Pulmonary vein isolation implemented by second-generation cryoballoon for treating hypertrophic cardiomyopathy patients with symptomatic atrial fibrillation: a case-control study

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Abstract

Background Atrial fibrillation (AF) is a generally acknowledged turning-point of the natural history of hypertrophic cardiomyopathy (HCM); however, data from the cryoballoon ablation (CBA) for AF in HCM patients are relatively scarce. The study aimed to evaluate the efficacy and safety of CBA in HCM patients with AF.

Methods We retrospectively analyzed HCM patients among 1253 patients with symptomatic AF who underwent CBA for pulmonary vein isolation in a single center. The study analyzed the AF recurrence and assessed the CBA indexes, including nadir temperature, time-to-isolation, CBA failure, pulmonary vein potentials (PVPs), and redo procedure.

Results A total of 108 patients were included (mean age: 59.0 ± 6.9 years), 27 patients (25%) had HCM, with the median follow-up duration of 25.5 months. The one-year AF-free rates were 79.0% vs. 63.0% (non-HCM vs. HCM), while the two-year AF-free rates were 77.8% vs. 55.1% [hazard ratio (HR) = 2.758, log-rank \( P = 0.024 \)]. Patients with persistent AF had poor AF-free rates compared to those with paroxysmal AF (\( P < 0.001 \)). The CBA failure was the most common in the right inferior pulmonary veins, which had the lowest PVPs. Multivariate Cox regression analysis indicated that HCM and persistent AF were risk factors for AF recurrence (HR = 2.74, 95% CI: 1.29–5.79, \( P = 0.008 \); and HR = 3.97, 95% CI: 1.85–8.54, \( P < 0.001 \), respectively).

Conclusions The CBA can be effectively and safely used to treat HCM patients with symptomatic AF. The freedom from AF for HCM patients after CBA is relatively low compared to that for non-HCM patients.

Keywords: Atrial fibrillation; Cryoballoon ablation; Hypertrophic cardiomyopathy; Pulmonary vein isolation

1 Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic heart disease with a high prevalence of comorbid atrial fibrillation (AF) (20%–25%).1,2 The AF increases the risk of embolic events or heart dysfunction in HCM patients.3 However, no randomized trials have examined the efficacy of antiarrhythmic drugs (AADs) in HCM patients with AF. Furthermore, the HCM patients with AF frequently show a poor response to AADs in clinical practice.4 For restoring and maintaining sinus rhythm, catheter ablation that was successively demonstrated as superior to AADs had an acceptably low complication rate.3,4 Additionally, cryoballoon ablation (CBA) was non-inferior to radiofrequency (RF) ablation with respect to its treatment efficacy of drug-refractory paroxysmal AF,5 while the prognostic index analysis displayed apparent superiority to RF ablation.6 However, clinical data are lacking about the efficacy and safety of CBA in HCM patients with AF.

This study aimed to evaluate the efficacy and safety of CBA using a 28-mm second-generation cryoballoon to reach pulmonary vein isolation (PVI) in HCM patients with AF in a single center.

2 Methods

2.1 Study population

We retrospectively included 108 consecutive patients (27...
HCM patients) among the 1253 patients with symptomatic AF who underwent CBA using a 28-mm second-generation cryoballoon catheter (Artic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) between January 2015 and February 2018 in Fuwai Hospital and completed at least two-year follow-up. Considering the relatively small number of HCM patients and complying with the statistical principle of an individual matching case-control study, each HCM patient was design-matched with three non-HCM patients. Selected non-HCM patients who were identified in the same period had matching clinical characteristics, including age, sex, AF type, body mass index, functional echocardiography data, and cardiovascular risk factors (e.g., hypertension, diabetes, coronary artery disease). The HCM diagnosis was defined as an asymmetrical and hypertrophied left ventricle with a wall thickness ≥ 15 mm in the absence of cardiac or systemic disease.[9] Patients with valvular AF (i.e., rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or a mitral valve repair history) were excluded. Moreover, patients with the following characteristics (i.e., left atrial thrombus, left atrial diameter > 50 mm, uncontrolled thyroid dysfunction, decompensated heart failure, severe coronary artery stenosis, contraindications to anticoagulation, pregnancy, post-ablation AF, and severe conduction system diseases) were also excluded. The definition of paroxysmal or persistent AF was made in accordance with the AF guidelines.[10,11] All patients’ baseline characteristics were recorded. This research was approved by the Ethics Committee of Fuwai Hospital (No.2016-829) and written consent was obtained from each individual patient.

2.2 Pre-procedural management

All patients underwent transthoracic echocardiography and cardiac computed tomography for the assessment of the left atrial anatomy and pulmonary veins (PVs) within one week before the procedure. Three days before the CBA, transesophageal echocardiography was used to rule out atrial thrombus and a proton-pump inhibitor was initiated to suppress gastric acid production. The AADs (except amiodarone) were discontinued a minimum of five half-lives before the procedure. Patients received vitamin K antagonists, and the international normalized ratio was maintained at 2.0–3.0. Oral anticoagulants, including novel oral anticoagulants, were withheld for 24 h before the procedure.

2.3 Mapping and CBA procedure

Surface and intracardiac electrocardiograms were amplified and displayed on the Bard system (Lab System PRO, Bard Electrophysiology, Lowell, MA, USA). Surface electrocardiograms and bipolar intracardiac electrograms were filtered at 0.05–40 Hz and 30–500 Hz, respectively. Vessel punctures were performed under local anesthesia. A 6F decapolar electrode catheter was advanced into the coronary sinus via the right internal jugular vein. Furthermore, a 6F quadripolar electrode catheter was positioned at the right ventricular apex via the left femoral vein. The transseptal puncture was guided by fluoroscopy. After access to the left atrium, a 100 UL/kg bolus of heparin was administered. The activated clotting time was monitored every 30 min to maintain a value of 300–350 s throughout the procedure.

Deep sedation was maintained with a continuous infusion of fentanyl and midazolam after a 12-hour fasting. Electrocardiography and oxygen saturation were continuously monitored. Noninvasive positive pressure ventilatory assistance was used in patients with sleep apnea or obesity throughout the CBA. The CBA was performed using a 28-mm second-generation cryoballoon catheter (Artic Front Advance, Medtronic, Inc., Minneapolis, MN, USA) inserted through a 12F steerable sheath (FlexCath, Medtronic, Inc., Minneapolis, MN, USA). The Achieve Mapping Catheter (Achieve Mapping Catheter, Medtronic, Inc., Minneapolis, MN, USA) was advanced into the left atrium via the inner lumen of the cryoballoon catheter to record the baseline pulmonary vein potentials (PVPs).

The cryoballoon was introduced into the PV ostium by rotating the steerable sheath and pushing the Achieve Mapping Catheter (Achieve Mapping Catheter, Medtronic, Inc., Minneapolis, MN, USA). The cryoballoon occlusion was evaluated using the selective angiography injection of contrast agent via the inner lumen of the cryoballoon catheter, and the ideal occlusion was indicated by the absence of contrast reflux into the left atrium with contrast agent retention.

Only one ablation cycle was used if the PVs were isolated within 60 s. The single ablation time for a second-generation balloon was ≤ 180 s. If PVI was achieved and PVP conduction did not recur, no bonus ablation was needed. In cases with a time-to-isolation (TTI) ≥ 60 s, a second cryoapplication within 180 s was performed. Additional cryoablation for focal PVs was performed at the physician’s discretion. The nadir temperature should not be lower than −60°C. The definition of CBA failure was unsuccessful PVI with five or more attempts of cryoapplication for a single PV. The heart rate to slow down caused by the vagal reflex during CBA could be increased by pacing the right ventricle or via the intravenous injection of raceanisodamine (a short-acting agent similar to atropine). During the CBA of right-sided PVs, the quadripolar catheter was positioned in the superior vena cava for phrenic nerve stimulation with 1500 ms cycle length and 20 mA high-
output. Phrenic nerve capture was monitored by intermittent fluoroscopy or tactile feedback. Whenever a decrease or loss of phrenic nerve capture was observed, the CBA was immediately terminated. Once AF continued at the end of the procedure, sinus rhythm was restored using 200-J cardioversion. Using an irrigated contact force ablation catheter (ThermoCool Smart Touch, Biosense Webster Inc., Diamond Bar, CA, USA), the RF touch-up ablation was performed to reach the PVI for CBA failure guided by the Achieve Mapping Catheter (Achieve Mapping Catheter, Medtronic, Inc., Minneapolis, MN, USA). In patients with recorded typical atrial flutter (AFL), the linear ablation of cavotricuspid isthmus (CTI) was required. A bidirectional block across the CTI was confirmed after the ablation. Thereafter, the pericardium was confirmed as normal on fluoroscopy.

2.4 Post-procedural management

After returning to the ward, all patients underwent trans-thoracic echocardiography to exclude pericardial effusion. Routine blood biochemistry variables, including clinical status, were assessed before discharge. On the other hand, the HCM patients received the continuous oral anticoagulant treatment if not contraindicated, irrespective of the CHA2DS2-VASc score, while non-HCM patients continued to take oral anticoagulants for at least two months without AADs. Thereafter, the specific anticoagulant strategies for non-HCM patients corresponded to individual CHA2DS2-VASc score. All patients continued to take pantoprazole 40 mg twice daily for at least two months. Moreover, patients with persistent AF received amiodarone continuously for three months to maintain the sinus rhythm and visited the doctors, if necessary, for monitoring the drug reactions.

2.5 Follow-up

All patients were scheduled for outpatient visits at one and three months, and then every three months after discharge. The follow-up included electrocardiography, Holter monitoring, and echocardiography. Telephone interviews were performed to screen for arrhythmia-related symptoms (e.g., palpitations, chest discomfort, fatigue, dizziness). Recurrence was defined as any episode of documented atrial arrhythmias (AAs) lasting for ≥ 30 s after the three-month blanking period. The ‘AF-free’ was defined as no-recurrence without AADs use. Patients with recurrence required readmission. The redo procedure confirmed recurrent conduction between the PVP and left atrium by mapping with a Decapolar Lasso Catheter (Biosense Webster Inc., Diamond Bar, CA, USA). After excluding the macro-reentry circuit and ectopic triggers outside the PVs, RF ablation of the PVs gap was performed in accordance with the PVI protocol using an irrigated contact force ablation catheter (ThermoCool Smart Touch, Biosense Webster Inc., Diamond Bar, CA, USA). Reaching the PVI of the target PV again was the endpoint of the redo procedure. If macro-reentry circuit was not excluded, three-dimensional activation electroanatomic mapping was useful for determining the macro-reentry isthmus. The linear ablation of isthmus was required to confirm the bidirectional block across the isthmus. Patients undergoing the redo procedure were not reenrolled into the AF-free group and simply identified as recurrence cases.

2.6 Statistical analysis

Continuous variables are expressed as mean ± SD, while categorical variables are expressed as percentage. The survival curve was delineated using the Kaplan-Meier method. The Cox proportional hazard regression model was used to analyze the risk factors of recurrence. Nonparametric tests were used to analyze continuous outcomes, and Fisher’s exact test or Pearson’s chi-squared test was used to examine categorical outcomes. A P-value of < 0.05 was considered statistically significant. All statistics were performed using SPSS version 20.0 (SPSS Inc, Chicago, IL, USA). The figures were generated using the GraphPad Prism version 5.0 (GraphPad Software, San Diego, CA, USA).

3 Results

3.1 Study population characteristics

Among the 108 enrolled and analyzed patients (mean age: 59.0 ± 6.9 years), 27 patients (25%) were HCM and 81 patients (75%) were non-HCM. A total of 89 patients (82.4%) had paroxysmal AF, while nineteen patients (17.6%) had persistent AF (four HCM patients and fifteen non-HCM patients). All patients had symptomatic palpitations that were refractory to one or two AADs. Transthoracic echocardiography confirmed that thirteen patients (48.1%), twelve patients (44.4%), and two patients (7.4%) had asymmetrical left ventricular apical hypertrophy, asymmetrical ventricular septal hypertrophy, and asymmetrical middle left ventricular hypertrophy, respectively. Of the 27 HCM patients, there were four patients with obstructive HCM (mean pressure gradient: 55.8 ± 7.1 mmHg) consisting of one patients with persistent AF and three patients with paroxysmal AF. One patient had obstructive sleep apnea syndrome.

All transesophageal echocardiography results excluded left atrial thrombus. For anticoagulation therapy, 33 patients (30.6%), 70 patients (64.8%), and five patients (4.6%) received rivaroxaban, dabigatran, and warfarin, respectively.
Table 1. Patients’ baseline demographic characteristics.

| Variable                        | HCM group (n = 27) | Non-HCM group (n = 81) | P-value |
|---------------------------------|--------------------|------------------------|---------|
| Paroxysmal AF                   | 23 (85.2%)         | 66 (81.5%)             | 0.777   |
| Type of HCM                     |                    |                        |         |
| Left ventricular apex            | 13 (48.1%)         | 0                      | -       |
| Interventricular septum         | 12 (44.4%)         | 0                      | -       |
| Left ventricle                  | 2 (7.4%)           | 0                      | -       |
| Anticoagulant drugs             |                    |                        |         |
| Warfarin                        | 2 (7.4%)           | 3 (3.7%)               | 0.597   |
| Rivaroxaban                     | 10 (37.0%)         | 23 (28.4%)             | 0.471   |
| Dabigatran                      | 15 (55.6%)         | 55 (67.9%)             | 0.255   |
| Age, yrs                        | 59.0 ± 6.9         | 59.0 ± 7.0             | 0.983   |
| Female                          | 4 (14.8%)          | 19 (23.5%)             | 0.424   |
| Body mass index, kg/m²          | 25.8 ± 3.0         | 25.6 ± 3.2             | 0.739   |
| AF duration, yrs                | 4.6 ± 3.9          | 5.6 ± 6.4              | 0.761   |
| Left atrial diameter, mm        | 40.9 ± 4.0         | 39.2 ± 4.8             | 0.091   |
| Left ventricular end-diastolic diameter, mm | 46.4 ± 4.7 | 47.5 ± 4.0 | 0.453 |
| Left ventricular ejection fraction, % | 64.5 ± 5.9 | 63.1 ± 4.6 | 0.347 |
| Interventricular septum, mm     | 15.6 ± 4.2         | 9.3 ± 1.2              | < 0.001 |
| Left ventricular posterior wall, mm | 11.1 ± 2.2 | 9.1 ± 1.0             | < 0.001 |
| Left common pulmonary vein      | 3 (11.1%)          | 4 (4.9%)               | 0.363   |
| Coronary artery disease         | 4 (14.8%)          | 7 (8.6%)               | 0.28    |
| Hypertension                    | 17 (63%)           | 43 (53.1%)             | 0.503   |
| Diabetes                        | 6 (22.2%)          | 21 (18.5%)             | 0.801   |

Data are presented as means ± SD or n (%). AF: atrial fibrillation; HCM: hypertrophic cardiomyopathy.

Three patients had right bundle branch block during sinus rhythm. All left ventricular ejection fractions were normal. The HCM group had a considerably thicker mean interventricular septum and left ventricular posterior wall than the non-HCM group. The maximal apex wall thickness of twelve apical HCM patients was 20.08 ± 3.18 mm, whereas that of the left ventricular posterior wall was 10.50 ± 1.38 mm; the maximal thickness of the interventricular septum was 18.33 ± 3.33 mm in thirteen septum HCM patients. Both patients with middle left ventricular hypertrophy had a maximal thickness > 20 mm. Eleven patients without the history of myocardial infarction had a confirmed diagnosis of mild coronary stenosis on coronary angiography. Baseline patient characteristics are summarized in Table 1.

3.2 CBA procedure

Before the procedure, 21 HCM patients (77.8%) and 60 non-HCM patients (74.1%) had sinus rhythm, while the remaining patients had AA rhythm. At the end of the CBA, 93 patients (86.1%) had sinus rhythm (23 HCM patients and 70 non-HCM patients), while the other fifteen patients (16.9%) required cardioversion to restore the sinus rhythm (ten persistent AF patients and five paroxysmal AF patients). The PVP recording rate of the left PVs and right superior pulmonary veins (RSPVs) in both groups was 90% or higher, while the right inferior pulmonary veins (RIPVs) result was approximately 80%. One left superior pulmonary vein (LSPV), one left inferior pulmonary vein (LIPV) and two RIPVs demonstrated CBA failure in HCM patients versus one LSPV and three RIPVs in non-HCM patients. All CBA failure episodes of PVs achieved PVI using touch-up RF ablation (Figure 1A).

![Figure 1](http://www.jgc301.com; jgc@jgc301.com | Journal of Geriatric Cardiology)
Two patients (1.9%) had transient phrenic nerve paralysis; after the immediate termination of CBA, the diaphragm resumed its normal rhythm of movement. Thirteen patients (12.0%) demonstrated a short-time vagal reflex. Two patients experienced mild hemoptysis prior to discharge. Thirty-seven patients (34.3%) underwent the linear ablation of CTI. The procedure time and fluoroscopy did not differ significantly ($P > 0.05$). No severe complications occurred during the procedure (e.g., hydropericardium, atrial esophageal fistula, and acute cerebrovascular event). Procedural characteristics are summarized in Table 2.

The nadir temperature and TTI of CBA did not differ between the HCM and non-HCM groups ($P > 0.05$). Furthermore, when divided into recurrence and no-recurrence subgroups, no significant difference was found in the nadir temperature ($P > 0.05$). Only the TTI of the LIPVs of the no-recurrence group was significantly lower than that of the recurrence group (48.4 ± 24.0 s vs. 63.4 ± 31.1 s; $P = 0.034$) (Figure 2). Data of the nadir temperature and TTI are shown in Tables 1S–4S (supplemental material).

### 3.3 Follow-up results

The median follow-up duration was 25.5 months (interquartile range: 12–36 months). Twelve of the 27 HCM patients (eleven HCM patients and one obstructive HCM patient) experienced AF recurrence, including four patients with persistent AF. The AA recurrence occurred in eleven patients with AF and in one patient with a combination of atrial tachycardia and AF. Five HCM patients underwent readmission for the redo procedure, and the gap sites were located at two LSPVs, two LIPVs, three RIPVs, and one contiguous site of the posterior roof of the LSPV and RSPV (Figure 1 B). Another seven recurrent HCM patients refused to undergo the redo procedure. The non-HCM group included 18 of the 81 patients with AF recurrence, including eleven patients with paroxysmal AF and seven patients with persistent AF. The AAs occurred in three patients, one patient, and fourteen patients with a combination of atrial tachycardia and AF, a combination of AF and typical AFL, and AF, respectively. The redo procedure ablated the gap sites of two LSPVs, one contiguous site of an LSPV and LIPV, two RSPVs, and two RIPVs (Figure 1B).

Finally, the one-year AF-free rates were 79.0% vs. 63.0% (non-HCM group vs. HCM group, respectively). The two-year AF-free rates were 77.8% and 55.1%, respectively [hazard ratio (HR) = 2.758, log-rank $P = 0.024$] (Figure 3A). Univariate Cox analysis showed that HCM, persistent AF, and cardioversion were risk factors for AF recurrence (HR =

### Table 2. Procedural characteristics of cryoballoon ablation.

| Variable                              | HCM group ($n = 27$) | Non-HCM group ($n = 81$) | $P$-value |
|---------------------------------------|----------------------|--------------------------|-----------|
| No sinus rhythm before procedure      | 6 (22.2%)            | 21 (25.9%)               | 0.801     |
| Pulmonary vein potential record       |                      |                          |           |
| LSPVs                                 | 25 (92.6%)           | 72 (88.9%)               | 0.727     |
| LIPVs                                 | 23 (85.2%)           | 68 (84%)                 | 0.879     |
| RSPVs                                 | 23 (85.2%)           | 74 (91.4%)               | 0.462     |
| RIPVs                                 | 21 (77.8%)           | 67 (82.7%)               | 0.575     |
| Nadir cryo-temperature, $^\circ$C    |                      |                          |           |
| LSPVs                                 | 47.7 ± 6.4           | 48.6 ± 5.8               | 0.581     |
| LIPVs                                 | 47.0 ± 6.4           | 45.1 ± 5.6               | 0.175     |
| RSPVs                                 | 51.3 ± 5.6           | 53.4 ± 4.5               | 0.063     |
| RIPVs                                 | 46.9 ± 5.7           | 49.1 ± 6.2               | 0.068     |
| Cardioversion                         | 4 (14.8%)            | 11 (13.6%)               | 0.872     |
| Cavo-tricuspid isthmus ablation       | 10 (37%)             | 27 (33.3%)               | 0.817     |
| Procedure time, min                   | 48.6 ± 10.7          | 49.0 ± 9.5               | 0.569     |
| Fluoroscopy time, min                 | 15.2 ± 5.3           | 17.9 ± 6.9               | 0.076     |
| Fluoroscopy dose, mGy                 | 238.5 ± 142.1        | 241.2 ± 156.0            | 0.873     |
| Phrenic paralysis                      | 1 (3.7%)             | 1 (1.2%)                 | 0.439     |
| Vagus reflex                          | 3 (11.1%)            | 10 (12.3%)               | 0.584     |
| Hemoptysis                            | 0                    | 2 (2.5%)                 | -         |
| Hydropericardium                      | 0                    | 0                        | -         |
| Acute cerebrovascular event           | 0                    | 0                        | -         |
| Atrial esophageal fistula             | 0                    | 0                        | -         |

Data are presented as means ± SD or $n$ (%). HCM: hypertrophic cardiomyopathy; LIPVs: left inferior pulmonary veins; LSPVs: left superior pulmonary veins; RIPVs: right inferior pulmonary veins; RSPVs: right superior pulmonary veins.
Figure 2. Comparison of the nadir cryotemperature and time-to-isolation. (A): The analysis of nadir temperature between the groups of HCM and non-HCM; (B): the analysis of nadir temperature between the groups of recurrence and no-recurrence; (C): the analysis of time-to-isolation between the groups of HCM and non-HCM; and (D): the analysis of time-to-isolation between the groups of recurrence and no-recurrence. HCM: hypertrophic cardiomyopathy; LIPV: left inferior pulmonary vein; LSPV: left superior pulmonary vein; RIPV: right inferior pulmonary vein; RSPV: right superior pulmonary vein.

Figure 3. The Kaplan–Meier estimates of AF-free rate. (A): The presentation of AF-free survival curve of patients with HCM and non-HCM; and (B): the presentation of AF-free survival curve of patients with persistent AF and paroxysmal AF. The black dots represent the censored patients. The solid and dotted lines show the survival probability. AF: atrial fibrillation; HCM: hypertrophic cardiomyopathy.

2.09, 95% CI: 0.98–4.40, \( P = 0.055 \); HR = 3.16, 95% CI: 1.49–6.71, \( P = 0.003 \); and HR = 2.14, 95% CI: 0.92–5.00, \( P = 0.078 \), respectively). The AF-free rate of persistent AF was 42.1% after two-year follow-up (HR = 6.09, 95% CI: 2.18–17.05, \( P < 0.001 \)) (Figure 3B). On multivariate Cox regression analysis, the HCM (HR = 2.74, 95% CI: 1.29–5.79, \( P = 0.008 \)) and persistent AF (HR = 3.97, 95% CI: 1.85–8.54, \( P < 0.001 \)) were independently associated with AF recurrence (Table 3). Of interest, the occurrence of AAs during the three-month blanking period was highly predictive.
Table 3. Univariate and multivariate Cox regression analysis results.

| Variable                        | B   | SE  | Wald | HR  | 95% CI for HR | P-value |
|---------------------------------|-----|-----|------|-----|---------------|---------|
|                                  |     |     |      |     | Lower         | Upper   |
| Univariate analysis             |     |     |      |     |               |         |
| HCM                             | 0.82| 0.37| 4.81 | 2.27| 1.09          | 4.71    | 0.028   |
| Age ≥ 60 yrs                    | −0.28| 0.37| 0.58 | 0.75| 0.37          | 1.55    | 0.446   |
| Male sex                        | −0.02| 0.46| 0.00 | 0.98| 0.40          | 2.39    | 0.961   |
| Persistent AF                   | 1.22| 0.38| 10.20| 3.37| 1.60          | 7.11    | 0.001   |
| Duration > 3 yrs                | 0.34| 0.40| 0.75 | 1.41| 0.65          | 3.08    | 0.388   |
| Hypertension                    | −0.10| 0.37| 0.07 | 0.91| 0.44          | 1.86    | 0.787   |
| Diabetes                        | 0.07| 0.46| 0.03 | 1.08| 0.44          | 2.63    | 0.873   |
| Coronary heart disease          | 0.02| 0.61| 0.00 | 1.02| 0.31          | 3.37    | 0.971   |
| Body mass index > 25 kg/m²      | 0.27| 0.38| 0.01 | 1.31| 0.62          | 2.76    | 0.473   |
| Left atrial diameter > 40 mm    | 0.54| 0.37| 2.15 | 1.71| 0.83          | 3.50    | 0.143   |
| Cardioversion                   | 0.76| 0.43| 3.10 | 2.14| 0.92          | 5.00    | 0.078   |
| Multivariate analysis           |     |     |      |     |               |         |
| HCM                             | 1.01| 0.38| 6.94 | 2.74| 1.29          | 5.79    | 0.008   |
| Persistent AF                   | 1.38| 0.39| 12.46| 3.97| 1.85          | 8.54    | <0.001  |

The factors with the statistical significance or clinical implications would enter the multivariate Cox regression analysis with the stepwise forward method. AF: atrial fibrillation; B: regression coefficient; CI: confidence interval; HCM: hypertrophic cardiomyopathy; HR: hazard ratio; SE: standard error.

4.1 Difference in AF-free rate after CBA of HCM versus non-HCM patients

The CBA of HCM patients with AF has been sparsely characterized. Maagh, et al.[12] did not recommend CBA in HCM patients with AF because of specific hemodynamic changes in HCM patients that commonly resulted in an early AF recurrence. However, RF ablation of paroxysmal AF in obstructive HCM patients obtained an ideal result after the short-term follow-up of 5.8 ± 2.7 months.[13] The outcome of nonpharmacologic treatment in HCM patients with AF from a prospective study also showed symptomatic improvement, but with low success and high complication rates during the long-term follow-up.[14] We conducted this study based on the FIRE AND ICE Study,[6] and found that HCM patients with AF had relatively low AF-free rate after CBA than non-HCM patients. Furthermore, the STOP AF Post-Approval Study showed AF-free rates of 81.6%, 73.8%, and 68.1% at 12, 24, and 36 months after CBA, respectively.[15] Omran, et al.[16] reported a success rate of 68.9% for the CBA of AF, and the Multicenter CRYO4 PERSISTENT AF Trial reported a single-procedure success rate of 61%.[17] Similarly, our result was reasonably close to the results of these studies.

4.2 Major pathophysiological mechanisms

The pathophysiological determinants are complicated for HCM patients. Firstly, the left ventricular diastolic dysfunc-
tion in HCM patients due to a non-compliant and asymmetrical hypertrophic left ventricle, such as the hypertrophic left ventricular apex, interventricular septum, and middle left ventricle reported in the present study, was always associated with an increased filling pressure. Abnormal diastolic performance was independent of cardiac symptoms or a subaortic pressure gradient. Secondly, the impaired cardiac vasodilator reserve and myocardial ischemia could result from overt or covert obstruction of the left ventricular outflow tract and the AAs. Thirdly, changes in the atrial structure under the background of complex cardiovascular abnormalities led to the inflammation waterfall, which induced necrosis and apoptosis of the atrial myocyte and heterogeneously altered impulse conduction and refractoriness, generating an arrhythmogenic substrate. In addition, basic research found that the activation of the signal pathway of atrial fibrosis and renin-angiotensin-aldosterone system generated multiple downstream profibrotic factors. Therefore, atrial fibrosis decreased the response to AF ablation, and affected the long-term AF-free survival. Although it was challenging to individually trace the specific pathophysiological mechanisms, all of the above-mentioned disease components partially contributed to the clinical course of post-ablation in HCM patients.

4.3 AF recurrence and AAs in the blanking period

Similar to the previously published study, recurrence during the blanking period, the only long-term AF recurrence or early AF recurrence predictor, was the only independent predictor for late AF recurrence apart from other clinical and echocardiographic variables. Our study found that the occurrence of AAs during the blanking period was associated with a high rate of AF recurrence, and HCM patients who experienced AAs during the blanking period had higher AF recurrence than non-HCM patients. Early AAs recurrence was associated with a lower long-term success rate in this study. Nevertheless, although the cornerstone ablation strategy of PVI is well-acknowledged for patients with paroxysmal AF, the single strategy of PVI implemented by CBA for HCM patients and those with persistent AF had controversies that whether performing the modification of ganglionated plexi and/or implementing relatively extensive atrial lesion.

4.4 PVP recording rate, CBA failure and risk factors of recurrence

Of note, our study showed that the RIPVs had the lowest PVP recording rate, at approximately 80%. The result was similar to that of a previous study, and in keeping with the anatomical findings regarding the relatively less extensive distribution of muscular sleeves around the inferior PVs than around the superior PVs. Moreover, the majority of CBA failures and PV reconnections occurring in the RIPVs might result from the posterior site of interatrial puncture. After all, interatrial puncture was not under intracardiac echocardiography guidance. The study of anatomical features of cardiac computed tomography further found that the extraordinary angle of the right-sided PVs was considered an anatomical feature significantly related to CBA failure. In addition, patients with persistent AF in this study had an AF-free rate of 42.1%. Similarly, recent studies found that the CBA of antral PVI versus RF catheter ablation of PVI in patients with persistent AF successfully maintained the sinus rhythm in 40%-50% of patients. In addition, the previous studies found that the enlarged left atrium was an independent predictor of AF occurrence and AF recurrence after PVI. But regrettably, this study could not detect the significant effect of left atrial diameter on AF recurrence.

4.5 Complication

The major complications of this study included phrenic paralysis and transient vagal reflex, including two cases of hemoptysis. The rate of phrenic paralysis, < 2%, was similar to that reported previously. Aryana, et al. reported a persistent phrenic paralysis rate of 1.6% versus 2.7% in the FIRE AND ICE Study, and 2.09% in another meta-analysis. Additionally, although a transient vagal reflex was commonly induced during the CBA of the left PVs, no severe adverse events occurred in the perioperative or follow-up periods.

4.6 Limitations

This study has some mentionable limitations. Firstly, this observational and retrospective study has a relatively small sample size and is conducted in a single center, and its preliminary results require further validation. Moreover, patients censored during follow-up and cases of persistent AF may have affected the AF-free rate of the study population. Secondly, we did not analyze the results of functional echocardiography and cardiac magnetic resonance owing to the drawback of retrospective data (i.e., filling pressures, E wave, A wave, and E/E'). The availability of data may have avoided the interpretation of AF recurrence of HCM patients. Furthermore, the survival curve after the two-year follow-up showed poor performance of a decreasing AF-free survival trend. The use of the implantable monitoring device may compensate for the undetected data.
4.7 Conclusions

The CBA can be effectively and safely applied for the treatment of HCM patients with symptomatic AF. The freedom from AF for HCM patients after CBA is relatively low compared to that for non-HCM patients. Clinically, prospective, randomized, multicenter trials will be useful for further investigating the efficacy and safety of CBA for HCM patients with AF.

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