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Original Article

State-of–the-Art Management of Hypertrophic Cardiomyopathy in Children

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Hypertrophic cardiomyopathy is a common abnormality in children, and is know to be associated with a genetic predisposition. It can present in childhood, adolescence, or adulthood. It is a frequent cause of disability and death in those of all ages. Indeed, it is the most common cause of sudden cardiac death in the young athlete.[1] In addition to the diversity in the time of presentation, there is also diversity in terms of the the mode of clinical presentation, the natural history, and most importantly, the prognosis. In this respect, debate continues with regard to the treatment and prognosis of the asymptomatic patient with hypertrophic cardiomyopathy. Similarly there is continued discussion with regard to the criterions for diagnosis, as well as management, for children known to have hypertrophic cardiomyopathy. Our objective in producing this review, therefore, is to address hypertrophic cardiomyopathy as it pertains to children and adolescents.

Prevalence and Genetics

Hypertrophic cardiomyopathy is one of the more common genetic cardiac conditions, having a prevalence of 1 in 500 of the population at-large. Included within this number are patients who have no symptoms, as well as those who are at risk for sudden cardiac death. In this review, we concentrate on the so-called sarcomeric forms of hypertrophic cardiomyopathy. The non-sarcomeric forms of the disease are both phenotypically and genetically different from the group to be discussed.[2] Those with non-sarcomeric disease present with concentric left ventricular hypertrophy, and are associated with syndromes such as Pompe's syndrome, Fabry's syndrome, and Noonan's syndrome, many of which are storage diseases, or else represent different genetic abnormalities. For these reasons, we confine our current discussions to the sarcomeric variants.

The sarcomeric form of hypertrophic cardiomyopathy is genetically inherited in an autosomal dominant fashion. It is associated with mutations in any of the genes that are involved with the proteins of the sarcomere. These include many of the components of the thick and thin filaments of the sarcomere.[3] Though many specific mutations have been uncovered, a direct relationship has yet to be determined between specific mutations and phenotypic presentation or prognosis. A large number of the cases involve mutations in either the beta myosin heavy chain, cardiac troponin T, or the myosin binding protein. Mutations in the genes that encode for the other components of the contractile apparatus make up a smaller number of the cases.

The identification of these genetic mutations has led to interest in the development of DNA-based genetic testing of patients in order to aid in their diagnosis and management, as well as the screening of their families. While genetic testing is currently commercially available, its value is still not clear. There are certainly circumstances where genetic

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testing for hypertrophic cardiomyopathy is useful.[4] For example, if a patient with hypertrophic cardiomyopathy has a defined genetic mutation, genetic testing of phenotypically normal children is likely to avoid the need for serial echocardiography should the genetic tests reveal absence of the offending mutation. The clinical use of such genetic testing in other clinical situations, nonetheless, remains to be defined.

Diagnosis

Hypertrophic cardiomyopathy, in its classic and most common form, is associated with hypertrophy of the left ventricle, most notably the ventricular septum.[5] The morphologic, haemodynamic, and clinical manifestations of the disease, nonetheless, can vary widely. Depending on the site and extent of muscular hypertrophy, patients can develop any combination of obstruction of the left ventricular outflow tract, diastolic dysfunction of the left ventricle, myocardial ischaemia, and mitral regurgitation. Cross-sectional echocardiography is the mainstay of diagnosis, and typically shows the extent of ventricular hypertrophy. Making the diagnosis of hypertrophic cardiomyopathy implies that alternative causes of left ventricular hypertrophy, such as systemic hypertension or aortic stenosis, have been ruled out. There are different morphologies of hypertrophic cardiomyopathy as defined by echocardiography. Asymmetric septal hypertrophy, both in its obstructed and non-obstructed forms, accounts for four-fifths of the cases (Fig. 1). The concentric form of hypertrophic cardiomyopathy, sometimes difficult to differentiate from so-called athlete's heart, makes up about one-sixth of cases, while the patients with apical hypertrophy account for 3% of cases. The mid-ventricular form makes up the remaining 1 to 2% of cases.[6]

Extensive physical training can result in significant left ventricular hypertrophy, and can produce the so-called athletic heart syndrome. This can be difficult to differentiate from hypertrophic cardiomyopathy. Additional findings supporting the diagnosis of the athletic heart syndrome include dilation of the left ventricular cavity, absence of left atrial enlargement, absence of electrocardiographic findings supportive of hypertrophic cardiomyopathy, absence of echocardiographic evidence of left ventricular diastolic abnormalities, absence of a family history of hypertrophic cardiomyopathy, and a maximum consumption of oxygen of 50 ml/kg/minute.[7] A decrease in left ventricular hypertrophy associated with deconditioning is definitive evidence for the athletic heart.

The degree of mural thickness can be markedly variable in those with hypertrophic cardiomyopathy, ranging from mild to massive. In children, the thickness can also change with time. Left ventricular remodeling can occur as children grow,[8,9] such that dramatic increases in left ventricular mural thickness can develop during adolescence in those who initially showed minimal hypertrophy. This phenomenon has implications for the utility of echocardiographic screening of children of family members with known hypertrophic cardiomyopathy, and underscores the importance of serial studies. Genetic testing, as discussed previously, may also impact on this situation.

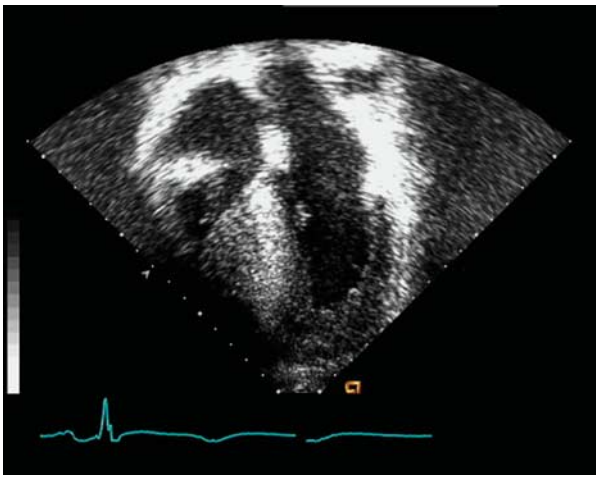

Figure 1.
An apical 4-chamber echocardiogram showing severe asymmetric septal hypertrophy in a patient with hypertrophic cardiomyopathy.

Asymmetric septal hypertrophy, as already emphasized, is the commonest form of hypertrophic cardiomyopathy, and may be obstructive or non-obstructive. Basal septal hypertrophy typically narrows the left ventricular outflow tract, with systolic anterior motion of the aortic leaflet of the mitral valve potentiating the obstruction, and also resulting in mitral regurgitation. The obstruction may be latent and variable, and is influenced by preload, afterload, and the inotropic state. The gradient measured across the outflow tract has shown to be an independent determinant of progressive cardiac failure and functional disability in adults.[10] Such obstruction is associated with an increase in left ventricular pressure and mural stress, an increased myocardial consumption of oxygen, and myocardial ischaemia. Because of the variable dynamic nature of the obstruction, a gradient measured at a single point in time must be interpreted cautiously, and in its appropriate clinical context. In addition, the role of an exercise-induced or pharmacologically provoked gradient is not yet clear when making decisions for management of children with hypertrophic cardiomyopathy. Identification of a gradient, nonetheless, justifies intervention for its reduction.

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The presence of diastolic dysfunction and impaired filling of the left ventricle in hypertrophic cardiomyopathy have been well documented.[11] In addition, the role of echocardiographically measured diastolic parameters in early detection of the disease, as well as stratification of risk for those known to have hypertrophic cardiomyopathy, is currently under investigation.

A burgeoning role is now being recognized for other imaging modalities, such as cardiac magnetic resonance imaging. This technique has been used to quantify delayed enhancement and scarring, and to determine the coronary arterial flow reserve.[12] Its value in guiding the prognosis and management of patients with hypertrophic cardiomyopathy, however, is yet to be determined.

Clinical Profiles

While many children with hypertrophic cardiomyopathy are asymptomatic, some typical prognostic profiles are well recognized (Fig. 2). One group of patients has symptoms of cardiac failure, including exertional dyspnoea, orthopnoea, chest pain, and general fatigue. This group of patients usually has normal or hypercontractile left ventricular function, with or without obstruction of the left ventricular outflow tract. While significant obstruction typically causes symptoms, there are also symptomatic patients who do not have obstructed outflow tracts. In this setting, symptoms are due to factors such as diastolic dysfunction, mitral regurgitation, on microvascular dysfunction. The haemodynamic consequences of significant diastolic dysfunction in those with hypertrophic cardiomyopathy are well known. Because of the associated abnormalities of left ventricular diastole and filling, both the left ventricular end-diastolic and left atrial pressures are elevated, with a concomitant reduction in stroke volume and cardiac output. Pulmonary congestion can occur, resulting in dyspnoea, orthopneoa and exercise intolerance. Chest pain, if present, is likely secondary to severe ventricular hypertrophy, with myocardial ischaemia due to the microvascular dysfunction, and can also contribute to worsening cardiac failure.

A second well recognized group is made up of the patients with atrial fibrillation and its complications, such as embolic stroke. It is uncommon, however, to find children in this group, as it is uncommon to find them with end-stage systolic and diastolic dysfunction. We will not discuss this group further. The final group with a typical clinical profile is made up of those who are at risk for sudden cardiac death. Those falling in this important group will be discussed later in our review.

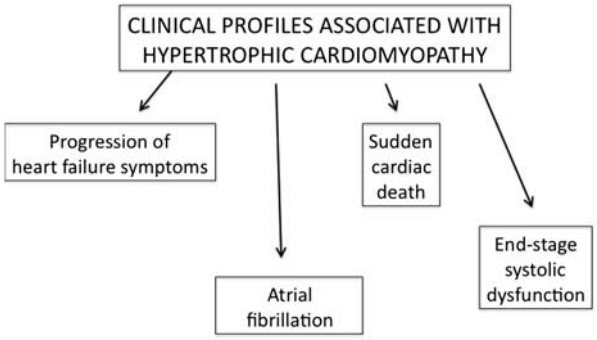

Figure 2.
The clinical prognostic profiles associated with hypertrophic cardiomyopathy.

Medical Therapy

There are many important caveats regarding medical therapy in patients with hypertrophic cardiomyopathy. Firstly, medical therapy has not been shown to alter the prognosis, being focused primarily on the relief of symptoms. There are no large randomized trials on which to base therapeutic strategies, which hence are based on observational data and clinical experience. Because every patient is different, an empiric approach to therapy is critical.

If there are exertional symptoms of cardiac failure, the initial therapy typically includes negative inotropic agents, usually beta-blockers, verapamil, or disopyramide. The mechanism, or mechanisms, of benefit include slowing of the heart rate, and prolongation of diastole, which allows for an increase in ventricular filling. These agents potentially relieve the symptoms of an obstructed left ventricular outflow tract, since they have a negative inotropic effect, but often do not have a significant impact on reducing the degree of obstruction. Beta-blockers may relieve anginal symptoms by decreasing myocardial demand for oxygen, while blockers of the calcium channels, such as verapamil, may reduce angina by their beneficial effects on microvascular dysfunction. A beta-blocker or verapamil is typically used first, and is titrated until symptoms improve, or until side-effects appear. If this strategy is unsuccessful, then another drug should be considered. In the presence of an obstructed left ventricular outflow tract, beta blockers are preferred because of the undesirable effects of verapamil on the systemic vascular resistance.

Beta-blockers, therefore, are usually the initial drug chosen for medical therapy. Whether short or long acting agents are selected is at the discretion of the cardiologist. Side-effects in children include depression, impaired performance at school, and untoward effects on growth and development. There

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are beneficial effects of disopyramide in the presence of severe symptomatology due to an obstructed left ventricular outflow tract, although the anticholinergic side effects limit its use.[13] Because disopyramide can accelerate atrioventricular nodal conduction, it should be used in conjunction with a beta-blocker. There is little data, however, on either its use or dosage in children. It is usually used in patients with mild or absent obstruction of the left ventricular outflow tract, and is usually well tolerated, but may be associated with side-effects that include sinus arrest, atrioventricular block, and pulmonary oedema.

In patients with obstructive hypertrophic cardiomyopathy, several classes of medications are contraindicated, or else should be used with great caution. Vasodilators decrease the systemic vascular resistance, worsen the obstructiobn in the left ventricular outflow tract, and exacerbate symptoms. Diuretics may be used cautiously in patients with persistent cardiac failure and volume overload, albeit that dehydration and a critical reduction in preload can worsen symptoms. Digoxin, and other positive inotropic agents, should be avoided, since they worsen any obstruction of the left ventricular outflow tract. As already discussed, medical therapy is generally unsuccessful in reducing the resting gradient across the left ventricular outflow tract. Its major role is to reduce symptoms.

Medical therapy is controversial in the asymptomatic patient with hypertrophic cardiomyopathy. Most clinicians would choose not to institute medical therapy for those without symptoms. Exceptions include those with clinical or morphologic features known to put them at an increased risk, for example, patients with massive hypertrophy or severe obstruction of the left ventricular outflow tract in the absence of symptoms. More often than not, however, the patients making up the latter group with massive hypertrophy or severe obstruction of the left ventricular outflow tract are likely to have some degree of symptomatology.

Sudden Cardiac Death

In an unselected population of patients with hypertrophic cardiomyopathy, the incidence of sudden cardiac death is around 1% each year.[14,15] Given the lower incidence of sudden death from all causes in young patients compared to adults, however, hypertrophic cardiomyopathy accounts for a significant percentage of sudden deaths in children.

The mechanism of sudden death in this setting is thought to be the sudden onset of a malignant ventricular arrhythmia. This notion has been confirmed by electrographic recordings of appropriate discharges obtained from patients with implanted defibrillators.[16] Polymorphic ventricular tachycardia or ventricular fibrillation are more commonly seen compared to monomorphic ventricular tachycardia. This is not surprising, as the substrate for these arrhythmias is severe diffuse hypertrophy with disarray of the aggregated myocytes, along with ischaemic-induced myocardial necrosis and fibrosis. Intense exercise, by increasing the demand for oxygen, and worsening obstruction across the outflow tract, and decreased coronary perfusion due to peripheral vasodilation, are common triggers, albeit that in many instances no obvious trigger is identified.

Identifying the Risk for Sudden Death

Given the annual incidence of 1% for sudden death, identification of those patients at risk is challenging. Factors contributing to increased risk include a family history of sudden death, syncope, especially when exertional, repetitive nonsustained ventricular tachycardia, exercise-induced hypotension, and extreme left ventricular septal hypertrophy.[17,18] It is unclear in children whether indexed or absolute measurements of mural thickness should be used to assess risk. This is an issue of considerable importance, since extreme hypertrophy may be the most important risk factor for sudden death. Although it may contribute to symptoms and further progression of left ventricular hypertrophy, there is no evidence that the degree of obstruction across the outflow tract contributes directly to the risk of sudden death.

Prevention of Sudden Death

Given the dismal outcome for patients suffering cardiac arrests out of hospital, primary prevention of sudden death offers the best chance of improving survival. The low frequency of occurrence in a relatively uncommon disease, with the risk of sudden death spread over many years, has precluded the ability of prospective randomized trials to assess the efficacy of any treatment. The prolonged period of risk also implies that the patient is also exposed for a prolonged period to the potential detrimental effects of the chosen therapeutic modality. Use of beta blockers has shown a modest reduction in sudden death in a diverse group of cardiac diseases, especially ischaemic heart disease. Given their long-term safety profile, use of beta blockers appears justified in preventing sudden death in those with hypertrophic cardiomyopathy. Indeed, one retrospective report showed no sudden death in children receiving high doses of beta blockers.[19] The topic, nonetheless, is controversial. This opinion is not

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shared by many experts in the field. In the limited experience available from patients having appropriate discharges from implantable cardioverter defibrillators, many were receiving beta blockers or amiodarone, thus providing indirect evidence of the lack of efficacy of antiarrhythmic therapy. Amiodarone is probably the most rigorously studied of all the antiarrhythmic drugs in those with both ischaemic and non-ischaemic substrates. A small but consistent reduction in arrhythmic sudden death has been offset by increase in mortality due to its systemic toxicity.[20,21] Consequently, it appears to have little to offer in a condition like hypertrophic cardiomyopathy, where the risk is spread over decades.

The proven efficacy in randomized prospective trials of the implantable cardioverter defibrillator in reducing mortality when used both for primary and secondary prophylaxis in ischaemic and non-ischaemic cardiomyopathy[22] has encouraged its use in other situations, where its efficacy cannot be tested in an equally rigorous fashion. Retrospective studies in the primary prevention of sudden death with the implantable cardioverter defibrillator in hypertrophic cardiomyopathy have shown that appropriate shocks are effective in terminating spontaneously occurring episodes of ventricular tachycardia or ventricular fibrillation that would, presumably, have resulted in sudden death.[22–24] Implantation of a cardioverter defibrillator, however, is far from ideal, especially in children, in whom a substantial number of device-related complications, including inappropriate shocks, dislodgement of fracture of leads, malfunctions of the device, and infections have been reported.[25] In addition, it can be difficult to place either endocardial or epicardial devices in small children. In the absence of any other effective therapy, nonetheless, implantation of a cardioverter defibrillator should be considered to be the mainstay of therapy for secondary and primary prevention of sudden death.

Septal Myectomy in Obstructive Hypertrophic Cardiomyopathy

Left ventricular septal myectomy is the gold standard for treatment of patients with severe symptoms due to obstructive hypertrophic cardiomyopathy that are unresponsive to medical therapy.[26,27] While the early surgical experience was associated with complications of complete heart block, production of ventricular septal defects, injury to the aortic or mitral valves, and incomplete relief of obstruction, this is uncommon in the current era. The transaortic approach remains the primary method of extended left ventricular septal myectomy. A decrease in the gradient is accomplished by physical enlargement of the outflow tract, and by interruption of the pathophysiological sequence of events, primarily systolic anterior motion of the aortic leaflet of the mitral valve, which are responsible for the obstruction.[26] Complete relief of the obstruction by septal myectomy also eliminates the mitral regurgitation caused by the systolic anterior motion of the mitral valvar leaflet. Residual mitral regurgitation after adequate myectomy is usually due to intrinsic mitral valvar pathology, for example, ruptured cords, prolapse of leaflets, or annular dilation. These can be corrected by direct and appropriate valvar repair. Replacement of the mitral valve is reserved for patients with primary valvar pathology that is not amenable to repair.

Indications for Operation

Symptoms of dyspneoa, chest pain, pre-syncope, syncope, fatigue, and orthopneoa or paroxysmal nocturnal dyspneoa may result from an obstructed left ventricular outflow tract. Despite appropriate adjustment of medications, symptomatic relief can be incomplete, transient, or accompanied by intolerable side-effects. In such patients, septal myectomy is the preferred treatment when the resting or provocable gradient is greater than 50 mmHg.[28,29] Surgery may also be advised in children who are asymptomatic, or mildly symptomatic with gradients of between 75 and 100 mmHg at rest.[28] In these patients, the operative risk is around 1%, and relief of obstruction is predictably good. Importantly, surgery for obstructive hypertrophic cardiomyopathy, especially for children, should be confined to centers with significant volume, and with known risk of mortality of no more than 1 to 2%.

Surgical Technique

Over the last 3 decades, septal myectomy has evolved from the classic myectomy to a more extended left ventricular septal myectomy.[30] Intraoperative transoesophageal echocardiography is used routinely to evaluate the anatomy and thickness of the septum, and mitral valvar function. Standard median sternotomy is performed, and intracardiac pressures are measured directly in the left ventricle and aorta. If the measured gradient is less than 30 mmHg because of the conditions of anaesthesia, provocation with isoproterenol is performed to determine the maximal gradient. Cardiopulmonary bypass is used with cross clamping and cardioplegia. Exposure is via an aortotomy. Visualization of the ventricular septum is facilitated by posterior displacement of the left ventricle with a forceps, a rake retractor being used to engage the distal septum. The septal incision is begun at the

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base of the right aortic sinus, and continued leftward towards the mitral valve. Importantly, the incision is carried apically beyond the point of contact of the mitral valvar leaflet with the septum, usually marked by a fibrous friction lesion. The resection is extended leftward toward the hinge of the mitral valve, and apically to the bases of the papillary muscles. Resection of the apical third of the septum to the right of the incision in the aortic sinus is then performed, effectively making a much wider trough at the midventricular level. The methods of extended myectomy as described can be difficult in children, when the orifice of the aortic valve is small. This results in the inability to perform a complete myectomy, and a greater likelihood of residual obstruction. In addition, there is more likelihood of injury to the mitral and aortic valves. For all of these reasons, minimally invasive techniques, for example, robotics, are not used in this setting. The most common reason for residual obstruction is incomplete extension of the septectomy toward the middle of the left ventricle. After separation from bypass, pressures are measured again in the left ventricle and aorta, and transoesophageal echocardiography is repeated. If successful myectomy has been performed, there will be little or no residual gradient, and little or no systolic anterior motion of the leaflet of the mitral valve. In general, bypass would be resumed for re-resection if the gradient were from 15 to 20 mmHg, or if there was persistent systolic anterior motion of the aortic leaflet of the mitral valve.

Outcome of Septal Myectomy

Symptomatic children with obstructive hypertrophic cardiomyopathy have a higher annual rate of death, at 6%, compared to adults.[31] Although the operation is technically more challenging because of the difficulty of exposure of the smaller structures, there is a role for surgery in children. Experience with left ventricular septal myectomy at the Mayo Clinic now exceeds 2,000 patients. Between December, 1972, and January, 2009, 95 consecutive patients below the age of 21 years of age, with a median age 15 years, and a range from 2 months to 21 years, of whom three-fifths were male, underwent septal myectomy at our institution without early mortality. In order to determine if surgical relief of the obstructed left ventricular outflow tract had a favourable influence on outcome, we analysed the initial cohort of 56 patients who underwent myectomy between April, 1975, and April, 2003.[32] Medical therapy had failed in all patients, and 12 patients had undergone implantation of dual-chamber pacemakers without improvement. Intraoperative

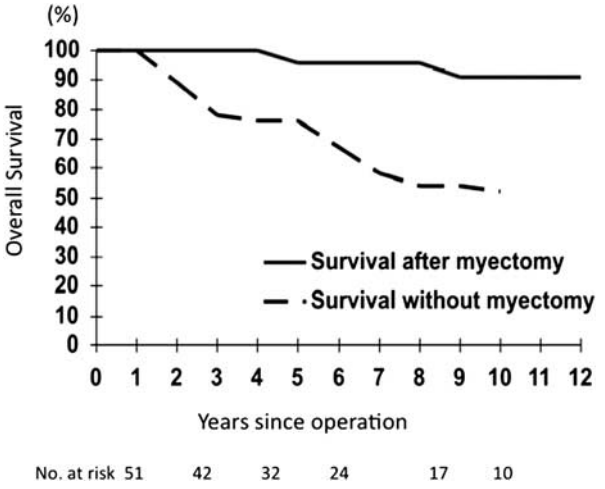

Figure 3.
Probability of survival after septal myectomy compared with the survival curve for symptomatic children treated non-surgically as reported by McKenna and colleagues.[31]

gradients were 60 ± 27 mmHg before the myectomy, and 6 ± 6 mmHg afterwards. Late cardiac reoperations were required in 8 patients, transplantation of the heart in 2, repeated myectomy in 2, epair or replacement of the mitral valve in 2, a Konno-Rastan procedure in 1, and replacement of the aortic valve in the other. An age of 14 years or less at operation was the only predictor for reoperation. Follow-up ranged to 29 years, with a mean of 8.6 years. We found that 2 patients had died subsequently, one suddenly without residual obstruction across the left ventricular outflow tract, and the other from chronic rejection after cardiac transplantation. At late follow-up, the gradients measured by echocardiography remained low, with a mean of 11 mmHg. All patients but one were in the first or second classes of the system devised by the New York Heart Association. As is true for adults, therefore, we have shown that extended septal myectomy is a safe and effective means of relieving cardiac symptoms and obstruction in the left ventricular outflow tract in children with hypertrophic cardiomyopathy. Late survivorship compared very favourably with the natural history of the disease, in which there is an annual mortality rate as high as 6% in symptomatic patients evaluated in tertiary referral centers (Fig. 3).

As we have already discussed, obstruction within the left ventricular outflow tract has been found to be a strong independent predictor of progression to severe cardiac failure, stroke, and the relative risk of death.[10] Whether relief of obstruction by septal myectomy also prolongs life has been an important but largely unresolved issue, due to the impracticality and ethical considerations involved in designing a controlled trial comparing patients

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randomized to surgery and other treatments. Previous reports,[33,34] and a recent large retrospective and controlled analysis in adult patients,[35] suggest that myectomy results in excellent long-term survival. and may improve the natural history of the disease. After septal myectomy, long-term actuarial survival was 99%, 98%, and 95%, at 1, 5, and 10 years, respectively, when considering mortality related firectly to hypertrophic cardiomyopathy. This survival did not differ from that expected in a matched general population in the United States of America. It was superior to that achieved in patients with hypertrophic cardiomyopathy and obstructed left ventricular outflow tracts not submitted to surgery.[35] Furthermore, myectomy was also associated with reduced long-term risk for sudden cardiac death.[35] These findings, of course, were noted in adult patients. Larger numbers of children undergoing myectomy are required before a similar analysis can be performed to assess the benefits in childhood. Surgical myectomy, furthermore, does not eliminate the need to assess the risk of each patient for sudden cardiac death. Nor does it eliminate the need to consider implanting a cardioverter defibrillator in those with a significant burden of risk, such as those with a positive family history of sudden cardiac death, "massive" left ventricular hypertrophy, non-sustained ventricular tachycardia, and so on.

Although the basic transaortic approach for performing a septal myectomy has been known for over 40 years, the operation remains technically challenging, and the results are dependent on the skill of the surgeon. While myectomy can be performed successfully in children, and even infants, adequate resection may be compromised by the small size of the aorta and limited visibility of the midventricular region. Poor visualization of the anatomy below the aortic valve can result in injury to the aortic or mitral valves, while incorrect placement of incisions, or excessive muscular resection or traction, can produce heart block or a ventricular septal defect. These limitations account in part for the need for reoperation at a later age for some children.[36]

Septal myectomy, nonetheless, effectively relieves obstructed left ventricular outflow tracts and cardiac symptoms in both adults and children with obstructive hypertrophic cardiomyopathy. In experienced centers, operative mortality for isolated myectomy in both children and adults is low, and late results continue to improve. Children are more likely to need reoperation when complete elimination of the gradient cannot be achieved at the initial operation because of difficulties in exposure, or because of ventricular remodeling resulting in recurrent obstruction.

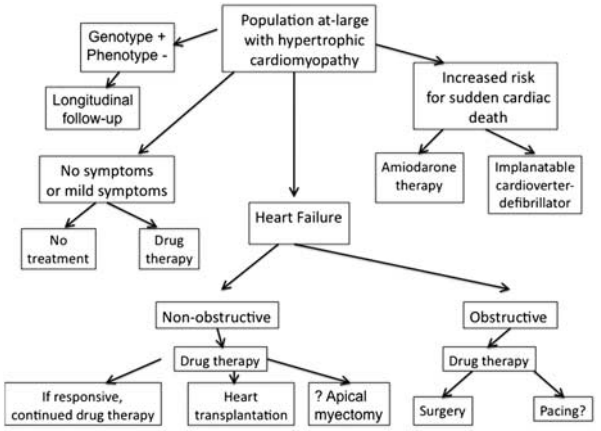

Figure 4.
A flow chart summarizing the potential treatment for children and adolescents with hypertrophic cardiomyopathy.

Conclusions

Hypertrophic cardiomyopathy is a complex disease with variation in presentation, symptoms, severity, and response to therapy. In Figure 4, we summarise the options for treatment, providing in our opinion a reasonable approach to the care of children and adolescents with this disease.

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