Postgrad Med J (1991) **67**, 713 - 718

Review Article

Problems in diagnosis and management of hypertrophic cardiomyopathy

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Diagnosis

i) Introduction

In the first systemic characterization of what is now known as hypertrophic cardiomyopathy, Teare reported gross asymmetric hypertrophy in 9 young adults who had died suddenly.[1] His report captured the essence of a disease in which cardiac hypertrophy, normally the heart's way of reducing wall tension during pressure overload, could occur inexplicably, within families as well as sporadically, and cause sudden death.

In the 1960s, the diagnosis was based on a midsystolic murmur and the demonstration of a subaortic gradient at cardiac catheterization; giving rise to names such as idiopathic hypertrophic subaortic stenosis (IHSS), muscular subaortic stenosis (MSS) and hypertrophic obstructive cardiomyopathy (HOCM).[2] With the advent of M-mode echocardiography in the 1970s came new diagnostic criteria. The most widely used of these was asymmetric hypertrophy of the interventricular septum, defined as a ratio of septal to posterior left ventricular wall thickness of at least 1.3. By the mid 1970s, asymmetric septal hypertrophy was considered by some to be the genetically determined, pathognomonic feature of the disease.[3] M-mode echocardiography imaged the upper anterior septum – usually the thickest part of the left ventricle, and the upper posterior wall – usually the thinnest, and thus reemphasized the asymmetric nature of hypertrophy in the condition. The two other major echocardiographic diagnostic criteria for hypertrophic cardiomyopathy were the *M*-mode echocardiographic features of a left ventricular outflow tract (LVOT) gradient, systolic anterior motion of the mitral valve (SAM) and premature systolic closure of the aortic valve (Figure 1). When cross-sectional echocardiography became available in the 1980s, with its ability to image the whole heart, it became clear that apart from asymmetric septal hypertrophy, which was seen in 50 to 60% of the patients, hypertrophy could be concentric (20 to 30%),[4] predominantly involve the distal left ventricle (10 to 15%), or affect single myocardial segments such as the middle or distal part of the posterior septum or lateral wall. Cross sectional echocardiography also showed that about a third of the patients with hypertrophic cardiomyopathy (HCM) had right ventricular hypertrophy (Figure 2), a feature which Teare had described in his original report.[1,5] The diagnostic criteria for hypertrophic cardiomyopathy have evolved over 3 decades as new techniques became available. The diagnosis now includes patients with unexplained left or right ventricular hypertrophy with or without intracavitary gradients.

ii) Presenting features

A history of syncope, especially in children, a systolic murmur detected during routine examination, or a family history of sudden death can lead to the diagnosis of hypertrophic cardiomyopathy. In the young, sudden death is all too often the first presentation while in adults diagnosis is most often following the incidental discovery of an abnormality on physical examination, electrocardiogram (ECG) or chest X-ray. Symptomatic presentation is usually chest pain, dyspnoea or syncope which may understandably be attributed to ischaemic heart disease, mitral, or aortic valve disease. The classical findings on physical examination of a rapid upstroke pulse and a late systolic murmur reflect a dynamic left ventricle with outflow tract turbulence and are present in approximately a third of patients. In the absence of a left ventricular outflow gradient, the abnormalities on examination are subtle with a hyperdynamic cardiac impulse and occasionally a palpable atrial beat

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Received: 28 February 1991

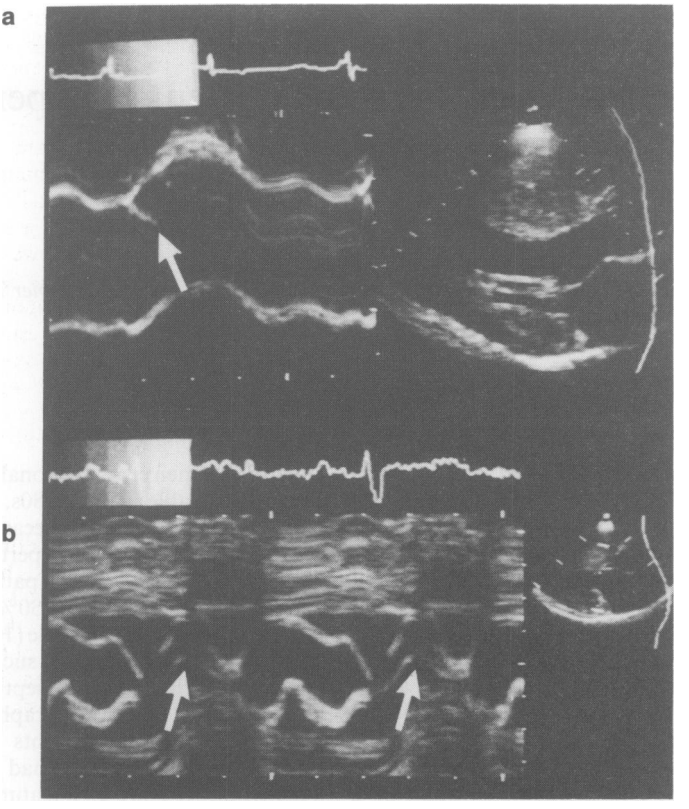

Figure 1 Parasternal long-axis views demonstrating (a) midsystolic closure of the aortic valve (arrow) and (b) marked septal hypertrophy and systolic anterior motion of the mitral valve.

reflecting a hypertrophied and non-compliant left ventricle. The ECG is abnormal in 80% of patients, showing features of left ventricular hypertrophy or myocardial infarction or giant T wave inversion.[6] The finding of a bizarre ECG in a young patient should raise the suspicion of HCM.

iii) Limitations of echocardiographic diagnosis

A diagnosis of exclusion has its own limitations. The diagnosis of hypertrophic cardiomyopathy is difficult when other potential causes of left ventricular hypertrophy coexist, as in athletes, or in patients with hypertension, aortic valve disease, obesity, or systemic amyloid disease.[7] Furthermore, neither the magnitude nor the pattern or extent of asymmetric septal hypertrophy, are pathognomonic of hypertrophic cardiomyopathy.[8] Age-related changes in cardiac shape can also confound interpretation of the cross-sectional echocardiogram and render the diagnosis of hypertrophic cardiomyopathy insecure. In the elderly, basal hypertrophy of the anterior ventricular septum and a narrowing of the left ventricular outflow tract[9] may increase the ratio of the septal to posterior walls and simulate asymmetric hypertrophy. At the other end of the age spectrum, the diagnosis of hypertrophic cardiomyopathy cannot be reliably excluded in those aged under 18 years as cardiac hypertrophy may not become apparent until adolescent growth is complete.[10] Echocardiography is warranted at regular intervals until adulthood is reached, particularly following growth spurts, in individuals with clinical or ECG abnormalities suggestive of HCM or in those with a family history of sudden death.

iv) Histological diagnosis

Myocardial fibre hypertrophy and disarray are the characteristic histological findings in patients with hypertrophic cardiomyopathy but the specificity of these findings has been disputed. Myocardial disarray may be a normal finding at the junction of the free wall of the right ventricle and the interventricular septum, and is also seen in patients with hypertension or aortic valve disease.[11,12] Nevertheless, the mean proportion of the septum with disarray in normal hearts is only 1.5%, and rises to about 30% of the total tissue area in patients with

hypertrophic cardiomyopathy.[13] Therefore, a confident histological diagnosis can be made if at least 10% of the ventricular septum shows disarray and there are short, broad, and irregularly shaped myocardial fibres with hyperchromatic nuclei.[14] Such a diagnosis can only be confirmed by a postmortem examination, ideally of the whole heart; cardiac biopsy, with its susceptibility to sampling error, is not a reliable alternative. The recent description of two families with autosomal dominant inheritance of myocardial disarray without myocardial hypertrophy indicates, however, that the spectrum of abnormality in hypertrophic cardiomyopathy may be wider than is currently recognized.[15]

v) Genetic diagnosis

The aforementioned difficulties in diagnosis have spurred attempts to find more specific, yet sensitive and unequivocal, criteria for diagnosing hypertrophic cardiomyopathy. One approach has been to try and identify the molecular basis of the disease. Evidence is mounting that some forms of familial hypertrophic cardiomyopathy are due to mutations in the myosin heavy chain (MHC) gene, a gene which encodes important myofibrillar components. Recently, a large family in which the gene for hypertrophic cardiomyopathy segregated as an autosomal dominant trait was studied, using linkage analysis and molecular genetic mapping techniques.[16] This revealed that the gene responsible for hypertrophic cardiomyopathy was located on chromosome 14 (band q1) and coinherited with a DNA locus 14S26. Refined mapping of this region revealed a missense mutation in exon 13 of the beta cardiac myosin heavy chain gene – an adenine for guanine replacement which was found in only the affected individuals.[17] This base pair change encodes an arginine for glutamine change in the amino acid sequence of the resulting myosin heavy chain polypeptide. Arginine is one of 5 amino acids common to the amino acid sequence of exon 13 from the myosin polypeptides of species as divergent as the human and the amoeba and changes to an amino acid so highly conserved in evolution must be functionally important. A separate mechanism – an alpha/beta cardiac myosin heavy chain hybrid gene – apparently resulting from an unequal crossover event during meiosis has been implicated as the cause of familial HCM in an unrelated family.[18] Further advances in these techniques will lead to better understanding of the molecular basis of hypertrophic cardiomyopathy and hopefully a molecular basis for diagnosis, risk stratification and ultimately prevention.

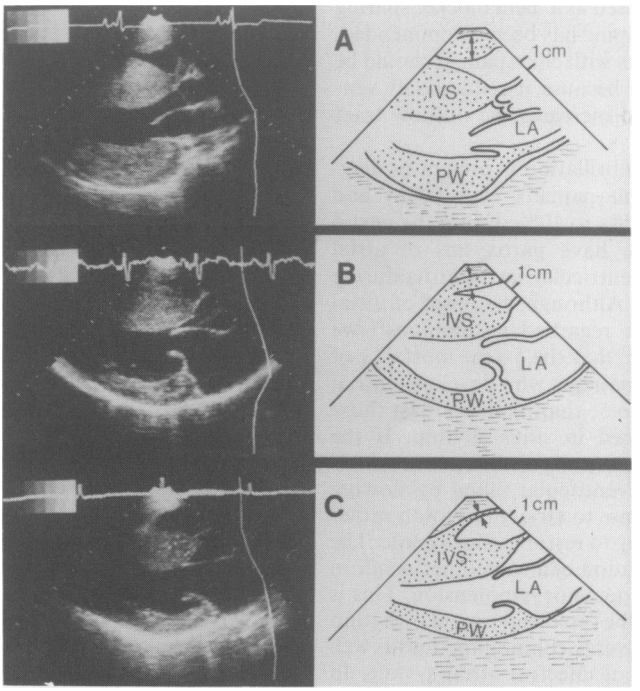

Figure 2 Parasternal long-axis views demonstrating (A) severe, (B) moderate and (C) no right ventricular hypertrophy from the proximal right ventricular outflow tract (arrows) in three patients with hypertrophic cardiomyopathy.

Management

The two main aims of treatment are the relief of symptoms and the improvement of prognosis.

i) Control of symptoms

Over 50% of adult patients with hypertrophic cardiomyopathy experience dyspnoea or exertional chest pain; incapacitating symptoms are, however, uncommon (<20%). The predominant mechanisms behind these symptoms are usually not clear. Treatment is aimed at reversing or reducing abnormal systolic or diastolic left ventricular function, the elevated end-diastolic pressures and the cardiac ischaemia to which these symptoms are attributed. Propranolol relieves dyspnoea presumably because it slows the heart rate, prolongs diastole and improves left ventricular filling. Verapamil may be even more effective, but its use has been associated with pulmonary oedema, syncope and sudden death.[19] A few patients, including those with early rapid and restricted filling, do, however, become more breathless when treated with negative chronotropic agents and are better off with a relative tachycardia. Both propranolol and verapamil are effective in patients with chest pain but can worsen pre-existing atrioventricular conduction abnormalities. Diltiazem has not been compared with beta-blockers but may be used as a 'beta blocker sparing agent'. Though nifedipine has been recommended, particularly in patients with chest pain, it should be used with great care because it reduces left ventricular afterload and increases the outflow tract gradient.

Established atrial fibrillation is present at diagnosis in 7% of adult patients with HCM and develops in another 5% to 10% during the next 5 years. Another 30% have paroxysms of atrial fibrillation or supraventricular tachycardia during 48 hour monitoring. Although the onset of atrial fibrillation was once regarded as ominous[20] we have recently shown[21] that the 5-year mortality of 14% amongst adult patients who developed atrial fibrillation was no worse than that amongst those patients who remained in sinus rhythm. If the patient is haemodynamically stable, treatment is aimed at improving ventricular filling by slowing the ventricular response to atrial fibrillation rather than necessarily trying to restore atrial systole. The onset of atrial fibrillation can sometimes result in severe pulmonary oedema or hypotension. This is presumably because the rapid and irregular rhythm causes a reduction in ventricular filling time as well as a precipitate loss of effective atrial systole. In such situations DC cardioversion and intravenous amiodarone have the best chance of restoring sinus rhythm.

Betablockers, verapamil and digoxin all reduce the ventricular response in established atrial fibrillation but are not as effective as amiodarone either in restoring sinus rhythm or as prophylaxis against paroxysmal atrial fibrillation. Patients with paroxysmal or established atrial fibrillation should be anticoagulated to prevent embolic complications. Pacemaker implantation is sometimes necessary for sino-atrial or atrio-ventricular nodal disease; surprisingly, the incidence of such complications is relatively low. The use of pacemakers to reverse the activation sequence and therefore reduce the outflow gradient is still experimental.[22]

Myectomy carries a 5% to 10% perioperative mortality. Survival is usually associated with an improvement in haemodynamics and exercise capacity and a reduction in the severity of mitral regurgitation. Papillary muscle excision and mitral valve replacement is effective for severe mitral regurgitation with a lower perioperative mortality than for myectomy and is particularly useful in elderly patients with mitral annular calcification. A myectomy which is too deep or which involves a thin part of the septum may result in a ventricular septal defect as can complete heart block, particularly if there is preexisting right bundle branch block. Aortic valve regurgitation is a potential complication of an incision made too close to the aortic valve. Controlled trials of surgical versus medical treatment have not been performed, but it appears that whilst surgery provides excellent symptomatic relief for patients with incapacitating symptoms, it does not prolong life.[23]

Syncope is the most worrying symptom, because it is associated with sudden death. Naturally, tachyarrhythmias or conduction abnormalities are sought assiduously in any patient with such a history but systemic characterization reveals a likely mechanism in less than 50%.

ii) Prognosis

Hypertrophic cardiomyopathy carries a 2 to 3% mortality in adults and a 6% mortality, usually from sudden death, in children and adolescents referred to tertiary centres.[24,25] Sudden death is not predicted by the degree or pattern of hypertrophy, by symptoms of chest pain or dyspnoea or by invasive haemodynamic measurements. Non-sustained ventricular tachycardia is detected during Holter monitoring in about 25% to 30% of consecutive adult populations and is the single most useful predictor for sudden death, with a sensitivity of 69%, a specificity of 80%, a negative predictive accuracy of 97% and a positive predictive accuracy of 22%.[26] The finding of nonsustained ventricular tachycardia represents a marker of the high risk adult and is unlikely to be the initiating event for sudden death. The absence of

nonsustained ventricular tachycardia indicates low risk. To improve the prediction of sudden cardiac death, other workers[27] entered symptoms, left ventricular hypertrophy, haemodynamic measurements and other indices of left ventricular function in a step-wise discriminant analysis in 14 patients with, and 74 patients without, ventricular tachycardia. Digitized angiographic analysis revealed that peak left ventricular ejection rate was significantly reduced in patients who died suddenly compared with those who survived. Thus, the degree of left ventricular dysfunction may be an important determinant of which patients with ventricular tachycardia are at an increased risk. Nevertheless, the low predictive accuracy of nonsustained ventricular tachycardia for sudden death indicates that not all patients carry the same increased risk factor. Age, sex, severity of symptoms, and the presence of ventricular gradients do not distinguish patients with nonsustained ventricular tachycardia who die suddenly from those who survive.[26,28] More detailed haemodynamic and electrophysiological measurements and stratification of patients with nonsustained ventricular tachycardia are needed to identify those patients who need treatment on prognostic grounds.

The role of electrophysiological testing in identification of high risk patients with hypertrophic cardiomyopathy is unclear. Ventricular fibrillation is induced in up to 47% of such patients using aggressive stimulation protocols.[29] Fananapazir *et al.*[30] induced sustained ventricular tachycardia in 66 (43%) of 155 patients with HCM; ventricular tachycardia degenerated into ventricular fibrillation in 31 of these 61 patients. Although tachycardia was induced more often in the 'higher risk' patients, the possibility cannot be discounted that such patients were stimulated more aggressively because they had a history of cardiac arrest or syncope. The clinical relevance of these results needs prospective study.

Predicting sudden death in children and adolescents with hypertrophic cardiomyopathy is even more difficult. Arrhythmias during ECG monitoring are uncommon in children and adolescents and do not appear to be of prognostic value. But syncope is ominous; in one retrospective series it was 86% specific for sudden cardiac death within 6 years.[31] Most of the children who die suddenly, however, have neither a history of syncope nor significant limitation of exercise tolerance. Yet even in such 'apparently low risk' individuals there is still an annual mortality from sudden death of 4%. It is possible that sudden death is precipitated by a drop in blood pressure and stroke volume in relation to emotion or exercise-related tachycardia leading to life-threatening arrhythmias in patients with vulnerable hearts. That young patients with hypertrophic cardiomyopathy who die suddenly have more myocardial disarray than adults with the disease who die suddenly from other causes indicates that the extent and severity of myocardial disarray may also be an important determinant of myocardial electrical stability and the risk of sudden death. However, more reliable strategies for identifying high-risk patients are needed before studies of the prognostic effects of various interventions, such as long-term amiodarone therapy or automatic implantable defibrillators, can be undertaken.

The prognosis in adults with ventricular arrhythmias on Holter monitoring[32,33] can be improved by treatment with low dose amiodarone. Over a 3-year follow-up period, we found that there was a mortality of 7% per year amongst patients on Class 1 antiarrhythmic agents, but no deaths over the next 5 years amongst well-matched patients taking amiodarone. Similarly, there were no deaths after 3 years amongst 15 high-risk adolescents who received between 500 mg and 1000 mg of amiodarone per week, with plasma concentrations of 0.5 mg/ml.[25] The mechanisms of amiodarone's prognostic benefit are unclear but its anti-adrenergic, Class III, anti-ischaemic actions may combine to suppress supraventricular and ventricular tachycardia and increase the threshold for ventricular fibrillation. Serious pulmonary and hepatic complications are rare if amiodarone is used carefully with daily maintenance doses not exceeding 400 mg and with blood levels kept between 0.5 mg/ml and 1.5 mg/ml. Class 1 antiarrhythmic agents and betablockers have been disappointing in suppressing serious ventricular arrhythmias and in preventing sudden death. Further improvements in risk stratification and treatment of adult HCM patients will probably come from studies of the prognostic value of combined clinical, haemodynamic, and electrophysiological data which prospectively examine potential mechanisms of sudden death.

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