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EC CARDIOLOGY
Research Article

Prognostic Value of Different Electrocardiographic Patterns in Hypertrophic Cardiomyopathy Patients

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Received: September 01, 2022; **Published:** October 10, 2022

Abstract

Introduction: One of the essential screening tools in hypertrophic cardiomyopathy (HCM) diagnostics is a standard 12-lead electrocardiography (ECG). Some ECG patterns could have prognostic information even at the initial evaluation of the patient.

Purpose: The purpose of this study was to evaluate the clinical characteristics and prognosis in Ukrainian HCM patients with different ECG patterns.

Methods: In this retrospective study 250 HCM patients were included from 2006 to 2017. HCM was defined based on echocardiography left ventricular hypertrophy (LVH) with wall thickness ≥ 15 mm in adults in the absence of other cardiovascular or systemic diseases that might cause hypertrophy of such degree. The patients underwent a general clinical examination, standard 12-lead ECG, transthoracic echocardiography, 24 hours Holter ECG monitoring. Patients with HCM were divided into five groups according to the ECG types detected: I type (presence of high R waves, ST depression and T inversion - "strain pattern") - 107 patients (42.8%), type II (presence of pathological Q waves) - 49 (19.6%), type III (presence of infarct-like convex ST-elevation) - 23 (9.2%), mixed ECG - 50 (20%), atypical ECG (normal ECG or minor changes) - 21 (8.4%).

Results: The most severe phenotype had patients with III type ECG. They had significantly higher prevalence of chest pain (78,3% vs. 65.3% in type II and 61.9% in atypical ECG groups, p = 0.048), larger left atrial diameter (4.5 (4 - 5.1) cm vs. 4,3 (3,9 - 4,6) in II type, 4,3 (4 - 4,7) in mixed type, 4,2 (3,9 - 4,3) in atypical ECG groups, p = 0.038), LV EDD (4.8 (4.6 - 5.2) cm vs. 4.5 (4.1 - 4.7) in II type, 4.3 (4 - 4.8) in mixed type ECG groups, post-hoc p = 0.02). They also had a higher burden of SVE on Holter ECG monitoring (111 (8 - 931) vs. (17 (2 - 45) in I type; 6 (1 - 20) in II type, 28 (3 - 162) in mixed ECG type, 13 (4 - 120) in atypical ECG, p = 0.021). On Kaplan-Meier survival plot patients with III type ECG had a significantly worse prognosis (Chi-square = 18.5, p = 0.001). I and II types of ECG associated with better cardiovascular outcomes. In Multiple Cox's proportional regression analysis independent predictors of cardiovascular death were found - minimum heart rate during Holter ECG monitoring (HR 1.09, 95% CI 1.04 - 1.14, p = 0.0005), III type ECG (HR 3.83, 95% CI 1.49 - 9.88, p = 0.005) and QRS ≥ 120 ms (HR 2.62, 95% CI 1.10 - 6.22, p = 0.03).

Conclusion: In our study, we found that some parameters of standard 12-lead ECG and ambulatory ECG monitoring had prognostic value in patients with HCM. I and II types ECG were found to have better cardiovascular prognosis. III type ECG, prolonged QRS complex ≥ 120 ms and minimum heart rate on Holter ECG monitoring were shown to be independent predictors of cardiovascular adverse outcomes.

Keywords: *Hypertrophic Cardiomyopathy; ST-Elevation; QRS Prolongation; Minimum Heart Rate; Cardiovascular Outcomes; ECG Patterns*

Abbreviations

AH: Arterial Hypertension; AF: Atrial Fibrillation; BP: Blood Pressure; CMR: Cardiac Magnetic Resonance Imaging; DT: Deceleration Time of Early Diastolic Blood Flow; ECG: Electrocardiography; HCM: Hypertrophic Cardiomyopathy; HF: Heart Failure; HR: Heart Rate; IVS: Intraventricular Septum; LA: Left Atrium; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LV EDD: Left Ventricular End Diastolic Diameter; LV EF: Left Ventricular Ejection Fraction; LV ESD: Left Ventricular End Systolic Diameter; LVH: Left Ventricular Hypertrophy; LVOT: Left Ventricular Outflow Tract; NSVT: Non-Sustained Ventricular Tachycardia; NYHA: New York Heart Association Functional Class of Heart Failure; SCD: Sudden Cardiac Death; SD: Standard Deviation; STEMI: ST-Elevation Myocardial Infarction; SVE: Supraventricular Extrasystoles; SVT: Supraventricular Tachycardia; VE: Ventricular Extrasystoles

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disease characterized by increased left ventricular (LV) wall thickness that is not solely explained by abnormal loading conditions [1]. The disease occurs in approximately 0.2% of the general population [2]. Myocardial hypertrophy is often asymmetric with localization in the inter-ventricular septum (IVS), LV free wall, anterolateral wall, apex, papillary muscles, right ventricle. Rarely concentric hypertrophy also can be seen [3]. The course of the disease is variable from asymptomatic to severe with the development of diastolic dysfunction, progressive heart failure (HF), atrial fibrillation (AF) and cardio-embolic stroke, sudden cardiac death (SCD), especially in young patients [1,4,5].

One of the essential screening tools that make us suspect HCM is a standard 12-lead electrocardiography (ECG). This instrumental method is distinguished by its general availability, low cost, and reproducibility. The ECG can be used to screen a wide range of people, especially athletes participating in competitions [6].

Most HCM patients have ECG abnormalities that sometimes are apparent even at the initial stage of the disease. But ECG changes are nonspecific. Electrocardiographic markers of left ventricular hypertrophy (LVH), downsloping ST depression and T inversion ('strain pattern'), abnormal Q waves, "giant" negative T waves are often described in HCM [7-9]. There is also ST-elevation resembling ST-elevation myocardial infarction (STEMI) in small number of cases [10-12]. Almost 6% of HCM patients have a normal ECG at the time of diagnosis, and according to the authors, this type of ECG was associated with better outcomes [13].

Threshkur TV and co-authors in 2009 systematized various ECG changes in patients with asymmetric LVH and proposed three main types of ECG and a mixed ECG variant [14]: I type (high amplitude of R waves, downsloping ST depression and T inversion), II type (multiple pathological Q waves corresponding to positive T waves), type III "infarct-like" (simulates the acute phase of the infarct curve with convex type ST-elevation and preserved R waves in the same leads) and mixed ECG characterized by a combination of ECG signs of different types of ECG.

Recently, scientists have tried to identify ECG patterns in HCM patients and evaluate their relationship with the localization and prevalence of myocardial hypertrophy, presence of fibrotic changes and left ventricular aneurysm [8,15-21]. But few studies have evaluated the prognostic value of specific ECG patterns in development of adverse cardiovascular events [10,22-24].

Purpose of the Study

The purpose of this study was to evaluate the clinical characteristics and prognosis in Ukrainian HCM patients with different ECG patterns.

Materials and Methods

Study population

In this retrospective study 260 consecutive HCM patients were recruited and evaluated for this study, during the period of 2006 to 2017 at City Clinical Hospital # 8, Kharkiv, Ukraine. Patients were admitted to cardiology department from outpatient. The criteria of the diagnosis of HCM were according to 2014 European Society of Cardiology guidelines on diagnosis and management of HCM. HCM was defined based on echocardiography LVH with wall thickness ≥ 15 mm in adults in the absence of other cardiovascular or systemic diseases that might cause hypertrophy of such degree [1]. 10 (3,8%) patients were excluded from the study for the following reasons: severe valvular heart disease (n = 3), previous history of acute coronary syndrome (n = 2), presence of paced ventricular rhythm on ECG (n = 2), incomplete clinical or instrumental data (n = 3). Remaining study population included were 250 HCM patients.

Patients with HCM underwent a comprehensive examination at the beginning of the study, which included collection of complaints, medical history, family history of HCM and SCD, physical examination with estimation of blood pressure (BP) and heart rate (HR). BP and HR were measured at the sitting position of the patient after 5 minutes of the rest. Standard 12-lead ECG, transthoracic echocardiography, 24 hours Holter ECG monitoring were also obtained. Body weights and heights were measured in underclothes. Body weight was measured in kilo grams up to minimum of 0.5 Kg by a calibrated weighing machine. Height was measured in centimeters after removing shoes asking the subject to stand on his back side, close to measuring stand. Body mass index (BMI) was calculated and obesity was defined as a BMI of 30 kg/ m^2 and above, overweight when body mass index 25 kg/m^2 to 29.9 Kg/m^2.

Patients with HCM were divided into five groups according to the ECG types detected: 1 group (I type, presence of high R waves, ST depression and T inversion - "strain pattern") - 107 patients (42.8%), group 2 (type II, presence of pathological Q waves) - 49 patients (19.6%), group 3 (type III, presence of STEMI-like convex ST-elevation) - 23 patients (9.2%), group 4 (mixed ECG variant) - 50 patients (20%). 21 patients (8.4%) had either a normal ECG or minor changes that could not be attributed to any type, so they were allocated to a group with an atypical ECG (group 5).

The endpoint of the study was cardiovascular death, which included sudden cardiac death, death due to progression of heart failure, myocardial infarction or stroke.

Patients were followed up via personal visits to the clinic or telephone interviews. Median follow-up time was 5.1 (0.8 - 7.6) years (from 1 month to 11 years).

The patients provided their written informed consent to participate in this study. This study was approved by Kharkiv City Clinical Hospital # 8 Review Board.

12-lead ECG

All patients, when included in the study, had a 12-lead ECG taken at a speed of 50 mm/s, standard calibration of 10 mm/1 mV. LVH, abnormal Q waves, ST segment depression and elevation, T wave inversion, QRS duration, QT interval and corrected QT interval (Bazett's formula) were assessed. LVH was determined according to modified Sokolow-Lyon score, Cornell voltage score and Romhilt-Estes scale. An abnormal Q wave was defined as at least 25% or more of the adjacent R wave in depth and/or greater than 30 ms in width in at least 2 contiguous leads. ST-depression or elevation was defined as ≥ 1 mm below or above the baseline at 80 ms from the J point in at least 2 adjacent leads. ST-elevation in leads V1-V3 was determined ≥ 2 mm in the absence of complete left bundle branch block. "Strain pattern" was defined as downsloping ST-depression ≥ 1 mm with an inverted asymmetric T wave opposite to the QRS axis. Inversion of T waves

was determined at a depth of negative T waves of at least 1 mm. Several types of ST elevation were observed - convex (STEMI-like), concave and flat.

Echocardiography

All patients underwent echocardiography on commercially available equipment according to the standard technique in M-mode and 2-dimensional studies. All studies were performed by one ultrasound specialist. The examination was carried out from the parasternal and apical position with estimation of LV end-diastolic (LV EDD) and end-systolic (LV ESD) diameters, left and right atrial diameters and maximum LV thickness. Left ventricular ejection fraction (LV EF) was measured from the apical position by Simpson's method. Septal LVH was determined in the presence of asymmetric hypertrophy of the septum, apical LVH - in case of hypertrophy of the apex, free wall LVH - in case of asymmetric hypertrophy of LV free wall, mixed LVH - in case of asymmetric hypertrophy of septum and apex/free wall of the LV, symmetric LVH - in case of all LV walls involvement.

The blood pressure gradient in left ventricular outflow tract (LVOT) was assessed using continuous-wave Doppler echocardiography. The magnitude of the pressure gradient ≥ 30 mm Hg at rest or during provocation (Valsalva maneuver, physical exertion) was considered as the presence of LVOT obstruction.

Assessment of LV diastolic filling was performed using the pulsed Doppler mode with evaluation of the maximum velocity of early diastolic flow - Ve, the maximum velocity of late diastolic flow - Va, E/A ratio, deceleration time of early diastolic blood flow - DT.

Ambulatory ECG monitoring

Patients underwent 24-hour Holter ECG monitoring using commercially available systems. Mean HR and minimum HR during 24 hours were assessed. The presence of cardiac arrhythmias - the total number of ventricular extrasystoles (VE), supraventricular extrasystoles (SVE) and presence of non-sustained ventricular tachycardia (NSVT), supraventricular tachycardia (SVT), episodes of AF were analyzed.

Calculation of SCD risk

SCD risk was calculated for patients using the SCD HCM risk calculator_V2. High risk was considered in case ≥ 6% over 5 years, medium - < 6% - ≥ 4% and low - < 4%.

Statistical analysis

STATISTICA 12.0 (StatSoft Inc, USA) was used for statistical analysis. Categorical data are described as number and percentage and assessed using Pearson's χ^2 test and Fisher's exact test. Continuous variables are presented as mean (M) ± standard deviation (SD) for normally distributed variables and as median (50^{th} percentile) and interquartile range (IQR, $25\text{-}75^{th}$ percentile) for non-normally distributed variables. The difference between groups was tested with Kruskal-Wallis test. The normality of the distribution was analyzed using Kolmogorov-Smirnov test. Bonferroni's adjustment for multiple comparisons was used for post-hoc analysis. Multivariable Cox proportional hazard regression analysis was performed to identify independent predictors of cardiovascular death after the most significant predictors were identified in univariate analysis. The possible influence of the studied indicators on the probability of the development of events was estimated by hazard ratio (HR,) with a confidence interval (Cl) of 95%. Survival analysis was described using the Kaplan-Meier method with a long-rank test. For all types of analysis, the differences were considered statistically significant at $p < 0.05$.

Results

Clinical characteristics of HCM patients

A total of 250 HCM patients were enrolled. The mean age of all patients was 51.5 ± 15.5 years, 124 men (49.6%) and 126 women (50.4%). Clinical characteristics of HCM patients are shown in table 1. Patients with type III ECG were older at diagnosis (60.9 ± 13.5 years vs. 52.6 ± 14.8 in group I, 47.0 ± 15.9 in group II, 48.2 ± 14.4 in mixed type ECG and 51.3 ± 13.4 atypical ECG groups, post-hoc $p < 0.05$) and had predominance of women but not statistically significant ($p > 0,05$). Patients with type III ECG and mixed type ECG had a greater prevalence of chest pain (78,3% and 88% vs. 65.3% in type II ECG and 61.9% in atypical ECG groups, $p = 0.048$). NYHA III-IV heart failure showed a trend for an increase in III type ECG group but not statistically significant (26.1% vs. 10.2% in type II and 4,8% in atypical ECG, $p = 0,077$). There were no differences in LVOT obstruction, AF, end stage HCM, dyspnea, syncope and palpitations, AH, BP and HR.

	I type (n = 107)	II type (n = 49)	III type (n = 23)	Mixed type (n = 50)	Atypical (n = 21)	p-value (group comparison)
Age, years	52,6 ± 14,8[a b]	47,0 ± 15,9	60,9 ± 13,5[e i h]	48,2 ± 14,4	51,3 ± 13,4	0,002
Male	58 (54,2)	27 (55,1)	6 (26)	24 (48)	9 (42,9)	0,13
LVOT obstruction	36 (33,6)	15 (30,6)	4 (17,4)	15 (30)	7 (33,3)	0,65
AF	20 (18,7)	14 (28,6)	7 (30,4)	10 (20)	2 (9,5)	0,29
End stage	4 (3,7)	2 (4,1)	1 (4,3)	2 (4)	0	0,92
Family History HCM	21 (19,6)	12 (24,5)	5 (21,7)	15 (30)	3 (14,3)	0,54
Family History SCD	6 (5,6)	3 (6,1)	2 (8,7)	10 (20)	0	0,016
AH	68 (63,6)	21 (42,9)	16 (69,5)	25 (50)	11 (52,4)	0,075
Chest pain	78 (72,9)	32 (65,3)	18 (78,3)	44 (88)	13 (61,9)	0,048
Dyspnea	77 (72,0)	31 (63,2)	17 (73,9)	37 (74)	16 (76,2)	0,72
Syncope	8 (7,5)	4 (8,2)	3 (13)	10 (20)	3 (14,3)	0,19
Palpitation	58 (54,2)	28 (57,1)	13 (56,5)	31 (62)	12 (57,1)	0,93
SBP, mmHg	131,8 ± 22,7	127,9 ± 16,1	131,3 ± 21,1	122,1 ± 20,2	128,8 ± 22,1	0,20
DBP, mmHg	79,2 ± 12,5	79,3 ± 9,9	79,3 ± 12,1	75,1 ± 12,4	80,5 ± 12,4	0,37
Heart rate, bpm	73,5 ± 16,6	71,1 ± 12,0	73,8 ± 18,6	74,4 ± 14,4	75,7 ± 10,6	0,39
No HF	9 (8,4)	7 (14,3)	0	5 (10)	1 (4,8)	0,23
NYHA III-IV	24 (22,4)	5 (10,2)	6 (26,1)	11 (22)	1 (4,8)	0,077
HCM Risk-SCD score, %	2,1 (1,5-4,0)	2,5 (1,7-4,6)	2,2 (1,4-3,6)	3,1 (1,9-5,1)	1,9 (1,6-3,1)	0,04

Table 1: *Clinical characteristics of the groups.*

Mean ± SD, median (IQR) or number of patients (%). AF: Atrial Fibrillation; AH: Arterial Hypertension; DBP: Diastolic Blood Pressure; HCM: Hypertrophic Cardiomyopathy; HF: Heart Failure; LV: Left Ventricle; LVOT: Left Ventricular Outflow Tract; NYHA: New York Heart Association Functional Class of Heart Failure; SBP: Systolic Blood Pressure; SCD: Sudden Cardiac Death.

[a]Group I vs. II, [b]I vs. III, [e]II vs. III, [h]III vs. Mixed, [i]III vs. Atypical, $p < 0.05$ on post-hoc pairwise comparisons (p-values multiplied by 10 for Bonferroni adjustment of 10 tests).

Interestingly, patients with mixed type ECG had a higher prevalence of family history of SCD (20% vs. 5.6% in type I, 6,1% in type II and 0 group with atypical ECG, p = 0.016) and HCM Risk-SCD score (3,1 (1,9 - 5,1) vs. 1,9 (1,6 - 3,1) in atypical ECG group, 2,1 (1,5 - 4,0) in I type, 2,2 (1,4 - 3,6) in III type, p = 0,04).

Distribution of LVH depending on the type of ECG

The distribution of LVH depending on the type of ECG is shown in table 2. It was found that septal LVH had prevalence in patients with type II ECG (with pathological Q waves) - 83.7%, atypical ECG 85.7% and mixed type of ECG 70%. The difference was significant in type II vs. I - 56% (post-hoc p = 0.003), type II vs. III - 34.8% (post-hoc p = 0.0005) and atypical ECG vs. type III (post-hoc p = 0.01) (Table 2). Apical hypertrophy was not found in type II and atypical ECG, but had a significantly higher prevalence in type III 21.7% and type I 17.8%. The difference between type I and type II (post-hoc p = 0.0008), type II and type III is significant (post-hoc p = 0.02). Also, isolated apical hypertrophy rarely occurred in a mixed type of ECG - in 2 patients (4%). Mixed septal and apical/free wall LVH was more common among patients with type III - 34.8% and type I ECG 20.6% (vs. 6.1% in II group, post-hoc p = 0.03).

	I type (n = 107)	II type (n = 49)	III type (n = 23)	Mixed type (n = 50)	Atypical (n = 21)	p-value (group comparison)
Septal LVH	60 (56)	41 (83,7)[ae]	8 (34,8)	35 (70)	18 (85,7)[i]	0,00005
Apical LVH	19 (17,8)	0 [ae]	5 (21,7)	2 (4)	0	0,00057
Mixed septal and apical/free wall LVH	22 (20,6)	3 (6,1)	8 (34,8)[e]	6 (12)	1 (4,8)	0,0079
Free wall LVH	1 (0,9)	0	0	3 (6)	0	0,093
Symmetric LVH	5 (4,7)	5 (10,2)	2 (8,7)	4 (8)	2 (9,5)	0,73
RV involvement	5 (4,7)	1 (2,0)	1 (4,3)	5 (10)	0	0,30

Table 2: *Distribution of LVH depending on the type of ECG.*

Number of patients (%); LVH: Left Ventricular Hypertrophy; RV: Right Ventricle.

[a]Group I vs. II, [e]II vs. III, [i]III vs. Atypical, [k]Mixed vs. Atypical, p < 0.05 on post-hoc pairwise comparisons (p-values multiplied by 10 for Bonferroni adjustment of 10 tests).

HCM patients did not differ in the prevalence of symmetric LVH, as well as right ventricular (RV) involvement. Isolated LV free wall hypertrophy was extremely rare in the study population.

Echocardiographic and Holter ECG monitoring features of HCM patients

According to echocardiography, the III type ECG group had greater left atrial (LA) diameter (4.5 (4 - 5.1) cm vs. 4,3 (3,9 - 4,6) in II type, 4,3 (4 - 4,7) in mixed type, 4,2 (3,9 - 4,3) in atypical ECG groups, p = 0.038), LV EDD (4.8 (4.6 - 5.2) cm vs. 4.5 (4.1 - 4.7) in II type, 4.3 (4 - 4.8) in mixed type ECG groups, post-hoc p = 0.02) (Table 3).

The group with an atypical ECG tended to have a smaller maximum LV wall thickness and LV mass index but the difference was not significant. LVEF and LV diastolic function did not differ significantly between groups.

Holter ECG monitoring features are shown in table 4. The number of supraventricular extrasystoles (SVE) was greater in the III group (111 (8 - 931) vs. (17 (2 - 45) in I type; 6 (1 - 20) in II type, 28 (3 - 162) in mixed ECG type, 13 (4 - 120) in atypical ECG, p = 0.021). SVT, NSVT and VE did not differ significantly between groups.

	I type (n = 107)	II type (n = 49)	III type (n = 23)	Mixed type (n = 50)	Atypical (n = 21)	p-value (group comparison)
LA diameter, cm	4,4 (4-4,7)	4,3 (3,9-4,6)	4,5 (4-5,1)	4,3 (4-4,7)	4,2 (3,9-4,3)	0,038
LV EDD, cm	4,6 (4,2-5)	4,5 (4,1-4,7)	4,8 (4,6-5,2)[eh]	4,3 (4-4,8)	4,5 (4,1-4,8)	0,005
LV ESD, cm	2,9 (2,6-3,3)	2,8 (2,6-3)	3,1 (3-3,3)	2,8 (2,4-3,2)	3,0 (2,7-3,2)	0,08
Max LV wall thickness, cm	2,1 (1,9-2,5)	2,1 (1,8-2,4)	2,3 (1,9-2,5)	2,1 (1,8-2,5)	1,9 (1,8-2,2)	0,11
LV EF, %	64 (60-71)	66 (60-70)	64 (59-71)	65 (61-72)	62 (58-65)	0,23
LV mass index, g/m^2	127,3 ± 43,3	125,1 ± 32,1	136,9 ± 61,4	124,8 ± 33,2	114,6 ± 36,8	0,15
E/A>2	6 (5,6)	9 (18,4)	3 (13)	6 (12)	0	0,05
DT, мс	191,97 ± 8,87	163,77 ± 7,84	180,92 ± 11,88	192,48 ± 12,64	187,36 ± 14,23	0,77

Table 3: *Echocardiographic parameters in groups of patients with different types of ECG.*

Mean ± SD, median (IQR) or number of patients (%). HCM: Hypertrophic Cardiomyopathy; LA: Left Atrium; LV: Left Ventricle; LV EF: Left Ventricular Ejection Fraction; LVH: Left Ventricular Hypertrophy; LVOT: Left Ventricular Outflow Tract; LV EDD: Left Ventricular End Diastolic Diameter; LV ESD: Left Ventricular End Systolic Diameter; DT: Deceleration Time.

[e]Group II vs. III, [h]III vs. Mixed, p < 0.05 on post-hoc pairwise comparisons (p-values multiplied by 10 for Bonferroni adjustment of 10 tests).

	I type (n = 107)	II type (n = 49)	III type (n = 23)	Mixed type (n = 50)	Atypical (n = 21)	p-value (group comparison)
Mean HR/24 hr, bpm	68,6 ± 10,9	69,3 ± 9,6	68,5 ± 10,2	70,6 ± 14,8	69,8 ± 11,6	0,88
Minimum HR/24 hr, bpm	46,8 ± 7,0	46,7 ± 5,8	49,7 ± 5,8	49,1 ± 10,7	48,4 ± 9,1	0,42
SVE	17 (2-45)	6 (1-20)	111 (8-931)[be]	28 (3-162)	13 (4-120)	0,021
SVT	30 (28)	10 (20,4)	10 (43,5)	16 (32)	4 (19)	0,12
VE	4 (1-30)	2 (0-23)	26 (3-90)	11 (2-71)	6 (0-19)	0,12
NSVT	15 (14)	8 (16,3)	5 (21,7)	11 (22)	3 (14,3)	0,73

Table 4: *Holter monitoring parameters in groups of patients with different types of ECG.*

Mean ± SD, median (IQR) or number of patients (%). HR: Heart Rate; SVE: Supraventricular Extrasystoles; SVT: Supraventricular Tachycardia; VE: Ventricular Extrasystoles; NSVT: Non-Sustained Ventricular Tachycardia.

[b]Group I vs. III, [e]II vs. III, p < 0.05 on post-hoc pairwise comparisons (p-values multiplied by 10 for Bonferroni adjustment of 10 tests).

Prognosis and cardiovascular mortality

In this retrospective study median follow-up time was 5.1 (0.8 - 7.6) years. The longest follow-up was 11 years. During follow-up period, 32 patients died (16%). Overall, 26 patients (13%) died from cardiovascular death - 6 (5,6%) in I type, 4 (8,1%) in II type, 8 (34,8%) in III type, 7 (14%) in mixed ECG type, 1 (4,8%) in atypical ECG group.

When performing Kaplan-Meier survival analysis in relation to cardiovascular death, significantly worse long-term survival was found in patients with ECG type III (Chi-square = 18.5, p = 0.001) (Figure 1). In pairwise comparison of survival in different groups, the differ-

ence was significant between III and I type of ECG (log-rank test p = 0.00005) and III and II type of ECG (log-rank test p = 0.006). I and II types of ECG associated with better cardiovascular outcomes. No significant difference was found between the other groups.

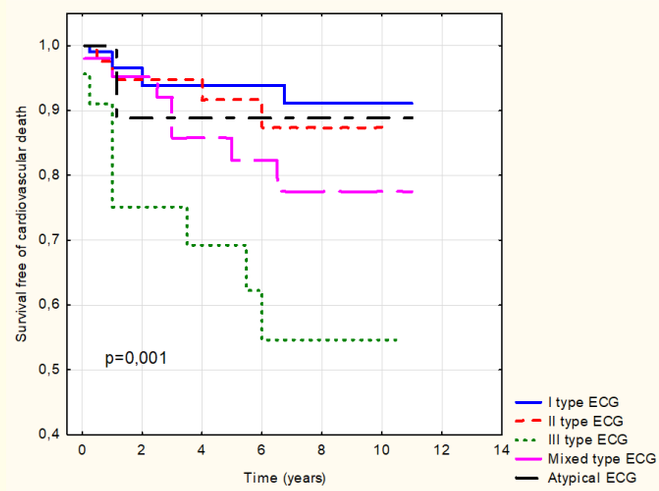

Figure 1: *Kaplan-Meier survival curves free of cardiovascular death.*

Univariate Cox regression analysis was performed to study predictors of cardiovascular death. Statistically significant predictors were identified among indicators of 12-lead ECG and 24-hour ECG monitoring, which were subsequently included in multivariable Cox regression analysis. In multivariable Cox regression analysis was found that independent predictors of cardiovascular death are the minimum heart rate according to Holter ECG monitoring (HR 1.09, 95% CI 1.04 - 1.14, p = 0.0005), III type ECG (HR 3.83, 95% CI 1.49 - 9.88, p = 0.005) and QRS ≥ 120 ms (HR 2.62, 95% CI 1.10 - 6.22, p = 0.03) (Table 5).

	Univariate Cox regression analysis			Multivariable Cox regression analysis		
	HR	**95% CI**	**P value**	**HR**	**95% CI**	**P value**
Age	0,99	0,97-1,02	0,86			
Prolonged QRS ≥ 120 ms	3,01	1,34-6,76	0,008	2,62	1,10-6,22	0,03
Prolonged QTc ≥ 440 ms	1,46	0,66-3,25	0,35			
ECG criteria of LVH	0,74	0,22-2,48	0,63			
I type ECG	0,36	0,14-0,90	0,03			
II type ECG	0,71	0,24-2,06	0,53			
III type ECG	4,6	2,0-10,6	0,0003	3,83	1,49-9,88	0,005
Mixed type ECG	1,50	0,63-3,57	0,36			
Atypical ECG	0,63	0,09-4,72	0,66			
Mean HR/24 hr	1,02	0,99-1,05	0,24			
Minimum HR/24 hr	1,08	1,04-1,13	0,0003	1,09	1,04-1,14	0,0005
AF	2,38	1,09-5,19	0,029			
SVE	1,0002	1,00002-1,0003	0,024			
SVT	0,99	0,96-1,03	0,79			
VE	1,0	0,99-1,001	0,26			
NSVT	2,21	1,01-4,81	0,045			

Table 5: *Independent predictors of cardiovascular death.*

AF: Atrial Fibrillation; AH: Arterial Hypertension; ECG: Electrocardiogram; HCM: Hypertrophic Cardiomyopathy; HR: Heart Rate; LV: Left Ventricle; LVH: Left Ventricular Hypertrophy; NSVT: Non-Sustained Ventricular Tachycardia; NYHA: New York Heart Association Functional Class of Heart Failure; SBP: Systolic Blood Pressure; SCD: Sudden Cardiac Death; SVE: Supraventricular Extrasystoles; SVT: Supraventricular Tachycardia; VE: Ventricular Extrasystoles.

To study the effect of age on cardiovascular mortality, it was included in the regression model. Regression analysis showed no effect of age on cardiovascular mortality in our study population (HR 0.99, 95% CI 0.97 - 1.02, p = 0.86).

Discussion

The most common type of ECG among patients with HCM was type I (with ST depression and deep negative T) - 107 patients (42.8%), the rarest type III (STEMI-like) - 23 patients (9.2%) and a group with atypical ECG - 21 (8.4%). II type (with abnormal Q waves) and mixed ECG type were found in almost equal number of patients - 49 (19.65%) and 50 (20%).

The study showed that septal LVH was present predominantly in II type of ECG (with pathological Q waves), atypical ECG (without significant abnormalities) and mixed type ECG (Figure 2).

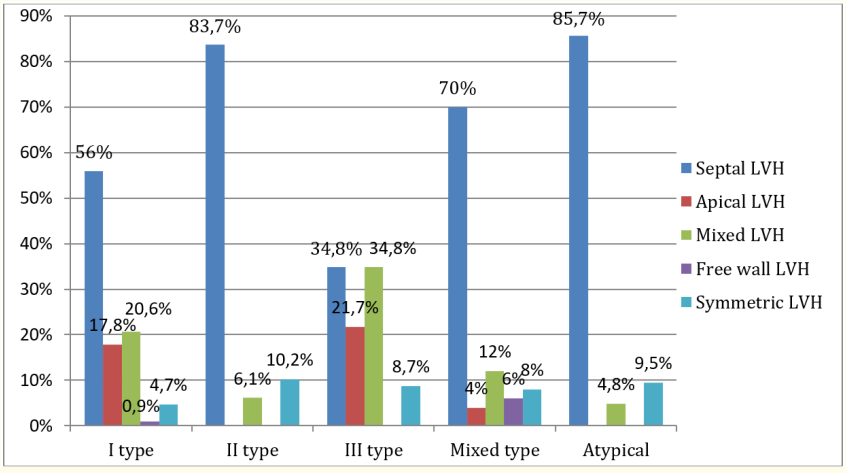

Figure 2: *Distribution of LVH depending on the type of ECG.*

The pathophysiological mechanism of abnormal Q waves in HCM is still a subject of debate. There are two main mechanisms discussed: the loss of electrical forces due to transmural myocardial fibrosis and the changed direction of the resulting initial QRS vector due to disproportionate hypertrophy of the basal IVS and/or the basal LV free wall, which are not counteracted by the apical electric forces [25]. In early studies using echocardiography, it was found that pathological Q correlated with hypertrophy of the anterior-superior septal region and its relationship with hypertrophy of the right ventricle and hypertrophy of the posterior-superior septal region [26]. Similar data were obtained in studies involving cardiac magnetic resonance imaging with gadolinium contrast (LGE CMR) [27] that was also consistent with our data. In a CMR study of asymptomatic and mildly symptomatic HCM patients, abnormal Q waves were associated with greater basal anterior-septal thickness, maximal basal thickness, and a greater number of segments with large late gadolinium enhancement (LGE) (> 75% of wall thickness), which characterizes myocardial fibrotic changes [28]. Scientists have determined that pathological Q and/or repolarization abnormalities can be detected even in carriers of sarcomere gene mutations without hypertrophy according to CMR data [9]. However, the study of Furuki., *et al*. showed the association of pathological Q with disease progression, left ventricular dilatation and myocardial dysfunction [24]. In the population of patients with "end stage HCM", pathological Q waves were found to be predictors of adverse cardiovascular events [29]. In our study, ECG type II with abnormal Q waves was not associated with worse echocardiographic results and did not reveal an adverse impact on prognosis. According to Kaplan-Meier analysis, the survival rate of patients

with type II ECG was better (log-rank test p = 0.006). Such discrepancies could be explained by use of different criteria for definition of abnormal Q waves - width ≥ 30 ms in our study and ≥ 40 ms in studies that found a poor prognosis. Probably, it is the longer duration of Q waves that is associated with myocardial fibrosis in HCM patients and progressive course of the disease.

Patients with atypical ECG in our study were represented by patients with a normal ECG or minor abnormalities on ECG. In these patients septal LVH also prevailed (85.7%) and the apical form was not found. Atypical ECG group had better course of the disease with fewer chest pain. There were no patients with "end stage" and only one patient with NYHA III-IV among them. These patients had significantly smaller LA diameter and a tendency to have decreased LV mass index and maximum LV thickness, which can be attributed to the absence of LVH as well as repolarization abnormalities on ECG. These data are consistent with the study of McLeod CJ., *et al*. where they proved that patients with a normal ECG in HCM show a less severe phenotype with a better cardiovascular prognosis [13]. However, in Kaplan-Meier survival analysis atypical ECG patients did not differ significantly from other groups that could be explained by the inclusion of patients with minor ECG abnormalities.

Apical LVH and mixed LVH of the septum and apex/free wall were common among patients with ECG type I and III (apical LVH 17.8% and 21.7%, mixed LVH 20.6% and 30.4%). Nevertheless, they were almost never found in patients with II type, mixed type ECG, and atypical ECG.

The I type ECG in our study was characterized by the presence of high R waves, downsloping ST depression and inversion of T waves ('strain pattern'). In previous studies, the presence of a 'strain pattern' and deep negative T in the left chest leads were associated with the apical HCM [17,20,21]. In CMR study 'strain pattern' was observed in 100% patients with apical HCM, the height of R waves and the depth of T waves in leads V5-V6 were associated with apical hypertrophy [21]. Similar data were obtained in the large cohort of HCM patients from South Korea with the use of echocardiography: 'strain pattern' and T inversion were more common in patients with apical HCM [17]. However, according to the same group of authors, any influence of ECG abnormalities on the prognosis was not found [30]. According to our data, patients with I type ECG had significantly better outcome in Kaplan-Meier analysis (log-rank test p = 0.00005).

As shown in our study the most severe phenotype had patients with III type ECG (with infarct-like convex ST elevation). They had significantly higher prevalence of chest pain and trend to have NYHA III-IV class of heart failure. According to echocardiography, they had a larger LA diameter and an enlarged LV cavity, which indicates unfavorable remodeling [31]. They also had a higher burden of SVE on Holter ECG monitoring. When analyzing survival, patients with III type ECG had a significantly worse prognosis compared to other types of ECG. When performing Cox's proportional regression analysis, III type ECG was found to be an independent predictor of cardiovascular death in HCM patients. According to literature, ST segment elevation was associated with left ventricular remodeling and development of apical aneurysm. In the study of Furuki M., *et al*. three different ST-segment elevation models were identified: concave, straight, and convex. There was a strong association between electrocardiographic detection of ST-segment elevation and/or abnormal Q waves and the occurrence of LV enlargement and/or wall motion abnormalities on echocardiograms, suggesting disease progression. However, straight, and concave ST segment elevation showed a less significant relationship with echocardiographic data [24]. Significant correlation between the occurrence of apex aneurysm and ST-elevation on ECG was found, especially in the presence of midventricular obstruction [11,12]. In our study, no apical aneurysm was detected in any patient with III type ECG. It could be partly explained by insufficient visualization of the apex on echocardiogram in comparison with CMR. Consistent with our data, the multicenter study by Biagini E., *et al*. showed that pseudo-STEMI pattern on ECG was associated with worse prognosis and was found to be independent predictor of SCD and major cardiovascular events [10]. However, unlike in our study, patients with the pseudo-STEMI pattern were younger, more frequently men, and with a higher rate of LVOT obstruction. In this study pseudo-STEMI pattern was defined not only as ST-elevation but also as giant positive T waves. In our study, these patients were older, more frequently women, LVOT obstruction rate did not differ significantly from other groups. Scientists tried to explain the repolarization abnormalities with the expression of a genetically determined ion-channel dys-

function accidentally associated with HCM. Other proposed mechanisms are the presence of myocardial cell damage and fibrosis, which may disrupt normal transmission of membrane potentials, as well as mechanical distress associated with high intracavitary pressure and impaired wall motion, which are associated with the development of convex-type ST-segment elevation [24]. Further investigations need to be performed to clear the electrophysiological and/or genetic mechanisms of this ECG phenomenon and facilitate therapeutic interventions to improve the prognosis of HCM patients.

In addition to III type ECG, other predictors of cardiovascular death were found in the presented study. Prolonged QRS ≥ 120 ms and minimal HR on Holter ECG monitoring. Prolonged QRS duration on ECG is associated with the presence of myocardial fibrosis and progressive heart failure in patients with HCM in previous studies, so the negative prognostic role of this indicator is quite clear [32].

An interesting finding in our study was the minimum HR during ambulatory ECG monitoring, which reflects the autonomic nervous system state of HCM patients at rest. This parameter might be associated with increased sympathetic activation in HCM patients even at rest, especially in the development of heart failure. Data from series of studies using scintigraphy with 123 I-meta-iodobenzylguanidine showed a close relationship between HCM progression and sympathetic activation. There are several mechanisms of the sympathetic activation effect on the myocardium in HCM patients. Norepinephrine (NE) induces myocardial cell growth, disarray, and scarring. Second, α-adrenergic coronary constriction induced by increased NE levels may cause myocardial ischemia. Third, NE increases the rate of spontaneous depolarization of myocardial cells, which may contribute to the development of ventricular arrhythmias. Fourth, most patients with HCM have increased total LVEF, indicating increased contractility, which may be a consequence of accelerated cardiac adrenergic activity. An increase in cardiac sympathetic activity correlates with impaired LV diastolic and systolic function and an increase in BNP. This indicates that increased sympathetic activity of the heart is the result of adverse hemodynamics in HCM [33]. It is important that this parameter can be corrected in daily clinical practice with the help of beta-blockers, which will improve the prognosis of HCM patients.

Study Limitations

This study has several limitations. Our study was conducted in an inpatient setting and has retrospective design, and selection bias was unavoidable. The relatively small size of study population may have limited the prognostic significance of the statistical analysis. Genetic analysis was not performed in our cohort of patients. Cardiac magnetic resonance imaging was not available in our study, and it was not possible to assess the presence of a small apical aneurysm at the initial stage.

Conclusion

In our study, we found that some parameters of standard 12-lead ECG and ambulatory ECG monitoring had prognostic value in patients with HCM. I and II types ECG were found to have better cardiovascular prognosis. III type ECG with the presence of infarct-like convex ST-elevation, prolonged QRS complex ≥ 120 ms and minimum heart rate on Holter monitoring were shown to be independent predictors of cardiovascular adverse outcomes. This prognostic information could be helpful even at the initial evaluation of HCM patients and play crucial role in the prevention of disease progression.

Conflict of Interest

Authors declare no financial interest or conflict of interest.

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