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ELECTROCARDIOGRAPHIC FEATURES OF PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

ELEKTROKARDIOGRAFSKE KARAKTERISTIKE PACIJENATA SA HIPERTROFIČNOM KARDIOMIOPATIJOM

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Summary

Introduction. Hypertrophic cardiomyopathy is a disorder of the myocardium characterized by asymmetric or symmetric left ventricular hypertrophy. It is often an inherited disorder with an autosomal dominant pattern. The aim of this study was to evaluate the electrocardiographic characteristics of patients with hypertrophic cardiomyopathy, as well as to assess the accuracy of current electrocardiographic criteria for left ventricular hypertrophy used as indicators of hypertrophic cardiomyopathy. **Material and Methods.** This retrospective study was conducted using hospital medical records of 42 patients with the diagnosis of hypertrophic cardiomyopathy. Detailed electrocardiography analysis, apart from all the usual parameters, included the calculation of indices used to diagnose left ventricular hypertrophy including Sokolow augmented vector left, Cornell voltage, Cornell product, and Sokolow-Lyon index. **Results.** Sinus rhythm was present in 95.2% of patients, while atrial fibrillation was found in 4.8%. The majority of patients presented with left axis deviation. A slight positive correlation was found between the Sokolow augmented vector left index and posterolateral wall thickness ($r = 0.475$; $p < 0.05$), and also between the Cornell voltage index and posterolateral wall thickness ($r = 0.368$; $p < 0.05$). A borderline positive correlation was found between the Cornell product index and posterolateral wall thickness ($r = 0.290$; $p = 0.063$). Interventricular septum thickness showed no significant correlation with any of the electrocardiographic indices of left ventricular hypertrophy. **Conclusion.** In patients with hypertrophic cardiomyopathy, the Sokolow augmented vector left and Cornell voltage indices were the best indicators of posterolateral wall hypertrophy, whereas none of the examined indices correlated well with the interventricular septum thickness.

Key words: Cardiomyopathy, Hypertrophic; Electrocardiography; Hypertrophy, Left Ventricular; Atrial Fibrillation; Echocardiography; Correlation of Data

Sažetak

Uvod. Hipertrofična kardiomiopatija predstavlja poremećaj srčanog mišića, koji karakteriše asimetrična ili simetrična hipertrofija miokarda leve komore. Hipertrofična kardiomiopatija je najčešće nasledni poremećaj koji se prenosi autozomno dominantno. Cilj ovog istraživanja bio je procena elektrokardiografskih karakteristika pacijenata sa hipertrofičnom kardiomiopatijom kao i provera preciznosti postojećih elektrokardiografskih kriterijuma koji se koriste kao pokazatelji hipertrofije leve komore. **Materijal i metode.** Ovu retrospektivnu studiju sproveli smo koristeći medicinsku dokumentaciju grupe od 42 pacijenta sa potvrđenom dijagnozom hipertrofična kardiomiopatija. Detaljna elektrokardiografska analiza, osim svih uobičajenih parametara, obuhvatila je i izračunavanje indeksa koji se koriste za dijagnozu hipertrofije leve komore uključujući *Sokolow augmented vector left, Cornell voltage, Cornell product* i *Sokolow-Lyon* indeks. **Rezultati**. Sinusni ritam je zabeležen kod 95,2% pacijenata, dok je atrijalna fibrilacija bila prisutna kod 4,8%. Srčana osovina je u najvećem broju slučajeva pokazala devijaciju ulevo. Dobijena je blaga pozitivna korelacija između *Sokolow augmented vector left* indeksa i debljine posterolateralnog zida ($r = 0,475$; $p < 0,05$), kao i između *Cornell voltage* indeksa i debljine posterolateralnog zida ($r = 0,368$; $p < 0,05$). Granično značajna pozitivna korelacija je dobijena između *Cornell product* indeksa i debljine posterolateralnog zida ($r = 0,290$; $p = 0,063$). Debljina interventrikularnog septuma nije imala značajnu korelaciju ni sa jednim elektrokardiografskim indeksom hipertrofije leve komore. **Zaključak**. Kod pacijenata sa hipertrofičnom kardiomiopatijom, vrednosti *Sokolow augmented vector left* i *Cornell voltage* indeksa najbolje pokazuju nivo hipertrofije posterolateralnog zida, dok nijedan od ispitivanih indeksa nije povezan sa debljinom interventrikularnog septuma.

Ključne reči: hipertrofična kardiomiopatija; elektrokardiografija; hipertrofija leve komore; atrijalna fibrilacija; ehokardiografija; korelacija

Introduction

Hypertrophic cardiomyopathy (HCM) is the most common inherited disease of the myocardium with a prevalence of approximately 1 in 500 adults [1], which most often presents between the third and fifth decade. It is a disorder of the myocardium that

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Abbreviations

BMI – body mass index
ECG – electrocardiography
HCM – hypertrophic cardiomyopathy
LV – left ventricle
aVL – augmented vector left
NYHA – New York Heart Association

is characterized by asymmetric or symmetric hypertrophy of the left ventricle (LV) with no apparent reason. In order to make the diagnosis, any abnormal loading conditions, such as aortic stenosis and long-lasting arterial hypertension, as well as other systemic and metabolic diseases that may cause myocardial hypertrophy must be excluded [2, 3].

The HCM is caused by a genetic mutation that is transmitted with an autosomal dominant pattern, caused most commonly by a single mutation in one of the sarcomere protein genes, which can be present in either thick or thin filament genes [4, 5]. The two most common are the thick filament mutation myosin-binding protein C and β-myosin heavy chain, which are responsible for approximately three-quarters of the identified mutations in HCM patients [6].

Clinical presentation of HCM is often completely asymptomatic, while symptoms may include fatigue, dyspnea, chest pain, palpitations, syncope, and in the worst case even sudden cardiac death [7–9]. Septal hypertrophy may lead to obstruction of LV outflow tract, while other complications include myocardial fibrosis, microvascular ischemia, and deterioration of cardiac function [10].

The diagnosis of HCM is based mainly on imaging techniques including electrocardiography, computed tomography and cardiac magnetic resonance imaging. Electrocardiography (ECG) is used as a diagnostic algorithm primarily in the detection and follow-up of heart rhythm disorders that may range from atrial tachyarrhythmias, premature supraventricular and ventricular complexes, to malignant arrhythmias like ventricular tachycardia [11]. Nonetheless, there are specific ECG signs that indicate the presence of LV hypertrophy, based on which several criteria have been established. The best known ECG criteria for LV hypertrophy are Sokolow-Lyon, Sokolow augmented vector left (aVL), Cornell voltage, Cornell product, Romhilt and Siegel [12, 13].

The aim of this study was to evaluate the ECG characteristics of patients with HCM, as well as to assess the accuracy of current ECG criteria for LV hypertrophy used as indicators of HCM.

Material and Methods

This retrospective observational study was performed using hospital medical records of 42 patients with the diagnosis of HCM. The collected data included demographic characteristics, medical history, clinical and laboratory findings, ECG and echocardiographic findings. The diagnosis of HCM was established using echocardiography with LV wall thickness of ≥ 15 mm, in the absence of other cardiac or systemic diseases which could contribute to its development, such as aortic stenosis or arterial hypertension.

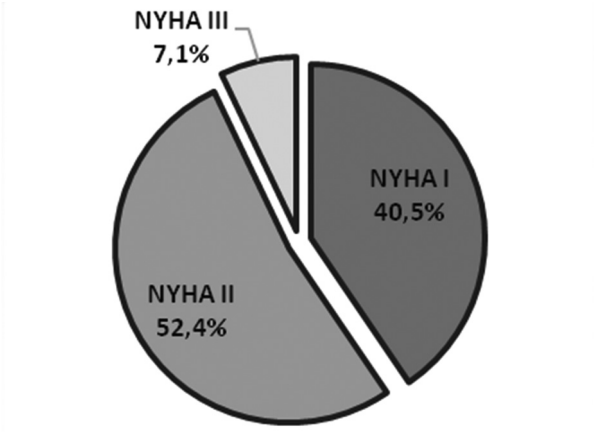
All the participants underwent a 12-lead ECG in supine position with standard calibration (voltage 0.1 mV/mm; paper speed 25 mm/s). Detailed ECG analysis, apart from all the usual parameters, involved calculation of the criteria used for diagnosing LV hypertrophy including Sokolow aVL, Cornell voltage, Cornell product, and Sokolow-Lyon index. These indices were calculated by measuring the voltages of the particular QRS complex components in specific leads. Detailed formulas for the calculation of specific indices and their cut-off values for LV hypertrophy are shown in **Table 1**. Reference values are the same for both sexes, with the exception of Cornell voltage criteria which are sex-specific.

Continuous variables are expressed as mean values ± standard deviation, while categorical variables are presented as absolute numbers and percentages. Acquired results were statistically analyzed using Pearson's linear correlation coefficient and independent samples t-test. Statistical significance was set at $p < 0.05$.

Results

The study included 42 patients of whom 69.0% (29/42) were male and 31.0% (13/42) were female. The patients were 61.7 (± 10.4) years old with a mean body mass index (BMI) of 29.5 (± 4.1) kg/m^2. There were 19.1% (8/42) of patients in the normal (healthy) weight, 38.1% (16/42) of patients were overweight, 35.7% (15/42) of patients were with grade I and 7.1% (3/43) of patients with grade II obesity.

In regard to clinical characteristics, 61.9% (26/42) of patients felt fatigue, 33.3% (14/42) felt chest pain, and 33.3% (14/42) had shortness of breath. There were 23.8% (10/42) of asymptomatic patients. According to the New York Heart Association (NYHA)



Graph 1. Distribution of HCM patients according to the NYHA classification
Grafikon 1. *Distribucija pacijenata sa hipertrofičnom kardiomiopatijom prema New York Heart Association klasifikaciji*

Table 1. Formulas used for calculation of the ECG criteria for LV hypertrophy
Tabela 1. *Formule korišćene za izračunavanje elektrokardiografskog kriterijuma hipertrofije leve komore*

Name *Naziv*	Calculation formula *Formula za izračunavanje*	Cut-off value for LV hypertrophy *Granična vrednost za hipertrofiju LV*
Sokolow augmented vector left	R (aVL)	> 11 mm
Cornell voltage	R (aVL) + S (V3)	> 28 mm (male/*muškarci*) > 20 mm (female/*žene*)
Cornell product	(R (aVL) + S (V3)) x QRS	> 2436 mm·ms
Sokolow-Lyon	S (V1) + R (V5/V6)	> 35 mm

Table 2. General characteristics of the HCM patients' cohort
Tabela 2. *Opšte karakteristike kohorte pacijenata sa hipertrofičnom kardiomiopatijom*

Females/*Žene*	13 (30.9%)
Age/*Starost* (years/*godine*)	61.7 (±10.4)
Body mass index/*Indeks telesne mase* (kg/m^2)	29.5 (±4.1)
Symptoms/*Simptomi*	
Fatigue/*Zamaranje*	26 (61.9%)
Dyspnea/*Gušenje*	14 (33.3%)
Chest pain/*Bol u grudima*	14 (33.3%)
Asymptomatic/*Bez simptoma*	10 (23.8%)
NYHA classification/*New York Heart Association klasifikacija*	
I	17 (40.5%)
II	22 (52.4%)
III	3 (7.1%)
Comorbidities/*Komorbiditeti*	
Diabetes mellitus/*Dijabetes melitus*	6 (14.3%)
Chronic obstructive pulmonary disease/*Hronična opstruktivna bolest pluća*	4 (9.5%)
Thyroid disease/*Bolest štitaste žlezde*	2 (4.8%)
Renal dysfunction/*Bubrežna disfunkcija*	2 (4.8%)

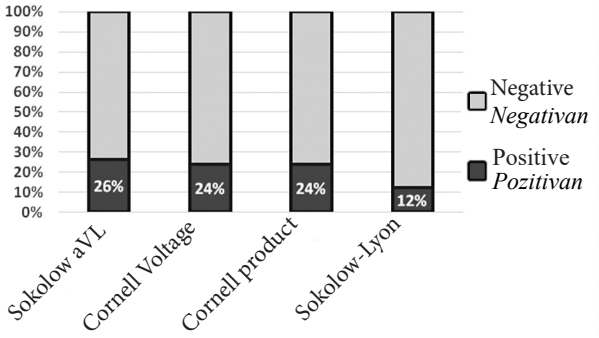
classification for heart failure **(Figure 1)** 40.5% (17/42) of patients had class I symptoms, 52.4% (22/42) of them had class II, while 7.1% (3/42) had class III symptoms. There were no patients with NYHA class IV. Demographic data and general characteristics of HCM patients are shown in **Table 2**.

Family history of HCM was positive in 19.0% (8/42) of patients, while only one patient (2.4%) had a positive family history of dilated cardiomyopathy. The most common comorbidity was diabetes mellitus, in 14.3% (6/42) of patients, followed by chronic obstructive pulmonary disease in 9.5% (4/42), renal insufficiency in 4.8% (2/42) and thyroid gland disease in 4.8% (2/42) of patients.

Mean systolic blood pressure was 136.7 (± 20.4) mmHg and diastolic 77.6 (± 10.0) mmHg. Sinus rhythm

Table 3. Correlation between ECG indices for LV hypertrophy and echocardiographically measured LV wall thickness
Tabela 3. *Korelacija između elektrokardiografskog indeksa za hipertrofiju leve komore i ehokardiografski merene debljine zidova leve komore*

	Interventricular septum thickness *Debljina interventrikularnog septuma*		Posterolateral wall thickness *Debljina posterolateralnog zida*	
	r	p	r	p
Sokolow augmented vector left	-0.143	0.366	0.475	0.001*
Cornell voltage	0.094	0.556	0.368	0.016*
Cornell product	-0.013	0.934	0.290	0.063
Sokolow-Lyon	0.206	0.191	0.042	0.793



Graph 2. Percentage of HCM patients with positive and negative criteria for LV hypertrophy
Grafikon 2. *Broj pacijenata sa hipertrofičnom kardiomiopatijom sa pozitivnim i negativnim kriterijumima za hipertrofiju leve komore*

was recorded in 95.2% (40/42) of patients, while atrial fibrillation was found in 4.8% (2/42). Normal heart axis was found in 42.8% (18/42) of patients, left heart axis was found in 52.4% (22/42), and right heart axis was observed in 4.8% (2/42) of cases.

Regarding the Sokolow aVL index, its mean value was 7.1 (± 5.8) mm, with 26.2% (11/42) of patients measuring over the reference value of 11 mm, and 73.8% (31/42) of them were below 11 mm. Mean Cornell voltage index in males was 18.1 (± 8.9) mm, and in females 20.0 (± 7.7) mm. There were 23.8% (10/42) of patients with a value over the reference limit, while 76.2% (32/42) were below it. Mean Cornell product index was 2161.8 (± 1662.4) mm·ms. In 23.8% (10/42) of patients, the value was over the reference limit (2436 mm·ms), and in 76.2% (32/42) of patients it was below it. Mean Sokolow-Lyon index was 20.5 (± 10.9) mm. There were 11.9% (5/42) of patients with a value over the reference limit, which is 35 mm, and in 88.1% (37/42) it was below it. **Figure 2** shows the distribution of HCM patients with various LV hypertrophy criteria.

The LV myocardial thickness was measured at posterolateral wall and interventricular septum. Both measures were increased, so the mean interventricular septum thickness was 17.4 (± 4.3) mm, and posterolateral wall thickness was 15.5 (± 3.4) mm. Mean LV ejection fraction was preserved 61.9 % (± 9.7).

All of the above-mentioned ECG criteria for LV hypertrophy were correlated with the true echocardiographically measured wall thickness **(Table 3)**. The obtained results showed a mild positive correlation between the Sokolow aVL index and posterolateral wall thickness ($r = 0.475$; $p < 0.05$), and also between the Cornell voltage index and posterolateral wall thickness ($r = 0.368$; $p < 0.05$). Borderline correlation was found between the Cornell product index and posterolateral wall thickness ($r = 0.290$; $p = 0.063$). Interventricular septum thick-

Table 4. Comparison of LV wall thickness on echocardiography between patients with positive and negative ECG indices for LV hypertrophy
Tabela 4. *Poređenje debljinve zidova leve komore na ehokardiografiji između pacijenata sa pozitivnim i negativnim elektrokardiografskim indeksima za hipertrofiju leve komore*

		N *Br*	Mean *Prosečna vrednost*	Standard deviation *Standardna devijacija*	p-value *p-vrednost*
Sokolow augmented vector left					
Interventricular septum *Interventrikularni septum*	Negative/*Negativan*	31	17.23	4.60	0.702
	Positive/*Pozitivan*	11	17.82	3.63	
Posterolateral wall *Posterolateralni zid*	Negative/*Negativan*	31	14.81	2.30	0.033*
	Positive/*Pozitivan*	11	17.36	5.26	
Cornell voltage					
Interventricular septum *Interventrikularni septum*	Negative/*Negativan*	32	17.44	4.41	0.882
	Positive/*Pozitivan*	10	17.20	4.29	
Posterolateral wall *Posterolateralni zid*	Negative/*Negativan*	32	14.84	2.30	0.032*
	Positive/*Pozitivan*	10	17.50	5.48	
Cornell product					
Interventricular septum *Interventrikularni septum*	Negative/*Negativan*	32	17.38	4.61	0.988
	Positive/*Pozitivan*	10	17.40	3.53	
Posterolateral wall *Posterolateralni zid*	Negative/*Negativan*	32	14.88	2.34	0.042*
	Positive/*Pozitivan*	10	17.40	5.48	
Sokolow-Lyon					
Interventricular septum *Interventrikularni septum*	Negative/*Negativan*	37	17.16	4.31	0.380
	Positive/*Pozitivan*	5	19.00	4.64	
Posterolateral wall *Posterolateralni zid*	Negative/*Negativan*	37	15.19	3.50	0.145
	Positive/*Pozitivan*	5	17.60	2.30	

ness showed no significant correlation with any of the ECG indices of LV hypertrophy.

The difference in the LV wall thickness between patients with positive and negative results was analyzed for each of the ECG index **(Table 4)**. A significantly higher posterolateral wall thickness was found in patients with positive compared to those with negative Sokolow aVL index (17.4 vs. 14.8 mm, $p < 0.05$), as well as for Cornell voltage (17.5 vs. 14.8 mm, $p < 0.05$) and Cornell product (17.4 vs. 14.9 mm, $p < 0.05$). No statistically significant difference was found in interventricular septum thickness in patients with positive and negative results for any of the studied ECG indices.

Discussion

This study investigated the value of classical ECG criteria in the detection of LV hypertrophy in patients with HCM. The main findings revealed a generally low reliability of all examined ECG criteria, especially regarding the interventricular septum thickness. Nevertheless, Sokolow aVL and Cornell voltage criteria can be used as solid indicators of posterolateral wall thickness in HCM patients.

In our cohort, there was a 2:1 male predominance, which confirmed the literature data that males account for 55 – 75% of patients with the diagnosis of HCM [12, 14, 15]. This uneven gender distribution is attributed to reduced disease penetrance in women, as well as slower progression of myocardial hypertrophy that could be related to protective role of female sex hormones. Moreover, the lack of gender specific HCM diagnostic criteria means that women require relatively higher level of myocardial hypertrophy in order to reach the diagnostic threshold of wall thickness > 15 mm, because on average they have smaller hearts than men. This translates into increased relative wall thickness compared with lower LV cavity sizes in females, leading to more severe symptoms and higher NYHA functional class [16].

The BMI analysis showed that the majority of HCM patients in this study were overweight and obese, which is outlined as a predominant risk factor for symptoms and negative outcome in HCM, as well as for the development of LV outflow tract obstruction [17].

The most common clinical symptom in our study was fatigue, which has not been suggested as a specific symptom of HCM in the literature [1]. Our results showed that the majority of patients had mild symptoms and were in NYHA class I and II; nearly one quarter of patients were completely asymptomatic, which correlates with the literature data [12]. Mild clinical presentation of HCM does not necessarily mean good prognosis, since these patients can be at high risk of sudden cardiac death regardless of the symptoms and their intensity.

Sinus rhythm was registered in the majority of patients. Only a small fraction of patients had atrial fibrillation, which is consistent with the literature [12, 18, 19]. The development of atrial fibrillation in patients with HCM is associated with other markers of more severe disease expression such as left atrial enlargement, higher LV wall thickness, and LV outflow tract obstruction [20]. Examination of cardiac axis in ECG showed that more than half of HCM patients had left heart axis that can be attributed to increase in LV myocardial mass, which is similar to the results of other studies [12, 21].

Examination of ECG criteria for determining LV hypertrophy showed that none of the ECG criteria positively indicate interventricular septum hypertrophy, while Sokolow aVL, Cornell voltage and Cornel product may point to posterolateral wall hypertrophy, because the thickness of posterolateral wall is significantly increased in those with positive compared to those with negative findings. All four of the examined ECG criteria for LV hypertrophy were positive in about one quarter of patients, which means that, according to our results, as much as three quarters of patients with HCM present without ECG symptoms of LV hypertrophy. Such results are consistent with the literature data, and confirm the low sensitivity of ECG in regard to screening and diagnosis of HCM [12].

Correlation analysis showed that Sokolow aVL and Cornell voltage indices show a positive correlation to LV posterolateral wall thickness, and therefore, the grater the correlation, the greater the posterolateral wall hypertrophy. This is consistent with the results of Monzo et al. [12] who also concluded that these two ECG criteria best correspond to the maximal LV wall thickness. While the calculated Cornell voltage index in our study positively correlated with posterolateral wall thickness, results of other studies showed its correspondence with LV anterior wall and interventricular septum. On the other hand, none of the analyzed criteria in our study showed significant correlation with the interventricular septum thickness.

Although ECG criteria for determining LV hypertrophy have been thoroughly examined in various disorders that cause or contribute to myocardial hypertrophy, such as arterial hypertension and stenosis of the aortic valve, there are scarce data on their use in genetically transmitted HCM. Our study is one of the few across the literature that analyzed the properties and value of these ECG criteria in patients with HCM, and certainly the first one performed in the HCM population of Serbia.

While the present study focused on diagnostic performance of ECG in recognition of LV hypertrophy in patients with HCM, the interest of the scientific community is currently aimed at HCM disease progression and prognosis. In that light, our ongoing multicenter SILICOFCM trial [22, 23] seeks to provide novel data on whether the complementary addition of either sacubitril/valsartan or lifestyle intervention to the optimal standard therapy improves cardiovascular performance in patients with non-obstructive HCM as well as their clinical phenotypic characteristics, injury and stretch activation markers, habitual physical activity, and quality of life.

Conclusion

The electrocardiography characteristics of patients in our study showed that the majority of patients with hypertrophic cardiomyopathy were in sinus rhythm, while the most common arrhythmia was atrial fibrillation. Left heart axis was present in most hypertrophic cardiomyopathy patients due to left ventricular hypertrophy. The values of Sokolow augmented vector left and Cornell voltage criteria best indicated the level of posterolateral wall hypertrophy, whereas none of the examined criteria correlated well with the interventricular septum thickness.

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