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Hypertrophic cardiomyopathy: a modern view of the problem

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Abstract

Cardiomyopathy is considered one of the main causes of heart failure and sudden cardiac death, at least in young people. Approximately 50% of patients who die suddenly in childhood or adolescence or undergo heart transplantation suffer from this condition. The purpose of this literature review is to study and highlight the issues of etiology, pathogenesis, clinical features, diagnosis and treatment of hypertrophic cardiomyopathy from the point of view of modern ideas. The search and analysis of domestic and foreign literature materials using the PubMed and eLibrary databases was carried out. Of particular interest is the etiology of primary congenital cardiomyopathies, in respect of which research continues. As a result of the implementation of genetic factors, multiple structural and functional changes in the myocardium develop, which lead to changes in hemodynamics. Cardiomyopathy is a clinically heterogeneous disease, and one of the factors that determine the clinical phenotype is the genotype. In addition to standard laboratory testing, patients with suspected hypertrophic cardiomyopathy are advised to undergo medical genetic counseling to identify the causative mutation, and often to obtain prognostic information. The fundamental imaging method is echocardiography, but the role of magnetic resonance imaging in the diagnosis of the disease is also considered. Patients with symptomatic obstructive hypertrophic cardiomyopathy are usually recommended first-line pharmacotherapy with β-blockers or non-dihydropyridine calcium channel blockers. Currently, research on new drugs for the treatment of hypertrophic cardiomyopathy — inhibitors of cardiac myosin is ongoing. Surgical methods of treatment are developing progressively, however, methods of conservative treatment require further active research of drugs that have not been used before.

Keywords: review, hypertrophic cardiomyopathy, chronic heart failure, sudden cardiac death, desminopathy, rasopathy.

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Introduction

Cardiomyopathy (CMP) is a significant contributor to heart failure (HF) and sudden cardiac death (SCD), particularly in young adults [1]. However, epidemiological data are lacking; as a result, determining the public health effect of these diseases and prioritizing action at the national or international level are challenging [1].

The prevalence of hypertrophic CMP (HCMP) is 1:500 in the general population [1]. According to statistics from the Heart Failure Association of the European Society of Cardiology, HCMP has a prevalence of 2–5 per 1000 in the general population [2]. HCMP occurs with similar frequency in different countries. At least 300,000 people in Russia suffer from this disease [3].

The term “cardiomyopathies” was coined by W. Bridgen in 1957. Cardiomyopathies are defined as primary myocardial lesions of undetermined etiology that cause cardiac dysfunction and are not sequelae of diseases of the coronary arteries, valve apparatus, pericardium, systemic or pulmonary hypertension, or some rare variants of cardiac conduction system lesions [4].

Probands with this pathology are common in first-line families, indicating the high inheritability of the disease (up to 65%) [5]. In HCMP, progressive CH is less common than restrictive CMP; however, its development predicts an unfavorable prognosis [6].

W.J. McKenna et al. highlighted the urgency of CMP as a problem. According to their report, CMP was present in approximately 50% of patients who died suddenly during childhood or adolescence or underwent heart transplantation [7]. SCD, with an annual incidence of 0.5%–1%, typically affects

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Table 1. Classification of cardiomyopathies (CMP, American Heart Association, 2006)

CMP groups	CMP types
Primary CMPs	
Primary congenital CMPs (hereditary)	Hypertrophic CMP
	Arrhythmogenic dysplasia of the right ventricle
	Noncompact left ventricular myocardium
	Lenegre's disease
	Congenital pathology of the ion channels – Prolonged *QT* syndrome – Short *QT* syndrome – Brugada syndrome – Idiopathic ventricular paroxysmal tachycardia (primary electrical heart disease)
Primary mixed CMPs	Dilated CMP
	Restrictive CMP
Primary acquired CMPs	Inflammatory (outcome of myocarditis)
	Stress (takotsubo CMP)
	Peripartal
	Tachycardia-induced
	CMP of children from mothers with insulin-dependent diabetes mellitus
Secondary CMPs	
Infiltrative (e.g., amyloidosis)	
Accumulation of CMPs (e.g., in hemochromatosis)	
Toxic (e.g., alcohol and drugs)	
Endocrine (diabetic CMP and CMPs in hypo- and hyperthyroidism)	
CMPs in neuromuscular diseases (e.g., Duchenne muscular dystrophy and Friedreich's ataxia))	
Alimentary (e.g., vitamin B_1, selenium, and carnitine deficiency)	
CMPs in systemic connective tissue diseases	

young men (between the third and fourth decades of life) with HCMP and may be the initial disease manifestation [8].

Currently, several CMP variants have been reported [2]. This literature review summarizes current information on the etiology, pathogenesis, clinical features, diagnosis, and treatment of HCMP.

Classification of cardiomyopathies

To position HCMP among other CMPs, we will refer to two classifications of CMP. In 1980, a World Health Organization task force chaired by J. Goodwin presented the first classification of CMPs based on the predominant structural and hemodynamic phenotype, 23 years after W. Bridgen proposed the term "cardiomyopathies." This classification distinguishes three groups of CMP: dilated, hypertrophic, and restrictive CMPs [7].

The textbook by G.E. Roytberg and A.V. Strutynsky, "Internal Medicine: Cardiovascular System" [4], presents the 2006 classification of CMP developed by experts of the American Heart Association. This classification is considered the most acceptable and consistent with modern concepts of CMP etiology and pathogenesis (Table 1).

Etiology of hypertrophic cardiomyopathy

According to the American Heart Association classification (2006), the names of CMPs, such as primary acquired and secondary CMPs, reflect their causes. However, the etiology of primary congenital CMPs remains unknown and is still being investigated. Primary CMPs are hereditary diseases that occur fairly commonly, with a frequency of 0.5% in the population [9].

K.S. Kochergin-Nikitsky et al. distinguished a group of primary desminopathies, which are CMPs caused by *DES* mutations at locus 2q35. *DES* encodes the protein desmin, which serves as the main protein of the intermediate filaments of myocytes, primarily in the myocardium and skeletal muscles. Desminopathies are usually inherited

in an autosomal dominant manner, accounting for 80% of all cases. Dilated and restrictive CMPs are the most common in this pathology, and HCMP is somewhat less common [9].

Over 100 genes have been reported to cause CMPs since the discovery of pathogenic variants in the *myosin heavy chain 7* (*MYH7*) gene in HCMP [10].

J. Bonaventura et al. reported the eight sarcomeric genes (*ACTC1*, *MYBPC3*, *MYH7*, *MYL2*, *MYL3*, *TNNI3*, *TNNT2*, and *TPM1*) that are the most important and have the most convincing evidence of causing HCMP [11]. Mutations in one of the eight sarcomeric genes are present in 60% of genetically related HCMP cases [12]. According to B.J. Maron et al., affordable genetic testing has led to the identification of >11 causative genes with >2000 unique variants for individual families in patients with HCMP [13].

HCMP, caused by mutations in sarcomeric genes, is inherited in an autosomal dominant manner and exhibits a high degree of phenotypic heterogeneity [14]. In addition, up to 40% of all cases of HCMP are sporadic, which means the lack of mutations in the proband or the lack of family history [15].

M. Lioncino and E. Monda, et al. reported a group of HCMPs known as RASopathies. RASopathy is a multisystem disorder caused by mutations in genes related to the RAS/mitogen-activated protein kinase pathway. Compared with sarcomeric HCMP, RASopathy HCMP is associated with a higher prevalence of congestive HF and is characterized by the high prevalence and severity of left ventricular (LV) obstruction. RASopathies commonly involve biventricular issues and are often associated with congenital heart disease, particularly pulmonary artery stenosis [16].

R. Tadros et al. conducted a meta-analysis of three case–control studies (GWAS) and identified 14 new HCMP-associated loci [17].

Current views on hypertrophic cardiomyopathy pathogenesis

Genetic factors can cause structural and functional changes in the myocardium, leading to hemodynamic changes [4]. HCMP is characterized by the stiffening of the hypertrophied and sclerosed myocardium, which impairs the diastolic relaxation of the ventricles. Typically, systolic function is not affected in HCMP with diastolic dysfunction [4].

Relative coronary insufficiency results from the mismatch between increased myocardial mass and capillary bed, increased myocardial oxygen demand, compression of small subendocardial branches of coronary arteries, small coronary artery disease, and decreased gradient between the aorta and LV cavity [4].

According to C. Chou and M.T. Chin, no concepts can clearly explain how individual gene mutations lead to myocardial fibrosis, disruption of the cardiomyocyte structure, and asymmetric hypertrophy. The authors described the role of prolonged activation of calcium–calmodulin-dependent protein kinase II, autophagy characterized by the degradation of intracellular organelles and macromolecules in response to cellular stress, and sustained glycolysis in cardiomyocytes in this process. Intracellular changes may lead to cardiomyocyte hypertrophy, which can cause changes in the extracellular environment. These changes can promote tissue reorganization in intact cardiomyocytes, resulting in diffuse myocardial fibrosis [15].

Ventricular arrhythmias in HCMP are mainly caused by massive hypertrophy, fibrosis, and microvascular ischemia. However, functional arrhythmogenic mechanisms are likely to predominate in the early disease stages [18]. Current evidence suggests that rhythm disturbances are caused by increased late Na^+ current and Ca^{2+} current via L-type calcium channels inside the cells. Furthermore, the heightened sensitivity of myofilaments to Ca^{2+} may contribute to postdepolarization and recurrent arrhythmias. In addition, reduced K^+ currents occur during the neglected process, decreasing repolarization reserve and increasing early postdepolarizations [18].

S. Ranjbarvaziri et al. revealed significant dysregulation of fatty acid metabolism, decreased levels of acylcarnitines, and accumulation of free fatty acids, indicating changes in various biochemical reactions. HCMP has demonstrated signs of global energy decompensation, as evidenced by decreased levels of high-energy phosphate metabolites (adenosine triphosphate, adenosine diphosphate, and phosphocreatine) and low number of mitochondrial genes involved in the synthesis of creatine kinase and adenosine triphosphate [19].

Obstructive HCMP can cause low cardiac output due to dynamic LV outlet obstruction [4]. This obstruction is believed to be more pronounced in older patients, possibly because of frequent calcification of the mitral annulus [20].

Clinical picture of HCMP

CMP is clinically heterogeneous, and its clinical phenotype is determined by various factors, including genotype [10]. The clinical presentation of CMP can range from an asymptomatic course to SCD, which is most common in young individuals [21].

C.Y. Ho et al. reported that patients with pathogenic variants in sarcomeric genes who suffer from HCMP have higher rates of adverse events, such as HF, ventricular arrhythmias, and atrial fibrillation.

Pathogenic variants in sarcomeric genes are also important predictors of adverse outcomes [22]. The most common symptoms include chest pain, shortness of breath, palpitations, fatigue, and fainting [23].

The clinical presentation in most patients is caused by diastolic dysfunction and stasis in the pulmonary circulation [24]. Chest pain syndrome resembles typical angina pectoris because it is caused by inadequate coronary blood flow with significant LV myocardial hypertrophy [24].

Syncope in HCMP can have several causes, including paroxysmal cardiac rhythm disturbances such as ventricular arrhythmias, supraventricular arrhythmias, tachyarrhythmias, and bradyarrhythmias, low ejection syndrome, which is usually associated with severe LV outlet obstruction and neurocardiogenic autonomic dysfunction [24].

Cardiac rhythm disturbances are the leading cause of SCD in patients with HCMP. In addition to pronounced subjective sensations such as palpable palpitations and interruptions in rhythm, approximately a quarter of arrhythmias are asymptomatic [24]. Furthermore, P. Teekakirikul et al. reported that the signs and symptoms of HCMP do not always correlate with the severity of myocardial hypertrophy. Thus, no significant proportion of young patients with HCMP may experience symptoms throughout their lives [25].

According to reports, HCMP symptoms may appear later in older patients than in younger ones. However, risk stratification is inversely related to age [20].

Laboratory and instrumental diagnosis of HCMP

The Ministry of Health of the Russian Federation [26] recommends standard laboratory tests for patients suspected of CMP, including clinical blood analysis, urinalysis, and biochemical blood analysis (cholesterol, triglycerides, potassium, sodium, alanine aminotransferase, aspartate aminotransferase, urea, creatinine, bilirubin, and glucose). A high NT-proBNP[1] level indicates HF [26].

Medical and genetic counseling are recommended to identify the causative mutation [26]. According to B.J. Maron et al., genetic testing is also important in investigating next-generation family members who are at risk but usually asymptomatic (cascade genetic testing). Relatives of a proband who receive a negative genetic testing result for the same sarcomere gene mutation as the proband can be excluded from further follow-up with a high probability [13].

[1] NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide.

Patients suspected of HCMP should undergo electrocardiography (ECG) and Holter monitoring [26]. In HCMP, ECG data reveal the following [4]:

– Signs of LV hypertrophy

– Signs of left atrial overload and hypertrophy

– Abnormal *Q* or *QS* spike in leads II, III, and aVF in the case of hypertrophy of the proximal part of the interventricular septum (IVS) and in leads I and aVL in the case of hypertrophy of the lower part of the IVS and apex.

– Supraventricular and ventricular arrhythmias.

ECG should be performed annually [13]. Echocardiography is necessary to detect myocardial structure and function disorders and changes in the heart chambers and valve apparatus [27].

To diagnose HCMP, T. Ciarambino et al. suggested that the LV wall thickness should be >15 mm [27]. However, a wall thickness of 13–14 mm may also be diagnostically significant, particularly in cases with a family history of HCMP, dynamic outlet obstruction, and ECG changes [28]. In symmetric HCMP cases, LV outflow tract obstruction is typically absent [29].

Asymmetric HCMP is characterized by a ratio of IVS to posterior LV free wall thickness >1.3 [29]. It can be both nonobstructive and obstructive [30]. In idiopathic hypertrophic subaortic stenosis, the mobile distal part of the anterior mitral valve leaflet approaches the hypertrophic IVS during systole, causing dynamic obstruction of the LV outflow tract under the Bernoulli and Venturi effects. Echocardiography can detect anterior systolic displacement of the leaflet [31].

L.O. Gazun and E.V. Polukhina highlighted that Doppler echocardiography is the most informative method for assessing the degree of LV outflow tract obstruction. The degree of obstruction is determined by the pressure gradient, which does not exceed 5–6 mmHg under normal conditions. An increase of up to 30 mmHg should be considered an insignificant obstruction. An increase from 30 to 100 mmHg should be considered severe obstruction, and consultation with a cardiac surgeon is indicated when the gradient is >100 mmHg [30]. Stress echocardiography can be informative when the LV outlet gradient at rest is <30 mmHg [13].

In apex HCMP, wall thickening occurs in the apex region and a small residual cavity in the left ventricle. Dopplerography revealed accelerated return blood flow in this area [30].

In a prospective cohort study, R Karaca Özer et al. found that global longitudinal LV deformation <12.5% can distinguish HCMP from LV hypertrophy in athletes and patients with arterial hypertension with a sensitivity of 65% and specificity of 77%. According to the Kaplan–Meier

7-year survival analysis, patients with a global longitudinal strain value <12.5% had a higher risk of all-cause mortality than those with >12.5% (29% vs. 9%; p = 0.032). The LV global longitudinal strain value predicted mortality with a sensitivity of 64% and specificity of 70% for a value <12.5% (p = 0.012) [32].

The American Society of Echocardiography proposed four parameters [33] to detect diastolic dysfunction [33]:

– Maximal left atrial (LA) volume index >34 mL/m^2

– Peak tricuspid regurgitation velocity (>2.8 m/s

– Mean ratio of peak early diastolic ventricular filling velocity (E) to peak atrioventricular annulus early diastolic velocity (e') >14

– Atrioventricular ring peak early diastolic velocity (e'): septal <7 cm/s, lateral <10 cm/s.

After diagnosis, patients with HCMP should undergo annual echocardiography [13]. Chest radiography is also recommended [4, 27].

HCMP typically lacks specific radiological signs. However, LA shadow enlargement may be detected in cases of volume overload caused by severe mitral regurgitation. In addition, swelling of the second arch on the left, root dilation, and signs of venous stasis in the lungs may be noticeable in cases of severe pulmonary hypertension [4, 27].

To differentiate between diagnoses, coronary angiography and ventriculography are recommended [4]. Additional options for verifying the diagnosis include cardiac magnetic resonance imaging (MRI), computed/multispiral computed tomography, scintigraphy, and positron emission tomography [26].

MRI with late gadolinium enhancement can reveal typical contrast enhancement patterns that differentiate HCMP from other conditions that mimic it, such as Anderson–Fabry disease. MRI provides detailed visualization of the IVS, mitral valve, and papillary muscles, which is useful for preoperative evaluation before IVS myomectomy [27]. B.J. Maron et al. reported that regular MRI with contrast enhancement is not mandatory for patients aged >65 years of age, although it is recommended at intervals of 3–5 years [13].

Treatment of hypertrophic cardiomyopathy

Conservative methods are initially prescribed for the treatment of HCMP. Surgical methods are only used if conservative treatment is ineffective and disease symptoms are severe [34].

First-line pharmacotherapy for symptomatic obstructive HCMP usually involves the administration of β-adrenoblockers or nondihydropyridine calcium channel blockers. These drugs have been the mainstay of treatment for decades because of their general negative inotropic and chronotropic effects, which lead to a decrease in contact between the anterior mitral valve leaflet and the IVS [35]. In patients with nonobstructive HCMP who experience HF symptoms, β-adrenoblockers or verapamil should be prescribed. These drugs can reduce and control HF symptoms; however, little evidence suggests that they can reduce SCD risk [36].

According to T.J. Gluckman, β-adrenoblockers without vasodilatory effects, such as atenolol and propranolol, are primarily used to reduce symptoms. Titrating β-adrenoblockers according to tolerability while considering a target resting heart rate of approximately 60 beats/min is recommended. These drugs are effective in reducing dyspnea during exercise and chest pain, improving diastolic filling [34].

A.M. Dybro et al. found that metoprolol reduced LV obstruction both at rest and during exercise, relieved symptoms, and improved the quality of life in patients with obstructive HCMP [37].

Currently, new drugs are being studied in addition to previously described and well-established medications.

I. Olivotto et al. described the results of a phase 3 randomized double-blind placebo-controlled study on the use of mavacamten, the first cardiac myosin inhibitor in its class. The study analyzed patients with HCMP, LV outlet gradient ≥50 mm Hg, and functional class II–III chronic HF. The drug demonstrated efficacy in reducing LV obstruction, improving exercise tolerance, and reducing the functional class of chronic HF compared with placebo [38].

Mavacamten is the first drug specifically designed for treating HCMP, with the potential to benefit patients with symptomatic obstruction [39]. However, this drug, despite its positive effects, does not prevent disease progression [40]. The MAVA-LTE study, which evaluates the long-term safety of mavacamten, is scheduled to be completed in November 2025 [41].

M.S. Maron et al. also reported positive results from a phase 2 clinical trial of aficamtena, another cardiac myosin inhibitor, in patients with symptomatic HCMP. The phase 3 trial of afikamtena, SEQUOIA-HCM, is currently ongoing [42]. According to C. Ferrantini et al., treatment with the late sodium current inhibitor ranolazine decreased tension predominant in the IVS in obstructive HCMP [43].

B.J. Maron et al. revealed that the effective use of an implantable cardioverter-defibrillator reduces the risk of SCD caused by fatal rhythm disturbances. The authors found that the use of an

implantable cardioverter-defibrillator reduced the rate of HCMP-related mortality to 0.5% per year. An implantable cardioverter-defibrillator is generally not recommended for patients with HCMP aged ≥60 years who do not exhibit symptoms of rhythm disturbances because of the low incidence of arrhythmia-related SCD in this age group. However, there may be exceptions for individual cases, such as those involving the cardiac apex [36].

In addition to the conservative treatment of CMP, several surgical methods are available. These include myomectomy, which involves the resection of the proximal part of the IVS, mitral valve replacement, and implantation of a dual-chamber pacemaker operating in the DDD mode [4, 44].

According to B.J. Maron et al. [45], myomectomy-related mortality has significantly decreased from 6%–8% to 0.5% over the past 30 years. E.J. Rowin et al. [46] reported an improvement in HF symptoms, reduction in the functional class of chronic HF by ≥1 in ≥90% of the patients, and restoration of physical activity in 75% of the patients, regardless of age.

Some studies have reported transapical myomectomy in patients with apical HCMP. A. Nguyen et al reported a case fatality rate of 4% of patients within 30 days of surgery. At follow-up, 76% of the patients reported symptom improvement, and 3% subsequently underwent heart transplantation for the recurrence of HF symptoms. The estimated 1-, 5-, and 10-year survival rates were 96%, 87%, and 74%, respectively [47].

Alcohol ablation of the IVS is an alternative to myomectomy for patients with severe symptoms that are not candidates for surgery. However, this intervention may lead to ventricular tachyarrhythmias because of IVS scarring, which may require the use of an implantable cardioverter-defibrillator to prevent SCD [36].

Heart transplantation has been reported as a treatment option for patients with end-stage HCMP and severe symptoms of chronic HF [48]. In some cases, chronic HF caused by HCMP can progress to the terminal stage, which is characterized by diffuse fibrosis and LV remodeling, leading to severe systolic and diastolic dysfunction [41]. Heart transplantation has a 5-year survival rate of >90% [48].

Conclusions

After studying HCMP-related information, this disease requires the introduction of highly effective and modern diagnostic methods to differentiate it from other conditions. Despite the development of new drugs and surgical methods, the problem of therapy is far from being solved. Therefore, new research directions in this area remain relevant.

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REFERENCES

1. Lannou S, Mansencal N, Couchoud C, Lassalle M, Dubourg O, Stengel B, Jacquelinet C, Charron P. The public health burden of cardiomyopathies: Insights from a Nationwide Inpatient Study. *J Clin Med*. 2020; 9(4):920. DOI: 10.3390/jcm9040920.

2. Seferović PM, Polovina M, Bauersachs J, Arad M, Gal TB, Lund LH, Felix SB, Arbustini E, Caforio ALP, Farmakis D, Filippatos GS, Gialafos E, Kanjuh V, Krljanac G, Limongelli G, Linhart A, Lyon AR, Maksimović R, Miličić D, Milinković I, Noutsias M, Oto A, Oto Ö, Pavlović SU, Piepoli MF, Ristić AD, Rosano GMC, Seggewiss H, Ašanin M, Seferović JP, Ruschitzka F, Čelutkiene J, Jaarsma T, Mueller C, Moura B, Hill L, Volterrani M, Lopatin Y, Metra M, Backs J, Mullens W, Chioncel O, de Boer RA, Anker S, Rapezzi C, Coats AJS, Tschöpe C. Heart failure in cardiomyopathies: A position paper from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2019;21(5):553–576. DOI: 10.1002/ejhf.1461.

3. National clinical guideline on diagnosis and treatment of hypertrophic cardiomyopathy. *Russian cardiology bulletin*. 2016;11(1):3–22. (In Russ.) EDN: VLJOBD.

4. *Vnutrennie bolezni. Serdechno-sosudistaya sistema*. (Internal diseases. Cardiovascular system.) Tutorial. GE Roytberg, AV Strutynskiy, editors. 6nd ed. M.: MED-press-inform; 2019. 904 p. (In Russ.)

5. Martinez HR, Beasley GS, Miller N, Goldberg JF, Jefferies JL. Clinical insights into heritable cardiomyopathies. *Front Genet*. 2021;12:663450. DOI: 10.3389/fgene.2021.663450.

6. Stolfo D, Collini V, Sinagra G. Advanced heart failure in special population: Cardiomyopathies and myocarditis. *Heart Fail Clin*. 2021;17(4):661–672. DOI: 10.1016/j.hfc.2021.05.010.

7. McKenna WJ, Maron BJ, Thiene G. Classification, epidemiology, and global burden of cardiomyopathies. *Circ Res*. 2017;121(7):722–730. DOI: 10.1161/CIRCRESAHA.117.309711.

8. Sinagra G, Carriere C, Clemenza F, Minà C, Bandera F, Zaffalon D, Gugliandolo P, Merlo M, Guazzi M, Agostoni P. Risk stratification in cardiomyopathy. *Eur J Prev Cardiol*. 2020;27(2):52–58. DOI: 10.1177/2047487320961898.

9. Kochergin-Nikitsky KS, Zaklyazminskaya EV, Lavrov AV, Smirnikhina SA. Cardiomyopathies associated with the DES gene mutations: molecular pathogenesis and gene therapy approaches. *Almanac of Clinical Medicine*. 2019;47(7):603–613. (In Russ.) DOI: 10.18786/2072-0505-2019-47-025.

10. Yamada T, Nomura S. Recent findings related to cardiomyopathy and genetics. *Int J Mol Sci*. 2021;22(22):12522. DOI: 10.3390/ijms222212522.

11. Bonaventura J, Polakova E, Vejtasova V, Veselka J. Genetic testing in patients with hypertrophic cardiomyopathy. *Int J Mol Sci.* 2021;22(19):10401. DOI: 10.3390/ijms221910401.

12. Sabater-Molina M, Perez-Sanchez I, Hernandez Del Rincon JP, Gimeno JR. Genetics of hypertrophic cardiomyopathy: A review of current state. *Clin Genet*. 2018;93(1):3–14. DOI: 10.1111/cge.13027.

13. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, Rowin EJ, Maron MS, Sherrid MV. Diagnosis and evaluation of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79(4):372–389. DOI: 10.1016/j.jacc.2021.12.002.

14. De Oliveira GMM. A new look into hypertrophic cardiomyopathy based on clinical evidence. *Rev Port Cardiol (Engl Ed)*. 2018;37(1):11–13. DOI: 10.1016/j.repc.2018.01.001.

15. Chou C, Chin MT. Pathogenic mechanisms of hypertrophic cardiomyopathy beyond sarcomere dysfunction. *Int J Mol Sci*. 2021;22(16):8933. DOI: 10.3390/ijms22168933.

16. Lioncino M, Monda E, Verrillo F, Moscarella E, Calcagni G, Drago F, Marino B, Digilio MC, Putotto C, Calabrò P, Russo MG, Roberts AE, Gelb BD, Tartaglia M, Limongelli G. Hypertrophic cardiomyopathy in RASopathies: Diagnosis, clinical characteristics, prognostic implications, and management. *Heart Fail Clin*. 2022;18(1):19–29. DOI: 10.1016/j.hfc.2021.07.004.

17. Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, Kelu Bisabu K, Walsh R, Hoorntje ET, Te Rijdt WP, Buchan RJ, van Velzen HG, van Slegtenhorst MA, Vermeulen JM, Offerhaus JA, Bai W, de Marvao A, Lahrouchi N, Beekman L, Karper JC, Veldink JH, Kayvanpour E, Pantazis A, Baksi AJ, Whiffin N, Mazzarotto F, Sloane G, Suzuki H, Schneider-Luftman D, Elliott P, Richard P, Ader F, Villard E, Lichtner P, Meitinger T, Tanck MWT, van Tintelen JP, Thain A, McCarty D, Hegele RA, Roberts JD, Amyot J, Dubé MP, Cadrin-Tourigny J, Giraldeau G, L'Allier PL, Garceau P, Tardif JC, Boekholdt SM, Lumbers RT, Asselbergs FW, Barton PJR, Cook SA, Prasad SK, O'Regan DP, van der Velden J, Verweij KJH, Talajic M, Lettre G, Pinto YM, Meder B, Charron P, de Boer RA, Christiaans I, Michels M, Wilde AAM, Watkins H, Matthews PM, Ware JS, Bezzina CR. Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect. *Nat Genet*. 2021;53(2):128–134. DOI: 10.1038/s41588-020-00762-2.

18. Santini L, Coppini R, Cerbai E. Ion channel impairment and myofilament Ca^{2+} sensitization: Two parallel mechanisms underlying arrhythmogenesis in hypertrophic cardiomyopathy. *Cells*. 2021;10(10):2789. DOI: 10.3390/cells10102789.

19. Ranjbarvaziri S, Kooiker KB, Ellenberger M, Fajardo G, Zhao M, Roest ASV, Woldeyes RA, Koyano TT, Fong R, Ma N, Tian L, Traber GM, Chan F, Perrino J, Reddy S, Chiu W, Wu JC, Woo JY, Ruppel KM, Spudich JA, Snyder MP, Contrepois K, Bernstein D. Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation*. 2021;144(21):1714–1731. DOI: 10.1161/CIRCULATIONAHA.121.053575.

20. Lee DZJ, Rakowski H. Hypertrophic cardiomyopathy in elderly individuals: Is it a rose by another name? *J Am Heart Assoc*. 2021;10(3):e020204. DOI: 10.1161/JAHA.120.020204.

21. Muresan ID, Agoston-Coldea L. Phenotypes of hypertrophic cardiomyopathy: Genetics, clinics, and modular imaging. *Heart Fail Rev.* 2021;26(5):1023–1036. DOI: 10.1007/s10741-020-09931-1.

22. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS, Caleshu CA, Helms AS, Colan SD, Girolami F, Cecchi F, Seidman CE, Sajeev G, Signorovitch J, Green EM, Olivotto I. Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: Insights from the sarcomeric human cardiomyopathy registry (SHaRe). *Circulation*. 2018;138(14):1387–1398. DOI: 10.1161/CIRCULATIONAHA.117.033200.

23. Borsari W, Davis L, Meiers E, Salberg L, McDonough B. Living with hypertrophic cardiomyopathy: A patient's perspective. *Future Cardiol.* 2022;18(1):43–50. DOI: 10.2217/fca-2021-0091.

24. Balla EA, Taub GS. Hypertrophic cardiomyopathy: curreut issues and problems. *Lechebnoe delo: nauchno-prakticheskiy terapevticheskiy zhurnal.* 2017;(1):52–56. (In Russ.) EDN: YFOMYF.

25. Teekakirikul P, Zhu W, Huang HC, Fung E. Hypertrophic cardiomyopathy: An overview of genetics and management. *Biomolecules*. 2019;9(12):878. DOI: 10.3390/biom9120878.

26. Gabrusenko SA, Gudkova AY, Koziolova NA, Alexandrova SA, Berseneva MI, Gordeev ML, Dzemeshkevich SL, Zaklyazminskaya EV, Irtyuga OB, Kaplunova VYu, Kostareva AA, Krutikov AN, Malenkov DA, Novikova TN, Saidova MA, Sanakoev MK, Stukalova OV. 2020 Clinical practice guidelines for hypertrophic cardiomyopathy. *Russian Journal of Cardiology*. 2021;26(5):269–334. (In Russ.) DOI: 10.15829/1560-4071-2021-4541.

27. Ciarambino T, Menna G, Sansone G, Giordano M. Cardiomyopathies: An overview. *Int J Mol Sci.* 2021;22(14):7722. DOI: 10.3390/ijms22147722.

28. Maurizi N, Michels M, Rowin EJ, Semsarian C, Girolami F, Tomberli B, Cecchi F, Maron MS, Olivotto I, Maron BJ. Clinical course and significance of hypertrophic cardiomyopathy without left ventricular hypertrophy. *Circulation*. 2019;139(6):830–833. DOI: 10.1161/CIRCULATIONAHA.118.037264.

29. Haland TF, Edvardsen T. The role of echocardiography in management of hypertrophic cardiomyopathy. *J Echocardiogr.* 2020;18(2):77–85. DOI: 10.1007/s12574-019-00454-9.

30. Gazun LO, Polukhina EV. Some aspects of cardiomyopathy ultrasonic diagnosis. *Public health of the Far East.* 2017;(4):75–79. (In Russ.) EDN: YOJYNQ.

31. Konstant Dzh. *Klinicheskaya diagnostika zabolevaniy serdtsa (kardiolog u posteli bol'nogo).* (Clinical diagnosis of heart diseases (cardiologist at the patient's bedside).) Translation from English. M.: BINOM; 2017. 448 p. (In Russ.)

32. Karaca Özer P, Ayduk Gövdeli E, Engin B, Atıcı A, Baykız D, Orta H, Demirtakan ZG, Emet S, Elitok A, Tayyareci Y, Umman B, Bilge AK, Buğra Z. Role of global longitudinal strain in discriminating variant forms of left ventricular hypertrophy and predicting mortality. *The Anatol J Cardiol*. 2021;25(12):863–871. DOI: 10.5152/AnatolJCardiol.2021.21940.

33. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2016;17:1321–1360. DOI: 10.1093/ehjci/jew082.

34. Gluckman TJ. Hypertrophic cardiomyopathy: Diagnosis and therapeutic options. *Am J Manag Care*. 2021;27(6):S111–S117. DOI: 10.37765/ajmc.2021.88628.

35. Tuohy CV, Kaul S, Song HK, Nazer B, Heitner SB. Hypertrophic cardiomyopathy: The future of treatment. *Eur J Heart Fail*. 2020;22(2):228–240. DOI: 10.1002/ejhf.1715.

36. Maron BJ, Desai MY, Nishimura RA, Spirito P, Rakowski H, Towbin JA, Dearani JA, Rowin EJ, Maron MS, Sherrid MV. Management of hypertrophic cardiomyopathy: JACC state-of-the-art review. *J Am Coll Cardiol*. 2022;79(4):390–414. DOI: 10.1016/j.jacc.2021.11.021.

37. Dybro AM, Rasmussen TB, Nielsen RR, Andersen MJ, Jensen MK, Poulsen SH. Randomized trial of Metoprolol in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2021;78(25):2505–2517. DOI: 10.1016/j.jacc.2021.07.065.

38. Olivotto I, Oreziak A, Barriales-Villa R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, Kubanek M, Wojakowski W, Jensen MK, Gimeno-Blanes J, Afshar K, Myers J, Hegde SM, Solomon SD, Sehnert AJ, Zhang D, Li W, Bhattacharya M, Edelberg JM, Waldman CB, Lester SJ, Wang A, Ho CY, Jacoby D; EXPLORER-HCM study investigators. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):759–769. DOI: 10.1016/S0140-6736(20)31792-X.

39. Zampieri M, Berteotti M, Ferrantini C, Tassetti L, Gabriele M, Tomberli B, Castelli G, Cappelli F, Stefàno P, Marchionni N, Coppini R, Olivotto I. Pathophysiology and treatment of hypertrophic cardiomyopathy: New perspectives. *Curr Heart Fail Rep*. 2021;18(4):169–179. DOI: 10.1007/s11897-021-00523-0.

40. Goldspink PH, Warren CM, Kitajewski J, Wolska BM, Solaro RJ. A perspective on personalized therapies in hypertrophic cardiomyopathy. *J Cardiovasc Pharmacol*. 2021;77(3):317–322. DOI: 10.1097/FJC.0000000000000968.

41. Taddei-Allen P. Hypertrophic cardiomyopathy considerations for the managed care pharmacist. *Am J Manag Care*. 2021;27(6):S118–S125. DOI: 10.37765/ajmc.2021.88629.

42. Maron MS, Masri A, Choudhury L, Olivotto I, Saberi S, Wang A, Garcia-Pavia P, Lakdawala NK, Nagueh SF, Rader F, Tower-Rader A, Turer AT, Coats C, Fifer MA, Owens A, Solomon SD, Watkins H, Barriales-Villa R, Kramer CM, Wong TC, Paige SL, Heitner SB, Kupfer S, Malik FI, Meng L, Wohltman A, Abraham T; REDWOOD-HCM Steering Committee and Investigators. Phase 2 study of aficamten in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2023;81(1):34–45. DOI: 10.1016/j.jacc.2022.10.020.

43. Ferrantini C, Pioner JM, Mazzoni L, Gentile F, Tosi B, Rossi A, Belardinelli L, Tesi C, Palandri C, Matucci R, Cerbai E, Olivotto I, Poggesi C, Mugelli A, Coppini R. Late sodium current inhibitors to treat exercise-induced obstruction in hypertrophic cardiomyopathy: An *in vitro* study in human myocardium. *Br J Pharmacol*. 2018;175(13):2635–2652. DOI: 10.1111/bph.14223.

44. Jiang Z, Tang M, Liu H, Ma N, Ding F, Bao C, Mei J. Minimally invasive surgery for hypertrophic obstructive cardiomyopathy with mitral regurgitation. *Ann Thorac Surg.* 2021;111(4):1345–1350. DOI: 10.1016/j.athoracsur.2020.06.028.

45. Maron BJ, Dearani JA, Ommen SR, Maron MS, Schaff HV, Nishimura RA, Ralph-Edwards A, Rakowski H, Sherrid MV, Swistel DG, Balaram S, Rastegar H, Rowin EJ, Smedira NG, Lytle BW, Desai MY, Lever HM. Low operative mortality achieved with surgical septal myectomy: Role of dedicated hypertrophic cardiomyopathy centers in the management of dynamic subaortic obstruction. *J Am Coll Cardiol*. 2015;66(11):1307–1308. DOI: 10.1016/j.jacc.2015.06.1333.

46. Rowin EJ, Maron BJ, Romashko M, Wang W, Rastegar H, Link MS, Maron MS. Impact of effective management strategies on patients with the most extreme phenotypic expression of hypertrophic cardiomyopathy. *Am J Cardiol*. 2019;124(1):113–121. DOI: 10.1016/j.amjcard.2019.04.002.

47. Nguyen A, Schaff HV, Nishimura RA, Geske JB, Dearani JA, King KS, Ommen SR. Apical myectomy for patients with hypertrophic cardiomyopathy and advanced heart failure. *J Thorac Cardiovasc Surg.* 2019;S0022–5223(19)30772-X. DOI: 10.1016/j.jtcvs.2019.03.088.

48. Rowin EJ, Maron BJ, Carrick RT, Patel PP, Koethe B, Wells S, Maron MS. Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2020;75(24):3033–3043. DOI: 10.1016/j.jacc.2020.04.045.

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