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Treatment Options for Atrial Fibrillation in Hypertrophic Cardiomyopathy

Anurag Anand[1], Manish Kumar Maity[1], Jaspreet Kaur[1], Raman Mehra[1], Akshit Munjal[1], Parul Kharab[1], Parminder Nain*[1]
[1]Department of Pharmacy Practice, MM College of Pharmacy, Maharishi Markandeshwar (Deemed to be University), Mullana,-Ambala (Haryana)
(*Corresponding Author's E-mail – parminder.nain26@gmail.com)

ABSTRACT
Hypertrophic cardiomyopathy, is the most common genetic cardiac disease. Diastolic dysfunction, outflow tract obstruction, mitral regurgitation, atrial and ventricular arrhythmia, pulmonary hypertension, coronary insufficiency, and congestive heart failure are all possible outcomes of this phenotype of aberrant hypertrophy, which is often localized. While many patients are asymptomatic or mildly symptomatic, or have adapted their physical routine over decades to make the diagnosis of overt disease more subtle, a significant subset suffers from symptoms ranging from palpitations to pre-syncope or syncope to dyspnea, angina, and those associated with late or end-stage heart failure. Sudden cardiac death, which occurs at a rate of 1 percent per year in this group, can be as high as 3 to 5% in high-risk subsets, necessitating the implantation of an implanted cardioverter-defibrillator (ICD) in around 30% of patients. A thorough examination of anatomy and physiology is required for symptomatic individuals in order to determine the cause of their symptoms. This comprises both rest and physiologic provocation echocardiogram to identify the degree and location of hypertrophy. The presence of aberrant or abnormal papillary muscles, valve disease or membranes, and the severity of any outflow tract blockage. The extent of hypertrophy or intramyocardial scar may aid in decision-making, cardiac MRI and transesophageal echocardiography are useful, particularly when the potential benefits of an implantable defibrillator or a better understanding of mitral regurgitation are required, respectively. Lifestyle changes, such as adequate hydration in patients without overt indications of fluid overload, avoidance of caffeine and alcohol, and suitable exercise and nutrition to preserve fitness, are the first steps in the medical care of hypertrophic cardiomyopathy. In order to establish the degree of sickness in a specific family and to safeguard others proactively by carefully scheduled testing and counseling, family counseling and genetic testing are also crucial.
Keywords: Atrial fibrillation, hypertrophic cardiomyopathy, pharmacological therapy

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INTRODUCTION

With an underestimated incidence of 1:500, hypertrophic cardiomyopathy (HCM) is the most common hereditary cardiovascular condition, and it is a primary cause of sudden cardiac mortality in the young, as well as a common cause of heart failure (HF) and stroke [1]. The HCM phenotype is defined by a diverse pathoanatomic basis that manifests in a variety of clinical symptoms. Asymmetric left ventricular (LV) hypertrophy, LV outflow tract obstruction (LVOTO), mitral valve abnormalities, diastolic dysfunction, alterations in cardiomyocyte depolarization and metabolism, microvascular ischemia, myocardial fibrosis, altered sympathetic innervation, and multifactorial arrhythmogenesis are the most common pathophysiological anomalies in HCM patients [2]. LV outflow tract obstruction (LVOTO), is an example, which occursin around 70% of HCM patients: it can be present at rest or be dynamically induced by physical stress. Furthermore, LVOTO is a key factor in the development of symptoms including dyspnea, chest discomfort, syncope, and arrhythmic recurrences. As a result, it is also regarded as a primary therapeutic target [3,4].

The avoidance of sudden cardiac death and the treatment of supraventricular arrhythmias are also critical in HCM patients [5]. Atrial fibrillation (AF) is the most prevalent persistent arrhythmia in patients with HCM with a frequency of 20% to 25% [6,7] . It is more common in elderly patients and people with LVOTO. [8-10]

HCM and AF together are linked to an increased risk of stroke, heart failure, and overall mortality [1,11]. In the presence of AF, the risk of mortality is raised by four times [12]. Furthermore, AF is linked to an 8-fold higher risk of thrombosis in HCM patients, with an annual incidence of 3.75 percent [8,13,14]. As a

result, a thorough diagnosis of new-onset AF and precise risk stratification should be a top focus, as it may affect follow-up and therapy measures.

PATHOPHYSIOLOGY

Hemodynamic variables including diastolic dysfunction and LV outflow blockage are thought to be the first triggers for left atrial hypertrophy and AF development. With a threshold of 34 ml/m^2, increased left atrium (LA) volume is linked to a higher incidence of AF [15]. LA function, as well as LA volume, is a predictor of new-onset AF, with LA strain ≤ 23.4% being identified as an independent predictor of new onset AF [16]. HCM patients are more likely to experience unfavorable LA remodeling and enlargement, which is caused by pathophysiological changes such as higher filling pressures, mitral regurgitation, and LVOTO [15]. Furthermore, atrial fibrosis is common in HCM patients as a result of atrial ischemia and microvascular dysfunction, which adds to atrial hypertrophy and functional impairment [17]. As a result, electrophysiological abnormalities are a direct result of the structural abnormalities previously mentioned [Figure 1].

Finally, genetic variables may play a role in the development of AF by regulating intrinsic atrial myopathy, myofibril disarray, and LA maladaptive remodeling, all of these are associated with atrial arrhythmias [18]. Even though there is little scientific evidence, particular sarcomeric gene alterations have recently been linked to AF onset presently in the HCM population [19]. Non-sarcomeric genes, particularly encoding proteins implicated in the renin-angiotensin-aldosterone pathway and collagen formation, have also been found to operate as HCM disease modifiers, increasing the risk of AF [20].

Diagnosis

The European Society of Cardiology (ESC) proposed the following essential factors for AF screening in HCM patients [21]: In individuals who are in sinus rhythm and have a LA anterior-posterior diameter of ≥ 45 mm, 48-hour ambulatory ECG monitoring should be considered in AF screening (Class IIa recommendation) every 6 to 12 months. Instead, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines are less stringent, indicating that 24-hour ambulatory ECG monitoring in people with HCM to check for asymptomatic AF could be considered (Class IIb) [22].

Implanted Loop Recorder (ILR) might be used as a technique for enhancing paroxysmal AF diagnosis because 24-hour or 48-hour Holter electrocardiograms (ECGs) may not identify supraventricular arrhythmias. Only a few studies have focused at using ILR to correlate symptoms with tachyarrhythmias in individuals with HCM and other cardiomyopathies [23]. ILR may be explored for individuals with frequent palpitations (Class IIb) who have no reason detect after continuous ECG monitoring, according to ESC guidelines [21]. Weidemann et al. previously established that using ILR in patients with Fabry cardiomyopathy enhanced arrhythmia identification and resulted to clinically important treatment improvements when compared to using simply holter recordings [24]. Despite the underrepresentation of HCM patients in clinical trials, it is believe that, given the increased occurrence of paroxysmal AF in this situation, more stringent surveillance by repeating Holter-recordings or ILR should be explored in patients presenting with stroke. [25,26,27]

Only a little amount of evidence supports the use of very sensitive cardiac troponin T (cTnT) or other cardiac biomarkers in the diagnosis of AF [28]. Serum cTnT concentration was only found to be a predictor of an increased risk of AF in single population research [29]. The pathophysiological changes that cause elevated blood troponin levels in HCM patients are yet unknown. A concept that thecTnT increase is caused by LA maladaptive remodeling, atrial myocyte death, and fibrosis, among other things [28,29]. However, bigger studies are needed to establish the potential therapeutic utility of cTnT or other markers for AF treatment.

MATERIALS AND METHODS

We performed a literature search from reputed and indexed journal data sets including Pubmed, Scopus, Web of Science, and Medline electronically for identification of potential studies conducted from 1985 till March 2020 by using special keywords like Atrial fibrillation, hypertrophic cardiomyopathy, and pharmacological therapy for atrial fibrillation. In the underlying search, all articles that had these keywords in their literature were sorted by citations. Abstracts were evaluated only if they presented all required information.

RESULTS AND DISCUSSION

Pharmacological therapy

Therapeutic options for patients with brief AF paroxysms should typically focus on controlling the arrhythmia itself. However, in patients with persistent AF, the physician is typically torn between trying to restore and then maintain sinus rhythm (rhythm control) or accepting the arrhythmia (as in chronic

AF) and controlling the ventricular rate (rate control). Patients with one or more risk factors for thrombosis should be evaluated for anticoagulation, regardless of the arrhythmia pattern or treatment method selected, and in the absence of contraindications (fig 1). Patients with a low or intermediate risk of bleeding, as well as those with a higher risk of bleeding for whom warfarin is contraindicated, may benefit from antiplatelet therapy [Figure-2]

Rhythm and rate control

Symptom management (mostly dyspnea and chest pain), LVOTO (typically the major predictor of symptoms), and the prevention or treatment of HF and arrhythmias are the main goals for pharmaceutical therapies in HCM patients [30]. Although there are useful clinical guidelines for HCM but the strength of pharmacological therapy recommendations is only partially evidence-based. [21, 22] However, because of its negative influence on prognosis, AF in HCM patients should be treated as aggressively as feasible [8].

Although DC shock remains the gold standard in cases of hemodynamic instability, rate control is frequently the favored option in the context of acute AF. Beta-blockers or non-dihydropyridine calcium channel blockers are the first-line treatment for AF-related symptoms, as they reduce heart rate, ventricular inotropic, and, if present, the LVOTO gradient; these two classes of drugs are also the preferred ones in cases of AF associated with ischemic symptoms [21,22]. In the context of signs and symptoms of heart failure, cardiogenic shock, or pre-excitation, calcium channel blockers should be avoided [31]. In young patients, however, rhythm control may be the best option due to inadequate hemodynamic response to prolonged AF. Unfortunately, due to a lack of data on rhythm control in patients with HCM, evidence is inferred from research with non-selected individuals in this situation as well [32]. Amiodarone infusion should be used for pharmacological cardioversion of new-onset AF [30]. Flecainide and propafenone should not be used since they have been linked to a pro-arrhythmic impact in people with structural heart disease, and they can also enhance ventricular response by converting atrial flutter to atrial flutter ina 1:1 ratio [21]. However, if a cardioversion method is adopted, transesophageal echocardiography should be conducted prior to medication administration to ensure that there is no left atrial thrombus.

To avoid recurrences of paroxysmal AF, long-term anti-arrhythmic medication is typically favored [33]. Two medicines are commonly used as first-line agents in this strategy *i.e*,sotalol and amiodarone. Because of its few adverse effects, sotalol is the drug of choice among young people [34]. Amiodarone is the only alternative for rhythm regulation in HF patients: it has been shown to preserve sinus rhythm and reduce thromboembolic events [35]. Furthermore, according to the current ESC recommendations on HCM, amiodarone should be used after electrical cardioversion (Class IIa, level of evidence B) [21]. Amiodarone should be used with caution in young children, with the lowest effective dose (typically 200 mg five to seven times per week) and routine checks for thyroid, hepatic, pulmonary, and ocular toxicity [33]. There isn't a lot of clinical experience with dronedarone.Other oral antiarrhythmic drugs, such as flecainide or propafenone, are generally avoided in the HCM population because of their pro-arrhythmic and negative hemodynamic effects [21]: both of these drugs are linked to QT prolongation and the detection of ventricular arrhythmias on electrocardiographic monitoring [28]. Disopyramide, a class I antiarrhythmic with negative inotropic effects, is commonly administered in patients with LVOTO, although its effect on rhythm regulation is unclear [30]. It has the potential to be detrimental because it improves atrioventricular conduction and, as a result, increases ventricular rates during AF. As a result, it should be started in conjunction with beta-blockers and continuous telemetry in order to identify QT prolongation and arrhythmia [36].

Beta-blockers or non-dihydropyridine calcium channel blockers are the preferred choices in the setting of a chronic rate control approach, with the latter being avoided in HF patients. In individuals with HCM that is not complicated by LVOTO, low-dose digoxin combined with beta-blockers can be administered, albeit data on this therapy is limited.

Anticoagulation therapy

Few recorded data onthe incidence of AF in HCM patients, in which oral anticoagulation is recommended. Other risk factors for embolic strokes, such as age or gender, are not required for this indication. Furthermore, the CHA2DS2-VASc [congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female)]score is ineffective in predicting embolic risk in HCM patients [23,33]. A retrospective investigation of HCM patients finds that 9.8% of patients with a CHA2DS2-VASc score of 0 experienced, have a thromboembolic event during the 10-year follow-up period [37]. Indeed, advanced age, the presence of AF, increased LV wall thickness, previous thromboembolic event, advanced NYHA class, increased left atrial volume, and the presence of vascular disease were all statistically significant predictors of an increased risk of thromboembolic events, while the use of Vitamin K Antagonists (VKAs) was linked to a 54.8 percent relative risk reduction.

Warfarin has already been shown to be superior to antiplatelet medications in the prevention of thromboembolic events in the HCM group [37]. As a result, VKAs are the first-line therapy: the close of medicine should be titrated to keep the international normalized ratio (INR) between 2.0 and 3.0 Nevertheless, this long-term therapy comes with a number of drawbacks, including worries about medication adherence. The emergence of new oral anticoagulants (NOACs), such as Dabigatran (a direct thrombin inhibitor) and Rivaroxaban, Apixaban, and Edoxaban (factor Xa inhibitors), is fast transforming this picture. While care is required in the absence of safety and effectiveness evidence in HCM patients. NOACs can be a viable option to warfarin in a variety of therapeutic settings and need further exploration. In patients who cannot maintain a therapeutic aim of anticoagulation, in circumstances of inability in monitoring INR readings, or in cases of intolerance to warfarin, and propose the use of NOACs as a second-line therapy (Class IB) [21]. After a mean follow-up of 0.56 years, Gersh *et al.* found that the incidence rates of 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[38]. But not statistically significant. NOACs have demonstrated a lower tendency to intracranial bleeding, hemorrhage and stroke compared to warfarin. Another recent retrospective analysis of the Korean National Health Insurance Service database found a similar number of embolic and hemorrhagic events in HCM patients treated with VKAs or NOACs during 16 months of period, with the NOACs group having lower all-cause mortality and composite fatal cardiovascular events [40]. These findings support the use of NOACs instead of warfarin to prevent stroke in individuals with AF and HCM.

HCM patients were not included in clinical investigations on LAA closure. In HCM patients undergoing cardiac surgery for other reasons, surgical LAA exclusion may be undertaken.

Non-Pharmacological Treatment

HCM patients with symptomatic AF resistant to antiarrhythmic medications, as well as those with contraindications, intolerances, or a long list of side effects, might consider radiofrequency catheter ablation (RFCA) [21]. Multiple studies have proved the procedure's feasibility and safety, as well as the low incidence of peri-procedural problems. [41,42] On the other hand, around one out of every two patients has to have operations redone [43]. According to the findings of a recent meta-analysis based on data from 15 trials and including 531 patients, the single-RFCA success rate was 45.5 percent after a mean follow-up of more than 12 months, while only 66.1 percent of patients were free of AF after multiple RFCA. Following RFCA, antiarrhythmic treatment is frequently used. Following RFCA, antiarrhythmic treatment is frequently used. The success rate was reduced to 32.9 percent in the same research when only patients who did not use antiarrhythmic medicines in the follow-up after the surgery were considered [44].

In young patients with atria that are not or only mildly dilated, the RFCA technique should be used. In fact, substantial LA enlargement, NYHA class III/IV, long-term AF, non-pulmonary veins (PV) triggers, left ventricle systolic dysfunction, and patient age are all independent predictors of AF recurrence following RFCA.

Multiple arrhythmogenic zones around the pulmonary veins can be caused by myocardial disarray and sarcomere protein gene alterations [8,44]. On the other hand, Non-pulmonary vein routes, can induce AF recurrence in HCM patients [41,44]. Due to hypertrophy of atrial myocytes and LA thickening, the effectiveness of radio frequencies to create permanent transmural lesions in order to effectively isolate the pulmonary veins can be variable. This topic has been supported by the high incidence of pulmonary vein conduction recovery identified on repeat ablations [42].

According to the current ESC recommendations, atrioventricular node ablation may be a treatment option in individuals who have difficulty controlling both rhythm and heart rate with antiarrhythmic medications. [21] Surgical interventions in HCM patients with AF may be an option. In order to minimize gradients and systolic anterior motion-related mitral valve regurgitation, surgical septal myectomy should be considered. This improves functional status and symptoms in over 90% of HCM patients, but there is no evidence that it reduces AF [45]. As a result, combining septal myectomy with AF surgical ablation has been advised for symptomatic AF patients with outflow blockage.

Alfieri et al. documented a group of thirty-one individuals who had surgical myectomy and the Maze technique at the same time [46]. There were no strokes or thromboembolic events during a median follow-up of 4 - 6 months. Antiarrhythmic drug-free survival was 82 percent after one year and 52 percent after six years. The difference below 1-year and 6-year arrhythmia control rates (maintenance of sinus rhythm with or without antiarrhythmic drugs) were 96% and 80%, respectively, suggesting that surgical ablation of AF is a viable treatment option for drug-resistant AF in patients with HCM undergoing surgical myectomy and/or mitral valve surgery.

Prognosis and Follow-up of HCM patients

Patients had a 0.7 percent annual HCM-related death rate and a 1.1 percent annual HCM-unrelated mortality rate, according to recent research [47]. Age, the presence of apical aneurysms, non-sustained ventricular tachycardia at ECG monitoring, Late Gadolinium Enhancement at cardiac Magnetic Resonance Imaging, and sarcomeric protein gene mutation at genetic analysis are the most important factors described in the literature that affect the prognosis of HCM patients. [48 – 51]

HCM patients should be monitored throughout time with specialized visits, totally independent of the existence of AF in the setting [53]. The frequency of these medical examinations should be determined by the patient's symptoms, age, and illness severity. A cardiology outpatient follow-up including ECG and transthoracic echocardiography should be performed every 1-2 years for asymptomatic patients. The sameis recommended for the 24/48-hour ECG Holter, except for patients with atrial dilatation, who should have this exam every 6 months. Patients should have a cardiopulmonary test and a cardiac magnetic resonance scan every 2-3 years [21].In most HCM patients, antiarrhythmic medications are well-tolerated and do not need discontinuation. In practical practice, an ECG should be performed around 2-4 weeks after the first antiarrhythmic medicine is taken, with the goal of excluding bradyarrhythmias and QT prolongation.If the QTc interval exceeds 480 milliseconds during up-titration, pharmacotherapy should be stopped or the dosage lowered, and concomitant use of other QT-prolonging drugs should be avoided [21].

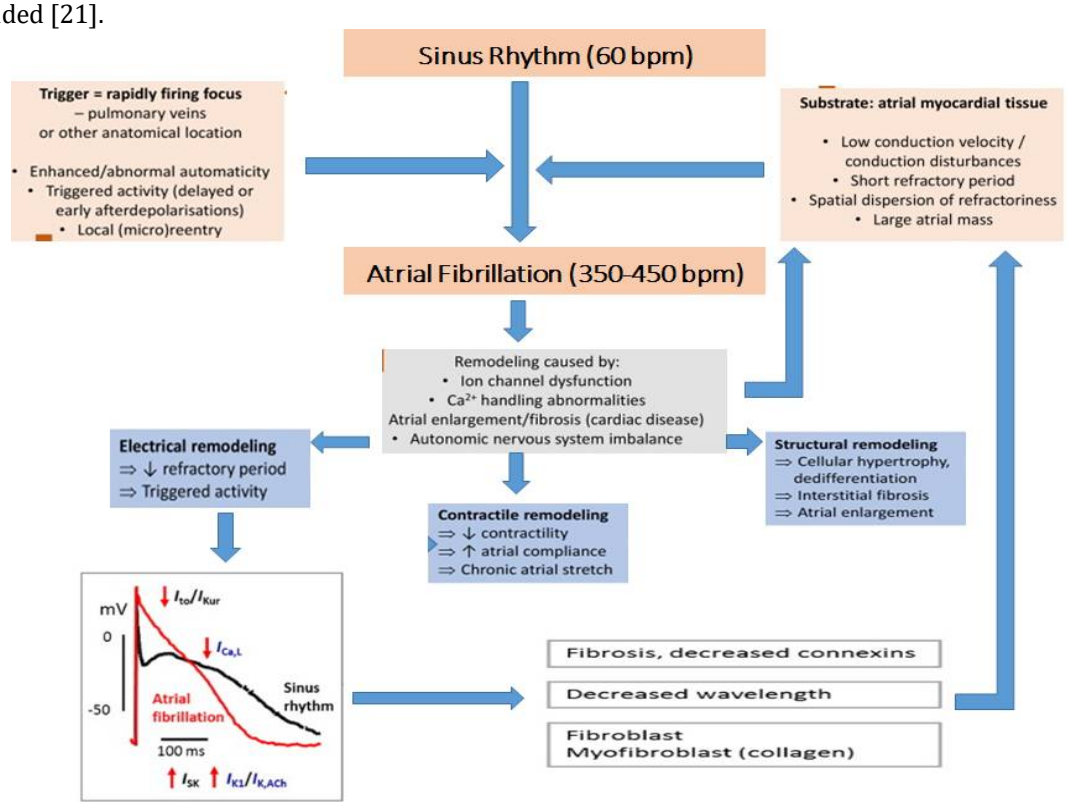

Figure 1: Pathophysiology of Atrial Fibrillation

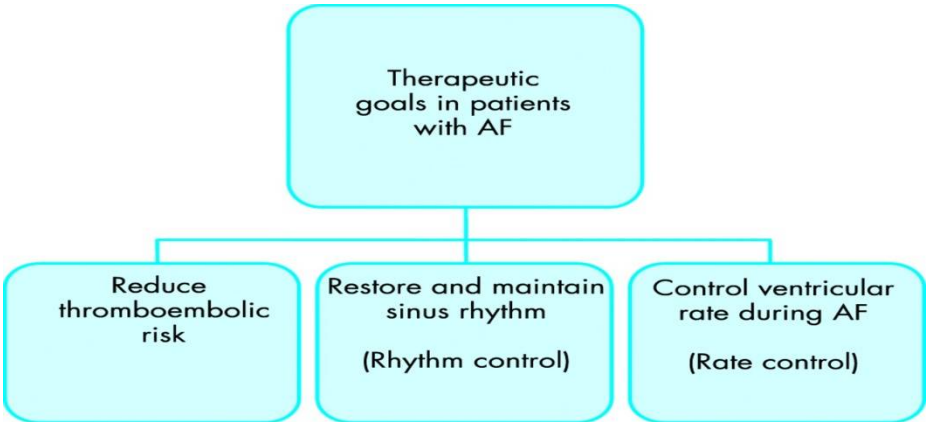

Figure 2: Therapeutic goals in patients with AF

CONCLUSIONS

Atrial Fibrillation (AF) is a common occurrence with the progression of HCM, but it is also linked to a poor prognosis. It has a complicated etiology, owing in part to the normal anatomic and hemodynamic modifications of HCM, but also to hereditary factors. As a result, during routine patient follow-up, the physician must have a high suspicion of cardiac arrhythmia.For the treatment of acute AF, the prevention of recurrences, and rate control in patients with persistent AF, a variety of pharmacological and non-pharmacological treatments are now available. Such treatment plans must be adapted to the specific needs of each patient. Furthermore, even after the first recorded AF event, anticoagulation is a cornerstone in the management of HCM patients. To further understand the effectiveness and safety of innovative oral anticoagulants in this group, more significant data is needed.

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