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ORIGINAL RESEARCH

Ablation of Atrial Fibrillation in Patients With Hypertrophic Cardiomyopathy: Treatment Strategy, Characteristics of Consecutive Atrial Tachycardia and Long-Term Outcome

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BACKGROUND: Atrial fibrillation (AF) is common in patients with hypertrophic cardiomyopathy (HCM) and is associated with a deterioration of clinical status. Ablation of symptomatic AF is an established therapy, but in HCM, the characteristics of recurrent atrial arrhythmias and the long-term outcome are uncertain.

METHODS AND RESULTS: Sixty-five patients with HCM (aged 64.5±9.9 years, 42 [64.6%] men) underwent AF ablation. The ablation strategy included pulmonary vein isolation in all patients and ablation of complex fractionated atrial electrograms or subsequent atrial tachycardias (AT) if appropriate. Paroxysmal, persistent AF, and a primary AT was present in 13 (20.0%), 51 (78.5%), and 1 (1.5%) patients, respectively. Twenty-five (38.4%) patients developed AT with a total number of 54 ATs. Stable AT was observed in 15 (23.1%) and unstable AT in 10 (15.3%) patients. The mechanism was characterized as a macroreentry in 37 (68.5%), as a localized reentry in 12 (22.2%), a focal mechanism in 1 (1.9%), and not classified in 4 (7.4%) ATs. After 1.9±1.2 ablation procedures and a follow-up of 48.1±32.5 months, freedom of AF/AT recurrences was demonstrated in 60.0% of patients. No recurrences occurred in 84.6% and 52.9% of patients with paroxysmal and persistent AF, respectively (P<0.01). Antiarrhythmic drug therapy was maintained in 24 (36.9%) patients.

CONCLUSIONS: AF ablation in patients with HCM is effective for long-term rhythm control, and especially patients with paroxysmal AF undergoing pulmonary vein isolation have a good clinical outcome. ATs after AF ablation are frequently observed in HCM. Freedom of atrial arrhythmia is achieved by persistent AF ablation in a reasonable number of patients even though the use of antiarrhythmic drug therapy remains high.

Key Words: ablation ■ atrial fibrillation ■ atrial tachycardia ■ catheter ablation ■ hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenetic cardiac disease affecting ≈1 out of 500 individuals in the general population.[1] Atrial fibrillation (AF) is common in patients with HCM with a prevalence ranging between 22% and 32%, and AF episodes are often associated with a major deterioration of the functional clinical status in these patients.[2-4] Thus, effective and durable rhythm control is desirable[5,6] but often challenging because of the complex substrate which is determined by atrial fibrosis, atrial dilatation, or intrinsic atrial myopathy.[7] Despite initial promising results >2 decades ago, no

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CLINICAL PERSPECTIVE

What Is New?

- The present real-world data comprising a relatively large number of patients with hypertrophic cardiomyopathy show the effectiveness of atrial fibrillation (AF) ablation with freedom of any atrial arrhythmia in 60% of patients during long-term follow-up.
- Macroreentry and localized reentry atrial tachycardias are frequently observed in patients with hypertrophic cardiomyopathy following AF ablation, and the ablation of stable atrial tachycardias usually leads to an effective rhythm control without antiarrhythmic drug therapy.

What Are the Clinical Implications?

- Patients with hypertrophic cardiomyopathy and paroxysmal AF should undergo pulmonary vein isolation because of the favorable long-term outcome.
- The use of antiarrhythmic medication is necessary in many patients for long-term rhythm control following the ablation of persistent AF.
- Consecutive atrial tachycardias after AF ablation often show complex mechanisms in hypertrophic cardiomyopathy. Therefore, a generous ablation planning is advocated and should be discussed with affected patients.

Nonstandard Abbreviations and Acronyms

AAD	antiarrhythmic drug
AT	atrial tachycardia
CFAE	complex fractionated atrial electrograms
CL	cycle length
HCM	hypertrophic cardiomyopathy
PV	pulmonary vein
PVI	pulmonary vein isolation

randomized trials exist examining antiarrhythmic drug (AAD) therapy for AF prevention in HCM.[8,9] Today, because of its limited long-term efficacy in permanently maintaining sinus rhythm and potential hazardous side-effects, AAD therapy remains challenging in this patient population.[10] AF ablation has become an established therapy for symptomatic AF,[11] and isolation of the pulmonary veins (PVs) emerged as the mainstay of the interventional or surgical treatment strategy.[12,13] Several observational studies have shown that AF ablation in HCM is safe and reasonably effective despite potentially progressed atrial involvement resulting in severely enlarged atria in many cases.[14-18] A recent meta-analysis of these studies found a single-procedure success of 38.7% while outcome after ≥1 procedure amounted to 51.8%.[19] However, data on long-term outcome of AF ablation in patients with HCM undergoing multiple ablation procedures remains limited. The occurrence and the mechanism of subsequent atrial tachycardias (ATs) in these patients are largely unknown. Thus, we analyzed the recurrent atrial arrhythmias and the long-term outcome of patients with HCM undergoing AF ablation.

METHODS

Anonymized patient data that support the findings of this study are available from the corresponding author upon reasonable request. Consent was not obtained for data sharing, but the presented data are anonymized, and the risk of identification is minimal.

Study Population

A total of 65 patients with HCM undergoing catheter-based or surgical AF ablation between 2007 and 2018 at our institution were included in this study. The diagnosis of HCM was based on the current guidelines and verified in our specialized outpatient clinic for patients with HCM.[20] The baseline parameters and the clinical functional status during symptomatic AF episodes were assessed.[11] Echocardiographic parameters such as characteristics of left ventricular hypertrophy, systolic and diastolic function, left atrial cavity size including the left atrial volume index (left atrial volume/body surface area), functional status of the mitral apparatus, and left ventricular outflow tract obstruction were assessed according to recommendations of the European Association of Cardiovascular Imaging.[21] Approval was received from the local ethics committee review board of the University Heart and Vascular Center Hamburg-Eppendorf.

Protocols of Catheter Ablation and AF Surgery

All patients gave written informed consent before the procedure. We performed transesophageal echocardiography to rule out intracardiac thrombi before the ablation. During catheter ablation, patients were under deep sedation by intravenous propofol (Propofol- Lipuro; B. Braun, Melsungen, Germany) administration and fentanyl (Fentanyl-Janssen, Neuss, Germany).[22] After access to the left atrium (LA) by transseptal puncture bolus injections of unfractionated heparin were used to maintain an activated clotting time >300 seconds. Surface ECGs and bipolar endocardial electrograms were monitored continuously and digitally recorded (Bard Electrophysiology, Lowell, MA, USA).

At index procedure, electrical isolation of the PVs was performed by either radiofrequency energy applying a point-by-point wide antral ablation line circumferentially around each pair of ipsilateral pulmonary veins or by cryoballoon ablation aiming for isolation of the individual PVs.[21] For radiofrequency catheter ablation, the non-fluoroscopic 3-dimensional mapping systems Ensite NavX (St. Jude Medical, St. Paul, MN, USA), Carto (Biosense Webster, Diamond Bar, California) or Rhythmia (Boston Scientific, Charlestown, MA, USA) were used at operator's discretion. Treatment of persistent AF primarily involved pulmonary vein isolation (PVI) and a modified stepwise approach at the discretion of the electrophysiologist, as previously described in detail.[23,24] In brief, the first step of the ablation procedure was antral PVI with complete electrical isolation of the PVs. Additional targets for AF ablation in the LA consisted of complex fractionated atrial electrograms (CFAE) as well as areas of continuous local activity and bursts, temporal activation gradient between proximal and distal ablation bipoles, or areas of local spatial centrifugal activation. The desired procedural end point was the termination of AF, either directly to sinus rhythm or via atrial tachycardia (AT). Using the same criteria, mapping and ablation were performed within the coronary sinus and the right atrium if AF required.

Subsequent ATs were specifically targeted using entrainment mapping, activation mapping, and the analysis of voltage maps to guide the ablation. A multi-polar mapping catheter was used for ultra-high-density mapping, at operator's discretion.[25,26] AT was defined as an organized atrial activity with stable cycle length (CL) >180 ms, monomorphic p-waves on a standard 12-lead ECG, and consistent endocardial activation sequence. An AT with a stable CL was considered macro-reentrant when the tachycardia CL could be demonstrated around the presumed circuit and/or a consistent repeat post-pacing interval as observed. Localized reentry was defined as an atrial activity confined to an area of continuous signals on the bipoles of the mapping catheter displaying ≥85% of the tachycardia CL and showing consistent post-pacing interval (PPI) ≤30 ms after repeat entrainment pacing or demonstration of continuous rotational activation within a small area of <2 cm with each rotation encompassing 1 full CL.[25,27] If a macro-reentry or a localized reentry was clearly identified during activation mapping, entrainment mapping was not always performed to confirm the diagnosis. Focal AT was recognized as an atrial activation originating from a discrete site activating the surrounding tissue centrifugally and showing other features consistent with a focal mechanism such as variation of CL ≥15% or inconsistent post-pacing interval.[28]

We considered an AT, which remained unchanged during mapping and thus could be appropriately characterized according to above-mentioned criteria as "stable AT". In contrast, atrial arrhythmia with frequently changing activation sequence or wavering cycle length were defined as "unstable AT".

Linear ablation addressing the anatomical or practical arrhythmia isthmus was performed if a macro-reentrant mechanism was suspected. Localized reentry or focal ATs were ablated at the site of earliest activation based on individual characteristics of the arrhythmogenic substrate.[29]

Repeat procedure was indicated in case of symptomatic arrhythmia recurrences and patients` preferences. As the first step of repeat procedures, electrical isolation of the PVs was evaluated and re-established if required. In case of recurrent paroxysmal AF episodes, repeat PVI only was pursued. If patients presented with persistent AF or AT, the ablation was performed according to the protocol mentioned above.

Concomitant surgical ablation was performed in patients with AF undergoing mitral valve surgery or surgical myectomy. The indication for AF surgery as a stand-alone procedure was reserved for a selected number of patients with severely dilated LA after interdisciplinary decision of the cardiac surgeon and the electrophysiologist. Patients with paroxysmal AF received PVI. Left atrial ablation with box lesions, left atrial appendage isolation, the ablation of the left atrial isthmus, additional biatrial ablation with right atrial intercaval lesions, ablation of the cavotricuspid isthmus, and ablation at the right atrial appendage and the terminal crest was performed at operator's discretion as was previously described.[30] The energy sources applied included unipolar radiofrequency ablation (Cardioblate unipolar RF pen, Medtronic Inc.) and bipolar ablation (Cardioblate BP2 device and Cardioblate Surgical Ablation System Generator, Medtronic Inc.).

Follow-Up

All patients were monitored for peri-procedural complications throughout the procedure and during hospitalization. Follow-up was scheduled in a 3- to 6-month interval in our outpatient clinic. AF and AT recurrences were assessed using 24-hour Holter ECG recordings every 1 to 2 months. In patients with an implantable electronic cardiac device, the continuous rhythm monitoring function was used for the assessment of AF/AT recurrences.[31] Patients were assessed for clinical status and current antiarrhythmic medication. A single AF/AT episode with a duration of >30 seconds on the 24-hour Holter ECG or an atrial high rate episode lasting longer than 5 minutes

as detected by a cardiovascular implantable electronic device such as a pacemaker or an implantable cardioverter defibrillator (ICD) was defined as AF/AT recurrence. The absence of AF/AT recurrences during the entire follow-up was considered freedom of AF/AT. If AAD therapy was continued after ablation and no further AF episodes were detected at follow-up, discontinuation of AAD therapy was recommended. Patients experiencing symptomatic recurrences with documented AF/AT or an AF burden >1% after a 3-month blanking period underwent a change of AAD or a repeat ablation at the discretion of the electrophysiologist and patients' preference.

Statistical Analysis

Continuous values are reported as mean±SD or as median and range as appropriate. Group comparison of continuous normally distributed variables was performed using the Student *t*-test. For group comparisons of ordinal variables, the Mann–Whitney *U* test was used, while dichotomous variables were compared using the Fisher exact-test. Differences in pre- and post-ablation parameters were assessed using the Wilcoxon signed-rank test for ordinal variables, while the McNemar test was used for dichotomous variables. Time to recurrence and event-free survival curves were calculated using the Kaplan–Meier estimation method. Uni- and multivariate Cox regression analyses were used to evaluate predictors for AF/AT recurrences. All statistical tests were 2-tailed. A $P<0.05$ was considered as statistically significant. The statistical analysis was performed using SPSS 26.0 (IBM, Chicago, IL, USA).

RESULTS

Study Population

The baseline characteristics of the study population are summarized in Table 1. At index procedure, 13 (20.0%) patients presented with paroxysmal AF and 51 (78.5%) with persistent AF. One (1.5%) patient had a primary AT when initially AF was suspected. Septal hypertrophy was diagnosed in 45 (69.2%) patients as compared with apical or concentric hypertrophy which was found in 4 (6.1%) and 16 (24.7%) of the patients, respectively. An enlarged LA was present in most of the patients with a mean volume of 110.3±55.3 mL and a LA volume index of 55.8±28.7 mL/m^2. In 28 (43.1%) patients an ICD was previously implanted for prevention of sudden cardiac death. In 22 (33.8%) patients the dual-chamber ICD with an atrial lead incorporated a continuous atrial rhythm monitoring function. The indication for ICD implantation was based on primary prevention in 82.1% of those patients. The majority of patients received beta-blocker therapy (80.0%), and

Table 1. Baseline Clinical Data

Baseline Clinical Data	n=65
Age, y	64.5±9.9
Sex, men, n	42 (64.6)
BMI	27.4±5.3
Arterial hypertension, n (%)	25 (38.4)
Diabetes mellitus, n (%)	6 (9.2)
Coronary artery disease	14 (21.5)
Prior TIA/stroke, n (%)	10 (15.3)
Creatinine, mg/dL	1.2±0.6
ProBNP, ng/L	2490±2130
Creatine kinase, UI/L	185±159
Type of HCM	
Septal, n (%)	45 (69.2)
Concentric, n (%)	16 (24.7)
Apical, n (%)	4 (6.1)
Paroxysmal AF, n (%)	13 (20.0)
Persistent AF, n (%)	51 (78.5)
Primary AT, n (%)	1 (1.5)
LVEF, %	54.4±14.6
LA diameter, mm	54.1±12.5
LA volume, mL	110.3±55.3
LA volume index, mL/m^2	55.8±28.7
Septal wall thickness, mm	18.6±4.2
Posterior wall thickness, mm	13.4±3.2
Resting gradient, mm Hg	8.1 (0–60)
Stress gradient, mm Hg	12.6 (0–62)
TASH	3 (4.6)
Septal myectomy	8 (12.3)
Diastolic dysfunction	
No	12 (18.5)
Mild	19 (29.2)
Moderate	32 (49.2)
Severe	2 (3.1)
Mitral insufficiency	
No	10 (15.3)
Mild	40 (61.5)
Moderate	14 (21.5)
Severe	1 (1.5)
SAM of the mitral valve	11 (16.9)
Mitral valve repair	6 (9.2)
Mitral valve replacement	7 (10.7)
Family history of SCD, n (%)	5 (7.7)
Syncope, n (%)	13 (20.0)
SCD risk score (5-y risk of SCD in %)	3.7±3.2
ICD	28 (43.1)
Primary prevention	23 (82.1)
Secondary prevention	5 (17.9)

Values are indicated as total number (n), percentage (%), mean±SD, or median (range). AF indicates atrial fibrillation; AT, atrial tachycardia; BMI, body mass index; BNP, B-type natriuretic peptide; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LA, left atrium; LVEF, left ventricular ejection fraction; proBNP, pro-B-type natriuretic peptide; SAM, systolic anterior motion; SCD, sudden cardiac death; TASH, transcoronary ablation of septal hypertrophy; and TIA, transient ischemic attack.

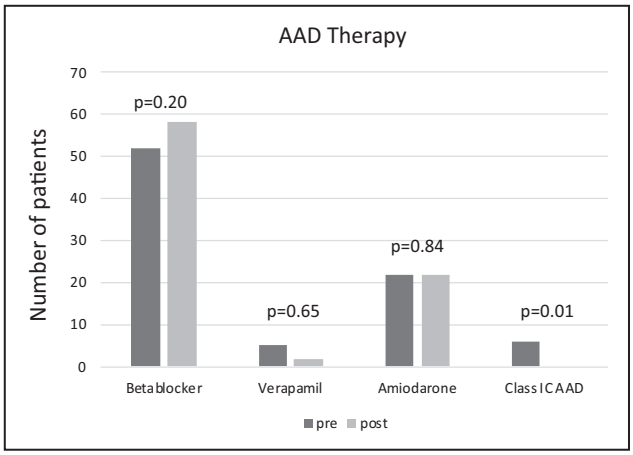

Figure 1. Antiarrhythmic drug therapy before and after ablation of atrial fibrillation.
Overall, the use of antiarrhythmic drug therapy did not change during follow-up (*P*=0.09, *P* values based on McNemar test). AAD indicates antiarrhythmic drug; Post, after ablation; and Pre, before ablation.

approximately half of the patients received AAD therapy (50.7%) before ablation. The selected AAD was (Figure 1): flecainide (9.2%), amiodarone (33.8%), or verapamil (7.6%). Patients at a young age experiencing symptomatic AF episodes were primarily selected for ablation to avoid possible long-term AAD usage.

Catheter Ablation and AF Surgery

Overall, 128 procedures were performed with a mean of 1.9±1.2 procedures per patient. Catheter ablation was conducted in the majority of cases with a total number of 119 (92.9%) procedures, as compared with a total of 9 (7.1%) AF surgeries. Procedure time, fluoroscopy time, and time of radiofrequency energy application of catheter ablation was 167.0±69.9, 27.7±18.6, and 52.1±28.2 minutes, respectively (Table 2).

The index procedure was a catheter-based ablation in 57 (87.6%) patients, whereas 8 (12.3%) patients underwent AF surgery. In 6 patients, AF surgery was accompanied by an operative mitral valve repair, mitral valve replacement, or surgical myectomy. In 2 patients, AF surgery was a stand-alone procedure. One patient had a biatrial ablation during a tricuspid and mitral valve repair as the second ablation procedure.

Table 2. Procedural Data

No. of procedures in total	128
Mean number of procedures	1.9±1.2
Catheter ablation, n (%)	119 (92.9)
Procedure time, min	167.0±69.9
Fluoroscopy time, min	27.7±18.6
Radiofrequency energy, min	52.1±28.2
Surgical ablation, n (%)	9 (7.1)

Values are in n (%), mean±SD, or n.

The index procedure involved PVI in 64 (98.5%) patients. Catheter ablation using radiofrequency energy was performed in 83.1%, while 2 (3.1%) patients underwent cryoballoon PVI at index procedure. A left atrial anterior line, connecting the mitral valve annulus to an area of dense scar in the central left atria as indicated by the voltage map, was performed in 1 (1.5%) patient with an isolated anterior left atrial macro-reentry tachycardia and no history of AF. Eleven (84.6%) patients with paroxysmal AF received PVI only with mean of 1.4±0.8 procedures. In 1 patient, CFAE ablation and ablation of ATs were performed during the third procedure. Another patient had an anterior linear ablation of a macro-reentry AT during the second ablation. During repeat ablation procedures continuous PVI of all PVs was found in 5 of 36 (13.9%) during the second, 6 of 18 (33.3%) during the third, in 5 of 10 (50.0%) during the fourth, and in one of four (25.0%) during the fifth ablation procedure. Details about the CFAE ablation and the creation of additional ablation lines beyond PVI of all patients are summarized in Figure 2. AF surgeries involved an isolated bilateral PVI in 2 patients, a left atrial ablation including PVI, box lesions and left atrial appendage excision, and left atrial isthmus ablation in 4 patients, and a biatrial ablation which additionally included right atrial intercaval lesions such as the ablation of the cavotricuspid isthmus, the right atrial appendage, and the terminal crest in 3 patients.

Mechanism and Ablation of Atrial Tachycardia

Ablation of ATs was conducted in 25 (38.4%) patients, targeting a total of 54 ATs. Out of 47 patients in which a PVI only had been performed previously, 14 (27.7%) patients developed AT, whereas 10 of 17 (58.8%) patients with a previous ablation of CFAE presented with AT. One patient had a primary AT, as mentioned above. The mechanism was characterized as a macro-reentry tachycardia in 37 (68.5%), as a localized reentry in 12 (22.2%), or as a true focal mechanism in 1 (1.9%) of the AT in question. The mechanism was not conclusively detectable and thus not classified for the remaining 4 (7.4%) ATs. As for macro-reentry ATs, a linear ablation was performed at the LA roof (n=10), the mitral isthmus (n=11), and the anterior LA (n=16). Localized reentry ATs were identified in various different locations (Figure 3), and ablation in the left or right atrium was conducted as appropriate. These ATs were located at the atrial septum (n=3), the inferior LA (n=2), the anterior LA (n=2), near the ostium of coronary sinus (n=1), in close vicinity of the right superior PV (n=1), near the superior vena cava (n=1), at the base of the left atrial appendage (n=1), and at the posterior LA roof (n=1). A

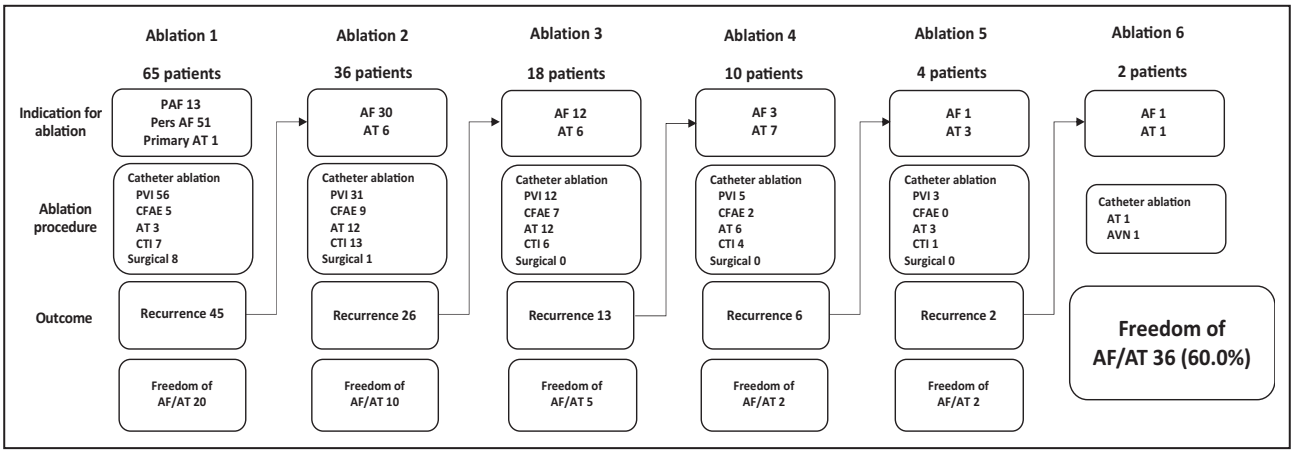

Figure 2. Ablation strategy during procedures, outcome, and indication for re-ablation.
Values are indicated as total number (n), or percentage (%). AF indicates atrial fibrillation; AT, atrial tachycardia; AV, atrioventricular node; CFAE, complex fractionated atrial electrograms; CTI, cavotricuspid isthmus; PAF, paroxysmal AF; Pers AF, persistent AF; and PVI, pulmonary vein isolation.

true focal AT was located at the ostium of the coronary sinus (n=1). An additional ablation of the cavotricuspid isthmus was performed in 14 (56.0%) of those patients either empirically (n=2), because of previously reported typical atrial flutter (n=9), or after the identification of cavotricuspid isthmus dependent atrial flutter (n=3) during the electrophysiologic study (a repeat ablation of the cavotricuspid isthmus was necessary for 1 patient during a subsequent ablation procedure).

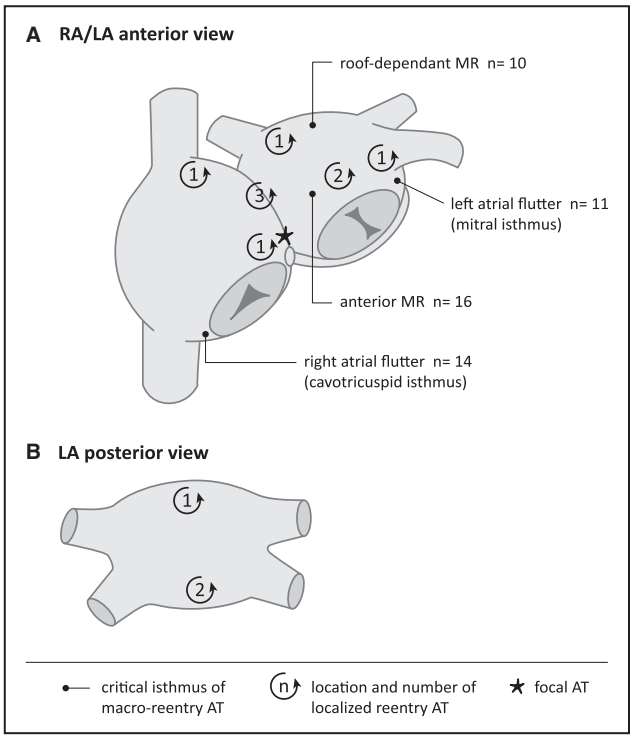

Figure 3. Location and mechanism of atrial tachycardias as shown in an anterior (A) and posterior (B) view of the atria.
Values are indicated as total number (n). AT indicates atrial tachycardia; LA, left atrium; MR, macro-reentry; and RA, right atrium.

Out of the 25 patients presenting with AT, we found 15 (60.0%) with stable AT and 10 (40.0%) with unstable AT. Procedure duration and radiofrequency energy application were higher for the ablation of unstable AT as compared with stable AT, 225±58 versus 153±56 minutes (P<0.01) and 69±35 versus 48±26 minutes (P=0.03), respectively. Fluoroscopy times did not differ (33±17 versus 30±16 minutes, P=0.29).

Nine (90.0%) patients with unstable AT during the ablation procedure had undergone a previous AF ablation involving the ablation of CFAE. In those 10 patients 25 ATs occurred, of which 13 (52.0%) were characterized as macro-reentry, 8 (32.0%) as localized reentry, and 4 (16.0%) were not classified because of an inconclusive mechanism. The linear ablation for macro-reentry ATs was performed at the roof in 9, the mitral isthmus in 1, and the anterior LA in 3. The ablation of localized reentry AT was performed at the atrial septum in 3, the inferior LA in 2, near the ostium of the coronary sinus in 1, near the superior vena cava in 1, and at the posterior LA roof in 1.

In contrast, no ablation of CFAE was previously performed in 12 (80.0%) of the 15 patients with stable AT. Besides the 1 patient who presented with primary AT with a macro-reentry stable AT circling around an anterior low-voltage region, all of those patients only had PVI or cavotricuspid isthmus ablation before the ablation of the stable AT. A total of 29 ATs were reported with 24 (82.8%) described as macro-reentry, 4 (13.8%) as localized reentry, and 1 (3.4%) as a true focal AT. A linear ablation for the macro-reentry AT was performed at the roof in 7, the mitral isthmus in 12, and the anterior LA in 5. Ablation of localized

reentry ATs was performed at the anterior LA in 2, in close vicinity of the right superior PV in 1, and at the base of the left atrial appendage in 1. The focal AT was ablated at the ostium of the coronary sinus. During the ablation primarily targeting the stable AT, a redo PVI was performed in 10 (66.6%) patients because of electrical reconnection of PVs even though AF was not reported anymore.

The occurrence of macro-reentry and localized reentry ATs were not significantly different in patients with unstable AT and stable AT (P=0.11). A redo ablation of 3 (5.5%) ATs was performed at the LA roof (n=1), the CS ostium (n=1), and the mitral isthmus (n=1).

Long-Term Outcome

The mean follow-up was 48.1±32.5 months after the index procedure and 30.6±26.8 months after the last ablation procedure. Continuous atrial rhythm monitoring of a previously implanted ICD was used to detect AF episodes in 22 (33.8%) patients. In the remaining 43 (66.2%) patients, the follow-up was based on sequential Holter ECG recordings. Freedom of AF/AT was found in 39 (60.0%) patients during long-term follow-up (Figure 4). No recurrences occurred in 11 (84.6%) patients with paroxysmal and 27 (52.9%) patients with persistent AF (P<0.01). In the subgroup of 25 patients with ablation of AT, we found freedom of AF/AT in 4 (40.0%) patients with unstable AT and in 9 (60.0%) patients with stable AT (P=0.43). One patient with primary AT was free of recurrences after 14 months. All patients with exclusively a surgical ablation (n=3) had arrhythmia recurrences during follow-up (2 with AF, 1 with AT). One (1.5%) patient progressed from paroxysmal to persistent AF, whereas 2 (3.1%) patients were shifted from persistent to mostly paroxysmal AF episodes.

No clinical predictors of AF/AT recurrences or clinical predictors for the occurrence of AT after AF ablation were found in univariate and multivariate Cox regression analysis. The majority of patients (92.3%) were on beta-blocker or verapamil as medical therapy for the underlying HCM. The overall usage of AADs was not reduced as shown in Figure 1 (P=0.09). After ablation class IC AAD therapy were discontinued in all patients because of hypertrophy of the ventricular septum ≥13 mm. For the suppression of AF recurrences, the antiarrhythmic medication was limited to amiodarone in 22 (33.8%) and verapamil in 2 (3.1%) patients.

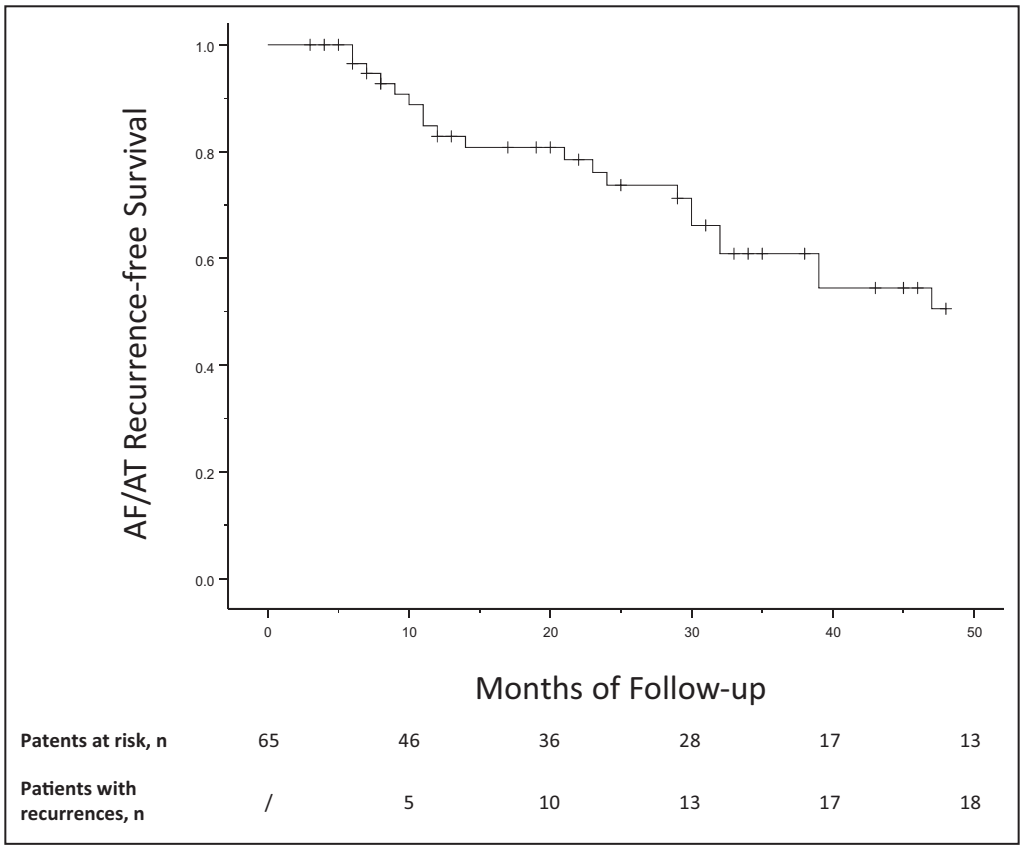

Figure 4. Kaplan–Meier graph showing the atrial fibrillation/atrial tachycardia recurrence-free survival.
Values are indicated as total number (n). AF indicates atrial fibrillation; and AT, atrial tachycardia.

Following the ablation 22of 52 (42.3%) patients with persistent AF and 2 of 13 (15.4%) patients with paroxysmal AF (with AF recurrences) received AAD therapy (P<0.01). Even though 6 patients were able to abandon amiodarone treatment after ablation the same number of patients required amiodarone for effective maintenance of sinus rhythm. Thus, the number of patients on amiodarone therapy remained equal before and after ablation.

The clinical functional status of most patients improved during follow-up (P=0.0498). Changes in pre- and post-ablation clinical functional status of every single patient are summarized in Figure 5. Freedom from symptomatic AF/AT episodes was found in 44 (67.7%) patients, whereas in 5 (7.7%) patients, asymptomatic episodes were reported after AF/AT ablation.

After a total of 119 catheter ablation procedures, 1 patient (0.8%) had a pericardial tamponade with immediate percutaneous pericardiocentesis and favorable clinical outcome. One patient (0.8%) experienced a transient ischemic attack without any residual neurological impairment. One patient (0.8%) suffered air embolization into the right coronary artery with an unremarkable clinical outcome. One patient (0.8%) had an arteriovenous fistula, which was treated surgically.

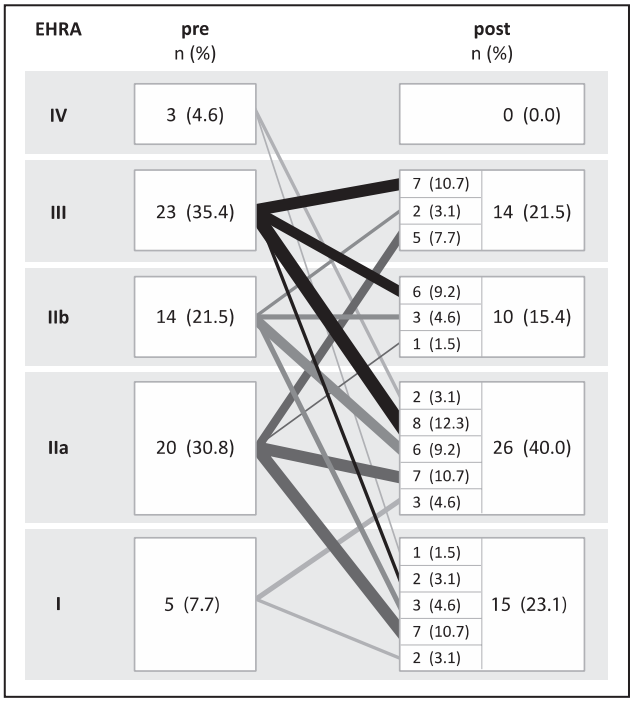

Figure 5. Change of European Heart Rhythm Association functional class of every single patient before and after ablation of atrial fibrillation.
Overall the clinical functional status of most patients improved during follow-up (P=0.0498, Wilcoxon signed-rank test). EHRA indicates European Heart Rhythm Association; Post, after ablation; and Pre, before ablation.

No acute stroke or atrio-esophageal fistula was observed after ablation.

During follow-up, 4 (6.1%) patients died attributable to causes not related to the ablation procedure. Two (3.1%) died as a result of severe infection and septic shock of the ICD and its transvenous leads. The lethal event in these 2 patients was >24 months after the last ablation procedure, and an infectious complication related to the catheter ablation seems unlikely as mentioned in a previous work of our group[32]. One patient (1.5%) died as a consequence of congestive heart failure after a prolonged hospitalization with hospital-related complications, and 1 (1.5%) patient suffered a severe stroke after acute obstruction of the left common carotid artery potentially because of a cardiac embolus despite oral anticoagulation with novel oral anticoagulants. In these patients the lethal event also occurred >24 months after the last ablation procedure.

DISCUSSION

To our knowledge, we present one of the largest single-center studies with the longest follow-up (Table 3) investigating outcome of AF ablation in patients with HCM and the mechanism of subsequent atrial arrhythmias. The main findings of this study are: (1) AF ablation is effective for long-term rhythm control in patients with HCM; (2) patients with paroxysmal AF have an especially good clinical outcome comparable with ablation of paroxysmal AF in the general population; (3) about a third of patients with HCM develop AT after the ablation of AF which are unstable in about 40% of patients; (4) while ablation of stable AT show a promising long-term outcome, in patients with unstable AT especially following CFAE ablation the efficacy of long-term rhythm control is relatively low.

Long-Term Outcome of AF Ablation

In patients with HCM, the occurrence of AF is common[3] and was thought to be associated with increased mortality.[2,33,34] A more recent study of Rowin et al reports a relatively low annual mortality <1% directly attributable to AF when applying current treatment strategies with no difference in the outcome of patients with HCM without AF.[35] Even though the effect of rhythm versus rate control on mortality in HCM is largely unknown, this study casts a more favorable light on AF and its impact on mortality in HCM. However, recurring AF often leads to a major deterioration in clinical functional status in HCM, and thus a therapeutic strategy aiming for long-term rhythm control is desirable in most patients.[2-6] As AAD therapy fails to maintain sinus rhythm durably,

Table 3. Previously Published Studies of AF Ablation in Patients With HCM Compared With the Present Study

Author (Y)	Study Design	No. of Patients, male (%)	Age, y	Persistent AF, n (%)	LA Diameter, mm	Septal Wall Thickness, mm	Ablation Procedure	No. of Procedures	AAD Usage at Last FU, %	FU Duration, y	Occurrence of AT, %	Freedom of AF/AT, %
Kilcaslan et al (2006)[14]	Retrospective multicenter	27 (70)	55±10	13 (48)	50±9	17±5	PVI	1.3	39	0.9±0.6	n.a.	70
Gaita et al (2007)[16]	Prospective cohort single-center	26 (69)	58±11	13 (50)	52±6	23±4	PVI, roof, mitral line	1.2	38	1.6±0.8	15	65
Di Donna et al (2010)[18]	Retrospective multicenter	61 (72)	54±13	26 (43)	52±5	20±5	PVI, roof, mitral line, CTI (in 15 patients)	1.5	54	2.4±1.3	15	67
Derejko et al (2013)[17]	Prospective observational	30 (67)	49±11	16 (53)	51±7	21±6	PVI, CTI, mitral line, roof, CFAE	1.4	37	1.9±1.2	n.a.	53
Santangeli et al (2013)[15]	Prospective multicenter	43 (67)	59±8	31 (72)	47±8	20±4	PVI, box lesion, SVC isolation, CFAE, non-PV trigger	1.6±0.7	24	1.3 (0.7–1.6)	37	94
Bassiouny et al (2015)[6]	Retrospective single-center	CA 79 (54), SA 68 (46)	55±11	62 (42%)	50±10	20±5	PVI, mitral line, roof, CTI, Cox-Maze	1.2	38	2.9 (1.2–5)	8	46
Dinshaw et al (2020)	Retrospective single-center	65 (65)	64±10	51 (79)	54±13	19±4	PVI, CFAE, AT as appropriate	1.9±1.2	37	4.0±2.7	38	60

Values are indicated as total number (n), percentage (%), or mean±SD. AAD indicates antiarrhythmic drug; AF, atrial fibrillation; AT, atrial tachycardia; CA, catheter ablation; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; CTI, cavotricuspid isthmus; FU, follow-up; HCM, hypertrophic cardiomyopathy; LA, left atrium; n.a., not available; PVI, pulmonary vein isolation; SA, surgical ablation; and SVC, superior vena cava.

several studies investigated the role of AF ablation in HCM (Table 3).[10] We now show in our large retrospective single-center study that the ablation of AF involving a solely catheter-based approach in most and a combined approach using a surgical and catheter-based ablation in some patients results in a reasonable long-term freedom of AF/AT of 60% after a mean follow-up of 30.6±26.8 months after the last ablation procedure. This is comparable with previous work published by our group in the past assessing the long-term AF ablation outcome of patients without HCM.[31,36] Also, large clinical trials or current real-world registries of unselected cohorts show long-term arrhythmia-free survival ranging between ≈40% to 75% underlining the acceptable AF ablation outcome of patients with HCM as demonstrated by our present study.[37-40] Even though the majority of our patients had persistent AF (78.5%), we showed that especially patients with paroxysmal AF in this cohort have a good clinical outcome with freedom of AF/AT recurrences in 84.6% of patients. Large randomized controlled trials involving unselected cohorts generally found no recurrences after AF ablation in >80% of patients with paroxysmal AF,[41-43] which is also supported by previous work of our group.[24] This suggests that the AF ablation outcome in patients with HCM and paroxysmal AF is comparable with the ablation outcome of paroxysmal AF in the general population. Nevertheless, the total number of patients requiring AAD therapy for long-term rhythm control remains high in our study (36.9%), but this is comparable with other studies (Table 3).[18,44] In a meta-analysis, Providencia et al analyzed several retrospective cohort studies of AF ablation in HCM and found diverging success rates, ranging between 14% and 94%.[19] Only a limited number of patients were included in most of those studies (ranging between 4–61 patients) and the ablation protocol differed significantly between groups, therefore assessment of ablation outcome in HCM necessitates a more differentiated approach. Di Donna et al demonstrated in a multicenter study of patients with HCM that 67% of patients were in sinus rhythm after a mean follow-up of 29±16 months.[18] More than half (56%) of the patients were in paroxysmal AF (25% with persistent and 19% with long-standing persistent AF), and the use of AAD was necessary for 54%. In contrast to our study, the ablation protocol for the index procedure included PVI, linear ablation at the LA-roof, ablation of the right atrial isthmus in all, and effective linear ablation of the mitral isthmus in 32 (52%) patients. In this study, especially younger age and a smaller LA diameter were shown to be associated with a better outcome. Three patients died during follow-up attributable to causes unrelated to the ablation procedure which, like in our study, indicated

the potential severe morbidity of this patient cohort. However, the ablation procedure itself has a good safety profile and a low-complication rate also in patients with HCM, which is supported by our data and which was previously shown by previous studies.[19] Therefore, we perceive that ablation in patients with HCM with symptomatic AF is a reasonable approach for long-term rhythm control despite potential additional AAD therapy. Patients with HCM and paroxysmal AF should be treated with PVI because of the potential good long-term clinical outcome in this subgroup of patients.

Occurrence of AT After AF Ablation in HCM

In our study, about a third of patients with HCM (38.4%) undergoing AF ablation showed AT as recurring atrial arrhythmia during follow-up. Subsequent ATs are well described after ablation of AF. Gerstenfeld et al and Wasmer et al investigated the occurrence of ATs in a total of >1100 patients after circumferential antral ablation of the ipsilateral PVs and reported a prevalence of 2.9% and 4%, respectively.[45,46] In contrast, a study by Deisenofer et al found 31% of patients with ATs after circumferential PVI.[47] In this study, however, structural heart disease was known in 58% of patients, whereas in the study of Wasmer et al, only 10% of patients with structural heart disease were included. Furthermore, in the study of Wasmer et al, patients with ATs more commonly had structural heart disease (25% versus 10%) suggesting a higher occurrence of AT after AF ablation in patients with structural heart disease.

The data about predictors of AT after AF ablation are limited. After an extensive atrial substrate modification involving CFAE and linear ablation, the occurrence of ATs is more commonly seen ranging between 24% and 40%.[30,37,49] Recently, Ipek et al showed that right atrial dilatation is predictive for typical flutter, whereas LA dilatation, linear ablation lesions, and persistent AF were predictive for atypical flutter.[49] We now demonstrated for the first time, to our knowledge, that patients with HCM experience a relatively high number AT after AF ablation as compared with patients without or with another type of structural heart disease.[46-48] Even after an isolated PVI, about 30% of patients have AT requiring targeted ablation. This number rises to almost 60% when an ablation of CFAE was performed previously. Clinical parameters such as LVEF, diastolic dysfunction, mitral valve insufficiency, septal wall thickness, or LA volume were not found to be predictors for the occurrence of AT in our cohort.

Mechanism of AT After AF Ablation

The mechanism of ATs has been classically described as focal or macro-reentry. More recently, we gained deeper insight into those atrial arrhythmias differentiating true focal versus localized reentry using novel mapping strategies and multipolar catheters with high-density electrogram acquisition.[50,51] The critical isthmus of reentry ATs can be demonstrated in the majority of cases and the ablation of the localized or macro-reentrant AT individually planned during the procedure.[25] Patients with HCM often have extensive structural changes resulting in sometimes severe dilatation of the atria potentially also because of an underlying primary atrial cardiomyopathy associated to hereditary cardiac disease beyond secondary changes because of a mitral insufficiency and/or diastolic dysfunction of the hypertrophied ventricle. However, the strategy for mapping and ablation of AT in patients with HCM generally does not differ as compared with the general population.

As ATs are common after AF ablation in HCM, appropriate characterization of the arrhythmia in question is essential for an optimized ablation procedure. This is surprisingly difficult in patients with HCM after AF ablation, as 40% of those patients present with unstable AT. Almost all of these patients (90.0%) had a previous CFAE ablation suggesting an initially more complex type of AF and the location of subsequent ATs are more commonly found at atypical sites such as the inferior and posterior LA. In those patients with unstable AT, a repeatedly changing cycle length and activation sequence sometimes cause the inability to characterize the atrial arrhythmia. Ablation in those cases is guided according to a multitude of criteria after entrainment-, activation- and voltage-mapping. Even though Deisenhofer et al reported a relatively large proportion of unstable AT (31%) in her study, to our best knowledge, the literature about the ablation of unstable AT is limited, and recommendations about mapping and ablation strategies do not exist.[25,47] After often prolonged ablation procedures, the unstable AT often has to be terminated by external electric cardioversion. The long-term freedom of AF/AT of 40% during follow-up in our study remains unsatisfactory, while we are not aware of any comparative results in the literature of long-term freedom of arrhythmia recurrence in this subgroup of patients. Randomized controlled studies recently questioned the role of extensive substrate ablation in patients with persistent AF.[52,53] The role of CFAE or linear ablation beyond PVI in patients with HCM was not addressed in randomized trials yet. Our current results suggest that potentially the ablation of CFAE leads to unstable AT for which the current ablation strategies do not achieve a satisfactory freedom of AF/AT. This might lead to the assumption that the role and the extent of atrial substrate modification have to be substantially revisited, possibly using multipolar mapping catheters with an optimized signal

resolution. Santangeli et al performed an extensive AF ablation in patients with HCM in their study, including PVI, isolation of the left atrial posterior wall, isolation of the superior vena cava, CFAE ablation in the LA and coronary sinus, and in redo procedures the ablation of non-PV triggers after isoproterenol challenge.[15] Late recurrences (>1 year after the last ablation) were found in around 50% of patients, and atypical atrial flutter was the dominant mode of recurrence, occurring in almost 90% of these cases. In this study, atypical flutter was mapped and ablated in approximately two thirds of cases which is comparable to our findings. Santangeli and colleagues found that flutter termination during ablation did not predict the ablation outcome, whereas the ablation of non-PV triggers was associated with an arrhythmia-free survival benefit resulting in arrhythmia freedom in 94% of patient off AAD therapy with a median follow-up of 15 months. Thus, possibly additional ablation of non-PV triggers might play an important role in the ablation of persistent AF in HCM, which should be addressed in future studies.

In contrast, we found 60% of patients with stable AT in which the mechanism of the AT could be characterized in all cases, and the ablation was performed accordingly. In the majority (80%) of patients, only a PVI was performed during a prior ablation, and those patients had a promising long-term rhythm control with freedom of AF/AT of 60% after >24 months with only 1 (6.6%) patient on AAD therapy with amiodarone.

In summary, we perceive that all patients with HCM should primarily undergo PVI as effective rhythm control is possible in some patients, and the occurrence of stable AT is common. In case of recurrence of stable AT, a targeted ablation strategy aiming for characterization and respective ablation of the AT in addition to a redo PVI if appropriate is a reasonable approach. However, a CFAE ablation for recurrent persistent AF in HCM and a careful mapping of all subsequent ATs in case of unstable mechanisms is questionable and larger prospective multicenter trials are necessary to determine the best ablation strategy.

Limitations

The present study has several limitations: First, this is a single-center, retrospective, observational study. However, we present a relatively large patient population with a relatively long follow-up giving insights into AF ablation of patients with HCM. Second, a matched comparison with patients without HCM undergoing AF ablation was not performed in our study. As index ablation procedures go back several years, technological advancements of mapping systems and catheter design were made. Whether this influenced our results was not assessed. The differentiation between slow AF and unstable AT is challenging and was based on the best knowledge of the electrophysiologist during the procedure. Even though the diagnosis was made by at least 2 experienced electrophysiologists, interobserver bias cannot be ruled out and further mechanistically studies are warranted.

CONCLUSIONS

We conclude that AF ablation in patients with HCM is effective for long-term rhythm control. Especially patients with paroxysmal AF undergoing PVI have a good clinical outcome. The occurrence of ATs after AF ablation in HCM is high. Macro-reentry and localized reentry ATs can be demonstrated, and the ablation of stable ATs usually leads to an effective rhythm control without AAD therapy. The long-term freedom of AF/AT for persistent AF and unstable ATs in HCM is reasonable even though the optimal ablation strategy remains debatable.

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