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ORIGINAL ARTICLE

Endothelial damage and thromboembolic risk after pulmonary vein isolation using the latest ablation technologies: a comparison of the second-generation cryoballoon vs. contact force-sensing radiofrequency ablation

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Abstract
Experimental data suggest that cryoenergy is associated with less endothelial damage and thrombus formation than radiofrequency energy. This study aimed to compare the impact of pulmonary vein isolation (PVI) on the endothelial damage, myocardial damage, inflammatory response, and prothrombotic state between the two latest technologies, second-generation cryoballoon (CB2) and contact force-sensing radiofrequency catheter (CFRF) ablation. Eighty-six paroxysmal atrial fibrillation (AF) patients (55 men; 65 ± 12 years) underwent PVI with either the CB2 ($n = 64$) or CFRF ($n = 22$). Markers of the endothelial damage (L-arginine/asymmetric dimethylarginine [ADMA]), myocardial injury (creatine kinase-MB [CK-MB], troponin-T, and troponin-I), inflammatory response (high-sensitive C-reactive protein), and prothrombotic state (D-dimer, soluble fibrin monomer complex, and thrombin–antithrombin complex) were determined before and up to 24-h post-procedure. The total application time was shorter (1,460 ± 287 vs. 2,395 ± 571 [sec], $p < 0.01$) and total procedure time tended to be shorter (199 ± 37 vs. 218 ± 38 [min], $p = 0.06$) with CB2 than CFRF ablation. The amount of myocardial injury was greater (CK-MB: 45 ± 17 vs. 11 ± 3 [IU/l], $p < 0.01$) with CB2 than CFRF ablation. The L-arginine/ADMA ratio was lower (160 ± 51 vs. 194 ± 38, $p = 0.028$) after CB2 than CFRF ablation. Inflammatory and all prothrombotic markers were significantly elevated post-ablation; however, the magnitude was similar between the two groups. During a mean follow-up of 20 ± 6 months, the single-procedure AF freedom was similar between the CB2 and CFRF groups (60/64 vs. 20/22, $p = 0.82$). CB2-PVI produces significantly lesser endothelial damage with greater myocardial injury than CFRF-PVI; however, similar anticoagulant regimens are required during the peri-procedural periods in both technologies.

Keywords Pulmonary vein isolation · Endothelial damage · Atrial fibrillation · Cryoballoon

Introduction

Pulmonary vein isolation (PVI) has become the cornerstone of atrial fibrillation (AF) ablation therapy in paroxysmal AF [1, 2]. The cryoballoon (CB) is a recently introduced technology for PVI [3], and a prospective randomized study [4] clarified that radiofrequency (RF) ablation and CB ablation were comparable with respect to the efficacy and safety of catheter ablation of paroxysmal AF. Both technologies have currently benefited from significant material improvements with the advent of the second-generation CB [5] and contact force (CF)-sensing RF catheters [6], both showing improved outcomes compared with the older models. The selection of the energy for achieving PVI in paroxysmal AF still remains at the discretion of the operator, whereas the spectrum and relevance of complications significantly differ between the two technologies [7].

RF ablation creates endothelial damage, which leads to platelet adhesion, activation, aggregation, and fibrin generation, and, thus, to thrombus formation at the site of injury

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[8]. A histological observation clarified that cryoablation results in well-delineated, discrete lesions with preservation of the tissue ultrastructure, including the endothelial cell layer, while RF lesions have serrated edges with more extensive endothelial cell destruction [9]. However, no studies have examined the impact of the PVI on endothelial dysfunction or compared the magnitude of the endothelial dysfunction following ablation between CB and CF-guided RF ablation. Furthermore, the comparisons of the myocardial damage, inflammatory reactions, or thrombogenic state during the peri-procedural period between these two latest different technologies have also not been sufficiently clarified. Accordingly, the purpose of this study was to clarify these points.

Methods

Study population

This retrospective observational study consisted of 86 patients with drug-refractory paroxysmal AF in whom the biomarkers were evaluated during the peri-procedural period of the PVI using either the second-generation CBs ($n=64$) (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) or CF-sensing irrigated-tip RF catheters ($n=22$) (SmartTouch or SmartTouch Surround Flow, Biosense Webster, Diamond Bar, CA, USA) between May 2015 and March 2017. The ablation device was selected according to the operators' preference. Patients with persistent AF, additional LA substrate modification, and hemodialysis were excluded from the study. AF was classified according to the latest guidelines [2]. All patients gave their written informed consent. The study protocol was approved by the hospital's institutional review board. The study complied with the Declaration of Helsinki.

Procedural protocol

All antiarrhythmic drugs except for amiodarone were discontinued for at least five half-lives prior to the procedure. Cardiac enhanced computed tomography and transesophageal echocardiography were performed pre-procedurally to evaluate the PV anatomy and to exclude any left atrial (LA) thrombi. The surface electrocardiogram and bipolar intracardiac electrograms were continuously monitored and stored on a computer-based digital recording system (EP-WorkMate, St. Jude Medical, Minneapolis, MN, USA). Direct oral anti-coagulants (DOACs) were interrupted on the procedural day, but warfarin was uninterrupted throughout the peri-procedural period. The procedure was performed under moderate sedation obtained with dexmedetomidine and thiopental. A bolus of 5000 U of heparin was administered immediately following the venous access, and heparinized saline was additionally infused to maintain the activated clotting times at 300–350 s. A 5-Fr 10-pole bipolar catheter (Inquiry, St. Jude Medical) was placed in the coronary sinus via the femoral vein. A single transseptal puncture was performed using an RF needle (Baylis Medical., Montreal, QC, Canada) guided by intracardiac echography (SoundStar, Biosense Webster).

In the CB group, a 15-Fr steerable sheath (Flexcath Advance, Medtronic) was inserted into the LA. A spiral mapping catheter (achieve, medtronic) was used for mapping the PV potentials. Complete occlusion with a 28-mm second-generation CB was confirmed by injecting contrast medium and pressure monitoring. This was followed by double 3-min freezes. To avoid any phrenic nerve injury, CB applications were applied while monitoring the right diaphragmatic electromyography during phrenic nerve pacing. When the balloon nadir temperatures exceeded −60 °C or the luminal esophageal temperature on the esophageal probe (SensiTherm, St. Jude Medical, or Esophastar, Japan Life Line, Tokyo, Japan) reached 25 °C, the cryoapplications were discontinued. Touch-up ablation was performed with an 8-mm tip cryocatheter (Freezor MAX, Medtronic) or 8-mm tip RF catheter (Ablaze, Japan Life Line) if necessary.

In the RF group, three long sheaths (SL0, St. Jude Medical) were introduced into the LA. Ipsilateral PVs were circumferentially ablated with a double-Lasso technique (Lasso, Biosense Webster, or Libero, Japan Life Line) guided by a 3-D mapping system (CARTO3, Biosense Webster) (Fig. 1). RF current was delivered point-by-point with a CF-sensing irrigated-tip RF catheter with a power of up to 35 W and CF > 10 g. The power was limited to 25 W on the posterior wall close to the esophagus.

In both groups, the procedural endpoint was bidirectional conduction block between the PVs and LA verified by the circular mapping catheter, including a 30-min waiting time from the last application. Any adenosine triphosphate-provoked dormant PV conduction was eliminated by additional applications.

Post-ablation management and follow-up

After the procedure, intravenous heparin was administered for 24 h, and in-hospital ECG monitoring was continued for 3–5 days. All patients were prescribed proton-pump inhibitors for 1 month after the procedure. No antiarrhythmic drugs were prescribed after the procedure except for patients with a highly symptomatic early recurrence of AF. Regular follow-up consisted of outpatient clinic visits at 1, 2, and 3 months after the procedure. Subsequent follow-up visits consisted of a clinical interview, 12-lead ECG, and/or 24-h Holter ECG recordings every 3 months. Anticoagulation was continued for at least 3 months. Recurrence was defined if an atrial

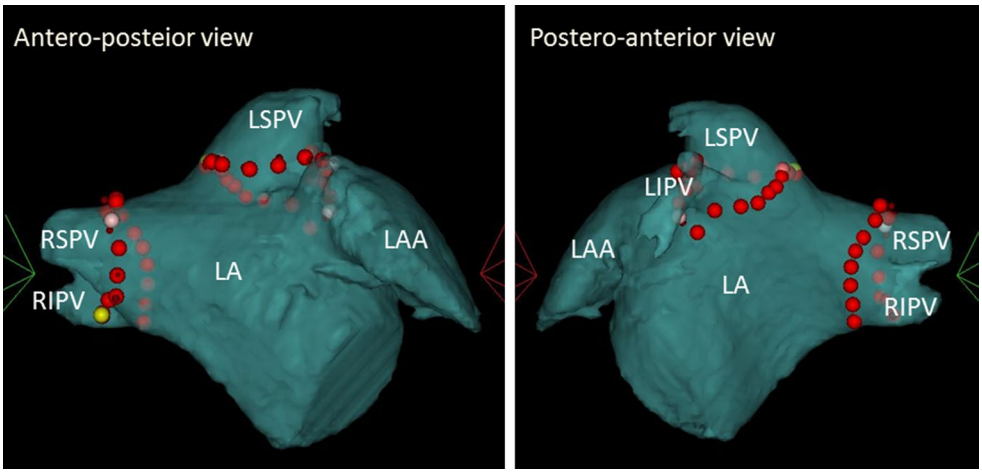

Fig. 1 Representative encircling-PV isolation lines on a 3-dimensional mapping system in a patient undergoing radiofrequency catheter ablation. The red tags indicate the ablation sites. *LA* left atrium, *LAA* LA appendage, *LI(S)PV* left inferior (superior) pulmonary vein, *RI(S)PV* right inferior (superior) pulmonary vein

arrhythmia lasting longer than 30 s was documented after a 3-month blanking period following the latest guidelines.

Blood sampling and biomarkers

Blood samples were taken for analysis of the creatine kinase-myoglobin binding (CK-MB), high-sensitive C-reactive protein (hs-CRP), brain natriuretic peptide (BNP), troponin-T, troponin-I, D-dimer, soluble fibrin monomer complex (SFMC), and thrombin–antithrombin complex (TAT) levels 1 day before and 1 day after the procedure. To evaluate the endothelial damage, blood samples were taken from the LA before and immediately after the PVI during the procedure, and the asymmetric dimethylarginine (ADMA) level was also measured.

Statistical analysis

Continuous data are expressed as the mean ± standard deviation for normally distributed variables or as the median (25th and 75th percentiles) for non-normally distributed variables. The continuous and categorical variables were compared with the Student's *t* test and Chi-square test, respectively. The time-course patterns of each parameter were compared with a two-way layout ANOVA between the CB group and RF group. Sequential data measurements in each group were analyzed with Bonferroni's multiple comparison. A Kaplan–Meier analysis was used to determine the percentage of patients free from recurrence. The difference in the arrhythmia-free survival was evaluated using the log-rank test.

Results

Patient characteristics and procedural results

Among the total 86 patients (55 men, 65 ± 12 years), 64 (74%) underwent cryoballoon ablation (CB group), and the other 22 (26%) RF ablation (RF group). The baseline clinical, echocardiographic, and laboratory data did not significantly differ between the two groups (Table 1). In the CB group, 30 (47%) patients required touch-up ablation to complete the PVI either with a cryocatheter ($n = 2$) or RF catheter ($n = 28$). The total application time of the touch-up ablation was 239 ± 0 and 167 ± 73 s for the cryocatheter and RF catheter, respectively. Finally, an electrical PVI was successfully achieved in all 86 patients.

The total application time was significantly shorter and total procedure time tended to be shorter in the CB group than RF group (Table 2). The number of patients who experienced an electric cardioversion during the procedure was comparable between the two groups. Transient right phrenic nerve injury and gastric hypomotility were observed in two

Table 1 Patient characteristics of the total study population

	CB group	RF group	*p value*
Number of patients, *n*	64	22	
Age, (years)	64 ± 12	67 ± 12	0.41
Male gender, *n* (%)	40 (63)	15 (68)	0.80
BMI, (kg/m^2)	23 ± 3	24 ± 4	0.83
Hypertension, *n* (%)	32 (50)	10 (45)	0.81
History of AF, (month)	40 ± 45	28 ± 30	0.24
CHADS2	0.9 ± 1.1	1.3 ± 1.2	0.17
CHA2DS2-VASc	1.9 ± 1.5	2.2 ± 1.6	0.41
LVEF, (%)	68 ± 8	67 ± 8	0.73
Left atrial diameter, (mm)	35 ± 5	36 ± 5	0.45
LAA flow velocity, (cm/s)	62 ± 24	65 ± 23	0.52
BNP level, (pg/ml)	43 ± 47	73 ± 116	0.09
Creatinine, (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	0.71

The values are the mean ± standard deviation or number (%) of patients

BMI body mass index, *BNP* brain natriuretic peptide, *CB* cryoballoon ablation, *LAA* left arterial appendage, *LVEF* left-ventricular ejection fraction, *PAF* paroxysmal atrial fibrillation, *RF* radiofrequency

patients each in the CB group. No other complications were observed.

Myocardial damage and inflammatory response

The CK-MB was evaluated in 84 patients and hs-CRP in all 86 patients, and the troponin-T and troponin-I levels were measured in 27 (20 in the CB group and 7 in the RF group) patients. The CK-MB levels significantly increased after the procedure in both groups, and the time-course pattern significantly differed between the CB and RF groups ($p < 0.01$) (Fig. 2a). Both troponin-T and troponin-I levels also significantly increased after the procedure in both groups, and the time-course pattern significantly differed between the CB and RF groups ($p = 0.03$ and $p < 0.01$) (Fig. 2b, c). The hs-CRP level became significantly elevated from 0.18 ± 0.52 to 1.25 ± 0.89 mg/dl after the procedure in a total of 86 patients ($p < 0.01$), and the time-course pattern was similar between the two groups ($p = 0.53$). In 69 patients (54 in the CB group and 15 in the RF group) in whom the BNP level was assessed, the value was similar before and after the procedure (48 ± 76 vs. 50 ± 43 pg/ml, $p = 0.73$), and the time-course pattern was similar between the two groups ($p = 0.47$).

Table 2 Procedural data in the two groups

	CB group $n = 64$	RF group $n = 22$	*p value*
Total ablation time (sec)	$1{,}460 \pm 287$	$2{,}396 \pm 571$	< 0.001
Total fluoroscopy time (min)	19 ± 8	23 ± 13	0.09
Total procedure time (min)	199 ± 37	218 ± 38	0.06
Number of patients who experienced cardioversion, *n* (%)	17 (27)	4 (13)	0.57

The values are the mean ± standard deviation or number (%) of patients

CB cryoballoon ablation, *RF* radiofrequency

Endothelial damage

In 38 patients (26 in the CB group and 12 in the RF group), the L-arginine and ADMA levels were evaluated, and the baseline patient characteristics were similar between the two groups (Table 3). The baseline L-arginine/ADMA ratio was comparable between the two groups (178 ± 36 vs. 177 ± 43; $p = 0.93$). The time-course pattern of L-arginine/ADMA ratio significantly differed between the two groups ($p = 0.02$) (Fig. 3). The ratio after the PVI significantly increased in the CB group ($p = 0.04$), but was similar in the RF group ($p = 0.16$) as compared to that before the PVI. After excluding 12 patients who required touch-up ablation with an RF

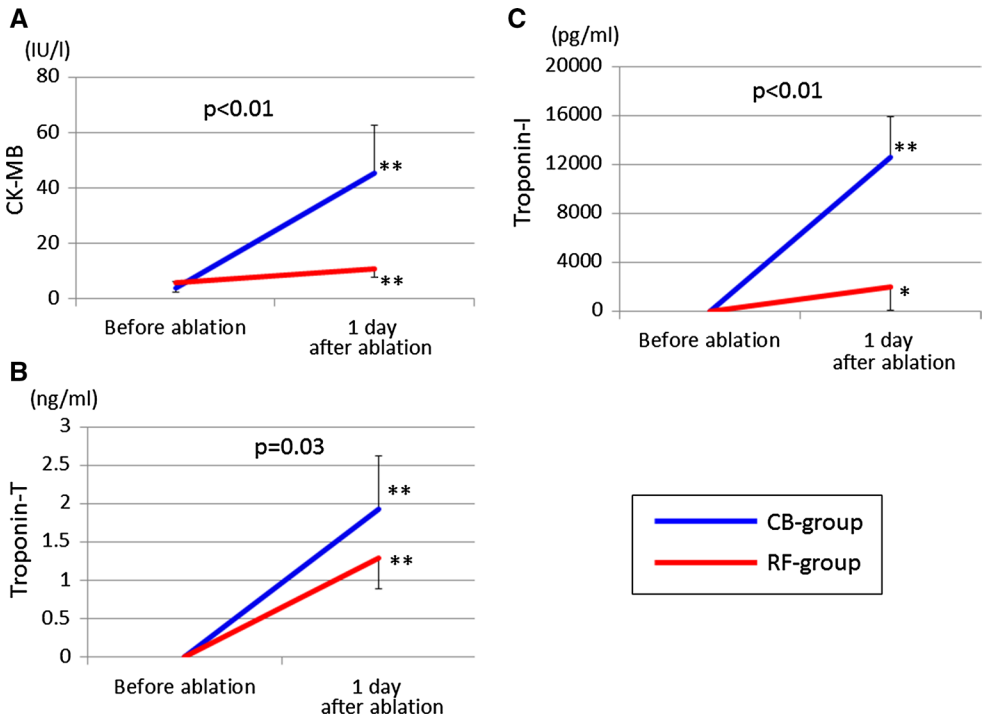

Fig. 2 Transition of the myocardial injury markers (**a** CK-MB, **b** troponin-T, and **c** troponin-I) before and 1 day after the procedure. The *p* values indicate the comparison between the CB and RF groups. There were significant differences between the two groups. $*p < 0.05$ (compared with the baseline), $**p < 0.01$ (compared with the baseline)

catheter in the CB group, the study results remained the same.

Prothrombotic markers

During the peri-procedural period, DOACs were used in all patients except for 2 (2%) patients with warfarin therapy in the CB group. The D-dimer level was evaluated in 80 (62 in the CB group and 18 in the RF group) patients, and SFMC and TAT levels in 72 (56 in the CB group and 16 in the RF group) patients. The D-dimer values became significantly elevated after the procedure in the total population ($p=0.047$), and the time-course pattern was similar between the 2 groups ($p=0.85$) (Fig. 4a). The SFMC and TAT levels significantly increased after the procedure in the CB group ($p=0.01$ and $p<0.01$) and RF group ($p<0.01$ and $p<0.01$), and the time-course pattern was similar between the two groups ($p=0.60$ and $p=0.92$) (Fig. 4b, c).

Table 3 Patient characteristics of the patients in whom L-arginine/ADMA was evaluated

	CB group	RF group	*p value*
Number of patients, *n*	26	12	
Age, (years)	62 ± 11	66 ± 14	0.39
Male gender, *n* (%)	15 (58)	8 (67)	0.60
BMI, (kg/m^2)	24 ± 3	24 ± 3	0.84
Hypertension, *n* (%)	11 (42)	4 (33)	0.60
History of AF, (month)	48 ± 58	27 ± 31	0.25
CHADS2	0.8 ± 1.2	1.4 ± 1.6	0.19
CHA2DS2-VASc	1.7 ± 1.6	2.3 ± 1.9	0.31
LVEF, (%)	68 ± 7	67 ± 9	0.61
Left atrial diameter, (mm)	36 ± 5	37 ± 6	0.49
LAA flow velocity, (cm/s)	60 ± 20	64 ± 25	0.59
BNP level, (pg/ml)	39 ± 32	43 ± 39	0.73
Creatinine, (mg/dl)	0.8 ± 0.1	0.9 ± 0.2	0.19

The values are the mean ± standard deviation or number (%) of patients

ADMA asymmetric dimethylarginine, *BMI* body mass index, *BNP* brain natriuretic peptide, *CB* cryoballoon ablation, *LAA* left arterial appendage, *LVEF* left-ventricular ejection fraction, *PAF* paroxysmal atrial fibrillation, *RF* radiofrequency

Follow-up data

After a 3-month blanking period, 60 patients (94%) in the CB group and 20 (91%) in the RF group were free from any recurrent arrhythmias during a mean follow-up period of 20 ± 6 months (range 8–30 months), and the single-procedure AF freedom was similar between the two groups ($p=0.82$) (Fig. 5). No thromboembolic events were observed during the peri-procedural period in both groups. The LA diameter became significantly decreased 1 month after the procedure as compared to baseline (from 35.2 ± 5.0 to 34.0 ± 4.0 mm, $p<0.01$).

Discussion

The results of this study demonstrated the following findings: (1) CB ablation was associated with less endothelial damage than RF ablation; (2) the amount of the myocardial injury was significantly greater after CB than RF ablation; (3) the inflammatory response and coagulate sate were comparable between the two groups during the peri-procedural

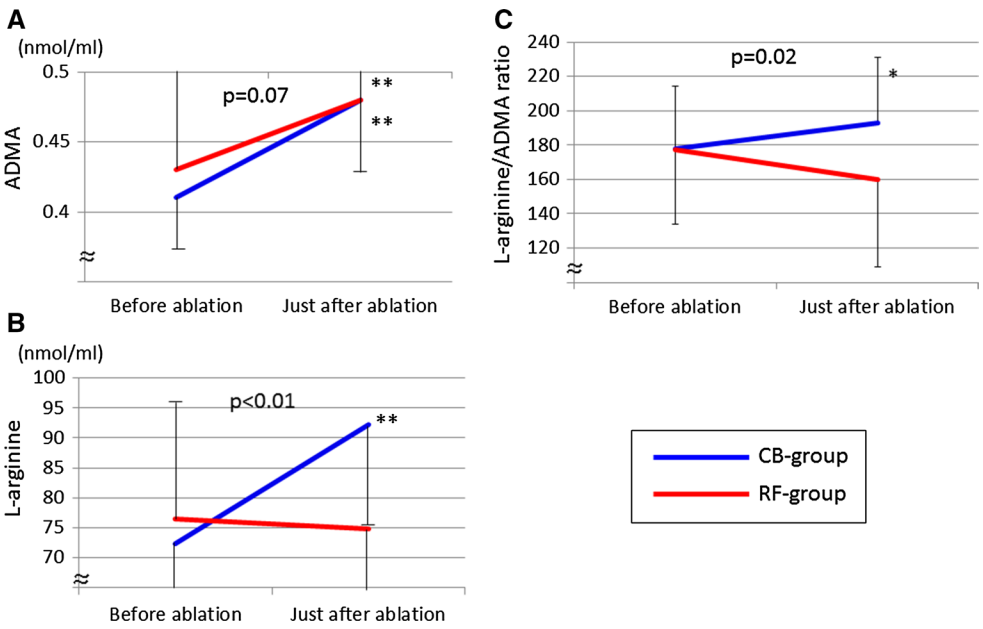

Fig. 3 Transition of the ADMA, L-arginine, and L-arginine/ADMA ratio before and after the procedure. The *p* values indicate the comparison between the CB and RF groups. The time course of the L-arginine/ADMA ratio was significant different between the two groups. *$p<0.05$ (compared with the baseline), **$p<0.01$ (compared with the baseline)

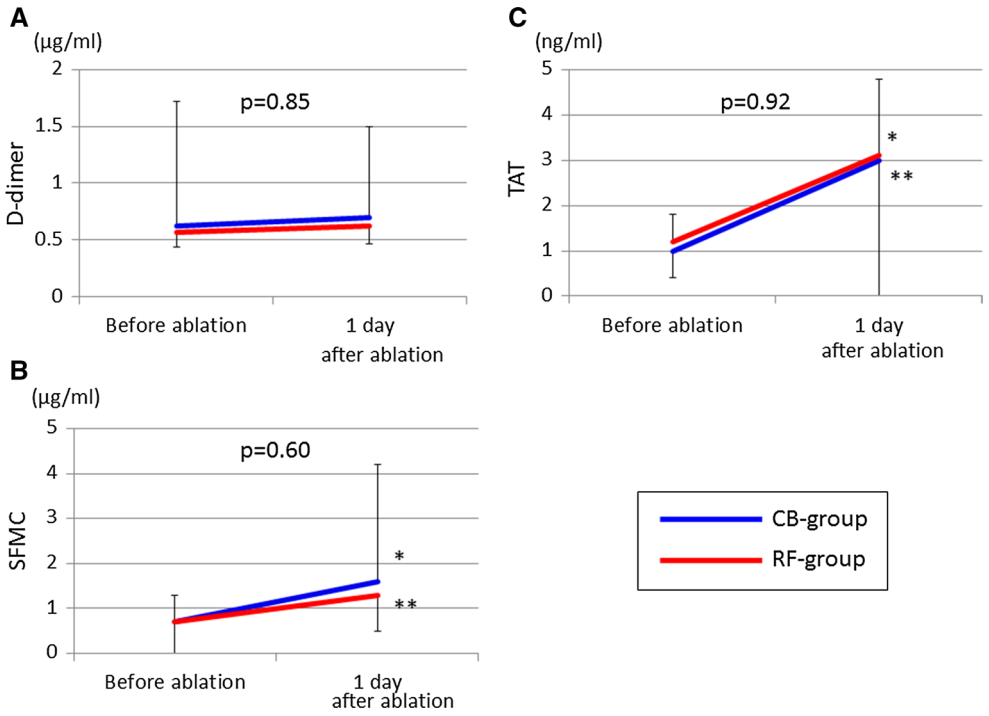

Fig. 4 Transition of the prothrombotic markers (**a** D-dimer, **b** SFMC, and **c** TAT) before and 1 day after the procedure. The *p* values indicate the comparison between the CB and RF groups. There were no differences in the prothrombotic markers between two groups. $*p<0.05$ (compared with the baseline), $**p<0.01$ (compared with the baseline)

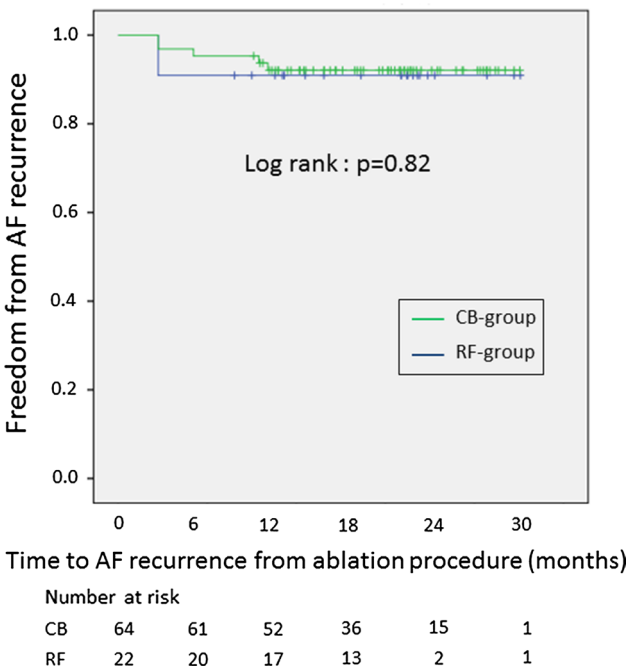

Fig. 5 Kaplan–Meier curves showing the freedom from AF recurrence after the cryoballoon ablation (CB group) or the radiofrequency ablation (RF group). The single-procedure AF freedom at 20 ± 6 months of follow-up was similar between the two groups

period; (4) the single-procedure AF freedom was equivalent between the two groups.

Cryoablation and RF ablation

The mechanisms of tissue injury in cryoablation and RF ablation considerably differ. Tissue heating with RF energy is a result of resistive heating at the interface between the catheter and tissue, and hyperthermia-induced tissue necrosis and coagulation. This can cause activation of the cascade of thrombin generation and platelet activation. The mechanisms of thrombogenesis during RF ablation include endothelial disruption, coagulation necrosis, electroporation injury, mechanical damage of the vessel wall, and heating of the circulating blood elements [10]. In contrast, the mechanism of hypothermic tissue injury is highly complex [11]. Cryoablation has been shown to result in lesions characterized by dense homogeneous fibrosis with well-delineated border zones and preservation of the tissue ultrastructure, including the endothelial cells [9]. A positive correlation was found between the amount of the RF injury and thrombus volume, whereas no such correlation existed for the lesions produced by cryoenergy [9]. In an in vitro blood circulation model, the RF procedure induced significantly more blood cell damage, platelet activation, and clotting, which

may determine the endothelial activation and oxidative stress induction, than did the cryoapplication procedure [12].

Myocardial injury and inflammation

The cardiac enzyme, CK-MB, and myofibrillar proteins, troponin-T and troponin-I, are sensitive and specific markers of myocyte damage, and an elevated level reflects the amount of myocardial injury. The second-generation CB provides more effective cooling than the first-generation balloon [5], and CF-sensing RF catheters create more effective lesions than the conventional RF catheters [6]. The present study initially compared the amount of the myocardial injury between the two latest technologies, and clarified that more extensive lesions were created by the second-generation CB as compared to the CF-sensing RF catheter. This might be explained by the different lesion configurations between balloon ablation and point-by-point linear lesions. Given these results, a subsequent higher inflammatory response and prothrombotic state might be expected after CB ablation.

Inflammation is being increasingly recognized to play a significant role in the genesis and perpetuation of AF [13]. RF ablation triggers an inflammatory response, and histopathologic studies have established that RF ablation induces necrosis followed by inflammatory infiltrates leading to a fibrotic scar. In the present study, the magnitude of the hs-CRP value elevation was comparable before and 1 day after the procedure in the two groups despite a different amount of myocardial injury. These results suggest that cryoablation provokes a relatively lesser inflammatory response than RF ablation per the same amount of myocardial injury.

Endothelial damage

ADMA is an endogenous inhibitor of eNOS and is known to result in endothelial dysfunction in experimental human studies [14]. Nitric oxide has potent antithrombotic properties on the endothelium and inhibits platelet and monocyte adhesion [15]. Several studies support the view that the ratio between L-arginine and ADMA is important for the regulation of eNOS activity [16]. Clinically, increased levels of ADMA or an impaired ratio of L-arginine/ADMA have been reported in different disease states with a high risk for numerous cardiovascular diseases [17]. The relationship between AF and ADMA, or the rhythm control outcome after electrical cardioversion and L-arginine/ADMA ratio have been reported in the previous studies [18, 19]. However, to the best of our knowledge, this is the first study to compare the impact of the PVI on the L-arginine/ADMA ratio between the different energy sources. Our study found that CB ablation was associated with less endothelial damage than RF ablation, suggesting different thromboembolic risks after PVI. This observation is consistent with the histological findings that the endothelial structure was preserved after cryoablation as compared to RF ablation in canine hearts [9].

Prothrombotic markers

TAT, SFMC, and D-dimer generally indicate thrombogenesis, coagulability, and fibrinolysis. TAT is formed by an irreversible interaction of antithrombin III and thrombin, after thrombin is cleaved from prothrombin. The formation of D-dimer follows chronologically after thrombin is generated and reflects lysis of fibrin. The activation of blood clotting may be attributable to several factors, such as catheter manipulation, myocardial injury caused by ablation, and the anticoagulant regimen [20]. In the present study, the level of the prothrombotic markers was comparable between the CB group and RF group at baseline. After the ablation procedures, we noticed a significant rise in the blood-clotting activation with respect to the baseline values, but there were no differences in the magnitude of the elevation between the groups. Although it seems plausible that cryoablation provokes a lesser prothrombotic state, considering the greater amount of myocardial injury, our study results suggested that a similar anticoagulation regime was required during the peri-procedural period of the PVI for the second-generation CB as well as RF ablation.

Study limitations

First, this was a retrospective observational study, and the study population, especially in the RF group, was relatively small. Second, each biomarker was evaluated during the peri-procedural period, but the data during the chronic phase were lacking. A further study is necessary to elucidate whether or not the acute damage from the CB ablation or CF-guided RF ablation might have an impact on the endothelial dysfunction during the chronic phase or have the potential to cause cardiovascular events. Third, the ablation device was selected according to the operators' preference and was not randomized.

Conclusions

The L-arginine/ADMA ratio after the PVI was significantly lower for the second-generation CB than CF-sensing RF ablation despite a significantly greater amount of myocardial injury post-CB ablation. On the contrary, both technologies induced a similar inflammatory response and blood-clotting activation. Our study results suggested that cryoablation produces significantly lesser endothelial damage than RF ablation; however, a similar anticoagulant regimen is required during the peri-procedural period of both technologies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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