Published in final edited form as:

Heart Fail Clin. 2010 October ; 6(4): 433–444. doi:10.1016/j.hfc.2010.05.004.

Hypertrophic Cardiomyopathy in Childhood

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Keywords

cardiomyopathy; hypertrophic cardiomyopathy; sudden death; pediatrics; children; infants

Hypertrophic cardiomyopathy (HCM) is defined as the presence of a hypertrophied, non-dilated ventricle in the absence of another disease that creates a hemodynamic disturbance that is capable of producing the existent magnitude of wall thickening (eg, hypertension, aortic valve stenosis, catecholamine secreting tumors, hyperthyroidism, etc). HCM accounts for 42% of childhood cardiomyopathy and has an incidence of 0.47/100,000 children¹ and represents a heterogeneous group of disorders with a diversity that is more apparent in childhood than at any other age. It is possible to further subdivide these diseases based on a number of characteristics. A classification is presented in List 1 based on groupings of familial, syndromic, neuromuscular, and metabolic (storage disease and mitochondrial disorders). Other classification schemes are commonly used, including division into primary and secondary forms, where the primary form is a familial disorder ("familial hypertrophic cardiomyopathy", FHC) typically devoid of findings outside of the heart, and the secondary forms include diseases such as Friedreich ataxia² where ventricular hypertrophy is common but is not the dominant clinical manifestation and others, such as glycogenosis Type IX³, in which a systemic disorder has primarily or exclusively cardiac manifestations.

Most of the available information for HCM derives from studies in adult populations, and the implication of these observations for pediatric populations is often uncertain. The purpose of this review is not to attempt to review the vast body of literature that has accumulated about HCM but rather to summarize key findings and to discuss their implications for diagnosis and management of children with HCM.

Epidemiology and Survival

The Pediatric Cardiomyopathy Registry is a multicenter observational study of pediatric cardiomyopathies initiated in 1995 that in 2003 reported the sex, age, and race-specific incidence of the several forms of cardiomyopathy based on 2 geographically diverse sections of the United States¹. Of note, the incidence of HCM was found to be 69% more common in males, occurred at 10 times the rate in subjects under age 1, and was significantly more common in blacks than in whites or Hispanics. Subsequently, the distribution of etiologies and the etiology-specific survival in 849 children, the largest series to date, was reported⁴. Overall,

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there was nearly equal distribution between inborn errors of metabolism (IEM, 9%), malformation syndromes (MFS, 9%), and neuromuscular disorders (NMD, 8%), with the remaining 75% represented by the idiopathic and FHC patients. The mean age at diagnosis was under 6 months in the IEM and MFS groups whereas the other groups were typically older at the time of diagnosis. Survival was found to be etiology- and age-specific confirming that survival in infants is much poorer than in older groups but documenting that this can be attributed to the high incidence of IEM and NMD at this age whereas the survival for patients with NMD and FHC was similar regardless of age at diagnosis (Figure 1). A notable observation was that annual mortality in children with FHC was 1.1 per 100 patient-years, which compares favorably with contemporary reports in adults with FHC. This finding contrasted to earlier and smaller series in children that reported much higher annual mortality.

Infantile Hypertrophic Cardiomyopathy

The infant with HCM represents a particularly difficult challenge with regard to determining an etiologic diagnosis due to the wide range of disorders for which an association has been reported (List 1). Successful determination of a specific diagnosis is likely to have significant impact on management and survival because of the differences in etiology-specific survival. Although the pace of advances in genetic and metabolic diagnostics has quickened and the chances that a specific diagnosis can be achieved has improved substantially in recent years, about 50% of HCM cases under age 1 remain idiopathic⁴. Amongst those patients for whom a defined etiology is identified, a few disorders (Pompe disease, Noonan syndrome, and FHC) account for the largest percent and etiologic diagnosis in the remainder is far more difficult. From the cardiac perspective, the association of particular patterns of the cardiac phenotype with specific etiologies has been an area of considerable interest because of the potential to guide the evaluation. For example, the finding of a hypertrophic, hypokinetic left ventricle has been most frequently associated with IEM, and in particular with mitochondrial defects. Biventricular outflow tract obstruction is more common in Noonan syndrome than in other forms of infantile HCM. Asymmetric patterns of hypertrophy are more commonly seen in syndromic and familial HCM than in IEM. Although these sorts of observations can provide some guidance, for most infants with HCM early referral for multi-specialty evaluation including specialists in cardiology, neurology, genetics, and metabolism is warranted.

Familial Hypertrophic Cardiomyopathy

Genetics

The genetic transmission of FHC is usually autosomal dominant, with a significant percentage of cases representing apparently new mutations. Maternally inherited mitochondrial pattern of transmission has also been reported⁵, adding to the complexity of the disease. There has been a virtual explosion of information since the early 1990's concerning the genetic abnormalities associated with this disorder. One of the most striking findings has been the sheer number of diverse mutations that manifest clinically as HCM. The results of molecular studies so far have implicated a number of sarcomeric proteins in the etiology, including beta-myosin heavy chain, alpha-myosin heavy chain, myosin essential light chain, myosin regulatory light chain, cardiac troponin T, cardiac troponin I, alpha-tropomyosin, and myosin binding protein C, titin, and actin⁶. These gene mutations display allelic heterogeneity; that is, multiple distinct mutations of each of these genes can cause the disease. The frequent finding of mutations in the sarcomeric proteins resulted in the paradigm of FHC as a disease of the sarcomere⁷, an understanding that has been disrupted by the more recent identification of mutations in genes encoding non-sarcomeric proteins within the z-disc and calcium handling control mechanisms that result in a similar phenotype⁶. There are also familial forms of HCM due to non-sarcomeric genes, such as those due to mitochondrial defects, potassium channel⁸, and the gamma subunit of protein kinase A⁹. Although sarcomeric defects appear to be the most common cause of FHC,

they are not the only cause. Furthermore, at present the genotype responsible for the HCM phenotype cannot be determined in 30–40% of patients.

Commercially available genetic testing for some of the more common mutations causing FHC is a relatively recent event and one that has stimulated considerable discussion concerning who should have this testing performed. Although certain mutations may imply greater or lesser risk, the expectation that genotyping would markedly improve risk stratification and clinical management has been largely undercut by recent data¹⁰. For example, mutations in troponin T were initially reported to have a consistent phenotype of mild or absent hypertrophy associated with a high incidence of sudden death¹¹, but families have been described with troponin T defects who have a low risk of early death¹². Other factors, such as the coexistence of mitochondrial DNA mutations in some families¹³, multiple mutations¹⁴, or the impact of coexistent genetic polymorphisms within the renin-angiotensin system¹⁵ account for some of the variability in disease expression. It has been argued that detection of gene carriers in FHC may have too little impact on clinical care to justify the cost and the potential for adverse psychological and social consequences¹⁶.

Implications for pediatrics—For infants, children, and young adults there are several benefits that are not considered in the foregoing analysis. One of the most feared complications of HCM in children and young adults is diagnosis of the disease at the time of sudden death. The potential to avert such events rests on diagnosis of the disease in asymptomatic children. Because development of the phenotype can be noted throughout childhood, current practice is to periodically screen offspring of affected individuals throughout childhood. Identification of a familial gene allows children who are genotype negative to avoid longitudinal evaluation for development of hypertrophy, markedly reducing the overall cost of care, in addition to anxiety reduction and elimination of concerns about exercise participation. Those children who carry the gene can be followed more closely for development of disease and they also become eligible for trials of interventions to prevent development of the phenotype. The potential to prevent the onset of hypertrophy remains an unproven hypothesis in humans although a mouse model of myosin heavy chain HCM treated prior to the onset of hypertrophy with diltiazem had less hypertrophy, fibrosis, and myocyte disarray than placebo-treated mice¹⁷, and a clinical trial in phenotype negative, genotype positive children and young adults is currently in progress.

The phenomenon of incomplete penetrance (a negative phenotype in genotype positive adult members of a pedigree) has been well described in familial HCM and appears more common than has been previously believed. One of the implications of this finding is that all children in the pedigree, even offspring of phenotype negative parents, must be considered at risk and should undergo longitudinal evaluation for development of the phenotype unless the parents can be shown to be genotype negative. As a corollary, adult members of the pedigree who are found to carry the gene can be advised that they are at risk for transmitting the gene even if they are phenotypically negative. Finally, identification of the gene permits use of the relatively new technique of embryo pre-selection to allow carriers of the gene to avoid transmission to their offspring.

Diagnosis

The diagnosis of HCM in infants is generally made during evaluation for a murmur or for congestive heart failure. Older children are diagnosed during investigations for murmurs, symptoms (impaired exercise capacity, chest pain, palpitations, or syncope), electrocardiographic abnormalities, and screening of offspring of affected adults. The echocardiogram provides definitive noninvasive assessment of ventricular size, wall thickness, systolic and diastolic function, outflow obstruction, and valvar insufficiency in nearly all children. Diagnosis has typically been based on increased regional or global wall thickness and

excess regional variation in thickness. The usual adult criteria for diagnosis are based on an absolute wall thickness above the normal range (>12 mm), resulting in a significant false positive rate. Improved longitudinal observations and the advent of more widespread genotyping have improved the ability to refine these echocardiographic criteria. This issue is of particular importance in distinguishing physiologic from pathologic hypertrophies. Cardiac hypertrophy associated with intense athletic participation is well described in both children and young adults¹⁸. In athletic subjects with mild hypertrophy on echocardiography, findings that increase the probability of HCM include unusual patterns of hypertrophy, small left ventricular cavity size, abnormal diastolic function indices, female gender, family history of hypertrophic cardiomyopathy, and evidence of delayed enhancement with gadolinium on cardiac magnetic resonance imaging (CMRI)¹⁹. Findings that increase the probability of physiologic hypertrophy include left ventricular cavity size near or above the upper limits of normal and elevated peak oxygen consumption on exercise testing. The electrocardiogram is not helpful in making this distinction. Ultimately, if reasonable certainty is not achieved based on these additional criteria, cessation of exercise participation for 6 months can be used to identify subjects with HCM, who will not experience a decrement in wall thickness. Unfortunately, obtaining adequate compliance with this recommendation is challenging in most athletes.

Implications for pediatrics—Use of age and body surface area adjusted normal values is necessary in children. The use of z-scores (defined as the number of standard deviations from the population mean) has been particularly helpful in this regard²⁰. The sensitivity and specificity for specific z-score values relative to diagnosis of HCM in children has not been tested, although in general the range of uncertainty between physiologic and pathologic hypertrophy corresponds to a z-score between 2 and 3, with physiologic hypertrophy rarely resulting in a wall thickness relative to body surface area that is more than 3 standard deviations above the population mean. Studies performed in genotypically positive children have identified a number of echocardiographic and electrocardiographic findings that can be abnormal despite the absence of hypertrophy^{21–23}. In particular, abnormal noninvasive diastolic function indices such as reduced early diastolic tissue velocities, prolonged isovolumic relaxation times, and increased left atrial volume have been described^{23;24}. These findings have important implications concerning the pathophysiology of the disease but the implications concerning diagnosis are more ambiguous. In children with mild hypertrophy, abnormal diastolic function indices make it highly likely that the hypertrophy is not physiologic. However, in the absence of hypertrophy, genotypically positive individuals do not meet the definition of hypertrophic cardiomyopathy, are not known to be at increased risk for sudden death, and do not manifest symptoms. Furthermore, it is unclear whether all genotype positive, phenotype negative individuals will manifest hypertrophy over time. Although the term “hypertrophic cardiomyopathy without hypertrophy” has been used, the implication that disease status should be based on genetic status rather than phenotype remains unclear. This uncertainty is apparent in the conflicting exercise guidelines issued by the 36th Bethesda Conference and the European Society of Cardiology recommendations for sports participation, with the European but not the American group recommending against participation in phenotypically negative, genotypically positive individuals²⁵.

Management of symptoms

The goals of therapy in this disorder are to reduce symptoms and prolong survival. The symptoms of chest pain, dyspnea, and exercise intolerance can often be managed medically, and surgery has been successful in certain patient groups. Digitalis is not helpful and is usually contraindicated unless atrial fibrillation occurs. Although dyspnea is a common symptom, diuretic therapy is usually not beneficial, can increase the outflow gradient due to a reduction in chamber volume, and can reduce cardiac output. Outflow tract obstruction plays an important

role with regard to symptom status in HCM. The clinical importance of outflow obstruction has been highly controversial over the years, as recently recounted in some detail by Maron²⁶. Patients with outflow tract obstruction are at greater risk for symptoms and progression to heart failure and death²⁷, and exercise-induced or exacerbated outflow tract obstruction is both common and associated with a higher risk of symptoms²⁸. Reduction in outflow tract obstruction is one of the primary targets of therapy for symptomatic patients. The gradient can be at detected rest or only with provocation such as inotropic stimulation, vasodilation, or exercise and often demonstrates marked spontaneous lability²⁹. Although provocation of latent outflow obstruction with maneuvers such as amyl nitrate has been recommended, the clinical significance of gradients elicited in this fashion remains uncertain, in part due to the difficulty in standardization.

Beta-blockers—The mainstay of therapy for many years has been beta-adrenergic blockade. Chest pain and dyspnea are often relieved by propranolol, but improved exercise capacity is seen less often. The response appears to be dose dependent, and very high dosage levels have often been tried. Side effects such as fatigue, depression, sleep disorders, and impaired school performance are often encountered at these high dosage levels, particularly in children and adolescents, and can be intolerable. Despite early improvement, symptoms often recur, and may not respond to dose escalation. Studies of the impact of beta-blocker therapy on survival in adults and children have invariably been uncontrolled but have not identified a measurable effect of propranolol on survival. In a single uncontrolled study in children, comparison of a small number of pediatric patients in each of two geographically distinct areas, one of which treated all HCM patients with high dose propranolol, found unusually high mortality (52% 10 year survival) in the untreated cohort with no mortality in the treated cohort³⁰. It is difficult to reconcile these findings with the many prior, larger studies that have failed to identify a survival benefit from propranolol and the high mortality in the untreated group is difficult to reconcile with large pediatric studies that have found a 10 year survival of 80% in unselected populations⁴. Differential therapy based solely on geographic location is potentially highly biased due to the potential for genetically similar patients in each geographic region, and the differences in outcome do not exceed those observed between other studies in small groups of pediatric patients with HCM.

Calcium channel blockers—Calcium channel blockers in general and verapamil in particular have been used extensively in patients with FHC. Sustained improvement in diastolic relaxation is generally noted in response to verapamil administration with secondary reduction in diastolic pressure and mean left atrial pressure^{31;32}, resulting in a reduction in dyspnea and increase in exercise capacity. Improved distribution of subendocardial flow and diminished inducible ischemia have been noted as well³³. Although verapamil may exacerbate congestive heart failure in older patients, pediatric tolerance has been excellent, even in neonates³⁴.

Angiotensin converting enzyme inhibitors—Inhibition of the renin-angiotensin system has a favorable impact on ventricular hypertrophy and diastolic function in secondary hypertrophy, but has rarely been used in FHC. Angiotensin converting enzyme inhibitors given to patients with dynamic left ventricular outflow tract obstruction result in a fall in cavity size and increase in outflow gradient, as well as impaired left ventricular relaxation and compliance³⁵. Based on theoretical considerations and data such as these, it is generally believed that these agents as well as other systemic vasodilators are contraindicated in HCM when left ventricular outflow tract obstruction is present. However, there are also recent data indicating a significant role for aldosterone¹⁵ and the renin-angiotensin system in general³⁶ in modulating the phenotypic manifestations of HCM, leading to the suggestion that blocking this system might reduce hypertrophy and fibrosis³⁷.

Pacemaker therapy—Despite a wave of enthusiasm for asynchronous ventricular pacing for treatment of symptoms in patients with left ventricular outflow tract obstruction, this therapy has largely fallen into disfavor. Results in small cohorts of children with outflow obstruction who were symptomatic despite medical therapy noted symptomatic improvement, reduced outflow obstruction, reduced left ventricular hypertrophy, and improved exercise tolerance^{38–40}. Despite early studies⁴¹, subsequent controlled studies found that only about 60% of subjects improved. Furthermore, in 2/3 of these the benefit appeared to reflect placebo effect and an adverse effect on symptoms was seen in 5%⁴². The significant placebo effect has been seen in other studies⁴³, perhaps explaining reports of persistent symptom relief after pacing termination⁴⁴, an effect not confirmed in later studies⁴⁵. Based on current information, dual chamber pacing should at best be considered as an alternative to surgical or transcatheter septal reduction in patients with obstructive FHC who are symptomatic despite maximum medical therapy and are poor candidates for other interventions.

Alcohol Septal Ablation—Direct transcatheter infusion of absolute alcohol directly into septal coronary perforators can result in tissue infarction, reduction in septal thickness, and relief of left ventricular outflow tract obstruction, with symptomatic improvement and increased exercise tolerance. Toxicity has included a 1–2% rate of procedural death, 20–50% incidence of transient heart block and a 10–20% incidence of permanent complete heart block^{46;47}, peri-procedure ventricular arrhythmias that may require cardioversion, unintended distal infarction due to inadvertent alcohol infusion into the anterior descending coronary, and late appearance of complete heart block. Success is highest when obstruction is related to basilar septal hypertrophy. Patients with mitral valve abnormalities or obstruction that is more apical are poor candidates. Late outcome is unknown for this new technique, but current results indicate this may represent a reasonable alternative to surgery for relief of outflow tract obstruction in selected patients⁴⁸. Recently, coil occlusion of these vessels has been reported as an alternative method of inducing controlled infarction⁴⁹. Heart block was not seen in this series, the size of the infarction was smaller than with alcohol ablation, and the reduction in outflow gradient was less. The relative advantages to these two techniques remains to be determined.

Surgical myectomy—In symptomatic subaortic stenosis, septal myotomy-myectomy results in symptomatic improvement in nearly all patients and most contemporary studies have documented a high success rate, near zero mortality, and few complications with the procedure in adults^{50–52}. Results in children have been similar to those reported in adults^{53;54}. Mitral regurgitation often improves in response to myectomy due to improved intraventricular flow patterns and surgery permits concomitant mitral valve repair in patients with underlying mitral valve abnormalities. Although recurrence of obstruction is rare in older patients (2%⁵⁵), it is more frequent in the neonate and infant.

Implications for children—In the absence of symptoms, medical therapies have no proven benefits. Propranolol or verapamil are the first line therapy for symptomatic patients. If symptoms are unresponsive to medical therapy and outflow tract obstruction is present, particularly if associated with mitral regurgitation, reduction or elimination of the outflow gradient should be considered. The technical feasibility of transcatheter septal reduction in adolescents has been demonstrated, though experience in this age group is at present limited to case series. The higher procedural complication rate compared with myectomy and concerns for potential late risks associated with a large infarction have led most clinicians to await longer term results prior to use in children. Younger patients are not considered candidates for this procedure due to the inability to cannulate the smaller coronary feeder vessels in these patients. Therefore, surgical myectomy is generally recommended for management of medically intractable symptoms.

Prevention of Sudden death

Exercise restriction—Avoidance of high intensity exercise is generally recommended for patients with FHC. The rationale for this restriction is based on the observations that sudden death is the usual cause of death in FHC and has a higher than expected association with exercise⁵⁶. Nevertheless, the basis for this recommendation has several serious weaknesses⁵⁷. The true incidence of FHC in athletes who experience sudden death is uncertain since genetic confirmation was not available and diagnosis was based on morphologic criteria that cannot unequivocally differentiate FHC from physiologic hypertrophy. It is clear that some patients with FHC tolerate intense, competitive athletic participation without symptoms or sudden death⁵⁸. Population studies have documented the apparent paradox that although there is a transient increase in the risk for sudden death during intense exercise in patients with coronary artery disease who regularly participate in low and high level exertion, these individuals experience an overall reduction in the risk for sudden death^{59;60}. Additionally, individuals who do not exercise regularly have an exaggerated risk of sudden death during exercise⁶¹. In fact, it is precisely those individuals with cardiovascular risk factors who derive the largest risk reduction from regular participation in moderate to intense exercise⁶¹. Several population studies have now documented that exercise and sports participation during childhood are predictive of activity level in adults⁶². Detraining and social stigmatization are particularly difficult problems for the adolescent who is excluded from the usual school activities and peer interactions. Competitive team sports elicit an emotional overlay that appears to increase the risk associated with the sport itself, in addition to demanding more intense exercise, and can therefore be justifiably proscribed. Certain activities, such as weight lifting, are associated with high levels of circulating catecholamines that can predispose to arrhythmias and elicit a marked stimulus to eccentric cardiac hypertrophy. However, in patients who do not manifest high grade arrhythmias or exercise-induced arrhythmias or hypotension, there is little evidence to indicate that moderate aerobic-type exercise represents a significant risk and it does provide measurable hemodynamic and psychological benefits.

Antiarrhythmics—Although most instances of sudden death in FHC are arrhythmic events, antiarrhythmic therapy has not been effective⁶³. Amiodarone was initially reported to reduce the incidence of sudden death in certain high-risk subgroups, but subsequent studies indicated an increased risk of sudden death⁶⁴. Furthermore, the pediatric experience with amiodarone therapy for FHC is very limited due to the toxicity associated with chronic therapy. The promising early experience with implantable cardioverter defibrillators (ICD) has resulted in a shift to recommending an ICD for patients with ventricular tachycardia on Holter monitor or resuscitated cardiac arrest⁶⁵.

ICD Implantation

The incidence of sudden death in HCM is less than 1% per year in both adults and children and ICDs are not without hazard, including, reduced quality of life, depression, anxiety, and inappropriate discharges that can at times be fatal. Optimization of the risk-benefit for ICD use is therefore dependent on the ability to identify individuals at high risk for sudden death. A number of risk factors for sudden death in adults with HCM have been proposed (List 2), and it is worth noting that this list continues to evolve with the introduction of newly proposed risk factors in addition to both the promotion and demotion of those previously proposed^{66;67}. Very few series have been focused on children, with severity of hypertrophy (wall thickness z-score >6) and an abnormal blood pressure response to exercise having been confirmed as risk factors in young patients^{68;69}. The understanding of several of the proposed risk factors in List 2 has changed based on recent data and these newer findings are worth specific discussion.

Arrhythmias—Ventricular arrhythmias including ventricular tachycardia and fibrillation are common, and are the presumed mechanism of sudden death in most cases. Despite this, there are conflicting data concerning the prognostic implications of non-sustained ventricular tachycardia (NSVT) found on Holter monitor recording in patients with FHC. The presence of asymptomatic NSVT on Holter monitoring has been reported as a risk factor in some series⁷⁰ but not in others^{71;72}. These differences may relate to age distribution included in each study since NSVT is generally associated with a low incremental risk (relative risk 2–2.5) which appears to be higher in adults under age 30 (22% versus 5% 5-year risk of sudden death)⁷⁰. Similarly, in children NSVT on Holter monitoring is less frequent than in adults⁷³ but when present appear to be associated with a higher annual risk of sudden death.

Extreme hypertrophy—Several recent reports have evaluated the impact of the severity of left ventricular hypertrophy on survival and risk of sudden death. Extreme wall thickness, in particular, has been suggested as an important risk factor⁷⁴ and therefore as a potential indication for an implantable cardioverter-defibrillator⁷⁵. Other reports have not confirmed this association^{76–78}. These conflicting data may in part be related to the observation that the increase in risk is primarily incurred in patients presenting under age 30.⁷⁹ Further supporting this concept, severity of hypertrophy has also been found to be a risk factor in children⁶⁸.

Outflow tract obstruction—The clinical importance of outflow obstruction has been highly controversial over the years, as recently recounted in some detail by Maron²⁶. The reduced survival in patients with outflow tract obstruction has been primarily related to death due to congestive heart failure²⁷ with at most a small increase in risk of sudden death. Most studies have failed to identify any relationship to sudden death⁸⁰. Surgical or pharmacologic reduction in the outflow gradient in symptomatic patients is usually associated with a reduction in symptoms and possibly improved overall survival, although there are no data to suggest that the incidence of sudden death is reduced. In patients with an ICD, a reduction in “appropriate discharges” after myectomy has been documented and has been proposed as a surrogate for a reduction in sudden death⁸¹. However, the accuracy of this surrogate is questionable since “appropriate discharges” occur at a far higher rate than the expected rate of sudden death. Based on current data, intervention based on gradient alone or for the purpose of averting sudden death cannot be recommended.

Myocardial Bridging—Muscle bands overlying epicardial coronary arteries (myocardial bridges) are congenital and sufficiently common that they are considered an anatomic variant rather than a congenital anomaly, having been observed in 20 to 66% of hearts⁸². In a provocative report of a relationship between sudden death and the presence of myocardial bridging in children with FHC⁸³, Yetman et al suggest that surgical unroofing of the coronary can prevent sudden death. It is unclear why myocardial bridges would have a greater impact on children than has been described in adults, where bridging is extremely common and does not appear to represent a risk for sudden death⁸⁴. Perhaps more troubling is the observation in this report⁸³ that patients with bridges were older than the patients without, and the overall incidence (28%) was identical to the frequency described in adults (30%⁸⁵) in contrast to the diminishing prevalence that would be anticipated in a congenital disorder that represents a risk for sudden death. Thus, although surgical intervention is possible⁸⁶, further confirmation is required before myocardial bridging can be accepted as an adverse risk factor worthy of surgical intervention.

Syncope—Unexplained syncope (that is, excluding neurally-mediated syncope) has been identified as a risk factor for sudden death in adult series, but the relative risk was only 1.8⁸⁷, although the risk was much higher in patients <18 years of age (hazard ratio 8), although

the limited number of children and adolescents in this series limits the strength of the conclusion. Interestingly, recurrent episodes did not appear to increase this risk.

Delayed hyper-enhancement on magnetic resonance imaging (DHE-MRI)—DHE-MRI has been identified as a sensitive imaging technique for myocardial scar, correlating with histologically proven myocardial fibrosis⁸⁸. Myocardial scar is a known risk factor for ventricular arrhythmias and DHE-MRI is noted more frequently in patients with HCM who manifest NSVT than those who do not^{89;90}. Based on current data, the increase in 5-year risk of sudden death in adults with DHE-MRI has been estimated at 1.6⁹¹.

Implications for children—With the exception of aborted sudden death, the various clinical parameters associated with increased risk of sudden cardiac death have low positive predictive value. The presence of multiple risk factors incurs higher risk, leading to the recommendation that ICD use should be limited to patients who manifest multiple risk factors⁷⁸. Nevertheless, current methods for risk stratification remain inadequate insofar as, based on current ICD utilization rates after implantation in high risk subjects and an anticipated device lifespan of 5 years, 83% of devices will not be used prior to replacement⁹². This dilemma is further compounded in children, for whom the risk-benefit ratio for the use of ICD's is less favorable than in adults. In a recent review, 28% of children experienced appropriate, potentially life-saving ICD discharges, 25% experienced inappropriate discharges, and there was a 21% incidence of lead failure⁹³. Children are also at higher risk for device-related infections and adverse psychosocial impact than adults. Therefore, although potentially life-saving, pediatric-specific implantation indications must be developed and tested before this technology will achieve its full potential in children. At present, our institution has adopted an age-adjusted management approach. Aborted sudden death is considered an indication for ICD regardless of age. An ICD is recommended for adolescents with two or more of the other accepted risk factors. For pre-adolescents, additional evidence of risk is required before primary prevention is considered.

Summary

This review emphasizes the recent data concerning the etiology, natural history, management, and outcome in the diverse set of diseases that fall within the clinical phenotype of hypertrophic cardiomyopathy. Changes in the understanding of the genetics of familial hypertrophic cardiomyopathy and the escalating clinical utility of genotyping, particularly in children, are discussed. There is a large observational literature concerning familial hypertrophic cardiomyopathy in adults with a much smaller body of data in children. This review summarizes those situations in which the findings in children have been found to be different from the information available from adult cohorts and emphasizes how certain of the management recommendations must be modified when applied to pediatric patients.

Synopsis

Hypertrophic cardiomyopathy has important differences in children compared with adults, particularly with regard to the range of causes and the outcomes in infants. Survival is highly dependent on etiology, particularly in the youngest patients, and pursuit of the specific cause is therefore necessary. The clinical utility of defining the genotype in children with familial hypertrophic cardiomyopathy exceeds that at other ages and has a highly favorable cost-benefit ratio. Although most of the available information concerning treatment and prevention of sudden death is derived in adults, management of children requires consideration of the differences in age-specific risk:benefit ratios.

Acknowledgments

This work was supported by Grant No. 5 R01 HL53392-09 from the National Institutes of Health

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Figure 1.
Percent survival as a function of age in children with hypertrophic cardiomyopathy (HCM) due to various classes of etiology.

List 1**Phenotypically-based classification of hypertrophic cardiomyopathy**

Familial Hypertrophic Cardiomyopathy

Sarcomeric Hypertrophic Cardiomyopathy

Maternally-Inherited Hypertrophic Cardiomyopathy Syndromes

Syndromic Hypertrophic Cardiomyopathy

Noonan's Syndrome

Beckwith-Wiedemann Syndrome

Cardio-facial-cutaneous syndrome

Costello syndrome

Lentiginosis (LEOPARD Syndrome)

Neuromuscular disease

Friedreich's Ataxia

Metabolic Disorders

Anabolic steroid therapy and abuse

Carnitine deficiency (Carnitine palmitoyl transferase II deficiency, carnitine-acylcarnitine translocase deficiency)

Fucosidosis type 1

Glycogenoses type 2, 3 and 9 (Pompe's disease, Forbes' disease, Phosphorylase kinase deficiency)

Glycolipid lipidosis (Fabry Disease)

Glycosylation disorders

I-Cell disease

Infant of diabetic mother

Lipodystrophy, total

Lysosomal disorders (Danon's Disease)

Mannosidosis

Mitochondrial disorders (multiple forms)

Mucopolysaccharidoses type 1, 2 and 5 (Hurler's syndrome, Hunter's syndrome, Scheie's syndrome)

Pre and postnatal Corticosteroid therapy

Selenium deficiency

List 2

Risk factors for Sudden Death in HCM

Generally Agreed	Conflicting or Insufficient Data
Aborted sudden death	Left ventricular outflow tract obstruction
Non-sustained ventricular tachycardia	Late hyper-enhancement on MRI
Family history of sudden death	Specific, "high risk" mutations
Syncope	Atrial fibrillation
Extreme hypertrophy	Myocardial bridging
Abnormal blood pressure response to exercise	