Diagnosis and Management of Hypertrophic Cardiomyopathy

Edited by

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Blackwell Futura

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Foreword

I am delighted to have the opportunity to write the foreword for this unique treatise on the complex subject of hypertrophic cardiomyopathy. This multi-authored book provides state-of-the-art discussions on all aspects of the disease. Each chapter is a contribution from experts in the field.

The subject matter is presented in a highly organized fashion. It includes the clinical (phenotypic) expression of hypertrophic cardiomyopathy, genetic aspects, outflow obstruction, diastolic function, the impact of atrial fibrillation, risk factors for sudden death and other prognostic markers, pharmacologic treatment, septal myectomy surgery and non-surgical septal ablation, and the role of implantable defibrillators in the prevention of sudden death. These topics are expertly discussed by knowledgeable investigators. The manuscripts are, in general, balanced and comprehensive. There is much that is contemporary, and aspects that are likely to be controversial by the nature of their novelty are also included.

The editor has included additional, related topics of interest, such as the athlete's heart, arrhythmogenic right ventricular cardiomyopathy, sudden death due to chest blows (commotio cordis) and naturally occurring animal models of cardiovascular disease. An important chapter on the role of the Internet and support groups for patients with hypertrophic cardiomyopathy should be particularly useful to patients, primary clinicians and cardiologists.

This outstanding monograph, edited by Dr Barry Maron, an internationally recognized authority on the subject, provides a comprehensive discussion of the ever-changing spectrum of hypertrophic cardiomyopathy. It should serve as an excellent reference book on the subject for many years to come.

Pravin M. Shah, MD, MACC
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Dedication and Acknowledgments

This informative, comprehensive, and contemporary multi-authored book—largely devoted to the diagnosis, pathophysiology, clinical course and management of hypertrophic cardiomyopathy—is formally dedicated to the many thousands of patients afflicted with this disease throughout the world.

In addition, I would like to personally acknowledge the longstanding and continued support of my family for this and other related projects, including my wife Donna and all of the other young Maron doctors—Martin, Bradley and Jill—as well as my staff at the Hypertrophic Cardiomyopathy Center of the Minneapolis Heart Institute Foundation, particularly Terri Hanson and Sue Casey. Without their efforts, neither this book nor the substantial amount of data generated from our center over the last 10 years (ultimately important to the care of patients with hypertrophic cardiomyopathy) would have been possible.

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CHAPTER 1

Phenotypic Expression and Clinical Course of Hypertrophic Cardiomyopathy

Barry J. Maron, MD

Hypertrophic cardiomyopathy (HCM) is a complex and relatively common genetic cardiac disease and has been the subject of intense scrutiny and investigation for over 40 years.[1–50] HCM is an important cause of disability and death in patients of all ages and is the most common cause of sudden cardiac death in young people, including trained athletes.[51–60] Because of marked heterogeneity in clinical and phenotypic expression, natural history and prognosis,[51–66] HCM often represents a dilemma even to cardiovascular specialists, including those for whom this disease is a focus of their investigative efforts. This chapter is designed to place in perspective and clarify the rapidly evolving concepts predominantly related to the prevalence, phenotypic expression, and clinical course of HCM.

Prevalence

Epidemiologic investigations using echocardiography and with diverse study designs have produced similar estimates for the prevalence of phenotypically expressed HCM in general adult populations: about 0.2% (or 1: 500) (Fig 1.1).[20,39,67–69] These include population surveys of young adults in the USA, echocardiographic screening for cardiovascular disease in rural Minnesota, and other investigations using population samples in Japan and China. Therefore, HCM is not rare; in fact, it is the most common of the genetic cardiovascular diseases, with reports from many countries throughout the world, including most prominently the USA, Canada, Western Europe, South America, Australia, Japan, and China. Taken together, these reports from diverse geographic regions and cultures have suggested a similar clinical presentation and course. Nevertheless, a substantial proportion of individuals harboring a mutant gene for HCM are probably undetected clinically, as evidenced by the uncommon occurrence of HCM in routine cardiology practice, constituting about 1% of an outpatient population.[70] This limited exposure to HCM by practicing clinicians outside of major centers understandably accounts for the uncertainty that prevails regarding this disease and its management.

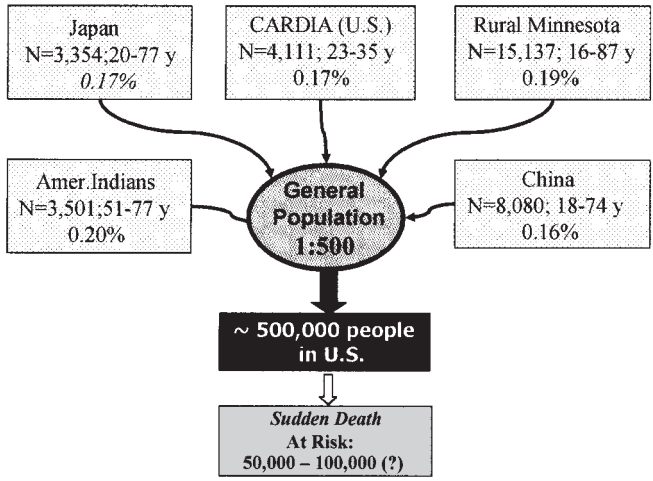

Fig. 1.1 Evidence of the worldwide prevalence of hypertrophic cardiomyopathy and its clinical implications. y = years of age; Amer. = American. Population prevalence data presented are cited in references 20, 39, 67, and 69.

Nomenclature

Since the first modern description in 1958,[1] HCM has been known by a vast and confusing array of names, reflecting its clinical heterogeneity and the skewed experience of early investigators (Fig. 1.2). 'Hypertrophic cardiomyopathy'[71] has become established as the preferred name because it describes the overall disease spectrum without introducing the misleading inference that left ventricular (LV) outflow tract obstruction is an invariable clinical feature (such as hypertrophic obstructive cardiomyopathy; or idiopathic hypertrophic subaortic stenosis). Indeed, under resting (basal) conditions HCM presents as a predominantly nonobstructive disease in which only about 25% of patients demonstrate a sizeable outflow gradient.[2,3,7,25,27,34,37]

Genetics

HCM is inherited as a Mendelian autosomal dominant trait caused by mutations in any one of 10 genes, each encoding proteins of the cardiac sarcomere (components of thick or thin filaments with contractile, structural or regulatory functions).[3,9,35,43,45,46,48–50,59,72] The physical similarity of these proteins represents a unifying principle that makes it possible to regard the diverse HCM spectrum as a single disease entity and a primary disorder of the sarcomere. Recently, missense mutations in the gene that encodes the γ-2 regulatory subunit of the AMP-activated protein kinase (*PRKAG2*) have been reported to cause familial Wolff–Parkinson–White syndrome and LV hypertrophy (due to glycogen accumulation in myocytes).[3,73] This syndrome is a metabolic storage disease distinct from typical HCM, and is caused by mutations in genes

TERMS USED TO DESCRIBE HYPERTROPHIC CARDIOMYOPATHY

Acquired aortic subvalvular stenosis
Apical asymmetric septal hypertrophy
Apical hypertrophic cardiomyopathy
Apical hypertrophic nonobstructive cardiomyopathy
Apical hypertrophy
Asymmetric left ventricular hypertrophy
Asymmetric septal hypertrophy
Asymmetrical apical hypertrophy
Asymmetrical hypertrophic cardiomyopathy
Asymmetrical hypertrophy of the heart
Brock's disease
Diffuse muscular subaortic stenosis
Diffuse subvalvular aortic stenosis
Dynamic hypertrophic subaortic stenosis
Dynamic muscular subaortic stenosis
Familial hypertrophic subaortic stenosis
Familial muscular subaortic stenosis
Familial myocardial disease
Functional aortic stenosis
Functional aortic subvalvar stenosis
Functional hypertrophic subaortic stenosis
Functional obstructive cardiomyopathy
Functional obstruction of the left ventricle
Functional obstructive subvalvular aortic stenosis
Functional subaortic stenosis
Hereditary cardiovascular dysplasia
Hypertrophic apical cardiomyopathy
HYPERTROPHIC CARDIOMYOPATHY
Hypertrophic constrictive cardiomyopathy
Hypertrophic disease
Hypertrophic hyperkinetic cardiomyopathy
Hypertrophic infundibular aortic stenosis
Hypertrophic nonobstructive apical cardiomyopathy
Hypertrophic nonobstructive cardiomyopathy
Hypertrophic nonobstructive cardiomyopathy with giant negative T waves
Hypertrophic obstructive cardiomyopathy
Hypertrophic obstructive cardiomyopathy of left ventricle
Hypertrophic restrictive cardiomyopathy
Hypertrophic stenosing cardiomyopathy
Hypertrophic subaortic stenosis
Idiopathic hypertrophic cardiomyopathy
Idiopathic hypertrophic obstructive cardiomyopathy
Idiopathic hypertrophic subaortic stenosis
Idiopathic hypertrophic subvalvular stenosis
Idiopathic muscular hypertrophic subaortic stenosis
Idiopathic muscular stenosis of the left ventricle
Idiopathic myocardial hypertrophy
Idiopathic ventricular septal hypertrophy
Irregular hypertrophic cardiomyopathy
Left ventricular muscular stenosis
Low subvalvular aortic stenosis
Mid-ventricular hypertrophic cardiomyopathy
Mid-ventricular hypertrophic obstructive cardiomyopathy
Mid-ventricular obstruction
Muscular aortic stenosis
Muscular hypertrophic stenosis of the left ventricle
Muscular stenosis of the left ventricle
Muscular subaortic stenosis
Muscular subvalvular aortic stenosis
Non-dilated cardiomyopathy
Nonobstructive hypertrophic cardiomyopathy
Obstructive cardiomyopathy
Obstructive hypertrophic aortic stenosis
Obstructive hypertrophic cardiomyopathy
Obstructive hypertrophic myocardiopathy
Obstructive myocardiopathy
Pseudoaortic stenosis
Stenosing hypertrophy of the left ventricle
Stenosis of the ejection chamber of left ventricle
Subaortic hypertrophic obstructive cardiomyopathy
Subaortic hypertrophic stenosis
Subaortic idiopathic stenosis
Subaortic muscular stenosis
Subvalvular aortic stenosis
Subvalvular aortic stenosis of the muscular type
Teare's disease
Typical hypertrophic obstructive cardiomyopathy

Fig. 1.2 Terms which have been used to describe hypertrophic cardiomyopathy. From Maron and Epstein. Hypertrophic cardiomyopathy: A discussion of nomenclature. *Am J Cardiol* 1979; **43**: 1242–4, reproduced with permission of the *American Journal of Cardiology.*

encoding proteins of the cardiac sarcomere; future studies are likely to ascribe other HCM subgroups to metabolic disorders (e.g. glycogen storage diseases).

At present, three of the HCM-causing mutant genes predominate: β-myosin heavy chain (the first identified), cardiac troponin T, and myosin-binding protein C. The other genes each account for a minority of HCM cases—cardiac troponin-I, regulatory and essential myosin light chains, titin, α-tropomyosin, α-actin, and α-myosin heavy chain. This diversity is compounded by intragenic heterogeneity, with more than 150 mutations identified, most of which

are missense with a single amino acid residue substituted for another (see Chapter 2 for details). The molecular defects responsible for HCM are usually different in unrelated individuals, and many other sarcomeric genes and mutations (each accounting for a small proportion of familial HCM) remain to be identified. The mechanisms by which disease-causing sarcomere mutations cause LV hypertrophy and the HCM disease state are presently unresolved, although several hypotheses abound.[74]

Contemporary molecular genetic studies over the past decade have provided important insights into the considerable clinical heterogeneity of HCM, including the preclinical diagnosis of affected individuals without evidence of the disease phenotype (e.g. LV hypertrophy by echocardiography or ECG).[3,11,35,43,49,75–78] While DNA analysis for mutant genes is the definitive method of establishing the diagnosis of HCM, it is not yet a routine clinical strategy.[72] Because the techniques are complex, time-consuming and expensive, genotyping is confined to research-oriented investigations of highly selected pedigrees. The development of rapid, automated screening for genetic abnormalities will permit more widespread access to the power of molecular biology for resolving diagnostic ambiguities.

Diagnosis

Conventionally, the clinical diagnosis of HCM is established most easily and reliably with two-dimensional echocardiography, by imaging the hypertrophied but nondilated LV chamber, in the absence of another cardiac or systemic disease capable of producing that magnitude of hypertrophy (e.g. systemic hypertension or aortic stenosis) (Fig. 1.3).[2,3,12,15,21,34,37] Initially, the clinical suspicion of HCM may be raised by a heart murmur (occasionally during preparticipation sports examinations), a positive family history, new symptoms or cardiac events, or abnormal ECG.[20,25,79] The physical examination may not be a reliable method for clinical identification, unless a murmur is elicited in the standing position or with the Valsalva maneuver, given that most HCM patients do not have outflow obstruction or loud murmurs in the supine position under resting (basal) conditions.[79]

With regard to pedigree assessment, it is obligatory for the proband and family members to be informed of the genetic nature and autosomal dominant transmission of HCM. Screening of first-degree relatives with history and physical examinations, two-dimensional echocardiography and ECG should be strongly encouraged, particularly if adverse HCM-related events have occurred in the family.

In clinically diagnosed patients, increased LV wall thicknesses range widely from mild (13–15 mm) to massive (≥30 mm; normal ≤12 mm),[2,3,6,10,12,15,52,53,55] and include the most substantial in any cardiac disease—up to 60 mm (Figs 1.4–1.7).[19,80] In trained athletes, modest segmental wall thickening (13–15 mm) occurs occasionally,[81] raising the differential diagnosis between extreme physiologic LV hypertrophy (i.e. athlete's heart) and mild morphologic expressions

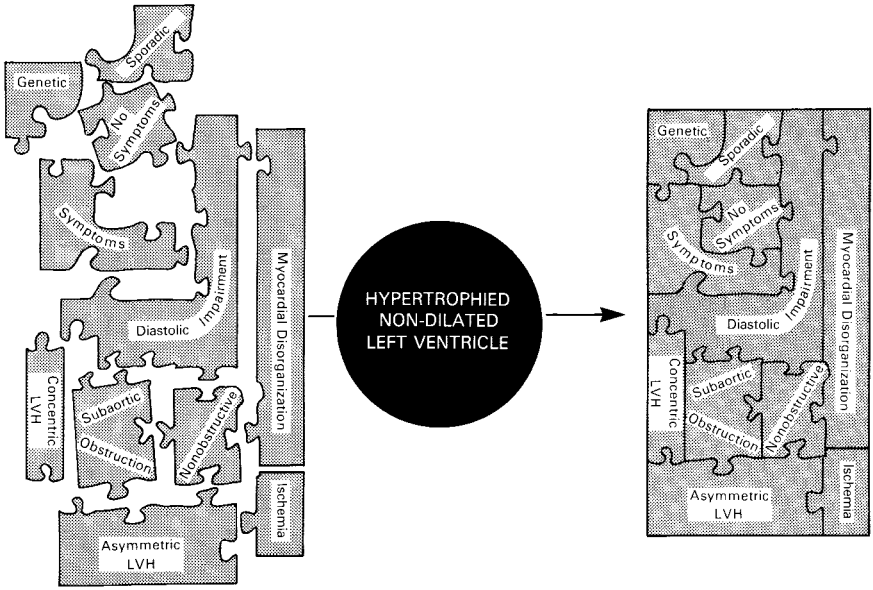

Fig. 1.3 Diagrammatic representation of the basic morphologic definition of hypertrophic cardiomyopathy (in dark circle), as it unifies the clinical and morphologic heterogeneity characteristic of the disease spectrum.

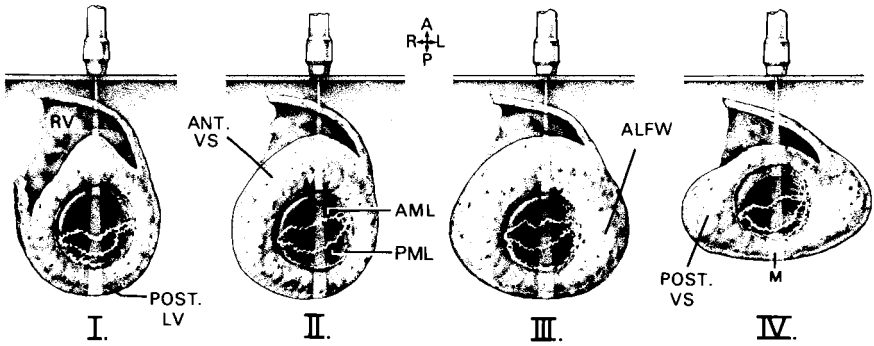

Fig. 1.4 Morphologic variability in hypertrophic cardiomyopathy, based on observations made from two-dimensional echocardiography (Maron classification). All images appear in the short-axis cross-sectional plane at mitral valve level. **I**, Relatively mild left ventricular hypertrophy confined to anterior portion of ventricular septum (VS); **II**, hypertrophy of anterior and posterior septum in the absence of free wall thickening; **III**, diffuse hypertrophy of substantial portions of both the ventricular septum and the anterolateral free wall (ALFW); **IV**, includes more unusual patterns of hypertrophy in which the anterior septum is spared from the hypertrophic process and the thickened portions of the left ventricle are in the posterior septum or anterolateral free wall (as shown here), or the apex. AML = anterior mitral leaflet; A or ANT = anterior; L = (patient's) left; LVFW = LV free wall; P or POST = posterior; PML = posterior mitral leaflet; R = (patient's) right; RV = right ventricle. From Maron *et al.* Patterns and significance of distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy: A wide-angle, two-dimensional echocardiographic study of 125 patients. *Am J Cardiol* 1981; **48**: 418–28, reproduced with permission of the *American Journal of Cardiology.*

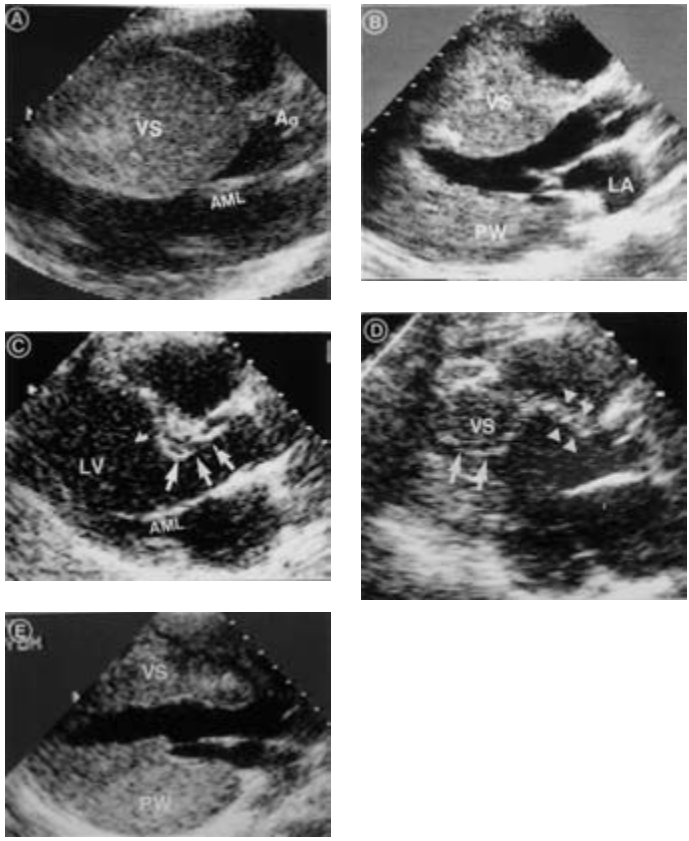

Fig. 1.5 Distribution and extent of ventricular septal thickening as shown in a composite of parasternal long-axis stop-frame images obtained in diastole. (**A**) Massive asymmetric hypertrophy of ventricular septum (VS) with wall thickness exceeding 50 mm. (**B**) Heterogeneous pattern of septal thickening, with distal portion substantially thicker than the proximal region at mitral valve level. (**C**) Hypertrophy sharply confined to the basal (proximal) septum just below the aortic valve (arrows). (**D**) Distal septal thickening (arrows) and particularly abrupt transition to thin proximal septum (<10 mm) (arrowheads). (**E**) 'Inverted' pattern of hypertrophy in which the distal anterior ventricular septum is only mildly thickened but the posterior free wall (PW) is substantially thickened and the posterior free wall (PW) is substantially thickened (to 40 mm). Calibration dots are 1 cm apart. Ao = aorta; AML = anterior mitral leaflet; LA = left atrium; LV = left ventricle. From Klues *et al*. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: Morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995; **26**: 1699–708, reproduced with permission of the American College of Cardiology.

of HCM,[48] which usually can be resolved with noninvasive testing.[82] Magnetic resonance imaging may be of diagnostic value when echocardiographic studies are technically inadequate or in identifying segmental LV hypertrophy that is undetectable by echocardiography.[83]

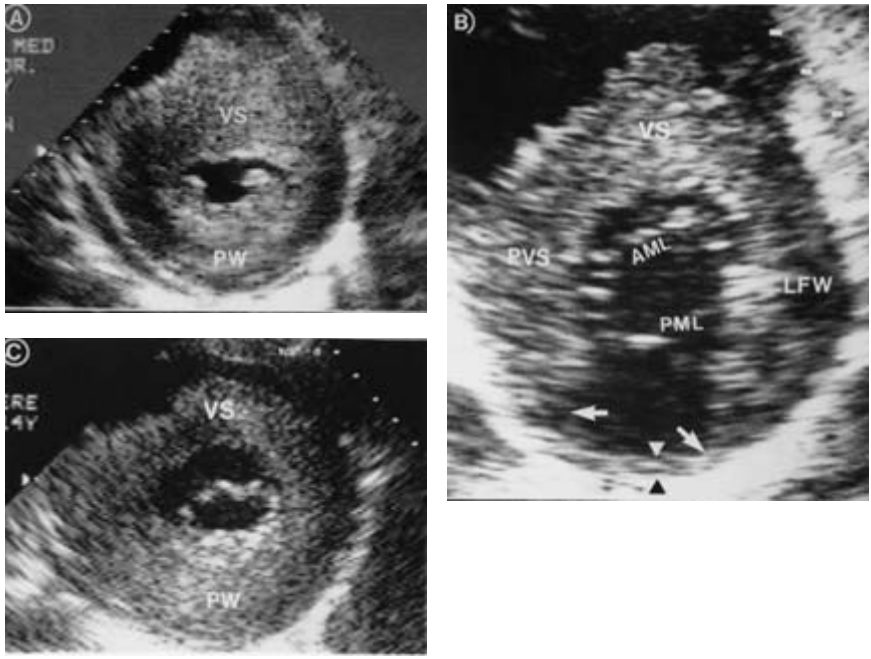

Fig. 1.6 Variability of patterns of left ventricular hypertrophy in patients with hypertrophic cardiomyopathy, shown in a composite of diastolic stop-frame images in the parasternal short-axis plane. (**A, B** and **D**) Wall thickening is diffuse, involving substantial portions of the ventricular septum and free wall. At the papillary muscle level (**A**), all segments of the left ventricle are hypertrophied, including the posterior free wall (PW), but the pattern of thickening is asymmetric with the anterior portion of the ventricular septum (VS) massive (50 mm). (**B**) Hypertrophy is diffuse, involving three segments of the left ventricle but with the posterior wall spared and thin (<10 mm) (arrowheads) and with particularly abrupt changes in wall thickness evident (arrows). (**C**) Marked hypertrophy in a pattern distinctly different from that in **A**, **B** and **D**, in which the thickening of the posterior wall is predominant and the ventricular septum is of nearly normal thickness. (**D**) Diffuse distribution of hypertrophy involving three segments of the left ventricle similar to that in **B** but without sharp changes in the contour of the wall. (**E**) Hypertrophy predominantly of the lateral free wall and only a small portion of contiguous anterior septum (arrows). (**F**) Hypertrophy predominantly of the posterior ventricular septum (PVS) and, to a lesser extent, the contiguous portion of the anterior septum. (**G**) Thickening of anterior and posterior septum to a similar degree but with sparing of the free wall. Calibration dots are 1 cm apart. AML = anterior mitral leaflet; LFW = lateral free wall; PML = posterior mitral leaflet. From Klues *et al*. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: Morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995; **26**: 1699–708, reproduced with permission of the American College of Cardiology. (*Continued*.)

The 12-lead ECG is abnormal in 75–95% of HCM patients depending on the particular selection of patients; the ECG typically demonstrates a wide variety of patterns, often bizarre in appearance, although none are characteristic of most patients with HCM.[84,85] The ECG abnormalities most commonly described are LV hypertrophy, ST segment alterations and T wave inversion, left atrial enlargement, abnormal Q waves, and diminished or absent R waves

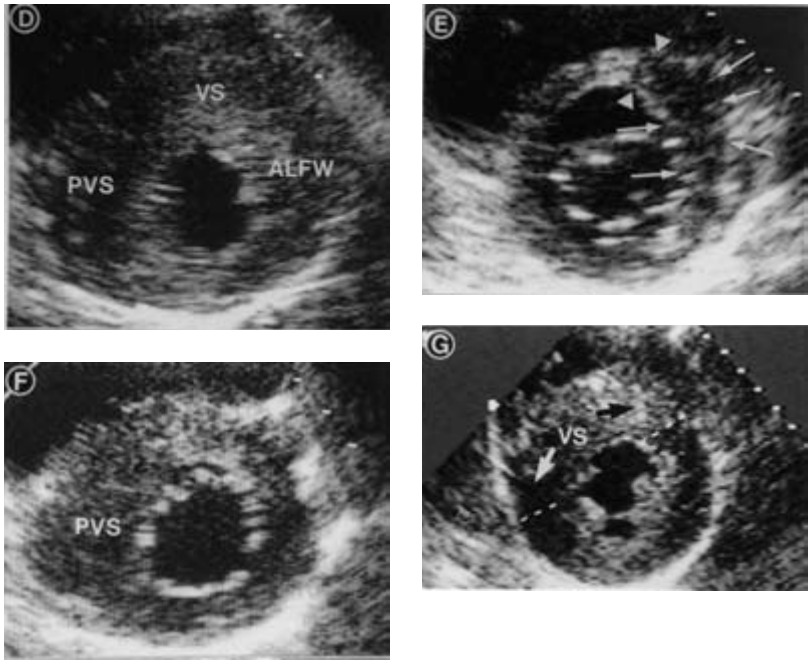

Fig. 1.6 (*Continued.*)

in the lateral precordial leads. Infants and young children with HCM often have the paradoxic finding of right ventricular hypertrophy, which may reflect obstruction to right ventricular outflow. Normal ECGs are most commonly encountered in family members identified as part of pedigree screening and/or when associated with mild localized LV hypertrophy.[43,75–77]

Only a modest relation between ECG voltages and the magnitude of LV hypertrophy assessed by echocardiography is evident, and no particular ECG pattern reliably discriminates patients with or without obstruction to LV outflow or those at risk of sudden death. All of this limits the usefulness of the 12-lead ECG as a routine clinical test.[86] Nevertheless, the 12-lead ECG has been shown to have diagnostic efficacy in raising the suspicion of HCM in family members known to carry a disease-causing mutant gene but without LV hypertrophy, as well as in targeting athletes for diagnostic echocardiography as part of preparticipation sports screening.[43,75–77,85,87] Also, non-preload-dependent measures of diastolic dysfunction with tissue Doppler echocardiography may precede the appearance of LV hypertrophy, providing clues to the impending appearance of the HCM phenotype.[78]

However, not all individuals harboring a genetic defect will at all times express the clinical features of HCM, such as LV hypertrophy by echocardiography, abnormal ECG, or cardiac symptoms.[2,3,21,35,37,43,72,85] Molecular genetic studies have demonstrated that there is no minimum wall thickness obligatory for the diagnosis of HCM at any given time in life; indeed, it is not unusual for

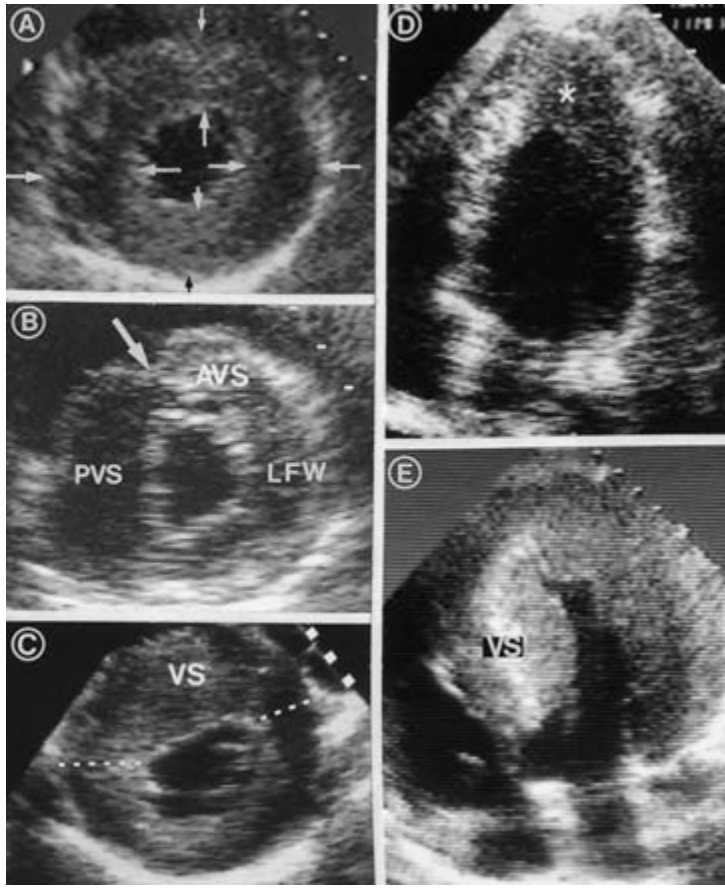

Fig. 1.7 Patterns of left ventricular hypertrophy in five patients with hypertrophic cardiomyopathy. (**A, B** and **C**) Diastolic stop-frame images obtained in the parasternal short-axis plane. (**D** and **E**) Apical four-chamber views. In **A**, relatively mild hypertrophy in a concentric (symmetric) pattern, each segment of septum and free wall having similar or identical thickness (paired arrows). (**B**) 'Butterfly' pattern with prominent indentation (arrow) and localized area of thinning interpositioned at the 11 o'clock position between adjacent thicker areas of the ventricular septum. (**C**) Hypertrophy of the entire ventricular septum (VS) and sparing of most of the left ventricular free wall. (**D**) Myocardial hypertrophy confined to the left ventricular apex (asterisk). (**E**) Image from another patient with hypertrophy of the left ventricular apex but also diffusely involving the ventricular septum and free wall. Calibration marks are 1 cm apart. AVS = anterior ventricular septum; LA = left atrium; LFW = lateral free wall; LV = left ventricle; PVS = posterior ventricular septum. From Klues *et al*. Phenotypic spectrum and patterns of left ventricular hypertrophy in hypertrophic cardiomyopathy: Morphologic observations and significance as assessed by two-dimensional echocardiography in 600 patients. *J Am Coll Cardiol* 1995; **26**: 1699–708, reproduced with permission of the American College of Cardiology.

children under 13 years to carry a mutant HCM gene without demonstrating hypertrophy. This underscores the potential limitation of echocardiographic screening for this disease in pre-adolescents.[2,3,21,35,37,43,49,72,75–77,85]

Substantial LV remodeling with the spontaneous appearance of hypertrophy typically occurs with the accelerated body growth occurring during adolescence, and this morphologic expression is believed to be complete in most instances at the time of physical maturity (about 17–18 years of age) (Fig. 1.8).[2,3,21]

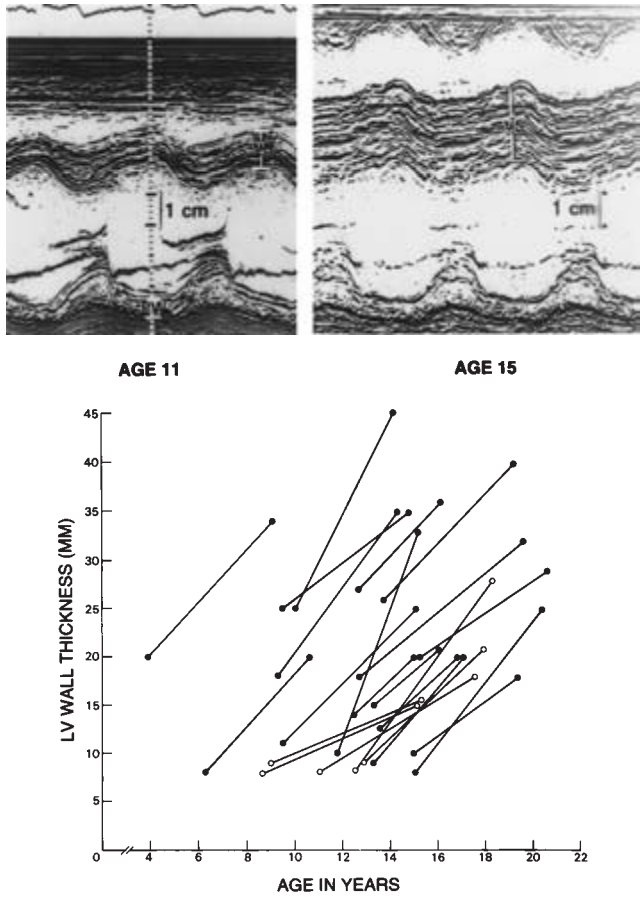

Fig. 1.8 Development and progression of left ventricular hypertrophy in children with hypertrophic cardiomyopathy. (Top) Dynamic, striking changes in left ventricular wall thickness with age in 22 children; each patient is represented by the left ventricular segment that showed greatest change in wall thickness. Open symbols denote five patients who had no evidence of hypertrophy in any segment of the left ventricle at initial evaluation but subsequently developed *de novo* hypertrophy typical of hypertrophic cardiomyopathy. (Bottom) Development of marked hypertrophy of the anterior basal ventricular septum (VS). M-mode echocardiograms were obtained at the same cross-sectional level in girl with a family history of hypertrophic cardiomyopathy. At age 11, ventricular septal thickness was at the upper limit of normal (10 mm); at age 15, septal thickness had increased markedly (to 33 mm). Appearance of the echocardiogram is typical of hypertrophic cardiomyopathy. The patient remained asymptomatic throughout this period but died suddenly and unexpectedly at age 17. PW = posterior left ventricular free wall. From Maron *et al.* Hypertrophic cardiomyopathy: Interrelation of clinical manifestations, pathophysiology, and therapy. *N Engl J Med* 1987; **316**: 780–9 and 844–52, reproduced with permission of the Massachusetts Medical Society.

Recently, novel diagnostic criteria for HCM, based on genotype–phenotype studies, have demonstrated incomplete disease expression with the absence of LV hypertrophy in adult individuals, due most commonly to cardiac myosin-binding protein-C or troponin-T mutations.[2,3,11,43,49] Mutations in the myosin-binding protein C gene have also been associated, in both cross-sectional and serial echocardiographic studies, with age-related penetrance of the HCM phenotype, in which delayed and late *de novo* onset of LV hypertrophy occurs in mid-life and even beyond (Fig. 1.9).[2,3,11,43,88] Such adult morphologic conversions dictate that it is no longer possible to issue definitive reassurance to asymptomatic family members at maturity (or even in middle age) that they are free of a disease-causing mutant HCM gene solely based on clinical findings and a normal echocardiogram. This probably necessitates a strategy of subsequent

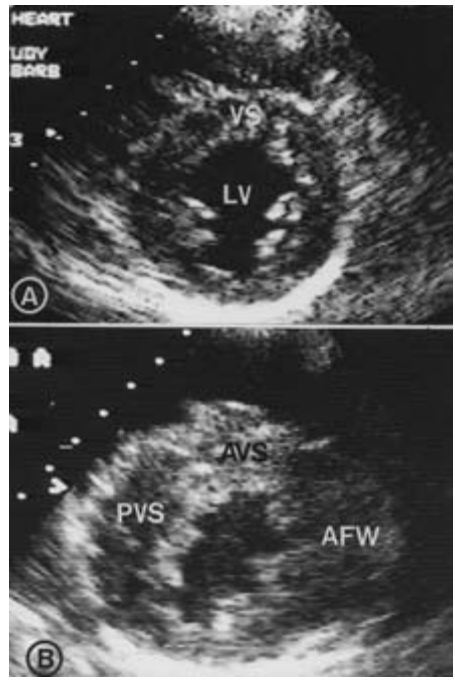

Fig. 1.9 Development of the hypertrophic cardiomyopathy phenotype in adulthood. Stop-frame two-dimensional echocardiograms at end-diastole, at the papillary muscle level in the parasternal short-axis plane, from a woman with familial hypertrophic cardiomyopathy at age 27 years, when genotyping was initiated (**A**) and at age 33 years, after the myosin-binding protein C mutation was known (**B**). (**A**) Left ventricular (LV) thickness is normal (≤12 mm) in all segments of the wall, including the ventricular septum (VS). (**B**) Six years later, at age 33, wall thickness was abnormally increased (19–20 mm) in the anterior ventricular septum (AVS) and posterior septum (PVS) as well as the anterolateral free wall (AFW). Mild mitral valve systolic anterior motion (without septal contact or outflow gradient) appeared at this time, although it is not shown here. Calibration marks are 10 mm apart. From Maron *et al*. Clinical course of hypertrophic cardiomyopathy with survival to advanced age. *J Am Coll Cardiol* 2003; **42**: 882–8, reproduced with permission of the *Journal of the American College of Cardiology*.

echocardiographic examinations every 5 years.[72] Otherwise, the recommended strategy for screening relatives in most HCM families calls for such evaluations at intervals of 12–18 months, usually beginning at age 12.

Paradoxically, a small, distinctive subset of HCM patients (2%) evolve to the end-stage (or 'burned-out') phase, characterized by LV wall thinning, ventricular cavity enlargement and systolic dysfunction. This often resembles the dilated form of cardiomyopathy and produces relentlessly progressive and irreversible heart failure (Fig. 1.10).[2,3,66,89,90] Such disease progression is probably due to extensive myocardial scarring on the basis of ischemia related to 'small vessel disease,' but is not associated with atherosclerotic coronary artery disease. This profound remodeling process, progressing from a thick-walled,

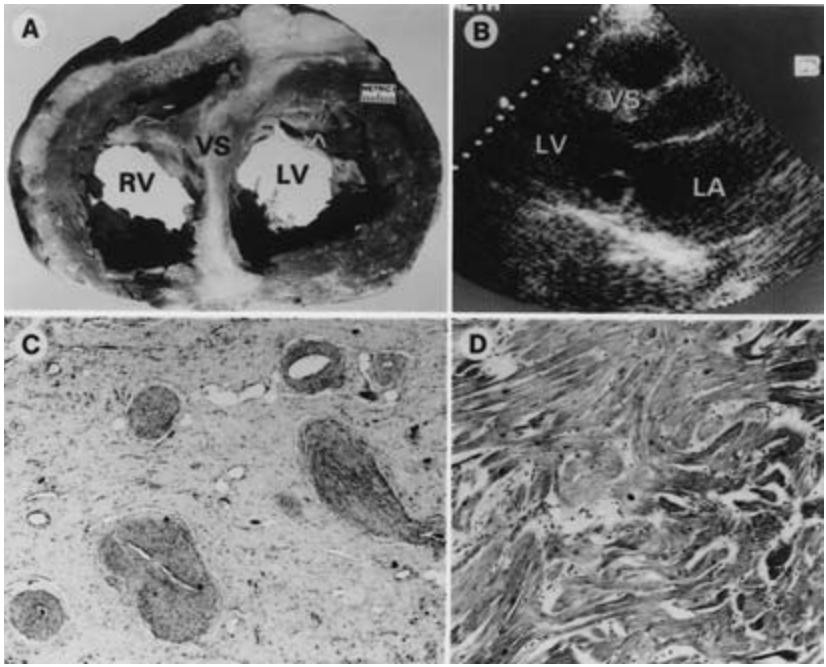

Fig. 1.10 End-stage hypertrophic cardiomyopathy in a 46-year-old man. (**A**) Transverse section of the heart obtained after heart transplantation, showing extensive scarring and thinning of the ventricular septum (VS), which extends into the anterior and posterior free wall. The left ventricular (LV) cavity appears enlarged. RV = right ventricle. (**B**) Stop-frame echocardiogram in parasternal long-axis view (obtained 2 weeks before heart transplantation, showing relatively mild (13 mm) wall thickening confined to the basal anterior ventricular septum. The left atrium (LA) is enlarged (65 mm). (**C** and **D**) Photomicrographs of the left ventricular myocardium. (**C**) Several abnormal coronary arteries with markedly thickened walls and a narrowed lumen, dispersed in an area of replacement fibrosis. Hematoxylin–eosin stain; magnification ×45. (**D**) Bundles of hypertrophied cardiac muscle cells arranged in a chaotic pattern, with adjacent cells oriented at oblique and perpendicular angles to each other. Hematoxylin–eosin stain; magnification ×30. From Hecht *et al*. Coexistence of sudden cardiac death and end-stage heart failure in familial hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1993; **22**: 489–97, reproduced with permission of the American College of Cardiology.

nondilated LV with normal or increased ejection fraction to a thinned and dilated LV with impaired contractility, can develop abruptly or evolve over several years, and may present at any age. Furthermore, end-stage patients and patients with HCM-related sudden cardiac death may coexist in the same family (and therefore share the same genetic substrate); individual patients have even experienced aborted sudden death and subsequently died in the end-stage phase of their disease, all within their lifetime.[60]

Therapeutic options are considerably limited for drug-refractory, severely symptomatic patients with the nonobstructive end-stage form of HCM.[2,3] Only this subset of patients, among the broad HCM clinical spectrum, may become candidates for heart transplantation.[2,3] Other adults, most commonly women,[91] may experience more gradual and subtle LV remodeling, with regression in wall thickness associated with aging (but not linked to systolic dysfunction or clinical deterioration).[2,37,91] Therefore, LV hypertrophy is not a static manifestation of HCM, can appear at virtually any age, and can also increase or decrease dynamically throughout life.[89]

Left ventricular outflow obstruction

LV outflow tract gradients are produced by systolic anterior motion of the mitral valve, and apposition with the ventricular septum (due predominantly to a drag effect[92] or possibly also the Venturi phenomenon)[2,3] has been the most recognizable feature of HCM from its initial clinical description.[93–95] Although previously subject to periodic controversy, there is now widespread recognition that the subaortic gradient and the associated elevation in intracavity LV pressure reflect true mechanical impedance to outflow and are of pathophysiologic and prognostic importance to patients with HCM.[7] Indeed, outflow obstruction under basal (resting) conditions (gradient ≥30 mm Hg) is a strong, independent predictor of HCM-related progression to severe limiting symptoms of New York Heart Association (NYHA) classes III and IV, and of death due specifically to heart failure and stroke (relative risk >4.0).[7] However, the likelihood of severe symptoms and death due to outflow tract obstruction was greater when the magnitude of the gradient was increased above the threshold of 30 mm Hg.[7] Over time, disease consequences due to chronic outflow gradients (and concomitant mitral regurgitation) are likely to be related to the resulting increase in LV wall stress, myocardial ischemia, and eventually cell death and replacement fibrosis.[96,97] Indeed, longer durations of obstruction appear to confer a more unfavorable clinical course, leading frequently to heart failure-related disease progression and death.[7]

It is important to underscore that a variety of interventions have been traditionally employed to elicit latent (inducible) gradients in echocardiography, cardiac catheterization, and exercise laboratories (e.g. amyl nitrite inhalation, Valsalva maneuver, post-premature ventricular contraction response, isoproterenol or dobutamine infusion, standing posture, and physiologic exercise). However, rigorous standardization for these maneuvers has been lacking, and many have come to be regarded as nonphysiologic. To define latent gradients

during and/or immediately after exercise for the purpose of major management decisions, treadmill or bicycle exercise testing in association with Doppler echocardiography is probably the most physiologic, meaningful, and preferred provocative maneuver, given that HCM-related symptoms are typically elicited with exertion. Intravenous administration of dobutamine is undesirable, because subaortic gradients provoked with this agent are widely regarded as nonphysiologic.[3] Therefore, the presence of LV outflow obstruction justifies intervention with septal myectomy (or alcohol septal ablation in selected patients) to reduce or abolish clinically relevant subaortic gradients (≥50 mm Hg at rest or with physiologic exercise)[98] in severely symptomatic patients who are refractory to maximum medical management.[3] Outflow gradients associated with atrial fibrillation are particularly deleterious in HCM patients.[99]

HCM phenotype and morphologic features

Left ventricular hypertrophy

Structural heterogeneity in HCM is considerable, no single pattern of LV hypertrophy being regarded as typical (Figs 1.4–1.11).[2,3,15] While many patients show diffusely distributed LV hypertrophy, almost one-third have mild wall thickening localized to a single segment,[15] including the apical form,[17,18,65,88] which appears to be most common in Japanese patients (Fig. 1.7).[65,100] Apical HCM refers to a nonobstructive form of hypertrophy confined to the most distal portion of LV, and may (or may not) be associated with giant negative T-waves on ECG. Also, very rarely, patients with HCM may develop apical aneurysms of various sizes, associated with mid-ventricular LV hypertrophy and repetitive monomorphic ventricular tachycardia, for which the prognosis appears to be particularly unfavorable.[6,101]

LV hypertrophy in HCM is characteristically asymmetric (with the anterior septum usually the predominant area of thickening) (Figs 1.4–1.9, 1.11), although an occasional patient may show a symmetric (concentric) pattern in which wall thicknesses are virtually identical in all LV segments (Fig. 1.7).[15] The distribution of LV wall thickening shows no direct link to clinical outcome, although distal located hypertrophy is always associated with the absence of LV outflow obstruction. Other relatively common echocardiographic hallmarks of HCM which *per se* are not prerequisites for diagnosis, include a hyperdynamic LV and mild systolic anterior motion of the mitral valve.

Young children may present with LV hypertrophy clinically resembling HCM as part of other disease states (e.g. Noonan's syndrome, mitochondrial myopathies, metabolic disorders) but unrelated to HCM-causing sarcomere protein mutations. The fact that disproportionate thickening of the ventricular septum is also a characteristic anatomic feature of the normal embryonic and fetal human heart (Fig. 1.12) suggests the possibility that, in some instances,

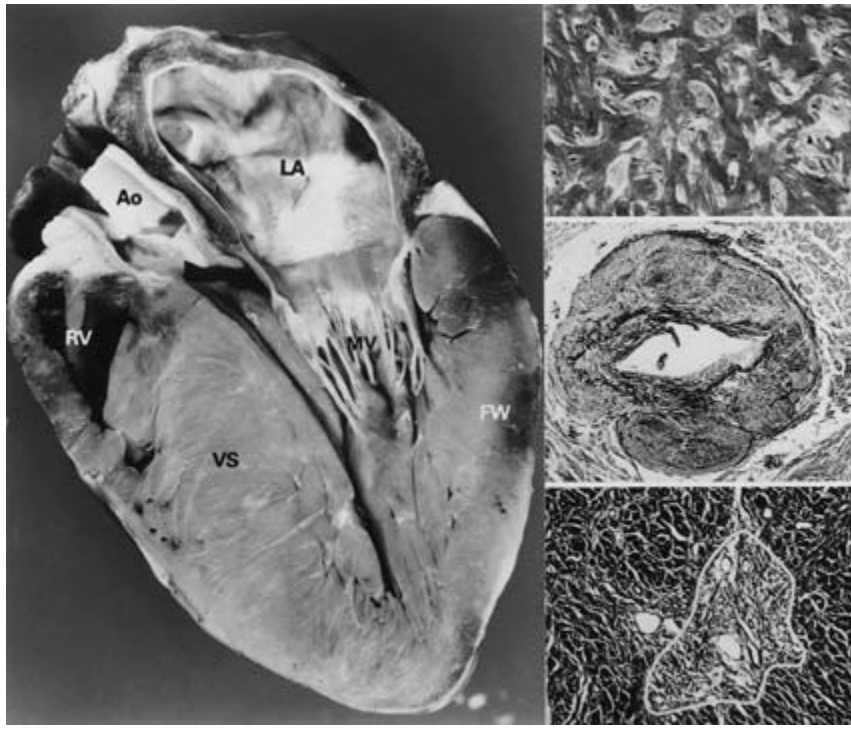

Fig. 1.11 Morphologic features of the myocardial substrate for sudden death in hypertrophic cardiomyopathy. (**Left**) Gross heart specimen from a 13-year-old male competitive athlete showing disproportionate thickening of the ventricular septum (VS) with respect to the left ventricular free wall (LV). RV = right ventricular wall. (**Top right**) Marked disarray of cardiac muscle cells in the disproportionately thickened ventricular septum with adjacent hypertrophied cells arranged in a chaotic pattern at oblique and perpendicular angles, forming the typical disorganized architecture of hypertrophic cardiomyopathy. (**Middle right**) Abnormal intramural coronary artery with markedly thickened walls and narrowed lumen. (**Lower right**) Replacement fibrosis, the consequence of bursts of myocardial ischemia, cell death, and small vessel disease. Hematoxylin–eosin stains. Adapted from Maron BJ. Hypertrophic cardiomyopathy. *Curr Probl Cardiol* 1993; **18**: 637–704, reproduced with permission of Mosby, Inc.

asymmetric LV hypertrophy in young infants with HCM represents postnatal persistence of a normal anatomic feature of the developing heart.[102]

Histopathologic components

The cardiomyopathic substrate in HCM is defined anatomically by several histologic features.[22,62,63,102–106] Based largely on autopsy observations, LV myocardial architecture is disorganized and comprises hypertrophied cardiac muscle cells (myocytes) with bizarre shapes and multiple intercellular connections, often arranged in chaotic alignment at oblique and perpendicular angles (Fig. 1.10).[62,63,106] Cellular disarray may be widely distributed, occupying substantial portions of the LV wall (on average, 33% of the septal myocardium

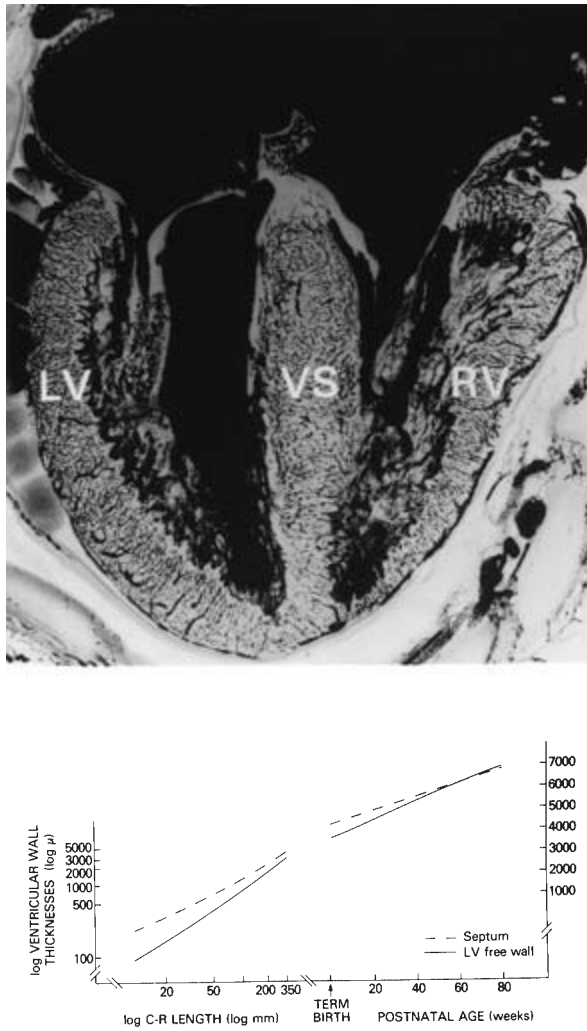

Fig. 1.12 Ventricular anatomy in the normal human fetus. (Top) Frontally sectioned heart of a fetus at 10 weeks of gestation, showing a ventricular septum (VS) that is disproportionately thicker than the left ventricular free wall (LV). Ventricular cavities are filled with India ink that was injected into the umbilical vein at the time of preparation for the specimen. RV = right ventricle. (Bottom) Changes in ventricular septum, left ventricular free wall, and right ventricular wall thickness before and after birth. From Maron *et al*. Disproportionate ventricular septal thickening in the developing normal human heart. *Circulation* 1978; **57**: 520–6, reproduced with permission of the American Heart Association.

and 25% of the free wall),[62,107] and is more extensive in young patients who die of their disease.[62] Disarray is not, however, limited to thickened regions of the left ventricle, and abnormal cellular arrangement may be present in both hypertrophied and nonhypertrophied segments.[106]

Abnormal small intramural coronary arteries, characterized by thickened walls with increased intimal and medial collagen and narrowed lumen, may be regarded as a form of small vessel disease (Fig. 1.11).[108,109] Such architectural alterations of the microvasculature (as well as a mismatch between myocardial mass and coronary circulation) are likely responsible for impaired coronary vasodilator reserve[109,110] and bursts of myocardial ischemia[104,111] leading to myocyte death and repair in the form of patchy or even transmural replacement scarring (Fig. 1.11);[104,105,107] these are identifiable at autopsy or as thallium-201 myocardial perfusion defects.[111] The presence of myocardial scarring supports the clinical evidence that ischemia occurs in HCM and may serve as the substrate for premature heart failure-related death. It is also evident that the cardiomyopathic process in HCM is not confined to areas of gross wall thickening, because nonhypertrophied regions also contribute to ischemia or impaired diastolic function.[2,3]

Disorganized cellular architecture,[62,63,106] myocardial scarring,[104,105,107,108] and the expanded interstitial (matrix) collagen connective tissue compartment[22] probably also serve as an arrhythmogenic substrate predisposing to life-threatening electrical instability by impairing the transmission of normal electrophysiologic impulses, and thereby predisposing to disordered patterns of electrical depolarization and repolarization (Fig. 1.11). This substrate is likely to be the source of primary re-entrant arrhythmias with ventricular tachycardia/fibrillation (VT/VF), the predominant mechanism of sudden death,[23] either primarily or in association with triggers that are intrinsic to the disease process, such as myocardial ischemia, systemic hypotension, supraventricular tachyarrhythmias, or environmental variables (e.g. intense physical exertion). It is also likely that this pathologic architecture of the left ventricle in HCM is responsible for (or contributes substantially to) increased ventricular chamber stiffness and impaired relaxation.[112–115]

Penetrance and variability of phenotypic expression are undoubtedly influenced by factors other than disease-causing mutant genes, such as modifier genes (e.g. the *ACE* genotype), coexistent hypertension, lifestyle, or other environmental factors.[2,3] Indeed, several phenotypic manifestations of HCM do not primarily involve sarcomeric proteins, including increased interstitial collagen,[22] abnormal intramural coronary arteries,[107,108] and mitral valve malformations, such as elongated leaflets[14,61] and papillary muscle insertion directly into mitral valve.[13]

Indeed, a constellation of structural malformations of the mitral valve and apparatus demonstrates that the pathologic process in HCM is not confined to cardiac muscle, thereby expanding the morphologic definition of this disease.[13,14,116,117] In morphometric analysis of mitral valves removed at operation or at necropsy from patients with HCM, about two-thirds showed alterations in size, shape and morphology (Fig. 1.13).[14] These abnormalities included increased overall mitral valve area, ranging up to more than twice the normal size, and due primarily to elongation of the leaflets (but without evidence of myxomatous mitral valve degeneration) (Fig. 1.13). The enlarged and elon-

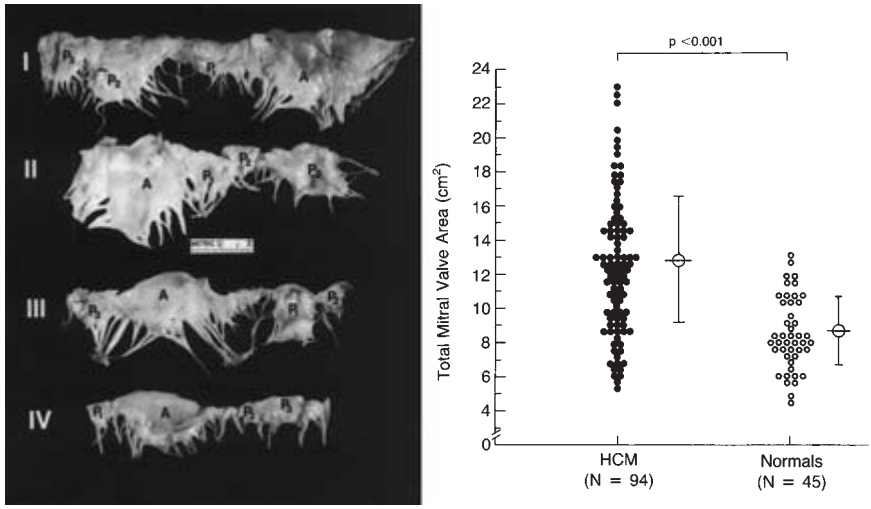

Fig. 1.13 Enlarged and elongated mitral valve in hypertrophic cardiomyopathy. (Left) Photographs of mitral valves from three patients with obstructive hypertrophic cardiomyopathy aged 31, 29 and 60 years (**I**, **II**, and **III**) and from a normal control patient without cardiovascular disease (**IV**), showing variation in valvular size and structure. Valves have been opened with the circumference displayed in a horizontal orientation, exposing the atrial surface. (**I**) Large valve (area = 22 cm^2) in which both the anterior (A) and posterior (P) leaflets are greatly elongated and increased in area. (**II**) Large valve in which increased valve size (area = 18 cm^2) is due primarily to elongation and enlargement of the anterior leaflet. (**III**) Segmental elongation and increased area confined to a lateral scallop of posterior mitral leaflet, which has virtually the same length as the normal-sized anterior leaflet. (**IV**) Valve is normal in area (11 cm^2), length and thickness. (Right) Scatterplot of total mitral valve leaflet area in patients with hypertrophic cardiomyopathy and normal controls. From Klues *et al*. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. *Circulation* 1992; **85**: 1651–60, reproduced with permission of the American Heart Association.

gated mitral valves, found primarily in younger patients with HCM (i.e. those under age 50), show considerable variability with regard to structure, including elongation of both anterior and posterior leaflets or asymmetric and segmental enlargement of either the anterior leaflet or the mid-scallop of the posterior leaflet. Compared with more normal-sized mitral valves in HCM, the enlarged and elongated valves are situated more posteriorly in a larger LV outflow tract and also have greater flexibility and systolic excursion, usually with a distinctive sharp-angled bend of the anterior leaflet making localized systolic contact with ventricular septum. This striking pattern of valvular motion is possible because the central and distal portions of the leaflet are relatively free of fibrous thickening.

In addition, some other patients with a virtually normal-sized mitral valve show anomalous insertion of the papillary muscle directly into the anterior mitral leaflet (without interposition of chordae tendineae) (Fig. 1.14), the predominant cause of muscular mid-cavitary outflow obstruction.[13] This is a congenital abnormality resulting from an arrest during embryonic development

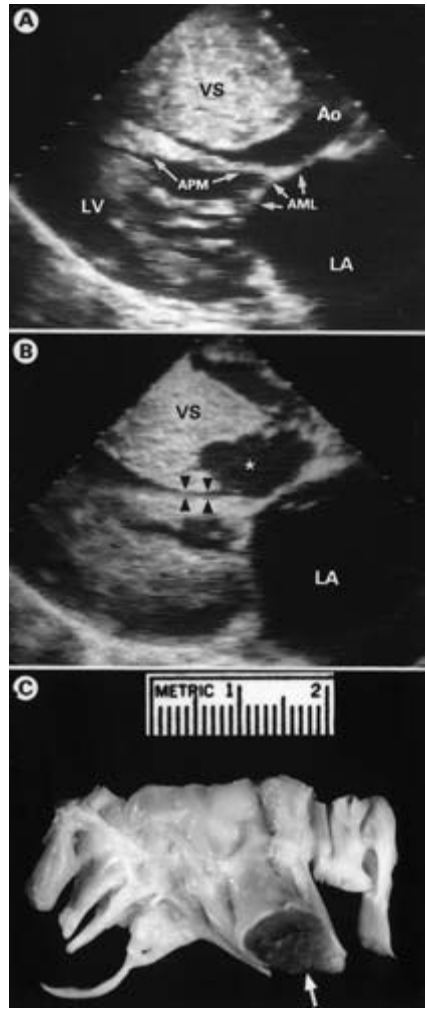

Fig. 1.14 Anomalous papillary muscle (APM) insertion directly into the anterior mitral leaflet in a patient with hypertrophic cardiomyopathy, producing muscular mid-cavity left ventricular outflow obstruction. (**A**) Before myotomy–myectomy. AML in direct continuity with the anterolateral papillary muscle (APM), which is displaced anteriorly within the left ventricular cavity, producing a long area of midcavity contact with the ventricular septum (VS) and outflow obstruction (arrowheads); tips of mitral leaflets coapt in the usual position and typical systolic anterior motion is absent (small arrows). (**B**) After myotomy–myectomy. Extensive muscular resection (*) extends from the base of the septum beyond the distal margins of the anterior mitral leaflet; nevertheless, a large area of direct contact between the papillary muscle and the ventricular septum remains (arrowheads), which is responsible for persistent obstruction of left ventricular outflow. (C) Mitral valve specimen excised at operation. A massively hypertrophied APM (arrows) inserts directly into the body of anterior leaflet. Ao = aorta; LA = left atrium; LV = left ventricle. From Klues *et al*. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy: Significance in producing left ventricular outflow obstruction. *Circulation* 1991; **84**: 1188–97, reproduced with permission of the American Heart Association.

in which the chordae tendineae fail to develop, or do so in only a rudimentary fashion, and it is important to recognize it prior to major interventions, such as septal myectomy.

Clinical course

Overall HCM population

HCM is unique among cardiovascular diseases by virtue of its potential for clinical presentation during any phase of life from infancy to old age (>90 years).[2–6,20,25,30,31,36,38,42,64,91,118] While adverse clinical consequences have been recognized for many years (sudden cardiac death in particular, but also progressive heart failure disability), a more balanced perspective regard-

ing prognosis has evolved recently. Historically, misperceptions regarding the clinical significance of HCM have prevailed because of the obstacles of relatively low prevalence,[67] extreme heterogeneity[2,3] and skewed patterns of patient referral creating important patient selection biases.[119] Indeed, much of the data assembled over 40 years was disproportionately generated by a few tertiary centers, and relates largely to patients preferentially referred because of high-risk status or severe symptoms requiring specialized care (such as surgery).[2,3,119] For example, while considerable data have been reported over more than four decades from highly selected patient cohorts, such as the National Institutes of Health, the latter program has recently been terminated permanently. Hence, the older HCM literature was dominated by the most adverse consequences of the disease, while clinically stable, asymptomatic and elderly patients were largely under-represented. Nevertheless, it is now recognized that HCM occurs in both genders and many races, including under-served minorities.[91,120,121] However, while HCM is underdiagnosed in women and minorities, there is no evidence that the disease is expressed differently (either morphologically or clinically) in such subgroups.

The risks of HCM would appear to have been overestimated by dependence on frequently cited, ominous mortality rates of 3–6% per year.[119] These figures, based on skewed tertiary center experience, have contributed importantly to the misguided perception that HCM is a generally unfavorable disorder. Recent reports over the last 8 years from less selected regional or community-based HCM patient cohorts cite mortality rates that are in a much lower range, of about 1% (or less),[25,26,29,30,37] and are not dissimilar to that of the general adult US population (Fig. 1.15).[25]

Such data provide a more balanced view, in which HCM may be associated with important symptoms and premature death, but more frequently with

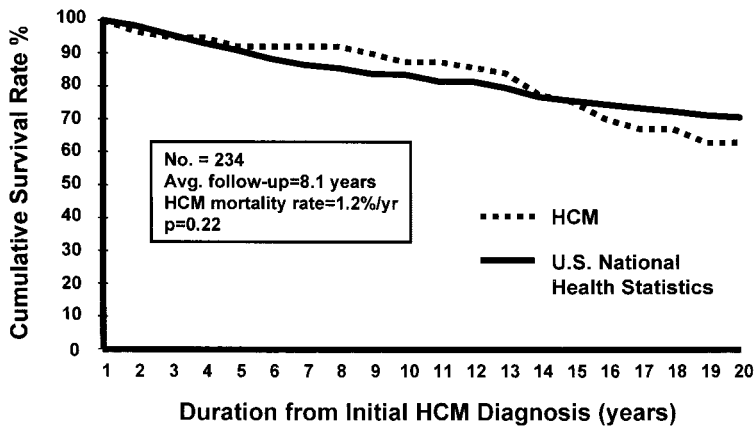

Fig. 1.15 Total mortality (death from any cause) for adult patients with hypertrophic cardiomyopathy in a community-based cohort does not differ with respect to the expected survival in the US general population after adjustment for age, sex, and race. The annual mortality is only about 1%. From Maron *et al.* Clinical course of hypertrophic cardiomyopathy in a regional United States cohort. *JAMA* 1999; **281**; 650–5, reproduced with permission of the American Medical Association.