Radiofrequency catheter ablation is effective for atrial fibrillation patients with hypertrophic cardiomyopathy by decreasing left atrial pressure

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Abstract

Background: Radiofrequency catheter ablation (RFCA) for atrial fibrillation (AF) refractory to medical therapy remains controversial in patients with hypertrophic cardiomyopathy (HCM); the acute effects on the direct left atrial (LA) pressure are not completely understood.

Methods: We consecutively studied patients with HCM (n=15) and without HCM (NHCM, n=106) who underwent extensive encircling pulmonary vein isolation for drug-refractory AF. We compared clinical parameters, echocardiographic parameters, electrophysiological parameters, LA pressures using hemodynamic catheterization and recurrence rate in both groups.

Results: The LA volume index was significantly higher (51.9 ± 13.6 mL/m² vs. 41.6 ± 12.7 mL/m², p=0.02) in the HCM group than the NHCM group. The pre-ablation mean LA pressure was significantly higher in the HCM group than the NHCM group. Among the AF patients, the mean LA pressure decreased more significantly in the HCM group than the NHCM group (post-ablation minus pre-ablation pressures: 4.2 ± 3.7 mmHg vs. 0.9 ± 4.1 mmHg, p=0.03). The early recurrence rate (within 30 days after ablation) tended to be higher in the HCM group than the NHCM group (20% vs. 5.7%, p=0.08), but the rates of late recurrences (> 30 days after ablation) were similar (13.3% vs. 7.6%, p=0.83). Discontinuation of antiarrhythmic drugs occurred at rates of 13% and 62% in the HCM and NHCM groups, respectively (p < 0.001).

Conclusions: The LA pressure in the HCM group decreased immediately after AF RFCA. Patients with HCM and drug-refractory AF may benefit from RFCA.

1. Introduction

Atrial fibrillation (AF) is a common complication in patients with hypertrophic cardiomyopathy (HCM), occurring at a prevalence greater than 20% [1]. When AF is refractory to medical therapy in these patients, it is associated with a worse clinical status and a significant increase in the risk of stroke, heart failure, and death [2]. Moreover, maintaining long-term sinus rhythm with antiarrhythmic drug (AAD) therapy alone is often difficult in HCM because the associated diastolic dysfunction facilitates increased left atrial (LA) pressures and exacerbates LA remodeling, eventually leading to further AF [3].

Radiofrequency catheter ablation (RFCA) has recently emerged as an important non-pharmacological treatment for AF. However, the maintenance of sinus rhythm after RFCA is considered difficult because of the left ventricular diastolic dysfunction in HCM.

Consequently, whether or not RFCA leads to favorable outcomes remains controversial [4,5]. We evaluated the long-term efficacy of extensive encircling pulmonary vein isolation (EEPVI) for drug-refractory AF in HCM patients. Furthermore, we investigated the acute effects of the direct LA pressure in patients with HCM and without HCM (NHCM).

2. Materials and methods

2.1. Study population

Patients from Hiroshima University Hospital were retrospectively included. We included 15 patients with HCM who underwent their first session of RFCA for drug-refractory symptomatic AF between January 2009 and January 2013. No patient with HCM underwent additional substrate modification beyond EEPVI. We included 173 patients without HCM who underwent their first session of RFCA for drug-refractory symptomatic AF between January 2011 and December 2011. We excluded patients

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with severe valvular disease \( (n=10) \), congenital heart disease \( (n=1) \), left ventricular ejection fraction \(< 40\%\) \( (n=10) \), old myocardial infarction \( (n=3) \), or those who were on long-term hemodialysis \( (n=2) \). We also excluded patients who underwent additional substrate modification beyond EEPI (e.g., superior vena cava isolation, \( n=10 \); roof line ablation, \( n=24 \); and mitral annulus ablation, \( n=7 \)). Finally, we enrolled 121 patients who were divided as follows: 15 patients with HCM (HCM group, 12 male patients, 62 ± 8 years of age) and 106 patients without HCM (NHCM group, 82 male patients, 61 ± 9 years of age). HCM was diagnosed based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle (LV maximum wall thickness \( \geq 15 \) mm) in the absence of any other cardiac or systemic disease capable of producing an evident magnitude of hypertrophy [6]. Paroxysmal AF was defined as recurrent AF (\( > 2 \) episodes) that spontaneously terminated within 7 days. Persistent AF was defined as AF that was sustained beyond 7 days or lasted \(< 7 \) days but necessitated pharmacological or electrical cardioversion. Longstanding persistent AF was defined as continuous AF with a duration \( > 1 \) year [7]. This study was approved by the ethical committee of Hiroshima University Graduate School of Biomedical and Health Sciences.

2.2. Echocardiography

Transesophageal and transthoracic echocardiography were performed within 24 h before ablation to exclude the presence of an LA thrombus or structural heart disease, using commercially available ultrasonographic systems (iE33; Philips Medical Systems, Best, The Netherlands). Echocardiography measurements were taken in accordance with the recommendations of the American Society of Echocardiography.

2.3. Electrophysiological study and RFCA

Patients were treated with warfarin for at least 1 month before the procedure and throughout the periprocedural period, without interruption, maintaining a prothrombin time–international normalized ratio of 2.0–3.0. AADs such as \( \beta \)-blockers, but excluding amiodarone, were stopped at least five half-lives before the procedure. Amiodarone was routinely discontinued at least 2 weeks prior to the procedure.

EEPI and bidirectional cavotricuspid isthmus blocks were performed, as reported previously [8]. After two circular mapping catheters (Lasso; Biosense Webster, Diamond Bar, CA, USA) were positioned within the ipsilateral superior and inferior pulmonary veins (PVs) under the guidance of selective PV angiography, continuous EEPI was performed during the first ablation to achieve electrical isolation of the left- and right-sided PVs (in pairs); EEPI was performed 0.5–2 cm from the PV ostia, as defined by PV angiography and a three-dimensional electro-anatomical mapping system (CARTO3; Biosense Webster) with computed tomography integration (CARTOMERGE; Biosense Webster). At the anterior aspect of the left PVs, ablation was attempted along the ridge between the LA appendage (LAA) and PV ostia. EEPI was performed using an irrigated 3.5-mm tip electrode catheter (THERMOCOOL; Biosense Webster). Radiofrequency energy was delivered for 15–20 s at each point around EEPI line to achieve a reduction in the amplitude of the local bipolar atrial electrogram of \( > 80\% \) or \(< 0.1 \) mV. If AF persisted after completion of EEPI line, cardioversion was performed to restore sinus rhythm. Successful PV isolation was defined as the loss of all PV potentials (entrance block) and failure to capture the LA when pacing from the PV (output 10 mA; pulse width 2 ms; exit block) using circular multipolar mapping catheters. These maneuvers were repeated after 20–60 min to exclude acute PV reconnections. We performed only EEPI or trigger-based RFCA in the first session because there was no useful evidence of effective additional substrate modification beyond EEPI. For patients who recurred after EEPI without reconnection of the PV or the other PV foci, we performed additional substrate modification beyond EEPI. These patients were excluded from this study.

We performed a bidirectional cavotricuspid isthmus block with an endpoint of bidirectional conduction block in all patients following EEPI. After stable sinus rhythm, an electrophysiological study was performed (within 1 h). AA (onset or peak of one atrial signal to the same aspect of the next consecutive signal), AH (atrial signal to the His bundle), and HV (His bundle to the first ventricular activation) intervals were measured. The corrected sinus node recovery time (cSNRT) was defined as the recovery interval in excess of the sinus cycle (i.e., cSNRT = max SNRT – sinus cycle length). Significant ablation-related complications were considered to include the following: death, stroke, peripheral emboli, cardiac tamponade or perforations, valvular damage, arteriovenous fistulae requiring surgical intervention, and a large vascular access-site hematoma resulting in a drop in the hemoglobin level by 20 g/L.

2.4. Measurement of LA, right atrium, and arterial pressures

All patients were prohibited from eating and drinking for 12 h before ablation. They were infused with 500 mL of normal saline solution 3 h before the ablation; the infusion was maintained at a rate of 20 mL/h during the ablation. No diuretics were used. The LA, right atrium (RA), and arterial pressures were measured using a water-filled system at two time points (i.e., just after the transseptal puncture and after completion of the EEPI). Mean values were obtained by averaging at least three beats.

2.5. Follow-up

Patients were restarted on suitable AADs prior to discharge according to the results of the electrophysiological study. The primary endpoint was to assess the maintenance of sinus rhythm regardless of whether they were taking AADs or not. In HCM patients, AADs were continued regardless of whether the arrhythmia recurred. Each patient was followed by clinic visits with 12-lead electrocardiogram, echocardiography, and 24-hour

| Table 1A Clinical characteristics. |
|-----------------------------------|
| NHCM group \( (n=106) \) | HCM group \( (n=15) \) | \( p \) Value |
|---|---|---|
| Age (years) | 61 ± 9 | 62 ± 8 | 0.88 |
| Male | 82 (77%) | 12 (80%) | 0.82 |
| AF type (paroxysmal, persistent, long) | 68/18/19 | 9/4/2 | 0.66 |
| Duration of AF (months) | 26 (8-52) | 36 (6-60) | 0.69 |
| Hypertension | 50 (47%) | 7 (48%) | 0.97 |
| Diabetes mellitus | 18 (17%) | 2 (13%) | 0.72 |
| Dyslipidemia | 31 (30%) | 3 (20%) | 0.44 |
| Body mass index (kg/m\(^2\)) | 23 ± 3 | 26 ± 4 | < 0.01 |
| Current smoker | 14 (13%) | 3 (20%) | 0.51 |
| Procedure duration (h) | 3.5 ± 0.7 | 4.3 ± 1.2 | 0.01 |
| eGFR < 60 mL/min per 1.73 m\(^2\) | 19 (18%) | 6 (40%) | 0.06 |
| Medications before RFCA |
| Class I AADs | 32 (31%) | 7 (46%) | 0.23 |
| Amiodarone | 17 (16%) | 5 (33%) | 0.14 |
| Bepridil | 11 (11%) | 1 (6%) | 0.64 |
| \( \beta \)-blocker | 28 (27%) | 9 (60%) | 0.01 |

AF, atrial fibrillation; eGFR, estimated glomerular filtration rate; RFCA, radiofrequency catheter ablation; AADs, antiarrhythmic drugs. Values are expressed as mean (standard deviation) or median (inter-quartile range) or absolute number of cases (relative percentage) as appropriate. \( p \) Values were two-tailed, and \( p < 0.05 \) was considered statistically significant.
Holter monitoring at 1, 3, and 6 months and every 6 months thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. In addition, patients were instructed to seek medical attention thereafter. 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differences were observed between the two groups in the SNRT, cSNRT, %SNRT, atrial–ventricular node (AVN) 1:1 conduction, or the AH interval. The HV interval and AVN effective refractory period were significantly longer in the HCM group than the NHCM group.

Table 3
Electrophysiological study.

|                     | NHCM group (n=106) | HCM group (n=15) | p Value |
|---------------------|--------------------|-----------------|---------|
| SNRT (ms)           | 1401 ± 741         | 1588 ± 730      | 0.42    |
| A-A interval (ms)   | 826 ± 163          | 928 ± 340       | 0.68    |
| CSNRT (ms)          | 448 (309-591)      | 528 (267-614)   | 0.60    |
| %SRT (%)            | 159 ± 53           | 164 ± 48        | 0.95    |
| AVN1:1 conduction   | 154 ± 25           | 149 ± 37        | 0.82    |
| AH interval (ms)    | 89.4 ± 24.4        | 107.8 ± 44.1    | 0.10    |
| HV interval (ms)    | 41.3 ± 8.5         | 48.0 ± 7.2      | 0.01    |
| AVN-ERP (ms)        | 275 ± 80           | 360 ± 65        | <0.01   |

SNRT, sinus node recovery time; CSNRT, corrected sinus node recovery time; %SRT, sinus node recovery time expressed in percentage of spontaneous cycle length; AVN1:1, the point of the Wenckebach block; AVN-ERP, the effective AV node refractory period.

Values are expressed as mean (standard deviation) or median (inter-quartile range) as appropriate. P values were two-tailed, and p < 0.05 was considered statistically significant.

Table 4
Medications administered after RFCA.

|                        | NHCM group (n=106) | HCM group (n=15) | p Value |
|------------------------|--------------------|-----------------|---------|
| Medications at discharge |                    |                 |         |
| Class I AADs           | 61 (59%)           | 9 (60%)         | 0.92    |
| Amiodarone             | 20 (19%)           | 5 (33%)         | 0.23    |
| Bepridil               | 30 (29%)           | 2 (13%)         | 0.20    |
| β-blocker              | 13 (13%)           | 9 (60%)         | <0.001  |
| Discontinuation of AADs| 66 (62%)           | 2 (13%)         | <0.001  |

RFCA, radiofrequency catheter ablation; AADs, antiarrhythmic drugs. Values are expressed as absolute number of cases (relative percentage). p Values were two-tailed, and p < 0.05 was considered statistically significant.

Fig. 1. Change in the mean left atrial (LA) pressure during the pre- and post-extensive encircling pulmonary vein isolation (EEPVI) phases between the two groups with pre-atrial fibrillation (AF). Among the patients with AF, the LA pressures decreased more significantly in the hypertrophic cardiomyopathy (HCM) group than the non-HCM (NHCM) group (post-LA pressure – pre-LA pressure: 4.2 ± 3.7 mmHg vs. 0.9 ± 4.1 mmHg, p=0.03).

Table 5
Echocardiography parameters and NT-proBNP change 6 months after RFCA.

|                        | NHCM group (n=106) | HCM group (n=15) | p Value |
|------------------------|--------------------|-----------------|---------|
| Post-ablation Transthoracic Echocardiography |              |                 |         |
| Left atrial volume index (mL/m²)    | 35.6 ± 9.3        | 55.7 ± 20.5     | <0.01   |
| Septal mitral E/e ratio             | 12.0 ± 9.8        | 18.1 ± 6.6      | <0.01   |
| Lateral mitral E/e ratio            | 8.9 ± 9.6         | 13.2 ± 7.3      | <0.01   |
| Pre-ablation NT-proBNP (pg/mL)     | 180 (56-498)      | 789 (297-1000)  | <0.01   |
| Post-ablation NT-proBNP (pg/mL)    | 82 (33-271)       | 490 (288-605)   | <0.01   |
| p Value of comparison between pre- and post-NT-proBNP | 0.11   | 0.02 |

NT-proBNP, N-terminal pro B-type natriuretic peptide; RFCA, radiofrequency catheter ablation. Values are expressed as mean (standard deviation) or median (inter-quartile range) as appropriate. p Values were two-tailed, and p < 0.05 was considered statistically significant.

Fig. 2. Early recurrences (ER) after hospital discharge in the hypertrophic cardiomyopathy (HCM) and non-HCM (NHCM) groups. No significant difference was observed in the rates of early recurrence between the HCM and NHCM groups (20% vs. 5.7%, p=0.08).

prescription rate was significantly higher in the HCM group than the NHCM group (60% vs. 13%, p < 0.001). The frequency of discontinuing AADs was significantly lower in the HCM group than the NHCM group (15% vs. 62%, p < 0.001). Table 5 shows echocardiography parameters and N-terminal pro B-type natriuretic peptide...
(NT-proBNP) change 6 months after RFCA. The LAVI, mitral septal E/e’ ratio, and lateral E/e’ ratio did not decrease from pre-ablation. However, post-ablation NT-proBNP dramatically decreased from pre-ablation (pre-ablation minus post-ablation NT-proBNP in the HCM group: 291 [60–1233] pg/mL). Although three HCM patients (20%) had early recurrence, they maintained sinus rhythm after a single cardioversion. Early recurrence rate tended to be higher in the HCM group than the NHCM group (20% vs. 5.7%, \( p = 0.08 \); Fig. 2). However, during a mean follow-up of 564 ± 252 days, two of the HCM patients (13.3%) had a recurrence of atrial tachycardia and AF (after hospital discharge). No significant difference was observed in the rates of late recurrences between the HCM and NHCM groups over 2 years (13.3% vs. 7.6%, \( p = 0.83 \); Fig. 3).

4. Discussion

A major finding of the present study was that a single EEPVI, albeit with the continued use of medication, could achieve sinus rhythm maintenance in patients with HCM and drug-resistant AF. The HCM patients in our study had diastolic dysfunction, large LAs, and high LA pressures. The LA pressure was higher in the HCM group than the NHCM group before EEPVI, but it decreased promptly in the acute phase after EEPVI. These findings suggest that EEPVI may be a feasible option for the treatment of drug-resistant AF in patients with HCM despite a high LA pressure.

Some studies have reported that radiofrequency ablation is effective for restoring long-term sinus rhythm in patients with HCM and AF, despite a high rate of late recurrences (13–52%) within 2 years [4,5]. Diastolic dysfunction has been reported to be an important cause of AF, even without any structural heart disease, because of increased LA afterload, which eventually increases LA pressures and dimensions [9]. Abnormalities of LV relaxation, filling, and compliance usually exist in HCM patients; this severe diastolic dysfunction is considered a main cause of their high rates of AF occurrence. In our study, the mitral septal and lateral E/e’ ratios, reflecting diastolic function, were significantly higher in the HCM group than the NHCM group. Consistent with results of previous studies, this provided conclusive evidence that diastolic dysfunction existed in our patients with HCM and refractory AF [10].

We analyzed and directly measured LA and RA pressures as hemodynamic parameters. To the best of our knowledge, this is the first published study to assess LA and RA pressures before and after EEPVI in HCM patients. Geske et al. reported that the correlations between the Doppler-derived diastolic parameters and direct LA pressure were poor in HCM patients [11]. The LA stiffness index, calculated by combining the invasive LA direct pressure and the noninvasive speckle tracking echocardiography, was reported to be related to the E/e’ ratio and to be a more significant predictor of AF recurrence than the E/e’ ratio alone [12]. In addition, a recent study suggested that greater LA stiffness index, calculated by the ratio of change in LA pressure to volume during passive filling of the LA, was independently associated with previous LA ablation and recurrence of AF after ablation [13]. In the present study, the LA pressure was higher in the HCM group than the NHCM group before EEPVI, but decreased after EEPVI when it became similar to that in the NHCM group. This acute effect suggests that LA pressure increases during the AF phase, particularly in HCM patients; the increased LA pressure is a reversible change outside of severe HCM. We speculate that the changes of LA pressure between before and after EEPVI were essentially based on the rhythm change of AF to sinus rhythm in HCM patients. In addition to sinus rhythm restoration, heart rate decrease might also affect the post-LA pressure.

We hypothesize that the pathogenesis in HCM patients who are prone to AF occurs as follows. First, HCM patients develop severe diastolic dysfunction. Second, once AF occurs, the LA pressure drastically increases and worsens the clinical condition, causing HCM patients to enter a negative cycle of increased vulnerability and persistent AF. Therefore, if we can temporarily decrease the LA pressure in these patients by ablating the AF foci, we may return them to the initial state before they developed increased vulnerability, making it more likely that they will maintain a regular sinus rhythm under AAD treatment.

Notably, after a single EEPVI, the rates of long-term sinus rhythm maintenance were similar between patients with and without HCM. In particular, no patient with HCM developed recurrence of AF after 6 months. AADs were discontinued in 66 patients in the NHCM group (62%) and in two patients in the HCM group (13%). The AAD discontinuation rate was higher in the NHCM group than the HCM group. We did not attempt to discontinue AADs or β-blockers in any of the HCM patients to avoid concomitant ventricular arrhythmias and cardioembolic events associated with their underlying pathology, even though the AF had been successfully controlled. The different AAD discontinuation rates may be another reason for the lack of a significant difference in outcomes between the two groups. Furthermore, the interventricular septal thicknesses in HCM patients were relatively small, which might influence the rates of long-term sinus rhythm maintenance. Even so, it is undeniable that the patients with HCM and drug-resistant AF were maintained in sinus rhythm after EEPVI when medication was continued.

The electrophysiological parameters indicated that electrical remodeling did not progress excessively. Because AF causes progressive atrial structural remodeling (i.e., LA fibrosis/scarring and dilatation) [14], RFCA in HCM patients is more effective when performed early before structural remodeling of the LA has progressed [4]. In our study, the LA pressure in the HCM group could decrease based on rhythm and heart rate change, and it might mean that the capacity of the LA was maintained. It might be thought that RFCA is effective in these patients whose capacity of the LA was maintained. The vast majority of arrhythmias that occur after RFCA are re-entrant via gaps in prior ablation lines [15]. It remains controversial whether additional substrate modification beyond PV isolation could improve single-procedure efficacy; indeed, long linear lesions, as opposed to segmental PV isolation, may result in complex gap geometries that promote conduction block and facilitate re-entry [16]. It is particularly important to ensure a perfect EEPVI line without conduction gaps in HCM patients, because they tend to possess a thickened and enlarged LA. Unexpectedly, in our study, even HCM patients susceptible to LA remodeling were able to maintain sinus rhythm by EEPVI without LA modification. The early recurrence rate tended to be
higher in the HCM group than the NHCM group, but the difference was not significant. Recent studies have reported that RFCA of AF causes a systemic and local inflammatory response that was closely associated with early recurrence after the procedure. Therefore, corticosteroids have been reported to be effective in preventing AF recurrences after AF ablation [17]. In the present study, the procedure duration was longer because of difficulties completing EE PV in the HCM group compared with the NHCM group. The inflammatory response can therefore reasonably be expected to be stronger in the HCM group than in the NHCM group, which may eventually lead to a higher rate of early recurrence in the HCM group.

The following study limitations should be acknowledged. This study was conducted based on an RFCA database and included a relatively small number of patients in a highly selected population. Furthermore, the interventricular septal thicknesses in HCM patients were relatively small when compared with that in previous studies [4,5], suggesting the possibility of selection bias. Furthermore, the intensive pharmacological treatment of HCM patients makes it difficult to assess the efficacy of RFCA alone. We speculate that these might affect the beneficial effects of RFCA for HCM patients. We did not search low voltage areas routinely. Therefore, the effectiveness of the only EE PV in patients with non-PV foci AF is unknown. The LA and RA pressures were measured in only 10 of the 15 patients with HCM (66%) and 73 of the 106 patients without HCM (69%). Because the rate of late recurrences in HCM patients was too low, we cannot analyze the direct relationship with the LA pressure and effectiveness precisely. Additionally, the volume overload might affect the LA pressure change. Finally, we retrospectively examined a small number of patients in a single institution in a non-randomized manner. Therefore, the present findings need to be validated in a larger prospective study with a longer follow-up. However, to our knowledge, this is the first report demonstrating a significant change in direct LA pressure in HCM patients after RFCA for AF.

5. Conclusions

In conclusion, the prevalence of the long-term maintenance of sinus rhythm after RFCA for AF was similar in patients with HCM and NHCM. EE PV appeared to be effective in treating AF in HCM patients, regardless of the AF subtype. Notably, because of the recovery of sinus rhythm, the LA pressure also decreased immediately after ablation in HCM patients. Our results suggest that RFCA of AF is effective and safe for restoring and maintaining sinus rhythm. RFCA should be considered a potential therapeutic option in HCM patients who have a large LA with high LA pressure. Further studies will be required to investigate the long-term outcomes and to clarify the optimal therapeutic options for these high-risk patients with AF.

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Conflict of interest

All authors declare no conflict of interest related to this study.

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