Review

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IMPORTANCE OF QTC INTERVAL DURATION IN PACING PARAMETERS OPTIMIZATION AND THERAPEUTIC MANAGEMENT OF THE PATIENTS WITH PERMANENT CARDIAC PACING

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Clinical importance of QT interval duration in patients with permanent pacemakers (PM) is discussed in the review. Physiological interpretation, methods of heart rate frequency normalization, changes under PM and role of pacing optimization parameters, reactions on medications in patients with spontaneous and stimulated rhythm, meaning for life quality and survivability of patients with permanent PM are considered.

KEY WORDS: cardiac pacing, electrocardiography, QT interval duration, QT interval dispersion

ЗНАЧЕННЯ ТРИВАЛОСТІ ІНТЕРВАЛУ QT В ОПТИМІЗАЦІЇ ПАРАМЕТРІВ СТИМУЛЯЦІЇ І ТЕРАПЕВТИЧНОМУ МЕНЕДЖМЕНТІ ПАЦІЄНТІВ З ПОСТІЙНОЮ ЕЛЕКТРОКАРДІОСТИМУЛЯЦІЄЮ

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В цьому огляді обговорюється клінічне значення тривалості інтервалу QT у пацієнтів з постійною електрокардіостимуляцією (ЕКС). Розглядається фізіологічна інтерпретація, методи нормування до частоти серцевих скорочень, зміни при ЕКС і роль в оптимізації параметрів ЕКС, реакції на медикаментозні препарати у пацієнтів зі спонтанним і стимульованим ритмом, значення для якості життя і виживаність пацієнтів з постійною ЕКС.

КЛЮЧОВІ СЛОВА: електрокардіостимуляція, електрокардіографія, тривалість інтервалу QT, дисперсія інтервалу QT

ЗНАЧЕНИЕ ПРОДОЛЖИТЕЛЬНОСТИ ИНТЕРВАЛА QT В ОПТИМИЗАЦИИ ПАРАМЕТРОВ СТИМУЛЯЦИИ И ТЕРАПЕВТИЧЕСКОМ МЕНЕДЖМЕНТЕ ПАЦИЕНТОВ С ПОСТОЯННОЙ ЭЛЕКТРОКАРДИОСТИМУЛЯЦИЕЙ

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В обзоре обсуждается клиническое значение продолжительности интервала QT у пациентов с постоянной электрокардиостимуляцией (ЭКС). Рассматриваются физиологическая интерпретация, методы нормирования на частоту сердечных сокращений, изменения при ЭКС и роль в оптимизации параметров ЭКС, реакции на медикаментозные препараты у пациентов со спонтанным и стимулированным ритмом, значение для качества жизни и выживаемости пациентов с постоянной ЭКС.

КЛЮЧЕВЫЕ СЛОВА: электрокардиостимуляция, электрокардиография, продолжительность интервала QT, дисперсия интервала QT

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INTRODUCTION

Permanent cardiac pacing (CP) is one of the leading methods of bradyarrhythmia and chronic heart failure (CHF) treatment [1]. It reliably improves the life quality of the patients and reduces mortality indices [1-2], though, it always demands concurrent medical therapy both about preexisting diseases and the states induced by CP.

Despite the fact that main approaches in the using of pharmacological agents in patients with pacemaker correspond to those outside the ECS [1-2], they have a number of features. Among other factors demanding individualization of medical therapy in patients with PM the output of QT interval duration and dispersion of QT interval (QTD) outside the limits of physiological range of meanings takes an important place.

The available literature data on QT interval duration and dispersion in the patients with implanted PM and their interconnection with the use of cardiac medications are summarized in the review.

NOTION OF DURATION AND METHODS OF QT INTERVAL NORMALIZING

The QT interval is the time interval of ECG starting from the beginning of the Q wave and ending when downward knee of the T wave return to the isolines [3]. It includes QRS complex (quick depolarization and initial repolarization of interventricular septum, walls of the right and left ventricles), ST segment (repolarization plato) and T wave (final repolarization), joining them into the notion of heart electric systole.

The most important physiological determinants of QT interval duration are sex (according to Hiroto I. et al. [4] data it is greater in women than in men in norm and comprises, consequently,- 413 ± 36 ms and 401 ± 35 ms), age (according to Moss A.J. and Robinson J.L. data [5] norms of corrected QT interval in accordance with regulation on Bazett formula comprise 1-15 years - <440 ms, adult men <430 ms and women - <450 ms), as well as heart rate frequency (HRF), the rise of which in 20 bits a min decreases QT duration in 40 ms in average.

Close dependence of QT interval duration from HRF has put the task of its normalization (QTc), first successful attempts of which were taken by Bazett H.C. and Fredericia L.S. just in 1920, who suggested practically simultaneously and independently from each other similar mathematical correlation for these purposes.

Simple Bazett H.C. formula QT=0,39*RR^½ was oriented for the calculation of appropriate interval for HRF. For corrected (independent from HRF) QT interval definition a modified formula QTc=QT/(RR)^1/2 [6] was suggested. Incorrectness under high and low HRF meanings was its failing. Fredericia L.S. suggested more accurate formula - QTf=QT/(RR^1/3)^1/2 [7]. Though, it can be used only under sinus rhythm, like Bazett H.C. formula.

Sagie A. et al. suggested linear formula for QT interval duration normalization in patients with atrial fibrillation (AF) - QTc=QT+0,154*(1000-RR) according to Framingham research results [8].

There are a number of other mathematical expressions for QTc definition: Hodges M. hyperbolic (QTc=QT+a*(1/RR-1)), parabolic ($QTc=QT/RR^a$), logarithmic (QTc=QT-a*ln(RR)), Nomogram modified logarithmic ($QTc=\ln(e^{qt}+a*(1-RR))$), Sarma J.S.M. exponential ($Tc=QT+a*(e^{-RR}-1/e)$) [9].

Comparative evaluation of five methods of normalization (Bazett H.C. simple and modified, Framingham, Frederica L.S. linear and Sarma J.S.M. exponential) in 21 healthy volunteers was conducted by Molnar J. et al. [10] under computer registration of electrocardiogram (ECG). The results demonstrated absence of meaningful differences in use of any mentioned formulas as well as their insufficient accuracy in HRF output outside the limits of physiological range. The main conclusion is optimality of modified Bazett H.C. formula for QTc interval duration definition under standard 12-channel ECG.

The problem of QT interval duration normalization in patients with PM first raised more than 30 years ago by Milne J.R. et al in 1981 [11]. They explained inaccuracy of Bazett H.C. formula in patients under increase of ventricular rate (VR) on the background of right ventricle (RV) stimulation by influence on QT interval duration not only by VR, but also by sympathetic tonus.

Chiladakis J. et al. conducted a series of studies [12-13] on optimal method of QT normalization definition to VR in patients with dual chamber PM. In work [12] they studied various methods of QT interval normalization

(Bazett H.C., Frederica L.S., Sagie A.-Framingham, Hodges M. and Nomogram formulas) on 123 patients with DDD PM in groups with lengthened and normal QT interval duration under VR 60, 80 and 100 bits per min. Bazett H.C. formula showed optimal variability of QTc dependence of QT interval duration from VR in both groups, Hodges and Nomogram formula demonstrated the lowest QTc level of dependence from cardiac cycle duration. Methods of QT normalization in patients with medically determined lengthening of QT interval duration on the background of double-chamber stimulation were studied in [13]. Hodges M. and Nomogram formulas preferred to Bazett H.C. formula under VR meanings lower than 60 bits a min on the background of PM.

Common unambiguous solution about optimal method of QT interval duration normalization in patients with permanent PM is absent till now. Probably the task will be solved by QT-TENDENCY multicenter randomized study began with this purpose in March 2012 [14].

QT interval dispersion (QTD) is the change of QT interval duration from one cycle to another in one ECG lead or in various leads during the same cardiac cycle. Increase of QTD reflects the homogeneity of the process of ventricles myocardium repolarization and is one of the most important predictors of electrical instability of myocardium and increasing of ventricular arrhythmia development and sudden cardiac death (SCD) risk [15].

PROGNOSTIC SIGNIFICANCE OF QT INTERVAL DURATION IN PATIENTS WITH PACEMAKERS

Lengthening of QTc interval duration in patients both with permanent PM and without it is an important predictor of serious rhythm violations which can lead to SCD.

Solti F. et al. [16] recorded episodes of ventricular tachycardia in 11 from 12 patients with right ventricular stimulation and QT interval lengthening of stimulated complexes, which they connected with the response on early ventricular impetus under refractory period shortening.

In Prochnau D. et al. study [17] proarrhythmogenic role of QTc lengthening was demonstrated in 127 patients with severe refractory to CHF medication therapy and lengthening of QRS complex > 130 ms after biventricular (BiV) implantation of PM for cardioresynchronization therapy (CRT). In the group with registered episodes of ventricular tachyarrhythmia during 24 months after the set implantation (42 episodes in 35 patients) QTc interval duration was greater (505 ± 55 ms) than in the group of patients without arrhythmia episodes (486 ± 44 ms).

In 2013 г. Tayeh O. et al. [18] published the identical results having established a great QTc interval duration in patients with ventricular arrhythmias episodes against patients without arrhythmic events (527 ± 63.29 against 496.95 ± 45.2 ms), which proved prognostic signifycance of QTc interval in patients with CRT.

INFLUENCE OF PERMANENT PM ON QT AND QTC INTERVALS DURATION

Influence of permanent CP on QT interval duration was first described by Milne J.R. et al in 1981 [11] on 19 patients with constant right ventricular (RiV) stimulation and increase of ventricular rate (VR) after implantation not less than 50 bits a min. Metering of QTc interval duration of spontaneous and stimulated rhythm was done in all the patients which demonstrated shortening of the prolonged in rest duration of QTc after physical loading trial. The authors of the study paid attention that QTc interval duration was determined not only by VR but also by sympathetic tonus which influenced the accuracy of its estimation under the use of Bazett formula, though better normalizing criterion was not suggested. The main conclusion is that new physiological PM providing shortening of QTc interval duration but not only the syndromes of pathological repolarization correction are needed.

The same year Rickards A.F. et al [19] presented the estimation results of QT interval duration on the background of trial with increasing physical loading on 25 patients with frequency adaptive atrial PM which did not demonstrate on its background the expected essential shortening of QT interval. The result was the conclusions about the necessity of PM creation in which the stimulated rhythm frequency control is reached considering QT interval duration regardless atrial activity.

In Lelakowski J. et al [20] study the reaction of QTc interval duration in 30 patients with VVIR PM and in 6 and 24 months after radiofrequency ablation of atrio-ventricular junction (RFAVJ) regarding refractory to therapy atrial fibrillation (AF) was absent.

Correlation in RR and QTc intervals duration in 9 patients with PM in VVI mode with preserved function of sinus junction under making of stress test was studied by Oda E. et al. [21]. Authors explain the found variability of correlation degrees (in 2 patients – good (r = +0.816 and +0.897), in 4 – satisfactory (r = +0.672, +0.615, +0.615 and –0.669), in other 3 – weak (r = +0.494, +0.467 and –0.424) by individuality of sympathetic tonus influence on QTc interval duration.

Zabel M. et al [22] demonstrated direct verified dependence between QTc interval duration and VR of stimulated complexes at rest and after physical loading on 35 patients with single-chamber atrial stimulation.

Negative influence of BiV PM on ventricles repolarization was first described by Medina-Ravell V.A. et al. [23] in 2003 on the example of 29 patients with CHF, in which QTc interval duration was detected as well as transmural dispersion of repolarization (TDR) on the background of RiV endocardial stimulation, BiV stimulation and left ventricular epicardial stimulation. BiV stimulation alongside epicardial left ventricular (LV) stimulation was associated with lengthening of QTc interval duration and increase of TDR. The fact of early ventricular extrasystole appearance in 4 patients on the background of BiV stimulation and LV epicardial stimulation was explained by increase of transmural early postdepolarization which is in favor of arrhythmogenic effect of stimulation in the mentioned modes. Influence of epicardial LV stimulation on repolarization was experimentally proved on rabbit myocardium by the researchers.

Fish J.M. et al. [24] studied possible connection between QT interval prolongation and TDR increase as well as risk of arrhyth-mias development with the change of active-tion direction in the wall of stimulated LV in experiment on 12 specimens of dogs' myocardium. Under dislocation of electrode from endocardium to epicardium QT interval duration increased 297,6 ± 3,9 ms to 314,0 ± 5,7 ms and TDR - from 35,5 ± 5,2 ms to 70,3 ± 6,2 ms, which authors explained by delaying of potassium channels conduction under extremely quick activation closer to epicardium. In accordance with this, to their mind, fluttering and fibrillation of ventricles can be induced by epicardium, but not endocardium stimulation.

Interconnection between BiV stimulation and QT interval duration in 176 patients with ischemic and non-ischemic cardiomyopathy and CHF of II-III functional classes (FC) according to New York Heart Association (NYHA) with average EF = 24 ± 9 % were studied by Bhatia A et al. [25]. QT interval duration was measured before and after 30 min, 24 hours and 1 month of BiV PM implantation. The results demonstrated statistically significant lengthening of QT interval duration from 445 ± 32 ms to 470 ± 34 ms on the background of BiV PM.

The results of potential proarrhythmogenic CRT effect were demonstrated in the work by Tayeh O. et al. [18]. In 75 patients on the background of BiV PM and spontaneous rhythm QT interval duration was measured and episodes of ventricular arrhythmias were fixed. Increase of QTc interval duration was demonstrated in all the patients after CRT (from 476.2 ± 41.6 to 498.9 ± 50.8 ms), as well as greater meanings of QTc interval duration among the patients with ventricular arrhythmias episodes (527 ± 63.29 against 496.95 ± 45.2ms). Lengthening of QTc interval duration on the background of BiV PM was a predictor of ventricular arrhythmias develop-ment.

Bai R. et al. [26] compared QT interval duration on the background of RiV endocardial, LV epicardial and BiV stimulation in groups of patients without structural heart changes (15 patients) and with CHF (21 patients). The results also demonstrated the increase of QT interval duration which, however, was observed only in CHF group, it did not sufficiently differ in stimulation modes.

QTc interval duration was defined in 14 patients with CHF on the background of sinus rhythm, atrium-synchronized stimulation of RiV apex, LV epicardium and BiV stimulation in the work by Harada M. et al. [27]. The results demonstrated the increase of QTc interval duration in 10,2 % under stimulation of RV apex and in 26,1 % under LV epicardial stimulation. The fact of the absence of changes of QTc interval duration in patients with BiV stimulation pointed on minimal proarrhythmogenic effect of the given mode.

In the work by Berger T. et al. [28] the increase of QTc interval duration was described (112 ± 12 % and 114 ± 14 % consequently) in 25 patients with implanted CRT and complete left bundle branch block (LBBB) in regimes of left ventricle and right ventricle

stimulation and absence of its changes under both ventricles stimulation (99 ± 12 %).

Local QT interval duration (in LV, RiV areas and interventricular septum area) and its connection with global QT interval duration of spontaneous and stimulated complexes were studied by Douglas R.A. et al. [29] on the example of 52 patients with BiV PM. The results demonstrated the decrease of global duration of QT on the background of BiV stimulation. Local QT interval duration did not differ in all areas before and after implantation as well as QT interval duration in LV and RV areas, only in the middle area it was less on the background of BiV stimulation. Under global QT interval duration decrease absence of local changes is connected with possible absence of positive influence of CRT on ventricles repolarization in these areas.

Possibility of QT interval duration decrease under CRT was demonstrated by Samir S. et al. [30] on 33 white rabbits, divided into three equivalent groups. In one group single-chamber RiV PM were implanted, in another - BiV PM, the third group served as a control (false operated). In 4 weeks after the operation increase of QT duration was found in RiV group of stimulation from 159 ms to 174 ms and decrease – in BiV group of stimulation group from 174 ms to 156 ms. The results demonstrated advantages of BiV stimulation connected with the decrease of QT interval duration as a risk marker of ventricular arrhythmia development.

Dilaveris P. et al. [31] studied QT interval duration in 70 patients with CHF and syncope episodes or ventricular tachycardia (VT) in case history with implanted biventricular stimulators – cardioverters - defibrillators (BiV-ICD). In a year of ECG investigation maximal and minimal meanings of QT interval duration decreased and did not reliably differ in the patients group with ICD activation episodes during the study (38,6 %).

In their work Scott P.A. et al. [32] demonstrated absence of QTc interval duration changes in 43 patients under BiV with endocardial transseptal LV stimulation, under stimulation of only coronary sinus and under epicardiac LV stimulation.

Ventricle stimulation from some points as possible solution of the problem of repolarization violations under CRT was described in 2013 in the work by Ogano M. Et al. [33]. Patients with CHF of II-IV FC according to NYHA and EF ≤ 35 % and QRS complex duration > 120 ms after implantation by traditional CRT with biventricular stimulation (BiV) - 36 cases and CRT with triple site stimulation (Tri-V) (1 electrode – in RV, 2 electrodes – in LV) - 22 cases were studied. During the research period in 3,5 years QTc interval duration decreased in 14,1 % in BiV group and in 23,6 % - in Tri-V CRT group, ventricular arrhythmias were observed in 14 (39 %) cases in BiV group and in 2 (9 %) cases in Tri-V CRT group. The received results pro-ved the improvement of repolarization para-meters and antiarrhythmic effect Tri-V CRT.

INFLUENCE OF PERMANENT CP ON QT INTERVAL DISPERSION

Dispersion of normalized QT interval QT (QTcD) is not less important than QTc interval duration prognostic factor of ventricles arrhythmias development. In the work by Zabel M. et al. [22] absence of correlation of QTcD stimulated complexes with HRF at rest and after physical loading on 35 patients with single-chamber atrial stimulation were presented.

In Demir A.D. et al. [34] study QTcD was also defined in patients with atrial stimulation in groups: control group with intact coronary arteries (13 patients) and with ischemic heart disease (IHD) (12 patients - affection of one vessel, in 16 – affection of two vessels and in 14 – affection of three vessels). The results demonstrated absence of QTcD reaction on atrial stimulation in control group (43.4 ± 8.1 and 49.3 ± 9.5 ms), increase in the group of one-vessel affection from 46.1 ± 8.1 to 74.3 ± 7.7 ms, in the group of two-vessel affection - from 48.5 ± 10.4 to 93.8 ± 22.1 ms and in the group of three-vessel affection - from 49.7 ± 13.6 to 128.5 ± 31 ms. The main conclusion is that QTcD of stimulated rhythm depends on coronary disease.

Lelakowski J. with colleagues made a series of studies published in [20, 35-37] on the patients with implanted PM dedicated to the influence of various diseases and changes of functional indices connected with them on interconnection of stimulation parameters with QTD. In the work [35] in 60 patients with DDD PM QTD and heart stroke volume (SV) in DDD stimulation mode were estimated and also in a day in VVI stimulation mode with various variants of programmed AV-delay.

Patients were divided into two subgroups with IHD, arterial hypertension (AH) and their combination. Increase of QTD was associated with SV increase, mode of VVI stimulation, presence of IHD and AH. Direct inter-connection between QTD and hemodynamic status of the patient as well as possibility of QTD optimization by way of stimulation mode and AV-delay in patients with HID and/or AH became the main conclusion of the study. In the work [36], left ventricle myocardium hypertrophy (LVMH) and control according to the same protocol QTD and AV-delay were estimated in 34 patients with PM in subgroups of post-infarct cardiosclerosis (PICS) In PICS and LVMH groups in comparison with control group direct correlation between QTD and SV was demonstrated which was further used for the choice of optimal AV-delay with QTD decrease on the background of PM. In the work [37] direct connection between QTD increase and EF decrease was demonstrated in 34 patients in subgroups with ejection fraction (EF) < 50 % and > 50 % under single-chamber stimulation in VVIR mode after radiofrequency catheter ablation (RFCA) concerning atrial fibrillation in modes of stimulation frequencies decrease from 80 to 40 per min under estimation of QTmin, DeltaQTm (QTm-40 – QTm-80), QTmax, DeltaQTM (QTM-40 – QTM-80), QTD and AQTD (QTD-40 – QTD-80). QTD changes in the study [20] were absent in 30 patients with VVI PM in 6 and 24 months after radiofrequency ablation of atria-ventricular junction (RFAVJ) of refractory to therapy AF.

Data of CRT influence on QTD are also contradictory. In Chalil S. et al [38] study QTcD was registered before implantation and in 48 months after CRT implantation in 75 patients with resistant to medical therapy CHF (III-IV FC according to NYHA). QTcD increased on the background of CRT in 47 % of patients among which reliable increase of arrhythmias development was demonstrated.

Absence of QTD reaction on the background of QT interval prolongation under BiV stimulation was demonstrated in Pastore C.A. [39] study in 50 patients with BiV PM implanted concerning CHF with III-IV FC according to NYHA and complete LBBB.

Dilaveris P. et al [31] demonstrated absence of QTD changes in 70 patients with CHF and syncope episodes or VT in case history with implanted BiV-ICD. In group of patients with ICD activation episodes (38,6 %) no QTD statistically significant differences were observed during the study.

In the work by Harada M. et al. [27] QTcD was defined in 14 patients with CHF on the background of sinus rhythm, atrium synchronized stimulation of RV apex, LV epicardium and BiV stimulation. Increase of QTcD in 66,5 % cases under LV epicardial stimulation and QTcD absence of changes in patients with BiV stimulation in comparison with sinus rhythm proved about low proarrhythmogenic CRT effect.

A number of studies demonstrated the decrease of QTD after CRT PM implantation. Thus, Santangelo L. et al [40] described QTD and TDR under BiV stimulation in the group of 50 patients with dilatational cardiomyopathy and expressed atrio-ventricular, intra- and interventricular dyssynchrony. The study demonstrated a reliable decrease of ventricular repolarization heterogeneity indices: QTD and TDR on the background of BiV stimulation in comparison with sinus rhythm.

Possibility of QTcD decrease under CRT was also described by Scott P.A. et al. [41], who compared QTcD reaction under BiV with endocardial transseptal LV stimulation under stimulation of only coronary sinus and under epicardial LV stimulation in 43 patients. In group of endocardial transseptal LV stimulation (7 patients) reliable QTcD decrease was received (-45.2 ± 35.6) against the group with coronary sinus stimulation (28 patients), in groups with epicardial stimulation and under coronary sinus stimulation they did not essentially differ statistically. According to the study results the conclusion about the decrease of arrhythmias development risk was done under LV electrode setting into transseptal area in patients with CRT.

Frommeyer G. et al. [42] studied the influence of amiodarone on QTD and activity potential duration (APD) as indices of proarrhythmogenic potential in the model of stimulator-induced CHF. 35 rabbits with CHF caused by PM and 34 false-operated rabbits were divided in experiment into 2 groups: in 37 cases amiodarone was infused in dose 50 mg/kg a day, the rest of them got the infusion of sotalole in dose 50-100 mg/kg. ECG in 6 weeks demonstrated absence of QTD increase under amiodarone infusion in both groups and APD increase in group of false-operated rabbits; QTD increase in +29 ms in

groups with CHF and APD – in both groups with sotalol infusion. Effects of amiodarone were explained by the absence of triangle configuration of activity potential characteristic for sotalol and activation of the III quick phase of repolarization which testifies in favor of low proarrhythmogenic potential of amiodaron under CHF.

Because of a great number of patients who are «non-responders» to CRT a possibility of CRT response prognosticating was studied before BiV implantation of the sets with the help of QTD definition. Hina K. et al. [43] studied the connection between QTcD of spontaneous rhythm and clinical improvement in 26 patients after CRT implantation. Absence of CHF EF decrease according to NYHA during 3 months (8 cases) was considered as absence of clinical improvement on CRT. Increase of QTcD in group of non-responders proves its high significance under prognosticating of clinical response on CRT before implantation.

In 2012 Timineri S. et al. published the data of the study [44], where FC of CHF according to NYHA, tolerance to physical loading in test with 6-minute walking in 53 patients with CRT in groups with QTcD > 60 ms and QTcD ≤ 60 ms spontaneous complexes, QRS and QTcD complexes duration, indices of echocardiography (LV ejection fraction (EF), finally-diastolic size (FDS), intra- and interventricular dyssynchronia before and after cardioresynchronizing set implantation were registered. In QTcD > 60 ms group in comparison with QTcD ≤ 60 ms group in a year after implantation a reliable increase of CHF FC according to NYHA, LV EF, FDS and intraventricular LV desyncronia, decrease of tolerance to physical loading in test with 6 minute walking were observed. In accordance with these data, QTcD as an addition to QRS complex duration is an important index in choice of patients for CRT.

PERMANENT CP UNDER INITIALLY LENGTHENED QT INTERVAL DURATION

The problem of ECS implantation under initially increased QT interval duration (congenital and acquired forms of lengthened QT syndrome (LQT)) was first described in 1981 by Weber H. et al. [45] on the example of 12 patients from 3 families with congenital form of LQT syndrome. Atrial single-chamber PM was set in 4 patients with sinus bradycardia and syncopal states, the rest patients received beta-adrenergic receptors blockers therapy. Test with physical loading in patients with PM demonstrated the increase of average QTc interval duration to 540 ms on the background of loading in comparison with 430 ms in patients with LQT medical therapy. Episode of ventricular tachycardia in one of the patients on the background of CP was due to hypersensitivity of conductivity system to sympathetic tonus in the given group.

The results of one of the most essential studies of congenital LQT syndrome were published by Garson A. Jr. et al. [46] when in 281 child with LQT syndrome beta-adrenergic receptors blockers therapy caused the development of atrio-ventricular blockades in 5 % of cases demanding PM implantation. In 5 % cases more the necessity of cardioverters – defibrillators implantation aroused in connection with syncopal states and episodes of SCD, including 8 % of cases in the subgroup of QT > 600 ms interval duration.

Influence of constant CP on initially increased duration of QT interval under acquired LQT syndrome with Morganji – Adam – Stocks (MAS) syndrome in 8 patients with stimulation in AAI and DDD modes on the background of beta- blockers therapy was described in the work by Eldar M. et al [47]. QT interval duration was estimated in connection with syncopal states episodes. During 35.1 ± 18.9 months of therapy QT intervals duration shortened from 534.4 ± 51.4 to 425.6 ± 18.9 ms, thus, one patient demonstrated syncopal state on the background of hyperventilation and another patient revealed giddiness which did not repeat after exchange of AAI to DDDR PM. The study results demonstrated the effectiveness of LQT syndrome therapy with reliable decrease of QT interval duration by permanent PM method in connection with beta-adrenergic receptors blockers therapy.

Pinski S.L. et al. [48] estimated minimal frequency of stimulated rhythm, preventing TdP development in 18 patients with permanent PM under initially increased QT interval duration and ventricular flutter-fibrillation (torsades-de-pointes (TdP)) in case history. 7 TdP episodes were registered under stimulation frequency 55 ± 11 bits per min and 1 episode - under 63 ± 13 bits per min frequency. No episode of arrhythmia of TdP type was

registered under frequency > 70 bits per min, which proves in favor of its protective effect as base stimulation frequency in patients with initially lengthened QT interval.

ROLE OF QT INTERVAL DURATION FOR AV-DELAY CORRECTION UNDER PERMANENT CP

The role of QT interval duration of stimulated complexes in the choice of optimal AV-delay in patients with dual-chamber PM was studied in the series of trials by Ishikawa T. et al. [49-51]. In [49] QT interval duration and LV EF under graded increase of AV-delay in 30 ms, beginning with 90 ms was estimated in 12 patients with PM in DDD mode. The same increase of QT interval duration was observed on the grade with the greatest EF (increase from 440 ± 40 to 456 ± 39 ms). In [50] QT interval duration, LV EF and pulmonary artery jamming pressure (PAJP) under various degrees of AV-delay were estimated in the same way in the group of 10 patients with stimulation in DDDR mode. The results demonstrated maximal increase of QT interval duration (from 346 ± 60 to 353 ± 62 ms) under AV-delay with the greatest EF and minimal PAJP. In [51] 13 patients with DDDR PM with sensing transducer of QT interval duration were examined according to the same protocol. All patients demonstrated decrease of QT interval duration and LV EF both under decrease and increase of automatically defined optimal AV-delay. The series of trials demonstrated reasonability of optimal AV-delay existence with the help of QT interval duration sensing.

SENSING OF QT INTERVAL DURATION FOR PM RATE ADAPTATION

Necessity in rate-adaptive PM with sensing of QT interval duration creation was first described in 1981 in the work by Rickards A.F. et al. [52] in connection with the absence of sufficient shortening of QTc interval on the background of loading and VR in the given group of patients.

First studies of automatic sensing efficiency of QT interval duration for PM rate correction were published practically simultaneously in 1985 by Fananapazir L. et al. [53] and GoicoleadeOro A. [54]. In the work [53] sensing efficiency of QT interval duration for VR correction were studied in 13 patients with rate adaptive PM. Tolerance to physical loading was defined with the help of treadmill-test under frequency by QT interval duration sensing under atrio-synchronized stimulation (in DDD mode) and asyncronized stimulation (in VOO and VVI modes). Increase of tolerance to physical loading in patients with rate adaptation of PM in comparison with asyncronized mode, which, however, reliably did not differ from the identical one under atrio-syncronized stimulation, indicated at physiology of CP with sensing of QT interval duration for PM rate correction. In [54] tolerance to physical loading on early and distant post-operative period in groups after single-chamber (9 patients) and dual chamber (10 patients) PM implantation with QT interval duration sensing for VR correction was studied. Treadmill-test was made under VVI mode and under rate adaptation in both groups in 1-3 months and after 10-24 months. The results also demonstrated the same reliable improvement of tolerance to physical loading in groups of single- and dual chamber PM in patients with rate-adaptive sets and QT interval duration sensing.

Bloomfield P. et al. [55] described the experience of five-year observation of 8 patients with implanted rate-adaptive PM with QT interval duration sensing. Increase of tolerance to physical loading and satisfactory rate adaptation in comparison with fixed rhythm was observed in 5 patients who needed no correction of stimulation parameters in the study period. One patient needed the increase of basic stimulation rate during 5 years of study because of CHF development after acute myocardium infarction endurance, after reprogramming tolerance to physical loading under rate adaptation was reliably higher. The received data prove the reliability of QT interval duration sensing for rate adaptation in patients with long-term CP.

With the aim of greater physiology of PM rate adaptation various algorithms of QT interval duration sensing took root. The study carried out by Baig M.W. et al [56] describes the efficacy of linear and non-linear algorithms of QT interval duration sensing for stimulated rhythm adaptation to physical loading in 11 patients with PM. HRF increase, tolerance to physical loading, oxygen saturation (SaO2) were estimated in a month after every algorithm programming. Non-linear algorithm of QT interval duration sensing was associated with VR less increase time in 10 bits per min,

less rhythm fluctuations, besides tolerance to physical loading, SaO2 and correlation of VR to SaO2 did not differ under various algorithms. Non-linear QT interval duration sensing algorithm in rate-adaptive PM was presented as more physiological, though its programming did not solve the problem of stimulation rate decrease at the beginning.

The next stage for the improvement of stimulated rhythm frequency regulation as a response on physical loading was automatically dual sensing of physical activity and QT interval duration. Connelly D.T. [57] described in 1993 the results of the first 90 implantations of single-chamber stimulators with two sensing introducers programming independently, consequently, according to physical activity level and QT interval duration. In a month after implantation a sample with physical loading was done which demonstrated more gradual increase of VR in response to physical loading in sensing group with two transducers versus sensing group with physical loading introducers. Dual sensing, besides, excluded pressure factors, PM body vibration, which indicated its essential preferences.

Efficacy of automatic dual sensing of physical loading and QT interval duration were studied in the work by Lascault G. [58] on the example of 12 patients after PM implantation considering full AV-blockade in control group with normal sinus rhythm. HRF of spontaneous and VR of stimulated rhythm with sensing of only physical activity and dual sensing under various levels of treadmill-test loading were registered in a month. VR with dual sensing on the stages of physical loading was identical to sinus rhythm and greater than under sensing of only physical activity which proved sufficient physiology of PM rate adaptation with automatic dual sensing of physical activity and QT interval duration.

INFLUENCE OF MEDICAL THERAPY ON QT INTERVAL DURATION AND QTD IN PATIENTS WITH SPONTANEOUS AND STIMULATED RHYTHM

B01A A Anticoagulation and B01A C antiplatelet therapy

Anticoagulants do not usually influence QT interval duration.

Radhakrishnan M. with colleagues [59] described in 2006 the case of QT interval lengthening in a patient with intracranial aneurism which was connected with heparin-stimulated hypocalcaemia. Its correction caused its normalization. Further influence of heparin therapy on LQT duration was not studied.

The data of connection between K vitamin antagonists preparations taking and increase of QT interval duration were not earlier described in literature.

As for modern anticoagulants Morganroth J. et al. [60] found no essential changes of QTc interval duration in 96 patients on the background of betrixaban in dose 80 mg and 140 mg (therapeutic and supertherapeutic dose, consequently) in 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours after taking.

Similar results were received by Ring A. et al. [61] in respect of dabigatran etexilate in doses 150 mg and 600 mg (therapeutic and supertherapeutic, consequently) were studied in 40 healthy people. According to QT interval duration in 1,5 and 3 upper boundary of trust interval comprised 1,4 ms - for the group with therapeutic dose and 1,3 ms – with supertherapeutic dose (0,9 value level).

Effects of antiplatelet therapy on QT interval duration were estimated in a big randomized multicenter LANCELOT ACS trial [62]. In 603 patients with acute coronary syndrome and/or high cardiovascular risk, taking a new antiplatelet atopaxar, dose-dependent lengthening of QT interval duration was presented which reached reliable value ($p = 0,05$) in high doses groups (200 mg a day) in comparison with groups of acetylsalicylic acid therapy and group of dual antiplatelet therapy (acetylsalicylic acid and tienopiridon derivatives). The frequency of bleeding was demonstrated the same in both groups.

Anticoagulating and antiplatelet therapy in most of the patients after PM implantation as a factor of QT interval duration lengthening as well as its influence of QTD in all the patients were not earlier studied.

C01A Cardiac glycosides

In cardiac glycosides group digoxin is the only preparation used in modern practice [63-65]. Its influence studies on QT interval duration demonstrate contradictory results [66-73].

Saner H.E. with colleagues [66] were the first who in 1988 estimated the connection between digoxin taking in average therapeutic doses and ECG parameters in 97 patients with CHF without IHD clinical manifestations of ST segment shift versus 40 nondegytalized persons

of control group. The results demonstrated QT and QTC intervals duration decrease under digoxin influence.

Clinical cases of symptomatic brady-arrhythmia manifestation with QT interval duration decrease on the background of digoxin taking and hypercalcaemia, conditioned by bronchus planocellular carcinoma were described by Vella A. with colleagues [67]. After the end of digoxin taking and hypercalcaemia correction arrhythmia was cut short. The main conclusion is that proarrhythmogenic effect of digoxin under hypercalcaemia is connected with pathological shortening of QT interval, conditioned by calcium transport acceleration to carciomyocites under digoxin activity and calcium level increase in blood serum.

Guo L. et al [68] demonstrated the effect of cardiac glycosides on electric potentials of cardiomyocites on preparations received from human pluripotent sterm cardiomyocites cells (hiPSC-CMs) and preparations of Langendorff ginea pigs myocardium being in QT interval duration shortening under ouabain and digoxin effection. They saw the reason in sodium ions transport decrease and calcium ions increase in cardiomyocites which, to their mind, conditioned proarrhythmogenic activity of cardiac glycosides.

QT interval duration before and after tilt test in 20 patients with AF and CHF, 17 of which took digoxin was studied by Malik M. et al [69]. Automatic detection of QT interval duration demonstrated its shortening from 409.8 ± 11.1 ms to 401.9 ± 9.89 ms in a min and to 394.8 ± 10.0 ms in 2 min after active transition into vertical position.

Duraković Z. et al. [70], on the contrary, found no QTc interval duration correlation calculated on Bazett H.C. and Fredericia L.S. formulas with digoxin concentration in 84 patients with CHF.

QT interval duration increase on the background of digoxin therapy with TdP development on the example of classical case in 74 years old woman was described by Patanè S. et al. [71].

The alike influence of digoxin on ventricles repolarization was demonstrated according to the results of the biggest trial of medical preparations influence on QT interval duration published in 2013 by Iribarren C. et al. [72]. Digoxin was referred to the group of remedies, lengthening the QT interval from 15 to 20 ms basing on the study of 59 467 patients for the period from 1995 to the middle of 2008 in the study of 90 various remedies.

Makkar R.et al [73] demonstrated lengthening of QTC interval duration under the study of sexual differences in influence of medical preparations as well as the greater frequency of arrhythmias of TdP type on the background of digoxin therapy among women.

The data of heart glycosides influence on QT and QTD intervals duration in patients with implanted PM was not found.

C01B A-C Antiarhythmic preparation of class I

Antiarrhythmic preparations of IA class – procainamide, quinidine, disopyramide, pirmenol (classification according to VaughanWilliams, 1971) lengthen repolarization and refractory period duration through decrease of potassium and sodium flow in cardiomyocites [74].

Reiter M.J. et al. [75] compared influence of procainamide and quinidine on QTc interval duration in 18 patients. The results demonstrated dose-independent increase of QTc interval duration, longer on the background of quinidine (78 ± 10 ms), than procainamide therapy (39 ± 7 ms).

Platia E.V. et al. [76] also found dose-dependent increase of QT interval duration under the study of immediate electrophysiological effects of procainamide and quinidine in 16 patients with chronic forms of IHD.

Salerno D.M. et al. [77] described anti-arrhythmic properties of pirmenol and quinidine in 18 patients with ventricular ectopic activity, which effectiveness for the first preparation comprised 88 % and for another – 50 % with average increase of QTc interval duration, consequently, to 8 ± 9 ms and 46 ± 30 ms.

QTc interval duration increase in 20 % on the background of disopyramide introduction was demonstrated by Miyamoto S. with colleagues [78] in experiment on dogs with adrenaline-induced arrhythmias.

Disopyramide influence of QT interval duration in patients with implanted PM was studied by Furushima H. et al. [79]. In group of 8 patients with initial bradycardia-dependent LQT syndrome QT interval duration was reliably greater versus the group of 5 patients without LQT syndrome and depended on HRF (451 versus 416 ms under HRF = 90 per min, 490 versus 432 ms under HRF = 70 per min). QT interval duration increase was observed in

both groups after disopyramide taking on the background of CP and was greater in patients with LQT syndrome (78 versus 35 ms).

Antiarrhythmic preparations of IB class (lidocaine, mexiletine) have minimal influence on sodium ions transport in cardiomyocites and accelerate the repolarization process activating potassium channels [80]. Owczuk R. et al. [81] demonstrated absence of QT interval duration reaction on intravenous infusion of lidocaine in 43 women during trachea intubation while in control group with inhalational narcosis and trachea intubation without lidocaine the latter increased essentially. Mexiletine is used in congenital forms of LQT syndrome therapy due to repolarization process shortening [82].

The first clinical observation of QTc interval duration shortening under mexiletine activity was published in 1995 by Schwartz P.J. et al. [83] in 6 patients with LQT3 syndrome and 7 patients with LQT2 syndrome. It was reliable in LQT3 group (535 ± 32 and 445 ± 31 ms) and unreliable in LQT2 group (530 ± 79 and 503 ± 60 ms).

Absence of mexiletine influence on mortality in distant period among new-born children with various forms of LQT syndrome was demonstrated by Chien-Chih Ch. with colleagues [84].

Arend D.J. Ten Harkel et al. [85] described absence of QT interval duration reaction on mexiletine infusion to a new-born child with LQT3 syndrome and ventricular arrhythmias which were cut short only by medical therapy and ICD implantation combination.

Gao Y. et al. [86] studied efficacy of mexiletine for hereditary Timothy syndrome therapy, which was accompanied by frequency-dependent lengthening of QT interval with average life expectancy 2,5 years. On a clinical case of 2-year old girl example decrease of QT interval duration from 584 to 515 ms on the background of the preparation taking was demonstrated.

Preparations of IC class (propafenone, flecainide) have identical activity mechanism with preparations of IA class: slow down sodium transport of cardiomyocites acting on potassium transport in less degree [87].

Stuart J. Connoly et al. [88] describing clinical pharmacology of propafenone in 13 patients marked worsening of arrhythmia course in 2 patients (15 %) and dose-dependent increase of QT interval duration.

Proarrhythmogenic potential of propafenone was studied by Femenia F. et al. [89] on the example of clinical case of 69 year old woman with arterial hypertension and paroxysmal form of ventricles fibrillation on the background of constant enalapril, atenolol, amiodarone therapy. Infusion of 600 mg of propafenone for atrial fibrillation paroxysm cupping caused lengthening of QT interval duration with atrial fluttering paroxysm development with irregular rhythm and wide QRS complex, which further transformed into ventricular tachycardia. Arrhythmia was cut short after propafenone and antiarrhythmic preparations of III class taking.

Chimienti M. with colleagues [90] demonstrated similar increase of QT interval duration and frequency of arrhythmogenic events on the background of therapy by both preparations studying the influence of flecainide and propafenone on ventricles repolarization in 335 patients.

C01B D Antiarrhythmic preparation of class III

Among antiarrhythmic preparations of III class, lengthening the action potential, repolarization process and, consequently, QT interval duration [91], amiodaron is more often used.

Problem of amiodaron influence on QT interval duration was raised for the first time in 1986 by Torres V. et al. [92]. In 33 patients who took amiodaron in doses 2,5 and 3,2 mcg/ml during 12 ± 7 months, QT and QTc intervals duration were estimated. During the study period 6 patients died because of SCD, 3 – of out-cardiac reasons and 1 – of CHF progresssing. QT and QTc intervals duration increased in all the patients on the background of amiodaron therapy besides it was reliably greater in SCD group, though, not correlating with amiodaron dose.

The reason of lower proarrhythmic potential of amiodaron in comparison with other antiarrhythmic preparations of III class, especially, sotalole, was studied by Milberg P. et al. [93]. In experiment amiodarone was infused to 8 rabbits for 6 weeks and sotalole - to 13 rabbits, increase of QT interval duration was demonstrated in both groups which was greater in sotalole group (31 ± 6 ms and 61 ± 9 ms, consequently). Less proarrhythmic amiodarone side effect was explained by lengthening of monophase activity potential (MAP) according to rectangular scheme, while sotalole lengthens MAP according to triangle scheme which is

accompanied by great lengthening of repolarization phase.

Tong K.L. with colleagues [94] described a series of clinical cases of 13 patients with medically-induces increase of QT interval duration (average meaning - 545 ms) and development of arrhythmia of TdP type, 7 of which (57 %) were caused by amiodarone.

In the greatest randomized multicenter trial on the influence of medical preparations on QT interval duration published by Iribarren C. et al. [95] amiodarone demonstrated its greatest increase - in 25,2 ms among 90 preparations.

Mattioni T.A. et al. [96] studied the possibility of long-term amiodarone taking in 12 patients after episodes of medically-induced TdP. The results demonstrated decrease of QTc interval duration in the first 7 days (from 570 ± 40 ms at the moment of TdP to 490 ± 70 ms) and increase in 3 months of therapy (to 580 ± 80 ms). QTc interval duration in 16 ± 7 months was reliably greater in the study group in comparison with control group, though frequency of repeated TdP, episodes of syncope and SCD did not differ which allowed the authors to come to a conclusion about possibility and independence of amiodarone usage in patients with episodes of medically-conditioned TdP.

Opposite point of view was demonstrated in the work by Ramy F. Ayad et al. [97] on the example of clinical case of VT with wide complexes in a woman with QT interval increase induced by taking of antipsychotic remedies. The repeated VT episode was observed on the background of amiodarone therapy after which it was invalidated. The main conclusion is that amiodarone is contraindicated under VT with medically conditioned lengthening of QTc interval duration.

In clinical case was described by Van de Loo A. et al. [98] reaction of QT interval duration was absent in a patient with sotalole-induced TdP on the background of amiodarone therapy in 3 months, though QTD was reliably less (47 ms), in comparison with sotalole therapy (77 ms), and did not differ from control without antiarrhythmic therapy (43 ms). Informativity of QTD for identification of proarrhythmic risk of antiarrhythmic preparation of III class prescription is the main conclusion of the work.

Tran H.T. with colleagues [99] described the case of amiodarone-induced TdP with QTD duration increase in more than 100 % after quinidine-induced TdP episode which testified in favor of the necessity of QTD estimation as a potential marker of TdP development on the background of amiodarone therapy in patients having quinidine-induced TdP.

Influence of amiodarone on QTD was studied by Hii J.T. et al. [100] in 38 patients having TdP induced by taking of antiarrhythmic preparations of Ia class in case history. The results demonstrated preferences of amiodarone therapy with absence of QTD reaction (49 ± 26 ms versus basic 44 ± 12 ms) and repeated arrhythmias episodes of TdP type in comparison with control group with proceeding antiarrhythmic preparations of Ia class therapy where QTD increased to 101 ± 37 ms, the repeated TdP episodes were observed in 9 patients.

Higher risk of TdP development under amiodarone therapy in women was demonstrated by Makkar R.R. et al. [73].

Cairns J.A. et al. [101] published the results of CAMIAT trial. VF and SCD development risk was estimated in 1202 patients (606 patients took amiodarone, 596 patients comprised control group) after having acute myocardium infarction for 1,79 year. The results demonstrated less frequency of arrhythmic events in amiodarone group - 25 (4,5%) in comparison with control group - 39 (6,9%), on the basis of which the conclusion about VF and SCD risk decrease on the background of amiodarone therapy in patients after acute myocardium infarction was made.

Influence of amiodarone on QT and QTD interval duration in patients with implanted PM was not earlier studied.

Combinations of amiodarone with other preparations

Shah S.A. et al. [102] compared influence of antiarrhythmic preparations of III class monotherapy (sotalole, dofetilide, ibutilide) and their combination with amiodarone on ventricles repolarization. The results demonstrated identical increase of QT interval duration in both cases, though QTD and TdP frequency were less under combined therapy which testified for its less proarrhythmic potential.

Clinical case of QT interval duration increase in 74 years old patient on the background of digoxin and amiodarone therapy was published by Bajaj B.P. et al. [103]. The appearance of weakly controlled TdP testified

in favor of possible proarrhythmogenic effect of the given combination of preparations.

A number of cardiovascular medical preparations such as metronidazole, antiretrovirus, antihistamine remedies, etc. are not recommended for simultaneous usage with amiodarone because of possible lengthening of QT interval duration and increase of arrhythmias development risk [104-108].

C03 Diuretic preparations

Diuretics indirectly influence on QT interval duration and increase of TdP risk by the way of potassium and magnesium introduction increase. Hypopotassemia and hypomagnesaemia caused by diuretics usage can aggravate the activity of other preparations increasing QT interval duration [109].

Sato T. Et al. [110] published a clinical case of TdP type arrhythmia in a woman with the decrease of potassium level of blood serum on the background of arterial hypertension therapy by thiazide diuretics.

The results of JacksonHeartStudy trial, published by Akylbekova E.L. with colleagues [111] demonstrated direct correlation between the increase of QT interval duration and taking of diuretics in 4660 African Americans.

C07 A Beta adrenergic receptors blockers

Nonselective

The most utilized preparation of the given group is sotalole. It consists of sinister rotatory isomer - 60 %, having halved beta adrenergic receptors blockers activity and halved lengthening the activity potential, primarily in account of repolarization phase and in 40 % from dextrorotatory isomer with antiarrhythmic preparations of III class activity [112].

Graff C. et al. [113] studied the influence of sotalole on QT interval duration in the group of 39 healthy people and 30 people with congenital LQT syndrome of type 2. QT interval duration increase was the greatest in the group of healthy people for all doses of the preparation: in 72 % under taking of 160 mg and in 87 % - 320 mg of sotalole.

Increase of QTc interval duration with the increase of sotalole concentration in blood serum of 15 healthy people under oral and parenteral taking was demonstrated by Somberg J.C. et al. [114].

Knudson J.D. et al. [115] did not demonstrate reliable lengthening of QTc interval duration under the study of efficacy and independence of high doses of sotalole (15 – 200 mg/m^2 a day) in 48 new-born children and 36 children under the age of 2 years old with refractory to therapy supraventricular tachycardias, thus arrhythmias control was reached in 90 % of cases.

Weeke P. et al. [116] demonstrated statistically essential increase of QTc interval duration and QTD in 541 patients with AF or atrial flutter in 2 hours and 48 hours after sotalole infusion in dose 86 ± 39 mg.

Essential increase of QTc interval duration (to 840 ms) in a patient after wrong taking of 120 mg of sotalole was described by Kukla P. with colleagues [117].

According to Iribarren C. et al. [95] data received in 59467 patients, sotalole increased QT interval duration in 15 – 20 ms.

Somberg J.C. et al. [118] demonstrated essential increase of QT interval duration in 2,5 hours after intravenous infusion of 75 mg of sotalole in 15 health /volunteers – more in women (411 ± 13 versus 438 ± 13 ms, $p < 0.001$) and less in /men (395 ± 23 versus 413 ± 27 ms, $p < 0.05$).

Influence of CP on the change of QTc interval duration under sotalole taking was studied by Tsai S.F. et al. [119]. 22 patients with implanted permanent PM (right ventricle stimulation < 10 %) took part in the trial. The results demonstrated essential increase of QT interval duration after taking the preparation on the background of spontaneous rhythm (from 431 ± 28 to 463 ± 33 ms, $p = 0.002$) and decrease – under stimulated rhythm (from 520 ± 48 to 538 ± 45 ms, $p = 0.07$).

Selective

Selective beta blockers shorten QT interval duration and are used for congenital and acquired LQT syndrome [120-121].

Efficacy and usage limitations of beta adrenergic blockers in patients with QT interval duration increase were studied by Moss A.J. et al. [122]. Reliable decrease of mortality from cardiovascular events were demonstrated in 869 patients, receiving beta adrenergic receptors blockers for 5 years, though episodes of syncope and SCD were observed in 5,7 % of cases among the patients with LQT in case history, which is comparable with control group data.

Michael Vincent G. et al. [123] also demonstrated the efficiency of beta adrenergic receptors blockers therapy in decrease of SCD risk on 216 patients with various forms of congenital and medically conditioned LQT syndrome. The authors come to the conclusion

about the absence of necessity of routine ICD implantation to all patients with LQT syndrome in condition of sufficient compliance to therapy by this class of preparations.

Silvia G. Priori with colleagues [124] described decrease of QT interval duration and cardiovascular events risk for 5 years of beta adrenergic receptors blockers preparations therapy only under LQT1 in 335 patients with various forms of congenital LQT syndrome. QT interval duration did not relatively change and syncope risk and SCD remained high (23 % and 32 %, consequently) in patients with LQT2 and LQT3.

QT interval duration under various HRF in 20 patients taking beta adrenergic receptors preparations concerning LQT syndrome of type 1 was studied by Matthew T. Bennett et al. [125]. Increase of QT interval duration (398 ms versus 391 ms; p = 0,02) after taking 5 mg of bisoprolol was observed in the group with lower HRF (< 90 bits a min), decrease (339 ms versus 349 ms; p = 0,001) – in group with higher HRF (> 105 bits a min).

Comparative estimation of LQT syndrome therapy by selective (metoprolol - 147 patients) and non-selective (propranolol - 134 patients, nadolol - 101 patients) beta adrenergic receptors blockers for 14 years was conducted by Chockalingam P. et al. [126]. The results demonstrated the most prominent shortening of QT interval duration in those who took propranolol, as well as similarly better decrease of cardiovascular events risk on the background of propranolol and nadolol therapy.

C07A G Combined alpha and beta adrenergic receptors

Mechanism of carvedilol and its new analogue VK-II-36 combining blocking activity of alpha and beta adrenergic receptors influence on QT and QTD interval duration was studied by Maruyama M. et al. [127] in Langendorff mice and rats. Shortening of initially lengthened QT interval duration, QTD decrease was in all cases connected with inhibiting of these preparations of spontaneous increase of intracellular calcium in systole which suppressed trigger activity of ventricle myocardium and thereby prevented ventricular tachyarrhythmias development.

Influence of selective and combined beta adrenergic receptors blockers on QT and QTD interval duration in patients with implanted PM was not earlier studied.

C08 Calcium antagonists

Among potassium antagonist preparations bepridil and ranolazin have maximal proarrhythmogenic effect in QT interval duration lengthening. [128-129].

Yoshiga Y. With colleagues [130] demonstrated the increase of QTc interval duration in 50 ± 8 %, QTD in 14 ± 8 % in 10 patients with resistant to therapy proximal AF on the background of bepridil taking.

Mechanism of bepridil proarrhythmogenic activity was studied by Kang L. et al. [131] on specimens of new-born white rats myocardium. The authors came to the conclusion that the preparation increases QT interval duration on account of ventricle repolarization time increase conditioned, in its turn, by calmodulin inhibiting which shortens Na (V) degradation of 1.5 alpha components of sodium receptors and increases sodium flow in cardiomyocites.

Ranolazin is an antianginous and antiarrhythmic preparation which activity is conditionned by calcium channels blockage and inhibiting of the later phase of inner sodium flow [132].

Clinical case of QT interval duration increase and arrhythmia of TdP type development on the background of ranolazin taking was described by Liu Z. et al. [133].

Koskinas K.C. et al. [134] identified comparative for both preparations increase of QT interval duration under absence of acute cardiovascular events during 48 hours of electrophysiological effects studies of ranozolin in comparison with amiodaron in 121 patients.

Influence of amlodipin on QT and QTc intervals duration in 90 patients with arterial hypertension was studied by Milovanović B. et al. [135]. The results demonstrated statistically insignificant QT interval shortening (from 391.49 ± 31.4 to 388.31 ± 35.0 ms) and QTc (from 426.94 ± 25.3 to 424.08 ± 33.7 ms) during a day after preparation taking.

In the work by Peters F.P. with colleagues [136] clinical case of QT interval duration increase from 380 to 480 ms with further ventricle fibrillation development after 20 mg of nifedipin taking sublingually in 34 years old woman with malignant arterial hypertension was described.

According to the trial eHealthMe United States Food and Drug-Administration (FDA) [137] data 93 (0,55 %) from 16 792 cases of nifedipin side effects is increase of QT interval duration.

In Redfern W.S. et al [138] trial changes of QT interval duration in dogs were studied, its reactions and cases of TdP in human on the background of 100 of various preparations taking. Nifedipin and verapamil identically increased QTc interval duration in all observations and did not influence the TdP risk.

Shortening of QT interval duration as a result of verapamil taking was described by Fauchier L. et al. [139] in 19 patients with paroxysmmal nodal re-entry-determined tachycardia without structural heart violations on the ground of which authors make a conclusion about protective effect of verapamil against TdP.

O. Erbas [140] demonstrated the decrease of QT interval duration after diltiazem taking (125 ± 4 ms) in 18 rats with cyprazidon-induced LQT syndrome in comparison with control group (160 ± 10 ms).

According to FDA data of 5791 registered cases of diltiazem side effects only in 2 (0,03 %) the increase of QT interval was found up to 2014 [141].

Interconnection between calcium antagonists taking and QT and QTD intervals duration in patients after implantation of permanent PM were not studied before.

C09 Remedies functioning on rennin-angiotensinic system

Angiotensin-transforming enzyme effect on QTc interval duration was studied by DiasdaSilva V.J. et al. [142]. Captopril was given to rats of various ages for 2-20 months. QTc interval duration was longer in adult rats in comparison with new-born ones (117+/-4 versus 64+/-6 ms, $p < 0.05$), though it decreased under captopril (71+/-6 ms, $p < 0.05$).

Bashir Y. With colleagues [143] demonstrated reliable increase of QTc interval duration from 351 ms to 358 ms after taking 25 mg of captopril in 8 patients with decreased LV function (EF < 40 %) and ventricular tachycardia, induced by programming CP.

Data about influence of remedies acting on rennin-angiotensive system on QTD QT and QTD intervals duration in patients with implanted PM were not found.

C10 Hypolipidemic remedies

Vrtovec B. et al. [144] studied QT interval duration in 80 patients with CHF, 40 of which took atorvastatin (statins group) and 40 did not take hypolipidemic preparations (control group). The fact of QT interval duration shortening in statins group after 3 months of therapy (from 450+/-30 to 437+/-29 ms) and its absence in control group (from 446+/-27 to 450+/-25 ms) testifies about antiarrhythmic effect of statins in patients with CHF. The same group of authors described shortening of QT interval duration on the background of statins therapy during a year in 114 patients after heart transplantation [145].

In Health Me United States Food and Drug Administration trial (FDA) in 256 cases (0,36 %) from 71 991 of registered side effects of simvastatin use increase of QT interval duration was observed [146].

Reaction of QT and QTD interval duration on hypolipidemic preparations taking in patients after PM implantation were not earlier reported in literature.

LIFE QUALITY OF THE PATIENTS WITH PM AND QT INTERVAL DURATION AND QTD OF STIMULATED COMPLEXES

Influence of PM implantation on the patients life quality regardless QT interval duration and QTD was studied by Manolis A.G. with colleagues [147]. The data of individual life quality questionnaire were estimated as well as CHF FC according to NYHA and LV EF before and after PM implantation and RFAVJ concerning atrial tachyarrhythmias. 46 patients (33 - in DDDR mode with function of automatic mode switch and 13 - in VVIR stimulation mode) during 6 months after RFAVJ procedure the reliable improvement of life quality was demonstrated according to the data of individual questionnaires, LV EF increase from 42 ± 16 % to 50 ± 14 %, CHF EF increase according to NYHA in 1.4 ± 0.8, only 7 patients needed medical antiarrhythmic therapy, and only 1 patient - repeated ablation.

The greatest trial in which the connection between the patients quality of life and QT interval duration and QTD in 156 patients after PM implantation and RFAVJ concerning EF refractory to therapy, was done by Ablate and Pace Trial (APT) [148]. Individual questionnaires like Health Status Questionnaire, Quality of Life Index и Symptom Checklist: Frequency and Severity were used. Besides QT interval duration and QTD, LV EF and tolerance to physical loading in test with 6 minutes walk were estimated. Improvement of life quality was demonstrated in all three questionnaires as well as improvement of

functional indices beyond QT interval duration and QTD increase in all the patients during 12 months after ECS implantation and RFAVJ.

Lelakowski J. et al. [149] studied LV EF, QTc interval duration, QTD of stimulated rhythm, tolerance to physical loading in test with 6 minute walking, the patients quality of life according to individual questionnaires SF-36, Manolis, DASI scale in 6 and 24 months after RFAVJ considering EF refractory to therapy in 30 patients with VVI ECS. The results demonstrated increase of life quality indices on all the stages according to SF-36 and Manolis scales, increase - in 6 months and decrease - in 12 months according to DASI scale. LV EF did not essentially statistically change and in 24 months decreased. Average QTc interval duration, QTD and tolerance to physical loading remained stable during the study.

MORTALITY OF THE PATIENTS WITH PM AND QT INTERVAL DURATION AND QTD OF STIMULATED COMPLEXES

Increase if QTc interval duration is associated with increase of mortality, first of all because of SCD both in patients with spontaneous rhythm and after PM implanttation.

QT interval duration as a predictor of SCD was first described by Schwartz P.J. et al. in 1978 in 55 patients after myocardium infarction (MI) [150]. The results of 7 years study demonstrated the increase of SCD frequency in 2,16 times in group of lengthened QTc interval against the group with its normal duration.

Interconnection between lengthened QTc interval and SCD risk were studied in randomized trial Rotterdam QT Project [151] on 6693 patients with registration of 12-channel ECG and 24-hour Holter monitoring. SCD frequency was 2,3 times higher in patients with increase of QTc interval duration, though differences concerned only the group with preserved systolic function (EF $\geq$ 40%). Sex, age HRF, presence of MI in case history and taking of remedies did not influence relative risks.

Connection of QTc interval duration changes in the limits of physiological range with level and structure of mortality in 7828 patients was described in randomized multicenter trial [152]. During 13,7 years in group of QTc interval duration 410 – 439 ms the results demonstrated the increase of mortality level in 2,03 times in comparison with general mortality, in 2,55 times in mortality level from cardiovascular diseases, in 1,63 times in mortality level from coronary heart disease and in 1,65 times in the level of beyond-cardiac mortality; in group of QTc interval duration 320-377 ms – increase of mortality level in1,39 in general mortality level, in 1,35 times in mortality level from cardiovascular diseases, in 1,02 times in mortality level from heart coronary disease and in 1,42 times in beyond-cardiac mortality level. The received data prove the unfavorable influence of lengthening and shortening of QTc interval on mortality level.

The increase of QTc interval duration after PM implantation is also associated with the increase of patients mortality, first of all from SCD. In the work by Dorostkar P.C. [153] SCD was observed in 24 % cases during 6.3 ± 4.6 years after implantation in 37 patients with combined therapy of LQT syndrome by beta-adrenergic receptors blockers and permanent PM. The main conclusion is the necessity of ICD sets implantation to patients with LQT on the background of beta-adrenergic receptors blockers therapy and permanent CP, especially in the early age.

Tereshchenko L.G. et al. [154] described the increase of VT development frequency and episodes of ICD activation in 69 patients with BiV-ICD in group of lengthened QTc interval and QTD increase as well as SCD frequency increase in patients with BiV sets without ICD.

Risk of VT, ventricular fibrillation (VF) and SCD development under various QTD were studied among the patients in Multicenter Automatic Defibrillator Implantation Trial (MADIT) II [155]. 817 patients with implanted ICD after ECG registration were divided into the groups of normal and increased QTD. The received numbers of VT, VF, SCD with documented episode of ICD activation were reliably greater in the group of increased QTD.

CONCLUSION AND PROSPECTS FOR FUTURE STUDIES

The survey demonstrates an important estimation of QT interval duration and QTD in pacing optimization parameters and the choice of medical therapy tactics in patients with permanent CP. Thus, the available works in this sphere are extremely few, the data about medical therapy influence are contradictory and concern generally the patients without PM.

The outlined above proves in favor of availability of further purposeful studies of clinical applications of QT interval duration and QTD in conduction of the patients with implanted PM.

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