Pulsed-field ablation of atrial fibrillation: kinetics of release of multiple cardiac biomarkers

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Several studies have yielded data on the variation of cardiac biomarkers after a thermal energy to the ablation of atrial fibril-lation (AF) [1, 2]. To date, however, when a form of non-thermal energy is used, such as electroporation obtained by means of pulsed-field ablation (PFA), few biomarkers of myocardial injury have been evaluated [3, 4]. From July 2022 to May 2023, we enrolled 72 consecutive patients referred to our center for the ablation of AF; all patients underwent ablation with the novel FARAPULSE™ PFA system (Boston Scientific) and blood sample evaluation of 14 cardiac biomarkers of cardiovascular stress, myocardial fibrosis, inflammation, and coagulation activity (Fig. 1). A standard PFA protocol was applied [3]. Blood samples were collected the day before the scheduled procedure and 3 h, 24 h, and 48 h after ablation.

By the end of the procedure, pulmonary vein isolation (PVI) had been achieved in all patients by means of PFA alone. No major procedural or anesthesia-related complications were recorded.

The kinetics of biomarkers of myocardial injury (i.e., hs-troponin, myoglobin, and CK-MB) showed a rapid and significant increase from baseline values 3 h after ablation and a significant decrease during the subsequent 24 h and 48 h. The maximum peak of these biomarkers was seen 3 h after ablation (15,000-fold increase in hs-cTnI and tenfold increase in both myoglobin and CK-MB) (Fig. 1A–C). Ferritin levels showed a rapid increase during the first 3 h, a peak at 24 h, and a decrease at 48 h, whereas no differences were found between baseline and 3 h, 24 h, and 48 h levels of NT-ProBNP. WBC levels (Fig. 1F) were markedly increased at 3 h and slowly decreased up to 24 h and 48 h. By contrast, C-reactive protein (Fig. 1G) increased over time, peaking at 48 h. At the baseline and at 3 h, 24 h, and 48 h, the majority of biomarkers of myocardial injury and inflammation displayed no significant differences between patients who had undergone PV ablation only and those in whom ablation extended beyond the PVs. Only C-reactive protein levels 3 h after ablation showed a significant difference between these two patient groups (0.54 ± 0.8 mg/dl for PV only vs 0.86 ± 1.6 mg/dl for extended ablation, $p = 0.035$). However, at 24 h and 48 h, this difference was no longer significant.

This study provided novel insights into the precise time-course of inflammation, myocardial injury, and electrolyte and prothrombotic responses following the PFA of AF. Patients undergoing AF ablation by means of cellular electroporation exhibited a myocardial injury within the first 2 days after ablation, with a peak in biomarkers at 3 h; subsequently, a decline towards lower values was already evident at 24 h. A significant inflammatory response occurred over a 48-h period; however, biomarker levels remained within the normal range for this population. Following the procedure,

markers indicating coagulation activity, such as hemoglobin, hematocrit, and platelet count, exhibited a decline and this decrease was similar to that observed after AF ablation using other energy sources. By contrast, the level of fibrinogen remained stable throughout the first 2 days. Cardiac enzyme elevations did not seem to be correlated with lesion extension after AF ablation. In our study, we found that the degree of myocardial injury did not appear to depend on the specific ablation area targeted (i.e., limited to PVs versus ablation extending beyond PVs). Besides the duration of energy delivery, other factors may contribute to the higher degree of myocardial injury in PFA, as indicated by increased levels of biomarkers following the ablation procedure [1, 5]. Significantly larger lesions are created by PFA than by both cryoablation [5, 6] and multielectrode radiofrequency balloon-based [4] PVI at the PVs, which often involves part of the posterior wall area, also resulting in higher troponin release [4].

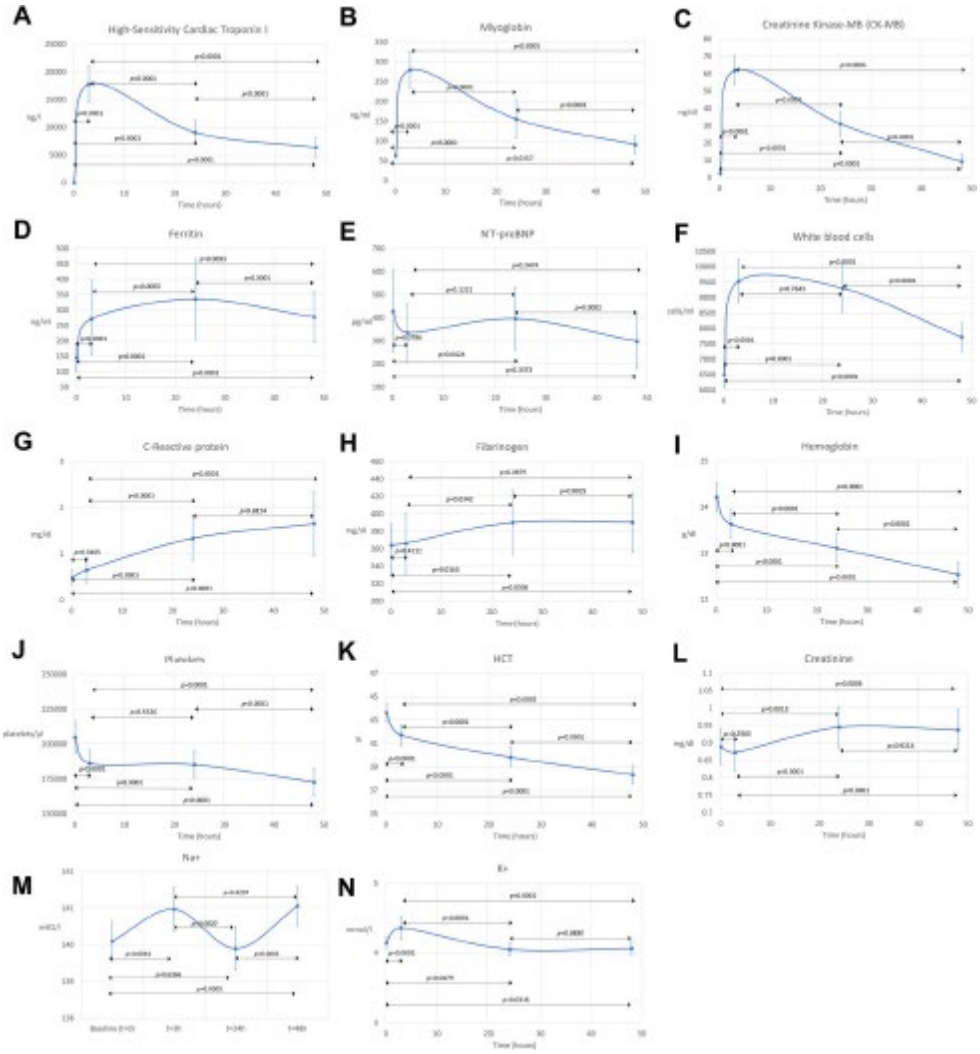

Fig. 1 Kinetics of the various biomarkers: high sensitivity cardiac troponin I (hs-cTnI, ng/L), creatinine kinase-MB (CK-MB, ng/dl), fibrinogen (mg/dl), myoglobin (ng/ml), N-terminal (NT)-pro hor-mone B-type natriuretic peptide (NT-ProBNP, pg/ml), C-reactive protein (mg/dl), creatinine (mg/dl), ferritin (ng/ml), white blood cells (WBC, number of cells/ml), hematocrit (HCT, percentage of red blood cells), hemoglobin (g/dl), platelets (platelets/µl), potas-sium concentration (K + , mmol/L), and sodium concentration (NA + , mEq/L). Baseline values and values 3 h, 24 h, and 48 h after the pro-cedures are shown: A–C biomarkers of myocardial injury (troponin, myoglobin, and CK-MB). Ferritin levels are shown in D, NT-ProBNP levels in E, white blood cell levels in F, and C-reactive protein in G. The time-courses of prothrombotic markers (fibrinogen,

hemoglobin, platelets, and hematocrit (HT)) are shown in H–K. L–N The kinetics of renal function (creatinine level) and electrolyte balance (NA + and K +). Data are presented as mean with its 95% confidence interval

In our work, we did not find higher release of hs-cTnI according to lesion exten-sion with the same ablation technology. It is therefore possible that the release of hs-cTnI, CK-MB, myoglobin, and ferritin, as quantitative measures of cumulative myocardial injury, does not accurately predict the continuity of lesions that extend beyond a few centimeters around the antral area of the ipsilateral veins. Albeit we did not directly compare PFA vs thermal ablation, at parity of lesion extension, the kinetics of biomarkers of myocardial injury (i.e., hs-cTnI, CK-MB, myoglobin) might differ, with different process of release and recover between these two determinants of lesion (thermal vs PFA). In addition, inflammatory response to lesion (i.e., WBC or C-reactive protein) might be different also depending on the primary cell death process (apoptosis vs necrosis) associated with electroporation vs thermal injury, possibly impacting the kinetic of enzymes release.

We noticed a significant decrease in both hemoglobin and hematocrit level after ablation. While it is important to note that this decline is not solely attributed to hemolysis, our findings are consistent with those reported by Sairaku et al. in the context of radiofrequency ablation [5]. Hemoglobin serves as a direct indicator of clinical severity in hemolytic diseases, and its levels are crucial for monitoring hemolytic patients and assessing treatment responses. In our study, however, post-ablation hemoglobin levels remained within the normal range. Although we did not directly compare ablation modalities, we do not anticipate an increased risk of hemolysis compared to radiofrequency ablation.

C-reactive protein increased over time, peaking at 48 h. We did not assess its recovery after 48 h; thus, we can reasonably infer that its kinetics are comparable to the anticipated pattern derived from literature. This assumption is supported by the measured values falling within the expected range for this population, with no patient displaying a C-reactive protein level indicative of a high risk of cardiovascular disease [7].

In studies involving thermal ablation [1], it was observed that a greater increase in cardiac biomarkers with cryoablation did not necessarily result in improved clinical outcomes. However, the impact of PFA on cardiac enzyme kinetics, particularly during PFA of PVs and atrial substrate, may differ, potentially influencing long-term outcomes. Therefore, long-term follow-up is essential to determine whether cardiac enzyme kinetics can serve as non-invasive markers for evaluating the outcomes of cardiac ablation using PFA. Finally, there is strong evidence that prove the specificity and selectivity of PFA on cardiac tissue only; therefore, other specific non-cardiac markers (e.g., neuronal, rather than growth factors linked to the coronary intima) could be useful to reiterate the safety of the lesion compared to thermal ablations.

In summary, CK-MB, hs-cTnI, myoglobin, and WBC levels displayed an increase at 3-h post-ablation, followed by a decline towards lower values within 24 h. By contrast, C-reactive protein exhibited a gradual increase over time, peaking at 48 h. Markers of hemolysis and potential end organ damage exhibited fluctuations within the expected range for this specific population. Interestingly, there appears to be no correlation between cardiac enzyme elevations and the extension of PFA beyond the PVs.

Declarations

Conflict of interest M. Malacrida is an employee of Boston Scientific. The other authors have no conflicts of interest to declare that are relevant to the content of this article.

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