FEBRUARY 2001 volume VI, issue 2

CARDIOLOGY Rounds™

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Hypertrophic cardiomyopathy in 2001

BY GEOFF PULEY, MD, ROBERT CHISHOLM, MD

Hypertrophic cardiomyopathy is a clinically heterogeneous disease caused by a wide variety of mutations in genes encoding cardiac sarcomeric proteins. These ultimately result in inappropriate hypertrophy of the myocardium, usually involving the interventricular septum in an asymmetric fashion. Diastolic dysfunction, dynamic left ventricular outflow tract obstruction, mitral regurgitation, myocardial ischemia, and arrhythmias are all potential consequences of inappropriate hypertrophy and combine to produce a wide spectrum of clinical manifestations. Drug therapy can improve symptoms by augmenting diastolic filling and improving obstruction when present. For patients with significant obstruction refractory to medication, septal myectomy, dual chamber pacing, and percutaneous chemical septal ablation are further options. Finally, amiodarone and implantable cardioverter-defibrillators may have an important role in preventing sudden death in these patients.

Definition, pathology, and prevalence

The characteristic distinguishing feature of hypertrophic cardiomyopathy (HCM) is myocardial hypertrophy that is out of proportion to the hemodynamic load. Macroscopically, there is typically a marked increase in myocardial mass and the ventricular cavity is normal or reduced in volume. The left ventricle usually shows more involvement than the right, but the pattern and extent of hypertrophy varies markedly from patient to patient. There is great heterogeneity even within subgroups of patients with mutations in the same genes.[1] Most patients show disproportionate involvement of the interventricular septum and anterolateral wall (Figure 1), but predominant involvement of the apex (particularly in Japanese patients), posterior wall, or even symmetric left ventricular hypertrophy are also well recognized variants. [2]

Microscopically, affected myocardium shows characteristic disorganization in the alignment of cardiac myocytes, typically oriented around islands of loose connective tissue.[3] High-power magnification of individual myocytes also demonstrates disarray in the orientation of their myofibrillar architecture (Figure 2).[4] Fibrosis is prominent throughout affected areas and may be the result of ischemia due to the abnormally small, thickened, intramural coronary arteries seen in HCM.[5] These microscopic changes are found not only in areas with macroscopically obvious hypertrophy, but also in other areas of seemingly uninvolved myocardium. They have also been found at autopsy in hearts of patients with a positive family history for HCM who died suddenly, but had no obvious hypertrophy themselves.[4]

Hypertrophic cardiomyopathy is found throughout the world. The prevalence of the echocardiographic appearance of HCM in North America is 0.2% or 1 in 500 people.[6] However, as more subtle manifestations of the disease are recognized and further advances are made in genotyping and screening, this number will likely increase.

Genetics

The majority of cases of HCM (60%-80%) are clearly familial and are inherited in a Mendelian single-gene autosomal dominant fashion. To date, 9 culprit genes and well over 100 specific

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The opinions expressed are only those of the Divisional members. This publication is made possible through unrestricted grants.

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Figure 1: Longitudinal cross-section through the left ventricle of a patient with HCM showing asymmetric hypertrophy of the interventricular septum.[38]

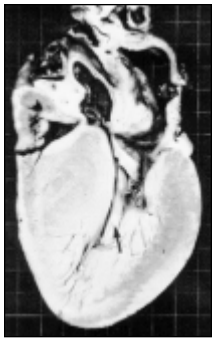
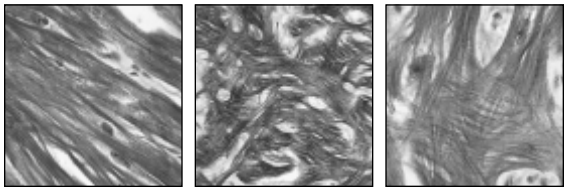


**Figure 2: A: Photomicrograph of normal cardiac myocytes.
B: Myocyte disarray, cells oriented in a characteristic whorled pattern.
C: Higher power shows myofibrillar disarray.**



A B C

mutations have been identified.[1,2] Each of the culprit genes thus far described encode sarcomeric proteins. The most prevalent of these are the beta-myosin heavy chain (~35% of cases), cardiac troponin-T (~15%) and the cardiac myosin binding protein C (~15%) genes (Figure 3).[7] Genetic screening and genotype-based clinical decision algorithms are not yet a part of routine practice in HCM, but with the ongoing accumulation of large databanks of affected families, this holds great potential for the future care of patients with HCM.[8] It is likely that a great deal of meaningful incremental information will come from the knowledge of a patient's genotype, in addition to the overt phenotypic manifestations they demonstrate. For example, it is known that some mutations of the beta-myosin heavy chain and all mutations of the troponin-T genes are associated with sudden death in up to 50% of patients.[9]

The challenge of the future will be to develop therapies aimed at preventing the expression of HCM once a genetic defect has been identified. Understanding the pathway from mutations in genes encoding the contractile proteins to the development of inappropriate hypertrophy is therefore critical. This has been facilitated by the development of mouse models. The incorporation of mutant proteins into sarcomeres results in increased intracellular calcium concentrations and increased myocyte stress. As a result of this, there is up-regulation of stress-responsive trophic and mitotic factors that are ultimately responsible for the collagen synthesis, myocardial disarray, and hypertrophy that are characteristic of the disease.[10]

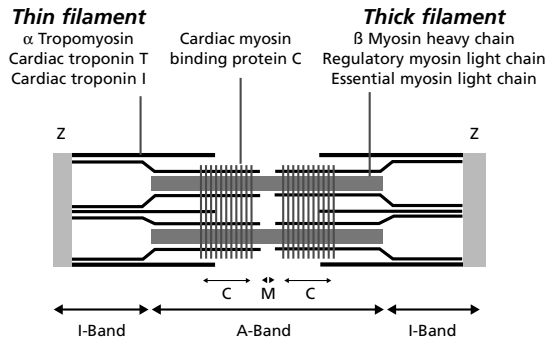
Clinical manifestations

The majority of patients with HCM are asymptomatic or only mildly symptomatic and are often identified during screening of relatives of a symptomatic patient with HCM. Patients can first become symptomatic at any age, from early childhood to age mid-80s, but the majority of patients present in their 30s or 40s. Dyspnea is the most common presenting symptom. Chest pain, fatigue, palpitations, and syncope are also common. Sudden death is the first clinical manifestation of the disease in up to 10% of patients. Clinical deterioration is usually slow, but approximately 10-15% of patients go on to develop gradual thinning of the walls and the picture of dilated cardiomyopathy.[11]

Diastolic dysfunction is the single most important pathophysiological abnormality in patients with HCM. It is found in over 80% of patients by nuclear studies or Doppler echocardiography and is largely independent of the severity and distribution of hypertrophy.[12] The rapid-filling phase of diastole is significantly prolonged, resulting in reduced ventricular filling with a compensatory increase in the relative contribution of the atrial kick, hence the often precipitous acceleration of symptoms in patients who develop atrial fibrillation.

Approximately 25% of patients develop dynamic obstruction of the left ventricular outflow tract (LVOT). A number of factors (hyperdynamic LV contraction, reduced LVOT dimension, and anterior displacement of the mitral valve) contribute to the creation of an intraventricular pressure gradient and ultimately to systolic anterior motion (SAM) of the mitral valve (Figure 4). There has been great debate over the years as to the clinical significance of the obstruction caused by SAM.[13-15] Some authors believe that the gradient does not represent a true obstruction, but rather, is an inevitable consequence of rapid ventricular ejection. They argue that the clinical improvement achieved by pharmacological or surgical relief of outflow obstruction is in fact due to an improvement in diastolic function that these interventions also achieve. Indeed, for many patients with dynamic outflow obstruction, more than 80% of ventricular ejection is completed before the onset of mitral-septal contact.

Figure 3: Schematic organization of some of the sarcomeric proteins associated with HCM. (Adapted from Reference #1)



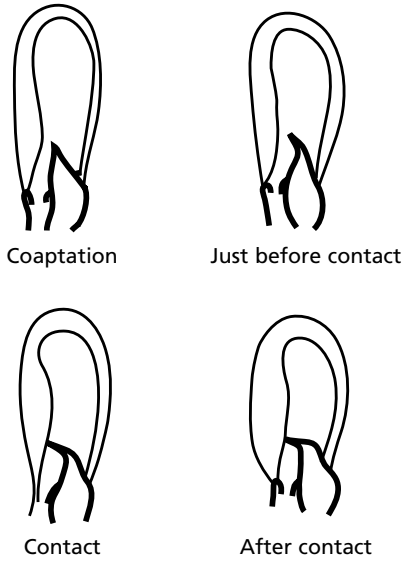
However, when the outflow gradient is greater than 50 mm Hg, the percentage of ventricular ejection that occurs before the obstruction develops, rapidly declines.[13]

Medical management

The diverse genetic and clinical features of HCM make it impossible to define precise guidelines for management, making it necessary to individualize therapy. However, certain principles hold true for the management of many of these patients. First, the primary goal of medical therapy is to improve diastolic filling of the stiff left ventricle and, secondarily, to relieve outflow tract obstruction in the subset of patients where this is significant. The negative inotropic and heart-rate lowering properties of verapamil and beta-blockers have been shown to achieve subjective and objective benefit in patients.[16] Disopyramide, as a negative inotropic agent, has also been shown to improve symptoms.[17] There has been no prospective clinical data supporting the use of any one of these agents over the other. Many physicians will avoid the afterload reduction achieved with verapamil in patients with significant obstruction. Inotropic agents (digoxin, beta-agonists) and decreased preload conditions (diuretics) should be avoided, except in those patients who go on to develop dilated cardiomyopathy. Patients with HCM are considered "moderate risk" for bacterial endocarditis by the AHA guidelines and should receive prophylaxis when appropriate.

When medical therapy ultimately proves insufficient to control symptoms, subsequent therapeutic strategies are largely determined by the presence or absence of outflow obstruction. For patients with nonobstructive disease, limited options are available. Cardiac transplantation should be considered in severely symptomatic patients.

Figure 4: Diagrammatic representation of the anterior motion of the mitral valve during systole and the development of mitral-septal contact.



For patients with obstruction whose symptoms are refractory to drug-therapy, surgical myectomy, dual-chamber pacing, and percutaneous septal ablation are therapeutic options.

Surgical myectomy

The relief of outflow tract obstruction by surgical excision of a portion of the basal interventricular septum was first described by Morrow in 1978.[18] The procedure is now most commonly performed through an aortic approach and achieves nearly complete relief of the outflow tract gradient in the great majority of patients. Indications for surgery include refractory NYHA class III or IV heart failure despite medical therapy, basal septal thickness of at least 18 mm, and a resting gradient of at least 50 mm Hg. Operative mortality at experienced surgical centres is 2% or less.[19] Approximately 5% of patients require a permanent pacemaker for high-grade AV block post-operatively. While no randomized data of surgery vs medical therapy has been performed, short- and long-term follow-up studies of surgical cohorts have shown impressive subjective and objective measures of improvement that are sustained for many years for most patients.[20,21]

Dual-chamber pacing

The potential for pacing to improve dynamic LVOT obstruction has been recognized for over 30 years. Pacing the right ventricle from the apex may cause paradoxic or

diminished inward movement of the ventricular septum resulting in an increase in LVOT dimensions. Additionally, asynchronous contraction from the apex to the base may result in further separation of the septum and the anterior mitral leaflet in systole (Figure 4). There has also been a suggestion that pacing may have chronic effects on remodeling, increasing LV volume in patients with HCM.[22] In the early 1990s, two large cohort studies showed favorable results achieved with dual-chamber pacing.[22,23] The outflow tract gradient was reduced by greater than 50% on average and there was symptomatic improvement in 90% of patients. However, later controlled studies comparing AAI and DDD pacing in a cross-over fashion, suggested that the majority of the benefit seen was simply due to a placebo-effect.[24] While dual chamber pacing can unequivocally achieve some reduction in the LVOT gradient, subjective and objective measures of improvement in symptoms and exercise-capacity were not significantly modified by dual-chamber pacing. Additionally, a non-randomized comparison of DDD pacing and septal myectomy (in which patients chose their own therapy after the risks and benefits of each were explained to them) showed that surgery resulted in a significantly greater improvement in outflow gradient, NYHA class, and VO_2-max than that seen with pacing.[25]

Chemical septal ablation

Chemical septal ablation involves the infusion of 96% ethanol through an angioplasty catheter into one or more septal perforator branches of the left anterior descending artery. This results in a controlled infarction and thinning of the proximal interventricular septum. As with all therapies in HCM, no prospective randomized data has established the value of septal ablation. Several studies have documented an average of 65% reduction in the resting LVOT gradient and significant improvement in symptoms and exercise capacity that are sustained in follow-up exceeding one year.[26,27] However, there are significant complications associated with this procedure. The mortality rate in the largest trials is similar to that from surgery, up to 4%. The majority of patients are left with significant conduction abnormalities (RBBB and LBBB) and 0-40% (average 21%) suffer persistent high-grade AV block requiring a permanent pacemaker. The lack of long-term follow-up leaves outstanding questions about the effect of septal infarction on arrhythmogenicity, left ventricular remodeling, and systolic function.

Sudden death in HCM

Sudden cardiac death (SCD) is the initial presenting feature in up to 10% of patients with HCM. The commonly quoted 2%-4%/year risk of sudden death in patients with HCM is likely a significant overestimate based on referral bias to tertiary care centres from which these data arise. Risk factors for sudden cardiac death include: resuscitated arrest, family history of SCD, unexplained syncope and a hypotensive response to exercise.[28,29] A recent prospective study examining the relationship between maximal left ventricular wall thickness and the risk of SCD showed significant incremental risk with increasing wall thickness. Sudden death occurred in less than 1% of patients with maximal thickness <20mm and in 16% of patients with maximal thickness >30mm over an average follow-up of 7 years.[30] Neither the severity of symptoms, nor the presence of outflow tract obstruction have been shown to be predictive of SCD. In fact, 21 of the 23 (91%) patients in the above study who died suddenly had no or only mild symptoms. Non-sustained ventricular tachycardia (NSVT) is common in patients with HCM and, while controversial, has not been shown to be an independent predictor of SCD.[31,32] Identification of NSVT seems to have a low positive, but high negative predictive value for SCD. However, this might again be a product of referral bias and not reflect the significance of NSVT in the larger population of patients with HCM. Finally, inducibility of ventricular arrhythmias at electrophysiology study has not consistently been shown to be useful in predicting SCD in HCM.[33,34]

Amiodarone and the implantable cardioverter-defibrillator

The role of amiodarone in SCD prevention is a controversial one. In a non-randomized study of amiodarone vs Class 1a antiarrhythmic + ß-blocker in patients with HCM and NSVT, McKenna et al reported improved survival with amiodarone.[35] However, the event rates were low and there is a question about whether the "benefit" was in fact related to the pro-arrhythmia of Class 1a agents. Some authors have even questioned the safety of amiodarone in these patients.[36] Randomized, prospective data examining the role of amiodarone in high risk patients is needed before any meaningful recommendations can be made.

Recently, considerable attention has been given to the role of the automatic implantable cardioverter-defibrillator (AICD) devices in preventing sudden

death in HCM patients. Unfortunately, there is once again a paucity of controlled clinical data examining this issue. The best available evidence comes from examining appropriate discharge rates in retrospective series. The largest such study has recently been published by Maron et al.[37] The choice for AICD after resuscitated arrest (secondary prevention) is a clear one: 44% of these patients had an appropriate discharge after a mean follow-up of 4 years (11%/year). Twelve percent of patients who received an AICD for primary prevention had an appropriate discharge after a mean follow-up of 2.6 years (5%/yr). These discharge rates are lower than those seen in patients with ischemic heart disease, but the HCM patients are younger and potentially have more years to "save." In their discussion, the authors extrapolate the primary prevention discharge rate and predict that at 10 years, 50% of patients receiving AICD for primary prevention will receive an appropriate discharge. Such an extrapolation is, however, not a statistically sound one as it assumes a constant risk across the population over time.

Few clinicians would argue about the life-saving abilities of the AICD when applied to an appropriate, high-risk population. Identifying the clinical and genetic profile of the high risk patient will be the most important step toward effectively applying this technology to the population of patients with HCM.

Summary

Hypertrophic cardiomyopathy is a relatively common disease that is usually inherited in an autosomal dominant fashion from mutations in cardiac sarcomeric proteins. It is both genotypically and phenotypically diverse in its presentation, manifestations, and prognosis. Most symptomatic patients can be treated with negative inotropic and chronotropic agents which achieve improved diastolic function. For the subset of patients with obstruction to outflow, surgical myectomy and percutaneous septal ablation are of proven benefit. Dual-chamber pacing does not appear to be as effective as these measures, but rather seems to have a significant placebo effect. Finally, the genotypic and clinical predictors of risk for sudden cardiac death need further clarification before clear guidelines on the role of amiodarone and implantable cardioverter-defibrillators can be constructed.

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This publication is made possible by an educational grant from

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