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Short and long-term changes in platelet and inflammatory biomarkers after cryoballoon and radiofrequency ablation

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ABSTRACT

Background: Cryoballoon (CB) versus radiofrequency (RF) ablation response on prothrombotic biomarkers obtained different results at short-term, while long-term is still unknown in atrial fibrillation (AF) treatment. We evaluated short and long-term changes in platelet and inflammatory biomarkers after CB and RF ablation.
Methods: Fifty-eight paroxysmal AF patients were randomized for pulmonary vein (PV) isolation using either CB ($n = 29$) or RF ($n = 29$) ablation. Biomarkers of platelet activation [P-selectin (CD62P), CD40 ligand (CD40L), platelet factor-4 (PF-4), mean platelet volume (MPV), platelet-leukocyte ratio (P-LCR), and platelet distribution width (PDW)]; and inflammatory [high sensitivity CRP (hs-CRP) and interleukin-6 (IL-6)] were measured at baseline, 18–24 h and 6-Months postablation.
Results: Twenty-four (86.2%) and twenty-six (89.7%) patients remained in sinus rhythm at 6-Months in CB and RF group respectively ($p = 0.500$). After 18–24 h postablation, CD62P, CD40L, PF-4, hs-CRP, and IL-6 levels were significantly activated in both groups ($p < 0.001$). However, CD62P was significantly lower in CB than RF ($p = 0.017$). At 6-Month postablation in CB group, all platelet biomarkers CD62P ($p = 0.021$), CD40L ($p < 0.001$), PF-4 ($p < 0.001$), MPV ($p = 0.010$), PDW ($p = 0.004$), and P-LCR ($p = 0.033$) were significantly decreased compared to baseline levels. However in RF group, CD40L and PF-4 ($p < 0.001$) significant decreased, CD62P ($p = 0.022$) increased, and no change in MPV and P-LCR ($p > 0.05$) compared to baseline levels. hs-CRP and IL-6 levels were comparable between baseline and 6-Months in both groups ($p > 0.05$).
Conclusions: CB ablation might influence the risk of thromboembolism due to less platelet activation after PV isolation and decreased platelet activation at long-term in maintained sinus rhythm patients compared to RF.

1. Introduction

Pulmonary vein (PV) isolation by catheter ablation has become cornerstone therapeutic option for the treatment of atrial fibrillation (AF), leading to a decrease the number of arrhythmic episodes, increase in the time of sinus rhythm and improvement in the quality of life as compared to antiarrhythmic medications [1]. Radiofrequency (RF) ablation is the most frequently used energy to achieve point-by-point PV isolation worldwide; recently, cryoballoon (CB) ablation has emerged as a highly effective single shot alternative approach to RF particularly in paroxysmal AF patients [1,2].

Abnormal platelet and inflammatory activations are well known to play an essential role in thrombus formation and the risk of thromboembolism in AF patients [3,4]. To investigate prothrombotic biomarkers at short-term after CB and RF ablations; Tse et al. noted significant reduced platelet activation in CB [5], and Herrera et al. resulted in a comparable rise of platelet and inflammatory biomarkers in both ablations [6]. Currently, there are limited data comparing the long-term changes in prothrombotic biomarkers between patients remaining in sinus rhythm and those AF recurrences after RF ablation [7,8]. Therefore, this study was to evaluate the short and long-term changes in platelet and inflammatory activation biomarkers after CB and RF ablation in paroxysmal AF patients.

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2. Methods

2.1. Study population

The present study recruited 58 consecutive symptomatic paroxysmal AF patients at the First Affiliated Hospital of Dalian Medical University and defined according to the expert consensus statement as recurrent AF that terminates spontaneously within 7 days [1]. Recruited paroxysmal AF patients were scheduled for the first-time catheter ablation (September 2016–December 2017) and randomly assigned to undergo transseptal PV isolation using either RF or CB ablation. Exclusion criteria included long-standing (>12 months) and persistent AF, acute cause of AF (e.g. infection, alcohol excess, pulmonary emboli), heart failure, vascular diseases (myocardial infarction, peripheral artery disease, and cerebrovascular events within the last 3 months), inflammatory diseases, cancer, renal dysfunction (estimated glomerular filtration rate < 30 mL/min per 1.73 m^2), left atrial diameter ≥55 mm, and patients taking antiplatelet and nonsteroidal anti-inflammatory drugs within one month of enrollment into study. The First Affiliated Hospital of Dalian Medical University ethics committee approved this study and all participants gave written informed consent.

2.2. Ablation procedures

All procedures were performed under general anesthesia with midazolam and propofol. Patients were treated with oral anticoagulant (OAC), warfarin with an international normalized ratio level ≥2 or novel OAC for at least 3 weeks prior to the ablation procedure. During the procedure a bolus of intravenous heparin (100 IU/kg) was administered immediately following the transseptal puncture with uninterrupted OAC, and continuous infusion of heparin (1000 IU/kg) to maintain the activated clotting time (ACT) ≥300 s. The ACT level was measured before the ablation procedure and then every 20 min after the first heparin dose. All patients continued the postablation OAC for at least 3 months and those with a CHA2DS2-VASc score ≥2 including CB ($n = 12$) and RF ($n = 11$) received continuous therapy throughout the study period. Antiarrhythmic drugs were stop at least 5 half-lives before the procedure and re-started from evening post-procedure and discontinued if the 3-month follow-up visit confirmed the absence of atrial arrhythmia. The transesophageal and transthoracic echocardiography examinations were performed in each patient before the ablation to exclude left atrial thrombus.

2.2.1. Radiofrequency (RF) ablation

RF was performed as previously described [1,2,6]. In brief, PV isolation was performed by ablation catheter Navistar Thermocool 3.5-mm D-F curve with Smart Touch technology (Biosense Webster) using contiguous circumferential lesions guided by (lasso™, Biosense and Webster, Inc., CA, USA). RF energy was applied in a power-controlled mode with a power limited of 35 W (30 W at the posterior wall) and a maximal temperature of 45 °C. At each point, a radiofrequency current was applied until a voltage of <0.1 mV was achieved, with a maximum of 30 s per point.

2.2.2. Cryoballoon (CB) ablation

CB was performed as previously described [1,2,6]. In brief, PV isolation by CB was performed under fluoroscopy guidance using the cryocatheter (Arctic Front Advance balloon or Arctic Front TM, Medtronic, MN, USA). When using Arctic Front TM cryocatheter, the size of balloon was selected according to patient's PV anatomy. PV diameters ≤18 mm was ablated with a 23-mm balloon and those >18 mm were ablated with a 28-mm balloon. The balloon was introduced into the PV ostium over the Achieve guidewire (Medtronic Ablation Frontiers, LLC, Carlsbad, CA), which was utilized for mapping PV. Contrast medium was injected into the distal site of the balloon in order to visualize occlusion through the cryocatheter. CB was delivered for 180–300 s for each PV. Additional bonus shot was delivered if potentials were still present. Before targeting the right PVs, a catheter was positioned in the superior cava in order to promptly detect phrenic nerve injury during CB.

In both groups, procedural success of all PV isolation was confirmed using entrance and exit blocks by pacing maneuvers. No further ablation beyond PV isolation was performed.

2.3. Postablation follow-up

All patients underwent surface 12-leads electrocardiogram (ECG), transthoracic echocardiography and 24 h Holter monitoring on the first postablation day. During follow-up, serial 7 day Holter monitoring and 12-leads ECG were performed at 1, 3, and 6 months after the procedure. An additionally 12-leads ECG was advised if any patient became symptomatic during follow-up, Procedural success was defined as the absence of any atrial arrhythmia ≥30 s on 12-leads ECG or 7 days Holter monitoring after a 3-month blanking period.

2.4. Blood sampling and biomarkers measurements

Peripheral blood samples were collected with a slow withdrawal technique with discarding the first 5 mL at baseline (at the start of the procedure, prior to administration of heparin and any ablation), at 18–24 h (Inpatient stay) and 6-Months postablation during outpatient follow-up. Laboratory personnel were blinded to patient characteristics, those who analyzed the platelet and inflammatory biomarkers.

2.4.1. Platelet biomarkers

EDTA blood samples were collected to determine mean platelet volume (MPV), platelet-leukocyte ratio (P-LCR) and platelet distribution width (PDW) within 30 min after withdrawal of blood samples from complete blood count analysis by hematology auto-analyzer (Sysmex XE-2100). Citrated blood samples were collected to determine platelet surface expression of P-selectin (CD62P) within 4 h by flow cytometry (FACSCanto, Becton Dickinson, UK) as described previously [7]. An extra citrated blood sample was collected from each subject and centrifuged immediately at 2500*g* for 10 min at room temperature and stored at −80 °C incubator for batch analysis enzyme-linked immunosorbent assay (ELISA). CD40 ligand (CD40L) and platelet factor-4 (PF-4) were measured by ELISA kits per company instructions (Cloud-Clone Corp).

2.4.2. Inflammatory biomarkers

Serum high sensitive CRP (hs-CRP) by particle-enhanced immunonephelometry (Cardiophase* hsCRP, Siemens Healthcare Diagnostics, Germany) and interleukin 6 (IL-6) by latex particle-enhanced immunoassay auto-analyzer (Immulite, Siemens Medical Solutions Diagnostics GmbH, Germany) were used for the measurement within 30 min after withdrawal of blood samples.

2.5. Statistical analysis

Kolmogorov-Smirnov test was applied to continuous data for determining normality. Continuous variables were expressed as mean ± standard deviation or median with interquartile range for normally and non-normally distributed data respectively. Categorical data were expressed as percentages. Data between groups were compared using Student's *t*-test, Fisher's exact test or the Pearson χ^2 test as appropriate. Comparison of biomarkers between CB and RF groups was performed using the independent *t*-test or Mann-Whitney-*U* test at baseline, 18–24 h and 6-Months postablation. The paired *t*-test or Wilcoxon signed rank test was used for repeated measurements from baseline to the same study time-points after ablation in both groups. A *p*-value ≤0.05 was considered statistically significant. All statistical analyses were performed using SPSS 23 (IBM).

3. Results

3.1. Patient and procedure characteristics

All patients except one in CB group could complete 6 months follow-up, twenty-four (86.2%) and twenty-six (89.7%) patients remained in sinus rhythm, while 4 (13.8%) and 3 (10.3%) patients sustained AF recurrence in CB and RF group respectively ($p = 0.500$). During blanking period ≤3 months, AF recurrence rate was 7 (24.1%) in CB and 4 (13.8%) in RF, ($p = 0.252$). The antiarrhythmic drugs were effective to restore sinus rhythm in 4 (36%) recurrent patients and no additional procedure was performed. Due to lower number of AF recurrence, this study included maintained sinus rhythm patients in both groups.

The clinical and procedural characteristics of the included patient cohort are shown in Table 1. The mean age was 61.8 ± 6.6 years old with a median (interquartile range) AF history of 24 (8–60) months. In the CB group, the mean procedural time (66.9 ± 13.2 vs. 98.5 ± 23.5 min, $p < 0.001$) and mean PV isolation time (24.4 ± 7.1 vs. 39.9 ± 9.5 min, $p < 0.001$) were significantly shorter, whereas mean fluoroscopy time (15.4 ± 4.2 vs. 10.6 ± 5.1 min, $p = 0.001$) was significantly longer than the RF group.

3.2. Platelet biomarkers

The levels of platelet biomarkers at baseline and 18–24 h postablation are shown in Fig. 1, and [Table 1 in ref. (9)]). No significant difference in CD62P (% 18.5 ± 4.4 vs. 17.9 ± 5.9, $p = 0.654$), CD40L (pg/mL 68 ± 33.8 vs. 70.3 ± 47.8, $p = 0.844$), PF-4 (pg/mL 102 ± 23.5 vs. 108.5 ± 18.3, $p = 0.305$), MPV (fL 10.1 ± 0.5 vs. 10.1 ± 0.7, $p = 0.986$), PDW (fL 11.9 ± 1.1 vs. 11.6 ± 1.6, $p = 0.420$), and P-LCR (% 25.9 ± 5.2 vs. 25.7 ± 6.4, $p = 0.895$) was observed at baseline between CB and RF group respectively. CD62P, CD40L and PF-4 were significantly higher at 18-24 h postablation in both groups ($p < 0.001$). However, CD62P (%29.1 ± 5.4 vs. 34.4 ± 7.7, $p = 0.017$) was significantly lower in CB than RF. Furthermore, a significant decrease was noted in PDW (fL 11.4 ± 1.1 vs. 11.9 ± 1.1, $p = 0.025$) compared to baseline level in CB group. No change was observed in MPV and P-LCR in both groups ($p > 0.05$).

At 6-Month postablation, all six platelet biomarkers CD62P (% 16.4 ± 3.8 vs. 18.5 ± 4.4, $p = 0.021$), CD40L (pg/mL 23.8 ± 19.6 vs. 68 ± 33.8, $p < 0.001$), PF-4 (pg/mL 72.7 ± 34.8 vs. 102 ± 23.5, $p < 0.001$), MPV (fL 9.9 ± 0.5 vs. 10.1 ± 0.5, $p = 0.010$), PDW (fL 11.3 ± 1.1 vs. 11.9 ± 1.1, $p = 0.004$), and P-LCR (% 24.3 ± 4.5 vs. 25.9 ± 5.2, $p = 0.033$) decreased significantly compared to baseline levels in the CB group patients who remained in sinus rhythm. However in the RF group, a significant decreased in CD40L (pg/mL 31.6 ± 29.7 vs. 70.3 ± 47.8, $p < 0.001$) and PF-4 (pg/mL 87 ± 26.5 vs. 108.5 ± 18.3, $p < 0.001$); increased in CD62P level (% 21.3 ± 6.1 vs. 17.9 ± 5.9, $p = 0.022$); and no change in MPV and P-LCR ($p > 0.05$) compared to baseline levels are shown in Fig. 1, and [Table 2 in ref. [9]).

3.3. Inflammatory biomarkers

No significant difference was observed in the pro-inflammatory biomarkers IL-6 [pg/mL 3.3 (1.9–3.9) vs. 3 (1.9–6.7), $p = 0.617$] and hs-CRP [mg/L 0.8 (0.5–2) vs. 0.6 (0.4–2.1), $p = 0.907$] at baseline between two groups (Table 1 in ref. [9]). Significant increase was observed in IL-6 and hs-CRP at 18–24 h postablation compared to baseline ($p < 0.05$), but no statistical difference between two groups ($p > 0.05$). IL-6 and hs-CRP were comparable at 6-Months compared to baseline levels in both groups ($p > 0.05$) are shown in Fig. 2, and (Table 2 in ref. [9]).

Table 1
Clinical and procedural characteristics.

	CB ($N = 24$)	RF ($N = 26$)	p-Value
Age (years) SD	61.2 ± 5.5	62.4 ± 7.5	0.525
Male	16 (66.7%)	18 (69.2%)	0.543
Body mass index	25 ± 3.8	25.8 ± 3	0.414
AF history (months)	42 (12–69)	24 (7–51)	0.325
SBP (mm Hg)	132 ± 12	142 ± 19	0.064
DBP (mm Hg)	79.7 ± 11.5	84.5 ± 12.5	0.164
HR (bpm)	70 (59–74)	68 (62–80)	0.946
Comorbidities			
HTN	12 (50%)	15 (57.7%)	0.397
Age ≥ 75	1 (4.2%)	0 (0%)	0.480
DM	3 (12.5%)	2 (7.7%)	0.461
Stroke/TIA	5 (17.2%)	2 (6.9%)	0.211
Age 65–74	4 (16.7%)	10 (38.5%)	0.080
Female sex	9 (31%)	10 (34.5%)	0.543
Mean CHA2DS2-VASc	1.5 (0.2–2)	1 (1–2.2)	0.948
Mean CHADS2	1 (0–1.7)	1 (0–1)	0.341
Smoking habits	9(37.5%)	4(15.4%)	0.072
Medications			
ACEI	1 (4.2%)	0	0.480
CCB	9 (37.5%)	4 (15.4%)	0.072
Beta blocker	12 (50%)	8 (30.8%)	0.136
Propafenone	4 (16.7%)	7 (26.9%)	0.298
Amiodarone	4 (16.7%)	6 (23.1%)	0.418
Warfarin	7 (29.2%)	8 (30.8%)	0.574
Dabigatran	12 (50%)	11 (42.3%)	0.397
Rivaroxaban	5 (20.8%)	7 (26.9%)	0.433
Echocardiographic parameters			
LA diameter (mm)	36.5 ± 3.3	36 ± 2.5	0.588
LVEF (%)	59 (59–59)	59 (59–59)	0.617
Procedure details			
Mean procedure time (min)	66.9 ± 13.2	98.5 ± 23.5	**0.000**
Mean PV isolation time (min)	24.4 ± 7.1	39.9 ± 9.5	**0.000**
Mean fluoroscopy time (min)	15.4 ± 4.2	10.6 ± 5.1	**0.001**

Data are expressed as mean ± SD, median and interquartile range (25th–75th), or percentile (%), bold letters are significant and unless otherwise stated.
ACEI = angiotensin converter enzyme inhibitor; CCB = calcium channel blocker; CB = cryoballoon; CHA2DS2-VASc: congestive heart failure (CHF), hypertension (HTN), age ≥ 75 (doubled points), diabetes mellitus (DM), stroke/TIA (transient ischemic attack), vascular disease, age 65–74; DBP = diastolic blood pressure; HR = heart rate; LA = left atrial; LVEF = left ventricular ejection fraction; N = number; mm = millimeter; Min = minutes; PV = pulmonary vein; RF = radiofrequency; SBP = systolic blood pressure.

4. Discussion

4.1. Main findings

The main findings in this study i) CB ablation was associated with a significantly decreased level of platelet activation biomarkers at short and long-term in patients who remained in sinus rhythm compared with RF ablation. ii) By contrast no significant change in inflammatory biomarkers was observed between both groups.

4.2. The role of platelet activation in AF

Platelets play a vital role in the pathogenesis of thromboembolism [3,4,10]. Recently, a meta-analysis study confirmed the link between increased platelet activation and thromboembolism complications in AF compared to sinus rhythm [10]. The CD62P, CD40L, PF-4, MPV, P-LCR, and PDW are main platelet indices for assessment of platelet cellular, functional and activation characteristics [3,10,11]. Previous studies have demonstrated that changes in these platelet indices are associated with spontaneous echo contrast, left atrial thrombus, silent cerebral infarction, and ischemic stroke in AF patients [3,10,11].

There is a growing-evidence illustrating difference in peri-procedural complications is due to tissue injury induced by CB and RF energy. RF lesions are characterized by ragged boundaries, with extensive endothelial cell destruction, consequently exposed to local collagen and tissue factor that leads to increase activation of platelet and inflammation, which can promote thrombus formation [5,12]. By contrast, lesions induced by cryoinjury are characterized by well circumscribed, discrete lesion with sharp borders, with minimal endothelial disruption, lower levels of platelet and inflammation pathway activation, which can explain the lower incidence of thrombus formation compared to RF [5,12,13].

Our study provides the evidence that enhanced activation of CD62P, CD40L, and PF-4 levels occur after PV isolation; however, CD62P was significantly lower in CB than RF, further a subsequent decrease was also observed in PDW compared to baseline level in the CB group. CD62P, which can be measured by flow cytometry is emerging as a novel marker for platelet activation. Flow cytometry permits detection of platelet surface biomarkers in their physiological milieu in whole blood and is highly sensitive, being able to detect as few as 1% of activated platelets [14]. Studies have shown an association of higher CD62P and PDW levels with thromboembolic events in patients with AF [3,10].

Our results are consistent with those of existing clinical studies, which reported lower platelet activation using CB than RF ablation, suggesting that CB might be a safer alternative to RF, especially for pulmonary veins ablation [5,12]. Recently, a lower number of microembolic signals was detected when AF ablation was performed with CB as compared with RF [15]. Moreover, additional RF ablation of the left atrium for PV isolation after failed CB procedures was an independent risk factor of cerebral ischemic events [16].

To the best of our knowledge, the present study might be the first study to evaluate prothrombotic biomarkers change at long-term between CB and RF ablation. In the present study, we found that CB ablation significantly decreased all platelet biomarkers CD62P, CD40L, PF-4, MPV, PDW, and P-LCR at long-term in maintained sinus rhythm patients compared to the RF group. Indeed, previous studies have reported reduced platelet activation after AF cardioversion [17] or successful PV isolation with RF ablation [7]. In fact, the tissue repair process is known to stabilize usually within 3 months after ablation. However, some studies reported permanent scarring with cellular necrosis and severe edema that may remain consistent in extent, location and intensity at 3 months or slightly expansion in percentage at later follow-up after RF ablation [18,19]. A worsened level of left atrial edema was detected 6 months after RF ablation [19]. Moreover, extensive RF ablation lesion that may impact the atrial size and systolic function despite maintenance of sinus rhythm than may directly influence short and long-term cerebral embolism as well as prothrombotic state, which are often silent [18,20]. Our results

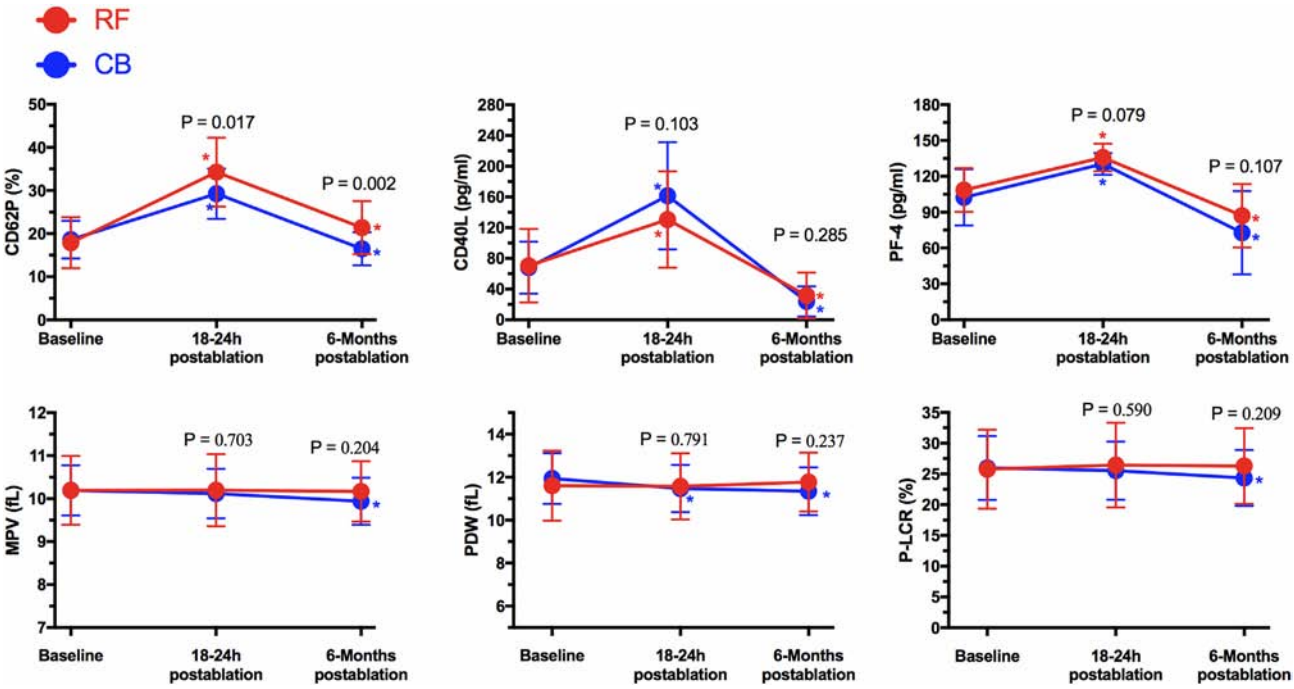

Fig. 1. Platelet biomarkers at different time periods in maintained sinus rhythm patients. Curves are displaying mean and standard deviation (CB in blue and RF in red), * $p < 0.05$ represents significant difference compared with baseline in each group, and p values indicate the comparison at 18–24 h and 6-Months postablation between two groups.

an increased level of platelet activation in the RF group, thus postulate that patients undergoing RF ablation might benefit from the use of antiplatelet agents. Currently, there are controversial reports and variation in clinical practice as to whether antiplatelet therapy are more or less efficacious compared to OAC in AF patients who have successfully remained in sinus rhythm following catheter ablation [1,21–24]. To date, there is no randomized trial to update clinicians regarding anti-thrombotic therapy for successful catheter ablation in AF. In fact, the Optimal Anti-Coagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation (OCEAN; NCT02168829) randomized controlled trial will provide some insight on this issue [21]. The OCEAN trial is evaluating antiplatelet versus anticoagulant strategies for patient with risk factors for stroke and bleeding after successful AF ablation.

By contrast, CB ablation is associated with lower thrombotic risks explicable by reduced platelet activation, better scar healing with no signs of inflammation and edema at 3 months postablation [5,12,13]. Moreover, the Germany ablation registry showed that combinations of death, myocardial infarction and stroke occurred with slightly lower incidence (0.7%) after CB than (1.4%) after RF ablation at 12 months follow up, with no statistically significant. They also pointed out that spectrum and consequence of complications were significantly different between two ablation methods. Which might influence the choice of the ablation method offered for paroxysmal AF patients [25]. Similarly, the FIRE AND ICE trial subgroup analysis significantly favored CB in term of 34% reduction in cardiovascular rehospitalizations, 21% reduction in all-cause rehospitalizations, and 33% reduction in repeated ablations than RF ablation [2]. In addition, CB has been demonstrated in numbers of studies with relatively short procedural and ablation time, and comparable arrhythmia outcome during follow up than RF ablation [1,2,25].

4.3. The role of inflammation in AF

This study noted a comparable response at short-term between CB and RF group, which is consistent with the published data [6,8]. Furthermore, no significant changes were observed in IL-6 and hs-CRP levels at 6-Months postablation compared to baseline in both groups. Indeed, it has been previously reported that inflammatory biomarkers return to baseline level after RF ablation, consistent the notion that the inflammatory process may persist over the long-term as a result of aging or systemic abnormalities such as hypertension and diabetes even in

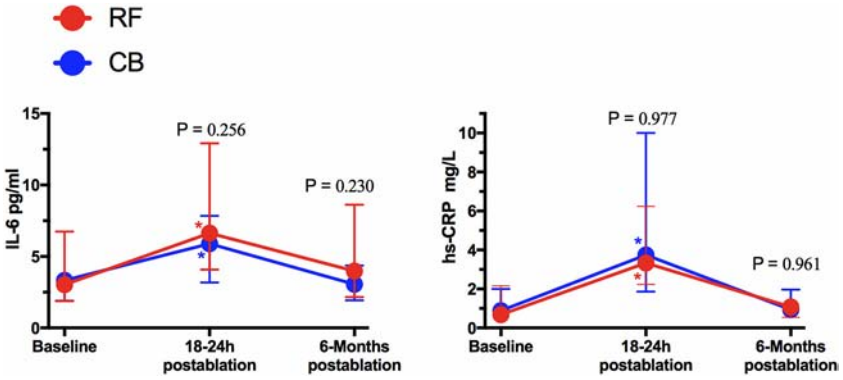

Fig. 2. Inflammatory biomarkers at different time periods in maintained sinus rhythm patients. Curves are displaying median and interquartile ranges (CB in blue and RF in red), * $p < 0.05$ represents significant difference compared with baseline in each group, and p values indicate the comparison at 18–24 h and 6-Months postablation between two groups.

patients who do not experience a postablation AF recurrence [8,26]. Indeed, persistent levels of inflammation can predispose to atrial remodeling and late AF recurrence even in patients remaining in sinus rhythm after catheter ablation [8].

4.4. Limitations

Several limitations of this study should be noted. First, the present study was carried out in a single center and included comparatively small number of patients. Second, the main objective of this study to evaluate short and long-term changes in prothrombotic biomarkers between CB and RF energies; Though the changes in the platelet activation and inflammation response are complex and the measurement of these biomarkers are represented by histopathologically, which may not adequately present the thromboembolism state in AF patients. Moreover, no magnetic resonance imaging has been taken to detect ischemic stroke risk after procedure and at end of the fellow-up. However, none of the patient experienced major clinical complications including cerebrovascular accident, phrenic nerve palsy, and atrioesophageal fistula in either group during or after procedure and throughout the fellow-up. Third, the effect of OAC particularly dabigatran or other medications used on these biomarkers might not be excluded. Recently a study showed that dabigatran treatment in AF patients increases platelet reactivity by enhancing the thrombin receptor density on platelets [27]. In present study, the pre- and postablation treatments profiles were comparable between both groups that might similarly affect platelet thrombin receptor reactivity. In addition, this study excluded patients on antiplatelet and nonsteroidal anti-inflammatory drugs. Forth, the AF recurrence percentage might be underestimated during the follow-up period because of lack of an implantable loop monitor and despite the use of 7 days Holter recording in the present study. Therefore, we recommend large prospective randomized trials for the clinical endpoints to evaluate the platelet and inflammatory biomarkers at short and long-term after RF and CB ablation, and consideration of pre- and post-ablation anti-thrombotic therapy duration between different energy ablation treatments in AF patients.

5. Conclusions

CB ablation was associated with less platelet activation after PV isolation and decreased platelet activation in maintained sinus rhythm patients at long-term compared to RF group. Future studies are needed to explore whether differences in the risk of thromboembolism are found between CB and RF techniques, and whether these are associated with platelet activation biomarkers.

Author contributions

All authors have made substantial contributions to the conception (YX, KB, GT, YD, CR) and/or design (YX, KB, YD, CR, SW) of the work; acquisition of data (KB, XY, BD, LG, ZW, XG); analysis of data (KB, YX, XY, YL, LG); interpretation of data (YL, BD, LW, ZW, XY, GT); and drafting of the work (KB, YX, GT, YD, LW, SW). All authors contributed in revising the work and also approved the final version to be published and agreed to be accountable for all aspects of the work.

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Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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