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ОСОБЕННОСТИ ГИПЕРТРОФИИ ЛЕВОГО ЖЕЛУДОЧКА И ХАРАКТЕРИСТИКА ФЕНОТИПИЧЕСКИХ ВАРИАНТОВ У БОЛЬНЫХ ГИПЕРТРОФИЧЕСКОЙ КАРДИОМИОПАТИЕЙ

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Specifics of Left Ventricular Hypertrophy and Characteristic of Phenotypic Variants in Patients with Hypertrophic Cardiomyopathy

Резюме

Гипертрофическая кардиомиопатия характеризуется генетической и фенотипической гетерогенностью, что проявляется в различных вариантах локализации и протяженности гипертрофии миокарда. **Цель**. На основании данных эхокардиографии оценить особенности гипертрофии левого желудочка, распространенность и клинико-инструментальные показатели фенотипических вариантов гипертрофической кардиомиопатии. **Материалы и методы**. Обследовано 295 больных с гипертрофической кардиомиопатией в возрасте от 18 до 88 лет (60,3±13,4 лет), мужчин 183 (62 %), женщин 112 (38 %). Диагноз устанавливался на основании двухмерной эхокардиографии. Оценивались выраженность, локализация и протяженность гипертрофии миокарда, максимальная толщина гипертрофированного сегмента, масса миокарда, индекс массы миокарда левого желудочка, наличие и выраженность среднежелудочковой обструкции и обструкции выносящего тракта левого желудочка. В зависимости от преимущественной локализации и протяженности гипертрофии больные были распределены в 8 групп согласно рекомендациям по гипертрофической кардиомиопатии МЗ РФ. Проведен анализ и сравнение полученных результатов в зависимости от фенотипа кардиомиопатии. **Результаты**. Средняя продолжительность заболевания — 10,5±7,52 лет. Средние значения индекса массы тела у всех пациентов составили 28,2±2,82 кг/м^2. Наиболее часто отмечался фенотип с базальной гипертрофией межжелудочковой перегородки (n=130, 44,1 %), 1 группа. У 47 (15,9 %) больных выявлена гипертрофия межжелудочковой перегородки «обратной кривизны» (3 гр.), у 41 (13,9 %) — «нейтральная межжелудочковая перегородка» (2 гр.), у 36 (12,2 %) — симметричная гипертрофия левого желудочка (8 гр.), по 11 (3,7 %) пациентов имели комбинированную гипертрофию межжелудочковой перегородки и других отделов левого или правого желудочка (4 гр.) и свободной стенки ЛЖ (7 гр.), у 10 (3,4 %) — среднежелудочковая гипертрофия левого желудочка (6 гр.) и у 9 (3,1 %) — апикальная гипертрофия (5 гр.). Наибольшее значение максимальной толщины миокарда отмечено у больных 6 группы 19,3 (19-20,4 мм). Среднежелудочковая обструкция выявлена в 6 группе (90,0 %), обструкция выносящего тракта левого желудочка чаще регистрировалась в 4 и 8 группах (81,8 % и 77,8 %), а реже — в группе 5 (22,2 %) (p <0,01). У больных 7 группы не было выявлено случаев с обструкцией выносящего тракта левого желудочка в базальном состоянии. Максимальные значения показателей массы миокарда и индекса массы миокарда левого желудочка отмечены в группе 8 — 402 (356-439) г и 195 (173-218) г/м^2, соответственно (p <0,01). **Заключение**. Эхокардиография представляет информативный метод оценки наличия, выраженности гипертрофии миокарда и определения фенотипического варианта гипертрофической кардиомиопатии. Наиболее часто регистрируются варианты гипертрофии межжелудочковой перегородки, среди которых самым распространенным является фенотип гипертрофии базальной её части. Каждый фенотип гипертрофической экспрессии характеризуется особенностями эхокардиографических параметров.

Ключевые слова: *гипертрофическая кардиомиопатия, гипертрофия миокарда, фенотип, эхокардиография, обструкция*

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Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract
Hypertrophic cardiomyopathy is characterized by genetic and phenotypic heterogeneity which manifests in different variants of localization and extent of myocardial hypertrophy. **Aim**: to evaluate specifics of left ventricular hypertrophy, the prevalence and characteristics of clinical and instrumental features of phenotypic variants of hypertrophic cardiomyopathy. **Materials and methods**. The study includes 295 patients with hypertrophic cardiomyopathy aged 18 to 88 years (60.3±13.4 years), 183 men (62 %), and women 112 (38 %). The diagnosis of which was established by 2D echocardiography. The severity, localization and extent of myocardial hypertrophy, the maximum thickness of the hypertrophied segment, left ventricular myocardial mass, left ventricular myocardial mass index, the presence and severity of mid-ventricular and left ventricular outflow tract obstruction were evaluated. Depending on the predominant localization and extent of hypertrophy, patients were divided into 8 groups according to the recommendations for hypertrophic cardiomyopathy of the Ministry of Health of the Russian Federation. The analysis and comparison of the obtained results are carried out. **Results.** The average duration of the disease is 10.5±7.52 years. The mean values of the body mass index in patients — 28.2±2.82 kg/m^2. The phenotype with basal hypertrophy of the septum (n=130, 44.1 %), group 1 was most often noted. In 47 (15.9 %) patients, hypertrophy of the septum of "reverse curve" (2 group) was detected, in 41 (13.9 %) — "neutral septum" (3 group), in 36 (12.2 %) — symmetrical hypertrophy of the left ventricle (8 group), 11 (3.7 %) of patients had combined hypertrophy of the septum and other parts of the left or right ventricle (4 group) and the free left ventricular wall (7 group), in 10 (3.4 %) — middle ventricular hypertrophy of the left ventricle (6 group) and in 9 (3.1 %) — apical hypertrophy (5 group). The highest value of the maximum thickness of the myocardium was noted in patients of the 6th group 19.3 (19-20.4 mm). Mid-ventricular obstruction was detected in group 6 (90 %), left ventricular outflow tract obstruction was more often registered in groups 4 and 8 (81.8 % and 77.8 %), and less often in group 5 (22.2 %) (p <0.01). In group 7, there were no cases of rest obstruction of left ventricular outflow tract. The maximum values of myocardial mass and left ventricular myocardial mass index were noted in group 8 — 402 (356-439) g and 195 (173-218) g/m^2, respectively (p <0.01). **Conclusion**. Echocardiography is an informative tool for assessing the presence, severity myocardial hypertrophy and determination of the phenotypic variant of hypertrophic cardiomyopathy. Variants of septal hypertrophy are most commonly registered one, among which the most frequent is the phenotype of basal septal hypertrophy. Each phenotype of hypertrophic expression is characterized by its echocardiographic parameters.

Key words: *hypertrophic cardiomyopathy, myocardial hypertrophy, phenotype, echocardiography, obstruction*

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OT — outflow tract, HCM — hypertrophic cardiomyopathy, LVH — left ventricular hypertrophy, LVMMI — left ventricular myocardium mass index, EDD — end-diastolic dimension, LV — left ventricle, MV — mitral valve, LVMM — left ventricular myocardium mass, BSA — body surface area, RV — right ventricle, PWTd — LV posterior wall thickness, diastolic, IVSTd — interventricular septum thickness, diastolic, echoCG — echocardiography

Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic myocardial disease defined by left and/or right ventricular (RV) myocardium hypertrophy, usually asymmetric due to a thick interventricular septum (IVS), which cannot be attributed solely to a higher pressure-induced load, and observed in the absence of any other cardiac or system disease, metabolic or multisystemic syndrome associated with left ventricular (LV) hypertrophy [1–3].

LV myocardium hypertrophy is a primary pathomorphological and diagnostic sign of HCM, which defines a cascade of subsequent pathophysiological events: LV outflow tract (OT) obstruction, diastolic dysfunction, microcirculation involvement, and various cardiac rhythm and conduction disorders [4].

HCM is diagnosed on the basis of unexplained and usually symmetric LV hypertrophy (LVH) using imaging methods, the use of which makes it possible to assess the presence, intensity, primary localisation, and extension

of hypertrophic myocardium. Besides, visualisation methods, especially echocardiography (echoCG), are capable of assessing the presence and intensity of LVOT obstruction and cardiac valve condition (especially that of the mitral valve, MV), subvalvular structures, systolic and diastolic function of LV [5].

When echoCG was introduced in clinical practice in 1970s, it was then possible to identify the array of forms of myocardium hypertrophy in HCM [6–8]. According to the HCM Clinical Guidelines approved by the Ministry of Health of Russia in 2020, cardiomyopathy can be symmetric and asymmetric, and the latter form includes seven variants of LVH [3]. Understanding the various forms of HCM improves disease diagnosis, which is not limited only to detection of basal IVS hypertrophy, and makes it possible to study pathogenesis taking into genotype/phenotype correlation as well as to select a most optimal therapy. However, to date there is insufficient information on the rate of proposed phenotypes, only a general idea that HCM is a disease, the primary sign of which is asymmetric hypertrophy with IVS involvement [5, 9, 10].

Objective

Using a 2D echoCG, to assess the features of LVH, morbidity and the characteristics of clinical and instrumental parameters of various HCM phenotypes.

Materials and Methods

A cross-sectional study was conducted. Analysis covered all diagnosed HCM cases found in the database of a multiprofile inpatient clinic during a period from 2000 to 2022 and medical records of 295 patients (183 males (62 %) and 112 females (38 %)) 18 to 88 years of age (mean age: 60.3 ± 13.4 years) with HCM.

The disease was diagnosed on the basis of 2D echoCG results where one or several LV segments was ≥ 15 mm thick and any other pathological process which could cause hypertrophy was absent [1-3].

Exclusion criteria for the study were: patients with inadequate echo window; stage 2–3 arterial hypertension (systolic blood pressure: > 160 mm Hg, diastolic blood pressure: > 100 mm Hg), stage II–III hypertensive disease; aortic valve stenosis; marked aortic regurgitation, congenital heart disorders; history of active sporting activities within the previous year, clinical, laboratory, morphological data or a history of Anderson Fabry disease Anderson, Danon disease, Friedreich's ataxia, isolated cardiac glycogenosis, cardiac amyloidosis and other infiltrative, endocrine and metabolic diseases which can cause myocardium thickening or hypertrophy.

All patients underwent echoCG using Vivid-3 Pro apparatus (General Electric, USA) with a 3 MHz phase sensor, with the patient lying on the left side, breathing quietly and with the exhalation recommended for transthoracic echoCG by the American Society of Echocardiography (2019) [11].

The thickness of LV segments was measured during diastole, with the sensor oriented perpendicularly to the parasternal long axis (IVS, posterior wall of LV), parasternal short axis (IVS septum, anterior, side and posterior wall of LV), apical axis (2- and 4-chamber position) in order to measure the thickness of myocardium in the LV apex.

The left ventricular myocardium mass (LVMM) was calculated in accordance with the recommendations of the American Society of Echocardiography [12] using the following formula: LVMM = 0.8 x [1.04 x (EDD + PWTd + IVSTd)^3 — EDD^3)] + 0.6 g, where EDD is end-diastolic dimension, PWTd is LV posterior wall thickness, diastolic, and IVSTd is interventricular septum thickness, diastolic.

Left ventricular myocardium mass index (LVMMI) was calculated as follows: LVMMI = LVMM/BSA (g/m^2), where LVMM is body surface area, m^2.

LVOT gradient was calculated using the modified Bernoulli distribution: gradient = 4V^2, where V is the LVOT blood flow velocity (m/s). The blood flow velocity was measured using a constant wave Doppler mode, with the control volume positioned at the LVOT level.

Obstruction at rest was at gradient ≥ 30 mm Hg; obstruction with stimulation was at the normal resting value (< 30 mm Hg) and ≥ 30 mm Hg after physical exercises; no obstruction was observed at a normal value (< 30 mm Hg) both at rest and after physical exercises.

If the thickness of any segment of LV was ≥ 15 mm, hypertrophy localisation and extension were identified. Then patients were divided into 8 groups depending on phenotypic expression of hypertrophy in accordance with the morphological HCM classification [3]: hypertrophy of the basal segment of IVS (group 1), hypertrophy of entire IVS, or neutral IVS (2), reverse curvature hypertrophy of IVS (3), combined hypertrophy of IVS and other segments of LV or RV (4), apical hypertrophy with or without involvement of other LV segments (5), mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV (6), hypertrophy of free wall of LV (7), and symmetric (or concentric) LV hypertrophy (8).

8 phenotypic variants of LVH were compared in groups depending on gender. Mean values of the maximum thickness the hypertrophic myocardium segment,

LVMM, LVMMI, pressure gradient in LVOT were assessed in each of the 8 phenotypic groups of HCM patients; also, the rate of LVOT obstruction was analysed.

Statistical processing and result presentation were performed using licensed Jamovi 2.3.21.0. The values were assessed for correspondence with the normal distribution, and Shapiro-Wilk test was used. The data are presented as a mean arithmetic and standard deviation (M±SD) for values with normal distribution, and as a median with interquartile range (Me (IQR)) for parameters with non-normal distribution. Categorical variables are presented as absolute values and per cents. For intergroup comparison for quality, chi-square (χ^2) was used, while for quantitative comparison, single-factor analysis of variance or Kruskal-Wallis test were used. Results with $p < 0.05$ were statistically significant.

Results

Males prevailed in all phenotypic variants of HCM, except for apical LVH; however, the differences were not statistically significant ($p > 0.05$). Mean disease duration from the first complaint to HCM diagnosis was 10.5±7.52 years. Mean body mass index (BMI) in all patients was 28.2±2.82 mg/m^2.

EchoCG revealed that the most common phenotypic variant is hypertrophy of the basal segment of IVS, which was recorded in 130 (44.1 %) cases (group 1). 47 (15.9 %) patients had reverse curvature hypertrophy of IVS (group 3); 41 (13.9 %) patients — neutral IVS (group 2); 36 (12.2 %) patients — symmetric LVH (group 8); 11 (3.7 %) patients had combined hypertrophy of IVS and other segments of LV or RV (group 4) and hypertrophy of free wall of LV (group 7); 10 (3.4 %) patients — "sand glass" LVH (group 6); and 9 (3.1 %) patients — apical LVH (group 5). Clinical characteristics of patients with HCM divided into phenotypic groups are presented in Figure 1 and Table 1.

Most common complaints were weakness, fatigue in 221 (74.9 %) patients, chest pain and shortness of breath in 202 (68.5 %) patients. Also, patients complained of palpitations, arrhythmias — 133 (45.1 %) patients and dizziness — 118 (40 %) patients. Presyncope and syncope were observed in 27 (9.15 %) patients.

Comorbidities included arterial hypertension in 48 (16.3 %) patients, coronary heart disease (CHD) in 22 (7.46 %) patients, type 2 diabetes mellitus in 61 (20.68 %) patients, cerebrovascular diseases in 67 (22.77 %) patients, thyroid diseases in 38 (12.8 %) patients, and cancer in 6 (2.03 %) patients.

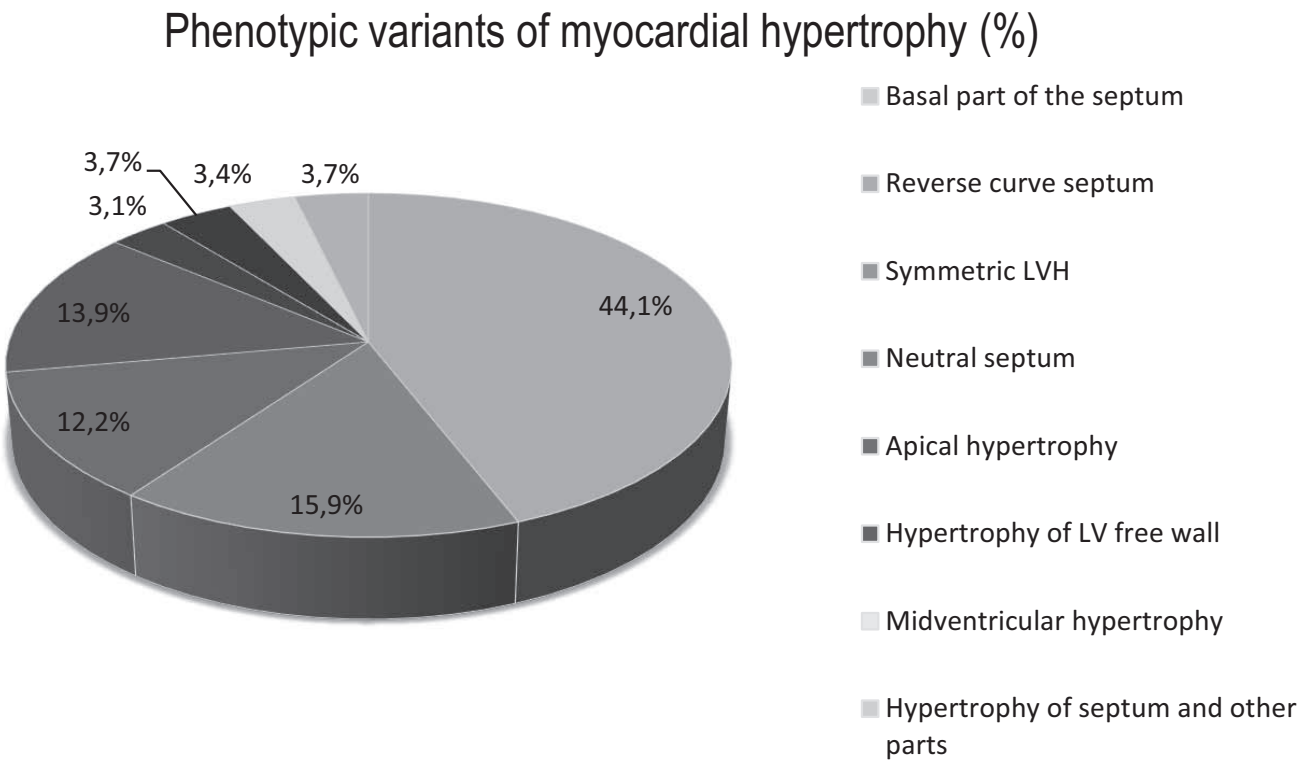

Figure 1. *Prevalence of phenotypic variants of myocardial hypertrophy in patients with hypertrophic cardiomyopathy*
Notes: LV — left ventricle; LVH — LV hypertrophy

Table 1. General characteristic of patients with hypertrophic cardiomyopathy

Parameters	Total (n=295)
Sex, male (%)	183 (62 %)
Age, years, mean±MD	60,3±13,4
Duration of the disease, years §	10,5±7,52
BMI, kg/m², mean±MD	28,2±2,82
Complaints, n (%):	
• Chest pain	202 (68,47 %)
• Dyspnoe	202 (68,47 %)
• Weakness, fatigue	221 (74,91 %)
• Palpitation, heart rate irregularity	133 (45,08 %)
• Dizziness	118 (40,0 %)
• Pre-, syncope	27 (9,15 %)
Concomitant diseases, n (%):	
• Arterial hypertension	48 (16,27 %)
• Coronary artery disease	22 (7,46 %)
• Diabetes mellitus	61 (20,68 %)
• Cardiovascular disease	67 (22,77 %)
• Thyroid disease	38 (12,8 %)
• Malignant disease	6 (2,03 %)
Heart failure	168 (56,95 %)

Note: § — the duration of the disease is considered to be the time from the diagnosis of hypertrophic cardiomyopathy or the presence of severe left ventricular hypertrophy (≥ 15 mm) in the absence of obvious causes that can cause hypertrophy of such severity, and signs of another systemic, metabolic or infiltrative disease

Table 2. Results of electrocardiographic and echocardiographic investigations in patients with hypertrophic cardiomyopathy

Parameters	Total, n (%)	Variant 1	Variant 2	Variant 3	Variant 4	Variant 5	Variant 6	Variant 7	Variant 8
	295 (100)	130 (44,1)	41 (13,9)	47 (15,9)	11 (3,7)	9 (3,1)	10 (3,4)	11 (3,7)	36 (12,2)
Electrocardiography									
Sinus rhythm, n	204 (69,15)	87 (42,64)	24 (11,76)	36 (17,65)	8 (3,92)	5 (2,45)	6 (2,94)	10 (4,90)	27 (13,24)
	in % to group	87 (66,92)	24 (58,54)	36 (76,60)	8 (72,73)	5 (55,56)	6 (60,0)	10 (90,91)	27 (75,0)
Atrial fibrillation, n	91 (30,84)	43 (47,25)	17 (18,68)	11 (12,08)	3 (3,29)	4 (4,39)	4 (4,39)	1 (1,09)	9 (9,89)
	in % to group	43 (33,08)	17 (41,46)	11 (23,40)	3 (27,27)	4 (44,44)	4 (40,0)	1 (9,09)	9 (25,0)
AV-blocks, n	31 (10,5)	14 (45,16)	5 (16,13)	5 (16,13)	2 (6,45)	0	0	2 (6,45)	3 (9,68)
	in % to group	14 (10,77)	5 (12,20)	5 (10,64)	2 (18,18)	0	0	2 (18,18)	3 (8,33)
Intraventricular conduction blocks, n	122 (41,36)	55 (45,08)	15 (12,30)	21 (17,21)	2 (1,64)	5 (4,10)	8 (6,56)	3 (2,46)	13 (10,66)
	in % to group	55 (42,31)	15 (36,59)	21 (44,68)	2 (18,18)	5 (55,56)	8 (80,0)	3 (27,27)	13 (36,11)
Pseudo-infarction Q, n	59 (20)	30 (50,85)	10 (16,95)	5 (8,47)	3 (5,08)	1 (1,69)	3 (5,08)	3 (5,08)	4 (6,78)
	in % to group	30 (23,08)	10 (24,39)	5 (10,64)	3 (27,27)	1 (11,11)	3 (30,0)	3 (27,27)	4 (11,11)
QRS fragmentation, n	18 (6,1)	8 (44,44)	0	4 (22,22)	2 (11,11)	0	1 (5,56)	0	3 (16,67)
	in % to group	8 (6,15)	0	4 (8,51)	2 (18,18)	0	1 (10,0)	0	3 (8,33)
T inversion in precordial leads, n	236 (80)	100 (42,37)	36 (15,25)	41 (17,37)	7 (2,97)	7 (2,97)	9 (3,81)	8 (3,39)	28 (11,86)
	in % to group	100 (76,92)	36 (87,80)	41 (87,23)	7 (63,64)	7 (77,78)	9 (90,0)	8 (72,73)	28 (77,78)
Prolonged QTc, n	14 (4,75)	5 (35,71)	2 (14,29)	1 (7,14)	2 (14,29)	0	1 (7,14)	1 (7,14)	2 (14,29)
	in % to group	5 (3,85)	2 (4,88)	1 (2,13)	2 (18,18)	0	1 (10,0)	1 (9,10)	2 (5,56)
Amplitude signs of LV hypertrophy, n§	213 (72,2)	93 (43,66)	27 (12,68)	33 (15,49)	7 (3,29)	7 (3,29)	8 (3,76)	9 (4,23)	29 (13,61)
	in % to group	93 (71,54)	27 (65,85)	33 (70,21)	7 (63,64)	7 (77,78)	8 (80,0)	9 (81,82)	29 (80,56)

Table 2. (The end)

Parameters	Total, n (%)	Variant 1	Variant 2	Variant 3	Variant 4	Variant 5	Variant 6	Variant 7	Variant 8
	295 (100)	130 (44,1)	41 (13,9)	47 (15,9)	11 (3,7)	9 (3,1)	10 (3,4)	11 (3,7)	36 (12,2)
Echocardiography									
Mitral valve insufficiency, n	85 (28,81)	30 (35,29)	16 (18,82)	14 (16,47)	3 (3,53)	4 (4,71)	4 (4,71)	2 (2,35)	12 (14,12)
	in % to group	30 (23,08)	16 (39,02)	14 (29,79)	3 (27,27)	4 (44,44)	4 (40,0)	2 (18,18)	12 (33,33)
Diastolic dysfunction, n	235 (79,66)	106 (45,11)	32 (13,62)	37 (15,74)	7 (2,98)	7 (2,98)	7 (2,98)	10 (4,26)	29 (12,34)
	in % to group	106 (81,54)	32 (78,05)	37 (78,72)	7 (63,64)	7 (77,78)	7 (70,0)	10 (90,91)	29 (80,56)
Pulmonary artery pressure, mm Hg	25 (20,5-31)	24 (22-30)	25 (22-38)	24 (20-31,5)	25 (19,5-29,5)	25 (24-30)	23,5 (22,3-25)	21 (18-27)	24,5 (19-35)
EDV, ml	149 (116-184)	145 (115-175)	162 (109-189)	168 (132-201)	113 (97,5-178)	148 (143-168)	186 (146-222)	163 (126-186)	148 (124-177)
ESV, ml	56 (40-71,0)	55 (38,5-65)	58,5 (46-76)	63,1 (44-76,5)	43 (28,5-73)	65 (56-71)	47,5 (39,5-62,5)	58 (34,5-63)	54 (43,8-66,8)
Stroke volume, ml	91,2 (73,5-114)	90,5 (69-110)	87 (68-109)	94,6 (83,5-127)	75 (67,1-104)	94,6 (86-98)	108 (101-133)	113 (79,5-125)	90 (81,3-112)
Ejection fraction, %	64 (56,5-69,6)	64 (55-70)	61 (50,8-67,9)	64 (57,1-69)	68 (61,5-73,5)	60,1 (55-64)	69,6 (68,4-73,3)	67 (65-68,6)	62,5 (57-72,3)
Mean maximal thickness of hypertrophied myocardium, mm (Me (IQR))	17,8 (16,4-19,0)	16,9 (16-18,2)	18,0 (16,4-19,3)	18,0 (16,6-19,3)	18,7 (18,2-19,3)	19,1 (18,0-20,1)	19,3 (19,0-20,4)*	18,6 (16,4-19,5)	18,0 (16,9-19,0)
Obstruction of left ventricular outflow tract, n	183 (62,03)	83 (45,36)	27 (14,75)	25 (13,66)	9 (4,92)	2 (1,09)	9 (4,92)	0	28 (15,30)
	in % to group	83 (63,84)	27 (65,85)	25 (53,19)	9 (81,81)	2 (22,22)*	9 (90,0)	0	28 (77,78)
Rest gradient, mm Hg (Me (IQR))	20,0 (8,50-36,0)	20,8 (8,50-35,0)	17,0 (9,0-32,0)	15,0 (5,0-35,0)	23,0 (16,3-44,0)	6,50 (3,50-15,5)*	39,5 (35,6-42,8)	11,0 (6,0-11,5)	25,8 (13,9-38,0)
MMLV, g (Me (IQR))	345 (284-411)	349 (284-400)	363 (297-421)	338 (270-390)	290 (273-336)	280 (234-288)	342 (282-376)	317 (257-369)	402 (356-439)*
MMLVI, g/m2 (Me (IQR))	168 (143-202)	169 (141-200)	187 (150-204)	164 (133-200)	146 (142-152)	138 (127-152)	163 (138-197)	151 (129-164)	195 (173-218)*
Left atrium, mm	4,52 (4,17-4,97)	4,50 (4,10-4,98)	4,60 (4,10-5,10)	4,40 (4,07-4,81)	4,58 (4,30-5,0)	4,78 (4,39-5,11)	4,58 (4,46-4,70)	4,33 (4,10-4,65)	4,63 (4,30-4,91)

Notes: AV — atrioventricular; LV — left ventricle; EDV — end-diastolic volume; ESV — end-systolic volume; MMLV — LV myocardial mass; MMLVI — MMLV index. Variant 1 — hypertrophy of the basal part of the septum; 2 — hypertrophy of the entire septum ("neutral" septum); 3 — hypertrophy of the septum "reverse curve"; 4 — combined hypertrophy of the septum and other parts of the left (LV) or right ventricle; 5 — apical hypertrophy of the LV; 6 — mid-ventricular hypertrophy of the LV with hypertrophy of the free LV wall; 7 — hypertrophy of the free LV wall; 8 — symmetrical (or concentric) LV hypertrophy. Values are mean ± standard deviation, n (%) or median (interquartile range). * p <0.05 in comparison with intergroup values; § — amplitude signs of LV hypertrophy were determined by Cornell and/or Sokolow-Lyon voltage criteria

EchoCG results were used to analyse the correlation of the most marked LV myocardium hypertrophy depending on the phenotypic variant (Table 2). The most marked hypertrophy (mean values) demonstrated statistically significant differences (p = 0.003) depending on the phenotypic variant: patients with mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV (group 6) — 19.3 (IQR: 19.0-20.4) mm, 19.1 (IQR: 18.0-20.1) mm (group 5), 18.7 (IQR: 18.2–19.3) mm (group 4), 18.6 (IQR: 16.4–19.5) mm (group 7), 18.0 (IQR: 16.6–19.3) mm (group 3), 18.0 (IQR: 16.9–19.0) mm (group 8), 18.0 (IQR: 16.4–19.3) mm (group 2), 16.9 (IQR: 16.0–18.2) mm (group 1) (Figure 2).

The correlation between the presence and type of obstruction in the middle section of LV and LVOT (both at rest and after stimulation) and a certain morphological phenotype of myocardial hypertrophy was studied. The most common was mid-ventricle obstruction (MVO) in group 6 — 9 (90.0 %) patients; LVOT obstructions were observed more often in group 4 — 9 (81.8 %) patients and group 8 — 28 (77.8 %) patients; more rarely in group 5 — 2 (22.2 %) patients; the difference was statistically significant at p < 0.01. Patients in group 7 (hypertrophy of free wall of LV) did not have basal LVOT obstructions.

Comparison of gradients at rest also revealed differences, depending on the LVH phenotype: the highest values were observed in group 6 — 39.5 (IQR: 35.6–42.8) mm Hg, while the lowest values were recorded in group 5 — 6.50 (IQR: 3.50–15.5) mm Hg (p < 0.01). The gradient distribution is presented in Figure 3.

LVMM values had their own peculiarities: the lowest values were recorded in group 5 — 280 (IQR: 234–288) g, while the highest values were recorded in group 8 — 402 (IQR: 356–439), the difference was statistically significant at p < 0.01.

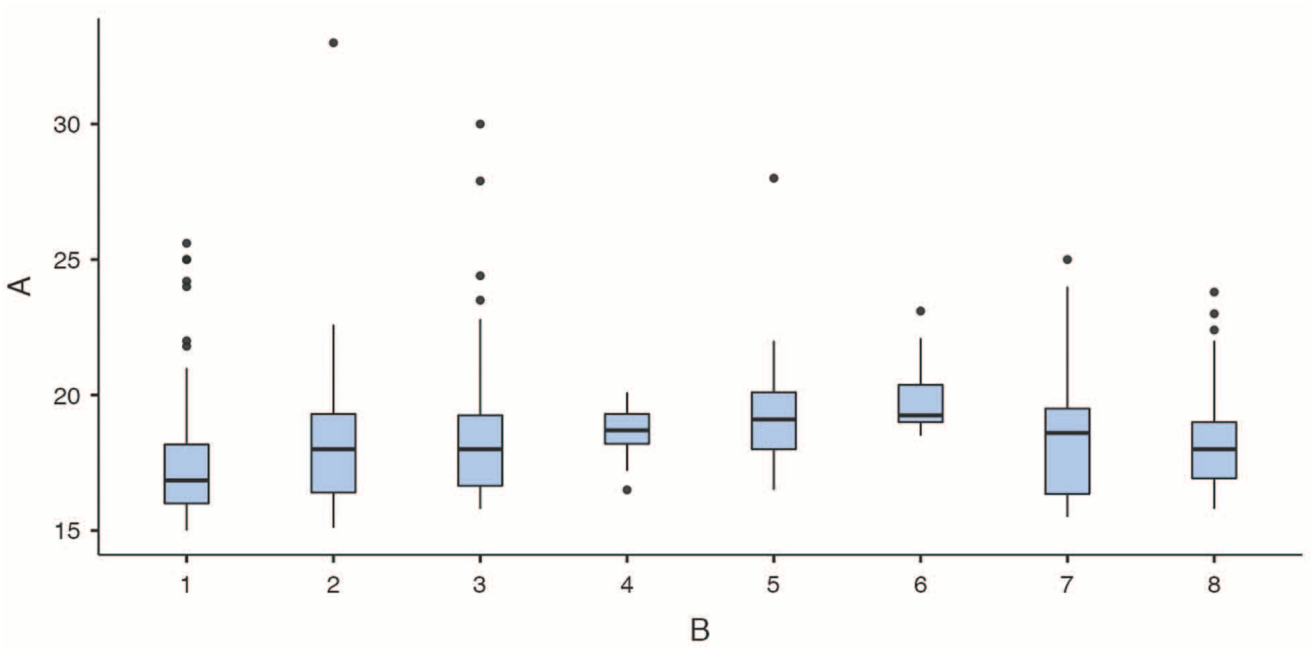

Figure 2. *Medians and quartiles of maximum thickness of hypertrophied myocardium in different phenotypic variants of left ventricular hypertrophy. A — myocardial thickness, mm. B — phenotypic variant, group number (p=0.003)*

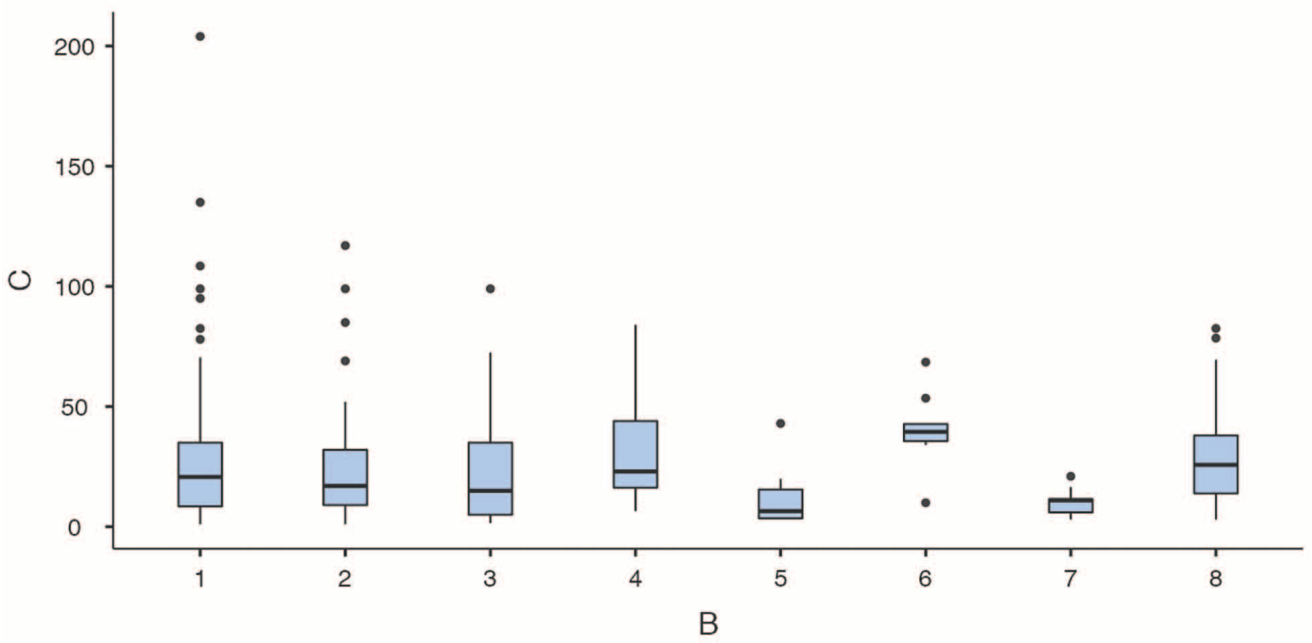

Figure 3. *Medians and quartiles of rest gradient values in different phenotypic variants of left ventricular hypertrophy. C — gradient, mm Hg, B — phenotypic variant, group number (p <0.01)*

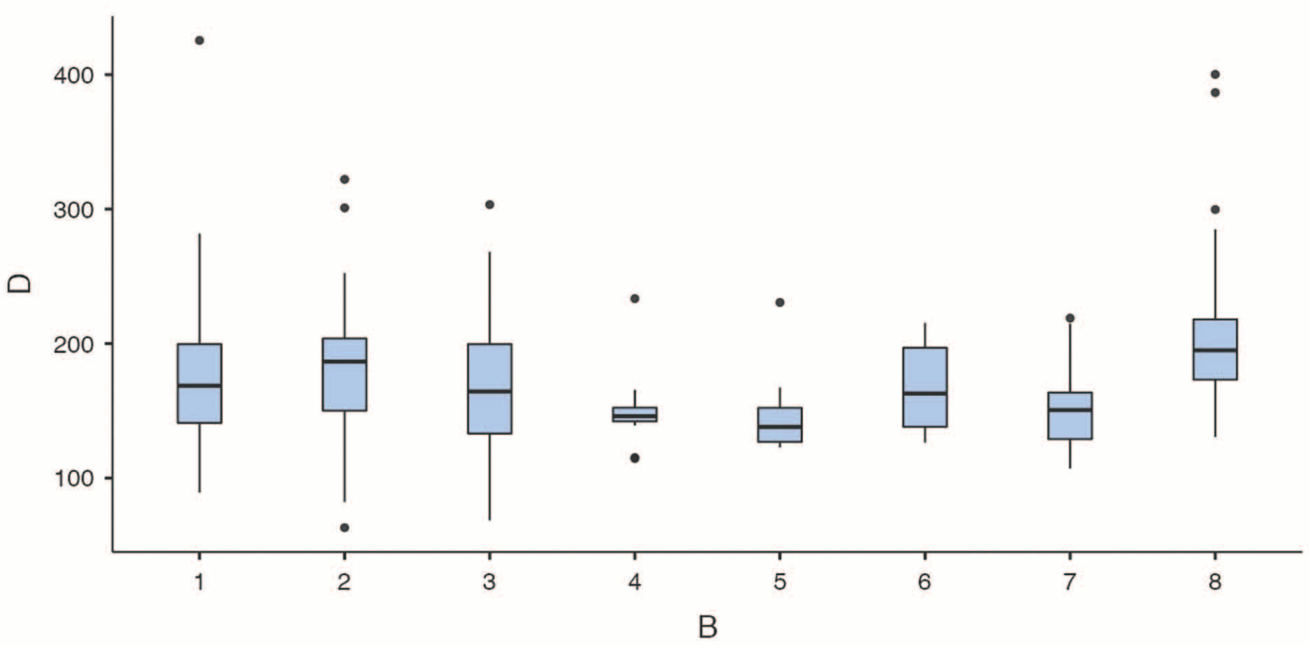

Figure 4. *Medians and quartiles of left ventricular myocardium mass index in different phenotypic variants of left ventricular hypertrophy. D — left ventricular myocardial mass index, g/m², B — phenotypic variant, group number (p <0.01)*

Like LVMM, the highest LVMMI values were observed in group 8 — 195 (IQR: 173–218) g/m², and the result was statistically more significant vs. other LVH phenotypes (p < 0.01) (Figure 4).

Discussion

After the introduction of 2D echoCG and, later, of heart MRI for HCM diagnosis, various phenotypes of myocardial hypertrophy can now be distinguished. In 1981, B.J. Maron et al. proposed four LVH patterns in this pathology: LVH limited to the anterior section of IVS (type 1); hypertrophy of anterior and posterior section of IVS (type 2); combined IVS hypertrophy and free wall of LV (type 3), and variants of anterior wall of IVS and other LV walls (type 4) [13]. Later H.G. Klues et al. [7] separated concentric and apical LVH, however, the share in the total number of patients was low. The authors identified 12 LVH patterns in 600 patients with HCM. Besides, they found out that in a majority of cases (71.7 %) hypertrophy involves two and more segments of myocardium; 34 % of patients had ≥ 3 segments affected, thus confirming that the pathological process is mostly diffuse [7]. I.S. Syed et al. [6] analysed IVS hypertrophy variants and identified its sub-types: reverse curvature, neutral and sigmoid.

With the understanding of the genetic and clinical heterogeneity of HCM and with the advent of highly informative imaging methods, the knowledge of a variety of myocardial hypertrophy phenotypes extended. MRI, a diagnostic method with high space resolution, ensures complete reconstruction of LV chamber and makes it possible to more precisely identify the presence, intensity and extent of myocardial hypertrophy. M.S. Maron et al. [14] used MRI results to present an abundance of morphological variants of HCM in 333 patients. The authors mentioned that myocardial hypertrophy in this condition is usually segmental. Generally, one or several LV segments are thicker than other, with a marked difference in the point where the thickness changes. Some patients present with fragmented patterns of segmental hypertrophy and LV wall involvement. According to the authors, none of the morphological forms of HCM is a classic or typical one; however, all researchers agree that IVS hypertrophy is prevailing [7].

Literature sources do not provide any common classification of HCM phenotypes. Researchers are of the opinion that any classification fails to highlight the diversity of the forms of hypertrophy in this disease. The ease of classification use in clinical practice by functional healthcare providers and cardiologists should be taken into account as well. On the other hand, it would be advantageous

to study the phenotypical variety with an assessment of constitutional, anamnestic data and the relation to other clinical and laboratory parameters. According to the Recommendations for HCM [3] developed by experts of the Ministry of Health of Russia, there are eight morphological types of cardiomyopathies which we use in our study; they are based on echoCG results of 295 patients. Russian experts thoroughly studied the information on HCM phenotypes and prepared their recommendations taking into account the abundance of hypertrophy patterns. The proposed classification covers asymmetric and symmetric forms of the disease. Diagnosing symmetric or concentric LVH is often challenging as regards result interpretation, provided that this hypertrophy variant is typical of secondary hypertrophy and for various HCM phenocopies [15, 16].

Despite the various available classifications of HCM phenotypes, their prevalence in patients has not been established yet. The published echoCG study results [6, 7, 17, 18, 43] for the prevalence of phenotypes in this cardiomyopathy are based on the classification taking into account morphological variants of IVS and describe 4–5 patterns. With the introduction of heart MRI, it is now possible to find areas of local myocardial hypertrophy due to better space imaging as compared to echoCG [14, 15, 19–21]. In recent years, extended classifications of phenotypes in HCM have been proposed, which include basal IVS hypertrophy, diffuse IVS hypertrophy (neutral type), concentric HCM, mid-ventricle hypertrophy, apical HCM, hypertrophy of free LV wall [3, 20, 21]. However, there are limited data on the rate of these phenotypes in HCM. Thus, our study presents information related to the prevalence and morphological features of various phenotypic variants in HCM using 2D echoCG in a relatively large group of patients.

When patients were divided into groups depending on prevalence of a hypertrophic expression phenotype, it was found out that 130 (44.1 %) patients had basal IVS hypertrophy. Reverse curvature IVS hypertrophy was observed in 47 (15.9 %) patients, neutral IVS hypertrophy and concentric hypertrophy was recorded in 41 (13.9 %) and 36 (12.2 %) patients, respectively. Phenotypes with IVS hypertrophy combined with other sections of LV and RV and hypertrophy of free LV wall — 11 (3.7 %) patients, hypertrophy of middle section of IVS and free LV wall — 10 (3.4 %) patients and apical LV hypertrophy — 9 (3.1 %) patients — were rare (Figure 1). Therefore, most often hypertrophy was limited to IVS (218 cases, 73.9 %), and the most common phenotype was basal IVS hypertrophy.

Analysis of results of previous studies of prevalence of HCM phenotypes demonstrated that the most common pattern is anterior septal hypertrophy and hypertrophy of entire IVS (neutral type) [2, 6–8, 22]. Probably, rare observation of hypertrophy of anterior, anteriolateral LV wall (group 7) in our study is due to the limited capabilities of 2D echoCG in the location of these walls and space imaging of all myocardial segments [23].

Out of 295 patients with HCM in our study, 183 (62 %) patients were males, like in the majority of studies, where male subjects prevail [1, 24]. According to a number of scientists, a higher share of male subjects is a result of a lower level of diagnosis in women, for whom correct diagnosis is less frequent, than gender predisposition of men to HCM [25].

Mean patient BMI was 28.2±2.82 kg/m^2. In other words, the patients were overweight. The papers on the impact of BMI on the course and clinical manifestations of HCM note that overweight is associated with a higher phenotypical expression of cardiomyopathy [26]. Researchers believe that BMI in HCM has a U-shape correlation with hospital mortality: underweight patients and patients with stage III obesity had significantly higher mortality rates. At the same time, patients with stage I and II overweight (preobesity) demonstrated lower mortality compared to patients with normal BMI [17]. According to our information, there were no significant differences in BMI in phenotypic groups.

Patients with HCM may have no complaints, thus complicating timely diagnosis [27]. The main symptoms of this disease are caused by the four major pathophysiological disorders: diastolic dysfunction, LVOT obstruction, imbalance between oxygen supply and demand by myocardium, and arrhythmias [4]. Usually, patients with HCM complain of shortness of breath during physical activities, chest pain, dizziness, presyncope and syncope, and palpitations/arrhythmias [3, 21]. In our study, most often patients complained of chest pain and shortness of breath (202 patients, 68.8 %), weakness, fatigue (n = 221, 74.9 %), palpitations/arrhythmias (n = 133, 45.1 %), and dizziness (n = 118, 40 %). Presyncope and syncope were recorded in 27 patients (9.15 %).

In our study, the maximum thickness of hypertrophic myocardium was statistically higher in group 6 (mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV): 19.3 (IQR: 19.0–20.4) mm, while the minimum myocardium thickness was observed in group 1: 16.9 (IQR: 16.0–18.2) mm. These values correlate with mean values observed in other studies (20–21 mm) [9, 28, 29]. It is assumed that higher hypertrophy intensity can be associated with a more unfavourable prognosis [15]. Besides, assessment of the thickness and changes in phenotype are of clinical and scientific interest [9].

In our study, prevalence of mid-ventricle hypertrophy ("sand glass" type) was low and was recorded in 10 (3.4 %) patients. Patient examination showed that mid-ventricle obstruction was found in 9 out of 10 cases (90 %) in group 6 (mid-ventricular hypertrophy of IVS with hypertrophic free wall of LV), demonstrating that practically all patients with mid-ventricular IVS hypertrophy have MVO. According to literature sources, MVO is observed nearly in 10 % of patients with HCM [30]. It is assumed that patients with MVO have a higher risk of progressive cardiac failure and sudden cardiac death [1, 30]. Approximately 25 % of cases are accompanied by formation of apical LV aneurysms which are associated with a higher rate of cardiovascular mortality [30]. In our study, none of patients had an apical aneurysm.

In general, the results of our work confirm the idea of HCM as a disease which is mostly obstructive: MVO and LVOT obstruction was observed in 182 (62 %) patients. LVOT obstruction was most common in group 4 (n = 9, 81.8 %) and group 8 (n = 28, 77.8 %). Most often LVOT obstruction was observed in patients with various phenotypes of isolated LV hypertrophy (groups 1–3), and in group 5 (n = 2, 22.2 %) and group 7 (n = 0) it was quite rare.

LVOT obstruction is recorded approximately in 2/3 of patients with HCM [1–4]. It is assumed that it is caused by the two main mechanisms: IVS hypertrophy with narrowed LVOT, creating conditions for abnormal blood flow, and anatomical changes in MV and subvalvular structures, including cusp elongation, anterior displacement of papillary muscles, making MV more susceptible to pathologically oriented vectors of systolic blood flow [2].

When assessing LVMM and LVMMI values, it is essential to take into account that usually HCM is associated with asymmetric LVH. LVMM and LVMMI are calculated with the help of thickness of IVS, posterior LV wall (diastolic) and end-diastolic dimension [12]. That is why the values of parameters in symmetric (or concentric) LVH is quite relative when assessing hypertrophy intensity. For instance, in apical HCM these values can be within a normal range, while limited basal IVS hypertrophy can present with higher LVMM and LVMMI values. According to the results of our study, LVMM and LVMMI values for all patients and within groups were normal. The lowest values were recorded in group 5 and the highest values were observed in group 8 (concentric hypertrophy) (Table 2). Taking into account the low significance of traditionally calculated LVMM and LVMMI values in HCM, special systems for assessment of LVH intensity were proposed which are based on determination of the number of hypertrophic segments and myocardium thickness [31].

Study Limitations

Study limitations are a result of a mostly retrospective nature of our study. The results are based on 2D echoCG, which is readily available and informative, but cannot visualise all sections of myocardium. In some patients, examination is obstructed by constitutional characteristics, chest shape and pulmonary diseases. Compared to MRI, echoCG is incapable of comprehensive assessment of free LV wall, anterior and lateral LV wall as well as apical area. Besides, a major disadvantage is reduced accuracy in wall thickness measurement due to inadequate distinction of endocardial surface and cardiac cavity and occasional oblique sections which distort measurement results.

We are unable to study the presence and characteristics of genetic mutations of sarcomere proteins and to compare results with phenotypical manifestations. Genetic testing is an additional method of examination of patients with HCM, the results of which allow diagnosing disease where myocardial hypertrophy is below the diagnostic level (13–14 mm) and is an important stage in differential diagnosis of HCM and its phenocopies.

Conclusion

This study conducted in a representative cohort using 2D echoCG allowed assessing prevalence and characteristics of phenotypes of hypertrophic expression in HCM. EchoCG makes it possible to assess the myocardial thickness, presence and localisation of hypertrophy, to identify the main phenotypic variants of the disease. The most common is isolated IVS hypertrophy, with prevailing basal IVS hypertrophy. Very common are phenotypes of IVS hypertrophy with reverse curvature, hypertrophy of entire IVS and concentric LV hypertrophy.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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