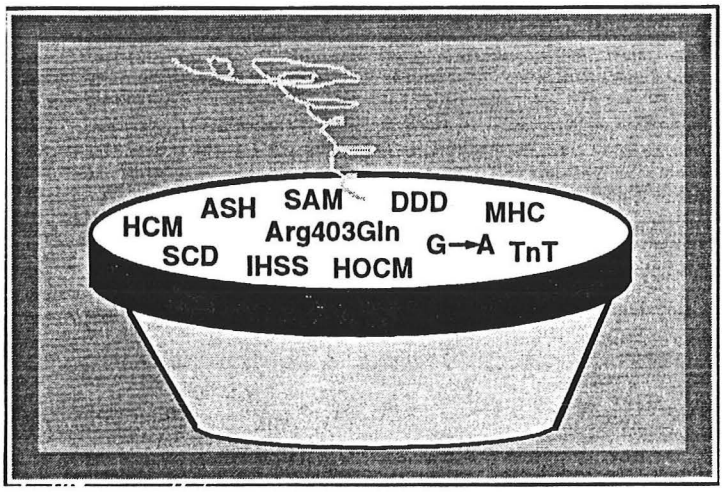
Medical Grand Rounds
The University of Texas Southwestern Medical Center
Dallas, TX



Sick sarcomeres, alphabet soup, and sudden death: Hypertrophic cardiomyopathy in 1995

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Introduction

The disease we recognize today as hypertrophic cardiomyopathy (HCM) was first appreciated by the medical community less than 40 years ago, but our understanding of its pathophysiology has increased dramatically in each subsequent decade, paralleling advances in the analytical tools and methods available to cardiovascular investigators (Fig. 1). The disease may carry a high mortality, even in asymptomatic individuals, and it is not rare (1-10 per 10,000 in the general population), such that all internists should be familiar with its cardinal manifestations. In addition, recent advances in the molecular genetics of HCM make this disorder particularly interesting as an example of both the power, and the current limitations, of molecular medicine.

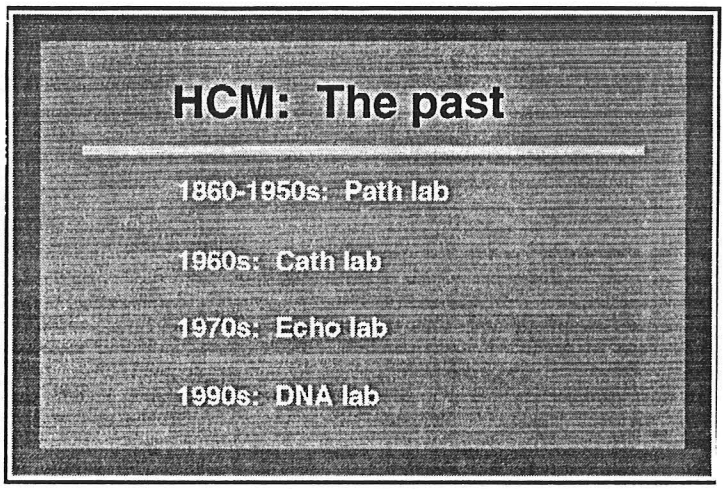


Fig. 1

History and definitions

HCM was probably observed by pathologists as early as the mid-nineteenth century [1], and families with a high incidence of sudden death, perhaps attributable to HCM, were described in the first half of this century [2]. The first systematic description of the disorder, however, is attributed to Donald Teare, who served as chief coroner of the City of London. In 1958, Teare described autopsy findings from 8 patients with marked hypertrophy of the ventricular septum [3]. He correctly established the relationship between this gross anatomic finding and sudden death, and also described the histological hallmark of this disease: cellular disorganization within the myocardium. He interpreted these findings as indicative of a benign tumor or hamartoma. A contemporaneous report from Russell Brock, a surgeon at Guy's Hospital, described a patient referred for surgical correction of aortic stenosis, but found to have a structurally normal aortic valve [4]. The patient died and ventricular hypertrophy was found at autopsy. Brock speculated that outflow obstruction from the thick ventricular wall was the basis for this patient's symptoms and physical findings, and his paper is generally cited as the first description of the obstructive form of HCM.

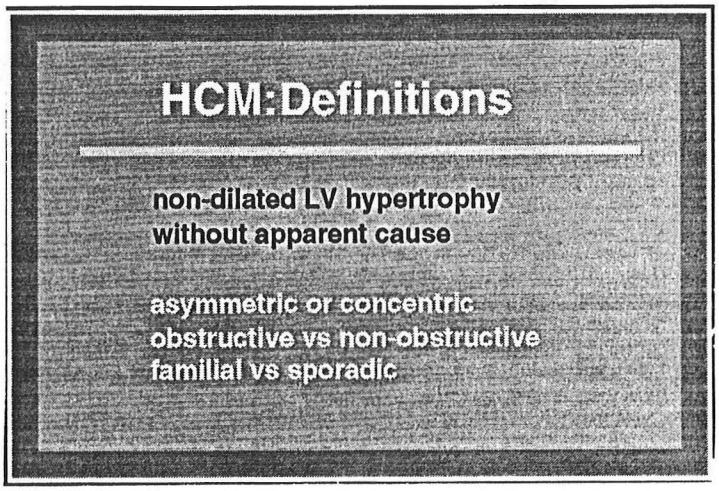
These reports generated considerable excitement among cardiovascular investigators, and coincided with the beginning of a period of significant advances in techniques of cardiac catheterization. Over the next decade, investigations were focused primarily on the obstructive component of this disease: its dynamic nature was recognized; the fascinating

responses to provocative stimuli were noted; and criteria for diagnosis using invasive methods were defined [5, 6]. Many clinical descriptors and acronyms were coined, but by the disease became generally known in this period as IHSS: idiopathic hypertrophic subaortic stenosis.

The development and refinement of non-invasive echocardiographic techniques in the 1970s and 1980s brought new insights into the pathophysiology of obstructive HCM, and a new appreciation for the complexities of this disease. Different forms of hypertrophy were recognized [7], and it became apparent that many patients had features of IHSS without aortic outflow obstruction [8]. The echocardiographic hallmarks of this disease were established [9, 10], the frequency of sudden death was defined [11], and the special risk of vigorous exercise in HCM patients was noted [12].

The next important steps awaited the development of linkage analysis and other molecular techniques for identification of disease-causing gene mutations. In the case of familial HCM, the initial success in this endeavor by Christine Seidman and colleagues [13, 14] was made possible by the preceeding decades of careful clinical studies and by a large body of basic research in muscle biology that had identified candidate genes.

Fig. 2



Current nomenclature defines hypertrophic cardiomyopathy as non-dilated cardiac hypertrophy without an apparent cause (e.g. hypertension or valvular disease) (Fig. 2). While most patients with HCM have asymmetric septal hypertrophy (ASH), the process also may involve the left ventricular free wall, resulting in concentric hypertrophy. A subset of patients with HCM will manifest aortic outflow tract obstruction, which may be apparent at all times or evoked only by provocative stimuli. The disease frequently is familial, and many of the apparently sporadic cases also have a genetic basis (new mutations) [15]. Several large kindreds with familial HCM have disease-causing mutations in the ß myosin heavy chain (ßMHC) gene, most frequently single nucleotide base substitutions that alter the amino acid sequence at positions within the head or hinge region of the myosin molecule (e.g. glutamine replacing arginine at position 403: Arg403Gln). The Venn diagram shown in Fig. 3 illustrates relationships between these subsets of patients with HCM.

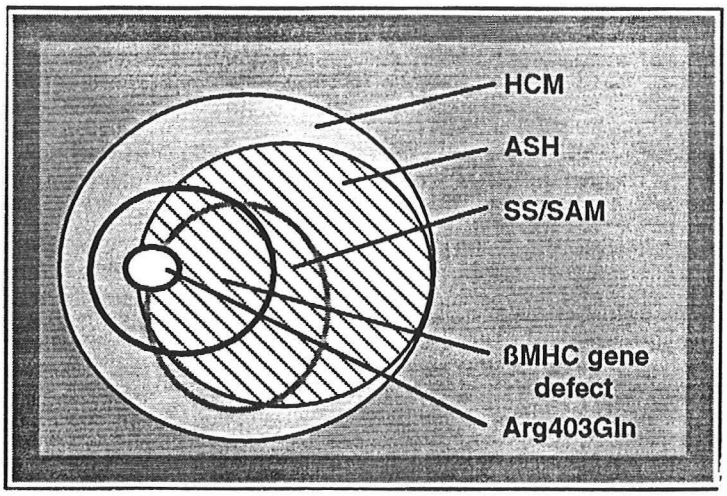


Fig. 3. Venn diagram of relationships between various descriptors of HCM patients.

Clinical features and diagnosis

The literature on clinical features of HCM is vast, but is summarized in several recent textbooks and reviews [11, 16-22]. HCM may be evident at birth or not detected until advanced age. The majority of patients, however, come to medical attention as young adults (Fig. 4). Systematic screening of large kindreds with HCM by echocardiography reveals many affected individuals who are asymptomatic, and even in sporadic cases, sudden cardiac death may be the first manifestation of the disorder. When symptoms occur, dyspnea or angina on exertion predominate, and syncope or presyncope are also common. A positive family history can be elicited in approximately 50% of cases.

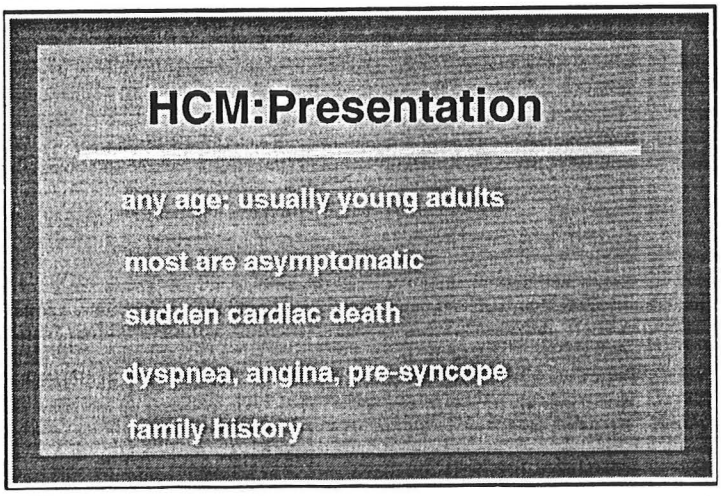


Fig. 4

The disorder is life-threatening (Fig. 5). Earlier surveys suggest an annual mortality rate of 3-4%, but other data indicate that not all patients are at equal risk [11, 23-25]. In some

families with HCM, few affected individuals survive past the age of 30 (Fig. 6), while other families exhibit near normal survival curves. Although certain characteristics (e.g. prior cardiac arrest) may predict a poor outcome, factors such as the extent of hypertrophy, the magnitude of obstruction, or the severity of symptoms bear only weak relationships to prognosis [26]. Interestingly, survival may be much longer in symptomatic patients with HCM than in patients with valvular aortic stenosis manifesting similar symptoms (e.g. syncope). In addition, while a number of therapeutic modalities are available to relieve symptoms, evidence for enhanced survival based on medical or surgical interventions is limited or circumstantial. It is clear, however, that many, if not all, patients with HCM are at risk for lethal events during vigorous exercise. In fact, unrecognized HCM represents the most common cause of sudden death of young athletes [12].

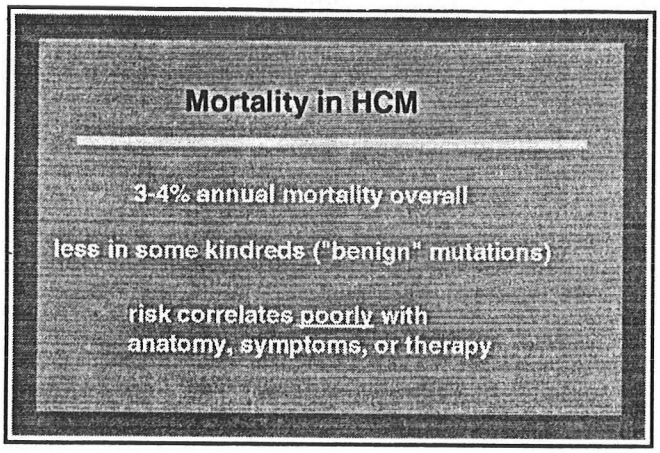


Fig. 5

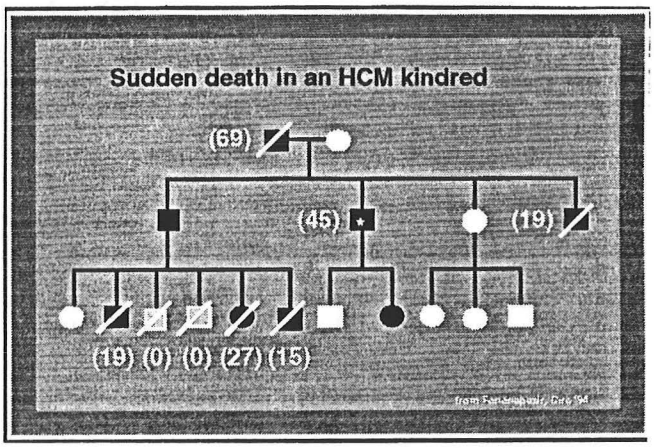


Fig. 6. Pedigree of a high risk HCM kindred [46]. Horizontal marks indicate patients who died suddenly, with age of death in parenthesis. The asterix indicates a patient resusitated from ventricular fibrillation and fitted with an AICD device.

The physical exam, in some cases, may be normal. In other patients, only signs of diastolic dysfunction are evident, manifested by S4 or S3 gallops. Florid congestive heart failure is uncommon except in association with acute events (arrhythmia/infarction) or in patients who have progressed to systolic dysfunction and a dilated ventricle: a condition termed end-stage HCM. Other physical findings are present only in the subset of patients with left ventricular outflow tract obstruction. The systolic ejection murmur of obstructive HCM (sometimes abbreviated as HOCM) is heard best along the left sternal border at the cardiac base, and is distinguished from the murmur of valvular aortic stenosis by its increased intensity during maneuvers that reduce ventricular filling, such as the strain phase of the Valsalva response or sudden standing. The carotid upstroke is distinctive: during early systole the hyperdynamic ventricle ejects blood forcefully, but progressive obstruction in mid- and late-systole impairs flow, resulting in the spike and dome pattern characteristic of this condition. In obstructive HCM, systolic anterior motion of the anterior leaflet of the mitral valve (SAM), a cardinal finding at echocardiography, disrupts

the normal geometry of the mitral apparatus, producing mitral regurgitation, which results in the characteristic apical holosystolic murmur.

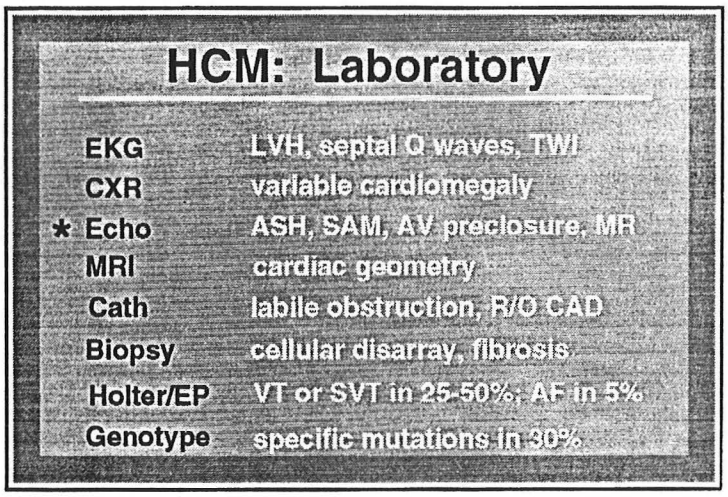


Fig. 7

A variety of laboratory abnormalities (Fig. 7) should lead the clinician to suspect HCM, or are useful in establishing the diagnosis. The electrocardiogram most frequently shows signs of left ventricular hypertrophy, but this may be indistinguishable from LVH resulting from other conditions. Other EKG findings are less common, but more distinctive, and include the massive T wave inversions seen in the anatomic variant of apical HCM, or large Q waves resulting from depolarization of the hypertrophied septum, but mimicing myocardial infarction (pseudoinfarct pattern).

The chest radiogram often shows cardiomegaly, but because HCM is associated with diminished chamber volumes, massive hypertrophy may be present with only minimal enlargement of the cardiac silhouette.

Echocardiography remains the workhouse for detection and characterization of HCM [27, 28]. Except in patients with poor sound transmission, the ventricular geometry can be defined, and the presence of outflow obstruction and mitral regurgitation evaluated. Similar data can now be acquired with magnetic resonance imaging, which should be employed if the echocardiagraphic findings are equivocal.

Cardiac catheterization is employed to quantify the severity and lability of the obstructive process, and to evaluate the epicardial coronary vessels for coexistent atherosclerotic disease.

Ventricular biopsy has little role in routine cases. While biopsy specimens may reveal the characteristic fiber disarray that is a cardinal feature of HCM [29, 30], this abnormality is inhomogeneous within the heart, and apparently normal biopsies may be obtained from affected individuals. In addition, other insults to the myocardium may provoke a histologically similar cellular response, so the finding lacks specificity as well. Endomyocardial biopsy is not necessary for identification of genetic defects causing HCM. In kindreds with known mutations, Southern analysis or sequencing of PCR amplification products from genomic DNA of peripheral blood leukocytes may permit accurate genotyping. Low levels of ectopic transcription in peripheral blood leukocytes of genes

encoding sarcomeric proteins are also sufficent to permit PCR-generated amplification of cDNA, and identification of disease-causing mutations [31].

Atrial and ventricular arrhythmias are very common in HCM patients [32]. Electrophysiological evaluation is warranted in patients manifesting symptoms potentially attributable to arrhythmias, and possibly in asymptomatic patients with ventricular tachycardia and a malignant family history [33]. Atrial fibrillation in other diseases may cause minimal hemodynamic compromise, but often is an ominous rhythm in hypertrophic cardiomyopathy. Marked diastolic dysfunction [34] renders the HCM heart highly vulnerable to the loss of atrial systole and the shorter duration of diastole, such that atrial fibrillation may provoke circulatory collapse and even death in these patients.

The variation in ventricular geometry among patients with HCM is striking, even within single kindreds harboring an identical genetic lesion. At least three general categories of ventricular anatomy should be recognized (Fig. 8). Most patients have disproportionate septal involvement but a significant subset have more concentric hypertrophy. Hypertrophy limited to the cardiac apex often presents the distinctive electrocardiographic picture mentioned earlier, and represents a discrete category of disease.

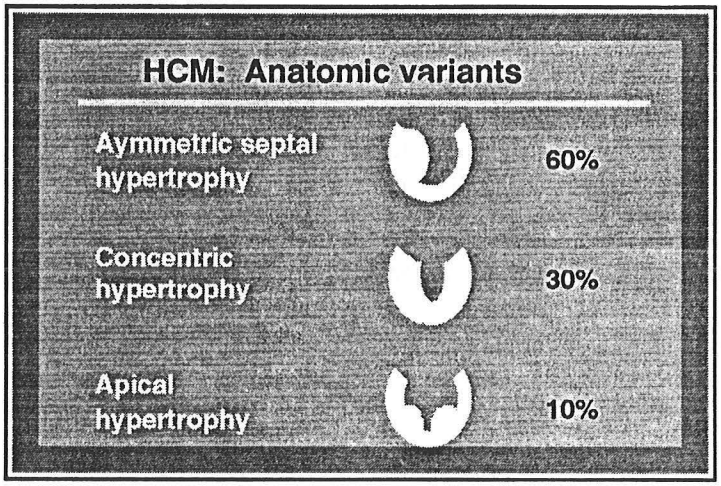


Fig. 8

Non-obstructive HCM, particularly when the left ventricular free wall is involved, may be difficult to distinguish from hypertrophy evoked by systemic hypertension in the elderly, but usually not in young persons. Obstructive HCM presents findings shared with valvular aortic stenosis or mitral regurgitation, but echocardiography almost always should discriminate between these disorders in a definitive manner in cases where a careful physical examination is ambiguous.

Restrictive cardiomyopathies or infiltrative processes that restrict diastolic filling or generate asymmetric thickening of the ventricular septum may be confused with HCM, but usually lack the hypercontractile ventricle that is characteristic of the latter disease.

Since angina pectoris is a common presenting complaint in patients with HCM, these individuals may be misdiagnosed as having atherosclerotic coronary artery disease, a much more common condition. Exertional angina in young persons, a family history of sudden

death, or evidence of myocardial ischemia in the absence of atherosclerotic risk factors should raise suspicion for HCM and trigger appropriate diagnostic studies.

Finally, physical conditioning may induce physiological ventricular enlargement. The cardiac hypertrophy evoked by endurance training (distance running, rowing, cycling) is associated with large intraventricular volumes and is therefore easily distinguishable from HCM. On the other hand, weight lifters may develop concentric hypertrophy that may not be readily differentiated from HCM on anatomical grounds, and other clinical criteria must be applied.

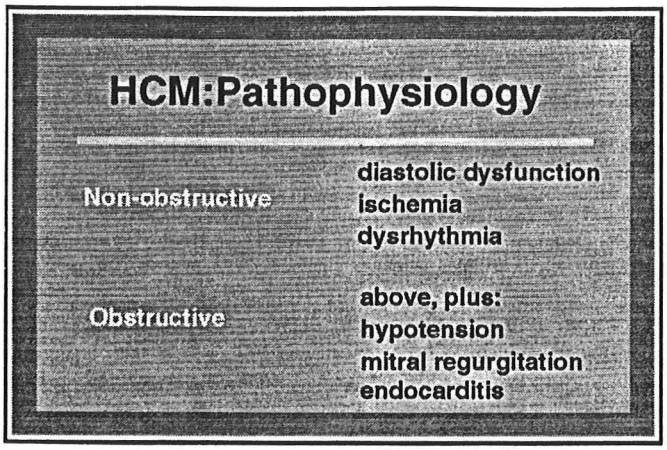


Fig. 9

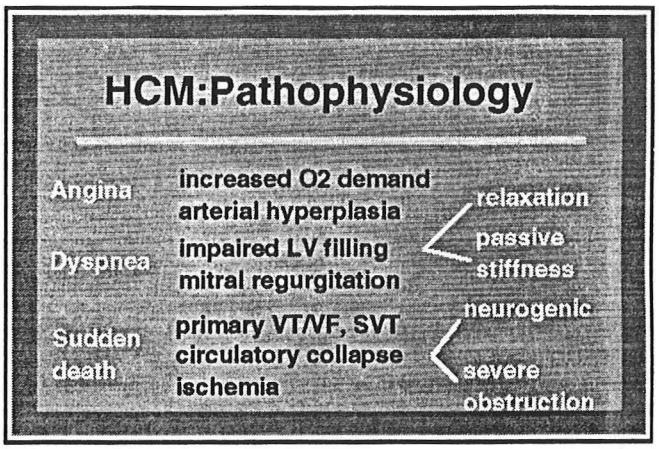


Fig. 10

Some of the physiological abnormalities and the resulting clinical symptoms associated with HCM are attributable to the hypertrophic process itself, in the absence of outflow tract obstruction (Figs. 9 & 10). Myocardial ischemia causing angina pectoris results from an increased myocardial oxygen demand in the hypertrophied ventricle that cannot be met by physiological coronary vasodilation, even when the large epicardial coronary vessels are normal. In addition, hyperplastic changes in the smaller penetrating coronary vessels may restrict flow [35]. Dyspnea is primarily the consequence of diastolic dysfunction: active relaxation is impaired and passive stiffness of the ventricle also may be increased. This results in elevated left atrial pressures and pulmonary congestion, particularly when the heart rate is increased during exercise. Pulmonary venous pressure increases further when mitral regurgitation is superimposed as a component of obstructive HCM.

Both ventricular and supraventricular arrhythmias are common in HCM and produce symptoms directly or indirectly by provoking ischemia or increasing left atrial pressures. The special vulnerability of HCM patients to systemic hypotension following the onset of atrial fibrillation has already been noted.

Sudden death in HCM may result from several mechanisms. Primary dysrhythmias probably account for most fatalities, but neurogenic vasodepressor reflexes, circulatory collapse resulting from severe obstsruction, or myocardial ischemia are implicated as well [36].

Genetics

Roughly half of patients with newly diagnosed HCM will have affected relatives, but this figure underestimates the contribution of genetic factors to the disease. Familial HCM, with a few exceptions we will discuss later, is inherited as an autosomal dominant trait, with variable penetrance [37] (Fig. 11). Thus, 50% of offspring of affected individuals will inherit the disease, and between 60 and 100% of these will exhibit clinically detectable manifestations of HCM. In patients known to carry a defective gene causing HCM, ventricular hypertrophy may or may not be evident in infancy, but usually increases during childhood and particular following puberty. Even when the family history is negative, HCM is likely to have a genetic basis. Spontaneous mutations in the disease-causing genes appear to be relatively common [15].

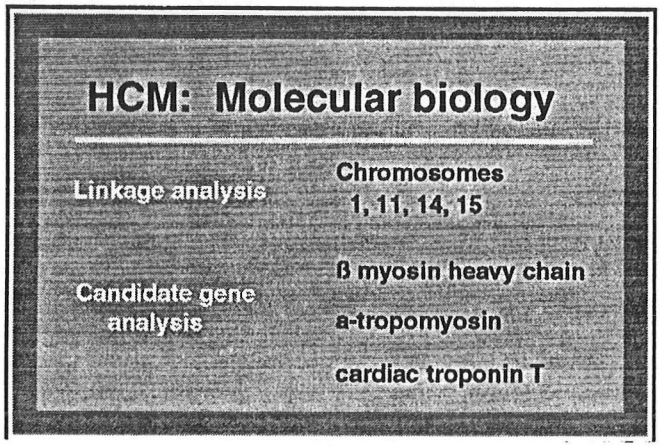


Fig. 11

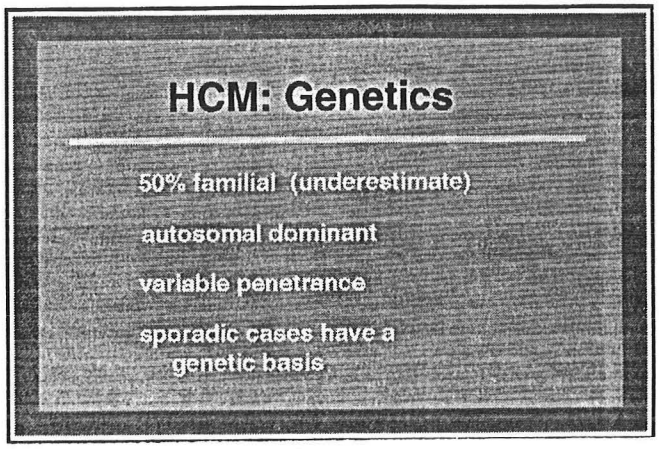


Fig. 12

HCM is genetically heterogeneous [38, 39], and linkage analysis has mapped disease-related genes to four different chromosomes (Fig. 12). The mutations that cause disease have then been defined using a candidate gene approach. The first mutation to be definitively associated with HCM was identified in 1990 by Christine Seidman and colleagues within the ß myosin heavy chain gene on chromosome 14 [14]. Subsequently, over 30 different mutations in this gene have been identified in kindreds with HCM [40]. Most kindreds have novel mutations, and even when identical mutations have been found in different kindreds, haplotype analysis has indicated that these arose as independent mutational events [41], rather than from a common ancestor.

In 1994 the Seidman group has reported that mutations within two other genes, α-tropomyosin from chromosome 15, and cardiac troponin T from chromosome 1, segregate uniformly with the disease in other kindreds [42]. The disease-related gene on chromosome 11 remains to be identified.

Cell and molecular biology

How do these mutations cause disease? The genetic information acquired to date indicates that HCM is fundamentally a disease of the sarcomere -- the complex macromolecular structure that generates the mechanical force of muscle contraction. The three disease-related genes identified so far each encode proteins with different but essential roles in sarcomeric function. ß-myosin heavy chain is a large molecule that comprises the major constituent of the thick filament. Mutations in the ß-MHC gene, a partial list of which is illustrated in Fig. 13, result in amino acid substitutions within the globular head domain that contacts actin and hydrolyzes ATP, or in the hinge region by which the head is connected to the rod-like carboxyl terminal region that forms the thick filament. Most of the disease-causing mutations alter either the charge or hydrophobicity of the affected amino acid side chain, but this is not uniformly true.

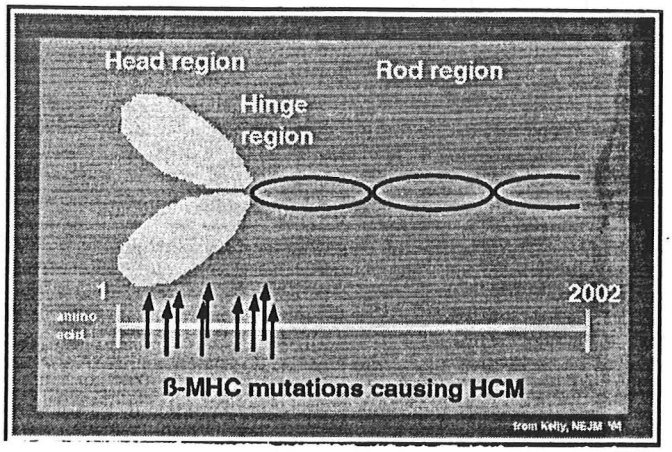


Fig. 13

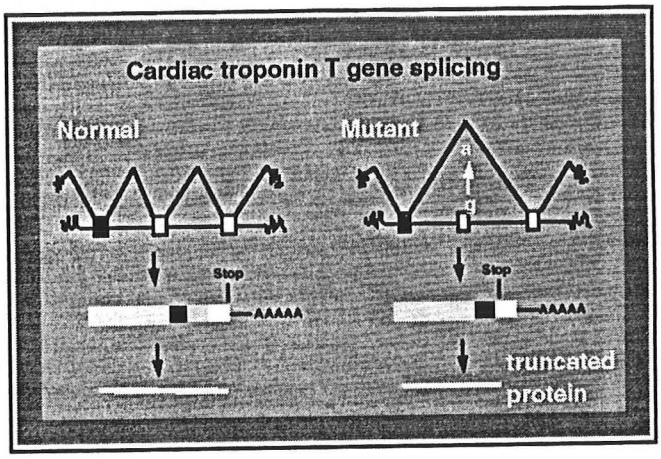
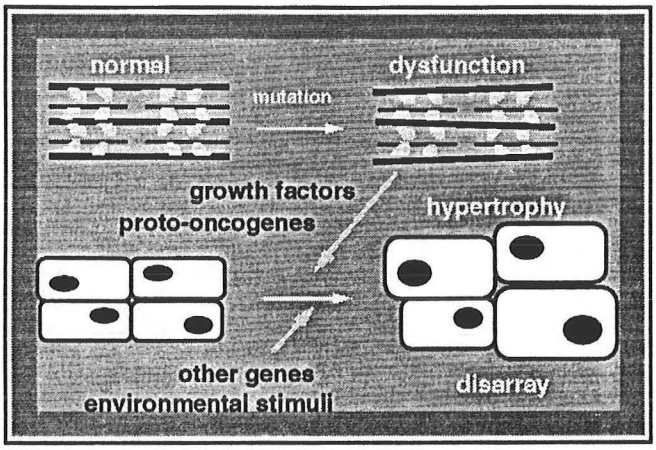


Fig. 14

Troponin T and α-tropomyosin are constituents of the thin filament, where they function in calcium-dependent regulation of the actin-myosin interaction. Similarly to the HCM-associated mutations in the ß-myosin heavy chain gene, most of the mutations in these genes alter a single amino acid within the protein. One HCM kindred, however, carries a different kind of mutation in the cardiac troponin T gene that results in aberrant splicing of primary RNA transcripts (Fig. 14). In this family, a G-to-A nucleotide base substitution in the intron sequence that comprises the splice donor site of exon 15 leads to exclusion of this exon from the mature mRNA [42]. The polypeptide produced from this aberrantly spliced mRNA is truncated, both because the codons contained within exon 15 are missing, and because the junction of exons 14 and 16 produces a frameshift and a premature stop codon. At this time, it is not known whether this truncated troponin T protein is incorporated into the sarcomere or whether the protein is unstable. An analogous splicing mutation (*upheld*^{2}) that truncates the carboxyl terminal of troponin T in flight muscles of *Drosophila melanogaster* functions as a null allele [43]. If this human mutation in the cardiac troponin T gene essentially generates a null allele, the implication is that abnormal stoichiometry among the contituents of the sarcomere, as well as incorporation of

structurally abnormal proteins, can serve as the proximate stimulus to the development of HCM.

Mutations in these sarcomeric proteins act in a dominant negative manner, meaning that they cause disease even in the presence of a normal allele. Sarcomeres of affected patients carrying ßMHC mutations include both normal and mutant forms of the protein. The presence of an abnormal protein within the sarcomere apparently disrupts contractile function, triggering a process that involves autocrine elaboration of peptide growth factors [44], activation of latent proto-oncogenes [45], and increased gene transcription and protein synthesis to promote enlargement of mycardial cells (Fig. 15). In some areas within the heart, this cellular hypertrophy is accompanied by disruption of the normal intracellular and supracellular architecture, producing the bizarre myofibrillar and cellular disarray first observed by Teare in 1958 [3].



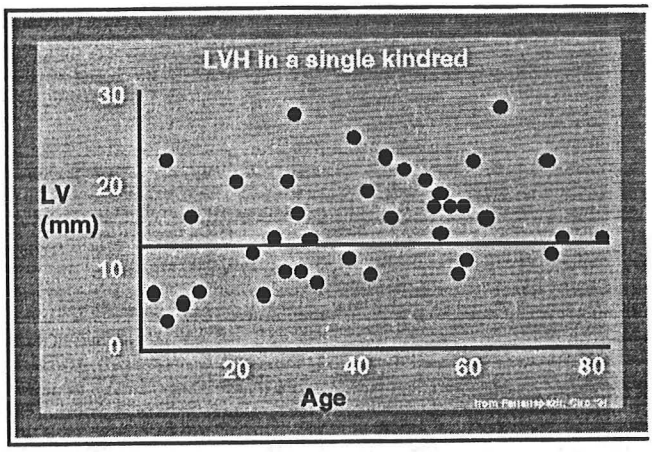


Fig. 15. From sick sarcomeres to hypertrophy and fiber disarray.

Fig. 16

Although the process leading to cardiac hypertrophy is triggered by the presence of the abnormal protein, the extent to which hypertrophy actually develops is influenced by many factors. Even among affected members of a single kindred [46], all of whom harbor an identical mutation, the magnitude of hypertrophy may be dramatically variable (Fig. 16). At least part of this variance is likely to be determined by allelic variation at other gene loci. One recent study described greater hypertrophy in HCM patients with the DD genotype at the angiotensin converting enzyme gene locus than in patients with ID or II alleles [47]. Environmental stimuli also influence the phenotypic consequences of a given mutation, as evidenced by the observed progression of hypertrophy in some patients during puberty.

Several different model systems are currently available to explore the mechanisms by which cellular hypertrophy and disorganization arise in HCM. Mutant myosin molecules have been observed to have abnormal interactions with actin in sarcomeres reconstituted *in vitro* [48, 49]. Likewise, abnormalities of sarcomeric assembly and structure result from forced expression of mutant myosin transgenes in cultured cells [50]. Leslie Leinwand and colleagues have generated lines of transgenic mice engineered to express α-MHC genes

carrying substitution mutations that recapitulate disease-causing mutation in human ß-MHC. Note that α-MHC is the dominant isoform expressed in the adult rodent heart whereas ß-MHC dominates in humans and other large mammals. Although no published data are yet available, preliminary reports (L. Leinwand: personal communication) indicate that these animals develop cardiac hypertrophy within the first few weeks of life, and exhibit cellular disarray in the myocardium resembling that seen in human HCM.

HCM also occurs as a consequence of mutations in mitochondrial DNA [51] (Fig. 17). Asymmetric or concentric ventricular hypertrophy is particularly common in patients with the maternally inherited MELAS (mitochondrial encephalopathy with lactic acidosis and stroke-like episodes) or MERRF (mitochondrial encephalopathy with ragged red fibers) syndromes, which arise secondary to mutations in the mitochondrial $tRNA^{Leu}$ and $tRNA^{Lys}$ genes, respectively [52]. HCM also occurs in patients with point mutations in protein-coding regions of mtDNA [53], or with defects in nuclear genes encoding proteins involved in energy metabolism [54, 55]. The association of HCM with these defects that impair oxidative phosphorylation suggests that a deficiency in energy supply, as well as abnormal sarcomeric proteins, can provide the trigger to cellular responses leading to hypertrophy.

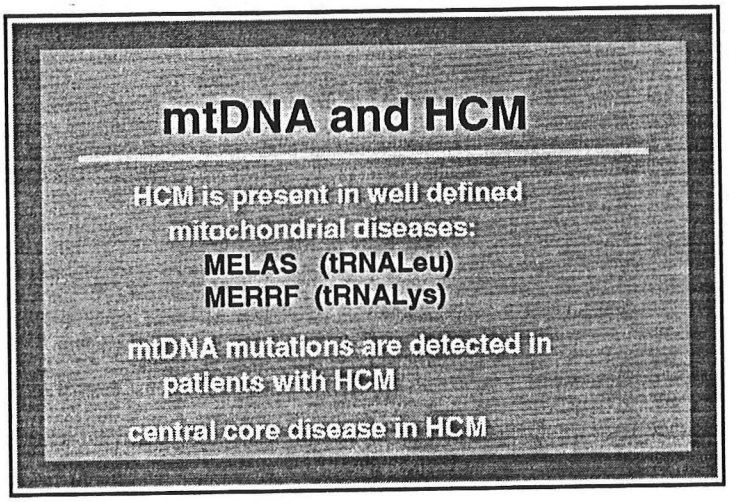


Fig. 17

In patients with otherwise unexplained HCM, sensitive assays based on the polymerase chain reaction identify an unexpectedly high prevalence of mutated forms of mitochondrial DNA [56]. It remains to be determined, however, whether this finding represents an secondary response to cellular injury that bears no physiological consequence, or whether acquired mutations in the mitochondrial genome influence the course of the disease. Interestingly, some patients with HCM exhibit a histological picture in their skeletal muscles known as central core disease [57], in which mitochondria degenerate within the central region of the muscle fibers.

Management

Current management of patients with HCM is complex, and depends on a variety of factors (Fig. 18). In asymptomatic patients detected fortuitously or by screening relatives of probands, counseling and risk stratification are the paramount goals (Fig. 19). Quantifying risk for sudden death in HCM is a very imperfect art [58, 59], since factors such as the magnitude of hypertrophy or obstruction, which intuitively should be helpful, in fact are not. There has been some recent enthusiasm for genotyping as an aid to prognostication (Figs. 20 & 21). Indeed, certain mutations in the myosin heavy chain gene, as studied in multiple kindreds, appear to be compatible with survival to advanced age and with virtually normal overall survival curves. Other mutations appear to carry a different prognosis within different kindreds from the same ethnic background, or from different ethnic backgrounds [46, 60-62]. At this time, therefore, genotyping of individual patients outside of well defined kindreds would only rarely provide prognostic information.

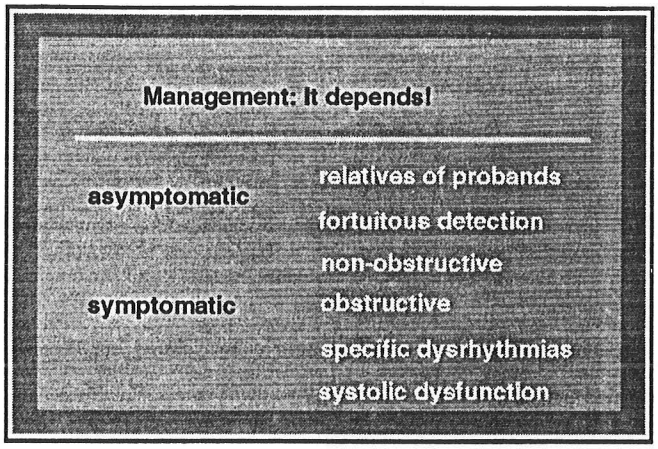


Fig. 18

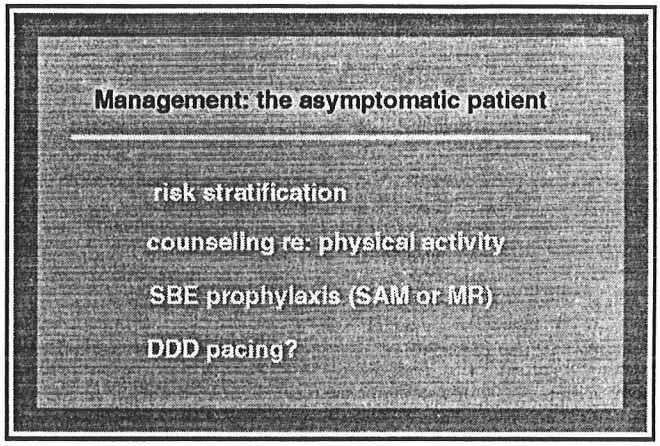


Fig. 19

Even asymptomatic patients with structually abnormal ventricles should be advised to forego vigorous physical exercise because of the risk of sudden death. Only in rare circumstances may it be appropriate to relax this prohibition. In obstructive HCM, abnormal contacts between the ventricular septum and the mitral valve lead to endothelial changes that increase risk for endocarditis [63], and antibiotic prophylaxis is advised during procedures associated with bacteremia.

Should asymptomatic patients with HCM receive more aggressive therapy to reduce their risk for sudden death or to slow progression of the disease? This question carries particular importance for patients detected in childhood, when ventricular hypertrophy may be minimal or absent. At this time, no definitive answer is available. Recently, however, clinical investigators working in this field have proposed treatment of asymptomatic patients, including children, with DDD pacing, with the goal of delaying progression of hypertrophy [64]. This interesting new treatment modality will be discussed in detail subsequently. In addition, implantation of automated defibrillators in affected but

minimally symptomatic members of kindreds with highly malignant family histories and inducible ventricular arrhythmias may be justifiable.

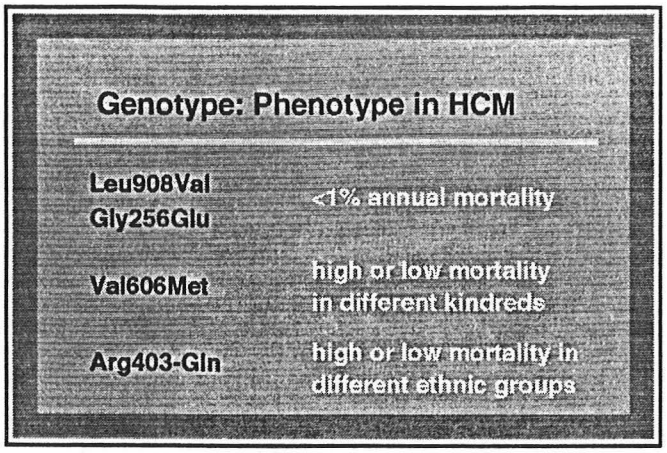


Fig. 20

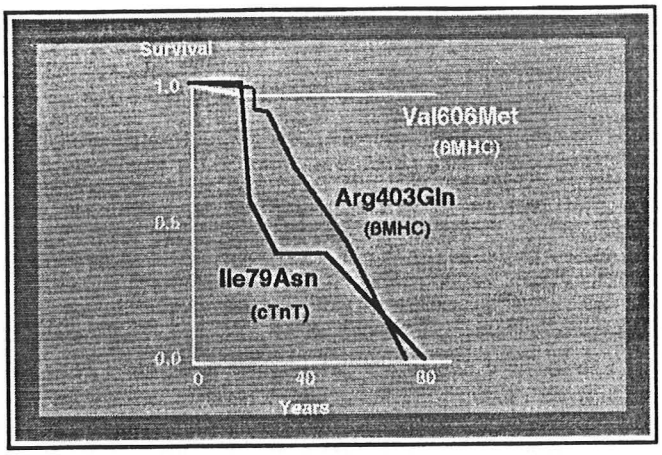


Fig. 21

Patients with angina or dyspnea occurring in the hypercontractile phase of HCM (Fig. 22) can gain symptomatic relief with negative inotropes, including ß-blockers, Ca++ channel antagonists, or disopyramide [65, 66]. Accurate diagnosis is essential, particularly in discriminating patients with HCM from those with angina or dyspnea due to other conditions, in that cardiac glycosides, diuretics, nitrates and other vasodilators used appropriately in patients with coronary atherosclerotic disease or congestive heart failure may be ineffective or have deleterious effects in patients with HCM. Patients with obstructive HCM and symptoms refractory to medical therapy can be treated surgically by septal myotomy-myectomy [67, 68]. In this procedure, a tissue block is removed from the left ventricular face of the intraventricular septum. leading to substantial reduction in fixed or provocable aortic outflow gradients and improvement in functional class.

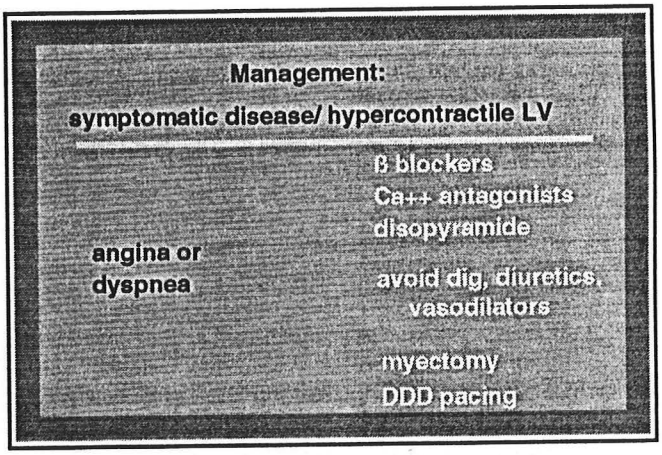


Fig. 22

Mitral valve replacement may accompany myectomy in patients with severe mitral regurgitation, and may play a role in relief of outflow tract obstruction. Operative mortality has been reported at 5-10%.

Within the last 3 years, Lameh Fananapazir and colleagues from the NIH have developed an innovative new approach to the treatment of medically refractory patients with obstructive HCM through the use of DDD pacing [69-71]. The conceptual basis for this strategy is illustrated in Fig. 23. In the typical patient with obstructive HCM, the temporal and spatial pattern of ventricular activation resembles that of the normal heart. Impulses arising from the sinoatrial node traverse the atrium, are slowed during passage through the AV node, and then enter the His-Purkinje system. Activation of the working myocardium is initiated at the ventricular apex and progresses upward and from left to right within the ventricular septum (leftward panel of Fig. 23). By contrast, if ventricular activation is initiated from a pacing electrode placed in the right ventricle, the geometrical progression of septal activation is altered. Such an aberrant pattern of activation was observed to reduce ventricular outflow tract obstruction in acute studies, and long term clinical trials were initiated.

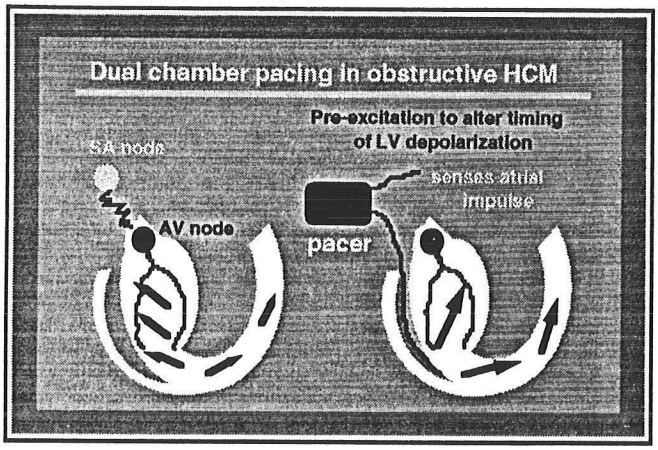


Fig. 23

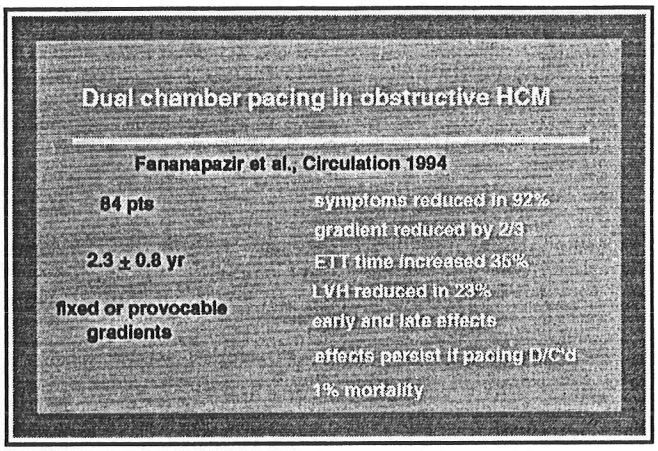


Fig. 24

To maintain physiological heart rate responsiveness while promoting this change in the ventricular activation pattern, the pacemaker is programmed to DDD mode in most patients. Atrial activity controlled by the sinus node is sensed by an atrial electrode, and triggers ventricular activation driven by the pacemaker. The AV interval is programmed to achieve preexication: that is, septal depolarization in advance of the native impulse which is delayed in crossing the AV node. In patients with rapid AV nodal conduction, it may not be possible to achieve preexcition with the pacemaker without compromising ventricular filling, and AV nodal ablation [72] is performed.

In 1992, favorable effects of this intervention were reported in 44 patients who underwent DDD pacing for 6-12 weeks [70], and in December of 1994, a study with longer followup was published [71], the results of which are summarized in Fig. 24. A total of 84 adult patients with obstructive HCM and unremitting symptoms despite medical management were subjected to acute and chronic DDD pacing. Most of these patients would otherwise have been considered appropriate candidates for surgical myotomy-myectomy procedures.

The results are impressive. With a mean follow-up period of 2.3 ± .8 yrs, almost all (92%) of patients improved symptomatically and exercise performance was enhanced. Outflow tract gradients were reduced in most patients and on average declined by 2/3. In addition, this intervention seemed to reduce the extent of ventricular hypertrophy in some patients. Although no contemporaneous control group was studied, mortality in this group of paced patients was low (about 1% annually) relative to historical data on comparable patients.

Several other points raised in this study are of interest. First, the acute response to pacing was not a reliable predictor of long term benefit, leading the investigators to conclude that this intervention can be recommended without a preliminary assessment of hemodynamic response to pacing. Second, in a subset of patients who were analyzed after a few weeks of pacing, and again after several months, greater hemodynamic improvement was evident at the second follow-up study than at the first. In other words, at least some of the physiological benefits of this procedure accrue progressively over time, perhaps due to structural remodeling of the ventricle. Further support for this concept was based on the observation that, after long term pacing, manifestations of outflow tract obstruction were reduced, even when the pacemaker was turned off.

Other clinical studies of DDD pacing are underway in the US and abroad, and more information on this promising therapeutic approach should be available in the next few years. Some investigators have commented that the symptomatic and functional benefits of pacemaker therapy of HCM may be based, at least in part, on more aggressive pharmacologic therapy [73]. Admistration of ß blockers or calcium channel antagonists to patients with HCM can be limited by conduction block and bradycardia, which become irrelevant during DDD pacing.

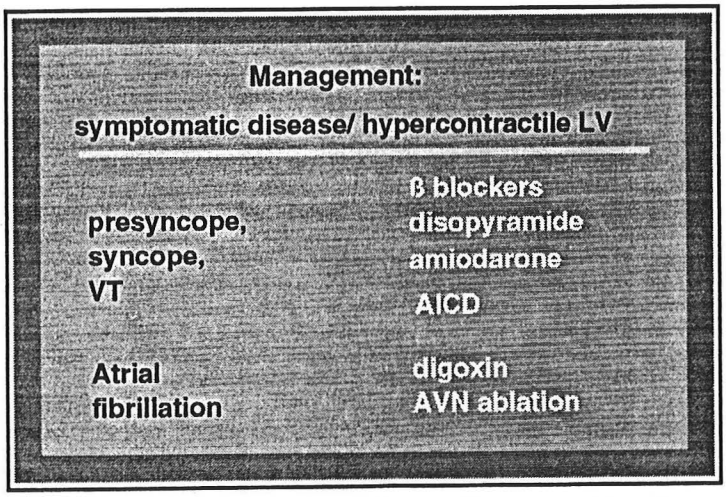
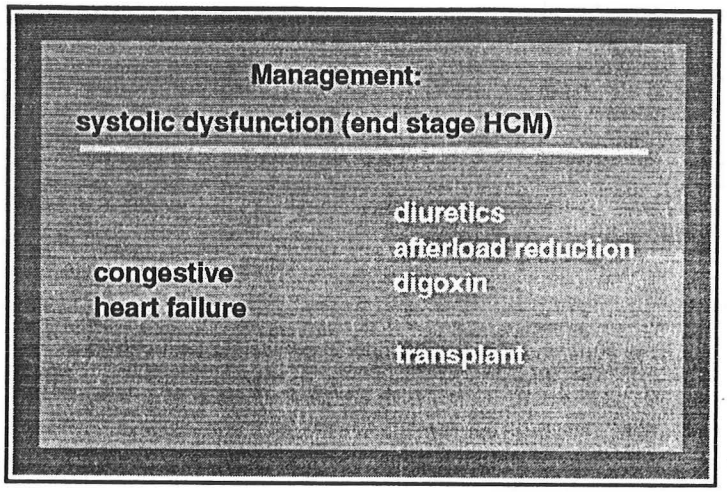


Fig. 25

Symptoms of HCM atributable to dysrhythmias (Fig. 25) sometimes may be controlled by anti-arrhythmic drugs [74, 75] but may require implantable defibrillators. We have already addressed the potentially lethal consequences of atrial fibrillation in HCM. If drug therapy is unable to restore sinus rhythm or to slow the ventricular response sufficiently to overcome the hemodynamic of the loss of atrial systole, then HCM patients with atrial fibrillation should be considered for AV nodal ablation and permanent pacing [72].

Finally, the natural history of HCM in some patients concludes with the development of systolic dysfunction, a dilated ventricle, and frank congestive heart failure [76]. HCM patients presenting in this stage may be difficult to distinguish from those in whom other insults have led to dilated cardiomyopathy. Symptoms attributable to end-stage HCM are managed differently (Fig. 26) from those occuring in the context of a hypercontractile ventricle with predominately diastolic dysfunction. Patients in the dilated phase of HCM are more likely to response to conventional therapy with diuretics or vasodilators than to negative inotropic drugs. Ultimately, cardiac transplantation may be the only recourse.

Fig. 26



The future

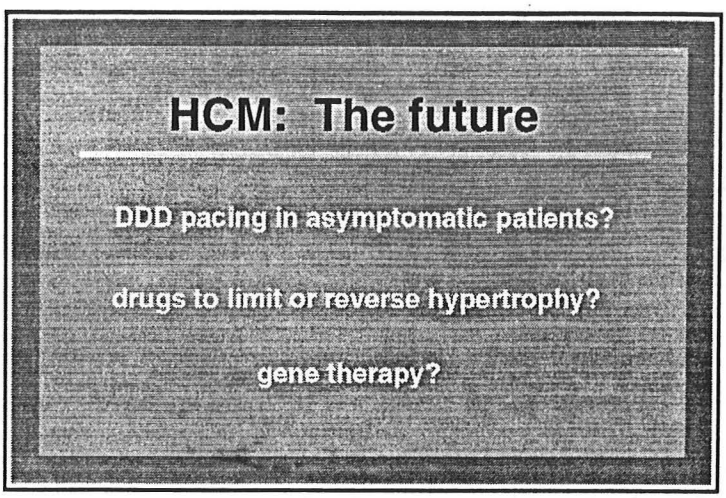
Over the 4 decades since hypertrophic cardiomyopathy was first recognized as a clinical entity, we have acquired a substantially enhanced understanding of this disorder, including an appreciation of its varied manifestation and the stunning discovery of its proximate genetic cause. In addition, we have gained important insights into the pathophysiology of HCM, and effective, albeit palliative, therapeutic measures are now available. What about the next ten years?

The dramatic effects of DDD pacing merit more detailed study, and already some investigators are extending clinical trials of this intervention to patients with non-obstructive or latent disease, including children [73]. This mode of therapy, whatever its merits, will not, however, correct the underlying defect, and even the most optimistic projections of its application will leave a substantial burden of morbidity and mortality in patients with HCM.

The recent identification of specific genetic lesions that cause HCM raises our hopes for more definitive therapies, based either on the development of drugs that would render the effects of the defective gene innocuous, or on gene therapy. Pharmacologic agents already exist to mitigate the effects of signaling molecules that modulate myocardial hypertrophy (e.g. angiotensin converting enzyme inhibitors and endothelin antagonists), and these have been applied successfully to control pathological cardiac hypertrophy and ventricular remodeling in hypertension or following myocardial infarction. Unfortunately, the vasodilating effects of currently approved drugs with these effects limit their use in HCM,

but perhaps other agents can be developed with more selective effects on the hypertrophic process.

Fig. 27



Direct gene therapy is appealing, in principle, but may be even more difficult to achieve in this condition than in other cardiovascular diseases, for several reasons. Most importantly, the dominant negative effect of the mutant proteins demands that the defective allele must be disabled or eliminated. It will not be sufficient simply to insert an additional copy of the wild type gene. Moreover, silencing of the mutant allele must be accomplished in post-mitotic cells in which homologous recombination for modification or replacement of endogenous genes is infeasible at the current time. A further complexity arises from the likelihood that a reasonably strict stoichiometry in the expression of sarcomeric proteins must be maintained to avoid triggering the series of events that leads to clinical HCM. Thus, silencing of the defective allele would have to be accompanied by some additional measure to restore expression of the wild type protein to physiological levels. Finally, it seems likely that therapeutic transgenes, if they could be identified, must be delivered to virtually the entire population of cardiomyocytes within the heart, and no current gene transfer methods come close to achieving this goal.

On a more optimistic note, we can reasonably expect to learn a great deal from experiments now in progress in several laboratories with respect to the mechanisms by which mutant sarcomeric proteins produce disease. Perhaps it will prove possible to exploit this information to engineer novel proteins designed to circumvent the dominant negative effects of specific HCM-causing mutations, and restore normal sarcomeric function using transgenes, even in the face of continued activity of the mutant allele. The ultimate goal, of course, would be direct correction of the mutant DNA sequence *in situ* within the host chromosome. Perhaps the burgeoning knowledge of the enzymology of recombination, integration, and DNA repair eventually can be harnassed for this purpose.

References

1. Liouville H. Retrecissement ventriculo-aortique. *Gazette Med Paris.* 1869; 24: 161-163.
2. Davies LG. Familial heart disease. *Br Heart J.* 1952; 14: 206-212.
3. Teare RD. Assymmetrical hypertrophy of the heart in young adults. *Br Heart J.* 1958; 20: 1-8.
4. Brock R. Functional obstruction of the left ventricle (acquired aortic subvalvular stenosis). *Guy's Hosp Rep.* 1957; 106: 221-238.
5. Braunwald E, Morrow AG. Idiopathic hypertrophic subaortic stenosis: hemodynamic and angiographic manifestatations. *Am J Med.* 1960; 29: 924-945.
6. Wigle ED, O. HR, Gunton RW. Idiopathic ventricular septal hypertrophy causing muscular subaortic stenosis. *Circ.* 1962; 26: 325-340.
7. Nishiyama S, Yamaguchi H, Isimura T, Nayasaki F, Takatsu F, Umeda T, Machii K. Echocardiographic features of apical hypertrophic cardiomyopathy. *J Cariogr.* 1978; 8: 177-183.
8. Abbasi AS, MacAplin RN, Eber LM, Pearce ML. Echocardiographic diagnosis of idiopathic hypertrophic cardiomyopathy without outflow obstruction. *Circ.* 1972; 46: 897-904.
9. Abbasi AS, MacAplin RN, Eber LM, Pearce ML. Left ventricular hypertrophy diagnosed by echocardiography. *N Engl J Med.* 1973; 289: 118-121.
10. Henry WL, Clark CE, Epstein SE. Asymmetric septal hypertrophy (ASH): echocardiographic identification of the pathognomonic anatomic abnormality of IHSS. *Circ.* 1973; 47: 225-233.
11. Maron BJ, Fananapazir L. Sudden cardiac death in hypertrophic cardiomyopathy. *Circulation.* 1992; .
12. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. *A Am Coll Cardiol.* 1986; 7: 204-14.
13. Jarcho JA, McKenna W, Pare JA, Solomon SD, Holcombe RF, Dickie S, Levi T, Donis KH, Seidman JG, Seidman CE. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. *N Engl J Med.* 1989; 321: 1372-8.
14. Geisterfer LA, Kass S, Tanigawa G, Vosberg HP, McKenna W, Seidman CE, Seidman JG. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell.* 1990; 62: 999-1006.
15. Watkins H, Thierfelder L, Hwang DS, McKenna W, Seidman JG, Seidman CE. Sporadic hypertrophic cardiomyopathy due to de novo myosin mutations. *J Clin Invest.* 1992; 90: 1666-71.
16. Maron BJ, Bonow RO, Cannon R, Leon MB, Epstein SE. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (1). *N Engl J Med.* 1987; 316: 780-9.
17. Maron BJ, Bonow RO, Cannon R, Leon MB, Epstein SE. Hypertrophic cardiomyopathy. Interrelations of clinical manifestations, pathophysiology, and therapy (2). *N Engl J Med.* 1987; 316: 844-52.
18. Maron BJ, Goldenberg IF, Pedersen WR. Management of hypertrophic cardiomyopathy. *Heart Dis Stroke.* 1993; 2: 203-8.
19. Maron BJ. Hypertrophic cardiomyopathy. *Curr Probl Cardiol.* 1993; 18: 639-704.
20. J. Wynne and E. Braunwald. The cardiomyopathies and myocarditides, in *Heart Disease: a textbook of cardiovascular medicine.* E Braunwald, Editor. 1988, W.B. Saunders Company: Philadephia. 1410-14690.
21. Louie EK, Edwards LC. Hypertrophic cardiomyopathy. *Prog Cardiovasc Dis.* 1994; 36: 275-308.
22. Kelly DP, Strauss AW. Inherited cardiomyopathies. *N Engl J Med.* 1994; 330: 913-919.

23. Maron BJ, Lipson LC, Roberts WC, Savage DS, Epstein SE. Malignant hypertrophic cardiomyopathy: identification of a subgroup of families with unusually frequent premature death. *Am J Cardiol.* 1978; 41: 1133-1140.
24. Spirito P, Chiarella F, Carratino L, Berisso MZ, Bellotti P, Vecchio C. Clinical course and prognosis of hypertrophic cardiomyopathy in an outpatient population [see comments]. *N Engl J Med.* 1989; 320: 749-55.
25. McKenna WJ. The natural history of hypertrophic cardiomyopathy. *Cardiovasc Clin.* 1988; 19: 135-48.
26. Epstein SE, Maron BJ, Hypertrophic cardiomyopathy: an overview, in *Hypertrophic Cardiomyopathy,* M Kaltenbach and SE Epstein, Editors. 1982, Springer-Verlag: Berlin. p. 5-17.
27. Rakowski H, Sasson Z, Wigle ED. Echocardiographic and Doppler assessment of hypertrophic cardiomyopathy. *J Am Soc Echocardiogr.* 1988; 1: 31-47.
28. Sasson Z, Rakowski H, Wigle ED, Popp R. Echocardiographic and Doppler studies in hypertrophic cardiomyopathy. *Cardiol Clin.* 1990; 8: 217-32.
29. Ferrans VJ, Morrow AG, Roberts WC. Myocardial ultrastructure in idiopathic hypertrophic subaortic stenosis. *Circ.* 1972; 45: 769-792.
30. Maron BJ, Roberts WC. Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy. *Circ.* 1979; 59: 689-706.
31. Rosenzweig A, Watkins H, Hwang DS, Miri M, McKenna W, Traill TA, Seidman JG, Seidman CE. Preclinical diagnosis of familial hypertrophic cardiomyopathy by genetic analysis of blood lymphocytes. *N Engl J Med.* 1991; 325: 1753-60.
32. Bjarnason I, Hardarson T, Jonsson S. Cariac arrhythmias in hypertrophic cardiomyopathy. *Br Heart J.* 1982; 48: 198-218.
33. Fananapazir L, Epstein SE. Value of electrophysiologic studies in hypertrophic cardiomyopathy treated with amiodarone. *Am J Cardiol.* 1991; 67: 175-82.
34. Murgo JP. The hemodynamic evaluation in hypertrophic cardiomyopathy: systolic and diastolic dysfunction. *Cardiovasc Clin.* 1988; 19: 193-220.
35. Maron BJ, Wolfson JK, Epstein SE, Roberts WC. Intramural ("small vessel") coronary artery disease in hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1986; 8: 545-552.
36. Dilsizian V, Bonow RO, Epstein SE, Fananapazir L. Myocardial ischemia detected by thallium scintigraphy is frequently related to cardiac arrest and syncope in young patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 1993; 22: 796-804.
37. Maron BJ, NIchols PF, Pickle LW, Wesley YE, Mulvihill JJ. Patterns of inheritance in hypertrophic cardiomyopathy: assessment by M-mode and two-dimensional echocardiogrphy. *Am J Cardiol.* 1984; 53: 1087-94.
38. Solomon SD, Jarcho JA, McKenna W, Geisterfer LA, Germain R, Salerni R, Seidman JG, Seidman CE. Familial hypertrophic cardiomyopathy is a genetically heterogeneous disease. *J Clin Invest.* 1990; 86: 993-9.
39. Epstein ND, Fananapazir L, Lin HJ, Mulvihill J, White R, Lalouel JM, Lifton RP, Nienhuis AW, Leppert M. Evidence of genetic heterogeneity in five kindreds with familial hypertrophic cardiomyopathy. *Circulation.* 1992; 85: 635-47.
40. Solomon SD, Wolff S, Watkins H, Ridker PM, Come P, McKenna WJ, Seidman CE, Lee RT. Left ventricular hypertrophy and morphology in familial hypertrophic cardiomyopathy associated with mutations of the beta-myosin heavy chain gene. *J Am Coll Cardiol.* 1993; 22: 498-505.
41. Watkins H, Thierfelder L, Anan R, Jarcho J, Matsumori A, McKenna W, Seidman JG, Seidman CE. Independent origin of identical beta cardiac myosin heavy-chain mutations in hypertrophic cardiomyopathy. *Am J Hum Genet.* 1993; 53: 1180-5.
42. Thierfelder L, Watkins H, MacRae C, Lamas R, McKenna W, Vosberg HP, Seidman JG, Seidman CE. Alpha-tropomyosin and cardiac troponin T mutations cause

familial hypertrophic cardiomyopathy: a disease of the sarcomere. *Cell.* 1994; 77: 701-12.
43. Fyrberg E, Fyrberg CC, Beall C, Saville DL. Drosophila melanogaster troponin-T mutations engender three distinct syndromes of myofibrillar abnormalities. *J Mol Biol.* 1990; 216: 657-675.
44. Sadoshima J, Xu Y, Slayter HS, Izumo S. Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. *Cell.* 1993; 75: 977-84.
45. Aoyagi T, Izumo S. Mapping of the pressure response element of the c-fos gene by direct DNA injection into beating hearts. *J Biol Chem.* 1993; 268: 27176-9.
46. Fananapazir L, Epstein ND. Genotype-phenotype correlations in hypertrophic cardiomyopathy. Insights provided by comparisons of kindreds with distinct and identical beta-myosin heavy chain gene mutations. *Circulation.* 1994; 89: 22-32.
47. Lechin M, Yu QT, Workman R, Greve G, Roberts R. Angiotensin converting enzyme genotype DD is associated with increased left ventricular mass in patients with hypertrophic cardiomyopathy. *Circ.* 1994; 90: I-174 (abstract).
48. Cuda G, Fananapazir L, Zhu WS, Sellers JR, Epstein ND. Skeletal muscle expression and abnormal function of beta-myosin in hypertrophic cardiomyopathy. *J Clin Invest.* 1993; 91: 2861-5.
49. Sweeney HL, Straceski AJ, Leinwand LA, Tikunov BA, Faust L. Heterologous expression of a cardiomyopathic myosin that is defective in its actin interaction. *J Biol Chem.* 1994; 269: 1603-5.
50. Straceski AJ, Geisterfer LA, Seidman CE, Seidman JG, Leinwand LA. Functional analysis of myosin missense mutations in familial hypertrophic cardiomyopathy. *Proc Natl Acad Sci U S A.* 1994; 91: 589-93.
51. Williams RS. Cardiac involvement in mitochondrial diseases, and vice versa. *Circ.* 1995; 91: (in press).
52. Anan R, Nakagawa M, Miyata M, Higuchi I, Nakao S, Suehara M, Osame M, Tanaka H. Cardiac involvement in mitochondrial diseases: A study on 17 patients with documented mitochondrial DNA defects. *Circulation.* 1995; XX: XXX-XX.
53. Pastores GM, Santorelli FM, Shanske S, Gelb BD, Fyfe B, Wolfe D, Willner JP. Leigh syndrome and hypertrophic cardiomyopathy in an infant with a mitochondrial DNA point mutation (T8993G). *Am J Med Genet.* 1994; 50: 265-71.
54. Angelini C, Melacini P, Valente ML, Reichmann H, Carrozzo R, Fanin M, Vergani L, Boffa GM, Martinuzzi A, Fasoli G. Hypertrophic cardiomyopathy with mitochondrial myopathy. A new phenotype of complex II defect. *Jpn Heart J.* 1993; 34: 63-77.
55. Elleder M, Shin YS, Zuntova A, Vojtovic P, Chalupecky V. Fatal infantile hypertrophic cardiomyopathy secondary to deficiency of heart specific phosphorylase b kinase. *Virchows Arch A Pathol Anat Histopathol.* 1993; 423: 303-7.
56. Obayashi T, Hattori K, Sugiyama S, Tanaka M, Tanaka T, Itoyama S, Deguchi H, Kawamura K, Koga Y, Toshima H, et al. Point mutations in mitochondrial DNA in patients with hypertrophic cardiomyopathy. *Am Heart J.* 1992; 124: 1263-9.
57. Fananapazir L, Dalakas MC, Cyran F, Cohn G, Epstein ND. Missense mutations in the beta-myosin heavy-chain gene cause central core disease in hypertrophic cardiomyopathy. *Proc Natl Acad Sci U S A.* 1993; 90: 3993-7.
58. Vassalli G, Seiler C, Hess OM. Risk stratification in hypertrophic cardiomyopathy. *Curr Opin Cardiol.* 1994; 9: 330-6.
59. DeRose JJ, Banas JJ, Winters SL. Current perspectives on sudden cardiac death in hypertrophic cardiomyopathy. *Prog Cardiovasc Dis.* 1994; 36: 475-84.
60. Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med.* 1992; 326: 1108-14.

61. Epstein ND, Cohn GM, Cyran F, Fananapazir L. Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the beta-myosin heavy chain gene. A 908Leu----Val mutation and a 403Arg----Gln mutation. *Circulation.* 1992; 86: 345-52.
62. Watkins H, McKenna W, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, Spirito P, Matsumori A, Moravec CS, Seidman JG, Seidman CE. The role of cardiac troponin T and alpha tropomyosin mutations in hypertrophic cardiomyopathy. 1995; *(pre-publication preprint made available by the authors).*
63. Alessandri N, Pannarale G, del MF, Moretti F, Marino B, Reale A. Hypertrophic obstructive cardiomyopathy and infective endocarditis: a report of seven cases and a review of the literature. *Eur Heart J.* 1990; 11: 1041-8.
64. Rishi F, Hulse JE, Sharma S, Kanter KR, Williams WH, Dooley KJ, Auld D, McRae GJ, Clark LJ, Campbell RM. Permanent dual chamber pacing in pediatric patients with hypertrophic obstructive cardiomyopathy. *Circ.* 1994; 90: I-98 (abstract).
65. Goodwin JF. Pharmacologic treatment of hypertrophic cardiomyopathy: beta-blockade or calcium blockade or what? [editorial]. *Cardiovasc Drugs Ther.* 1988; 1: 665-8.
66. Bonow RO. Effects of calcium-channel blocking agents on left ventricular diastolic function in hypertrophic cardiomyopathy and in coronary artery disease. *Am J Cardiol.* 1985; 55: .
67. Bonow RO, Maron BJ, Leon MB, Cannon R, Epstein SE. Medical and surgical therapy of hypertrophic cardiomyopathy. *Cardiovasc Clin.* 1988; 19: 221-39.
68. Seiler C, Hess OM, Schoenbeck M, Turina J, Jenni R, Turina M, Krayenbuehl HP. Long-term follow-up of medical versus surgical therapy for hypertrophic cardiomyopathy: a retrospective study. *J Am Coll Cardiol.* 1991; 17: 634-42.
69. McAreavey D, Fananapazir L. Altered cardiac hemodynamic and electrical state in normal sinus rhythm after chronic dual-chamber pacing for relief of left ventricular outflow obstruction in hypertrophic cardiomyopathy. *Am J Cardiol.* 1992; 70: 651-6.
70. Fananapazir L, Cannon R3, Tripodi D, Panza JA. Impact of dual-chamber permanent pacing in patients with obstructive hypertrophic cardiomyopathy with symptoms refractory to verapamil and beta-adrenergic blocker therapy. *Circulation.* 1992; 85: 2149-61.
71. Cannon R, Tripodi D, Dilsizian V, Panza JA, Fananapazir L. Results of permanent dual-chamber pacing in symptomatic nonobstructive hypertrophic cardiomyopathy. *Am J Cardiol.* 1994; 73: 571-6.
72. Chang AC, McAreavey D, Tripodi D, Fananapazir L. Radiofrequency catheter atrioventricular node ablation in patients with permanent cardiac pacing systems. *Pace Pacing Clin Electrophysiol.* 1994; 17: 65-9.
73. Gras D, Leclerq C, Baisset JM, Paillard F, Mabo P, Daubert C. Is benefit of DDD pacing in obstructive hypertrophic cardiomyopathy due to the possibility of optimizing drug therapy? *Circ.* 1994; 90: I-443 (abstract).
74. Counihan PJ, McKenna WJ. Low-dose amiodarone for the treatment of arrhythmias in hypertrophic cardiomyopathy. *J Clin Pharmacol.* 1989; 29: 436-8.
75. Stewart JT, McKenna WJ. Management of arrhythmias in hypertrophic cardiomyopathy. *Cardiovasc Drugs Ther.* 1994; 8: 95-9.
76. Bingisser R, Candinas R, Schneider J, Hess OM. Risk factors for systolic dysfunction and ventricular dilatation in hypertrophic cardiomyopathy. *Int J Cardiol.* 1994; 44: 225-33.