Catheter Ablation of Atrial Fibrillation in Hypertrophic Cardiomyopathy:  
Long-Term Outcomes and Mechanisms of Arrhythmia Recurrence

Running title: Santangeli et al.; Catheter ablation of AF in hypertrophic cardiomyopathy

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Abstract:

**Background** - Pulmonary vein antrum isolation (PVAI) in patients with hypertrophic cardiomyopathy (HCM) and atrial fibrillation (AF) has been reported to have satisfactory results at the mid and short-term follow-up. We determined the outcomes at the long-term follow-up of PVAI in these patients.

**Methods and Results** - We enrolled 43 patients with HCM and AF (28% paroxysmal AF). PVAI (paroxysmal AF) and posterior wall isolation with CFAE ablation (persistent and longstanding persistent AF) was the endpoint at the time of the index procedure and for repeat procedures during the first year of follow-up. In case of recurrent arrhythmia >1 year, high-dose isoproterenol challenge was used to disclose non-PV trigger sites. During the first year the success rate reached 91% (mean of 1.6 procedures). After a median follow-up of 42 months (range 38-48), 49% of the patients remained free from AF/atrial tachycardia. All patients underwent an additional procedure. PVA and posterior wall remained isolated in 82% of the cases, and extra-PV triggers were documented in all patients and targeted for ablation. After a median follow-up of 15 months (range 8 to 19) after the last procedure, 94% of the patients remained free from AF/atrial tachycardia off AADs.

**Conclusions** - PV isolation in patients with HCM is feasible and safe, although is not effective in preventing very late (≥1 year) AF recurrences in about 50% of patients. Non-PVs triggers seem to be responsible of very late recurrences, which supports the appropriateness of a more extensive ablation beyond PV isolation to improve the long-term arrhythmia-free survival.

**Key words:** atrial fibrillation, catheter ablation, cardiomyopathy, hypertrophic cardiomyopathy
Introduction

Atrial fibrillation (AF) is highly prevalent in patients with hypertrophic cardiomyopathy (HCM), and constitutes one of the most common reasons for hospitalization. There is a paucity of data regarding the effectiveness of rhythm-control with antiarrhythmic agents in this patient population. Amiodarone represents the most studied one and is considered the drug of choice by current guidelines. Few data support the efficacy of sotalol or dofetilide in HCM patients with AF, as well as the antiarrhythmic effectiveness of disopyramide, which has been shown to be safe when prescribed for control of left ventricular outflow tract obstruction. Pulmonary vein antrum isolation (PVAI) has been recently reported as feasible and safe therapeutic strategy in HCM patients with drug-refractory AF, with satisfactory short- and mid-term results. Thus far, scant data are available regarding the long-term results of PVAI in patients with HCM. In this study, we aimed to evaluate the long-term outcomes and the mechanism of arrhythmia recurrence after radiofrequency catheter ablation of AF in patients with HCM, in order to assess the optimal ablation strategy.

Methods

We included 43 consecutive patients (age 59 ± 8 years) with HCM and drug-refractory symptomatic AF. The diagnosis of HCM followed the guidelines by ACC/ESC. Definitions of paroxysmal, persistent and longstanding persistent AF followed the AHA/ACC/ESC guidelines. Patients were in long-term treatment with therapeutic warfarin, which was not discontinued during the periprocedural period. Antiarrhythmic drugs were discontinued for at least five half-lives before the procedure. Patients receiving amiodarone therapy discontinued the drug 4 to 6 months before the ablation procedure. Informed consent was obtained from all patients and all the data were entered in a central hub database approved by the Institutional Ethical Committee.
Instrumentation for electrophysiological study

Procedures were performed under either general anesthesia or conscious sedation. An esophageal probe was inserted in all patients to monitor esophageal temperature during ablation. Four venous accesses were obtained: two in the right femoral vein, one in the left femoral vein and one in the right internal jugular vein. Right internal jugular vein access was used to place a 20-pole catheter in the coronary sinus with the proximal 10 poles positioned along the crista terminalis. The left femoral venous access was catheterized with a 11Fr venous sheath to insert a 10Fr 64-element phased-array ultrasound imaging catheter (ICE) (AcuNav, Acuson, Mountain View, CA, USA) in the right atrium under fluoroscopic guidance. A bolus of unfractioned heparin (10,000 U in males and 8,000 U in females) was administered before the transseptal access and intermittent infusion was adopted to maintain an activated clotting time (ACT) >300. Left atrial access was obtained with a double transseptal puncture.

Catheter ablation

Index procedure and repeat procedures during the first year of follow-up

Patients with paroxysmal AF underwent PVAI and isolation of the superior vena cava. The technique of PVAI has been described extensively elsewhere. Briefly, a 3.5-mm irrigated-tip catheter (NaviStar ThermoCool, Biosense Webster, Diamond Bar, California) and a circular mapping catheter (Lasso, Biosense Webster) were used. ICE was used to identify the PV antra, to guide the positioning of the circular catheter and radiofrequency delivery and to look for all potential complications. Electroanatomic mapping was performed using the CARTO system (Biosense Webster, Diamond Bar, California) or the EnSite NavX Navigation system (St. Jude Medical, St. Paul, Minnesota). Radiofrequency energy was set at 40 W of power (up to 45 W) and to no more of 41°C catheter tip temperature. On the posterior wall, power was reduced to 35
W; energy delivery was further reduced when the baseline esophageal temperature increased and discontinued when the temperature reached 39°C. The end point of the procedures was elimination of all PV potentials along the antra with entry block. After isolation of all the PV antra and the posterior wall contained between the PVs, the circular mapping catheter was placed above the junction between the right atrium and superior vena cava, at the level of the lower border of the pulmonary artery as imaged by ICE. Before radiofrequency delivery, maximum output pacing (up to 20 mA) was performed at any site of the posterolateral side of the superior vena cava. If diaphragmatic stimulation was present, ablation in this site was not performed in order to avoid injury to the phrenic nerve. The endpoint of ablation was to eliminate any potential along the mapping catheter (entry block).

In patients with persistent and longstanding persistent AF the electrical isolation of the PVs was extended to the entire posterior wall down to the coronary sinus and the left side of the septum.11 Ablation of complex fractionated atrial electrograms (CFAE) in the left atrium and in the coronary sinus was also performed.

If the AF organized into an atrial tachycardia, activation and entrainment mapping were performed to attempt termination. Otherwise, patients were cardioverted after elimination of all CFAE sites. For recurrences occurring during the first year of follow-up, repeat procedures targeted only sites of reconnection around the PV antrum, posterior wall, interatrial septum and coronary sinus. If patients presented with organized atrial arrhythmia (i.e., atrial flutter/tachycardia), activation and entrainment mapping were performed to terminate the arrhythmia.

*Repeat procedures for recurrences beyond 1 year (late recurrences)*

For repeat procedures ≥1 year after the index procedure, in addition to the ablation strategy
mentioned above (i.e., ablation of sites of reconnection, mapping and ablation of organized atrial tachyarrhythmias), high doses of isoproterenol (20-30 \( \mu\)g/min) for 15-20 minutes were administrated to check for extra-PV firings (Figure 1), which were mapped as previously reported.\(^\text{12}\) No specific hemodynamic compromise beyond what expected during isoproterenol test was encountered in this series of patients. The anesthesiologist participating to the procedure used phenylephrine to manage blood pressure decrease and allow the completion of the isoproterenol test. Non-PV triggers were defined as either consistent (at least 10 in one minute) atrial premature depolarizations or as firing inducing AF/atrial tachyarrhythmia.

**Follow-up**

The follow-up was performed at 3, 6, 9, 12, and then every 6 months after the procedure, with physical examination, 12-lead electrocardiogram, and 7-day Holter monitoring. All patients received an event recorder for the first 5 months to record any symptomatic events. In addition, random recordings were performed 2 to 3 times per week to monitor for any asymptomatic episodes of AF. Recurrence was considered to be any episode of AF/atrial tachycardia lasting for at least 30 seconds after a blanking period of 3 months from the procedure. Repeat ablation was not allowed during the blanking period.

Late recurrence was defined as AF/atrial tachycardia recurrence occurring beyond 1 year after the index procedure. Antiarrhythmic drugs (class III agents – sotalol or dofetilide in 41 cases, amiodarone in 2) were systematically used for the blanking period, and discontinued after the end of the blanking period if patients were in sinus rhythm.

**Statistical analysis**

Descriptive statistics are reported as mean ± SD (or median and interquartile range for skewed distributions) for continuous variables, and as absolute frequencies and percentages for
categorical variables. Between-group comparisons were performed with the unpaired Student t test for continuous data (Mann-Whitney U test when normality assumption not possible), and with the Fisher’s exact for categorical variables. Long-term arrhythmia-free survival was reported as crude event rates, and assessed through a time-to-event analysis by the Kaplan-Meier method. All tests were 2-sided, and a P value <0.05 was considered statistically significant. To adjust for type I error while making multiple pair-wise comparisons for type of recurrent arrhythmia in paroxysmal vs. persistent and longstanding persistent AF populations, the P value for rejecting null hypothesis was set at a conservative level (P = 0.01). Statistical analyses were done by STATA version 11.1 (StataCorp, College Station, Tex) software.

Results

The majority of the patients had persistent (18 [41%]) and longstanding persistent (13 [31%]) AF (Table 1). The mean left atrial diameter was 50.8 ± 6.8 mm, and the left ventricular ejection fraction was 59 ± 6%. Maximum left ventricular wall thickness was 19.8 ± 3.9 mm. All patients had failed treatment with at least one antiarrhythmic drug.

Index Procedure and First Year of Follow-Up

PVAI and isolation of the posterior wall between the PVs and of the superior vena cava was achieved in all patients with paroxysmal AF. In those with persistent and longstanding persistent AF, ablation was extended to the entire posterior left atrial wall and to areas with CFAE in the left atrium and coronary sinus.13 The average radiofrequency time in patients with paroxysmal AF was 34 ± 6 min, and was significantly longer in patients with persistent and longstanding persistent AF (71 ± 9 min, P < 0.001 for comparison with paroxysmal AF). The median fluoroscopy time was 49 min (range 29-53 min), with a median procedural time of 176 min (range 161-189 min).
All patients completed the follow-up monitoring, with all being compliant to the 7-day Holter monitoring. The compliance to all the required trans-telephonic transmission during the initial 5 months was about 88%. At 1 year, the overall freedom from recurrent AF/atrial tachycardia after a single procedure was 53% (75% in patients with paroxysmal AF versus 45% in those with persistent and longstanding persistent AF, \( P = 0.08 \) for comparison), with most of the recurrences occurring between 3 months and 9 months after the index procedure. Specifically, the recurrent arrhythmia was atypical atrial flutter in 65% of cases (69% in paroxysmal AF versus 71% in persistent and longstanding persistent AF, \( P > 0.99 \), and AF in the remaining 35% (33% in paroxysmal AF versus 29% in persistent and longstanding persistent AF, \( P > 0.99 \)). All patients with recurrence underwent repeat ablation (average 1.6 ± 0.7 procedures [1 to 3]). Recovery of conduction across the previously targeted areas (most frequently in the PV antrum) was noted in all patients undergoing a repeat ablation; all areas demonstrating reconnection were re-isolated during the repeat procedure (Figure 1). In patients presenting with atypical atrial flutter, repeat isolation of areas with reconnection always resulted in acute termination of the flutter. The overall secondary success rate at 1 year was 76% off antiarrhythmic drugs, and reached 91% including patients who were successfully treated with previously ineffective antiarrhythmic drugs. No major complications occurred. Minor complications (minor hematoma at the femoral vein access sites) occurred in 2 (4.6%) patients.

**Long-term Follow-up**

After the first year of follow-up, an additional 18 patients experienced recurrent arrhythmia, with a cumulative success rate of 49% at a median follow-up of 42 months (range 38-48 months) (Figure 2A). In particular, long-term arrhythmia-free survival was achieved in 67% of paroxysmal AF patients, 56% of persistent AF, and 23% of longstanding persistent AF (Figure
Most of the late recurrences occurred between 16 and 23 months (Figure 2A and 2B), and all patients underwent an additional procedure (Figure 1). Atypical atrial flutter was the dominant mode of recurrence in these patients, occurring in 89% of cases, while the remaining 11% presented with recurrent AF. Among the clinical variables, only type of AF was found to predict long-term success, with the highest risk of recurrence among patients with longstanding persistent AF (odds ratio = 2.58, 95% confidence interval 1.11 to 6.05, \( P = 0.028 \)).

**Mechanism of Long-term Recurrence, Ablation Strategy and Outcomes**

Persistent isolation of the previously targeted areas (i.e., PV antra and posterior wall) was confirmed in 82% of patients. In the 16 patients presenting with atypical atrial flutter, activation and entrainment mapping were performed, and the arrhythmia was successfully terminated with ablation in 69% of cases. In the 2 patients presenting with recurrent AF, persistent isolation of the previously targeted areas was confirmed at repeat ablation, and the patients were converted to sinus rhythm with electrical cardioversion. At high-dose isoproterenol challenge, non-PV sites of firing were detected in all patients. Non-PV triggers were most commonly mapped in the coronary sinus, left atrial appendage, interatrial septum, and right atrium/crista terminalis (Figure 3). Trigger ablation was performed with the aim of achieving electrical isolation when triggers arose from the coronary sinus or LAA, or with focal ablation in other areas, such as the interatrial septum and the crista terminalis. In these cases, the amount of ablation increased by an average of 14 ± 3 min for the coronary sinus (with the endpoint of complete isolation), or by an average of 31 ± 4 min for achieving LAA isolation. No patient experienced any major complication, while 2 patients had a minor complication not requiring intervention (i.e., 1 femoral pseudoaneurysm, 1 groin hematoma). No clinical variable was found to significantly
predict non-PV triggers, although patients with non-PV triggers were older (62 ± 9 vs. 57 ± 7 years, \( P = 0.07 \)), had larger left atrial diameters (52 ± 7 mm vs. 49 ± 6 mm, \( P = 0.29 \)), and lower left ventricular ejection fraction (58 ± 5% vs. 61 ± 6%, \( P = 0.08 \)).

At a median follow-up of 15 months (range 8 to 19 months) after the last procedure, 94% of the patients remained free from AF/atrial tachycardia off antiarrhythmic drugs.

**Discussion**

The present study reports the results of catheter ablation of AF in a large series of patients with HCM, with the longest follow-up to date. The major findings are as follows: 1) catheter ablation of AF in HCM patients is a safe and effective approach to achieve long-term freedom from recurrent arrhythmia; 2) PV and posterior wall isolation alone are insufficient to obtain satisfactory long-term results, even when permanent isolation is achieved; 3) non-PV triggers can be demonstrated in the majority of HCM patients with late arrhythmia recurrence; 4) ablation of non-PV triggers is associated with a significant improvement in the long-term arrhythmia-free survival.

Atrial fibrillation has a major impact on morbidity and mortality in patients with HCM.\(^{14}\) Radiofrequency catheter ablation has been proposed as an effective rhythm-control treatment for HCM with AF.\(^{4,6,15}\) Specifically, PV antrum isolation (with or without additional left atrial linear ablation)\(^{4,6,15}\) has shown satisfactory results at mid-term follow-up. The present study shows that the benefit of PV antrum and posterior wall isolation is limited at the long-term follow-up, even when persistent isolation is achieved. Rather, non-PV triggers appear highly prevalent in these patients. These results support the concept that HCM patients with AF represent a specific population in whom PV isolation alone should not be considered sufficient as
a stand-alone approach, and a more extensive ablation beyond the PV antrum and posterior wall is necessary to increase the long-term arrhythmia-free survival.

From a pathophysiological perspective, the effect of chronic atrial stretch due to diastolic dysfunction leading to diffuse atrial fibrosis,\textsuperscript{16} the presence of mitral regurgitation due to systolic anterior motion of the mitral valve, and the underlying atrial myopathy caused by the sarcomere protein gene mutations,\textsuperscript{14} might provide the substrate for multiple arrhythmogenic areas beyond the PVs in such patients. Previous studies evaluating the role of PV isolation in HCM patients have shown that enlarged left atria, increasing age, and more advanced heart failure symptoms are predictors of arrhythmia recurrence after PV isolation;\textsuperscript{4} the presence and role of non-PV triggers was not investigated in such studies, and the electrophysiological mechanisms underlying the lack of clinical response to PV isolation during follow-up remained undefined. Non-PV triggers could provide an explanation to lack of sustained response to PV isolation shown in previous studies,\textsuperscript{4} since older age,\textsuperscript{17} enlarged left atria\textsuperscript{18} and more advanced heart failure\textsuperscript{19} have all been linked to a higher prevalence of non-PV triggers.

The present study allows also to draw clinically relevant conclusions regarding the optimal ablation strategy in these patients, by showing that non-PV triggers ablation is associated with a significant arrhythmia-free survival benefit. Indeed, more than 90\% of patients were free from any recurrent arrhythmia without antiarrhythmic medications at an average of 14 months after the last procedure. The large majority of patients with very late arrhythmia recurrence presented with atypical atrial flutter, which was successfully mapped and ablated in about two thirds of cases. Flutter termination was not found to predict the long-term outcome in our patient cohort ($P = 0.49$); again, trigger ablation appeared the only reliable predictor of success. These findings are in line with the concept that post-ablation organized reentrant arrhythmias are the
consequence of spontaneous triggering from specific structures, such as the PV, the coronary sinus, the LAA or the interatrial septum/right atrium.\textsuperscript{20}

**Study Limitations**

This study had a prospective non-randomized design and included a relatively small sample of patients. The presence of non-PV triggers was not assessed at the time of the index procedure and for repeat procedures during the first year of follow-up, due to concerns of inducing or worsening intraventricular obstruction during isoproterenol test. On the other hand, no complications were observed during high-dose isoproterenol test at repeat procedures beyond 1 year, thus suggesting that isoproterenol challenge is safe in these patients, albeit we did not actively assess the presence of a dynamic gradient during the isoproterenol challenge. In addition, we could not evaluate whether non-PV triggers were already present at the time of the first ablation or only represented a late phenomenon responsible for arrhythmia recurrence at long-term follow-up. The lack of assessment for PV exit block might represent another limitation. Most of the late recurrences were observed between 16 and 23 months after the index procedure, which might be explained by the fact that most of the follow-up beyond 1 year occurred within that time frame. It is possible that, if the follow-up was longer, more late recurrences might be seen. Finally, assessment of the left atrial function after ablation was not an endpoint of the study, and was performed only in patients undergoing extensive anterior ablation including isolation of the LAA.

**Conclusions**

PV isolation in patients with HCM is feasible and safe, although is not effective in preventing very late (≥1 year) AF recurrences in about 50% of patients. Non-PVs triggers seem to be responsible of very late recurrences in the majority of these patients. This supports the
appropriateness of a more extensive ablation strategy targeting multiple structures other than the PV antra to improve long-term success.

**Conflict of Interest Disclosures:** Dr. Andrea Natale has received consultant fees or honoraria from Biosense Webster, Boston Scientific, Medtronic, Biotronik and LifeWatch. Dr. Luigi Di Biase is a consultant for Biosense Webster and Hansen Medical. The other authors declare no conflicts of interest.

**References:**


Table 1. Clinical characteristics of the patients included in the study.

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<tr>
<th>Variable</th>
<th>N = 43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Sex, males</td>
<td>29 (67)</td>
</tr>
<tr>
<td>AF Type</td>
<td></td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Persistent</td>
<td>18 (42)</td>
</tr>
<tr>
<td>Longstanding persistent</td>
<td>13 (30)</td>
</tr>
<tr>
<td>NYHA functional class I</td>
<td>9 (21)</td>
</tr>
<tr>
<td>NYHA functional class II</td>
<td>31 (72)</td>
</tr>
<tr>
<td>NYHA functional class III</td>
<td>3 (7)</td>
</tr>
<tr>
<td>AF duration, months (median, IQR)</td>
<td>36 (51)</td>
</tr>
<tr>
<td>LA Diameter, mm</td>
<td>50.8 ± 6.8</td>
</tr>
<tr>
<td>Max LV thickness, mm</td>
<td>19.8 ± 3.9</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Implantable cardioverter-defibrillator</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Failed antiarrhythmic drugs</td>
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</tr>
<tr>
<td>Amiodarone</td>
<td>36 (84)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>31 (72)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Class IC agents</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation or n (%). AF = atrial fibrillation; IQR = interquartile range; LA = left atrial; LV = left ventricle; NYHA = New York Heart Association.
Figure Legends:

**Figure 1.** Study design and ablation strategy adopted in the study.

**Figure 2.** Panel A: Kaplan-Meier survival curve showing multiple-procedure freedom from any atrial arrhythmia recurrence after PV and posterior wall isolation (without ablation of non-PV triggers). Panel B: Kaplan-Meier survival curve showing multiple-procedure freedom from any atrial arrhythmia recurrence after PV and posterior wall isolation (without ablation of non-PV triggers) according to the type of presenting AF. *Note:* time zero is the last ablation targeting the PV and posterior wall without non-PV triggers ablation.

**Figure 3.** Electrophysiological findings at repeat procedures in patients presenting with very late (≥1 year) atrial arrhythmia recurrence.
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