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Review

Atrial Fibrillation in Hypertrophic Cardiomyopathy: A Review

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Abstract

Hypertrophy cardiomyopathy (HCM) is the most common cardiomyopathy characterized by left ventricular hypertrophy and a spectrum of clinical manifestation. Atrial fibrillation (AF) is the most common sustained arrhythmia in HCM patients and is primarily related to left atrial dilation and remodeling. There are several clinical, electrocardiographic (ECG), and echocardiography (ECHO) features that have been associated with development of atrial fibrillation in HCM patients. The strongest predictors are left atrial size and heart failure class. AF can lead to progressive functional declines, worsening the heart failure and increased for systemic thromboembolism. The mechanism by which atrial fibrillation occurs in HCM is incompletely understood but data suggest that heart failure induced atrial fibrosis and atrial ionic remodeling are the underlying abnormalities that facilitate atrial fibrillation. The management of AF in patients with HCM includes risk factor modification and guideline directed medical therapy, rate control and rhythm control and prevention of complication such as thromembolism. The decision whether to target a rate control or rhythm control strategy is an evolving aspect of management. As recent evidence suggest that early rhythm control strategy may result in more favorable short- and long-term prognosis.

Key words: Hypertrophy Cardiomyopathy, Atrial Fibrillation, Heart Failure, Thromboembolism, Antiarrhythmic Agents, Calcium Channel Blockers.

1. Introduction

Hypertrophic cardiomyopathy is the most common inherited cardiomyopathy due to the mutation in one of the sarcomere genes and transmitted in autosomal dominant pattern with variables penetrance (1, 2). It is characterized by left ventricular hypertrophy that is wall Thickness > 13 mm on echocardiogram, usually asymmetric involving the septum, in the absences of abnormal loading conditions and other known photocopies of HCM (e.g.-lysosomal associated membrane protein-2 cardiomyopathy or amyloidosis)(3, 4).Septal hypertrophy may causes dynamic left ventricular outflow tract obstruction (Hypertrophic obstructive cardiomyopathy) and mitral regurgitation due to abnormal systolic anterior motion of the anterior mitral valve leaflet. The clinical presentation of HCM is heterogeneous and includes asymptomatic state, heart failure syndrome due to diastolic dysfunction or left ventricular outflow obstruction, arrhythmia(atrial fibrillation, embolism) and sudden cardiac death as shown in table 1(1, 5). Atrial fibrillation (AF) leads to sustained arrhythmia in HCM patients and is responsible for worsening the symptom and lifestyles (6, 7). There are so many risk factors that cause sudden death in hypertrophic cardiomyopathy as shown in table 2 (8).

Table 1: Clinical feature of hypertrophic cardiomyopathy (8).

1. Symptoms:
• Angina on effort.
• Dyspnea on effort.
• Syncope on effort.
• Sudden death.
2. Signs:
• Jerky pulse.
• Palpable left ventricular hypertrophy.
• Double impulse at the apex.
• Mid- systolic murmur at the base.
• Pansystolic murmur.

2. Incidences and Prevalence

HCM is most common form of cardiomyopathy with a prevalence of approximately up to 0.2 % or 1 in 500 persons (6). It is common causes of exercise intolerance, heart failure and sudden cardiac death in young patients. AF is the most common sustained arrhythmia in both HCM and in general population. The prevalence of AF in HCM patients is four to six folds higher than similarly aged general population. The annual incidences are 2-4 % and lifetime prevalence are 20-30 % with high rate 40 % chances of HCM in patients over the ages of 70 % years. The AF incidence is about 3.08 % per 100 patients per year and lifetime prevalence is 22.5 % (9). AF is regarded as a reason for a progressive arrhythmia in HCM patients with major clinical impacts and progressive arrhythmia tend to be paroxysmal in two-thirds of patients while rests have persistent or permanent AF (7, 10).

3. Pathophysiology of Atrial Fibrillation in Hypertrophic Cardiomyopathy

The condition is a genetic disorder with autosomal dominant transmission with a high degree of penetrance and variable expression. The

Table 2: Risk factors which cause Sudden death in Hypertrophic cardiomyopathy (8).

a. A history of previous cardiac arrest or sustained ventricular tachycardia.
b. An adverse genotype and family history.
c. Exercise induced hypotension.
d. Recurrent syncope.
e. Multiple episodes of Non-sustained ventricular tachycardia on ambulatory ECG monitoring.
f. Marked increase in left ventricular wall thickness.

Genetic mutations in HCM lead to myofibril disarray and eventually left ventricular hypertrophy over time. There are three most predominant mutations involving the sarcomere contractile proteins constitute 60% of the HCM cases, involving the beta myosin heavy chin (NYH7), cardiac Troponin T and myosin binding protein C (11). Beta-myosin heavy chin mutations are associated with elaborate ventricular hypertrophy. Troponin mutations are associated with little and sometimes even no hypertrophy but marked myocardial fiber disarray, abnormal vascular response (exercise induced hypotension) and high risk of sudden death. Myosin binding protein C mutation present late in life and often associated with hypertension and arrhythmia. The developments of AF in HCM patients are multifactorial including genetic factors, structural abnormalities and electrophysiological abnormalities. The missense mutation Arg663His in MHY7 gene has been reported to be associated with greater risk of AF (47 % prevalence over a follow up period of 7 years (12). Polymorphisms in the Angiotensin receptor gene (AGTR1) have also been linked to the development of AF in patients with HCM (13).

Hypertrophic cardiomyopathy is associated with diastolic dysfunction due to left ventricular hypertrophied and reduced LV compliance. Diastolic dysfunction lead to elevated left ventricular end diastolic pressure and increased afterload for left atrium. This results in progressive dilation and remodeling of left atrium causing structural and electrophysiological abnormalities. This is further exacerbated by left ventricle outflow tract obstructions and mitral regurgitation due to systolic anterior motion of the mitral valves (4, 14). Left atrial remodeling shortens the atrial refractory period and in turn increase the dispersion of repolarization. This can potentiate the ability of ectopic and trigger to initiate AF (15, 16). HCM itself can cause atrial myofibril disarray and atrial fibrosis which as substrate for AF by impairing intra-atrial conduction (15, 17, 18). The mechanism for AF in HCM includes atrial ischemia due to microvascular dysfunction, hypertrophy of muscle sleeves responsible for conduction from pulmonary vein triggers to Left atrium and abnormal calcium handling resulting in triggered activities (16, 19, 20).

The mutation in PRKAG2 encoding the subunit of AMP activated kinase. The mutation result in significant change with conserved region of protein sequence and cosegregates with disease with complete penetration. This is associated with left ventricular systolic and diastolic dysfunction, left ventricular outflow tract obstruction and myocardial ischemia. This will explain the molecular mechanism of sudden death of patient in hypertrophic cardiomyopathy.

4. Risk Factor for Development of Atrial Fibrillation

There are several clinical cases, electrocardiographic (ECG) and echocardiography

(ECHO) features that have been described as independent predictors for development of AF in HCM patients. The strongest independent predictors of those are left atrial size, age and heart failure classes as shown in table 3. The size of the left atrium (LA) is strongly associated with the development of AF in HCM patients. There is a different cutoff of left atrial size to predict AF risk in HCM patients, but most accepted size is anteroposterior diameter > 45 mm (7, 9). In metanalysis of 7381 patients, the left atrium diameter was 38 mm in HCM patients with sinus rhythm compared to 45 mm in patients with AF (9). In another study of 480 patients, a LA diameter > 45 mm was significantly associated with higher risk of AF and is a part of guidelines (7).

The left atrial volume index (LAVI) provides more information about left atrial remodeling and is a better predictor of AF in HCM patient than LA diameter alone. In a study of 141 HCM patients, LAVI > 34 ml/m 2 identified patients at a risk of developing paroxysmal AF with sensitivity and specificity of 80% and 73% respectively (21).

Age is also a well-known predictor of AF in general population and in HCM patients. The age is a risks factor in development of AF and threshold ranging from > 40 to > 50 years are independently predictive index of AF in HCM patients (7, 22). Finally, NYHA class III/IV, moderate-several mitral regurgitation and LV ejection fraction < 50% which have associated with higher risk of AF in multiple studied (23, 24). The septal hypertrophies on ECHO and Cardiac magnetic resonance imaging (CMR) are also associated with higher risk of AF (25). The left ventricular outflow tract (LVOT) obstruction in HCM is associated with worse outcome but the evidence to predict AF is inconsistent.

Abnormal atrial activation on electrocardiographic basis has shown to predict the risk of AF. A study of 110 patients observed that HCM patients with signal average P-wave > 140 ms are at higher risk of developing AF. It is more sensitive when combined with dilated LA > 40 mm (26). Another study of 80 patients reported that P-wave duration > 134.5 ms separated the patients with AF from control with a sensitivity of 92 % and specificity of 89%. They also reported that P-wave dispersion value > 52.5 ms separated AF patients from control with a sensitivity of 96% and specificity of 91% (27).

5. Clinical Impacts of Atrial Fibrillation

The development of atrial fibrillation in HCM has a significant impact on quality of life and often associated with functional declines. AF is associated with higher rates of symptomatic heart failure, thromboembolism and mortality (29).

Symptoms of progressive heart failure were the major source of morbidity in hypertrophic cardiomyopathy. During AF, the loss of coordinated atrial contraction and rapid ventricular response lead to variable ventricular filling. This

Table 3: predictors of atrial fibrillation in patients with hypertrophic cardiomyopathy

Predictors	cutoff	References
Left atrial size:	> 45mm	(7, 9)
Left atrial volume index:	≥ 34 ml/m^2	(21)
Left atrial emptying fraction:	< 38 %	(28)
Septal hypertrophy		
P-wave duration:	≥ 140 ms	(26)
P-wave dispersion:	≥ 52.2 ms	(27)

Compounded with reduced LV compliance in hypertrophied ventricle can causes a wide range of hemodynamic consequences (10, 13). HCM patients with LVOT obstruction can develop hypotension, presyncope or syncope due to decreased cardiac output. HCM patients with AF have a greater rate of progression to end stage heart failure. Patients with paroxysmal AF have poor exercise tolerance despite being in normal rhythm at the time of testing (30).

Atrial fibrillation is an independent predictor of mortality in HCM patients and is associated with four-fold increase of death compared to sinus rhythm. Most cardiovascular deaths in AF groups are related to thromboembolism and worsening heart failure. There are few cases of sudden cardiac death due to deterioration of AF caused ventricular tachycardia, especially in the presence of pre-excitation. In a study of 480 HCM patients, 107 developed AF during mean follow up 9.1 years. The presence of AF was associated with significantly higher risk of mortality in these patients. The patients who developed AF at a younger age > 50 years have a highest risk of thromboembolism and carried worse prognosis (7).

Multiple studied shown that AF increased the risk of systemic thromboembolism in HCM patients. In large meta-analysis of 7381 patients the incidence of systemic thromboembolism was 3.8 % per years and overall prevalence was 27.1 % (9). In another study of 480 patients, the ischemic stroke was eight times more frequent in AF grouped compared to HCM patients without AF (7). Thromembolism risk in AF is unrelated to the type of AF and the number of paroxysms and cannot predict accurately by using clinical prediction score like CHA2DS2-VASc (31).

Left atrial enlargement (> 44 mm), several diastolic dysfunction and higher filling pressure have a bad prognosis of atrial fibrillation in hypertrophic cardiomyopathy (32).

6. Management of Atrial fibrillation

The lifestyle modification like healthy eating, weight reduction along with treatment of underlying comorbidities like diabetes, hypertension and sleep apnea should be undertaken to prevent atrial fibrillation.

6.1. Pharmacological treatment

Long term complication of concern determining management strategy for AF includes stroke, tachycardia-induced cardiomyopathy and worsening heart failure. The management of AF is focused on two principles-control of rate and rhythm and the prevention of complication such as thromboembolism with anticoagulant therapy were as shown in **table 4**. The rate and rhythm control strategies for control AF will lower the *rate* of cardiovascular death, admission to heart failure, thromboembolic event, several bleeding, pacemaker implantation and several side effects of antiarrhythmic drugs (33, 34). The Rate control strategies may also need antiarrhythmic drugs to improve the quality of life and prolong asymptomatic phase.

Acute management

In a new onset AF, rate control is often desired to provide symptomatic relief to the patients. The rate control is achieved by initiating oral beta blockers, or non-hydropyridine calcium channel blockers (CCB). The intravenous preparation is considered to give patients with symptoms of ischemia or heart failure or significant discomfort. Care should be taken to avoid these agents' causes' pre-excitation or cardiogenic shocks (3, 35).

In some patients immediately convers to sinus rhythm may be necessary and includes hemodynamic instability, actively progressing ischemic seen on ECG and inadequate response to intravenous beta blockers and CCBs (3, 35). Urgent cardioversion should be carried out when required, irrespective of anticoagulation status and although absence of anticoagulation is associated with risk of thromboembolism. If

available transesophageal echocardiogram, can be performed to rule out thrombus in the left atrium before cardioversion. Pharmacologic cardioversion can be considered, Amiodarone, preferred agent with added benefit of delayed rate control (8-12 hour later) when used intravenous. Class IC antiarrhythmic like flecainide and propafenone, though more effective to cardioversion are associated with pro- arrhythmic effect in structural heart disease and should be avoided (36).

Vernakalant as an atrial selective antiarrhythmic and is recommend by 2014 ESC Guidelines for rapid and effective conversion of AF. Ibutilide as an effective antiarrhythmic is recommended in pre-excitation.

Table 4: Summary of management of AF in Hypertrophic cardiomyopathy patients (35)

Issue	Recommendation	Comments
Rate control:	BBs and CCBs	Caution in patient with LVSD and cardiogenic shock.
Rhythm control:	Amiodarone/Disopyramide.	Sotalol is preferred due to long term Side effect.
Catheter ablation:	Refractory symptomatic AF.	Useful in young patients with normal LA size.
Anticoagulation:	Prevent Thromembolism (INR 2-3)	Direct oral anticoagulant

BBs= beta Blockers. CCBs= Calcium channel blockers. LVSD=Left ventricular systolic dysfunction.
LA= left atrium. AF= atrial fibrillation.

Chronic rate control

Despite a widespread use for rhythm control method in HCM patients with AF, excepting asymptomatic patients and those who cannot tolerate antiarrhythmic drugs due to adverse effect. This group should be considered for rate control, given lack of clear benefit from rhythm control. The preferred medications are oral non-hydropyridine calcium channel blockers (verapamil and Diltiazem) or beta blockers (metoprolol, propranolol, atenolol, nadolol), in individual or combination. Calcium channel blockers due to their negative inotropic action should be avoided in patients with LV systolic failure (3, 35).

In critically patients, short term intravenous Amiodarone could be used for rate control. Dronedarone is used to control rate in permanent AF when associated with worse outcomes (37). Digoxin can be considered to use alone or in combination with beta blockers or CCBs in long term management of permanent AF of patients presenting with symptom of NYHA class II-IV, provided there is no significant LVOT obstruction (38).

HCM patients who have failed rhythm control and for whom ablative procedures are contraindicated can be considered to AV nodal ablation with subsequent insertion of a dual chamber pacemaker, if rate control method is unsuccessful, assuming LVEF > 50%. In case with LVEF < 50%, AV nodal ablation can be followed by either HIS bundle pacemaker or cardiac resynchronization therapy pacemaker implantation (38, 39).

Chronic rhythm control

Once the sinus rhythm is achieved, the goal of starting use antiarrhythmic drug is to reduce the number and duration of AF recurrences. In short term, arrhythmia free phase allows patients to live a life of higher quality while in long term, natural progression from paroxysmal to persistent/permanent AF is been prevented. Choice of antiarrhythmic drug in each patient is guided by duration of pharmacological treatment planned, patients characters like age, sex, pre-existing comorbidities and side effect profile of the drug.

Sotalol is the most prescribed antiarrhythmic in young HCM patients with AF. Sotalol is ineffective in cardioversion; long term used is

associated with lower rate of recurrence of AF and improved the exercise tolerance (40). Patients should be followed up regularly to monitor serum potassium, magnesium, electrocardiogram changes and renal function (40). Dofetilide is other Ikr inhibitors that can be used for rhythm control in patients with AF. The rate maintenance of sinus rhythm with Dofetilide at 1 year was 58 % compared to 25% in the placebo group (41).

If a short duration of treatment is expected, Amiodarone can be considered initially. Multiple RCT have demonstrated the superiority of Amiodarone over Sotalol followed up for 1 year (42, 43). The long-term use of Amiodarone is limited due to Extracardiac side effect and the increased mortality (43). Short term use with Amiodarone can also be practiced only in a limited manner. A randomized trial demonstrated the episodic short-term use of Amiodarone results in higher recurrences of AF which with higher than expected morbidity and overall significantly higher rates of all causes mortality and cardiovascular hospitalizations (44).

A close relative of Amiodarone and Dronedarone have a more tolerable side effect profile, enhanced exercise tolerance and reduced mortality in paroxysmal and persistent atrial fibrillation. Dronedarone is used in permanent AF is associated with increased combined end point of MI, stroke, systemic embolism and cardiovascular death (37). Disopyramide supplemented with AV node blocking drug like beta blockers or CCBs, is used to treat LVOT obstruction in HCM.

6.2. Non-pharmacologic rhythm control

Percutaneous catheter ablation is an effective treatment for rhythm control in patients with drug-refractory symptomatic AF. Several studies have analyzed the role of catheter ablation in HCM patients for drug refractory AF (45, 46). Pulmonary vein isolation was reported to be a safe and effective therapy for drug refractory AF, with good short-term result (45). In a study of 61 HCM patients, catheter ablation was successful with no recurrence of AF in 67% patients over 29 months follow up. The major's predictors of AF recurrence after catheter ablation was the LA size, NYHA class III/IV, AF duration and LV systolic dysfunctions. The incidences of serious peri procedure complications was 5.1% and there was no death reported (47).

In addition, there are some data suggesting the role of surgical ablation for AF. In a study of 68 HCM patients who underwent surgical ablation during myectomy, 51% had freedom from AF after a single procedure at 35-month mean follow-up (48). However, this procedure is associated with high rate of major complications (18%)

7. Thromembolism prophylaxis

Hypertrophic cardiomyopathy patients with AF are having sustained risk for thromboembolism. Major's guidelines strongly recommended long term anticoagulation for thromboembolism prevention in HCM patients with AF (3, 35). Anticoagulation with warfarin is known to be effective for stroke prevention compared to antiplatelet therapy in HCM patients (49, 50). In a study of 4821 patients, warfarin was associated with 54.8% stroke risk reduction compared to no therapy (31). In patients with warfarin intolerability, difficult to maintain INR in therapeutic range, an oral direct thrombin inhibitor (Dabigatran) or factor Xa inhibitors (rivaroxaban /anixaban) is recommended. The both warfarin therapy (goal INR2 to 3) and direct oral anticoagulants therapy is to be effective strategies for stroke prevention in HCM patients (35). In a small study of 52 HCM patients with AF, the use of Amiodarone was associated with fewer embolic episodes (10). No other antiarrhythmic was shown to reduce the risk of thromboembolism.

CHA2DS2-VASc score is commonly used

for stroke risk stratification in AF; however, it is not validated and does not effectively predict stroke risk in HCM patients (31). Therefore, current guidelines recommended that all HCM patients with even a single brief episode of AF should be treated with long term anticoagulation (35). In patients who cannot be prescribed anticoagulation due to a high risk of bleeding, left atrial appendage occlusion procedure can be considered. Hypertrophic cardiomyopathy patients presenting with stroke symptom should be carefully monitored for AF as 7.4% of these have new onset AF at the time of event and 14.7% developed AF during evaluation after stroke (51).

Conclusion

Atrial fibrillation is the most common arrhythmia in HCM patients and is very poor tolerated. It is related to several processes including genetic factors, left atrial structural and electrical remodeling. AF in these patients is associated with worsening heart failure, function decline, increased risk of Thromembolism, and increase mortality. We recommended an early and aggressive rhythm control strategy with long term anticoagulation, especially in younger HCM patients to prevent morbidity and mortality.

Abbreviations

HCM: Hypertrophic cardiomyopathy.
AF: Atrial Fibrillation.
LA: Left atrium.
LVOT: Left ventricular outflow tract
HF: Heart failure.
NYHA: New York heart associations.
LVEF: Left ventricular ejection fraction.
BBs: Beta blockers.
CRT: Cardiac resynchronization therapy.

Declarations

1) Consent to publication

We declare that all authors agreed to publish the manuscript at this journal based on the signed Copyright Transfer Agreement and followed publication ethics.

2) Ethical approval and consent to participants

Not applicable.

3) *Disclosure of conflict of interests*

We declare that no conflict of interest exists.

4) Funding

None

5) Availability of data and material

We declare that the data supporting the results reports in the article are available in the published article.

6) Authors' Contributions

Authors contributed to this paper with the design (LNG), literature search (LNG), drafting (LNG), revision (LNG and SY), editing (LNG and SY) and final approval (LNG).

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8) Authors' biography

None

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