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Miroshnichenko E.P., Dranenko N.Y., Goryanskaya I.Y., Gagarina A.A., Ushakov A.V.

SERUM ALDOSTERONE LEVEL DYNAMICS AND CARDIAC REMODELING IN MYOCARDIAL INFARCTION PATIENTS WITH UNDIFFERENTIATED CONNECTIVE TISSUE DYSPLASIA TREATED WITH SELECTIVE ALDOSTERONE RECEPTOR BLOCKER

V.I. Vernadsky Crimean Federal University,
Medical Academy named after S.I. Georgievsky (Academic Unit),
Simferopol, Russian Federation

SUMMARY

Aim. To study serum aldosterone level dynamics and cardiac remodeling characteristics in myocardial infarction (MI) patients with undifferentiated connective tissue dysplasia (UCTD) treated with selective aldosterone receptors antagonist eplerenone.

Study population and methods. A total of 110 MI patients with and without UCTD and 32 healthy controls without cardiovascular pathology and without signs of UCTD were enrolled in the study. Clinical examination, phenotyping, echocardiography and serum aldosterone levels evaluation were performed. MI patients were divided into 3 groups: I (n=20) - patients with UCTD who was treated by eplerenone additionally to basic therapy of MI; II (n=60) - patients without UCTD treated by basic therapy of MI; III (n=30) - patients with UCTD treated by basic therapy of MI only.

Results. All MI patients regardless of UCTD presence had increased serum aldosterone in the first day of MI. In 28 days the significant increase of serum aldosterone level in group I in comparison with groups II, III and control group was observed.

Analysis of structural and functional characteristics of the heart in MI patients in a 6 month after MI had shown more significant left ventricle enlargement and decrease of cardiac pump function in group III compared to group I.

Conclusion. Presence of UCTD in MI patients does not affect serum aldosterone levels dynamics. Inclusion of eplerenone in the treatment of MI patients with UCTD during 6 months inhibits left ventricular dilatation and attenuates reduction of its ejection fraction.

Keywords: *myocardial infarction, undifferentiated connective tissue dysplasia, aldosterone, cardiac remodeling.*

Information about authors:

Dranenko Natal'ja Jur'evna	PhD (Candidate of Medical Sciences), Associate professor of the Department of Internal Medicine No. 1 with Clinical Pharmacology course of Medical Academy named after S.I. Georgievsky of V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation, e-mail: nup-d@yandex.ru, tel. 8-3652-225310
Goryanskaya Irina Jaroslavovna	PhD (Candidate of Medical Sciences), Associate professor of the Department of Internal Medicine No. 1 with Clinical Pharmacology course of Medical Academy named after S.I. Georgievsky of V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation, e-mail: irina_gor@inbox.ru, tel. 8-3652-225310
Gagarina Alina Anatolievna	PhD (Candidate of Medical Sciences), Associate professor of the Department of Internal Medicine No. 1 with Clinical Pharmacology course of Medical Academy named after S.I. Georgievsky of V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation, e-mail: alinaga@ukr.net, tel. 8-3652-225310
Ushakov Alexey Vitalievich	Doctor of Medical Sciences, Professor, Head of the Department of Internal Medicine No. 1 with Clinical Pharmacology course of Medical Academy named after S.I. Georgievsky of V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation, e-mail: ushakovav8@ukr.net, tel. 8-3652-225310
Corresponding author: Miroshnichenko Elizaveta Petrovna	Assistant professor of the Department of Internal Medicine No. 1 with Clinical Pharmacology course of Medical Academy named after S.I. Georgievsky of V.I. Vernadsky Crimean Federal University, Simferopol, Russian Federation. Address: Russian Federation, Simferopol, 295006, Lenin Blvd. 5/7, Medical Academy named after S.I. Georgievsky, Department of Internal Medicine No. 1 with Clinical Pharmacology course. E-mail: Miroshnichenko_E_P@i.ua, tel: 8-3652-225310; 8-3652-255377.

✉ **Miroshnichenko_E_P@i.ua**

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Nowadays, the role of aldosterone in pathogenesis of myocardial infarction (MI) and post-infarction cardiac remodelling is being extensively discussed [1, 2, 3]. It has been proved that aldosterone affects myocardial connective tissue the condition of which is of great importance in reparative and restorative processes taking place in the cardiac muscle following MI. A significant feature of regulatory functions of aldosterone is its ability to exert both genomic and extragenomic influence on tissues and systems, cardiovascular system in particular [4, 5]. The genomic effect is realized through the mineralocorticoid receptors and is slow. It manifests within a few hours or even days. Extragenomic effects of aldosterone develop within a few minutes and are realized mainly in the target organs – the heart, blood vessels, kidneys [6].

A number of aldosterone effects have been identified in pathogenesis of cardiovascular pathology. The most important of them are: induction of endothelial dysfunction, inhibition of nitric oxide synthesis, pro-inflammatory effect, stimulation of fibrosis of blood vessel walls, myocardial hypertrophy and remodelling [7, 8].

It is also known that a number of diseases concomitant with connective tissue dysplasia have different clinical manifestations and are more often accompanied by various complications and unfavourable outcomes [9, 10]. In this regard, it is reasonable to assume that congenital defects of connective tissue can alter post-infarction cardiac remodelling process and worsen the prognosis in patients after MI.

The described mechanisms and peculiarities of aldosterone effect on myocardial connective tissue caused the selective aldosterone receptor antagonist eplerenone to be included into the treatment of patients with MI [7, 11].

The positive clinical effect of eplerenone in patients with MI is manifold and manifests at various pathogenetic levels. Blocking the adverse effect of aldosterone on the extension of necrotic zone and on the excessive fibrosis provides mechanical protection of the affected area, thereby improving systolic and diastolic functions of the left ventricle. NO bioavailability and engulfment of norepinephrine by cardiomyocytes increase at the cellular level. There is also an improvement of heart rate variability parameters, reduced risk of arrhythmias [12], and better myocardial reperfusion [13].

In connection with the above, eplerenone appears particularly useful in improving reparative and regenerative processes in cardiac muscle following MI and in optimising post-infarction remodelling of the connective tissue matrix of the heart in patients with undifferentiated connective tissue dysplasia (UCTD).

Objective: to study peculiarities of serum aldosterone level dynamics and the character of cardiac remodelling in MI patients with UCTD treated with the selective aldosterone receptor antagonist eplerenone.

MATERIALS AND METHODS

110 patients with ST-segment elevation Q-wave MI including 28 (25.4%) women and 82 (74.5%) men were examined.

Group I included 20 MI patients with UCTD (17 (85%) men and 3 (15%) women, average age 53.35±2.52 y.o.) who received eplerenone in the dose of 25 mg once a day (Inspra, Pfizer, USA) in addition to standard MI therapy during 6 months starting from the first day of MI development.

Group II consisted of 60 MI patients (19 (31.7%) women and 41 (68.3%) men, average age 63.0±1.82 y.o.) without UCTD who received standard MI therapy.

Group III consisted of 30 MI patients with UCTD (6 (20%) women and 24 (80%) men, average age 59.68±2.35 y.o.) who received standard MI therapy only.

The control group comprised 32 apparently healthy subjects without cardiovascular pathology and signs of UCDT (10 (31.2%) women and 22 (68.8%) men, average age 52.7±1.2 y.o.).

The study was conducted in accordance with the standards of Good Clinical Practice and the principles of the Helsinki Declaration. The Bioethics Committee of V.I. Vernadsky Crimean Federal University approved the study protocol. Before entering the study, all participants signed written informed consent.

Patients with hemodynamically significant heart defects (including mitral valve prolapse with mitral regurgitation, often revealed in patients with UCTD), non-coronary myocardial diseases, malignant neoplasms, kidney and liver diseases if their functions were impaired, acute and chronic infectious and inflammatory diseases were not enrolled in the study. In addition, the patients were not included into group III if they had absolute indications for mineralocorticoid-receptor antagonist therapy [14].

In addition to clinical examinations and electrocardiography monitoring, standard laboratory tests and echocardiography were performed.

All patients with MI were treated in accordance with the guidelines for the management of acute coronary syndrome with ST-segment elevation [15]. The groups of patients under survey did not vary in the frequency of use of the main classes of drugs included into standard MI therapy, as well as in the frequency of use of other drugs. Thrombolysis in group I was performed in 25% of the patients, in group II – in 33% of the patients, in group III – in 20% of the cases. As far as the frequency of thrombolysis was concerned, the groups did not differ significantly by this parameter either. Time interval from the onset of MI symptoms to thrombolytic therapy comprised 2 to 6 hours and was not significantly different between groups.

Evaluation of the connective tissue state was made by identifying the stigma of disembryogenesis on the basis of a phenotypic map proposed by M.J. Glesby [16] and modified by A.I. Martynov and co-authors. UCTD were diagnosed if six or more stigmas had been present [9].

ELISA using DRG ELISA test systems (Germany) determined aldosterone serum levels.

Structural and functional characteristics of the heart were assessed by means of echocardiography (Philips EnVisor) with evaluation of the following parameters: right ventricular (RV) diameter, left atrial (LA) diameter, left ventricular end-systolic size (LVESS), left ventricular end-diastolic size (LVEBS), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT), left ventricular ejection fraction (LVEF).

The relative thickness of walls (RTW) of the LV was calculated by the formula:

RTW =LVPWT + IVST/LVEBS

The left ventricular myocardial mass index (LVMMI) was calculated by the formula: LVMM/S, where LVMM refers to the left ventricular myocardial mass, S refers to the body surface area.

At that, the LV myocardial mass (LVMM) was calculated by Devereux formula and was indexed to the body surface area:

$$\mathbf{LVMM = 1.04 \times ((IVST + LVPWT + LVEBS)^3 - LVEBS^3) - 13.6}$$

LVMM index values of more than 125 g/m² in men and more than 110 g/m² in women were considered as the signs of LV hypertrophy.

Statistical analysis of the data obtained was carried out using the software package STATISTICA 6.0 (StatSoft Inc., USA). To assess the reliability of differences between the groups, the nonparametric Mann-Whitney U test was applied. The reliability of changes in the parameters over time was assessed by Wilcoxon signed

rank test non-parametric criterion. As a nonparametric criterion characterizing the existence and strength of the relationship between the parameters studied, the Spearman's rank correlation coefficient (r) was used. Differences and correlations were considered significant at $p<0.05$.

RESULTS AND DISCUSSION

The dynamics of serum aldosterone levels in the studied groups are presented in Table 1.

The obtained results show that on the first day of MI aldosterone level was elevated in all MI patients groups with and without UCTD. At the same time, there was no significant difference between the groups. Serum aldosterone concentration remained increased in 14 days after MI in groups of patients both with and without UCTD, when compared with the control group. By the 28th day of MI, the aldosterone level in groups II and III reduced to the level of control group. At that, on the 28th day of MI aldosterone concentration in the group of MI patients with UCTD receiving eplerenone was significant higher as compared to groups II and III, as well as compared to control group.

According to the literature data, the active influence of aldosterone on the processes of local intravascular inflammation, especially in patients with MI, is accompanied by changes in the structural and functional parameters of the heart [6, 7, 17]. In this regard, the echocardiographic parameters were studied in MI patients with concomitant UCTD and without it. The study was carried out on the 7th day and at 6 months after the onset of MI. The results are shown in Table 2.

In 6 months after MI, one of the patients included into group I refused to be followed-up; in group II 9 patients refused to be re-examined and 3 patients died (two of recurrent MI, one of ischemic stroke); in group III 6 patients refused to be followed-up, 2 patients died (one of recurrent MI, one of hemorrhagic stroke).

The analysis of structural and functional state of the heart in 6 months after MI revealed a reliable increase in LA, LVEDS, LVESS, and reduced LVEF in all MI groups in comparison with the control group. At that, in groups II and III, the size of LA, LVEDS, LVESS had increased over time. However, the differences between 6 months after the onset of MI and the 7th day of the disease were reliable only in the group of patients with UCTD who did not receive eplerenone: LVEDS increased by 6%, LVESS increased by 9%. When assessing LV systolic function in group II, there was a reliable decrease in LVEF by 3% compared with the 7th day, the decrease in group III was by 6%, but the reliability of differences in the group of the patients with UCTD was not achieved. When comparing the parameters of the groups 6 months after the onset of MI, a reliable increase in LVEDS, LVESS and a decrease in LVPWT, IVST, RTW, LVEF were observed in group III compared with group II ($p<0.05$).

In contrast, the group of patients with UCTD received eplerenone showed the decreases of LVEDS by 4%, of LVESS by 5%, of LVPWT

Table 1. Serum aldosterone levels dynamics in the patients with myocardial infarction with undifferentiated connective tissue dysplasia in the course of ongoing drug therapy

The day after MI	Serum aldosterone level (pg/mL)			
	Group I (n=20)	Group II (n=60)	Group III (n=30)	Control group (n=32)
	M±m	M±m	M±m	M±m
1st day	154,78±16,95*	157,09±10,74*	151,26±6,05*	135,08±2,49
14th day	145,78±12,87*	142,33±10,09*	146,64±5,22*‖†	
28th day	143,72±30,72*	138,36±4,95§▪	131,98±4,08§▪	

Note:
** - the reliability of difference with control group ($p<0.05$); ▪ - the reliability of difference with Group I ($p<0.05$);*
† - the reliability of difference with group II ($p<0.05$); § - the reliability of difference with the 1st day of MI ($p<0.05$);
‖ - the reliability of difference with the 28th day after MI ($p<0.05$).

Table 2. Structural and functional characteristics of the heart in the patients with myocardial infarction with and without undifferentiated connective tissue dysplasia in the course of treatment

Parameter	Group I (n=32)		Group II M±m		Group III M±m		Control group
	7th day after MI (n=20)	6 months later (n=19)	7th day after MI (n=60)	6 months later (n=48)	7th day after MI (n=30)	6 months later (n=22)	M±m
LA, cm	*4,41±0,13**	*4,39±0,13**	*4,27±0,07**	*4,30±0,08**	*4,27±0,12**	*4,32±0,10**	*3,77±0,06*
LVEDS, cm	*5,74±0,16**	*5,53±0,14*§*	*5,32±0,09*°*	*5,39±0,09**	*5,63±0,13*▪*	*5,95±0,09*§▪°*	*4,99±0,04*
LVESS, cm	*4,72±0,18**	*4,48±0,15*§*	*4,05±0,09*°*	*4,20±0,09**	*4,51±0,14*▪*	*4,94±0,08*§▪°*	*3,45±0,07*
LVPWT, cm	*0,96±0,04*	*0,90±0,03*§*	*0,97±0,02*	*0,99±0,02§°*	*0,92±0,02**	*0,89±0,03*▪*	*0,97±0,02*
IVST, cm	*0,95±0,07**	*0,90±0,07*§*	*1,06±0,03°*	*1,10±0,03*§°*	*0,93±0,04*▪*	*0,92±0,02*▪*	*0,98±0,02*
LVEF, %	*36,85±1,70**	*38,89±1,37**	*45,67±0,93*°*	*44,37±0,75*§°*	*36,77±1,47*▪*	*34,59±1,30*▪°*	*59,75±1,01*
RV, cm	*2,30±0,08*	*2,27±0,08*	*2,22±0,03*	*2,23±0,03*	*2,18±0,07*	*2,30±0,02**	*2,14±0,04*
LVMMI, g/m2	*139,66±8,95**	*140,02±8,44**	*130,99±8,01**	*128,79±8,89*	*121,89±5,25**	*122,57±6,39*	*106,75±3,05*
RTW	*0,36±0,02**	*0,35±0,02 **	*0,38±0,01*	*0,38±0,01*	*0,34±0,02*▪*	*0,30±0,01*§▪*	*0,39±0,01*

Note:
** - the reliability of difference with control group ($p<0.05$); § - the reliability of difference with the 7th day after MI ($p<0.05$);*
° - the reliability of difference with group I ($p<0.05$); ▪ - the reliability of difference between groups II and III ($p<0.05$).

by 6% and of IVST by 5% ($p < 0.05$) 6 months after the onset of MI, when compared with the 7th day. LVEF values correspondingly increased by 5%, but the reliability of the differences was not achieved.

It also should be noted that in 6 months after MI in the group of patients with MI and UCTD who did not receive eplerenone we observed more pronounced increase of LVEDS (by 7%) and of LVESS (by 10%) and a decrease in LVEF (by 11%) than in Group I; $p<0,05$.

The data obtained in this study indicate that the development of Q-wave MI is accompanied by an increase in serum aldosterone level starting from the first day of the disease. By the 28th day, the aldosterone level in groups II and III returned to the control group values. At the same time, on the 28th day of MI there was a reliable increase in serum aldosterone concentration in the group of the MI patients with UCTD receiving eplerenone in comparison with the control group and with the group of MI patients with UCTD received only standard MI treatment.

Numerous studies have shown that an increase in serum aldosterone levels is associated with deterioration in hemodynamic parameters and with maladaptive pattern of cardiac remodelling, characterized by the preponderance of the stretch of myocardium over its hypertrophy and, as a consequence, by inadequate restoration of the cardiac pump function [7, 12, 13]. The results obtained indicate that this type of post-infarction remodelling of the heart is a typical for patients with UCTD. It can be assumed that this phenomenon is due to the genetically determined collagen pathology in this category of patients, manifested by insufficient rigidity and excessive extensibility of collagen. This leads to the fact that under the condition of intracardiac hemodynamics changes with the increase of endomyocardial stress and of the LV end-diastolic pressure, effectiveness of compensatory mechanisms aimed at adapting the structural and functional parameters of the heart reduces. Besides, another evidence of reduced compensatory reserve of post-infarction cardiac remodelling due to a qualitatively different condition of myocardial connective tissue in the presence of UCTD is the dynamic decrease in RWT, combined with progressive LV dilatation. At that, long-term administration of the selective mineralocorticoid receptor antagonist eplerenone inhibits the development of the above-mentioned unfavourable type of post-infarction cardiac remodelling in patients with UCTD.

CONCLUSION

UCTD has no effect on serum aldosterone levels and their dynamics in MI. At the same time, patients with UCTD develop more unfavourable type of post-infarction cardiac remodelling with dilatation of LV and with a decrease of its contractility prevailing over hypertrophic response. The administration of eplerenone to MI patients with UCTD inhibits the adverse effects of aldosterone, thereby inhibiting myocardial fibrosis and slowing the development of maladaptive postinfarction cardiac remodelling.

REFERENCES

1. *Kokorin V.A., Lusov V.A., Shaydyuk O.Yu. The prognostic importance of neurohumoral activation in patients with myocardial infarction. Scientific Bulletin. Medicine. Pharmacy. 2011; 10(105):37-43. [in Russian]*
2. *Perutsky D.N., Makeev T.I., Konstantinov S.L. Main concepts of postinfarction myocard remodeling. Scientific bulletin. Medicine. Pharmacy. 2011; 10(105):51-59. [in Russian]*
3. *Beygui F., Labbe JP., Cayla G. et al. Early mineralocorticoid receptor blockade in primary percutaneous coronary intervention for ST-elevation myocardial infarction is associated with a reduction of life-threatening ventricular arrhythmia. Int J Cardiol. 2013. Vol. 167. P. 73-79.*
4. *Nguyen Dinh Cat A., Jaisser F. Exstrarenal effects of aldosterone. Current Opinion in Nephrology and Hypertension. 2012. Vol. 21. P. 147-156.*
5. *Zadionchenko V.S., Yalymov A.A., Shekhyan G.G. et al. Mineral corticoid receptors antagonists: the place in the practice of a cardiologist. Russian medical journal. 2018; 1(11):120-125. [in Russian]*
6. *Pitt B., Pfeffer M., Assmann S. et al. Spironolactone for heart failure with preserved ejection fraction. N. Engl. J. Med. 2014. Vol. 370. P. 1383-1392.*
7. *João P.F., Kévin D., Gilles M. et al. Effect of eplerenone on extracellular cardiac matrix biomarkers in patients with acute ST-elevation myocardial infarction without heart failure: insights from the randomized double-blind REMINDER Study. Clinical Research in Cardiology. 2018. Vol. 107. P. 49-59.*
8. *Kuzmin O. B., Clinical efficacy of renin-angiotensin-aldosterone system inhibitors in patients with heart failure with impaired renal function. Heart failure 2013; 4 (78):228-233. [in Russian]*
9. *Zemtsovsky E.V. Dysplastic phenotypes. Dysplastic heart. SPb.: Olga; 2007. C. 80. [in Russian]*
10. *Trisvetova E.L. Magnesium deficiency and cardiovascular diseases: time to act. Rational pharmacotherapy in cardiology. 2014; 10:99-105. [in Russian]*
11. *ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2012. Vol. 33. P. 1787–1847.*
12. *Tanaka-Esposito C., Varahan S., Jeyaraj D. et al. Eplerenone-mediated regression of electrical activation delays and myocardial fibrosis in heart failure. J. Cardiovasc. Electrophysiol. 2014. Vol. 25. P. 537–544.*
13. *Lavall D., Selzer C., Schuster P. et al. The mineralocorticoid receptor promotes fibrotic remodeling in atrial fibrillation. J. Biol. Chem. 2014. Vol. 289. P. 6656–6668.*
14. *Mareev V. Y., Ageev F. T., Arutyunov G. P. et al. National Guidelines of Heart Failure Society Specialists, Russian Society of Cardiology and Russian Scientific Society of Internal Medicine on Diagnosis and Treatment of Chronic Heart Failure (fourth revision). Journal of Heart Failure. 2013; 7 (81):379-472. [in Russian].*
15. *ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology. European Heart Journal. 2012. Vol. 33. P. 2569-2619.*
16. *Glesby M.J., Pyeritz R.E. Association of mitral valve prolapse and systemic abnormalities of connective tissue. J. Amer. Med. Assoc. 1989. Vol. 262. P. 523-528.*
17. *Antonio Lax., Jesus Sanchez-Mas., Maria C. Asensio-Lopez et al. Mineralocorticoid Receptor Antagonists Modulate Galectin-3 and Interleukin-33/ST2 Signaling in Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction. Jacc: HEART Failure. 2015. Vol. 3. P. 51-58.*

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