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Hypertrophic Cardiomyopathy

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Key Points

- Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium that is characterized by ventricular hypertrophy in the absence of identifiable precipitating factors, such as hypertension and aortic stenosis.
- Hypertrophic cardiomyopathy is important as a cause of sudden death in young adults.
- Hypertrophic cardiomyopathy is a familial disorder that is inherited as an autosomal dominant trait. Sporadic cases may occur presumably as a consequence of de novo gene mutations.
- More than 250 HCM-causing mutations have been reported, and mutations in the β-myosin heavy chain and cardiac myosin-binding protein C predominate and account for approximately 80% of the reported cases.
- Obstructive HCM is caused by proximal ventricular septal hypertrophy; some individuals have midventricular obstruction due to hypertrophy, and some individuals have midventricular obstruction due to hypertrophy at the level of the papillary muscles. Impaired diastolic relaxation is also present.
- Myocardial ischemia may occur in both obstructive and nonobstructive types.
- Transthoracic echocardiography is the primary diagnostic modality.

Definition

Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium that is characterized by ventricular hypertrophy in the absence of identifiable precipitating factors such as hypertension and aortic stenosis. Myocardial hypertrophy may affect either ventricle but usually involves the left ventricle (LV). The hallmark diagnostic feature of HCM has been considered to be asymmetric hypertrophy of the interventricular septum (Fig. 56.1). However, two-dimensional echocardiographic studies have demonstrated that the distribution and severity of LV hypertrophy may vary widely.[1–3] Ventricular septal hypertrophy may be associated with systolic anterior motion of the mitral valve and subaortic obstruction of the LV outflow tract. Histologic examination of ventricular myocardium typically shows myocyte hypertrophy, myocyte and myofibrillar disarray, and interstitial fibrosis (Fig. 56.2).

The clinical manifestations of HCM range from minor symptoms such as palpitations and dizziness to syncope and sudden death. Hypertrophic cardiomyopathy is particularly important as a cause of sudden death in young adults.[4] The differential diagnosis of myocardial hypertrophy in young adults may be difficult, particularly for those engaged in competitive athletic activities. The occurrence of sudden death in a number of elite athletes with HCM has focused considerable medical and media attention on this disease. Although initially considered to be a relatively uncommon disorder, recent observations have estimated the prevalence of HCM in the general population to be 1 in 500.[5] Since its first description in 1869,[6] numerous clinical and hemodynamic studies have been performed in attempts to elucidate the pathophysiology of HCM. The various terms ascribed over this time period—*hypertrophic obstructive cardiomyopathy* (HOCM), *asymmetric septal hypertrophy* (ASH), and *idiopathic hypertrophic subaortic stenosis* (IHSS)—reflect the traditional emphasis on the anatomic and hemodynamic features of the interventricular septum and LV outflow tract. Over the last decade, the results of molecular genetics studies have revealed fundamental insights that challenge previous concepts of the pathogenesis of HCM. The discovery that HCM is primarily caused by mutations in genes that encode

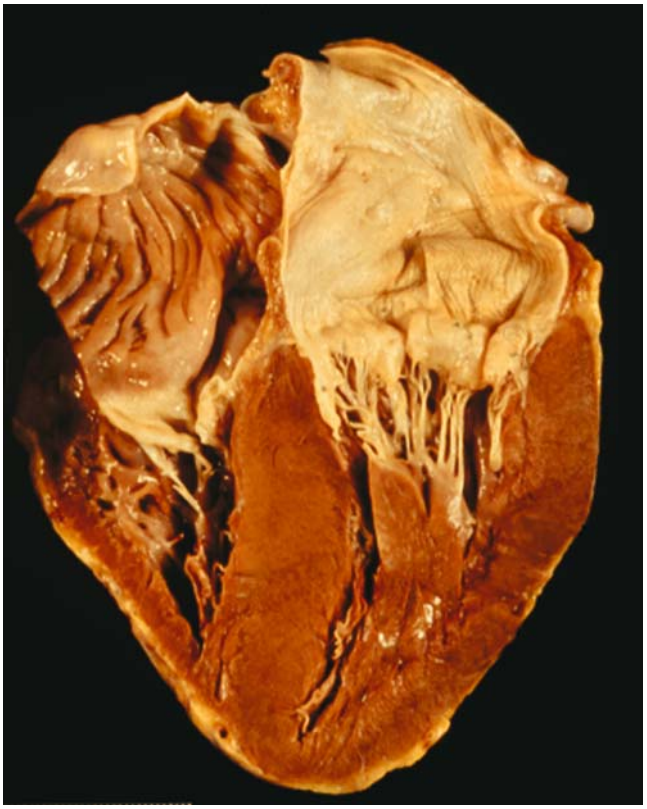

FIGURE 56.1. Gross heart morphology in an individual who had HCM. This section is cut in a longitudinal plane and shows the four cardiac chambers. The left ventricle is markedly hypertrophied with a reduced cavity size. An asymmetric pattern of hypertrophy is present, with predominant involvement of the interventricular septum. The left atrium is enlarged. The right ventricle and right atrium appear relatively normal.

sarcomere proteins has provided an important new framework for understanding the diverse pathologic and clinical manifestations of HCM and a basis for new strategies for diagnosis, prognostic stratification, and therapy. Hypertrophic cardiomyopathy is one of the first examples of an inherited heart disease caused by a single gene defect, and thus it serves as a paradigm for the study of cardiovascular genetic disorders. Current concepts of the pathogenesis, clinical evaluation, natural history, and treatment of HCM are reviewed in this chapter.

Pathogenesis

Genetic Linkage Analyses

Hypertrophic cardiomyopathy is a familial disorder that is inherited as an autosomal dominant trait. Hence, the chance that a child of an affected parent will develop HCM is 50%, and males and females are equally likely to be affected (Fig. 56.3). Sporadic cases of HCM may occur,[7,8] arising presumably from de novo gene mutations. Individuals with sporadic disease also have a 50% likelihood of transmitting HCM to each of their offspring. Genome-wide linkage analyses and mutation screening in families have demonstrated that HCM is a genetically heterogeneous disorder (Table 56.1 and Fig. 56.4).

Hypertrophic Cardiomyopathy Disease Genes

The first HCM disease gene described was the β-myosin heavy chain (MHC) gene that mapped to chromosome 14q12.[9,10] Mutations have been found subsequently in five additional genes that encode proteins associated with the thick filament: α-MHC (chromosome 14q12),[11] cardiac myosin binding protein C (cMyBP-C, chromosome 11p11),[12–14] essential myosin light chain (chromosome 3p21),[15] regulatory myosin light chain (chromosome 12q23-q24),[15] and myosin light chain kinase (chromosome 20q13).[16] Mutations have also been found in five genes that encode thin filament proteins: cardiac troponin T (chromosome 1q32),[17,18] cardiac troponin I (chromosome 19q13),[19] cardiac troponin C (chromosome 3p21-p14),[20] α-tropomyosin (chromosome 15q22),[18,21] and cardiac actin (chromosome 15q14).[22] Recently, mutations in four genes that encode intra- and extrasarcomeric cytoskeletal proteins have been associated with an HCM-like

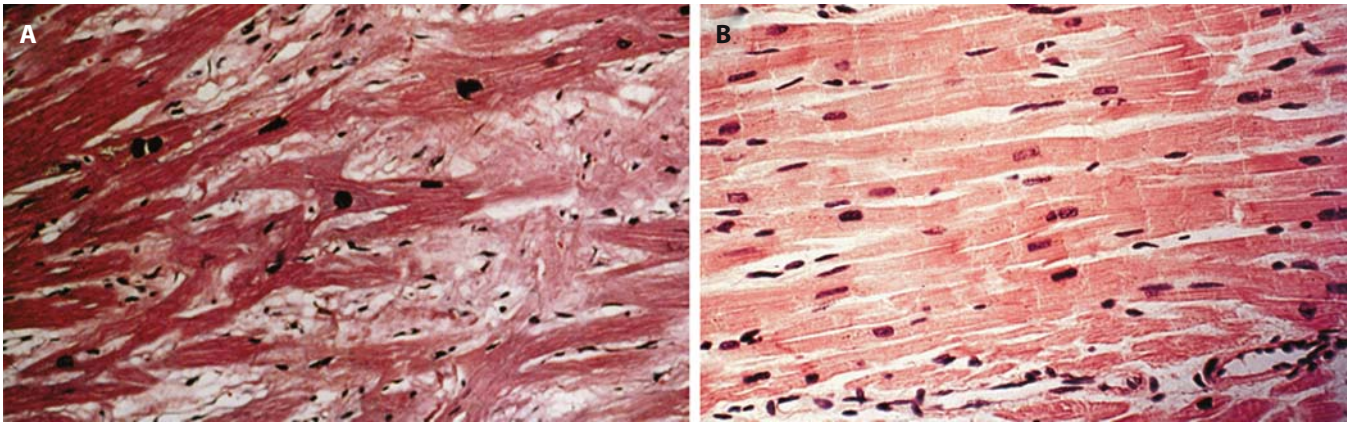

FIGURE 56.2. Histologic specimens of left ventricular myocardium from an individual with HCM (A) and a normal heart (B). The myocardial sections are stained with hematoxylin and eosin. Histopathologic findings in HCM are typified by myocyte hypertrophy with loss of the orderly alignment of sarcomeres (myofibrillar disarray). Myocyte nuclei are enlarged and hyperchromatic. An increased amount of loose intercellular connective tissue is present.

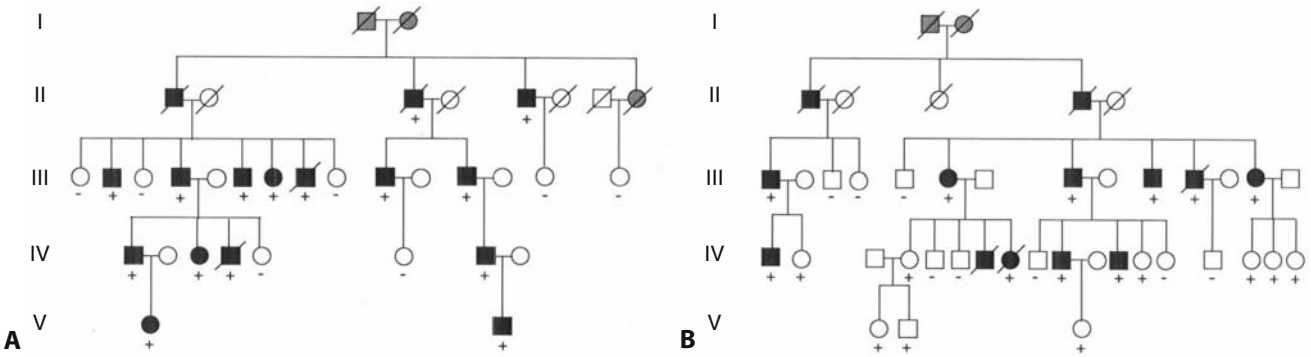

FIGURE 56.3. Pedigrees in 2 families with HCM caused by mutations in the β-myosin heavy chain (β-MHC) gene (A) and cardiac myosin binding protein C gene (B). Generation numbers are indicated in Roman numerals. Squares denote male family members and circles, females. Affected individuals are indicated by solid symbols, and unaffected individuals by clear symbols; individuals in whom the affection status is unknown are indicated by gray symbols. Diagonal slashes denoted deceased family members. Individuals who have the disease (affected) haplotype in genetic linkage analyses are shown as "+" (positive), whereas those without the disease haplotype are shown as "–" (negative). In families with β-MHC gene mutations, the disease penetrance is high; that is, the majority of genotype-positive individuals are also phenotype-positive. In families with cardiac myosin binding protein C gene mutations, symptoms and signs of HCM may not appear until late adulthood; consequently, some individuals in younger generations may be genotype-positive but phenotype-negative.

TABLE 56.1. Disease genes associated with hypertrophic cardiomyopathy

Chromosome locus	*Gene*	*Protein*	*Prevalence (%)*
14q12	MYH7	β-MHC	40
11p11	MYBPC3	Cardiac MyBP-C	>30
1q32	TNNT2	Cardiac troponin T	<15
19q13	TNNI3	Cardiac troponin I	<10
15q22	TPM1	α-tropomyosin	<5
12q23-q24	MYL2	Regulatory MLC	<3
15q14	ACTC	Cardiac actin	<3
3p21	MYL3	Essential MLC	<1
14q12	MYH6	α-MHC	<1
3p21-p14	TNNC1	Cardiac troponin C	<1
20q13	MYLK2	Myosin light chain kinase	<1
2q24	TTN	Titin	<1
11p15	CLP	Cardiac muscle LIM protein	<1
17q12	TCAP	Telethonin	<1
3p25	CAV3	Caveolin-3	<1
6q22	PLB	Phospholamban	<1

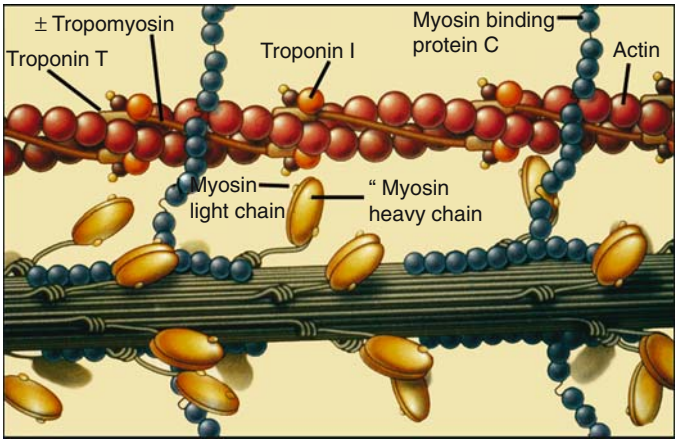

FIGURE 56.4. HCM is caused by mutations in genes that encode sarcomere proteins. The components of the sarcomere in which HCM-causing mutations have been identified most commonly are shown in this schematic: thick filament proteins (myosin heavy chain, regulatory myosin light chain, essential myosin light chain), thin filament proteins (cardiac troponin T, cardiac troponin I, α-tropomyosin and cardiac actin), and cardiac myosin binding protein C.

phenotype: titin (chromosome 2q24),[23] muscle LIM protein (chromosome 11p15),[24] Tcap (chromosome 17q12),[25] and caveolin-3 (chromosome 3p25).[26] A mutation in a sarcoplasmic reticulum Ca^{2+}-regulatory protein gene, phospholamban (chromosome 6q22),[27] has also been identified.

Gene Mutations

More than 250 HCM-causing mutations have been reported (go to http://www.cardiogenomics.org). At least 50% of familial HCM and 20% to 30% of sporadic HCM result from mutations in one of the known disease genes. Mutations in the β-MHC and cMyBP-C genes predominate, and together account for approximately 80% of genotyped cases. A variety of mutation types have been found, including missense mutations that result in a single nucleotide substitution, deletions, insertions, and splicing variants, which encode full-length or truncated proteins. In most cases, individuals with HCM-causing mutations are heterozygous at the disease locus, that is, one copy (allele) of the gene has a DNA sequence change and the second copy has normal DNA sequence. Isolated cases have been described of individuals who are homozygous at a disease locus, that is, both copies of the gene have DNA sequence variants.[28,29] Cases of compound-heterozygosity, that is, mutations in more than one disease gene, and double-heterozygosity, that is, more than one mutation in one gene, have also been identified.[30] Homozygosity and complex genotypes have been associated with more severe clinical phenotypes. In general, unrelated individuals have "unique" mutations, although sequence variants may occur relatively more frequently at certain sites, that is, mutation "hot spots." Taken together, these findings have important implications for genetic screening strategies. Screening should not be stopped when one mutation is identified, and the coding sequence of all known disease genes should ideally be evaluated in all cases.

One important question in understanding the pathogenesis of HCM is determination of the mechanism by which a defect in a single gene allele produces a dominant phenotype. Because the majority of HCM mutations are missense mutations, the mechanism by which these cause disease has been assumed to be through dominant negative actions. In this model, the mutant protein is incorporated into the sarcomere but prevents appropriate assembly or function of myofibrils by acting as a "poison polypeptide." An alternative hypothesis is that these mutations function as null alleles ("haploinsufficiency"), which result in an imbalance of stoichiometry of sarcomere proteins. The haploinsufficiency model has been proposed as a potential mechanism to explain HCM caused by gene mutations that encode truncated proteins, such as cMyBP-C and cardiac troponin T.

Differential Diagnosis

Affected individuals in families that map to the chromosome 7q36 locus have a distinct phenotype comprised of LV hypertrophy and ventricular preexcitation [Wolff-Parkinson-White (WPW) syndrome.[31] While this was long considered to be an HCM variant, the discovery of mutations in the γ_2-regulatory subunit of an adenosine monophosphate (AMP)-activated protein kinase (AMPK) has now shown this disorder to be an autosomal dominant–inherited myocardial metabolic storage disease, that is, characterized by glycogen accumulation in cardiomyocytes.[32–34] The clinical course of patients with AMPK mutations is remarkable for progressive development of conduction system disease, manifested as atrioventricular block, which is an atypical finding in HCM.

Mutations in the lysosome-associated membrane protein 2 (*LAMP2*) gene typically cause an X-linked multisystem glycogen-storage disease (Danon's disease), but can also present with predominant cardiac involvement. Clinical features that are suggestive of *LAMP2* defects include male gender, early-onset severe LV hypertrophy, ventricular preexcitation, and elevated serum levels of creatine kinase and alanine aminotransferase.[35] The typical clinical course for affected males is progressive deterioration of cardiac function and significant arrhythmias early in adulthood; in many, fulminant heart failure ensues. The natural history of women who carry one mutant *LAMP2* gene may not be entirely benign; cardiac dysfunction early in middle age has been observed in affected women in some families.

Glycogen storage disorders should be considered in the differential diagnosis of unexplained LV hypertrophy, and have been shown to account for approximately 50% of cases of LV hypertrophy with preexcitation.[35] Identification of these disorders has important implications not only for the long-term management of affected individuals, but also for defining genetic risk in family members. Gene-based diagnosis provides precise resolution of whether unexplained LV hypertrophy is HCM or a glycogen-store cardiomyopathy.

Functional Consequences of Hypertrophic Cardiomyopathy Gene Mutations

Mechanisms of Muscle Contraction

To determine the consequences of HCM gene mutations, an understanding of the cardiomyocyte sarcomere is first required. The sarcomere is the fundamental structural and functional unit of cardiac muscle that consists of an interdigitating system of thick and thin filaments. A widely accepted theory to explain the mechanism of muscle contraction is the cross-bridge hypothesis.[36] In this model, force generation results from the sliding movement of thick filaments relative to thin filaments; this is achieved by cyclical attachment and detachment of myosin cross-bridges to actin. Adenosine triphosphate (ATP) binds to the myosin head during the cross-bridge attachment phase. Hydrolysis of ATP then provides energy for the detachment and subsequent reattachment of the cross-bridges that causes a step-like displacement of the thin filament relative to the thick filament.[37] The troponin-tropomyosin complex constitutes the Ca^{2+}-sensitive switch that regulates this process. Troponin I is an inhibitory component of the troponin-tropomyosin complex, which binds actin and inhibits actomyosin adenosine triphosphatase (ATPase) activity in the absence of Ca^{2+}. Ca^{2+} binding to troponin C causes the troponin-tropomyosin complex to release the myosin binding domain of actin, permitting the interaction of actin and myosin heads.[38] The myosin light chains maintain optimal speed and effi-

ciency of cross-bridge cycling.[39–41] Myosin binding protein C contributes to the organization and assembly of thick filaments[42–45] and modulates cross-bridge function by regulating the position of the myosin head relative to the thin filament.[46–48]

β-MHC Gene Mutations

Cardiac myosin is a hexamer composed of two MHCs, two essential light chains, and two regulatory light chains. Myosin heavy chains contain a globular head connected through a neck region to a rod-like tail. The myosin heads contain binding sites for actin and ATP and constitute the motor domain of the myosin molecule.[37,49] The majority of β-MHC mutations are located in the myosin head, and hence are predicted to disrupt mechanical and catalytic components of actin-myosin interaction[50] (Fig. 56.5).

A widely used method for assessment of the rate of cross-bridge cycling is the in vitro motility assay, which measures the velocity of translocation of single actin filaments by single myosin filaments bound to a nitrocellulose-coated surface. Reduced filament sliding velocities have been demonstrated in a number of studies that have examined the properties of human and recombinant mutant β-MHC.[51–53] Functional studies of skinned skeletal muscle fibers from patients with β-MHC gene mutations have also generally shown decreased velocity of shortening and force generation.[54] For example, the Arg403Gln β-MHC mutation has been associated with depressed contractile function in patients' skeletal muscle,[54] and also in muscle strips from mice bearing the equivalent α-MHC mutation (α-MHC$^{403/+}$).[55,56] Surprisingly, myosin purified from α-MHC$^{403/+}$ hearts was shown to have faster actin sliding velocity, increased actin-activated ATPase activity, and increased force generation compared with control samples.[57] These apparently conflicting findings can be reconciled most readily by differences in the techniques used to evaluate contractile performance. While studies of purified actin and myosin might intuitively seem to be the optimal technique for assessing the functional consequences of β-MHC gene mutations, these do not take into account the effects of factors such as other protein components of the sarcomere, structural changes in the myocardial walls, and hemodynamic loading conditions that affect contractile performance in the intact muscle and in vivo. Abnormalities of myocyte regulation of Ca^{2+} have also been shown in α-MHC$^{403/+}$ mice. Mutant mouse hearts have normal cytosolic Ca^{2+} levels but reduced sarcoplasmic reticulum Ca^{2+} stores, reduced levels of the Ca^{2+}-binding protein calsequestrin, require higher Ca^{2+} concentrations to achieve the same contractile force as control hearts, and exhibit an exaggerated hypertrophic response to agents that affect myocyte Ca^{2+} levels.[58,59] Administration of the L-type Ca^{2+} channel inhibiter, diltiazem, to young α-MHC$^{403/++}$ mice significantly attenuates the development of functional changes and hypertrophy.[59] On the basis of these findings, it has been proposed that mutant sarcomeres sequester Ca^{2+} and act as an ion trap. Differences in the Ca^{2+} sensitivity for force production have recently been demonstrated for other HCM-causing MHC mutations.[60,61]

It has been proposed that abnormal myocardial energetics may have an important role in the pathophysiology associated with β-MHC gene mutations. Hypo- or hyperfunction of the sarcomere and heterogeneity in the effects of mutant protein between individual fibers within a single muscle could result in mechanical inefficiency of force generation and an energy-requiring state. Altered mitochondrial structure and function, potentially due to accumulation of Ca^{2+}, have been observed in α-MHC mice and might also contribute to energy depletion.[62] Changes in myocardial energetics have been demonstrated in α-MHC$^{403/+}$ mice,[63] but have yet to be evaluated comprehensively in human HCM.

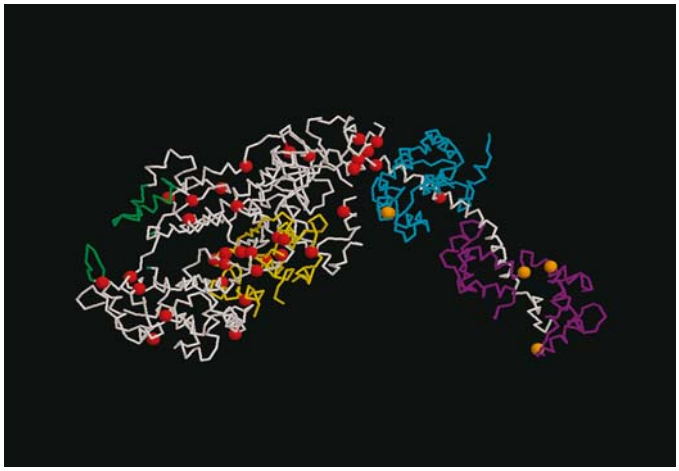

FIGURE 56.5. Computer reconstruction of the three-dimensional crystal structure of myosin, based on x-ray coordinates for chicken skeletal muscle myosin reported by Rayment et al.[266] The protein backbone is shown in white. Binding sites for myosin (green) and adenosine triphosphate (ATP) (yellow) are indicated. Essential and regulatory myosin light chains are shown in blue and purple, respectively. HCM-causing mutations in the myosin heavy chain are denoted by red spheres; mutations in the essential and regulatory myosin light chains by orange spheres. Note the clustering of mutations in the ATP binding domain. This image was generated using RasMol software.[267]

Cardiac Myosin Binding Protein C Gene Mutations

Cardiac MyBP-C is located in the A-bands of the sarcomere, where it is arrayed in a series of seven to nine transverse stripes spaced at 43-nm intervals. It is thought to have both structural and regulatory roles in the sarcomere. Cardiac MyBP-C has multiple immunoglobulin C2-like and fibronectin type 3 domains, a cardiac-specific region, a phosphorylation region, and binding sites for myosin and titin. Although missense mutations, insertions, deletions, and splice mutations have been identified, the majority of cMyBP-C mutations cause truncation of the encoded protein with loss of the myosin and titin binding domains.[13,14,64,65] Western blot analyses of transfected myoblasts and cardiac tissue from humans and mice have yielded varying results for the expression levels of mutant cMyBP-C protein. The truncated proteins have been able to be identified in some studies, but not in others.[66,67] Overexpression of truncated cMyBP-C may be accompanied by a compensatory reduction of wild-type protein.[68]

Three mouse models of cMyBP-C deficiency have been reported. One of these models was generated by expression

of a cMyBP-C transgene that encoded a truncated protein lacking the myosin and titin binding domains.[68] The mutant protein was stable but did not incorporate efficiently into sarcomeres, resulting in a striking pattern of sarcomere disorganization. Functional studies showed normal contraction and relaxation parameters with a leftward shift in the pCa-force curve and reduced power output. In a second model, a similar cMyBP-C truncation was generated using homologous recombination techniques.[69] Homozygous ($MyBPC^{t/t}$) mice exhibited dilated cardiomyopathy from birth with subsequent development of progressive LV hypertrophy, myofibrillar disarray, and fibrosis. On electron microscopy, sarcomere assembly appeared normal with the exception of absence of the M bands. In vivo hemodynamic studies in the $MyBPC^{t/t}$ mice demonstrated significant impairment of both systolic and diastolic LV function. $MyBPC^{t/t}$ myocytes showed prolonged time to 50% decay of Ca^{2+} transients, and reduced SERCA2a protein levels. Heterozygous ($MyBPC^{t/+}$) mice developed late-onset LV hypertrophy (>125 weeks), with normal cardiac function and histology.[70] Studies of cMyBP-C knockout mice demonstrate that homozygous ($MyBPC^{-/-}$) mice develop significant LV hypertrophy with depressed systolic and diastolic function, while heterozygous ($MyBPC^{+/-}$) mice are indistinguishable from wild-type littermates.[71] A rightward shift in the pCa-tension relationship was found in $MyBPC^{-/-}$, but not in $MyBPC^{+/-}$ mice. Evaluation of skinned myocytes showed increases in the peak normalized power output and rate constant of force development in $MyBPC^{-/-}$ mice.[72] These data suggest that the extent of sarcomeric perturbation is dependent on the relative amounts of mutant and normally functioning wild-type cMyBP-C protein. While abnormalities of Ca^{2+} homeostasis have been implicated in the pathophysiology of cMyBP-C mutations, it is notable that normalization of Ca^{2+} cycling parameters by genetic crosses between cMyBP-C and phospholamban-deficient mice fails to rescue the cardiomyopathic phenotype.[73] Further studies are required to identify the critical molecular defects that result from cMyBP-C insufficiency.

Cardiac Troponin T, I, and C Gene Mutations

The troponin complex is comprised of three subunits—troponin T, troponin I, and troponin C—and has a key role in the regulation of muscle contraction. Mutations in all three components of the troponin complex have been associated with the development of HCM. Troponin T mutations have been reported most frequently. The cardiac troponin T molecule consists of a long N-terminal region (residues 1 to 187) that lies adjacent to tropomyosin along the thin filament, and a globular C-terminal region (residues 188 to 288). Residues 70 to 170 are critical for the stability and function of the troponin complex, and for interactions with actin.[74] Hypertrophic cardiomyopathy–causing mutations have been identified in the both the N- and C-terminal regions. A number of in vitro studies have been performed to determine the functional consequences of troponin T mutations. Similar to β-MHC studies, the effects of mutant protein on Ca^{2+} sensitivity and force development have varied with the different experimental methods used.[75–82]

Several groups of investigators have generated transgenic mouse models to study the effects of troponin T mutations in vivo. Mice that express either truncated troponin T or Arg92Gln troponin T transgenes exhibit characteristic functional and histologic features of HCM, including LV diastolic dysfunction, myofibril disarray, and a variable extent of fibrosis.[83–85] Mice with truncated troponin T and those with low levels (1–10%) of the Arg92Gln transgene show LV systolic dysfunction, whereas mice with higher levels (30%, 67%, and 92%) of the Arg92Gln transgene develop dose-related hypercontractile function, consistent with a dominant-negative effect of mutant protein on systolic performance.[83–86] Notably, none of these murine models of cardiac troponin T mutations have developed LV hypertrophy, analogous to observations of minimal or absent hypertrophy in patients with cardiac troponin T mutations. Left ventricle hypertrophy has not been detected also in transgenic mice that bear an Ile79Asn mutation, either under resting conditions or with chronic exercise training.[87] Skinned fibers from the hearts of these mice showed increased Ca^{2+} sensitivity of ATPase activity and force, with an increased rate of force development, slowed relaxation and increased resting tension.

Interventions that further increase heart rate or contractility appear to exacerbate the cardiac dysfunction associated with troponin T deficiency. Stimulation with adrenergic agonists was found to induce sudden death both in mice with truncated troponin T and also in those with Arg92Gln troponin T.[88] Sudden death was observed in male, but not in female, mice, indicating additional gender-related factors in adrenergic responsiveness. In addition, Arg92Gln transgenic mice not only show baseline changes in mitochondrial ultrastructure and in the free energy of ATP hydrolysis, but also exhibit an inability to increase contractile performance with inotropic challenge.[89] Taken together, these findings suggest that a common feature of troponin T mutations is altered Ca^{2+} regulation of force production and reduced energetic efficiency of muscle contraction. These changes appear to activate hypertrophic pathways to a lesser extent than other HCM-causing gene mutations, but do result in an increased propensity for cardiac arrhythmias and sudden death, which may be exacerbated by increased cardiac workloads.

Troponin I is composed of three domains: an N-terminal region (residues 34 to 71) that contains protein kinase C phosphorylation sites, an inhibitory region (residues 128 to 147) that also contains a protein kinase C phosphorylation site, and a switch region (residues 147 to 163) that contains a p21-activated kinase site. Ca^{2+}-dependent binding of the inhibitory region with actin and troponin C is critical for muscle contraction and relaxation, respectively. Troponin I interacts with troponin C at multiple sites to form an antiparallel dimer. Hypertrophic cardiomyopathy–causing mutations have been located in the inhibitory and switch regions of troponin I. In vitro functional studies suggest that these mutations may variably alter actin binding, the Ca^{2+} sensitivity of actomyosin ATPase activity, and the stability of troponin I/troponin C interactions.[90–93] Transgenic mice expressing an Arg145Gly cardiac troponin I at a low level (1.2-fold) have no overt phenotype, while a higher level of transgene expression (3.5-fold) causes hypercontractility, diastolic dysfunction, histologic changes, and premature death.[94] Similar to troponin T mice, troponin I mutant mice do not show LV hypertrophy. Skinned muscles from the hearts of Arg145Gly mice show a significant increase in Ca^{2+} sensitivity, with no

changes in shortening velocity, or maximum power, compared with control littermates. It has been proposed that mutations in cardiac troponin I impair its function as a Ca^{2+} sensitive switch, causing the thin filament to remain longer in an "on" position.

Mutations in cardiac troponin C are a rare cause of HCM, and to date, only one sporadic case has been identified.[20] Troponin C mutations would be predicted to alter Ca^{2+} binding or interactions with other components of the troponin complex.

α-Tropomyosin Gene Mutations

α-Tropomyosin proteins form long rods composed of α-helical coiled-coil dimers that lie in a head-to-tail arrangement in the major groove of actin filaments, spanning seven actin monomers. α-Tropomyosin has two binding sites for troponin T, only one of which is Ca^{2+} sensitive. The effects of two mutations in the Ca^{2+}-sensitive troponin T binding region, at residues 175 and 180, have been studied in most detail. In a transgenic mouse model, overexpression of Asp175Asn α-tropomyosin was associated with reciprocal reductions in endogenous α-tropomyosin RNA and protein levels.[95] The mutant mice showed LV hypertrophy and histologic features of HCM, with slowed contraction and relaxation times, a leftward shift in the pCa-force relationship, and blunted responses to exercise and β-adrenergic stimulation. Skeletal muscle fibers from patients with Asp175Asn α-tropomyosin also showed increased Ca^{2+} sensitivity of force production, when compared with controls.[96] In one study, Glu180Gly α-tropomyosin transgenic mice showed severe LV hypertrophy and histologic changes,[97] whereas in another study, mice with the same mutation failed to develop these phenotypic features.[98] Single myocytes from these mice exhibited increased Ca^{2+} sensitivity of force production and diastolic dysfunction. The Asp175Asn and Glu180Gly α-tropomyosin mutations have recently been compared in transgenic rats.[99] With both mutations, molecular markers of cardiac hypertrophy were induced. In skinned fibers from Asp175Asn mutant rats, Ca^{2+} sensitivity was decreased and was accompanied by an increase in the frequency and amplitude of spontaneous Ca^{2+} waves. Ca^{2+} sensitivity in Glu180Gly mutant rats was unchanged. In yeast, a number of α-tropomyosin mutations, including Glu180Gly, did not change the cooperativity of thin filament activation with increasing Ca^{2+} concentrations, but did exhibit thermally induced unfolding of the α-tropomyosin molecule.[100] Collectively, these studies suggest model-dependent and mutation-dependent effects. While it has been proposed that altered Ca^{2+} sensitivity is the principal consequence of α-tropomyosin mutations, an alternate possibility is that structural instability of the mutant molecule critically alters protein interactions and Ca^{2+} handling.

Myosin Light Chain Gene Mutations

Myosin light chains belong to a large family of Ca^{2+}-binding proteins that is characterized by a helix-loop-helix of Ca^{2+} binding sites (EF hands). They are thought to contribute to the mechanical efficiency of cross-bridge cycling and the velocity of contraction. Cardiac muscle has two regulatory (phosphorylatable) and two essential (alkali) light chains. Mutations in the slow/ventricular isoforms have been associated with HCM. Two mutations, Met149Val in the essential myosin light chain and Glu22Lys in the regulatory myosin light chain, have been evaluated in vitro and in transgenic mice.[15,101–103] As noted for other mutant proteins, the results of functional analyses have varied with the techniques used. A number of studies have found, however, increased Ca^{2+} sensitivity of myofibrillar ATPase, and a leftward shift in the pCa-force relationship, indicating that myosin light chain mutations are likely to alter power output via a Ca^{2+} -dependent mechanism.

"Compensatory" Hypertrophy

Primary Defects

A large body of experimental data indicate that HCM mutations are associated with altered sarcomere structure and function. These findings provide the basis for the current and widely accepted concept that LV hypertrophy in HCM is a "compensatory" rather than a primary phenomenon. The precise nature of the defects that elicit a hypertrophic response in cardiomyocytes has not as yet been established. Alterations of sarcomere structure may result in hypo- or hypercontractile function, altered Ca^{2+} affinity or localization, or an energetically inefficient state. Any one, or a combination, of these factors could potentially be the critical molecular trigger for hypertrophy development. Although HCM has traditionally been regarded as a disease of the sarcomere, because the majority of disease genes have encoded protein components of the thick and thin filaments, recent reports of mutations in genes encoding extrasarcomeric proteins, such as titin, muscle LIM protein, Tcap, caveolin-3, and phospholamban,[23–27] which are involved in the maintenance of myocyte cytoarchitecture, stretch sensing, and Ca^{2+} homeostasis, have challenged this view and posed new questions about the definition of this disease. Can any cause of heritable but otherwise "unexplained" LV hypertrophy (with or without myofibrillar disarray) be considered under the umbrella of HCM? Or should a diagnosis of HCM be reserved for the classic disease associated with sarcomere protein gene mutations? These distinctions are important, because there may be different implications for the natural history of disease and patient management. Further insights into the nature of the hypertrophic "triggers" and interactions between the sarcomere and the extrasarcomeric cytoskeleton may help to resolve these questions.

Hypertrophic Response

The severity of LV hypertrophy can vary considerably in murine models, in humans with different mutations, and between individuals with the same mutation within families. This spectrum may be related to trigger factors, such as the nature, severity, or "dose" of the primary defect. For example, the finding that heterozygous mice bearing α-MHC and cMyBP-C binding protein-C mutations develop HCM, whereas homozygous mice with the same mutations develop dilated cardiomyopathy, might be explained by a

gene-dosage effect.[58,69,70,104] Comparative studies of myosin from individuals heterozygous and homozygous for β-MHC mutations indicate, however, that the amount of mutant protein can correlate poorly with muscle performance and clinical phenotype.[105] The extent of hypertrophy development might also be related to factors that modify the "effector" arm of the hypertrophic response. A combination of genetic, environmental and comorbidity factors are likely to be involved.

Left Ventricular Pathophysiology

Systolic Function

Left ventricular systolic function in HCM is usually normal or hyperdynamic. Reduced systolic function and wall thinning may occur in patients with long-standing chronic disease ("burnt out" HCM) due to replacement of myocytes by myocardial fibrosis. Hypertrophic cardiomyopathy may be classified as obstructive or nonobstructive, depending on the presence or absence of a systolic pressure gradient across the LV outflow tract. Obstructive HCM occurs in less than 25% of cases. The subaortic gradient results from a mechanical impediment to LV outflow produced by the combination of (1) asymmetric hypertrophy (ASH) of the proximal interventricular septum, and (2) systolic anterior motion (SAM) of the mitral valve with subsequent mitral leaflet-septal contact. The mechanism of SAM has been controversial but it has been postulated that the anterior mitral valve leaflet is drawn upward toward the septum by a Venturi effect produced by high-velocity blood flow through the narrowed outflow tract.[106,107] Subaortic obstruction to LV blood outflow gives rise to the "spike-and-dome" pattern on arterial pulse tracings. This waveform is characterized by a brisk upstroke due to rapid early ejection of blood from the LV, a decline in pressure with the onset of obstruction to outflow, and then a secondary pressure rise with late systolic ejection of the residual LV blood volume. Angulation and SAM of the anterior mitral valve leaflet also causes the mitral leaflets to coapt in the body of the leaflets rather than at the leaflet tips. A funnel-shaped opening created by the distal portions of both leaflets results in a posterior-directed jet of mitral regurgitation during middle and late systole.[108] The severity of mitral regurgitation has been shown to correlate with the length over which the mitral leaflets coapt, the relative mismatch of anterior to posterior leaflet length, and decreasing posterior leaflet mobility.[109]

The subaortic gradient in HCM has been described as "dynamic" because the magnitude of the pressure gradient can be varied by provocative maneuvers. The outflow tract obstruction is increased by maneuvers that reduce LV preload or afterload or that increase myocardial contractility (such as standing from a sitting or squatting position, Valsalva maneuver, exercise, or pharmacologic interventions such as administration of nitroglycerin or amyl nitrate). Conversely, the outflow tract obstruction is reduced by maneuvers that increase LV preload or afterload or that reduce myocardial contractility (such as squatting, passive leg elevation, handgrip, or administration of phenylephrine or beta-blocking drugs).[107] In asymptomatic individuals, provocative maneuvers may be used to unmask latent obstruction.

Although obstructive HCM is caused by proximal ventricular septal hypertrophy in the majority of cases, a minority of individuals may exhibit midventricular obstruction due to hypertrophy at the level of the papillary muscles. Left ventricle preload, afterload, and contractility influence the severity of midventricular obstruction. Other features of subaortic obstruction such as the "spike-and-dome" arterial pulse waveforms and mitral regurgitation are not observed, however, with midventricular obstruction.[107]

Diastolic Function

Impaired diastolic relaxation is a characteristic feature of human HCM that has been reproduced in mouse models.[55,63,69,83,84,110] The diastolic dysfunction has been attributed to a combination of prolonged LV relaxation and increased LV chamber stiffness. Studies in mouse models of HCM have provided insights into both of these processes. First, the detection of diastolic dysfunction prior to overt evidence of histologic change in mutant mice suggests that this physiologic abnormality is a primary consequence of sarcomere gene mutations. Slowed cross-bridge cycling rates in mutant sarcomeres may directly lead to prolonged activation of the thin filament and reduced diastolic relaxation.[63] Increased or prolonged Ca^{2+} availability to the myofibril may also prolong diastolic relaxation. Left ventricle relaxation is influenced also by load-dependent factors that may be abnormal in HCM, including end-systolic LV pressure and volume, wall stress, coronary artery blood flow, and regional asynchrony of LV wall motion.[106] The secondary development of structural changes, such as hypertrophy and fibrosis, causes LV chamber remodeling and increased chamber stiffness that further exacerbate diastolic filling. Georgakopoulos and colleagues[110] performed sequential in vivo hemodynamic studies in α-MHC$^{403/+}$ mice and found delayed pressure development in mice aged 6 weeks; by 20 weeks, reductions of cardiac output and increased end-systolic chamber stiffness were also present, coincident with the development of LV hypertrophy and fibrosis (Fig. 56.6). Blanchard and colleagues[55] also demonstrated increased diastolic stiffness in resting LV papillary muscle strips from α-MHC$^{403/+}$ mice. Intracellular Ca^{2+} overload and myocardial ischemia are two factors that may contribute to myocyte dysfunction and ultimately to myocyte death. Myocyte loss and replacement fibrosis have been observed to a greater extent in homozygous (α-MHC$^{403/403}$) than in heterozygous α-MHC$^{403/+}$ mutant mice, suggesting that there may be a threshold level for cell viability with increases in the proportion of mutant protein.[104] Elevated LV end-diastolic pressures due to diastolic dysfunction, increased end-systolic pressure with LV outflow obstruction, and mitral regurgitation may contribute to elevation of left atrial pressure, left atrial enlargement, and a subsequent increased risk for the development of atrial fibrillation. The onset of atrial fibrillation may precipitate severe hemodynamic compromise in individuals with LV diastolic dysfunction since LV filling is reliant to a greater extent on left atrial contraction. Atrial fibrillation is also associated with an increased risk of thromboembolic events.

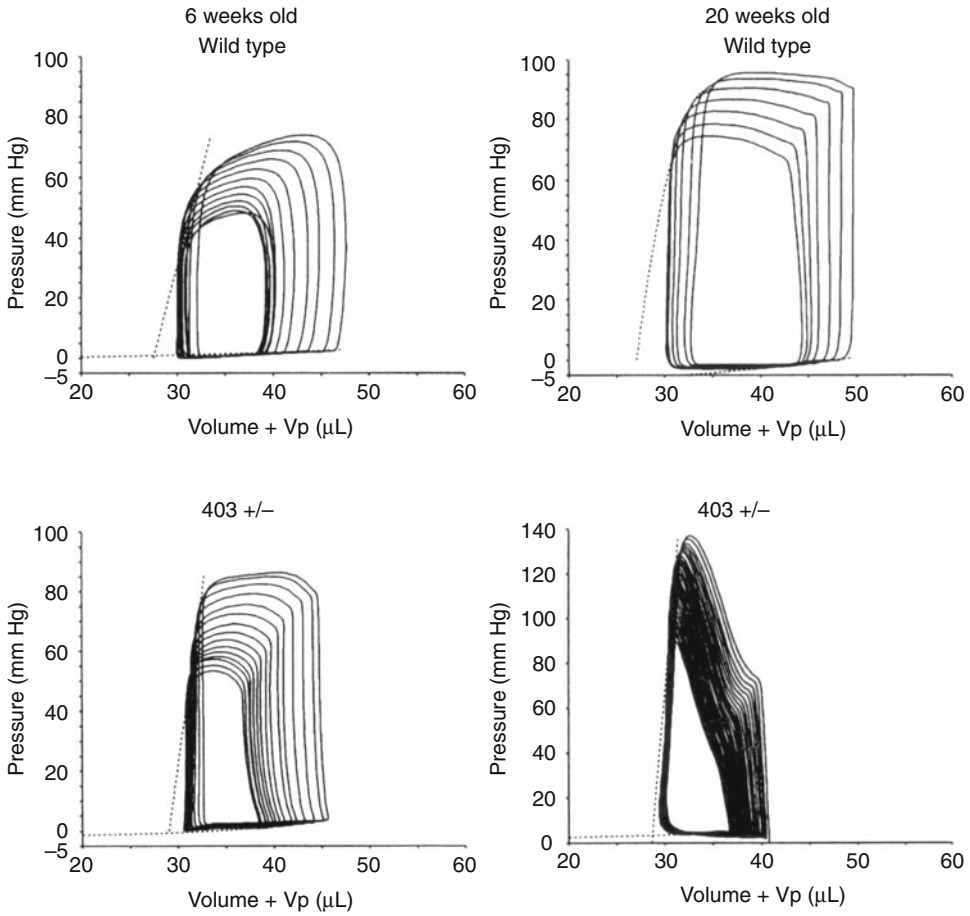

FIGURE 56.6. In vivo left ventricular pressure-volume relations measured during transient reduction of cardiac preload in wild-type and α-MHC$^{403/+}$ mutant mice. At 6 weeks (left), data for wild-type and α-MHC$^{403/+}$ mice were similar. At 20 weeks (right), α-MHC$^{403/+}$ mice showed a change in loop shape with systolic pressure elevation during ejection and a substantial increase in the end-systolic elastance (dashed vertical line), consistent with an increase in systolic stiffness.

Myocardial Ischemia

Myocardial ischemia may occur in both obstructive and nonobstructive HCM. Several mechanisms for myocardial ischemia in HCM have been proposed, including (1) increased myocardial oxygen demand, due to increased LV mass and wall stress; and (2) reduced myocardial oxygen supply, due to decreased coronary perfusion pressure secondary to LV outflow obstruction, elevated diastolic filling pressures, systolic compression of large intramural coronary arteries, myocardial bridging, reduced capillary density, and abnormally narrowed small intramural coronary arteries.[106,107] Symptoms of myocardial ischemia in HCM are precipitated frequently by exertion, which causes further imbalance of the myocardial oxygen demand and supply ratio.

Clinical Evaluation

Clinical History

Genotype-positive individuals with HCM may be asymptomatic or experience symptoms ranging from mild dizziness and palpitations to sudden death. The most common presenting features are exertional dyspnea, angina pectoris, fatigue, and presyncope or syncope. Since a variety of pathophysiologic mechanisms contribute to symptoms in HCM, including LV subaortic outflow obstruction, LV diastolic dysfunction, and myocardial ischemia (see previous section), the severity of symptoms generally does not correlate well with single factors such as the extent of LV hypertrophy or the magnitude of the LV outflow tract pressure gradient.[106,107] In individuals with LV diastolic dysfunction, symptoms and signs of congestive cardiac failure such as paroxysmal nocturnal dyspnea, orthopnea, and peripheral edema may be precipitated by atrial tachyarrhythmias. Syncope and sudden death may result from ventricular arrhythmias.

The age of onset of symptoms differs between HCM disease genes. For example, individuals with β-MHC gene mutations generally present in the first two decades of life. In contrast, individuals with cMyBP-C gene mutations may be asymptomatic until the fifth or sixth decades (Fig. 56.7).[65,111] A detailed family history is an essential component of the clinical history in HCM. Identification of young affected family members is particularly important in

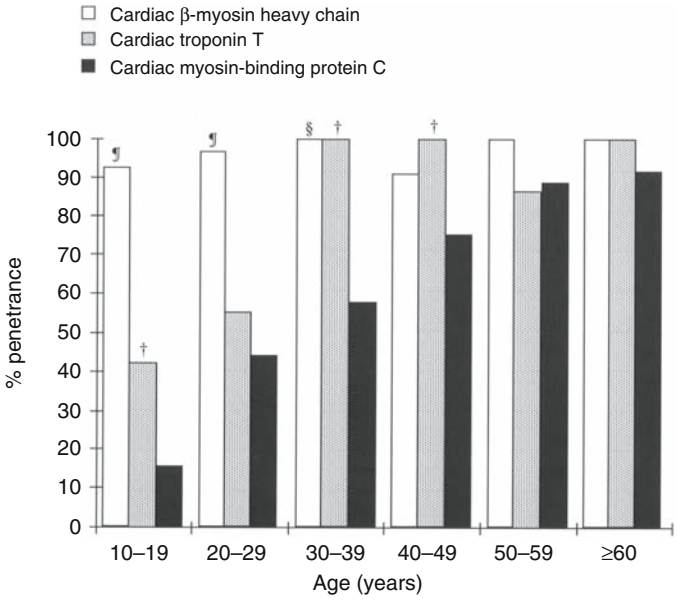

FIGURE 56.7. Age-related penetrance of HCM caused by mutations in the genes for β-MHC, cardiac troponin T, and cardiac myosin binding protein C. Solid bars denote the percentage of phenotype-positive individuals within the total population of genotype-positive individuals. In HCM caused by β-MHC and cardiac troponin T gene mutations, the onset of left ventricular hypertrophy is observed in early adulthood. In contrast, in HCM caused by cardiac myosin binding protein C gene mutations, the onset of left ventricular hypertrophy may be delayed until late adulthood. Significant differences in the penetrance of HCM caused by β-MHC, cardiac troponin T, and cardiac myosin binding C gene mutations are indicated as follows: † denote $p<0.05$, § $p<0.005$, and ¶ $p<0.001$.

families that have mutations with a malignant course characterized by a high incidence of sudden death. In elderly individuals, although a positive family history for HCM may not be obtained, this diagnosis should be considered, particularly if the symptoms and signs cannot be accounted for by the presence of other pathologic processes, such as coronary artery disease or hypertension. It should be noted also that in the elderly, HCM may coexist with other pathologies. The absence of a positive family history in an individual with symptoms and signs of HCM suggests the possibility of a sporadic gene mutation.

Physical Examination

Physical findings may be unremarkable in the absence of LV outflow tract obstruction. On examination of the precordium, the LV apex may be forceful and is variably displaced. A double, or triple, apical impulse may be present with the addition of a palpable left-sided S_4 or forceful late systolic LV contraction. With extensive LV hypertrophy, the jugular venous pulse may have a prominent *a* wave, due to reduced right ventricular compliance, and a bouncing carotid pulse may be present, analogous to the spike-and-dome pattern on arterial pressure tracings.

On auscultation, the first heart sound is generally normal. The second heart sound may have a narrow split or reversed splitting if LV contraction is prolonged by severe LV outflow obstruction. A loud fourth heart sound is often present and is due to augmented LV filling during left atrial systole when LV diastolic relaxation is prolonged. A systolic crescendo-decrescendo ejection murmur caused by turbulent blood flow through the LV outflow tract may be audible between the left sternal border and the apex. This murmur can be distinguished from valvular aortic stenosis by its response to provocative maneuvers that increase or reduce the extent of LV outflow obstruction (see previous section). In addition to the systolic ejection murmur, a pansystolic, blowing murmur due to mitral regurgitation may also be audible at the apex, with radiation to the axilla.

Electrocardiography

Electrocardiographic abnormalities are present in the majority of individuals with HCM and may occur in the absence of echocardiographic evidence of LV hypertrophy.[112] An example of an abnormal electrocardiogram found in a young genotype-positive, phenotype-negative individual is shown in Figure 56.8. Voltage criteria for the presence of LV hypertrophy have been defined according to the height of the QRS complexes, particularly in the precordial leads.[113] ST-segment and T-wave changes are commonly observed. Giant negative T waves in leads V_4 to V_6 are characteristically found with the apical pattern of LV hypertrophy observed predominantly in Japanese patients with HCM.[114,115] A pseudoinfarction pattern with prominent Q waves may be present in the inferior (II, III, aVF) and precordial (V_2–V_6) leads.[116,117] The etiology of these Q waves is uncertain since a close correspondence with ventricular septal hypertrophy has not been observed. Abnormal P-wave morphology may be present if the left atrium is dilated. Atrial tachyarrhythmias (atrial fibrillation, atrial flutter), and ventricular arrhythmias may also be found.

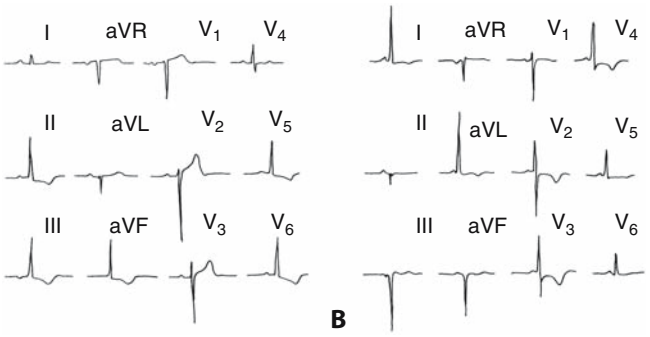

FIGURE 56.8. Twelve-lead electrocardiographic tracings from two individuals with HCM who were genotype-positive, phenotype-negative (A) and genotype-positive, phenotype-positive (B). The ECG in (A) was recorded from a 17-year-old boy who was asymptomatic but had a positive family history of HCM. His echocardiogram was normal. This ECG shows inferolateral T wave inversion and voltage criteria for left ventricular hypertrophy. The ECG in (B) was recorded from a 32-year-old woman with symptoms and signs of HCM, including echocardiographic evidence of left ventricular hypertrophy. This ECG shows anterior and inferior Q waves, anterolateral T wave inversion, and voltage criteria for left ventricular hypertrophy.

Chest X-Ray

The chest X-ray in HCM may be normal or may demonstrate an abnormal cardiac silhouette due to LV or left atrial enlargement. Infrequently, anterior ventricular septal hypertrophy may cause a bulge along the left heart border. Redistribution of pulmonary vascular markings and enlargement of the right ventricle and right atrium may be observed with secondary pulmonary hypertension or right ventricular hypertrophy.

Echocardiography

Transthoracic echocardiography is the primary diagnostic modality for evaluation of individuals with suspected HCM. Two-dimensional echocardiographic imaging provides assessment of left and right ventricular hypertrophy, ventricular and atrial chamber size, and systolic contractile function. The presence of an LV outflow tract gradient and LV diastolic dysfunction can be identified by color-flow Doppler studies. Both two-dimensional echocardiographic imaging and color-flow Doppler are used to examine valvular morphology and function. Although HCM is primarily a myocardial disorder, structural abnormalities of the mitral valve and subvalvular apparatus may be present, including increased leaflet area, elongation and prolapse of leaflets, and anomalous papillary muscle insertion directly into the anterior leaflet.[118,119] Mitral regurgitation is a relatively frequent finding that results primarily from abnormal coaptation of the mitral valve leaflets.[108,109] Transesophageal echocardiography is indicated for (1) more precise delineation of mitral valve morphology and function, (2) exclusion of left atrial thrombus and spontaneous echo contrast in patients with atrial fibrillation or recent thromboembolic events, (3) intraoperative monitoring during surgical myectomy-myotomy, and (4) technically inadequate transthoracic echocardiographic images. Stress echocardiography may be useful to investigate individuals with symptoms suggestive of myocardial ischemia[120] (Fig. 56.9).

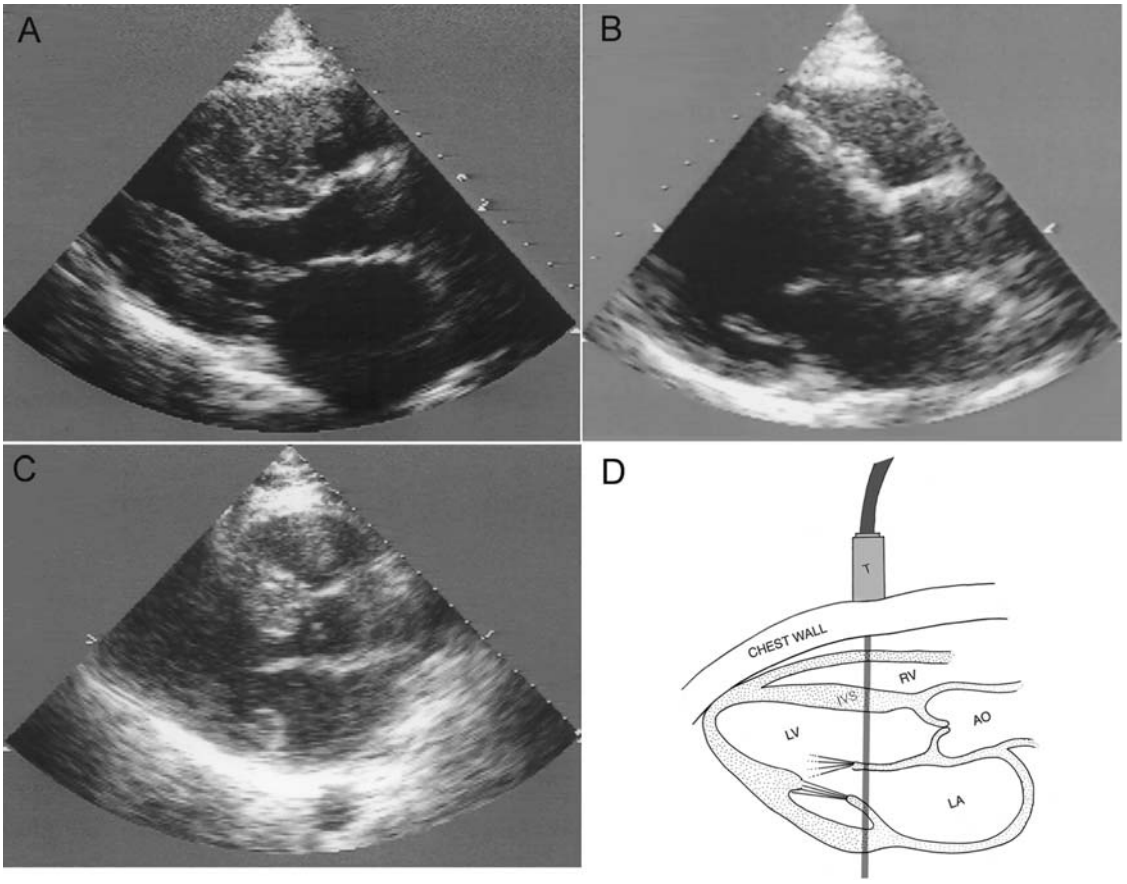

FIGURE 56.9. Two-dimensional echocardiographic images in the parasternal long-axis view from three individuals with HCM. (A) A 20-year-old woman presented to the emergency room following a syncopal episode. A positive family history of HCM was elicited. On auscultation of the precordium, a systolic ejection murmur was audible. Echocardiography showed asymmetric hypertrophy of the interventricular septum, systolic anterior motion of the mitral valve and left atrial dilation. (B) An asymptomatic 35-year-old man was evaluated following the sudden death of his sister. Postmortem examination of the deceased sister's heart had revealed histologic evidence of HCM. Echocardiography showed left ventricular dilation and reduced fractional shortening, consistent with dilated cardiomyopathy. (C) A 30-year-old man presented with presyncope after repeated episodes of standing from a squatting position. Echocardiography showed marked hypertrophy of the proximal interventricular septum, with systolic anterior motion of the mitral valve and left ventricular outflow tract obstruction (gradient = 90 mm Hg). Highly echogenic foci present in the septal myocardium caused a "ground-glass" appearance. An echogenic plaque at the site of anterior mitral vale leaflet-septal contact was also noted. (D) Schematic of the cardiac chambers visualized by two-dimensional echocardiography in the parasternal long-axis view. AO, aorta; IVS, interventricular septum; LA, left atrium; LV, left ventricle; RV, right ventricle.

Asymmetric septal hypertrophy has been considered the sine qua non of HCM, with a septal-to-posterior wall ratio ≥1.3:1 regarded as diagnostic.[121] Transthoracic echocardiographic studies performed in large populations with HCM have demonstrated, however, that while LV hypertrophy in the vast majority of cases is asymmetric, a variety of patterns of LV hypertrophy, ranging from extensive and diffuse to mild and segmental, can be found.[1,2,122–125] Such data indicate not only that traditional diagnostic criteria lack sensitivity and specificity but also that no single morphologic pattern can be considered pathognomonic for diagnosis of this disease.

Genotype-phenotype analyses have demonstrated that genetic heterogeneity contributes to phenotypic heterogeneity in HCM. For example, LV hypertrophy in β-MHC gene mutations may be moderate or severe, whereas LV hypertrophy in cardiac troponin T gene mutations is generally only mild.[111,124,126] Cardiac troponin I and myosin light chain gene mutations cause unusual forms of LV hypertrophy localized to the LV apex or mid-ventricular cavity, respectively.[15,19] Clinical evaluation of large families highlights the variable expressivity of HCM. Young genotype-positive individuals may have only mild thickening of LV wall segments, whereas older members of the same family may exhibit severe LV hypertrophy. In young individuals, the diagnosis of cardiac hypertrophy may be made more reliably by comparison of LV wall thickness measurements with unaffected siblings rather than with conventional HCM wall thickness criteria. Age-related penetrance also varies with different HCM disease genes. For example, individuals with β-MHC gene mutations are likely to develop LV hypertrophy within the first or second decades of life. In contrast, individuals with cMyBP-C gene mutations may have normal echocardiograms until the fifth or sixth decades (Fig. 56.7).[65,111] In any HCM pedigree, a small number of nonpenetrant genotype-positive individuals may be found who do not exhibit LV hypertrophy at any age. In individuals with a family history but unknown genotype, a positive echocardiogram can confirm HCM, but a negative echocardiogram does not necessarily exclude this diagnosis. Genotype-phenotype correlations in large numbers of affected individuals are required to accurately define patterns of LV hypertrophy across the spectrum of HCM gene mutations. Genetic heterogeneity is unlikely to account fully for phenotypic heterogeneity in HCM. The role of additional genetic factors and environmental factors such as blood pressure, exercise, diet, and body mass need to be considered when assessing LV hypertrophy in individuals with HCM.

Electrophysiologic Studies

Individuals with HCM who experience syncopal episodes should be evaluated noninvasively with Holter monitoring to identify sustained or potentially lethal ventricular arrhythmias.[127–130] While other techniques may be appropriate for investigation of syncope, including signal averaged electrocardiography,[131–134] heart rate variability determination,[135,136] and assessment of blood pressure response to exercise, the use of provocative studies such as tilt table testing has great potential for precipitating hemodynamic compromise in patients with HCM. Histopathologic changes in HCM may cause variation in conduction properties with dispersion of conduction velocity throughout the myocardium. Assessment of QT dispersion may be a useful component in risk assessment for ventricular arrhythmias.[137] Invasive electrophysiologic studies have been used to identify spontaneous and provocable arrhythmias in patients at high risk of sudden death, including those with a strong family history or syncope, or survivors of sudden death. The predictive value of inducible ventricular arrhythmias in HCM, however, has been found to be low.[130,138–141]

Other Investigations

Radionuclide scanning with tomographic imaging (single photon emission computed tomography, SPECT) or magnetic resonance imaging is useful for delineating the location and extent of LV hypertrophy if the technical quality of transthoracic echocardiographic images is inadequate.[142–145] Stress thallium studies may be useful to identify reversible defects caused by myocardial ischemia.[146–148] Myocardial blood flow and metabolism may also be assessed using positron emission tomography.[149–153] Gated radionuclide ventriculography is an alternative to echocardiography for assessment of LV size and contractile function.[154] Cardiac catheterization and angiography are generally reserved for assessment of myocardial ischemia and for evaluation prior to surgical procedures such as myectomy and cardiac transplantation.

Genetic Studies

Genotype-phenotype correlations in large populations will provide important data for diagnostic and prognostic evaluation in HCM. Genotyping may be particularly useful in cases where the clinical diagnosis is ambiguous, such as in individuals without a family history of disease, when LV hypertrophy is accompanied by atypical electrophysiologic manifestations (e.g., WPW syndrome or atrioventricular block), or when LV hypertrophy occurs in trained athletes or in individuals with hypertension.[155] Currently, gene-based diagnosis is expensive and available in few centers [Harvard Partners Center for Genetics and Genomics, Laboratory of Molecular Medicine (www.hpcgg.orgLMM/tests)]. With continued evolution of technologies that enable low-cost rapid automated DNA sequencing, gene-based diagnosis of HCM should become the standard of care and transform molecular genetics research into clinical medicine.

The availability of genetic testing creates a number of psychosocial, ethical, and medicolegal issues. While a genotype-positive diagnosis may stimulate beneficial lifestyle changes and therapeutic interventions, it may also create patient anxiety about having a genetic disorder and may potentially lead to discrimination by employers and insurance companies. Identification of genotype-positive, phenotype-negative individuals creates particular difficulties since the clinical significance of this diagnosis is uncertain. Many of these questions will be resolved over time as genetically oriented research studies provide a better understanding of the clinical implications of genetic diagnoses. From a community perspective, these genetic data will need to be viewed in the context of an appropriate ethical and legal framework.

Natural History

The natural history of HCM is variable; while some individuals remain asymptomatic throughout life, others have progression of symptoms with or without development of heart failure. A significant number of individuals die suddenly, often without premonitory symptoms. Estimated mortality rates in HCM differ according to the population studied. In hospital-based referral centers in which a large proportion of cases have moderate or severe symptoms, annual mortality rates of 3% to 6% have been found.[156–165] In contrast, studies performed in community clinics have emphasized the relatively mild symptoms and good survival in unselected populations with annual mortality rates of 1% or less.[166–170]

Longitudinal echocardiographic studies have demonstrated that LV remodeling may occur during the course of this disease. Progressive increases in LV wall thickness are observed predominantly in adolescents and young adults with HCM. In later adult life, LV wall thickness generally remains stable or decreases.[171–175] It is notable that the majority of studies that have examined the natural history of LV hypertrophy in HCM have been performed in patients whose genotype is unknown. We have observed progression of LV hypertrophy in selected subgroups of genotyped individuals over the age of 40 years, such as those with cMyBP-C mutations[65] or the Arg663His β-MHC mutation[176] (Fig. 56.10). Left ventricle wall thinning in individuals with long-standing disease may result from myocyte loss and fibrosis. Approximately 10% to 20% of individuals with HCM may ultimately develop symptoms and signs of dilated cardiomyopathy.[174,177] Disease progression in HCM may also include the onset of atrial fibrillation. The prevalence of atrial fibrillation in affected individuals has been estimated to be 10% to 16%.[125,178] Some HCM gene mutations or morphologic variants appear to have an increased propensity for atrial fibrillation. For example, we observed a high incidence of atrial fibrillation (47%) and proximal septal hypertrophy in a family with the Arg663His β-MHC mutation (Fig. 56.10).[176]

Sudden death is the most devastating result of HCM and may occur in young asymptomatic individuals or in those with chronic heart failure. Ventricular tachyarrhythmias are the cause of sudden death in the majority of cases. A complex interaction of electrical and hemodynamic factors may trigger ventricular tachyarrhythmias in HCM, including reentrant depolarization pathways around foci of myofibrillar disarray and fibrosis, supraventricular tachyarrhythmias, LV outflow tract obstruction, LV diastolic dysfunction, myocardial ischemia, and systemic arterial hypotension.[106,179,180] Bradyarrhythmias related to sinus node and atrioventricular node conduction abnormalities may cause sudden death in some individuals.[181–183] Given the complexity of mechanisms that may precipitate ventricular arrhythmias, it is not surprising that few clinical parameters have been found to reliably predict individuals at increased risk for sudden death. Most investigators agree that high-risk patients include survivors of a cardiac arrest with documented ventricular fibrillation and young patients (<30 years) with a strong family history of sudden death.[106,107,126,162,184–188] For the large proportion of individuals who do not fall into the high-risk category, consideration of the risk associated with other clinical parameters is relevant. In various study populations, conflicting results have been found, however, for the positive predictive value of factors such as young age at diagnosis, history of syncope, severity of symptoms, LV outflow tract gradient, LV wall thickness, left atrial size, and atrial fibrillation.[107,162,167,168,170] Although these clinical variables may not identify individuals at increased risk for sudden death, their high negative predictive value does enable identification of individuals at low risk for sudden death. Adult individuals with HCM can be categorized as low risk if they are asymptomatic or have mild symptoms and also have none of the following: a family history of premature death due to HCM, nonsustained ventricular tachycardia on ambulatory monitoring, a marked LV outflow tract gradient, substantial LV hypertrophy (>20 mm), marked left atrial dilation, and an abnormal blood pressure response during exercise.[180]

Genotype determination may be the single most important component of risk stratification in HCM. It is likely that the majority of individuals considered at high risk due to a strong family history of sudden death also have a high-risk HCM gene mutation. It has been demonstrated that prognosis varies considerably between different HCM gene mutations. For example, some β-MHC mutations such as Arg403Gln and Arg453Cys are associated with a reduced life expectancy and high incidence of sudden death, whereas other β-MHC mutations, such as Val606Met, have a relatively benign course.[185] Reduced survival has been shown with cardiac troponin T mutations and some α-tropomyosin mutations (Ala63Val, Lys70Thr).[126,189,190] Survival was reduced

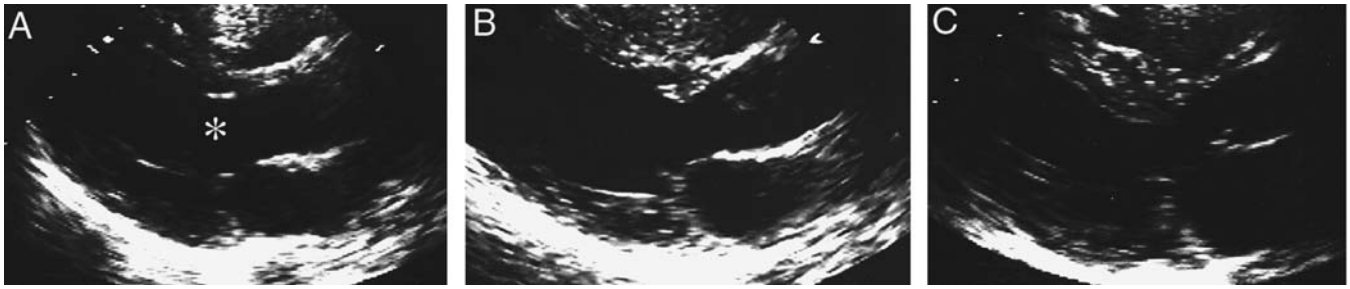

FIGURE 56.10. Two-dimensional echocardiographic images in the parasternal long-axis view demonstrating progressive left ventricular morphologic changes caused by the β-MHC Arg663His missense mutation. (A) Mild proximal septal thickening (maximal wall thickness <1.3 cm). (B) Focal proximal septal hypertrophy. (C) Predominant proximal septal hypertrophy with additional midseptal hypertrophy.

in one family with the Asp175Asn α-tropomyosin mutation[190] but was normal in three other families with the same mutation,[191] suggesting that genetic susceptibility may be modified by other genetic or environmental factors.

The location of a HCM gene mutation in the sarcomere has been proposed as an important determinant of the degree of sarcomere dysfunction and the severity of clinical outcome. The HCM mutations that alter amino acid charge have been associated with poor outcomes.[185] However, while mutations that do not alter amino acid charge usually have a benign clinical course, some mutations that do alter amino acid charge also have a good prognosis.[192] Electrophysiologic studies in mouse models may provide important clues into the mechanisms and differential propensity for sudden death between HCM gene mutations.

Treatment

The overall strategy for treatment of individuals with HCM is shown in Figure 56.11. In general, the approach to treatment varies according to the classification of a patient into one of four categories: (1) genotype-positive, phenotype-negative; (2) asymptomatic and mildly symptomatic; (3) obstructive or nonobstructive HCM with heart failure; and (4) high clinical or genetic risk for sudden death.

Genotype-Positive, Phenotype-Negative Individuals

Genetic testing has led to the identification of a subgroup of individuals who are genotype-positive for HCM gene mutations but who have no clinical evidence of disease (phenotype-negative). Most of these individuals ultimately develop symptoms and signs of HCM. Young genotype-positive members of families in which a β-MHC mutation has been found should undergo longitudinal follow-up with serial echocardiograms throughout adolescence and early adult life. Genotype-positive members of families with known cMyBP-C mutations should have serial echocardiograms throughout life. At present, there are no data to suggest that pharmacologic treatment of genotype-positive, phenotype-negative individuals will delay or prevent the onset of LV hypertrophy or complications such as sudden death. However, regular assessment of clinically silent arrhythmias is warranted in individuals with mutations associated with a high incidence of sudden death. The clinical implications of genetic abnormalities in the small percentage of individuals who remain nonpenetrant are not known.

Asymptomatic and Mildly Symptomatic Individuals

Genetic testing has also led to the identification of a large number of genotype-positive, phenotype-positive individuals who are asymptomatic. Further, community-based studies have shown that a significant proportion of individuals with HCM have only mild symptoms.[166–170] These observations suggest that asymptomatic and mildly symptomatic individuals comprise the majority of the total HCM population.[180] Pharmacologic therapy is indicated for relief of mild symptoms but is generally not required in asymptomatic individuals. One possible exception is the young asympto-

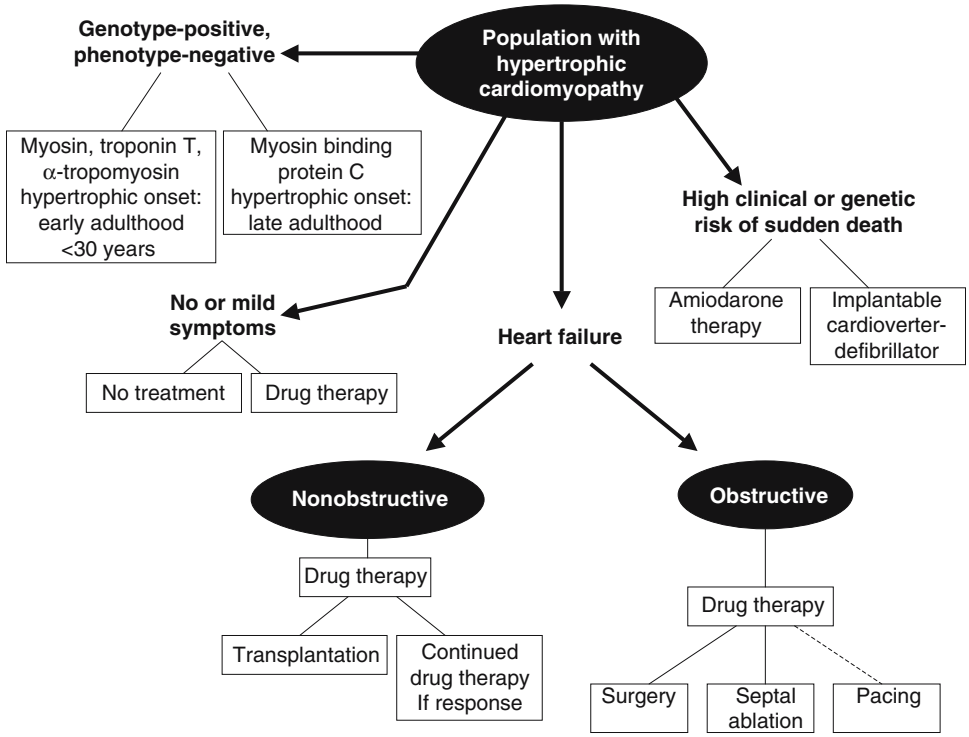

FIGURE 56.11. Schematic of the four principal clinical presentations of HCM with corresponding treatment strategies.

matic patient with massive LV hypertrophy or significant LV outflow tract gradient, in whom the onset of symptoms would appear inevitable.[180] There is no clinical trial evidence that prophylactic treatment with β-adrenergic blocking drugs or Ca^{2+} antagonists will prevent progression of disease or improve prognosis in asymptomatic or mildly symptomatic individuals.[180] It should be noted, however, that prospective trials of prophylactic therapy have not been performed, largely because of the small study populations and relatively infrequent clinical end points. Asymptomatic or mildly symptomatic individuals should be discouraged from competitive athletic activities but may participate in recreational sport provided that risk factors for sudden death are absent (see previous section). Detailed guidelines for exercise recommendations in young patients with HCM have recently been formulated.[193]

Heart Failure in Obstructive and Nonobstructive Hypertrophic Cardiomyopathy

Drug Therapy

Pharmacologic therapy is indicated for relief of symptoms in patients with heart failure in both obstructive and nonobstructive HCM. β-adrenergic blocking drugs are useful predominantly for symptoms of angina and dyspnea and may improve exercise performance. The beneficial effects of β-adrenergic blockers are mediated principally by their negative chronotropic effect, with reduced heart rates resulting in prolongation of the LV diastolic filling time.[194–196] The negative inotropic effect of these drugs also contributes to a reduction of myocardial oxygen demand and may prevent increases in severity of the LV outflow tract gradient, which may occur during exercise when sympathetic tone is increased.[195–197]

Ca^{2+} antagonist drugs are an alternative to β-adrenergic blocking drugs for treatment of symptoms in HCM. Patients who do not respond to β-adrenergic blockers may experience symptomatic improvement with Ca^{2+} antagonists. There is no evidence that the combined use of these two drug classes has synergistic effects. Verapamil has been the most widely used of the Ca^{2+} antagonist drugs. Verapamil improves symptoms by increasing LV relaxation and diastolic filling.[198–204] The vasodilatory effects of verapamil improve myocardial blood flow but may also potentially exacerbate LV outflow tract gradients in patients with obstructive HCM and precipitate hypotension and pulmonary edema in patients with elevated pulmonary pressures. The negative inotropic effects of verapamil may decrease LV outflow tract gradients but may also contribute to the development of heart failure. Other adverse effects of verapamil include suppression of sinus node automaticity and inhibition of atrioventricular conduction. Nifedipine causes less depression of atrioventricular conduction but has a more potent vasodilatory action and may be particularly harmful in patients with obstructive HCM.[205] Diltiazem has been used less frequently in HCM but may improve LV diastolic function.[206,207]

Disopyramide is a class IA antiarrhythmic drug that blocks the fast sodium channel and prolongs action potential duration. Disopyramide may improve symptoms in obstructive HCM by exerting a negative inotropic effect.[208] Disadvantages of disopyramide include anticholinergic side effects and prolongation of the QT interval, which increases the propensity for ventricular arrhythmias such as torsades de pointes. A reduction of hemodynamic benefits with prolonged use of disopyramide has also been observed.[107]

Patients with nonobstructive HCM who develop heart failure should be treated with standard therapeutic agents, including diuretics, angiotensin-converting enzyme inhibitors, and digitalis. These drugs should be administered with caution in patients with severe LV diastolic dysfunction who require high filling pressures for adequate ventricular filling and in patients with obstructive HCM. Although obstructive HCM has been regarded as a contraindication for these drugs, some data suggest that diuretics may reduce symptoms of pulmonary congestion when combined with β-adrenergic blockers or Ca^{2+} antagonists.[209] A subset of patients with long-standing HCM and dilated cardiomyopathy who have severe heart failure that is inadequately controlled by medical therapy may ultimately become candidates for cardiac transplantation.

Atrial Fibrillation

Prevention of atrial fibrillation is an ideal goal in management of patients with HCM that may be difficult to achieve due to the persistence of risk factors for arrhythmia development, particularly increased left atrial size. Both electrical and pharmacologic cardioversion may be used to restore sinus rhythm in patients with paroxysmal episodes of atrial fibrillation but the risk of recurrence is high. Amiodarone is currently considered to be the most effective antiarrhythmic agent for prevention of recurrence in paroxysmal atrial fibrillation.[128,210–213] Because of the serious side effects of amiodarone, however, alternative drugs such as sotalol are often used in younger patients. Both β-adrenergic blockers and verapamil may be used for rate control in patients with chronic atrial fibrillation.[106,107,210] In patients with rapid atrial fibrillation that is refractory to pharmacologic treatment, ablation of the atrioventricular node and insertion of a permanent pacemaker may be required. Aspirin therapy should be considered for all HCM patients with echocardiographic evidence of left atrial enlargement; for those with paroxysmal and chronic atrial fibrillation, anticoagulation with warfarin is recommended to reduce the risk of thromboembolism.

Surgical Procedures

Ventricular septal surgery has been the gold-standard therapy for more than 40 years in patients who have high LV outflow tract gradients (>50 mm Hg) and severe symptoms that are inadequately controlled by medical therapy.[106,107] The procedure has evolved from a septal myotomy without muscular resection, to a myectomy in which a wedge of muscle is removed from the hypertrophied basal septum.[214–223] Intraoperative transesophageal echocardiography is helpful in planning the extent of resection, assessing the immediate result, and detecting complications.[108] Septal myectomy is often combined with mitral valve repair and/or coronary artery bypass graft surgery. In experienced surgical centers, the operative mortality of myectomy is now less than 2%.[107,216,218,220,222,223] Operative mortality may be greater in

elderly patients and in those in whom combined procedures are performed.[223,224] Septal myectomy has been shown in large patient series to improve symptoms and functional capacity in obstructive HCM. The hemodynamic benefits of septal myectomy are achieved by basal septal thinning, which reduces or abolishes the LV outflow tract gradient and systolic anterior motion of the mitral valve, with consequent reductions in LV pressures and mitral regurgitation, and increases in LV filling and myocardial perfusion.[107,146,225–228] Symptomatic improvement persists for 5 years or more after surgery in approximately 70% of patients.[215–223] Long-term survival after myectomy has been reported as 99%, 98%, and 95%, at 1, 5, and 10 years, respectively, and does not differ from that expected in the general U.S. population.[229,230]

Nonsurgical Techniques for Reduction of Left Ventricle Outflow Tract Gradients

Not all patients with severely symptomatic obstructive HCM are suitable candidates for open-heart surgery, due to comorbidity or advanced age. Moreover, access to surgery may be a limiting factor, since expertise in these procedures is restricted to a relatively small number of specialized referral centers. These considerations, together with economic pressures within the health care system, have contributed to growing interest in the development of alternative nonsurgical methods for LV outflow tract gradient reduction.

In the early 1990s, there was a wave of enthusiasm for dual-chamber pacing. With this procedure, gradient reduction putatively results from paradoxical motion of the interventricular septum, due to preexcitation of the right ventricle. Initial observations in nonrandomized, unblinded studies reported that dual-chamber pacing caused substantial reductions in both the LV outflow tract gradient and symptoms.[231,232] Subsequent more stringent evaluation, including three randomized crossover studies, has found the effects of pacing to be less favorable.[233–236] There are no data to suggest that pacing either alters the course of the disease or reduces the risk of sudden death. Dual-chamber pacing is not currently considered to be a first-line therapy, but may have a limited role in a subgroup of elderly patients.[237]

More recently, percutaneous alcohol septal ablation has been introduced as an alternative to myectomy in obstructive HCM.[238] This is a catheter-based intervention in which 1 to 3 mL of 96% to 98% alcohol is injected into a septal perforator branch of the left anterior descending coronary artery, to create a myocardial infarction in the proximal ventricular septum. Myocardial contrast echocardiography enhances the efficacy and safety of the procedure by identifying the most appropriate target arteries.[239,240] Acute gradient reduction may be observed, associated with septal stunning and altered LV ejection dynamics. Longer-term gradient reduction results from wall thinning and hypokinesis of the basal septum, which enlarges the LV outflow tract and improves mitral valve function. Alcohol septal ablation has been shown to have beneficial effects on symptoms and functional capacity over follow-up periods ranging from 2 to 5 years.[241–248] This procedure is widely available, has less discomfort and is less expensive than surgery, avoids cardiopulmonary bypass, and requires relatively short hospital admissions. The procedure-related mortality rate is 1% to 2% in experienced centers, equivalent to that of surgery.[245,247,248] Treatment failures can occur, and repeat ablations may be required. Because of the close proximity of the atrioventricular bundles, conduction-system abnormalities are common complications, with right bundle branch block and transient heart block in 60% to 100% of patients, and high-grade atrioventricular block requiring permanent pacemaker implantation in 5% to 30% of patients.[241–244,249–251] Less frequent but significant complications include anterior myocardial infarction, due to alcohol reflux into the left anterior descending coronary artery, coronary dissection, perforation, and thrombosis. Recently, considerable debate has been generated about the potential role of alcohol septal ablation as a primary treatment modality for obstructive HCM.[230,237,252] Although the number of ablation procedures performed has been rapidly escalating, and by far exceeds the number of myectomies, no randomized trials comparing these techniques have been performed, and long-term follow-up data for septal ablation are lacking. Several recent case reports of monomorphic ventricular tachycardia in patients who have undergone septal ablation have raised concerns that the alcohol-induced myocardial infarction generates an arrhythmogenic substrate that might exacerbate a preexisting disease-related propensity for malignant tachyarrhythmias.[253–255]

Prevention of Sudden Death

Patients with high clinical or genetic risk for sudden death due to ventricular arrhythmias may be treated with amiodarone (100 to 300 mg per day) or an implantable cardioverter-defibrillator.[237,256–263] Two large clinical trials, Antiarrhythmics versus Implantable Defibrillators (AVID)[264] and multicenter automatic defibrillator implantation trial (MADIT),[265] have shown survival advantages with the use of implantable cardioverter-defibrillators compared with antiarrhythmic drug therapy in selected populations of patients at high risk of life-threatening ventricular arrhythmias. Neither of these studies specifically examined individuals with HCM. Patients enrolled in the AVID study were survivors of episodes of ventricular fibrillation or ventricular tachycardia associated with hemodynamic compromise. Those enrolled in MADIT had episodes of nonsustained ventricular tachycardia, low ejection fractions, and inducible, nonsuppressible ventricular arrhythmias during electrophysiologic testing. A multicenter study to evaluate the use of implantable cardioverter-defibrillator devices in patients with HCM is currently underway. Empiric use of antiarrhythmic drugs or implantable cardioverter-defibrillators in HCM must therefore reflect careful risk stratification based on an individual's symptoms, age, family history, and genotype. Anticipated event rates, availability, and cost will certainly influence these decisions. Although a small number of individuals who do not fall into the high-risk category may experience sudden death, it is difficult to identify these individuals on the basis of clinical parameters. Further, since the majority of individuals with HCM do not die suddenly, and given the side effects and expense of current therapies, prophylactic treatment to prevent sudden death in all genotype-positive individuals is not indicated.

Acknowledgment

Diane Fatkin is supported by the Sylvia and Charles Viertel Charitable Foundation.

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