Intraprocedural Conversion Efficacy of Intravenous Nifekalant Administration for Persistent Atrial Fibrillation after Pulmonary Vein Isolation

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Summary
The aim of this study was to prospectively assess the efficacy, safety, and predictive effect of intravenous nifekalant administration for persistent atrial fibrillation (PerAF) after pulmonary vein isolation (PVI) with second-generation cryoballoon ablation (CBA) on 1-year atrial tachyarrhythmia (ATa)-free survival by examining the pharmacological conversion rate.

One hundred and two drug-refractory, consecutive PerAF patients undergoing PVI were enrolled in this prospective observational study. After PVI, nifekalant (50 mg) was given followed by 30 minutes of observation and no further intervention. PerAF was successfully converted to sinus rhythm (SR) in 60 patients (58.8%) after a median time of 7.75 (4.13-12) minutes (group N). In the remaining 42 patients (41.2%) (group C), PerAF was successfully converted to SR by external electrical cardioversion. Nonsustained ventricular tachycardia occurred in 1 patient in group N. The left atrial volume (LAV) in group C was larger than that in group N (128.2 ± 28.2 versus 111.8 ± 24.5 mL, \( P = 0.002 \)). Phrenic nerve injury occurred in 4 of 102 patients (3.9%). No other complications occurred during the procedure or within the 1-year follow-up period. At the 1-year follow-up, after a 3-month blanking period (BP), ATa-free survival during 1-year follow-up in group C was significantly lower than that in group N (50.0% versus 71.7%, \( P = 0.026 \)), and the overall ATa-free survival rate was 62.7%. Two patients in group C and 4 patients in group N underwent a second procedure with radiofrequency catheter ablation. Multivariate Cox regression analysis demonstrated that unsuccessful conversion to SR (\( P = 0.025 \)), ATa relapse during the BP (\( P = 0.000 \)), and larger LAV (\( P = 0.016 \)) were independent predictors of ATa recurrence at the 1-year follow-up.

In conclusion, at the 1-year follow-up, the ATa-free survival rate after PVI with CBA for PerAF patients was 62.7%, and successful conversion to SR with nifekalant could serve as a clinical predictor of reduced ATa recurrence.

Keywords: Ablation, One-year follow-up, Second generation, Electrophysiology

Cryoballoon ablation (CBA) has emerged as a safe and effective ablation strategy for patients with atrial fibrillation (AF) with persistent atrial fibrillation (PerAF). Related studies have demonstrated the ablation efficacy of PVI as an index procedure using a cryoballoon (CB) for patients with paroxysmal AF (ParAF) and persistent AF (PerAF). For PerAF patients, in addition to PVI, other targets for radiofrequency catheter ablation (RFCA) have included complex fractionated atrial electrograms (CFAEs), empiric additional line ablation, and driving rotors, with reported 1-year efficacy rates of 29%-60%. Recent data have brought into question the utility and safety of the aforementioned RFCA strategies other than PVI, which may lead to an increased incidence of RFCA-related atrial flutter (AFL), pericardial effusion, and other complications. Only sparse data are available regarding the pharmacological conversion of PerAF achieved by intravenous nifekalant administration during the RFCA procedure. This study was undertaken to evaluate the efficacy, safety, and predictive effect on the 1-year atrial tachyarrhythmia (ATa)-free survival of intravenous nifekalant administration for PerAF after PVI with second-generation CBA by examining the pharmacological conversion rate.

Methods
Study subjects: From July 2015 to December 2018, among 425 consecutive AF patients who presented for catheter ablation, 102 drug-refractory, consecutive PerAF patients (24.0%) were enrolled in this study. Patients with AF episodes lasting longer than 7 days requiring external electrical cardioversion (EEC) or chemical cardioversion to restore sinus rhythm (SR) were defined as having
Pre-CBA preparation: from groin bleeding. Arteriovenous fistula, retroperitoneal bleeding, or death 2 g/dL due to groin pseudoaneurysm/hematoma (> 3 cm), cation was defined as a decrease in hemoglobin of at least and the guide wire was advanced into the femoral vein was performed using the modified Seldinger technique, obtained with fentanyl citrate during the procedure. FVP (NOAC) treatment before the procedure, NOAC treatment For patients undergoing novel oral anticoagulation cardiac sinus and right ventricle via the left FV , respectively. Nonsteerable quadripolar catheter were placed in the coronary sinus and right atrium. Once total PV occlusion was achieved, CBA was started, and a small amount of pressure was applied to the balloon after 5 seconds of CBA to completely occlude the PV (proximal-seal technique). In this setting, a larger and less compliant CB carries a significantly lower chance of creating a more distal lesion in the PV. For the smaller LIPV and RSPV, CBA was started (without retrieving the CB when total PV occlusion was achieved, as determined by selective CM injection showing total CM retention with no back flow into the LA. CBA procedure: The left superior pulmonary vein (LSPV) was treated first, followed by the left inferior pulmonary vein (LIPV), right inferior pulmonary vein (RIPV), and right superior pulmonary vein (RSPV). For the larger LSPV and RSPV, the first step consisted of obtaining complete occlusion of the vein, as demonstrated by contrast medium (CM) injection showing total CM retention with no back flow into the LA. The phrenic nerve stimulation was recorded at least 48 hours before CBA for all patients. The demographic and clinical data, including patient age, sex, height, weight, biochemical blood examination results, echocardiographic parameters, and clinical arrhythmias, were collected prior to the index procedure. The study protocol was reviewed and approved by the hospital’s ethics committee according to the principles of the Declaration of Helsinki. All patients provided written informed consent before CBA.

Preprocedural management: All antiarrhythmic drugs (AADs) were discontinued at least 5 half-lives before the procedure. TTE was performed within 1 week before CBA, enabling the assessment of left ventricular (LV) function and intracavitary dimensions. Transesophageal echocardiography (TEE) was performed 2 days before the procedure to exclude the presence of thrombi in the LA and/or the LAA. All patients underwent a preprocedural computed tomographic (CT) scan to assess the detailed LA and pulmonary vein (PV) anatomy. Periprocedural anticoagulation was managed as per individual physician discretion.

LA volume (LAV) measurement: A series of LA images were collected based on the preprocedural CT scan result and imported into the Ensite system (St. Jude Medical, MN, USA) to reconstruct and establish the 3D LA shell. Endocardial contours of the LA were semiautomatically traced in each axial image, and the mitral valve annulus was used as a landmark to separate the LA from the LV. The LAA and the PVs were excluded at their ostia, defined as the site of reflection of these structures with the surrounding LA wall. Finally, the software was used to calculate the LAV from the 3D LA shell.

Femoral vein puncture (FVP) and major groin complications: Patients were treated with conscious analgesia obtained with fentanyl citrate during the procedure. FVP was performed using the modified Seldinger technique, and the guide wire was advanced into the femoral vein (FV) after the completion of FVP. A major groin complication was defined as a decrease in hemoglobin of at least 2 g/dL due to groin pseudoaneurysm/hematoma (> 3 cm), arteriovenous fistula, retroperitoneal bleeding, or death from groin bleeding.

Pre-CBA preparation: A steerable decapolar catheter and nonsteerable quadripolar catheter were placed in the coronary sinus and right ventricle via the left FV, respectively. For patients undergoing novel oral anticoagulation (NOAC) treatment before the procedure, NOAC treatment was not discontinued, and heparin was not infused as required. For patients not undergoing NOAC treatment before the procedure, heparin was administered as an intravenous bolus (100 U/kg) after LA access (via the right FV) was obtained, and the activated clotting time was maintained between 300 and 350 seconds by supplemental heparin infusion as required. After LA and PV angiography were performed, a steerable 15-Fr sheath (FlexCath Advance, Medtronic, Inc., Minneapolis, MN, USA) was exchanged. The inner-lumen mapping catheter (Achieve, Medtronic, Inc., Minneapolis, MN, USA) within the CB (Arctic Front Advance, Medtronic, Minneapolis, MN, USA) was advanced into the LA via the steerable sheath and sequentially positioned in each PV antrum to obtain baseline PV potential (PVP) information.

Intravenous nifekalant administration: A single intravenous dose of nifekalant (50 mg, initial dose of 0.3 mg/kg for 5 minutes, followed by a continuous infusion at 10 μg/kg per minute for the residual dosage; Sichuan Baili Pharmaceutical Co. Ltd., Sichuan, China) was intravenously
After CBA, patients were continuously monitored with ECG telemetry for at least 48 hours. TTE was performed routinely to look for evidence of pericardial effusion. For patients not undergoing NOAC treatment before the procedure, NOAC was administered 4 hours after CBA and was continued for at least 3 months for all patients. Patients were discharged 2 days after CBA if their clinical status was stable. Oral amiodarone or propafenone was continued for 6 months, and after that time, their discontinuation was recommended if SR was maintained. The decision to restart oral amiodarone after the blanking period (BP) was usually made when the first subsequent episode of ATas was recorded.

**Follow-up:** The primary endpoint was the first ATa episode after the index procedure. After discharge, patients were scheduled for follow-up visits at 0.5, 1, and every month thereafter to 1 year, during which routine baseline ECG and 24-hour Holter recordings were obtained. The pulse rhythm was measured by the patients themselves one time, twice a day for at least 1 minute. Patients were encouraged to immediately obtain an ECG or Holter recording upon experiencing palpitations or measuring an irregular pulse rhythm. All reports of ECG and Holter recordings performed in referring centers were sent to our center for confirmation of the diagnosis of recurrent ATas. ATa recurrence was defined as a symptomatic or documented ATa episode > 30 seconds during planned, symptom-driven or irregular pulse rhythm-driven consultation. ATas occurring in the first 3 months after the ablation (i.e., the BP) were censored, and the follow-up period was truncated at 1 year. In the case of symptomatic drug-refractory ATa recurrence, the patient was evaluated for a second procedure. All repeat procedures were performed with RFCA guided by the CARTO 3 mapping system.

**Statistical analysis:** Normal data are expressed as the mean ± SD and were compared by the independent samples t-test. Non-normally distributed data are expressed as the median and interquartile range in parentheses. Event-free survival was estimated by the Kaplan-Meier method, and the log-rank test was applied for comparisons between groups. Multivariate Cox regression analysis was used to identify predictors of PerAF recurrence. Categorical variables are presented as numbers and percentages and were evaluated by the chi-square test and Fisher’s exact test as appropriate. A 2-tailed probability value of $P < 0.05$ was considered as statistically significant. Statistical analyses were conducted using SPSS software (version 17, SPSS, Inc., Chicago, IL, USA).

**Results**

**Study population:** In this prospective observational study, a total of 114 consecutive patients with PerAF undergoing PVI with CBA were screened, and 102 patients were included in the final analysis. The remaining 12 patients were excluded because they lacked 12 months of follow-up data. The baseline clinical and patient characteristics of the study population are summarized in Table I and were

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**Table I.** Baseline Clinical Characteristics of the Study Population

|                      | Group C (n = 42) | Group N (n = 60) | t/Z/me value | P value |
|----------------------|------------------|------------------|--------------|---------|
| Age (years)          | 61 ± 11          | 63 ± 9           | 0.947        | 0.346   |
| Male sex (%)         | 28/42 (66.7%)    | 37/60 (61.7%)    | 0.267        | 0.605   |
| Hypertension (%)     | 24/42 (66.7%)    | 31/60 (51.7%)    | 0.298        | 0.585   |
| DM (%)               | 8/42 (19.0%)     | 13/60 (21.7%)    | 0.104        | 0.747   |
| CHD (%)              | 8/42 (19.0%)     | 10/60 (16.7%)    | 0.096        | 0.756   |
| Stroke (%)           | 7/42 (16.7%)     | 7/60 (11.7%)     | 1.073        | 0.300   |
| PerAF duration (weeks) | 12.0 (2.0-37.0)* | 12.0 (2.0-42.8)* | 0.113        | 0.910   |
| Longstanding PerAF patients (%) | 6/42 (14.3%) | 10/60 (16.7%)    | 0.106        | 0.745   |
| CHARS-VAs score      | 2 (1-3)*         | 2 (1-3)*         | 0.443        | 0.658   |
| HAS-BLED score       | 2 (1-2)*         | 2 (1-2)*         | 0.209        | 0.835   |
| BMI (kg/m²)          | 27.7 ± 3.6       | 26.2 ± 3.2       | 2.235        | 0.028   |
| K (mmol/L)           | 4.1 (3.9-4.3)*   | 4.1 (3.8-4.4)*   | 0.509        | 0.610   |
| Cr (μmol/L)          | 68.9 ± 11.6      | 72.6 ± 13.1      | 1.487        | 0.140   |
| UA (μmol/L)          | 340.0 (295.6-430.0)* | 377.4 ± 94.7    | 0.955        | 0.339   |
| Glu (mmol/L)         | 5.3 (4.9-5.8)*   | 5.4 (5.0-6.1)*   | 0.535        | 0.593   |
| LA (mm)              | 43.3 ± 3.1       | 42.0 (39.5-45.0)* | 1.322       | 0.186   |
| LVEDD (mm)           | 48.6 ± 4.0       | 47.0 (45.0-49.0)* | 1.959        | 0.050   |
| LVEF (%)             | 59.6 ± 7.9       | 58.5 (55.0-65.0)* | 0.092        | 0.927   |
| LAV (ml)             | 128.2 ± 28.2     | 111.8 ± 24.5     | 3.128        | 0.002   |

Values are given as the mean ± SD. *Non-normally distributed data with the median and interquartile range in parentheses. BMI indicates body mass index; LA, left atrium; DM, diabetes mellitus; CHD, coronary heart disease; PerAF, persistent atrial fibrillation; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; and LAV, LA volume.
are summarized in Table II. The TTI was not available in 0.247. The TTI, nadir temperature, and total CBA time in group C and 61.0 (45.3-71.0) minutes in group N (0.777). The mean LA dwell time was 57.4 ± 20.8 minutes in group C and 80.0 (65.0-88.0) minutes in group N (1.157 0.247). The mean fluoroscopy time was 23.8 ± 10.0 minutes in group C and 24.4 ± 11.4 minutes in group N (1.629 0.103). The RR interval after EEC in group C was 12.0 (2.0-37.0) weeks, and that in group N was 12.0 (2.0-42.8) weeks (P = 0.910).

Procedural characteristics: All CBA procedures were exclusively performed with a 28-mm balloon, and PVI was successfully achieved in 101 patients; in the remaining 1 patient, additional focal RFCA applications were needed in the RIPV. The characteristics of the procedure and CBA (overall and per vein) of the 102 patients are summarized in Table II. The procedural time, fluoroscopy time, and LA dwell time were available for all 102 patients. The mean procedural time was 74.9 ± 27.7 minutes in group C and 80.0 (65.0-88.0) minutes in group N (P = 0.103). The mean fluoroscopy time was 23.8 ± 10.0 minutes in group C and 24.4 ± 11.4 minutes in group N (P = 0.777). The mean LA dwell time was 57.4 ± 20.8 minutes in group C and 61.0 (45.3-71.0) minutes in group N (P = 0.247). The TTI, nadir temperature, and total CBA time are summarized in Table II. The TTI was not available in several cases due to distal positioning of the ACHIEVE catheter to obtain better supporting force, especially for the RIPV and LIPV. During CBA, conversion to atrial tachycardia (AT)/AFL without PerAF termination was documented in 2 patients in group N.

Intravenous nifekalant administration: Within 30 minutes of observation, conversion to AT/AFL but without conversion to SR occurred in 2 patients in group C. Conversion to AT/AFL followed by SR occurred in 6 patients in group N. The time to conversion to SR in group N was 7.75 (4.13-12) minutes. The RR interval after EEC in group C was 1.5 (1.2-2.1) seconds, and that after conversion by nifekalant in group N was 1.2 (0.93-1.6) seconds (P = 0.005). Nonsustained ventricular tachycardia (VT) occurred in 1 patient in group N. The QTc interval before intravenous nifekalant administration was 420 ms, and the longest QTc interval after intravenous nifekalant administration was 708 ms, occurring after 18 minutes. The QTc interval returned to normal 22 minutes later. No proarrhythmia-related deaths were recorded with the use of nifekalant. In group C, the QTc interval and longest QTc interval before and after intravenous nifekalant administration was 427.1 ± 24.9 ms and 447.9 ± 24.3 ms, respectively (P = 0.011). In group N, the QTc interval and longest QTc interval before and after intravenous nifekalant administration was 440.3 ± 31.0 ms and 454.2 ± 23.0 ms, respectively (P = 0.026). The detailed conversion parameters are summarized in Table III. Finally, the

|                           | Group C (n = 42) | Group N (n = 60) | t/Z/χ² value | P value |
|---------------------------|-----------------|-----------------|--------------|---------|
| LSPV                      |                 |                 |              |         |
| Time at TTI (seconds)     | 53.6 ± 12.0     | 56.5 (45.3-76.5)* | 1.099        | 0.272   |
| Temperature at TTI (°C)   | −38.3 ± 4.2     | −38.0 (36.0-42.0)* | 0.321        | 0.749   |
| Nadir temperature (°C)   | −49.0 (46.0-51.5)* | −46.5 (45.0-51.0)* | 1.366        | 0.172   |
| Total CBA time (seconds) | 210.0 (180.0-332.5)* | 300.0 (180.0-381.0)* | 1.700        | 0.089   |
| LIPV                      |                 |                 |              |         |
| Time at TTI (seconds)     | 53.2 ± 21.8     | 58.8 ± 26.2     | 1.048        | 0.298   |
| Temperature at TTI (°C)   | −35.0 (32.0-38.0)** | −37.0 (32.0-39.0)* | 1.045        | 0.296   |
| Nadir temperature (°C)   | −43.2 ± 4.3     | −45.0 ± 4.6     | 1.939        | 0.055   |
| Total CBA time (seconds) | 180.0 (180.0-307.8)* | 180.0 (180.0-270.0)* | 0.175        | 0.861   |
| RIPV                      |                 |                 |              |         |
| Time at TTI (seconds)     | 46.5 (39.0-60.8)* | 50.0 (39.0-82.0)* | 1.123        | 0.261   |
| Temperature at TTI (°C)   | −37.5 (35.3-41.0)* | −37.5 ± 4.3     | 0.228        | 0.820   |
| Nadir temperature (°C)   | −46.8 ± 5.3     | −47.0 ± 5.4     | 0.193        | 0.848   |
| Total CBA time (seconds) | 180.0 (180.0-270)* | 180.0 (180.0-277.5)* | 0.602        | 0.547   |
| RSPV                      |                 |                 |              |         |
| Time at TTI (seconds)     | 37.0 (37.0-50.0)* | 40.5 (30.0-55.0)* | 1.350        | 0.177   |
| Temperature at TTI (°C)   | −34.7 ± 6.1     | −37.5 (33.8-40.0)* | 1.674        | 0.094   |
| Nadir temperature (°C)   | −51.0 (47.8-55.0)* | −52.0 (47.0-55.0)* | 0.597        | 0.551   |
| Total CBA time (seconds) | 180.0 (180.0-300.0)* | 180.0 (180.0-300.0)* | 0.594        | 0.552   |
| Mean procedure duration (minutes) | 74.9 ± 27.7 | 80.0 (65.0-88.0)* | 1.629        | 0.103   |
| Mean LA dwell time (minutes) | 57.4 ± 20.8 | 61.0 (45.3-71.0)* | 1.157        | 0.247   |
| Mean fluoroscopy time (minutes) | 23.8 ± 10.0 | 24.4 ± 11.4 | 0.284        | 0.777   |
| Mean fluoroscopy radiation dosage (mgY) | 22.5 (16.8-33.1)* | 23.8 (18.0-31.4)* | 0.092        | 0.927   |
| Phrenic nerve injury (%)   | 1/42 (2.4%)     | 3/60 (5.0%)     | 0.023        | 0.879   |

Values are given as the mean ± SD. *Non-normally distributed data with the median and interquartile range in parentheses. Data were for 35 out of 42 patients; ◆ data were for 51 out of 60 patients; ▼ data were for 30 out of 42 patients; ▽ data were for 37 out of 60 patients; △ data were for 58 out of 60 patients; in the remaining patients, the TTI parameters were not available due to distal positioning of the ACHIEVE catheter to obtain better supporting force. TTI indicates time to isolation; CBA, cryoballoon ablation; LIPV, left inferior pulmonary vein; LIPV, left inferior pulmonary vein; RSPV, right superior pulmonary vein; RIPV, right inferior pulmonary vein; CBA, cryoballoon ablation; and LA, left atrium.
EPS revealed no coexisting PSVT.

**Complications during CBA and follow-up:** PNI occurred in 1 of 42 patients (2.4%) in group C and 3 of 60 patients (5.0%) in group N during RSPV CBA ($P = 0.879$). Three patients recovered within 30 minutes of observation, and the remaining 1 patient recovered during the 1-month follow-up period. No other complications, including pericardial effusion, groin complications, cerebrovascular events, or atrial esophageal fistula, occurred during the procedure or within the 1-year follow-up period.

**ATa recurrence within 48 hours after CBA and the following treatment:** After CBA, patients were continuously monitored with ECG telemetry for at least 48 hours. Eighteen of 42 patients (42.9%) in group C and 15 of 60 patients (25%) in group N showed recorded episodes of ATas. Due to atrial edema secondary to CBA, ATa conversion by EEC would be difficult, or the converted SR would be difficult to maintain. Patients were discharged 2 days after CBA as scheduled if their clinical status was stable. Patients were scheduled for a follow-up visit at 0.5 months after CBA. In group C, 3 of the 18 patients showed a restored SR, and the remaining 15 patients and another 4 patients with SR before discharge showed episodes of ATas followed by successful EEC. In group N, 5 of the 15 patients showed a restored SR, and the remaining 10 patients and another 3 patients with SR before discharge showed episodes of ATas followed by successful EEC if intravenous nifekalant administration did not successfully convert the ATas to SR.

**Three-month BP follow-up:** During the 3-month BP, 89 of 102 patients took oral amiodarone (87.3%), 2 of 102 patients took oral propafenone (1.9%) instead of amiodarone due to hypothyroidism, and the remaining 11 patients (10.8%) were not treated with AADs due to baseline sinus bradycardia of less than 55 beats per minute. At the end of the 3-month BP, ATa episodes were documented as ParAF in 5 of 42 patients (11.9%) and as PerAF in 11 of 42 patients (26.2%) in group C. ATa recurrence was documented as ParAF in 2 of 60 patients (3.3%) and as PerAF in 6 of 60 patients (10.0%) in group N. Patients with ATa episodes underwent successful EEC if intravenous nifekalant administration did not successfully convert the ATas to SR and continued treatment with AADs for another 3 months; AADs were discontinued if SR maintenance was observed at the 6-month follow-up.

**One-year follow-up:** ATa recurrence was documented as ParAF in 7 of 42 patients (16.7%) and as PerAF in 14 of 42 patients (33.3%) in group C. ATa recurrence was documented as ParAF in 5 of 60 patients (8.3%) and as PerAF in 12 of 60 patients (20.0%) in group N. The mean time to the first ATa episode was $6.1 \pm 2.7$ months in group C and 7.0 (3.0-10.5) months in group N, respectively.

**RFCA:** Of the 38 patients who had ATa recurrence, 32 patients (84.2%) decided to pursue medical treatment, and SR could be maintained in 7 patients (18.4%) with previously ineffective AAD treatment (propafenone or amiodarone), whereas 6 patients (15.8%) had been scheduled for a second procedure with RFCA to ablate the clinical ATas. In group C, 1 patient showed LSPV reconnection, and another patient showed a left atrium roof line-dependent flutter. In group N, 2 patients showed RIPV reconnection, 1 patient showed a mitral annulus-dependent flutter, and another patient showed a tricuspid isthmus-dependent flutter.

**Predictors of arrhythmia recurrence:** Multivariate Cox regression analysis demonstrated that unsuccessful conversion to SR ($P = 0.025$), ATa relapse during the BP, and larger LAV were independent predictors of PerAF recurrence. Unsuccessful conversion to SR independently predicted ATa recurrence with a 1.012-fold risk (95% CI $1.002-1.023$, $P = 0.025$). ATa relapse during the BP independently predicted ATa recurrence with a 6.032-fold risk (95% CI $2.891-12.587$, $P = 0.000$). For each additional 1 mL of LAV, the risk of ATa recurrence increased by 1.017-fold (95% CI $1.003-1.031$, $P = 0.016$) (Table IV).

**Discussion**

**Main findings:** This is the first study to assess the efficacy, safety, and predictive effect on the 1-year ATa-free survival of intravenous nifekalant administration for PerAF after PVI with second-generation CBA by examining the pharmacological conversion rate. The main findings of the current study are as follows: (1) At the 1-year follow-up, the ATa-free survival rate after PerAF with CBA without additional substrate modification was 62.7%.

(2) The conversion rate of intravenous nifekalant admini-
Table IV. Multivariate Cox Regression Analysis Indicating Predictors for PerAF Recurrence

| Variable                          | β coefficient | SE  | Wald  | Hazard ratio (95% CI) | P value |
|----------------------------------|---------------|-----|-------|-----------------------|---------|
| Age (years)                      | 0.007         | 0.020 | 0.107 | 1.007 (0.968-1.047)   | 0.743   |
| Unsuccessful conversion to SR    | 0.012         | 0.005 | 5.044 | 1.012 (1.002-1.023)   | 0.025   |
| BMI (kg/m²)                      | 0.016         | 0.056 | 0.079 | 1.016 (0.910-1.134)   | 0.778   |
| LA volume (cm³)                  | 0.017         | 0.007 | 5.761 | 1.017 (1.003-1.031)   | 0.016   |
| LA (mm)                          | 0.045         | 0.056 | 0.649 | 0.956 (0.856-1.067)   | 0.420   |
| LV (mm)                          | 0.009         | 0.047 | 0.033 | 0.991 (0.903-1.088)   | 0.856   |
| LVEF (%)                         | 0.016         | 0.026 | 0.358 | 0.984 (0.935-1.037)   | 0.549   |
| Female sex                       | 0.199         | 0.436 | 0.209 | 0.819 (0.348-1.926)   | 0.647   |
| Relapses in BP                   | 1.797         | 0.375 | 22.936| 6.032 (2.891-12.587)  | 0.000   |

SR indicates sinus rhythm; BMI, body mass index; LA, left atrium; LV, left ventricle; LVEF, left ventricular ejection fraction; and BP, blanking period.

Figure. ATa-free survival at the 1-year follow-up. Kaplan-Meier curve showing ATa-free survival of PerAF patients after the 3-month BP. Twenty-one patients (50%) in group C and 43 patients (71.7%) in group N showed ATa-free survival without AAD treatment at the 1-year follow-up (log-rank, P = 0.026). ATa indicates atrial tachyarrhythmia; BP, blanking period; PerAF, persistent atrial fibrillation; and AAD, antiarrhythmic drug.

CBA as an index procedure for PerAF: To date, PVI is the cornerstone of ablation for AF and represents the first step in AF ablation, and CBA has demonstrated satisfactory acute and mid-term clinical results by achieving PVI in nearly all PVs approached, with a very low incidence of acute reconnection. However, the role of additional line ablation and CFAE ablation at the time of the index procedure is still controversial and poorly standardized. Related studies compared three different RF ablation strategies in the treatment of PerAF: PVI alone, PVI plus linear ablation, and PVI plus CFAE ablation. PVI alone was not inferior to the other two strategies that involved additional substrate modification, which assumed that more extensive ablation may induce new substrate formation for arrhythmogenesis. Furthermore, previous studies have reported that PVI can lead to simultaneous cardiac ganglionated plexi modification, which will result in improved ATa-free survival after CBA for AF patients, which in turn can be considered an adjunctive effect of PVI. Thus, with the aim of applying PVI as the index procedure in the treatment of PerAF without concomitant arrhythmias that need RFCA, CBA is feasible. It is well known that the large 28-mm CB allows wide antral ablation by targeting the PVs that are important areas for AF initiation and maintenance. This leads to potential substrate modification in these regions, which certainly are involved in the persistence of PerAF. The clinical outcome might also be due to modification of the atrial substrate for arrhythmogenesis near the PV antrum or alteration of the influence of the intrinsic cardiac autonomic nervous system.

Pharmacological effect of intravenous nifekalant: PerAF is characterized by electrical remodeling marked by decreases in the atrial effective refractory period (ERP). Nifekalant is a pure class III AAD (pure IC₃ channel blocker) similar to ibutilide, used abroad; these drugs are distinguished from most other class III AADs, such as amiodarone, which block sodium and calcium currents as well as potassium currents. Nifekalant is usually used for ventricular arrhythmia but has the potential to convert ATas by increasing the atrial ERP. Usually, the effect of QT interval prolongation reaches a maximum within 2.5 minutes after the intravenous administration of a single bolus dose, and the effect of QT interval prolongation largely disappeared 5-30 minutes after administration. In our study, nonsustained VT occurred in 1 patient in group N. In this case, the QTc interval before intravenous nifekalant administration was 420 ms, and the longest QTc interval after intravenous nifekalant administration was 708 ms, occurring after 18 minutes. The QTc interval
In our study, although the LA diameter did not reach statistical significance as an independent predictor of PerAF recurrence, we still assume a low success rate of CBA in terms of clinical significance. Further long-term evaluations are necessary, including an assessment of PerAF recurrence and PV reconnection.

Conclusions
CBA is a safe and effective option as an index procedure for PVI for drug-refractory PerAF patients, with a favorable success rate of 62.7% at the 1-year follow-up. Multivariate Cox regression analysis demonstrated that unsuccessful conversion to SR ($P = 0.025$), ATa relapse during the BP, and larger LAV were independent predictors of ATa recurrence. Successful conversion to SR with intravenous nifekalant administration may indicate less severe electrical remodeling of the LA substrate and could serve as a clinical predictor of reduced ATa recurrence at the 1-year follow-up (50.0% versus 71.7%, $P = 0.026$).

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