Atrial fibrillation in hypertrophic cardiomyopathy: mechanisms, embolic risk and prognosis

Hipertrofik kardiyomiyopatide atriyal fibrilasyon: Mekanizmalar, emboli riski ve prognoz

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ABSTRACT

Hypertrophic cardiomyopathy (HCM) is associated with an increased incidence of supraventricular and ventricular arrhythmias. Atrial fibrillation (AF) is the most common arrhythmia in HCM with a prevalence of 20% and an annual incidence of two percent per year. Increased left atrial size and volume along with impaired left atrial function confer an increased likelihood of AF. The onset of AF is often accompanied by a decrease in functional status in conjunction with an increased risk of stroke and overall mortality. *(Anadolu Kardiyol Derg 2006; 6 Suppl 2: 40-3)*

Key words: Atrial fibrillation, hypertrophic cardiomyopathy, thromboembolism

ÖZET

Hipertrofik kardiyomiyopati supraventriküler ve ventriküler aritmilerin yüksek insidansı ile birlikte görülür. Prevalansı %20 ve yıllık insidansı %2 olup atriyal fibrilasyon (AF) HKM'de en çok rastlanan aritmidir. Sol atriyal fonksiyon bozukluğu ile beraber sol atriyum büyümesi ve hacminin artması AF olasılığını artırır. Atriyal fibrilasyonun başlangıcına sık olarak fonksiyonel durumda bozulma ile beraber inme ve mortalitede artma riski eşlik eder. *(Anadolu Kardiyol Derg 2006; 6 Özel Sayı 2: 40-3)*

Anahtar kelimeler: Hipertrofik kardiyomiyopati, atriyal fibrilasyon, tromboembolizm

Introduction

Hypertrophic cardiomyopathy (HCM) is clinically defined as the presence of myocardial hypertrophy in the absence of hemodynamic stress that would be responsible for the magnitude of hypertrophy (1). Genetically, HCM is a disease of the sarcomere that is an autosomal dominant disorder with a reported phenotypic prevalence of 1:500 based on population studies (2). Hypertrophic cardiomyopathy is invariably associated with left ventricular diastolic dysfunction due to impaired relaxation and reduced compliance, and it may be associated with dynamic left ventricular outflow tract gradient and mitral regurgitation (3). Common symptoms are dyspnea, angina and syncope. The clinical course of HCM may be complicated by sudden cardiac death, progressive heart failure with three percent reaching a "burnt-out" phase, and atrial fibrillation with embolic consequences.

Atrial fibrillation (AF) is the most common arrhythmia observed in hypertrophic cardiomyopathy (4). Roughly 20% of patients develop AF with an annual incidence of two percent. When compared with the general population, HCM patients have a greater likelihood of developing atrial fibrillation (5). In addition, atrial fibrillation may develop prior to the diagnosis of HCM and may be its initial manifestation. Development of atrial fibrillation in HCM is associated with an increased risk of systemic thromboembolism, congestive heart failure and death. Thus, HCM patients should be monitored for the development of AF and appropriate treatment should be initiated early in these patients.

Mechanisms important in the development of Atrial Fibrillation

Patients with HCM have a four to six fold greater risk of developing atrial fibrillation compared to the general population (6). The mechanisms that predispose HCM patients to develop AF are variable and include genetic factors, structural abnormalities, as well as prolonged and impaired atrial conduction due to atrial myopathy.

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Structural abnormalities consisting of hypertrophied, noncompliant chambers play an important role in AF pathogenesis as impaired diastolic function leads to left atrial pressure overload and enlargement with subsequent atrial myopathy. Another important structural factor involved in AF genesis is the degree of myocardial fibrosis. Surgical studies have shown that patients with HCM have thicker, more fibrotic tissue compared with normal subjects (7), and autopsy studies have demonstrated a higher degree of myocardial fibrosis in HCM patients with AF compared with ones without AF (8).

Genetic factors may also influence the propensity for AF. Roughly 60% of HCM cases are associated with mutations in sarcomeric protein genes (1), and at least ten genes have been associated with HCM; β-myosin heavy chain (β-MHC), cardiac troponin T and myosin-binding protein C are the three most predominant genes involved (9). The β-MHC missense mutation Arg663His has been associated with an increased risk of AF in HCM patients. In a study of 24 patients with Arg663His there was a high prevalence of atrial fibrillation; 47% developed AF over a seven-year follow-up period (10). Polymorphisms in the angiotensin receptor gene have also been implicated in the development of AF in HCM (11).

Predictors of Atrial Fibrillation

Predictors of AF in HCM include left atrial diameter, volume and function, age, and NYHA class (Table 1). Maximum left ventricular (LV) wall thickness and the degree of LV outflow tract obstruction have not been shown to correlate to the presence of AF (12). Left atrial (LA) size was the strongest predictor of AF, independent of age and NYHA functional class. In a study on 480 HCM patients a LA size greater than 45mm (on m-mode measurement) appeared to represent the threshold value associated with substantial risk of subsequent AF development (5), findings confirmed by other studies (13).

In addition, an increased LA volume or volume index (calculated as LA volume divided to body surface area) is also associated with AF. Maximum left atrial volume is recognized as one of the most sensitive and specific parameter for the occurrence of paroxysmal atrial fibrillation in patients with HCM. In a study of 141 consecutive patients with HCM, patients with paroxysmal atrial fibrillation (PAF) had greater LA volumes and LA volumes index compared with those without PAF (14). A maximum LA volume of 56 ml or more identified patients at risk for PAF with a sensitivity and specificity of 80 and 73%, respectively, and LA volume index more than 34 ml/ cm^2 demonstrated similar results.

Table 1. Left atrial predictors of atrial fibrillation in patients with hypertrophic cardiomyopathy*

LA size (M-mode)	> 43-45 mm
LA volume	> 56 mL
LA volume index	> 34 mL/cm^2
Filtered P wave duration	> 140 ms
P wave dispersion	> 52.5 ms

LA- left atrial
*data from references - 5, 13, 14, 16, 17

Left atrial function, as shown in a study of 150 consecutive HCM patients, serves as another reliable predictor for AF development independent of age, LA diameter or volume. Over a 5.2 year follow-up AF occurred in 20 patients (13%). Those with LA dysfunction (measured as decreased global LA fractional shortening) had a higher risk of AF (15).

Apart from echocardiographic parameters, filtered P wave duration measured using high resolution signal average electrocardiography has also been used to predict AF in HCM patients. Patients with P wave durations greater than 140ms are prone to develop AF (16). The predictive value is even greater (93% sensitivity) when combined with left atrial dilatation. In a study of 80 patients with HCM, 27 with AF were compared to 53 controls. In this study a LA diameter of 42mm or greater was predictive of AF with sensitivity of 96% and specificity of 91%, and a P wave dispersion of greater than 52.5 ms independently separated patients with AF from controls with a positive predictive accuracy of 84% (17). Maximum P wave duration was also longer in those with AF.

Impact of Atrial Fibrillation

The onset of AF can be associated with a multitude of symptoms including dyspnea, chest pain, heart failure and pulmonary edema, syncope and implantable cardioverter defibrillator discharges. Several studies evaluated the clinical impact of AF on HCM patients. In a 1970 study of 167 patients with HCM, the occurrence of atrial fibrillation was 10% (18). This percentage was similar to that described by Frank and Braunwald in 1967, where ten of 123 patients studied developed atrial fibrillation (19). The onset of atrial fibrillation was late in the course of the disease and was not associated with the severity of left ventricular outflow tract obstruction or the amount of mitral regurgitation present. All patients had significant deterioration upon the onset of atrial fibrillation. Over a follow-up period of five year after the onset of atrial fibrillation, three patients had died and four suffered cerebral embolic events. The authors concluded that the onset of atrial fibrillation was ac-

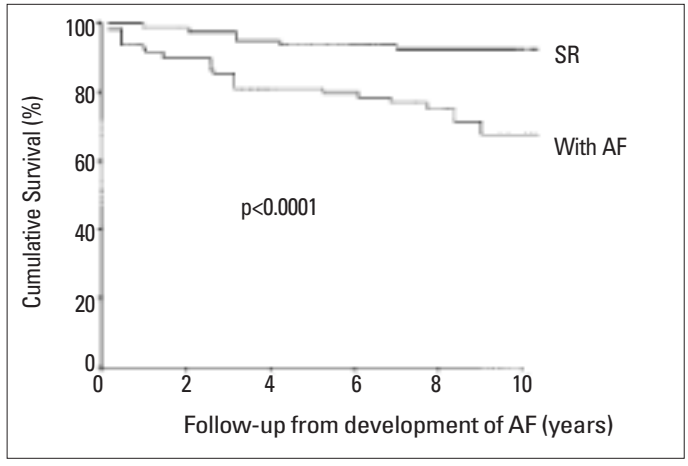

Figure 1. Impact of AF on overall HCM-related mortality over a 10-year period

AF- atrial fibrillation, HCM- hypertrophic cardiomyopathy, SR- sinus rhythm

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companied by a decrease in cardiac output and clinical deterioration due to the loss of atrial systolic filling of the left ventricle. In addition, controlling the ventricular rate was not sufficient to prevent clinical deterioration and persistent AF led to decompensated heart failure.

Robinson and colleagues subsequently studied the clinical outcome of 52 consecutive patients with HCM who developed paroxysmal atrial fibrillation over a 15-year period (20). Forty-nine patients (89%) had symptomatic deterioration associated with the onset of atrial fibrillation. Sinus rhythm could be restored in 29 (63%) of the patients who developed acute atrial fibrillation. In logistic regression analysis amiodarone therapy and shorter duration of arrhythmia were the most powerful predictors of sinus rhythm restoration; amiodarone therapy was also associated with fewer embolic events. In contrast to earlier studies (18), this report suggested that AF was not always associated with clinical deterioration, failure to maintain sinus rhythm did not uniformly lead to a decreased functional status, and mortality was not affected. However, the previous studies exclusively had patients with significant outflow tract gradient, only half of patients in this study had significant obstruction and there was less mitral regurgitation (35%). In addition, amiodarone was widely used, accounting for a decrease in atrial fibrillation and possibly ventricular tachyarrhythmias, leading to improved morbidity and mortality.

In the largest study of AF and HCM , 480 consecutive patients with HCM were followed for an average of 9.1 ± 6.4 years. Atrial fibrillation occurred in 107 patients (22%) with a two percent annual incidence rate (5). Patients with AF were found to be at increased risk of HCM-related death primarily due to excess heart failure mortality and stroke rather than sudden cardiac death (Fig. 1). Compared with patients in sinus rhythm, patients with AF had an odds ratio of 17.7 (95% CI, 4.1 to 75.9; p=0.0001) for cerebrovascular events. Ischemic stroke was eight times more frequent among AF patients (21% vs. 26%, p=0.0001). Stroke risk was independent of the number of paroxysms (1 compared with more than or equal to 2, 23% vs. 18%, p=0.6). Overall, patients with chronic atrial fibrillation had a significantly higher combined probability of HCM-related death, functional impairment, and stroke when compared to those with PAF (5). In patients who developed AF, stroke was less common in those patients treated with warfarin as compared to untreated patients or those treated with antiplatelet agents (5).

The annual HCM-related death was three percent in patients with AF versus one percent in control HCM patients. In multivariate analysis AF was associated with increased HCM-related mortality odds ratio of 3.7. During follow up, 84% of patients with AF experienced deterioration of functional status, and had clinical manifestations of reduced cardiac output including syncope, impaired consciousness, dyspnea and chest pain. Patients with AF had a greater rate of progression to NYHA III or IV heart failure over long-term follow-up compared with non-AF patients. Similar to older studies, rate control with beta-blockers, calcium channel blockers and/or amiodarone had no effect on AF-related morbidity and mortality. Patients who developed atrial fibrillation at a younger age (age<50) had an unfavorable prognosis compared to those who developed AF at an older age (> 50 years).

Similar findings were seen in recent smaller studies (13, 21). In 91 Japanese patients with HCM followed over 6.7 ± 4.8 years, AF was documented in 22 (24%) of patients. Those with AF were older, had larger left atrial dimensions (43 ± 6 vs. 36 ± 5 mm, p < 0.01), and had worse cardiovascular outcomes described as higher rates of embolic events, heart failure and death (13).

Conclusion

There is a body of evidence that development of atrial fibrillation in HCM patients is associated with increased cardiovascular complications and decreased survival. Even in the absence of significant outflow obstruction, AF is associated with a markedly increased risk for HCM-related death, ischemic strokes, and significant functional deterioration compared to normal sinus rhythm.

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