
Hypertrophic Cardiomyopathy

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Abstract: Hypertrophic cardiomyopathy is a fascinating disease of marked heterogeneity. Hypertrophic cardiomyopathy was originally characterized by massive myocardial hypertrophy in the absence of known cause, a dynamic left ventricular outflow obstruction, and increased risk of sudden death. It is now well accepted that multiple mutations in genes encoding for the cardiac sarcomere are responsible for the disease. Complex morphologic and pathophysiological differences, disparate natural history studies, and novel treatment strategies underscore the challenge to the practicing cardiologist when faced with the management of the patient with hypertrophic cardiomyopathy. (Curr Probl Cardiol 2004; 29:233-91.)

Hypertrophic cardiomyopathy continues to fascinate and challenge cardiologists in clinical practice and research. Its initial clinical appreciation by master bedside clinicians began over 4 decades ago. With the inception of 2-dimensional echocardiography 3 decades ago, there was the realization that this disease comprised a wide spectrum of anatomy, pathophysiology and natural history. Just over 1 decade ago was the discovery of specific sarcomeric mutations that result in hypertrophic cardiomyopathy.

Hypertrophic cardiomyopathy is the most common heritable cardiovascular disease, with a reported prevalence of 0.1% to 0.2% in the general population but remains a disease of controversy. Hypertrophic cardiomyopathy has been implicated as the most common cause of sudden death in the young, yet most patients live a normal life. There have been a number of evolving treatments for patients with hypertrophic cardiomyopathy for both symptom relief, as well as prevention of sudden death, but the indications for these have not yet been clarified. The purpose of this

The authors have no conflicts of interest to disclose.
0146-2806/\$ – see front matter
doi:10.1016/j.cpcardiol.2004.01.001

monograph is to review the basic understanding of hypertrophic cardiomyopathy and discuss current therapies and challenges.

Historical Perspectives

Initial Description

The first widely recognized, unequivocal description of hypertrophic cardiomyopathy was offered by Teare¹ in 1958 when he described the cardiac anatomy of 8 young patients with severe, asymmetric left ventricular hypertrophy with bizarre muscle bundle orientation and variable myocyte size. Contemporary with the description by Teare,¹ Brock² reported on patients with functional subvalvular left ventricular outflow tract gradients, who had been diagnosed as having aortic valvular stenosis. Braunwald et al^{3,4} in the 1960s defined the specific disease process in which asymmetric septal hypertrophy, myofibril disarray, and a dynamic subvalvular pressure gradient was documented.

R. A. O'Rourke: Hypertrophic cardiomyopathy (HCM) has been given a wide variety of names. These include asymmetric septal hypertrophy (ASH), idiopathic hypertrophic subaortic stenosis (IHSS), muscular subaortic stenosis, and hypertrophic obstructive cardiomyopathy (HOCM). The term *HCM* has been designated by the World Health Organization as the most precise term to describe this unique process of primary muscle hypertrophy that may occur with or without a dynamic left ventricular outflow tract gradient.

Progression of Knowledge

The emergence of 2-dimensional echocardiography ushered in a new phase of discovery for hypertrophic cardiomyopathy.^{5,6} It became recognized that the disease was more common than originally appreciated and that left ventricular outflow obstruction was present in only about 25% to 40% of patients with hypertrophic cardiomyopathy. Echocardiography offered new insight to the cause of left ventricular outflow obstruction, the highly variable distribution and extent of hypertrophy, and the complex hemodynamics.⁶⁻⁸ Application of echocardiography enabled researchers to conduct careful epidemiologic studies that show hypertrophic cardiomyopathy is relatively common with generally good overall prognosis.⁹⁻¹⁶

The Genetic Era

It was long appreciated that hypertrophic cardiomyopathy tended to run in families,¹⁷ but it was not until the late 1980s that the true

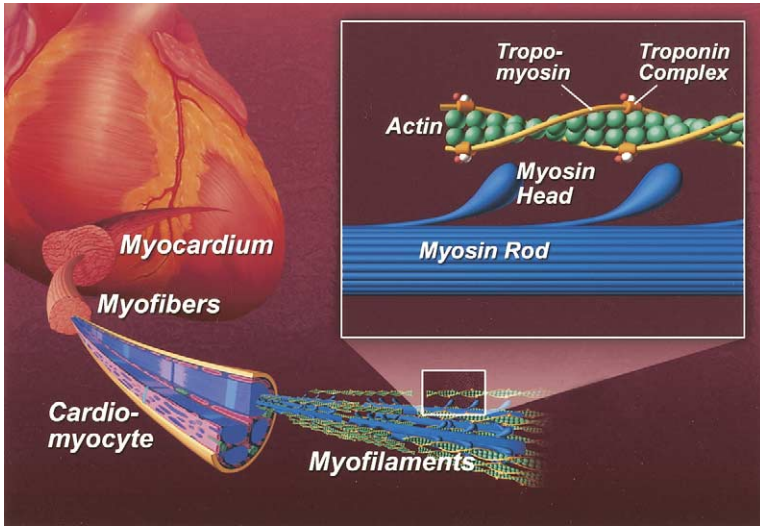


FIG 1. Schematic representation of cardiac sarcomeric proteins implicated in hypertrophic cardiomyopathy.

genetic nature of the gene came to full light. In 1989 a careful linkage analysis revealed a responsible gene on chromosome 14q1 (subsequently shown to be the locus of beta-myosin heavy chain).¹⁸⁻²¹ Since that description, 10 other genes, encompassing hundreds of mutations, have been shown to be associated with hypertrophic cardiomyopathy. The vast majority of these mutations involve the proteins of the cardiac sarcomere (Fig 1): beta-myosin heavy chain, myosin binding protein C, cardiac troponin T, alpha tropomyosin, cardiac troponin I, essential myosin light chain, regulatory myosin light chain, cardiac alpha actin, and titin.¹⁸⁻³¹

Etiology

Realization of the Genetic Link

Hypertrophic cardiomyopathy is inherited in an autosomal dominant pattern, and it has been estimated that up to 60% to 70% of patients with hypertrophic cardiomyopathy have another affected family member. Hundreds of mutations involving one of several sarcomeric proteins result in similar and overlapping phenotypic expression indicating that hypertrophic cardiomyopathy is a primary disease of the cardiac sarcomere.^{26,32-42} The pathway from mutation to disease expression is not understood completely.

Cardiac Sarcomere Structure and Function

Cross-bridging between the head of the myosin heavy chain with the actin molecules and the subsequent conformational change in myosin heavy chain (power stroke) result in myocyte contraction (Fig 1). The troponin-tropomyosin complex regulates this interaction such that the binding site for myosin and actin is “covered” in the absence of intracellular calcium. When intracellular calcium rises, structural changes in the complex allow the systolic interaction between myosin and actin. Myosin binding protein C and titin are viewed as providing structural support to the sarcomere unit.³⁸

Proposed Pathogenesis

The bulk of data suggest that the causal mutations alter sarcomeric function and secondarily lead to hypertrophy and fibrosis.³⁷ Potential abnormalities include alteration of the protein structure that may change the delicate interactions,^{43,44} change the sensitivity to regulators such as calcium or adenosine triphosphate,³⁷ impair energy metabolism,^{45,46} or decrease the force or velocity of myocyte contraction.⁴⁷ Hypertrophy as a compensatory mechanism is supported by the finding that subtle functional abnormalities have been detected before the development of hypertrophy in hypertrophic cardiomyopathy in isolated myocyte gene transfer preparations, in intact whole-heart animal models, and in human patients.⁴⁸⁻⁵⁴

Pathology

Microscopic

In the original report by Teare,¹ bizarre arrangements of the muscle fiber bundles were described. The myocardial disarray consists of short runs of severely hypertrophied fibers interrupted by connective tissue (Fig 2). There are large, bizarre nuclei with degenerating muscle fibers and fibrosis. This disorganization results in a “whorling” of muscle fibers that is characteristic of hypertrophic cardiomyopathy. Myocardial disarray is noted not only in the ventricular septum but also in the left ventricular free wall. Disarray is not specific to hypertrophic cardiomyopathy and can be seen in any pressure-overloaded ventricle, although the proportion of myocardial disarray is much greater in hypertrophic cardiomyopathy.^{55,56} Another key histologic feature is intramyocardial fibrosis, which is believed to play an integral in arrhythmogenesis and abnormal myocardial compliance.⁵⁷⁻⁵⁹ Finally, the intramural vessels are abnormal in hypertrophic cardiomyopathy, with frequent thrombosis and obliteration

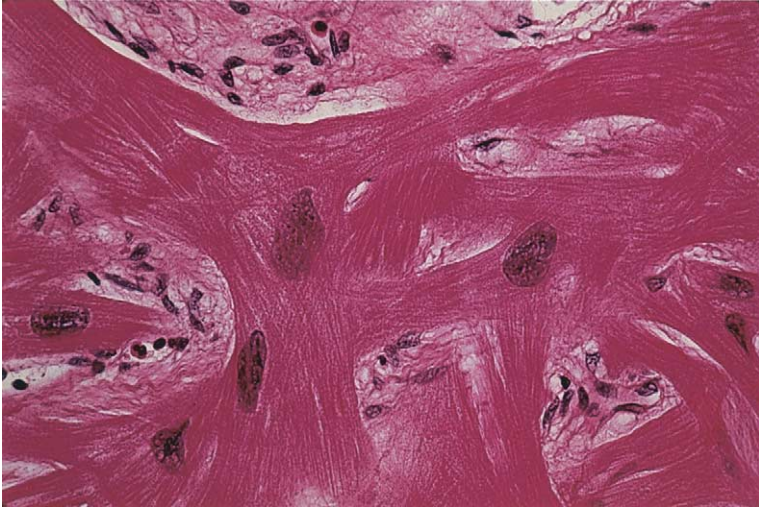


FIG 2. Microscopic section of myocardium from a patient with hypertrophic cardiomyopathy demonstrates myocyte disarray.

of the small vessels within the myocardium.^{60,61} This latter feature predisposes to subendocardial ischemia and may be one of the causal factors for fibrosis.

One of the more intriguing aspects of hypertrophic cardiomyopathy has to do with the distribution of these features. The genetic mutation is ubiquitous, the myofiber disarray and intramyocardial fibrosis are patchy, and yet the hypertrophy is usually asymmetric and can be focal. The triggers for the development of disarray and hypertrophy are not yet understood, but may be related to isolated load or stress/strain conditions with up-regulation of mitotic and trophic signal factors.³⁷ The phenotypic expression of hypertrophic cardiomyopathy is probably not solely the product of the mutations, but also of modifier genes and environmental factors.⁶²⁻⁶⁴

Anatomic

Distribution of hypertrophy. Any pattern of left ventricular hypertrophy can be seen in hypertrophic cardiomyopathy; however, asymmetric septal hypertrophy is more common than diffuse concentric patterns (Fig 3).^{6,65,66} Involvement of the basal to mid-ventricular anterior septum appears most commonly. Thickening confined to the left ventricular apex has been described worldwide and is more common in Japanese popula-

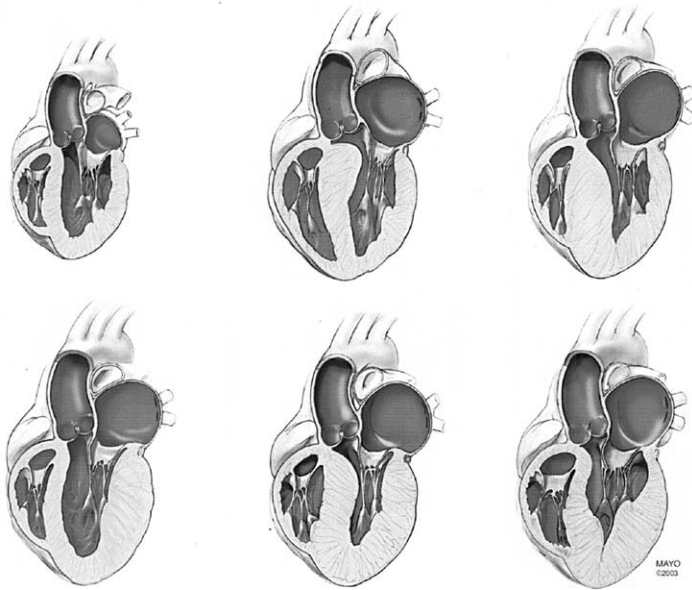


FIG 3. Schematic representation of variable distribution of left ventricular hypertrophy in hypertrophic cardiomyopathy. Upper left is normal heart for comparison. Reproduced by permission of Mayo Foundation.

tions (Fig 4).⁶⁷⁻⁷³ Involvement of the right ventricle has been described more frequently in pediatric-aged patients.⁷⁴

The extent of hypertrophy is highly variable. While the lower limit is constrained by the definition of disease, most walls measure between 20 to 30 mm. Less commonly walls in excess of 35 to 40 mm are encountered. The importance of the magnitude of hypertrophy in the assessment of risk for sudden cardiac death is an area of substantial interest and controversy.^{75,76}

Mitral valve and apparatus abnormalities. Abnormalities of the mitral valve and its support structures are common in hypertrophic cardiomyopathy (Fig 5). Elongation of the mitral leaflets and anterior displacement of the papillary muscles are common.^{77,78} These abnormalities can position the mitral valve such that it is more prone to systolic anterior motion and outflow tract obstruction. Some patients have very short chordae tendineae, or direct insertion of the papillary muscle onto the mitral leaflets or septum. Recognition of these abnormalities has important implications for management of symptomatic patients.⁷⁹



FIG 4. Apical four-chamber view with echocardiographic contrast enhancement of a patient with apical hypertrophic cardiomyopathy. Top frame is taken at end-diastole, bottom frame is from end-systole. LV, Left ventricle; RV, right ventricle.

Pathophysiology

The pathophysiology of hypertrophic cardiomyopathy is complex, with a number of different processes contributing to the symptoms and natural history in this disorder. There is a wide spectrum of the extent to which each pathophysiological process is present in an individual patient. These processes consist of abnormal diastolic function, myocardial ischemia, outflow tract obstruction, mitral regurgitation, arrhythmias, and abnormal autonomic function.

Diastolic Dysfunction

Altered diastolic function is evident in all patients with hypertrophic cardiomyopathy.^{8,80-83} In fact, there is evidence that abnormal diastolic

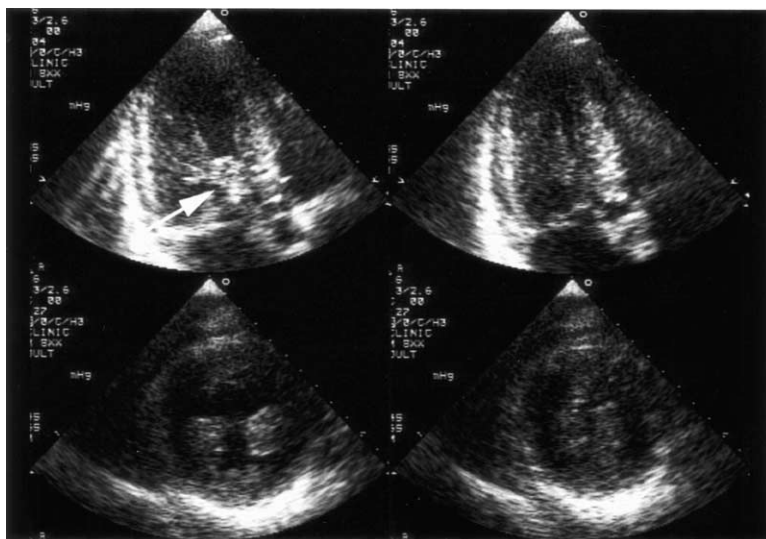


FIG 5. Papillary muscle hypertrophy and abnormal attachment to mitral valve (*arrow*) can contribute to outflow tract obstruction. These abnormalities have direct bearing on treatment choice because only an operative approach can address this type of obstruction. Top images are apical long-axis images. Bottom images are parasternal short-axis images demonstrating degree of papillary muscle hypertrophy. Left frames are taken at end diastole, and right frames are from end systole.

function is present even before the onset of hypertrophy in individuals harboring mutations known to cause hypertrophic cardiomyopathy. Doppler studies have shown that at this early, preclinical stage, there is slowed myocardial relaxation. As diastolic dysfunction worsens, there is increased dependence on the atrial contribution to ventricular filling, then on increased driving pressure (increased left atrial pressure). Ultimately, increasing myocardial fibrosis and increasing operating chamber stiffness may result in further increases in left atrial and pulmonary artery wedge pressure. These abnormalities can be a primary cause for dyspnea.

Myocardial Ischemia

The combination of increased left ventricular wall thickness (increased myocardial oxygen demand) and decreased capillary network (decreased myocardial oxygen supply) predispose to ischemia and the resulting symptoms.^{8,60,61,84-86} The addition of other provoking factors (increased heart rate, increased afterload, or decreased perfusion pressure) can readily induce ischemia.

Left Ventricular Outflow Obstruction and Mitral Regurgitation

Left ventricular outflow tract obstruction is present in 25% to 40% of patients with hypertrophic cardiomyopathy. It may be present at rest, provokable (mild in the resting state but significant with physiological provocation), or latent (not present at rest, but evident with provocation). Obstruction can produce symptoms by several mechanisms. The obstruction itself can limit the cardiac output and result in effort-related symptoms such as dyspnea or presyncope. Obstruction increases left ventricular pressures, which can induce ischemia through increased demand and decreased perfusion pressure. The high contraction load imposed by obstruction may affect ventricular relaxation and diastolic filling. Finally, the mitral regurgitation that is associated with the obstruction can cause further elevation of left atrial pressure.^{8,83}

The mechanism of outflow obstruction involves basal septal hypertrophy and flow-mediated displacement of the mitral valve anteriorly into the left ventricular outflow tract such that the mitral leaflet can come into contact with the ventricular septum (Fig 6). The accelerated flow around the hypertrophied basal septum pushes the mitral leaflet at the same time that there may be “suction” forces that contribute to the systolic anterior motion of the mitral valve.^{8,83,87-91} Mitral coaptation is diminished and results in variable degrees of posteriorly directed mitral regurgitation. If the mitral regurgitant jet is directed anteriorly, primary mitral valve pathology such as a flail or prolapsing segment may be present, and this may have direct bearing on treatment options.

R. A. O'Rourke: The mitral regurgitation (MR) in HCM is usually due to distortion of the mitral valve apparatus resulting from the systolic anterior motion secondary to the left ventricular outflow tract obstruction. The jet of MR is directed laterally and posteriorly and predominantly during mid and late systole. The severity of MR is usually proportional to left ventricular outflow obstruction. Alterations in left ventricular load and contractility that affect the severity of outflow tract obstruction will similarly affect the degree of MR. Thus an increase in the afterload or increase in preload will decrease MR that is secondary to systolic anterior motion of the mitral valve, but this response does not occur when there is a primary abnormality of the mitral valve apparatus. When patients with HCM have severe limiting symptoms of dyspnea, MR is usually the primary cause. It is important to identify patients who have concomitant primary abnormality of the mitral valve leaflet such as an unsupported segment due to ruptured chordae because this finding will influence subsequent treatment.

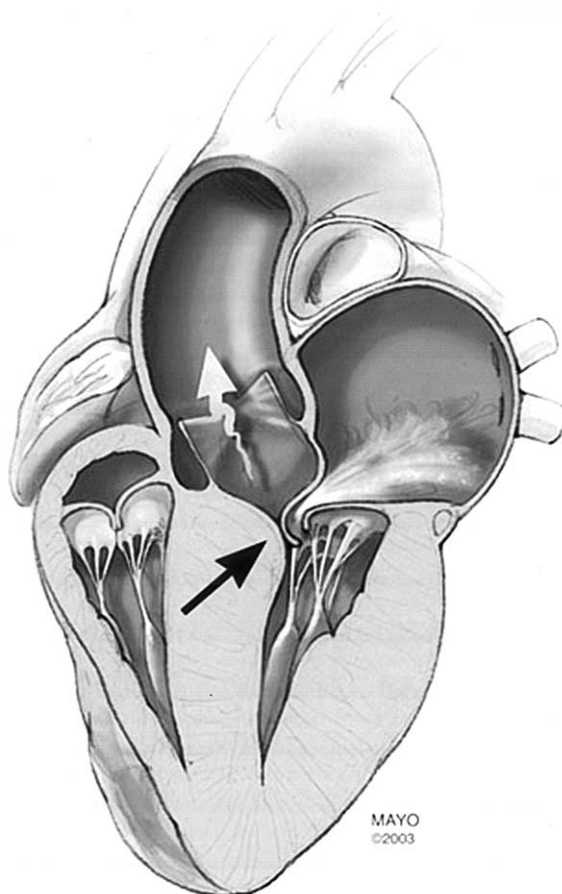


FIG 6. Schematic drawing of hypertrophic cardiomyopathy in systole. Mitral leaflet is distorted toward septum (systolic anterior motion, *black arrow*) resulting in outflow tract obstruction and posteriorly directed mitral regurgitation. Reproduced by permission of Mayo Foundation.

Autonomic Dysfunction

Approximately 25% of patients with hypertrophic cardiomyopathy will have an abnormal blood pressure response to exercise as defined by either a failure of systolic blood pressure to rise greater than 20 mm Hg or a fall in systolic blood pressure.^{92,93} The inability to augment or sustain systolic blood pressure is due to systemic vasodilation during exercise and occurs in spite of an appropriate rise in cardiac output. Abnormal blood pressure response and autonomic tone are associated with a poorer prognosis of hypertrophic cardiomyopathy.^{75,92,94,95}

Diagnosis

Definition

The World Health Organization has designated the term “hypertrophic cardiomyopathy” to describe this unique process of primary muscle hypertrophy, which may exist with or without a dynamic left ventricular outflow tract gradient.^{96,97} Hypertrophic cardiomyopathy is a clinical disease that is defined by the finding of left ventricular hypertrophy in the absence of identifiable cause. The diagnosis can be suspected on the basis of an abnormal physical examination or electrocardiogram. However, the primary diagnostic test is 2-dimensional echocardiography. Magnetic resonance imaging and computed tomography can also confirm the presence of left ventricular hypertrophy.

Physical Examination

The classic physical examination findings of hypertrophic cardiomyopathy are based on the presence of left ventricular outflow tract obstruction. However, because most patients with hypertrophic cardiomyopathy do not have outflow obstruction, the most common features simply involve those findings consistent with left ventricular hypertrophy.

Examination clues that typify the obstructive form of hypertrophic cardiomyopathy involve arterial and carotid pulsation, the apical impulse, and dynamic auscultation. The classic carotid pulsation is brisk and bifid, characterized by a rapid upstroke followed by a midsystolic drop, related to premature closure of the aortic valve that is in turn followed by a secondary wave. The mid-systolic drop of the carotid pulse contour coincides with systolic anterior motion of the mitral valve. The late peak is due to relief of the outflow tract gradient as the mitral valve leaflet returns to its original position.

The apical impulse reflects the myocardial hypertrophy. It is a sustained systolic thrust, which continues throughout most of systole. There is frequently a bifid impulse due to a forceful atrial contraction. A trifid impulse with a third component occurring near the end of systole may occur if outflow tract obstruction is present. A systolic thrill may be palpable at apex from severe mitral regurgitation or the lower left sternal border from outflow tract obstruction.

R. A. O'Rourke: In a patient with bisferiens arterial pulse who has a left ventricular outflow tract systolic murmur, no evidence of coincident aortic

regurgitation or no concomitant high cardiac output state, the diagnosis of HCM is highly likely from the physical examination.

Auscultation usually reveals a normal or loud first heart sound. Usually, the second heart sound is split physiologically, although patients may have a paradoxical split due to either a concomitant left bundle branch block or severe left ventricular outflow tract obstruction. Often, a fourth heart sound is present, especially if there is severe hypertrophy. In young patients, an early diastolic filling sound is frequently heard, indicating early rapid filling. If there is severe mitral regurgitation, a diastolic flow rumble may be appreciated.

The classic murmur from left ventricular outflow tract obstruction is a crescendo-decrescendo murmur, peaking in mid to late systole, located primarily at the left sternal border. The murmur usually ends before the second heart sound. The murmur can radiate across the precordium, but in contrast to valvular aortic stenosis, there is seldom radiation to the carotid arteries. Mitral regurgitation may be a separate holosystolic murmur audible at the apex. The presence of an aortic diastolic decrescendo murmur consistent with aortic regurgitation should suggest another disease, such as aortic valve disease or a discrete subvalvular stenosis.

Dynamic auscultation should be performed to differentiate the murmur of hypertrophic cardiomyopathy from that of valvular aortic stenosis and mitral regurgitation. Maneuvers that decrease the left ventricular volume will increase the dynamic gradient and the intensity of the murmur. The change in murmur intensity during the strain phase of the Valsalva maneuver has been used as a method to diagnose the murmur of hypertrophic cardiomyopathy. However, due to the variability in the performance of this maneuver, the classic response of the murmur to the Valsalva maneuver may not occur in all patients. The most reliable method for diagnosing a dynamic left ventricular outflow tract obstruction is the response of the murmur to the stand-squat-stand maneuver. From the standing position to a prompt squat, there is an increase in both afterload and preload, resulting in a marked reduction in the intensity of the murmur. From the squatting to standing position, afterload is immediately reduced, and there will be a prompt increase in intensity of the murmur. A progressive increase in intensity of the murmur will continue for the next 4 to 5 beats as preload to the left side of the heart is reduced. Other maneuvers that are used to change the intensity of the murmur include simple exercise, leg raising to increase preload, or the inhalation of amyl nitrite to decrease afterload and increase heart rate.

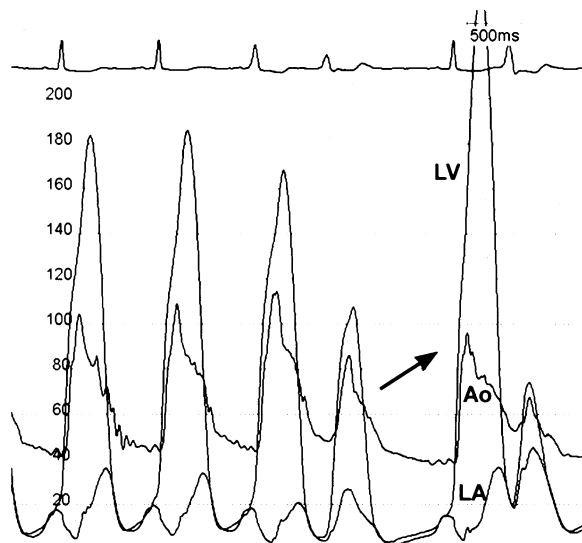


FIG 7. Hemodynamic pressure curves obtained in patient with left ventricular outflow tract obstruction demonstrate Brockenborough phenomenon following premature ventricular contraction (arrow). Increased contractility and decreased afterload result in worsening outflow obstruction and decrease in peak aortic pressure, and a decrease of aortic pulse pressure. Micromanometer-tipped catheters are in aorta (Ao), left ventricle (LV), and left atrium (LA).

Premature ventricular contractions can reveal characteristic findings that are classic for obstructive hypertrophic cardiomyopathy. While there is focus on the change in the auscultatory findings, careful palpation of the arterial pulsation can reveal the Brockenborough phenomenon (Fig 7). The post-extrasystolic contraction is more forceful, due to increased contractility and decreased afterload, resulting in more outflow obstruction and a decreased pulse pressure. This can be demonstrated readily in the cardiac catheterization laboratory. The response of the intensity of the murmur after premature ventricular contraction or after any long pause is useful. The systolic murmur in obstructive hypertrophic cardiomyopathy increases, while the murmur of organic mitral regurgitation will remain unchanged or decrease in intensity.

Electrocardiography

The electrocardiogram is abnormal in most patients with hypertrophic cardiomyopathy.³ On the resting 12-lead electrocardiogram, 70% to 80% of patients will demonstrate left ventricular hypertrophy. Although bundle branch block and atrioventricular block are unusual, more than 80% of



FIG 8. Hemodynamic pressure curves demonstrate dramatic effects of atrial fibrillation. At start of study (left) patient was in normal sinus rhythm with minimal resting outflow obstruction. Paroxysmal atrial fibrillation occurred with rapid ventricular response (right). Result was loss of atrial contribution to filling, shortened diastolic filling time, development of severe outflow obstruction, and decreased systemic blood pressure.

patients undergoing electrophysiological studies actually demonstrate subclinical conduction system disease with a prolonged H-V interval.⁹⁸ Abnormal Q-waves simulating myocardial infarction are seen in 25%, may appear in any lead, and are likely reflective of the disturbance of activation of ventricular septum. The electrocardiogram in a variant of hypertrophic cardiomyopathy involving primarily the apex (apical hypertrophic cardiomyopathy) will show a distinctive pattern of diffuse symmetric T-wave inversions across the precordium.

Normal sinus rhythm predominates, but ambulatory monitoring demonstrates a high incidence of supraventricular tachycardia (46%), premature ventricular contractions (43%), and nonsustained ventricular tachycardia (26%).⁹⁹⁻¹⁰¹ Atrial fibrillation may occur in up to 25% to 30% of the older population and carries significant consequences (Fig 8).^{99,102-107} Preexcitation has also been associated with hypertrophic cardiomyopathy, and a rapid

ventricular response with atrial fibrillation may lead to deterioration and sudden death.

Echocardiography

Two-dimensional and Doppler echocardiography are the gold standard for the diagnosis of hypertrophic cardiomyopathy.^{8,83} The hypertrophy can occur in any distribution throughout the myocardium.^{6,65,66} While no phenotypic expression can be considered “classic” or particularly typical of this disease, the most common pattern is diffuse involvement of the entire ventricular septum. The average maximal wall thickness of the left ventricular wall in a population of patients with hypertrophic cardiomyopathy is usually 20 to 22 mm, with 5% to 10% of patients demonstrating markedly thickened wall measuring 30 to 50 mm.

The echocardiographic morphology appears different in the younger versus the older age group.¹⁰⁸ Nonetheless, dynamic left ventricular outflow obstruction associated with systolic anterior motion of the mitral valve can occur at any age. Because the older patients with the sigmoid septum frequently have systemic hypertension, it is speculated that the hypertrophy may represent an abnormal response to the pressure overload.

Recent genotype-phenotype studies examining hypertrophic cardiomyopathy have shown that the phenotype is not always expressed as severe thickening of the left ventricle.^{23,109-112} While studies may demonstrate trends in severity of wall thickness, for instance, there is wide variability and overlap, which may be related to the heterogeneity in the onset and degree of penetrance. The phenotypic expression of myocardial hypertrophy does not appear to be evident at a young age in all patients. Data regarding the myosin binding protein C mutation suggest the phenotypic expression of hypertrophy may not appear until middle age.^{23,109-112} Doppler tissue imaging of the intrinsic myocardial contraction and relaxation velocities may be useful in detecting gene-positive individuals even in the absence of hypertrophy.⁵²⁻⁵⁴

Other conditions can result in increased wall thickness on echocardiography. Increased afterload from either hypertension or valvular aortic stenosis may cause an increase in the left ventricular wall thickness. Patients with chronic kidney failure, especially those on dialysis, will also present with increased wall thickness. Infiltrative and glycogen storage diseases such as cardiac amyloidosis, Fabry’s disease and Friedreich’s ataxia may present with increased wall thickness and thus will mimic nonobstructive hypertrophic cardiomyopathy on echocardiography.¹¹³⁻¹¹⁶ It is important to correlate the findings of increased left ventricular wall

thickness with the clinical history and the electrocardiogram. If there is relatively low voltage on the electrocardiogram in the presence of increased wall thickness, then an infiltrative type disease (cardiac amyloidosis) should be suspected.

In young athletes, a physiological form of left ventricular hypertrophy may occur that is an adaptation to intense training.^{117,118} The resultant findings on echocardiography in these athletes may be difficult to differentiate from hypertrophic cardiomyopathy. Elite athletes who have a dilated ventricular cavity with septal thickness less than 14 to 15 mm most likely have the athlete's heart, but this combination of findings may not always be present. A reduction in wall thickness after cessation of training is useful to identify the "athletic heart" but may not be practical in all patients.¹¹⁷⁻¹¹⁹ Future investigation with Doppler tissue imaging and myocardial strain, which examine intrinsic myocardial systolic and diastolic function, may provide insight into this difficult diagnostic challenge.¹²⁰

Echocardiography is useful for defining the presence and severity of left ventricular outflow tract obstruction.^{77,121} If true dynamic obstruction is present, there will be systolic anterior motion of the mitral valve apparatus including one or both leaflets (Fig 6).¹²² The exact site of the obstruction may be determined by visualizing the region of the mitral leaflet-septal contact.¹²³ In the classic form of hypertrophic cardiomyopathy, the obstruction will occur at the most basal portion of the septum as it projects into the left ventricular outflow tract. However, the obstruction may also extend into the left ventricle from systolic anterior motion of the chordal apparatus or mid ventricular obstruction due to a hypertrophied papillary muscle abutting the ventricular septum.¹²⁴ Two-dimensional and Doppler echocardiography are useful for excluding other causes of left ventricular outflow tract obstruction such as discrete or tunnel subaortic stenosis.¹²⁵

Doppler echocardiography is the primary tool used to define the pathophysiological hemodynamics that are present in hypertrophic cardiomyopathy. A high-velocity, late-peaking, "dagger-shaped" signal on continuous-wave Doppler interrogation of the left ventricular outflow tract is the hallmark of dynamic outflow obstruction (Fig 9).¹²⁶ In patients with low-outflow tract velocities (less than 3 m/sec), provocation with physiological maneuvers should be performed during the Doppler study to determine if there is a labile or latent obstruction. The most common maneuvers used are the strain phase of the Valsalva maneuver, inhalation of amyl nitrite, or exercise (Fig 10).

Mitral regurgitation, due to the systolic anterior deformation of the

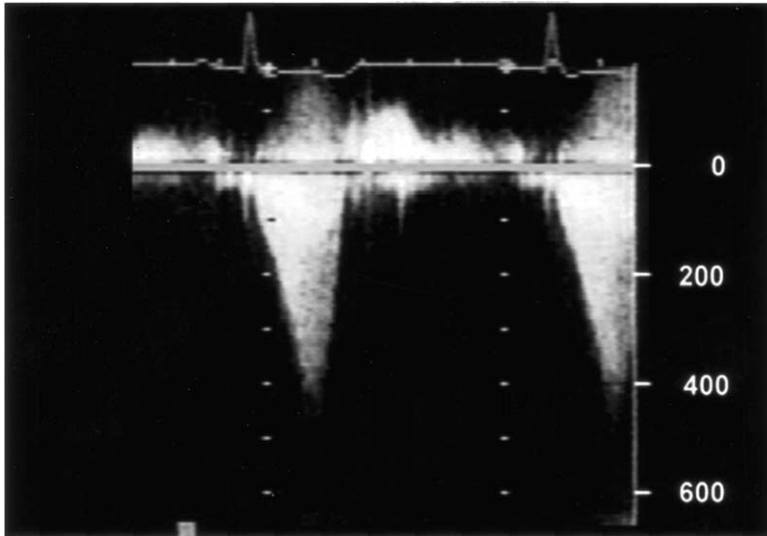


FIG 9. Continuous-wave Doppler signal through left ventricular outflow tract demonstrates characteristic late-peaking, "dagger-shaped" contour of dynamic outflow obstruction. In this example peak velocity is 4.8 m/sec, which corresponds to peak gradient of 92 mm Hg.

leaflets, is frequently present in patients with dynamic outflow tract obstruction. Doppler color-flow imaging can be used to determine the presence of mitral regurgitation and provide a semiquantitative estimate of the severity.¹²⁷ Mitral regurgitation that results from the systolic anterior motion is an eccentric jet that is directed to the posterolateral aspects of the left atrium and will occur primarily in mid to late systole. If mitral regurgitation is directed centrally or anteriorly, then a primary structural abnormality of the mitral valve apparatus should be suspected. The mitral regurgitation signal by continuous-wave Doppler may contaminate the outflow tract velocity signal, and care must be taken to differentiate the true outflow tract velocity from the mitral regurgitation jet.

Diastolic function can be assessed noninvasively by Doppler echocardiography. However, the transmitral flow velocity curves alone cannot be used for analysis of diastolic function in hypertrophic cardiomyopathy due to the complex interplay of relaxation and compliance abnormalities that are present.¹²⁸ Pulmonary vein flows and tissue Doppler imaging together with the transmitral flow velocity curves may aid in evaluating left ventricular filling pressures.¹²⁹

Transesophageal echocardiography is usually not necessary in the

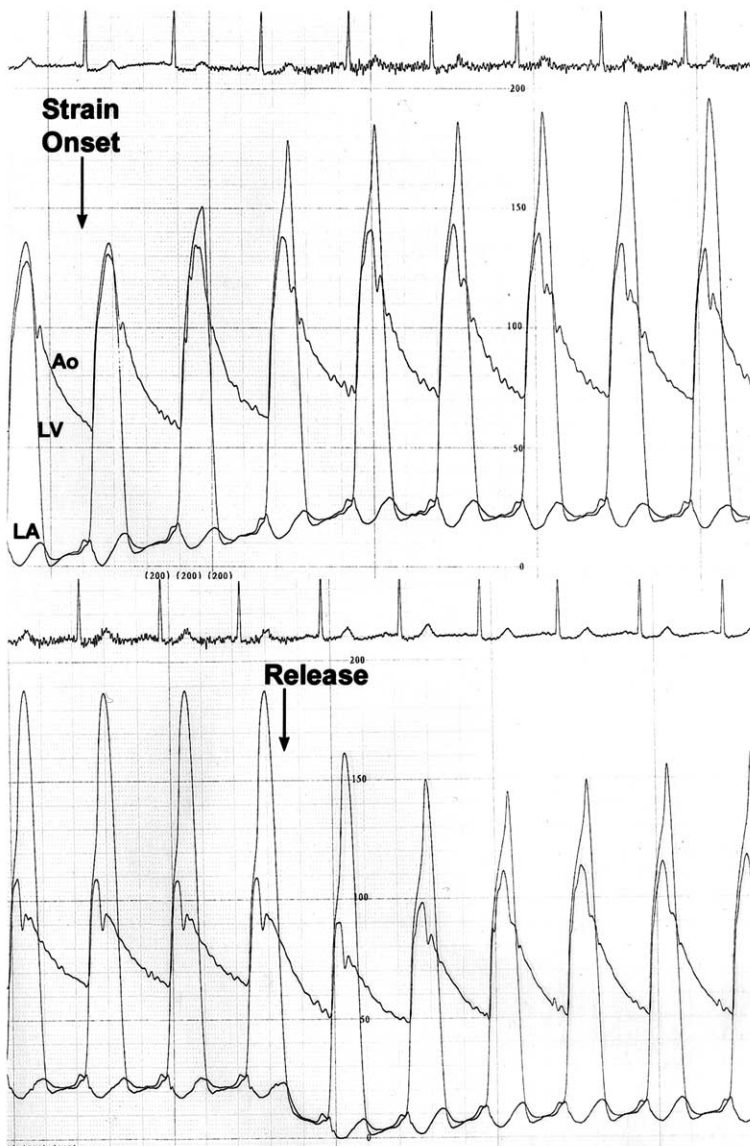


FIG 10. Hemodynamic catheterization demonstrates latent left ventricular outflow tract obstruction that is revealed with simple Valsalva maneuver. Dynamic left ventricle to aortic pressure gradient gradually appears after onset of strain phase, and gradually dissipates after release of strain. Micromanometer-tipped catheters are in aorta (Ao), left ventricle (LV), and left atrium (LA).

evaluation of the patient with hypertrophic cardiomyopathy. In most patients, the clinically necessary anatomic and hemodynamic information

can be obtained by transthoracic echocardiography. However, patients in whom discrete subvalvular stenosis or a primary abnormality of the mitral valve is suspected may benefit from transesophageal echocardiography.

Computed Tomography/Magnetic Resonance Imaging

Cardiac magnetic resonance imaging provides high-resolution moving images of the myocardium and accurately determines the site and extent of hypertrophy in patients with hypertrophic cardiomyopathy. Areas of myocardial ischemia can be detected, and abnormal blood flow velocities can be evaluated. The clinical utility of this imaging modality remains to be determined; however, there are emerging data with respect to risk stratification.¹³⁰

Genetics in Hypertrophic Cardiomyopathy

It is now well accepted that hypertrophic cardiomyopathy is a disease of the sarcomere and occurs when there is a gene mutation in one of the sarcomeric protein genes. At the present time there are more than 11 genes that have been shown to be affected in patients with hypertrophic cardiomyopathy, encompassing hundreds of mutations. The vast majority of these mutations involve the proteins of the cardiac sarcomere: beta-myosin heavy chain, myosin binding protein C, cardiac troponin T, alpha tropomyosin, cardiac troponin I, essential myosin light chain, regulatory myosin light chain, cardiac alpha actin, and titin. Although there has been an exponential increase in our knowledge of the gene abnormalities that are found in hypertrophic cardiomyopathy, the clinical role of genetic testing is still unclear.

Genotype-Phenotype Correlations

Initial reports have suggested that certain genotypes are associated with specific phenotypes in hypertrophic cardiomyopathy (ie, myosin binding protein C with the elderly, troponin T with mild hypertrophy, and increased sudden death). The possibility that the individual genotype could determine the phenotypic expression and clinical course of hypertrophic cardiomyopathy has come under increasing scrutiny, and it appears that there are no mutation-specific phenotypes. In fact, mutations in myosin heavy chain, cardiac actin, troponin T, alpha-tropomyosin, and titin can result in either hypertrophic or dilated cardiomyopathy. The factors that determine whether a specific mutation results in hypertrophy versus cavity dilation are not understood, but this underpins the notion that there is not a one-to-one relationship between specific gene mutation and clinical structure in hypertrophic cardiomyopathy.

Genetic Screening and Risk of Sudden Death

The potential that individual mutations may predispose to sudden cardiac death is another area of intense interest. Several studies done on families with multiple sudden deaths (or the lack thereof) have suggested that certain mutations may be more “malignant,” whereas others may be “benign” mutations.^{39,131,132} The clinical usefulness of these findings has come under question as studies involving unrelated hypertrophic cardiomyopathy patients have confirmed that specific “malignant” or “benign” mutations are rare, and the clinical course cannot be reliably predicted.^{133,134} The crucial issue, yet to be resolved, is one of potential biases in all of these studies.

Diagnosis of Hypertrophic Cardiomyopathy by Genetic Testing

While echocardiography remains the diagnostic test of choice for hypertrophic cardiomyopathy, there has been hope that genetic testing would be the primary diagnostic technique. However, the vast number of genes and mutations involved makes routine screening impractical with current methods. The genetic era does, however, bring a new frontier to scientific pursuits regarding hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy genetics research centers have identified individuals who have specific mutations, abnormal myocardial velocities, but no hypertrophy.⁵²⁻⁵⁴ This raises several important questions; does the presence of the putative mutation equate with the diagnosis of disease (and as such, is “hypertrophic” cardiomyopathy the appropriate label); and can hypertrophy be prevented.¹³⁵

Natural History

Survival

The life expectancy of patients with hypertrophic cardiomyopathy is highly variable but in general is not dissimilar from age- and sex-matched controls. This fact was not always appreciated. Early reports suggesting high mortality rates were based on data from referral-based patients with extraordinarily adverse histories.^{101,136-138} Subsequent population-based studies revealed the relatively common prevalence (1:500) and relatively benign prognosis (annual mortality rates of only about 1%) that approaches age-expected survival in the elderly.^{9-16,139} There are, however, families with multiple early sudden deaths. Identifying the few patients who fall into this latter group remains one of the more difficult challenges in the management of hypertrophic cardiomyopathy.

Death can be sudden and unexpected, is most common in young adults, but can occur at any age.^{15,75,140-142} Sudden death usually occurs in patients who have no or mild symptoms, and a substantial proportion of patients will die during or just after vigorous physical activity. Hypertrophic cardiomyopathy is the most common cause of sudden death among young competitive athletes and thus represents a medical exclusion from participation in competitive athletics.¹⁴²⁻¹⁴⁸

The mechanism of sudden death has been inferred from patients experiencing implantable defibrillator discharges.¹⁴⁹⁻¹⁵¹ Ventricular tachycardia and fibrillation appear to be the primary mechanism; however, other arrhythmias may also play a role, including asystole, rapid atrial fibrillation, and electrical mechanical dissociation.

Symptom Course

Just as the survival of hypertrophic cardiomyopathy is variable, the symptom course is also highly heterogeneous. Many patients can maintain active, healthy lifestyles and remain completely symptom free. However, some patients progress to complicated symptomatic courses. While there is clear overlap, one may view the symptomatic patient as having a clinical course that predominantly involves sudden cardiac death, exertional symptoms, development of atrial fibrillation, or rarely progression to an end-stage dilated phase.

Atrial fibrillation occurs in up to 30% of older patients, is associated with clinical deterioration, and usually indicates advanced disease.^{14,105} Acute atrial fibrillation can present as a medical emergency, especially in the presence of hemodynamic deterioration (Fig 8) where immediate cardioversion to normal sinus rhythm is indicated. Systemic embolism occurs in 6% of patients and is usually associated with atrial fibrillation.¹⁰⁶ Anticoagulation is recommended for patients with atrial fibrillation and hypertrophic cardiomyopathy but will not fully eliminate the risk of stroke.

Infective endocarditis may occur in 4% to 5% of patients with hypertrophic cardiomyopathy.^{3,152} The lesions are usually located at the point of opposition of the mitral valve against the septum but can involve the mitral valve and less often the aortic valve.

R. A. O'Rourke: One of the major mistakes often made in the management of patients with HCM is the failure to prescribe antibiotic therapy at the time of dental and other operative procedures (see below).

A small number (<5%) of patients with hypertrophic cardiomyopathy in a referral-based population will develop an “end-stage” phase.^{153,154} In these patients, there are progressive symptoms of congestive heart failure with significant limitation of exercise tolerance. The left ventricular cavity enlarges, and the dynamic outflow tract gradient disappears. Eventually, the morphologic appearance of the ventricle will be similar to that of a dilated cardiomyopathy. These patients have a poor outlook with a high risk of death due to heart failure or arrhythmias.

Treatment of Hypertrophic Cardiomyopathy

The treatment of patients with hypertrophic cardiomyopathy is complex and requires a thorough understanding of the pathophysiology in each individual patient. There are general guidelines that should be followed for all patients. Treatment is aimed primarily at the relief of symptoms, particularly in those with dynamic outflow tract obstruction. Risk stratification to attempt to prevent sudden death is an essential part of managing patients with hypertrophic cardiomyopathy.

General Guidelines

Because hypertrophic cardiomyopathy is now considered to be a genetic disorder with an autosomal dominant inheritance pattern, screening of first-degree relatives by echocardiography is recommended. Adolescents should undergo surveillance echocardiography every 12 to 18 months (particularly if they wish to participate in competitive athletics). Adult family members should be reevaluated every 5 years thereafter and sooner if signs or symptoms of cardiovascular disease arise.

Patients with hypertrophic cardiomyopathy should be prohibited from engaging in strenuous activity and competitive athletics. The most common cause of sudden death in young athletes is hypertrophic cardiomyopathy. Although an exact cause-and-effect relationship has not been demonstrated, it is speculated that severe exertion may preclude patients to development of ventricular arrhythmias from the oxygen supply-demand mismatch. Low to moderate aerobic exercise is encouraged.

All patients with evidence of dynamic left ventricular outflow tract obstruction should be given infective endocarditis prophylaxis. They should also be instructed to keep themselves well hydrated at all times, to avoid precipitating further outflow tract obstruction.

Nonobstructive Hypertrophic Cardiomyopathy

Most patients with hypertrophic cardiomyopathy do not have obstruction, and symptoms are related to diastolic dysfunction. Treatment of diastolic dysfunction is not well proven. Negative chronotropic agents (beta-adrenergic antagonists, nondihydropyridine calcium channel antagonists) and aggressive rhythm control, if atrial fibrillation develops, are the mainstays of therapy. If the degree of diastolic dysfunction progresses to the states with elevated filling pressures, then the judicious use of diuretics can be added to the treatment plan. It is always important to appropriately treat other contributing factors such as concomitant hypertension.

Future treatments of symptomatic nonobstructive hypertrophic cardiomyopathy may involve the use of antagonists of the renin-angiotensin-aldosterone system. There is evidence that tissue-level angiotensin can modulate both myocardial relaxation and fibrosis.¹⁵⁵ Therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, statins, and calcium blockers may be of benefit based on animal models of hypertrophic cardiomyopathy but await human trials.^{32,33,35,41,42,156,157}

Obstructive Hypertrophic Cardiomyopathy

The presence of left ventricular outflow obstruction provides a target for therapy. The obstruction makes the use of diuretics or other vasodilator therapy problematic because these will worsen the degree of obstruction. Treatment strategies directed at the outflow obstruction have involved pharmacotherapy, dual-chamber pacing, surgical septal myectomy, and catheter-based alcohol septal ablation (Table 1).

Pharmacologic Therapy

The first line of therapy in symptomatic obstructive hypertrophic cardiomyopathy involves pharmacotherapy. Therapy is targeted at the effort-related increase in left ventricular outflow obstruction as exertion causes decreased filling of the ventricle (decreased preload), increased contractility, and decreased afterload. The resting gradient on a supine echocardiogram should not be used to judge the effectiveness of a given therapy. Agents that interfere with the exercise-induced phenomenon by decreasing contractility (negative inotropic properties) and blunting the heart rate response (negative chronotropic properties) can effectively diminish the exercise gradient and also directly prevent the myocardial oxygen supply-demand mismatch (ischemia).

TABLE 1. Results of invasive strategies to relieve left ventricular outflow tract obstruction

Reference	Author	Year	No. of patients	Length of follow-up	Gradient 1	Gradient 2	NYHA 1	NYHA 2	Complications	Mortality	Comment
Dual chamber pacing											
239	McDonald	1988	9	3-24 mo	-	-	3	1.5	-	-	Improved exercise capacity
240	Jeanerud	1992		82	47	3					
241	Cannon	1994	12	4 mo	-	-	3.3	-	-	8%	Symptoms improved by 1-2 classes
194	Fananapazir	1994	84	28 mo	96	27	3.2	1.6	-	-	
242	Posma	1996	6	3 mo	65	19	3.5	2	-	-	Improved homogeneity of perfusion with pacing
202	Slade	1996	56	11 mo	78	36	2.75	1.69	-	-	Only patients responding to temporary pacing were entered
198	Gadler	1997	19 (<40 mm Hg)	6 mo	22	-	3	1.9	-	0%	Comparison of outcome of minimal versus significant resting gradient
				22 (>40 mm Hg)	86	26	2.8	1.8			
195	Kappenberger	1997	83	3 mo AAI	59	33	2.6	2.4	36%	0%	Randomized crossover
				3 mo DDD	59	30	2.6	1.7			
201	Nishimura	1997	21	3 mo DDD	76	55	2.9	2.4	-	-	Double-blind crossover study demonstration placebo effect to AAI pacing
				3 mo AAI	76	83		2.6			
243	Rishi	1997	10	23 mo	53	16	-	-	-	-	Pediatric aged patients
197	Gadler	1999	80	3 mo DDD			2.54	1.7			Randomized crossover with one year of follow up in preferred mode
				3 mo AAI				2.2			

Table 1 (continued)

Reference	Author	Year	No. of patients	Length of follow-up	Gradient 1	Gradient 2	NYHA 1	NYHA 2	Complications	Mortality	Comment
199	Linde	1999	81	12 mo 3 mo DDD	70	33	2.6	1.62 1.7	-	-	Subjective symptom reporting disproportionate to objective parameters in inactive pacing mode (PIC)
200	Maron	1999	48	3 mo AAI 3 mo DDD	71 82	52 48	2.5	2.2			Double blind crossover with 6 additional months of active pacing-objective exercise data obtained
				3 mo AAI 6 mo unblinded	82 82	76 48	-	-			
244	Pavin	1999	23	16 mo	93	31	2.9	1.6	-	-	Mitral regurgitation significantly improved with pacing
Surgery											
245	Tajik	1974	43	84 mo	77		3	1.7		16%	
176	Morrow	1975	83	72 mo	96	0	3.3	1.5	10%	7%	
246	Cooley	1976	27	8–61 mo	74	7	-	72%	10%	4%	Mitral valve replacement
247	Agnew	1977	49	89 mo	85	<10	2.8	1.4	10%	4%	
248	Maron	1978	124	62 mo	73	23	3	1.7	-	8%	
249	Redwood	1979	41	6 mo	37–118	-	-	-	5%	-	Improved cardiac output and hemodynamics
250	Maron	1983	240	60	-	-	≥3	70%	-	8%	
251	Cooper	1987	11 HCM +CAD	54 mo	65	3	3.2	1.9	-	27%	All patients age > 65

(Continued)

Table 1 (continued)

Reference	Author	Year	No. of patients	Length of follow-up	Gradient 1	Gradient 2	NYHA 1	NYHA 2	Complications	Mortality	Comment
			41	HCM no CAD	95	17				8%	
252	Cannon	1989	20	6 mo	64	4	≥3	-	-	-	Improved O ₂ supply-demand
188	Krajcer	1989	127	Myectomy	118 mo	69	10	3.2	2.1	3%	5%
			58	Mitral valve replacement	75	10	3.4	2.2	3%	7%	
253	McIntosh	1989	58	6 mo	66	4	3.1	1.8	~20%	9%	Mitral valve replacement
254	Mohr	1989	115	61 mo	70	9	2.3	1.4	11%	5%	
255	Mohr	1989	47	60 mo	70	10	1.9	1.3	13%	0%	Mean age 21.5 years; range 0-38 years
256	Siegman	1989	28	58 mo	86	3	3.3	2	21%	14%	HCM and CAD
177	Cohn	1992	31	78 mo	96	5	3.1	1.7	6%	0	
257	Diodati	1992	30	6 mo	79	15	-	-	-	-	Improved exercise capacity
258	McIntosh	1992	36	6-12 mo	81	16	2.9	1.8	-	3%	Myectomy plus mitral valve plication
185	Schulte	1993	364	98 mo	54	9	3	1.6	-	5%	
189	Schoendube	1994	58	84	85	-	91%	23%	21%	0%	
							Class III-IV	Class III-IV			
186	ten Berg	1994	38	82 mo	72	6	3	1.5	5%	0	Myectomy
259	Heric	1995	178	44 mo	93	21	2.8	1.4		6%	
260	Schoendube	1995	58	84 mo	79	5	3.1	1.8	7%	0	Myectomy
261	Kofflard	1996	8		95	18	2.6	1	0	0	Myectomy + mitral leaflet extension
					87	23	2.8	1.7	0	0	Myectomy alone
181	McCully	1996	65	20 mo	73	9	3.2	1.6	6	4.6	0% mortality in isolated myectomy

Table 1 (continued)

Reference	Author	Year	No. of patients	Length of follow-up	Gradient 1	Gradient 2	NYHA 1	NYHA 2	Complications	Mortality	Comment
262	Robbins	1996	158	72 mo	64	10	28			3.2	0% mortality in patients < 60 years old; 95% of patients with improved symptoms
263	Theodoro	1996	25	77 mo	100	14	2.2	1.1	4%	0	Pediatric-age patients
183	Merrill	2000	22	79 mo	78	12	-	-	9%	0	
187	Yu	2000	104	5 days							Mitral regurgitation related to severity of obstruction and relieved with myectomy
264	Ommen	2002	73		57	4	2.6		0	0	29% of patients developed transient postoperative atrial fibrillation
191	Ommen	2002	256		68	10	2.7		1%	0	Intraoperative transesophageal echocardiography detected secondary cardiac anomalies
Ablation											
211	Sigwart	1995	3	3 mo	27	8	-	-	-	4.40%	
209	Knight	1997	18	3 mo	67	22	2.6	1.1	11%	0	
223	Kuhn	1997									
215	Faber	1998	91	3 mo	74	15	2.8	1.1	15%	1%	
265	Seggewis	1998	25	3 mo	62	18	2.8	1.2	28%	4%	
220	Gietzen	1999	37	7 mo	45	5	3	1.7	38%	4%	
265	Henein	1999	20	6 mo	60	22	-	-	-	-	
266	Kim	1999	20	3 mo	58	14	2.7	1.6	10%	0	Improved exercise capacity
225	Kuhn	1999	62	6 mo	54	6	-	-	-	-	
129	Nagueh	1999	29	6 mo	54	6	3.1	1.2	-	-	Improved parameters of diastolic function following ablation
216	Faber	2000	25	3 mo	60	20	2.8	1.4	20%	4%	3 patients required repeat ablation

(Continued)

Table 1 (continued)

Reference	Author	Year	No. of patients	Length of follow-up	Gradient 1	Gradient 2	NYHA 1	NYHA 2	Complications	Mortality	Comment
				12 mo	60	9	2.8	1.4			
218	Faber	2000	162	30 mo	60	3	2.8	1.2			
				3 mo	77	12	2.8	1.3	9%	2%	Use of echocardiographic myocardial contrast
228	Lakkis	2000	50	12 mo	74	6	3	1.1	22%	4%	Improved exercise capacity
267	Ruzyllo	2000	25	3 mo	85	36	2.8	-	28%	0	
				6 mo	85	32	2.8	1.2			
268	Boekstegers	2001	50	4–6 mo	80	18	2.8	1.9	10%	0	
				12–18 mo	80	17	2.8	-			
269	Flores-Ramirez	2001	30	6 mo	66	12	-	-	-	-	
270	Mazur	2001	26	24 mo	36	0	3	1	27%	0	LVH regression demonstrated
Comparisons											
204	Ommen	1999	19 Pacing	3 mo	77	55	2.9	2.4	-	-	Exercise time and oxygen consumption better in surgical group
			20 Myectomy	14 mo	76	9	2.8	1.3	-	-	
232	Nagueh	2001	41 Ablation	12 mo	76	8	3.4	1.1	22%	2%	9 new pacemakers, one death
			41 Myectomy	13 mo	78	4	3.1	1.2		0	1 new pacemaker, 8 transient AF, no deaths
230	Qin	2001	25 Ablation	3 mo	64	24	3.5	1.9	24%	0	Similar outcomes between the two procedures
			26 Myectomy		62	11	3.3	1.5	7%	0	
231	Firoozi	2002	20 Ablation		91	21	2.3	1.6	15%	5%	Surgical patients with better objective measures of exercise capacity
			24 Myectomy		83	12	2.4	1.5	4%	5%	

As the exercise related physiological changes are mediated by catecholamines, beta-adrenergic antagonists are ideal agents to treat symptomatic obstructive hypertrophic cardiomyopathy.^{3,136,158-162} Doses are gradually titrated to keep the resting heart rate at or below 60 beats/min such that exercise heart rates are also limited. Acute hemodynamic studies have shown that beta-blocking agents block the increase in gradient that occurs with isoproterenol and exercise but have little effect on the resting gradient. Beta-blockers result in an improvement in angina, exercise tolerance, and syncope in 60% to 80% of patients. However, only about 40% of patients would continue to have sustained symptomatic improvement.^{158,161,163}

For individuals in whom beta-adrenergic antagonists are ineffective, or produce unsatisfactory side effects, other options are available. Verapamil and diltiazem have both been used to control symptoms.^{81,164-169} However, both of these agents do have some vasodilatory properties that can worsen the obstruction and thus must be used with caution.¹⁷⁰ Sudden death has been reported when verapamil is used in patients with severe resting obstruction. As with beta-blockers, verapamil will result in sustained symptomatic improvement in less than 50% of patients at long-term follow-up.

The Class Ia antiarrhythmic agent disopyramide, a negative inotrope, has also been used successfully to relieve symptoms in hypertrophic cardiomyopathy.¹⁷¹⁻¹⁷⁴ It is relatively well tolerated, although anticholinergic side effects can limit its utility in older male patients due to urinary retention.

In our practice, the treatment of symptomatic obstructive hypertrophic cardiomyopathy begins with beta-blockade as the initial therapy. The beta-blocker should be gradually increased to optimal dosages, with a goal of a resting heart rate of 60 beats/min. If patients cannot tolerate beta-blockers due to fatigue or other side effects, a calcium channel blocker, usually verapamil, should then be started. If there is a severe resting outflow tract obstruction and symptoms, the calcium blocker should be started in the hospital under monitored conditions. If a patient does tolerate a large dosage of either a beta-blocker or calcium channel blocker but continues to be severely symptomatic, there are no data to show that the combination of the 2 classes is better than 1 drug alone. Disopyramide may be added to either the beta-blocker or verapamil if symptoms persist. Some centers successfully use disopyramide as an initial drug strategy. In those patients in whom medical therapy is ineffective, other treatment options, such as septal myectomy, dual-chamber pacing, or septal ablation should be considered.

Surgical Septal Myectomy

Surgical septal myectomy is the definitive treatment for the relief of left ventricular outflow obstruction.¹⁷⁵⁻¹⁸⁶ Performed via an aortotomy, this procedure removes (debulks) the basal-to-mid-ventricular septum, thus widening the effective outflow tract area and eliminating the systolic anterior motion of the mitral valve. Concomitant mitral regurgitation, if it is due to systolic anterior motion, is also relieved by this technique. While this procedure was initially associated with high procedural mortality rates, reports now suggest that death and severe complication rates are on the order of 1% or less for patients undergoing isolated myectomy. If concomitant procedures are also performed (coronary artery bypass grafting, mitral valve repair), these rates are still less than 5%.¹⁷⁷⁻¹⁸⁶ Over 90% of patients report significant symptomatic improvement with durable results. Long-term postoperative survival is excellent. Emerging data suggest that myectomy improves survival among patients with outflow tract obstruction.^{186a} In patients with concomitant mitral regurgitation secondary to systolic anterior motion of the mitral valve, the regurgitation disappears as a result of the myectomy.^{187,188} A more extensive myectomy procedure is performed at some centers whereby the septal resection is wide and extended to the level of the papillary muscles. In those patients with abnormalities of the papillary muscle, dissection and reduction of the anomalous papillary muscle apparatus may also be performed.^{79,189}

Complications of the surgery are rare. Heart block, ventricular septal defect, and aortic regurgitation have been reported. However, with increasing experience and newer surgical techniques, these complications occur in less than 1 % of patients undergoing operation. These results are not only dependent on surgical expertise but also related to the use of intraoperative transesophageal echocardiography, which guides the surgeon as to adequacy of resection or concomitant structural heart disease.¹⁹⁰⁻¹⁹² This operation should be performed in referral centers with extensive surgical expertise.

Dual Chamber Pacing

Dual chamber pacing has been proposed, tried, and tested as a primary treatment for the relief of symptoms in obstructive hypertrophic cardiomyopathy (Fig 11).¹⁹³⁻²⁰² The rationale for this therapy is based on optimizing atrioventricular delay to take full advantage of the atrial contribution to filling, a change in the activation sequence of the left ventricle with septal asynergy, and chronic remodeling. While there are clearly some patients who benefit from this therapy, the majority does not

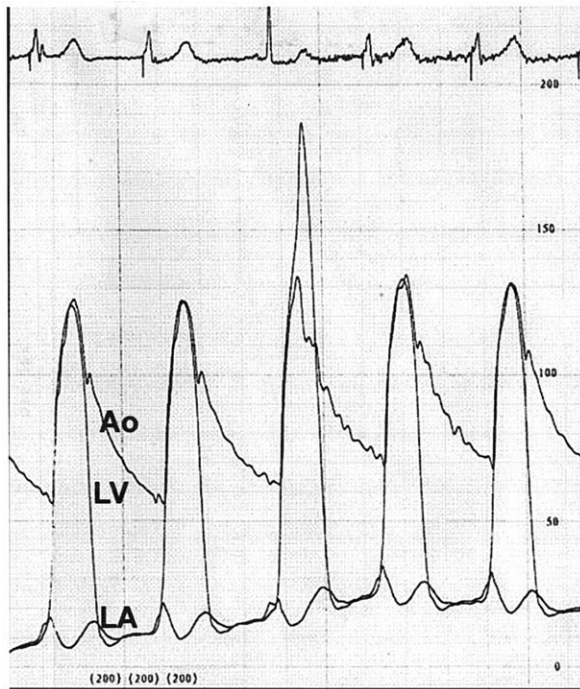


FIG 11. Acute hemodynamic study shows sometimes dramatic effects of pacing. Third complex shows native conduction (loss of ventricular capture by temporary pacing wire) with significant outflow gradient that is abolished when ventricular pacing is present. Micromanometer-tipped catheters are in aorta (Ao), left ventricle (LV), and left atrium (LA).

have lasting symptom benefit.²⁰³ Randomized cross-over trials have been performed whereby a pacemaker is implanted and the patients were randomly assigned to active dual-chamber pacing, or placebo (AAI mode).^{195,197,199-201} Subjective and objective data were collected after periods of weeks to months, and then the patients were “crossed-over” to the alternative pacing mode. Data from these trials suggest that there is a strong placebo effect. However, active pacing does result in variable gradient reduction and improvements of exercise capacity is a small subset of patients. Unfortunately, there are no known parameters that suggest which patients will benefit from pacing.

A retrospective comparison of therapy with dual-chamber pacing versus surgical myectomy suggests that pacing does not provide as predictable or complete relief of outflow obstruction. Symptom response and exercise were better in patients after surgical myectomy.²⁰⁴ Based on all these factors, pacing has become a secondary therapy that is reserved for patients with

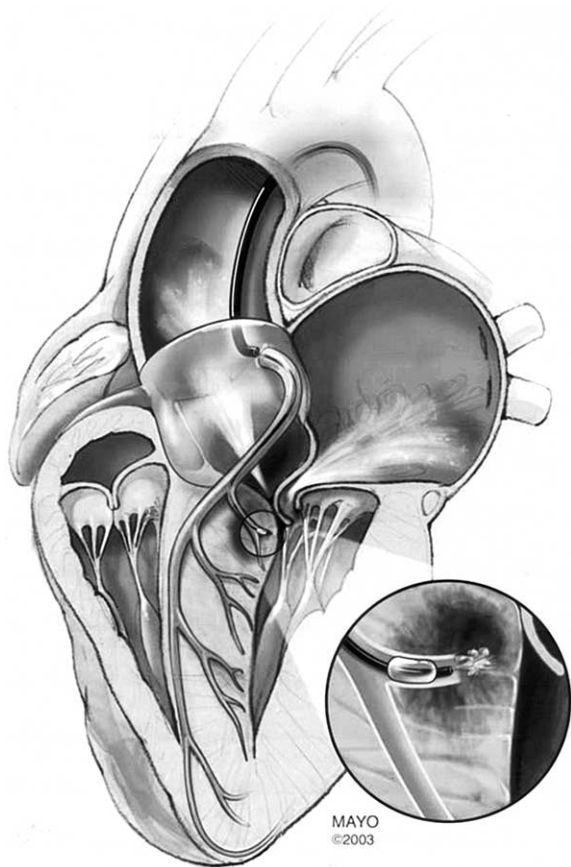


FIG 12. Schematic drawing of catheter-based septal ablation shows selective cannulation of branch of first septal perforator. Artery that supplies myocardium adjacent to point of anterior mitral leaflet septal contact is target artery for ablation. Reproduced by permission of Mayo Foundation.

confounding factors or contraindications that render surgical therapy unacceptably risky.

Septal Ablation

The newest novel therapy for the relief of obstruction is the catheter-based alcohol septal ablation.²⁰⁵⁻²¹² Similar to the surgical myectomy, this procedure attempts to debulk the septum in the area where the obstruction occurs (Figs 12 and 13). In this case, a localized myocardial infarction is created by injection of ethanol into the septal perforator supplying the muscle mass adjacent to the point mitral leaflet-septal

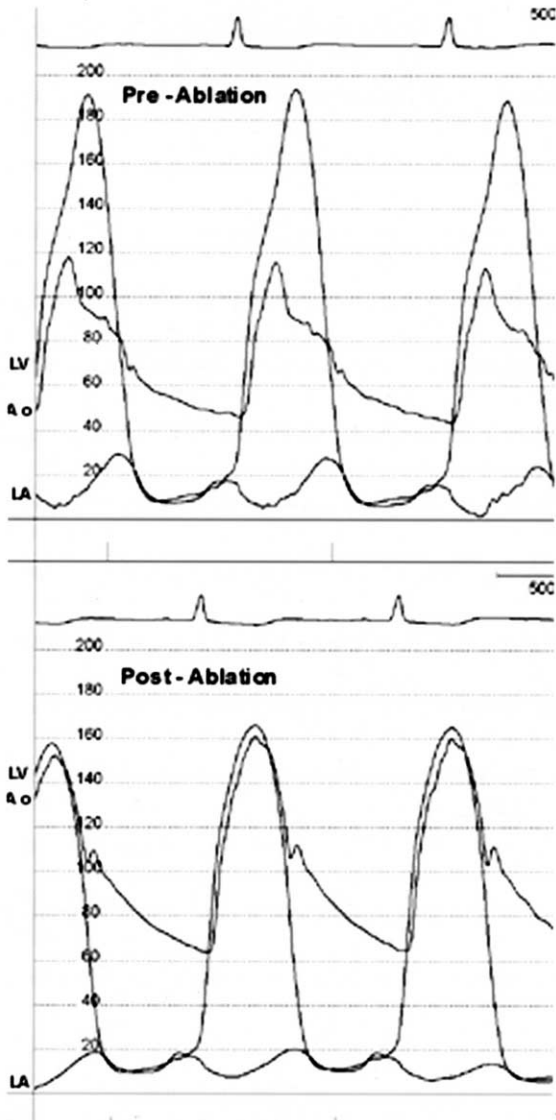


FIG 13. Hemodynamic recordings from patient before (top) and immediately after (bottom) catheter-based septal ablation. Procedure resulted in near-complete relief of left ventricular outflow obstruction, and marked reduction of the v-wave on left atrial (LA) pressure tracing. Micromanometer-tipped catheters are in aorta (Ao), left ventricle (LV), and left atrium (LA).

contact. Acutely, this causes the basal septum to become akinetic and effectively widens the outflow tract during systole. Over time (6 weeks to

6 months), as infarct-related remodeling occurs, the infarcted segment thins and provides further relief of obstruction.

This procedure has evolved such that the infarct size and complications related to the procedure have decreased over time. Initial experiences reported that advanced heart block (as a complication of infarction of the conduction system) occurred in upwards of 25% of patients. More recent experiences, with the use of echocardiographic contrast agents to help better identify the correct artery, and the use of subselective alcohol injections, have reduced the need for permanent pacemakers to around 10%. The procedure mortality rate appears to be in the range of 1% to 4%.²¹³⁻²¹⁵ Retrospective, nonrandomized comparisons suggest that the intermediate-term (3 to 12 months) results show impressive reduction in gradients and improvements in functional classification.^{209,215-229} The advantage of the catheter-based approach is shorter hospital stay, quicker return to work/activity, and avoidance of sternotomy and general anesthesia. There is no apparent survival benefit compared with myectomy. The disadvantages include increased need for permanent pacing, the indirect approach, the inability to address concomitant anatomic abnormalities (mitral valve prolapse, abnormal papillary muscle anatomy, coronary artery disease) and the uncertainty about the long-term effects of iatrogenic myocardial infarction. Approximately 15% to 20% of patients will not have a successful procedure due to lack of suitable septal arteries in the region of obstruction. Whether the results of septal ablation are comparable to septal myectomy remains controversial,²³⁰⁻²³² and the ultimate role of this procedure in the treatment of hypertrophic cardiomyopathy is unclear.^{10,212,233,234}

Treatment Summary

The treatment of obstructive hypertrophic cardiomyopathy starts with general measures such as adhering to prophylaxis for infective endocarditis and avoidance of dehydration, alcohol, and isometric or anaerobic exercise. The first line of therapy for patients with exertional symptoms is pharmacologic therapy with maximally tolerated doses of 1 or more negative inotropic agents. For patients who are refractory or intolerant of pharmacologic therapy, direct relief of obstruction through septal debulking should be considered. If there is unusual anatomy or concomitant structural heart disease, such as mitral valve abnormalities or revascularizable coronary artery disease, a surgical approach offers the best chance of addressing all issues. If there is isolated basal septal hypertrophy, then either surgical myectomy or catheter-based septal ablation can be used. There must be a thorough discussion of the goals, risks, and proven

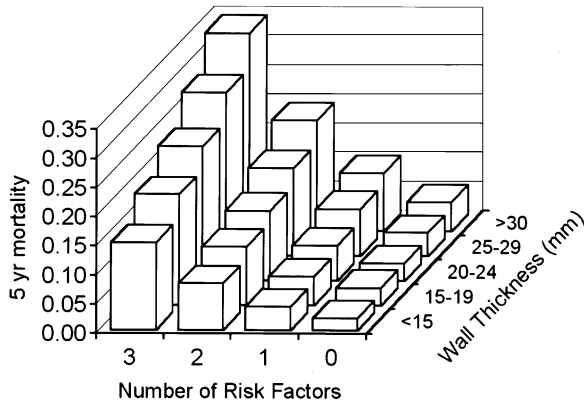


FIG 14. This chart demonstrates relationship between maximal left ventricular wall thickness, cumulative number of adverse risk factors, and mortality. Data are from Elliot et al.⁷⁵

benefits of each strategy. Dual-chamber pacing can be considered in patients with severe comorbidities or other extenuating circumstances that unacceptably increase the risk of the other procedures.

Risk of Sudden Cardiac Death

Sudden cardiac death is one of the most perplexing issues in the management of hypertrophic cardiomyopathy. Referral bias issues initially gave the false impression that hypertrophic cardiomyopathy was a disease with high incidence of sudden death. While subsequent epidemiologic studies have provided a more realistic, lower estimate, there are patients who die at a young age without warning. The identification of those at increased risk remains challenging and controversial. There is a long list of variables that have been proposed to help in this risk stratification.^{75,76,99,100,137,139,140,235} These include (1) a prior cardiac arrest or sustained ventricular tachycardia, (2) a family history of premature sudden death due to hypertrophic cardiomyopathy, (3) repetitive nonsustained ventricular tachycardia on ambulatory Holter monitoring, (4) massive degree of ventricular hypertrophy (wall thickness greater than 30 mm), and (5) hypotensive response to exercise (Fig 14). Other findings such as myocardial bridging in young patients or severe ischemia on radionuclide imaging have been associated with an increased risk of sudden death.²³⁶ Electrophysiological studies have not been shown to be of benefit and risk stratification in these patients.^{237,238} A retrospective analysis of implantable cardioverter defibrillator use in secondary prevention strategies has shown that up to 70% to 80% of such patients will

have an appropriate ICD therapy within the first 10 years after implantation. The use of ICD as a primary prevention strategy, based on perceived risks, has also been shown to result in cumulative appropriate device therapy rates of 20%.¹⁴⁹ Primary prevention based on single factors are difficult to justify epidemiologically, leading to proposals to look at cumulative numbers of risk factors or developing risk score systems based on retrospective data sets.^{75,141} Equally as difficult, however, is a strict adherence to algorithms when sitting with a worried patient.

Summary

Hypertrophic cardiomyopathy continues to be a fascinating disease marked with heterogeneity. The understanding and treatment of the disease provides challenges for clinicians, basic scientists, statisticians, epidemiologists, and patients. It is clearly established as a disease related to mutations in genes encoding for the cardiac sarcomere, although the path from mutation to functional defect to clinical presentation remains elusive. Novel treatment strategies for both the relief of symptoms and the prevention of sudden cardiac death continue to emerge. Perhaps the next era in hypertrophic cardiomyopathy will see the elucidation of the true molecular mechanisms responsible for disease expression and the development of strategies to directly combat this process.

R. A. O'Rourke: In patients with HCM who are severely symptomatic in spite of medical therapy, septal myectomy and septal ablation are alternative beneficial procedures for patients with persistent left ventricular outflow tract gradients (usually >30 mg Hg) at rest or with provocation. Both have advantages and disadvantages, and there is considerable controversy over which is most effective in which patients. In any case, either procedure should be performed only at those institutions with considerable experience with its use and by operators who have obtained favorable results in prior patients.

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