Catheter ablation for atrial fibrillation in hypertrophic cardiomyopathy: a systematic review and meta-analysis

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ABSTRACT

Objective Atrial fibrillation (AF) is common in hypertrophic cardiomyopathy (HCM) and is associated with a high risk of stroke. The efficacy and safety of catheter ablation in this setting is poorly characterised. We aimed to systematically review the existing literature and to perform a meta-analysis to determine the efficacy and safety of catheter ablation of AF in patients with HCM.

Methods Random-effects meta-analysis of studies comparing HCM versus non-HCM controls. The outcomes of freedom from AF/atrial tachycardia, and acute procedure-related complications were assessed. Studies were searched on MEDLINE, EMBASE, COCHRANE and clinicaltrials.gov.

Results Fourteen studies were considered eligible for the systematic review, of which five were included in the meta-analysis. Freedom from AF/atrial tachycardia relapse was higher in patients without HCM (after a single procedure: 38.7% HCM vs 49.8% controls, OR=2.62, 95% CI 1.52 to 4.51, p=0.0006; I2=33% and 26%, respectively). Risk of procedure-related adverse events was low. Repeat procedures (mean difference=0.16, 95% CI 0.00 to 0.32, p=0.05, I2=53%) and antiarrhythmic drugs (OR=4.70, 95% CI 2.31 to 9.55, p<0.0001, I2=0%) are more frequently needed in patients with HCM to prevent arrhythmia relapse.

Conclusions The observed complication rate of catheter ablation of AF in patients with HCM was low. Even though the risk of relapse is twofold higher, catheter ablation can be effective in patients with HCM and AF, particularly in patients with paroxysmal AF and smaller atria.

BACKGROUND

Hypertrophic cardiomyopathy (HCM) is the most frequent monogenic cardiovascular disease affecting 1 out of every 500 individuals in the general population.1 Atrial fibrillation (AF) is the most common arrhythmia in patients with HCM with a prevalence and annual incidence 22.5% and 3.1%, respectively.2 New-onset AF is often associated with heart failure symptoms3 and requires prompt treatment with direct current cardioversion in haemodynamically unstable patients or ventricular rate control with oral ß-blockers or non-dihydropyridine calcium channel antagonists followed by elective cardioversion.4 There are no randomised controlled trials examining the effect of antiarrhythmic drugs on long-term prevention of AF in patients with HCM and the encouraging results in observational studies which took place decades ago5–7 are conflicting with our daily practice, as antiarrhythmic agents are frequently ineffective in eradicating arrhythmias. Similarly, studies assessing the impact of catheter ablation of AF in patients with HCM are sparse and provide contradictory results. The joint Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society expert consensus statement on catheter ablation suggests that registries could facilitate the collection of more robust information on the safety and efficacy of AF ablation in the setting of less common underlying conditions, such as HCM.8

The aim of this study is to systematically review the existing literature and to perform a meta-analysis of observational studies to determine the efficacy and safety of catheter ablation of AF in patients with HCM.

METHODS Study selection

We performed a search in the databases MEDLINE, EMBASE and COCHRANE (from inception to 7 July 2015) using the following search string: ‘catheter ablation’ AND ‘HCM’ AND ‘AF’. Reference lists of all accessed full-text articles were searched for sources of potentially relevant information. Ongoing studies assessing the outcomes of catheter ablation of AF in patients with HCM were searched on ClinicalTrials.gov, and experts in the field were contacted to ensure that all important studies had been included. Authors of full-text papers and congress abstract authors were also contacted by email to retrieve additional information.

The population, intervention, comparison and outcome approach was used for conducting the meta-analysis.9 The population of interest included patients with HCM and the intervention was catheter ablation of AF. Comparisons were performed...
between HCM and controls (patients without HCM undergoing catheter ablation of AF). The outcomes were mid-term procedural success, need of antiarrhythmic drugs after successful ablation, number of catheter ablation procedures and procedural complications.

Procedural success was defined as freedom from AF or atrial tachycardia relapse, with ECG documentation, after a blanking period. Procedural complications included in the analysis were thromboembolic events (including stroke and transient ischaemic attack), pericardial tamponade requiring pericardiocentesis or pericardial effusion causing haemodynamic imbalance and necessitating prolonged monitoring, pulmonary vein (PV) stenosis, atrio-oesophageal fistula and procedure-related death occurring in the first 30 days post procedure.

To meet inclusion criteria, studies were required to provide information on age, gender and AF type (ie, paroxysmal, persistent or permanent).

Studies providing no information regarding follow-up duration, and number of events in each group were excluded. Similarly, studies consisting of catheter ablation of the atrioventricular node or surgical ablation, and conference abstracts not published as full-text articles in the 5 years following presentation were not examined. Studies presenting data in patients with HCM but not in controls were included in the systematic review, but excluded from the meta-analysis.

Search results were reviewed and consensus reached by three investigators (RP, KP and GB) to ensure that all studies met the prespecified inclusion criteria.

Study quality was formally evaluated using a modified Newcastle–Ottawa Quality Assessment Scale for Cohort Studies by three reviewers (RP, KB and NS). An agreement between these three reviewers was mandatory for the final classification of studies.

Data extraction
Data extraction and presentation for the preparation of this manuscript followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) group. From each study, we retrieved study design, study population characteristics (age range, gender and AF type, mitral regurgitation, left ventricular outflow tract obstruction, previous myectomy or septal ablation), follow-up duration, lesion set used in the ablation procedure, definition of relapse, postprocedural monitoring, use of antiarrhythmic agents after blanking, predictors of relapse, mid-term outcomes and procedural complications.

Statistical analysis
Data were pooled using random-effects according to the Mantel–Haenszel model (Review Manager, RevMan, V.5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). A random-effects model was chosen for the analysis of titles and abstracts. Of these, 177 were excluded as they were either duplicates or deemed unsuitable for the purpose of the meta-analysis (editorials, letters, reviews or case reports). The remaining 32 studies were carefully screened and after analysis of their abstracts and/or full-text only (one was a conference abstract) were considered adequate for inclusion in the systematic review (figure 1). Of these, only six studies were prospective, provided enough details to be included in the meta-analysis. There was full agreement between investigators (RP, KP and GB) on the inclusion of the selected studies.

Baseline data: patients with HCM undergoing catheter ablation of AF
The design of selected investigations and baseline data are summarised in tables 1 and 2. The final population of the systematic review included 403 patients with HCM; 139 patients with HCM and 393 controls were included in the meta-analysis. All included studies were observational and non-randomised, and only five were prospective.

Quality assessment of the included studies is shown in table 3. Study quality was modest, with only two studies being assigned 7 out of 9 possible points with the Newcastle–Ottawa scale.

The median HCM cohort size was 27 patients (IQR 22–39.5). Only one observational study included more than 50 patients with HCM. In the six studies included in the meta-analysis, treatment groups were balanced for all baseline variables (tables 1 and 2). Diagnosis of HCM was mostly based on the American College of Cardiology Foundation (ACCF) and European Society of Cardiology consensus, the recent ACCF/American Heart Association guidelines, or other preceding documents. One study had genotype information in 11 patients and one provided no diagnostic criteria for diagnosing HCM.

Medián age was 57 years (IQR 54–59). Women accounted for the majority of the patients with HCM, with a median prevalence of 30% (IQR 26%–33%). Persistent AF was the most common AF type in seven studies. The median prevalence of non-paroxysmal AF was 53% (IQR 37%–69%) (table 1).

In studies reporting time since AF diagnosis, the median duration was 5.9 years (IQR 4.0–6.9). Median left atrial size was 47 mm (IQR 46–51 mm) and median maximum left ventricular thickness was 18 mm (IQR 18–21 mm). Only conference abstracts for left atrial size, prevalence of individuals with persistent AF and left atrial size (comparison of studies below vs above median level for the last two scenarios).

Statistical heterogeneity on each outcome of interest was assessed and quantified using the I² statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. Values below 25%, between 25% and 50%, and higher than 50% are, by convention, classified as low, moderate and high degrees of heterogeneity, respectively.

Funnel plots and meta-regression analyses were not performed as part of the assessment for the presence of publication bias, and possible association of baseline differences with modulator variables in procedural outcomes, respectively, as comparisons involved less than 10 studies, which is the minimum number for assuring the appropriateness of these methods.
nine studies reported on mitral regurgitation, and this was reported as moderate in 7%–36% of patients in six out of the nine studies reporting on this variable. The presence of left ventricular outflow tract obstruction at baseline and previous myectomy or alcohol septal ablation were reported in 11–14, 16, 18–20, 22–26 and 6 studies, respectively, and had a median prevalence of 24% (IQR 20%–37.5%) and 14.5% (IQR 1.8%–28.8%) (table 1).

Procedural data
All AF ablation procedures consisted of PV isolation and used radiofrequency as the energy source. In two studies, the PVs were the only targeted structures, but in the remainder ablation lines were created in the left atrium (LA) and/or right atrium, or lesions deployed to terminate atrial tachycardias (table 2). Ostial PV isolation was performed in two publications, while in the remainder further ablation was performed in a more antral location. In three studies, complex atrial fractionated electrogram ablation was also performed.

Procedural outcomes
The median follow-up was 1.8 years (IQR 1.05–3.30 years). Except for three studies, mean follow-up duration was >1 year (table 4). In two studies, mean/median follow-up was >3 years. Definition of relapse and monitoring post ablation across all studies are described in table 5.

In four studies, freedom from AF (no documentation of further AF episodes after ablation) at the end of follow-up and after ≥1 procedure was ≥70%. In two studies, this figure was 60% and in all remaining studies success rate was lower, in spite of several repeat ablation procedures.

Figure 2 illustrates freedom from arrhythmia in patients with HCM and controls. Control patients had no structural heart disease, except for left ventricular hypertrophy secondary to systemic hypertension in Müssigbrodt et al, and in Gaita et al valvular heart disease was observed in 10 patients and dilated cardiomyopathy in 6. Both after a single procedure and after ≥1 procedure, sinus rhythm maintenance was lower in patients with HCM: 38.7% (36/93) HCM vs 49.8% (148/297) controls, OR=2.25, 95% CI 1.09 to 4.64, p=0.03; 51.8% (72/139) HCM vs 71.2% (280/393) controls, OR=2.62, 95% CI 1.52 to 4.51, p=0.0006, respectively. Heterogeneity was moderate for both comparisons: I²=33% and 26%, respectively.

The median number of procedures was 1.4 (IQR 1.2–1.5) in patients with HCM and 1.2 (IQR 1.2–1.3) in controls. A second or third ablation procedure was required in 25%–50% of patients with HCM in 10 studies. Figure 3 illustrates the comparison of the total number of procedures in
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study design</th>
<th>Number of HCM and control patients diagnosis of HCM</th>
<th>Age (years)</th>
<th>∆</th>
<th>Non-paroxysmal AF</th>
<th>AF duration (years)</th>
<th>LA size</th>
<th>LVT (mm)</th>
<th>% mitral regurgitation</th>
<th>LVOT obstruction</th>
<th>Previous myectomy or septal ablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (2005)</td>
<td>Retrospective Multicentre (two centres)</td>
<td>4 patients with HCM based on echocardiographic criteria</td>
<td>58±8</td>
<td>50% (2)</td>
<td>0% (0)</td>
<td>8±8.5</td>
<td>46±9 mm</td>
<td>27±5</td>
<td>N.A.</td>
<td>100% (4)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Kilicaslan et al (2006)</td>
<td>Retrospective Multicentre (four centres)</td>
<td>27 patients with primary HCM according to ACCF/ESC consensus</td>
<td>55±10</td>
<td>30% (8)</td>
<td>48% (13)</td>
<td>5.4±3.6</td>
<td>50±9 mm</td>
<td>170±48 mm</td>
<td>17±5</td>
<td>Grade 1–2: 67% (18)</td>
<td>At rest—44.4% (12) Proved—37.0% (10)</td>
</tr>
<tr>
<td>Gaita et al (2007)</td>
<td>Prospective Cohort Single-centre</td>
<td>26 patients with HCM based on TTE (LV ≥13 to 15 mm) ±family history and absence of other cardiac or systemic disease Controls: 52 patients</td>
<td>58±11</td>
<td>31% (8)</td>
<td>50% (13)</td>
<td>7.3±6.2</td>
<td>52±6 mm</td>
<td>70±26 mL/m²</td>
<td>23±4</td>
<td>Mild: 69% (18) Moderate: 12% (3)</td>
<td>At rest—23% (6) N.A.</td>
</tr>
<tr>
<td>Bunch et al (2008)</td>
<td>Prospective Single-centre</td>
<td>33 patients with HCM Diagnosis criteria—guidelines/specialised clinic (Mayo)</td>
<td>51±11</td>
<td>24% (8)</td>
<td>36% (12)</td>
<td>6.2±5.2</td>
<td>51±7 mm</td>
<td>140 mL (125–180)</td>
<td>N.A.</td>
<td>Mild–moderate: 21% (7)</td>
<td>At rest—24% (8) N.A.</td>
</tr>
<tr>
<td>Di Donna et al (2010)</td>
<td>Retrospective Multicentre (two centres)</td>
<td>61 patients with HCM based on TTE (LV ≥13 to 15 mm) and absence of other cardiac or systemic disease Genotype available in 11 patients</td>
<td>54±13</td>
<td>28% (17)</td>
<td>43% (26)</td>
<td>5.7±5.5</td>
<td>52±5 mm</td>
<td>180±40 mL</td>
<td>20±5</td>
<td>Mild: 50% (28) Moderate: 36% (22)</td>
<td>At rest—20% (12) N.A.</td>
</tr>
<tr>
<td>McCready et al (2011)</td>
<td>Retrospective Cohort Single-centre</td>
<td>14 patients with HCM—according to ACCF/ESC consensus 177 controls</td>
<td>58±13</td>
<td>21% (40)</td>
<td>100% (191)</td>
<td>N.A.</td>
<td>47±7 mm</td>
<td>17±4</td>
<td>Mild: 14.3% (2) Moderate: 7.1% (1)</td>
<td>28.6% (4)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Dereko et al (2013)</td>
<td>Prospective observational Multicentre</td>
<td>30 patients with HCM according to ACCF/ESC consensus</td>
<td>49±11</td>
<td>33% (10)</td>
<td>53% (16)</td>
<td>6±4.2</td>
<td>51±7 mm</td>
<td>21±6</td>
<td>N.A.</td>
<td>20% (6)</td>
<td>7% (2)</td>
</tr>
<tr>
<td>Santangeli et al (2013)</td>
<td>Prospective Multicentre (eight centres)</td>
<td>43 patients with HCM according to ACCF/ESC consensus</td>
<td>59±8</td>
<td>33% (14)</td>
<td>72% (31)</td>
<td>Median 3.0, IQR 4.3</td>
<td>47±8 mm</td>
<td>20±4</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Yan et al (2013)</td>
<td>Retrospective Multicentre (eight centres)</td>
<td>25 patients with HCM Diagnosis criteria—N.A. 50 controls</td>
<td>53±8</td>
<td>24% (6)</td>
<td>36% (9)</td>
<td>40% (20)</td>
<td>N.A.</td>
<td>47±8 mm</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
</tr>
<tr>
<td>Hayashi et al (2014)</td>
<td>Retrospective Cohort Single-centre</td>
<td>17 patients with HCM based on TTE (LV ≥15 mm) and absence of other cardiac or systemic disease 34 controls</td>
<td>63±12 66±9</td>
<td>29% (5)</td>
<td>53% (9)</td>
<td>3.5±3.5</td>
<td>41±3.7</td>
<td>46±7 mm</td>
<td>19±4</td>
<td>Moderate or severe 18% (3) 9% (2)</td>
<td>23.5% (4) 41% (7)</td>
</tr>
<tr>
<td>Contreras-Valdes et al (2015)</td>
<td>Retrospective Cohort Single-centre</td>
<td>40 patients with HCM according to the ACC/AHA guidelines</td>
<td>54±7</td>
<td>30% (12)</td>
<td>68% (27)</td>
<td>70% (45)</td>
<td>N.A.</td>
<td>N.A.</td>
<td>N.A.</td>
<td>37.5% (15)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Müssigbrodt et al (2015)</td>
<td>Prospective Cohort Single-centre</td>
<td>22 patients with HCM based on TTE (LV ≥15 mm) ± LVOT obstruction and absence of other cardiac or systemic disease</td>
<td>57±8 63±10</td>
<td>32% (7) 36% (8)</td>
<td>55% (12)</td>
<td>N.A.</td>
<td>46±8 mm</td>
<td>19±4</td>
<td>Significant: 14% (3) 0% (0)</td>
<td>36% (8) 32% (7)</td>
<td></td>
</tr>
<tr>
<td>Okamatua et al (2015)</td>
<td>Retrospective Single-centre</td>
<td>22 patients with HCM based on the presence of myocardial hypertrophy and absence of local or systemic aetiology</td>
<td>65±11</td>
<td>55% (12)</td>
<td>77% (17)</td>
<td>6.7±4.4</td>
<td>48±6 mm</td>
<td>98±38 mL</td>
<td>13±4</td>
<td>Greater than or equal to moderate: 23% (5)</td>
<td>14% (3) N.A.</td>
</tr>
</tbody>
</table>

Continued
controlled studies, showing that patients with HCM underwent repeat procedures more often: mean difference=0.16, 95% CI 0.0 to 0.32, p=0.05, I²=53%.

In two studies, patients remained in sinus rhythm free from antiarrhythmic drugs, or these were used in only a minority of patients. However, in the remaining studies, antiarrhythmic agents were needed for optimisation of the rhythm control strategy in >25%–50% of patients with HCM. In controlled studies, chances of remaining on antiarrhythmic drugs following a successful ablation were fivefold higher in patients with HCM: OR=4.70, 95% CI 2.31 to 9.55, p<0.0001, I²=0% (figure 3). Of note, in some patients with HCM these drugs were used because of concomitant ventricular arrhythmias.

Predictors of procedural success

Left atrial size was the most frequently identified predictor of procedural success. Sensitivity analyses

Sensitivity analysis after excluding results published as a conference abstract confirmed that frequency of sinus rhythm maintenance after one or more catheter ablation procedures was twofold higher in patients without HCM: HCM 52.9% (63/119) versus controls 71.1% (248/349); OR=2.52, 95% CI 1.28 to 4.93, p=0.007, I²=39% (see online supplementary figure S1).

Pooling of studies including ≤53% (median % of persistent AF) of subjects with persistent AF displayed a higher relapse rate in patients with HCM: HCM 61.9% (39/63) versus controls 76.2% (99/130); OR=2.05, 95% CI 1.05 to 4.01, p=0.04, I²=0%. However, data from studies with >53% of patients with persistent AF showed an even higher relapse rate in patients with HCM (HCM 43.4% (33/76) versus controls 76.7% (181/233); OR=3.46, 95% CI 1.22 to 9.78, p=0.02, I²=58%), suggesting that persistent AF is associated with a lack of procedural success (see online supplementary figures S2A and S2B).

Similarly, a sensitivity analysis for left atrial size showed that studies with more severely dilated left atria (≥47 mm, the median LA diameter in the HCM cohort) presented with higher relapse rate in patients with HCM (HCM 66.7% (26/39) versus controls 78.6% (44/56); OR=1.51, 95% CI 0.57 to 3.98, p=0.41, I²=0%), suggesting comparable success rate in patients with HCM to the normal population when the LA is not excessively dilated (see online supplementary figures S3A and S3B).

Funnel plots and meta-regression were not performed, as only six entries were eligible for the meta-analysis.

Complications of AF ablation

While six studies reported no major complications, thromboembolic complications without permanent sequel occurred in two studies (table 5). PV stenosis was reported in three entries, ranging from 3.0% to 4.5% to 4.8%.

Contreras-Valdes et al reported that patients with HCM may have longer postablation hospitalisation and higher readmission.
rate at 30 days, at the expense of heart failure and congestive symptoms. 24

Due to the low incidence of major complications, no forest plots could be created as no comparisons were possible between patients with HCM and controls.

DISCUSSION

This systematic review demonstrates that the success rate of AF ablation is lower in patients with HCM than in patients without HCM with an overall efficacy of AF ablation in HCM at least 50% lower than in controls for ≥1 procedure. The need for repeat procedures and maintenance of antiarrhythmic drugs is frequent. Left atrial size and AF type were the most frequently identified

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Ablation procedure</th>
<th>Number of procedures</th>
<th>Use of AADs after blanking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al (2005) 14</td>
<td>PVI</td>
<td>1.3</td>
<td>Second procedure: 25% (1) Oral amiodarone in one patient (25%) to prevent AT relapses after second procedure</td>
</tr>
<tr>
<td>Kilicaslan et al (2006) 15</td>
<td>PVI</td>
<td>1.3</td>
<td>Second procedure: 25.9% (7) Out of 13 patients (38.5%) with relapse after the first procedure remained in SR on AADs</td>
</tr>
<tr>
<td>Gaita et al (2007) 16</td>
<td>PVI+roof line+mitral isthmus</td>
<td>1.2</td>
<td>Second procedure: 19.2% (5) 10 of 16 patients (62.5%) in SR were off AADs</td>
</tr>
<tr>
<td>Bunch et al (2008) 17</td>
<td>Ostial PVI in 15 patients+roof line and mitral isthmus in seven patients</td>
<td>1.4</td>
<td>Second procedure: 39% (13) Of the 78% patients in SR at 1 year, 14% were under AADs</td>
</tr>
<tr>
<td>Di Donna et al (2010) 18</td>
<td>PVI+roof line+mitral isthmus+CTI (under fluoroscopic guidance in 15 patients)</td>
<td>1.5</td>
<td>Second procedure: 52% Of the 74% patients in SR at 3 years, 27% were under AADs</td>
</tr>
<tr>
<td>McCreedy et al (2011) 19</td>
<td>PVI+roof line, mitral isthmus and CFAE ablation at the discretion of the operator</td>
<td>HCM 1.5; controls 1.3</td>
<td>Second procedure: 71.4% (10) The success rate at 30 days, at the expense of heart failure and congestive symptoms. 24</td>
</tr>
<tr>
<td>Derejko et al (2013) 20</td>
<td>Ostial PVI+CTI line ± mitral isthmus, roof line and CFAE ablation at the discretion of the operator</td>
<td>1.4</td>
<td>Second procedure: 43% (13) 11 of 17 patients (64.7%) in SR after the first procedure were on AADs</td>
</tr>
<tr>
<td>Santangeli et al (2013) 21</td>
<td>All patients: PVI+posterior wall isolation between PVs+SVC isolation Persistent AF: +all posterior wall (CS and left side of septum)+CFAE (LA and CS) Redo: +non-PV triggers</td>
<td>1.6±0.7 Second procedure: 58% (25) (All patients with recurrence) 11 of 24 patients (45.8%) in SR after the second procedure were on AADs</td>
<td></td>
</tr>
<tr>
<td>Yan et al (2013) 22</td>
<td>PVI+roof line, mitral isthmus or CTI line</td>
<td>1.1</td>
<td>Eight of nine patients with HCM (88.9%) were free from AF recurrence without AADs</td>
</tr>
<tr>
<td>Hayashi et al (2014) 23</td>
<td>PVI+roof line+posterior inferior line+CTI+mitral isthmus, if persistent AF</td>
<td>HCM 1.5; controls 1.4 Second procedure: 47% (8) HCM, 35% (12) controls (p=0.87) Chronic AADs in 45% HCM vs 18.8% controls (p=0.007)</td>
<td></td>
</tr>
<tr>
<td>Contreras-Valdes et al (2015) 24</td>
<td>PVI Ablation of sustained organised AT</td>
<td>HCM 1.3±0.5 Controls 1.2±0.4 (p=0.71) 6 of 22 (27%) patients with HCM treated with AADs vs none in non-HCM group (p=0.008)</td>
<td></td>
</tr>
<tr>
<td>Müssigbrodt et al (2015) 25</td>
<td>PVI+roof line, septal line and CTI line</td>
<td>HCM 1.4, controls 1.1 Second procedure: five patients with HCM vs three controls Third procedure: three patients with HCM (p=0.045)</td>
<td></td>
</tr>
<tr>
<td>Okamura et al (2015) 26</td>
<td>PVI±CTI</td>
<td>1.1</td>
<td>Second procedure: three patients with HCM 15 (68%) patients used concomitant AADs</td>
</tr>
<tr>
<td>Wen et al (2015) 27</td>
<td>Paroxysmal AF: PVI+CTI (if documentation of typical flutter) Persistent AF: +roof line, mitral isthmus and CTI</td>
<td>1.0 N.A.</td>
<td></td>
</tr>
</tbody>
</table>

AADs, antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; CTI, cavitricuspid isthmus; HCM, hypertrophic cardiomyopathy; LA, left atrium; N.A., not available; PVI, to be interpreted as wide antral circumferential ablation, unless stated ostial PVI; PV, pulmonary vein; SVC, superior vena cava; SR, sinus rhythm; WACA, wide antral circumferential ablation.
predictors of procedural success. Patients with HCM also underwent ablation late in the course of their disease (median of 5.9 years after the diagnosis of atrial arrhythmias) with non-paroxysmal AF being present in at least 50% of patients in half of the included studies. Therefore, by the time of the first procedure patients were likely to have a greater degree of electrophysiological and structural remodelling which further increases the chances of failure. Furthermore, a significant proportion had mitral regurgitation and left ventricular outflow obstruction, promoting atrial stretching, which can shorten the effective atrial refractory period, increasing the dispersion of repolarisation thus potentiating the ability of ectopic triggers to maintain AF.3,33 Indeed, it is this diastolic dysfunction which results in the marked deterioration in clinical status with the transition to AF and loss of atrial transport contributing to the cardiac output.3

Given these major factors limiting success, it is remarkable that after a median of 1.4 procedures, the success rate is 52%. These data would suggest that if AF can be treated earlier in the natural history of the disease before it becomes established, then the success rates may be higher but this has to be balanced against the degree of left atrial dilatation on initial presentation and degree of mitral regurgitation and LV diastolic dysfunction affecting the likelihood of at least medium-term success. Indeed the challenge remains to identify those patients who are most likely to benefit from ablation in the context of their HCM status and disease course. The high use of long-term antiarrhythmic drugs highlights the fact that ongoing remodelling may be successful in these complex patients.
A number of structural and mechanistic factors further impact on the success rates of AF ablation in HCM. Patients with HCM have a high prevalence of atrial fibrosis, which may serve as a substrate for slow conduction and intra-atrial re-entry, thereby playing a crucial role in the development and maintenance of AF. Sarcomeric gene mutations account for 60% of HCM cases. The β-myosin heavy chain (MHC) missense mutation Arg663His has been associated with an increased risk of AF in patients with HCM with 47% Arg663His carriers developing AF over a 7-year follow-up period. Polymorphisms in the angiotensin receptor gene have also been implicated in the development of AF in HCM. Anatomical variations in left atrial thickness have been suggested. However, preliminary data from Hayashi et al using CT to measure left atrial thickness in a small sample of patients indicate that left atrial wall in HCM is no thicker than in matched patients without structural heart disease.

Abnormal calcium handling is a recognised pathophysiological mechanism in HCM and could account for triggered activity (from delayed after depolarisations) precipitating AF in the proarrhythmic myocardial tissue architecture.
Myocardial ischaemia and autonomic dysfunction are two other factors that have been previously suggested as relevant triggers of AF, and may make AF ablation more difficult in the context of HCM. Clearly, understanding the pathophysiology of AF in HCM and identifying predictors of relapse remain important to improve overall procedural outcomes. Santangeli et al. have suggested that these patients present with frequent non-PV

![Freedom from AF/AT relapse after a single procedure](image1)

![Freedom from AF/AT relapse after one or more procedures](image2)

![Number of catheter ablation procedures](image3)

![Need for AADs in patients with successful ablation](image4)

Figure 2  Forest plots comparing procedural outcomes (freedom from AF/AT relapse) of catheter ablation of AF in patients with and without HCM. AF, atrial fibrillation; AT, atrial tachycardia; HCM, hypertrophic cardiomyopathy.

Figure 3  Forest plots comparing number of ablation procedures (upper panel) and need of AADs following a successful ablation procedure in patients with HCM versus controls. AADs, antiarrhythmic drugs; HCM, hypertrophic cardiomyopathy.
triggers, which may be responsible for late recurrences. These authors have favoured extensive ablation beyond PV isolation. However, as we demonstrate in this review a consensus on the optimal approach for AF ablation in patients with HCM remains elusive. It is unclear if performing PV isolation and targeting sustained atrial tachycardias is superior to employing a more aggressive approach with extensive lesion sets including lines, targeting complex fractionated electrograms and non-PV triggers in both atria. This is particularly important as even the optimal strategy to identify these sites and their relevance in procedural outcomes is contentious.43 Furthermore, the optimal energy source to use is also not clear as all studies in this review have been performed using radiofrequency ablation. A randomised controlled trial to address this matter would be of interest. Although the incidence of major complications was low and comparable to the general population, cases of PV stenosis, most of them asymptomatic, have been noted (ranging from 3% to 4.8%). In two reports these occurred in the setting of non-ostial PV isolation.14 25 As pulmonary venogram was not routinely performed in all cases we cannot report on the prevalence of this complication and this reflects the Registry data in the general AF ablation populations as asymptomatic PV stenosis is not reported routinely.

Given the small numbers of patients in all included studies, it is unclear if the apparently high rate of PV stenosis truly reflects a higher risk in this population or if it is a product of small sample sizes in the reporting studies.44 It has been suggested by Kilicaslan et al15 that patients with HCM might be prone to more exaggerated hypertrophic tissue responses leading to tissue stenosis. This is yet to be confirmed, but it may also be a contributory factor for more frequent gap formation and PV reconnection in the HCM population. The possible increase in PV stenosis in this subset of patients warrants clarification, and the electrophysiologist performing cases in these patients should be aware of this potential complication and try to deliver lesions as far away as possible from the PVs.

Two systematic reviews on the role of catheter ablation of AF in patients with HCM have been recently published.45 46 However, unlike these, where the overall success rate of the procedure is reported, ours is the first meta-analysis with a case-control design. This is of importance, as it is the first paper allowing comparisons between patients with HCM versus other patients undergoing AF ablation, providing a better understanding of the true effectiveness of the catheter ablation in this setting. As included studies in the aforementioned systematic reviews45 46 span for almost a decade, simply pooling the success rates in those cohorts of patients with HCM without having any control group/comparator, makes the pooled OR impossible to interpret.

LIMITATIONS

There are some limitations to this meta-analysis. First, there is a paucity of data and studies allowing the comparison of patients with HCM and patients without HCM. As a result of this (small number of included studies and patients) this analysis has low power. However, these data are able to demonstrate differences in outcomes of catheter ablation of AF in patients with HCM and patients without HCM. Second, the ratio of patients with HCM to controls differs across studies. Third, moderate to high heterogeneity was observed across the included studies. A careful analysis of figures 2 and 3, shows that the rate of relapse and number of redo procedures in patients with HCM stands out as higher in the cohort published by McCready et al.19 This can be attributable to the fact that all patients in that study had persistent AF, and in most circumstances this was long-standing persistent. Lastly, data quality was modest, with no data derived from randomised controlled trials or large registries. The above-mentioned factors suggest that the reliability of the estimated effect sizes may be suboptimal.

CONCLUSIONS

Data regarding catheter ablation of AF in the HCM population are scarce and of modest quality. The observed complication rate was low. Although outcomes seem less favourable than for the general population, with a twofold higher risk of relapse, more frequent need of repeat procedures and concomitant use of antiarrhythmic drugs, ablation can be a valuable option for symptomatic drug-refractory patients with HCM, particularly in those with paroxysmal AF and smaller atria.

Key messages

What is already known about this subject?

- Atrial fibrillation is a common finding in patients with hypertrophic cardiomyopathy, and anti-arrhythmic drugs are frequently not effective enough for a rhythm control strategy.

What does this study add?

- This meta-analysis confirms that catheter ablation can be a valuable option in patients with hypertrophic cardiomyopathy and atrial fibrillation.
- However, the overall success rate of atrial fibrillation ablation procedure in patients with hypertrophic cardiomyopathy is worse than for the general population. Best candidates are patients with small atria and paroxysmal AF.

How might this impact on clinical practice?

- These results reinforce the role of appropriate patient selection and ideal timing of the procedure. Referral in early stages of disease progression may optimize the chances of an effective rhythm control strategy.

Contributors RP and PDL planned this meta-analysis population, intervention, comparison and outcome (PICCO) approach. RP and KP were responsible for data collection. GB, NS, KB and NP confirmed data collection, study selection criteria and performed study quality assessment. JM provided patient level data for one of the studies. RP performed the statistical analysis and wrote the first draft of the paper, which was thoroughly revised by PDL and PE, who provided important critical input. A new and revised version of the paper was prepared and sent to all authors, who provided suggestions and approval after the final version of the paper was written.

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