Cardiology

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Investigation and treatment of hypertrophic cardiomyopathy

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Classification of cardiomyopathies

Historically, cardiomyopathies have been classified in accordance with specific structural and functional myocardial abnormalities in the absence of coronary artery disease, hypertension, valvular disease and congenital heart defects. Hypertrophic cardiomyopathy (HCM) has been defined by the presence of myocardial hypertrophy in the absence of a haemodynamic stress or systemic disease sufficient to account for the degree of hypertrophy.[1] This nosology has served well but it is increasingly apparent that many patients with 'unexplained' heart muscle disease in fact have rare, but well described systemic diseases.

In this article, the term HCM will be used to describe myocardial hypertrophy in the absence of abnormal loading conditions (hypertension, valve disease) but will include left ventricular hypertrophy (LVH) associated with genetic syndromes and systemic diseases in which the heart is commonly affected. This approach mirrors that recommended by the European Working Group on Myocardial and Pericardial Diseases in a forthcoming position statement.

Key Points

- **Hypertrophic cardiomyopathy is a common genetically transmitted disease, defined clinically by the presence of left ventricular hypertrophy in the absence of loading conditions sufficient to cause the observed degree of hypertrophy**
- **The disease has a heterogeneous clinical course, with many patients having few cardiovascular symptoms and others profound exercise limitation and recurrent arrhythmia**
- **The overall annual rate of disease-related complications such as sudden death, end-stage heart failure and fatal stroke is approximately 1–2%, but risk in individual patients varies as a function of age, disease severity and the underlying cause of the hypertrophy**
- **Genetic counselling and clinical risk stratification are relevant for all patients.**
- **Subsets of patients require septal alcohol ablation, septal myectomy and implantable cardioverter defibrillators**

KEY WORDS: heart failure, hypertrophic cardiomyopathy, left ventricular outflow tract obstruction, sarcomeric proteins, sudden death

Aetiology

LVH in the absence of moderate to severe hypertension and valve disease occurs in about one in 500 adults.[1,2] The prevalence of unexplained LVH in children is unknown, but clinical studies report an annual incidence of 0.3–0.5 per 100,000.[3]

The spectrum of diseases that cause HCM varies with the age of presentation. In infants and young children, HCM is often caused by congenital syndromes, metabolic disorders and neuromuscular diseases (Table 1).[2,4] Familial disease is not uncommon, with various patterns of inheritance including autosomal dominant, recessive, X-linked and maternal. Up to 60% of adults with moderate to severe hypertrophy have autosomal dominantly inherited mutations in one of 10 genes that encode proteins of the cardiac sarcomere. Recent studies suggest that the frequency of sarcomere protein gene mutations is much less in unselected populations with milder hypertrophy.[2] In adults without sarcomeric protein gene mutations, metabolic diseases such as Anderson-Fabry disease, mitochondrial cytopathies and infiltrative disorders such as amyloidosis should be considered in the differential diagnosis.[4]

Investigation of hypertrophic cardiomyopathy

The investigation of patients with HCM has to address several management issues (Fig 1).

Initial diagnosis

HCM may be detected during the investigation of cardiovascular symptoms, but increasingly it is an incidental finding during a routine medical examination or during the evaluation of relatives of individuals already known to have the disease.

Electrocardiography

The first clue to the diagnosis is an ECG in most cases. There are no changes specific to the disease, but common abnormalities include right and left atrial enlargement, LVH, pathological Q-waves

(most commonly in the inferolateral leads) and giant negative T-waves in the mid-praecordial leads (characteristic of apical involvement).

Echocardiography

The diagnosis of HCM is usually confirmed by two-dimensional echocardiography (Figs 2–4). Any pattern of LVH is consistent with the diagnosis, but most patients have asymmetrical septal hypertrophy.[4,5] Approximately 25% of patients have dynamic left ventricular outflow tract obstruction (LVOTO) caused by contact between the anterior mitral valve leaflet and interventricular septum during systole. Many patients without outflow obstruction at rest develop a pressure gradient during physiological and pharmacological interventions that reduce left ventricular end-diastolic volume or augment left ventricular contractility. Mitral regurgitation occurs in almost all patients with obstructive HCM as a consequence of abnormal mitral leaflet coaptation. Conventional echocardiographic measures of systolic function are normal or increased in both obstructive and non-obstructive HCM. Myocardial thinning and ventricular cavity dilatation occur in some adult patients as the disease progresses ('burnt-out phase').

Other tests

Cardiac catheterisation is used to exclude coronary atherosclerosis in older patients with chest pain and to assist in the assessment of valve dysfunction and end-stage disease. Cardiac magnetic resonance (CMR) imaging may be useful in selected cases to assess right ventricular involvement or when areas such as the left ventricular apex and lateral wall are poorly imaged. CMR can also determine the extent of myocardial fibrosis.

Table 1. Causes of hypertrophic cardiomyopathy (HCM).

• Sarcomeric protein gene mutations	β-myosin heavy chain Cardiac myosin binding protein C Cardiac troponin I Troponin T Troponin C α-tropomyosin Essential myosin light chain Regulatory myosin light chain Cardiac actin α-myosin heavy chain Titin
• GSD	eg GSD II (Pompe's disease), GSD III (Forbes' disease), AMP kinase (WPW, HCM, conduction disease)
• Lysosomal storage diseases	eg Anderson-Fabry disease, Hurler syndrome
• Disorders of fatty acid metabolism	
• Carnitine deficiency	
• Phosphorylase B kinase deficiency	
• Mitochondrial cytopathies	eg MELAS, MERFF, LHON
• Syndromes	Noonan syndrome LEOPARD syndrome Friedreich ataxia Beckwith-Wiedermann syndrome Swyer's syndrome (pure gonadal dysgenesis)
• Other	Muscle LIM protein Phospholamban promoter Familial amyloid Infants of diabetic mothers Obesity Athletic training Amyloidosis (AL/pre-albumin)

AL = amyloid L; AMP = adenosine monophosphate; GSD = glycogen storage disease; LEOPARD = lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, genitalia abnormalities, growth retardation, deafness (syndrome); LHON = Leber hereditary optic neuropathy; MELAS = mitochondrial encephalomyopathy-lactic acidosis- and stroke-like symptoms (syndrome); MERFF = myoclonus epilepsy with ragged red fibres (syndrome); WPW = Wolff-Parkinson-White (syndrome).

Differential diagnosis

Some clinical features are clues to particular causes of HCM (Table 2). Their presence should trigger appropriate biochemical and genetic testing.

Family screening

All patients with HCM should be counselled on the implications of the diagnosis for their families. Careful pedigree analysis can reassure relatives who are not at risk of inheriting the disease. For those who are at risk, clinical screening with ECG and echocardiography may be appropriate.

- *Children and adolescents*: screening should be performed annually, particularly in adolescents when there may be rapid changes in heart size and morphology.
- *Relatives over the age of 20 years*: for those with completely normal ECGs and echocardiograms advice on continued screening should take into account the concerns and needs of individuals as well as the clinical phenotype in the family (ie the presence of late-onset disease).

It is now possible to offer relatively rapid genetic testing to individuals with unequivocal disease. If a disease causing a mutation is identified, relatives can be offered predictive testing – again, only after appropriate genetic counselling.

Identification of patients at risk of complications

Patients with HCM are prone to a number of complications including sudden cardiac death (SCD), atrial fibrillation (AF), thromoboembolism, infective endocarditis and progressive heart failure. The annual mortality rate is less than 2%,[1,4,6] but the risk of individual

complications varies with age, severity and the underlying cause. The most predictive marker of sudden death risk is a history of previous cardiac arrest. Other clinical features associated with an increased risk of SCD include non-sustained ventricular tachycardia during Holter monitoring, abnormal blood pressure response during exercise, severe LVH, unexplained syncope and severe LVOTO.[1,4,7]

Treatment

Symptomatic outflow tract obstruction

Beta-blockers, verapamil and disopyramide can all be effective in relieving symptoms in patients with exertional symptoms and moderate to severe outflow tract obstruction.[8] Verapamil should be used cautiously in patients with severe obstruction as it can precipitate haemodynamic compromise. Disopyramide is usually co-administered with beta-blockers to prevent accelerated atrioventricular (AV) conduction during supraventricular tachycardia or AF.

Septal myotomy-myectomy, in which a trough of muscle is removed from the interventricular septum, should be considered in patients with obstruction who cannot tolerate drugs or whose symptoms persist despite treatment. The operative mortality in expert centres is below 1%. Complete heart block occurs in less than 5% of patients.

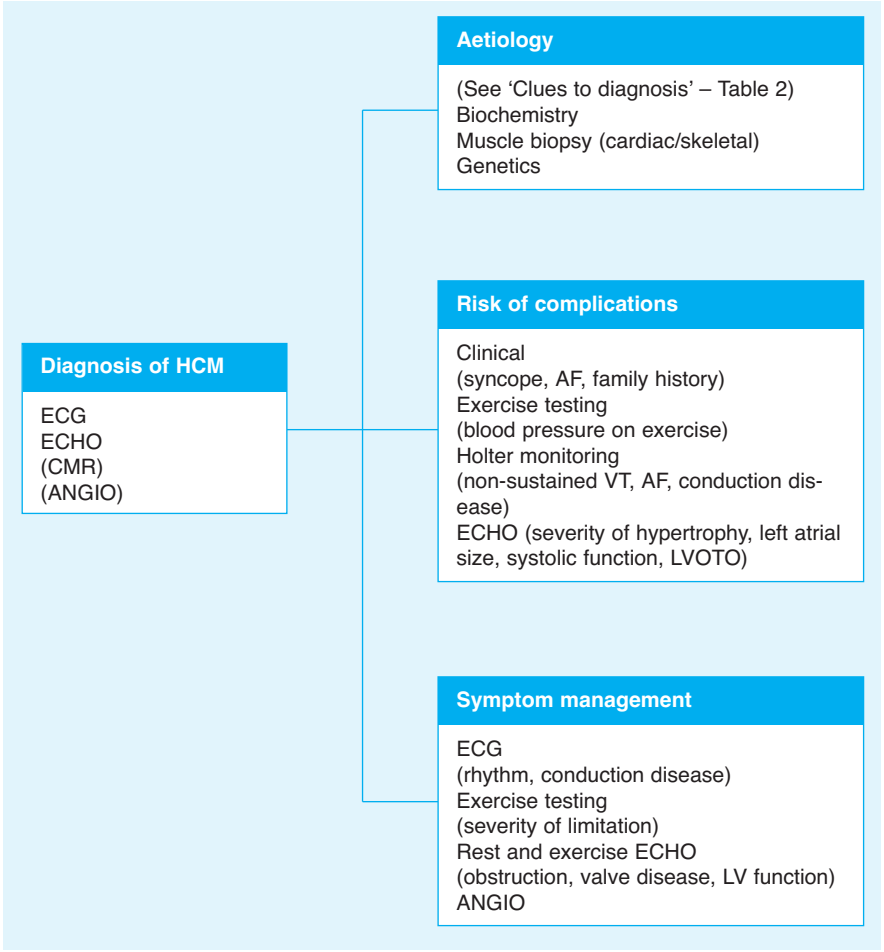

Fig 1. Summary of investigations necessary in patients with hypertrophic cardiomyopathy (HCM). The diagnosis of HCM is usually made with an standard 12-lead ECG and echocardiogram. In patients with poor echo images or equivocal findings, cardiac magnetic resonance (CMR) imaging, and less frequently angiography, may be required. Confirmation of the presence of left ventricular hypertrophy (LVH) should be followed by additional tests designed to determine the underlying cause of hypertrophy, to assess the risk of disease-related complications and to guide treatment of symptoms. AF = atrial fibrillation; ANGIO = angiography; ECHO = echocardiography; LVOTO = left ventricular outflow tract obstruction; VT = ventricular tachycardia.

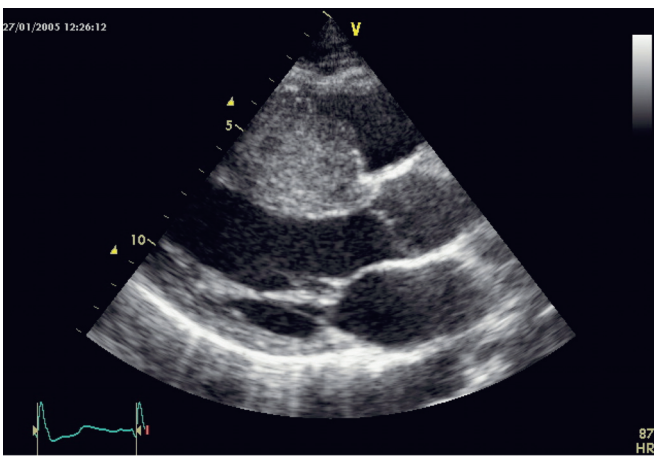

Fig 2. Two-dimensional echocardiogram (parasternal long axis view) showing disproportionate hypertrophy of the interventricular septum.

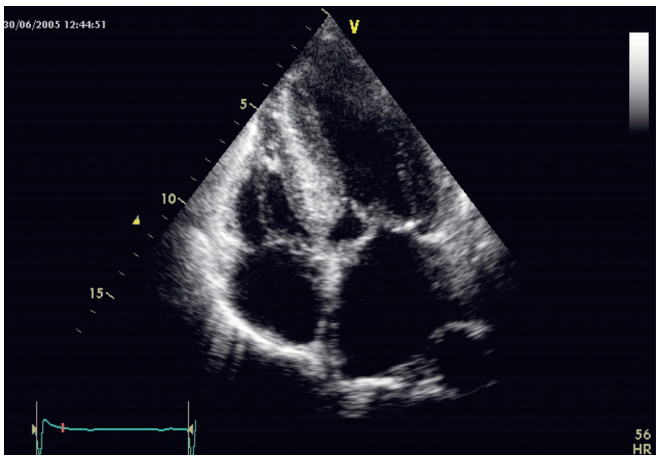

Fig 3. Subaortic obstruction caused by contact between the anterior mitral valve and septum in systole.

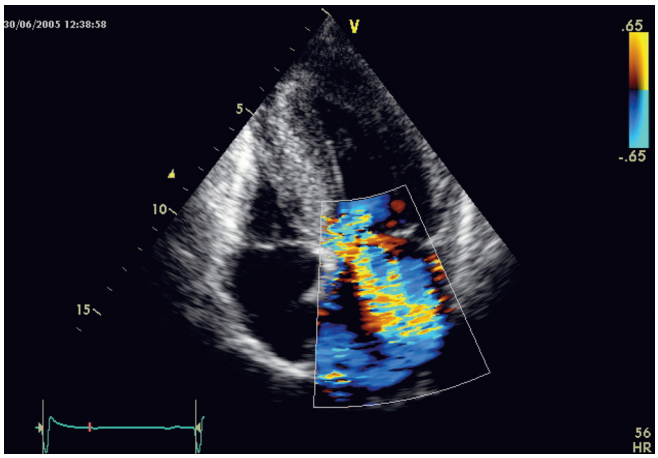

Fig 4. Mitral regurgitation caused by abnormal leaflet coaptation during systolic anterior motion of the anterior leaflet.

Percutaneous transcoronary septal myocardial ablation is an alternative in older patients: alcohol is injected into one or more septal perforator vessels to produce a localised area of myocardial necrosis within the basal interventricular septum. The procedure is guided by contrast echocardiography to reduce the risk of remote infarction. Published mortality rates are similar to surgery but the incidence of complete heart block is higher (5–30%). The effects of an intramyocardial scar on long-term arrhythmia risk and left ventricular function are unknown.

Several studies have suggested that dual chamber pacing using a short programmed AV delay improves symptoms in a minority (10–20%) of patients. It is generally considered in patients with an unacceptable operative risk or other pacing indications.

Table 2. Clues to the underlying cause of hypertrophic cardiomyopathy.

Diagnostic clue	Examples
Symptoms	Acroparaesthesiae, tinnitus, deafness (Anderson-Fabry) Skeletal muscle weakness (desminopathy, mitochondrial cytopathy)
Signs	Retinitis pigmentosa (mitochondrial, Danon disease) Postural hypotension (amyloid) Angiokeratoma (Anderson-Fabry) Lentigines (LEOPARD syndrome) Facial morphology (Noonan, Anderson-Fabry)
ECG	Pre-excitation/premature conduction disease (AMP kinase) Low voltage/infarct pattern (amyloid)
Echocardiography	Concentric/biventricular hypertrophy (infiltrative, metabolic disease) Valve thickening (Anderson-Fabry disease, amyloid)
Family history	X-linked inheritance (Anderson-Fabry, Danon disease) Diabetes, epilepsy and deafness (mitochondrial)
Biochemistry	Creatine kinase (GSD, mitochondrial) Lactate (mitochondrial) Renal dysfunction (Anderson-Fabry disease, mitochondrial) Paraproteinaemia (amyloid)
Exercise testing	Severe, premature acidosis (mitochondrial)

AMP = adenosine monophosphate; GSD= glycogen storage disease; LEOPARD = lentigines, ECG abnormalities, ocular hypetelorism, pulmonary stenosis, genitalia abnormalities, growth retardation, deafness (syndrome).

Non-obstructive hypertrophic cardiomyopathy

In patients without outflow obstruction, angina and dyspnoea may respond to beta-blockers or calcium channel antagonists. Nitrates and diuretics can be useful, but both should be used cautiously to avoid excessive reductions in preload. Cardiac transplantation should be considered in patients with refractory heart failure symptoms.

Atrial arrhythmias

AF in patients with HCM can cause sudden deterioration in symptoms and is associated with a high risk of thromboembolism. Restoration of sinus rhythm is usually ideal, but control of the ventricular rate with beta-blockers or calcium channel antagonists can be as effective. Digoxin is not recommended for rate control in HCM. Anticoagulation should be considered in all patients with persistent, permanent and frequent paroxysms of AF and in those with marked left atrial enlargement. Amiodarone and sotalol are effective in preventing AF and thromboembolism. The role of ablation is under investigation.

Prevention of sudden cardiac death

Prophylactic implantation of an implantable cardioverter defibrillator is advisable in patients with a history of sustained ventricular arrhythmia and should be considered in patients with multiple clinical risk factors. The treatment of patients with only one risk factor is guided by age and clinical context.

Other management issues

Although rare, most cases of infective endocarditis in patients with HCM occur in patients with left ventricular outflow tract gradients. Patients with outflow obstruction should be advised to take antibiotic prophylaxis.[9]

Complications during pregnancy are rare (1–2% of all pregnancies) but caution is advised when administering cardioactive drugs or conventional epidural

anaesthesia.[10] Young patients with HCM should not participate in competitive sports because 40% of HCM sudden deaths occur following moderate to severe exertion. Individuals over the age of 30 should be assessed on the basis of recognised or potential clinical risk factors, in accordance with published guidelines.[11,12]

Conflict of interest

Dr Elliott is a consultant for and/or has received honoraria from Medtronic Inc, Shire Human Genetics therapies and Genzyme Inc.

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