Treatment of atrial fibrillation in hypertrophic cardiomyopathy


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Introduction

Hypertrophic cardiomyopathy (HCM) is transmitted by an autosomal dominant pattern of inheritance and has a prevalence, estimated to be 1 in 500 in the general population (1). Patients with HCM are prone to a variety of arrhythmias. Atrial fibrillation (AF), which is present in approximately 5 percent of patients at the time of diagnosis, is the most common potentially serious atrial arrhythmia (2). The annual incidence of AF in this patient population is 2 percent per year (3), almost five times higher than the general population. The importance of atrial systole is increased in HCM, and particularly those with diastolic dysfunction are intolerant of atrial fibrillation with rapid ventricular rates. Loss of atrial systole, rapid heart rate, irregular ventricular contraction, and reduction in ventricular filling causing a greater degree of outflow obstruction, all may contribute to the hemodynamic deterioration seen during AF.

Management Principles

In AF, therapeutic goals should include rate control, stroke prevention, and quality of life improvement. Therapy goals can also include rhythm control.

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1. Control of heart rate, if tachycardic (Rate control)

During AF, inappropriately rapid heart rate can cause hemodynamic deterioration, which can be manifested as fatigue, lightheadedness, syncope, severe dyspnea and chest pain. These symptoms may result in severe functional limitation in the affected patient. In addition, a persistently elevated heart rate during AF can lead to tachycardia-induced cardiomyopathy especially in patients who are unaware of the arrhythmia (4).

**Atrioventricular (AV) nodal blockers**

In most instances, rate control is achieved by means of AV nodal blockers (beta-receptor and calcium channel antagonists). Some patients may require permanent pacing due to development of symptomatic bradycardia.

**AV junctional ablation/permanent pacemaker ("Ablate + Pace")**

In AF patients with symptoms secondary to rapid ventricular rate that cannot be adequately controlled with appropriate medical therapy, AV nodal ablation and permanent pacemaker implantation can be considered. This treatment modality is especially useful when ventricular systolic function is compromised by the excessive ventricular rate. Advantages of this treatment modality are as follow:

**Elimination of tachycardia**

Regularization of rhythm by eliminating ventricular cycles longer than the pacing cycle

In Ablate and Pace Trial (APT) (5), radiofrequency catheter ablation of the AV conduction system and permanent pacemaker implantation were associated with significant improvement of overall quality of life in patients with AF who remained highly symptomatic despite standard medical therapy.

Limitations of these treatments include lifelong dependency on the pacemaker, permanent need for anticoagulation therapy, ventricular dyssynchrony, and atrioventricular dyssynchrony. The latter will be a concern in patients who are most dependent on AV synchrony for maintenance of cardiac output. Such HCM patients might experience persistent symptoms after ablate + pace treatment.

2. Reduction of thromboembolic complications (stroke prevention)

In non-HCM patients, the annual rate for ischemic stroke was 3.2% and 3.3% in patients with recurrent and permanent AF respectively (6). Independent risk factors for ischemic stroke in nonvalvular AF include increasing age, diabetes mellitus, hypertension, heart failure, previous thromboembolic event, and moderate to severe left ventricular (LV) dysfunction on echocardiogram (7). Atrial fibrillation is frequently seen in patients with HCM and the risk of stroke is significantly increased. In a series of 480 patients, the incidence of stroke had an eight-fold increase in HCM patients with paroxysmal or persistent AF (8). This has led to recommendation that, warfarin should be used in all patients with AF and HCM, unless a contraindication exists.

3. Control of symptoms, if present (quality of life)

Atrial fibrillation patients may experience palpitation, dizziness, fatigue, dyspnea, diaphoresis, angina, confusion, and syncope. In a series of 69 patients with paroxysmal AF, 68% of the patients considered the dysrhythmia disruptive of their lives (9). The likelihood of developing symptoms is related to the ventricular rate and underlying heart disease. Most patients whose rates are well-controlled have no or only mild symptoms. Often times, worsening heart failure or angina secondary to tachycardia may aggravate the symptoms. Therefore rate control and treatment of the underlying heart condition will significantly improve the quality of life in AF patients.

4. Restoration and maintenance of normal sinus rhythm (rhythm control)

The mechanistic model that explains the development of AF includes two processes:

- Focal triggers in which one or multiple rapidly depolarizing foci exist due to local reentry or triggered automaticity and multiple wavelets causing reentry involving many simultaneous circuits.

Prior to the publication of the outcomes of Atrial Fibrillation Follow-up Investigation of Rhythm Management (10) study which will be discussed below, most physicians preferred rhythm control over rate control for patients presenting with the first few episodes of AF. There had always been a hypothetical argument for importance of rhythm control. Reestablishing and maintenance of normal sinus rhythm (NSR) had been presumed to maintain hemodynamics, prevent heart failure, and diminish symptoms. It was also believed that restoration of NSR would avoid precipitation of fatal ventricular tachyarrhythmias, limit stroke risk by reducing the frequency of embolization, and decrease the overall mortality rate. Cardioversion, either electrical or pharmacological is a frequent cause for admission. In the United States AF accounted for greater than 2 million hospital admissions between 1996 and 2001 of which 10% required direct-current electrical cardioversion (11). Transesophageal echocardiogram may be required as a substitute for 3 weeks of anticoagulation prior to cardioversion, in order to exclude left atrial appendage thrombus if AF is greater than 48 hours in duration and/or if there is evidence of mitral valve disease, severe left ventricular dysfunction, or previous embolism (12).

a. Antiarrhythmic drug therapy

The latest algorithm for antiarrhythmic drug therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent AF was recommended in 2001 by AHA/ACC/ESC guidelines (7). These guidelines recommend amiodarone as the only antiarrhythmic drug for treatment of AF in patients with left ventricular hypertrophy (LVH) (LVH greater than or equal to 1.4 cm). In contrast flecainide, propafenone or sotalol are the first line of treatment in AF patients with no or minimal history of heart disease. Moreover, the guidelines recommend that flecainide and propafenone are the drugs of choice in AF patients with hypertension in whom LVH is less than 1.4 cm. In addition, sotalol is used before amiodarone in AF patients with known coronary artery disease (CAD). No specific antiarrhythmic medication has been recommended in the guidelines for HCM in particular.

It has been shown that cardiac hypertrophy is associated with heightened risk of proarrhythmic effects of antiarrhythmic drugs, especially class III agents. In a study performed on dogs (13), dofetilide resulted in significantly more prolongation of ventricular repolarization of the hypertrophied heart. Repolarization prolongation was greater at endomyocardial and midmyocardial regions compared with epicardial regions resulting in increased transmural dispersion of repolarization, which is a major substrate for development of functional conduction block and reentrant ventricular tachyarrhythmias.
Disopyramide is a good alternative in patients with a contra-indication or non-response to amiodarone (7). Disopyramide has additional value in reducing outflow tract gradient in the majority of patients (14).

**Rhythm control versus rate control**

Expectations that reestablishing and maintaining sinus rhythm in patients with AF might improve survival were disproved in the AFFIRM study (15). This study was a randomized multi-center comparison of treatment strategies for AF. Patients were randomized to either (1) a rhythm-control strategy group in which antiarrhythmic drug therapy selected by the treating physician was used to achieve and attempt to maintain sinus rhythm; or (2) a rate-control strategy, in which atrioventricular nodal blocking agents were used to attempt to control the heart rate. It was found that, drug-based management of AF with a rhythm control strategy conferred no advantage over a rate-control strategy in cardiac or vascular mortality. At the end of the study, fatal cardiac outcomes were the same in both arms of AFFIRM.

As a matter of fact, there was a trend toward increased all-cause mortality in the rhythm-control group (Fig.1). In the final report of AFFIRM study, cause-specific mortality rates were described, which showed differences only in noncardiovascular death rates (Fig. 2) with a 1.5 fold increase in the rhythm-control arm. The specific causes that were more frequently experienced were cancer and pulmonary related. The reason for this increase is uncertain. Some possible explanations are as follow:

Noncardiovascular death may be hastened by adverse effects of antiarrhythmic drugs in this cohort’s age group (>65 years).

Complications of antiarrhythmic drug therapy may be more lethal in patients with serious conditions such as cancer or pulmonary disease.

Lack of the beneficial antineoplastic effects of warfarin in rhythm-control patients who were less often treated with warfarin.

Earlier recognition and treatment of cancer as a consequen-ce of bleeding from a pathologic site caused by warfarin in the rate-control group leading to earlier recognition of potentially fatal illnesses.

The secondary endpoint of AFFIRM was to compare the mortality and morbidity in the two arms of the study. Morbidity was considered a deleterious effect secondary to AF such as disabling stroke and anoxic encephalopathy or a complication of treatment such as major bleeding. The morbidity curves began to diverge at 2 years and gradually separated during the reminder of the study. After adjustment for other significant covariates, the difference was not statistically significant (p=0.28) (Fig. 3).

**b. Mapping and ablating AF**

The recognition that AF often times arises from the pulmonary veins (PVs) has led to innovation of ablation techniques that target this zone to electrically isolate the PV from the LA. Usually a double transseptal puncture is made through the fossa ovalis which is used to introduce an ablation catheter and a circumferential mapping catheter. Mapping is performed by placing the catheter close to the PV ostium. The LA-PV connections are targeted and eliminated by radiofrequency energy. The goal is to completely isolate each and every PV and therefore ablation is

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**Figure 1. Cumulative cardiac and non cardiac mortality in rhythm-control and rate-control groups**

(data from AFFIRM study, reference 15)

**Figure 2. Cumulative noncardiovascular mortality in the rhythm-control and rate-control groups**

(data from AFFIRM study, reference 15)

**Figure 3. Cumulative morbidity and mortality in the rhythm-control and rate-control groups**

(data from AFFIRM study, reference 15)
performed until there is complete and abrupt loss of PV potentials recorded by the mapping catheter. This procedure is technically feasible in virtually all patients.

In a series of 170 AF patients (16) who went through an intracardiac ultrasound (ICUS) and local electrocardiographic-guided LA-PV disconnection, complete freedom from recurrence was achieved in 81% and 79% of patients with persistent and paroxysmal AF, respectively. In addition, significant reduction in symptoms and burden of AF was achieved in 92% and 93% of patients with paroxysmal and persistent AF, respectively.

In a series of 100 patients (17) it was shown that hypertension and hypertensive heart disease in patients with and without AF are associated with PV dilation. In addition, a previous report by the same investigators demonstrated that ostial pulmonary vein diameter is increased in patients with AF (18). These findings support the theory that the cascade of events leading to diastolic dysfunction might predispose a person to AF by stretching the PVs and inducing arrhythmia however, the association is yet to be clarified. This mechanism is likely relevant to AF in HCM as well.

**Surgical treatment**

Some HCM patients undergo surgical septal myectomy to correct outflow obstruction. In addition, a surgical procedure known as the MAZE operation may be employed to eliminate AF. Lesions are made to disconnect arrhythmogenic foci in the PVs from the atria or isolate atrial regions (7).

In a series that looked at 1337 patients with HCM over a follow-up period of 6 ± 6 years (19), among 228 patients who had obstruction but did not undergo operation 25% had AF, whereas only 20% of the 289 patients who underwent myectomy had AF at the end of the follow up period (p < 0.05). These observations suggest a beneficial effect of myectomy in reducing the incidence of AF in HCM patients; however, this comparison is limited by potential bias in referral for surgery and was not randomized.

In another series of 110 patients (20), 5 out of 10 patients (50%) with recurrent AF before the surgery, developed persistent postoperative AF. Additionally in 31 patients, the onset of persistent AF was observed after a follow up period of 7.5 ± 5 years after operation. This incidence is slightly higher than the annual incidence of 2% per year among HCM patients previously described in the literature (3).

Further investigation is needed to determine the benefit of concomitant MAZE and myectomy in HCM patients. It is likely that a subset of HCM patients with AF might benefit from surgical correction of arrhythmia simultaneous with correction of the mechanical obstruction (20).

**Linking AF mechanism to therapy**

As mentioned earlier, the mechanistic model that explains the development of AF includes 2 concepts: focal triggers and multiple wavelets. Different AF treatment modalities will target one or both of these processes.

Pulmonary vein isolation will eliminate the rapidly depolarizing trigger foci. Left atrial modification by surgery will block the propagation of the multiple wavelets and antiarrhythmic drugs (AADs) may affect both of these processes.

**HCM-AF treatment algorithm**

Anticoagulation is the cornerstone of AF treatment. Additional AF treatment in HCM patients depends on the initial decision regarding need for surgical intervention, whether or not AF is permanent, and the severity of symptoms in patients with non-permanent AF. If surgery is planned, correction of the arrhythmia with MAZE procedure at the time of myectomy is an option to consider. The goal in HCM patients with permanent AF is to control the heart rate whether by chronic medications or through ablate + pace procedure as described earlier. Based on the severity of symptoms, HCM patients with non-permanent AF will be treated with either the rate control strategy (β-blockers/calcium channel blocker) or the rhythm control strategy (PV ablation, antiarrhythmic drugs, or radiofrequency ablation of the left atrium). This is because adverse effects of AADs and complications after invasive procedures are justifiable only in HCM patients who experience severe symptoms (Fig. 4).

**References**

5. Kay GN, Ellenbogen KA, Giudici M, Redfield MM, Jenkins LS, Manulli M, et al. The ablate and pace trial: A prospective study of cat-

![Figure 4. Hypertrophic Cardiomyopathy-Atrial Fibrillation treatment algorithm](image-url)


