Hypertrophic cardiomyopathy: diagnosis, risk stratification and treatment

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Hypertrophic cardiomyopathy is a common inherited cardiomyopathy, occurring in about 1 in 500 individuals.[1] The first gene mutation for this condition was identified in a large French Canadian family cohort in 1989.[2] Clinical presentation typically includes left ventricular hypertrophy in the absence of abnormal loading conditions, such as hypertension or aortic stenosis. Hypertrophic cardiomyopathy has come to public recognition in large part because of sudden cardiac death in a subset of young, otherwise healthy individuals with the condition.

Depending on the severity and location of hypertrophy, dynamic obstruction of the left ventricular outflow tract can occur, and it may be quite limiting in some cases. Less widely appreciated sequelae of hypertrophic cardiomyopathy include atrial arrhythmia and consequent embolic phenomena, as well as progression to heart failure and, in some cases, requirement for cardiac transplant.[3] Increasingly, the use of imaging and mutation analysis have made very early and preclinical genetic diagnosis possible. The same diagnostic advances are poised to contribute meaningfully to risk stratification (e.g., likelihood of sudden cardiac death).

Given the frequency of hypertrophic cardiomyopathy and the development of additional diagnostic and prognostic strategies, practitioners require a reasonable evidence-based approach to diagnose, assess and treat this disease. In this review, we address these needs and identify areas of ongoing controversy. Evidence in this area comes from highly varied sources, including relatively large populations in retrospective cohort and population studies, as well as family-focused observational analyses (Box 1). These studies guide expert opinion and, in many cases, are the result of careful clinical observation of specialty care offered at select high-volume centres. Prospective randomized controlled trials are largely absent from the literature on hypertrophic cardiomyopathy.

Box 1: Evidence used in this review

We performed a PubMed search using the term "hypertrophic cardiomyopathy." We reviewed all articles published between Jan. 1, 2005, and May 1, 2012, for relevance. We considered articles to be relevant if they addressed clinical aspects of diagnosis, assessment or treatment. We also examined major review articles and guidelines dating back to 1995, as well as the references from relevant articles. We also included seminal articles that have made important contributions to our knowledge of hypertrophic cardiomyopathy, even if such articles were not identified in our search.

Who is at risk?

Hypertrophic cardiomyopathy affects males and females of all ages and ethnic backgrounds. Autosomal dominant disease is predominant, with most sporadic and alternate inheritance patterns (X-linked, mitochondrial) representing phenocopies. Disease penetrance is incomplete and expression is variable, making the familial nature of this disease occasionally challenging to appreciate.[4] Although some reports indicate that hypertrophy may develop later in life in a subset of patients (in particular, those with *MYBC3* mutations),[5] general experience is that late development or progression of hypertrophy is uncommon, with most cases of hypertrophy developing during adolescence and early adulthood.

Studies of the clinical prevalence of hypertrophic cardiomyopathy indicate that clinical recognition of disease may occur earlier in men

Key points

- Clues to the possible diagnosis of hypertrophic cardiomyopathy include the presence of left ventricular hypertrophy on electrocardiography or echocardiogram in the absence of abnormal loading conditions.
- Once identified, hypertrophic cardiomyopathy is generally a benign or manageable condition, provided appropriate clinical evaluation is carried out.
- Genetic diagnoses may be obtained for most affected patients, allowing cascade screening of family members and subsequent release of those with a negative genotype from clinical follow-up.
- Regular clinical evaluation with specific investigations enables initiation of targeted therapies to reduce morbidity and mortality.
- Invasive therapies for obstructive symptoms should be chosen based on clinical characteristics, physician and institutional expertise, and patient preferences.

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than women.[1,5,6] Although no race or nationality is overrepresented, variable phenotypes have long been appreciated. Because of a relative prevalence of apical hypertrophic cardiomyopathy among East Asian populations, apical involvement is occasionally referred to as Japanese hypertrophic cardiomyopathy. However, the skew of prevalence of phenotypes is mild, making the use of this term misguided.[7–9] Hypertrophic cardiomyopathy has been most extensively studied in white populations with associated genetic subtypes best appreciated in this population. The normal cardiac phenotype may differ among races. Recognition of electrocardiographic abnormalities (Q waves, T-wave inversion) in apparently healthy black athletes may cause diagnostic uncertainty.[10]

A small but important minority of patients may present with earlier and more severe hypertrophy, in some cases, during infancy. In these situations, the presence of storage disease, multiple pathogenic sarcomere mutations, or important modifier mutations may be present and should be actively investigated.[11]

Clinical presentation of hypertrophic cardiomyopathy during mid and late life is not uncommon. As noted above, the proportion of patients who present late in life with new-onset hypertrophy remains an area of debate.[5] In some cases, symptomatic hypertrophic cardiomyopathy may have previously been misdiagnosed as asthma, chronic obstructive pulmonary disease, deconditioning or sleep apnea, and it may be difficult to distinguish from valvular and hypertensive heart disease in elderly patients.[12] Commonly, the development of symptoms occurs because of ischemia, gradual failure of compensatory mechanisms, or the onset of downstream pathology (e.g., atrial fibrillation).

Guidelines for diagnostic evaluation take into account the above issues when recommending yearly follow-up for at-risk individuals during adolescence. Reduction in the intensity of follow-up during adulthood is reasonable. No prespecified age for release from follow-up has been established, and continuation of follow-up should be based on family history and patient-specific factors (Box 2).[13]

Box 2: American College of Cardiology/European Society of Cardiology's 2003 recommendations for screening[13]

- Clinical screening of first-degree relatives and other family members should be encouraged if a DNA diagnosis cannot be established or is not feasible, including:
  - history and physical
  - 12-lead electrocardiogram
  - echocardiogram.
- Annual clinical screening is recommended in these individuals from 12 to 18 years of age.
- Clinical screening every 5 years is recommended in individuals older than 18 years.
- Clinical screening under the age of 12 is not usually pursued unless there is a high-risk family history or the individual will be pursuing intensive competitive sports.
- Clinical screening of identified affected individuals is recommended in 12- to 18-month intervals.

Box 3: Diagnostic criteria for hypertrophic cardiomyopathy[13]

Left ventricular hypertrophy in the absence of another cardiac or systemic disease that could cause hypertrophy:

- Wall thickness of 1.5 cm or greater in adults or the equivalent relative to body surface area in children with a nondilated hyperdynamic left ventricle.
- Distribution of hypertrophy can be variable.

Electrocardiography

- Characteristic changes may include left ventricular hypertrophy with repolarization changes, T-wave inversions and abnormal Q waves.

How is it diagnosed?

Hypertrophic cardiomyopathy should be considered if a patient has unexplained symptoms, a family history of premature cardiac disease, or electrocardiographic abnormalities. The diagnosis is confirmed by demonstration of increased wall thickness of 1.5 cm or more, or more than 3 standard deviations from predicted (Box 3).[12]

An electrocardiogram (ECG), echocardiogram and cardiac magnetic resonance imaging (MRI) from a patient with hypertrophic cardiomyopathy are shown in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120138/-/DC1). Voltage criteria showed T-wave inversion with left ventricular hypertrophy, echocardiography and MRI showed major hypertrophy, and late-gadolinium enhancement showed evidence of scar tissue. Such pronounced findings are not always present, however. Incomplete disease expression is common (> 30% of mutation carriers) and lesser degrees of left ventricular hypertrophy are often seen, sometimes in association with other echocardiographic features of the disease, including reduced left ventricular cavity dimensions, hyperdynamic indices of systolic function, abnormalities of papillary muscles and mitral valve anatomy, and abnormal indices of diastolic function with atrial enlargement.[14,15]

Genotype

A genetic diagnosis can be obtained for patients with hypertrophic cardiomyopathy. With current testing, pathogenic mutations will be identified

in 60%–70% of patients in 1 of 9 genes encoding the components of the cardiac sarcomere.[3] Although identification of a pathogenic sarcomere mutation is helpful, an inability to identify a pathogenic sarcomere gene mutation in a patient who meets the clinical criteria for diagnosis does not negate the diagnosis.

The availability of genetic testing with a reasonable signal-to-noise ratio enables the identification of genotype-positive, phenotype-negative individuals. Although the genes associated with hypertrophic cardiomyopathy are well described, the pathways that lead from gene mutation to hypertrophy, restrictive physiology, and atrial and ventricular arrhythmias remain incompletely understood. Those with a positive genotype, but who do not meet diagnostic criteria, should not be considered to have hypertrophic cardiomyopathy, because clinical issues that are important in phenotypically positive disease (e.g., restriction from competitive sports) are considerably less relevant in this population.[16,17] Variable penetrance and expressivity mean that we cannot reliably predict the clinical course for genotype-positive, phenotype-negative individuals based on the clinical histories of members of the same family who have hypertrophic cardiomyopathy.

Phenotype

The phenotype of hypertrophic cardiomyopathy overlaps with that of normal individuals who are elite athletes[18,19] and with that of some black individuals with mild hypertension.[10] Additionally, phenocopies of hypertrophic cardiomyopathy (e.g., Fabry disease,[20] Friedrich ataxia,[21] Noonan syndrome,[22] cardiac specific glycogen storage disease[23]) can closely mimic the classic phenotypes of this disease. Phenocopy identification is critically important because management strategies may differ and potentially change the disease course (i.e., use of replacement therapy with agalsidase α or β in Fabry disease).[24] The unique clinical manifestations of these phenocopies that may aid in the differentiation from classic hypertrophic cardiomyopathy are outlined in Appendix 2 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120138/-/DC1). Although the presence of such diverse phenotypes in the general population can make the identification of classic hypertrophic cardiomyopathy difficult, genetic testing can help to differentiate this disease from other subtypes of pathologic ventricular hypertrophy.

While a combination of ECG and echocardiography is more readily available and serves as adequate testing for the diagnosis of hypertrophic cardiomyopathy in most cases, cardiac MRI can provide additional information that can be quite useful. For example, cardiac MRI may identify noncontiguous regions of hypertrophy that are difficult to appreciate on echocardiography, and may be useful in identifying infiltrative processes, as well as scar tissue.[25]

How is it treated?

Treatment depends on disease expression, which can differ greatly among individuals, even within a single family. The natural history of hypertrophic cardiomyopathy includes those who remain asymptomatic and those who develop symptoms. The latter group can be further divided into those who develop outflow tract obstruction and exertional limitations (25% of all affected);[26] an additional 25% with provokable outflow tract obstruction;[27] those with restrictive physiology and minimal hypertrophy (1%–2%);[15] those who have a tendency for ventricular arrhythmias and sudden cardiac death; and the remainder who have hypertrophy without obstruction, but who remain at risk for atrial and ventricular arrhythmias and who may experience exertional limitation because of diastolic dysfunction. There is a small subset (up to 5%) who may progress to the so-called burnt out phase of hypertrophic cardiomyopathy with ventricular wall thinning, systolic and diastolic left ventricular failure, and heart failure requiring heart transplantation.[28] Although there is considerable overlap among these phenotypes, patients generally fall predominantly into one category or another. Treatment is dependent on the clinician's ability to identify and treat the underlying physiology (Figure 1).[13,29–68]

Left ventricular outflow tract obstruction

The evidence base for the management of outflow obstruction is variable (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120138/-/DC1); however, in all cases, treatment should be restricted to patients who exhibit the associated symptoms. Recognition of obstruction-related symptoms may be made challenging by both a patient's accommodation to limitations and a consequent lack of awareness of remediable limitations, and by the presence of latent obstruction (obstruction present only with provocation such as exercise, Valsalva manoeuvre, or premature ventricular contractions).[69,70] The prevalence of occult exertion-related obstruction (25% without provocation and another 25%–50% on exercise testing)[27,69] and adverse outcomes associated with reduced exertional capacity[30] supports quantitative assessment of exercise capacity (cardiopulmonary exercise testing, exercise echocardiography).[71,72]

Retrospective cohort studies and physiologic data support a first-line role for β-blockers in the treatment of symptomatic left ventricular outflow tract obstruction.[33,41,65] Reduced inotropy and longer ventricular filling times associated with β-blockade can reduce obstructive symptoms. Some centres have taken the approach of using verapamil as a first-line agent, but this strategy can be associated with acute exacerbation of obstruction due to preferential lowering of systemic vascular resistance.[73] At present, there is little evidence to support combined therapy; use of the combination comes with an associated risk of heart block and hypotension.[38]

Retrospective cohort data support the use of disopyramide to reduce left ventricular outflow tract gradients and symptoms, with good effect and reasonable safety profile in combination with β-blockers in patients with refractory symptoms (Appendix 3). Disopyramide should be considered for patients with obstructive hypertrophic cardiomyopathy before more invasive interventions.[62] It should not, however, be administered with other antiarrhythmic drugs (e.g., sotalol, amiodarone).

Patients who cannot tolerate or whose condition is refractory to medical therapy are candidates for surgical or catheter-based treatment of outflow obstruction.[74,75] In experienced centres, both procedures are associated with low rates of complications and successful relief of obstruction and associated symptoms.[76] There is debate over which procedure is best. Concerns regarding the potential for creation of an arrhythmogenic focus with septal ablation,[66] as well as the increased risk of complete heart block with that procedure, make the appropriate selection of patients for catheter-based treatment complex. For clinical practitioners, the major factors to be considered are operator and centre experience. If both procedures are available, surgical myectomy is generally recommended for young patients with low surgical-risk profiles, while catheter-based treatment is favoured for elderly patients and those at higher surgical risk (Appendix 4, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120138/-/DC1).[30]

Although early observational reports were promising, the subsequent blinded, randomized crossover trials failed to support the use of dual chamber pacing for treatment of left ventricular outflow tract obstruction. However, pacing may be beneficial for selected patients (i.e., those with end-stage disease or for whom myectomy or alcohol septal ablation cannot be performed).[49,77,78]

Structural abnormalities of the mitral valve and valve apparatus are not uncommon in patients with hypertrophic cardiomyopathy.[79] In the presence of substantial mitral regurgitation, surgery is the preferred approach. However, when the regurgitant jet is closely related to systolic anterior motion of the mitral valve (posteriorly directed in association with normal valve structure and major left ventricular outflow tract

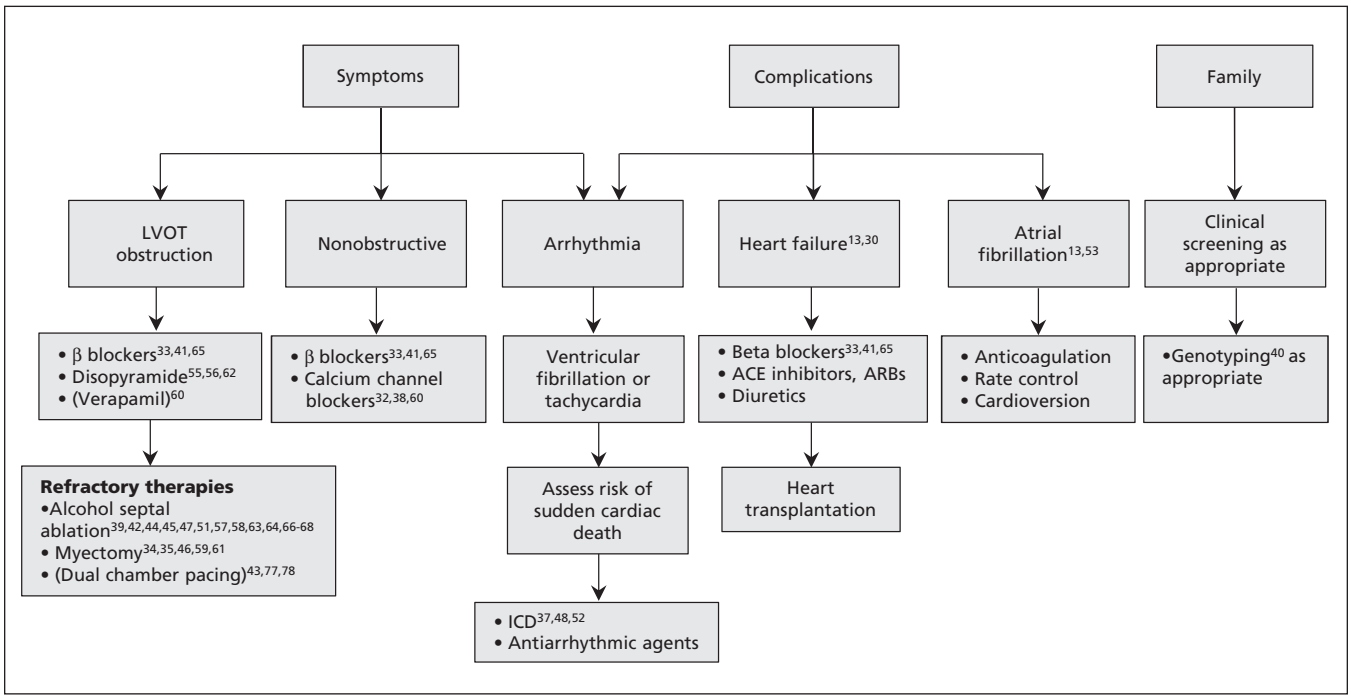

Figure 1: Management of hypertrophic cardiomyopathy. Brackets indicate third-line therapy with, at best, borderline evidence to support their use. Note: ACE = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, ICD = implantable cardioverter defibrillator, LVOT = left ventricular outflow tract.

gradient), either method of septal reduction should alleviate the mitral regurgitation.[80]

Restrictive disease with atrial arrhythmia

In the subset of people with hypertrophic cardiomyopathy and predominantly restrictive features, atrial arrhythmias may be tolerated poorly and are associated with a significantly increased risk of stroke.[53] Management of these arrhythmias and prevention of thromboembolism are achievable therapeutic targets.

Anticoagulation is recommended for all patients with hypertrophic cardiomyopathy and atrial fibrillation.[13,81] Because rate-versus-rhythm control strategies have not been studied in this population, existing management strategies for atrial fibrillation based on large prospective studies involving patients with heart failure from more usual causes cannot be applied. Some patients with hypertrophic cardiomyopathy and atrial fibrillation will tolerate permanent atrial fibrillation with rate control; however, some have reduced exertional capacity with atrial arrhythmias. Maintenance of sinus rhythm using cardioversion and antiarrhythmic agents, and ablation in select cases, may be indicated. The first step in the management of hypertrophic cardiomyopathy and atrial fibrillation should include attempts at rhythm control.

Ventricular arrhythmia

Sudden cardiac death remains the most visible outcome of hypertrophic cardiomyopathy, occurring in young, otherwise healthy individuals.[48] Reasonably well-defined clinical risk factors for sudden cardiac death allow clinicians to target implantable cardioverter defibrillator therapy to those who are at the highest risk.[37] Not all risk factors predict this outcome equally, and placement of this type of device in young patients is associated with an important lifetime risk of complications.[52] As is the case for other forms of heart disease, a personal history of cardiac arrest or sustained ventricular arrhythmia is the most powerful risk factor; massive (> 3 cm) septal hypertrophy is one of the weakest predictors.[36] Family history of sudden cardiac death is an important risk factor, particularly if there are multiple affected individuals in the same family.[82,83] The presence of multiple risk factors in an individual strengthens the case for an implantable defibrillator.[82,83]

Discussion of the risk of sudden cardiac death versus potential adverse effects of implanting a defibrillator is complex, particularly for adolescents and young adults. As such, the decision about the placement of an implantable defibrillator can be one of the most difficult in the care of a patient with hypertrophic cardiomyopathy (Figure 2).[30,36,37,84–91] It should be noted that there

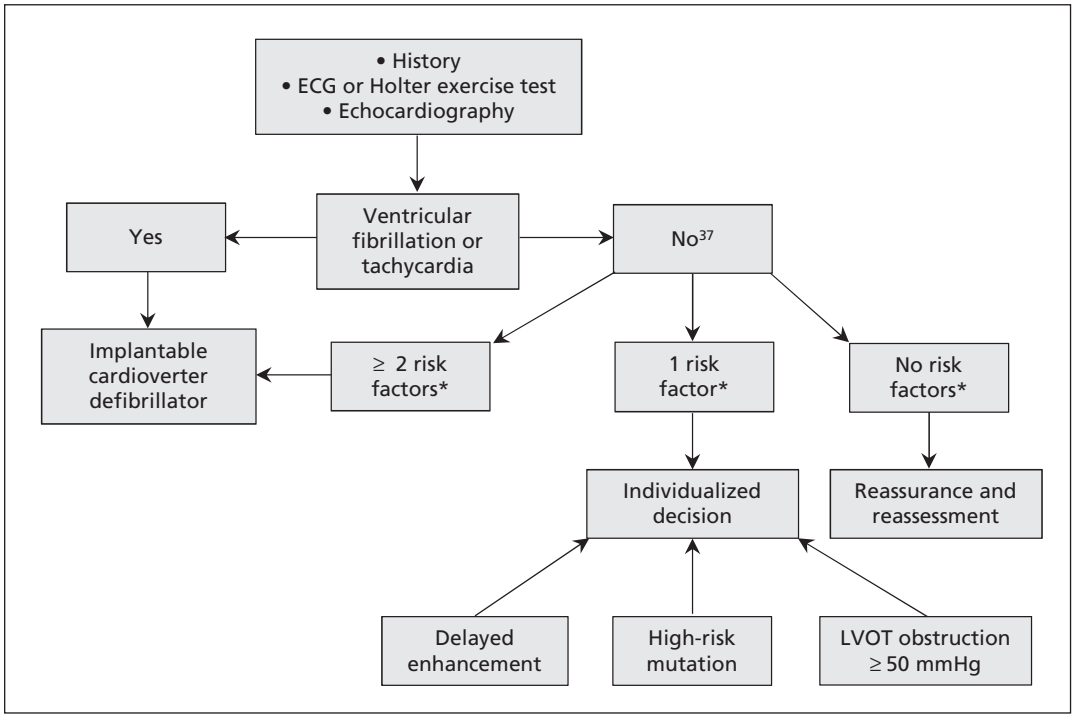

Figure 2: Risk stratification algorithm for prevention of sudden cardiac death. *Risk factors include cardiac arrest,[84,86] spontaneous sustained ventricular tachycardia,[84,86] family history of premature sudden cardiac death,[30] unexplained syncope,[91] left ventricular thickness of 3 or more cm,[36] abnormal blood pressure response to exercise[85] and nonsustained ventricular tachycardia (≥ 3 beats, at least 120 beats/min).[87] Possible risk factors include LVOT obstruction (≥ 50 mm Hg at rest),[86] contrast cardiac magnetic resonance imaging with extensive delayed enhancement,[90] and high-risk mutation. Note: ECG = electrocardiogram, LVOT = left ventricular outflow tract.

are no prospective data on reduction in mortality with the use of implantable cardioverter defibrillators in this population; however, retrospective cohort data using age- and risk factor–matched controls are strongly compelling for their use in high-risk patients.[36,37,48,52]

Heart failure

Congestive symptoms, refractory exertional limitation and end-stage heart failure occur in few patients with hypertrophic cardiomyopathy.[92] Once symptoms of advanced disease are seen, expert consensus recommends referral to a heart transplant centre.[30] Late referral may be associated with end-organ damage and pulmonary hypertension. Treatment of secondary pulmonary hypertension or placement of a left ventricular assist device is difficult in patients with small ventricular cavities, although small series support its limited use in this setting.[93]

Standard medical heart failure therapy may be used in this population; however, cautious use of afterload reduction and diuretics are necessary in patients with restrictive physiology.

What areas of management are controversial?

The selection of patients for placement of an implantable defibrillator, the method of septal reduction therapy, and the yield and utility of genetic testing remain areas of debate. The identification of risk factors is the starting point for determining the utility of an implantable defibrillator as primary prophylaxis in any patient. Data supporting the use of either a single risk-factor trigger or a multiple risk-factor trigger exist.[94,95] Both approaches are subject to risk tolerance, which itself is variable across individuals and cultures. The decision to place the device in an otherwise healthy individual should be made in the setting of a candid patient-centred discussion of absolute and relative risks of both sudden cardiac death and implantable defibrillator therapy. If the decision is made to delay placement of the device, reassessment of risk factors is necessary as disease expression may change over time.

Although use of alcohol septal ablation as a first-line treatment for symptomatic outflow obstruction is held up as controversial, both alcohol and surgical approaches to septal modification have similar safety and effectiveness. While there are reports of arrhythmia following alcohol septal ablation,[66] the data do not suggest significantly increased arrhythmia burden when the procedure is correctly performed.[76] Although there is longer-term experience with myectomy than with septal ablation, published data on both procedures suffer from incomplete follow-up. Operator and institutional experience are important factors, as are patient preference and individual predictors of therapeutic success. The figure in Appendix 4 provides a list of potential determinants that may lead to favouring one type of procedure over another.[37] The overall focus should be to present the best option to the individual patient.

Mutation analysis is another area of controversy. For information about this, please see Appendix 5 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.120138/-/DC1)

Conclusion

Over the years, our understanding of hypertrophic cardiomyopathy has shifted. What was initially viewed as a rare disease with severe clinical consequences is now known to be a relatively common cardiomyopathy with variable and an often benign, or at least manageable, clinical course.[40] The advent of implantable defibrillator therapy, expertise in septal reduction therapy, and advanced imaging have benefited patients. Perhaps most important, patient advocacy groups have created an environment in which patients are educated and empowered to work with their physicians as partners in their care.[73] Research goals and the availability of progressive specialty programs in inherited cardiomyopathy have both been positively affected by patient advocacy.

Prevention of hypertrophy, regression of hypertrophy and non–device-driven reduction in the risk of sudden cardiac death are the ultimate goals of treatment of this condition. Development of new therapies to address these goals based on knowledge of the genetic basis of hypertrophic cardiomyopathy has been disappointing. Ongoing investigation into pathogenetic mechanisms is likely to yield progress along these lines, but clearly the issues are complicated and the timeline unpredictable. Simple, astute, clinical observation of the relation between genotype and phenotype within families is of great importance.

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