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Efficacy of catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: impact of age, atrial remodelling, and disease progression

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Aims In patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF), radiofrequency catheter ablation (RFCA) represents a promising option. However, the predictors of RFCA efficacy remain largely unknown. We assessed the outcome of a multicentre HCM cohort following RFCA for symptomatic AF refractory to medical therapy.

Methods and results Sixty-one patients (age 54 ± 13 years; time from AF onset 5.7 ± 5.5 years) with paroxysmal ($n = 35$; 57%), recent persistent ($n = 15$; 25%), or long-standing persistent AF ($n = 11$; 18%) were enrolled. A scheme with pulmonary vein isolation plus linear lesions was employed. Of the 61 patients, 32 (52%) required redo procedures. Antiarrhythmic therapy was maintained in 22 (54%). At the end of a 29 ± 16 months follow-up, 41 patients (67%) were in sinus rhythm, including 17 of the 19 patients aged ≤50 years, with marked improvement in New York Heart Association (NYHA) functional class (1.2 ± 0.5 vs. 1.9 ± 0.7 at baseline; $P < 0.001$). In the remaining 20 patients (33%), with AF recurrence, there was less marked, but still significant, improvement following RFCA (NYHA class 1.8 ± 0.7 vs. 2.3 ± 0.7 at baseline; $P = 0.002$). Independent predictors of AF recurrence were increased left atrium volume [hazard ratio (HR) per unit increase 1.009, 95% confidence interval (CI) 1.001–1.018; $P = 0.037$] and NYHA functional class (HR 2.24, 95% CI 1.16–4.35; $P = 0.016$). Among 11 genotyped HCM patients (6 with MYBPC3, 2 with MYH7, 1 with MYL2 and 2 with multiple mutations), RFCA success rate was comparable with that of the overall cohort ($n = 8$; 73%).

Conclusion RFCA was successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF, including the subset with proven sarcomere gene mutations, although redo procedures were often necessary. Younger HCM patients with small atrial size and mild symptoms proved to be the best RFCA candidates, likely due to lesser degrees of atrial remodelling.

Keywords Hypertrophic cardiomyopathy • Atrial fibrillation • Radiofrequency ablation • Outcome • Genetics

Introduction

In patients with hypertrophic cardiomyopathy (HCM), atrial fibrillation (AF) is the most common clinical complication, with a prevalence exceeding 20% in most recent cohorts.[1,2] The occurrence of AF represents a turning point in the clinical course of the disease, in which it is generally associated with deterioration of clinical status, functional capacity, quality of life, and long-term outcome.[3–6] Maintenance of sinus rhythm is highly desirable in HCM patients, particularly when onset of the arrhythmia occurs at a young age.[7–8] However, pharmacological therapy for AF is particularly challenging in this patient population, due to the

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early onset of the disease, limited long-term efficacy, and potentially hazardous side effects of currently available treatment options.

In the last decade, radiofrequency catheter ablation (RFCA) of AF approaches have been successfully introduced in clinical practice, mostly in patients without underlying structural heart disease.[9–12] To date, evidence regarding the efficacy of RFCA in patients with HCM is limited. We and others have recently shown the feasibility of RFCA in selected HCM cohorts with severely symptomatic AF refractory to pharmacologic antiarrhythmic therapy.[13–15] Over time, however, progressive atrial remodelling,[16] specific to the HCM disease process, may influence the outcome of RFCA, even when the procedure is initially successful. Thus, issues such as whether an electrical 'cure' of AF can be plausibly offered to HCM patients by RFCA, and which patients are likely to benefit from the procedure, remain unresolved. Aim of the present study was to analyse the long-term results of RFCA in a sizable HCM patient cohort with AF, with specific regard to age and degree of left atrial remodelling.

Methods

Patient population

The study group included 61 patients with HCM and AF from three tertiary referral centres (Asti $n = 29$, Florence $n = 16$, and Bordeaux $n = 16$), consecutively treated by RFCA between January 2001 and March 2008. Of these, three underwent RFCA before 2003. Diagnosis of HCM was based on two-dimensional echocardiographic evidence of a hypertrophied, non-dilated left ventricle (maximum wall thickness $\geq$15 mm), in the absence of any other cardiac or systemic disease capable of producing the magnitude of hypertrophy evident.[17,18] Patients were recruited if they had symptomatic AF refractory to medical treatment, often in the context of disease progression and heart failure. Documentation of AF was based on ECG recordings obtained either after acute onset of symptoms or during routine examination. All patients had been unsuccessfully treated with multiple antiarrhythmic drugs, including amiodarone. According to the HRS/EHRA/ECAS 2007 Consensus Statement on Catheter and Surgical ablation of AF,[19] AF was defined as paroxysmal ($\geq$2 episodes terminating spontaneously within 7 days; $n = 35$; 57%), persistent (lasting $>$7 days but $<$1 year, or necessitating cardioversion; $n = 15$; 25%), or long-standing persistent (lasting $>$1 year; $n = 11$; 18%). All patients were on chronic oral anticoagulant therapy maintaining a target international normalized ratio (INR) of two to three.

Echocardiography

Comprehensive two-dimensional and Doppler echocardiographic studies were performed in each patient using commercially available instruments. LV hypertrophy was assessed with two-dimensional echocardiography, and the site and extent of maximal wall thickness were identified. Peak instantaneous LV outflow gradient, due to mitral valve systolic anterior motion and mitral-septal contact, was estimated with continuous wave Doppler under basal conditions.[20] Left atrial volume was measured at end-systole using the biplane area-length method.[21] The baseline atrial volume calculated at the time of patient enrolment was used for all analyses.

Electrophysiological study and radiofrequency catheter ablation

All procedures were performed in Asti ($n = 45$) and Bordeaux ($n = 16$). Before admission, warfarin was stopped for 3 days and substituted with low-molecular-weight heparin, and transoesophageal echocardiography was performed in all patients to rule out atrial thrombi. An informed consent was obtained. The electrophysiological study was performed in the post-absorptive conscious state with minimal sedation. The following catheters were introduced via the right femoral vein: (i) a deflectable quadripolar or decapolar catheter (2-5-2 mm electrode spacing, Xtrem, ELA Medical, France) or an octapolar catheter (Boston Scientific) positioned within the coronary sinus (CS) with the distal electrode positioned at 4 o'clock along the mitral annulus in the 30° left anterior oblique radiographic projection; (ii) 10 pole, fixed-diameter circumferential mapping catheter to guide pulmonary vein (PV) isolation (Lasso; Biosense-Webster, Diamond Bar, CA or Orbiter, Bard Electrophysiology), introduced with the aid of a long sheath (Preface multipurpose, Biosense-Webster, or SLO, St Jude, Minnesota, USA) continuously perfused with heparinised saline; and (iii) an 3.5 mm irrigated-tip quadripolar ablation catheter (2-5-2 mm inter-electrode spacings, ThermoCool, Biosense-Webster, Diamond Bar, CA, USA). A single transseptal puncture was performed with pressure monitoring. Left atrial access was confirmed by an appropriate atrial pressure waveform and by contrast injection. The circumferential mapping catheter was introduced to the left atrium (LA) via the transseptal sheath, and the sheath withdrawn to the right atrium to facilitate passage of the ablation catheter into the LA through the same puncture point.

In 46 patients, a three-dimensional shell representing the LA and PV ostia was constructed using an electroanatomic mapping system (Carto, Biosense-Webster), while the remaining 15 patients underwent catheter ablation under fluoroscopic guidance. Radiofrequency (RF) was applied using an open irrigated-tip catheter (Navistar Thermocool, Biosense Webster) with power output up to 30 W close to the PV ostia and up to 45 W while creating the roof line and the left mitral isthmus line, using an irrigation rate of 20–30 ml/min (0.9% saline infused with the Cool Flow Pump, Biosense Webster) in order to maintain a tip temperature below 45°C. A surface electrocardiogram and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system (Bard Electrophysiology). Intracardiac electrograms were filtered at 30–500 Hz. Following transeptal puncture a single bolus of 50 IU/kg of heparin was administered and repeated only for procedures lasting $\geq$4 h.

Catheter ablation protocol and periprocedural management

The ablation protocol consisted of a point-to-point PV isolation and linear lesions interconnecting the upper PV ostia (roof line) and the left inferior PV down to the mitral annulus, plus a cavotricuspid isthmus line, as previously described (*Figure 1*).[13] PV isolation was carried out anatomically and confirmed electrophysiologically by complete elimination or dissociation of PV potentials determined with the circular mapping catheter positioned at the PV ostia. Electrical block of the roof line, mitral isthmus line block, and cavotricuspid line was confirmed using pacing manoeuvres as previously described.[13] In none of the patients was RF delivered within the CS. When conduction recovery was documented, additional lesions were performed along the same lines; no additional lines were carried out.

Following RFCA, the ECG was continuously monitored and standard heparin infusion maintained for at least 24 h. Low-molecular

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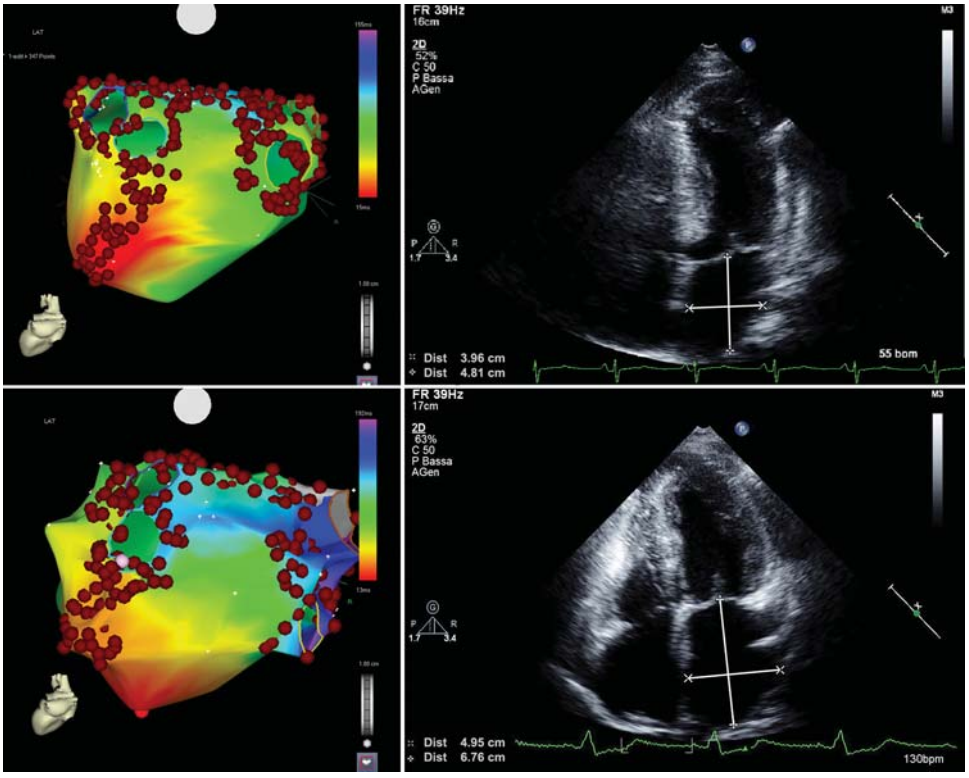

Figure 1 Radiofrequency catheter ablation of AF in two patients with HCM. Upper panels: A 50-year-old man with paroxysmal AF, in whom radiofrequency catheter ablation successfully restored sinus rhythm. Left: Three dimensional electroanatomic map reconstruction (PA view) of the LA showing pulmonary vein isolation and additional linear lesions. Right: Echocardiographic apical four-chamber view showing normal LA size. Lower panels: A 54-year-old woman paroxysmal AF, in whom AF recurred during follow-up. Left: Three dimensional electroanatomic map reconstruction (PA view) of the left atrium showing pulmonary vein isolation and additional linear lesions. Right: Echocardiographic apical four-chamber view showing markedly enlarged atrial size. HCM, hypertrophic cardiomyopathy; AF, atrial fibrillation; PA, postero-anterior; LA, left atrium.

weight heparin and warfarin therapy were instituted on the following day; heparin was stopped when the INR reached the therapeutic range of two to three. A 1-month blanking period was considered for each patients following catheter ablation.[13] Following the blanking period, a repeat ablation procedure was undertaken in the event of a recurrence of AF or atrial tachycardia whether symptomatic or not. PV isolation and completeness of linear lesions were assessed and further ablation delivered as necessary.

Follow-up

Due to the large number of patients requiring a second procedure, and of the variable time interval between procedures, beginning of clinical follow-up for the purpose of the present study was established as the time elapsed from the last RFCA to the final evaluation. Following hospital discharge, patients were followed at 1, 3, 6, and 12 months, with 12-lead ECG, echocardiography, and 24-h Holter monitoring and every 6 months thereafter through telephone contact, clinic follow-up visits, and/or communication with the patient's primary referring physician. In addition, patients were instructed to seek medical attention $<$24 h following the onset of new symptoms. Antiarrhythmic therapy was discontinued after 3 months unless there was evidence of recurrent non-sustained ventricular tachycardia requiring treatment. The study endpoint was represented by the recurrence of AF, atrial tachycardia, or atrial flutter lasting more than 3 min and detected due to symptoms or ECG-Holter recording.

Statistical methods

Student's *t*-test was employed for comparison of continuous variables expressed as mean $\pm$ SD. The χ^2 test was utilized to compare non-continuous variables expressed as proportions. Relative risks and 95% confidence intervals (CIs) were calculated using Cox proportional hazard regression analysis. Multivariate analyses were performed with a stepwise forward regression model, which selectively included variables with a *P*-value of $\leq$0.05 at univariate analysis. Survival curves were constructed according to the Kaplan–Meier method, and comparisons were performed using the log-rank test. All *P*-values were two-sided and considered significant when $<$0.05. Calculations were performed with SPSS 12.0 software (Chicago, IL, USA).

Results

Patient features

Mean age of the 61 HCM study patients was 54 $\pm$ 13 years; 19 patients (31%) were $\leq$50 years and 42 (69%) $>$50 years; 17 (28%) were female (*Table 1*). All patients had AF refractory to medical therapy, including 35 patients (56%) with paroxysmal, 15 (25%) with recent persistent, and 11 (19%) with long-standing persistent AF. The median value for LA volume was 140 mL (25th–75th percentile: 125–180 mL), exceeding 200 mL in 22 patients

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Table 1 Demographic and clinical features of 61 patients with HCM

Variable	Total population $n = 61$	Age <50 years $n = 19$	Age >50 years $n = 42$	*P*-value[a]
Age (years)	54 ± 13	38 ± 8.6	61 ± 6.6	<0.05
Female	17 (28%)	5 (26%)	12 (29%)	0.29
Years since first diagnosis of HCM	14 ± 8.7	6 ± 7.4	15 ± 8.6	0.11
Family history of HCM	27 (44%)	12 (63%)	15 (36%)	0.05
New York Heart Association Functional Class				
I	14 (23%)	3 (16%)	11 (26%)	0.37
II	32 (53%)	11 (58%)	21 (50%)	0.57
III	15 (24%)	5 (26%)	10 (24%)	0.83
Baseline echocardiographic measurements				
Middle LV thickness (mm)	20 ± 5.4	20 ± 5.3	21 ± 5.4	0.85
With basal LV outflow gradient >30 mmHg	12 (20%)	3 (16%)	9 (21%)	0.76
Left atrial diameter (mm)	51 ± 6.7	50.8 ± 7.9	52 ± 6.9	0.64
Left atrial volume (mL)[b]	140 (125–180)	131 (120–146)	147 (129–191)	0.19
Smoke effect in left atrium	24 (59%)	6 (32%)	18 (43%)	0.40
Mitral regurgitation				
None	11 (18%)	4 (21%)	7 (17%)	0.68
Mild	28 (50%)	12 (63%)	16 (38%)	0.07
Moderate	22 (36%)	3 (16%)	19 (45%)	0.03
LV ejection fraction (%)	59 ± 8	61 ± 10	59 ± 8	0.34
Prior interventions				
Surgical septal myectomy and MV replacement	4 (7%)	2 (11%)	2 (5%)	0.39
Alcohol septal ablation	2 (3%)	1 (5%)	1 (2%)	0.56
Implantable cardioverter-defibrillator for primary prevention of sudden death	17 (28%)	6 (32%)	11 (26%)	0.66

HCM, hypertrophic cardiomyopathy; LV, left ventricular; MV, mitral valve.
[a]Patients aged <50 vs. >50 years.
[b]Expressed as median (25th–75th percentile).

(36%). Patients with paroxysmal or recent persistent AF had experienced an average of 12 ± 7 arrhythmic episodes at the time of enrolment. Average time from clinical detection of AF to RFCA was 5.7 ± 5.5 years, ranging from 4.7 ± 4.1 years for those with paroxysmal to 7.2 ± 7.1 years for those with long-standing AF. In patients with long-standing AF, duration of the current episode was 2.6 ± 1.4 years.

At baseline, 46 patients (75%) were in New York Heart Association (NYHA) functional Class I or II, whereas 15 (25%) were in Class III (*Table 1*). Seven patients (11%) had been hospitalized due to acute cardiac decompensation and pulmonary oedema associated with acute onset of AF. Twelve patients (20%) had resting left ventricular outflow obstruction, and six (10%) patients had previously undergone percutaneous alcohol septal ablation or surgical myectomy. Seventeen patients (28%) had an implantable cardioverter-defibrillator.

Procedural outcome

At beginning of RFCA, 31 (51%) patients were in sinus rhythm, while 30 (49%) patients were in AF. Of these 30, 26 patients required an electrical cardioversion to restore sinus rhythm at the end of the procedure. All patients were in sinus rhythm at the end of the first RFCA, and had evidence of complete PV isolation and conduction block along the atrial roof. We did not observe any specific electrophysiological behaviour that we could identify as peculiar for HCM, as compared with other patients with structural heart disease, and linear lesions were not more difficult than usual to complete. Creation of an effective mitral isthmus linear lesion was obtained in 29 patients (48%); in the remaining 32 (52%), acute conduction slowing along the mitral isthmus was observed, with a mean atrial electrogram interval of 82 ± 27 ms during CS pacing. Conversely, right atrium isthmus block was achieved in all patients. Total procedural time was 149 ± 67 min and fluoroscopy time was 63 ± 27 min. No major periprocedural complications occurred; 5 (8%) patients developed mild pericardial effusion without haemodynamic compromise.

Of the 61 patients, 17 (28%) remained in stable sinus rhythm after a single procedure, including 11 on and 6 off antiarrhythmic medications. Conversely, 44 (72%) had AF recurrences within 14 ± 15 months from the first procedure. In 12 patients, a rate control approach was chosen at this stage, due to adverse clinical features or patient preference. In the remaining 32 patients, a redo procedure was performed. All showed conduction recovery of the PV or conduction gap along the ablation lines, which seemed to represent the prevalent cause for recurrence.

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Long-term follow-up

Total duration of follow-up was 40 ± 8 months; follow-up from last RFCA was 29 ± 16 months. During this period, three patients died, all while in stable sinus rhythm: an 82-year-old woman, due to the complications of intestinal perforation 8 months after RFCA; a 44-year-old woman with prior history of cardiac arrest and recurrent ventricular arrhythmias, who died suddenly at home 9 months following RFCA despite an implantable defibrillator; and a 46-year old man with advanced end-stage progression and refractory heart failure, who died of cerebral haemorrage while in stable sinus rhythm and on warfarin treatment, 20 months following RFCA. None of the patients had sustained ventricular arrhythmias or appropriate impiantable cardioverter defibrillator shocks.

At the time of final evaluation, 41 patients (67%) were in stable sinus rhythm, and therefore considered as RFCA successes, including the 3 patients with paroxysmal AF treated before 2003. The total number of ablation procedures in this group was 65. Conversely, the remaining 20 patients (33%) were considered as RFCA failures due to AF recurrence, whether after one ($n = 12$) or more ($n = 8$) procedures (*Figure 2*). Among the 41 patients with successful RFCA, 17 (41%) had undergone a single procedure, whereas 24 (59%) had required a redo. The overall RFCA success rate (including repeat procedures) at 1, 2, and 3 years was 95, 83, and 71%, respectively (*Figure 3*). There was no difference in the outcome between centres (success rate 30/45 = 67% in Asti vs. 11/16 = 69% in Bordeaux; $P = 0.63$). All patients with successful RFCA had marked improvement in functional status (NYHA functional class at final evaluation 1.2 ± 0.5 vs. 1.9 ± 0.7 at baseline; $P < 0.001$), including 5 (12%) patients who improved from Class III to II and 20 (49%) patients who improved from Class II to I. Two patients required hospitalization for acute heart failure during this time. However, this occurred in the context of end-stage progression and overt systolic dysfunction of the LV, and was not related to AF recurrence.

The 20 (33%) patients who experienced AF recurrences during follow-up, despite a redo procedure, were considered as RFCA failures according to the study endpoint. The mean number of procedures in this group did not differ from that with successful RFCA (1.4 ± 0.5 vs. 1.6 ± 0.5; $P = 0.7$). Of the 20 patients with arrhythmic recurrence, five developed paroxysmal AF, six persistent AF and nine lef artrial tachycardia/flutter. Despite recurrence of AF, patients with RFCA failure still showed an overall improvement in functional status which, although less marked than patients with successful RFCA, proved nonetheless significant (NYHA class 1.8 ± 0.7 at final evaluation vs. 2.3 ± 0.7 before RFCA; $P = 0.002$). Specifically, 11 of the

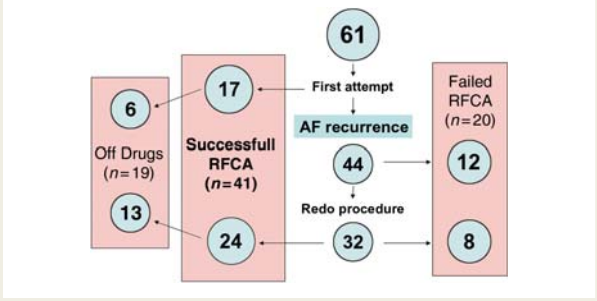

Figure 2 Overall procedural results. Flowchart depicting the prevalence of successful radiofrequency catheter ablation with regard to the number of procedures. AF, atrial fibrillation.

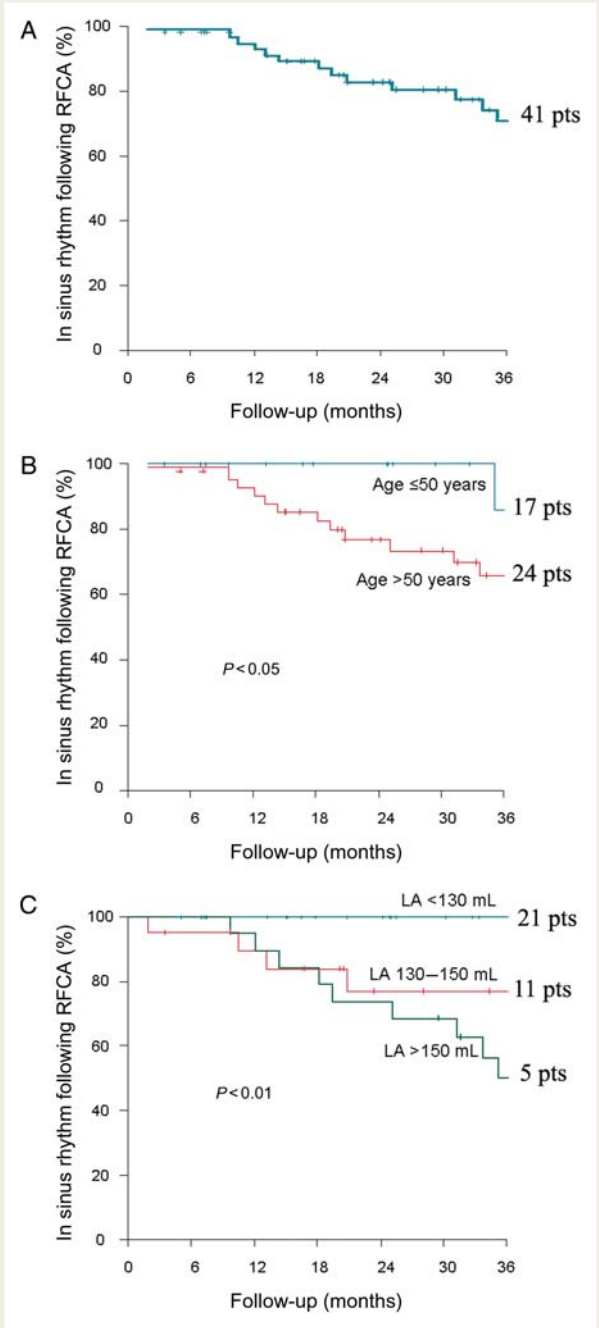

Figure 3 Cumulative probability of RFCA success over time. Kaplan–Meier curves depicting the overall survival free of atrial fibrillation recurrences following RFCA in the cohort as a whole (*A*), and based on age at enrolment (*B*), and left atrial volume (*C*). LA, left atrium; RFCA, radiofrequency catheter ablation.

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20 patients in this group reported subjective improvement in symptoms, due to reduction in perceived frequency and duration of AF recurrences.

Antiarrhythmic therapy

At the time of final evaluation or death, 19 of the 41 patients with successful RFCA (46%) were in sinus rhythm without antiarrhythmic treatment, while only 6 patients were off antiarrhythmic therapy after the first procedure (*Figure 2*). In the remaining 22 (54%) patients, pharmacological treatment with amiodarone ($n = 15$), sotalol ($n = 3$), or flecainide ($n = 4$) was not discontinued, due to the presence of repetitive non-sustained VT. Among the 20 patients with RFCA failure, 9 with paroxysmal or persistent AF recurrences were on long-term antiarrhythmic therapy with amiodarone, and 11 patients with permanent AF received beta-blockers and/or verapamil for ventricular rate control.

Predictors of RFCA outcome

RFCA success rates were higher among patients who were younger, had smaller LA size, better functional status, and without long-standing persistent AF at the time of the procedure. Specifically, the procedures were successful in 17 of the 19 patients aged $\leq$50 years (90%) and in all of the 21 with LA volume $<$130 mL. Moreover, 86% of the 14 patients originally in NYHA Class I and 71% of the 32 patients in Class II were in sinus rhythm at end of follow-up, compared with 40% of the 15 patients in NYHA Class III ($P < 0.05$; *Figure 4*). There was no difference in RFCA success rate between patients with and without left isthmus block (20/29 or 69% vs. 21/32 or 66%, respectively, $P = 0.6$).

In a multivariate Cox regression model, the only independent predictors of AF recurrence were LA volume [hazard ratio (HR) per unit increase 1.009, 95% CI 1.001–1.018; $P = 0.037$) and NYHA functional class (HR 2.24, 95% CI 1.16–4.35; $P = 0.016$), while age showed a similar trend but failed to reach statistical significance (HR 1.02, 95% CI 0.98–1.07; $P = 0.23$). Of note, LA volume $>$150 mL was associated with an almost four-fold independent increase in the likelihood of RFCA failure during follow-up (HR 3.8, 95% CI 1.4–10.4; $P = 0.009$). Conversely, other potential relevant variables such as gender, type and duration of AF, presence of LV outflow obstruction, maximum LV wall thickness, and LV ejection fraction failed to show a statistical association with RFCA outcome in our multivariate model.

RFCA in genotyped patients

Among our 61 study patients, mutations responsible for HCM were identified in 11 study patients, out of 14 who completed a comprehensive mutational screening for 8 sarcomere protein genes.[22] Of these 11 patients, 6 had MYBPC3, 2 had MYH7, and 1 had MYL2 mutations in isolation; the 2 remaining patients had complex genotypes including 1 with a double MYBPC3 defect and 1 with mutations in 3 different HCM-causing genes (MYBPC3, MYH7, and TNNI3) (*Table 2*). Average LA volume of the 11 genotyped patients was 158 $\pm$ 44 mL; 5 (45%) required a redo procedure. Mean follow-up in this group was 25 $\pm$ 14 months. Of note, RFCA was successful in 73% of these genotyped patients (i.e. 8/11), comparable with the success rate obtained in the overall study cohort. Nevertheless, most of these genotyped patients (7 or 64%) required antiarrhythmic therapy at the end of follow-up (*Table 2*).

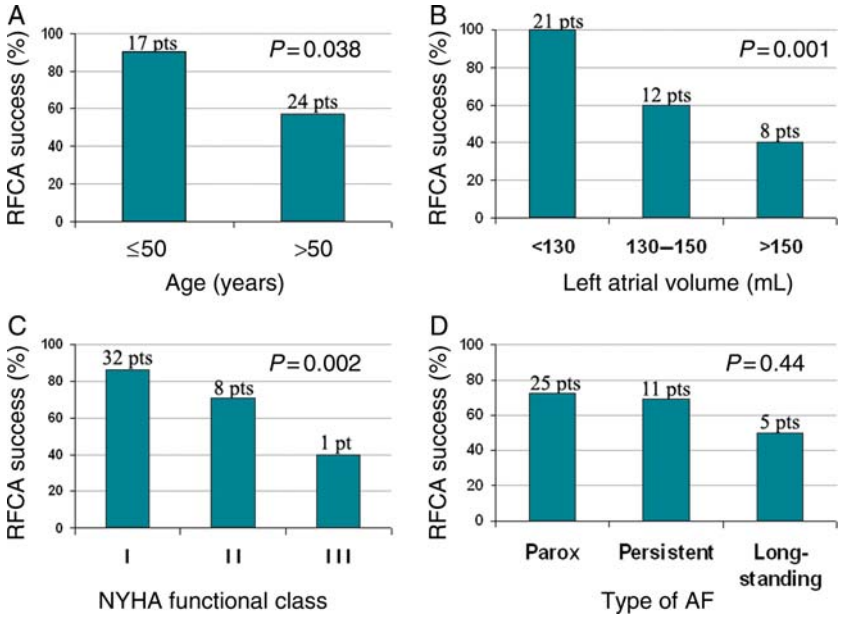

Figure 4 Rate of radiofrequency catheter ablation success based on age, left atrial volume, functional class, and type of AF at enrolment. Vertical bars represent the proportion of HCM patients in sinus rhythm at last evaluation for each category. HCM, hypertrophic cardiomyopathy.

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Table 2 Clinical features of 11 genotyped patients with hypertrophic cardiomyopathy

ID	Gender	Age at RFCA (years)	Gene	Exon/ intron	Mutation	Nucleotide change	Mutation type	Family history of HCM	Family history of SD	AF type	LA volume (cc)	Max LV thickness (mm)	LV outflow obstruction	ICD	Redo RFCA	Left isthmus block with RFCA	Follow-up (months)	RFCA outcome	On AA at final visit	NYHA FC at final visit
1	M	43	MYL2	E6	E134A*	GAG > GCG	Missense	+	+	Paroxysmal	122	18	0	0	+	+	18	Successful	0	1
2	M	43	MYBPC3	E30	K1065fs	insC	Frameshift/ter	+	0	Recent persistent	200	17	0	+	0	0	8	Successful	+	2
3	M	52	MYH7	E23	I909M*	ATC > ATG	Missense	+	+	Recent persistent	258	24	0	+	0	0	19	Failure	+	1
4	M	54	MYBPC3	E17	G531R	GGG > AGG	Missense	0	0	Long-standing persistent	124	11	0	0	+	0	16	Successful	+	1
5	M	56	MYBPC3	E23	V753fs	insT	Frameshift/ter	+	0	Long-standing persistent	194	36	0	+	+	+	41	Failure	0	3
6	M	59	MYBPC3	E6	E258K	GAG > AAG	Splice or missense	+	0	Paroxysmal	130	16	0	0	0	+	15	Successful	0	1
7	M	60	MYH7	E22	R869H	CGC > CAC	Missense	+	+	Paroxysmal	120	17	0	0	0	+	21	Successful	+	1
8	F	65	MYBPC3	E23	V753fs	insT	Frameshift/ter	+	0	Long-standing persistent	164	13	0	+	0	0	52	Successful	0	1
9	F	66	MYBPC3	E6	E258K	GAG > AAG	Splice or missense	0	+	Paroxysmal	121	23	+	+	+	+	15	Successful	+	1
10	M	44	MYBPC3	E6	E258K	GAG > AAG	Splice or missense	+	+	Paroxysmal	160	16	0	+	0	+	29	Successful	+	1
			MYBPC3	E15	E441K^{+}	GAG > AAG	Missense													
11	F	26	MYBPC3	E6	E258K	GAG > AAG	Splice or missense	+	0	Paroxysmal	148	21	0	+	+	+	39	Failure	+	1
			MYH7	E22	R869H	CGC > CAC	Missense													
			TNN13	E5	A86fs	delC	Frameshift/ter													
		52 ± 12						Positive: 9 (82%)	Positive: 5 (46%)	Paroxysmal 6 (54%) Persistent 5 (46%)	158 ± 44	19 ± 7	1 (9%)	7 (64%)	5 (45%)	7 (64%)	25 ± 14	Successful 8 (73%)	7 (64%)	1.3 ± 0.6

AA, antiarrhythmic treatment; AF, atrial fibrillation; F, female; ICD, implantable cardioverter-defibrillator; ID, patient number identification; HCM, hypertrophic cardiomyopathy; LA, left atrial; LV, left ventricle; M, male; NYHA FC, New York Heart Association functional class; redo RFCA, 2° radiofrequency catheter ablation procedure; RFCA, radiofrequency catheter ablation; SD, sudden death.

Discussion

The present multicentre study assessed the long-term efficacy and clinical outcome of selected HCM patients in whom RFCA was performed because of refractory, symptomatic AF despite medical treatment with various antiarrhythmic agents including amiodarone. The ablative procedures proved safe in our patients, despite severe LA dilatation reflecting the presence of advanced disease, often associated with heart failure.[3,13,16] Overall, about half of our HCM cohort required more than one procedure, due to the challenging atrial substrate favouring short-term recurrence of AF or atrial tachycardia/flutter. Whether this may have been due to disease-specific characteristics of the atrial tissue (e.g. hypertrophy of the muscle sleeves responsible for conducting PV triggers to LA), or simply to the considerable degree of atrial remodelling and dilatation, remains to be determined. Nevertheless, >3 years following the last procedure, 67% of the patients were in sinus rhythm and showed marked improvement in NYHA functional class. Of specific relevance, we were able to document the efficacy of RFCA in a subgroup of 11 genotyped patients, with a success rate comparable with that of the overall HCM patient population (73%). To our knowledge, this is the first demonstration of successful RFCA in a series with identified sarcomere gene mutations, which mostly comprised defects in the MYBPC3 gene. In such patients, there is considerable indirect evidence suggesting that a primary atrial myopathy, directly related to the genetic defect, may represent an important disease component, and a critical determinant of AF.[23] However, further studies are required to assess whether gene-specific differences exist with regard to the efficacy of RFCA in HCM patients.

Previous studies have demonstrated that RFCA for severely symptomatic AF is both a feasible and safe approach in patients with HCM,[13–15] and may provide similar benefits to those obtained in secondary structural heart disease.[13] However, due to the peculiar nature of the HCM disease process, the efficacy of RFCA in maintaining sinus rhythm over time, and the predictors of RFCA failure, remained largely unknown. The present study expands our knowledge in the field, by demonstrating that catheter ablation in HCM patients may result in long-term freedom from AF, although there is frequent need for redo procedures, and antiarrhythmic medications often cannot be discontinued due to additional indications. Because of the advanced disease state exhibited by many our patients, and the arrhythmogeneic nature of HCM, it would have probably been unrealistic to expect a large proportion of drug-free patients following RFCA, as many patients were receiving antiarrhythmic medications to control ventricular arrhythmias documented at ECG Holter monitoring or to minimize the likelihood of appropriate defibrillator shocks, rather than for control of AF.[24] Rather, the fact that 31% of our patients were able to totally withdraw antiarrhythmic treatment by the end of follow-up should be regarded as a considerable success of the procedure.

The present, sizeable study cohort allowed us to draw clinically relevant conclusions regarding the most important independent predictors of RFCA failure in HCM patients, which comprised age, functional status, and left atrial volume. Indeed, RFCA was highly successful in patients <50 years of age, and in NYHA Class I/II patients who had LA volumes <130 mL, reflecting less advanced disease process and more favourable substrate for the procedure.[23] These findings should help guide patient selection for RFCA and provide accurate pre-procedural counselling. Younger HCM patients with recent onset of AF in the context of mildly increased atrial size and mild or no symptoms have the greatest potential of obtaining stable sinus rhythm and to reduce or postpone the need for pharmacological antiarrhythmic therapy. These individuals should definitely be considered for RFCA when medical therapy fails or is poorly tolerated.[13–15] Conversely, older patients with long-standing AF associated with severe atrial dilatation and NYHA Class III symptoms are unlikely to benefit from RFCA, and should be informed of the reduced likelihood for success, weighing against potential procedural risks.[19] Interestingly, most patients technically considered as RFCA failures reported subjective reduction in the burden of AF and showed limited but significant improvement in functional class after the procedure. Thus, even when procedural outcome appears to be sub-optimal, RFCA may exert positive effects on the arrhythmia and improve the quality of life.[14] Whether RFCA for refractory, AF-related symptoms may have a role in HCM patients with advanced heart failure, despite a clearly unfavourable substrate, remains to be ascertained.

A redo ablative procedure was necessary in about half of our HCM patients, in order to restore stable sinus rhythm. This finding is in agreement with prior studies,[13,14] and is hardly surprising, given the unfavourable atrial substrate of most HCM patients in these cohorts. Of note, even in the HRS/EHRA/ECAS 2007 Consensus Statement, largely based data from patients with 'lone' AF, the reported failure rate of a single RFCA procedure was considerable, with most centres reporting values of 70% or more for persistent/long lasting AF.[19] The high failure rate of a single RFCA reinforces the need for accurate counselling of candidate patients, including full disclosure of the likely need for redo procedures. In this regard, we now favour the concept of offering the patient a *therapeutic strategy*, rather than a *procedure*. Indeed, the efficacy of RFCA in HCM patients over time is jeopardized by the peculiar characteristics of an ongoing cardiomyopathic process with progressive left atrial disease,[21] leading to long-term increase in atrial mass and favouring AF recurrence.[3,16,25] Other potential adverse mechanisms include recurrent ischemia due to severe coronary microvascular dysfunction which may lead to abrupt worsening of LV (prevalently diastolic) function, increased filling pressures and left atrial stretch, collagen metabolism abnormalities favouring atrial fibrosis and arrhythmogeneicity, and mitral regurgitation due to systolic anterior motion of the mitral valve.[23,26]

In conclusion, RFCA was successful in restoring long-term sinus rhythm and improving symptomatic status in most HCM patients with refractory AF, including those with proven sarcomere gene mutations. Younger HCM patients with small atrial size, mild symptoms, and shorter duration of AF proved to be the best candidates for RFCA of AF.

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References

1. Maron BJ, Casey SA, Poliac LC, Gohman TE, Almquist AK, Aeppli DM. Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 1999;**281**:650–5. Erratum: JAMA 1999; 281(24):22887.
2. Maron BJ, Olivotto I, Bellone P, Conte MR, Cecchi F, Flygen BP *et al.* Clinical profile of stroke in 900 patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol* 2002;**39**:301–7.
3. Olivotto I, Cecchi F, Casey SA, Dolara A, Traverse JH, Maron BJ. Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. *Circulation* 2001;**104**:2517–24.
4. Glancy DL, O'Brien KP, Gold HK, Epstein SE. Atrial fibrillation in patients with idiopathic hypertrophic subaortic stenosis. *Br Heart J* 1970;**32**:652–9.
5. Stafford WJ, Trohman RG, Bilsker M, Zaman L, Castellanos A, Myerburg RJ. Cardiac arrest in an adolescent with atrial fibrillation and hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1986;**7**:701–4.
6. Furlan AJ, Craciun AR, Raju NR, Hart N. Cerebrovascular complications associated with idiopathic hypertrophic subaortic stenosis. *Stroke* 1984;**15**:282–4.
7. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. *J Am Coll Cardiol* 2003;**42**:30–2.
8. Robinson K, Frenneaux MP, Stockins B, Karatasakis G, Poloniecki JD, McKenna WJ. Atrial fibrillation in hypertrophic cardiomyopathy: a longitudinal study. *J Am Coll Cardiol* 1990;**15**:1279–85.
9. Haïssaguerre M, Jaïs P, Shah DC, Takahashi A, Hocini M, Quiniou G *et al.* Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med* 1998;**339**:659–66.
10. Oral H, Scharf C, Chugh A, Hall B, Cheung P, Good E *et al.* Catheter ablation for paroxysmal atrial fibrillation: segmental pulmonary vein ostial ablation versus left atrial ablation. *Circulation* 2003;**108**:2355–60.
11. Pappone C, Oreto G, Rosanio S, Vicedomini G, Tocchi M, Gugliotta F *et al.* Atrial electroanatomical remodeling after circumferential radiofrequency pulmonary vein ablation: efficacy of an anatomic approach in a large cohort of patients with atrial fibrillation. *Circulation* 2001;**104**:2539–44.
12. Gaita F, Caponi D, Scaglione M, Montefusco A, Corleto A, Di Monte F *et al.* Long-term clinical results of two different ablation strategies in patients with paroxysmal and persistent atrial fibrillation. *Circ Arrhythmia Electrophysiol* 2008;**1**:269–75.
13. Gaita F, Di Donna P, Olivotto I, Scaglione M, Ferrero I, Montefusco A *et al.* Usefulness and safety of transcatheter ablation of atrial fibrillation in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2007;**99**:1575–81.
14. Bunch TJ, Munger TM, Friedman PA, Asirvatham SJ, Brady PA, Cha YM *et al.* Substrate and procedural predictors of outcomes after catheter ablation for atrial fibrillation in patients with hypertrophic cardiomyopathy. *J Cardiovasc Electrophysiol* 2008;**19**:1009–14.
15. Kilicaslan F, Verma A, Saad E, Themistoclakis S, Bonso A, Raviele A *et al.* Efficacy of catheter ablation of atrial fibrillation in patients with hypertrophic obstructive cardiomyopathy. *Heart Rhythm* 2006;**3**:275–80.
16. Losi MA, Betocchi S, Aversa M, Lombardi R, Mirando M, D'Alessandro G *et al.* Determinants of atrial fibrillation development in patients with hypertrophic cardiomyopathy. *Am J Cardiol* 2004;**94**:895–900.
17. Klues HG, Schiffers A, Maron BJ. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995;**26**:1699–708.
18. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. *Heart* 1997;**77**:130–2.
19. Calkins H, Brugada J, Packer DL, Cappato R, Chen SA, Crijns HJ *et al.*, Heart Rhythm Society, European Heart Rhythm Association, European Cardiac Arrhythmia Society, American College of Cardiology, American Heart Association, Society of Thoracic Surgeons HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation developed in partnership with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS); in collaboration with the American College of Cardiology (ACC), American Heart Association (AHA), and the Society of Thoracic Surgeons (STS). Endorsed and approved by the governing bodies of the American College of Cardiology, the American Heart Association, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society. *Europace* 2007;**9**:335–79.
20. Maron MS, Olivotto I, Betocchi S, Casey SA, Lesser JR, Losi MA *et al.* Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;**348**:295–303.
21. Ujino K, Barnes ME, Cha SS, Langins AP, Bailey KR, Seward JB *et al.* Two-dimensional echocardiographic methods for assessment of left atrial volume. *Am J Cardiol* 2006;**98**:1185–8.
22. Olivotto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E *et al.* Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc* 2008;**83**:630–8.
23. Olivotto I, Maron BJ, Cecchi F. Pathophysiology and clinical consequences of atrial fibrillation in hypertrophic cardiomyopathy. In Maron BJ (ed.). *Diagnosis and Management of Hypertrophic Cardiomyopathy*. Massachusetts, USA: Blackwell Futura; 2004. p105–20.
24. Cecchi F, Olivotto I, Montereggi A, Squillatini G, Dolara A, Maron BJ. Prognostic value of non-sustained ventricular tachycardia and the potential role of amiodarone treatment in hypertrophic cardiomyopathy: assessment in an unselected non-referral based patient population. *Heart* 1998;**79**:331–6.
25. Allessie MA, Boyden PA, Camm AJ, Kléber AG, Lab MJ, Legato MJ *et al.* Pathophysiology and prevention of atrial fibrillation. *Circulation* 2001;**103**:769–77.
26. Sciagrà R, Sotgia B, Olivotto I, Cecchi F, Nistri S, Camici PG *et al.* Relationship between atrial fibrillation and blunted hyperemic myocardial blood flow in patients with hypertrophic cardiomyopathy. *J Nucl Cardiol* 2009;**16**:92–6. Epub 20 Jan 2009.

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