

Review Article

Atrial fibrillation in hypertrophic cardiomyopathy: pathophysiology, diagnosis and management

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Abstract: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disorder, representing a leading cause of sudden cardiac death in the young and a prevalent cause of heart failure and stroke. Atrial fibrillation (AF) is frequently associated with HCM with a reported prevalence of about 20% to 25%. AF genesis is multifactorial, mostly genetically determined or secondary to hemodynamic alterations. AF has also a negative impact on HCM patients' prognosis because it may lead to an increased incidence of heart failure or stroke. We currently have several strategies which can be used during atrial fibrillation episodes and to prevent the arrhythmic recurrences.

Keywords: Atrial fibrillation, hypertrophic cardiomyopathy, pharmacological therapy

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disorder, with an underestimated incidence of 1:500, representing a leading cause of sudden cardiac death in the young and a prevalent cause of heart failure (HF) and stroke [1]. HCM phenotype is characterized by a heterogeneous patho-anatomic background reflecting into various clinical manifestations. Most frequent pathophysiological anomalies in HCM patients include asymmetric left ventricular (LV) hypertrophy, LV outflow tract obstruction (LVOTO), mitral valve abnormalities, diastolic dysfunction, alterations of cardiomyocytes depolarization and metabolism, microvascular ischemia, myocardial fibrosis, altered sympathetic innervation and multifactorial arrhythmogenesis [2]. In particular, LVOTO is typical in approximately 70% of HCM patients: it can be present either at rest or can be dynamically elicited by physical stress. Moreover, LVOTO is one of the major determinants of symptoms, such as dyspnea, chest pain, syncope or arrhythmic recurrences. For this reason, it is also considered a main therapeutic target [3, 4].

However, in HCM patients is also fundamental the prevention of sudden cardiac death and the management of supraventricular arrhythmias [5]. In particular, atrial fibrillation (AF) is the most common sustained arrhythmia in HCM [6, 7]. AF has a reported prevalence of about 20% to 25% in HCM population, more frequent in older patients and in patients with LVOTO [8-10].

The combination of HCM and AF is associated with an increased risk of stroke, HF and overall mortality [1, 11]. In particular, the risk of death in the presence of AF is increased by 4 times [12]. Moreover, AF in HCM patients is associated with an 8-fold increased risk of thromboembolism, with an annual incidence of 3.75% [8, 13, 14] (**Table 1**). Therefore, a careful diagnostic assessment for new-onset AF and an accurate risk stratification should be a priority and may have an impact on follow-up and management strategies.

Pathophysiology

Hemodynamic factors such as diastolic dysfunction and LV outflow obstruction are consid-

AF in HCM patient

Table 1. Natural History of Atrial Fibrillation in HCM patients

	Year	Number of patients	AF prevalence (%)	Stroke incidence in AF patients (%)	Stroke incidence in whole cohort (%)	NYHA III-IV in AF patients (%)	Mortality risk in AF patients (OR)	References
Olivotto et al.	2001	480	22	7	N/A	7	3.7	8
Maron et al.	2002	900	21	23	6	N/A	N/A	27
Kubo et al.	2009	261	28	20	7	23	N/A	9
Tian et al.	2013	654	24	N/A	N/A	N/A	1.2	13
Guttmann et al.	2014	4815	12.5	8	3.6	N/A	N/A	14
Siontis et al.	2014	3673	18	10	5	46	1.5	12
Masri et al.	2015	1005	19	N/A	3	N/A	N/A	4

AF = Atrial Fibrillation; HCM = Hypertrophic Cardiomyopathy; OR = Odds Ratio.

ered the early mechanisms leading to a progressive left atrial enlargement and to AF onset. Increased left atrium (LA) volume with a cutoff of 34 ml/m² is associated to a higher prevalence of AF [15]. Not only LA volume but also LA function is a predictor of new onset AF with LA strain $\leq 23.4\%$ reported as an independent predictor in addition to LA volume [16]. HCM patients are particularly prone to adverse LA remodeling and LA enlargement and this condition is secondary to typical pathophysiological alterations like increased filling pressures, mitral regurgitation and LVOTO [15]. Moreover, in HCM patients is frequently encountered an increased amount of atrial fibrosis due to atrial ischemia and microvascular dysfunction, which contributes to atrial enlargement and functional impairment [17]. Electrophysiological anomalies are therefore the direct consequence of the structural abnormalities just highlighted.

Finally, also genetic factors may play a role in AF incidence, modulating the intrinsic atrial myopathy, the myofibril disarray and the LA maladaptive remodeling usually preceding atrial arrhythmias [18]. Even if there are only few scientific evidences, specific sarcomeric gene mutations have recently been associated to earlier onset of AF in HCM population [19]. Moreover, also non-sarcomeric genes, mostly encoding for proteins involved in the renin-angiotensin-aldosterone system and collagen synthesis, have shown to act as HCM disease modifiers, increasing the AF incidence [20].

Pathophysiology of atrial fibrillation in hypertrophic cardiomyopathy is schematized in **Figure 1**.

Diagnosis

In 2014 guidelines, European Society of Cardiology (ESC) recommended the key points for AF

screening in HCM patients [21]: 48-hour ambulatory ECG monitoring should be considered in AF screening (Class IIa recommendation) every 6 to 12 months in patients who are in sinus rhythm and have LA anterior-posterior diameter ≥ 45 mm. Instead, 2011 American College of Cardiology/American Heart Association (ACC/AHA) guidelines are less rigorous, stating that 24-hour ambulatory ECG monitoring might be considered (Class IIb) in adults with HCM to assess for asymptomatic AF [22].

Because 24-hour or 48-hour Holter electrocardiograms (ECGs) might not detect supraventricular arrhythmias, Implanted Loop Recorder (ILR) utilization could be thought of as a tool for improving paroxysmal AF diagnosis. Only few studies have evaluated the use of ILR for the purpose of correlating symptoms and tachyarrhythmias in selected patients affected by HCM and others cardiomyopathies [23]. According to 2014 ESC guidelines, ILR may be considered for patients with frequent palpitations in whom no cause is identified after prolonged ECG monitoring (Class IIb) [21]. In this same setting, Weidemann et al. already demonstrated that the use ILR in patients with Fabry cardiomyopathy improved detection of arrhythmias and led to clinical relevant therapeutic changes compared to the only use of Holter recordings [24]. However despite the under representation of HCM patients in clinical trials [25], we think that in patients presenting with stroke a more strict monitoring by repetitive Holter-recordings or ILR should be considered, in light of the higher prevalence of paroxysmal AF in this setting [26, 27].

Very few data are reliable about the utility of highly sensitive cardiac troponin T (cTnT) or other cardiac biomarkers in the AF assessment [28]. Only in a single population study, serum

AF in HCM patient

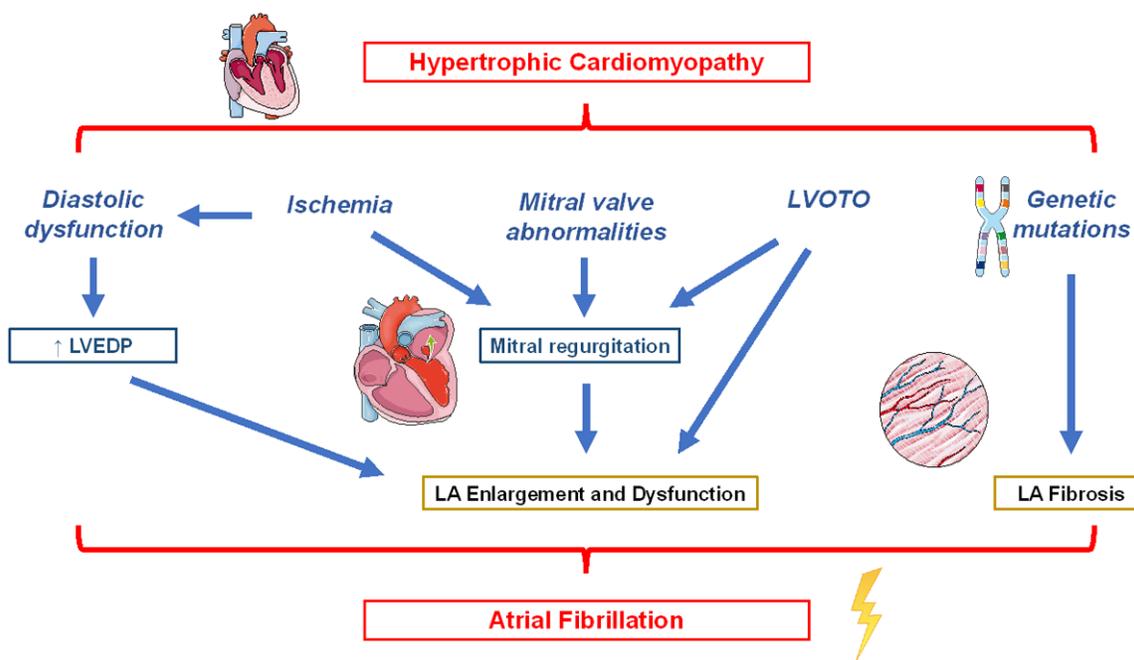


Figure 1. Pathophysiology of atrial fibrillation in hypertrophic cardiomyopathy. LA = Left Atrium; LVEDP = Left Ventricular End-Diastolic Pressure; LVOTO = Left Ventricular Outflow Tract Obstruction.

cTnT concentration proved to be a predictor for an increased incidence of AF [29]. The pathophysiological alterations underlying the increased serum troponin levels in HCM patients has yet to be understood. Among the others, one proposed theory would be that cTnT elevation may be secondary to the LA maladaptive remodeling, atrial myocyte death and fibrosis [28, 29]. However, the possible clinical use of cTnT or other markers for AF management must first be supported by further larger studies.

Pharmacological therapy

Rhythm and rate control

Main targets for pharmacological interventions in HCM patients are symptoms (mainly dyspnea and chest pain) control, LVOTO (usually the main determinant of symptoms), prevention and treatment of HF and arrhythmias [30]. Although valuable clinical guidelines exist for HCM [21, 22], the strength of recommendations for pharmacological treatment is only partially evidence based. However, AF in HCM patients should be treated as aggressively as possible, due to its adverse impact on prognosis [8].

In the setting of acute AF, although DC shock remains the gold standard in case of haemodynamic instability, rate control is often the preferred choice. Beta-blockers or non-dihydropyridine calcium channel blockers represent the first-line treatment to reduce AF-related symptoms by reducing heart rate, ventricular inotropy and by decreasing LVOTO gradient, if present; these two classes of drugs are also the preferred ones in cases of AF associated to ischemic symptoms [21, 22]. Calcium channel blockers should be avoided in the presence of signs and symptoms of heart failure, cardiogenic shock or in case of pre-excitation [31]. On the other hand, rhythm control could be the first choice in young people because of poor hemodynamic adaptation to persistent AF. Unfortunately, also in this case, because of the lack of data on rhythm control in patients with HCM, evidences are extrapolated from studies with non-selected populations [32]. For pharmacological cardioversion of new onset AF, amiodarone infusion should be preferred [30]. The use of flecainide and propafenone is not recommended because they are associated with proarrhythmic effect in subjects suffering from structural heart disease; moreover they can also increase ventricular response by converting AF to atrial flutter 1:1 [21]. However when

cardioversion strategy is chosen, if available transesophageal echocardiography should be performed before drug administration, in order to assess the absence of left atrium thrombus.

In the setting of paroxysmal AF, the administration of long-term anti-arrhythmic therapy is generally preferred to prevent recurrences [33]. For this strategy, two drugs are generally indicated as first-line agents: sotalol and amiodarone. Sotalol is the preferred choice in young people because of its limited side effects [34]. On the other hand, amiodarone is the only option for rhythm control in patients with HF: it has proven effective in maintaining sinus rhythm and in reducing thromboembolic events [35]. Furthermore, the 2014 ESC guidelines on HCM recommend the use of amiodarone following electrical cardioversion (Class IIa, level of evidence B) [21]. In young patients, amiodarone use must be strictly monitored: minimum effective dose should be employed (usually, 200 mg five to seven times per week) and regular controls for thyroid, hepatic, pulmonary, and ophthalmic toxicity should be done [33]. Significant clinical experience with dronedarone is lacking.

Other oral antiarrhythmic drugs like flecainide or propafenone are generally avoided as result of their pro-arrhythmic and negative hemodynamic effects in HCM population [21]: the use of both these drugs are associated to QT prolongation and ventricular arrhythmias detection at electrocardiographic monitoring [28].

In patients with LVOTO, Disopyramide, a class I antiarrhythmic with negative inotropic effects, is often used, but its effect for rhythm control is unknown [30]. It is potentially harmful because of the enhancement of atrioventricular conduction and consequently increased ventricular rates during AF. For this reason, it should be initiated associated with beta-blockers and continuous telemetry to allow the detection of QT prolongation and arrhythmia [36].

In the setting of chronic rate control strategy, beta-blockers or non-dihydropyridine calcium channel blockers are the first choice, taking into account that the latter should be avoided in HF patients. Low dosage digoxin in association to beta-blockers can be used in patients

with HCM not complicated by LVOTO, though data on this strategy are lacking.

Anticoagulation therapy

The onset of AF in HCM patients constitutes an indication for oral anticoagulation, also in cases of only one documented episode. This indication doesn't require other risk factors for embolic stroke such as age or gender. Moreover, in HCM patients CHA2DS2-VASc score is not effective to predict embolic risk [23, 33]: in a retrospective analysis of 4821 HCM patients, 9.8% subjects with a CHA2DS2-VASc score of 0 had a thromboembolic event during the 10-years follow-up [37]. Indeed this study found out that advanced age, presence of AF, increased LV wall thickness, previous thromboembolic event, advanced NYHA class, increased left atrial volume and presence of vascular disease were statistically significant predictors of an increased risk of thromboembolic events, while the use of Vitamin K Antagonists (VKAs) was associated with a 54.8% relative risk reduction.

Warfarin has already demonstrated superiority in the prevention of thromboembolic events in HCM population over antiplatelet agents [37]. Thus, VKAs represents the first-line therapy: drug should be titrated to maintain an international normalized ratio (INR) between 2.0 and 3.0; however, this long-term therapy has several disadvantages including concerns regarding medication adherence. This is typically true in many young patients who refuse warfarin or in older people who have experienced bleeding complications [14]. The introduction of the novel oral anticoagulants (NOACs), including the direct thrombin inhibitor Dabigatran and factor Xa inhibitors Rivaroxaban, Apixaban and Edoxaban, is rapidly changing this landscape. If on one hand caution is mandatory in the absence of safety and efficacy data in HCM patients, on the other hand NOACs can be considered a valid alternative to warfarin in multiple clinical setting and deserve specific investigations. 2014 ESC guidelines [21] recommend the use of NOACs as a second line, in patients who cannot maintain a therapeutic target of anticoagulation, in case of impossibility in monitoring the INR values or in cases of intolerance to Warfarin (Class IB). A recent published retrospective analysis by Gersh et al. [38] from a

large U.S. database showed how, after a mean follow-up of 0.56 years, the incidence rates for thromboembolic events were similar in HCM patients treated with NOACs or warfarin (1.93 and 2.03 events per 100 person years for NOACs and warfarin, respectively); however, although not statistically significant, NOAC have demonstrated compared with warfarin a lower tendency to intracranial bleeding, hemorrhagic stroke and major bleeding [39]. Another recent retrospective analysis from Korean National Health Insurance Service database showed a similar number of embolic and hemorrhagic events during 16 months of medium follow-up between HCM patients treated with VKAs or NOACs, with lower all-cause mortality and composite fatal cardiovascular events in NOACs group [40]. These data encourage the use of NOACs as an alternative to warfarin in order to prevent stroke in patients with AF and HCM.

Also with regard to clinical studies on LAA closure, HCM patients were not included. Surgical LAA exclusion might be performed in HCM patients undergoing cardiac surgery for other reasons.

Non-pharmacological treatment

Radiofrequency catheter ablation (RFCA) is indicated in HCM patients with symptomatic AF unresponsive to antiarrhythmic drugs or in patients with contraindications, intolerances or with many side effects [21]. Multiple studies have demonstrated the feasibility and the safety of this procedure and the small number of peri-procedural complications [41, 42]. On the other hand, about one in two patients requires "redo" procedures [43]. According to the results of a recent meta-analysis, based on data from 15 studies and involving 531 patients, single-RFCA success rate at mean follow-up > 12 months was 45.5%, freedom from AF was reached in 66.1% of patients only after multiple RFCA. Antiarrhythmic therapy is often administered after RFCA. In the same study, considering only patients who did not take antiarrhythmic drugs in the follow-up after the procedure, the success rate dropped to 32.9% [44].

RFCA procedure should be preferred in young patients and with atria that are not or only mild dilated. In fact severe LA enlargement, NYHA class III/IV, AF of long date duration, non-pulmonary veins (PV) triggers, left ventricle systol-

ic dysfunction and older patient age are independent predictors of AF recurrence after RFCA.

Myocardial disarray and sarcomere protein gene mutations [8, 44] can be the substrate for multiple arrhythmogenic areas around the pulmonary veins. However, recurrence of AF in HCM patients can also be triggered by non-pulmonary veins pathways [41, 44]. The effectiveness of the radio frequencies to create permanent transmural lesions, in order to effectively isolate the pulmonary veins, can be variable due to hypertrophy of atrial myocytes and LA thickening: this topic has been supported by the high incidence of pulmonary veins conduction recovery identified on repeat ablations [42].

Similarly, in patients in whom it is difficult to control both rhythm and heart rate with antiarrhythmic drugs, atrio-ventricular node ablation might be a therapeutic choice according to the ESC guidelines [21].

Even though limited data are available, the surgical procedures in HCM patients with AF can be an option. Surgical septal myectomy should be evaluated in order to reduce gradients and systolic anterior motion-related mitral valve regurgitation: this impacts positively on functional status and symptoms in over 90% of HCM patients, but there is no evidence about the reduction of AF [45]. Therefore, for symptomatic AF patients with outflow obstruction, combining septal myectomy with AF surgical ablation has been suggested.

Alfieri et al. [46] described a series of thirty-one consecutive patients submitted to surgical myectomy combined with Maze procedure. At a median follow-up of 6,4 months, no stroke and thromboembolic events were documented. The arrhythmia-free survival off antiarrhythmic drugs was 82% at 1 year and 52% at 6 years. The 1- and 6-year arrhythmia control (maintenance of sinus rhythm with or without antiarrhythmic drugs) was 96% and 80%, respectively, suggesting surgical ablation of AF as a reasonable treatment option for drug refractory AF in patients with HCM undergoing surgical myectomy and/or mitral valve surgery.

In **Figure 2** we have summarized a therapeutic algorithm concerning the treatment of AF in HCM patients based on the studies and evidences highlighted.

AF in HCM patient

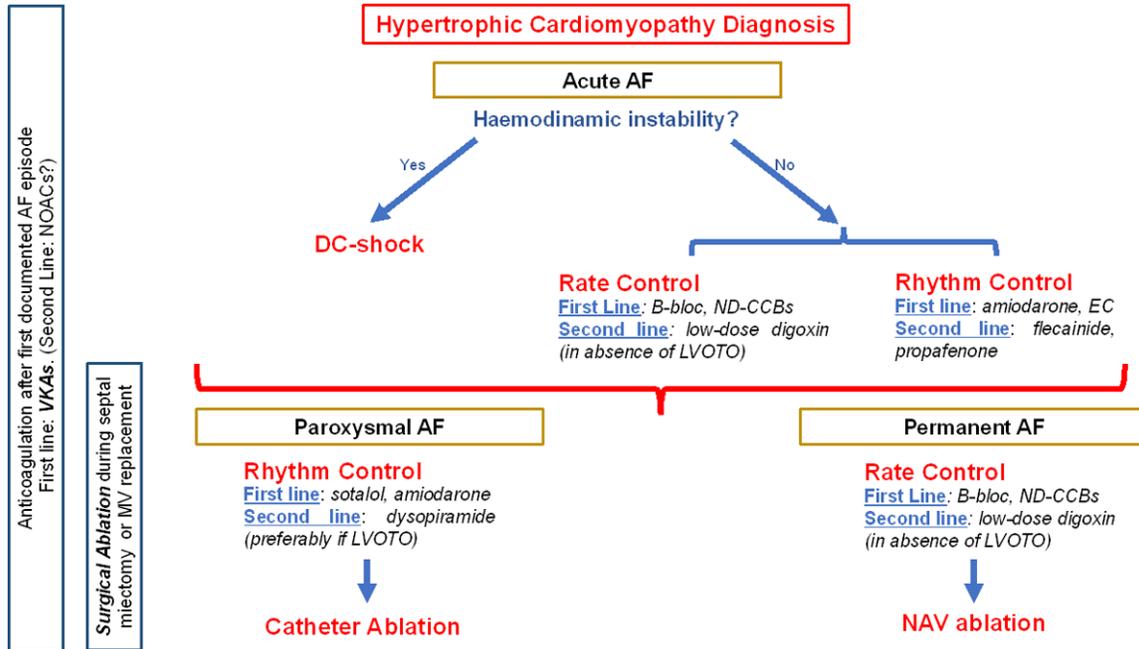


Figure 2. Treatment of Atrial Fibrillation in Hypertrophic Cardiomyopathy patients. AF = Atrial Fibrillation; B-bloc = Beta-Blockers; EC = Electrical Cardioversion; HCM = Hypertrophic Cardiomyopathy; LVOTO = Left Ventricular Outflow Tract Obstruction; ND-CCBs = Non-Dihydropyridine Calcium Channel Blockers; NOACs = New Oral Anticoagulants; VKA = Vitamin K Antagonists; MV = Mitral Valv.

Prognosis and follow-up of HCM patients

A recent study showed that patients had 0.7%/year HCM-related mortality rate and 1.1%/year HCM-unrelated mortality rate [47].

Most important factors described in the literature that affect the prognosis of HCM patients are age [48], the presence of apical aneurysms [49], non-sustained ventricular tachycardia at ECG monitoring [50], Late Gadolinium Enhancement at cardiac Magnetic Resonance Imaging [51], sarcomeric protein gene mutation at genetic analysis [52, 53].

HCM patients, regardless of the contextual presence of AF, should be followed over time through specialistic visits [54]. The frequency of these medical checks should be chosen according to the symptoms, age and severity of the disease of the specific patient. In general, for asymptomatic patients, a cardiology outpatient follow-up including ECG and transthoracic echocardiography should be performed every 1-2 years; as previously described, the same is recommended for 24/48-hour ECG Holter, except for patients with atrial dilatation, to whom this exam should be performed every 6 months. If available, every 2-3 years patients

should undergo cardiopulmonary test and Cardiac Magnetic Resonance [21].

Basically, antiarrhythmic drugs are well tolerated without need of withdrawal in most HCM patients. In clinical practice it is recommended to perform an ECG about 2-4 weeks after the first intake of antiarrhythmic drug: this control should be focused to exclude bradyarrhythmias and QT prolongation.

Pharmacotherapy should be discontinued or the dose reduced if the QTc interval exceeds 480 milliseconds during uptitration and moreover the concurrent use of other QT-prolonging medications should be avoided [21].

Conclusions

AF is a frequent event during the evolution of HCM but at the same time it is associated with an adverse prognosis. Its genesis is multifactorial, in part due to the typical anatomic and hemodynamic alterations of HCM but also genetically determined. According to this, clinicians must have high suspicion for this arrhythmia during the regular follow-up of their patients.

Nowadays multiple pharmacological and non-pharmacological strategies can be chosen for the treatment of acute AF, the prevention of recurrences and the rate control in patients with permanent AF. Such treatment protocols must be individually tailored for each patient. Moreover, anticoagulation is a cornerstone within the treatment of HCM patients already after the first documented AF episode. Further and larger data are needed in order to better study the efficacy and safety of novel oral anti-coagulants in this specific population.

Disclosure of conflict of interest

None.

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