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=2.25, 95% CI 1.09 to 4.64, p=0.03; after ≥1 procedure: 51.8% HCM vs 71.2% 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 0.0 to 0.32, p=0.05, I²=53%) and antiarrhythmic drugs (OR=3.70, 95% CI 2.31 to 5.95, p<0.0001, I²=0%) are more frequently needed in patients with HCM to prevent arrhythmia relapse. Sensitivity analyses suggested that the outcome in patients with HCM with less dilated atria and paroxysmal AF may be more comparable to the general population.

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 β-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) stenos,

**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 time to AF relapse, number of events in each group and baseline characteristics.

Comparisons between patients with HCM and patients without HCM were performed using OR, or mean difference when appropriate, and respective 95% CIs were shown. Outcomes were maintenance of sinus rhythm after one catheter ablation procedure, or after one or more catheter ablation procedures, number of ablation procedures, need of antiarrhythmic drugs following a successful ablation and procedural complications. Weights of each study in forest plots were calculated using the inverse variance method. Sensitivity analyses were performed excluding data from studies published only as 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).

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,16 17 20 21 25 Four studies were multicentre.14 15 18 21

Quality assessment of the included studies is shown in table 3. Study quality was modest, with only two studies16 23 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.18 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,34 35 the recent ACCF/ American Heart Association guidelines,29 or other preceding documents.28 30–32 One study had genotype information in 11 patients18 and one provided no diagnostic criteria for diagnosing HCM.23

**Baseline data: patients with HCM undergoing catheter ablation of AF**

The median HCM cohort size was 27 patients (IQR 22–39.5). Only one observational study included more than 50 patients with HCM.18 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,34 35 the recent ACCF/ American Heart Association guidelines,29 or other preceding documents.28 30–32 One study had genotype information in 11 patients18 and one provided no diagnostic criteria for diagnosing HCM.23

Median age was 57 years (IQR 54–59). Women accounted for the minority 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,18 20 21 23–26 The median prevalence of non-paroxysmal AF was 53% (IQR 37%–69%) (table 1).

In studies reporting time since AF diagnosis,14–18 20 21 23 26 27 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
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 myect-
omy or alcohol septal ablation were reported in 1114–20 23–26 and
6 studies,14–16 18 19 22 24 26 respectively, and had a median preva-
lence 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,14 15 the
PVs were the only targeted structures, but in the remainder abla-
tion 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 publica-
tions,17 20 while in the remainder further ablation was per-
fomed in a more antral location. In three studies, complex
atrial fractionated electrogram ablation was also performed.19–21

Procedural outcomes
The median follow-up was 1.8 years (IQR 1.05–3.30 years).
Except for three studies,14 15 25 mean follow-up duration was
>1 year (table 4). In two studies, mean/median follow-up was
>3 years.18 21 Definition of relapse and monitoring post abla-
tion 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%.14 15 21 In two studies, this
figure was 60%16 18 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 sys-
temic hypertension in Müssigbrodt et al,25 and in Gaita et al16
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: $I^2=33\%$ 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.14 15 17–21 23 25 Figure 3
illustrates the comparison of the total number of procedures in
### Table 1: Study design and sample characteristics

<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>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 HOCM 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>
</tr>
<tr>
<td>Kiliaris 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 mL</td>
<td>Grade 1–2: 67% (18) Grade 3–4: 7% (2)</td>
<td>At rest—44.4% (12) Provoked—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</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>Mild: 69% (18) Moderate: 12% (3)</td>
<td>At rest—23% (6)</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±10 mL</td>
<td>Mild–moderate: 21% (7)</td>
<td>At rest—24% (8)</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</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>Mild: 50% (28) Moderate: 36% (22)</td>
<td>At rest—20% (12)</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</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>
</tr>
<tr>
<td>Dereko et al (2013)</td>
<td>Prospective observational Single-centre</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>
</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>
</tr>
<tr>
<td>Yan et al (2013)</td>
<td>Retrospective Cohort Single-centre</td>
<td>25 patients with HCM Diagnosis criteria—N.A.</td>
<td>53±8</td>
<td>24% (6)</td>
<td>36% (9)</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</td>
<td>63±12</td>
<td>29% (5)</td>
<td>53% (9)</td>
<td>3.5±3.5</td>
<td>4.1±3.7</td>
<td>46±7 mm</td>
<td>19±4</td>
<td>Moderate or severe 18% (3) 9% (2)</td>
</tr>
<tr>
<td>Contreras-Valdes et al (2015)</td>
<td>Retrospective Cohort Single-centre</td>
<td>40 patients with HCM according to the ACCF/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>
</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</td>
<td>32% (7)</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>
</tr>
<tr>
<td>Okamatsu et al (2015)</td>
<td>Retrospective Cohort 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>Greater than or equal to moderate: 23% (5)</td>
<td>14% (3)</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,17 or these were used in only a minority of patients.22 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.17 18 24–27 In two studies, persistent AF was associated with worse procedural outcomes (OR = 7.7, 95% CI 1.13 to 50, p = 0.0220 and OR = 2.58, 95% CI 1.11 to 6.05, p = 0.02821). Other predictors of relapse were identified separately in single studies: age and New York Heart Association (NYHA) class,18 left atrial pressure and left ventricle (LV) outflow tract obstruction,24 AF duration in months and E/E’,23 and corrected QT interval (QTc) duration27 (table 4).

Sensitivity analyses

Sensitivity analysis after excluding results published as a conference abstract22 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% (181/263); OR = 3.46, 95% CI 1.22 to 9.78, p = 0.0281). Other predictors of relapse were identified 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 45.0% (27/60) versus controls 64.5% (189/293); OR = 3.52, 95% CI 1.16 to 10.67, p = 0.03, I² = 62%), whereas pooling of studies with less pronounced degrees of left atrial dilation produced neutral results (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 studies17 20 (table 5). PV stenosis was reported in three entries, ranging from 3.0%17 and 4.5%25 to 4.8%.15 Contreras-Valdes et al reported that patients with HCM may have longer postablation hospitalisation and higher readmission

<table>
<thead>
<tr>
<th>Table 1 Continued</th>
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<tbody>
<tr>
<td>Study design</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Retrospective</td>
</tr>
</tbody>
</table>

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ACCF, American College of Cardiology Foundation; AHA, American Heart Association; AF, atrial fibrillation; ESC, European Society of Cardiology; HCM, hypertrophic cardiomyopathy; HOCM, hypertrophic obstructive cardiomyopathy; LA, left atrium; LV, left ventricle; LVOT, left ventricle outflow tract; LVT, left ventricle thickness; N.A., not available; TTE, transthoracic echocardiogram.
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>Table 2</th>
<th>Procedural aspects and use of AADs</th>
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<tbody>
<tr>
<td>Author (year)</td>
<td>Ablation procedure</td>
</tr>
<tr>
<td>Liu et al (2005)14</td>
<td>PVI</td>
</tr>
<tr>
<td>Kilicaslan et al (2006)15</td>
<td>PVI</td>
</tr>
<tr>
<td>Gaita et al (2007)16</td>
<td>PVI+roof line+mitral isthmus</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>
</tr>
<tr>
<td>Di Donna et al (2010)18</td>
<td>PVI+roof line+mitral isthmus+CTI (under fluoroscopic guidance in 15 patients)</td>
</tr>
<tr>
<td>McCreary et al (2011)19</td>
<td>PVI+roof line, mitral isthmus and CFAE at the discretion of the operator</td>
</tr>
<tr>
<td>Derejk et al (2013)20</td>
<td>Ostial PVI+CTI line ± mitral isthmus, roof line and CFAE ablation at the discretion of the operator</td>
</tr>
<tr>
<td>Santangeli et al (2013)21</td>
<td>All patients: PVI+posterior wall isolation between PVI+SVC isolation Persistent AF: +all posterior wall (CS and left side of septum)+CFAE (LA and CS) Redo: +non-PV triggers</td>
</tr>
<tr>
<td>Yan et al (2013)22</td>
<td>PVI+roof line, mitral isthmus or CTI line</td>
</tr>
<tr>
<td>Hayashi et al (2014)23</td>
<td>PVI+roof line+posterior inferior line+CTI+mitral isthmus, if persistent AF</td>
</tr>
<tr>
<td>Contreras-Valdes et al (2015)24</td>
<td>PVI</td>
</tr>
<tr>
<td>Müssigbrodt et al (2015)25</td>
<td>PVI+roof line, septal line and CTI line</td>
</tr>
<tr>
<td>Okamatsu et al (2015)26</td>
<td>PVI±CTI</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>
</tr>
</tbody>
</table>

AADs, antiarrhythmic drugs; AF, atrial fibrillation; AT, atrial tachycardia; CFAE, complex fractionated atrial electrograms; CS, coronary sinus; CTI, cavotricuspid 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.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Study classification: Newcastle–Ottawa scale for cohort studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Article (year)</td>
<td>Newcastle–Ottawa Quality Assessment*</td>
</tr>
<tr>
<td>Gaita et al (2007)16</td>
<td>7</td>
</tr>
<tr>
<td>McCreary et al (2011)19</td>
<td>6</td>
</tr>
<tr>
<td>Yan et al (2013)24</td>
<td>6</td>
</tr>
<tr>
<td>Hayashi et al (2014)23</td>
<td>7</td>
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</tbody>
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*From 0 to 9 points.
Increasing the dispersion of repolarisation thus potentiating the stretching, which can shorten the effective atrial refractory period, and left ventricular failure. Furthermore, a significant proportion presented with 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. Indeed, it is this diastolic dysfunction which results in the marked deterioration in clinical status with the transition to AF and loss of atrial output contributing to the cardiac output.

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 limits the efficacy of ablation but should not be seen as a ‘failure’ of the procedure since a combined treatment approach may be successful in these complex patients.

Table 4: Mid-term procedural results and predictors of procedural failure

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>FUP duration (years)</th>
<th>Predictors of relapse</th>
<th>Mid-term procedural results</th>
</tr>
</thead>
</table>
| Liu et al (2005)
Gaita et al (2007)
Di Donna et al (2010)
McCready et al (2011)
Derejko et al (2013)
Santangeli et al (2013)
Yan et al (2013)
Hayashi et al (2014)
Okamatsu et al (2015)
Wen et al (2015) | 0.5±0.2
0.9±0.6
1.6±0.8
1.5±1.2
Total FUP: 3.3±0.7
Post last procedure: 2.4±1.3
1.1±0.7
1.9±1.2
3.5 (3.2–4.0)
3.3±1.2
2.2±1.2
Median: 4.5
HCM: 1.8–2.3
Controls: 2.9–5.6
HCM: 0.9±1.3
Controls: 1.4±0.6
1.8±1.0
Mean: 1.2 | N.A.
N.A.
LA dilation
Uni: older age (>50 years), atrial size ≥130 mL and NYHA ≥III
Multi: LA volume (HR=1.009, 95% CI 1.001 to 1.018, p=0.037)
NYHA (HR=2.24, 95% CI 1.16 to 4.35, p=0.016)
N.A.
Uni: non-paroxysmal AF
Multi: non-paroxysmal (OR=7.9, 95% CI 1.13 to 50, p=0.02)
Uni: long-standing persistent AF (OR=2.58, 95% CI 1.11 to 6.03, p=0.028)
N.A.
N.A.
LA pressure ≥12 mm Hg (HR=3.1, 95% CI 1.4 to 7.1, p=0.005) and dilated LA (HR=1.06, 95% CI 1.003 to 1.11 per mm; p=0.04)
Multi: LVOT obstruction (HR=4.3, 95% CI 1.6 to 11.4, p=0.007)
LA ≥45 mm in patients with HCM (p=0.041) but not in controls
Uni: duration of AF in months, E/E', LA volume and LA diameter
Multi: E/E' (HR=1.16, 95% CI 1.01–1.37, p=0.03)
Uni: LA diameter, QTC
Multi: LA diameter (HR=1.072, 95% CI 1.004 to 1.145, p=0.038), longer QTC (HR=1.02, 1.004 to 1.036, p=0.013); every 10 min (HR 1.227, 95% CI 1.053 to 1.431, p=0.009) |
All patients (4/4) were free from recurrence
52% (14/27) remained in SR after the first procedure; after ≥1 procedure this rose to 70% (19/27)
58% (15/26) of patients with HCM remained in SR after the first procedure; this rose to 62% (16/26) after ≥1 procedure vs 65% (17/26) of patients with secondary LVH and 77% (20/26) with idiopathic AF
Maintenance of SR free from AADs was 64% (95% CI 58% to 72%) at 1 year and 47% (36% to 58%) at 3 years
67% (41/61) were in SR following ≥1 procedure
Only 14% (2/14) of patients with HCM were free from recurrence, one after one procedure and the other requiring two ablation procedures
First procedure success rate was 33% (10/30), and increased to 53% (16/30) after ≥1 procedure
Long-term success rate after a single procedure was 49% and after ≥1 procedure 94%
SR in 45% (9/20) HCM vs 72% (32/44) controls after ≥1 procedure (p=0.032)
SR in 53% (9/17) HCM vs 56% (19/34) controls after one procedure (log rank p=0.78) and SR in 82% (14/17) HCM vs 88% (30/34) controls after ≥1 procedure (log rank p=0.35)
42.5% HCM vs 70.3% controls remained in SR at 1 year after a single procedure (p=0.005); after a redo procedure this changed to 45% HCM vs 75% controls (p=0.001)
At the end of FUP 35% of HCM vs 67.2% of controls (p=0.001) remained in SR after a single procedure; after a redo procedure this increased to 47.5% vs 73.4% (p=0.005)
After first procedure: SR in 41% (9/22) HCM vs 50% (11/22) controls (NS), but earlier relapses in HCM (Mantel–Cox p=0.015). After the last procedure, 54% (12/22) HCM vs 64% (14/22) controls (NS and Mantel–Cox p=0.121)
SR in 59% (13/22)
41% (16/39) remained in SR

AADs, antiarrhythmic drugs; AF, atrial fibrillation; E/E'; The ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; FUP, follow-up; HCM, hypertrophic cardiomyopathy; LA, left atrium; LVH, left ventricular hypertrophy; LVOT, left ventricle outflow tract; Multi, multivariate analysis; N.A., not available; NS, non-significant; SD, standard deviation; SR, sinus rhythm; Uni, univariate analysis.
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 also been implicated in the development of AF in HCM. 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

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.

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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. 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. 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. It has been suggested by Kilicaslan et al 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. 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 reviews span for almost a decade, simply pooling the success rates of 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. 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 an 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 states 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 (PICO) 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.

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