Influence of the left ventricular types on QT intervals in hypertensive patients

Juraj Kunisek, Luka Zaputovic[1], Zlatko Cubranic[1], Leon Kunisek[2], Marta Zuvic Butorac[3], Ksenija Lukin-Eskinja[4], Rade Karlavaris[4]

Thalassotherapia Crikvenica, Special Hospital for Medical Rehabilitation; Crikvenica-*Croatia*
[1]Clinical Hospital Center Rijeka, Department of Internal Medicine, Division of Cardiology; Rijeka-*Croatia*
[2]Clinical Hospital Center; Rijeka-*Croatia*
[3]University of Rijeka, Faculty of Engineering; Rijeka-*Croatia*
[4]Thalassotherapia Opatija, Special Hospital for Rehabilitation of Cardiac, Lung and Rheumatic Diseases; Opatija-*Croatia*

ABSTRACT

Objective: To investigate the possible electrophysiological background of the greater excitability of concentric and eccentric left ventricular hypertrophy types in relation to the asymmetric type.

Methods: 187 patients with essential hypertension, without ishaemic heart disease were divided into three groups with regard to left ventricule type: concentric (relative wall thickness >0.42, interventricular septum/left ventricular posterior wall ≤1.3), eccentric (left ventricular diameter in systoles >32, relative wall thickness <0.42), asymmetric left ventricular hypertrophy (interventricular septum/left ventricular posterior wall >1.3), and three subgroups: mild (interventricular septum or left ventricular posterior wall 11-12 mm), moderate (interventricular septum or left ventricular posterior wall 13-14 mm) and severe left ventricular hypertrophy (interventricular septum or left ventricular posterior wall ≥15 mm). In all patients QT intervals, QT dispersion, left ventricular mass index and ventricular arrhythmias were measured. An upper normal limit for QT corrected interval: 450/460 ms for men/women; for QT dispersion: 70 ms.

Results: The QT corrected interval and QT dispersion were increased in severe concentric and eccentric left ventricular hypertrophy (443 and 480 ms for QT corrected; 53 and 45 ms for QT dispersion, respectively), not significantly. QT dispersion in men with severe left ventricular hypertrophy was significantly enlarged (67.5 vs. 30 ms, p=0.047). QT interval was significantly longer in patients with complex ventricular arrhythmias (p=0.037).

Conclusion: No significant association of QT intervals or QT dispersion with the degree/type of left ventricular hypertrophy was found. QT corrected interval and QT dispersion tend to increase proportionally to the left ventricular mass only in the concentric and eccentric type.

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Key words: hypertension, left ventricular hypertrophy, QT interval, QT dispersion

Introduction

Marked left ventricular hypertrophy (LVH) is associated with potentially arrhythmogenic ventricular repolarization abnormalities and may generate conditions for QT interval (QTi) prolongation and increase QT dispersion (QTd) (1, 2). Prolongation of QT corrected (QTc) interval and QTd are risk markers for malignant ventricular arrhythmias and sudden cardiac death (3, 4). QT prolongation and dispersion are indicators for abnormalities in ventricular repolarization. This could suggest the presence of functional reentrant proarrhythmic circuits. Increased hyperpolarization-activated cyclic nucleotide-gated channel activity in hypertrophied myocytes prolongs the repolarization of the ventricular action potential and thereby may increase the arrhythmogenic potential (5). Defined as the difference between the longest and shortest QTi measured in any lead of the 12-lead electrocardiogram, QTd reflects the inhomogeneity in ventricular repolarization. Both parameters include also depolarisation. Increased QTd has been shown to correlate positively to complex ventricular arrhythmias in many clinical conditions (3, 6). QTd and QTi correlate with the left ventricular mass index (LVMI) determined echocardiographically in a group of selected patients with essential hypertension (7, 8). Normal QTd values vary extensively from 10 to 71 ms. QTd is higher in cardiac patients in comparison to normal subjects. The probability is that only explicitly abnormal values (i.e., those ≥100 ms) outside error margins may potentially have a practical value, suggesting a markedly abnormal repolarization (9). Scarce data was pub-

Address for Correspondence: Dr. Juraj Kunisek, Thalassotherapia Crikvenica, Special Hospital for Medical Rehabilitation, Gajevo setaliste 21, 51260 Crikvenica-*Croatia*
Phone: +385 51 407 844 E-mail: juraj_kunisek@net.hr
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lished regarding QTc interval prolongation/QTd and complex ventricular arrhythmias in hypertensive patients with LVH (10, 11), but which type of LVH has the greatest influence has been understudied (especially for the asymmetric type). The aim of this study was to investigate which type of LVH, considering at the same time the degree of LVH, induces the greatest QTi prolongation and QTd with a consequent proarrhythmic effect.

Methods

We performed an observational retrospective study. In a period of 5.5 years at the outpatient cardiology department suspected LVH on electrocardiography was observed in 1606 hypertensive patients. 1414 were excluded from the study for not satisfying the strict inclusion criteria (one of those under). Patients with congestive heart failure, atrial fibrillation, known coronary disease (history of angina pectoris at rest or at exercise testing, previous myocardial infarction according to documents or confirmed by echocardiograhy, and percutaneous coronary interventions), heart surgery, valvular diseases and other cardiac diseases (hypertrophic obstructive cardiomyopathy and previous myocarditis) were excluded. Patients with diabetes mellitus, alcoholics (exclusion was based on their medical history, clinical status and laboratory findings), patients with mental disorders, those overusing non-antihypertensive drugs, patients with malignant or accelerated hypertension and those that had suffered a stroke in the previous six months were also excluded. Patients with cancer, abnormal electrolytes, anemia, cardiopulmonary diseases (chronic lung diseases, sleep apnea), serum creatinine >140 μmol/L and abnormal thyroid function, those taking medication that can increase QTc (antiarrhythmics; antibiotics: macrolides, quinolones; some antipsychotics and antidepressants) were also ruled out (12). Echocardiography confirmed the diagnosis of LVH in the remaining 194 patients. After exclusion of 7 patients taking amiodarone, remaining 187 (82 men and 105 women, aged from 43 to 72 years) were included in the study. LVH was defined as LVMI greater than 132 g/m^2 for men and greater than 109 g/m^2 for women (moderately and severely abnormal) (13). Included were only patients who had essential hypertension and LVH. Hypertensive patients were those with blood pressure ≥140/90 mm Hg, measured three or more times by mercury sphygmomanometer, according to the guidelines of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (14). Blood pressure and heart rate were measured in office, and the mean arterial and pulse pressure were calculated. Upon previous patient's informed consent and the approval of the School of Medicine Ethical Committee, medication was discontinued in all subjects for 48 hours prior to ECG exercise testing and Holter monitoring. Alcohol intake was prohibited during the same period. Patients were advised to contact the principal investigator by phone or in person in the event any symptoms should appear.

Patients were divided into three main groups with regard to LVH type: concentric [relative wall thickness (RWT) ≥0.42 and interventricular septum/left ventricular posterior wall IVS/LVPW ≤1.3], eccentric (left ventricular diameter in systoles >32 mm and RWT <0.42) and asymmetric (IVS/LVPW >1.3), similar as in an earlier study (15) (and modified for asymmetric type). RWT was measured at end-diastole as the ratio of twice the thickness of LVPW/LVIDd left ventricular internal diastolic diameter, (LVIDd) (16). Each group was divided into subgroups according to the degree of LVH: mild (IVS or LVPW 11-12 mm), moderate (IVS or LVPW 13-14 mm) and severe (IVS or LVPW ≥15 mm).

Echocardiographic measurements ("M-mode", two-dimensional and Doppler echocardiography) were performed and interpreted by three cardiologists working independently, with no knowledge of the study aim, compliant with the recommendations of the American Society of Echocardiography (17). LVMI was calculated with the Devereux and Reichek's formulae (18).

In all patients a standard 12-lead ECG was performed after washout period for QTi measurements. ECG criteria to determine LVH according to Sokolow-Lyon and LV strain criterion were applied (19). ECG interpretation was performed manually and by a one qualified operator (cardiologist) who measured QTi in all 12 leads (and in 3 QRS complexes) with an accuracy of 20 ms (20), followed by the assessment of mean QTi values. The QRS complex onset point was defined as the beginning of the QTi, and the T-wave endpoint as the QTi end. In the presence of U waves, QTi was measured to the nadir of the curve between the T and U waves. The measurements of the T wave variants were also performed according previously described methods (9). QTi was adjusted for heart rate using the Bazett's square root correction formula: $QTc=QT/\sqrt{RR}$. QTd was defined as the difference between the shortest and the longest QTi in different leads (9). Lengths of up to 450 ms for men and up to 460 ms for women were considered normal QTc values (21), and for QTd up to 70 ms. All ECGs were obtained and QT intervals were measured in the morning.

Finally, the examined variables were left ventricular mass (LVM), left ventricular mass index, left ventricular geometry, LVH degree, ventricular arrhythmias (VA) prevalence (according to Lown's score), QTi and QTd. The type and duration of antihypertensive and anti-arrhythmic therapy received by the patients before entering the study were recorded for the analysis of possible effects on the outcome. The indications for anti-arrhythmic drugs were ventricular and supraventricular arrhythmias.

Statistical analysis

The collected data were statistically evaluated using data analysis software system STATISTICA, version 7.1. StatSoft, Inc. (2005), www.statsoft.com. The data were normally distributed (distribution checked for normality by Shapiro-Wilks test) and therefore presented by means and standard deviation or with 95% confidence interval. Categorical data were described with frequencies. Comparisons of numerical data were made using parametric ANOVA tests (one-way ANOVA for between-group comparisons and factorial ANOVA for between-group and

between-categories factors analysis). Results of nonparametric correlation (numerical by ordinal categories) were presented by Spearman rank correlation coefficient. The frequencies were analyzed by Yates corrected Pearson's chi-square test or Fisher exact test, where suitable. The level of statistical significance was set at 0.05 in all analyses.

Results

Clinical characteristics of the patients are shown in Table 1.

Prior to the study, all the patients were using two or more drugs (Table 2).

There was no difference in the treatment duration between the three groups (p=0.858), or in the type of applied medication (Table 2). Antihypertensives were evenly distributed within groups with particular types of LVH (Pearson χ^2 test, p=0.287). There was no difference in the frequencies of applied anti-arrhythmics between groups or subgroups (Fischer test, p=0.347 for propafenone in 20 patients; p=0.615 for verapamil in 8 patients; and p=0.469 for metil-digoxin in 12 patients. Only two patients were treated with mexiletin. There was no difference between type and degree of LVH in drug concentrations (doses) (analysis of variance, p=0.440 and 0.120 for propafenone; p=0.180 and 0.244 for verapamil; all patients were treated with the same dose of metil-digoxin (0.1 mg once a day). Two patients were taking combination of propafenon and digoxin, one patient was taking combination of verapamil and digoxin. Results were similar for beta-blockers in the frequencies of applied beta-blockers (Fisher's test for atenolol p=0.069, for carvedilol p=0.469 and for bisoprolol p=0.328), and in drug concentrations (analysis of variance according to the type of LVH for atenolol p=0.291, for carvedilol p=0.430 and for bisoprolol p=0.347; analysis of variance according to the degree of LVH for atenolol p=0.049, for carvedilol 0.055 and for bisoprolol p=0.280). Only one patient was treated with sotalol (half life 12 hours).

LVMI differed significantly with regard to the degree of left ventricular hypertrophy (it increased), presenting a statistically significant difference in all correlation comparisons. LVMI also differed significantly with regard to LVH type. Patients with eccentric LVH had a statistically significantly higher LVMI than those with concentric LVH, while patients with asymmetric LVH presented no significant difference in relation to the concentric and eccentric type (Table 3).

The average QT and QTc intervals for the entire group of patients had borderline values. The average QTd remained within normal values (Table 4). The analysis of variance demonstrated that the length of QTi and QTc interval did not differ with respect to type and degree of LVH. However, the analysis by

Table 1. Clinical characteristics of patients, with pressures

Number, total 187	**M 82 (43.8%) F 105 (56.2%)**
Parameter	**Mean value±SD**
Age / year	66±6
BMI / kgm^2	27.3±3.3
Elevated cholesterol (>5 mmol/L) / %	80.4
Elev. triglycerides (>1.7 mmol/L) / %	70.4
Elevated urea (>8 mmol/L) / %	67.4
Elev. creatinine (>140 µmol/L) / %	4.9
Smokers / %	18.8
Physically inactive / %	78.8
Duration of hypertension / year	16±4
Systolic blood pressure /mm Hg	176±15
Diastolic blood pressure /mm Hg	102±10
Mean arterial pressure /mm Hg	130±13
Pulse pressure /mm Hg	78±18
Frequency beats/min	76±4

BMI - body mass index

Table 2. Antihypertensive therapy (and anti-arrhythmics) applied in the examined population

Medication	**LVH type (n pts.)**				
	Concentric (n=91)	**Eccentric (n=46)**	**Asymmetric (n=50)**	**Total (n=187)**	***P***
ACE inhibitors or ARBs	67 (74%)	32 (70%)	42 (84%)	141 (75%)	0.52
Calcium antagonists	75 (82%)	36 (78%)	36 (72%)	147 (79%)	0.53
Beta blockers	46 (51%)	25 (54%)	29 (58%)	100 (53%)	0.74
Diuretics	41(45%)	23 (50%)	23 (46%)	87 (47%)	0.66
Anti-arrhythmics	17 (19%)	12 (26%)	8 (16%)	37 (20%)	0.37

ACE - angiotensin converting enzyme; ARBs - angiotensin receptor blockers; LVH - left ventricular hypertrophy

Table 3. Left ventricular mass index in patients with regard to the type and degree of left ventricular hypertrophy

LVH degree	**LVH type (LVMI g/m^2)**				
	Concentric (n=91)	**Eccentric (n=46)**	**Asymmetric (n=50)**	**Total (n=187)**	***P***
Mild (n=65)	145.18±12.53	164.49±22.35	145.29±18.21	150.41±17.92	0.001
Moderate (n=104)	172.35±26.27	206.18±25.43	163.33±26.06	179.57±30.12	
Severe (n=18)	204.18±44.63	214.75±0.11	204.97±30.92	207.22±36.43	
Total	165.82±23.46	181.42±37.41	170.27±14.59	173.25±27.18	

LVH - left ventricular hypertrophy; LVMI - left ventricular mass index
P=0.011 for eccentric versus concentric type

Table 4. Electrocardiographyc data (QT interval, QTc interval and QT dispersion)

Parameter	**Mean. v.±SD**	**Range**
QTi / ms	380.6±47.3	296-460
QTc / ms	425.0±34.4	255-496
QTd / ms	34.5±19.1	0-130

gender showed that the QTc interval in men with severe concentric and eccentric LVH was increased, but not significantly (p=0.081) (Fig. 1). Additionally, in the male group a simple regression analysis showed positive correlation between QTc interval and degree of LVH (Spearman rank r=0.26, p=0.031).

For the whole group of patients, QTd did not differ with regard to type and degree of LVH, although the analysis by gender again suggested that QTd values were significantly increased (p=0.047) in men with severe concentric and eccentric LVH (Fig. 2).

QTi was significantly longer (p=0.037) in patients with complex VA (Lown III-V) than in those with simple VA (Lown I-II) (Fig. 3). The QTc interval was also longer in patients with complex VA, but the difference was not statistically significant.

Discussion

In our study, the average QTc interval for the entire group of patients was in the normal limits. Considering the entire patient group there was no significant association of QTi or QTc interval with the degree and type of LVH. However, in men with severe concentric and eccentric LVH the QTc interval values were higher, although statistically not significantly. As a result, the importance of asymmetric pattern was not confirmed. Regarding the degree of LVH, a positive correlation with QTc length, near to statistical significance, was observed only in men (p=0.081). The difference between genders can be explained by echocardiographic measurements that confirmed anthropological differences (not shown in tables). Men had larger cardiac cavities (left ventricular internal diastolic diameter/left ventricular internal systolic diameter: 54.3/38.2 mm vs. 49.7/33.8 mm in women; p<0.001) and left ventricular mass (357.09 g/m^2 vs. 303.34 g/m^2, p<0.001).

LVMI differed significantly (it increased) with regard to left ventricular hypertrophy degree (a measure of left ventricular geometry), suggesting appropriate stratification of patients. The significantly highest LVMI was found in patients with the eccentric LVH type. The applied classification of left ventricular geometric patterns was not performed in compliance with guidelines (13) because there was no reference to the asymmetric type of LVH. Moreover, IVS/LVPW ratio was not used in calculations. The classification used (considered in the literature before the guidelines were published) is to our judgment more accurate in differentiating the three LVH types.

Failure to attain statistical significance for QTc is possibly due to the small number of patients with severe degree of LVH. Such patients are difficult to find in larger number because in urban areas they are recognized and treated rather early before severe LVH has managed to develop. Moreover, it should also be taken into account that these patients, except for hypertensive cardiomyopathy, should have no other diseases (12). Consequently, not many articles investigating this correlation

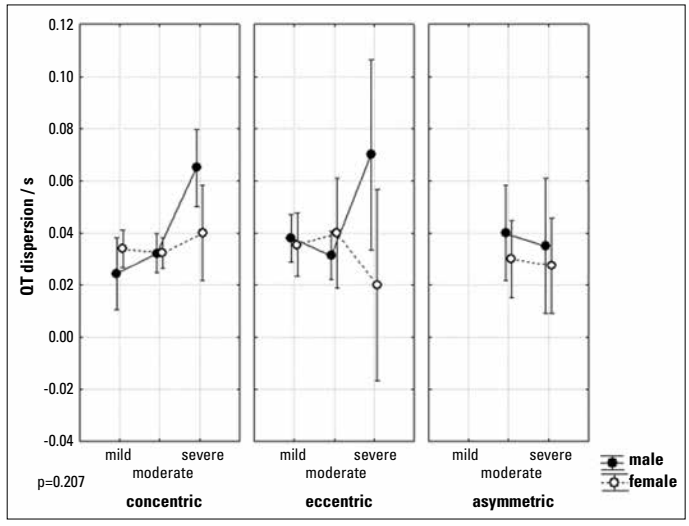

Figure 2. QT dispersion in patients according to the type and degree of left ventricular hypertrophy. Presented are mean values with 95% confidence intervals

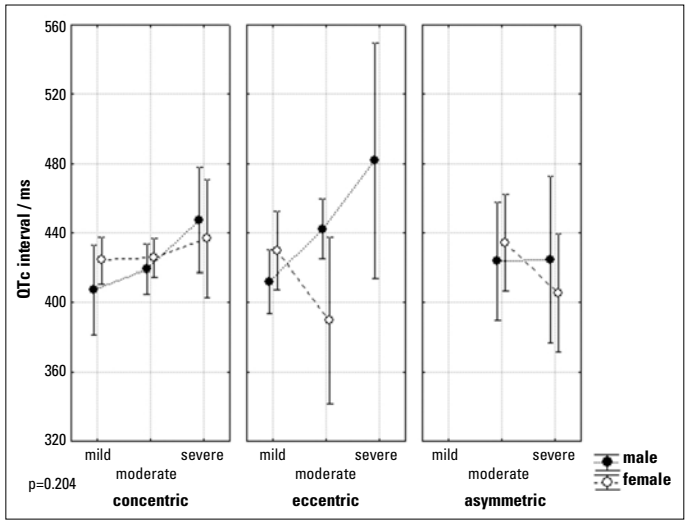

Figure 1. QTc interval in patients according to the type and degree of left ventricular hypertrophy. Presented are mean values with 95% confidence intervals

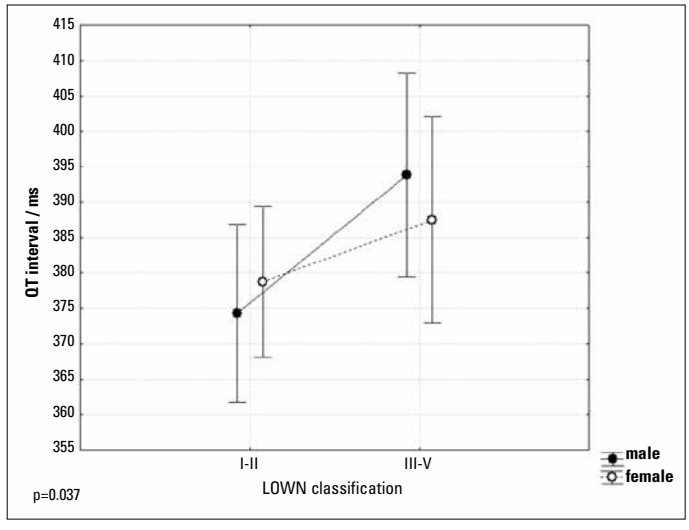

Figure 3. QT interval in patients with simple (n=112) and complex VA (N=75). Presented are mean values with 95% confidence intervals

have been published in the literature (1, 8). In some (22) QTc interval in patients with ventricular septal hypertrophy was significantly longer than in the normal group. Researchers in (1) also obtained the correlation between QTi and LVMI lengths. There was no significant difference between QTd values with regard to the LVH degree and type in our study. However, QTd in men had again higher values in severe concentric and eccentric LVH. Such flawed results were certainly influenced by accurate measurements performed manually, which were not beyond reproach. Manual assessment of the T-wave end is extremely unreliable. Regrettably, the existing automated methods have not proven to be advantageous. The main source of mistakes for readers and computers are the low amplitudes of T waves and the border between the T and U wave or the P wave (9) so some new methods are under investigation (23, 24). Increased QTc dispersion was associated with LVH, especially with its concentric variant in some studies (25, 26). In the LIFE study both concentric and eccentric LVH were associated with prolonged QTi and increased QTd (1). In another study (27) QTd >60 ms and QTi >440 ms were associated with greater probability of LVH.

In our patients, the QTi length correlates with the VA incidence. QTc interval was also longer in patients having complex arrhythmias but the difference in relation to simple arrhythmias was not significant.

Several factors may influence the increased left ventricular ectopic activity in patients with LVH. Increased stimulation of hypertrophic myocytes, fibrosis in hypertrophic myocardium that leads to electrophysiological inhomogeneity, distention of certain myocytes, increased oxygen requirement of the myocardium, damaged membrane porosity for various ions, and increased sympathetic activity are possible pathophysiological factors for the increased incidence of ventricular arrhythmias (28, 29).

In subjects without heart disease, during a 15-20 years follow-up period, prospective studies found significant correlation between prolonged QTc interval and increased risk for coronary events (30), cardiovascular mortality and all-cause mortality (mean follow-up of 4.9 years) (31), as well as for sudden cardiac death or cardiovascular death (32). Patients with a prolonged QTc (>or=450 milliseconds in women and >or=440 milliseconds in men) had a nearly 2-fold increase in risks of coronary events and cardiovascular death (33). Increased QTd in patients with LVH and higher incidence of ventricular premature beats or complex ventricular arrhythmias was also described by other authors (10). Both men and women with hypertension and left ventricular hypertrophy had significantly lower HR and higher values of QT interval dispersion compared with hypertensives with normal left ventricular geometry (30). Özdemir et al. (34) studying 80 patients with concentric LVH have found strong correlation between increased QTd and the incidence of ventricular arrhythmias. Other authors (35) obtained the highest influence of asymetric LVH on QTd, but without correlation between ventricular premature beats and QTd, neither between ventricular premature beats and LVMI.

Medications were discontinued 48 hours prior to ergometric examination and Holter monitoring with the intention to avoid the effects of treatment duration and type of antihypertensive and anti-arrhythmic drugs [applied in patients with complex ventricular arrhythmias (Lown III-V)] on the outcome. We observed whether these parameters differed between the examined groups. The obtained result was negative. A longer suspension of treatment could have threatened the patient or lead to reduced cooperation. Withdrawal of beta-blockers could have affected the increase of cardiac rate and rhythm control; however, all three study groups were under identical conditions. None of the antiarrhythmic medicines has half-life longer than 48 hours (digoxin 36-48 hours, verapamil 2.8-7.4, atenolol 6-7, carvedilol 7-10, bisoprolol 10-12, mexiletine 9-11 and propafenon 2-10 hours).

According to some investigations patients with increased QTd should be treated with angiotensin receptor blockers and nebivolol (36, 37). Telmisartan-based treatment induced an increased vagal activity without significant change of sympathetic activity and a reduction of QT dispersion and QTc dispersion (36).

Study limitations

It was impossible to rule out coronary heart disease completely. Coronary angiography is not indicated in all asymptomatic patients and myocardial stress-scintigraphy is too expensive and time-consuming. Modified methods from other similar studies were therefore applied. A 48-hour antihypertensive drug withdrawal period is relatively short. We studied the duration of treatment and the type of antihypertensive and anti-arrhythmic drugs and found no differences between the examined groups.

Our small subgroup of patients with severe degree of LVH was analyzed with appropriate statistical methods. An inadvertent inclusion of a patient with hypertrophic cardiomyopathy (HCM) and hypertension had probably no effect on the results considering the very small prevalence of this disease.

Conclusion

There was no significant association of QTi or QTc interval with the degree and type of LVH. Analyses by gender showed that men with severe concentric and eccentric LVH had higher values of QTc interval and QTd than those with asymmetric LVH (not significant). Considering only the degree of LVH, a positive and significant correlation for the QTc interval length was found again only in men. QTi was significantly longer in patients with complex ventricular arrhythmias (Lown III-V) than in those with simple VA (Lown I-II). QTc interval had the same tendency. Eccentric LVH showed maximal values of all studied parameters only in men. These findings could suggest the greater arrhythmogenecity of the concentric and eccentric in relation to the asymmetric LVH type.

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