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Hypertrophic Cardiomyopathy in Infants and Children

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1. Introduction

The definition and classification of the cardiomyopathies has been traditionally a complex and quite variable subject. In 2006, the American Heart Association issued a scientific statement elaborated by a task force of experts that contemplated the important development of molecular genetics in recent years, to explain the etiology of the diseases of cardiac muscle, or cardiomyopathies, previously considered idiopathic (B.J. Maron et al., 2006a). The document stated that “Cardiomyopathies are an heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction that usually, but not always, exhibit inappropriate ventricular hypertrophy or dilation, and are originated by a variety of causes, frequently genetic. Cardiomyopathies involve just the heart or are part of systemic disorders that often lead to cardiovascular death or heart failure related disability”. Myocardial damage secondary to coronary atherosclerosis, heart valve disease, congenital heart disease, and systemic hypertension, is excluded from this definition. Primary or metastatic cardiac tumors and diseases primarily affecting the endocardium with minimal or absent myocardial damage neither are included. The document also discourages the use of the classical terminologies hypertrophic, dilated, and restrictive cardiomyopathies because they have overlapping features and often mutate from one type to another during the course of the disease. Cardiomyopathies are then classified into 2 groups, *primary* when there is only heart involvement, and *secondary* if the heart is affected by systemic diseases with multiorganic involvement. (Table 1) *Primary cardiomyopathies* are divided into *genetic*, *acquired*, and *mixed* (genetic and acquired).

GENETIC	MIXED	ACQUIRED
Hypertrophic	Dilated	Inflammatory
Arrhythmogenic Right Ventricular	Restrictive	Tako-tsubo
Noncompaction		Peripartum
Glycogen Storage		Tachycardia-induced
Mitochondrial		Infants of diabetic mothers
Conduction Defects		
Ion Channelopathies		

Table 1. Classification of the primary cardiomyopathies (modified from B.J. Maron, et al., 2006a).

A salient feature of this classification is the inclusion of *ion channelopathies* caused by gene coding mutations of Na, K, and Ca channels. These channelopathies may result in deadly ventricular arrhythmias and can only be identified by molecular genetic studies since no structural cardiac damage is objectified. The Brugada syndrome, the long and short QT syndromes, the catecholaminergic polymorphic ventricular tachycardia, and the unexplained nocturnal sudden death in Southeastern Asian youngsters belong to the channelopathies. Some conduction disorders are also included in the classification.

In contrast with the American Heart Association point of view, the European Society of Cardiology issued a report in the year 2008 with an updated definition and classification of the cardiomyopathies (Elliot et al., 2008). (Table 2) It was there stated that “Cardiomyopathies are structural and functional myocardial diseases in the absence of systemic hypertension, coronary atherosclerosis, valvulopathies, or congenital heart disease sufficient to explain the observed abnormality”. Therefore, *hypertrophic cardiomyopathy* was defined as “Increased ventricular thickness or mass in the absence of loading conditions sufficient to cause the observed abnormality”. This definition better reflects the terminology used in pediatrics (Elliot et al., 2008; Franklin et al., 1999). With regard to the classification, it was based on the identification of phenotypes according to their structural and functional features recognizing the following cardiomyopathies: *hypertrophic, dilated, restrictive, arrhythmogenic right ventricular, and unclassified* (Colan et al., 2007). Every phenotype could be *familial* or *non-familial* emphasizing the role of genetics in some cardiomyopathies and orienting the etiologic diagnosis. The differentiation between primary and secondary cardiomyopathy is then abandoned. *Left ventricular non-compaction* and the *takotsubo cardiomyopathy* are included in the group of unclassified cardiomyopathies. The European Society of Cardiology experts do not believe that *channelopathies* and *conduction disorders* should be considered as cardiomyopathies. In our opinion, the European Society of Cardiology classification is more user-friendly for general physicians.

CARDIOMYOPATHIES				
HCM	DCM	ARVC	RCM	Unclassified
FAMILIAL/ Unidentified gene defect		GENETIC Disease sub- type		NON- FAMILIAL/ Idiopathic
				NON- GENETIC Disease sub- type

HCM: hypertrophic cardiomyopathy, DCM: dilated cardiomyopathy, ARVC: arrhythmogenic right ventricular cardiomyopathy, RCM: restrictive cardiomyopathy.

Table 2. European Society of Cardiology classification of primary cardiomyopathies (modified from Elliot, et al., 2008).

2. Classification

Though hypertrophic cardiomyopathy was first recognized by Liouville in France in 1869, (Liouville, 1869, as cited in Marian, 2007), it was not until the 1950's that was rediscovered in Britain by Brock and Teare (Brock & Fleming, 1956; Teare, 1958). Initial reports emphasized

the presence of left ventricular outflow tract obstruction until it was realized that this could be absent (B. J. Maron et al, 2009). Since then, two main types of hypertrophic cardiomyopathy were distinguished, with or without obstruction. Nowadays, we know that hypertrophic cardiomyopathy, is the most frequent monogenic disorder in cardiology and the commonest cause of sudden death in youngsters in either form of presentation (J. Seidman & C. Seidman, 2001).

Regardless of the presence or absence of obstruction, hypertrophic cardiomyopathy is classified into two main groups, *familial* and *non-familial*. (Table 3) The latter comprises 4 subgroups: hypertrophic cardiomyopathy associated with *obesity, infants born to diabetic mothers, athlete's heart, and amyloidosis*. This chapter will mainly address the *familial forms* of hypertrophic cardiomyopathy also composed of 4 subgroups: *sarcomeric*, and 3 others in association with *malformation syndromes, inborn errors of metabolism, and neuromuscular disorders* (Elliot et al., 2008). The sarcomeric forms are the most frequent and have an autosomal dominant inheritance. They are caused by missense mutations of genes encoding the contractile proteins of the sarcomere. A mutation involves the change of a DNA base for another resulting in the replacement of an aminoacid in a polypeptide for another. Though readable, the meaning (sense) of the genetic message is changed. Considerable genetic and phenotypic heterogeneity is found in hypertrophic cardiomyopathy. In other words, different gene mutations may cause similar phenotypes or on the contrary, the same gene may result in dissimilar ones. The presence of modifying genes, like that encoding angiotensin II, environmental influences, gender, and associated conditions might explain some of these dissimilarities (Alcalai et al., 2008). About 20 genes carrying a great number of mutations have already been identified in hypertrophic cardiomyopathy (Kim et al., 2011). (Table 4) However, just 3 of them, beta-myosin heavy chain (*MYH7*), myosin binding protein C (*MYBPC3*), and troponin T (*TNNT2*) are responsible for almost 75% of the cases, thence, the remaining are rare. The genes involved in pediatric hypertrophic cardiomyopathy have a similar frequency and distribution as in adult patients (Kaski et al., 2009).

FAMILIAL	NON-FAMILIAL.
Sarcomeric	Associated with obesity
Associated with malformation syndromes	Infants born to diabetic mothers
Associated with inborn errors of metabolism	Athlete's heart
Associated with neuromuscular disorders	Amyloidosis

Table 3. Classification of the hypertrophic cardiomyopathies (modified from Elliot et al., 2008).

It has been suggested that the genotype might have an influence in the prognosis in hypertrophic cardiomyopathy. Patients with *MYH7* mutation would have more severe ventricular hypertrophy and present earlier in life, those with *TNNT2* would have less left ventricular hypertrophy but higher risk of sudden death, and late onset of the disease and favorable prognosis would be found in patients with *MYBPC3* mutation (Moolman et al., 1997; Niimura et al., 1998; Watkins et al., 1992). Nevertheless, a more recent study showed that regardless of the gene mutation, patients with a positive molecular genetic study, had a higher risk of cardiovascular death, stroke, worse functional class, diastolic and systolic left ventricular dysfunction, and that the long term outcome was worse for patients carrying

more than one mutation. (Bos et al., 2009) The latter finding was not corroborated in children. (Kaski et al., 2009).

GENE	PROTEINS	GENE	PROTEINS
MYH7	β -Myosin heavy chain	TTN	Titin
MYH6	α -Myosin heavy chain	LBD3	LIM binding domain 3
MYBPC3	Cardiac myosin binding protein C	CSRP3	Muscle LIM protein
TNNT2	Cardiac troponin T	TCAP	Telethonin
TNNI3	Cardiac troponin I	VCL	Vinculin/metavinculin
TNNC1	Cardiac troponin C	ACTN2	α -Actinin 2
TPM1	α -Tropomyosin	MYOZ2	Myozenin 2
MYL3	Myosin essential light chain	JPH2	Junctophilin-2
MYL2	Myosin regulatory light chain	PLN	Phospholamban
ACTC	α -Cardiac actin		

Table 4. Susceptibility genes in hypertrophic cardiomyopathy (modified from Bos et al., 2009 & Kim et al., 2011).

3. Prevalence

The estimated prevalence of hypertrophic cardiomyopathy in the adult population as assessed by echocardiographic screening is 1:500 (B.J. Maron et al., 1995a). However, in pediatrics, the observed prevalence is much lower because hypertrophic cardiomyopathy usually has late gene expression. Large population registries from Australia and the US show a prevalence varying between 0.47 and 1.24:100,000 inhabitants and an occurrence of nearly 25% among all types of cardiomyopathies (Lipschultz et al., 2003; Nugent et al., 2003). In our institution, the incidence of hypertrophic cardiomyopathy was 1.1% for all children with heart disease attending the Division of Cardiology of the Children's Hospital (Bruno et al., 2002).

4. Pathology

4.1 Macroscopic findings

The gross anatomy generally shows severe left ventricular hypertrophy and small cavity size. (Fig. 1) The hypertrophy mainly involves the ventricular septum, and for this reason, one of the early denominations of the disease was *asymmetric septal hypertrophy* (Henry et al., 1973). Notwithstanding, hypertrophy may occur symmetrically or affect other segments like the posterior wall, and the apical or middle sections of the left ventricle (Falicov & Resnekov, 1977; Louie & Maron, 1987; Minami et al., 2011; Yamaguchi et al., 1979). Midventricular obstructive hypertrophic cardiomyopathy is more frequent in Asians with a prevalence of around 10% in tertiary centers and carries a higher risk for adverse events (B.J. Maron et al., 2003a; Minami et al., 2011). Patients with apical involvement are less commonly genotype positive than those with the more frequent variants of the disease but the affected genes are usually the same frequently found in the other patients (*MYBPC3* and *MYH7*) (Gruner et al., 2011). In infants and children, the right ventricle can also be involved (Biagini et al., 2005). Almost 5% of patients with hypertrophic cardiomyopathy evolve to end stage dilated cardiomyopathy with



Fig. 1. Longitudinal section of the heart of a 9 year-old boy, who died suddenly during ordinary activities, with predominant hypertrophy of the septum but also showing increased thickness of the free wall of both ventricles. During life, obstruction of both the left and right ventricular outflow tracts was present.

extensive fibrosis, myocardial wall thinning and cavity dilation (Harris et al., 2006). The left atrium is enlarged as a consequence of the elevated left ventricular end diastolic pressure caused by diastolic dysfunction and mitral regurgitation secondary to left ventricular outflow tract obstruction or associated mitral valve anomalies (Klues et al., 1992). The physiopathology of mitral insufficiency in hypertrophic obstructive cardiomyopathy was initially attributed to the Venturi effect produced by systolic flow acceleration in the left ventricular outflow tract dragging the anterior mitral valve leaflet towards the ventricular septum causing both obstruction and insufficiency (Grigg et al., 1992; Panza et al., 1992; Shah et al., 1969 & 1971). A subsequent echocardiographic and Doppler study suggested instead, that the mitral valve leaflets are protruding into a narrow left ventricular outflow tract at the onset of ejection causing that rapid forward flow becomes the dominant force that pushes the leaflets toward the septum being the immediate cause of obstruction. After the onset of obstruction the leaflets are forced against the septum by the pressure difference across the orifice. The raising gradient leads to a smaller orifice and a higher gradient (Sherrid et al., 1993). The systolic anterior motion of the mitral leaflets precludes the proper sealing of the mitral orifice generating mild to moderate mitral regurgitation (M. Maron et al., 2011). The mitral valve in these patients shows alterations in size and shape which are thought to be primary abnormalities of the disease. The main changes are elongation and increase of the leaflet area usually not symmetrical. The size of the left ventricular outflow, the hyperdynamic contraction and the alterations of the mitral valve are the causes of the obstruction.

4.2 Microscopy

The distinct feature of the microscopic examination of the myocardium is hypertrophy and marked disarray (greater than 5% of the myocardial tissue) of individual and grouped myocytes (myofibers) that instead of being normally aligned are interspersed in different directions forming whorls around areas of fibrosis. Cells and fibers lose their normal parallelism and can even be found almost perpendicular to each other. (Fig. 2) The disarray also includes the intracellular myofibrils. Other findings include increased connective tissue leading to interstitial fibrosis and thickening of the microvascular coronary artery walls with luminal reduction resulting in ischemia and fibrosis (Ferrans et al., 1972). Fibrosis and scar replacement of necrosed cells is more evident in areas with greater hypertrophy. Initially, it was postulated that the mechanism for the disarray and hypertrophy was caused by the increased effort of the myocytes to compensate the inefficient contractility of the affected sarcomere proteins. This would activate the insulin and tissue growth factors and angiotensin II resulting in the myocardial changes (J. Seidman & C. Seidman, 2001). Further experimental animal investigations and studies of hypertrophic cardiomyopathy mutations in man, by the same authors, found instead that the mutated sarcomeres had in fact increased function. It was then hypothesized that they would activate signals for hypertrophic remodeling. Abnormalities in calcium signaling were encountered leading to necrosis and replacement fibrosis producing diastolic dysfunction, a main feature of hypertrophic cardiomyopathy (C. Seidman & J. Seidman, 2011). An investigation by the same group, also found that a profibrotic marker like serum procollagen is significantly higher in patients with full blown hypertrophic cardiomyopathy and mutation carriers, with a still not developed phenotype, than in controls, pointing to increase collagen synthesis and fibrosis. Late gadolinium enhancement studies are positive when hypertrophy is already present (Ho et al., 2010). The myocardial disarray, interstitial fibrosis, and ischemia are also the substrate for the occurrence of arrhythmias.

4.3 Phenocopies

Patients with nonsarcomeric hypertrophic cardiomyopathy are considered to be phenocopies (Table 5), and might have the same pathologic findings as has been reported in some *malformation syndromes* or *neuromuscular disorders* like *Noonan's syndrome* and *Friedreich's ataxia* (Burch et al., 1992; Kawai et al., 2000). However, this is not the case for *inborn errors of metabolism* like *glycogen storage disease* where the gross anatomy resembles hypertrophic cardiomyopathy but microscopic examination shows the glycogen deposits in the myocytes without disarray. (Fig. 3) It should be noted that the present definition of phenocopy, according to the Webster's New World Medical Dictionary in its second acceptance is: "A person who has an environmental condition that mimics a condition that is produced by a gene". Since the examples just mentioned are genetic in origin, the term phenocopy could be inappropriate but is how these entities have been named for a long time.

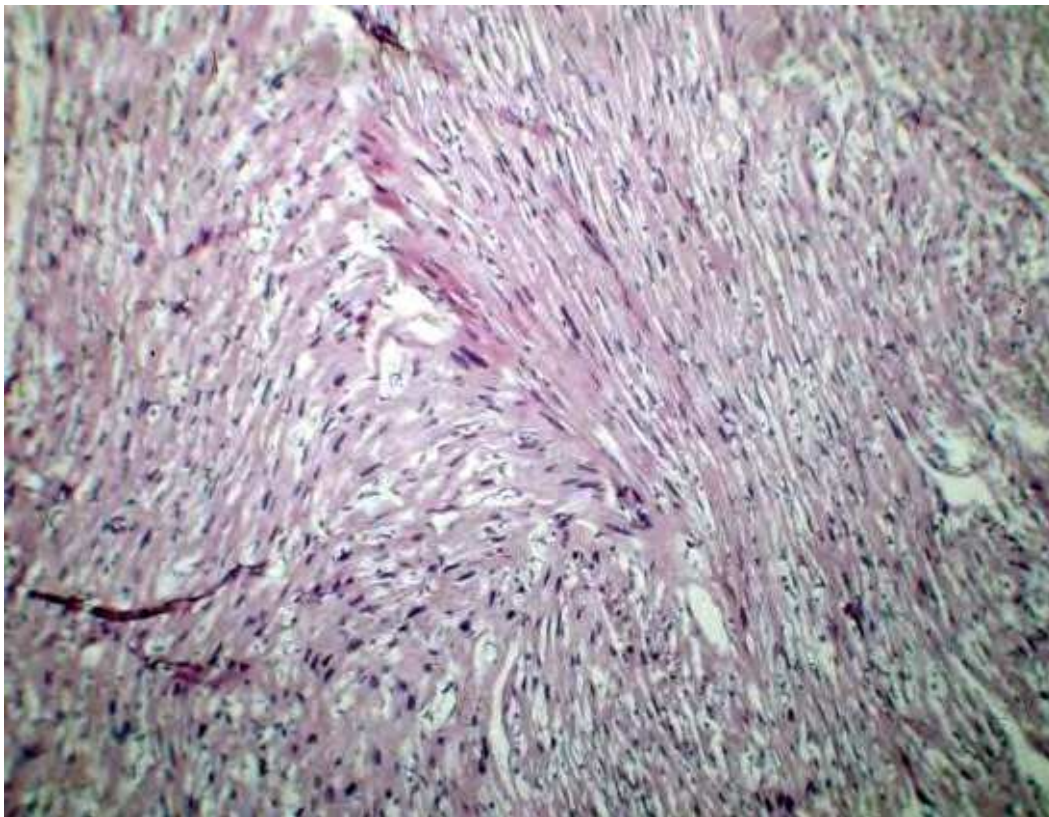


Fig. 2. Microscopic view of the myocardium with the typical disarray of hypertrophic cardiomyopathy in an infant who died in congestive heart failure. Myofibers have lost the usual parallel disposition and describe whorls around areas of fibrosis. The disarray is present in the myofibers, among myocytes and in the myofibrils within the myocytes.

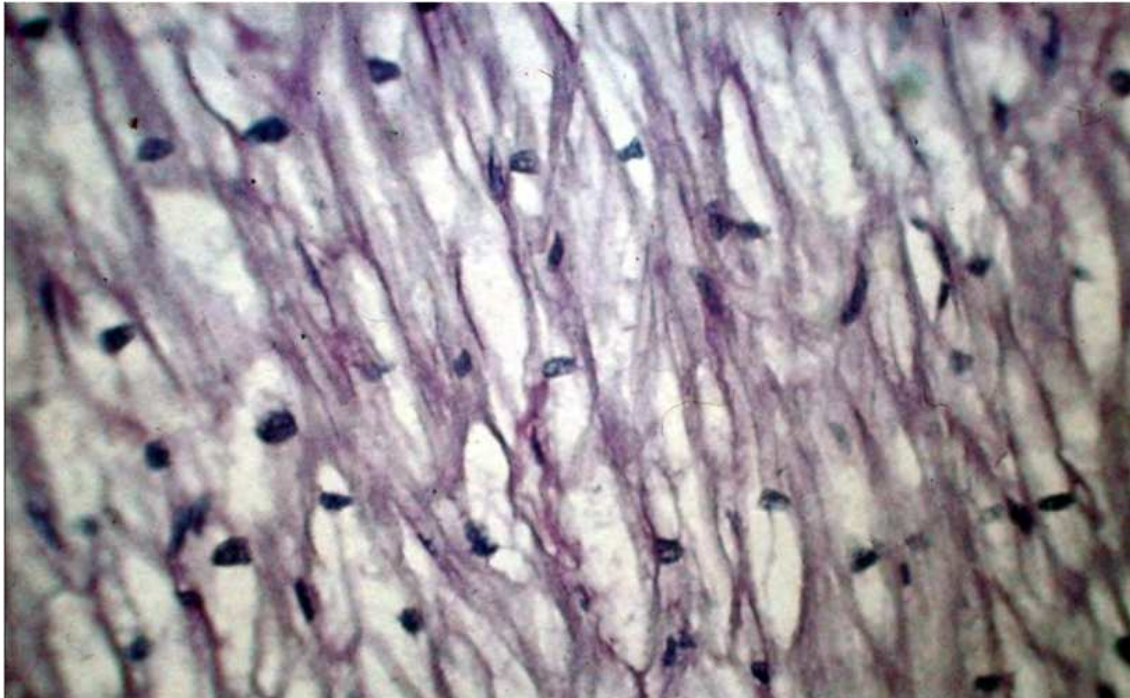


Fig. 3. Typical lacework appearance of the myocardium in a patient with type II Pompe's disease. There is normal alignment of the vacuolated myocardial fibers with glycogen storage.

GENE	PROTEIN	SYNDROME
TAZ	Tafazzin (G4.5)	Barth syndrome/LVNC
DTNA	α -dystrobrevin	Barth syndrome/LVNC
LAMP2	Lysosome-associated membrane protein 2	Danon's syndrome/WPW
GLA	α -galactosidase	Fabry's disease
AGL	Amylo-1,6-glucosidase	Forbes disease
FXN	Frataxin	Friedreich's ataxia
PTPN11	Protein tyrosine phosphatase, nonreceptor type 11, SHP-2	Noonan's syndrome, LEOPARD syndrome
RAF1	V-RAF-1 murine leukemia viral oncogene homolog 1	Noonan's syndrome, LEOPARD syndrome
KRAS	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog	Noonan's syndrome
SOS1	Son of sevenless homolog 1	Noonan's syndrome
GAA	α -1,4-glucosidase deficiency	Pompe's disease
PRKAG2	AMP-activated protein kinase	WPW/HCM

LVNC: left ventricular noncompaction, WPW: Wolff-Parkinson-White, HCM: hypertrophic cardiomyopathy.

Table 5. Genes involved in the production of phenocopies (modified from Bos et al., 2009).

5. Clinical findings

Aside from the genetic and phenotypic heterogeneity already mentioned in hypertrophic cardiomyopathy, the age, form of presentation, and outcome, are also quite diverse. The age of the patient at presentation is a determinant of prognosis (Colan et al., 2007). Newborn and infants are more likely to be referred for congestive heart failure while older children are usually asymptomatic at the time of diagnosis and the consultation is requested because of the presence of a heart murmur, cardiomegaly casually detected on a chest x-ray, or electrocardiographic abnormalities (Bruno et al., 2002). Initially, asymptomatic patients may go on without symptoms for a long period of time until they begin experiencing fatigue and dyspnea, and less frequently, palpitations, chest pain, and syncope or sudden death which might be the first symptom ever. Another cause of referral is the investigation of cardiac involvement in patients with conditions known to be associated with hypertrophic cardiomyopathy like the *malformation syndromes*, *inborn errors of metabolism* or *neuromuscular disorders*. However, in other circumstances, the associated disease may have been unnoticed and the cardiomyopathy is discovered first. The presence of physical findings suggesting an association then prompts referral to the geneticist (Alday & Moreyra, 1984). With regard to the physical examination itself, in hypertrophic obstructive cardiomyopathy, the peripheral pulses may rise and descend rapidly. When considerable cardiac enlargement is present, a precordial bulge and outward displacement of the point of maximal impulse are usually found. A double apical impulse caused by a 4th heart sound is often noted. A harsh, blowing systolic murmur with varying intensity, related to the degree of obstruction and mitral regurgitation, can be listened along the left sternal border and at the apex. A distinctive feature of these murmurs is the variability seen with maneuvers that increase or reduce the obstruction intensifying or decreasing their intensity (Moreyra et al, 1972). (Fig. 4) Patients with non obstructive hypertrophic cardiomyopathy may also have ejection systolic murmurs along the left sternal border though softer than when there is left ventricular outflow obstruction. An ambulatory electrocardiographic study performed in infants, children and adolescents with hypertrophic cardiomyopathy concluded that arrhythmias occur rarely before adolescence. However, from then on, prevalence of nonsustained ventricular tachycardia is as high as 18%. It is also worth mentioning that absence of arrhythmias is not synonymous of low risk for sudden death (McKenna et al., 1988). Supraventricular and ventricular tachycardias may be equally found. Atrial fibrillation may occur in end-stage dilated hypertrophic cardiomyopathy (Harris et al., 2006). Very rarely, patients with hypertrophic cardiomyopathy have associated Wolff-Parkinson-White syndrome (Bockowski et al., 2007). The development of high rate supraventricular tachycardias is poorly tolerated in these patients with left ventricular diastolic dysfunction. This might lead to syncope and sudden death which are the most feared complications of hypertrophic cardiomyopathy. Several mechanisms have been reported as a cause of syncope like tachyarrhythmias, left ventricular outflow tract obstruction, systemic hypotension, and 3rd degree AV block. Sudden unexpected death may be the first and only symptom in hypertrophic cardiomyopathy and this is the most frequent cause of death in young athletes during competition. However, sudden death also occurs during usual activities, at rest, or during sleep time. The estimated rate of sudden death in children is 3% per year, a similar figure to that found in adults cared for in tertiary centers (Bruno & al., 2002; B.J. Maron et al., 1982; McKenna & Deanfield, 1984). Heart failure in

this disease is usually provoked by diastolic dysfunction secondary to left ventricular hypertrophy, myocyte disarray and fibrosis. The presence of outflow obstruction is an additional factor leading to heart failure. In 3 to 5 % of patients the end stage is reached and systolic failure associated with left ventricular wall thinning and increased ventricular volume become a serious indication of poor prognosis (Biagini et al., 2005 & Harris et al., 2006).

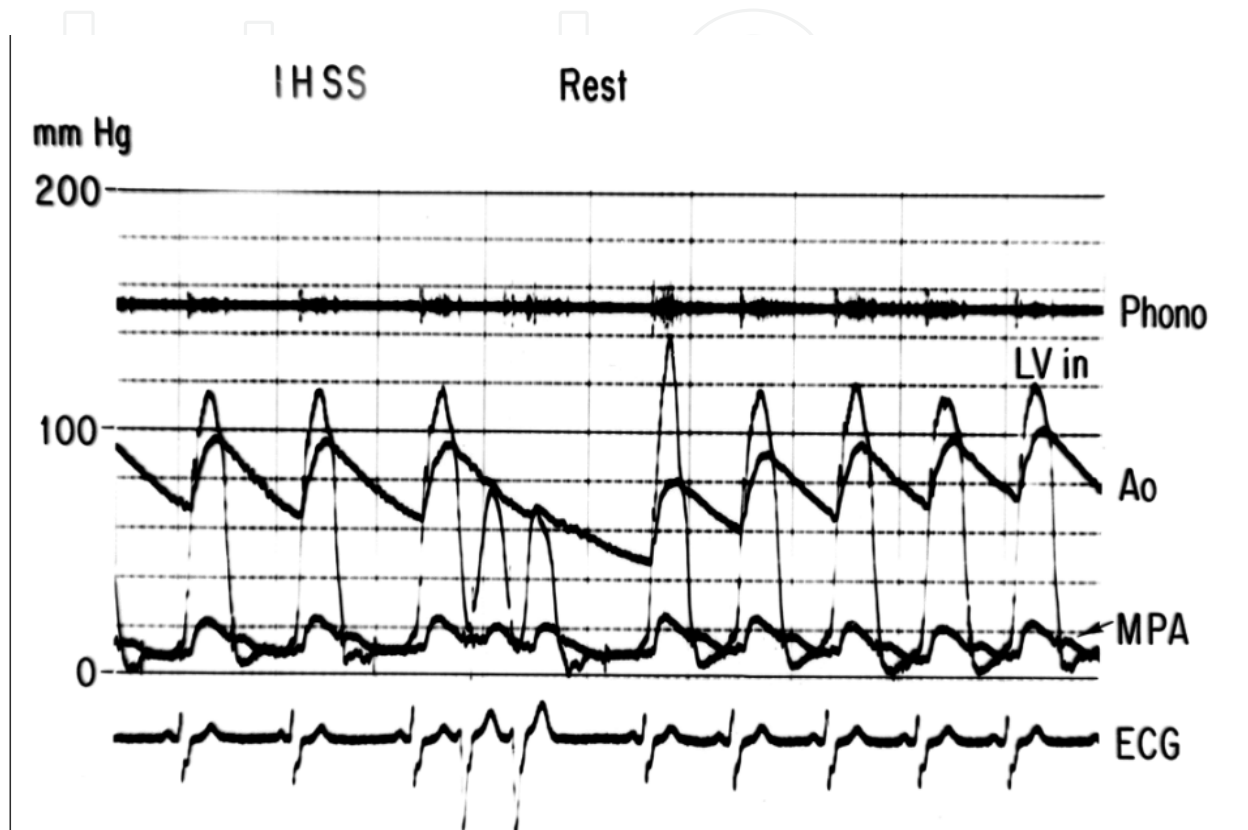


Fig. 4. Simultaneous hemodynamic recordings of the left ventricular inflow (LV in), aorta (Ao) and main pulmonary artery (MPA). An electrocardiogram (ECG) and a phonocardiogram (phono) were also recorded. There is a small basal gradient between the left ventricular inflow and the aorta which increases in a post-extrasystolic beat together with the intensity of the systolic murmur shown in the phonocardiogram, as a consequence of the stronger contraction following the post-extrasystolic pause. (IHSS: idiopathic hypertrophic subaortic stenosis).

6. Laboratory studies

6.1 Radiology

The chest x-ray is usually normal in early stages of the disease but following the pubertal growth spurt shows cardiomegaly at the expense of the left sided chambers (B.J. Maron et al., 1986). (Fig. 5) The same is true for patients evolving to end-stage hypertrophic cardiomyopathy (Biagini et al., 2005). Finally, infants with severe heart failure nearly always have considerable cardiac enlargement at presentation. Pulmonary venous hypertension secondary to elevation of the left ventricular end diastolic pressure is reflected by the well known resultant pulmonary vascular changes.

6.2 Electrocardiography and allied techniques

The electrocardiogram is usually abnormal in almost all patients with hypertrophic cardiomyopathy. (Panza & Maron, 1989) The electrocardiographic abnormality, even a slight one, may precede the echocardiographic findings showing left ventricular hypertrophy in family members carrying the genotype of probands with hypertrophic cardiomyopathy. Therefore, this should be kept on mind when screening relatives of hypertrophic cardiomyopathy patients (Gregor et al., 1989). Left atrial enlargement and left ventricular hypertrophy by voltage criteria usually associated with ST-T abnormalities are seen. (Fig. 6) Younger patients may have combined ventricular or isolated right ventricular hypertrophy with a rightwards QRS axis. (Fig. 7) Another frequent finding is the presence of pathological deep and narrow Q waves. An R + S sum higher than 10 mV on the limb leads of the electrocardiogram has been recently proposed as a risk factor for sudden death in children with hypertrophic cardiomyopathy (Ostman-Smith et al., 2005). (Fig. 8) An electrocardiographic Wolff-Parkinson-White pattern or syndrome is very rare in patients with sarcomeric hypertrophic cardiomyopathy. However, it has been described in mutations of genes like those encoding AMP-activated protein kinase (*PRKAG2*) and lysosome associated membrane protein 2 (*LAMP2*) producing *glycogen storage disease* and *Danon disease* respectively. Both of them recognized as phenocopies of hypertrophic cardiomyopathy (Alday et al., 2010). Ambulatory electrocardiography and exercise testing are used for arrhythmia detection and risk stratification in older children with hypertrophic cardiomyopathy. The presence of nonsustained ventricular tachycardia by Holter monitoring or an abnormal blood pressure response to exercise are considered risk factors for sudden death (Elliot et al., 2000).

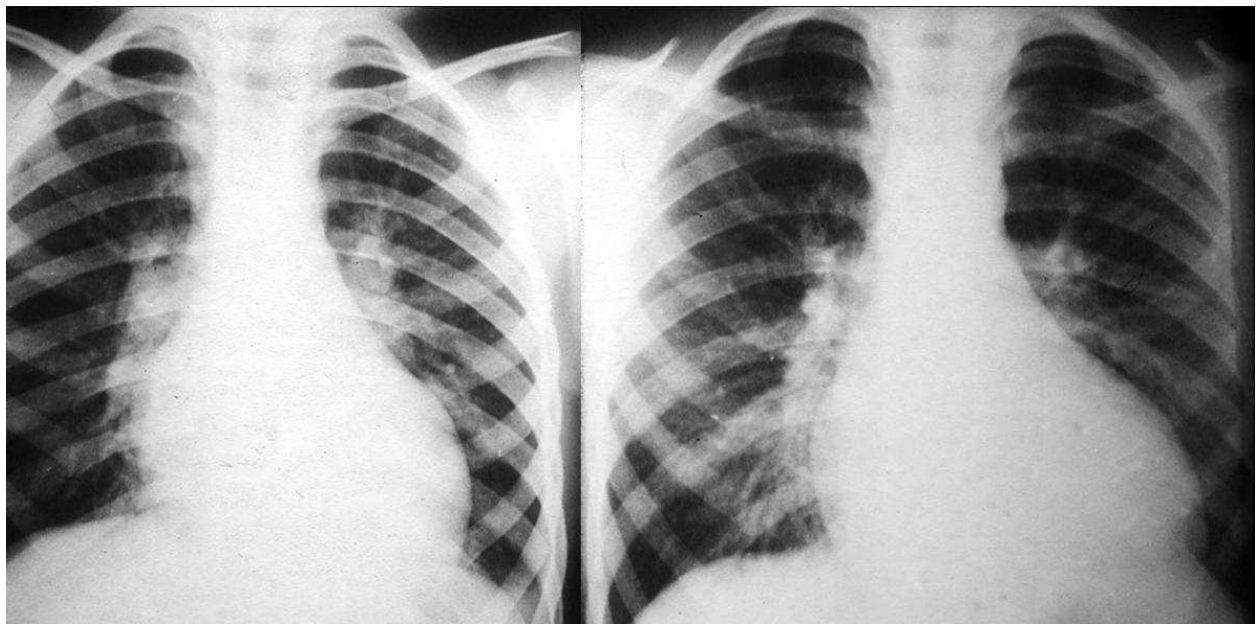


Fig. 5. Chest x-rays of a boy at 11 and 13 years of age showing great increase in the heart size coincident with pubertal growth spurt.

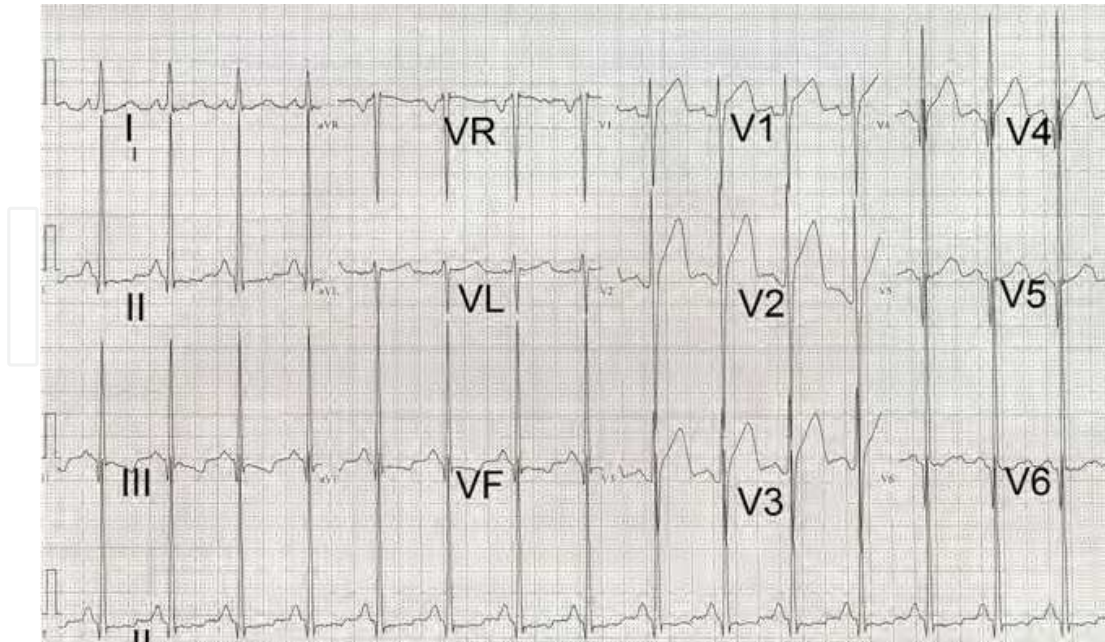


Fig. 6. Electrocardiogram of a 16 year-old male patient showing increased R wave voltages and secondary ST-T changes indicating severe left ventricular hypertrophy.

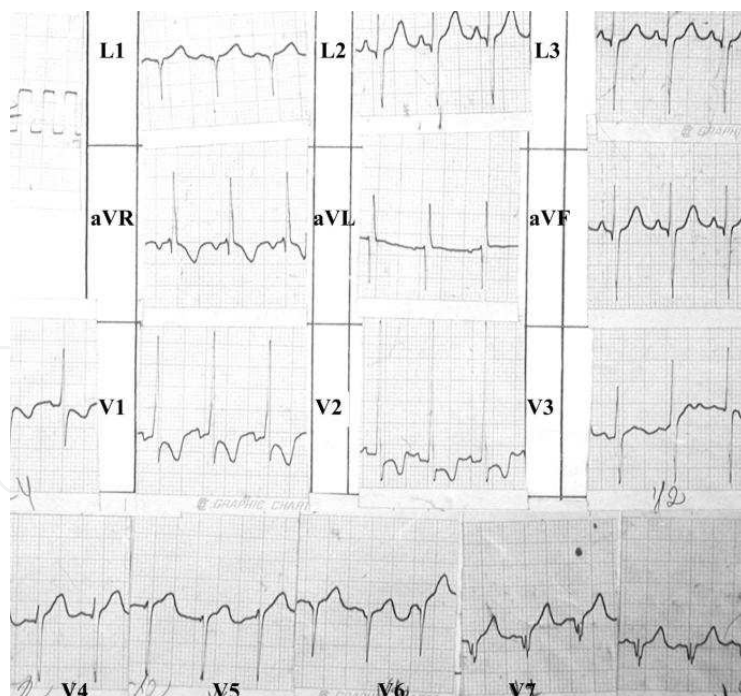


Fig. 7. Electrocardiogram belonging to a 4 year-old boy with a QRS axis of -120° with Q waves in leads II, III and aVF. There are signs of combined ventricular hypertrophy, loss of R wave voltage from V4 to V8 with appearance of QS complexes in V6 and pathological Q waves in V7 and V8.

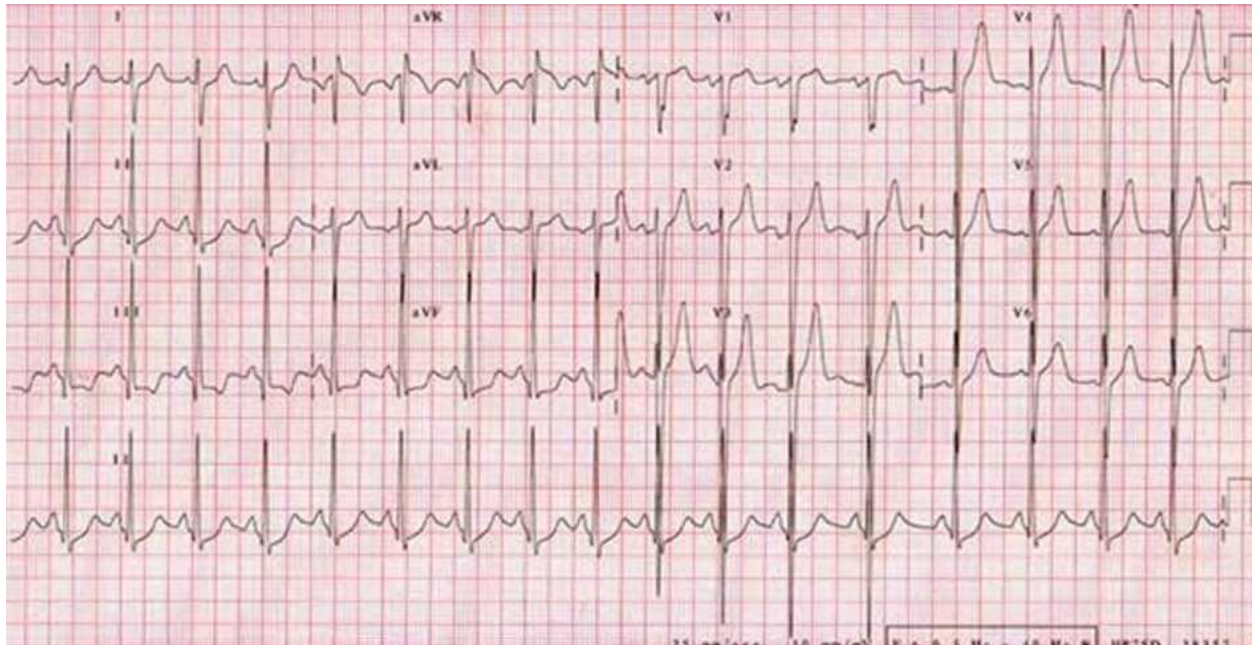


Fig. 8. Electrocardiogram of a 14 year-old male patient with a vertical QRS axis ($+120^{\circ}$) and voltage criteria for left ventricular hypertrophy. A limb lead voltage sum > 10 mV is considered a risk factor for sudden death in children.

6.3 Echocardiography

Echocardiography associated with color flow Doppler is the most effective test for the diagnosis of hypertrophic cardiomyopathy (B.J. Maron et al., 2003a). It allows detection of the disease, follow-up of progression, and risk stratification for sudden death (B.J. Maron et al., 1986, Ostman-Smith et al., 2005). The wall thickness echocardiographic criteria for the diagnosis of hypertrophic cardiomyopathy was set at greater than 2 SD above the mean for the body surface area of the population for a localized or general myocardial hypertrophy (Grenier et al., 2000). When in the absence of pulmonary valve stenosis the right ventricular wall thickness exceeds 4 mm the right ventricle is considered to be involved too (Nugent et al., 2005). Left ventricular hypertrophy is most frequently asymmetric with greater involvement of the interventricular septum than the rest of the walls, though it can also be concentric. (Fig. 9 - 11) More rarely, it is localized in the anterior wall, the apex, or in the mid left ventricle (M. Maron et al., 2009, Minami et al., 2011). The mid ventricular obstruction may lead to the development of an apical left ventricular aneurysm. (Fig. 12) In younger children the right ventricle may also be affected (Biagini et al., 2005). As a consequence of mitral insufficiency and/or diastolic dysfunction, there is left atrial enlargement. The systolic anterior movement of the mitral valve contacting the ventricular septum that causes left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy is readily seen (B.J. Maron et al., 2003). Color flow mapping allows detection of the site of obstruction. (Fig. 13) The gradient across the outflow tract is estimated by continuous wave Doppler that also allows assessment of the mitral regurgitation severity. (Fig. 14) Transesophageal echocardiography is more sensitive than transthoracic studies for evaluation of primary mitral valve anomalies producing mitral incompetence (Kuhl & Hanrath, 2004). The presence of left ventricular outflow tract obstruction is now considered a risk factor for adverse events in hypertrophic

cardiomyopathy (M. Maron et al., 2003). Furthermore, we now know that almost 70% of patients with hypertrophic cardiomyopathy have gradients across the left ventricular outflow considering the obstruction caused by exercise, when studied with stress echo. Actually, it should be performed in all patients with no significant gradient at rest (M. Maron et al., 2006). Estimation of diastolic dysfunction in hypertrophic cardiomyopathy is performed by studying the pulmonary vein and transmitral Doppler flow tracings but since they depend on loading conditions are not reliable to predict adverse outcomes in children with hypertrophic cardiomyopathy (McMahon et al., 2004). Tissue Doppler velocities measurements at the mitral annulus level are more sensitive in detecting diastolic dysfunction allowing early diagnosis in hypertrophic cardiomyopathy genetic carriers before they develop hypertrophy (Nagheb et al., 2003). (Fig. 15) Tissue Doppler studies can also predict adverse events like death, ventricular tachycardia, cardiac arrest, and exercise intolerance in affected children with the disease (McMahon et al., 2004).

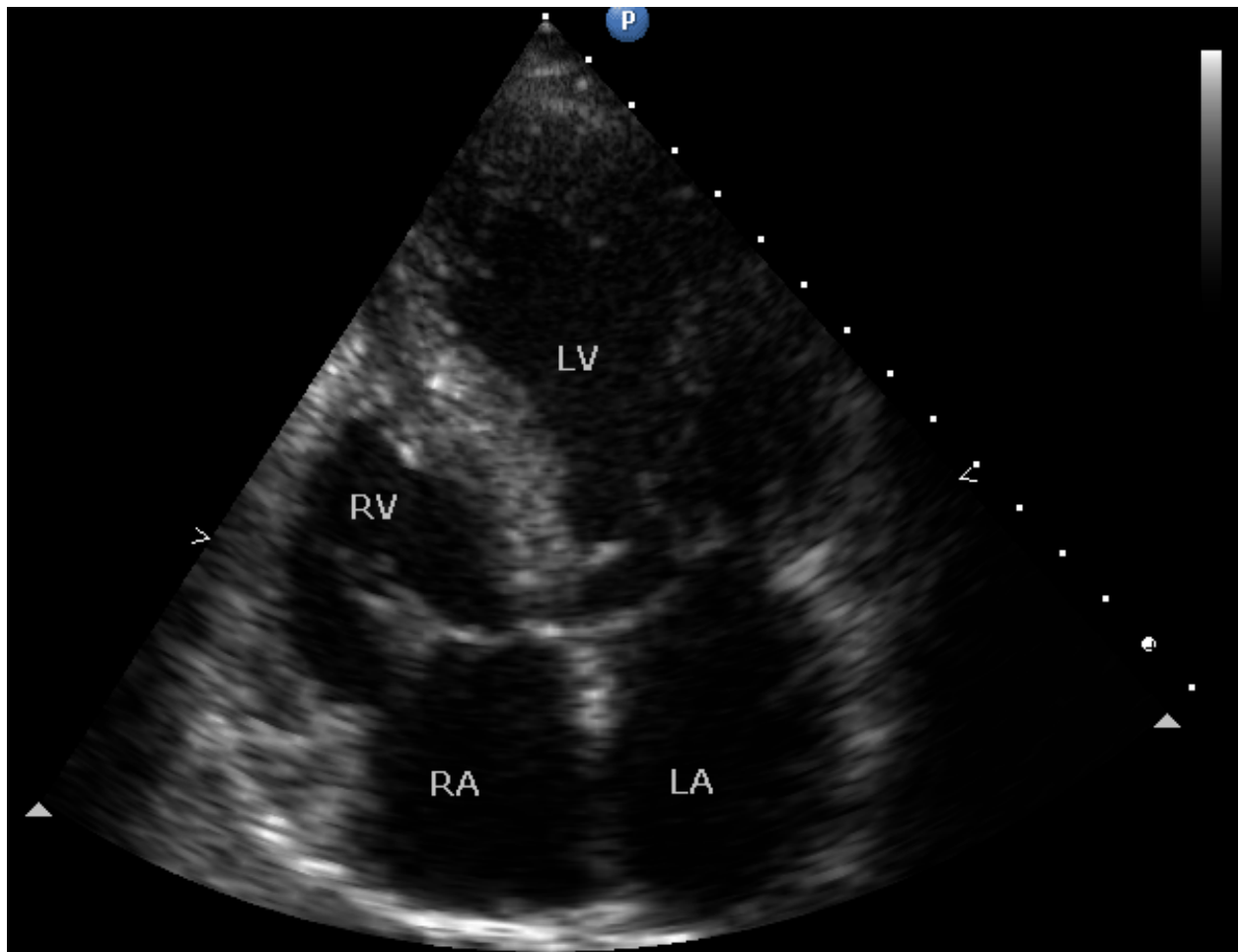


Fig. 9. Four-chamber bidimensional echocardiographic view of a 16 year-old asymptomatic male patient with hypertrophic cardiomyopathy with asymmetric septal hypertrophy. The septum and the posterior wall measure 21 mm and 9.5 mm respectively.

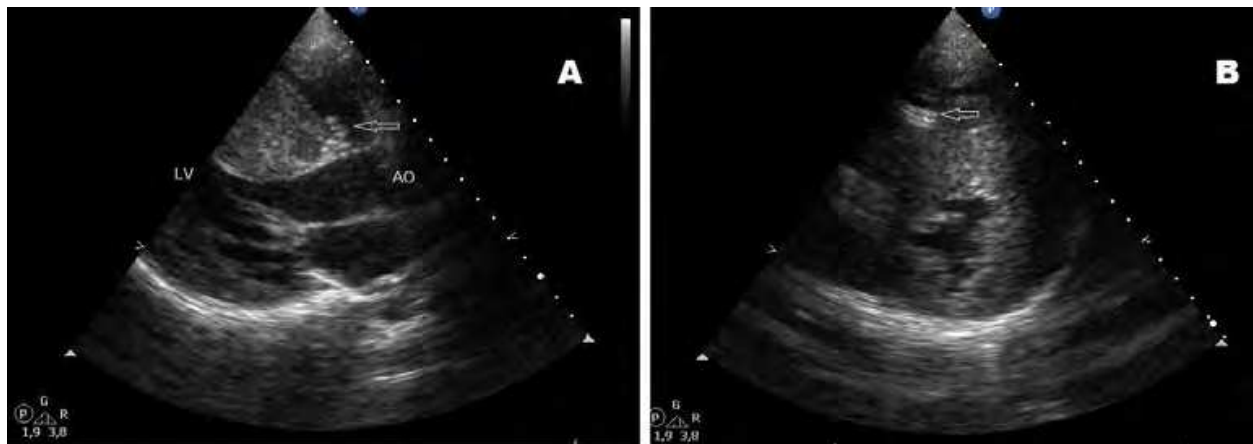


Fig. 10. Bidimensional echocardiogram showing long (A) and short (B) axis parasternal views of the left ventricle of a 22 year-old female followed since early childhood with severe asymmetrical hypertrophy of the septum measuring 31 mm in diameter. There is convexity toward the left ventricular cavity. The mitral leaflets initiate an anterior motion to provoke mitral septal contact and the resultant left ventricular outflow tract obstruction. The left atrium is mildly enlarged. The tip of a catheter for DDD pacing is seen in the right ventricular cavity (arrows).

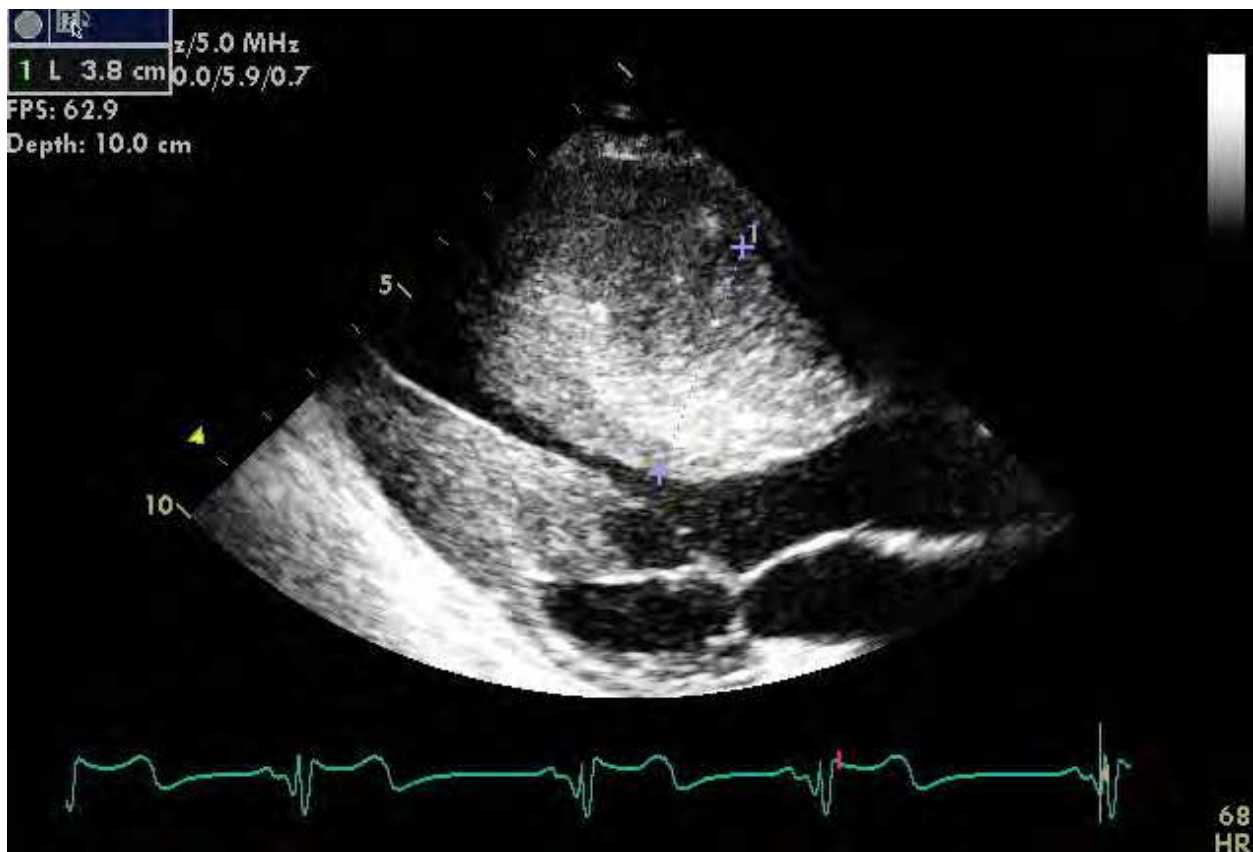


Fig. 11. Bidimensional echocardiographic long axis view with massive septal hypertrophy (38 mm) in a girl with a strong family history (2 siblings). Courtesy Dr Ricardo Pignatelli, Texas Children's Hospital.

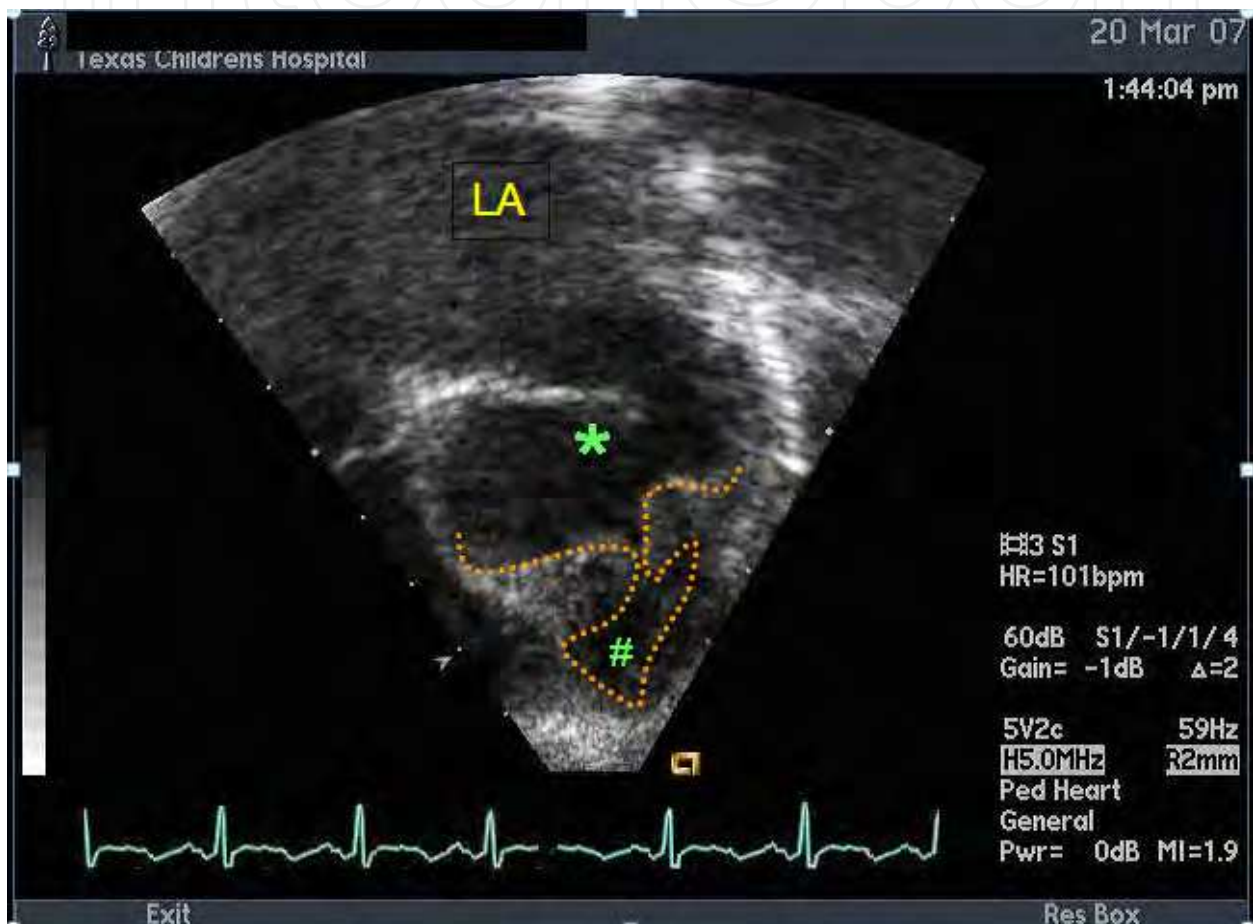


Fig. 12. Bidimensional echocardiographic view of a patient with midventricular obstruction. The left ventricle has an upper inflow (*) and a lower apical chamber (#) as a result of the obstruction. Courtesy Dr Ricardo Pignatelli, Texas Children's Hospital.

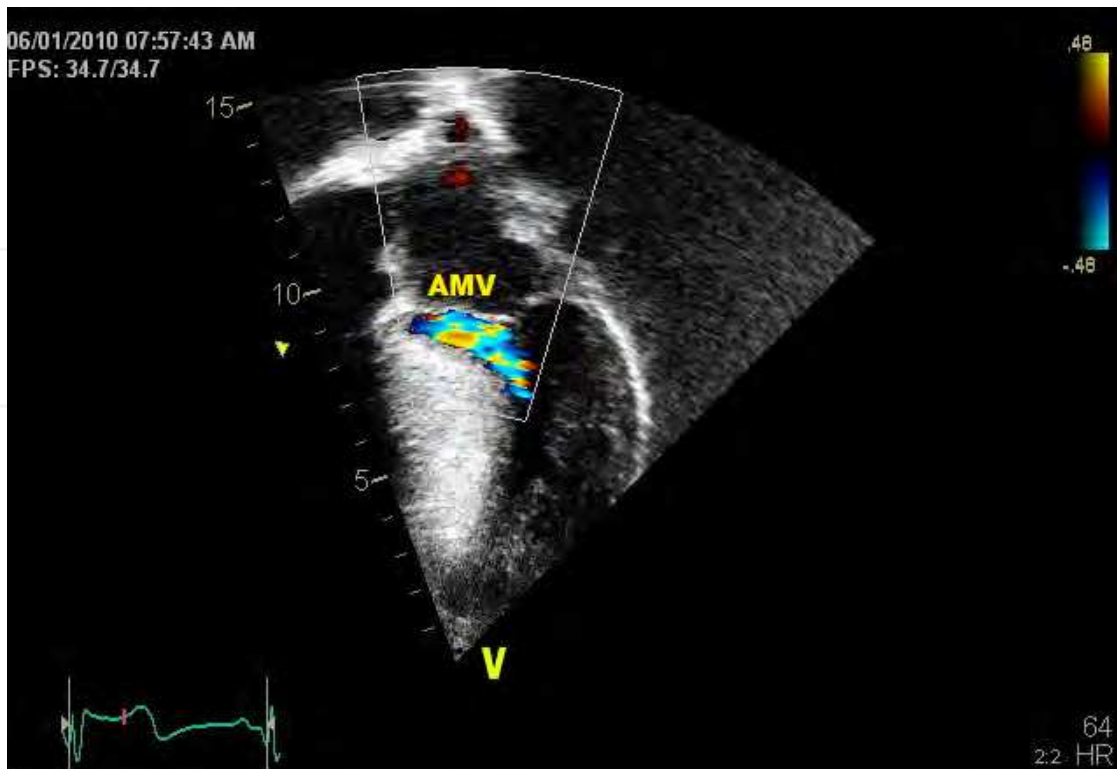


Fig. 13. Echocardiographic 4-chamber view of asymmetric septal hypertrophy with left ventricular outflow tract flow acceleration (arrow) by color Doppler. (AMV: anterior mitral valve). Courtesy Dr Ricardo Pignatelli, Texas Children’s Hospital.



Fig. 14. Continuous wave Doppler showing a severe gradient (87.6 mmHg) across the left ventricular outflow tract in the same patient shown on figure 10.

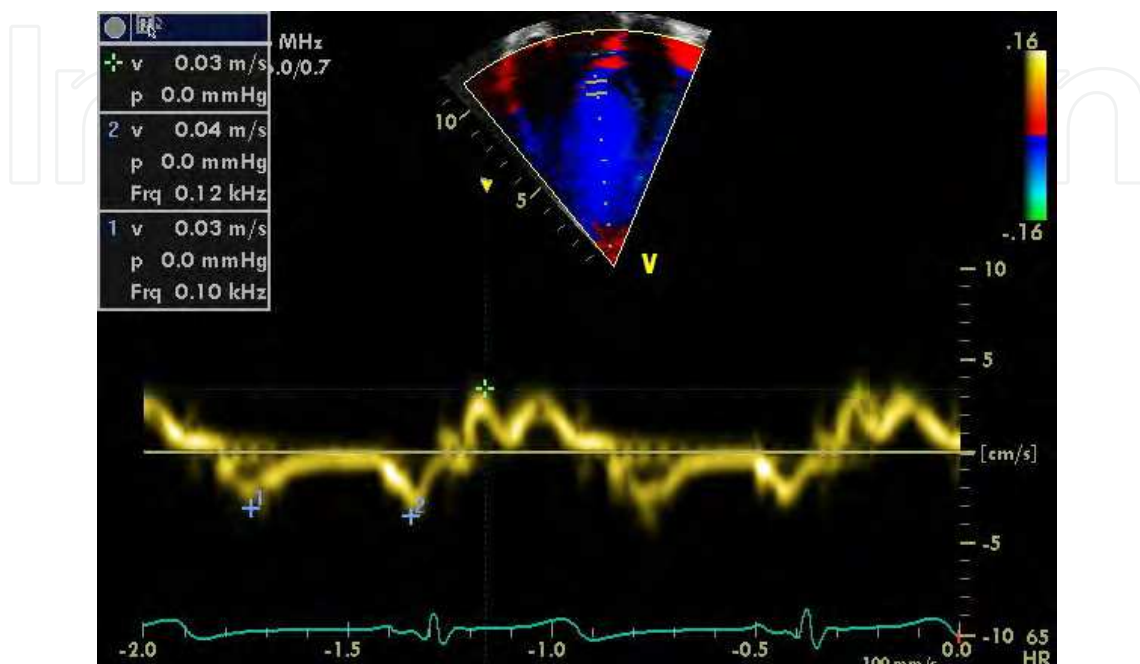


Fig. 15. Decreased Doppler tissue septal velocities (<5cm/second) in a patient with massive hypertrophic cardiomyopathy. Courtesy Dr Ricardo Pignatelli, Texas Children's Hospital.

6.4 Computed tomography and magnetic resonance imaging

Cardiac computed tomography and magnetic resonance imaging yield superior anatomic data than echocardiography since they allow better definition of the anterolateral wall and tip of the left ventricle and the right ventricle. However, these procedures are more costly and the former exposes the patient to radiation (M. Maron et al., 2009). (Fig. 16) Nevertheless, they are very useful when thoracic deformities prevent satisfactory cardiac visualization by transthoracic echocardiography. Cardiovascular magnetic resonance has also demonstrated that mitral leaflet elongation is present in hypertrophic cardiomyopathy independently of other phenotypic variants indicating that the mitral abnormalities are primary, thus, their important role in the pathophysiology of the left ventricular outflow obstruction (M. Maron, et al.; 2011). On the other hand, gadolinium magnetic resonance imaging late enhancement allows detection of the amount of myocardial fibrosis and is a predictor of systolic dysfunction (M. Maron et al., 2008). A more recent study reports that is also effective for prognostication of adverse outcomes and which patients might require a cardioverter-defibrillator (Fig. 17) (Bruder et al., 2010).

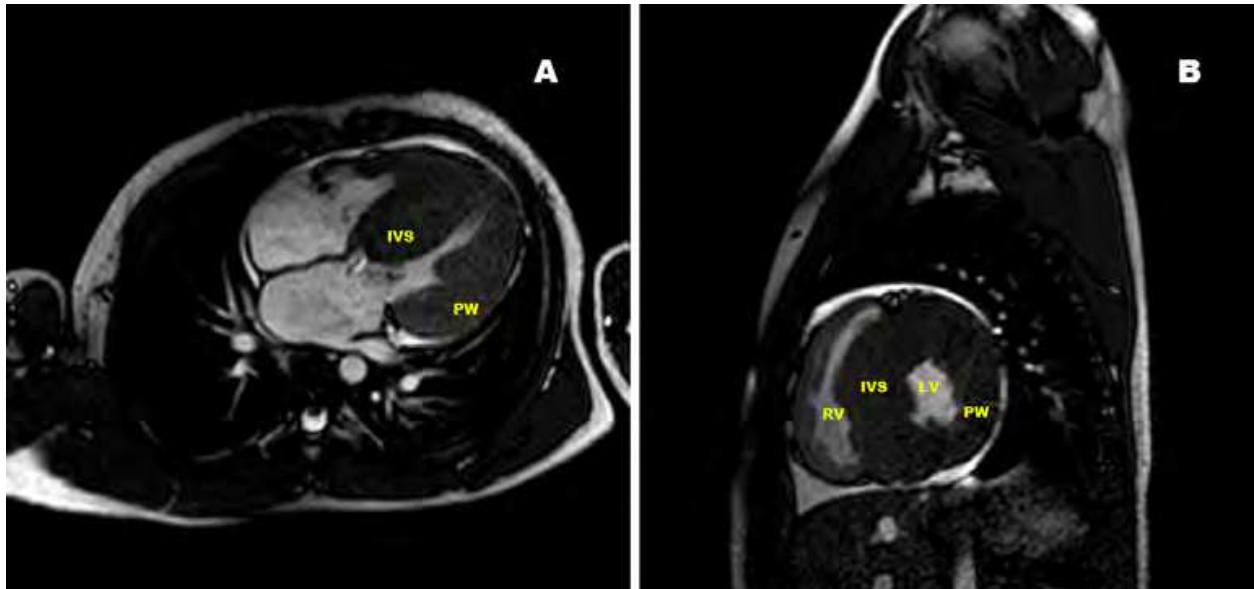


Fig. 16. **A.** Long axis view of a cardiac magnetic resonance image of a 5 year-old asymptomatic boy with severe hypertrophic cardiomyopathy. **B:** Magnetic resonance imaging of a short axis projection of the heart of a 3 year-old boy with severe heart failure. (IVS: interventricular septum, LV: left ventricle, PW: posterior wall, RV: right ventricle). Courtesy Dr Ricardo Pignatelli, Texas Children's Hospital.

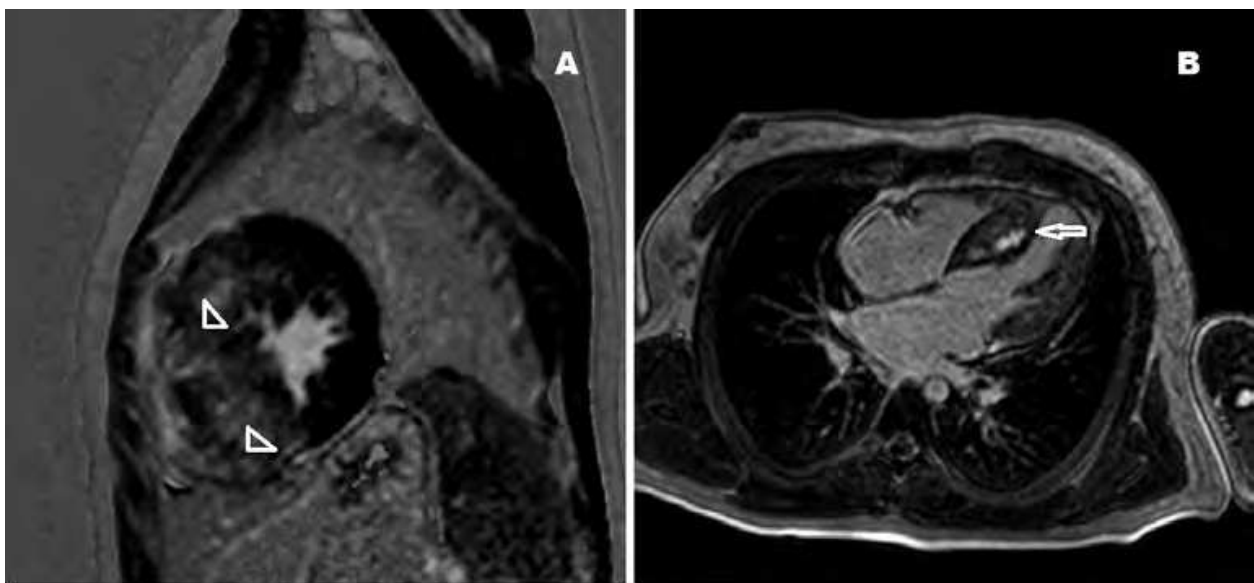


Fig. 17. **A.** Cardiac magnetic resonance image of the heart of a patient with positive delayed gadolinium enhancement indicating a diffuse pattern of fibrosis (arrowheads). **B:** Long axis view of a cardiac magnetic resonance image of the heart of a 9 year-old boy with a localized delayed gadolinium enhancement image in the interventricular septum (arrow). Courtesy Dr Ricardo Pignatelli, Texas Children's Hospital.

6.5 Cardiac catheterization and cineangiocardiology

We owe to cardiac catheterization and cineangiocardiology the initial understanding of the physiopathology of hypertrophic cardiomyopathy shortly after its rediscovery about half a century ago (Braunwald et al., 1964; Wigle, Auger & Marquis, 1967). These techniques were then considered the gold standard for the diagnosis of hypertrophic obstructive cardiomyopathy. (Fig. 18) With the advent of the just discussed noninvasive imaging techniques like Doppler-echocardiography, computed tomography, and magnetic resonance imaging, this invasive procedure is no longer necessary for diagnostic purposes. Nowadays, this method is only used before planned surgical treatment or percutaneous interventions for septal reduction.

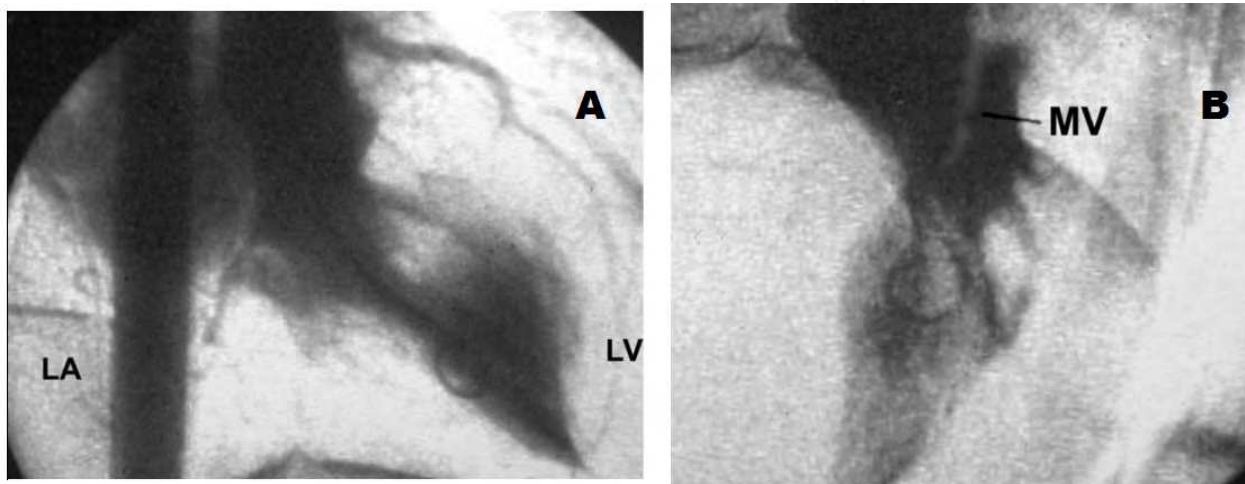


Fig. 18. A. Left ventricular cineangiogram in the right anterior oblique projection showing a hypertrophied chamber with subaortic obstruction and moderate mitral insufficiency with left atrial enlargement. B. In the left anterior oblique view the anterior mitral valve can be seen contacting the septum. LV: left ventricle; LA: left atrium; MV: mitral valve.

7. Complications

7.1 Sudden death and congestive heart failure

The main complications in children with hypertrophic cardiomyopathy are syncope and sudden unexpected death. The latter may be the first and only manifestation of the disease and is considered to be secondary to ventricular tachycardia and fibrillation caused by myocardial fibrosis and ischemia (Basso et al., 2000; B.J. Maron et al., 2000b). Sudden death occurs more often in older children with hypertrophic cardiomyopathy either during strenuous sport activities or at rest but is infrequent in infants (B.J. Maron et al., 2003a) who are more prone to present and die with congestive heart failure specially in secondary forms (Bruno et al., 2002).

7.2 Arrhythmias

Supraventricular and nonsustained ventricular tachycardias, were found in almost a third of pediatric and adolescent patients with hypertrophic cardiomyopathy studied by ambulatory electrocardiography (McKenna, et al., 1988). However, their outcome after a mean follow-up

of 3 years was rather benign. In a study from our group, a quarter of the patients had symptomatic atrial or ventricular tachycardia. Three out of 7 died suddenly during follow-up (Bruno et al., 2002). Rarely, 3rd degree atrioventricular block is found in children with hypertrophic cardiomyopathy. They could present with near syncope or syncopal attacks as the 1st manifestation of the disease (Rosen et al., 1997).

7.3 Evolving phenotype

Children with hypertrophic cardiomyopathy may evolve to dilated or restrictive cardiomyopathy phenotypes in 5% of the cases. In both circumstances they have a dimmer prognosis and become candidates for heart transplantation (Biagini et al., 2005; Denfield et al., 1997; Shirani et al., 1993).

7.4 Infectious endocarditis

Bacterial endocarditis is an uncommon complication in hypertrophic cardiomyopathy though can occur affecting the left ventricular aspect of the anterior mitral valve leaflet, especially in the presence of obstruction (Aoun et al., 1994; Morgan-Hughes & Motwani, 2002). Antibiotic prophylaxis for infectious endocarditis is then recommended.

7.5 Stroke

Ischemic stroke is somewhat frequent and a cause of death in adult hypertrophic cardiomyopathy but has not been mentioned in children (B.J. Maron et al., 2000a).

8. Differential diagnosis

The most important differential diagnosis is with the athlete's heart and is sometimes somewhat difficult to make. Highly trained competitive athletes may have electrocardiographic abnormalities that resemble those of hypertrophic cardiomyopathy. As in this situation, the left ventricle is hypertrophied but the wall thickness as determined by echocardiography does not exceed 15 mm in diameter and the hypertrophy is symmetrical. The left ventricular cavity is dilated and the ejection fraction is normal while hypertrophic cardiomyopathy is frequently accompanied by unusual distribution of hypertrophy, the left ventricle is smaller in size (<4.5 cm) and the ejection fraction is higher than normal. Furthermore, left ventricular diastolic function is normal in young athletes but is always impaired in hypertrophic cardiomyopathy (B.J. Maron, Spirito & Pelliccia, 1995b). Tissue Doppler studies has also been very useful to distinguish those patients in the "grey zone" (Cardim et al., 2003). When still in doubt regarding the diagnosis, cessation of physical activities usually results in regression of the left ventricular mass in a few weeks' time (B.J. Maron et al., 1993). Genetic screening might be useful when they are positive for a mutation which occurs in up to 70% of patients with hypertrophic cardiomyopathy. On the contrary, a negative test does not exclude the possibility of a mutation still not discovered.

9. Phenocopies and associations

A recent large epidemiologic study of the pediatric population with hypertrophic cardiomyopathy established that almost a quarter of patients with unexplained left

ventricular hypertrophy do not have a sarcomeric etiology (Colan et al., 2007). These variants are called phenocopies and are listed in Table 5. They are classified as *malformation syndromes, inborn errors of metabolism, and neuromuscular disorders* and each group numbers about one third of the total.

9.1 Malformation syndromes

9.1.1 Noonan's and LEOPARD syndromes

The most common *malformation syndromes* associated with hypertrophic cardiomyopathy included in the European Society of Cardiology classification of familial hypertrophic cardiomyopathy, are Noonan's syndrome and its allelic variant LEOPARD syndrome, acronym for lentiginosis, electrocardiographic anomalies, ocular hypertelorism, pulmonic stenosis, abnormal male genitalia, retardation of growth, and deafness. The prevalence of Noonan's syndrome, initially described as the Turner phenotype with normal karyotype (Noonan, 1968), is estimated in 1:2,000 births (Nora et al., 1974). (Fig. 19) It is inherited as an autosomic dominant form and nearly 80% have congenital heart disease, most frequently pulmonic valve and arterial stenoses, and atrial and ventricular septal defects. The introduction of echocardiography as a diagnostic tool, allowed the recognition of an association with hypertrophic cardiomyopathy in almost a quarter of patients (Nora et al., 1975). In the Australian epidemiologic study of childhood cardiomyopathies, 28% of 80 patients with hypertrophic cardiomyopathy had Noonan's syndrome (Nugent et al., 2005). These patients presented earlier and had more frequent biventricular involvement. However, they did not find greater adverse events rate than in sarcomeric hypertrophic cardiomyopathy. In about 40-50% of patients a mutation of protein tyrosine phosphatase nonreceptor type 11 (*PTPN11*) is found (Type 1 Noonan's syndrome), but this is present in 90% of LEOPARD patients (Sznajder et al., 2007; Tartaglia et al., 2001). This gene controls a series of developmental processes, among them the genesis of semilunar valves. The mutation is then mainly present in patients with heart defects but not in those with hypertrophic cardiomyopathy.

9.1.2 Related conditions

Some related genetic conditions to Noonan's syndrome like the Costello syndrome, the cardiofaciocutaneous syndrome, and palmo-plantar hyperkeratosis with woolly hair may also be associated with hypertrophic cardiomyopathy (Peirone et al., 2005, Roberts et al., 2006).

9.2 Inborn errors of metabolism

9.2.1 Pompe's disease

Pompe's disease or type II glycogen storage disease is an autosomal recessive inherited disorder caused by absence of the acid alpha-glucosidase enzyme (*GAA*) preventing the normal degradation of glycogen in the cardiac myocyte (Hers, 1963). There is an infantile type with massive cardiac enlargement as seen in hypertrophic cardiomyopathy with obstruction leading to congestive heart failure and early death (Ehlers et al., 1962). A typical electrocardiogram is shown in Fig. 20. Late onset Pompe's disease with a better outcome has also been described (Winkle et al., 2005). Enzyme replacement therapy is now available for treatment of *GAA* deficiency.



Fig. 19. **A.** Phenotype of a 10-year-old girl with Noonan's syndrome and hypertrophic cardiomyopathy. There is short stature, peculiar face, eyelid ptosis with downward slant, ocular and mammillar hypertelorism, low set ears, pterigium colli, and a prominent chest. **B.** Ten-year-old girl with LEOPARD syndrome. The multiple lentigines and hypertrophic obstructive cardiomyopathy became apparent long after she had been operated on for severe pulmonary valve stenosis when she was 6-month old (Reproduced with permission from *Am Heart J*, 1984; Vol.108, pp. 996-1000).

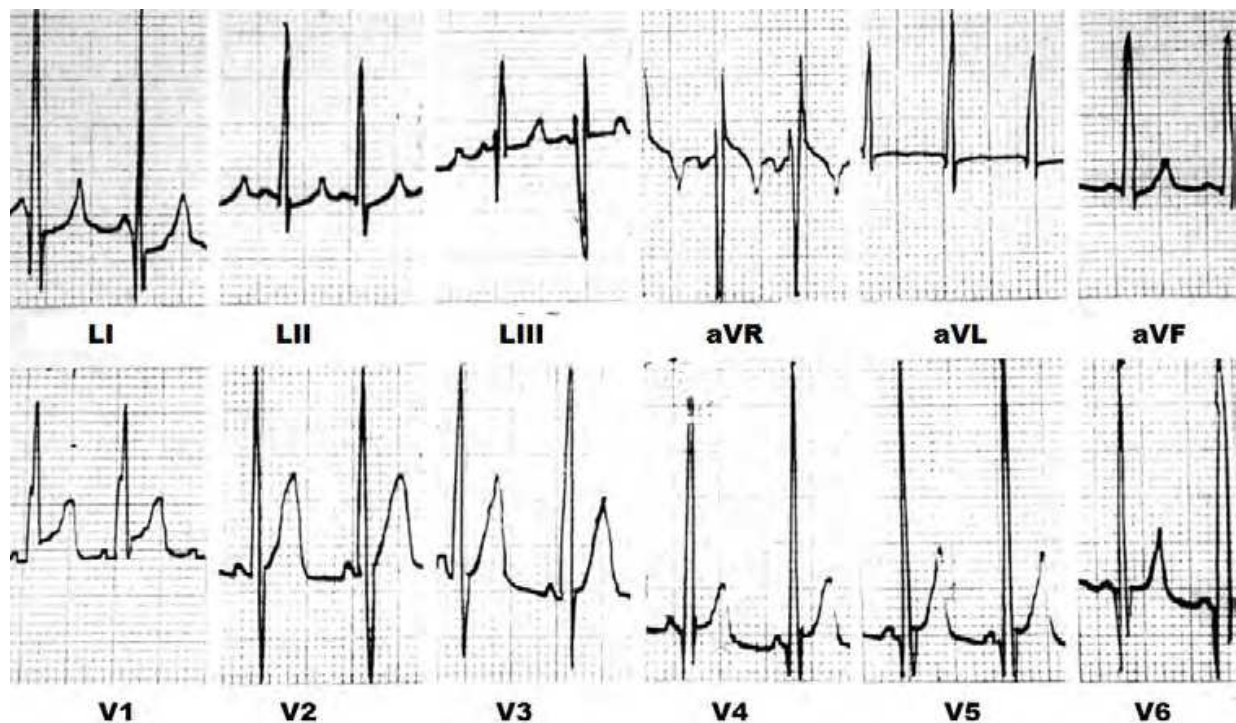


Fig. 20. Typical electrocardiogram of an infant with Pompe's disease. There is short atrioventricular conduction and biventricular hypertrophy with large voltages and no repolarization abnormalities.

9.2.2 Other glycogen storage diseases

A genetic study of 75 patients with hypertrophic cardiomyopathy found that 3 out of 35 patients with negative sarcomere protein mutations had genetical defects in lysosome-associated membrane protein 2 (*LAMP2*) responsible for the X-linked disorder Danon's disease/Wolff-Parkinson-White in 2 of the 3, and in AMP-activated protein kinase gamma 2 (*PRKAG2*) in the remaining, causing Wolff-Parkinson-White/hypertrophic cardiomyopathy (Arad et al., 2005). Both conditions produce glycogen storage and might wrongly be considered as sarcomeric hypertrophic cardiomyopathies. The presence of preexcitation should point to the correct diagnosis. Type IIIa and IV glycogen storage diseases are very rare conditions caused by deficiencies in debrancher and branching enzymes respectively. These patients have muscular hypotonia with elevated creatine kinase and heart and liver involvement. There is heterogenous severity of the disease and the hypertrophic cardiomyopathy is concentric. The inheritance is autosomal recessive (Kishnani et al., 2010). (Fig. 21)

9.2.3 Fabry's disease

Fabry's disease, an X-linked disorder characterized by intracellular accumulation of glycosphingolipids caused by deficiency of the lysosomal enzyme alpha-galactosidase A (*GLA*) may result in late onset hypertrophic cardiomyopathy, therefore it is rare in children. The reported prevalences in adult males and females with hypertrophic cardiomyopathy are 7.5 and 12% respectively (Chimenti et al., 2004; Sachdev et al., 2002). Enzyme replacement therapy for these patients is available (Eng et al., 2001).

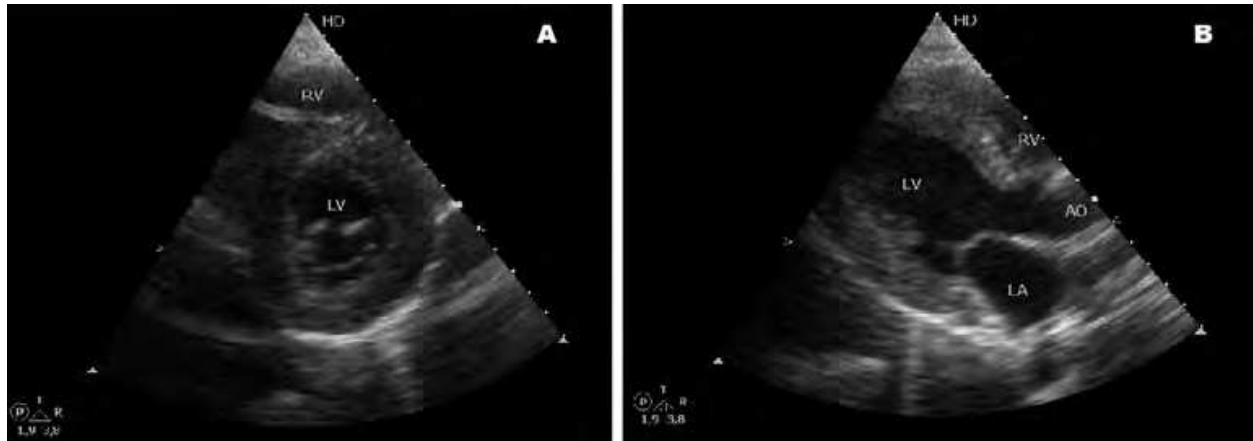


Fig. 21. Short and long axis parasternal echocardiographic views of the heart of a 19-year-old female with type III glycogen storage disease with concentric hypertrophic cardiomyopathy.

9.3 Neuromuscular disorders

Friedreich's ataxia is an autosomic recessive hereditary disorder with spinocerebellar degeneration and frequently associated with hypertrophic cardiomyopathy (Gottdiener et al., 1982). A mutation of the frataxin gene (*FXN*) alters the energy production through mitochondrial iron dysmetabolism resulting in mitochondrial damage producing muscle fiber fibrosis (Michael et al., 2006). The cardiomyopathy may precede the neurological manifestations (Alday & Moreyra, 1984).

9.4 Association with congenital heart disease

Not infrequently, hypertrophic cardiomyopathy and congenital heart disease are associated in children (Somerville & Becu, 1978). In most circumstances the defects are not severe. Ventricular and atrial septal defects and pulmonary valve stenosis have been reported, the last two mainly in patients with Noonan's and LEOPARD syndromes (Bruno et al., 2002; Tikanoja et al., 1999). However, associations with severe conditions like tetralogy of Fallot and atrioventricular septal defect have also been found (Alday et al., 1985; Eidem et al., 2000). (Fig. 22)

9.5 Association with left ventricular noncompaction

Left ventricular noncompaction belongs to the category of unclassified cardiomyopathies. It is characterized by the presence of prominent myocardial trabeculations and sinusoid tracts mainly in the left ventricle. (Fig. 23) Affected patients frequently develop a dilated cardiomyopathy with heart failure, arrhythmias, and systemic thromboembolism. Recent molecular studies have shown that mutations of genes producing phenocopies like Barth syndrome, or even dilated and hypertrophic cardiomyopathies, are present in patients with left ventricular noncompaction. We recently reported a family with overlapping phenotypes for left ventricular noncompaction, hypertrophic cardiomyopathy, and Wolff- Parkinson-White syndrome. We could not obtain genetic molecular studies but on the basis of features shared with affected patients suspected a mutation of either *PRKG2* and *LAMP-2* which cause hypertrophic cardiomyopathy with Wolff-Parkinson-White syndrome or Danon's disease respectively (Alday et al., 2010).

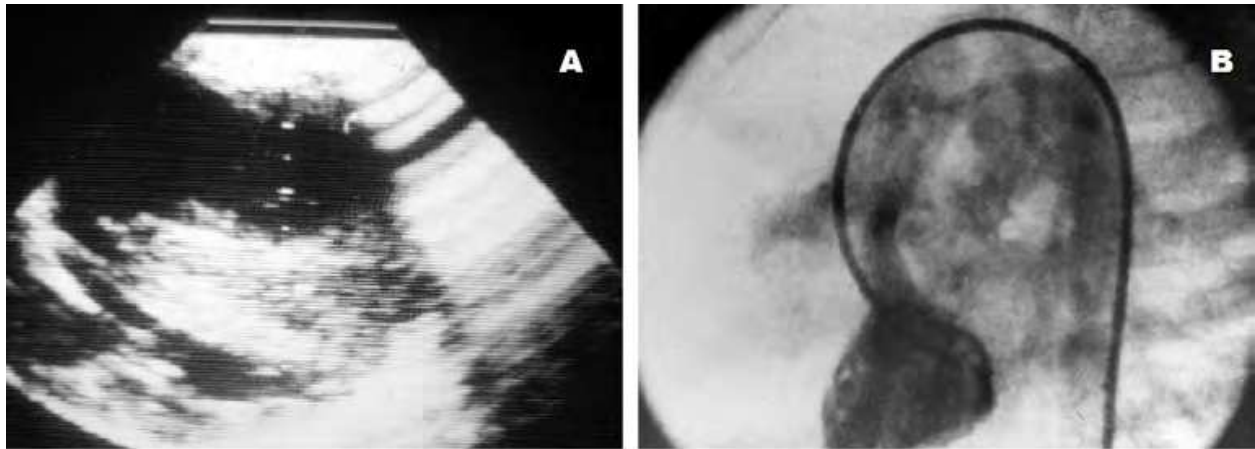


Fig. 22. Two dimensional echocardiogram (A) and left ventricular cineangiography (B) in a patient with tetralogy of Fallot six months after a right modified Blalock-Taussig shunt showing severe ventricular septal hypertrophy, a hypoplastic left ventricle and a dilated aorta overriding a ventricular septal defect.

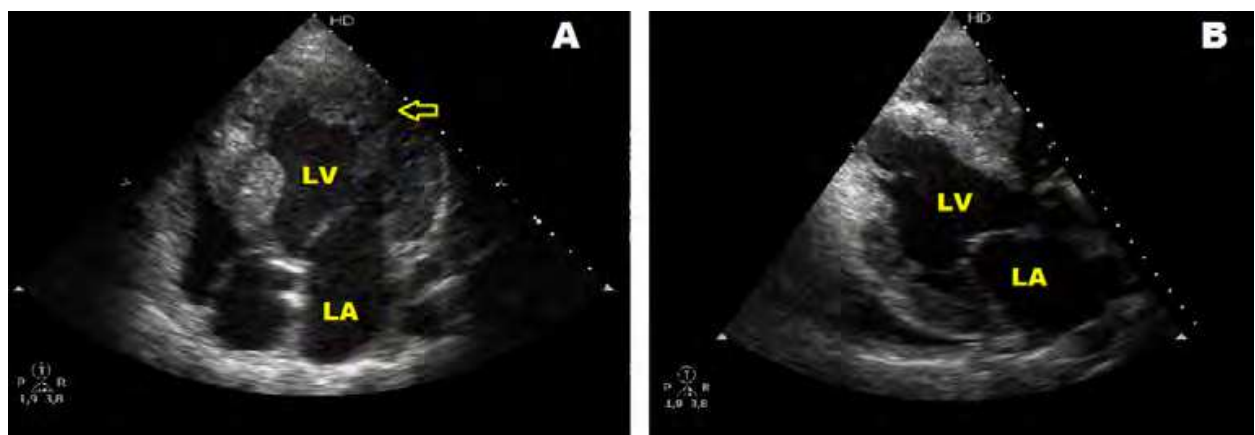


Fig. 23. A and B. Echocardiographic four-chamber view of two sisters followed since infancy showing hypertrophic cardiomyopathy and associated left ventricular noncompaction. The arrow in A points deep sinusoid tracts. LV: left ventricle, LA: left atrium.

10. Treatment

The treatment of hypertrophic cardiomyopathy aims to improve the quality of life alleviating symptoms and to stratify the risk for sudden death to prevent it from happening. Several algorithms have been proposed, a slightly modified one is shown in Fig. 24 (Berger et al., 2009). These authors emphasize the existing difficulties to implement prospective controlled randomized trials to define the benefits of different treatment options for this population, therefore most current therapies are empirical or the result of consensus. In older children intensive physical exercise is contraindicated. The disease presenting early has a severe prognosis this being the reason for indicating medical treatment even in asymptomatic children (Bruno et al., 2002). Patients who are symptomatic should receive pharmacological treatment with adrenergic beta blockers which do not decrease the basal outflow gradient but are able to prevent its accentuation in situations of exacerbated inotropism of the heart.

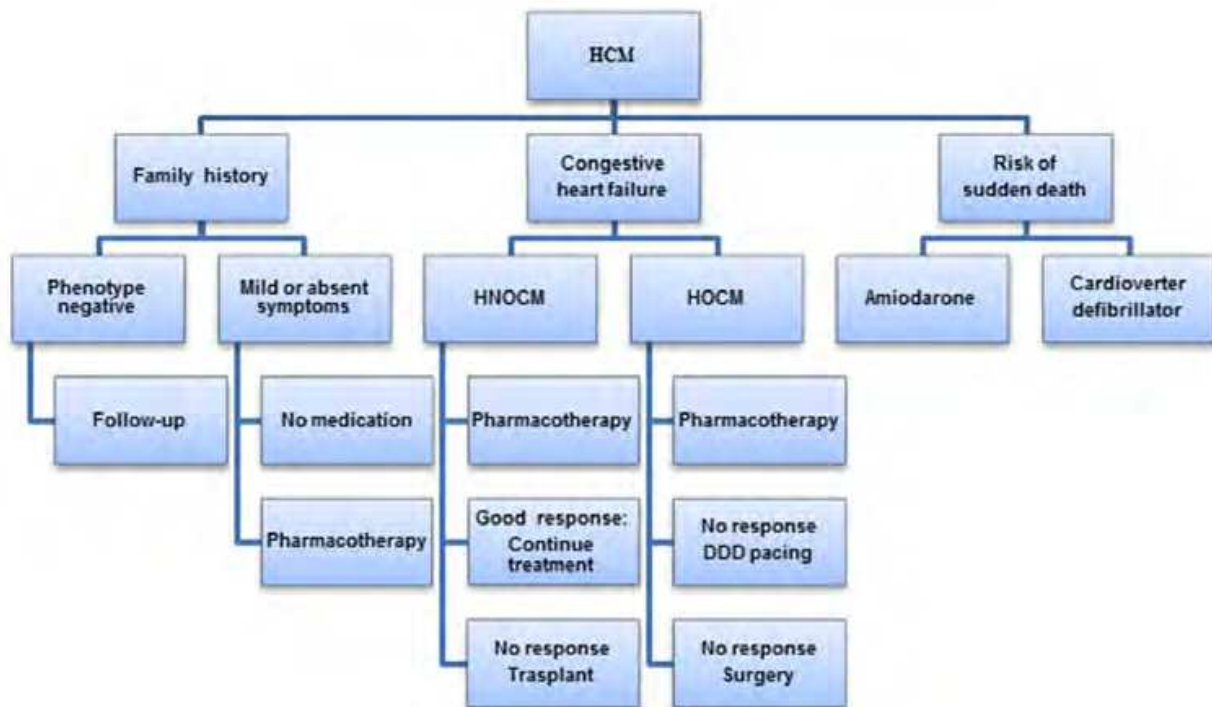


Fig. 24. Algorithm for the treatment of hypertrophic cardiomyopathy (Modified from Berger, et al. (2009) *Cardiol Young*, Vol.19, pp. 66-73).

Beta blockers also have anti-ischemic properties which increase ventricular filling by decreasing the heart rate. In these patients, calcium channel blockers like verapamil can be an alternative to beta blockers. It is not recommended to use them together. In patients with severe gradients and pulmonary hypertension are not advised because of the danger of precipitating acute pulmonary edema. If there is no improvement, disopyramide, which is an antiarrhythmic drug with negative inotropic effects, is able to decrease basal gradients. The combination of disopyramide and beta blockers has been used successfully in adults but there is no reported experience in children (Sherrid et al., (2005). For very symptomatic smaller children, in spite of full medical treatment, permanent DDD pacing with short atrioventricular interval to favor the consistent capture of the right ventricle has been used to lower the left ventricular outflow tract obstruction by changing the pattern of left ventricular activation (Alday et al., 1998 & Fananapazir et al., 1992). DDD pacing is a reasonable alternative to surgery in symptomatic children despite pharmacological treatment if they are still too young for surgery, taking into account that the approach to an extended septal myectomy is just the aortic valve with a small annulus at this age. A very recent study has also shown progressive relief of symptoms and gradient reduction at long term follow-up (Galve et al., 2010). However, as with other types of treatment, DDD pacing does not protect against the possibility of sudden arrhythmic death (Bruno et al., 2002). The gold standard for the treatment of hypertrophic obstructive cardiomyopathy is still the surgical septal myectomy (B.J. Maron et al., 2003a; Stone et al., 1993). In experienced centers the mortality is very low and the abolition of the gradient is instantaneous and persistent. The remaining obstruction is usually negligible. These excellent hemodynamic results are associated with improvement of symptoms. The results have been followed for many years and the need for repeat procedures is rare. It should be remembered that the child has to be old enough to permit the transaortic approach to the septum (Berger et al.,

2009). For this reason, reoperation might be necessary in children 14-year-old or younger (Minakata et al., 2005). With regard to catheter septal ablation with alcohol or radiofrequency the 2003 Expert Consensus Document on Hypertrophic Cardiomyopathy, addressing alcohol septal ablation, states that until the long-term effects of the myocardial scar are known, the procedure is not advised in children (Jensen et al., 2011; B.J. Maron et al., 2003a; Sigwart 1995) In patients with symptomatic hypertrophic nonobstructive cardiomyopathy, calcium antagonists like verapamil could be used to improve the diastolic performance of the left ventricle. Beta blockers are also indicated in this form of the disease. Recently the use of perhexiline which is a metabolic modulator has been introduced for the treatment of patients with this phenotype with improvement of the diastolic performance of the left ventricle and of symptoms (Abozguia et al.; 2010). This was a preliminary report that has still to be supported by further investigations. Infants with heart failure and older children with evolution to a dilated cardiomyopathy should be treated with drugs usually employed for treatment of systolic heart failure. These cases may eventually need heart transplantation (Shirani et al., 1993).

11. Prevention

Risk stratification of sudden death in infants and children differs from what is done in adults. In children, cardiac death occurs infrequently and non sudden cardiac death is as common as sudden arrhythmic death. The main risk factors for sudden death in children with hypertrophic cardiomyopathy are, according to Maron et al., previous cardiac arrest, syncope, or sustained ventricular tachycardia, family history of sudden death, frequent repetitive non sustained ventricular tachycardia, abnormal blood pressure response to exercise, end-stage hypertrophic cardiomyopathy, and massive left ventricular hypertrophy (B.J. Maron et al., 2003b). Other criteria for death prognostication proposed more recently, specifically in children, take into account the electrocardiographic voltage and echocardiographic parameters like the septal thickness and the left ventricular wall/left ventricular diastolic dimension ratio (Ostman-Smith et al., 2005). For non-sudden cardiac death, massive left ventricular hypertrophy and abnormal blood pressure response to exercise are considered significant risk factors for mortality (Decker et al., 2009). Sudden cardiac death due to hypertrophic cardiomyopathy occurs mostly in adolescence and early adulthood and very infrequently before 10 years of age. These cases are due to ventricular tachycardia or ventricular fibrillation. In fact, hypertrophic cardiomyopathy is the most common cause of sudden death in the young including athletes (J. Seidman & C. Seidman, 2001). This is the reason why the diagnosis of hypertrophic cardiomyopathy at this age is a strong indication to discontinue the practice of competitive sports. At this time it seems that to establish a prognosis by the knowledge of the specific disease causing mutation is not reasonable for the individual patient. Implantable cardioverter defibrillators are effective to prevent arrhythmic sudden death but in infants and children are indicated mainly in secondary prevention (B.J. Maron, et al., 2000b; Epstein, A.; et al., 2008). The cardioverter defibrillator implantation is plagued with complications in children, this being the reason for the reluctance of its use in primary prevention (Berul et al., 2008). In a nonrandomized controlled trial amiodarone was at one time reported to improve survival in hypertrophic cardiomyopathy associated with ventricular tachycardia (McKenna et al., 1985). However, the frequent toxic effects of amiodarone might counteract its benefits (Berger et al., 2009). It then could be concluded that the properly functioning cardioverter defibrillator is

nowadays the only effective treatment for the prevention of sudden arrhythmic death (B.J. Maron, et al., 2000b).

12. Screening strategies

It is well known that hypertrophic cardiomyopathy is a genetic disease of the sarcomeric proteins with great heterogeneity of genetic basis and fenotypic expression which does not only involve these structures but also include abnormalities of the connective tissue, mitral valve, and intramural coronary arteries. The genetic defect may be influenced by modifiers genes and unknown enviromental factors. The strategy for clinical screening for hypertrophic cardiomyopathy with 12 lead electrocardiogram and echocardiogram in non affected family members including < 12 year-old children, is optional, unless there is history of early death due to hypertrophic cardiomyopathy or other serious complications in the family, or is an athlete in training, or evidence of incipient left ventricular hypertrophy, or onset of suspicious symptoms. In family members 12 to 18 years of age, clinical follow-up should be performed every 12 to 18 months and from then on every 5 years. The period of screening should be extended to adulthood since we now know that certain mutant genes can provoke a disease of rather late onset (B.J. Maron et al., 2004).

13. Conclusion

Great strides have been made since the rediscovery of hypertrophic cardiomyopathy in the late 50's last century. Important advances in the understanding of the genetics and physiopathology of the disease have occurred as well as development of superb imaging technologies. Treatment is tailored according to the phenotype and stage of the disease. The very important differences between adult and childhood hypertrophic cardiomyopathy have been underlined in this chapter hoping that will help physicians in decision making when dealing with these patients.

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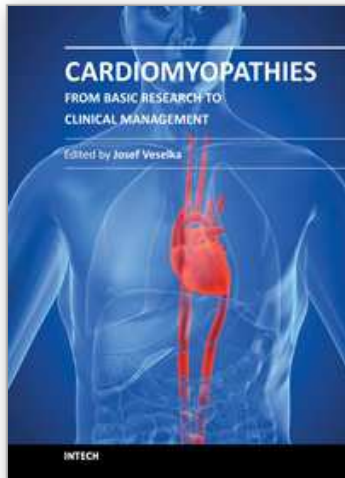
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Cardiomyopathy means "heart (cardio) muscle (myo) disease (pathy)". Currently, cardiomyopathies are defined as myocardial disorders in which the heart muscle is structurally and/or functionally abnormal in the absence of a coronary artery disease, hypertension, valvular heart disease or congenital heart disease sufficient to cause the observed myocardial abnormalities. This book provides a comprehensive, state-of-the-art review of the current knowledge of cardiomyopathies. Instead of following the classic interdisciplinary division, the entire cardiovascular system is presented as a functional unity, and the contributors explore pathophysiological mechanisms from different perspectives, including genetics, molecular biology, electrophysiology, invasive and non-invasive cardiology, imaging methods and surgery. In order to provide a balanced medical view, this book was edited by a clinical cardiologist.

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