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PRACA ORYGINALNA
ORIGINAL PAPER

Limitations of electrocardiographic criteria of left ventricular hypertrophy in differentiation between hypertrophic cardiomyopathy, cardiac amyloidosis and Fabry disease

Ograniczenia elektrokardiograficznych kryteriów przerostu lewej komory serca w różnicowaniu kardiomiopatii przerostowej, amyloidozy serca oraz choroby Fabry'ego

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ABSTRACT

INTRODUCTION: Left ventricular hypertrophy (LVH) is a common pathology and should be differentiated using non-invasive and invasive methods. Electrocardiography (ECG) is the first choice method for the clinical evaluation of patients with LVH.

MATERIAL AND METHODS: A retrospective analysis of 77 patients (pts; age: 54.1 ± 16.3; 50.6% men) with features of cardiac hypertrophy in an echocardiographic examination was performed. The population was divided into three subgroups: 60 pts with hypertrophic cardiomyopathy (HCM), 11 pts with cardiac amyloidosis (CA) and 6 pts with Fabry disease (FD). Multiple ECG records were evaluated and the presence and frequency of eight different LVH criteria were verified.

RESULTS: Among the study population LVH criteria were present in 67.6% pts with HCM, 53.8% pts with CA and 57.1% pts with FD. Analysis of the number of LVH ECG criteria revealed: none of LVH ECG criteria: in 32.4% pts of HCM, in 46.2% pts with CA, in 42.9% pts with FD; 1 LVH ECG criterion in 21.1% pts with HCM, 46.2% pts with CA and 14.3% pts with FD; 2–4 criteria in 33.8% pts with HCM, 7.7% pts with CA and 42.9% pts with FD; 5–7 criteria in 12.7% pts with HCM and no pts with CA or FD. No patient fulfilled the eight LVH ECG criteria.

CONCLUSIONS: Electrocardiographic LVH criteria are not sensitive indicators of LVH. The mismatch between transthoracic echocardiography (TTE) and ECG findings is characteristic for CA and FD that may raise the suspicion of these diseases. The lack of LVH ECG criteria do not exclude these diagnoses.

KEYWORDS

LVH ECG criteria, hypertrophic cardiomyopathy, amyloidosis, Fabry disease

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STRESZCZENIE

WSTĘP: Przerost lewej komory (*left ventricular hypertrophy* – LVH) jest powszechną patologią i powinien być rozróżniany za pomocą metod inwazyjnych i nieinwazyjnych. Elektrokardiografia (*electrocardiography* – ECG) jest metodą pierwszego wyboru w klinicznej ocenie pacjentów z LVH.
MATERIAŁ I METODY: Przeprowadzono retrospektywną analizę 77 pacjentów (wiek: 54.1 ± 16.3; 50,6% mężczyzn) z cechami przerostu serca w badaniu echokardiograficznym. Populację podzielono na trzy podgrupy: 60 pacjentów z kardiomiopatią przerostową (*hypertrophic cardiomyopathy* – HCM), 11 z amyloidozą serca (*cardiac amyloidosis* – CA) i 6 z chorobą Fabry'ego (*Fabry disease* – FD). Oceniono zapisy ECG oraz zweryfikowano obecność i częstość występowania ośmiu kryteriów LVH.
WYNIKI: W badanej populacji kryteria LVH ECG były spełnione u 67,6% pacjentów z HCM, 53,8% z CA i 57,1% z FD. Analiza liczby kryteriów LVH ujawniła: żadnego kryterium nie spełniało 32,4% pacjentów z HCM, 46,2% z CA oraz 42,9% z FD; 1 kryterium spełniało 21,1% pacjentów z HCM, 46,2% z CA oraz 14,3% z FD; 2–4 kryteria stwierdzono u 33,8% pacjentów z HCM, 7,7% z CA oraz 42,9% z FD; 5–7 kryteriów występowało u 12,7% pacjentów z HCM i u żadnego pacjenta z CA i FD. Żaden pacjent nie spełniał ośmiu kryteriów.
WNIOSKI: Elektrokardiograficzne kryteria LVH nie są swoistymi wykładnikami LVH. Różnice pomiędzy echokardiografią przezklatkową (*transthoracic echocardiography* – TTE) oraz zmianami elektrokardiograficznymi są charakterystyczne dla CA oraz FD, co może budzić podejrzenie wystąpienia tych chorób. Brak spełnionych kryteriów LVH w ECG nie wyklucza tych diagnoz.

SŁOWA KLUCZOWE

kryteria LVH w ECG, kardiomiopatia przerostowa, amyloidoza, choroba Fabry'ego

INTRODUCTION

Cardiac diseases are intricate and diverse, often requiring precise diagnostic tools to unravel their underlying complexities. Among these, left ventricular hypertrophy (LVH) is a common manifestation across various conditions, such as hypertrophic cardiomyopathy (HCM), cardiac amyloidosis (CA), and Fabry disease (FD). HCM is an inherited pathology of ventricular myocardium with the highest prevalence in the general population [1]. New guidelines from the European Society of Cardiology were released in 2023, which emphasize the role of genetic testing in determining the underlying disorders of such a group with the HCM genotype. Clinical situations that imitate HCM are common and pose a serious diagnostic problem, especially at the beginning of the diagnostic pathway, when molecular, isotopic or detailed imaging results are unavailable [2]. The clinician is assisted at the initial stage of differential diagnosis by a carefully collected interview, a detailed assessment of the clinical condition, and changes in the electrocardiographic (ECG) examination. The complex pathophysiology includes myocyte hypertrophy, abnormal myocyte arrangement, gap junctional abnormalities and secondary fibrosis [1]. Also in the case of CA, the thickening of ventricular walls due to infiltration by amyloid deposits is observed. Although there have been attempts to find ECG changes specific to this condition, such as reduced QRS voltages, the index of the Total QRS Score/LVWT and many others, still in a heterogeneous group of patients the problem remains [3]. FD is a multi-organ storage anomaly in which globotriaosylceramide (Gb3) accumulates inside cardiomyocytes and vascular endothelium, causing "true" cardiomyocyte hypertrophy, inflammation and subsequent fibrosis. This process leads to conduction abnormalities within the atria and ventricles; however, the electrocardiographic picture is often non-specific and varied [4]. Electrocardiographic criteria and echocardiography, have long been used as initial screening tools for LVH, aiding in the differentiation between these distinct entities. The aim of the study was to compare the LVH ECG criteria among patients with echocardiography features of cardiac hypertrophy in regards to the final clinical differential diagnosis (HCM, CA or FD).

MATERIAL AND METHODS

Study population

A retrospective analysis of 77 patients (pts) suffering from HCM, CA or FD with cardiac hypertrophy established during echocardiographic examinations was performed. The average age of the population was 54.1 ± 16.3 and 50.6% were males. The patients were hospitalized in the Department of Cardiology of the Medical University of Silesia in Katowice between 2010–2022. The patients with HCM were diagnosed based on the maximum left ventricular wall thickness ≥ 15 mm obtained by transthoracic echocardiography (TTE) in the absence of an increased loading condition. CA was confirmed by myocardial biopsy. FD was determined based on genetic and dried blood spot tests. The final clinical diagnosis led to division of the population into three subgroups: 60 pts with HCM (mean age 54.5 ± 15.6; 53.6% males), 11 pts

with CA (average age 61 ± 16.8; 45.5% males) and 6 pts with FD (mean age 37.8 ± 11.7; 50% males). The inclusion criteria were: 1) confirmed diagnosis of HCM, CA or FD; 2) complete clinical data. The exclusion criteria were: complete and incomplete bundle branch blocks, nonspecific intraventricular conduction disturbances (NIVCD) and a paced rhythm. Because the study is a retrospective analysis, permission of Research Ethics Committees was not required.

Electrocardiography data

Resting 12-lead ECGs using Mortara ELI 250c with a paper speed of 25 mm/s and voltage of 10 mm/mV were performed on admission. Each of the 91 ECGs of the whole population were manually analyzed by members of the research team. Any doubts were verified with experienced cardiologists. The ECGs were assessed with regard to the presence of LVH criteria.

Analysis of the ECGs included the following eight LVH criteria:

1) the Sokolow-Lyon index: the sum of the S wave in V_1 and the R wave in V_5 or V_6 > 3.5 mV (Sokolow & Lyon, 1949);
2) the Gubner-Ungerleider voltage: the sum of the R wave in I and the S wave in the III lead > 2.5 mV (Gubner & Ungerleider, 1943);
3) the Cornell voltage: the sum of the R wave in aVL and the S wave in V_3 > 2.0 mV (for women) and > 2.8 mV (for men) (Casale, Devereux, Alonso, Campo, & Kligfield, 1987);
4) the sum of the S wave in the V_2 and the R wave in V_5 or V_6 > 4.5 mV (Romhilt et al., 1969);
5) the amplitude of the R wave in V_5 or V_6 > 2.6 mV (Sokolow & Lyon, 1949);
6) a comparison of the amplitude of the R wave in V_5 and V_6; R V_6 > R V_5 (Holt & Spodick, 1962);
7) the sum of the largest amplitude of the R wave and the largest amplitude of the S wave in precordial leads > 4.5 mV (McPhie, 1958);
8) the amplitude of the R wave in aVL > 1.1 mV (Sokolow & Lyon, 1949).

The ECG was considered as positive for LVH if at least one of the LVH criteria was fulfilled. The quantity of fulfilled criteria among the respective subgroups was counted and evaluated. Assessment of the presence zero or at least one of the LVH ECG criteria in the subjects with HCM, CA and FD was performed. Furthermore, accurate numbers (0–8) of positive LVH ECG criteria among the patients in the foregoing subgroups were calculated. Because in patients suffering from CA and FD nobody fulfilled more than 5 criteria, the presence of 1; 2–4; 5–7 and 8 LVH ECG criteria was compared separately among the subjects in each of the three subgroups. Correlation of the number (1; 2–4; 5–7; 8) of fulfilled LVH ECG criteria between the subjects with HCM, CA and FD was estimated. Subsequently, analysis of the most frequent criterion of hypertrophy among the examined patients was performed. Finally, comparison of the presence of two LVH ECG criteria: Gubner-Ungerleider voltage and the amplitude of the R wave in aVL > 1.1 mV in particular subgroups was assessed.

Statistical analysis

Statistical analysis was performed using Statistica 13.3 software. Qualitative variables were presented in the form of absolute values and percentages and quantitative variables in the form of arithmetic mean and standard deviation. The intergroup differences for the quantitative variables were assessed by the chi-square test and if the data did not meet the criteria for it – the Fisher's exact test. The criterion of significance was assumed at the level of $p < 0.05$.

RESULTS

Overall echocardiographic data of study population among particular subgroups was illustrated in Table I. Eight electrocardiographic criteria were evaluated. One or more criteria were observed in 71.7% of the patients with HCM, 54.5% with CA and 50% with FD.

All of those criteria were characterized by low sensitivity (0–45.5%). The most common positive criterion was R amplitude in V6 > V5 (45.5%) among the patients with CA and the other presented criteria was below 10%. In the group which suffered from FD, the most common were the Sokolow-Lyon and Cornell index in a similar proportion (33.3%). Among those patients negative were V6 > V5, S in V2 + R in V5/V6 > 45 mm, the Gubner-Ungerleider and R in aVL > 11 mm indices. In the group with HCM the most common was the Cornell index (40%). The Gubner-Ungerleider index and R in aVL > 11 mm can be useful in differentiating HCM (Gubner-Ungerleider 23.3%, R in aVL > 11 mm among 26%) from CA and FD (Gubner, R in aVL > 11 mm 0.0%). Foregoing results was presented in Table II. LVH in ECG was accompanied by T-wave inversion (TWI) in 61%. TWI was observed among 61.5% patients with CA, 85.7% in the group with FD and 82.8% among the HCM group. TWI was associated with LVH in ECG among 36.4% of the patients with CA, 50% with FD and 66.7% of patients with HCM.

The patients which fulfilled the ECG criteria of LVH were divided into four groups. Only 1 criterion was observed in 25% of patients with HCM, 45.5% with CA and 16.7% that suffered from FD. 35.1% of the patients with HCM fulfilled 2 to 4 criteria, 9.1% with CA and 33.3% with FD. 5–7 criteria were observed only in 12.7% of the HCM group. No patient fulfilled all eight criteria. Previous results was shown in Table III.

Table I. Electrocardiographic findings in each groups

Variable	All patients [*n* =]	HCM patients [*n* = 60]	CA patients [*n* = 13]	FD patients [*n* = 7]
Heart rate *bpm*	68 ± 15	66 ± 13	82 ± 15	53 ± 5
Sinus rhythm *n (%)*	72 (93.5%)	56 (93.3%)	10 (90.9%)	6 (100%)
Atrial fibrillation *n (%)*	5 (6.5%)	4 (6.7%)	1 (9.1%)	0 (0%)
Normal axis *n (%)*	47 (61.0%)	40 (66.7%)	3 (27.3%)	4 (66.7%)
Left axis deviation *n (%)*	20 (26.0%)	18 (30%)	2 (18.2%)	0 (0.0%)
QRS complex *ms*	106 ± 23	108 ± 25	95 ± 13	105 ± 24
Positive ECG for LVH *n (%)*	52 (67.5%)	43 (71.7%)	6 (54.5%)	3 (50%)
TWI in any leads *n (%)*	63 (81.8%)	52 (86.7%)	6 (54.5%)	5 (83.3%)
LVH + TWI *n (%)*	47 (61.0%)	40 (66.7%)	4 (36.4%)	3 (50%)

ECG – electrocardiogram; TWI – T-wave inversion; LVH – left ventricular hypertrophy, HCM – hypertrophic cardiomyopathy; CA – cardiac amyloidosis; FD – Fabry disease.

Table II. Sensitivity for electrocardiographic criteria for left ventricular hypertrophy

ECG criteria	Positive results [*n*]				p
	all patients	HCM	CA	FA	
R in V5 lub R in V6 > 26 mm *n (%)*	11 (14.3%)	9 (16.7%)	1 (9.1%)	1 (16.7%)	NS
V6 > V5 *n (%)*	25 (32.5%)	20 (33.3%)	5 (45.5%)	0 (0%)	NS
Sokolow-Lyon index *n (%)*	17 (22.1%)	14 (23.3%)	1 (9.1%)	2 (33.3%)	NS
S in V2 + R in V5/V6 > 45 mm *n (%)*	8 (10.4%)	7 (11.7%)	1 (9.1%)	0 (0.0%)	NS
Cornell index *n (%)*	26 (33.8%)	24 (40.0%)	0 (0.0%)	2 (33.3%)	NS
Gubner-Ungerleider index *n (%)*	14 (18.2%)	14 (23.3%)	0 (0.0%)	0 (0.0%)	**p = 0.03**
maxR + maxS ≥ 45 mm *n (%)*	12 (15.8%)	10 (16.7%)	1 (9.1%)	1 (16.7%)	NS
R in aVL > 11 mm *n (%)*	20 (26.0%)	20 (33.3%)	0 (0.0%)	0 (0%)	**p = 0.03**

ECG – electrocardiogram; LVH – left ventricular hypertrophy; HCM – hypertrophic cardiomyopathy; CA – cardiac amyloidosis; FD – Fabry disease; NS – not significant.

Table III. Sensitivity of fulfilled electrocardiographic criteria for left ventricular hypertrophy

Number of ECG criteria [*n*]	Patients fulfilled ECG criterion/a [*n*]				p
	all patients	HCM	CA	FD	
1 *n (%)*	21 (27.5%)	15 (25.0%)	5 (45.5%)	1 (16.7%)	NS
2 *n (%)*	11 (15.0%)	10 (16.7%)	0 (0.0%)	1 (16.7%)	NS
3 *n (%)*	6 (7.5%)	5 (8.3%)	0 (0.0%)	1 (16.7%)	NS
4 *n (%)*	7 (8,8%)	6 (10.0%)	1 (9.1%)	0 (0.0%)	NS
2–4 *n (%)*	24 (31.3%)	21 (35.1%)	1 (9.1%)	2 (33.3%)	NS
5 *n (%)*	1 (1.3%)	1 (1.7%)	0 (0.0%)	0 (0.0%)	NS
6 *n (%)*	3 (3.8%)	3 (5.0%)	0 (0.0%)	0 (0.0%)	NS
7 *n (%)*	3 (3.8%)	3 (5.0%)	0 (0.0%)	0 (0.0%)	NS
5–7 *n (%)*	7 (8.8%)	7 (11.7%)	0 (0.0%)	0 (0.0%)	NS
8 *n (%)*	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NS

ECG – electrocardiogram; HCM – hypertrophic cardiomyopathy; CA – cardiac amyloidosis; FD – Fabry disease; NS – not significant.

DISCUSSION

There are many causes of LVH, hence the need for screening tools to diagnose particular diseases [5,6]. Importantly, in patients with diseases such as FD, CA and HCM, early diagnosis and treatment are essential for effective treatment. For example, for FD specific treatment of enzyme replacement therapy is available [6,7]. Because ECG is a clinical tool easily available and relatively inexpensive, we see its potential to aid in differentiating the causes of HCM [5,8]. To date, little is known about the difference of ECG findings in FD, CA, HCM and their differential diagnostic utility [3,9]. There are few studies comparing ECG findings in these diseases [6,8].

An important finding in our study is that criteria such as the Gubner-Ungerleider index and R in aVL > 11 mm can be useful in the differentiation between HCM and CA and FD because in patients with these HCM phenotypes, these criteria were not found. These results are not completely consistent with the literature. The studies by Beer et al. [10] and Junqua et al. [11] showed that the Gubner-Ungerleider index was more frequent in the FD group than in the HCM group and the study by Vitale et al. [12] demonstrated a higher prevalence of R wave in aVL ≥ 1.1 mV in patients with FD compared to patients with HCM. This discrepancy may result from the small size of our group of patients with FD. No similar data were found for the ECG of patients with CA.

Similar to previous reports, in our study, a lower QRS voltage was more common in the group of patients with CA than in the groups with HCM or FD [6,9,13]. Zero or only 1 criterion of LVH in our study was observed in 92.3% of patients with CA, 42.8% of patients with FD, and only 32.4% of patients with HCM. This can be explained by the increased wall thickness without true myocyte hypertrophy, which occurs in infiltrative disorders like CA, and therefore does not produce increased QRS voltage [6]. On the other hand, at least one criterion of LVH was observed in as much as 53.9% of patients with CA in our report. It demonstrates that a high QRS amplitude does not exclude this disease [8].

However, it should be noted that all of those eight LVH criteria were characterized by low differential diagnostic power (sensitivity 13.2–34.1%) as a single indicator. Single criteria have no differentiating power. Nevertheless, Namdar et al. [6] proposed a 2-step diagnostic algorithm with high sensitivity and specificity for the assessment of FD and CA using other ECG parameters. It requires additional research into whether a similar algorithm can be created for the criteria of LVH.

There is the study by Huang et al. [8], which showed that the group of CA patients had a higher prevalence of atrial arrhythmia and longer QRS duration than the HCM group. Still, neither our study nor the study by Hoigné et al. [9] showed such findings. Similar relationships were searched for concerning FD. Analogously, our study did not reveal a higher frequency of atrial arrhythmia or longer QRS duration in the FD group than in the HCM group. In contrast, the studies by Beer et al. [10] and Junqua et al. [11] found that QRS duration was significantly longer in the FD group than in the HCM group. In these reports, the frequency of atrial arrhythmia did not differ between the two groups.

The literature is consistent in that no single ECG parameter is perfect to distinguish between HCM, FD and CA [5,6,9]. Nonethless, the combination of symptoms, history, results of electrocardiographic signs, and echocardiography findings may help a differential diagnosis to be made [8]. Because there are a plenty of conflicting results on this subject, more research is needed to differentiate CA, FD and HCM. The limitation is that the issue concerns relatively rare diseases, which results in a small number of studies with a small number of participants, but the possibility of specific treatment should increase interest in the topic [6,8,9].

Limitations

The relatively small number of patients in the study population was the main limitation of the research. This was caused by the fact that different HCM phenocopies, especially CA and FD are extremely rare illnesses. This was also a reason for the disproportion between the number of subjects with HCM, CA and FD in the study population.

CONCLUSIONS

The ECG criteria of LVH are not sensitive in the diagnostics of LVH proved by echocardiography. A mismatch between TTE and ECG findings is especially present in CA and FD, which may be an indirect suggestion for the suspicion of these diseases. The lack of LVH ECG criteria did not exclude these diagnoses.

Author's contribution

Study design – K. Mizia-Stec
Data collection – M. Tometczak, J. Znamirowska, J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga
Data interpretation – M. Tometczak, J. Znamirowska, K. Mizia-Stec
Statistical analysis – J. Topa
Manuscript preparation – M. Tometczak, J. Znamirowska, J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga
Literature research – J. Topa, P. Pastor, D. Waksmundzki, A. Grzebinoga

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