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REVIEW

Genetic screening of patients with hypertrophic cardiomyopathy – a new diagnostic strategy for risk stratification?

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Abstract: Hypertrophic cardiomyopathy (HCM) is an autosomal dominant inherited disease of the heart muscle and its main characteristic is unexplained hypertrophy of the left and/or the right ventricle. HCM is the most common genetically determined cardiovascular disease and is prevalent in approximately in 1 of 500 of the population. The most serious complication of HCM is sudden cardiac death (SCD) which can be the first manifestation of the disease. However, there are other forms of benign prognosis which do not jeopardize patient's health or life. The clinical symptoms of HCM are partly dependent on mutations in affected sarcomere genes. Different mutations in the same gene can present as malign with a high risk of SCD, while other mutations can be benign. The clinical symptomatology can also be influenced by other factors such as the presence of polymorphisms in other genes. Nowadays the aim of intensive clinical research is to access the contribution of molecular genetic methods in HCM diagnostics as well as in risk stratification of SCD. It is expected that genetic analyses will have an important consequence in the screening the relatives of HCM patients and also in the prenatal diagnostics and genetic counseling *(Tab. 2, Fig. 1, Ref. 45).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: hypertrophy, cardiomyopathy, genetic mutations, sudden cardiac death, prognosis.

Hypertrophic cardiomyopathy (HCM) is a myocardial disease caused by mutations in genes encoding the sarcomere constituents of the heart muscle (Maron et al, 2003, Ho et al, 2006). The disease is associated with severe complications such as heart failure, arrhythmias and sudden cardiac death (SCD). The classification of SCD risk predictors and prognosis is difficult and it has not been definitively established yet. The individual risk is derived from genetic determination of the disease, myocardial pathology and pathophysiological abnormalities.

Pathologist Donald Teare gave the first pathologic-anatomical description of the disease in 1958. He published case histories of eight patients at the age of 14–44 years. Their autopsy showed "asymmetric septal hypertrophy", which he described as diffuse tumours of the myocardium (Teare et al, 1958). This clinical unit was given many synonyms until the end of the 1970s. Nowadays the generally accepted name of the disease is *hypertrophic cardiomyopathy* with or without obstruction. The main characteristic of this primary myocardial disease is unexplained hypertrophy of the heart wall. Nevertheless, special cases occurring in some patients without marked hypertrophy, however with microscopic signs typical for HCM, remain an unexplained paradox. Therefore, there still exists a small subgroup of patients with HCM, whose left ventricular wall's thickness ranges within border values 12–14 mm (Veselka et al, 2007).

Pathologic anatomy of HCM is based on myocardial hypertrophy of interventricular septum and/or the remaining walls of the left ventricle. Histopathological hallmarks of HCM are myocyte hypertrophy with "disarray", the regions of non-specific interstitial fibrosis and the disease of small intramural vessels ("small vessel disease"). From the pathophysiological point of view, HCM is characterized by supernormal contractility whereas diastolic filling of the left ventricle is restricted. Another important characteristic feature is high electrical vulnerability of ventricles and atria due to which HCM can manifest by a wide spectrum of clinically serious arrhythmias such as malignant ventricular tachyarrhytmias with SCD risk. Ventricular electrophysiological abnormalities are the direct consequence of inhomogeneity of cellular architecture ("disarray") that is genetically determined. However, atrial abnormalities and atrial remodelling are caused by diastolic dysfunction.

Approximately 25 % of patients have an obstructive form of HCM e.g. dynamic systolic gradient in the left ventricular outflow tract (LVOT) is present. The systolic pressure gradient cannot be detected in the predominantly non-obstructive form of the disease. However, the gradient can be provoked by several stimuli (e.g. exercise, Valsalva manoeuvre). It can cause symptoms that are important in patient's history without rest gradient. In most cases, the diagnosis is revealed in adults at the age of 20–40, often during the screening of patients' relatives for HCM.

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Tab. 1. Risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy (Crawford MH, DiMarco J, Paulus WJ et al. Cardiology 2004, Elsevier limited 2001, 961–975).

Risk factor	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Blood pressure (patients <40 age)	75	66	15	97
Ventricular tachycardia on Holter ecg	69	80	22	97
Syncope – general	29	83	25	86
patients <45 age	42	82	29	89
SCD in first degree relatives	42	79	28	88
Hypertrophy of left ventricle ≥30 mm	26	88	13	95

However, the familial form of the disease can also appear in newborns and sporadically also at high age. The establishment of exact diagnostic and therapeutic rules is hindered by the complexity of HCM and a relatively low number of patients. Therefore the management requires deep knowledge of genetics, pathophysiology and pathology. Genetic analyses of HCM patients and their next of kin relatives represent the promising base for the future of prevention and treatment strategy.

Clinical features of HCM

The spectrum of clinical signs is wide-ranging and varies from asymptomatic mutation carriers to patients with refractory symptomatology (Maron et al, 2003, Ho et al, 2006). The clinical symptoms result mostly from diastolic dysfunction, LVOT obstruction, myocardial ischaemia or rhythm disturbances, particularly atrial fibrillation. They can often be confused with other more frequently occurring clinical units, e.g. coronary artery disease (CAD) or aortic stenosis. Symptoms are usually present already at the stage of echocardiographically apparent myocardial hypertrophy. The disease prevalence in population is 0.2 %, whereby annual mortality ranges between 0.5–1.5 % (Čurila et al, 2007). The most formidable manifestation is an unexplainable syncope as a marker of SCD, heart failure and SCD as the first manifestation of the disease without any alarming signals.

Almost a half of the patients complain of *palpitations* that can be the manifestation of paroxysmal supraventricular tachycardia, atrial fibrillation or ventricular rhythm disturbances. The pathological substrate of arrhythmias is created by electrophysiological instability and heart muscle remodelling due to ischemia, fibrosis and diastolic dysfunction. The most serious complication of the disease is *sudden cardiac death* caused by malign ventricular arrhythmias usually provoked by an external factor (e.g. intensive exercise). Heart rhythm disturbances can also be the substrate of *syncope,* although syncope mostly occurs in cases with markedly developed hypertrophy. The prevalence of syncope is closely related to the degree of myocardial thickness as well as impaired left ventricular filling or sudden expression of LVOT obstruction during exercise. In almost 60 % of HCM patients, atrial fibrillation causes *embolisation. Dyspnoe* occurs in patients with HCM quite often, due to impaired diastolic filling of the left ventricle. Another frequent clinical feature is *chest pain* often mistaken for a sign of coronary artery disease. Coronary angiograms of a majority of HCM patients with documented myocardial ischaemia are normal (Bougard et al, 1996). From the pathophysiological point of view, ischaemia and chest pain are caused by the disproportion between the delivery of oxygen and its increased consumption by hypertrophied myocardium as well as by coronary spasms and systolic compression of anterior septal branches of ramus interventricularis. In addition to this, increased filling pressure of the left ventricle causes subendocardial ischaemia. Another mechanism contributing to the coronary reserve decrease is the "small vessel disease" characterized by the thickening of the vascular wall due to proliferation of smooth muscles and collagen.

According to current knowledge, HCM is the most common cause of SCD in young people below the age of 30. *The presence of non-invasive predictors* – SCD in next of kin relatives, malign genotype, unexplained syncope, abnormal blood pressure response to exercise, ectopic ventricular activity and massive left ventricular hypertrophy (≥30 mm) are associated with high risk of SCD and should be taken into account when ICD (implantable cardioverer defibrillator) implantation is considered (Maron et al, 2003) (Tab. 1). However, there is still no absolutely unequivocal parameter of individual risk prediction of specific clinical features, including life-threatening complications such as cardiac arrest, malign arrhythmias and SCD.

Deterioration of clinical stage and severe heart failure symptoms in patients with HCM can be exhibited suddenly without any previous symptoms. The dominant feature of HCM is left ventricular hypertrophy. However, the influence of pathological substrate as the definitive pathophysiological basis for SCD risk is still not absolutely clear. Varnava et al found a positive correlation between the presence of increased *disorganisation* of myocardial architecture and prevalence of ischaemia with abnormal tolerance to exercise in patients who died at the age <21 years (Varnava et al, 2001). The authors also noticed higher appearance of myocardial *fibrosis* in patients who died from cardiac arrest, and in patients with nonsustained ventricular tachycardia (Varnava et al, 2001). Another interesting finding was revealed by Maron et al (2008) in an asymptomatic 21-year-old male patient in whom ventricular fibrillation was interrupted by an ap-

propriate defibrillator shock of ICD. The decision of prophylactic ICD implantation was based largely on the presence of apparent extensive myocardial *fibrosis,* currently not considered as a risk factor in HCM. Except the fibrosis, the degree of *hypertrophy* seems to be the most determining prognostic factor in young people with HCM.

Left ventricular outflow tract obstruction is the predictor of deteriorated clinical outcome in HCM. Substantial hypertrophy and systolic and diastolic left ventricular dysfunctions have been observed in patients with the obstructive form of the disease (rest peak gradient ≥30 mmHg). Peak gradient is positively correlated with hypertrophy and negatively to tissue Doppler mitral annulus systolic and diastolic velocities. Left ventricular outflow tract obstruction is an independent determinant of left ventricular functional abnormalities, beyond the effects on hypertrophy (Araujo et al, 2006). Functional and intrinsic *mitral valve* abnormalities, which can also contribute to the magnitude of the obstruction are also quite common in HCM. It was found out that intrinsic mitral valve pathology is frequently observed in HCM patients with symptomatic obstruction who undergo myectomy. However, morphologic characteristics constituting the indications for surgical intervention are incompletely defined (Kaple et al, 2008).

At present the structure of *papillary muscles (PMs)* and the possible influence of their anatomic redevelopment on HCM phenotype attract attention. In the actual study of Harrigan et al (2008), the authors revealed a higher number and 2-fold thickness of PMs in HCM patients in comparison with the control group of the same age and gender. In the subgroup of patients with LVOT obstruction at rest, PMs were positioned closer to the ventricular septum, with more marked hypertrophy. The actual case of a young patient with HCM who died at the age of 15 because of sudden heart failure due to ventricular fibrillation has been assigned to severe participation of papillary muscles in HCM symptomatology. This patient did not fulfil the conventional criterions for high risk status according to the actual risk stratification. In this case the histopathological findings have surprisingly verified marked scarring in the apical portions of the anterolateral and posterolateral PMs. Furthermore, there was no evidence of either previous myocardial ischemia with replacement scarring, myocyte disarray, or coronary artery bridging. The authors contemplate that isolated fibrosis could have created the potential arrhytmogenic substrate (Maron et al, 2008). However, the way in which the fibrosis localized in this area of myocardium could have triggered the fatal arrhythmia remains an open question.

Rare cases of young patients who can be endangered by the risk of fatal complications despite the lack of current SCD risk factors give rise to the question whether the current risk stratification is satisfactory and whether it includes all the variants of clinical manifestation of HCM syndrome.

Hypertrophic cardiomyopathy is the most common cause of SCD also in *young otherwise healthy* competitive athletes (<35 years). There have been described cases of SCD in young sportsmen with normal coronary arteries caused by cardiac arrest. These rare situations refer to a serious fact that CAD does not have to be the only cause of an acute myocardial infarction in young people. Limongelli et al (2006) described the case of an 18-year-old athlete with non-obstructive form of HCM. He was resuscitated from a cardiac arrest during mild effort. Electrocardiogram showed atrial fibrillation and significant changes in ST segment and T wave, echocardiography revealed akinesis of interventricular septum, but the coronary angiogram verified normal coronary arteries (Limongelli et al, 2006). In the actual study of Basavarajaiah et al (2008) the authors examined 3500 asymptomatic top athletes at the age of 14–35 years. They found out that 53 (1.5 %) of them had left ventricular hypertrophy, while 50 had normal diastolic function. This means that the left ventricular hypertrophy is physiological. Three (0.08 %) athletes did not have a dilated hypertrophic left ventricle but the electrocardiogram showed a T-wave inversion which can be pathognomic for HCM. None of the respondents had other HCM phenotype features or a positive family history for HCM enabling the establishment of HCM diagnosis (Basavarajaiah et al, 2008).

The HCM prevalence in top athlete population has not been sufficiently examined. Incipient cardiomyopathy can stay clinically asymptomatic for several years, but it can present a potential basis of severe cardiac complications in the future. Cases of SCD in young athletes refer to the need of HCM screening in the subgroups of young top sportsmen. Marked repolarisation abnormalities on electrocardiogram can lead to the suspicion of incipient expression of HCM (Pelllicia et al, 2008). The proof of genes encoding the sarcomere proteins of the heart muscle can be useful in the differentiation of myocardial hypertrophy caused by intensive physical training from pathological hypertrophy typical for HCM.

Nowadays the aim of intensive research is to elucidate the relation of specific mutation in sarcomere genes with certain clinical symptomatology. It may shed new light on HCM diagnosis and patients' management.

Genetic determination of HCM

The position of mutated gene causing HCM remained a mystery until the end of the 1980s. The first association between HCM incidence and locus on the long branch of chromosome 14 was discovered in 1989 (Jarcho et al, 1989). The other candidate genes possibly responsible for HCM syndrome were discovered subsequently. Nowadays we know more than 400 mutations in 11 sarcomere genes of the heart muscle. The most common genes, which are responsible for the familial HCM form (75 %) are those encoding the heavy myosin chains (β-MyHC), myosin binding protein C (MyBPC) and cardiac troponin T (cTnT) (Fig. 1).

Mutations, which are unique for the genotype of a family, are typically "private" and they determine the familial form of HCM. However, HCM can also be seen in its sporadic form. Mutations in the genes encoding β-MyHC, cTnT and α-tropomyosin are responsible for more than 45 % of familial HCM (Niimura et al, 2002). In fact, the mutations are divided into two main subgroups according to their clinical penetrance and the

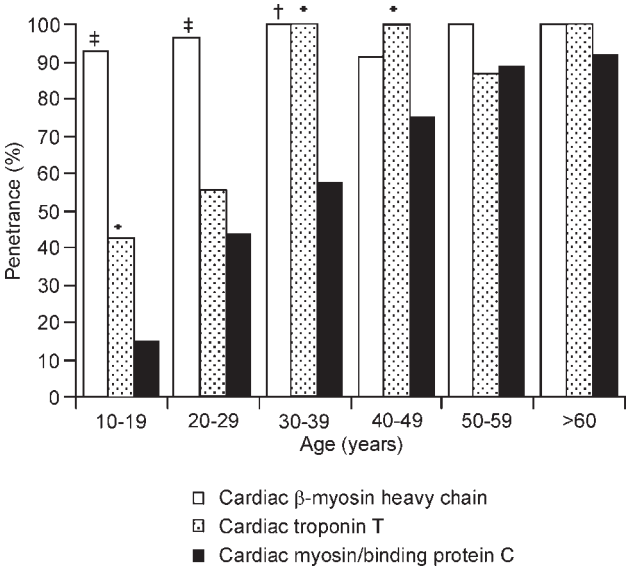

Fig. 1. Age-related penetrance of familiar hypertrophic cardiomyopathy caused by mutations in the genes for cardiac myosin-binding protein C, cardiac troponin T, cardiac β-myosin heavy chain (according to Niimura et al, 1998).

degree of clinical signs of severity – "malign" or "benign" mutations. It is a paradox that different mutations in the same gene can vary in their impact on symptomatology and the disease prognosis. However, described were also mutations, which despite being benign in their origin were presented by serious clinical features (Van Driest et al, 2002). These cases reflect an important fact that phenotype expression of HCM is the product of mutations in causal genes as well as modified genes and other environmental factors.

The studies concerning the genotype-phenotype correlation in the gene encoding β-MyHC confirmed the association of these mutations with marked myocardial hypertrophy at young age, high penetrance and unfavorable prognosis for SCD (e.g. R403Q, R453C, G716R). Missense mutation in the exon 13 (G1208A) is closely related to the severe familial form of HCM because it is associated with high penetrance, higher expression variability, serious symptomatology at young age and high incidence of SCD (Marian et al, 1994). Despite this, known are also mutations (N232S, G256E, V403Q) that lead to mild symptomatology, mild myocardial hypertrophy and good prognosis.

Mutations in the gene encoding cTnT are responsible for approximately 15 % of familial form cases. They are generally considered to worsen the prognosis and to have a higher incidence of SCD (Ho et al, 2000). The prognostic value of sarcomere gene mutations is usually directly proportional to the degree of expressivity and penetrance of myocardial hypertrophy. However, this is not the rule for cTnT gene. There is evidence from clinical studies that there are "malign" variants of cTnT gene that carry a high SCD risk but myocardial hypertrophy is only mild (Marian et al, 2001). These mutations are characterized by disorganisation of cardiomyocytes and myofibrils but not by significant hypertrophy and fibrosis. It is supposed that significant cardiomyocytes disorganisation in the absence of marked hypertrophy and fibrosis is the pathological substrate for SCD in the carriers of such mutations. The authors Varnava et al evaluated the histopathological hallmarks in patients with mutations in the gene encoding cTnT who succumbed to SCD (patients were 21-year-old on average). Patients with HCM had low heart weight and less fibrotic tissue, but a more severe degree of cardiomyocytes disorganisation in comparison with patients without cTnT gene mutations or with unknown genotype (Varnava et al, 2001). Mutations in this gene lead to a markedly different clinical as well as morphological manifestation of the disease and prognosis and this is why they show wide clinical heterogeneity. For instance, homozygous form of Ser179Phe mutation causes severe hypertrophy of the myocardium and juvenile lethality, however its heterozyous form is clinically and prognostically benign (Ho et al, 2000). On the other hand, there have also been identified mutations (Phe110Ile), which are typical by their variable cardiac morphology however with favorable prognosis (Ryuichiro et al, 1998).

Mutations in the gene encoding MyBPC cause clinical symptomatology in adults and elderly people with no family history of HCM and they are associated with low penetrance and mild clinical manifestation. However, there have also been described mutations (c.2067+1G—>A) that cause serious hypertrophy and are associated with lower incidence of SCD with the occurrence at higher age (Konno et al, 2006). This confirms the heterogeneity of clinical features in these gene mutations as well (Erdmann et al, 2001). Although the mutations in the gene encoding MyBPC predominantly occur sporadically at higher age and only in approximately 15 % of familial form cases – we should still be aware of this fact (Niimura et al, 1998). Late onset appearance of myocardial hypertrophy and mild clinical symptomatology can hide the inheritable substrate of these gene mutations. Genetic screening of adult patients with HCM may enable the recognition of asymptomatic members of the families with HCM caused by mutations in the gene encoding MyBPC. Mutations in the genes encoding the cardiac troponin I (cTnI) and α-MyHC are also associated with the incidence at higher age (Kokado et al, 2000, Niimura et al, 2002).

Familial and sporadic forms of left ventricular hypertrophy clinically represented by different conduction abnormalities (AV block, WPW syndrome) are new and important findings. These genetic forms of hypertrophy revealed the mutations in the gene encoding gamma2 regulatory subunit of AMP-dependent protein kinase (PRKAG2) and for the membrane protein associated with lysosome (LAMP2) (Ho et al, 2006). These are described as "metabolic cardiomyopathies". Mutations in the gene encoding LAMP2 are X-chromosome linked. They occur mostly in childhood and they are associated with rapidly progressive heart failure and unfavorable prognosis for the patient. These clinical units are a little bit far away from the classic HCM. Molecular signal pathways triggered by these genes are different from the pathways of sarcomere genes, and histopathological hallmarks are vacuoles containing glycogene and amylopectin. However,

their common basic feature is the unexplainable left ventricular hypertrophy. Thus, metabolic cardiomyopathies have to be subdued to further intensive screening.

The genotype-phenotype correlation in HCM is not simple because of great genotype-phenotype variability. A more severe phenotype appears in homozygote, double and combined mutations. If hypertrophy does not develop until the age of 20, mutation carriers can stay asymptomatic. Another unanswered question is the cause of disease in a group of patients with HCM in whom no mutations in sarcomere protein genes were detected. It is therefore necessary to trace mutations in other genes. The phenotype expression of HCM is based not only on mutated gene product but it is also influenced by modifier genes and environmental factors. The impact of modifier genes on phenotype expression has not been systematically discovered yet but it is deducted from phenotype variability in patients with familial form of HCM and thus it remains an open problem. Another important fact is that the presence of mutations found in individual populations differs.

Genetic screening is the only method, which may enable the recognition of mutation carriers in the preclinical phase before the hypertrophy becomes manifestant. Many studies confirm the contribution of genetic analyses such as the intellectual molecular screening of HCM patients (Erdmann et al, 2003, Pascale et al, 2003, Girolami et al, 2006). The importance of genetic analyses would also help in the differentiation of HCM from the "sport heart" of young competitive athletes, as well as in genetic counselling of patients and their next of kin family members. Therefore, genetics remains a big challenge in HCM.

Diagnosis and therapy of HCM

The key point of HCM patients' management is the prevention of HCM complications, especially the prevention of mortality (SCD, heart failure). The exact diagnosis (clinical examination, rest and stress echocardiography, electrocardiography, cardiac catheterization including coronary angiography) are the starting point. The patients' individual SCD risk can be stratified at once with the diagnosis. Table 2 shows the approach to family clinical screening for hypertrophic cardiomyopathy.

The most frequent cause for referring patients to cardiologist in case of HCM is abnormal electrocardiogram (ECG). Abnormal ECG image (repolarisation abnormalities, sign of left ventricular hypertrophy) occurs in 75–95 % and it often presents the first point for HCM suspicion although it is nonspecific. Echocardiography is the basic examination for HCM detection (two-dimensional and Doppler echocardiography), which can definitively confirm the diagnosis. The cardinal feature in two-dimensional echocardiography is left ventricular hypertrophy (13–15 mm). The dynamic obstruction of LVOT and systolic anterior motion (SAM) of the mitral valve with regurgitation belongs to other important features. The severity of hypertrophy is one of the stratifying parameters. Marked left ventricular outflow tract obstruction is associated with a higher SCD risk but it is concomitted by other risk factors. Clinical deterioration

Tab. 2. Approach to family clinical screening for hypertrophic cardiomyopathy (according to Ho et al, 2006).

Next of Kin Relatives (offspring, parents, siblings)	Screening – physical examination, echocardiogram, electrocardiogram
Below 12 years of age	Definitive findings are rare Screening optional (every 5 years) unless patient has malignant family history or is a competitive athlete or there is a suspicion of early onset left ventricular hypertrophy
Age 12 to 22 years	Screening optional every 12–24 months
Age 23 years or older	Screening to be repeated every 5 years or until genetic testing confirms the diagnosis

can be suddenly manifested in HCMP patients without any previous symptomatology. Hence, there is an effort to define echocardiographic predictors that would enable an early identification of patients at risk. The exact evaluation of global ventricular function as well as early, accurate and complex detection of diastolic dysfunction as a promising early marker seems to be crucial in the management of HCM. In this context, tissue doppler imaging (TDI) is a promising approach, because it enables an early detection of functional defects. Based on evaluation of 86 patients with HCM, Bayrak et al (2008) consider some parameters of diastolic dysfunction (longer E wave deceleration time) as well as those of occult systolic function (diminished LV lateral mitral annular systolic TD velocity (LMSa)) to be the predictors of heart failure symptoms in patients with sinus rhythm and normal systolic function (Bayrak et al, 2008).

The early markers of micro-structural changes of hypertrophied and scarred myocardium in HCM can be detected by high-resolution electrocardiography (HRECG). High-resolution electrocardiography detects high-frequency low-amplitude signals at the end as well as at the beginning of QRS complex called late potentials (LP). These micro-potentials arouse due to slow and fractionated motion of activated front in the areas of cardiomyocytes separation and distortion. The average electrocardiographic signal (SAECG) abnormalities can be useful in the prediction of malign arrhythmias triggered by late and fractionated electric activation. The time analysis of SAECG has a high negative predictive value (95–99 %) in the identification of patients with no risk of arrhythmias. However, it is useless in patients with blockades and intra-ventricular rhythm disturbances that can cause a falsely positive LP. Frequency analysis of ECG signal by fast Fourier transformation enables the resolution of signals in the frequency spectrum inside QRS complex and can be useful also in patients with blockades and ventricular rhythm disturbances. (Šulková et al, 2007, Mladosievičová et al, 1998 a, b).

Great attention is currently focused on the plasmatic value of NT-proBNP (N-terminal pro brain natriuretic peptide) in order to assess the severity and the progression of myocardial hypertrophy. Healthy people have approximately the same plas-

matic concentration of both BNP and NT-proBNP. Patients with left ventricular dysfunction or heart failure have the NT-proBNP values 2–10-fold higher than the values of BNP. Higher NT--proBNP plasmatic values could be the promising predictor of undesirable left ventricular remodelling in patients with non-obstructive form of HCM (Magga et al, 2008). Values of NT--proBNP are in the patients with HCM also in positive correlation with echocardiography and magnetic resonance parameters (Kim et al, 2006, Thaman et al, 2006).

Magnetic resonance imaging (MRI) represents the novel method in HCM diagnosis. It has been discovered that the characteristics of left ventricular hypertrophy according to the echocardiographic features is in good correlation with the mass of the left ventricle evaluated by MRI (Romano et al, 2008). Exact discrimination of papillary muscle and left ventricle morphology by MRI examination can identify the patients who are jeopardized by SCD on the basis of anatomic and fibrotic myocardial changes, but they do not accomplish current high-risk status criterions. Examination by MRI would also be useful in the planning of pre-operative strategy as for exact visualization of papillary muscles pathology.

Current therapeutic HCM strategies include pharmacological approach as well as non-pharmacological interventions. Treatment is tailored by the presence or absence of outflow tract gradient and individual symptoms. The antagonists of angiotensin II receptors seem to be a successful *pharmacological therapy* of non-obstructive HCM (Araujo et al, 2005). The current study of Japanese authors documented a regression of left ventricular mass hypertrophy after a one-year therapy with losartan (50 mg/day) in a non-obstructive HCM (Yamazaki et al, 2007). Obstruction, most commonly due to systolic anterior motion of the mitral valve deteriorates the symptoms and increases the mortality. Negative ionotropic drugs are effective in lowering the outflow gradients and relieving the symptoms, even in patients with high degree of resting obstruction. Beta-blockers are the first-line treatment in obstructive HCM predominantly by mitigating the provocable gradient. They potently slow down the heart rate, both at rest and during exercise with a positive impact on LV filling and suppression of ischaemia. Calcium channel inhibitors decrease the systemic vascular resistance, as did LVOT gradient, both at rest and with provocation. Beta-blockers combined with calcium channel inhibitors are thought to be the most effective medical treatment of obstruction and have been shown to be safe and not proarrhythmogenic (Musat et al, 2006).

Non-pharmacologic therapy includes percutaneous transluminal septal myocardial ablation (PTSMA), surgical myectomy and cardiostimulation. *Percutaneous transluminal septal myocardial ablation* belongs to one of the radical therapeutic strategy of HCM to reduce the LVOT obstruction in strictly indicated cases (symptomatic patient treated with conservative therapy, pressure gradient at rest >30 mmHg and during exercise >50 mmHg). This means controlled myocardial infarction in the area of myocardial hypertrophy of proximal septum. PTSMA relieves the obstruction of LVOT, diminishes the systolic anterior motion and mitral regurgitation. In some cases in spite of LVOT gradient reduction the systolic anterior motion of the mitral valve leaflet and the mitral regurgitation can still remain after ablation. The cause is probably hidden in the malposition of papillary muscle and in the malcoaptation of the mitral valve leaflet close to the ventricle septum (Delling et al, 2007). *Transaortic septal myectomy* has been recommended for symptomatic patients with fixed or inducible LVOT gradients who are not candidates for PTSMA (unsuitable anatomy of septal branches of coronary arteries) and are non-responders to medical treatment. Over the last three decades, the technique of septal myectomy has evolved from the classic Morrow myotomy and myectomy to a more extended left ventricular septal myectomy. A complete relief of LVOT obstruction also can result in correction of mitral regurgitation caused by SAM. In some cases mitral valvuloplasty can be performed in the same session. However, there is still the risk of complications such as complete heart block, ventricular septal defect, injury to the aortic or mitral valves and incomplete relief of obstruction.

The implantation of *cardioverter-defibrillator* is highly effective in HCM patients in primary as well as in secondary prevention of SCD (Maron et al, 2006, Maron et al, 2007, Przybylsky et al, 2005, Woo et al, 2007). The annual incidence of SCD is estimated to be 3–5 % in patients with two or more clinical predictors (Ho et al, 2006). Exact identification of high-risk patients for ICD implantation and mostly in primary SCD prevention are still not resolved questions. The actual criterions for implantation of SCD are: averted SCD, familial incidence of SCD, massive left ventricular hypertrophy (>30 mm), non-sustained ventricular tachycardia, unexplained syncopes, abnormal pressure response to exercise and LVOT pressure gradient >30 mmHg. Exact identification of high-risk patients for ICD implantation and mostly in primary SCD prevention are still not resolved questions. Recently published multicentric study of Maron et al evaluated 506 patients with HCMP who were implantable in the years 1986–2003. The results of this study confirm the effect of ICD implantation in 103 (20 %) patients with life-threatening ventricular tachycardia or fibrillation. The presence of adequate discharges in patients to whom ICD was implanted in primary prevention on the basis of only one risk factor was an encouraging finding (Maron et al, 2007). It means that one verified marker of current SCD risk algorithm would be sufficient enough for considering the prophylactic ICD implantation in selective subgroup of HCM patients. However, high frequency of possible inadequate discharges remains a controversy. The correct indication of ICD implantation in primary SCD prevention is judged according to the successful interruption of ventricular tachycardia/fibrillation and restoring the sinus rhythm. High incidence of inadequate discharges is associated mostly with atrial fibrillation with fast ventricular response, sinus tachycardia, conduction abnormalities and with higher sensitivity of device to T wave changes (Przybylsky et al, 2005). The authors Woo et al in the study of 61 HCM patients confirmed adequate device intervention in 8 % of patients in primary prevention and in 36 % of patients in secondary SCD prevention. They documented inadequate intervention in 20 cases (33 %). Subsequently, the authors thought that

the age of patients <30 years at the time of device implantation and the history of atrial fibrillation could be the significant predictors of possible inadequate interventions (Woo et al, 2007).

The first aim in diagnostic and therapeutic strategies is to improve the risk stratification of patients with HCM. Reserves are hidden in the elucidation of molecular-genetic substrate as well as the clinical heterogeneity of the disease in correlation with the known genotype. Electrophysiological phenotypisation of individual HCM genotypes is the promising future for the exact clinical management of patients.

Conclusion

Hypertrophic cardiomyopathy is a congenital cardiovascular disease with a wide spectrum of clinical signs and high prevalence of age variability. Nowadays it belongs to frequently discussed problems in cardiology. In young people and active sportsmen, HCM is the most common cause of SCD. An early detection and adequate management can avert the life-threatening cardiac arrest and malign tachyarrhythmias. Genetic analyses open new possibilities for the prevention of these severe complications. Genetic screening of HCM patients would enable an early detection of asymptomatic or preclinical HCM as well as the identification of patients at high-risk for SCD. From this point of view, genetic analysis fulfils the criterion of a crucial diagnostic tool in modern management of HCM patients.

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