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Cryoballoon Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy: From the Korean Cryoballoon Ablation Registry

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AUTHOR'S SUMMARY

This study addresses the unmet need for effective atrial fibrillation (AF) treatment in hypertrophic cardiomyopathy (HCM) patients, where data on cryoballoon ablation (CBA) are limited. The important finding is that approximately half of HCM patients remain free from atrial tachyarrhythmia recurrence 2 years post-CBA. Clinically, CBA is a viable rhythm control strategy with low complication rates in this population, although larger atrial sizes and persistent AF remain significant risk factors for recurrence.

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Conflict of Interest

The authors have no financial conflicts of interest.

Data Sharing Statement

The data generated in this study is available from the corresponding authors upon reasonable request.

Author Contributions

Conceptualization: Kim JY, Park SJ, Kwon CH, Shim J; Data curation: Kim JY, Kim MJ; Formal analysis: Kim JY, Lim HE; Funding acquisition: Kim JY; Investigation: Kim JY, Kim MJ; Methodology: Kim JY, Lim HE; Project administration: Kim JY; Supervision: Kim JY, Kim J, Park SJ, Lim HE; Visualization: Kim JY, Kim MJ; Writing - original draft: Kim MJ, Yang P; Writing - review & editing: Kim JY, Yang P, Kim J, Park SJ, Park KM, On YK, Lee S, Cha M, Kwon CH, Lee SH, Park J, Shim J, Oh I, Kim K, Kim J, Lim HE.

ABSTRACT

Background and Objectives: Atrial fibrillation (AF) occurs in more than 20% of hypertrophic cardiomyopathy (HCM) patients, further increasing the risk of stroke. Although radiofrequency catheter ablation in AF patients with HCM has been performed, data on cryoballoon ablation (CBA) in HCM patients are limited. We evaluated the efficacy and safety of CBA in HCM patients with AF.

Methods: The study included 2,649 patients with AF from the Korean CBA registry database with follow-up >12 months after de novo CBA. The primary efficacy outcome was recurrence of atrial tachyarrhythmias (ATs) ≥ 30 s after a 3-month blanking period.

Results: Totals of 1,176 paroxysmal AF (44.4%) and 1,473 persistent atrial fibrillation (PeAF, 55.6%) patients (mean age 61.7 years; 76.7% men) underwent de novo CBA. Compared to non-HCM patients (n=2,590), those with HCM (n=59) had larger left atrium and higher prevalence of heart failure, previous stroke or transient ischemic attack, and PeAF. Procedure-related complications were not statistically different between the 2 groups. During a mean follow-up period of 638 $\pm$ 308 days, 875 (33.0%) patients experienced recurrence of ATs (845 [32.6%] non-HCM patients and 30 [50.8%] HCM patients) (p=0.01). The overall AT-free survival rate at 2 years was 45.9% in HCM group and 63.3% in non-HCM group, respectively (p=0.014), whereas there was no significant difference between the two groups in PeAF.

Conclusions: CBA may be an effective rhythm control treatment for patients with AF and HCM, with an AT-free survival rate of approximately 50% at 2-year follow-up and low procedure-related complications.

Keywords: Atrial fibrillation; Catheter ablation; Hypertrophic cardiomyopathy

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a pathological condition characterized by myocardial hypertrophy, leading to thickening of the cardiac muscles and a variety of clinical outcomes. HCM is a common cardiac disease affecting about 1 in 500 adults and is known to be caused by a dominant mutation in sarcomere genes.¹⁾ These patients have an at least 4–6 times greater likelihood of developing atrial fibrillation (AF) than the general population,²⁾ and AF is the most common arrhythmia, observed in more than 20% of all HCM patients.³⁾ Additionally, patients with HCM often have diastolic dysfunction, and AF may occur at younger ages, resulting in persistent atrial cardiomyopathy.⁴⁾

Therefore, early initiation of rhythm control therapy is required when AF occurs in patients with HCM. Catheter ablation of AF has a high success rate as operator experience accumulates, and the ranges of indications and subjects are gradually expanding.⁵⁾ In addition, ablation modalities and energy sources are becoming more diverse. Previous studies have demonstrated that recurrence of AF was not significantly different between radiofrequency catheter ablation (RFCA) and cryoballoon ablation (CBA).^{6,7)} In particular, CBA demonstrated shorter procedure times, shorter learning curves, and less difference in outcomes among operators compared to RFCA.⁸⁾ These findings suggest that CBA is an effective treatment method for AF. However, data on AF ablation in patients with HCM are limited due to the exclusion of HCM patients from the FIRE and ICE trial.⁷⁾

Several observational studies showed that RFCA was safe and reasonably performed,⁹⁾ and AF was effectively controlled by reducing left atrial (LA) pressure in AF patients with HCM.¹⁰⁾ Meta-analysis revealed that the risk of AF recurrence was twofold higher and repeat procedures and antiarrhythmic drugs were more frequently needed in the HCM group compared to the control group; however, the procedure-related complication rate was very low.¹¹⁾ Therefore, RFCA can be effective in AF patients with HCM, particularly in patients with paroxysmal AF (PAF) and smaller LA. However, there are few reports about the effectiveness of CBA in AF patients with HCM. Therefore, we aimed to evaluate the efficacy and safety of CBA in AF patients with HCM from a large multicenter CBA registry.

METHODS

Ethical statement

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center in the Republic of Korea (IRB number: 2022-02-014-004). Retrieval of de-identified information was conducted retrospectively, and the requirement for informed consent was waived.

Study population

The Korean CBA registry consisted of cohort data from 12 tertiary institutes in Republic of Korea between May 2018 and June 2022. A total of 2,689 patients who underwent de novo CBA for treatment of drug-refractory AF was consecutively enrolled. HCM was defined as a wall thickness greater than or equal to 15 mm in one or more left ventricular (LV) myocardial segments, as measured by any imaging technique (echocardiography, cardiac magnetic resonance imaging, or computed tomography [CT]) that is not solely explained by abnormal loading conditions.¹²⁾ AF was classified as paroxysmal when it terminated spontaneously or occurred as intermittent episodes within 7 days of onset and as persistent when it was continuously sustained for more than 7 days, requiring intervention.¹³⁾ Heart failure (HF) was defined according to the definition used in the CHA₂DS₂-VASc score. It was characterized by clinical signs and symptoms of dysfunction in either the right or left side of the heart, confirmed through non-invasive or invasive methods.¹³⁾¹⁴⁾ Additionally, due to the rising prevalence of heart failure with preserved ejection fraction (HFpEF) and its increasing relevance to cardiovascular risk scores, we also included patients with HFpEF. HFpEF was defined as patients with a score of ≥ 5 on the HFA-PEFF score.¹⁵⁾ Data collection was conducted according to the principles outlined in the Declaration of Helsinki (2013) and Good Clinical Practices.

Cryoballoon ablation interventions

A pre-procedure transthoracic echocardiogram was performed, and baseline LA diameter, LA volume index (LAVI), E/e' ratio, and LV ejection fraction (LVEF) were measured according to the recommendations of the American Society of Echocardiography. Transesophageal echocardiography or chest CT was performed within 24 hours before CBA to rule out LA thrombus.

The CBA procedure generally conformed to the practice guidelines for CBA of AF,¹⁶⁾ and the application of detailed approaches and dosing protocols, including cryoenergy delivery time or number, fluoroscopic or intracardiac echocardiographic guidance for balloon positioning and occlusion, use of general anesthesia, and post-ablation testing, were at the discretion of each operator.

In the performance of all procedures, a 15-F steerable sheath (FlexCath, Advance Steerable Sheath; Medtronic, Inc., Dublin, Ireland) was used for introduction of a 28-mm CBA catheter (Arctic Front Advance; Medtronic, Inc.) into the LA. The CBA catheter was manipulated in the LA over a dedicated inner-lumen circular mapping catheter (Achieve; Medtronic, Inc.), which was used to record pulmonary vein (PV) potentials. The CBA catheter was inflated and advanced toward the antral surface of each PV. Freezing was initiated upon antral occlusion of the targeted PV. The number of cryoenergy applications and the duration of freezing were determined at the discretion of each operator, and PV isolation (PVI) was confirmed by blocking the entrance and exit after CBA.

Diaphragmatic stimulation with continuous pacing of the ipsilateral phrenic nerve occurred during right-sided CBA to avoid phrenic nerve paralysis. Freezing was immediately stopped upon detection of an attenuated diaphragmatic response. Additional RFCA of the cavotricuspid isthmus (CTI) was based on the operator's decision. The determination of the peri-procedural anti-coagulation regimen and discontinuation or re-initiation of antiarrhythmic drugs were at the discretion of each operator, and patients were discharged following the hospital's standard-of-care practice.

Patient follow-up and study outcomes

Patients were followed at the outpatient clinic at 1, 3, 6, 9, and 12 months and every 3–6 months thereafter. Whenever symptoms occurred after CBA, they were managed using the standard-of-care method of the hospital. Follow-up monitoring was performed according to the standard-of-care practice for each hospital. Rhythm monitoring was performed using any of the following methods, including 12-lead electrocardiogram (ECG), Holter or a single-lead ECG patch recording, or an insertable cardiac monitor. Any physician-proven atrial tachyarrhythmias (ATs) including AF, atrial flutter, and atypical atrial flutter in 12-lead ECG or lasting >30s in extended ECG monitoring after the initial 3-month blanking period was defined as clinical recurrence.

Statistical analysis

Continuous variables were reported as mean $\pm$ standard deviation, and group comparisons of continuous normal distribution variables were performed using Student's t-test or Wilcoxon rank-sum test (for non-parametric distribution data). Categorical variables were reported as numbers (percentages) and compared using the χ^2 test or Fisher's exact test (for non-parametric distribution data). Kaplan-Meier (K-M) analysis was used to evaluate the AT-free survival rate. To identify independent predictors of ATs recurrence, hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using multivariate Cox proportional hazards models, and variables that were statistically significant in univariate analysis or clinically relevant were used in the analysis. Mediation analysis was conducted to assess the indirect effect of LAVI on AT recurrence, using nonparametric bootstrapping to estimate CIs. Statistical significance was defined as a p value <0.05. All statistical analyses were conducted using R Statistical Software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline characteristics

Figure 1 shows the present study flow. A total of 2,649 patients was finally included in the analysis. **Table 1** describes the baseline characteristics of the study population. The mean

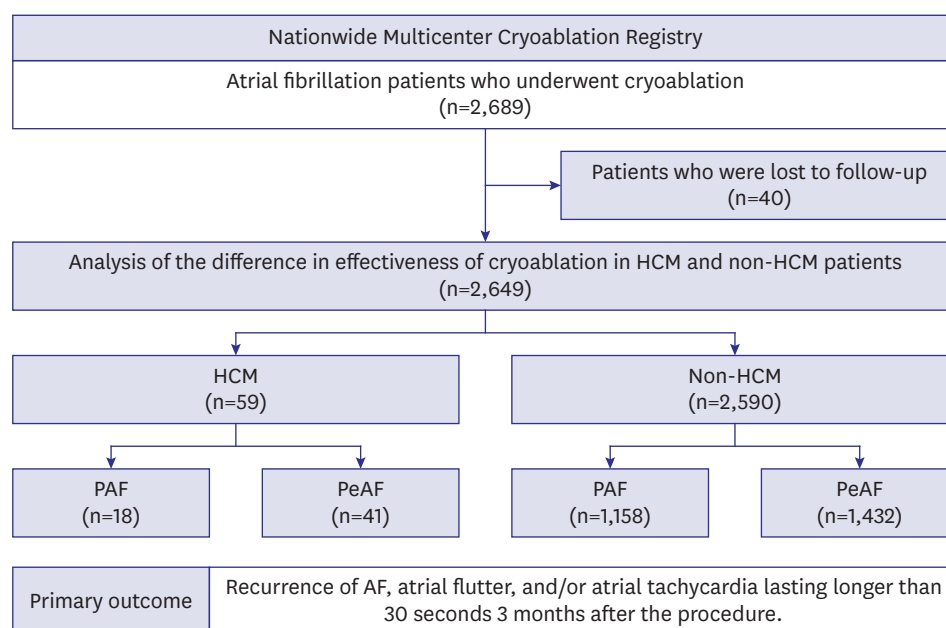


Figure 1. Study flow.

AF = atrial fibrillation; HCM = hypertrophic cardiomyopathy; PAF = paroxysmal atrial fibrillation; PeAF = persistent atrial fibrillation.

Table 1. Baseline clinical characteristics

Characteristic	Total (n=2,649)	Non-HCM (n=2,590)	HCM (n=59)	p value
Demographics				
Age (years)	61.7±10.0	61.7±10.0	61.6±9.7	0.937
Male	2,031 (76.7)	1,983 (76.6)	48 (81.4)	0.481
Body mass index (kg/m ²)	25.7±3.4	25.7±3.4	25.8±4.1	0.821
Left atrial AP diameter (mm)	43.8±6.8	43.6±6.7	51.3±7.6	<0.001*
LAVI (mL/m ²)	49.8±18.7	49.2±17.9	74.2±30.1	<0.001*
E/e' ratio	9.4±3.9	9.3±3.7	14.7±6.7	<0.001*
LVEF (%)	58.6±8.8	58.6±8.8	60.7±7.9	0.048*
CHA ₂ DS ₂ -VASc score	2.1±1.5	2.1±1.5	2.4±1.5	0.087
OAC use				
NOAC				0.113
Standard dose	1,961 (74.0)	1,920 (74.1)	41 (69.5)	
Reduced dose	436 (16.5)	421 (16.3)	15 (25.4)	
Warfarin	240 (9.1)	238 (9.2)	2 (3.4)	0.010*
Medical history				
DM	570 (21.5)	561 (21.7)	9 (15.3)	0.306
HTN	1,521 (57.4)	1,485 (57.3)	36 (61.0)	0.666
CKD	208 (7.9)	201 (7.8)	7 (11.9)	0.361
Coronary artery disease	216 (8.2)	211 (8.1)	5 (8.5)	>0.999
Prior stroke/TIA	309 (11.7)	296 (11.4)	13 (22.0)	0.043
Prior myocardial infarction	35 (1.3)	35 (1.4)	0 (0.0)	0.747
Heart failure	625 (23.6)	596 (23.0)	29 (49.2)	<0.001*
Mitral stenosis or prior MVR	26 (1.0)	26 (1.0)	0 (0.0)	0.916
Arrhythmia history				0.041*
Paroxysmal AF	1,176 (44.4)	1,158 (44.7)	18 (30.5)	
Persistent AF	1,473 (55.6)	1,432 (55.3)	41 (69.5)	

Values are presented as number (%) or mean ± standard deviation.

AF = atrial fibrillation; AP = anteroposterior; CKD = chronic kidney disease; DM = diabetes mellitus; E/e' ratio = E wave divided by e' velocity; HCM = hypertrophic cardiomyopathy; HTN = hypertension; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; MVR = mitral valve replacement; NOAC = non-vitamin K oral anticoagulant; OAC = vitamin K oral anticoagulant; TIA = transient ischemic attack.

*Statistically significant values (p value <0.05).

age of the patients was 61.7 ± 10.0 years, with a male predominance of 76.7%. PAF was observed in 44.4% of cases, and the mean body mass index was 25.7 ± 3.4 kg/m². The average diameter of LA was 43.8 ± 6.8 mm, the LAVI was 49.8 ± 18.7 mL/m², and the mean LVEF was $58.6 \pm 8.8\%$. The mean LA dimension in the HCM group was 51.3 ± 7.6 mm, with a mean LAVI of 74.2 ± 30.1 mL/m². These values were significantly higher than those observed in the non-HCM group (43.6 ± 6.7 mm, $p < 0.001$; 49.2 ± 17.9 mL/m², $p < 0.001$, respectively). In terms of diastolic function, the HCM group had a significantly higher E/e' ratio (14.7 ± 6.7) compared to the non-HCM group (9.3 ± 3.7). Additionally, the incidence of prior stroke/transient ischemic attack (TIA) was higher in the HCM group, along with a greater prevalence of HF. Furthermore, the proportion of patients with persistent AF (PeAF) in the HCM group (69.5%) was significantly higher than in the non-HCM group. Among the 1,473 patients in the PeAF group, 1,112 (75.6%) had long-standing PeAF, defined as AF lasting more than 1 year. Baseline characteristics in patients with PAF and PeAF are shown in **Supplementary Tables 1 and 2**, respectively. Compared with non-HCM patients, HCM patients had a larger LA size, more prevalent HF, and a higher E/e' ratio in PAF as well as PeAF.

Clinical outcomes

During a mean follow-up duration of 638 ± 308 days, ATs recurred in 875 (33.0%) patients after the 3-month blanking period. Of these, 845 (32.6%) were non-HCM patients and 30 (50.8%) were HCM patients. The K-M estimates for freedom from AT recurrence at 1 year were 60.0% in the HCM group and 72.6% in the non-HCM group. This trend continued at 2 years, with freedom from AT recurrence rates of 45.9% and 63.3% in the HCM and non-HCM groups, respectively (**Figure 2A**, log-rank $p = 0.014$). In subgroup analysis for patients with PeAF, the K-M estimates for freedom from AT recurrence at 1 year were 63.1% in the HCM group and 65.8% in the non-HCM group, and those at 2 years were 53.6% and 54.9%, respectively. There was no significant difference between the two groups (**Figure 2B**, log-rank $p = 0.76$). The results of the subgroup analysis, including comparisons according to age, sex, and LA size, are shown in **Figure 3**.

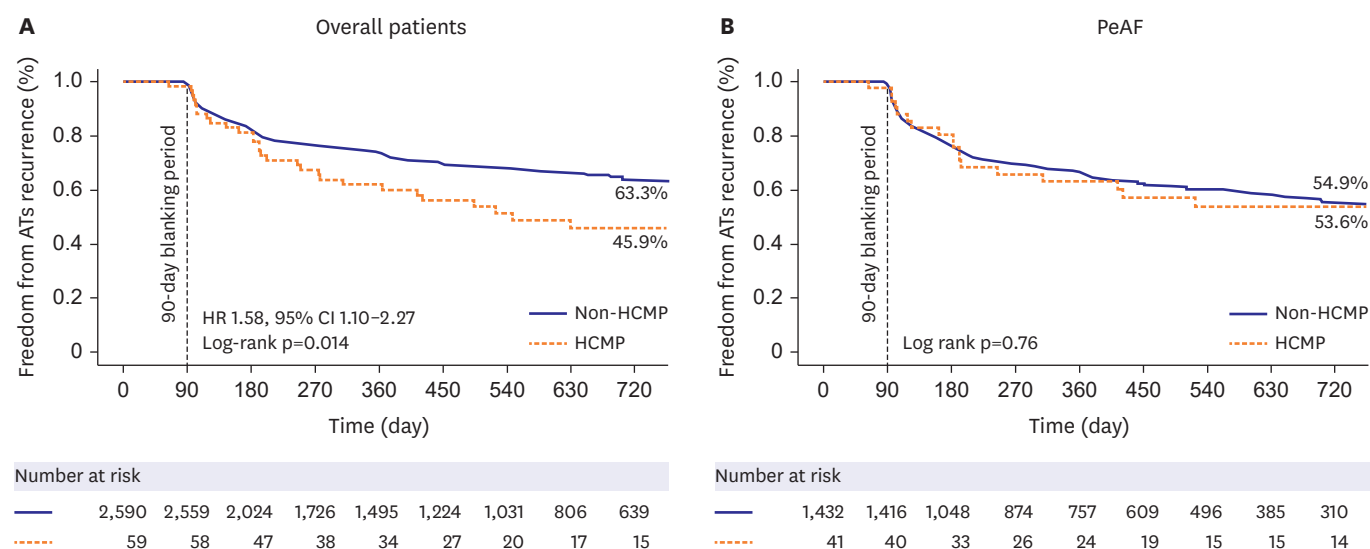


Figure 2. Primary outcome: freedom from AT recurrence based on the presence of HCM after the index cryoballoon ablation procedure. AT = atrial tachyarrhythmia; CI = confidence interval; HCM = hypertrophic cardiomyopathy; HR = hazard ratio.

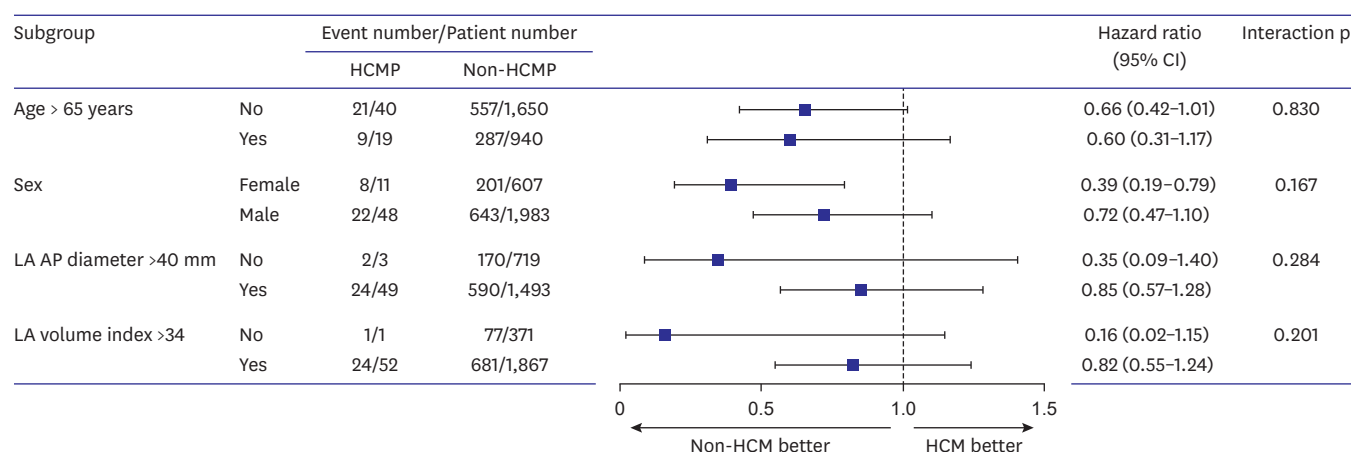


Figure 3. Subgroup analysis of primary outcome.

AP = anteroposterior; CI = confidence interval; HCM = hypertrophic cardiomyopathy; LA = left atrial.

Table 2 shows the univariate and multivariate analyses for assessing risk factors of AT recurrence. In univariate analysis, HCM was identified as a significant risk factor for recurrence of ATs (HR, 1.58; 95% CI, 1.10 to 2.27; $p=0.014$). However, a multivariate Cox proportional hazards model showed that the presence of HCM was no longer associated with AT recurrence (adjusted HR, 0.95; 95% CI, 0.58 to 1.56; $p=0.853$). After adjusting for other variables, PeAF and enlarged LA size were significant independent predictors of AT recurrence (adjusted HR, 2.01; 95% CI, 1.67–2.42 for PeAF; adjusted HR, 1.64; 95% CI, 1.37–1.96 for LAVI ≥ 46 mL/m²). To further explore the interplay between HCM, LA size, and AF recurrence, a mediation analysis was performed. The total effect was significant (0.133; 95% CI, [0.004, 0.270]; $p=0.046$), but this was predominantly driven by the mediated effect through LAVI (average causal mediation effect [ACME], 0.138; 95% CI, [0.090, 0.200]);

Table 2. Cox proportional hazard analysis of the recurrence of atrial tachyarrhythmia

	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	1.00 (0.99–1.00)	0.451		
Male	0.97 (0.83–1.13)	0.674		
DM	0.96 (0.82–1.13)	0.638		
HTN	0.88 (0.77–1.00)	0.053	0.94 (0.79–1.13)	0.513
CKD	0.95 (0.74–1.22)	0.674		
CAD	0.89 (0.69–1.14)	0.35		
Prior stroke/TIA	1.01 (0.83–1.24)	0.888		
Prior myocardial infarction	0.82 (0.44–1.52)	0.526		
Heart failure	0.96 (0.82–1.12)	0.625		
HCM	1.58 (1.10–2.27)	0.014*	0.95 (0.58–1.56)	0.853
Persistent AF	1.95 (1.69–2.24)	<0.001*	2.01 (1.67–2.42)	<0.001*
LA enlargement				
LAVI ≥ 46 mL/m ²	1.86 (1.61–2.15)	<0.001*	1.64 (1.37–1.96)	<0.001*
LVEF (%)	0.99 (0.99–1.00)	0.089	1.00 (0.99–1.01)	0.417
E/e' ratio	1.02 (1.00–1.04)	0.019*	1.00 (0.98–1.03)	0.735
CHA ₂ DS ₂ -VASc score	0.96 (0.92–1.00)	0.078	0.96 (0.90–1.03)	0.266
CTI ablation	0.65 (0.54–0.78)	<0.001*	0.90 (0.71–1.14)	0.392

AF = atrial fibrillation; AP = anteroposterior; CAD = coronary artery disease; CI = confidence interval; CKD = chronic kidney disease; CTI = cavotricuspid isthmus; DM = diabetes mellitus; E/e' ratio = E wave divided by e' velocity; HCM = hypertrophic cardiomyopathy; HR = hazard ratio; HTN = hypertension; LA = left atrium; LAVI = left atrial volume index; LVEF = left ventricular ejection fraction; TIA = transient ischemic attack.

*Statistically significant values (p value <0.05).

$p < 0.001$), as the direct effect (average direct effect [ADE]) was not significant (-0.005 ; 95% CI, $[-0.150, 0.140]$; $p = 0.854$) (**Supplementary Table 3**).

Procedure data and procedure-related complications are described in **Supplementary Table 4**. Catheter ablation at the CTI was performed in 563 (21.7%) non-HCM patients and 15 (25.4%) HCM patients, not statistically different between the 2 groups. Procedure-related complications occurred in 123 (4.6%) of the total population, with 119 (4.6%) in non-HCM patients and 4 (6.8%) in HCM patients and were not statistically different between the 2 groups. The rates of serious complications such as in-hospital cardiac surgery due to complications, acute myocardial infarction (AMI), cardiac arrest, stroke, and death were very low (less than 0.1%). The overall complication rates were similar between high-volume and low-volume centers. High-volume centers, defined as centers performing more than 150 CBAs annually, reported 97 complications out of 2,233 patients (4.34%), while low-volume centers reported 21 complications out of 456 patients (4.61%). Serious adverse events, including in-hospital death (1 case), stroke (3 cases), and myocardial infarction (1 case), occurred only in high-volume centers.

DISCUSSION

To the best of our knowledge, this is the first study from multicenter cohort data to report the effectiveness of CBA in Asian AF patients with HCM. Although a previous study has explored the effectiveness of CBA in Chinese AF patients with HCM, the sample size was relatively small and confined to a single center, which limited the generalizability of its findings.¹⁷⁾ The noteworthy findings of the present study are as follows. (1) After de novo CBA, approximately half of the AF patients with HCM were free from AF relapse at a follow-up of 2 years, although HCM patients had a higher recurrence rate of ATs compared with non-HCM patients, (2) However, there was no significant difference in the AT recurrence rate between HCM and non-HCM patients in the PeAF group, (3) PeAF and larger LA size were significantly associated with AT recurrence, but HCM was not an independent risk factor for AT recurrence.

AF is the most common sustained arrhythmia in patients with HCM, with a prevalence 4 to 6 times higher than in the general population.²⁾ Genetic predisposition, structural abnormalities, and electrophysiological irregularities all contribute to the high incidence of AF in HCM patients. In particular, chronic atrial dilatation, diastolic dysfunction, mitral regurgitation due to systolic anterior motion of the mitral valve, and underlying atrial myopathy facilitate electrical remodeling in HCM.¹⁸⁾ Furthermore, the risk of ischemic stroke in AF patients with HCM is higher than in AF patients without HCM, irrespective of the CHA₂DS₂-VASc score. This emphasizes the importance of anticoagulation therapy and careful management in all HCM patients with AF.¹⁹⁾²⁰⁾

For rhythm control management, conventional antiarrhythmic drug therapy is less effective in AF patients with HCM than in AF patients without HCM, and concerns about antiarrhythmic drug side effects often limit long-term use.²¹⁾ Therefore, previous studies regarding non-pharmacologic treatments, which focus on RFCA, have been conducted in AF patients with HCM.¹⁰⁾²²⁾ In a retrospective multicenter study of 61 patients with AF and HCM (43% non-PAF), RFCA resulted in an AT recurrence rate of 33% during a 29 ± 16 month follow-up period and a significant improvement in symptoms.²³⁾ Subsequently, Castagno et al.²²⁾ conducted a prospective multicenter study involving 116 AF patients with HCM (63% non-PAF).

They demonstrated that the AF recurrence rate after index RFCA was 32.3 per 100 patient/years, with 26% of patients free from AF relapse at the 6-year follow-up. Among patients experiencing AT recurrence, 51 (66%) underwent at least one repeat procedure. These results are comparable to our finding that the recurrence rate of ATs was 54.1% over a 2-year follow-up although the ablation method for PVI was different.

The present study also revealed that the AT recurrence rate following de novo CBA of AF was significantly higher in the HCM patients compared with the non-HCM patients, especially in the PAF group. Interestingly, when the analysis was confined to patients with PeAF, there was no difference in the AT recurrence rate between HCM and non-HCM patients. Moreover, after adjusting for potential confounders in the multivariate analysis, HCM was no longer directly associated with AT recurrence. Instead, persistent AF and LA enlargement were more strongly associated with recurrence. Given these findings, we conducted a mediation analysis to further explore the role of LAVI in linking HCM to recurrence. The analysis revealed that while HCM itself did not exhibit a statistically significant direct effect on recurrence (ADE), the indirect pathway mediated by LAVI (ACME) was highly significant. This indicates that the increased recurrence risk in HCM patients is primarily driven by LA remodeling. Overall, the findings emphasize the critical role of AF burden and electrical or anatomical atrial remodeling in predicting recurrence after ablation.

In terms of AF ablation, PV is the primary triggering focus, and substrate modification or targeting non-PV foci may not be necessary in the early stage of AF. However, HCM patients have not only ventricular myopathy, but also atrial myopathy, which facilitate electrical remodeling even in the early stage of AF. This leads to structural remodeling of LA such as increased LA size and a tendency to progress from PAF to PeAF. Previous studies have shown that LA size and AF burden are important predictors of AT recurrence after CBA.^{24)–26)} Our study also showed that HCM patients in the PAF group had a larger LA size, a higher E/e' ratio, and a higher prevalence of HF compared with non-HCM patients. This resulted in a significantly higher AT recurrence rate in HCM patients compared with non-HCM patients because only PVI by CBA was performed in our cohort. Moreover, it is noteworthy that we offered ablation to patients with such a dilated atrium, considering the extremely high LAVI in the HCM patients with PeAF (80.2 ± 31.7 mL/m²). These findings may be related to the distinctive characteristic of myocardial substrate generation in HCM, which contributes to fibrotic atrial cardiomyopathy. Efremidis et al. demonstrated extensive LA fibrosis detected by electroanatomical mapping in HCM patients, and the extent of fibrosis was the only predictor of AT recurrence.²⁷⁾

Castagno et al.²²⁾ conducted a study to evaluate the efficacy of RFCA with variable lesion sets as well as PVI in AF patients with HCM. A total of 116 patients was enrolled in their study, of whom only 19% underwent PVI alone. The remainder underwent additional linear ablation in various areas, including the roof of the LA, the left inferior PV to the mitral isthmus, and complex atrial fractionated electrogram ablation in a specific subset of patients. They demonstrated favorable outcomes, with 61% of patients maintaining sinus rhythm at the 6-year follow-up, although most patients required a repeat procedure. CBA is simpler and more specific for PVI compared to conventional RFCA. However, it is less effective in treating AF patients with extra-PV foci.²⁸⁾ In this context, CBA may have its own limitations in patients with AF and HCM. This is because AF triggering by non-PV foci has been reported in HCM patients,²⁹⁾³⁰⁾ and ablation of non-PV foci with CBA alone is challenging, potentially contributing to the high recurrence rate. Nevertheless, Creta et al. demonstrated that CBA

in patients with HCM is as safe and effective as RFCA, offering comparable success rates in maintaining sinus rhythm during the first year post-procedure. Although RF ablation may offer some versatility, particularly in addressing the complex atrial substrates commonly observed in HCM, CBA remains a robust and effective option, especially when only PVI is sufficient for the patient, such as in cases of PAF and low AF burden.³⁰⁾

Regarding complications, the rates of major complications, including pericardial effusion and cardiac tamponade, were remarkably low in our study. Specifically, the incidence of pericardial effusion was 0.8% in the overall cohort and 1.7% in the HCM group, while the rate of cardiac tamponade was 0.3%, with no cases reported in the HCM population (**Supplementary Table 4**). These results contrast sharply with those of Creta et al.,³⁰⁾ who reported a significantly higher rate of major complications, particularly cardiac tamponade, which occurred at a rate 4 times higher in HCM patients compared to non-HCM series (6.6% per patient and 4.0% per procedure). The increased risk of tamponade in Creta's study likely reflects the challenges posed by the complex anatomy of HCM patients during transseptal puncture, as well as the low hemodynamic tolerance to even small pericardial effusions due to diastolic dysfunction.

In our data, the lower complication rates may be attributed to the widespread use of intracardiac echocardiography (ICE). ICE was used in nearly 90% of procedures (89.8% in HCM patients), providing real-time imaging that likely minimized the risks associated with transseptal puncture, particularly in the anatomically challenging hearts of HCM patients. In addition, the higher rate of general anesthesia in patients with HCM (44.1% vs. 31.5% in non-HCM patients) may have contributed to better procedural control and patient stability, further reducing the risk of complications.

Importantly, high-volume centers (performing >150 procedures annually) and low-volume centers demonstrated similar overall complication rates (4.34% vs. 4.61%), demonstrating the consistency and reliability of CBA procedures across different operators and institutions. Serious adverse events, including in-hospital death, stroke, and myocardial infarction, were observed only in high-volume centers.

The sample size of HCM patients in the present study was relatively small (n=59), which not only limited the number of events available for analysis but also impeded a comparative analysis in the PAF group due to the limited number of patients with HCM and PAF (n=18). Although the multivariate analysis indicated that HCM is not a risk factor for recurrence, the small number of events in the HCM group may have affected the power of this analysis. Additionally, this study did not include data on arrhythmia burden before and after the ablation procedure. Moreover, data on procedural metrics such as procedure time, contrast medium doses, fluoroscopy duration, cryo-energy applications, and freezing duration were not collected, limiting a comprehensive evaluation of procedural performance. Furthermore, the absence of mortality data in our study precluded the possibility of conducting a competing risk analysis to address potential bias introduced by events such as death. Although our findings may not be generalizable, they may be very clinically meaningful as data on CBA in HCM patients are very limited. Further large-scale, multicenter cohort data are needed to address these issues.

Approximately half of AF patients with HCM had an AT-free survival rate over a 2-year follow-up after de novo CBA, although HCM patients had a higher recurrence rate of ATs

compared with non-HCM patients. There were no statistical differences in procedure-related complication rates between the HCM and non-HCM groups. The AT recurrence rate in patients with HCM and PeAF was similar to that in patients with non-HCM and PeAF. HCM is not an independent risk factor for AT recurrence. CBA might be considered an option for rhythm control strategy in HCM patients.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Baseline clinical characteristics for paroxysmal atrial fibrillation

Supplementary Table 2

Baseline clinical characteristics for persistent atrial fibrillation

Supplementary Table 3

Results of the mediation analysis

Supplementary Table 4

Procedural characteristics

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