

Effect of Antagonist Mineralocorticoid Receptors Eplerenon on the Dynamics of QT Interval Dispersion in Patients with Acute Elderly Aged

Larisa V. Shekhovtsova¹, Olga A. Osipova^{2*}, Nina I. Zhernakova³, Mikhail V. Pokrovskiy⁴, Tatyana G. Pokrovskaya⁵

¹Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia

²Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia: Email: osipova@bsu.edu.ru

³Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia

⁴Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia

⁵Belgorod State University, 85, Pobedy St., Belgorod, 308015, Russia

Abstract

The steady aging of the population of developed countries increases the proportion of cardiovascular diseases in the overall structure of the incidence, which leads to an increase in the number of elderly patients in the practice of doctors of many specialties. Currently, there is an increase in the frequency of cardiovascular diseases, including acute coronary syndrome (ACS), while in the Russian Federation due to ACS there is a high mortality rate from sudden cardiac death (SCD). The aim of the work is a comparative analysis of the effect of mineralocorticoid receptor antagonists (MRA) of eplerenone on the predictors of SCD development in patients with ST elevation myocardial infarction (STEMI) with a moderately abnormal ejection fraction (EF) of the left ventricle (LV) in the early stages of the disease. Materials and methods. A total of 52 patients with STEMI who underwent myocardial reperfusion were examined. Patients are divided into 2 groups by age. 26 patients of middle age and 26 patients of elderly. The average age of the patients of the 1st group was 57.6 ± 10.5 years, 2 groups: 69.04 ± 2.02 , the mean indicators of LVEF - $35.34 \pm 4.7\%$. All patients were examined in the first and thirtieth days of rehabilitation treatment. The dynamics of indicators of BCC predictors (dispersion of the QT interval and its parts with correction using the Bazett formula) were assessed: QTd, QTcd, QTapd, JTd, JTapd, SubTd, SubTcd (ms). Results. In a comparative analysis of the effect of MRA on day 30, eplerenone in middle-aged patients had a significantly greater effect on the corrected QT interval: reducing the QTd interval by 16.7%; $\Delta 18.06$ ms ($p = 0.38$), QTcd by 23.7%; $\Delta 27.94$ ms ($p = 0.024$), QTapd by 20.1%; $\Delta 3.1$ ms ($p = 0.031$), JTapd by 14.5%; $\Delta 17.4$ ms ($p = 0.043$), SubTcd by 12.8% $\Delta 14.7$ ms ($p = 0.043$) in relation to treatment in elderly patients.

1. INTRODUCTION

Currently, there is an increase in the frequency of cardiovascular diseases (CVD) [1], including acute coronary syndrome (ACS), while in the Russian Federation due to ACS, there is still a high mortality rate [2]. Since the number of elderly people is rapidly growing all over the world, and the clinical manifestations of CVDs increase dramatically with age, it is believed that prolongation of life expectancy of the population will have an increasingly significant burden on healthcare expenditures. It should be noted that today, aging is highlighted by the dominant factor of the risk of developing CVD. At the same time, in elderly people, an aging heart is characterized by both structural and functional changes. It should be noted that today in European countries in 51% of cases, ST elevation myocardial infarction (STEMI) (angioplasty or stenting), and in 41% - thrombolytic therapy [1]. However, a new approach in the treatment of patients with STEMI, Ming et al and Gonzalez et al detected that ASDs (DM) of the left ventricle (LV), opened in 2004,

when the influence of the mineralocorticoid receptor antagonists (MRA) eplerenone was found on the prognosis in patients with STEMI [3,4,5]. Until recently, there was an opinion about the need for only symptomatic treatment of CVD in elderly and elderly patients and the non-significant effect of medical intervention on the prognosis of life at this age. However, recent large clinical studies convincingly indicate that the patient's age is not a contraindication to the active medical and surgical treatment of many CVDs - coronary heart disease (CHD), stenotic arteriosclerosis of the arteries, heart rhythm and conduction disturbances.

Studying the effect of MRA on the incidence of sudden cardiac death of ARIA [6,7] established their positive effect on reducing overall mortality by 13%, and ARIA - by an absolute 3%. The main factor of the antifibrotic action of spironolactone is the inhibition of the formation of an extra-cellular matrix, which is confirmed by the highest survival of patients in the group with a reduced level of N-terminal particles of type III procollagen - plasma markers of collagen synthesis [8]. Thus, there is a slowdown in electrical remodeling of the myocardium and, accordingly, a

decrease in the probability of SCD [9]. In conditions of ischemia, where there is an elevation of the ST segment, measurement of the wave is difficult for determining the repolarization time only on the basis of the T wave. This is especially true of the central zone of ischemia, where the ST offset reaches its maximum in 20-30 minutes. In clinical terms, more significant changes in the dispersion are associated with the main pathophysiological states of the myocardium, such as acute myocardial ischemia, myocardial infarction [10,11].

At the same time, the effect of MRA on the blockade of aldosterone, the restoration of hibernated myocardium in patients with ACS after reperfusion has not been studied and is of particular significant interest. The question of the comparative effect of various MRA on electrical remodeling of myocardium remains unknown, especially in the early periods after STEMI in patients undergoing myocardial perfusion, depending on the structural, functional and hemodynamic features that formed the basis of this study.

Objective

To provide a comparative analysis of the effect of MRA eplerone and spironolactone on the dynamics of the dispersion of the QT interval and its parts in patients with STEMI with reduced EF in the early stages of the disease.

Materials and Methods

A comparative analysis of the effect of MRA - eplerone on the predictors of sudden cardiac death was performed in patients with STEMI with a moderately abnormal ejection fraction (EF) of the left ventricle (LV) in the early stages of the disease. Patients were examined at admission to the Center for Cardiovascular Surgery of the Belgorod Regional Clinical Hospital of St. Joasaph, with a reduced LV EF <40% (average LV EF - $35.34 \pm 4.7\%$). A total of 52 patients with STEMI who underwent myocardial reperfusion were examined. Patients are divided into 2 groups by age. 26 middle-aged patients and 26 elderly patients. The average age of patients in group 1 was 57.6 ± 10.5 years, 2 groups: 69.04 ± 2.02 . All patients were examined in the first and thirtieth days of rehabilitation treatment. The dynamics of indicators of BCC predictors (dispersion of the QT interval and its parts with correction based on Bazett's formula) were evaluated: QTd, QTcd, QTApd, JTd, JTapd, SubTd, SubTcd (ms). The average age of patients was 57.6 ± 10.5 years. The severity of heart failure during hospitalization before recovery of myocardial reperfusion was assessed according to the Killip classification: class I - 35%, II - 50%, III - 15%. The patients underwent myocardial reperfusion during the first 3 hours after the onset of the disease: thrombolytic therapy and percutaneous coronary intervention with stenting. Also, the criterion for inclusion in the study was the hemodynamically stable course of the disease after revascularization; in general, systolic arterial

pressure (BP) in the group was 132.8 ± 25 mm Hg. Art., diastolic blood pressure - 82.9 ± 14 mm Hg. Art., functional class (FC) of chronic heart failure (CHF) at discharge was on average 1.7 ± 0.15 .

All patients underwent standard therapy for STEMI: double anti-thiagregant therapy, direct anticoagulants (unfractionated heparin and low-molecular heparins, statins, β -adrenergic blockers, ACE inhibitors, diuretics, MRA - eplerone (Espiro, Akrichin), diuretics, diuretics; at two stages: before the reperfusion treatment on the 1st day of the STEMI upon admission to the Department of anaesthesiology and pain therapy and on the 30th day after revascularization. The control group consisted of 30 people comparable in age and sex with patients who underwent STEMI, after the survey, physical examination, research laboratory data registration electrocardiography (ECG) and echocardiography (echocardiographic) no evidence of clinically significant cardiovascular disease.

The study of the clinical condition of the patients was performed using standard techniques. A standard ECG with registration was performed using a SCHILLER AT-1 (2004) 12-channel electrocardiograph at a speed of 50 mm / s. The study determined the following intervals: QT, QTd, QTcd, JTd, JTacd, SubTd, SubTcd. Correction of the duration of the interval and its parts was carried out according to the formula of Bazett (ms). EchoCG was performed on an Philips En Visor C echocardiograph (USA, 2005) with a 3.5 MHz multi-frequency electronic sensor Vivid-7 (USA, 2004) according to the standard technique. The following indicators were evaluated: end-systolic volume (KSO, cm³), final-diastolic volume (KDO, cm³); ejection fraction (PV,%), systolic pressure in the pulmonary artery (SDLA, mm Hg).

Statistical processing of the data was carried out on a personal computer using the variation statistics method using the Microsoft Excel and Statistica 10.0 software [12]. The comparison of groups was performed using non-parametric criteria: two independent selections - Mann-Whitney and Wald-Wolfowitz, for linked samples - the sign criterion and the Wilcoxon criterion in the form of mean and standard deviation (M \pm SD). For a comparative analysis of the effect of the two drugs on the indices of the dispersion of the QT interval plots, and identifying the prevailing therapy for 30 days, we used the non-parametric Friedman test (Friedman's ANOVA Kendall method). The significance of differences was determined at a given level of significance, $p < 0.05$ [13].

Results

A comparative analysis of the indicators of the QT interval and its parts in patients with AIMSPST on the first day before the reperfusion with similar indicators of the control group demonstrated a statistically significant increase in the group of patients examined. Thus, the average value of the QTd interval before myocardial revascularization was higher than the control group by 2.73 times ($p = 0.000000$), and the QTcd indicators were 3.1 times ($p = 0.000000$). At the

same time, there is a significant change in the indicator in the DIMSPST group with a low LV ejection fraction of JTd which was increased 6 times ($p = 0.000000$), and

JTcd - 6.9 times ($p = 0.000000$), SubTd - 5 times ($p = 0.000000$), and SubTcd - 5.8 times ($p = 0.000000$) (table 1).

Table 1. Analysis of the cardiac cycle intervals in patients with STEMI in the first day before reperfusion (M±SD)

Indicators, ms	Control group n=30	Main group n=52	p
	1	2	1-2
QRS	113.70±19.90	110.66±19.24	0.000000
QTd	34.70±2.74	95.00±20.68	0.000000
QTcd	36.04±3.19	113.45±28.93	0.000000
QT apd	24.90±2.42	102.31±17.01	0.000000
QT apcd	25.87±2.79	103.28±20.78	0.000000
JTd	15.76±2.31	95.00±20.68	0.000000
JTcd	16.37±2.45	113.45±28.69	0.000000
JTapd	15.10±2.70	111.18±18.21	0.000000
JTapcd	15.71±3.08	112.36±22.21	0.000000
Sub Td	14.86±2.83	75.70±16.84	0.000000
Sub Tcd	15.46±3.12	90.19±22.59	0.000000

From the data obtained it is clear that the dispersion of the QT interval changes to a greater extent due to its final segment, which, apparently, primarily responds to myocardial ischemia and speaks in favor of the occurrence of fatal ventricular tachyarrhythmias in patients with STEMI without restoring myocardial reperfusion.

Analysis of the structural and geometric indices of the heart in patients with STEMI during hospitalization on the first day before reperfusion revealed a significant decrease in EF by more than 43.7% ($p = 0.000000$) compared to the

control group, and an increase in the volume of the LV cavity was established both due to BWW by 35.5% ($p = 0.000007$), and to a greater extent - CSR, which, due to myocardial infarction, was increased 2.3 times ($p = 0.000000$). Before the reperfusion of myocardium in the main group, a significantly high change in the indices of SDLA was determined compared to the control group, which was increased by 1.7 times ($p = 0.000000$) (Table 2).

Table 2. Analysis of structural and geometric parameters of the heart in patients with OIMspST on the first day before myocardial reperfusion (M±SD)

Indicators	Control group n=30	Main group n=52	P
	1	2	1-2
EF LV, %	61.44±5.16	35.18±5.46	0.000000
EDV LV, ml	107.83±8.26	150.43±40.25	0.000007
EDV	53.99±6.10	73.59±24.55	0.000125
ESV LV, ml	41.33±4.48	98.50±31.56	0.000000
TIS, sm	0.91±0.08	1.26±0.16	0.000000
TPWLV, sm	0.89±0.08	1.18±0.15	0.000000
SPPA, mm hg	25.47±1.87	43.24±14.88	0.000000
MMLV, g/m2	177.21±18.63	284.75±17.32	0.021644
iMMLV	88.77±12.41	135.69±0.52	0.021644

The effect on LV remodeling processes in patients after ACS by administering MRA is quite an important phenomenon, since remodeling is associated with

activation of neurohormones, as well as various cytokines and growth factors, synthesis of free radicals by oxygen,

apoptosis and collagen formation, and all these factors increase the risk of SCD [14,15].

MRA improves heart rate variability and baroreceptor function, reducing the activation of the sympathetic nervous system. All these effects, each of which can contribute to a reduction in mortality, are realized in the early period after ACS. Therefore, it is likely that it is the cumulative effect of the blockade of aldosterone, and not any one individual mechanism, that is responsible for the positive effect of eplerenone on total mortality within 30 days after randomization in the EPHEBUS study [4]. However, the study of the differentiated effect of MRA in patients with STEMI undergoing myocardial reperfusion was not carried out, which is of particular interest. In our study, subsequently, patients of the general group were divided into 2 subgroups depending on the received MRA.

Blocking the coronary blood flow entails a sequence of pathophysiological changes, in particular, areas of necrosis, apoptosis, hibernation of cardiomyocytes, ultimately leading to remodeling of the electrophysiological properties of the myocardium as a whole. Nevertheless, in spite of the complete recovery of myocardial reperfusion, in our patients in our work there

was a reliably significant trend towards an increase in the indicators of electrical instability of the myocardium, without positive dynamics.

A comparative analysis of the effect of MRA eplerenone in different age groups on the indicators of electrical instability of the myocardium in patients with STEMI with reduced LV EF for 30 days determined that the reception in elderly patients eplerenone did not have a significant positive effect, but it had a positive trend to decrease indicators of corrected parts of the QT interval. At the same time, a significant improvement in the contractile function of the LV by 10.14% ($p < 0.05$) was found. In the group of patients with STEMI with LV EF $< 40\%$ on the 30th day of eplerenone intake in middle age, a significant positive decrease in the corrected indices was found. So QTd decreased by 16.7%, which amounted to $\Delta 18.06$ ms ($p = 0.038$), QTcd - by 23.7%; $\Delta 27.94$ ms ($p = 0.024$), QTapd - by 20.1%; $\Delta 3.1$ ms ($p = 0.031$), JTapd - by 14.54%; $\Delta 17.4$ ms ($p = 0.041$), SubTcd - by 12.8%; $\Delta 14.7$ ms ($p < 0.05$), which significantly exceeds the figures for treatment in the group of elderly patients ($p < 0.05$) (table 3), to a greater extent in corrected indicators.

Table 3. Comparative analysis of the effect of EPLERENON on the electrical instability of the myocardium in patients with STEMI with an LV ejection fraction of $< 40\%$ elderly and middle age on day 30 after reperfusion therapy (M \pm SD)

Indicators	Group 1 n=26		Group 2 n=26		P		
	1 point	2 point	1 point	2 point	1 -2	3 -4	5-6
	1	2	3	4	5	6	7#
QRS, ms	115.78 \pm 2 1.61	112.36 \pm 2 0.54	100.0 \pm 10. 27	98.6 \pm 12 .94	1 .000	1 .000	0.1
QTd, ms	107.81 \pm 2 6.83	100.30 \pm 1 0.44	108.32 \pm 2 7.49	90.24 \pm 0 .03	0 .088	0 .038	0.0 10
QTcd, ms	117.14 \pm 1 4.82	110.20 \pm 4. 26	118.11 \pm 1 0.43	90.16 \pm 0 .04	0 .087	0 .024	0.0 10
QT apd, ms	107.12 \pm 1 9.66	107.04 \pm 1 5.43	105.42 \pm 1 1.14	79.31 \pm 9 .42	0 .179	0 .031	0.0 07
QT apcd, ms	110.22 \pm 1 6.42	108.34 \pm 1 4.72	107.84 \pm 2 1.24	80.04 \pm 1 0.18	0 .134	0 .01	0.0 00
JTd, ms	99.83 \pm 11. 94	91.23 \pm 7.3 7	94.71 \pm 18. 57	90.42 \pm 1 0.42	0 .059	0 .173	0.0 98
JTcd, ms	116.84 \pm 4. 83	110.37 \pm 5. 64	98.78 \pm 11. 32	81.22 \pm 6 .07	0 .067	0 .01	0.0 00
JTapd, ms	118.73 \pm 2 1.41	111.82 \pm 1 1.21	119.62 \pm 1 6.45	102.2 \pm 7 .86	0 .066	0 .041	0.0 38
JTapcd, ms	120.52 \pm 1 1.32	106.65 \pm 1 0.24	121.33 \pm 1 1.06	100.03 \pm 6.87	0 .119	0 .011	0.0 00
SubTd, ms	105.91 \pm 1 7.29	100.24 \pm 9. 59	104.63 \pm 2 0.43	98.83 \pm 1 4.43	0 .075	0 .089	0.0 67
SubTcd, ms	112.73 \pm 1 6.92	109.33 \pm 8. 87	115.21 \pm 1 0.28	100.52 \pm 9.61	0 .088	0 .039	0.0 43

In our study, a comparative analysis was conducted of the effect of the dynamics of MRA drug correction of eplerenone in patients of different age groups (elderly and middle age) on the structural and

geometric parameters of the heart in patients with STEMI 30 days after myocardial reperfusion (Table 4).

Table 4. Analysis of the effect of the dynamics of drug correction of eplerenone in elderly and middle-aged patients with STEMI on the structural and geometric parameters of the heart on day 30 after myocardial reperfusion (M±SD)

Indicators	Group 1 n=26		Group 2 n=26		P		
	1 point	2 point	1 point	2 point	1	3	5
	1	2	3	4	5	6	7
LVEF, %	35.09±5.8	38.65±6.1	35.37±4.9	43.04±5.5	0	0.	0
EDV LV, ml	146.26±39	152.39±3	159.22±4	150.00±3	0	0.	0
EDV	75.27±25.	78.91±21.	76.98±22.	64.88±18.	0	0.	0
ESV LV, ml	96.74±30.	94.24±29.	104.33±3	89.66±26.	0	0.	0
TWLV, sm	1.28±0.17	1.26±0.16	1.22±0.15	1.20±0.61	0	1.	1
TPWLV, sm	1.20±0.16	1.19±0.16	1.12±0.14	1.10±0.13	0	0.	1
SPPA, mm hg	42.09±11.	35.85±8.1	45.67±21.	32.71±5.1	0	0.	0
MMLV, g/m2	287.03±0.	280.04±1.	284.75±1	272.58±1	0	0.	0
iMMLV	139.21±0.	137.19±0.	135.69±0.	119.96±2.	0	0.	0

It was found that additional eplerenone therapy in middle-aged patients also had an additional positive effect on LV structural and functional parameters. Thus, LV EF increased by 21.68%; $\Delta 7.67\%$ ($p = 0.006$), LV CLV decreased by 5.8%; $\Delta 9,22$ ml ($p = 0.044$), the indexed index of the differential effect of LV decreased by 15.7%; $\Delta -12,1$ ml ($p = 0.037$). At the same time, the effect on the decrease in LV CSR by 14.06% was proved; $\Delta -14,67$ ml ($p = 0,015$), which was reflected in the decrease in SLEA by 28.4%; $\Delta -12.96$ mm Hg ($p = 0.023$). Significant decrease in both MM by 4.27%; $\Delta -12,17$, ($p = 0.044$) and IMM by 11.6%; $\Delta -15.73$ ($p = 0.037$).

Conclusion

The prognostic role of corrected QT interval in ST-elevation myocardial infarction is still unknown. This study aims to identify the prognostic value of corrected QT interval prolongation in acute coronary syndrome. A comparative analysis of the degree of influence of eplerenone therapy in patients of different age groups (middle-aged and elderly) for 30 days

showed in our study that the effect of eplerenone on 30 days in middle-aged patients was significantly superior to the effect of eplerenone in patients with corrected QT interval indicators: dQTd, dQTcd, dQTapd, dQTapcd, JTcd, dJTapd, dJTapcd, dSubTcd. It is noteworthy that when assessing the effect on markers of electrical myocardial instability in the elderly, they did not significantly reduce them, having only a tendency to decrease. It was established that eplerenone in the middle-age group had a significant impact on all indicators of the QT interval: dQTd, dQTapd, dJTapd, dSubTcd. There is also a significant improvement on the 30th day of the effect of eplerenone in the middle age group and on the structural and functional indicators of the left ventricle such as: dFV LV, dKDO LV, dKSO LV, dSDLA.

Increased dispersion of the QT interval (QTd) was found in patients with acute myocardial infarction, it was subsequently shown that this index decreases with thrombolytic therapy. So, Lörincz et al. Evaluated the effect of intravenous streptokinase on QT and JT dispersions and found that QTd increased in the first hours after a heart attack and thrombolytic therapy, but

decreased 8 ± 2 hours after it was performed [16,17]. Subsequently, QT and JT intervals were determined by predictors of the effect on all-cause mortality, regardless of the duration of the QRS interval, with some advantage of using JT. Our study aimed at identifying risk factors associated with the lack of dispersion dynamics of the QT interval after coronary artery reperfusion in patients with ACS, STEMI revealed that dilatation of the left ventricle is an independent factor that does not reduce the variance of the corrected QTcd index. The scientific work on the study and evaluation of individual intervals that make up the QT interval as separate indicators of repolarization is very important.

REFERENCES

- [1] Chazov, E.I., 2007. Acute coronary syndrome: problems, tasks, prospects. *Medichna newspaper "Health of Ukraine"*, 19: <http://health-ua.com/article/17223-ostryj-koronarnyj-sindrom-problemy-zadachi-perspektivy> (appeal date 11/14/2017) (In Russian).
- [2] Kozulin, V.Yu., 2017. The current state of the problem of acute coronary syndrome. *Russian Medical Server - cardiology news*, URL: http://www.rusmedserv.com/cardio/ac_sindr.htm.
- [3] Skvortsov, A.A., 2017. Mineralocorticoid receptor antagonists in the treatment of patients with chronic heart failure and myocardial infarction: a modern view on the old problem. *Cardiology*, 4:257-264.
- [4] Montalescot, G., Pitt, B., 2014. Early eplerenone treatment in patients with acute ST-elevation myocardial infarction without heart failure: the Randomized Double-Blind Reminder Study. *Eur Heart J.*, 7:35(34):2295-3002.
- [5] Pitt, B., Remme, W., Zannad, F., et al. 2003. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *New Engl J Med.*, 3:348(14):1309-1321.
- [6] Beygui, F., Cayla, G., Roule, V., et al. 2016. Early Aldosterone Blockade in Acute Myocardial Infarction: The ALBATROSS Randomized Clinical Trial. *J Am Coll Cardiol.*, 67:1917—1927.
- [7] Greenberg, B.H., 2016. A Treatment Approach for Patients With Chronic Systolic Heart Failure. *Rev Cardiovasc Med.*, 17(1):22-29.
- [8] Pitt, B., Zannad, F., Remme, W.J., et al. 1999. For the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *New England Journal of Medicine*, 341(10):709-717.
- [9] Pitt, B., White, H., Nicolau, J., et al. 2005. Eplerenone reduces mortality 30 days after randomization following acute myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. *Journal of the American College of Cardiology*, 46(3):425-431.
- [10] Lozhkina, N.G., 2013. Problems of predicting outcomes of acute coronary syndrome. *Modern problems of science and education*, 4:154.
- [11] Gegenava, B.B., Drapkina, O.M., 2015. Selective antagonist of mineralocorticoid receptors of eplerenone in cardiological practice. *Rational pharmacotherapy in cardiology*, 11(2):177-181.
- [12] Novikov, D.A., Novochadov, V.V., 2005. Statistical methods in biomedical experiments (typical cases). Volgograd: VolSMU Publishing, - 84 p.(In Russian)
- [13] Makarova, N.V., 2012. Statistical analysis of biomedical data using statistical software packages Statistica, SPSS, NCSS, SYSTAT. St. Petersburg: Polytechnic Service, 178 p.(In Russian).
- [14] Shekhovtsova, L.V., Osipova, O.A, 2015. Structural-functional and hemodynamic mechanisms of chronic heart failure in patients with ACS after stenting. *International Journal of Experimental Education*, 7:154-155.
- [15] Osipova, O.A., 2016. Pathomorphological mechanisms of regulation of myocardial fibrosis formation in patients with chronic heart failure on the background of ischemic heart disease. *Journal of heart failure*, 17(5):357-364.
- [16] Nikiforos, S., Hatzisavvas, J., Pavlides, G., Voudris, V., Vassilikos, V.P. 2003. QT-interval dispersion in acute myocardial infarction is only shortened by thrombolysis in myocardial infarction grade 2/3 reperfusion. *Clin Cardiol.*, 26(6):291-295.
- [17] Zulqarnain, M.A., Qureshi, W.T., O'Neal W.T., Shah A.J., 2015. Risk of mortality associated with QT and JT Intervals at different levels of QRS duration (from the third national health and nutrition examination survey [NHANES III]). *Am J Cardiol.*, 1;116(1):74–78.