# Impact of different energy sources on coagulation biomarkers and silent cerebral events in balloon-based ablation for atrial fibrillation

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**BACKGROUND** Different energy sources of balloon-based ablation for pulmonary vein isolation cause different kinds of endothelial damage and coagulation responses associated with thromboembolic risk.

**OBJECTIVES** The study sought to compare the impact of different balloon-based ablation, cryoballoon ablation (CBA) and laser balloon ablation (LBA), on coagulation/fibrinolysis biomarkers and silent cerebral events (SCEs) in paroxysmal atrial fibrillation.

**METHODS** Paroxysmal atrial fibrillation patients who underwent pulmonary vein isolation using either CBA (n = 52) or LBA (n = 53) without radiofrequency touch-up ablation were eligible. Time course (day 0 [before ablation], day 1, day 2, and day 28) of myocardial enzymes and inflammatory and coagulation/fibrinolysis biomarkers was evaluated during the perioperative period. Brain magnetic resonance imaging was performed within 2 days after the procedure to evaluate SCEs.

**RESULTS** There was no difference in patient characteristics between CBA and LBA.CBA had greater myocardial injury (troponin I and creatine kinase-MB) and lower inflammatory reaction (white blood cell count and neutrophil/lymphocyte ratio) than LBA. The coagulation biomarkers maximally increased by day 2 and then decreased in both groups. In day 28, the serum prothrombin fragment 1+2 and D-dimer levels in LBA were significantly higher than the values in CBA. The fibrinolysis biomarker (plasmin-α2 plasmin inhibitor complex) did not increase after the procedure in either group. The incidence of SCEs was comparable between CBA and LBA (11% vs 15%; $P = .591$). No thromboembolic event was observed.

**CONCLUSION** CBA and LBA had different effects on myocardial injury, inflammatory reaction, and coagulation activity but did not affect the incidence of thromboembolic events. LBA had significantly higher coagulation activity in day 28 and may require more careful postprocedural anticoagulation than CBA.

**KEYWORDS** Atrial fibrillation; Catheter ablation; Cryoballoon ablation; Laser balloon ablation; Coagulation biomarker; Silent cerebral event

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## Introduction

Balloon-based ablation with various energy sources have been introduced as an alternative to radiofrequency (RF) catheter ablation. Cryoballoon ablation (CBA) is a simple and effective procedure for pulmonary vein isolation (PVI) in atrial fibrillation (AF) patients.[1] Laser balloon ablation (LBA) uses laser energy to ablate tissue for PVI and offers real-time visualization of the balloon positioning and the energy delivery through the endoscopy equipped with the balloon catheter.[2] Both systems showed similar efficacy for treatment of paroxysmal AF.[1–3]

Although the technologies have been improved, catheter ablation causes endothelial/myocardial injury and inflammatory response in the left atrium (LA), which activates coagulation cascade, potentially leading to thrombus formation and thromboembolic events.

In previous experimental studies, the different energy sources of catheter ablation caused different endothelial injury and myocardial damages in histological examinations; lesions by LBA are caused by heat, whereas those by CBA are caused by extreme cold. The different characteristics of CBA and LBA lesions would have different effects on the coagulation and fibrinolysis cascades associated with thromboembolic risks.[4–6]

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## KEY FINDINGS

- The isolated antral surface area measured using electroanatomic mapping was unchanged between cryoballoon ablation (CBA) and laser balloon ablation (LBA).
- Myocardial injury biomarkers after CBA were significantly higher than those after LBA, but inflammatory biomarkers after LBA were significantly higher than those after CBA.
- There were significant differences in the time course of coagulation biomarkers between CBA and LBA: LBA remained significantly higher in coagulation activity than CBA in the first month after the procedure.
- The incidence of silent cerebral events was unchanged between CBA and LBA, and no thromboembolic event was observed in either group during the follow-up.

A silent cerebral event (SCE) is defined as an acute new brain lesion in a patient without clinically apparent neurological deficit. SCE lesions detected by brain magnetic resonance imaging (MRI) are usually small but are typical of cerebral thromboembolisms; they are frequently observed in asymptomatic patients who have undergone AF ablation. Although an SCE usually does not cause neurocognitive dysfunction, it may be a surrogate marker for the potential thromboembolic risk under specific ablation procedure.[7,8]

The aim of this study was to compare the impacts of CBA and LBA on serum coagulation/fibrinolysis biomarkers and SCEs in paroxysmal AF patients.

## Methods

### Patients

This was a single-center, nonrandomized, prospective study. A total of 150 consecutive PAF patients undergoing index catheter ablation using either CBA or LBA at Fujita Health University from June 2020 to February 2023 were eligible. The protocol was approved by the review board of Fujita Health University School of Medicine and written informed consent was obtained from all patients (HM20-273). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Baseline demographics and clinical information were obtained, and laboratory examinations were performed before the procedure. Transthoracic echocardiography was performed before catheter ablation to assess LA diameter, left ventricular systolic/diastolic dimensions, and left ventricular ejection fraction. A 3-dimensional image of the LA/pulmonary vein (PV) geometry was reconstructed by cardiac computed tomography imaging.

All patients received oral anticoagulation therapy with non–vitamin K antagonist oral anticoagulant at appropriate doses for $\geq$4 weeks prior to hospital admission. Transesophageal echocardiography was performed 1 day before catheter ablation to detect LA thrombus. In patients with factor Xa inhibitor, the anticoagulants were switched to dabigatran before catheter ablation.[9] Thus, all patients took dabigatran without interruption during the procedure and continued dabigatran for at least 1 month after the procedure. All antiarrhythmic drugs were stopped 5 days prior to the procedure. No patient was being treated with amiodarone. Oral anticoagulation therapy was continued for at least 3 months after the procedure.

Exclusion criteria were as follows: patients who required RF touch-up ablation; patients with common PV; patients with a left ventricular ejection fraction of $<$45%; patients with previously diagnosed structural heart disease, cardiac sarcoidosis, and moderate/severe valvular heart disease; patients under 18 years of age and those who were pregnant; patients with creatinine clearance (calculated by Cockcroft-Gault formula) $<$30 mL/min and those on hemodialysis; patients who had LA appendage thrombus on transesophageal echocardiography before the procedure; and patients with enlarged LA diameter ($>$ 50 mm) and mechanical valves.

### Procedure

PVI was performed using either CBA or LBA based on physician's choice/preference (Figure 1). In all patients, the procedure was performed under deep sedation with a continuous intravenous infusion of dexmedetomidine hydrochloride and propofol, and additional boluses of midazolam as previously described.[10] In all patients a temperature-monitoring catheter was inserted into the esophagus and the esophageal temperature was monitored throughout the procedure; the temperature limit was set to 18 °C for CBA and 39 °C for LBA. If a patient showed AF rhythm in the electrophysiological laboratory, electric cardioversion was performed to restore sinus rhythm.

After the initial value of activated clotting time (ACT) was measured, a bolus of 5000–10,000 international units of unfractionated heparin (50–100 U/kg) was administered before transseptal puncture to achieve an ACT $>$300 seconds. ACT was measured every 20 minutes after the first heparin shot and additional heparin boluses were administered to maintain the ACT $>$300 seconds.

A decapolar catheter was advanced into the coronary sinus via the internal jugular vein. An 8-F intracardiac echocardiography catheter (AcuNav [Biosense Webster], ViewFlex [Abbott]) was inserted into the right atrium via a 10-F short sheath in the right femoral vein; transseptal puncture was performed under intracardiac echocardiography and fluoroscopic guidance. An 8-F long sheath (SL1; Abbott) was then advanced into the LA. A ring-shaped decapolar catheter (Libero; Japan Life Line) was used for mapping. EnSite NavX (Abbott) was used to create a 3-dimensional electroanatomic voltage map of the LA and to integrate the voltage map with the computed tomography imaging reconstruction of the LA. The contrast fluoroscopy image of the LA was also obtained.[10]

In CBA, the transseptal sheath was exchanged over a guidewire for a 15-F steerable sheath (FlexCath Advance;

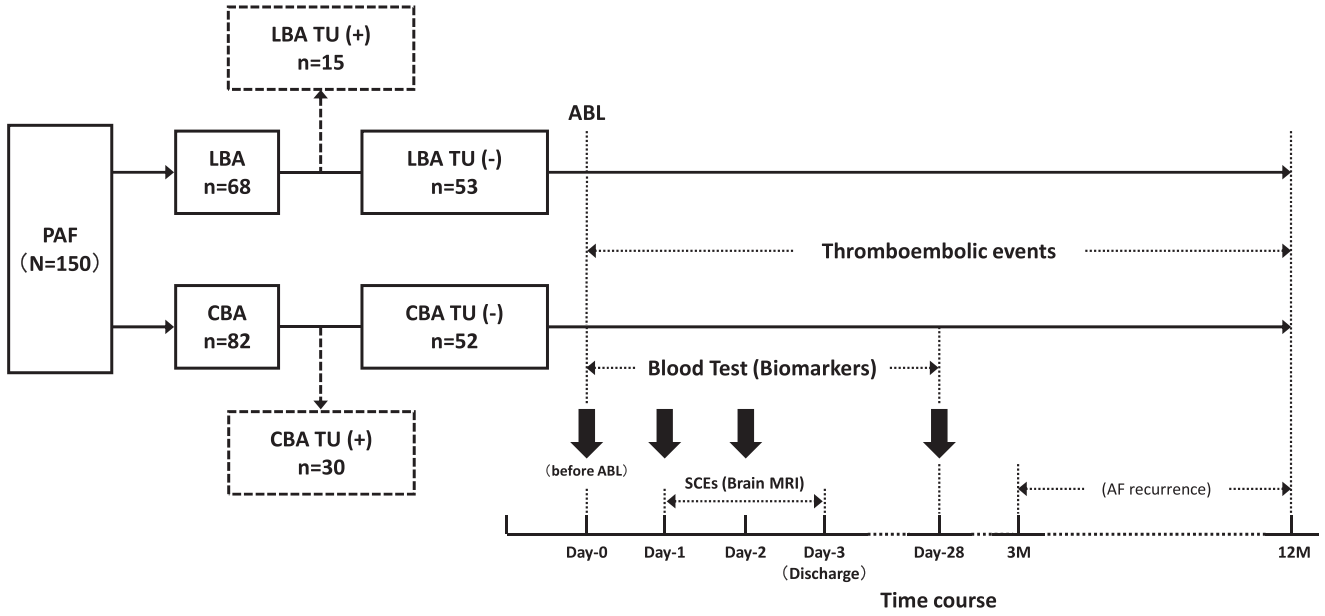


**Figure 1** Schematic diagram of the study protocol. ABL = catheter ablation; AF = atrial fibrillation; CBA = cryoballoon ablation; LBA = laser balloon ablation; PAF = paroxysmal atrial fibrillation; SCE = silent cerebral event; TU = radiofrequency touch-up ablation.

Medtronic). A second- or fourth-generation 28-mm cryoballoon catheter (Arctic Front Advance; Medtronic) was advanced into the 4 PVs under support by a guidewire-like ring catheter (Achieve; Medtronic). The ring catheter was also used for mapping of the PV potentials. The procedure was performed under guidance of an electroanatomic mapping system (EnSite NavX) and fluoroscopy. Contrast medium was used to confirm the position of the cryoballoon catheter and its complete occlusion of the PV ostium and then single short freezing for 180 seconds was applied to the PV. During the CBA to the right PVs, diaphragmatic movement and compound motor action potential during phrenic nerve pacing were monitored to prevent injury to the phrenic nerve.

In LBA, the transseptal sheath was exchanged with a 12-F deflectable steerable sheath (CardioFocus). The LBA catheter was delivered through the deflectable sheath and was located at the PV ostium in the LA. The compliant balloon was inflated with multiple pressures and the balloon size was adjusted to make adequate contact between the balloon and the tissue. The adjacent blood was maximally extruded by the balloon inflation so that the endocardial surface of the PV ostium could be visualized from the inside of the balloon catheter equipped with endoscopy. The degree of PV occlusion was defined as PV occlusion grade according to the following previous reports: (1) 360°, (2) 270–359°, (3) 180–269°, and (4) <180°.[2,11] Encircling PV isolation was individually performed for 4 PVs. The laser energy was titrated around the PV ostium in a point-by-point manner with a 30%–50% overlap of each contiguous lesion (5.5–2 W) or in a dragging manner using autocruise function to create a continuous lesion set (12 W). Regarding the point-by-point laser application, high energy (10 W) was used for the left PV anterior wall and roof, moderate energy (8.5 W) for the right PV, and moderate-to-low energy (5.5 W) for the left PV posterior walls and bottom. The low energy of 5.5 W was selected in case of esophageal temperature rise or severe pain while an overlap ratio was the same. The low energy was also used in the areas adjacent to blood. The laser energy delivery was stopped when the esophageal temperature reached >39 °C. During LBA of the right-sided PVs, phrenic nerve pacing was performed to monitor for early detection of phrenic nerve injury.

Successful PVI was defined as bidirectional conduction block between the outside and the inside of the circumferential PVI area, confirmed by constant pacing from both sides and by an electroanatomic mapping system using the circular mapping catheter. If successful PVI could not be achieved, RF touch-up ablation using an irrigation tip catheter (FlexAbility [Abbott]; 30–35 W, 30–60 seconds in each application) was performed but patients who required the touch-up ablation were excluded to avoid the impact of tissue injury by RF energy on coagulation/fibrinolysis biomarkers. Drug-evoked dormant conduction was not confirmed. No additional linear ablation and no additional non-PV foci ablation in the atrium were performed.

## Isolated antral surface area

The isolated antral surface area (IASA) and LA posterior wall surface area (LAPWSA) were calculated using EnSite NavX system (Figure 2A). The PV ostium was identified as the point of maximal inflection between the PV wall and LA wall. The PV antrum was defined as the region proximal to the PV ostium. The IASA was defined as the scar area (≤0.1 mV) proximal to the corresponding PV ostium. The left- and right-sided IASAs were summed as the total IASA. The LAPWSA was defined as the area formed by the superior and inferior margins of the LA and the section

of the posterior LA wall with bipolar voltage amplitudes >0.1 mV. The ratio of the total IASA, excluding the PVs, to the sum of the total IASA and LAPWSA was taken as the percentage of IASA (%IASA).[12]

### Brain MRI

Brain MRI was performed within 2 days after the procedure using a 1.5T scanner (Achieva 1.5T Nova Dual; Philips Healthcare) with an 8-channel brain coil, or a 3T scanner (Ingenia 3T; Philips) with a dS head coil, or a Vantage Titan 3T (Canon Medical Systems Corporation) with a 16- or a 32-channel coil to detect SCEs. In each patient, axial diffusion-weighted imaging was performed using single-shot, spin-echo, echo-planar imaging with 2 *b* values of 0 and 1000 s/mm$^2$ and 3 diffusion directions. Other scan parameters were as follows: repetition time/echo time 3600 to 5100/83 to 98 ms; 112 to 76 × 128 to 256 matrix; 288 to 512 × 288 to 512 reconstruction matrix; 220 × 220 mm field of view; slice thickness 5.0 mm; slice gap 1.0 mm; and 1 to 4 excitations. The apparent diffusion coefficient map was obtained to prevent the over-detection of T2 shine-through effects on diffusion-weighted imaging.

The definition for diagnosing SCE was based on the detection of new hyperintense lesions of the diffusion-weighted MRI with hypointense findings of the apparent diffusion coefficient map according to a neuroimaging expert's recommendation.[13] MRI images were independently and blindly evaluated by certified radiologists. A neurological examination was performed upon hospital admission and after the ablation procedure by certified neurologists or certified physicians blinded to the MRI findings.

### Inflammatory, myocardial injury, coagulation, and fibrinolysis biomarkers

Body temperature was measured at 3 different time points (on the day of procedure [before entering operating room, day 0], 1 day after the procedure [day 1], and 2 days after the procedure [day 2]). Blood samples were collected at 4 different time points (day 0, day 1, day 2, and 1 month after the procedure [day 28]) for the total white blood cell count (WBC) and for the serum levels of high-sensitivity C-reactive protein (hs-CRP), troponin I (TnI), creatine kinase-MB (CK-MB), fibrinogen (FN), prothrombin fragment 1+2 (PF1+2), D-dimer, and plasmin-α2 plasmin inhibitor complex (PIC).

### Follow-up

All patients were followed up by cardiologists at the outpatient department of Fujita Health University at 1, 3, 6, 9, and 12 months after ablation. All patients were asked about their symptoms and underwent a 12-lead electrocardiogram. Twenty-4 hour Holter electrocardiography monitoring was performed at 6-month follow-up and 7-day Holter electrocardiography was done at 12-month follow-up. In cases of AF recurrence within a 3-month blanking period, an antiarrhythmic drug was prescribed and discontinued after the blanking period. AF recurrence was defined as any atrial tachyarrhythmias lasting more than 30 seconds and occurring after the blanking period.

### Statistical analysis

Continuous variables, represented as mean ± SD, were compared using unpaired *t* tests. The analysis of sequential data was performed using mixed models with multiple comparisons. Categorical data, expressed as frequencies and percentages, were compared using chi-square tests. The AF-free survival rate was calculated using Kaplan-Meier survival analysis, and log-rank statistics were used for group comparisons.

All tests were 2-sided, and a $P$ value <.05 was considered statistically significant. Statistical analyses were performed using JMP11 (SAS Institute).

## Results

### Patient characteristics and procedure characteristics

Of the 150 patients, 82 underwent CBA and 68 underwent LBA. RF touch-up ablation was required in 30 out of 82 patients in CBA and in 15 out of 68 patients in LBA. Therefore, 52 patients in CBA and 53 patients in LBA were eligible (Figure 1). There was no significant difference in patient characteristics between the 2 groups (Table 1).

PVI was successfully performed in all patients. The CBA group had a significantly shorter total procedure time and shorter LA dwell time than the LBA group. The intraprocedural heparin/ACT kinetics were comparable between the 2 groups (Table 2).

### Isolated antral surface area

Representative images of voltage maps before and after PVI are shown in Figures 2B and 2C. The IASA was calculated and compared between CBA and LBA; there was no significant difference in the value between them (11.3 ± 2.8 cm$^2$ for CBA, 11.5 ± 2.2 cm$^2$ for LBA; $P$ = .732). %IASA was also comparable between CBA and LBA (48 ± 7% for CBA, 46 ± 8% for LBA; $P$ = .158).

### Inflammatory and myocardial injury biomarkers

WBC and neutrophil/lymphocyte (N/L) ratio maximally increased on day 1; hs-CRP peaked in day 2 in both groups, and decreased thereafter (Figure 3). There were significant differences in the time course changes of WBC ($P$ = .001) and N/L ratio ($P$ = .037) but not hs-CRP ($P$ = .370), between CBA and LBA; LBA had significantly higher WBC and N/L ratio on day 1 than CBA (WBC: 9082 ± 2568/μL for LBA, 7940 ± 1783/μL for CBA; $P$ = .010; N/L ratio: 5.8 ± 2.7 for LBA, 4.9 ± 2.4 for CBA; $P$ = .036). TnI and CK-MB peaked on day 1 in both groups (Figure 4). There were significant differences in the time course changes of TnI ($P$ < .001) and CK-MB ($P$ < .001) between CBA and LBA; CBA showed significantly higher TnI and CK-MB on day 1 and day 2 than LBA (TnI: 2.9 ± 1.8 pg/mL for LBA, 15.5 ± 9.9 pg/

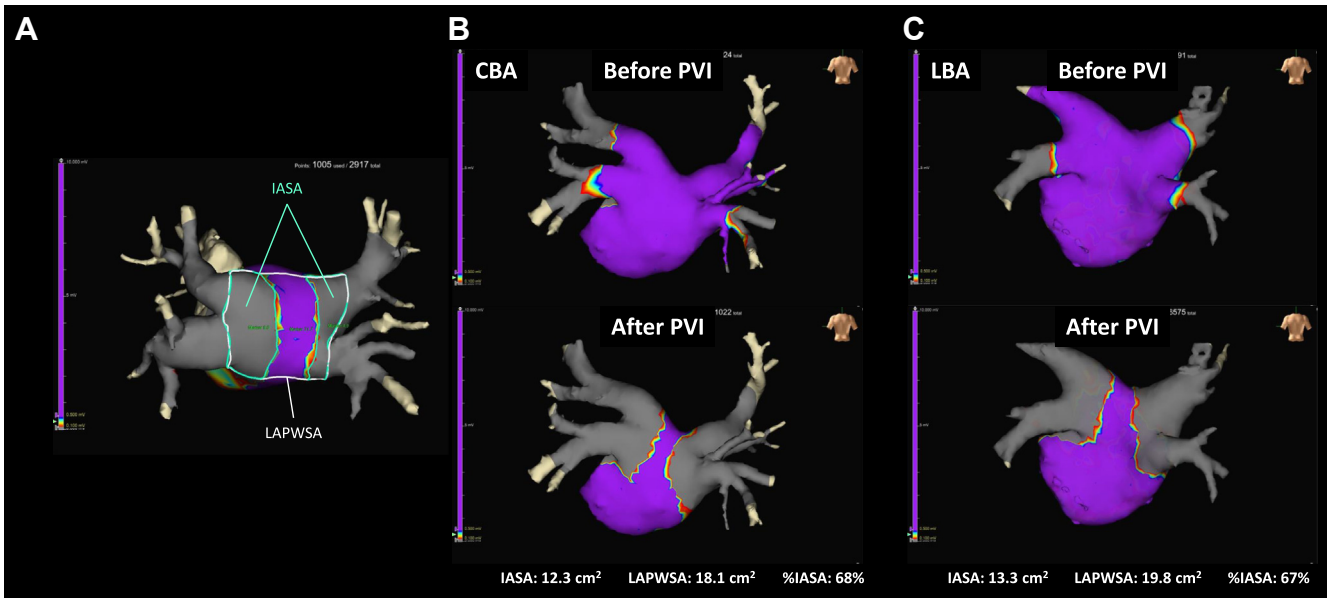


**Figure 2** Isolated antral surface area (IASA). A: Measurement of IASA. B: Representative images of voltage map before and after pulmonary vein isolation (PVI) in cryoballoon ablation (CBA). C: Representative images of voltage map before and after PVI in laser balloon ablation (LBA). LAPWSA = left atrial posterior wall surface area.

mL, for CBA; $P < .001$; CK-MB: 8.6 ± 3.1 U/L for LBA, 41.3 ± 20.8 U/L for CBA; $P < .001$)

### Coagulation and fibrinolysis biomarkers

Regarding coagulation biomarkers, FN and PF1+2 maximally increased on day 2 and then decreased on day 28 in both groups (Figure 5). There was a significant difference in the time course change of PF1+2 ($P = .028$), but not FN ($P = .160$), between CBA and LBA; LBA had significantly higher PF1+2 than CBA on day 28 (231 ± 127 pmol/L for LBA, 179 ± 62 pmol/L for CBA; $P = .01$). D-dimer peaked at day 1 in CBA and at day 2 in LBA, and then decreased on day 28 (Figure 4). There was a significant difference in the time course change of D-dimer ($P < .001$) between CBA and LBA; LBA had significantly higher D-dimer than CBA on day 28 (0.70 ± 0.43 μg/mL for LBA, 0.56 ± 0.12 μg/mL for CBA; $P = .02$). Regarding fibrinolysis biomarker, PIC did not increase after the procedure in either group; there was no significant difference in the time course change of PIC ($P = .544$) between CBA and LBA (Figure 5).

### Incidence of SCEs

The incidence of SCEs within 2 days after the procedure was 12% in CBA and 15% in LBA; there was no significant difference between the 2 groups ($P = .591$) (Figure 6A). No thromboembolic event was observed in CBA and LBA during the follow-up. The one-year AF-free survival rate was unchanged between CBA and LBA (90% for LBA, 90% for CBA, log-rank = 0.046; $P = .831$) (Figure 6B). There were no transient ischemic attack/stroke, systemic thromboembolism, and major bleeding during 12-month follow-up in both groups. Transient phrenic nerve injury was observed in 1 patient of LBA who recovered after the procedure. There were no other procedure-related complications in either group.

## Discussion

The major findings of this study are as follows. Myocardial injury after CBA was significantly greater than that after LBA, but the inflammatory reaction after LBA was higher than that after CBA. In addition, there were significant differences in the time course of coagulation biomarkers between the 2 groups: LBA had higher PF1+2 and D-dimer than CBA in the first month after the procedure. Finally, the incidence of SCEs was unchanged between CBA and LBA, and no thromboembolic event was observed in either group during the follow-up.

### Comparison with previous studies

Several comparative studies have demonstrated that both CBA and LBA have shown similar efficacy and safety for PVI with the same favorable rhythm outcome and periprocedural complications.[2,14] However, due to the different energy sources, tissue damage and inflammatory responses in LBA would differ from those in CBA, potentially leading to different risks of thromboembolism.

Previous studies have reported that different energy sources and different ablation techniques produced different myocardial lesions and inflammatory responses.[15–18] On the one hand, Miyazaki and colleagues[15] demonstrated that after the procedure, CBA increased serum CK-MB and TnI levels compared with RF catheter ablation but decreased high-sensitive CRP levels. On the other hand, Bin Waleed and colleagues[18] found no significant differences in inflammatory biomarkers between CBA and RF catheter ablation,

**Table 1** Patient characteristics after propensity score matching

| | CBA TU (–) (n = 52) | LBA TU (–) (n = 53) | *P* value |
|---|---|---|---|
| Age, y | 66 ± 10 | 69 ± 10 | .163 |
| Female | 18 (35) | 18 (34) | .944 |
| Body mass index, kg/m$^2$ | 23.6 ± 3.2 | 23.4 ± 5.0 | .798 |
| $CHADS_2$ score | 1.1 ± 1.1 | 1.3 ± 0.9 | .344 |
| $CHA_2DS_2$-VASc score | 2.1 ± 1.7 | 2.6 ± 1.4 | .147 |
| Congestive heart failure | 4 (8) | 4 (8) | .978 |
| Hypertension | 29 (56) | 34 (64) | .380 |
| Age ≥75 y | 12 (23) | 17 (32) | .302 |
| Diabetes | 8 (15) | 7 (13) | .750 |
| Stroke/TIA | 3 (6) | 4 (8) | .715 |
| Laboratory data | | | |
| NT-proBNP, pg/mL | 193 ± 234 | 287 ± 444 | .432 |
| BUN, mg/dL | 13.0 ± 3.3 | 13.3 ± 2.9 | .672 |
| Creatinine, mg/dL | 0.74 ± 0.17 | 0.77 ± 0.17 | .340 |
| CrCl, mL/min | 88 ± 27 | 81 ± 34 | .245 |
| Echocardiography | | | |
| LVEF, % | 58.7 ± 4.5 | 58.7 ± 9.3 | 1.000 |
| LVDd, mm | 45.6 ± 4.6 | 45.0 ± 4.7 | .497 |
| LVDs, mm | 29.4 ± 4.8 | 29.6 ± 5.3 | .907 |
| LAD, mm | 35.1 ± 5.4 | 35.1 ± 5.6 | .966 |
| LAVI, mL/m$^2$ | 2940 ± 10.0 | 30.9 ± 9.8 | .447 |
| Medication | | | |
| NOAC | 52 (100) | 53 (100) | 1.000 |
| Antiplatelet drug | 5 (10) | 10 (19) | .172 |
| ACE inhibitor/ARB | 20 (38) | 22 (42) | .750 |
| β-blocker | 24 (46) | 23 (43) | .776 |

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin 2 receptor blocker; BUN = blood urea nitrogen; CBA = cryoballoon ablation; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism; $CHA_2DS_2$-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category; CrCl = creatinine clearance; LAD = left atrial diameter; LAVI = left atrial volume index; LBA = laser balloon ablation; LS PeAF = long-standing persistent atrial fibrillation; LVDd = left ventricular diastolic dimension; LVEF = left ventricular ejection fraction; LVDs = left ventricular systolic dimension; NOAC = non–vitamin K antagonist oral anticoagulant; NT-proBNP = N-terminal pro–brain natriuretic peptide; TIA = transient ischemic attack; TU = touch-up.

**Table 2** Procedure characteristics and ACT/heparin kinetics

| | CBA TU (–) (n = 52) | LBA TU (–) (n = 53) | *P* value |
|---|---|---|---|
| OACs on the day of procedure | | | .258 |
| Dabigatran 300 mg | 43 (83) | 39 (74) | |
| Dabigatran 220 mg | 9 (17) | 14 (26) | |
| Initial ACT, s | 186 ± 32 | 199 ± 39 | .072 |
| Time to ACT >300 s, s | 19 ± 19 | 17 ± 22 | .600 |
| Total amount of heparin, IU | 9200 ± 3244 | 10,086 ± 4028 | .240 |
| LA dwell time, min | 82 ± 21 | 125 ± 30 | <.001 |
| Procedure time, min | 125 ± 33 | 165 ± 37 | <.001 |

Values are n (%) or mean ± SD.

ACT = activated clotting time; CBA = cryoballoon ablation; LA = left atrial; LBA = laser balloon ablation; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; OAC = oral anticoagulant; RF = radiofrequency ablation; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.

but patients treated with CBA had lower levels of platelet activation biomarkers than those treated with RF catheter ablation. The issue remains controversial and the information on LBA is largely limited. One previous study demonstrated that LBA had smaller myocardial injury (decreased high-sensitivity TnI levels) but higher inflammatory reaction (increased WBC and CRP levels) than CBA.[19] We also demonstrated that CBA caused greater myocardial injury than LBA, represented by the higher levels of TnI and CK-MB after the procedure. However, there was no significant difference in IASA and %IASA between CBA and LBA. On the one hand, CBA can create the wider band-like lesion in which the balloon surface contacts the myocardial tissue. On the other hand, LBA can create the narrower linear lesion by laser beam emitted from the balloon. Even though the IASA was unchanged between CBA and LBA, the myocardial volume injured by CBA would be bigger than that by LBA.

Thrombogenesis is associated with endothelial damage in catheter ablation. Khairy and colleagues[4] compared histological findings between the lesions created by RF ablation and cryoablation in dogs. At 1 week after the ablation, the cryoablated lesions were clearly circumscribed with dense areas of fibrotic tissue and had a distinctive smooth and sharp demarcation from surrounding intact myocardium. In contrast, the RF-ablated lesions were characterized by internal hemorrhage and ragged edges, and were less clearly demarcated from surrounding intact myocardium. Thrombus formation was only observed in RF-ablated lesions; cryoablated lesions exhibited intact endothelial cell layers.[4] These findings have also been observed in postmortem analyses of AF patients who underwent CBA.[20,21] Gerstenfeld and Michele[5] performed a histological examination of the lesion after PVI using LBA in swine models. The pathological changes are consistent with typical thermal injury including organizing granulation with persistent chronic inflammation, fibrosis, residual myocyte necrosis, and focal hemorrhage.[5] Aupperle and colleagues[6] examined acute histological findings induced by different energy sources in experimental atrial ablation in sheep. Endocardial RF and laser ablation resulted in severe endocardial necroses and thrombus formation. Myocardial necroses with internal hemorrhages were severe and were not demarcated. However, the lesion after cryoablation was demarcated; endocardial necrosis and thrombi were not obvious.[6] These suggest that a lesion created by laser ablation is likely similar to an RF-based thermal injury and that the thermal injury may be more thrombogenic than the cryoinjury, likely being reflected by coagulation and fibrinolysis biomarkers. We found significant differences in the time course of coagulation biomarkers between CBA and LBA. Both CBA and LBA almost equivalently increased PF1+2 and D-dimer on day 1 and day 2, but LBA had significantly higher PF1+2 and D-dimer levels than CBA on day 28. This may be attributable to the difference of the wound healing process in the ablated lesions between CBA and LBA.

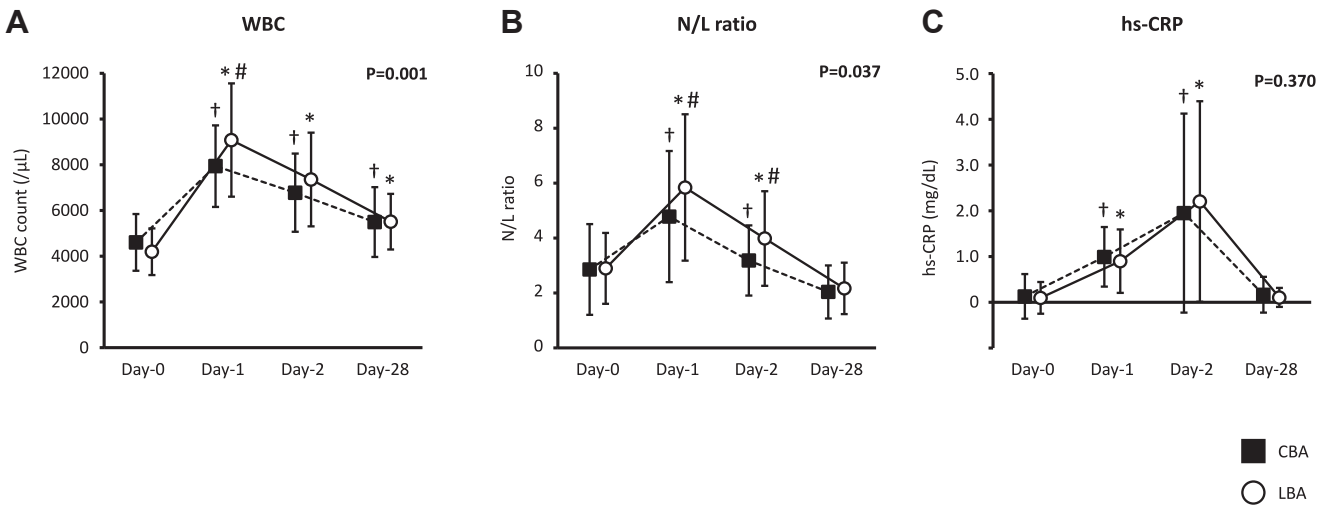


**Figure 3** Time course of body temperature and inflammatory biomarkers. A: White blood cell (WBC) count. B: Neutrophil/lymphocyte (N/L) ratio. C: High-sensitivity C-reactive protein (hs-CRP). *P* values indicate the comparison of the time course pattern between cryoballoon ablation (CBA) and laser balloon ablation (LBA). *$P < .05$ vs day 0 in LBA. †$P < .05$ vs day 0 in CBA. #$P < .05$ vs CBA.

More careful postprocedural anticoagulation therapy may be required to minimize thromboembolic risks in LBA. To the best of our knowledge, this study is the first to compare the time course changes of coagulation and fibrinolysis biomarkers between CBA and LBA.

SCE is a surrogate marker of clinical thromboembolic risk. The prevalence of SCEs after CBA has been reported with a range from 4.3% to 26.9%.[22–25] However, the information on this regard in LBA is limited. Only one study has reported that the prevalence of newly visible asymptomatic embolic brain lesions was 13.6% in LBA and 5.0% in CBA, but the number of eligible patients was very small (LBA: n = 44, CBA: n = 20).[26] We also demonstrated that there was no significant difference in SCE incidence between CBA (12%) and LBA (15%). Chun and colleagues[3] compared the safety outcome between CBA and LBA; there was no statistical difference in the thromboembolic events between the 2 groups. Moreover, no thromboembolic event was observed in this study.

## Limitation

This is a single-center study involving a small number of patients; its statistical power is therefore limited and any interpretations should be made with caution. Acute SCE lesions reportedly regress during the follow-up period, but we did not perform brain MRIs during the chronic phase. Different anticoagulation strategies may also have different effects on coagulation and fibrinolysis biomarkers and thromboembolic risk after ablation; however, all patients in this study used dabigatran without interruption during the procedure and continued dabigatran for at least 1 month afterward. Several mechanisms of SCEs after AF ablation are proposed other than microthrombus, such as gaseous emboli and microparticle, but the precise etiology has not been evaluated in all patients with SCEs.

## Conclusion

Different energy sources of balloon-based ablation, CBA vs LBA, had different impact on myocardial injury,

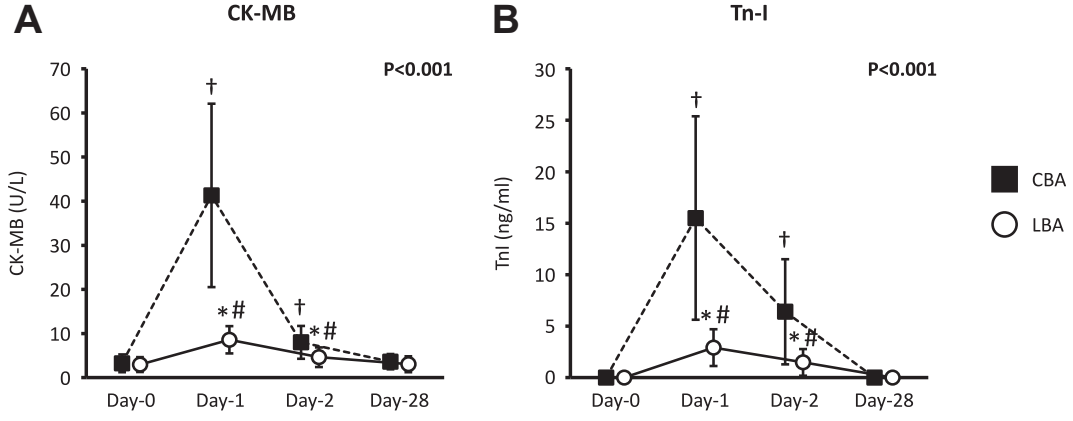


**Figure 4** Time course of myocardial injury biomarkers. A: Creatine kinase-MB (CK-MB). B: Troponin I (TnI). *P* values indicate the comparison of the time course pattern between CBA and LBA. *$P < .05$ vs day 0 in LBA. †$P < .05$ vs day 0 in CBA. #$P < .05$ vs CBA.

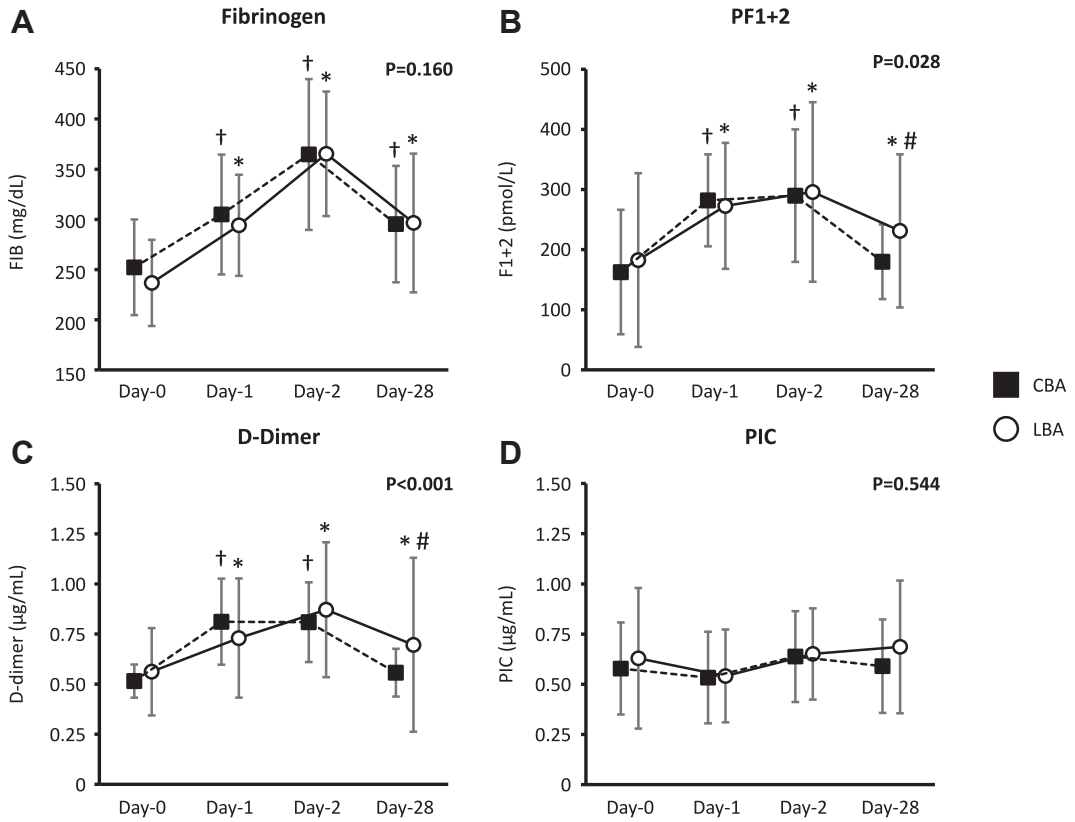


**Figure 5** Time course of coagulation and fibrinolysis biomarkers. A: Fibrinogen (FIB). B: Prothrombin fragment 1+2 (PF1+2). C: D-dimer. D: Plasmin-α2 plasmin inhibitor complex (PIC). *P* values indicate the comparison of the time course pattern between cryoballoon ablation (CBA) and laser balloon ablation (LBA). **P* < .05 vs day 0 in LBA. †*P* < .05 vs day 0 in CBA. #*P* < .05 vs CBA.

inflammatory reaction, and coagulation activity but did not affect the clinical thromboembolic events; both techniques similarly endorsed high therapeutic efficacy. LBA had significantly higher PF1+2 and D-dimer levels than CBA in the first month after the procedure, which may suggest that the more careful postprocedural anticoagulation may be required to minimize thromboembolic risks in LBA.

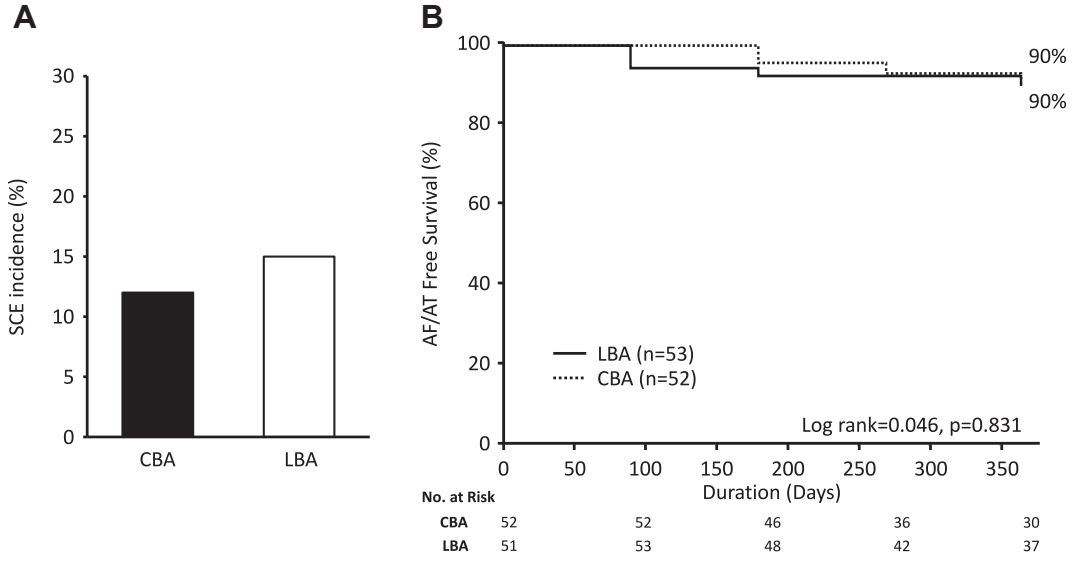


**Figure 6** Silent cerebral event (SCE) incidence and Kaplan-Meier atrial fibrillation (AF)–free survival curve in cryoballoon ablation (CBA) and laser balloon ablation (LBA). A: Incidence of SCEs. B: One-year AF-free survival curve in CBA and LBA. AT = atrial tachycardia.

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**Patient Consent:** Written informed consent was obtained from all patients.

**Ethics Statement:** The protocol was approved by the review board of Fujita Health University School of Medicine. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

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