Cardiac biomarker temporal dynamics after radiofrequency and pulsed field catheter ablation of atrial fibrillation

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BACKGROUND There is a lack of data on the temporal dynamics of cardiac biomarkers after radiofrequency and pulsed field ablation (PFA) catheter ablation of atrial fibrillation.

OBJECTIVE To evaluate the kinetics of release of several biomarkers following pulmonary vein isolation (PVI).

METHODS All patients underwent baseline and regular post-procedural blood sampling (at 3, 24, and 48 hours) to assess major markers of myocardial injury (troponin I, creatinine kinase-MB, and myoglobin) and inflammatory (C-reactive protein [CRP]). The population was stratified into 3 groups according to the ablation system: radiofrequency (RF) ablation catheter (RF group), pentaspline Farapulse™ PFA system (PFA-FAR group), and variable-loop Varipulse™ PFA system (PFA-VAR group).

RESULTS A total of 186 patients were included: 79 RF (42.5%), 69 PFA-FAR (37.1%), and 38 PFA-VAR (20.4%). A greater extent of myocardial injury was noticed in the PFA groups vs RF, and cellular electroporation via pentaspline PFA resulted in a greater biomarker increase compared with loop-variable PFA. Kinetics of biomarkers of inflammation increase following PVI with both PFA technologies and RF. However, both PFA systems resulted in a faster CRP biomarker recovery compared with RF, while CRP continued to increase beyond 24 hours post-ablation only in the RF group. PVI was achieved in all patients (100%) using only PFA or RF.

CONCLUSION Cellular electroporation induced by pentaspline PFA was associated with a significantly greater elevation in these cardiac biomarkers compared with variable-loop PFA and RF. After an initial increase, both PFA systems were associated with a more rapid decline in CRP levels compared with RF.

KEYWORDS Atrial fibrillation; Electroporation; Pulsed field ablation; Thermal ablation; Cardiac biomarkers; Lesion effect

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Introduction

Catheter ablation of atrial fibrillation (AF) using thermal energy sources, such as radiofrequency (RF) or cryoablation, is an established and effective rhythm control strategy.[1] Pulsed field ablation (PFA), a novel non-thermal modality based on irreversible electroporation, has recently been introduced and is now available across multiple approved systems from different manufacturers. Previous research has shown that PFA induces a transient inflammatory response in the initial days post-ablation, which resolves by 30 days and is generally lower than that observed with thermal ablation.[2,3]

All studies have evaluated individual PFA systems, leaving comparative data on different PFA technologies to a single study assessing high-sensitivity cardiac troponin-T (hs-cTnT) measured at a single point in time (on average: 20 hours post-intervention).[4]

There is a lack of data on temporal dynamics of cardiac biomarkers after RF and PFA catheter ablation of AF representing surrogates of acute myocardial injury (ie, high-sensitivity cardiac troponin-I, CK-MB, myoglobin), regional

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KEY FINDINGS

- A greater extent of myocardial injury (ie, high-sensitivity cardiac troponin-T, myoglobin, CK-MB) was noticed after pulsed field ablation (PFA) of atrial fibrillation versus radiofrequency (RF) ablation, and cellular electroporation via pentaspline PFA resulted in a greater biomarker increase compared with loop-variable PFA.
- Kinetics of biomarkers of inflammation (ie, C-reactive protein [CRP]) increase following pulmonary vein isolation with both PFA technologies and RF. However, PFA resulted in a faster CRP biomarker recovery compared with RF, while CRP continued to increase beyond 24 hours post-ablation only in the RF group.
- Time courses of blood biochemical or hematological parameters declined in all treatment groups, with no substantial and clinically relevant variation among different energy sources. Similarly, markers of renal function and electrolyte balance exhibited only minor fluctuations over time, remaining within the expected physiological range for the study population.

inflammation (ie, C-reactive protein [CRP]), coagulation activation (ie, hematocrit, hemoglobin, and platelets), and mid-term myocardial structural changes including fibrosis.

Therefore, we are reporting the temporal dynamics of several biomarkers released following pulmonary vein (PV) isolation (PVI) performed with different ablation technologies: Far pulse PFA (Boston Scientific), Varipulse PFA (Biosense Webster), and RF ablation (Thermocool Smarttouch™ and QDOT Micro™, Biosense Webstar and Tactiflex, Abbot Medical) in a relatively large group of patients.

Methods

Patient population and study design

We conducted a prospective, observational, single-center study. From July 2022 to February 2025, we enrolled 186 consecutive patients referred to a high-volume Italian arrhythmology center (University Hospital Ospedali Riuniti in Ancona) for de novo AF catheter ablation for PVI. All patients underwent baseline blood sampling and regular post-procedural sampling (at 3, 24, and 48 hours) to assess major markers of myocardial necrosis, renal function, and inflammatory indices. The population was stratified into 3 groups according to the ablation system: RF ablation catheter (RF group), pentaspline Farapulse PFA system (PFA-FAR group), and variable-loop Varipulse PFA system (PFA-VAR group). Comparisons were made among groups. Only patients with normal baseline values of myocardial injury were included. The study was performed respecting the institutional standards, national legal requirements, the Declaration of Helsinki for ethical standards, and the study protocol was approved by an institutional review board. All patients received and signed written informed consent to the procedure.

Ablation procedure

RF group

A 3D-electroanatomical mapping system (Carto 3, Biosense Webster) was used to guide mapping and ablation in all cases. Left atrial electroanatomic mapping and PVI were achieved via a multipolar catheter and an open-irrigated RF ablation catheter (Thermocool SmartTouch and QDOT Micro, Biosense Webstar and Tactiflex, Abbot Medical) according to the operator's preferences. Transcatheter RF ablations were consistently performed with a minimum power setting of 50W. Lesions were delivered according to an ablation index using the Thermocool SmartTouch and QDOT catheters, whereas lesions with the TactiFlex catheter were delivered at 50W for 10 seconds each. Lesions were created with an inter-lesion distance of 6 mm, encircling the PVs at the antral region, with additional lesions at the level of the carina.[5,6]

Pentaspline Farapulse PFA group

The procedure involved the use of the pentaspline 12F over-the-wire PFA catheter (Farawave, Boston Scientific). PVI was performed by means of 4 applications in a basket configuration and 4 applications in a flower configuration per PV, as described elsewhere.[7–10] Between pairs of PFA applications, the catheter was rotated by about 30°/45° after the first 2 applications in each configuration, to cover the entire PV circumference. Ablation was performed by using an amplitude setting of 2.0 kV for each of the 4 PVs. Additional lesions at PVs were deployed per the physician's discretion.

Variable-loop Varipulse PFA group

All procedures were performed with a variable-loop circular catheter (Varipulse, Biosense Webster) with a standardized, recommended workflow.[11,12]

In each vein, 4 ablations are performed: 2 with a closed loop (25 mm) and 2 with an open loop (35 mm). PVI was performed with the first ablation by initially positioning the catheter with a closed loop at the ostium of each vein. The second ablation was delivered by slightly rotating the catheter relative to the initial position to cover the gap between electrode #1 and #10. The same approach was used for the next 2 ablations with the open loop. The catheter was then repositioned with an open loop to achieve a more antral position for the third ablation, and then rotated in the fourth ablation to close the gap between electrodes #1 and #10.

A total of $\geq$16 ablations is recommended for PVI-only procedures. This workflow entails 4 full ablations per vein to create 2 concentric wide-band rings (ostial and antral).

The variable-loop circular catheter delivers bipolar energy via multiple, brief pulses over a few seconds across the electrodes without the use of an external patch. Each

pulse is composed of a proprietary waveform with an energy of 1800 V that has a predefined amplitude, pulse width, and duration measured in microseconds.

Blood sample diagnostic

Baseline blood tests were carried out on the day before the scheduled procedure. Post-procedure blood samples were collected at 3 hours, and at approximately 24 and 48 hours, with a margin of ±2 hours after ablation. Sampled cardiac biomarkers were hs-cTnT (ng/l), CK-MB (ng/dL), myoglobin (ng/mL), CRP (mg/dL), and NT-pro-hormone B-type natriuretic peptide (NT-proBNP, pg/mL). Additional blood biochemical measurements included creatinine (mg/dL), ferritin (ng/mL), potassium concentration (mmol/L), sodium concentration (mEq/L), white blood cells (WBC, number of cells/mL), hematocrit (percentage of red blood cells), hemoglobin (g/dL), and platelets (platelets/μL).

WBC count was assessed using an automated blood cell counter. Serum hs-cTnT was quantified using the Elecsys Troponin-T high-sensitive assay (cut-off value 514 ng/L, Roche Diagnostics). Assay-specific cut-off values for CK-MB activity were 170 and 24 U/L, respectively.

Study objectives

The primary objective of the study is to evaluate the trends of major biomarkers of myocardial injury and inflammatory indices in patients undergoing ablation of paroxysmal AF using RF and different PFA technologies, comparing the various groups. The secondary objective of the study is to assess, within the same groups, the trends of coagulation markers and renal function indices.

Statistical analysis

Descriptive statistics are reported as means ± standard deviation for normally distributed continuous variables, or medians with 25th to 75th percentiles in the case of skewed distribution. Normality of distribution was tested by means of the non-parametric Kolmogorov-Smirnov test. Differences between mean data were compared by means of a t-test for Gaussian variables, and the F-test was used to check the hypothesis of equality of variance. The Mann-Whitney non-parametric test was used to compare non-Gaussian variables. Differences in proportions were compared by applying χ^2 analysis or Fisher exact test, as appropriate. All statistical analyses were performed by means of R: A language and environment for statistical computing (R Foundation for Statistical Computing).

Results

Study population and procedural characteristics

A total of 186 patients (mean age 63 ± 10 years, men 138%–74.2%) were included: 79 patients (42.5%) in the RF group, 69 patients (37.1%) in the PFA-FAR group, and 38 patients (20.4%) in the PFA-VAR group. All groups were similar in baseline characteristics. Baseline clinical variables and procedural parameters of the cohort study groups are reported in Table 1. PVI was achieved in all patients (100%) using only PFA or RF. No major procedure-related adverse events were reported in all groups, no thromboembolic events occurred, and no signs of acute kidney injury or hemolysis were reported.

Kinetics of biomarkers of myocardial injury and hemodynamic stress

Baseline levels of biomarkers of myocardial injury (ie, hs-cTnT, myoglobin, CK-MB) and hemodynamic stress (ie, NT-proBNP) were comparable between groups. The kinetics of troponin, myoglobin, and CK-MB showed a rapid and significant increase from baseline values 3 hours after ablation and a significant decrease during the subsequent 24 hours and 48 hours. The maximum peak of these biomarkers was seen 3 hours after ablation (2000 to 15,000-fold increase in hs-cTnT, a 3- to 5-fold increase in myoglobin, and a 3- to 50-fold increase in CK-MB).

PFA-FAR was associated with the highest biomarker elevation, while PFA-VAR exhibited an intermediate trend between PFA-FAR and RF. By 48 hours, biomarker levels of troponin, myoglobin, and CK-MB were comparable between PFA-FAR and PFA-VAR. RF ablation was associated with a more rapid normalization of troponin and CK-MB levels at 48 hours compared with both PFA modalities (Figure 1A–C). NT-proBNP levels increased significantly up to 24 hours post-ablation, followed by a decline at 48 hours. No significant differences in NT-proBNP kinetics were observed between groups at any time point (Figure 1D).

Kinetics of biomarkers of inflammation and blood biochemicals of white blood cell level and ferritin

No differences emerged among groups in baseline levels of biomarkers of inflammation (ie, CRP) and blood biochemical (ie, WBC and ferritin). WBC levels (Figure 2A) were markedly increased at 3 hours and slowly decreased up to 24 hours and 48 hours in all groups. CRP levels (Figure 2B) increased progressively, peaking at 24 hours and remaining elevated at 48 hours in the PFA groups, with no significant differences between PFA-FAR and PFA-VAR. In contrast, CRP levels in the RF group continued to increase over time, with statistically significant elevations at 48 hours compared with PFA groups.

Ferritin levels showed a rapid increase within 3 hours, peaking at 24 hours, followed by a decrease at 48 hours (Figure 2C). Notably, both PFA-FAR and PFA-VAR were associated with a more pronounced early increase in ferritin compared with RF, a trend that persisted through 48 hours (Figure 2C).

Time courses of blood biochemicals of coagulation and hematological parameters

Following ablation, blood biochemical of coagulation or hematological parameters—including hemoglobin, hematocrit, and platelet count—declined in all treatment groups. Hematocrit and platelet count trajectories were similar across

Table 1 Baseline clinical characteristics and procedural parameters of the study population

Parameter	Overall population (n = 186)	(A) RF (n = 79)	(B) PFA-FAR (n = 69)	(C) PFA-VAR (n = 38)	*P* (A vs B)	*P* (A vs C)	*P* (B vs C)
Age, y	63.3 ± 10	61.9 ± 10	65.6 ± 9	62.1 ± 8	.0316*	.9049	.0637
Male sex, n (%)	138 (74.2)	62 (78.5)	47 (68.1)	29 (76.3)	.191	.8151	.5046
Indication for ablation:						.	
Paroxysmal AF, n (%)	143 (76.9)	59 (74.7)	54 (78.3)	30 (78.9)	.699	6524	1.00
Persistent AF, n (%)	43 (23.1)	20 (25.3)	15 (21.7)	8 (21.1)			
LVEF, %	58.7 ± 7	58.0 ± 7	58.7 ± 6	60.3 ± 6	.9226	.0233	.0566
LAVi, mL/m^2	36.1 ± 11	35.5 ± 11	37.9 ± 11	34.1 ± 12	.0878	.3479	.0586
LVEDVi, mL/m^2	57.2 ± 13	58.4 ± 14	56.6 ± 12	56.0 ± 9	.4028	.4465	.9381
BMI	26.7 ± 4	26.6 ± 4	26.6 ± 4	26.8 ± 5	.8914	1.00	.9377
Structural heart disease, n (%)	27 (14.5)	14 (17.7)	11 (15.9)	2 (5.3)	.8285	.0863	.1312
COPD, n (%)	6 (3.2)	1 (1.3)	5 (7.2)	0 (0.0)	.4662	.0976	.1583
Sleep apnea, n (%)	16 (8.6)	8 (10.1)	3 (4.3)	5 (13.2)	.2209	.7546	.129
Diabetes, n (%)	16 (8.6)	7 (8.9)	6 (8.7)	3 (7.9)	1.00	1.00	1.00
Hypertension, n (%)	110 (59.1)	45 (57.0)	43 (62.3)	22 (57.9)	.6149	1.00	.6832
Hyperlipidemia, n (%)	119 (64.0)	50 (60.3)	46 (66.7)	23 (60.5)	.7313	.8395	.5346
Antiarrhythmics, n (%)	114 (61.8)	53 (67.1)	38 (55.1)	24 (63.2)	.1755	.6823	.5396
Beta-blockers, n (%)	108 (58.1)	47 (59.5)	41 (59.4)	20 (52.6)	1.00	.5512	.5442

AF = atrial fibrillation; BMI = body mass index; COPD = chronic obstructive pulmonary disease; LAVi = indexed left atrial volume; LVEDVi = indexed left ventricle end diastolic volume; LVEF = left ventricular ejection fraction; PFA-FAR = pentaspline Farapulse pulsed field ablation system; PFA-VAR = variable-loop Varipulse pulsed field ablation system; RF = radiofrequency ablation catheter.
*$P < .017$ was considered significant after Bonferroni correction.

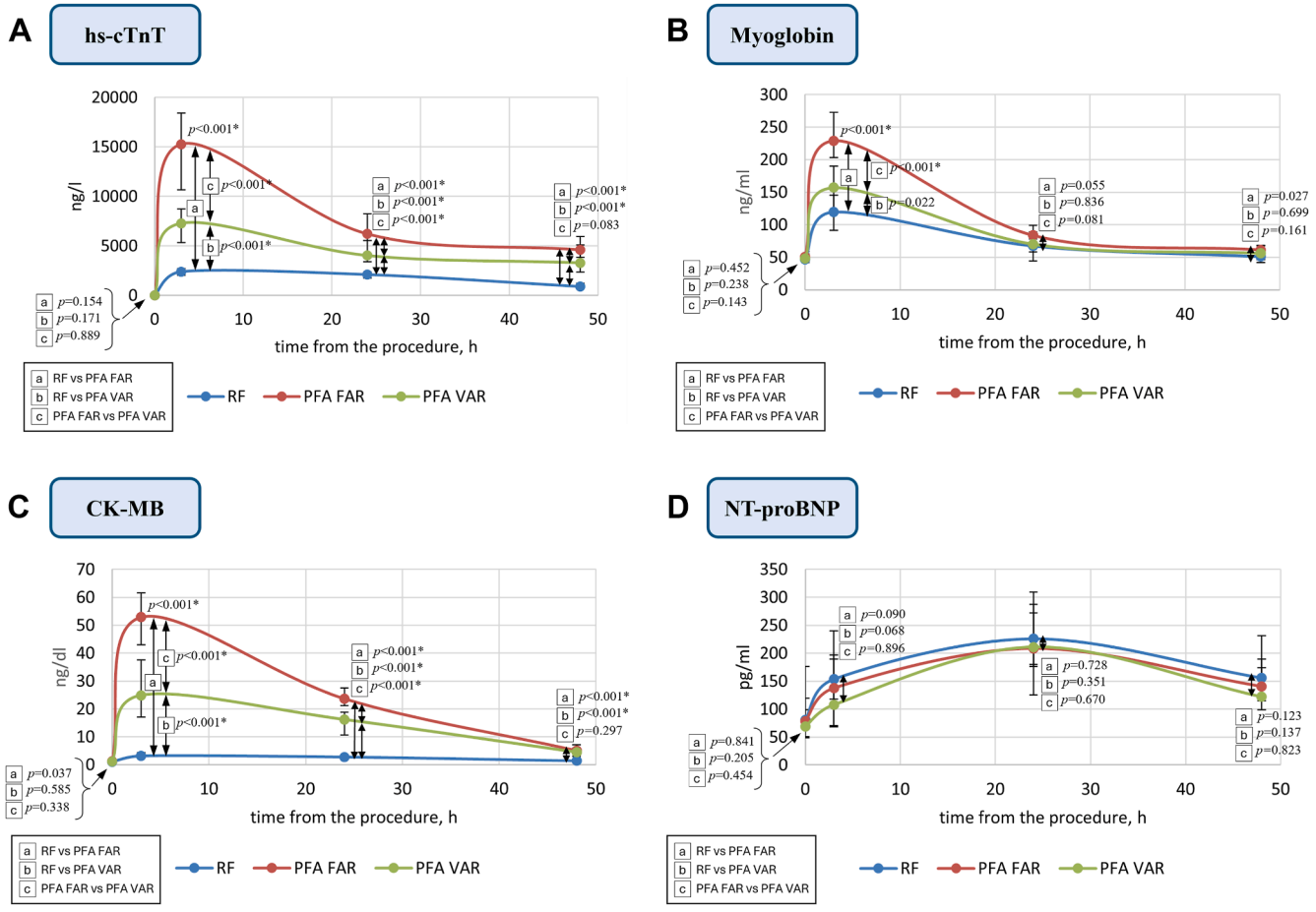

Figure 1 Kinetics of biomarkers of myocardial injury according to different energy sources. Baseline values and values 3 hours, 24 hours, and 48 hours after the procedures are shown. hs-cTnT = high-sensitivity cardiac troponin-T; NT-proBNP = NT-pro-hormone B-type natriuretic peptide; PFA-FAR = pentaspline Farapulse pulsed field ablation system; PFA-VAR = variable-loop Varipulse pulsed field ablation system; RF = radiofrequency ablation catheter.

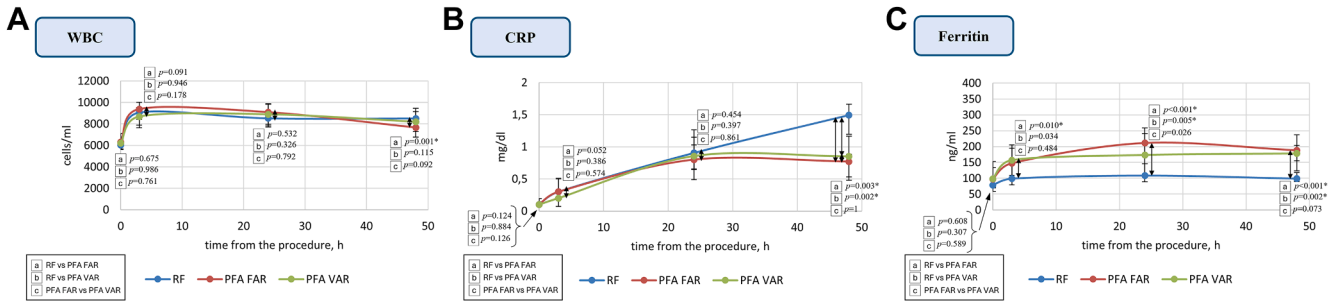

Figure 2 Kinetics of biomarkers of inflammation according to different energy sources. Baseline values and values 3 hours, 24 hours, and 48 hours after the procedures are presented. CRP = C-reactive protein; PFA-FAR = pentaspline Farapulse pulsed field ablation system; PFA-VAR = variable-loop Varipulse pulsed field ablation system; RF = radiofrequency ablation catheter; WBC = white blood cell.

groups over time (Figure 3A and B). However, the temporal profile of hemoglobin levels differed significantly between groups: post-procedural levels were highest in the PFA-VAR group, lowest in the RF group, with the PFA-FAR group demonstrating intermediate values (Figure 3C).

Markers of renal function and electrolyte balance

Renal function markers (ie, serum creatinine) and electrolyte parameters (ie, sodium and potassium) exhibited only minor fluctuations over time, remaining within the expected physiological range for the study population. No significant inter-group differences were observed for these parameters (Figure 4A–C).

Discussion

Main findings

This prospective, observational study provided novel insights into the precise time-course of myocardial injury, inflammation, and electrolyte and prothrombotic responses following de novo PVI for AF across different energy sources (RF vs PFA) and different PFA ablation technologies.

1) A greater extent of myocardial injury was noticed in the PFA groups vs RF, and cellular electroporation via pentaspline PFA resulted in a greater biomarker increase compared with loop-variable PFA.
2) Kinetics of biomarkers of inflammation increase following PVI with both PFA technologies and RF. However, both PFA systems resulted in a faster CRP biomarker recovery compared with RF, while CRP continued to increase beyond 24 hours post-ablation only in the RF group.
3) Time courses of blood biochemical or hematological parameters declined in all treatment groups, with no substantial and clinically relevant variation among different energy sources.
4) Markers of renal function and electrolyte balance exhibited only minor fluctuations over time, remaining within the expected physiological range for the study population.

Lesion formation and myocardial injury

In this study, PFA was associated with significantly greater release of myocardial injury biomarkers compared with conventional RF ablation. Similar to Popa et al,[13] levels of hs-cTnT and CK-MB were elevated approximately 5-fold and 15-fold, respectively, in the PFA groups. Additionally, we observed that the extent of myocardial injury, as assessed by myoglobin levels, was substantially greater in the PFA groups, with levels approximately twice as high as those observed with RF ablation. The most plausible explanation for this observation is the creation of a larger volume of myocardial injury with PFA, likely because of multiple contributing factors: the catheter design, the duration of energy delivery, and a more antral and extensive lesion formation with PFA that is less dependent on contact force or catheter orientation typical of RF ablation catheters.[13–16]

Although we have not evaluated the extension of the lesion consistently through a mapping system, supporting this concept, in RF ablation, PVI typically targets a narrow circumferential band around the PVs, producing thin linear lesions a few millimeters wide. In contrast, pentaspline or circular PFA catheters ablate a substantially broader surface area around the PVs, resulting in more extensive myocardial cell injury compared with point-by-point linear RF lesions. This means that the number of damaged cardiomyocytes is significantly higher.[3]

Moreover, pre-clinical and early clinical data have shown that PFA induces more pronounced transmural myocardial damage, and this, combined with a wider ablation zone, accounts for the higher levels of myocardial injury biomarkers observed. Animal studies[17] have demonstrated similar findings, with biomarker levels peaking between 1 and 3 days post-procedure, consistent with our results and previous literature.[3]

No significant differences in NT-proBNP levels were observed between PFA and RF ablation groups. This suggests that NT-proBNP, as a marker of cumulative myocardial stress or injury mostly produced by the ventricle, may not accurately reflect lesion extent in the atrium when ablation areas surpass several centimeters, particularly around the antral region of the ipsilateral veins.

Our findings align with those of Badertscher et al,[4] who reported significantly lower hs-cTnT levels following PVI

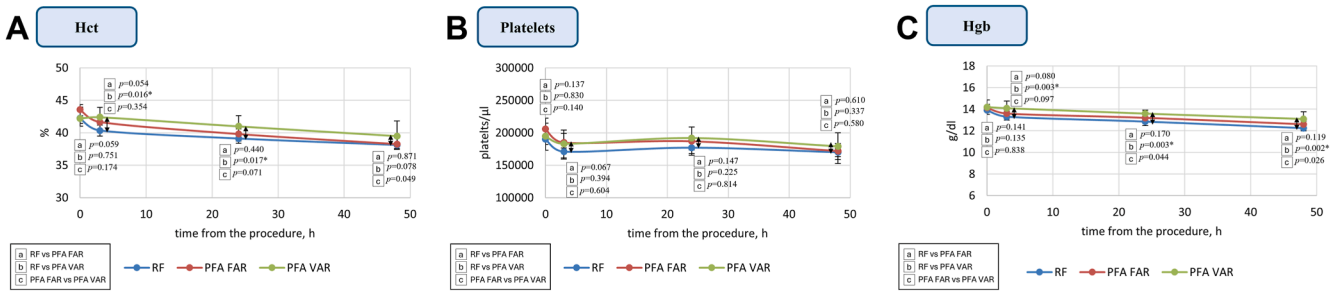

Figure 3 Time-course of biomarkers of prothrombotic markers according to different energy sources. Baseline values and values 3 hours, 24 hours, and 48 hours after the procedures are reported. Hct = hematocrit; HgB = hemoglobin; PFA-FAR = pentaspline Farapulse pulsed field ablation system; PFA-VAR = variable-loop Varipulse pulsed field ablation system; RF = radiofrequency ablation catheter.

with a loop-variable PFA system compared with pentaspline and loop catheter systems. In our study, hs-cTnT levels were approximately twice as high after pentaspline PFA compared with loop-variable PFA, although both exhibited similar biomarker kinetics over time. The most likely explanation is that pentaspline PFA catheters generate a greater volume of myocardial injury than variable-loop systems, which may contribute to enhanced durability of PVI. While hs-cTnT levels observed in the pentaspline PFA group are consistent with prior reports on myocardial injury following PFA,[18,19] the levels in the loop-variable PFA group were between pentaspline PFA and traditional thermal ablation.[20]

Level of inflammation

Multiple distinct forms and pathways of cell death can occur within cells and tissues, and these modes of cell death may be differentially induced, depending on the energy source and specific cellular context.[21] Among these, all membrane-disruptive forms of cell death—namely, necrosis, necroptosis, pyroptosis, and ferroptosis—are typically associated with an accompanying inflammatory response, with apoptosis being the exception.[22] RF ablation induces cell death predominantly through thermal injury, resulting in protein denaturation and coagulative necrosis. In contrast, PFA has been consistently associated with apoptosis as the primary mode of cell death. This fundamental difference may have important implications for the subsequent inflammatory response.

In our study, while WBC counts increased immediately following ablation across all treatment groups, regardless of energy source, CRP levels exhibited divergent trends. Specifically, CRP continued to increase beyond 24 hours post-ablation only in the RF group. This sustained elevation likely reflects the underlying mode of cell death and its associated immunologic response. Prior in vitro studies have shown that RF ablation elicits a pronounced inflammatory reaction. Histopathological investigations corroborate this, demonstrating that RF ablation induces coagulative necrosis followed by inflammatory cell infiltration and eventual fibrotic scar formation.[22] Comparative animal studies further support this observation. Koruth et al[23] reported that PFA lesions are characterized by uniform and organized fibrosis replacing the myocardium, whereas RF lesions display disorganized fibrosis, with a higher degree of mononuclear cell infiltration, indicative of a more intense inflammatory response.

Despite the greater extent of myocardial injury associated with PFA, our findings indicate that it does not elicit a corresponding increase in systemic inflammation as seen with RF. Notably, CRP levels in PFA-treated patients peaked at 24 hours and then began to decline by 48 hours. Moreover, although the degree of myocardial injury varied between pentaspline and variable-loop PFA technologies, no significant differences in CRP levels were observed between these groups. This consistency likely reflects the shared apoptotic mechanism underlying lesion formation in both PFA systems.

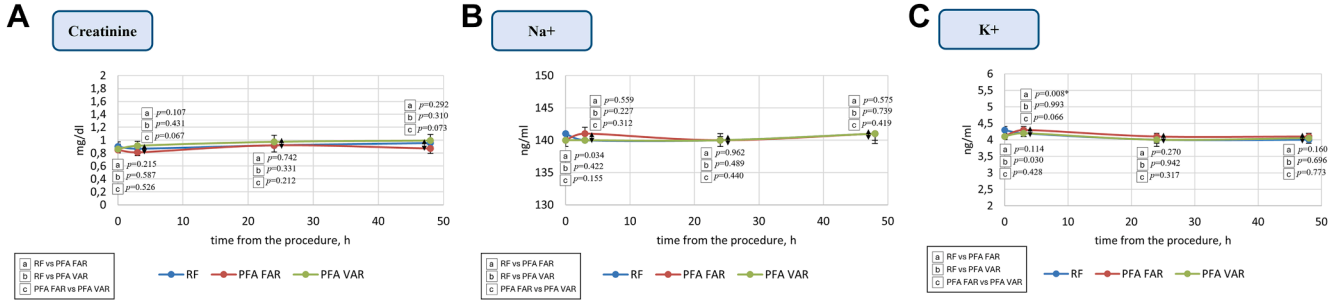

Figure 4 Time-course of markers of renal function and electrolyte balance according to different energy sources. Baseline values and values 3 hours, 24 hours, and 48 hours after the procedures are reported. K+ = potassium concentration; Na+ = sodium concentration; PFA-FAR = pentaspline Farapulse pulsed field ablation system; PFA-VAR = variable-loop Varipulse pulsed field ablation system; RF = radiofrequency ablation catheter.

Other blood biochemical or hematological parameters

In this study, the degree of platelet activation was comparable between patients undergoing RF and PFA, and plausibility did not correlate with the extent or size of myocardial lesions. This finding supports the concept of distinct biological responses elicited by thermal vs non-thermal energy sources, consistent with the observations reported by Osmancik et al.[3]

Regarding coagulation parameters, the temporal profile of hematological parameters did not differ significantly between the RF and PF groups, suggesting that PFA does not confer an increased risk of thrombus formation or other possible complications related to the coagulation response, compared with conventional RF ablation. Additionally, a significant post-procedural decrease in hemoglobin and hematocrit levels was observed in all groups. These results are in line with previous findings by Sairaku et al,[24] who reported similar hematological changes following RF ablation.[20,24]

Finally, markers of renal function and electrolyte homeostasis demonstrated only minimal variations over time and remained within physiological limits for the study population, indicating preserved systemic stability following different energy sources and ablation modalities.

Clinical perspective

The non-thermal mechanism underlying PFA leads to a distinct temporal and morphological profile of lesion formation compared with RF ablation. Furthermore, acute tissue responses to PFA are influenced by multiple variables, including pulse parameters (eg, pulse width, number of bursts), catheter design, procedural conditions, and other technical factors.

A thorough understanding of the biophysical principles and mechanistic basis of PFA is essential for the development of novel therapeutic strategies and for the optimization of clinical applications. Notably, despite inducing the greatest degree of myocardial injury, PFA is associated with a relatively attenuated inflammatory response. This observation is encouraging and supports further investigation into whether reduced inflammation following PFA may translate into a lower incidence of early arrhythmia recurrence or inflammatory symptoms during the post-ablation period.[21] This aspect may be particularly relevant and could guide the selection of energy modalities in patients with chronic inflammatory conditions, such as arthritis or psoriasis. Recent studies have highlighted the inflammatory component as a significant predictor of adverse outcomes.[25,26]

Consequently, the use of an ablation energy source associated with a reduced post-procedural pro-inflammatory and pro-fibrotic response may offer more favorable outcomes, particularly in patients with inflammation-associated atrial cardiomyopathy. In such patients, minimizing local inflammation post-ablation—as seen with PFA—might reduce additive inflammatory burden and potentially attenuate AF recurrence. Nevertheless, this proposed benefit remains theoretical at present, and further studies with supporting data would be valuable to substantiate this broader clinical implication.

The characterization of cell death pathways following PFA requires evaluation across a range of cell types with differing physiological properties to determine whether electric pulses primarily trigger general molecular stress responses or induce more specific, parameter-dependent forms of cell death. As elegantly discussed by Batista Napotnik et al[21] in a comprehensive review on electroporation-induced cell death, the wide range of pulse parameters used in PFA technologies suggests that the underlying mechanisms of cell death triggered by different pulsing protocols may be more closely related than previously understood.

Limitations

The principal limitations of this analysis arise from its intrinsic non-randomized design. Nevertheless, all patients were enrolled prospectively, adhering to the standard-of-care protocol ablation by the operators and patient management.

Data were available for biomarkers routinely assessed at our center in clinical practice. However, more specific markers of inflammation are required to confirm the current findings. While the primary aim of this study was to quantify differences in myocardial injury and inflammation, it was not powered to detect differences in procedural safety and outcomes. In addition, our study involved only an acute assessment; long-term follow-up is necessary to determine the predictive value of cardiac enzyme kinetics as non-invasive markers in evaluating the outcome of cardiac ablation by means of RF or PFA. Finally, information regarding lesion extension, as assessed by a high-density mapping system, was not available for all cases. Specifically, 3D mapping was not consistently employed during procedures performed with Farapulse PFA. As a result, it is not possible to draw inferences regarding the relationship between myocardial injury biomarkers and the extent of the lesions.

Conclusion

These findings demonstrate that serum levels of troponin I, CK-MB, and myoglobin increase following PVI performed with both Farapulse and Varipulse PFA technologies, as well as with RF ablation. Cellular electroporation induced by Farapulse PFA was associated with a significantly greater elevation in these cardiac biomarkers compared with Varipulse PFA and RF, with Varipulse PFA exhibiting an intermediate response. Additionally, CRP levels increased following PVI with all 3 modalities; however, both PFA systems were associated with a more rapid decline in CRP levels compared with RF, where CRP concentrations continued to increase beyond 24 hours post-procedure.

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Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients received and signed written informed consent to the procedure.

Ethics Statement: The study was performed respecting the institutional standards, national legal requirements, the Declaration of Helsinki for ethical standards, and the study protocol was approved by an institutional review board.

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