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THE FIVE YEARS PREDICTIVE VALUE OF QTc INTERVAL AND QTc INTERVAL DISPERSION IN HYPERTENSIVE PATIENTS WITH LEFT VENTRICULAR HYPERTROPHY

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Summary. *The aim of the paper is a study of QTc interval, QTcp interval (interval from Q wave to the peak of T wave), Tp-Tendc interval (interval from the peak of T wave to the end of T wave) and their dispersion with respect to the five-year predictive value of these intervals in patients with essential arterial hypertension and left ventricular hypertrophy. A total of 90 patients (56 males and 34 females) were examined, average age 55.2 ± 8.3 years, who suffered from essential arterial hypertension and left ventricular hypertrophy. The control group comprised 35 healthy subjects (20 males and 15 females), average age 54.5 ± 7.1 years. The average left ventricular mass index was 171.9 ± 32.4 g/m^2 in hypertensive patients and 102.4 ± 13.3 g/m^2 in healthy controls. The QTc interval and QTcp interval (interval from Q wave to the peak of T wave) were longer in the left ventricular hypertrophy group than in healthy controls ($p < 0.01$) in the baseline electrocardiogram. During exercise testing, QTc interval shortened in the hypertensive group ($p < 0.001$) but was unchanged in controls. QTc dispersion ($p < 0.001$) and QTcp ($p < 0.001$) had higher values in the hypertensive group before and after exercise testing, compared to healthy subjects. Fifteen (16.7%) patients had cardiovascular and cerebrovascular adverse events during the five-year follow-up. In the group of hypertensive patients with left ventricular hypertrophy, cardiovascular and cerebrovascular adverse events were more frequent in those patients who had higher values for the left ventricular mass, left ventricular mass index, wall thickness, and QTc dispersion before and after exercise testing, as well as a wider QRS complex, and slower rise of heart rate during exercise testing. Independent predictors of bad outcome were greater posterior wall thickness and QTc dispersion after exercise testing. Intervals and their dispersion as 'Q wave–peak of T wave' and 'peak of T wave–end of T wave' were less useful than QTc interval and QTc dispersion according to the prognosis.*

Key words: *Arterial hypertension, left ventricular hypertrophy, QTc interval, QTc dispersion, prognosis*

Introduction

Left ventricular hypertrophy (LVH) and prolonged QT interval at electrocardiogram are common in arterial hypertension, and they are markers of cardiovascular disease and sudden death. A longer QTc interval is a marker of unequal sympathetic activity in the myocardium and yields a lower threshold for ventricular tachyarrhythmias. QTc interval and QTc dispersion are simple and, above all, available electrocardiography parameters.

A QTc interval is obtained by measuring time distance from Q wave to the end of T wave and by correcting them by the square root of R-R interval (Basett's formula = $QT / R - R^{1/2}$). For QTc dispersion, QT interval and R-R interval need to be measured in all of the twelve leads, whereupon they are corrected by the Basett's formula, and a difference between maximal and minimal corrected values are found. The worst characteristic of QTc dispersion is low intra- and inter-observer reproducibility (relative error 25 – 35%) (1). QT dispersion is assumed to reflect a regional difference in the re-polarization process although QT interval is composed of depolarization and re-polarization. Greater QTc dispersion has been found in patients with neurohumoral activation, myocardial infarction, myocardial ischemia, myocardial fibrosis, myocardial hypertrophy, etc.

The first clinical significance of QTc dispersion was found by Dye *et al.* in 1990, in patients with ventricular arrhythmias (2). The first prognostic significance of QTc dispersion was shown by Barr *et al.* in 1994. They observed bad outcome in patients with heart failure and QTc dispersion greater than 100 ms (3). Darbar *et al.* confirmed the prognostic significance of QTc dispersion in patients with peripheral arterial disease. These patients showed greater cardiovascular mortality if their QTc dispersion was equal to or greater than 60 ms. Sensitivity of this marker was 92% and specifity 81% (4). There is no good prospective study which could confirm the

predictive value of QTc dispersion in any disease. QTc dispersion is not recommended as a strong predictive marker for cardiac death by the Task Force on Sudden Cardiac Death of the European Society of Cardiology (5).

There are numerous studies on QTc dispersion in hypertensive patients which confirm that QTc dispersion is greater in hypertensive patients with left ventricular hypertrophy than in healthy subjects (6,7). However, not many studies exist on QTc dispersion during exercise testing and its clinical significance (8).

Hypertensive subjects with LVH can have increased Tp-Tendc interval (interval from the peak of T wave to the end of T wave) dispersion, which is associated with cardiac death. Despite its prognostic value, Tp-Tendc interval dispersion is not widely used. QTp (i.e. beginning of QRS to the peak of T wave) is easier to measure.

Aim

The aim of the paper is a study of QTc interval, QTcp interval (interval from Q wave to the peak of T wave), Tp-Tendc interval (interval from the peak of T wave to the end of T wave) and their dispersion with respect to the five-year predictive value of these intervals in patients with essential arterial hypertension and left ventricular hypertrophy.

Patients and Methods

We examined 90 patients (LVH - 56 males and 34 females), average age 55.2 ± 8.3 years, with essential arterial hypertension and left ventricular hypertrophy (Table 1). The control group comprised 35 healthy subjects (CG - 20 males and 15 females), average age 54.5 ± 7.1 years. There were no differences between the two groups concerning age, gender, body surface area, percentage of smokers, and percentage of patients with hyperlididaemia and diabetes mellitus. The patients with hypertension had a greater body mass index and a positive family history of hypertension ($p < 0.001$).

The average left ventricular mass index was 171.9 ± 32.4 g/m^2 and the left ventricular mass was 337.9 ± 74.0 g in hypertensive patients. In healthy controls, the left ventricular mass index was 102.4 ± 13.3 g/m^2 and the left ventricular mass 193.6 ± 33.4 g.

Table 1. Baseline characteristics of the examined groups

Characteristics	LVH	CG	P <
Number of patients (N)	90	35	n.s.
Gender (m / f)	56 / 34	20 / 15	n.s.
Age (years)	55.2± 8.30	54.5 ± 7.10	n.s.
Body surface area (m^2)	1.95 ± 0.20	1.88 ± 0.14	n.s.
Body mass index	28.8 ± 3.80	26.5 ± 3.10	0.001
Duration of hypertension (years)	12.3 ± 7.9	–	–
Smocking (n / %)	34 / 37.8	11 / 30.5	n.s.
Hyperlipidemia (n / %)	20 / 22.2	6 / 17.1	n.s.
Diabetes mellitus (n / %)	12 / 13.3	2 / 5.5	n.s.
Hereditet (n / %)	58 / 64.4	11 / 30.5	0.001

Echocardiographic (Acuson-Sequoia) measurements (two independent examiners) included intraventricular septal thickness (IVSTd), posterior wall thickness (PWTd), end-diastolic diameter (LVIDd), and end-systolic diameter (LVISd). Measurements were performed according to the Penn convention and the Devereux and Reichek formula: the left ventricular mass = $1.04 \cdot [(IVSTd + PWTd + LVIDd)^3 - (LVIDd)^3] - 13.6$ g. The left ventricular mass (LVM) was divided by the body surface area to calculate the left ventricular mass index (LVMI). Criteria for LVH included LVMI of 134 g/m^2 or greater for men and 110 g/m^2 or greater for women (9).

Exercise testing was performed using the standard Bruce protocol. Reasons for termination of exercise included the achievement of the target heart rate based on 85% of the age- and sex-related maximal heart rate, the achievement of the limiting chest discomfort, participant request, dyspnea, fatigue, leg discomfort, excessive increase (> 250 mmHg) or decrease (> 10 mmHg from resting) of systolic blood pressure, > 1 mm of ST segment depression, and repetitive ventricular ectopy.

For QT measurements, the first electrocardiogram was done before exercise testing and the second one was done during the first minute of recovery. We assessed QT intervals, corrected them according to the Bazett's formula (QTc) and then subtracted the shortest from the longest QTc interval for the purpose of obtaining QTc interval dispersion. QTp interval (from Q wave to the peak of T wave) and Tp-Tend segment (from the peak of T wave to the end of T wave) were measured and their corrected values and dispersion were calculated.

Parameters were measured at the beginning of the study and the patients were monitored for five years. All patients received a regular medicament therapy during the follow-up period.

The results are expressed as mean ± SD and the statistical significance between the groups was estimated by using a Student's t-test and χ^2 – test. The independent predictive value was examined by multiple regression stepwise analyses.

Results

The patients and healthy subjects reached a statistically equal MET during exercise testing (Table 2). The double product was greater ($p < 0.001$) in the patients than healthy controls at the beginning of exercise testing, but there was no difference at the end of exercise testing. The patients reached an average 76.7% of the theoretically maximal bits per minute, which was statistically lower than in healthy controls who all reached the anticipated 85% ($p < 0.001$). The main reason for early termination of exercise testing in the patients group was fatigue. A rise in bits per minute for every minute of exercise testing was lower in the hypertensive group, but it was statistically insignificant.

Table 2. Parameters from exercise testing of the examined groups

Parameters	LVH	CG	P <
MET	6.6 ± 2.5	6.2 ± 1.6	n.s.
MDP	277.7 ± 53.3	262.4 ± 32.7	n.s.
DP	125.8 ± 25.9	105.8 ± 26.1	0.001
ΔDP	152.1 ± 56.4	153.7 ± 36.4	n.s
ΔSBP (mmHg)	44.4 ± 23.6	47.7 ± 18.0	n.s.
ΔDBP (mmHg)	5.2 ± 12.6	4.0 ± 7.2	n.s.
P of MBPM (%)	76.7 ± 21.6	85.3 ± 3.1	0.001
R of BPM (/min)	11.8 ± 6.4	13.9 ± 4.8	n.s.

MET – metabolic equivalent; MDP – maximal double product; DP – double product; ΔDP – difference between MDP and DP during exercise testing; ΔSBP – difference between maximal and minimal systolic blood presure during exercise testing; ΔDBP – difference between maximal and minimal diastolic blood pressure during exercise testing; P of MBPM – reached percentage of theoretically maximal bits per minute; R of BPM – rise of bits per minute for every minute during exercise testing.

The QTc interval and QTcp interval were greater in LVH group than in CG ($p < 0.01$) before exercise testing (Table 3). There were no differences between other parameters of QTc interval in the examined groups. During exercise testing, QTc interval shortened in LVH group ($p < 0.001$) and was unchanged in CG. QTcp interval shortened in LVH group ($p < 0.001$) and CG ($p < 0.05$). Tp-Tend interval was prolonged in both groups ($p < 0.001$).

Table 3. QTc interval in the examined groups during exercise testing

Parameters of QTc interval	LVH (ms)	CG (ms)	P <
QTc	420.4 ± 23.1	406.0 ± 27.0	0.01
QTc-et	414.0 ± 19.3	404.5 ± 30.2	n. s.
QTcp	327.2 ± 21.7	314.2 ± 24.7	0.01
QTcp-et	311.8 ± 19.2	300.0 ± 40.4	n. s.
Tp-Tendc	92.8 ± 15.9	91.2 ± 9.7	n. s.
Tp-Tendc-et	102.9 ± 11.9	101.4 ± 12.9	n. s.

QTc-et – QTc at the end of exercise testing; QTcp – rate-corrected interval from Q to the peak of T wave; QTcp-et – QTcp at the end of exercise testing; Tp-Tendc – rate-corrected segment from the peak of T wave to the end of T wave; Tp-Tendc-et – Tp-Tendc at the end of exercise testing.

QTc dispersion ($p < 0.001$), QTcp ($p < 0.001$) and Tp-Tend ($p < 0.01$) were greater in LVH group before and after exercise testing (Table 4). After exercise testing, QTc dispersion was decreased only in CG ($p < 0.001$), QTcp was decreased only in LVH group ($p < 0.01$) and Tp-Tend was decreased only in CG ($p < 0.05$).

The patients were followed up for five years during which time they received a regular anti-hypertensive therapy (beta blockers, ACE inhibitors, calcium channel blockers and diuretics). Fifteen (16.7%) patients had cardiovascular and cerebrovascular adverse events (Table 5).

During the five-year follow-up, the patients with cardiovascular and cerebrovascular events had greater values for the left ventricular mass index, left ventricular mass, wall thickness, duration of QRS complex, dQTc before and after exercise testing, as well as a slower rise per minute of heart rate during exercise testing (Table 6).

When these parameters were incorporated into multiple stepwise regression analyses, the main predictor for adverse events were QTc dispersion after exercise testing ($\beta = 0.319$; $p < 0.002$) and posterior wall thickness ($\beta = 0.262$; $p < 0.01$). For this model, statistical parameters included: $R = 0.419$; $R^2 = 0.179$; adjusted $R^2 = 0.156$, and standard error of the estimate = 0.3442.

Table 4. QTc interval dispersion in the examined groups during exercise testing

Dispersion	LVH (ms)	CG (ms)	P <
dQTc	59.5 ± 21.2	45.4 ± 5.9	0.001
dQTc-et	55.4 ± 18.9	32.6 ± 8.2	0.001
dQTcp	48.9 ± 27.0	29.8 ± 15.3	0.001
dQTcp-et	40.1 ± 18.6	27.2 ± 26.3	0.001
dTp-Tendc	56.3 ± 21.3	46.4 ± 14.6	0.01
dTp-Tendc-et	51.9 ± 18.7	39.2 ± 19.2	0.01

dQTc – QTc dispersion; dQTc-et –d QTc at the end of exercise testing; dQTcp – dispersion of rate-corrected interval form Q to the peak of T wave; d QTcp-et – dQTcp at the end of exercise testing; dTp-Tendc – dispersion of rate-corrected segment from the peak of T wave to the end of T wave; dTp-Tendc-et – dTp-Tendc at the end of exercise testing.

Table 5. Cardiovascular and cerebrovascular adverse events in patients

Adverse events	Number of patients	Description
Myocardial infarction	3	–
Cerebrovascular insult	5	2 patients died 1 patient - myocardial infarction
Angina pectoris	6	2 patients – coronary revascularization (one of them died during operation)
Sudden death	1	–

Table 6. Parameters in patients with and without adverse events

Parameters	Patients without adverse events	Patients with adverse events	P <
Septum thickness	13.4 ± 2.2	15.4 ± 3.1	0.05
Posterior wall thickness	11.6 ± 1.1	12.5 ± 1.3	0.05
LVM	329.6 ± 68.6	380.7 ± 87.8	0.05
LVMI	167.9 ± 29.3	194.0 ± 38.7	0.05
R of BPM	12.4 ± 6.7	8.8 ± 3.4	0.01
dQTc	56.6 ± 20.2	74.5 ± 20.3	0.01
dQTc-et	53.3 ± 19.3	65.8 ± 13.4	0.05
Duration of QRS	0.084 ± 0.008	0.089 ± 0.008	0.05

LVM – left ventricular mass; LVMI – left ventricular mass index; R of BMP – rise of bits per minute during exercise testing; dQTc – QTc dispersion; dQTc-et – QTc dispersion at the end of exercise testing.

After exercise testing, QTc dispersion greater than 60 ms was found in 9 (60.0%) patients with adverse events (15 patients) and 21 (28.0%) patients without adverse events (75 patients; $p < 0.02$). There were no healthy controls with QTc dispersion greater than 60 ms after exercise testing.

Discussion

Mangoni *et al.* examined the effects of age, gender, body mass index, smoking status, and blood pressure upon QT interval and QTc dispersion in healthy subjects. A multivariate regression analysis showed that age and the body mass index independently predicted QT interval, while gender was a weak predictor of QTd. They concluded that the increase in QT interval associated with ageing and the body mass index might be secondary to cardiac hypertrophy and potential prolongation of myocardial action (10). In our study, this was not confirmed. We found a greater body mass index in hypertensive patients but there was no correlation between the body mass index and QTc interval or dispersion.

In the study of Shouten *et al.,* 3091 patients, 40-65 years of age and with no evident cardiovascular disease, were followed for 28 years. A QTc interval greater than 420 ms was associated with allover mortality in both genders (11). The difference in the outcome was evident after 15 years of follow-up. The relative risk for QTc interval > 440 ms was 1.8. In our study, QTc and QTcp intervals were greater in hypertensive patients, and, during the five-year follow-up, the QTc interval did not show a predictive value of adverse cardiovascular and cerebrovascular events.

Perikiomaki *et al*. found greater QTc dispersion, especially QTcp dispersion, in patients with arterial hypertension and left ventricular hypertrophy (6). Similar results were found by Bugre *et al.* (7). In our study, all examined parameters of QTc dispersion were greater in hypertensive patients than in healthy subjects. Furthermore, patients with adverse events had greater QTc dispersion than patients with no adverse events during the five-year follow-up.

Yoshimura *et al.* examined QTc and QTcp dispersion in hypertensive patients and healthy subjects during exercise testing. They found a decreasing QT dispersion in patients without left ventricular hypertrophy and an unchanged QT dispersion in patients with left ventricular hypertrophy during exercise testing (8). QTc dispersion was increased in patients with left ventricular hypertrophy, while QTcp dispersion was decreased in patients without left ventricular hypertrophy and increased in patients with left ventricular hypertrophy. They found a positive correlation between QTcp and the left ventricular mass index and maximal blood pressure at the end of exercise testing. In our study, QTc dispersion was unchanged in patients with left ventricular hypertrophy and decreased in healthy controls. There is no prospective study which could explain the significance of the dynamics of QTc dispersion during exercise testing. We found a greater QTc dispersion after exercise testing in patients with bad outcome, especially if QTc dispersion was equal to or greater than 60 ms.

Oikarinen *et al.* measured QRS duration and QT intervals from the baseline 12-lead electrocardiograms as part of the Losartan Intervention For Endpoint Reduction in Hypertension Study, which included hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy randomized to either losartan-based or atenolol-based treatment of lower blood pressure (12). After a mean follow-up of 4.9±0.8 years, among a total of 5,429 patients, there were 417 deaths from all causes, including 214 cardiovascular deaths. In the multivariate Cox analyses including all electrocardiographic measures and adjustments for other risk factors, as well as treatment strategy, only QRS duration and maximum rate-adjusted QTp interval remained significant independent predictors of cardiovascular and all-cause mortality. We found QRS duration and QTc dispersion to be greater before and after exercise testing in patients with bad prognosis. In multivariate stepwise regression analyses, the independent predictor of bad outcome was QTc dispersion after exercise testing. There was a significant difference between these two studies concerning the definition of left ventricular hypertrophy: in our study, left ventricular hypertrophy was defined by echocardiography, while in Oikarinen's study it was defined by electrocardiography.

Moleiro *et al.* examined the behavior of QT interval during exercise testing and recovery in 42 healthy people performing computer analyses of QT interval. During exercise and recovery, the behavior of QT intervals permitted categorization into two groups. In the first group (about 2/3), the uncorrected QT interval showed a biphasic pattern consisting of a gradual decrease during incremental exercise followed by a gradual increase during recovery. In contrast, QTc interval had a triphasic pattern resulting from a slight increase during the early phase of exercise, a gradual decrease at the highest rates, and the final increase during recovery as the rate slowed down to control value. In the second group (about 1/3), the behavior was considered paradoxical since the uncorrected QT interval displayed a triphasic pattern, whereas the QTc interval yielded a tetraphasic pattern, which is due to the fact that both showed a second decrease during recovery while the rate was decreasing (13).

Lauer *et al.* examined the relationship between heart rate during exercise testing and its predictive value in asymptomatic men in the Framingham study. There were 1,575 subjects involved in the study. Of them, 327 men did not reach 85% of the maximal heart rate during exercise testing. The follow-up was 7.7 years during which time 55 deaths occurred. A greater risk for unstable angina, myocardial infarction, coronary death, and coronary revascularization was observed in patients who did not reach 85% of the maximal heart rate and patients who had slower rise of heart rate during exercise testing (14). The results in our study are similar. When this parameter was incorporated into multiple regression analyses together with the left ventricular mass, the left ventricular mass index, wall thickness, and QTc dispersion lost their independent predictive value.

Conclusion

Cardiovascular and cerebrovascular adverse events were more frequent among those hypertensive patients with left ventricular hypertrophy who showed higher values for left ventricular mass, left ventricular mass

index, wall thickness, and QTc dispersion before and after exercise testing, as well as a wider QRS complex and slower rise of heart rate during exercise testing. Independent predictors of bad outcome were greater posterior wall thickness and QTc dispersion after exercise testing. Intervals and their dispersion as 'Q wave–peak of T wave' and 'peak of T wave–end of T wave' were less useful than QTc interval and QTc dispersion according to the prognosis.

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PETOGODIŠNJA PROGNOSTIČKA VREDNOST QTc INTERVALA I DISPERZIJE QTc INTERVALA KOD HIPERTENZIVNIH PACIJENATA SA HIPERTROFIJOM MIOKARDA LEVE KOMORE

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Kratak sadržaj: *Cilj je bio ispitati QTc interval, QTcp interval (interval od Q zupca do vrha T talasa), Tp-Tendc interval (interval od vrha T talasa do kraja T talasa) i njihove disperzije u odnosu na petogodišnju prognozu ovih intervala kod parijenata sa esencijalnom arterijskom hipertrenzijom i hipertrofijom leve komore.*
U studiji je ispitano 90 pacijenata (56 muškaraca i 34 žene), prosečne starosti 55,2 ± 8,3 godine, sa esencijalnom arterijskom hipertenzijom i hipertrofijom miokarda leve komore. U kontrolnoj grupi bilo je 35 zdravih osoba (20 muškaraca i 15 žena), prosečne starosti 54,5 ± 7,1 godina. Prosečan indeks mase leve komore bio je 171.9 ± 32.4 g/m^2 kod hipertenzivnih pacijenata i 102,4 ± 13,3 g/m^2 kod zdravih osoba. QTc interval i QTc disperzija (interval od Q zupca do vrha T talasa) su bili veći u grupi sa hipertrofijom leve komore u odnosu na zdrave ispitanike ($p < 0,01$) na bazalnom elektrokardiogramu. U toku testa opterećenja QTc interval se skratio u hipertenzivnoj grupi ($p < 0,001$) i ostao nepromenjen u grupi zdravih ispitanika. QTc disperzija ($p < 0,001$) i QTcp disperzija ($p < 0,001$) su bile veće u hipertenzivnoj grupi pre i nakon testa fizičkim opterećenjem. Neželjeni kardiovaskularni i cerebrovaskularni događaji su se desili kod 15 (16,7%) bolesnika u toku petogodišnjeg praćenja.
Neželjeni kardiovaskularni i cerebrovaskularni događaji, kod hipertenzivnih pacijenata sa hipertrofijom miokarda leve komore, su bili češći kod pacijenata sa većom masom leve komore, većim indeksom mase leve komore, debljim zidovima leve komore, većom QTc disperzijom pre i nakon testa fizičkim opterećenjem, širim QRS kompleksom i manjim porastom frekvence srca tokom testa fizičkim opterećenjem. Nezavisni prognostički markeri loše prognoze bili su veća debljina zadnjeg zida i veća QTc disperzija nakon testa fizičkim opterećenjem. Intervali i njihove disperzije, kao što su Q zubac – vrh T talasa i vrh T talasa – kraj T talasa, bili su manje značajni od QTc intervala i QTc disperzije u prognostičkom smislu.

Ključne reči: *Arterijska hipertenzija, hipertrofija leve komore, QTc interval, QTc disperzija, prognoza*