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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

COMPARATIVE STUDY OF HEART RHYTHM VARIABILITY AND ELECTROLYTES IN THE TREATMENT OF PATIENTS WITH CHRONIC HEART FAILURE WITH FUROSEMIDE AND TORASEMIDE

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OVERVIEW OF THE WORK

Relevance of the topic. Nowadays, regardless of the economic situation, the high incidence of chronic heart failure (CHF) is observed all over the world. Despite advances in its treatment, the CHF continues to be an unfavorable prognosis and one of the leading causes of hospitalizations. The CHF progresses in cardiovascular diseases as a result of myocardial remodeling, endothelial dysfunction, metabolic changes caused by increased activity of the sympatho-adrenal, renin-angiotensin-aldosterone system (RAAS) etc., where the ischemic heart disease (IHD) is considered to be the most common of these diseases. Angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, and mineralocorticoid receptor antagonists improve the long-term prognosis of the CHF and are recommended as first-line drugs. However, the reduction of recurrent hospitalizations due to the deterioration of the clinical condition in patients can be achieved by preventing the accumulation of fluid in the body. In this regard, diuretics, especially loop diuretics, are of great importance in the treatment of the CHF[1]. Studies show that diuretic therapy along with the basic therapy allows reducing the frequency of hospitalization in terms of decompensation[2].

However, long-term treatment with diuretics, especially furosemide, leads to the violation of electrolyte balance, carbohydrate, lipid and purine metabolism and increases activity of the RAAS, which is reflected in changes in neurohumoral regulation

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[2] *Ponikowski, P.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC / P.Ponikowski, A.A.Voors, S.D. Anker [et al.] // Eur. J. Heart Fail., –2016. 37, – p. 2129-2200.

and heart rhythm variability (HRV) [3]. The close correlation between the HRV and sudden death rates was identified[4]. The HRV analysis is essential not only in the assessment of the tone of the autonomic nervous system, but also in the selection of the optimal dose of drugs and monitoring the treatment. The long-term treatment with furosemide is known to have a negative effect on HRV, as well as on the duration and dispersion of the QT interval[5].

All this suggests that pleiotropic loop diuretics, which have a long half-life, should be preferred in the treatment of CHF. Possibilities for the use of torasemide in the CHF treatment are being studied due to its high biological efficacy compared to furosemide, its ability to reduce the risk of hypokalemia, which often limits treatment with diuretics, as well as its ability to inhibit the endogenous hormonal system by blocking aldosterone receptors. The data on the clinical efficacy of torasemide is met in the literature[6,7]. However, there is no information on the analysis of the effect of the long-term use of torasemide on cardiac electrical instability markers: HRV, QT interval duration and dispersion, the development of various arrhythmias in a complex correlation with blood biochemical parameters. All this indicates the importance of studying the

[3]Алиева А.М. Вариабельность сердечного ритма в оценке клинико–функционального состояния и прогноза при хронической сердечной недостаточности / А.М. Алиева, Н.И. Булаева, О.И. Громова [и др.] // Креативная кардиология.– 2015.– № 3. – с.42–55.

[4]Виноградова Н.Г. Прогноз жизни пациентов с хронической сердечной недостаточностью и фибрилляцией предсердий в зависимости от контроля гемодинамических показателей и толерантности к физической нагрузке на фоне базисной терапии / Н.Г. Виноградова, Д.С. Поляков, И.В. Фомин [и др.]// Кардиология. – 2019. – том59. - №4. – с.51-58.

[5]Остроумова О.Д., Голобородова И.В. Влияние отдельных групп лекарственных препаратов на риск удлинения интервала QTc. // Consilium Medicum. 2019; 21 (10): 95–106.

[6]*Барышникова,Г.А.*Современные подходы к применению торасемида при сердечно-сосудистых заболеваниях / Г.А.Барышникова, С.А.Чорбинская, С.А.Степанова // Consilium Medicum, – 2017. 19 (10), – с. 66-72.

[7] *Mentz, R.J.* Torsemide versus furosemide in patients with acute heart failure (from the ASCEND-HF Trial) / R.J.Mentz, V.Hasselblad, A.D. De Vore [et al.] // Am. J. Cardiol., – 2016. 117 (3), – p. 404-411.

prospects for the use of diuretics in the treatment of the CHF.

In view of the above, we have set the following purpose of the research in order to study the effect of different generations of loop diuretics during CHF on HRV, QT interval duration and dispersion, the development of various arrhythmias, as well as the correlation between blood electrolyte balance and purine metabolism..

The purpose of the research is to comparatively study the effect of loop diuretics used during the complex treatment of CHF on the electrical stability of the myocardium, heart rhythm variability, and blood electrolyte balance.

Research objectives:

1. To study the characteristics of such markers of cardiac electrical instability as heart rhythm variability, corrected QT interval, QT dispersion and cardiac arrhythmias in the patients with CHF during furosemide and torasemide therapy
2. Assessment of the dynamic changes of blood parameters (electrolyte balance, NTproBNP, uric acid) in the patients with CHF during furosemide and torasemide therapy;
3. Comparative assessment of the functional status of the left ventricle of the heart in the patients with CHF during furosemide and torasemide therapy;
4. To study the correlation between blood biochemical parameters, electrical instability of the myocardium, heart rate variability, corrected QT interval, indicators reflecting the functional status of the left ventricle in the patients with CHF during furosemide and torasemide therapy;
5. Dynamic assessment of functional class and quality of life in the patients with CHF during furosemide and torasemide therapy.

Research methods. All patients underwent complex laboratory (electrolytes in blood, NTproBNP, uric acid) and instrumental examination methods (ECG in 12 standard procedures, ECG Holter monitoring, Echocardiography, 6-minute walking test). The clinical status assessment scale (based on V.Y. Mareyev modification, 2002) and the Minnesota questionnaire was used to assess quality of life.

Main points submitted for the thesis defense:

- Although furosemide and torasemide loop diuretics are effective in the treatment of CHF, they do not have an unambiguous effect on the electrical stability of the heart. The long-term furosemide treatment was accompanied by the heart rhythm disorder: an increase in the frequency of supraventricular and ventricular arrhythmias, while the treatment with torasemide was accompanied by a decrease in the incidence of such arrhythmias;
- The furosemide diuretic therapy in the patients with CHF makes the time and spectral indexes of the HRV in the direction of prevailing of the cardiac sympathetic and humoral-metabolic effects. The torasemide diuretic therapy results in improving of the time (SDNN, SDANN, rMSSD) and spectral (VLF, LF, HF) indexes of the HRV, which suggests that torasemide simultaneously reduces RAAS and sympathetic nervous system (SNS) activity;
- Increased levels of NTproBNP in the blood are associated with a decrease in parasympathetic activity and increased humoral-metabolic activity against the background of impaired systolic function of the left ventricle. During the long-term torasemide therapy of CHF patients, unlike the furosemide therapy, a decrease in NT-proBNP levels was more significant. This therapy had relatively neutral metabolic-minimal adverse effects, and no negative effects on blood electrolyte balance;
- The clinical and hemodynamic efficacy of torasemide was higher than that of furosemide in the use of various loop diuretics in the basic therapy of CHF, accompanied by a decrease in the functional class of CHF and improvement of patients' quality of life.

Scientific novelty of the research. During the use of furosemide and torasemide in the basic therapy of the CHF patients:

- Markers of electrical instability of the heart: heart rate variability, duration and dispersion of the QT interval , frequency of cardiac arrhythmias and systolic function of the left ventricle were studied in a complex way, as a result,

changes in RAAS and SNS were analyzed;

- The effect of the treatment on electrolyte balance, purine metabolism, functional status, quality of life was compared and correlated with heart rhythm variability, corrected QT interval and QT interval variance.

Practical significance. When there is a need in use of diuretics in basic therapy of CHF patients, it should be considered that torasemide, having a high clinical and hemodynamic efficacy and a positive effect on cardiac electrical instability, reduces the incidence of cardiac arrhythmias, does not affect the duration of the corrected QT interval, improves heart rhythm variability, left ventricular systolic function, reduces the functional class of CHF, and being relatively neutral in metabolism (no serious disturbances in electrolyte and purine metabolism) leads to an improvement in the quality of life of patients.

Implementation of the research results. The results of the dissertation work were applied in the clinical practices of the Scientific Research Institute of Cardiology named after the academician J. Abdullayev and the Therapeutic Department of Baku City Clinical Hospital No.5.

Approbation. The results of the research were discussed in XXVI International scientific and practical conference in the subject of "Actual problems of the science of XXI century" (Moscow, 2017) and the scientific and practical conference dedicated to the 40th anniversary of the foundation of the Scientific Research Institute of Cardiology named after the academician J. Abdullayev (Baku, 2018).

The preliminary discussion of the dissertation work was conducted in the meeting of the Scientific Council of the Scientific Research Institute of Cardiology named after the academician J. Abdullayev (18.03.2019, protocol No.1).

The approbation of the work was conducted in the scientific workshop of the ED 2.27 Dissertation Council conducting activity attached to the Azerbaijan Medical University (30.04.2021, protocol No.1).

Research Site. The dissertation work was performed at the

Cardiac Failure Department of the Research Institute of Cardiology named after acad. J. Abdullayev.

Publications. The key provisions of the dissertation work are reflected in 11 scientific works including 6 articles (including 2 abroad) and 5 theses (including 4 abroad).

Structure and length. The dissertation work is presented in 156 computer pages (186046 symbols) and consists of introduction (5 pages, 9907 symbols), literature review (30 pages, 58505 symbols), materials and methods of the research (13 pages, 13310 symbols), results of the research (61 pages, 69080 symbols), chapters on their discussion (15 pages, 27585 symbols), conclusions (2 pages, 3264 symbols), practical recommendations (1 page, 874 symbols) and references (24 pages) The work is visualized with 16 figures and 26 tables. 7 of the references in the reference list consisting of 194 sources are in Azerbaijani and 188 of them are in foreign languages.

MATERIALS AND RESEARCH METHODS

The research work was carried out in the Cardiac Failure Department of the Scientific Research Institute of Cardiology named after the academician J Abdullayev and the Therapeutic Department of Baku City Clinical Hospital No.5. The research included 100 patients: 59 men (middle age 57,1±2,1) and 41 women (middle age 61,7±2,5). They were diagnosed of complicated IHD with the chronic heart failure of II-IV functional classes (FC) according to NYHA.

Main nosologial forms in the examined patients were the IHD, stable tension stenocardia and postinfarction cardiosclerosis (PIC). All patients were randomized in 2 groups: the diuretic therapy was conducted with furosemide in the first group (50 patients) but with torasemide in the second group (50 patients). CHF of FC III was noted in the most patients (35 people in group I and 37 people in group II).

The clinical and demographic characteristics of the examined patients are demonstrated in Table 1.

As can be seen from the table, the patients in the study groups did not differ significantly in terms of key demographic and clinical characteristics before the treatment.

The control group included 21 patients with IHD of FC II-III stable angina without CHF. Patients in the control group and patients in the main groups were of the same age and sex. These patients had not been treated with diuretics.

Table 1

Clinical and demographic characteristics of patients

	I group (Furosemide)	**II group (Torasemide)**	**Statistical significance**
Number of patients	50	50	
The average dose of diuretics, mg	64,1±1,2	19,5±0,9	p<0,001
Demographic indicators			
Men/women	31/19	28/22	p>0,05
Average age	58,7±1,1	55,1±2,2	p>0,05
Clinical characteristics			
6-minute step test, m	201,1±75,4	225,4±69,7	p>0,05
CHF FC (NYHA)			
FC II, number of patients	15(30%)	13(26%)	p>0,05
FC III, number of patients	35(70%)	37(74%)	p>0,05
IHD, number of patients	43(86%)	40(80%)	p>0,05
PIC, number of patients	26(52%)	27(54%)	p>0,05
AH, number of patients	47(94%)	48(96%)	p>0,05
Clinical condition assessment scale, points	8,5±1,2	7,1±1,7	p>0,05
Quality of life according to the Minnesota survey, points	71,6±7,5	69,7±5,9	p>0,05

The preliminary doses of furosemide and torasemide for each patient were selected individually depending on the CHF FC and salient level of edema syndrome: for CHF of FC I were 20 and 5 mg, respectively, and for CHF of FC II-IV were 40 and 10 mg, respectively. The following correction of the doses was reached up to 120 mg for furosemide and 40 mg for torasemide depending on the diuretic response.

In both groups, patients were treated with ACEIs (enalapril 2.5-20 mg twice a day), beta-blockers (carvedilol 6.25-50 mg twice a day), aldosterone antagonists (spironolactone 25-50 mg a day), statins (rosuvastatin 10-20 mg a day), antiplatelet agents (acetyl salicylic acid 75-100 mg a day). At the same time, angiotensin receptor blockers (valsartan 40-160 mg a day), (in case of intolerance to ACEIs), nitrates (isosorbide mononitrate 20-40 mg twice a day) were prescribed.

All patients were conducted complex laboratory (electrolytes in the blood serum, NTproBNP, uric acid) and instrumental examination methods (ECG in 12 standard procedures, ECG Holter monitoring, EchoCG, 6 minute walk test) for the assessment of the condition of the cardiovascular system, as well as HRV indicators, Q-T interval duration and its variance, clinical condition assessment scale (based on V.Y. Mareyev modification, 2002) and Minnesota questionnaire for the assessment of the quality of life were applied before and 3-6 months after the diuretic therapy.

Echo-CG examinations were conducted by “Vivid 3” (USA) device at standard positions, M and B modes according to the recommendations of the American Society of Echocardiography.

6 minute walk test was conducted for specifying the functional class of chronic heart failure on the NYHA.

The ECG monitoring method was used for learning the variability of heart rate and the frequency of arrhythmias in the CHF patients over non-invasive “ECGproHolter” (Germany) system. The gradation of the ventricular rate disorder was specified over M. Ryan classification (1975).

The method of examination of the heart rhythm variability was based upon the Standards on Measurement, Physiological Interpretation and Clinical Use (1996) developed by the working group of the European Society of Cardiologists and North American Society on Stimulation and Electrophysiology. The following time parameters were investigated: SDNN; SDANN, rMSSD, pNN50.

It was possible to differ the following components of the spectral force under the spectral examination conducted under quick Fourier transformation: TP, VLF, LF, HF, VSS, LF/HF.

At the same time, the duration of the QT interval and its variance were studied. The corrected QT interval (QTc) was calculated by the Bazet H. formula: $QTc=QT/\sqrt{R\text{-}R}$. The maximum (QTcmax) and minimum (QTcmin) duration of QTc were determined. Repolarization variance QTcd was calculated by the following formula: QTcd=QTcmax–QTcmin

The concentration of the natrium, potassium and magnesium in blood serum was assessed with the help of AEK-01 ("Квер", Russia) electrolyte analyzer through potentiometric method but NTproBNP, C-reactive protein with harsh-phased immunoferment method in AQT90 FLEX (Radiometer Medical ApS, Denmark) analyzer.

The gained numerical indexes were developed statistically by using in non-parametric (Wilcoxon-Mann-Whitney, U-criterion) and correlation methods (r factor, Fischer factor). The calculation was made in Excel 2013 and SPSS-20 programs on computer.

RESULTS OF THE RESEARCH AND THEIR DISCUSSION

Against the background of the treatment in both groups, the characteristics of changes in the time and spectral parameters of HRV were studied. No significant differences in time and spectral values of HRV were observed in patients prior to furosemide and torasemide treatment.

The absolute limits of time parameters of HRV in group I tended to decrease by the end of 3-month and 6-month treatment compared to pre-treatment indicators. Thus, the indicator of SDNN, showing general heart rhythm variability, decreased from 92.8 to

83.3 by the end of 6 months treatment amounting to 10.2%. While SDNN in 26 (52.0%) patients was below the control level before the treatment, this number reached 29 (58.0%) in a 3 months treatment and 32 (64.0%) in a 6 months treatment. At the same time, the number of patients who approached the control level after the 3 and 6 months treatments was 21 (42.0%) and 18 (36.0%), respectively.

Accordingly, against the background of the long-term treatment with furosemide, there was a tendency of HRV decrease. Similar changes were observed in the components of parasympathetic parameters of HRV. Thus, such indicators as iSDNN, rMSSD, pNN50 tended to decrease to 11.5%, 16.8% and 19.8%, respectively (P> 0.05).

Therefore, by the end of the 6 months treatment the number of patients with iSDNN decreased against the control level increased from 29 (58.0%) to 31 (62.0%). Whereas, for rMSSD and pNN50 indicators these numbers increased from 10 (20.0%) to 20 (40.0%), and from 18 (36.0%) to 26 (52.0%), respectively.

Spectral parameters of HRV of CHF patients receiving treatment with furosemide were characterized primarily by an increase in the chromal-metabolic effects on heart rhythm, which is reflected in the absolute limits (VLF) and percentage (VLF%) of spectral analysis components of very low frequency, which showed 4.0% at the pre-treatment period and 2.9% (P <0.05) by the end of 6 months treatment.

The change in the sympathetic parameters of the spectral analysis of HRV was reflected in the decrease of both absolute (LF) and percentage (LF%) of the spectral components. Thus, a decrease by 15.5% and 16.1% (P <0.05), respectively, was observed by the end of 6-month treatment compared to pre-treatment indicators (Fig. 1).

During the 6-month treatment with furosemide, there was an increase in the number of patients with higher indicators against the control level [VLF (from 8 (16.0%) to 17 (34.0%) patients) and VLF% (from 6 (12.0%) to 18 (36.0%) patients)].

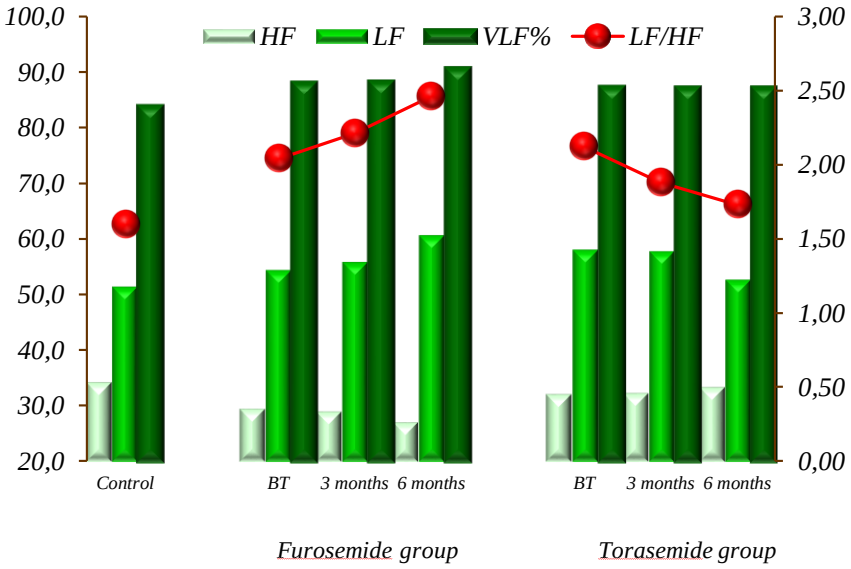

Fig. 1. Changes in the heart rhythm during the treatment

Against the background of the long-term 3 months and 6 months treatment with torasemide, the characteristics of changes in the time parameters of HRV were manifested by an insignificant increase in these indicators (Table 2).

Thus, by the end of the 6 months treatment, the general HRV indicator SDNN increased by 1.8% compared to pre-treatment period. Therefore, while before the treatment the SDNN level was close to the control level in 31 (62.0%) patients, the number of such patients increased to 34 (68.0%) after 6 months of treatment.

By the end of the 6 month treatment period, the indicators reflecting the parasympathetic activity of HRV time analysis, which are iSDNN, rMSSD, pNN50 increased compared to pre-treatment indicators (P> 0.05), reaching 5.9%, 12.8% and 13.9%, respectively. During the 6-month treatment period, the number of patients whose indicators were approaching the norm also increased: iSDNN from 24 (48.0%) to 29 (58.0%), rMSSD from 34 (68.0%) to 37 (74.0) %), and pNN50 from 40 (80.0%) to 45 (90.0%) people.

Table 2

Characteristics of heart rhythm variability against the background of treatment with furosemide and torasemide

Inidcator	I group (n=50)		II group (n=50)	
	Before the treatment	After the 6 month treatment	Before the treatment	After the 6 month treatment
SDNN, ms	92,8±3,9 (42-140)	83,3±4,1 (38-135)	99.5±3,4 (54-141)	104.4±3.4 (61-145)
iSDANN, ms	97,7±2,6 (65-142)	100,6±3,0 (52-152)	98.2±2,3 (54-125)	99.2±2.3 (60-125)
iSDNN, ms	32,2±1,8 (13-65)	28,5±1,8 (9-62)	33.1±1,7 (7-53)	35.2±1,7 (9-55)
rMSSD, ms	18,5±0,7 (10-28)	15,4±0,7^ (7-26)	17.0±1.0 (4-31)	19.5±1.0 (7-31)
pNN50, %	4,50±0,41 (1-9,01)	3,61±0,39 (0,11-8,95)	4,9±0,31 (1.07-9,01)	5.69±0,3 (1.98-9.12)
TP, ms^2	12243,0±59,2 (10015-12604)	12428,1±24,3 (11936-12607)	12372.5±120.4 (10236-15523)	12271.0±35.9 (11662-12580)
VLF, ms^2	10822,9±131,1 (8022-12078)	11278,0±99,7^ (9218-12228)	10717.4±155.2 (8429-12228)	10655.1±105.4 (9216-11822)
LF, ms^2	785,5±41,0 (265-1545)	663,8±40,8^ (265-1472)	870.6±61.1 (178-1905)	813.4±43.0 (55-1486)
HF, ms^2	442,1±38,3 (116-1357)	333,0±36,0^ (83-1183)	468.6±42.5 (12-1143)	564.0±42.4 (182-1281)
HFnu	29,4±1,0 (20,4-41,3)	27,0±1,0 (15,6-40,9)	32.0±1.7 (17.4-82.2)	33.3±1,1 (19.6-47.2)
LFnu	54,3±1,3 (37,7-67,7)	60,5±1,0^ (43,9-73,1)	58.0±0.9 (45.8-73.1)	52.6±1,1^ (33.1-69.9)
LF/HF	2,043±0,1 (1-3,33)	2,46±0,1^ (1,13-4,62)	2,12±0,09 (1.04-3.59)	1.73±0,09 ^ (0.81-3.34)
VLF, %	88,1±0,8 (72,1-96,4)	90,7±0,7 (75,8-97)	87.3±0,9 (72.3-97.7)	87.2±0,7 (75.5-94.5)
LF, %	6,46±0,36 (2,12-12,9)	5,42±0,33 (2,12-12,1)	7.15±0,51 (1.42-15.6)	6.74±0,33 (3.3-12.2)
HF, %	3,68±0,33 (0,93-11,3)	2,70±0,30^ (0,66-11,1)	3.90±0,35 (0.41-9.35)	4.61±0,35 ^ (1.46-10.5)

Note: Statistical significance: Furosemide compared to torasemide: ^ - p <0.05; ^^ - p <0,01; ^^^ - p <0.001.

Changes in the spectral parameters of HRV were characterized by an improvement in the humoral-metabolic effects on heart rate: a decrease in very low-frequency components of the spectrum in both absolute (VLF - 0.6%) and percentage (VLF% - 0.1%) values. Changes in the parasympathetic component of the spectral analysis of HRV were characterized by an increase in the frequency of the high-frequency spectrum component in both absolute (HF), normalized (HFnu) and percentage (HF%) values. Thus, by the end of the treatment period these values increased to 16.9%, 3.9% and 15.4%, respectively, compared to the previous indicators. In addition, only 36 (72.0%) patients had VLF indicators close to the control group normative values, whereas by the end of 6 months treatment, this number reached 46 (92.0%). Similarly, the number of patients with increased VLF reduced from 14 (28.0%) to 4 (8.0%). At the same time, the number of patients with normal levels of VLF% increased from 40 (80.0%) to 46 (92.0%). None of the patients, neither before nor after the treatment, had VLF and VLF% levels lower than those of the control group patients without CHF.

Thus, there was a more significant improvement in the time and spectral parameters of HRV after the 6 months of treatment with torasemide compared to the treatment with furosemide. Treatment of CHF patients with torasemide normalizes changes in sympathetic-parasympathetic balance by decreasing both absolute and relative sympathetic effects of cardiac arrhythmias against the background of the absence of symptoms of relative sympathotony and weakening of humoral-metabolic effects on heart rhythm, which has a significant correlation with blood electrolyte balance and hyperuricemia.

Cardiac electrical stability was also studied in the CHF patients during their treatment with furosemide and torasemide. The most common form of supraventricular arrhythmia is single supraventricular extrasystoles, which were recorded at the similar frequency of 20.5 and 20.8 times in patients of groups I and II. The number of supraventricular extrasystoles tended to increase insignificantly by 5.5% in the background of the treatment with furosemide, while there was a statistically significant decrease in the number of arrhythmias in the background of the treatment with

torasemide by 3.9 times (p <0.001). The subsequent form of the supraventricular arrhythmias by its frequency in the CHF patients was paired extrasystoles. These arrhythmias increased significantly by 2.9% during the treatment with furosemide and decreased by 2.3 times during the treatment with torasemide (p <0.01). Similar changes in the number of paired ventricular extrasystoles per day occurred against the background of the drug treatment. The treatment with furosemide resulted in a statistically significant increase in the number of such extrasystoles (P <0.05) by 17 times, while the treatment with torasemide resulted in a decrease by 1.4 times (P <0.05).

The number of ventricular extrasystoles was 3 times higher (P <0.05) as a result of the furosemide treatment while the torasemide treatment resulted in reduction in this type of arrhythmia by 2.6 times (P <0.05).

Thus, the analysis of changes in the electrical stability of the heart in patients with CHF against the background of the treatment with diuretics showed different dynamics of single and paired supraventricular and ventricular extrasystoles. Although a high number of these arrhythmias was observed as a result of the treatment with furosemide, a significant decrease in their number was observed against the background of the treatment with torasemide. The findings confirm that furosemide and torasemide, along with being effective diuretics, do not have the same effect on electrical instability of the heart. Unlike furosemide, the treatment with torasemide is accompanied by a decrease in the number of supraventricular and ventricular arrhythmias.

The main reason for the increase in the number of arrhythmias in the background of the treatment with furosemide is the development of hypokalemia and hypomagnesemia, which can lead to prolongation of the QT interval and lethal outcomes. At the same time in the study of the duration of the QT interval and its variance QTc-min and QTcmax values in the patients of group I were, 390.0 ± 7.06 and 417.0 ± 0.01 ms, respectively and in group II these indicators were 357.1 ± 9.60 and 399.0 ± 0.01 ms, respectively (p <0.001). QTcd did not significantly differ in either group. Against

the background of the treatment, the values of QTc-max were 425.0 ± 0.02 (p <0.05) in group I and 386.0 ± 0.19 in group II, while QTc values were 410.0 ± 2.06 and 396.7 ± 7.95, respectively.

When furosemide is added to the basic therapy of the CHF patients, an improvement is mostly observed in the intracardiac hemodynamism indexes, pumping ability of the left ventricle. Against the background of the use of torasemide, an improvement in the main indicators of intracardiac hemodynamics, as well as a decrease in left ventricular hypertrophy was observed.

The diastole and systole sizes of the left ventricle in the group taking torasemide (last diastolic size and last systolic size) fully decreased by 2,1% and 4,3% (p<0,05) the end of 6 month therapy comparing to the indexes before the therapy. The ejection fraction (EF) which is the main pumping parameter of the heart, also decreased by 6,4% at the end of 6 month therapy.

The long-term diuretic therapy with torasemide caused the thickness of the left ventricle to decrease that it became apparent with the decrease of the thickness of the posterior wall (PW) and the thickness of the intraventricular septum (IVS) (6,2% and 7,1% by the end of 6 month therapy, respectively). A decrease in the left ventricular myocardial mass (LVMM) was observed during the long-term treatment with torasemide in patients with CHF (7.1%; P <0.05).

Thus, the improvement of the key Echo-CG indexes of the systolic function and the structural-functional condition of miocardia was observed in the CHF patients with furosemide and torasemide added to the basal therapy in the background of long-term diuretic therapy. Along with that these changes became more important in the background of torasemide therapy. In contrast to furosemide, the long-term treatment of CHF patients with torasemide was characterized by a decrease in the left ventricular end-diastolic size and LVMM, resulting in improved systolic function (P <0.05).

In the present research, this index was appointed in the patients before and after the therapy as the appointment of natrium uretic peptides, especially, NTproBNP level as the laboratory tests of the CHF. Initially, a significant increase of NTproBNP level in the CHF

patients of both groups was observed. By the end of 6 month diuretic therapy with furosemide, the NTproBNP level was observed to decrease by 21,7% ($p<0,01$). The torasemide therapy caused the same index to decrease to a considerable extent (41,8%, $p<0,001$).

Full negative correlation was disclosed during the study of the correlation relation between the heart rhythm variability and NTproBNP that it was reflected in the activeness of the parasympathetic part of the vegetative nervous system, especially, in the SDNN relation showing the general condition of the heart rate variability ($p<0,05$). The level of correlation with the spectral parameters was insignificant.

Besides it, the increase of the concentration of this peptide in blood caused the shrinkage-pumping function of the heart to deteriorate, the dilatation of the left ventricle and the hypertrophy to develop that it confirms the significant positive correlation between NTpro BNP level and the volumes and sizes of the systole and diastole of the left ventricle as well as the IVS, PW, LVMM indexes that characterize the hypertrophy of miocardia. The relation with the EF which is the key parameter of the shrinkage-pumping function of the heart was significantly negative ($r=-330$, $p<0,01$).

Improvement of the levels of NTproBNP and potassium in blood, as well as improvement of HRD parameters [SDNN and NTproBNP: $r = -0.218$ ($P <0.05$)] enhancement of parasympathetic parameters, weakening of sympathetic parameters and humoral metabolic effects on heart rate during the treatment with torasemide in the CHF patients are associated with improvement of left ventricular pump-collection function.

Long-term treatment with loop diuretics can cause hyperuricemia. There were not revealed correct differences in the concentration of the uric acid (UA) before and after the therapy in the present research. However, there did not take place any considerable changes in the metabolism of the uric acid during the long term torasemide therapy in comparison with furosemide. Though the increase of the uric acid by 2,7% was observed at the end of the 3rd month of torasemide therapy, it decreased by 2,6% comparing to the indexes of 3 month therapy at the end of the 6th

month of the therapy. By considering the facts mentioned-above, preference must be given to torasemide for preventing of hyperuricemia during the loop diuretic therapy of the CHF.

As it is known, one of the diuretic therapy complications is the violation of water-electrolyte balance and it is reflected in the correct decrease of natrium, potassium and magnesium levels – the decrease of these indexes were noted in the background of long term therapy of the CHF patients accordingly: 26,4% ($p<0,01$), 40,4% ($p<0,01$) and 23,1% ($p<0,05$). As a result of the long-term treatment with torasemide, sodium levels reduced by only 12.9% ($p <0.01$), while potassium and magnesium levels decreased by 8.6% ($p <0.05$) and 11.2%, respectively ($p <0.05$).

As can be seen, the long-term treatment with diuretics led to a decrease in the content of electrolytes in the blood plasma. However, these changes were more pronounced during the treatment with furosemide than with torasemide (Fig. 2).

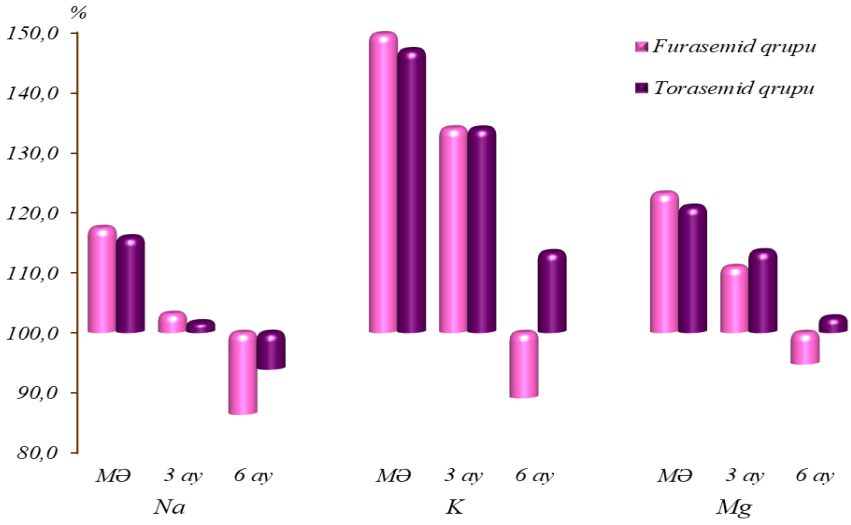

Fig.2. Blood electrolyte balance against the background of treatment with furosemide and torasemide during CHF

A significant negative correlation was found between sodium levels and iSDNN, an indicator of parasympathetic activity of HRV

(r = -209, p <0.05), a higher negative correlation in patients with CHF was accompanied by a decrease in both parasympathetic activity and total HRV.

During the observation period, the dynamics of the functional class of patients were assessed based on changes in the FC of the CHF. Before the treatment, 15 (30%) patients in group I and 13 (20%) patients in group II had FC II, but 6 months after the diuretic therapy, the number of patients with this FC increased due to transformation of FC III, reaching 18 (36%) and 21 (42%) patients respectively. It should be noted that the number of the CHF patients with FC III decreased from 35 (70%) to 25 (50%) in the first group and from 37 (74%) to 23 (46%) in the second group.

Analogical changes in the functional class of the CHF were also disclosed in the repeatedly appointed ASCC of the patients after diuretic therapy. The full improvement of the clinical condition of the patients took place in the background of long-term drug therapy (decrease from 8,5 to 13,7 points after furosemide therapy, 7,1 to 12,1 points after torasemide therapy, p<0,01).

The assessment of the quality of life showed that the improvement of the quality of life occurred in the background of long-term diuretic therapy and it was reflected in the decrease of the cases from 71,6 to 46,4 during the long-term furosemide therapy and 69,7 to 40,5 during the torasemide therapy. Along with that the improvement of the quality of life to a considerable extent mostly occurred because of decreasing of edema in shin and clutches, removal of difficulties, air insufficiency and anxiety occurring in walking or climbing the stairs as well as increasing of qualitative active rest opportunities. The quality of life during drug therapy mostly became worse because of sleeping disorders at nights and impossibility of long journeys.

Thus, it became clear from the results of the research conducted that torasemide has considerable advantages comparing to furosemide in the long-term therapy of the Chronic Heart Failure with regard to the improvement of the functional class, quality of life, heart rhythm variability and systolic function as well as the decrease of the frequency of arrhythmias without lipid, electrolyte

and purine metabolism disorders.

CONCLUSIONS

1. Various changes in the electrical instability of the heart were observed in patients with CHF during their treatment with furosemide and torasemide. Theree were rhythm disturbances observed against the background of the treatment with furosemide: an increase in single, paired and group supraventricular and ventricular extrasystoles, and an increase in the frequency of supraventricular tachycardia ($p < 0.01$), while during the treatment with torasemide the frequency of such arrhythmias significantly decreased ($p < 0.001$). In the study of the duration of the QT interval and its variance QTc-min and QTcmax values in the patients of group I were, 390.0 ± 7.06 and 417.0 ± 0.01 ms, respectively and in group II these indicators were 357.1 ± 9.60 and 399.0 ± 0.01 ms, respectively ($p < 0.001$). QTcd did not significantly differ in either group. Against the background of the treatment, the values of QTc-max were 425.0 ± 0.02 ($p < 0.05$) in group I and 386.0 ± 0.19 in group II, while QTc values were 410.0 ± 2.06 and 396.7 ± 7.95, respectively. There was no significant difference in QTcd in both groups [1, 2].
2. Against the background of the 6 months treatment of CHF patients with furosemide, HRV parameters were characterized by weakening of parasympathetic effects on the heart rhythm, and weakening of signs of relative sympathicotonia (16.9% increase in LF / HF, $P < 0.05$) as well as increased humoral-metabolic effects on the heart rhythm. On the other hand, during the treatment with torasemide there was an intensification of parasympathetic effects (increase in HF% by 15.4, $P < 0.05$), weakening of sympathetic effects (decrease in LFnu by 9.3%, $P < 0.05$) and weakening of humoral-metabolic effects on the heart rhythm, as well as removal of symptoms of relative sympathotony (decrease in LF / HF by 18.3%, $P < 0.05$), which suggests that torasemide reduces the activity of

both the renin-angiotensin-aldosterone system and the sympathetic nervous system. [4, 5].

3. There was a decrease in NTproBNP (21.7%, P <0.01) and potassium levels (40.4%, P <0.01) in blood, and an increase in uric acid concentration (19.2%, P <0.01) as a result of the long-term treatment with furosemide. At the same time, as a result of the long-term treatment with torasemide the level of NTproBNP (41.8%, P <0.001) remarkably reduced, and the level of potassium in the blood plasma changed insignificantly, while uric acid remained relatively stable. Changes in NTproBNP and potassium in blood, as well as improvement of HRD parameters [SDNN and NTproBNP: r = -0.217 (P <0.05)] enhancement of parasympathetic parameters, weakening of sympathetic parameters and humoral metabolic effects on heart rate during the treatment with torasemide in the CHF patients are associated with improvement of left ventricular pump-collection function [3, 7, 10, 11].
4. In contrast to the furosemide treatment, the long-term treatment of CHF patients with torasemide was characterized by a decrease in left ventricular end-diastolic size and left ventricular myocardial mass index (2.1% and 7.1%, respectively; P <0.05), resulting in improved systolic function [4, 5].
5. There was a significant improvement in the clinical condition of ASCC in both groups (from 8.5 to 13.7 points, and from 7.1 to 12.1 points, respectively; p <0.01,) against the background of treatment with furosemide and torasemide, which was accompanied by a decrease in the functional class of the CHF, based on the results of a 6-minute step test in both groups. This indicator had a negative correlation with a HRV parameter SDNN, VLF (r = -0.324, r = -0.257, respectively). At the same time, according to the MHFLQ survey, the effectiveness of the treatment, improvement of quality of life (from 71.6 to 46.4 points during the treatment with furosemide, and from 69.7 to 40.5 points during the treatment with torasemide) was noted. In this case, there was a negative correlation between the time

parameters and parasympathetic parameters of HRV, which are iSDNN, rMSSD and pNN50 (r = -0.315, r = -0.289, respectively), and a positive correlation between the time parameters and sympathetic parameter iSDANN (r = 0.308) [8, 9].

PRACTICAL RECOMMENDATIONS

1. It is necessary to determine the QT interval in order to assess the vegetative and humoral-metabolic effects on the electrical stability of the heart, as well as to study the heart rhythm variability and to assess prognosis when prescribing diuretics in the treatment of CHF. Torasemide is recommended as a drug of choice in the treatment by loop diuretics, given its positive effect on the heart rhythm variability and corrected QT interval in patients with arrhythmias as well as its ability to blockade the renin-angiotensin-aldosterone system and the sympathetic nervous system.
2. The use of torasemide in the treatment of CHF is of social-economic importance because by affecting the progression of heart failure and the process of remodeling of the heart, it allows for faster compensation, is more effective and has fewer undesirable effects (metabolic and electrolyte), and thus it reduces the frequency of hospitalization.

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LIST OF ABBREVIATIONS

ASCC - assessment scale of clinical condition
CHF - chronic heart failure
ECG - electrocardiography
Echo-CG - echocardiography
EF - ejection fraction
FC - functional class
HF - part of the spectrum at high frequency, ms2
HRV - heart rhythm variability
LF - low frequency components of heart rate variability
MHFLQ - Minnesota survey to assess life quality
NTproBNP-N-terminal pro b-type natriuretic peptide
NYHA - New York Heart Association
pNN50 - percentage of differentiation of consecutive NN intervals
rMSSD - root mean square of the average sum of successive differences between NN intervals, ms
SDANN, ms - deviations of normal intervals from the average limit standards in 5 minute notes taken in 24 hours
SDNN, ms - deviations of NN intervals from the average duration standard
VLF - spectral component at very low frequencies, ms^2

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