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Original article

Results of catheter ablation of atrial fibrillation in hypertrophied hearts – Comparison between primary and secondary hypertrophy

Andreas Müssigbrodt (MD)[a,1,*], Jedrzej Kosiuk (MD)[a,1], Emmanuel Koutalas (MD)[a,1], Sokrates Pastromas (MD)[a], Nikolas Dagres (MD)[b], Angeliki Darma (MD)[a], Johannes Lucas (MD)[a], Ole Alexander Breithardt (MD)[a], Philipp Sommer (MD)[a], Borislav Dinov (MD)[a], Charlotte Eitel (MD)[a], Sascha Rolf (MD)[a], Michael Döring (MD)[a], Sergio Richter (MD)[a], Arash Arya (MD)[a], Daniela Husser (MD)[a], Andreas Bollmann (MD, PhD)[a], Gerhard Hindricks (MD)[a]

[a] Department of Electrophysiology, University of Leipzig, Heart Center, Leipzig, Germany
[b] Second Cardiology Department, Attikon University Hospital, University of Athens, Athens, Greece

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ABSTRACT

Background and purpose: Approximately 20–25% of the patients with hypertrophic cardiomyopathy (HCM) develop atrial fibrillation (AF) during the clinical course of the disease, a percentage significantly larger than that of the general population. The purpose of the present study was to report on the procedural results of patients with AF and either primary or secondary left ventricular hypertrophy (LVH).

Methods and subjects: Twenty-two consecutive HCM patients (55% male, mean age 57 ± 8 years) with symptomatic AF, having undergone AF ablation procedures between September 2009 and July 2012 were compared with respect to procedural outcome and follow-up characteristics with 22 matched controls with secondary cardiac hypertrophy (64% male, 63 ± 10 years) from our prospective AF catheter ablation registry.

Results and conclusion: Radiofrequency catheter ablation (RFCA) was successful in restoring long-term sinus rhythm in patients with LVH due to HCM and due to secondary etiology. However, patients with HCM needed more RFCA procedures and frequently additional antiarrhythmic drug therapy in order to maintain sinus rhythm.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common genetically determined cardiomyopathy, with a prevalence of 0.2% in the general population. Approximately 20–25% of the patients with HCM will eventually develop atrial fibrillation (AF) during the clinical course of the disease, a percentage significantly larger than that of the general population [1–5]. AF is a major factor of morbidity and mortality in HCM, causing ischemic strokes and systemic embolisms, exacerbation of symptoms of heart failure, pulmonary congestion and edema, deterioration of the already compromised diastolic filling of the left ventricle, as well as provoking appropriate and inappropriate discharges in patients with implantable cardioverter-defibrillators (ICDs), dramatically affecting their quality of life [1,6–10]. As a consequence, recent AF treatment guidelines favor an aggressive approach to both rhythm control and stroke prevention in patients with HCM [11].

In this context, catheter ablation of AF is recommended for patients with drug refractory AF and for patients with antiarrhythmic agent (AAA) intolerance [11]. Catheter ablation has consistently shown satisfactory results regarding symptoms relief and survival free of arrhythmia for both paroxysmal and persistent AF in the general population [11]. It is unclear whether patients with HCM achieve the same results. Most of the data on AF ablation in patients with HCM are derived from cohorts with small numbers of patients, and success rates vary between 49% and 100% [13,17,23, Table3].

* Corresponding author at: Department of Electrophysiology, University of Leipzig, Heart Center, Strümpellstrasse 39, 04289 Leipzig, Germany. Tel.: +49 3418651413; fax: +49 3418651460.
E-mail address: andreas.muessigbrodt@gmail.com (A. Müssigbrodt).
[1] These authors contributed equally to this manuscript.

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Since AF is a major contributor to the progression of heart failure and is associated with an adverse outcome in HCM patients [1], maintenance of sinus rhythm is highly desirable. This study compared the efficacy and clinical outcomes between patients with LVH due to HCM and patients with secondary cardiac hypertrophy due to hypertensive cardiomyopathy.

Materials and methods

Population

A total of 22 consecutive HCM patients (55% male, mean age 57 ± 8 years) with highly symptomatic AF, having undergone AF ablation procedures between September 2009 and July 2012 were compared with respect to procedural outcome and follow-up characteristics with 22 matched controls with secondary cardiac hypertrophy (64% male, 63 ± 10 years) from our prospective AF catheter ablation registry. Table 1 displays the baseline characteristics. Matched parameters included LV hypertrophy, systolic LV function, and AF type. Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle (maximum wall thickness ≥15 mm) and/or relevant outflow tract obstruction, in the absence of any other cardiac or systemic condition capable of producing such magnitude of hypertrophy [14]. Diagnosis of secondary cardiac hypertrophy was based on two-dimensional echocardiographic evidence of an interventricular septum ≥14 mm and evidence of a causative condition. Hypertensive disease was diagnosed in 22 out of 22 patients (100%) with secondary cardiac hypertrophy. If arterial hypertension was also found in patients with HCM (73%), diagnosis of HCM was based on clinical judgment (i.e., LV outflow tract obstruction, apical LVH, magnitude of LVH) or the evidence of a mutation in gene analysis.

We did not use left atrial size as an exclusion criterion. Patients with large left atrium (LA) diameters were informed about the possibility of reduced success rate.

Paroxysmal AF and persistent AF were defined according to current guidelines [15]. Paroxysmal AF was defined as self-terminating within 7 days after onset. Persistent AF was defined as an AF episode either lasting longer than 7 days or requiring drug or direct current cardioversion for termination. All patients provided written informed consent prior to participation.

Table 1
Baseline parameters prior to ablation.

	HCM (n = 22)	Non-HCM (n = 22)	p value
Male, n (%)	15 (68)	14 (64)	0.750
Age (years)	57 ± 8	63 ± 10	0.032
Body mass index (kg/m^2)	30 ± 6	31 ± 6	0.592
Persistent AF, n (%)	12 (55)	12 (55)	1.000
Coronary heart disease, n (%)	2 (9)	2 (9)	1.000
Hypertension, n (%)	16 (73)	22 (100)	0.021
Previous stroke/TIA	0 (0)	2 (9)	0.148
Diabetes mellitus, n (%)	2 (9)	5 (23)	0.216
CHADS2 score	1 (median)	2 (median)	0.005
CHA2DS2-VASc score	1 (median)	2 (median)	0.005
LA diameter (mm)	46 ± 8 (range 31–67)	43 ± 6 (range 34–54)	0.183
Significant mitral insufficiency	3 (14)	0 (0)	0.073
LVEF (%)	60 ± 7	62 ± 7	0.286
IVSD (mm)	19 ± 4	14 ± 1	<0.001
ICD, n (%)	8 (36)	0 (0)	0.002
Pacemaker, n (%)	2 (9)	0 (0)	0.148
Morrow resection or TASH	7 (32)	0 (0)	0.004

Values are mean ± SD, median, or n (%).
HCM, hypertrophic cardiomyopathy; AF, atrial fibrillation; LA, left atrium; TIA, transient ischemic attack; LVEF, left ventricular ejection fraction; IVSD, interventricular septal end diastolic dimension; ICD, implantable cardioverter-defibrillator; TASH, transcoronary ablation of septal hypertrophy.

Catheter ablation procedure

Left atrial catheter ablation was performed using a previously described approach [16]. In brief, patients were studied under deep propofol sedation with continuous invasive monitoring of arterial blood pressure and oxygen saturation. Nonfluoroscopic 3D catheter orientation, computed tomography image integration, and tagging of the ablation sites were performed using Ensite NavX©, Ensite Velocity (St. Jude Medical, St. Paul, MN, USA) or CARTO 3© (Biosense Webster, Diamond Bar, CA, USA). Transseptal access and catheter navigation were performed with a steerable sheath (Agilis©, St. Jude Medical). If a double transseptal puncture approach was adopted, a second long nonsteerable sheath was used (Swartz Support Sheath SL0; St. Jude Medical), while the transseptal puncture was performed with a BRK transseptal needle (St. Jude Medical). After the first transseptal puncture a bolus dose of heparin was administered intravenously and activated clotting time was regularly measured in order to maintain it between 300 and 400 s.

A multisensor temperature catheter was inserted in the esophagus, with temperatures rising over 41 °C leading to temporal interruption of lesion placement. At the posterior wall, a starting energy delivery of 25 W was preselected, while at other sites energy was raised up to 50 W.

In all patients circumferential left atrial ablation lines were placed around the antrum of the ipsilateral pulmonary veins with an irrigated tip catheter (preselected tip temperature of 48 °C, and maximum power of 30–50 W). In case of AF induction after pulmonary vein isolation (PVI), additional linear lesions were added at the discretion of the operator, e.g. at the left atrial roof, the basal posterior wall, and the mitral isthmus. Ablation of complex fractionated electrograms was not performed.

After circumferential line placement, voltage and pace mapping along the ablation line were used to identify and close gaps. The isolation of all pulmonary veins with bidirectional block was verified with a multipolar circular mapping catheter and was defined as the procedural endpoint. Table 2 shows the procedural characteristics.

During repeat procedures, bidirectional electrical re-isolation of pulmonary veins was the primary endpoint. Atrial bursts of 300, 250, and 200 ms were used in order to induce atrial tachycardias. High-dose isoproterenol challenge was not administered. After complete electrical isolation of pulmonary veins, additional linear lesions were placed in the case of macroreentry tachycardia, after thorough activation and entrainment mapping.

Table 2
Procedural parameters.

	HCM (n = 22)	Non-HCM (n = 22)	p value
Persistent AF, n (%)	12 (55)	12 (55)	1.000
Number of interventions, n (%)			0.045
1	14 (64)	19 (86)	
2	5 (23)	3 (14)	
3	3 (14)	0	
Duration of procedure (min)	174 ± 56	152 ± 44	0.179
Duration of ablation (s)	2120 ± 1178	2575 ± 1171	0.344
Duration of fluoroscopy (min)	31 ± 10	35 ± 17	0.414
Additional lesions (roof line, septal line and cavo-tricuspidal isthmus line), n (%)	7 (32)	5 (23)	0.498

HCM, hypertrophic cardiomyopathy; AF, atrial fibrillation.

In addition to the latter, extrapulmonary vein foci were ablated in the left or right atrium, if a focal atrial tachycardia could be demonstrated.

Follow-up

Seven-day Holter recordings (Lifecard CF, Delmar-Reynolds Medical Inc., Irvine, CA, USA) were performed during 6-, 12-, and 24-month follow-up visits in our outpatient clinic. During nonrecorded periods, the patients were advised to contact our hospital themselves or through their family physicians in case of any symptom recurrence. Available information from interrogations of pacemakers or ICD with an atrial lead was also used for continuous monitoring. If necessary, the patient was readmitted to the hospital and synchronized electrical cardioversion to sinus rhythm (SR) was performed. If available, a 12-lead electrocardiogram (ECG) of the episode was recorded. Documented episodes of sustained (more than 30 s) AF or atrial flutter (including documentation from ECG, Holter recordings, and pacemaker or ICD interrogation) after a 3-month blanking period excluded were considered as recurrence of arrhythmia.

As standard protocol in our institution, any AAA therapy before the ablation procedure was discontinued afterward and patients received only titrated doses of beta-blocker. However, AAAs were continued in some patients at the discretion of the treating physician, e.g. in patients with recurrent arrhythmia.

In patients with symptomatic postinterventional arrhythmia recurrences refractory to AAA treatment re-ablations were considered after 3–6 months of follow-up.

According to current guidelines, anticoagulation was continued in all patients based on the CHADS-VASc score, independently of the rhythm during the follow-up [15].

Statistical analysis

Continuous variables are reported as mean ± one standard deviation and categorical variables are reported as frequencies. Continuous variables were compared using the Student *t*-test, while categorical variables were compared using the chi-square test.

Freedom from AF after last procedure was compared in both groups by means of Mantel–Cox test and presented as Kaplan–Meier curves. A two-tailed *p*-value less than 0.05 was considered statistically significant. Analysis was performed with SPSS v 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Population

In this study, patients with HCM were younger with a greater magnitude of LVH and a lower calculated thromboembolic risk score. A total of 5 of 22 patients with HCM (23%) underwent genetic testing. Genetic analysis was positive in three of five tested patients (60%). In two patients different heterocygote mutations were found in MYH7. In one patient a heterocygote mutation in MYBPC3 was found. The apical form of HCM was diagnosed in two patients (9%). HCM with left ventricular outflow tract obstruction was diagnosed in eight patients (36%). A total of seven of eight patients with left ventricular outflow tract obstruction (32% in total) had undergone previous Morrow procedure or transcoronary ablation of septal hypertrophy (TASH). Within the HCM cohort, two patients (9%) had a pacemaker implanted and eight patients (36%) were ICD carriers. None of the patients with secondary hypertrophy had undergone Morrow procedure, TASH, pacemaker, or ICD implantation. Table 1 displays the baseline characteristics.

Procedural aspects

Complete PVI as procedural endpoint was achieved in all patients. The periprocedural parameters in terms of procedure duration, required ablation time, and fluoroscopy were similar in both groups (Table 2). Additional lesions (roof line between both superior pulmonary veins, septal line between the mitral annulus and the right superior pulmonary vein, and cavo-tricuspidal isthmus line) were performed in seven patients (32%) in the HCM group and in five patients (23%) in the non-HCM group ($p = 0.498$).

Freedom from AF and left atrial flutter

Recurrences of arrhythmias after the first ablation were observed in 13 of 22 patients with HCM (59%) as opposed to 11 of 22 (50%) in the non-HCM group. Although the recurrence rate in both groups was similar after a single ablation procedure ($p = 0.545$), the Mantel–Cox analysis revealed that the time to recurrence after a single ablation procedure was significantly shorter in the HCM group with a mean freedom from AF of 12 ± 2 months compared to 19 ± 2 months in the non-HCM group ($p = 0.015$) (Fig. 1).

Recurrences of AF and/or atrial flutter after the last ablation occurred in 10 of 22 patients with HCM (46%) compared to 8 of 22 patients (36%) in the non-HCM group ($p = 0.376$). However, the time to recurrence after multiple procedures was similar in both groups. Recurrences after the last ablation were observed after a mean follow-up of 12 ± 11 months in the HCM group and after 17 ± 7 months in the non-HCM group ($p = 0.121$) (Fig. 2).

To reach a comparable level of freedom from AF in patients with HCM a higher number of repeated procedures was needed. In the HCM group five patients (23%) were re-ablated as compared to three patients (14%) without HCM. In three patients with HCM a 3rd procedure was required, which was not observed in the non-HCM group ($p = 0.045$).

Interestingly, 8 of 13 patients (62%) with recurrences in the HCM group after the first procedure experienced episodes of left atrial flutter during the follow-up. After the last procedure 7 of 10 patients (70%) still had episodes of left atrial flutter. Redo procedures revealed pulmonary vein re-conduction in two of five patients. Additional linear ablation was undertaken in all five patients with HCM and redo procedures due to inducible pulmonary vein independent left atrial flutter.

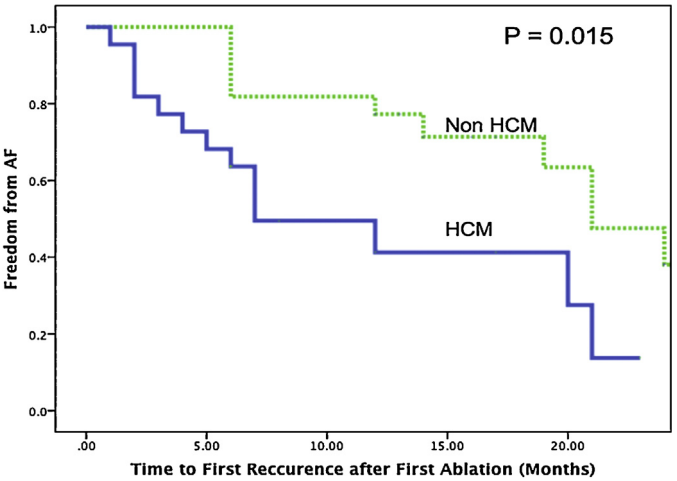

Fig. 1. Kaplan–Meier curve depicts the time to first recurrence after first ablation. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

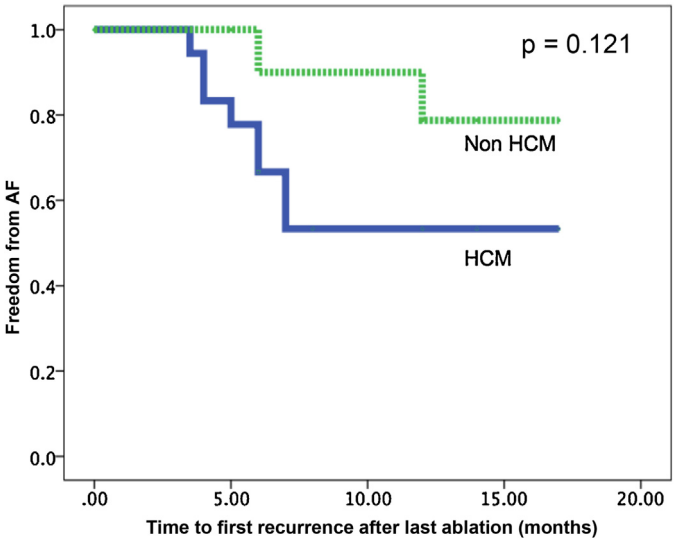

Fig. 2. Kaplan–Meier curve depicts the time to first recurrence after last ablation. AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy.

In contrast, in the non-HCM group only 3 of 11 patients (27%) experienced episodes of left atrial flutter after the first procedure, whereas recurrence of AF without evidence of left atrial flutter occurred in 8 of 11 patients (73%) ($p = 0.087$). After the last ablation, left atrial flutter was still detectable in three of five patients with recurrences in the non-HCM group and only the recurrence rate of AF decreased. In all three cases of re-ablation in non-HCM patients a pulmonary vein re-conduction was observed and PVI was completed. Two patients were treated with additional linear ablation because of pulmonary vein independent left atrial flutter.

AAAs were prescribed to 6 of 22 patients in the HCM group (27%) (amiodarone in four cases and sotalol in two cases), whereas none of the patients in the comparison group was under AAA during follow-up ($p = 0.008$).

Predictors for freedom from AF

Of nine HCM patients with a LA diameter greater than 45 mm there were only three patients (33%) without recurrent AF whereas six patients (67%) had AF recurrence ($p = 0.041$). In the non-HCM group LA size greater than 45 mm did not predict AF recurrence ($p = 0.402$). Patients' age and type of AF were no predictors for the outcome of RFCA in our study population.

Complications

Procedure-associated complications occurred in 1 of 22 patients (5%) in the HCM group (pulmonary vein stenosis that was subsequently treated with balloon dilation), whereas no complication occurred in the comparison group ($p = 0.351$).

Discussion

Main findings

The present study demonstrates that RFCA in the majority of HCM patients may result in a long-term freedom from AF, although there is frequent need for redo procedures, and antiarrhythmic medications often cannot be discontinued.

Comparison with previous studies

Previous studies have demonstrated that RFCA for symptomatic AF is both a feasible and safe approach in patients with HCM [1,12,13,17–20]. Table 3 shows the main baseline, procedural and outcome characteristics of previous studies of RFCA of AF in HCM patients. Various factors were found predicting the outcome of RFCA for AF in HCM patients: LA size, evidence of diastolic dysfunction, duration of AF, type of AF, and age of patients. Patients younger than 50 years with smaller LA, milder symptoms, and shorter duration of AF seemed to be the best candidates for RFCA [20]. RFCA was more successful in patients with paroxysmal AF compared to the subgroup with permanent AF [12]. Increased LA size was found as a risk factor for AF recurrence after RFCA in patients with HCM [20].

In our study population, LA dimension greater than 45 mm was also a significant predictor for a nonfavorable outcome after RFCA in patients with HCM. In the non-HCM group, however, LA size greater than 45 mm did not predict AF recurrence ($p = 0.402$).

In contrast to previous studies that have shown the influence of patients' age [20] and type of AF [12] on the outcome of RFCA, in our study population these parameters did not predict the outcome of RFCA.

Numerous potential mechanisms may explain why patients with HCM have higher AF recurrence rates after PVI: (1) Increased LA size is a frequent finding in patients with HCM and secondary hypertrophy due to impaired diastolic function and mitral insufficiency. Atrial stretch shortens the effective refractory period, increases the dispersion of the atrial effective refractory period, and potentiates the activity of ectopic triggers [21–23]. (2) The thickness of the left atrium exhibits a great variation between regions within the left atrium and among different patients [24]. Atrial tissue in hearts with LVH may differ from atrial tissue in hearts without LVH. (3) Increased prevalence of atrial fibrosis may provide a substrate for slow conduction and intra-atrial reentry and it may therefore increase the susceptibility to AF by increased vulnerability to triggers [25]. (4) Myocardial ischemia and autonomic dysfunction, both of which have been documented in HCM patients, may represent relevant factors triggering AF [26,27].

Table 3
Studies reporting on catheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy.

Study	Study design	No. of patients	Male *n* (%)	Age (years)	HOCM *n* (%)	PAF *n* (%)	Median follow-up (months)	Repeated procedures *n* (%)	Use of AAA	Significant complications	SR during complete FU
Liu et al. [17]	Retrospective cohort	4	2 (50)	57 ± 8	4 (100)	4 (100)	6 ± 3	1 (25)	1 (25)	N.n.	4 (100)
Kilicaslan et al. [18]	Retrospective cohort	27	19 (70)	55 ± 10	100%	14 (52)	11 ± 8	7 (26)	6 (22)	0%	19 (70)
Duytschaever et al. [13]	Case report	2	2 (100)	47 ± 10	1 (50)	1 (50)	11 ± 1	0	2 (100)	N.n.	2 (100)
Gaita et al. [12]	Prospective case control	26	18 (69)	58 ± 11	6 (23)	13 (50)	19 ± 10	5 (19)	6 (23)	0 (0)	14 (56)
Bunch et al. [19]	Prospective cohort	33	25 (76)	51 ± 11	8 (24)	21 (64)	18 ± 14	13 (39)	4 (13)	3 (9)	25 (75)
Di Donna et al. [20]	Retrospective cohort	61	44 (72)	54 ± 13	12 (20)	35 (56)	29 ± 16	32 (52)	31 (51)	0 (0)	41 (67)
Santangeli et al. [23]	Prospective cohort	43	29 (67)	59 ± 8	N.n.	12 (28)	42 ± 6	22 (51)	0 (0)	0 (0)	21 (49)

Varying units have been adapted.
N.n., Nomen nominandum – not reported.

Conclusion

In conclusion, RFCA was successful in restoring long-term SR in the majority of patients with LVH due to HCM and due to secondary etiology. However, patients with HCM needed more RFCA procedures and frequently additional AAA therapy in order to maintain SR. Left atrial flutter was found more frequently in patients with HCM than in patients with secondary hypertrophy.

Conflict of interest

None declared.

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