veins (2 applications in 4 different positions). The order in which the veins were treated was predefined by randomization before the procedure. Following each PFA application, potential sinus pauses or atrioventricular block episodes were recorded and measured (figure.1a).

Transjugular vagal stimulation (TJVS)

TJVS was performed using a quadripolar catheter inserted in the internal right jugular vein, and the anteromedial aspect of the internal jugular vein, at the level of the upper wisdom tooth. Stimulation was conducted using a dedicated voltage-controled neurostimulator with a pacing frequency of 50Hz, pulse duration of 0.05ms, pacing duration of 5 seconds, and a pulse amplitude of up to 1 V/kg (max 70V). TJVS was performed before PVI and after isolation of each pulmonary vein. At each step, stimulation was performed in sinus rhythm to assess potential sinus pauses and repeated during atrial pacing to assess the effect on atrioventricular conduction. Sinus pause durations were measured by taking the longest A-A interval recorded after TJVS (figure.1b), and atrioventricular pauses were measured by taking the longest V-V interval recorded after TJVS and simultaneous atrial pacing with a cycle length of 600ms.

Data acquisition for analysis

Electrogram recording and measurements were performed on using a dedicated digital electrophysiology recording system (LabSystem Pro, Boston Scientific).

Statistical analysis

Continuous data are represented as mean + standard deviation (SD) or median and interquartile range (IQR) as appropriate. Normality was evaluated using the Kolmogorov-Smirnov test. Comparisons between two groups were made with Student's t-tests and summarized with means and standard deviations for independent samples if normally distributed, or if not normally distributed, with the Mann-Whitney U test and summarized with medians and quartiles. Nominal values were expressed as n (%) and compared with chi-square tests, the Fisher exact test when expected cell frequency was < 5. A probability of < 0.05 was considered statistically significant.

Results:

Demographics

Table.1 shows patient demographics. The patients were all paroxysmal AF patients, with no prior ablation.

Vagal stimulation after PFA of each individual vein – sinus node block

Before the procedure vagal stimulation led to sinunodal pauses of 6.2 ± 3.5 seconds. Sinunodal block over 3 seconds was present in 23 out of 24 patients. Post-PFA, the Right Superior Pulmonary Vein (RSPV) showed the highest decrease of TJVS-induced sinus pauses (RSPV: before 8.41 ± 4.53 vs after 3.27 ± 3.53 sec, $p<0.001$, RIPV: before 6.76 ± 4.54 sec vs. 6.89 ± 5.07 sec, $p=0.90$; LSPV: before 6.76 ± 5.25 sec vs. after 6.93 ± 4.29 sec, $p=0.61$; LIPV: before 7.80 ± 4.06 sec vs. after 7.88 ± 3.84 sec, $p=0.91$). Notably, sinus

blocks over 3 seconds decreased significantly after RSPV ablation (19 before PFA, 10 after PFA, p<0.01), with less dramatic changes in other veins (RIPV: before 19, after 16, p=0.33; LSPV: before 14, after 19, p=0.11; LIPV: before 21, after 21, p=1.00).

Vagal stimulation after PFA of each individual vein – atrioventricular block

Before the procedure vagal stimulation led to atrioventricular pauses of 3.8 ± 2.2 seconds. Atrioventricular block over 3 seconds was present in 21 out of 24 patients. RSPV PFA also had the strongest impact on TJVS-induced AV block duration compared to the remaining veins (RSPV: before 6.49 ± 3.48 vs after 4.07 ± 3.27 sec, p<0.01, RIPV: before 6.00 ± 3.29 sec vs. 4.58 ± 3.99 sec, p=0.08; LSPV: before 5.15 ± 3.94 sec vs. after 5.14 ± 3.48 sec, p=0.93; LIPV: before 6.06 ± 3.98 sec vs. after 5.83 ± 3.44 sec, p=0.38). The incidence of AV blocks over 3 seconds was reduced, albeit non-significantly, after-RSPV and post RIPV ablation (RSPV: before:19 vs. after: 14, p=0.11, RIPV: before:19 vs. after: 14, p=0.11), with minor changes in other veins (LSPV: before 14, after 16, p=0.55; LIPV: before 17, after 18, p=0.77).

Pauses after electroporation

To assess the acute effect of electroporation we measured the duration between PFA application and the following atrial or ventricular activation. During PFA the Left Superior Pulmonary Vein showed the longest pauses after PFA application followed by the remaining pulmonary veins (RSPV: 1.89 ± 0.64 sec, RIPV: 1.81 ± 1.70 sec, LSPV: 1.95 ± 1.52 sec, LIPV: 1.72 ± 0.85 sec). Figure.2 shows the duration of pauses as an average after each PFA complication. PFA causes relatively long pauses during the first six applications, which shorten for the remaining six applications (1.99 ± 0.35 sec vs. 1.56 ± 0.22 seconds, p<0.01).

Pause duration after electroporation in dependence of first ablated vein

There was a difference between the measured pause durations in dependence of the vein that was targeted for ablation first. The results are presented figure.3 and the corresponding table.2. Targeting one of the left veins first led to relatively long pauses measured during PFA of the following veins, while ablation of the right pulmonary veins led to shorter pauses. Starting at the left superior pulmonary vein showed the longest pauses. Starting with the right superior pulmonary vein led to significantly shorter pauses during the ablation of subsequent veins in comparison with starting on the left pulmonary veins (p<0.03).

Discussion:

Effect of PFA on the parasympathetic nervous system

This study demonstrates the direct influence of PFA on the parasympathetic nervous system. Our findings confirm this by showing a notable reduction in sinus and atrioventricular blocks post PFA, particularly after ablating the right superior pulmonary vein (RSPV). The RSPV ablation resulted in a significant decrease in sinus block duration (from 8.41 ± 4.53 to 3.27 ± 3.53 sec, p<0.001) and atrioventricular block (from 6.49 ± 3.48 to 4.07 ± 3.27 sec, p<0.01). Sinus blocks over 3 seconds decreased significantly after RSPV ablation (19 before PFA, 10 after PFA, p<0.01), whereas there were no significant changes in other veins. PFA at the right superior pulmonary vein having the greatest effect on the autonomous nervous system suggests the PFA application at this location affects the right superior and or posterior nervous plexi, mainly responsible for sinunodal block[18]. These findings suggest a potent acute impact of PFA on the parasympathetic nervous system.

Are pauses during PFA linked to parasympathetic activation?

The pauses observed during PFA, particularly after RSPV ablation, were significantly shorter compared to other pulmonary veins. Ablation at the RSPV first showed a significant reduction in overall pause duration compared to ablation strategies targeting the left superior (p=0.01) or inferior(p=0.03) pulmonary vein first. There was a tendency towards shorter pauses compared with strategies starting at the right inferior pulmonary veins. These finding‘s resemblance to the effect of PFA on parasympathetic nervous system support the hypothesis that PFA-induced pauses are predominantly parasympathetic in nature. Studies that

showed atropine reduced the pause duration are in concordance with our results as they also imply the parasympathetic nature of these pauses[19].

Is there permanent nerve damage or is it acute?

Although the pauses during PFA are linked to parasympathetic activation and PFA affects the parasympathetic nervous system acutely, the question whether there are long-term effects has not yet been clarified. Studies evaluating biomarkers of neuronal detriment, which was similar before and after PFA procedures, suggest there is no or little durable damage to the GPs on the left atrium[15,20].

Optimizing Ablation Strategy

This is the first paper to assess different ablation strategies to minimize vagal reactions during PFA. The data we present advocate for initiating ablation at the right superior pulmonary vein, as this approach significantly reduces pause duration, a likely manifestation of parasympathetic activation. Subsequent targeting of the left pulmonary veins, where pauses were longer, and concluding with the right inferior pulmonary vein, appears to be the most effective sequence.

Limitations:

In our study several limitations were encountered. The study involved a small cohort, with only 24 patients. Larger cohorts are required to evaluate the findings of this study in the future. Additionally, the methodology included transjugular vagal stimulation (TJVS) between each PFA application, which extended the time between interventions. This approach might have influenced the observed effects of PFA on the sinus and atrioventricular node. Another critical factor to consider is the variability in autonomous nervous system innervation. Our study used TJVS from the right side. The right vagus nerve somewhat selectively innervates the right superior and posterior ganglionated plexuses, which then project to the sinus and AV node. In contrast, left vagus nerve inputs mostly connect to the left superior and left posteromedial GP, which then project to the AV node. If this study had been performed using left sided TJVS, denervation resulting from left sided GP damage (virtually absent in our study) may have been more apparent.

Conclusions:

PFA applications during PVI have acute effect on cardiac GPs, as evidenced by the decrease in TJVS-induced sinus and atrioventricular block at the level of the right superior pulmonary vein. PFA-induced pauses are more frequent during applications on the LSPV, and less frequent when prior isolation of the RSPV has been performed, suggesting a vagally-mediated mechanism involving the right superior and/or right posterior ganglionated plexi. To avoid vagal pauses during PFA ablation we suggest beginning the ablation by the right superior pulmonary vein.

Table.1 - Demographics

n=24	**Entire cohort**
Age (years)	62.8 ± 11.0
Male N (%)	16 (67%)
BMI (kg/mˆ2)	25.3 ± 5.6
Paroxysmal AF N (%)	24 (100%)
Prior AF Ablation N (%)	0 (0%)
AF History (years)	4.9 ± 5.8
Hypertension N (%)	10 (41.6%)
CHADSVASc score	1 (0-1)
Coronary disease N (%)	4 (16.7%)

Table.2 – Pauses recorded in dependence of vein targeted for first electroporation

	Pause duration at first PV (sec)	**Pause duration at second PV (sec)**	**Pause duration at third PV (sec)**	**Pause duration at fourth PV (sec)**	**p-value in comparison with starting at the RSPV**
Starting at RSPV	1.92 ± 0.68	1.06 ± 0.24	1.10 ± 0.22	1.21 ± 0.26	
Starting at RIPV	1.62 ± 0.65	2.09 ± 0.86	1.35 ± 0.33	1.52 ± 0.42	p = 0.11
Starting at LSPV	3.57 ± 2.31	1.79 ± 0.77	2.01 ± 0.69	1.77 ± 0.84	p = 0.01
Starting at LIPV	2.50 ± 0.84	2.87 ±2.79	2.09 ± 0.90	1.35 ± 0.38	p = 0.03

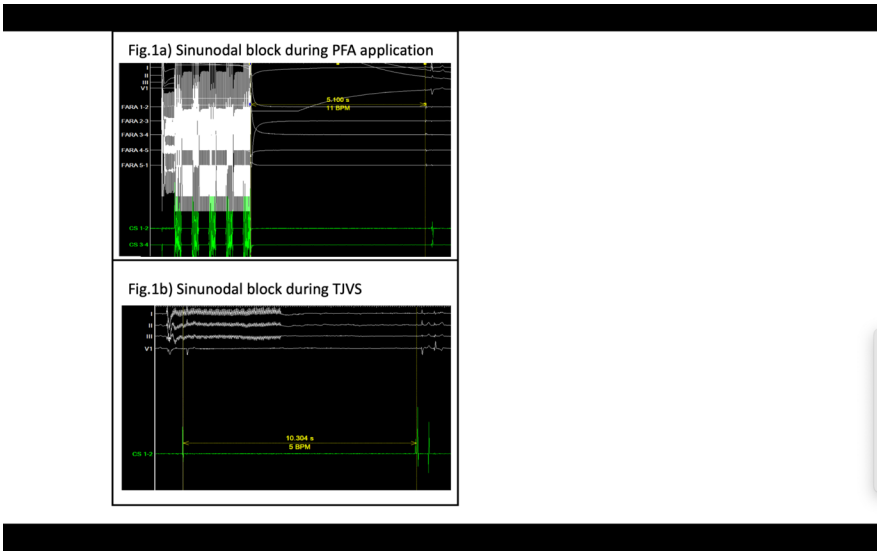

Figure.1 – This figure shows the different types of pauses recorded in our study.

On figure.1 a) a pause recorded during pulsed field ablation can be seen. The PFA artifact can be seen on the surface ecg and the catheter in the coronary sinus (green tracing). On figure 1b) you can see a pause caused by transjugular vagal stimulation.

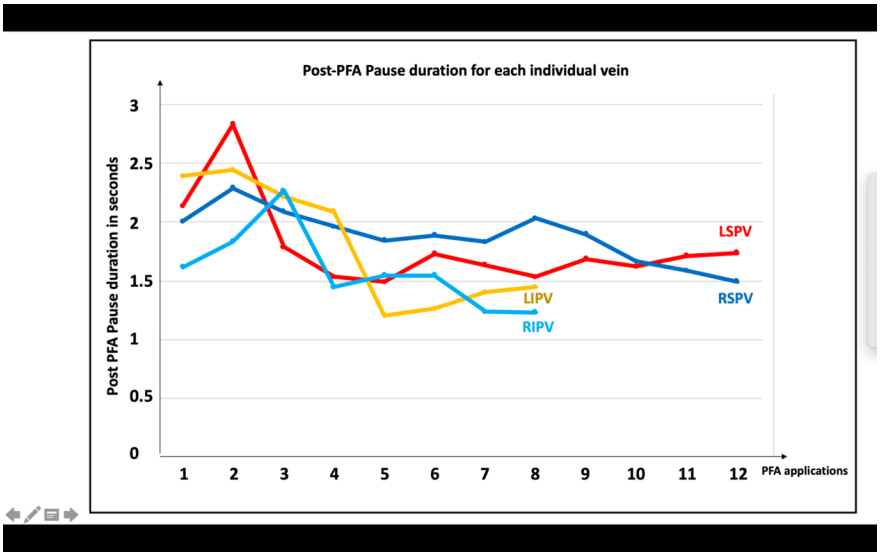

Figure.2 – This figure shows the duration of pauses after electroporation of each vein. The y-axis shows the average pause duration of each application shown on the x-axis.

12 applications were performed on the superior pulmonary veins therefore 3 applications in 4 positions, and 8 at the inferior pulmonary veins with 2 applications in 4 positions. The pauses during the applications at the right superior are shown in dark blue, the right inferior in light blue, the left superior in red, the left inferior in yellow.

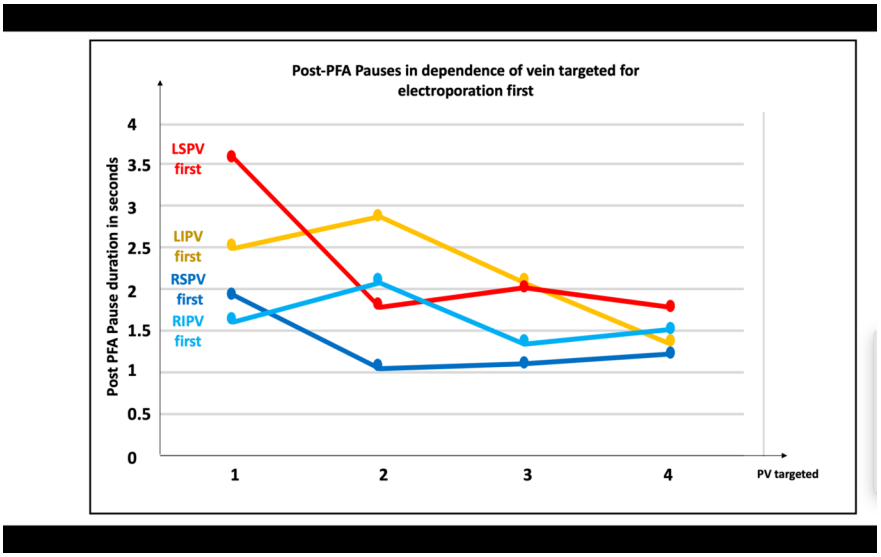

Figure.3 – Depiction of pause duration in dependence on vein targeted for PFA at the beginning. Starting with the left superior pulmonary vein in red, leads to relatively long pauses on subsequent veins, while a start at the right superior pulmonary vein leads to short pauses measured during the electroporation of the remaining veins.

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TSC1

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