Current management of hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy is a familial cardiac disorder with heterogeneous expression and a diversity of morphological, functional and clinical features. Some individuals with hypertrophic cardiomyopathy may be asymptomatic while others are disabled by symptoms of angina and breathlessness. This article summarizes the genetics, pathophysiology and present management of this important condition.

Hypertrophic cardiomyopathy (HCM) is a familial Mendelian-linked autosomal dominant disorder of the heart characterized by unexplained myocardial hypertrophy and, at a cellular level, myocyte disarray (Maron, 1997). Since the initial description of asymmetrical septal hypertrophy by Teare (1958), the definition, diagnostic criteria, nomenclature, genetics and pathophysiological characteristics have evolved. The diagnosis is based on the characteristic appearance of myocardial hypertrophy on two-dimensional echocardiography (Maron et al, 1987a,b), which has been, and remains, the standard diagnostic test for characterizing the HCM phenotype. It should be stressed that left ventricular outflow tract (LVOT) obstruction is not a prerequisite for diagnosis, and is not present in the majority of patients (Klues et al, 1995).

PREVALENCE

The disease is prevalent in about 1 in 500 (0.2%) of the general population and is therefore common. HCM may be the most common genetically determined, transmitted cardiovascular disease (Maron, 1997; Shapiro and Zezulka, 1983).

GENETICS

Recent advances in molecular genetics have shown that HCM is caused by abnormalities in genes (currently nine) encoding myocardial sarcomeric contractile proteins (McKenna, 2000). There are, however, over 50 disease-causing mutations in these genes complicating the genetic picture (Spirito et al, 1997). Genetic studies have not only provided insights into the pathology of HCM, but may also provide molecular diagnosis and risk stratification in the future (Watkins, 2000).

PATHOPHYSIOLOGY

The distribution of hypertrophy is almost always asymmetrical and in 90% of cases affects the septum (Wigle et al, 1995) (*Figure 1*). There is significant heterogeneity in left ventricular (LV) wall thickness between individuals, ranging from normal (7–12 mm; McKenna et al, 1990) to mildly increased (13–15 mm), to massive hypertrophy of up to 60 mm (Maron et al, 1995). The myocyte architecture is disorganized with hypertrophied cardiac muscle cells in bizarre shapes and irregular orientation. Coronary arteries may have thickened walls with increased amounts of connective tissue (Maron, 1997). The symptomatology and clinical course are dictated by the extent of disease expression and a variable combination of abnormalities of cardiac function caused by the disordered myocardium that include:

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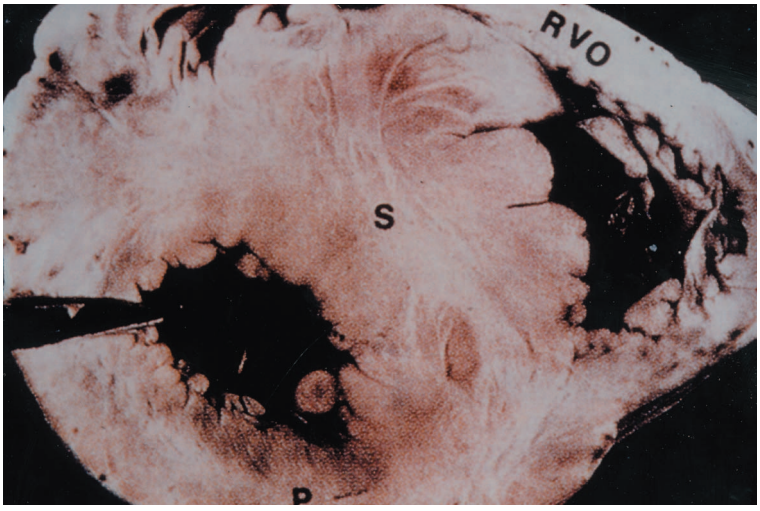

Figure 1. Cross-section of the heart showing the left and right ventricles in hypertrophic cardiomyopathy. The ventricular wall thickening is asymmetrical and confined primarily to the ventricular septum (S). The left ventricular cavity appears small. P=left ventricular posterior wall; RVO=right ventricular outflow tract.

- Arrhythmias and sudden death (Watkins, 2000)
- Increased chamber stiffness and impaired myocardial relaxation as a consequence of increased muscle mass and the small LV cavity (Wigle et al, 1995)
- LVOT obstruction (Maron, 1997)
- Abnormalities of small coronary arteries with luminal obstruction
- Impaired coronary flow reserve and myocardial ischaemia (Maron, 1997)
- Mitral regurgitation.

Primary mitral valve abnormalities may occur. Mitral regurgitation also occurs secondary to systolic anterior motion of the mitral valve.

A small proportion of patients with HCM may progress to 'endstage' HCM where LV dilatation and severe systolic dysfunction predominate.

SYMPTOMS

The majority of patients with HCM are asymptomatic and identified by family screening following a relative's diagnosis (Spirito et al, 1989). The most common symptoms are those caused by congestion from cardiac failure, and include dyspnoea, orthopnoea and lethargy. Angina, palpitations, syncope and presyncope all occur to varying degrees, but tragically the first manifestation of the disease may be sudden death. Although it is assumed that the mechanism of syncope (and sudden death) is a spontaneous ventricular arrhythmia, atrial fibrillation, bradycardia, myocardial ischaemia and peripheral vasodilatation during exercise have all been proposed as possible causes (Wigle et al, 1995).

MANAGEMENT

The most important and challenging aspect of the management of HCM is identification and treatment of patients at risk of sudden death. This may involve aggressive strategies (e.g. implantable defibrillators) in asymptomatic individuals.

Most symptomatic individuals can be managed pharmacologically, but some may require interventions such as surgical myectomy or non-surgical septal reduction.

The complex manifestations of the disease, the understandable anxieties of patients given a diagnosis of HCM, and the need for detailed family screening mean that treatment of patients with this condition should be conducted in, or under the direction of, specialist clinics working to established protocols.

RISK STRATIFICATION AND SUDDEN DEATH

Sudden death is the most important problem created by this disease, frequently occurring without warning symptoms. HCM is the most common cause of unexplained sudden death in otherwise healthy competitive athletes (Wigle et al, 1995). Although the overall annual mortality based on tertiary referral figures is in the order of 1% (Wigle et al, 1995), there are groups within the population of patients with HCM at much higher risk. Our ability to determine high-risk individuals is far from perfect but has improved as a consequence of the recognition of several risk factors for sudden death. These include:

- Patients who survive a cardiac arrest with documented ventricular fibrillation
- Non-sustained ventricular tachycardia (more than five episodes or a run of ten or more beats on Holter testing)
- Family history of sudden death
- A high-risk genetic mutation.

Identification of these individuals should lead to an aggressive management policy. Other variables that may be associated with an increased risk of sudden death, although with low positive predictive accuracy, are onset of disease in childhood, marked hypertrophy and exercise-induced hypotension (Spirito et al, 1997). Adults without these adverse profiles can be advised that their prognosis is good and that recreational or employment restrictions are not needed. When high risk is judged by these criteria the available treatment options are limited to long-term amiodarone or an implantable cardioverter-defibrillator (ICD).

Amiodarone

There are little data on the use of amiodarone in prophylaxis of sudden death in HCM. However, one non-randomized study did suggest that amiodarone, in a dose of up to 400 mg per day, did improve survival in patients with HCM and ventricular tachycardia (McKenna et al, 1985).

Implantable cardioverter-defibrillators

Implantation of the modern ICD with the pacing and defibrillation capabilities to abort lethal arrhythmias represents the most definitive option in sudden death prevention in HCM. It has been shown to be significantly superior to antiarrhythmic therapy in high-risk patients with ischaemic heart disease (AVID investigators, 1997). Retrospective studies in HCM suggest that the ICD prevents sudden death from ventricular tachyarrhythmias (Elliott et al, 1999). More recently, Maron et al (2000) presented the results of a large-scale retrospective study lending overwhelming support to the use of ICDs for primary and secondary prevention in high-risk patients.

SYMPTOMATIC TREATMENT

Pharmacological treatment

Beta-blockers: Negatively inotropic drugs reduce or eliminate obstruction in HCM, and may therefore improve symptoms and exercise tolerance in patients with symptoms owing to obstructive HCM (Sherrid et al, 1998). Beta-blockers are the mainstay of medical therapy and improve symptoms of chest pain and dyspnoea by decreasing heart rate, increasing the diastolic filling time, reducing the inotropic response, reducing myocardial oxygen consumption and decreasing the outflow gradient during exercise, when sympathetic tone is increased (Spirito et al, 1997).

Beta-blockers are particularly useful where angina supervenes and this may be guided by exercise testing (Spirito et al, 1997). They may also be useful in the control of the ventricular response to atrial fibrillation, especially if heart failure worsens. Sotalol (a beta-blocker with class 3 activity) may be helpful in preventing paroxysms of atrial fibrillation, although amiodarone is the most effective pharmacological agent to restore and maintain sinus rhythm in HCM. Despite the improvement in symptoms with beta blockade in randomized trials, there is little evidence that this treatment prevents sudden death (Spirito et al, 1997; Watkins, 2000).

Calcium antagonists: The most commonly used calcium antagonist is verapamil. Its negative inotropic and chronotropic effects lessen the outflow gradient, improve ventricular filling and improve myocardial ischaemia. However, calcium antagonists are vasodilating, and therefore have the potential for serious adverse side-effects, especially in those individuals with significant outflow tract obstruction. Most clinicians therefore favour the use of beta-blockers over calcium antagonists, to avoid excessive preload reduction in patients with an important outflow gradient, and reserve calcium antagonists for patients who have not responded to beta-blockers (Spirito et al, 1997). Coadministration of both types of drugs should be avoided.

Disopyramide: This class 1A antiarrhythmic may reduce the outflow tract gradient as it is negatively inotropic and a peripheral vasoconstrictor, and it has been used as the drug of choice for symptomatic obstructive HCM (Wigle et al, 1995). It has a number of unpleasant anticholinergic side-effects and should be instituted with a beta-blocker as it may increase the ventricular response to atrial fibrillation by shortening atrioventricular delay.

Atrial fibrillation: Patients with HCM may develop atrial fibrillation as a consequence of mitral regurgitation and an increase in left atrial size. This can result in cardiac failure, syncope and systemic emboli in both obstructive and non-obstructive HCM (Wigle et al, 1995). Beta-blockers and verapamil may slow the ventricular response to atrial fibrillation but amiodarone is the most effective agent to restore and maintain sinus rhythm (McKenna et al, 1984). Anticoagulation should be instituted early.

Non-pharmacological treatment

Surgical myotomy-myectomy: Patients with a severe outflow tract gradient (>50 mmHg) and symptoms refractory to medical therapy may be candidates for surgical myotomy-myectomy. Septal myotomy-myectomy, where a small portion of muscle is removed from the basal septum, is highly successful at relieving the obstruction and symptoms and has been used for over 40 years. In experienced centres operative mortality is low (1–2%) (Maron, 1997), although it may be increased in elderly patients and in those who need concurrent coronary bypass and/or mitral valve surgery (Spirito et al, 1997).

Despite its success in improving symptoms there is no evidence that surgery alters the risk of sudden death or prolongs survival.

Dual chamber pacing: In the early 1990s, a number of non-randomized studies suggested that both symptoms and LVOT obstruction could be diminished by dual chamber pacing (Nishimura and Danielson, 1993). More recently, randomized studies have demonstrated a strong placebo effect to be the predominant mechanism for symptom improvement, given that the decrease in outflow gradient was small (approximately 25%) and objective measurements of exercise tolerance did not alter (Maron et al, 1999). There is no evidence that pacing alters the clinical course of the disease or the risk of sudden death.

Non-surgical septal reduction: Sigwart (1995) introduced this percutaneous technique as an alternative to surgery. A reduction in septal mass is produced by creation of a localized septal myocardial infarction by the injection of absolute ethanol into the first septal branches of the left anterior descending coronary artery. The procedure is effective in reducing outflow tract obstruction and improving symptoms. To date, approximately 200 patients have undergone this procedure, with a mortality of 2% (Knight, 2000). The principal complication is

complete heart block, and up to 20% of patients may require a permanent pacemaker after the procedure. While an attractive strategy that avoids the need for open heart surgery, the procedure remains experimental and should be used only for carefully selected patients in specialist centres.

CONCLUSION

HCM is a common genetically determined cardiac disorder. The condition has been defined clinically and pathologically as a syndrome of unexplained myocardial hypertrophy associated with characteristic pathophysiological and pathological abnormalities. Disease expression is heterogeneous and many patients are asymptomatic. The most important clinical problem produced by the disease is the risk of sudden death and accurate risk stratification and aggressive treatment of high-risk individuals is essential to combat this problem.

Some patients with HCM are disabled by symptoms of angina and breathlessness. Usually these symptoms can be controlled pharmacologically but a small minority, with significant LVOT obstruction, may need surgical or interventional treatment. Future developments in genetic diagnosis may help identify those at highest risk and guide prognostic treatment. HM

Conflict of interest: none.

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KEY POINTS

- Hypertrophic cardiomyopathy is the most common genetically determined cardiovascular disease.
- It is caused by unexplained myocardial hypertrophy and, at a cellular level, cardiac myocyte disarray.
- The majority of patients achieve normal life expectancy or experience only mild symptoms without major intervention.
- A small proportion of patients are at risk of sudden death.
- The highest-risk patients can be identified and treated with amiodarone therapy and implantable cardioverter-defibrillators.