HYPERTROPHIC CARDIOMYOPATHY
A MODERN CLINICAL AND THERAPEUTIC PERSPECTIVE

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REZUMAT
Cardiomiopatia hipertrofică (CMH) e o afecțiune cardiacă familială relativ frecventă, cu un spectru clinic larg, marcată de un important potențial de risc prematur cardiovascular, respectiv de moarte subită, precum și de simptome incapacitante la persoane relativ tinere. Datorită aspectelor clinice variate, CMH reprezintă încă o problemă pentru cardiologi, și nu doar pentru ei, acum când noi modalități terapeutice ne stau la îndemnă, există încă o serie de probleme ridicate de alegerea modalității optime de diagnostic și tratament corespunzător.

Cuvinte cheie: cardiomiopatie hipertrofică obstrucțivă, gradient, ablație, miectomie

ABSTRACT
Hypertrophic cardiomyopathy (HCM) is a relatively common familial cardiac disease, with a broad clinical spectrum, with an important premature cardiovascular risk, including sudden death, but also with incapacitating symptoms, especially in young patients. Because of its heterogeneous clinical course and expression, HCM represents a management dilemma for cardiologists and other practitioners, especially now, when new treatment strategies are available and many questions still arise during the search for the right approach for diagnosis and treatment.

Key Words: obstructive hypertrophic cardiomyopathy, gradient, ablation, myectomy

LEARNING OBJECTIVES
After studying this article, the practitioner (cardiologist or not) should be able to recognize the clinical signs of hypertrophic cardiomyopathy, to differentiate between the two forms - obstructive and non-obstructive hypertrophic cardiomyopathy and to choose the best treatment option, including surgery or alcohol septal ablation, heaving in mind the echocardiographic and angiocoronarographic aspect (the anatomy of the coronary arteries) and, especially, the risk of sudden cardiac death.

INTRODUCTION
Hypertrophic cardiomyopathy (HCM) is a genetically transmitted primary cardiac disease, relatively common (about 1:500 in the general adult population), that affects men and women equally and occurs in many races and countries. HCM has a broad clinical spectrum and its risk of premature cardiovascular death and incapacitating symptoms in young patients- including trained athletes- but not only, has been repeatedly emphasized.

For the first time, around year 1900, German and French authors reported the results from the autopsy of four patients with striking hypertrophy involving the ventricular septum, which appeared to be responsible for the obstruction in the left ventricular ejection.

HCMs are myocardial diseases without an obvious cause, genetically, clinically, morphologically, functionally heterogeneous, variable in their evolution, from asymptomatic shapes to heart failure, arrhythmias and sudden death - the annual death toll averages...
around 1.2% of which half represents sudden deaths.\textsuperscript{7,8} Because of its heterogeneous clinical course and expression, HCM represents a management dilemma to cardiologists and other practitioners. Furthermore, with the recent treatment strategies, targeting different subgroups of patients, many questions arise.\textsuperscript{4} Hence, the difficulty of identifying as early as possible patients at risk, in order to prevent sudden death.

**CLINICAL DIAGNOSIS**

The distinctive sign of HCM is the unexplained left ventricular (LV) hypertrophy, typically asymmetric in distribution, demonstrated echocardiographically or frequently at necropsy (after death). (Fig 1, 2) Left ventricular wall thickening is associated with a nondilated and hyperdynamic chamber (often with systolic cavity obliteration) in the absence of another cardiac or systemic disease (e.g., hypertension or aortic stenosis) capable of inducing this kind of hypertrophy, independent of whether or not LV outflow obstruction is present.

![Figure 1. LV echocardiography - long parasternal axis view.](image1)

![Figure 1. LV echocardiography - apical 4 chambers view.](image2)

![Figure 3. Echocardiography - LV/Ao gradient (quantitative Doppler)](image3)

It is important to distinguish between the obstructive or non-obstructive forms of HCM, based on the presence or absence of the LV outflow gradient during resting and/or provoking conditions. Outflow gradients are responsible for a loud apical systolic ejection murmur associated with hypertrophy of the basal portion of the ventricular septum and small outflow tract and, also, an enlarged and elongated mitral valve. Obstruction may either be subaortic or midventricular in location. Subaortic obstruction is caused by systolic anterior motion (SAM) of the mitral valve leaflets and midsystolic contact with the ventricular septum. SAM is responsible, also, for the concomitant mitral regurgitation (mild-to-moderate in degree), due to incomplete leaflet apposition, typically directed posteriorly into the left atrium.\textsuperscript{4} Obstruction in HCM is characteristically dynamic – may be spontaneously labile and vary considerably with a number of factors (such as ingestion of a small amount of alcohol or a heavy meal).

It is important to divide the HCMs into hemodynamic subgroups based on the peak instantaneous gradient as assessed with continuous wave Doppler: (Fig.3)

1) Obstructive gradient under basal (resting) conditions ≥ 30 mm Hg (2.7 m/s by Doppler);
2) Latent (provoked) obstructive gradient < 30 mm Hg under basal conditions and ≥ 30 mm Hg with provocation;
3) Non-obstructive – gradient < 30 mm Hg in basal conditions or during provoking conditions.\textsuperscript{4}

**GENETICS, MOLECULAR AND ELECTROPHYSIOLOGICAL CHARACTERISTICS**

HCM is considered to be a genetic disease, transmitted mostly after Mendelian laws: the uniformity law, the law of dysfunction and characteristic independence (first generation hybrids present uniform characteristics, 50% of the individuals in second generation hybrids present the characteristics of the first, 25% present recessive characteristics, then in the next generations the hybrids characteristics are transmitted according to statistical probabilities).\textsuperscript{7,8}
HCM is inherited as a Mendelian autosomal dominant trait, caused by mutations in any one of 10 genes encoding protein components of the cardiac sarcomere composed of thick or thin filaments with contractile, structural or regulatory functions.\(^4\)

The discovery, about 10 years ago, of a mutation in \(\beta\)-myosin (MyHC) heavy–chain in a family suffering from HCM led to elucidation of a HCM molecular genetic basis, with later identification of another mutation in 10 sarcomere proteins. Up to now, the accused genes and mutations have been identified for approximately 2/3 of the HCM cases, the most frequent being gene mutations that encode \(\beta\)-myosin (heavy–chain–MyHC, gene located on chromosome 14), T cardiac troponin (cTnT, gene located on chromosome 1) and C link protein with myosin (MyBP–C, gene located on chromosome 11).\(^{7,10,11}\) Of course, there are still cases of yet unknown etiology. The discovery of the genetic molecular base of HCM allows a stratification of the genetic risk before the appearance of clinical phenotypes, including the establishment of the sudden death risk. Generally, mutation in \(\beta\)-myosin heavy chain gene associates with an early debut of the disease, a more severe hypertrophy and a greater incidence of sudden death, compared to mutation of the C-linking protein with myosin gene (MyBP–C). The phenotype with mutations in the gene that encodes cardiac T troponin (cTnT) is characterized by a relatively mild hypertrophy, but high incidence of sudden death and extended myocardial disorder. Another mutation in the gene encoding \(\alpha\)-tropomiosin (E62Q) would be associated with a high incidence of sudden death, as revealed by Jongbloed & co. in a HCM family, 50% of its members presenting young sudden death, with variable degree of myocardial hypertrophy.\(^{11}\) More to it, there is a great variability of phenotype expression through the affected individuals in a family and through the family members presenting identical causal mutations.

Clinical screening of first-degree relatives and other family members should be done. The recommended clinical strategy consists of: history, physical examination, 12-lead ECG, 2D-echocardiography at annual evaluations during adolescence (12-18 years of age). Affected patients identified through family screening are evaluated on \(\sim\)12-18-month basis.\(^4\)

Largely, existing data suggest genetic mutations lead to clinical, electrocardiographic and echocardiographic bursts, and prove that a phenotype associated with a genetic mutation does not exist. Moreover, the phenotype expression is affected by epigenetic factors (e.g., DNA methylation), epistasis (gene interaction), post-transcriptional and post-translational genetic products modifications, the presence of simultaneous diseases (hypertension), environment factors, etc.\(^{11-13}\)

As a result of the complexity of the molecular biology of hypertrophy, a large number of genes may influence the expression of the phenotype. The role of genetics in the genesis of electrophysiological abnormalities associated with LV hypertrophy is also recognized. For example, an increased risk for atrial fibrillation in HCM has been identified with \(\beta\)-myosin heavy chain Arg663 His mutation.\(^{4,14}\)

Missense mutations in the gene encoding the gamma-2-regulatory subunit of the AMP-activated protein kinase (PRKAG2), a regulator of cellular energy homeostasis, have been reported to cause familial LV hypertrophy associated with ventricular preexcitation.\(^{15,16}\)

Indeed, in patients with obstructive HCM the hypertrophic septum is characterized by a marked alteration of the regional electrophysiological properties. The local bipolar potentials display a significantly lower voltage than potentials recorded at the lateral LV. This finding is in concordance with the presence of myocardial replacement scarring, expanded interstitial fibrosis and/or myocardial fiber disarray (mostly in the thickest part of the septum), described by now by many authors.\(^{17-20}\)

There is an interest in gene therapy, but in HCM this technology is very problematic. Because most mutations cause substitution of a single amino acid within the encoded protein, gene therapy would theoretically have the daunting task to select and inactivate the mutated gene, the encoded protein, or both. Even more, the selection of the patients for gene therapy would be complex, because some forms of the HCM are compatible with normal longevity and absence of symptoms.\(^4\)

**EVOLUTION**

The clinical course of the disease is variable; patients could remain stable over long periods of time, with up to 25% of the HCM patients achieving normal longevity (\(\geq\) 75 years of age). The annual mortality is about 1%. However, the course of the evolution may encounter clinical events like: sudden death, embolic stroke, heart failure etc., events that dictate treatment strategies.

Let’s not forget that HCM may coexist with other cardiac conditions like systemic hypertension, coronary artery disease etc., that will also guide the choosing of a specific treatment strategy. For
example, in case of association of HCM with systemic hypertension we will avoid ACE inhibitors to control hypertension.

Based on different studies, up to now, multiple factors concerning sudden death have been identified in HCM patients: survived sudden cardiac death, young age death in family history, “malign” causal mutations, syncope history, severity of the myocardial hypertrophy (massive LV hypertrophy with septal wall thickness > 30 mm), extended myocytic disorders, extension of interstitial fibrosis, early start of the disease, arterial pressure’s abnormal response to effort, presence of nonsustained ventricular tachyarrhythmias in ECG Holter monitoring.12,21

A distinctive final phase of disease evolution appears in 10-15% of symptomatic patients with HCM (“end-stage” or “dilated” or “burned-out” phase), with progressive congestive symptoms, limited exercise capacity, atrial arrhythmias, left ventricular remodeling – enlarging of the left ventricular cavity, thinning of some regions of the wall, systolic dysfunction and, sometimes, spontaneous reduction of the subaortic gradient.22

HCM cases have also been reported in older patients (> age of 60). In some of these patients HCM may be well tolerated to particularly advanced ages (80 to 90 years and above), so it must be regarded as a condition compatible with normal longevity.23 In other elderly patients symptoms are not present early in life, but severe functional limitation and heart failure may intervene abruptly for the first time after age of 60. Characteristically, older patients with HCM have a relatively small heart, with modest increase in left ventricular wall thickness (≤ 20mm), outflow tract morphology severely distorted, anterior displacement of the mitral valve and often deposits of calcium in the mitral annular region.22,23 It is uncertain if older patients with HCM have the same genetic etiology as the other patients within the clinical spectrum.

MANAGEMENT STRATEGIES

Treatment should be directed to the abnormal diastolic compliance of the LV and reduction of the major LV/Ao gradient; β-blockers, Ca++ blockers, alone or in association, represent the most used conservative treatment; both categories reduce myocardial contractility with cavity dilatation and diminishing the ejection tract (ET) obstruction, thus improving the LV diastolic function; moreover, reducing cardiac frequency, they prolong the LV filling duration, reducing ejection tract (ET) obstruction.

Among Ca++ blockers the most chosen are those with weak vasodilation effect, with important depressing effect on myocardial contractility – e.g. Verapamil.

Other medications that reduce the preload (nitrates, diuretics, IECA, angiotensin receptor blockers - ARBs) reduce the dimension of the chambers and aggravate the symptoms!

Inotropic medication (digoxin, catecholamines) worsen the obstruction in the ejection tract of the left ventricle, do not reduce telediastolic pressure (TDP) and can induce arrhythmias.

Vasodilating drugs elevate the gradient at the ejection tract level and produce reflex tachycardia with even more depressed LV diastolic function.

Retrospective studies with antiarrythmic drugs (Amiodarone) have revealed a possible reduction in mortality rate in patients with ventricular tachycardia (VT) or syncope. Disopyramide has a negative antiarrythmic, inotrope negative effect.

Implanted defibrillators have been used in patients resuscitated for sudden death but it is not certain that their use would reduce the HCM mortality.24

Infectious endocarditis prophylaxis is recommended.

Overdosed exercise is not recommended because of the high risk of sudden death linked to excessive effort.

Septal miotomy or miomectomy is reserved for patients with severe, incapacitating symptoms, despite the prescribed and followed drug treatment. This procedure improves the symptoms, but it doesn’t seem to reduce mortality.25

The patients with HCM referred to surgical treatment have, usually, particularly marked outflow gradients (peak instantaneous usually ≥ 50 mm Hg), as measured with continuous wave Doppler echocardiography.4 In addition, these patients have severe limiting symptoms (exertional dyspnea and chest pain, regarded as NYHA functional classes III or IV, refractory to maximum medical therapy).

Over the past four decades, based on the experience of a number of centers throughout the world, the ventricular septal myectomy operation (the Morrow procedure) has proven useful for the amelioration of outflow obstruction in both adults and children with obstructive HCM and severe drug-refractory symptoms.4 But, myectomy should be confined to experienced centers in this procedure. Some advantages of myectomy surgery are represented by more immediate and complete relief of resting and provoked obstruction and mitral regurgitation; smaller incidence of complete heart block, requiring pacemaker; no risk of coronary dissection or unwanted myocardial infarction; no evidence in long-term studies.
that myectomy is arrhythmogenic; capacity to deal with concomitant problems such as midventricular obstruction, constricting muscle bridge over the left anterior descending coronary artery, mitral valve repair or replacement for additional valvular problems, etc.26

Selective septal embolization (percutaneous alcohol septal ablation) may represent an alternative to septal miciectomy, as it is obviously superior to it as far as we know for now.25,27 First reported in 1995 by Sigwart, this catheter interventional treatment involves the introduction of absolute alcohol into a target septal perforator branch of the left anterior descending coronary artery for producing a myocardial infarction within the proximal ventricular septum.28

Septal ablation mimics the hemodynamic consequences of myectomy by reducing the basal thickness of the septum, by producing akinetic or hypokinetic septal motion, with enlarging of the LV outflow tract and lessening the SAM of the mitral valve and the degree of the mitral regurgitation.3 The advantages of ethanol ablation consist in: avoidance of cardiopulmonary by-pass, especially in elderly patients; shorter hospitalization; shorter recovery time; smaller costs.26

Table 1 presents the comparison between septal myectomy and percutaneous alcohol septal ablation.4

Table 1. Comparison between septal myectomy and percutaneous alcohol septal ablation.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Myectomy</th>
<th>Ablation</th>
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<tbody>
<tr>
<td>Operative mortality</td>
<td>1-2%</td>
<td>1-2%</td>
</tr>
<tr>
<td>Gradient reduction (at rest)</td>
<td>≤ 10 mm Hg</td>
<td>≤ 25 mm Hg</td>
</tr>
<tr>
<td>Symptoms (subjective)</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>Symptoms (objective)</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>Effectiveness despite anatomic variability</td>
<td>usually</td>
<td>uncertain</td>
</tr>
<tr>
<td>Pacemaker (high grade A-V block)</td>
<td>1-2%</td>
<td>5-10%</td>
</tr>
<tr>
<td>Procedure frequency</td>
<td>x</td>
<td>15-20x</td>
</tr>
<tr>
<td>Sudden death risk (long-term)</td>
<td>very low</td>
<td>uncertain</td>
</tr>
<tr>
<td>Available follow-up</td>
<td>more than 40 years</td>
<td>about 6 years</td>
</tr>
<tr>
<td>Intramyocardial scar</td>
<td>absent</td>
<td>present</td>
</tr>
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In some cases, a mitral valve replacement was made – the cases with severe mitral valve dysfunction, with decrease of the gradient in the ET of the LV.

The dual-chamber cardiac pacemaker implant was used in order to modify the LV depolarization sequence for some of the patients with obstruction in the ET of the LV, with the decrease of the obstruction severity and the improvement of the symptomatology. The long term effect, including that on mortality, needs further studying.

**PREVENTION OF SUDDEN CARDIAC DEATH**

When risk level for sudden cardiac death is very high (see major risk factors for sudden cardiac death in HCM described above) and requires intervention, the ICD is the most effective and reliable treatment option available.4

**SPECIAL SUBGROUPS OF HCM PATIENTS**

When pregnancy is concerned there is no evidence that patients with HCM are at increased risk during pregnancy and delivery. Absolute maternal mortality is very low (although higher than in general population) and is related to high-risk clinical profile. Such patients should be carefully observed during pregnancy. Otherwise, most of the pregnant HCM patients undergo normal vaginal delivery, without need for cesarean section.4

Athletes – according to the Recommendations of the Expert Consensus Panel of the 26th Bethesda Conference, young patients with HCM should be restricted from intense competitive sports to reduce the risk of sudden cardiac death that may be associated, and increased by such extreme lifestyle.29 The stratification of the risk for athletes with HCM is difficult given the extreme environmental conditions to which they are often exposed (alterations in hydration, electrolyte-abnormalities). The consensus of the general medical community supports avoiding exposure to most competitive sports for young athletes with HCM to reduce the risk of sudden cardiac death, so withdrawal from the athletic arena can be regarded as a treatment modality in this disease.29,30

**CONCLUSIONS**

We must take into consideration that some patients with HCM present severe symptoms and are at increased risk for sudden death. Such patients need full medical evaluation in experienced diagnosis and treatment centers for improvement of their symptomatology, identification of those at risk for sudden cardiac death and for the best treatment choice in each case (from medical treatment to interventional or surgical approach, gene therapy, etc.). So far, both important strategies – myectomy and percutaneous alcohol septal ablation – managed to reduce LVOT obstruction by reducing the septal thickness and to improve NYHA functional class significantly. However,
there are benefits and drawbacks for each of them that must be counterbalanced when deciding on treatment for obstructive HCM.

REFERENCES


