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TRADITIONAL AND NEW ELECTROCARDIOGRAPHIC PREDICTORS OF NON-SUSTAINED POLYMORPHIC VENTRICULAR TACHYCARDIA CAUSED BY DRUG-INDUCED LONG QT SYNDROME

L.V.Kalatsei, V.A.Snezhitskiy

Grodno State Medical University, Belarus, Grodno, 80 Gorkogo str.

Aim. To identify electrocardiographic (ECG) predictors of drug-induced non-sustained polymorphic ventricular tachycardia (PVT).

Material and methods. The study included 110 patients with ischemic heart disease and /or arterial hypertension and cardiac arrhythmias who were taking class III antiarrhythmic drugs (amiodarone or sotalol). According to the presence or absence of the drug-induced QT interval prolongation (Bazett) (greater than 450 ms in men and greater than 470 ms in women), the patients were divided into 2 groups: «LQTS» (n=64) and «Non LQTS» (n=46). According to the presence or absence of non-sustained PVT, patients with drug-induced LQTS were additionally divided into the «PVT» (n=17) and «Non PVT» (n=47) groups. All patients underwent clinical, laboratory and instrumental examinations, which included taking anamnesis, physical examination, echocardiography, Holter monitoring, general clinical laboratory examinations, 12-lead ECG recording before and while taking antiarrhythmic drugs.

Results. In the «LQTS» group of patients, PVT was significantly more common than in the «non LQTS» group ($p=0.017$). When analyzing the baseline ECG parameters recorded before the initiation of antiarrhythmic therapy, no significant differences were found between the groups except for a greater QT interval dispersion in the group of patients with LQTS and non-sustained PVT compared with patients without LQTS ($p=0.03$). While receiving antiarrhythmic therapy, patients with LQTS and non-sustained PVT had a longer duration of the QT interval ($p<0.05$), as well as the duration of the corrected QT and JT intervals ($p<0.001$) compared with group of patients without LQTS and subgroup without non-sustained PVT. The values of the parameters of the balance of depolarization and repolarization of the ventricular myocardium (iCEB and iCEBc) were significantly higher in patients with LQTS and non-sustained PVT ($p<0.001$). Based on the results of the analysis of contingency tables, the most effective predictor of non-sustained PVT was an iCEBc value ≥5.81 (OR=7.294, 95% CI [4,245-11,532]). According to the results of one-way ROC-analysis, the iCEBc value ≥5.81 demonstrated high sensitivity (94.1%) and specificity (84.9%), as well as a fairly high area under the ROC-curve (0.901).

Conclusions. Our results indicate that the value of the corrected index of the cardioelectrophysiological balance ≥5.81 can be used in the prediction of non-sustained PVT in patients with QT interval prolongation induced by amiodarone and sotalol in addition to the existing ECG parameters.

Key words*:* QT interval; drug-induced long QT syndrome; antiarrhythmic drugs; non-sustained polymorphic ventricular tachycardia; electrocardiography; repolarization; QT interval dispersion; QRS fragmentation; corrected index of cardioelectrophysiological balance

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Corresponding author: Liudmila Kalatsei, E-mail: lkolotsey@mail.ru

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L.V.Kalatsei - ORCID ID 0000-0001-5211-709X, V.A. Snezhitskiy - ORCID ID 0000-0002-1706-1243

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Long QT syndrome (LQTS) is a potentially life-threatening channelopathy associated with QT interval prolongation on a 12-lead ECG, syncope, and a high risk of sudden cardiac death (SCD) due to the development of polymorphic ventricular tachycardia (PVT), including torsades de pointes [1-3]. According to its etiology, LQTS can be both congenital and acquired. The most common cause of acquired LQTS is the use of drugs that prolong the QT interval, especially antiarrhythmic drugs of IA and III class according to the M. Vaughan-Williams classification [4-6].

Risk stratification of SCD in drug-induced LQTS remains challenging. To date, there is no comprehensive, easily measured and widely available indicator that would have a sufficiently high ability to predict life-threatening ventricular arrhythmias in this category of patients.

QT interval prolongation on a 12-lead ECG, regardless of the reasons that caused it, is a generally accepted

risk factor and an independent predictor of life-threatening arrhythmias and SCD [5, 7]. However, QT interval duration characterizes only the total duration of depolarization and repolarization of the ventricular myocardium, without considering the peculiarities of the balance of these two components and the degree of their heterogeneity, and significantly depends on the heart rate.

Currently, it is proposed to use several other electrocardiographic markers in SCD risk stratification [7-13]. Thus, the duration and heterogeneity of the repolarization process, in addition to the QT interval duration, are characterized by such indicators as QT interval dispersion, JT interval dispersion, T wave alternation, T peak - T end interval duration and its dispersion, as well as the T peak-T end/QT ratio. Among the indicators reflecting the features of myocardial depolarization are the QRS complex duration and fragmentation, as well as the spatial QRS-T angle [7, 11].

A separate group consists of electrocardiographic parameters that characterize the balance between ventricular depolarization and repolarization, which include the index of cardioelectrophysiological balance (iCEB), defined as the duration of the QT interval divided by the duration of the QRS complex, and the corrected index of cardioelectrophysiological balance (iCEBc), which is calculated using the corrected QT interval (QTc) duration [8].

Table 1.

Clinical characteristics of the patient groups

Parameters	«LQTS» group (n=64)	«Non LQTS» group (n=46)	p 1/2
Male sex, n (%)	27 (42.1%)	27 (58.7%)	0.544
Age, years (M±SD)	57.2±9.4	56.1±9.2	0.687
BMI, kg/m^2 (M±SD)	29.8±4.6	29.5±4.8	0.739
Smoking, n (%)	13 (20.3%)	11 (23.9%)	0.482
SCD family history, n (%)	6 (9.3%)	4 (8.7%)	0.952
Hypertension			
No hypertension, n (%)	8 (12.5%)	4 (8.7%)	0.729
Stage 1, n (%)	10 (15.6%)	14 (30.4%)	0.176
Stage 2, n (%)	44 (68.8%)	26 (56.5%)	0.271
Stage 3, n (%)	2 (3.1%)	2 (4.3%)	0.907
CAD			
No CAD, n (%)	9 (14.1%)	8 (17.4%)	0.652
Coronary artery atherosclerosis, n (%)	8 (14.5%)	3 (7.9%)	0.686
Vasospastic angina	6 (10.9%)	6 (15.8%)	0.733
CCS Grade 1, n (%)	14 (25.4%)	13 (34.2%)	0,559
CCS Grade 2, n (%)	26 (47.3%)	14 (36.8%)	0,359
CCS Grade 3, n (%)	3 (5.4%)	2 (4.3%)	0,977
CCS Grade 4, n (%)	-	-	-
Myocardial infarction history, n (%)	10 (15.6%)	7 (15.2%)	0.972
HF NYHA Class 0, n (%)	3 (5.4%)	5 (10.9%)	0.566
HF NYHA Class I, n (%)	35 (54.7%)	20 (43.5%)	0.314
HF NYHA Class II, n (%)	21 (32.8%)	17 (37%)	0.706
HF NYHA Class III, n (%)	5 (7.8%)	4 (8.7%)	0.776
HF NYHA Class IV, n (%)	-	-	-
Paroxysmal AF, n (%) (%)	18 (28.1%)	10 (21.7%)	0.563
Persistent AF, n (%)	19 (29.7%)	17 (36.9%)	0.508
Frequent PVCs, n (%)	21 (32.8%)	15 (32.6%)	0.987
Non-sustained monomorphic VT history, n (%)	19 (29.7%)	16 (34.8%)	0.642
Frequent supraventricular extrasystoles, n (%)	5 (7.8%)	4 (8.7%)	0.776
Obesity, n (%)			
Diabetes mellitus, n (%)	26 (40.6%)	19 (41.3%)	0.949
Thyroid pathology, n (%)	6 (10.9%)	2 (4.3%)	0.644

Note: LQTS - long QT interval syndrome; BMI - body mass index; SCD - sudden cardiac death; CAD - coronary heart disease; CCS - Canadian Cardiovascular Society; MI - myocardial infarction; HF - heart failure; NYHA - New York Heart Association; AF - atrial fibrillation, VT - ventricular tachycardia, PVC - premature ventricular contraction.

The index of cardioelectrophysiological balance can serve as an equivalent of the cardiac wavelength λ, mathematically expressed as the product of the effective refractory period (ERP) and the conduction velocity. Studies conducted on preparations of rabbit left ventricular myocardium demonstrated that QT interval is associated with ERP duration; and changes in the duration of the QRS complex coincide with changes in the conduction velocity [8]. Results obtained in studies on animal models suggested that iCEB and iCEBc can act as potential predictors of ventricular arrhythmias, including those caused by drugs, and, consequently, drug-induced PVT [8, 9].

The aim of this study is to evaluate the values of traditionally used and new ECG markers characterizing the depolarization and repolarization of the ventricular myocardium in patients taking class III antiarrhythmic drugs according to the classification of M. Vaughan-Williams, with and without drug-induced LQTS and to identify electrocardiographic predictors of drug-induced non-sustained PVT.

MATERIAL AND METHODS

To achieve this goal, 110 patients were examined based on the Grodno Regional Clinical Cardiology Center, mainly with coronary artery disease (CAD), hypertension and cardiac arrhythmias. Patients with atrial

fibrillation (AF) were referred to the hospital for electrical cardioversion or to select antiarrhythmic therapy. Patients with ventricular arrhythmias were hospitalized to clarify the diagnosis and determine strategies for further treatment. All patients received class III antiarrhythmic drugs (amiodarone or sotalol).

Patients were divided into two groups depending on the presence or absence of the QT interval prolongation in response to antiarrhythmic therapy. The first group («LQTS») consisted of 64 patients, among them 37 (57.9%) women and 27 (42.1%) men, mean age 57.1±9.4 years, who had drug-induced prolongation of QTc interval (Bazett) (greater than 450 ms in men and 470 ms in women) while taking class III antiarrhythmic drugs. The second group («non-LQTS») included 46 patients, among them 19 (41.3%) women and 27 (58.7%) men, mean age - 56.1 ± 9.2 years, without drug-induced prolongation of QTc interval.

Table 2.

Drug therapy characteristics

	«LQTS» group (n=64)	«Non LQTS» group (n=46)	p
Beta-blockers, n (%)	8 (12.5%)	4 (8.7%)	0.729
ACE inhibitors, n (%)	39 (61%)	33 (71.7%)	0.327
Angiotensin II receptor blockers	40 (62.5%)	25 (54.3%)	0.463
Statins, n (%)	16 (25%)	10 (21.7%)	0.769
Antiplatelet agents, n (%)	58 (90.6%)	40 (87%)	0.738
Anticoagulants, n (%)	25 (39%)	16 (34.8%)	0.701
Amiodarone, n (%)	37 (57.8%)	26 (56.5%)	0.909
Sotalol, n (%)	42 (65.6%)	32 (69.6%)	0.719
Furosemide, n (%)	22 (34.4%)	14 (30.4%)	0.724
Torasemide, n (%)	6 (10.9%)	1 (2.2%)	0.507
Indapamide, n (%)	4 (6.3%)	1 (2.2%)	0.708
Hydrochlorothiazide, n (%)	9 (14.1%)	5 (10.9%)	0.772

Note: ACE - angiotensin converting enzyme

Table 3.

Comparative analysis of echocardiographic parameters of patients (Me (25%; 75%))

Parameters	«LQTS with PVT» group (n=17)	«LQTS without PVT» group (n=47)	«Non LQTS» group (n=46)
LA antero-posterior diameter, mm	38.6 [36; 40)	39.7 [37; 43)	40.1 [38; 42)
LV end-diastolic diameter, mm	52.8 [48; 56)	53.5 [49; 55)	53.6 [50; 56)
LV end-systolic diameter, mm	35.7 [32; 37)	35.8 (33; 38)	36.4 (33; 38)
LVEF (M-mode), %	60.8 [58; 67)	59.0 (56; 65)	60.0 (56; 65)

Note: LA - left atrium; LV - left ventricle; LVEF - left ventricular ejection fraction; PVT - polymorhic ventricular tachycardia.

Table 4.

Electrocardiographic parameters before antiarrhythmic therapy initiation (Me (25%; 75%))

Parameters	«LQTS with PVT» group (n=17)	«LQTS without PVT» group (n=47)	«Non LQTS» group (n=46)
Mean heart rate, b.p.m.	64.3 (60; 67)	62.1 (56; 69)	62.6 (56; 70)
Repolarization markers			
QT interval duration, ms	389.2 (370; 407)	399.9 (377; 427)	390.5 (370; 406)
QTc interval duration (Bazett), ms	405.1 (395; 417)	404.1 (392; 418)	396.1 (384; 408)
QT interval dispersion, ms	38.5 (30; 44)	32.9 (20; 43)	33.4 (30; 40)
JTc interval duration (Bazett), ms	319.1 (309; 334)*	314.1 (303; 330)	307.9 (293; 322)
JT interval dispersion, ms	32.1 (25; 40)	28.5 (18; 38)	29.5 (24; 37)
T peak - T end duration, ms	75 (67; 83)	77.4 (68; 86)	78.4 (67; 89)
T peak - T end dispersion, ms	21,5 (20; 22)	18.6 (10; 20)	19.2 (10; 28)
T peak - T end / QT ratio	0.19 (0,18; 0,21)	0.19 (0,18; 0,21)	0.20 (0,18; 0,22)
Depolarization markers			
QRS duration, ms	85.3 (80; 90)	90 (80; 100)	88.2 (80; 90)
QRS fragmentation, n (%)	4 (23,5%)	5 (10%)	3 (6%)
Repolarization and depolarization balance markers			
Index of CB (QT/QRS)	4.80 (4.44; 5.25)	4.61 (4,22; 4.89)	4,58 (4.33; 4.85)
Corrected index of CB (QT/QRS)	4.80 (4.17; 5.16)	4.54 (4.11; 4.89)	4,52 (4.23; 4.81)

Note: Here and below b.p.m. - beats per minute; QTc - corrected QT interval; JTc - corrected JT interval; CB - cardioelectrophysiological balance; * - $p<0.05$ value compared to the «Non LQTS» group.

Exclusion criteria from the study were: QTc interval greater than 450 ms in men and 470 ms in women before antiarrhythmic therapy initiation; genotyped congenital LQTS; Schwartz score more than 3 points; taking any drugs other than Class III antiarrhythmic drugs with a confirmed or probable risk of torsades de pointes, listed in the «CredibleMeds» database [14]; recent acute myocardial infarction, coronary artery bypass grafting, or coronary angioplasty (less than 3 months before enrollment in the study); left ventricular hypertrophy (Sokolov-Lyon index> 35mm); an increase in the duration of the QRS complex ≥100 ms; permanent and long-term persistent form of AF; 24 hours after restoration of sinus rhythm in patients with AF; disorders of atrioventricular conduction; uncorrected pathology of the endocrine system (hyperthyroidism, hypothyroidism, hyperparathyroidism); nervous system pathology (subarachnoid hemorrhage, trauma, infections, tumors); decompensated diabetes mellitus; active inflammatory process of any localization of infectious, autoimmune or other etiology.

Depending on the presence or absence of non-sustained PVT according to Holter monitoring while taking antiarrhythmic therapy, patients with drug-induced LQTS were additionally divided into 2 groups: «LQTS with PVT» (17 patients) and «LQTS without PVT» (47 patients). The average duration of an episode of non-sustained PVT was 7.3±4.1 seconds, the average number of episodes per day was 2.7±2.3, and the average heart rate was 245±32 beats per minute.

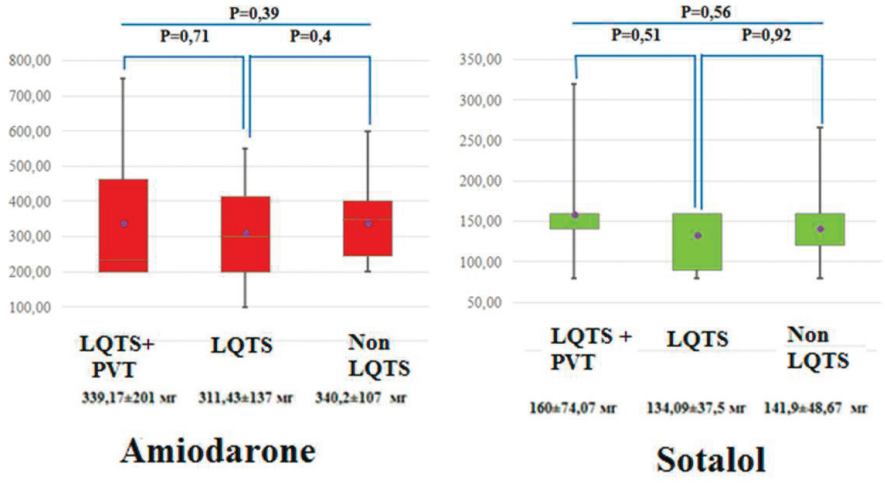

Figure 1. Tukey's range plots of average daily dosages of amiodarone (left) and sotalol (right) in patient groups.

All patients underwent clinical, laboratory and instrumental studies, including history taking, physical examinations, 12-lead ECG recording, Holter monitoring, and general clinical laboratory studies.

An electrocardiographic study was performed in patients initially - before the antiarrhythmic therapy initiation, and then during the administration of antiarrhythmic therapy. Before the initial ECG study, all antiarrhythmic drugs were withdrawn in patients, including beta-blockers, considering their half-life periods. We took into account

Table 5.

Electrocardiographic parameters while taking antiarrhythmic therapy (Me (25%; 75%))

Parameters	«LQTS with PVT» group (n=17)	«LQTS without PVT» group (n=47)	«Non LQTS» group (n=46)
Mean heart rate, b.p.m.	65.1 (60; 70)	64.5 (58; 69)	60.6 (55; 65)
Repolarization markers			
QT interval duration, ms	492.1 (457; 537)#*	461.7 (448; 482)*	416.7 (396; 433)
QTc interval duration (Bazett), ms	509.7 (479; 542)#*	475.6 (458; 489)*	412.6 (397; 429)
QT interval dispersion, ms	83.6 (59; 98)*	70.1 (59; 82)*	60.6 (50; 71)
JTc interval duration (Bazett), ms	427.9 (395; 462)#*	389.2 (373; 402)*	323.2 (307; 338)
JT interval dispersion, ms	77.2 (52; 90)*	65.7 (54; 75)*	56.7 (46; 66)
T peak-T end duration, ms	131.4 (113;147)*	123.5 (113; 137)*	97.9 (90; 107)
T peak-T end dispersion, ms	35.3 (30; 40)*	31.8 (20; 40)*	20 (10; 27.5)
T peak-T end/QT ratio	0.26 (0.25;0.29)*	0.27 (0.25; 0.29)*	0.23 (0.22; 0.25)
Depolarization markers			
QRS duration, ms	82.3 (80; 90)	86.2 (80; 90)	85.4 (80; 90)
QRS fragmentation, n (%)	7 (41.2%)#*	7 (14%)	3 (6%)
Repolarization and depolarization balance markers			
Index of CB (QT/QRS)	6.26 (5.88; 6,86)#*	5.55 (5.22; 5.67)*	4.85 (4.44; 5.20)
Corrected index of CB (QT/QRS)	6.24 (5.99; 6.55)#*	5.57 (5.13; 5.85)*	4.67 (4.33; 4.93)

Note: # - p<0.05 value compared to the "LQTS without PVT" group, * - p<0.05 value compared to the "non LQTS" group.

the ECG markers recorded before the development of PVT («LQTS with PVT» group) or at the first signs of drug-induced LQTS («LQTS without PVT» group), or indicators registered on the sixth day of taking antiarrhythmic therapy («non-LQTS» group).

An ECG study was performed using a 12-channel digital electrocardiograph for recording and analyzing ECG at rest «Intecard-3» («Cardian», Belarus). ECGs were standardized at a normal speed of 50 millimeters per second with an amplitude of 10 mm/mV. Determination of the duration of the waves and intervals was carried out manually using 12 standard ECG leads, with a record of at least five complete cardiac cycles. The definition of the end of the T wave was carried out using the slope method, at the intersection of the baseline with a tangent drawn from the top of the T wave along its descending part. Calculation of the QTc interval was carried out according to the Bazett formula. A QTc interval was considered prolonged if it was greater than 450 ms in men and greater than 470 ms in women.

Indicators of electrical instability of the ventricular myocardium (QT interval dispersion, JT interval dispersion, QRS complex fragmentation) were determined automatically using a computer program for the diagnosis and prediction of life-threatening cardiac arrhythmias «Intecard-7.3» («Cardian», Belarus). The analysis was performed on 10-second ECG recordings in 12 leads, followed by manual correction of automatic measurements.

Statistical analysis was performed using the STATISTICA 10.0 software package with a preliminary check for normal distribution using a distribution histogram. Quantitative data, the distribution of which was not normal, were given as a median, 25% and 75% quartiles. Since most of the quantitative characteristics did not obey the normal distribution law, non-parametric methods were used for comparison. The Mann-Whitney test was used to assess differences in quantitative traits between two independent groups. At a significance level of p less than 0.05, it was believed that the studied indicator in the compared groups had statistically significant differences. Correlation analysis between dichotomous values was carried out using the Russell-Rao similarity index, and between dichotomous and interval values using a point-biserial correlation coefficient. To compare the diagnostic value of indicators that showed statistically significant differences between groups, ROC curves of sensitivity and specificity were constructed.

The study was performed in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion in the study.

RESULTS

The clinical characteristics of the patient groups are presented in Table 1, 2. The main cardiovascular disease in patients with LQTS was CAD, which was detected in 55 (85.9%) patients. Of these, heart failure (HF) symptoms with I-III functional class (FC) were diagnosed in 47

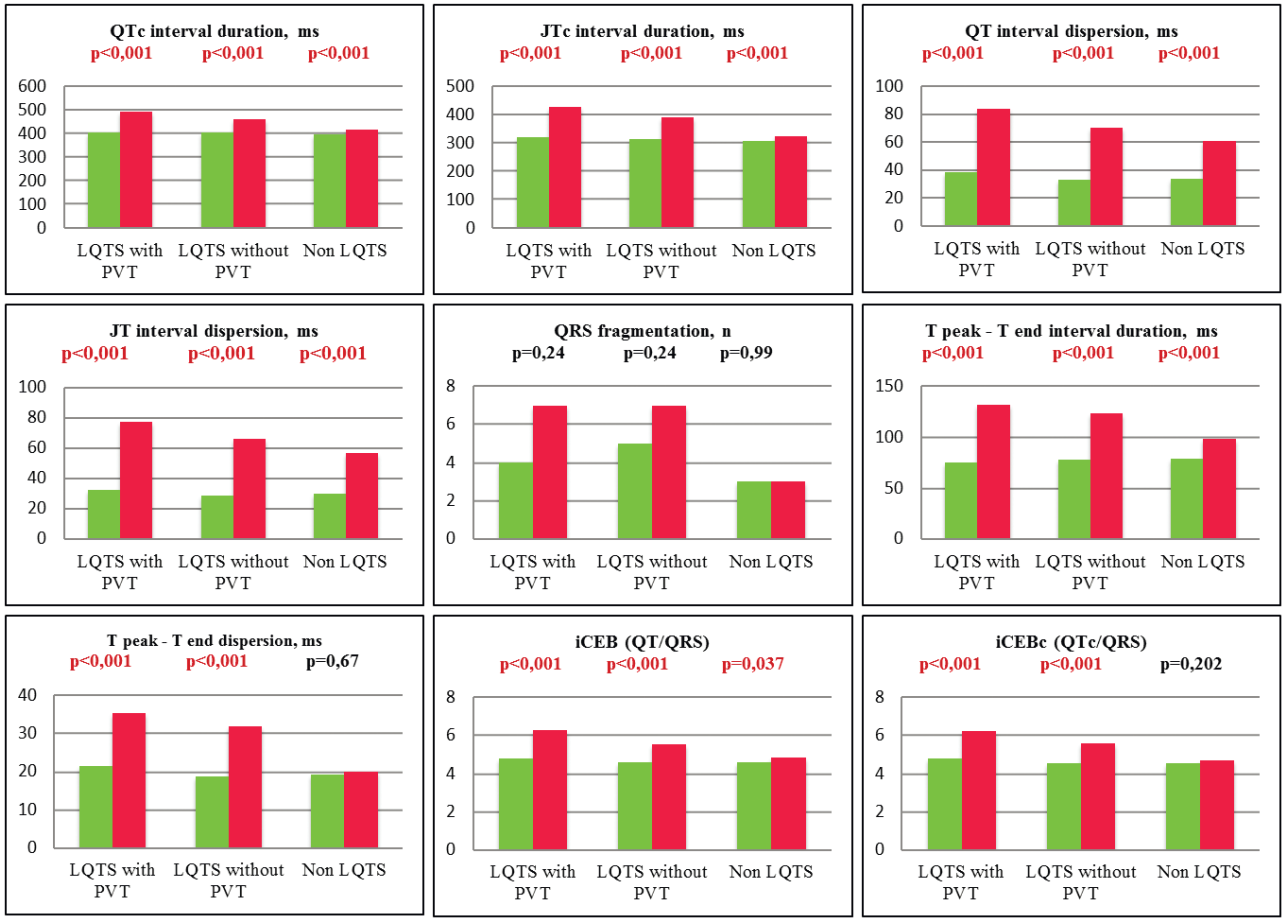

Figure 2. Histograms of the ratio of electrocardiographic parameters of patients of the studied groups before prescription (green columns) and during administration (red columns) of Class III antiarrhythmic drugs.

(85.4%) patients, most of them with II FC - 26 (47.2%). Ten (15.6%) patients had a history of myocardial infarction. Most patients (87.5%) had Stage I-III arterial hypertension, with normal blood pressure levels against the background of optimal drug therapy. Paroxysmal AF was detected in 18 patients (28.1%), persistent AF - in 19 patients (29.7%), paroxysms of non-sustained monomorphic VT were noted in 19 (29.7%) patients.

Concomitant pathology was mainly represented by obesity of I-III degree in 26 (40.6%) patients, chronic gastritis in 40 (62.5%) patients and the lower extremity varicose vein disease in 21 (32.8%) patients. Diabetes mellitus was detected in 6 (10.9%) patients, thyroid pathology (nodular goiter) was detected in 8 (12.5%) patients, and all of them were euthyroid. Among other diseases registered there were chronic pyelonephritis - 17 (26.5%), chronic obstructive pulmonary disease - 11 (17.2%), urolithiasis - 6 (10.9%), gout and psoriasis - 2 patients each (3.1%).

Patients received optimal medical therapy for CAD, hypertension, and HF. Fourty (62.5%) patients were taking angiotensin-converting enzyme inhibitors, 16 (25%) - angiotensin II receptor blockers, beta-blockers - 39 (61%), statins - 58 (90.6%), oral anticoagulants - 37 (57, 8%) and antiplatelet agents - 25 (39%).

All patients of the studied groups received Class III antiarrhythmic therapy: amiodarone or sotalol. In the «LQTS» group, amiodarone was prescribed to 42 (65.6%) patients, and sotalol - to 22 (34.4%) patients, which did not significantly differ from the «Non LQTS» group, where 32 patients (69.6%) received amiodarone and 14 (30.4%) - sotalol (p=0.724).

Patients with and without non-sustained PVT induced by LQTS did not have significant differences in gender, age, underlying disease, HF FC, history of myocardial infarction, and non-cardiac comorbidities at the time of inclusion in the study. It should be noted that before the initiation of antiarrhythmic therapy paroxysms of non-sustained monomorphic VT was recorded in 5 (29.4%) patients in the «LQTS with PVT» group, and in 14 (29.8%) patients in the «LQTS without PVT» group (p=0.986). There were no paroxysms of non-sustained PVT before the initiation of antiarrhythmic therapy in all patients included in the study. In the «LQTS with PVT» group, amiodarone was prescribed to 10 (58.8%) patients, and sotalol - to 7 (41.2%) patients, which did not significantly differ from the «LQTS without PVT», in which 32 patients (68.1%) received amiodarone (p=0.573), and 15 (31.9%) received sotalol (p=0.563).

A comparative analysis of echocardiographic parameters in the studied groups of patients is presented in Table 3. Patients of all three groups had no differences in the dimension of the left ventricle and left atrium and were comparable in terms of left ventricle ejection fraction (p>0.05).

While analyzing ECG parameters recorded before the start of antiarrhythmic therapy (Table 4), we found no statistically significant differences between all three groups of patients, except for a longer duration of the corrected JT (JTc) interval in patients with LQTS and non-sustained PVT compared with patients without LQTS (p=0.03). The duration of QTc in the studied patients was comparable and stayed within normal limits.

The total duration of Class III antiarrhythmic therapy in patients with LQTS was 3.40±1.35 days, which significantly differed from patients without LQTS (7.82±1.6 days, p<0.001), which can be explained by the abolition of the QT prolonging drug when registering QT interval prolongation on the ECG. In patients with LQTS and non-sustained PVT, there was a tendency to take class III antiarrhythmic drugs for a shorter period (2.88±1.22 days vs. 3.58±1.36 days in patients without PVT, p=0.053). The average daily doses of antiarrhythmic drugs used in all groups of patients were comparable and stayed within normal ranges (Fig. 1).

The values of electrocardiographic parameters recorded in patients of the studied groups while taking Class III antiarrhythmic drugs are presented in table 5.

Table 6.

Results of correlation analysis

Parameters	NSPVT	
	R	p
History and clinical values		
Female sex	0.254	<0.001
Diuretic intake	0.423	<0.001
History of monomorphic VT	0.320	<0.001
Electrocardiographic parameters while taking antiarrhythmic therapy		
QT interval duration, ms	0.444	<0.001
Corrected QT interval duration (Bazett), ms	0.528	<0.001
Corrected JT interval duration (Bazett), ms	0.554	<0.001
QT interval dispersion, ms	0.344	<0.001
JT interval dispersion, ms	0.326	0.004
QRS fragmentation, n (%)	0.423	<0.001
Index of CB (QT/QRS)	0.524	<0.001
Corrected index of CB (QT/QRS)	0.529	<0.001

Note: NSPVT - non-sustained polymorphic ventricular tachycardia.

The statistical analysis showed significant differences in the values of most electrocardiographic parameters in patients with and without drug-induced LQTS. When comparing the markers characterizing ventricular myocardium repolarization, it was found that patients with non-sustained PVT had a significantly longer QT interval duration (p=0.03), as well as QTc and JTc intervals (p<0.001) compared with patients of «LQTS with PVT» group. Attention was drawn to the trend towards greater values of the QT and JT intervals dispersion, however, not reaching the criteria of statistical significance. In patients with LQTS and PVT, there was also a trend towards greater values of the T peak-T end interval dispersion compared with patients without non-sustained PVT (p=0.06), however, the values of T peak-T end duration and T peak-T end/QT ratio were comparable.

The values of ventricular myocardial depolarization markers in the studied patients also had no significant difference, except for

QRS fragmentation, which was significantly more common in patients with LQTS and non-sustained PVT compared with the «LQTS without PVT» group (41.2% vs. 14.9%, p=0.04). The values of the balance of depolarization and repolarization of the ventricular myocardium (iCEB and iCEBc) were significantly higher in patients with LQTS and non-sustained PVT compared with the subgroup with the «LQTS without PVT» group (p<0.001).

We carried out a comparative analysis of the values of electrocardiographic parameters separately for subgroups of patients taking amiodarone and sotalol. Patients with non-sustained PVT who were taking amiodarone had a significantly longer duration of QTc and JTc intervals, T peak-T end interval, as well as iCEB and iCEBc (p<0.001) compared with other groups of patients. Differences in the values of the QRS complex duration, QRS fragmentation and T peak - T end dispersion were not significant. In patients with PVT taking sotalol, unidirectional changes with the «amiodarone» subgroup were found. At the same time, the studied ECG parameters in the «amiodarone» and «sotalol» subgroups had no significant differences. Therefore, further statistical analysis was performed in pooled groups.

When conducting a comparative analysis of the values of electrocardiographic parameters in patients of the studied groups before and after antiarrhythmic therapy initiation, significant differences were observed in the growth dynamics of most of them (Fig. 2). When conducting a correlation analysis, a statistically significant correlation was revealed between the development of non-sustained PVT and several electrocardiographic, clinical, and anamnestic parameters (Table 6). It should be noted that the highest correlation coefficient was observed for the corrected JT interval (R=0.554). Positive correlations were established between the development of non-sustained PVT and QRS fragmentation (R=0.423), iCEB (R=0.524), and iCEBc (R=0.529) values, as well as concomitant diuretic use (R=0.423).

When conducting a one-way ROC analysis, threshold values of electrocardiographic parameters associated with the development of non-sustained PVT were identified (Table 7).

Corrected JT interval ≥388.3 ms demonstrated the largest area under the ROC-curve (0.908) of all studied electrocardiographic parameters. QT interval dispersion ≥87 ms had the highest specificity (93%), but the lowest sensitivity (47.1%). iCEBc ≥5.81 showed the highest sensitivity (94.1%), as well as rather a high specificity (84.9%) and area under the ROC curve (0.901).

The prognostic significance of the studied electrocardiographic parameters about the development of drug-induced PVT is presented in Table 8. According to the contingency tables analysis, an iCEBc value greater than 5.81 was the most informative predictor of non-sustained PVT (odds ratio (OR) 7.294, 95% confidence interval (CI) [4,245-11,532]).

DISCUSSION

In recent years, many studies have been devoted to SCD risk stratification in drug-induced LQTS [10, 12, 17-20]. Prolongation of the corrected QT interval is most often associated with the risk of drug-induced non-sustained PVT. Moreover, QTc prolongation is one of the diagnostic criteria of congenital LQTS [11]. QTc prolongation greater than 500 ms is associated with the risk of syncope and SCD in patients with both congenital and acquired LQTS [12-13]. In the study by A.Sauer et al. drug-induced QTc interval prolongation was an independent predictor of SCD (OR 5.53; 95% CI [3.20-9.57]) [13]. Increased QT interval dispersion has been associated with SCD in large population-based studies [15, 16], but their direct association with the non-sustained PVT development has not been confirmed. In a recent study by A. Friedman et al., it was found that the QT interval dispersion when taking therapeutic doses of amiodarone was significantly higher than when taking sotalol and dofetilide (p=0.006), but it was not associated with an increased risk of torsades de pointes [17]. The results of our study demonstrated statistically significant differences in the values of QT and QTc intervals duration in the studied groups of patients, however, there were no significant differences in the values of QT interval dispersion.

The relationship of QRS fragmentation with torsades de pointes was studied by Haraoka K et al. [18]. There were no differences in the presence of structural heart disease between groups of patients with and without torsades de pointes, but QRS fragmentation was more common in the group of patients with torsades de pointes (81% vs. 21%) (p<0, 01) [18]. These data are consistent with our results (41.2% in the «LQTS with PVT» group and 14.9% in the «LQTS without PVT» group, p=0.04).

JT interval duration as a marker of ventricular repolarization is important, first, in patients with intraventricular conduction abnormalities (such as bundle branch block or a high percentage of ventricular pacing). QT interval duration in this category of patients is increased due to

Table 7.

Results of one-way ROC analysis

Parameters	TV	AUC	CI 95%	Se, %	Sp, %	PPV, %	NPV, %
Corrected QT interval duration, ms	474.7	0.884	[0.77-0.99]	82.3	80.6	44.8	95.1
Corrected JT interval duration, ms	388.3	0.908	[0.81-1.0]	88.2	79.6	49.7	96.6
QT interval dispersion, ms	87	0.683	[0.53-0.83]	47.1	93	57.1	91.2
JT interval dispersion, ms	84	0.681	[0.53-0.83]	52.9	86	42.8	91.7
iCEB (QT/QRS)	5.75	0.889	[0.78-0.99]	88.2	87.1	57.7	97.6
iCEBc (QTc/QRS)	5.81	0.901	[0.80-1.0]	94.1	84.9	57.1	98.7

Note: TV - threshold value; AUC - area under the curve; CI - confidence interval; Se - sensitivity; Sp - specificity; PPV - positive predictive value; NPV - negative predictive value.

the widened QRS complexes and prolongation of depolarization, but it should not automatically classify them as a group with high arrhythmic risk [11].

In a study by Zulqarnain M et al., which included more than 8025 participants, the effect of QT and JT intervals duration on the overall mortality was investigated [19]. JT interval prolongation was associated with an increased risk of death to a greater extent (OR 4.75, 95% CI [1.86-12.11]) than QT interval prolongation (OR 1.50, 95% CI [1.03, 2.17]) [19]. In our study, the JTc interval duration greater than 388.3 ms had the largest area under the ROC curve (0.908) of all studied electrocardiographic parameters. This marker also demonstrated a high predictive ability about the development of non-sustained PVT (OR 3.567, 95% CI [2.404-5.295]).

Literature data on the prognostic significance of transmural dispersion of repolarization markers (T peak-T end interval duration and its dispersion) are quite contradictory. A meta-analysis of three studies that included 144 patients with drug-induced LQTS caused by antiarrhythmic drugs did not reveal statistically significant differences between the T peak-T end interval duration in patients with and without torsades de pointes (p=0.12) [20]. However, the T peak-T end/QT ratio was greater in patients with PVT (p<0.001) [20]. In another study, which included 143 patients with drug-induced QT interval prolongation and atrioventricular conduction disorders, on the contrary, there were significant intergroup differences in the QTc interval (p=0.02) and T peak-T end interval (p<0.001), but there were no differences in the T peak-T end/QT ratio (p=0.27) [21]. In our study, transmural dispersion of repolarization markers significantly differed between groups of patients with and without LQTS but did not demonstrate prognostic value in non-sustained PVT risk assessment.

Electrocardiographic indicators that characterize the balance between ventricular depolarization and repolarization (iCEB and iCEBc) seem promising for ventricular arrhythmias risk prediction. Several studies [8, 9, 22] have demonstrated the relationship between the heart wavelength λ, mathematically expressed as the product of ERP and conduction velocity, and life-threatening ventricular arrhythmias. Research by H. Liu et al. showed that QT interval is associated with ERP duration, and changes in the QRS complex duration coincide with changes in conduction velocity [8].

Liu H et al [8] also demonstrated that the administration of potassium channel blocker dofetilide leads to an increase in QT interval, T peak-T end and iCEB, causing PVT in rabbit heart wedge. Robyns T et al. [9] found that sotalol increased iCEB, while flecainide decreased iCEB in patients with paroxysmal supraventricular arrhythmias. In addition, in the same study, the authors compared iCEB values in 70 genotype-positive congenital LQTS patients with 65 genotype-negative family members. Their data demonstrated that iCEB and iCEBc were significantly greater in LQTS compared with genotype-negative family members.

Study by Ardahanli I et al reported a statistically significant increase in iCEB (p=0.013) and iCEBc (p=0.023) values in patients with COVID-19 infection taking hydroxychloroquine and azithromycin for 5 days, in absence of significant changes in QT and QTc intervals (p=0.22) [23]. Afsin A et al studied the effect of amiodarone intake on iCEB and iCEBc values in patients with paroxysmal AF compared with the control group and found that iCEB values in both groups were comparable (4.4±0.6 vs. 4.2±0.4; p>0.05), and iCEBc values had statistically significant differences (4.8±0.6 vs. 4.3±0.6; p=0.001) [24].

In our study, iCEB and iCEBc values and their growth were significantly greater in the «LQTS with PVT» group (p<0.001). Moreover, iCEBc value greater than 5.81 was the most informative predictor of the drug-induced PVT (OR 7.294, 95% CI [4,245-11,532]) of all the studied parameters. According to the results of one-way ROC analysis, iCEBc ≥5.81 showed the highest sensitivity (94.1%), as well as rather high specificity (84.9%) and area under the ROC curve (0.901).

Our study had some limitations. First, a relatively small sample of patients with drug-induced LQTS was studied, and only patients treated with Class III antiarrhythmic drugs (amiodarone and sotalol) were included. Secondly, QRS complex, QT interval, and T peak - T end interval duration may change due to left ventricular remodeling in HF, hypertension, and other concomitant diseases. These factors limited the direct assessment of the antiarrhythmic therapy effect. Also, the reliability of the obtained values of iCEB and iCEBc was not evaluated during the invasive electrophysiological study with the ERP measurement of calculation of the cardiac wavelength λ.

Table 8.

Prognostic significance of electrocardiographic parameters in relation to the development of non-sustained polymorphic ventricular tachycardia

Parameters	OR	95% CI
Corrected QT interval duration > 474,67 ms	4.444	2.647-7.461
Corrected JT interval duration > 376,67 ms	3.567	2.404-5.295
iCEBc (QTc/QRS) > 5,81	6.459	4.171-10.343
iCEB (QT/QRS) > 5,75	7.294	4.245-11.532
QT interval dispersion > 87 ms	4.706	2.609-10.210
JT interval dispersion > 76 ms	4.412	2.202-8.837

Note: OR - odds ratio; CI - confidence interval.

CONCLUSION

Patients with LQTS and non-sustained PVT had greater values of the corrected QT and JT intervals duration, QT and JT intervals dispersion, as well as the index of cardioelectrophysiological balance and the corrected index of cardioelectrophysiological balance compared with other groups of patients.

The most informative predictor of non-sustained PVT is the value of the corrected cardioelectrophysiological balance index ≥5.81 (OR 7.294, 95% CI [4.245-11.532]). According to the results of a one-way ROC analysis, the value of the corrected cardioelectrophysiological balance index ≥5.81 demonstrated high sen-

sitivity (94.1%) and specificity (84.9%), as well as a high area under the ROC curve (0.901).

According to our results, the cardioelectrophysiological balance index value ≥5.81 can be used to predict non-sustained PVT in patients with drug-induced LQTS induced by amiodarone and sotalol in addition to existing electrocardiographic parameters. Considering the small size of the study sample, the possibility of using this marker requires testing on a larger group of patients, considering ongoing pharmacological therapy and structural heart disease.

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