Predictive Value of Non-invasive Parameters in Patients with Left Ventricular Hypertrophy during a Five-Year Follow-up Period

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SUMMARY

Introduction Regardless of other known factors, left ventricular hypertrophy is considered to be a significant factor which correlates with the risk of cardiovascular complications. In practice, it is very important to predict the outcome for every patient at the beginning of the treatment.

Objective The aim of the study was to follow the predictive value of non-invasive parameters obtained at the beginning of the study in patients with essential arterial hypertension and left ventricular hypertrophy who were treated by regular therapy through a five year follow-up period.

Methods Ninety patients (average age 55) with essential hypertension and left ventricular hypertrophy were examined. All patients were studied at baseline after temporary discontinuation of previous antihypertensive therapy. The follow-up period started at the baseline examination and lasted for five years. Adverse cardiovascular events occurred in 15 (16.7%) patients.

Results Non-invasive parameters were tested by stepwise multiple regression analysis. Three examined parameters had predictive value: QTc interval dispersion (beta=0.325, p=0.001), septal wall thickness (beta=0.294, p=0.003) and low increase of the heart rate during exercise testing (beta=-0.202, p<0.04). For this model, adjusted R square=0.203; $F_{3,84}$=8.406, p<0.0001.

Conclusion In spite of regular medical treatment, patients with larger QTc dispersion, greater septum thickness and lower increase of heart rate during exercise testing showed worse outcome through the follow-up period. These patients should be recognized as early as possible and treated more aggressively.

Keywords: arterial hypertension; left ventricular hypertrophy; predictive value

INTRODUCTION

Regardless of other known factors, left ventricular hypertrophy (LVH) is considered to be a significant factor which correlates the risk of cardiovascular complications [1]. The evidence shows that, after hypertensive treatment, the regression of LVH is accompanied by improvement in prognosis [2, 3]. LVH is multifactorial state and other risk factors may be the causes of adverse cardiovascular events during hypertensive condition. It is very difficult to achieve the target level of blood pressure in real patients, since different groups of medications have different potential to change left ventricular mass. In practice, it is of utmost importance to predict the outcome for every patient at the beginning of the treatment and, if necessary, start with more aggressive treatment in order to achieve the best prognosis.

OBJECTIVE

The aim of the study was to follow the predictive value of non-invasive parameters obtained at the beginning of the study in patients with essential arterial hypertension and LVH, who were treated by regular therapy, through a five year follow-up period.

METHODS

Population study

Patients were prospectively recruited from the Department for Treating High Blood Pressure at the Institute for Treatment and Rehabilitation "Niška Banja" based on the type of echocardiographic LVH. Ninety patients (average age: 55.2±8.3; 56 male and 34 female) with essential hypertension and LVH (35 patients with concentric LVH, 35 with eccentric LVH and 20 patients with septal LVH), and without cardiovascular and cerebrovascular adverse events were examined. The diagnosis of hypertension in the patients without therapy was established by at least three measurements at rest and in other circumstances. As for the patients who have never been treated, blood pressure higher than 140/90 mmHg is considered to be hypertension. All patients were studied at baseline, after discontinuation of previous antihypertensive therapy. The follow-up period started at the baseline examination and lasted for five years. Treatment was individualized and based on patents' lifestyle and pharmacological measures. The aim was to achieve blood pressure <140/90 mmHg. Therapy included diuretics, β-blockers, ACE inhibitors, calcium channel blockers and α1-blockers, alone or combined,

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while antihypertensive drugs were most frequently used. During the period of treatment and follow-up, all adverse events were verified by a medical expert in the field of cardiovascular diseases in the office of the Institute.

Exclusion criteria in this study were the following: secondary and malignant hypertension, valvular, coronary, or primary myocardial disease, serum creatinine >177 μm/L, age >74 years, poor exercise capacity as a result of lung disease or musculoskeletal problems, complete right or left bundle branch block, previous myocardial infarction, Wolff-Parkinson-White syndrome, atrial fibrillation and low left ventricular systolic function (EF<50%).

All patients were examined by means of echocardiography (two independent examiners Acuson-Sequoia), exercise testing, 24 hour ambulatory blood pressure monitoring, and QTc interval dispersion.

Electrocardiographic examination

Standard 12-lead ECG was recorded at 25 mm/s and 1 mV/cm calibration (EKG-300, EI Niš). LVH was determined by Lyon-Sokolow score and Cornell product. LVH was determined by Lyon-Sokolow score as SV1+RV5/V6>38 mm, and by Cornell product as SV3+RaVL X QRS duration ≥2.440 mm x ms [4]. The QT intervals were measured on all possible leads. The mean of three complexes was taken as the QT interval for each lead. The QT intervals were measured from the onset of the QRS complex to the end of the T wave, which is defined as the return to the T-P baseline. In case the U waves were present, the QT interval was measured to the nadir of the curve between T and U waves. The leads with unclear T wave were excluded. The minimum number of valuable leads was 11 leads. The QT intervals were also corrected (QTc) for the known effect of heart rate using Bazett's formula ($QTc=QT/(RR)^{1/2}$). The QTc dispersion (QTcd) was calculated as the difference between the maximum QTc interval and minimum QT interval in each subject [5].

Echocardiographic examination

Echocardiography was performed by means of Acuson Sequioa sonographic recorder with 3.5 MHz transducer, in a modified left lateral decubitus position with the head angled at 30° from the horizontal. M-mode, 2-dimensional image and Doppler examination were performed in all standard positions of the transducer. Transmitral flow velocity was used to quantify left ventricular diastolic function. The sample volume was placed at the tip of the mitral valve leaflets in a four-chamber apical view. Peak of the early diastolic velocity (E-wave), peak of the late diastolic velocity (A-wave), E/A ratio and early filling deceleration time were measured. M-mode images were obtained from the long-axis parasternal view at the level of the tips of the mitral valve leaflets. Measurements of septal wall thickness (SWT), posterior wall thickness (PWT), and left ventricular internal dimension (LVID) were performed at the peak of the R wave in accordance with Penn convention. Left ventricular mass index (LVMI) (in g/m^2) was calculated as: $LVMI = (1.04[(SWT+PWT+LVID)^3–(LVID)^3]–13.6)$ / Body Surface Area Cut-off values for the presence of LVH were taken as ≥110 g/m^2 for women and ≥134 g/m^2 for men [6].

Concentric remodeling of left ventricle is characterized by thickened ventricular walls in patients with normal LVMI and with small end-diastolic diameter [1]. Relative wall thickness (RWT) was calculated by doubling PWT and dividing it by end-diastolic diameter. Disproportionate septal LVH was determined by SWT/PWT ≥1.3 ratio. Concentric LVH was determined by RWT ≥0.45, and SWT/PWT <1.3 ratio. Eccentric LVH was determined by RWT <0.45 and SWT/PWT <1.3 ratio. M-mode image (long-axis parasternal view) was used for measuring left atrial size. Left ventricular volumes used to estimate ejection fraction (EF) were determined by Teichholz method [7].

Examination by exercise testing

Exercise testing was performed according to standard Bruce protocol. Exercises were terminated after achieving the target heart rate which is based on 85% of the age predicted maximum heart rate, limiting chest discomfort, participant request, dyspnea, fatigue, leg discomfort, excessive increase (>250 mmHg) or decrease (>10 mmHg from resting) of the systolic blood pressure, >1 mm of ST segment depression and repetitive ventricular ectopy. Increase of heart rate during exercise testing was defined as the difference between the maximum achieved heart rate at the end of exercise testing and heart rate at the beginning of exercise testing (beat/minute) divided by duration of exercise testing (minute). Double product at the beginning (DP min) and at the end (DP max) of the exercise testing was calculated by multiplying systolic blood pressure by heart rate.

Twenty-four hour ambulatory blood pressure monitoring

Twenty-four hour ambulatory systolic (SBP) and diastolic blood pressure (DBP) monitoring was performed by Del Mar Avionics, Irvine, California equipment (model P-VA and P6). Blood pressure recordings were made every 15 minutes between 7 AM and 11 PM and every 30 minutes between 11 PM and 7 AM. Data were edited by omitting all readings presumed to be erroneous, including readings of 0, DBP readings of more than 160 mmHg or less than 50 mmHg, SBP readings of more than 260 or less than 80 mmHg, and all readings where the difference between SBP and DBP was less than 10 mmHg.

Statistical analyses

Data were analyzed with SPSS release 12.0 (SPSS Inc.). Quantitative variables were presented as means ± standard

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deviation, while qualitative variables were presented as percentages. Mean values were compared between groups by means of Student's t-test. Proportions were compared by χ^2 tests. Multiple regression analyses were performed using a stepwise elimination procedure. A 2-tailed p<0.05 was considered significant for all tests.

RESULTS

Baseline characteristics of the examined patients are shown in Table 1. Analysis of adverse cardiovascular events was performed after exactly five years for each patient, except for the one who suddenly died after three years and seven months. Adverse cardiovascular events occurred in 15 (16.7%) patients. Three of them had myocardial infarction, five patients suffered from cerebrovascular insult, six patients had angina pectoris (positive exercise testing) and one died during coronary revascularization. All patients were divided in two groups according to the persistence of adverse cardiovascular events (Table 1). There were no differences in baseline parameters between two examined groups.

Parameters of 24-hour ambulatory blood pressure monitoring in patients with and without adverse cardiovascular events, are shown in Table 2. Parameters of 24-hour ambulatory blood pressure monitoring showed no statistically significant differences between the examined groups.

Table 1. Baseline characteristics of examined population

Characteristics		All (N=90)	Group without cardiovascular events (N=75)	Group with cardiovascular events (N=15)
Gender (male/female)		56/34	45/30	11/4
Age (years)		55.2±8.3	55.6±8.0	53.0±9.6
Body surface area (m²)		1.96±0.20	1.96±0.20	1.94±0.16
Body Mass Index (kg/m²)		28.8±3.8	28.8±3.7	29.0±4.1
Duration of hypertension (years)		12.0±7.7	11.8±7.8	12.8±7.6
Smoking (number/%)		34/37.8	28/37.3	6/40.0
Hyperlipidemia (number/%)		20/22.2	16/21.3	4/26.7
Diabetes mellitus (number/%)		8/8.9	6/8	2/13.3
Therapy	Beta-blockers	61/67.8	52/69.3	9/60.0
	ACE inhibitors	73/81.1	60/80.0	13/86.7
	Calcium channel blockers	48/53.3	41/54.7	7/46.7
	Diuretics	56/62.2	45/60.0	11/3.3

Data are mean ± standard deviation.

Lyon-Sokolow score was more frequent in the group with new cardiovascular events than in the group without cardiovascular events (p<0.05; Table 3). As for the presence of positive Cornell product for LVH, there was no statistical difference between the two groups. QTc interval was statistically equal in both groups. The QTc interval dispersion was larger in the group with cardiovascular events than

Table 2. Parameters of 24-hour ambulatory blood pressure monitoring in patients with and without adverse cardiovascular events

Parameters	All (N=90)	Group without cardiovascular events (N=75)	Group with cardiovascular events (N=15)
Average 24-hour SBP (mmHg)	139.3±12.2	139.0±17.4	141.0±16.4
Average 24-hour DBP (mmHg)	86.4±10.7	85.9±10.4	89.1±11.7
Morning SBP (mmHg)	141.4±23.9	141.3±23.9	141.7±24.8
Morning DBP (mmHg)	87.5±13.5	87.0±13.5	90.1±13.8
SD SBPD (mmHg)	15.3±3.8	15.5±4.0	15.4±2.6
SD SBPN (mmHg)	11.7± 4.7	11.5±4.7	12.8±5.1
SD DBPD (mmHg)	11.8±2.9	11.8±3.0	11.6±2.5
SD DBPN (mmHg)	10.3±3.2	10.3±3.2	10.3±3.4
PFSBP (%)	7.9±9.2	8.5±8.8	3.2±10.3
PFDBP (%)	9.9±10.5	10.3±10.6	7.9±10.4

Data are mean ± standard deviation.
SBP – systolic blood pressure; DBP – diastolic blood pressure; SD SBPD – standard deviation of systolic blood pressure during the day; SD SBPN – standard deviation of systolic blood pressure during the night; SD DBPD – standard deviation of diastolic blood pressure during the day; SD DBPN – standard deviation of diastolic blood pressure during the night; PFSBP – percent of fall systolic blood pressure; PFDBP – percent of fall diastolic blood pressure

Table 3. Electrocariographic parameters in examined groups

Parameters	All (N=90)	Group without cardiovascular events (N=75)	Group with cardiovascular events (N=15)	p
LVH – Lyon-Sokolow score	14 (15.5%)	9 (12%)	5 (33.3%)	<0.05
LVH – Cornell product	20 (22.2%)	14 (18.7%)	6 (40.0%)	NS
QTc interval	420.4±23.1	419.5±24.0	424.7±17.4	NS
QTc interval dispersion	59.5±21.2	56.5±20.2	74.5±20.2	<0.01

Data are mean ± standard deviation.
LVH – left ventricular hypertrophy

Table 4. Echocardiographic parameters in examined groups

Parameters	All (N=90)	Group without cardiovascular events (N=75)	Group with cardiovascular events (N=15)	p
LVID (mm)	52.9±4.6	53.0±4.4	52.6±6.1	NS
SWT (mm)	13.7± 2.5	13.4±2.3	15.4±3.1	<0.05
PWT (mm)	11.8 ±1.2	11.6 ± 1.1	12.5 ± 1.3	<0.05
LVM (g)	337.2±74.0	329.6±68.6	380.7±87.8	<0.05
LVMI (g/m^2)	172.3±32.4	167.9±29.3	194.0±38.7	<0.05
RWT	0.45±006	0.44±0.06	0.49±0.09	<0.05
EF (%)	65.7±6.1	65.8±5.8	65.1±7.5	NS
LA (mm)	40.0±5.2	39.5±4.5	42.3±7.4	NS
E/A	1.0±0.28	1.00±0.27	1.01±0.34	NS

Data are mean ± standard deviation.
LVID – left ventricular internal dimension; SWT – septal wall thickness; PWT – posterior wall thickness; LVM – left ventricular mass; LVMI – left ventricular mass index; RWT – relative wall thickness; EF – ejection fraction; LA – left atrium; E/A – early transmitral velocity/late transmitral velocity

Table 5. Parameters from exercise testing in examined groups

Parameters	All (N=90)	Group without cardiovascular events (N=75)	Group with cardiovascular events (N=15)	p
METs	6.6±2.5	6.5±2.5	6.9±2.4	NS
SHR	62 (68.9%)	50 (66.7%)	12 (80%)	NS
RHR	11.8±6.4	12.4±6.7	8.8±4.0	<0.01
Maximal DP	277.7±53.3	280.2±52.9	264.9±55.5	NS
Minimal DP	125.8±25.9	124.2±23.7	133.6±35.1	NS
Delta DP	152.0±56.4	156.2±55.2	131.3±59.8	NS

Data are mean ± standard deviation.
METs – metabolic equivalents; SHR – submaximal heart rate; RHR – rise of heart rate; DP – double product

without them (p<0.01). As for electrocardiographic parameters, there was no difference between the two groups.

Both groups had statistically equal end-diastolic left ventricular diameter (Table 4). Diastolic wall thickness of interventricular septum, as well as PWT and RWT, were greater in the group with cardiovascular events than in the group without them (p<0.05). Left ventricular mass and LVMI were larger as well. As far as EF, size of LA and diastolic function are concerned, there was no statistical difference between the two groups.

Both groups showed equal physical effort tolerance (Table 5). As for the percentage of the achieved 85% of maximum heart rate there was no difference between the groups. Heart rate raise during each minute of exercise testing was lower in the group with cardiovascular events than in the group without them. As for the maximum DP, minimum DP and raise of double product, there was no difference between groups.

All examined parameters were tested by the stepwise multiple regression analysis. Three examined parameters had predictive value: QTc interval dispersion (beta=0.325, p=0.001), septal wall thickness (beta=0.294, p= 0.003) and low increase of heart rate during exercise testing (beta=-0.202, p<0.04). Adjusted R square for this model was 0.203; $F_{3,84}$=8.406, p<0.0001.

DISCUSSION

This study showed that, aside from echocardiography and electrocardiography, exercise testing had prognostic significance in patients with LVH. The QTc interval dispersion was larger, and the raise of heart rate during exercise testing was slower in patients with adverse events than in patients without them.

High blood pressure has been one of the important factors of LVH occurrence. Correlation between 24-hour ambulatory blood pressure monitoring and LVH was better than the correlation between office measured blood pressure and LVH [8, 9]. The report of WHO states that high blood pressure has been listed as the first cause of death worldwide [10]. Daytime blood pressure adjusted for night-time blood pressure, predicted fatal combined with non-fatal cardiovascular events, except in treated patients, in whom antihypertensive drugs might reduce blood pressure during the day, but not at night, which was reported in the study of Boggia et al. [11]. As for the parameters of 24-hour ambulatory blood pressure monitoring, this study showed no differences between the groups with adverse cardiovascular events and without them. Thus, the values of blood pressure are not always sufficient to determine the outcome in the selected group of patients with LVH.

Sensitivity of electrocardiographic criteria for the detection of LVH is low [12]. In the study of Levy et al. [13], Lyon-Sokolow score and Cornell voltage QRS duration product was an independent predictor of adverse cardiovascular events. This study showed that only Lyon-Sokolow score was more frequent in patients with adverse cardiovascular events.

The other electrocariographic parameter, which was higher in patients with adverse cardiovascular events, was QTc interval dispersion. Several other studies confirmed a correlation between QTc dispersion and the presence or degree of LVH [14, 15]. Saadeh et al. [16] reported that QTc dispersion increased in patients with LVH during a 10-year follow-up period, but was not associated with the increased risk of sudden death. As far as this study is concerned, out of fifteen adverse cardiovascular events only one patient died suddenly. Stepwise multiple regression analysis, which was performed in this study, showed that the QTc interval dispersion had an independent predictive value of adverse events. In the study of Dimopoulos et al. [17] the authors concluded that prolonged corrected QT interval was an independent predictor of major cardiovascular events in older men and women. As for the QTc interval, this study showed no differences between the examined groups.

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LVMI has been a well known independent predictor of bad prognosis. The adjusted relative risk for cardiovascular morbidity associated with baseline LVH was 1.5 to 3.5 [18, 19]. After taking into account the traditional clinical risk factors [20], Fox et al. [20] found that echocardiographic LVMI was an independent predictor of incident ischemic stroke event. It is important to emphasize that ventricular walls may be thickened in patients with normal LVMI with small end-diastolic diameter, which is considered to be concentric remodeling of left ventricle, not LVH. Clinical studies have shown a stepwise increase in risk as patients advance from concentric remodeling to eccentric and concentric hypertrophy. This study showed that patients with adverse cardiovascular events had greater left ventricular mass and LVMI than patients without adverse events. Other important echocardiographic parameters were septum and posterior wall thickness and relative wall thickness. Stepwise multiple regression analysis showed that the septum wall thickness was an independent predictor of adverse events.

Several patients with hypertension and LVH did not reach submaximal heart rate during exercise testing, which was reported in the study of Lauer et al [21]. In the same study, double product was high and non-specific ST-T changes were frequent [21]. Over a period of 7.7 years, Framingham study [22] showed increased mortality of patients who did not reach 85% of maximum heart rate. Chronoscopic incompetence was examined by Lauer et al. [23]. Twenty percent of 1414 men and 23% of 1601 women did not reach sub-maximal heart rate. A low chronoscopic index was found in 14% of men and in 12% of women. Falcone et al. [24] reported a significantly increased risk of cardiovascular mortality in subjects with coronary artery disease who showed rapid heart rate increase during the first minute of nonindividualized semisupine cycle testing. They postulated that this early heart rate change was associated with an increased risk of death related to sympathetic hyperactivity or premature vagal withdrawal [24]. A recent study has shown that a rapid initial heart rate raise was associated with improved survival. However, heart rate increase at peak exercise and other conventional measurements, such as exercise capacity and the Duke treadmill score, were more powerful predictors of prognosis [25]. In this study, which used stepwise multiple regression analysis, patients with adverse cardiovascular events showed a slower increase of heart rate during exercise testing than patients with good prognosis, which is an independent predictor of adverse events.

Study limitation

The main limitation of the study was a small number of examined patients and adverse events. The examined hypertensive population was selected in accordance with the type of hypertrophy and LVMI. The prevalence of disproportionate septal LVH was more frequent than usual. The used formula was not appropriate for calculating LVMI in the patients with disproportionate septal LVH, which could make septum thickness a predictor of adverse events [6].

CONCLUSION

In spite of regular medical treatment, patients who had already suffered from left ventricular hypertrophy and had larger QTc dispersion, greater septum thickness and lower increase of heart rate during exercise testing showed worse five-year outcome. These patients should be recognized as early as possible, and treated more aggressively.

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Прогностички значај неинвазивних параметара код болесника с хипертрофијом леве коморе током петогодишњег периода

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КРАТАК САДРЖАЈ

Увод Хипертрофија леве коморе је удружена с повећаним ризиком за настанак кардиоваскуларних компликација независно од других познатих фактора ризика. У пракси је важно да се предвиди исход лечења сваког болесника пре почетка лечења.

Циљ рада Циљ рада био је да се испита прогностички значај неинвазивних параметара добијених на почетку студије код болесника с есенцијалном артеријском хипертензијом и хипертрофијом миокарда леве коморе током пет година клиничког праћења, уз редовну медикаментну терапију.

Методе рада Испитано је и лечено 90 болесника (просечне старости од 55 година) с есенцијалном артеријском хипертензијом. Након искључивања претходне медикаментне терапије сви болесници су подвргнути планираним испитивањима. Болесници су надгледани пет година, од почетка испитивања до завршетка пете године. Нежељени кардиоваскуларни догађаји забележени су код 15 болесника (16,7%).

Резултати Неинвазивни параметри испитани су тзв. *stepwise* мултиплом регресионом анализом. Три испитана параметра имала су прогностички значај: дисперзија интервала *QTc* (β=0,325; p=0,001), дебљина интервентрикуларног септума (β=0,294; p=0,003) и споро повећање срчане фреквенције током теста физичким оптерећењем (β=-0,202; p<0,04). За овај модел, корговано R^2=0,203; $F_{3,84}$=8,406; p<0,0001.

Закључак Код болесника с већом дисперзијом интервала *QTc*, већом дебљином септума и спорим повећањем срчане фреквенције током теста физичким оптерећењем уочен је лош исход лечења упркос редовној примени медикаментне терапије. Ове болеснике треба препознати што раније и подвргнути их интензивнијем лечењу.

Кључне речи: артеријска хипертензија; хипертрофија леве коморе; прогностички значај

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