Evaluation of the Neurohormonal System in Patients with Chronic Heart Failure Characterized by Postinfarction Cardiosclerosis

Latipov A.Ya

Pulatova Sh.H

ABSTRACT

A total investigation of 115 patients. Chronic heart failure (CHF) of the 1-st functional class (FC) was found in 19 patients (16.5%), 2-nd FC in 48 patients (41.8%), 3-d FC in 40 (34.7%) and 4-th FC in 8 (6.9%). In their peripheral venous blood plasma norepinephrine, aldosterone and brain natriuretic peptide were investigated. The amount of N in patients with cardiosclerosis post infarction increased in the 2-d, 3-d and 4-th FC; A increased in all the groups and with normal (FV) and didn't depend on diastolic or systolic kind of CHF. The amount of BNP also increased with the appearance of systolic heart insufficiency and grew as the level of CHF increased . The BNP level can be a diagnostic test for a low FC's grade of CHF.

Keywords: Chronic heart failure (CHF), norepinephrine, aldosterone, brain natriuretic peptide.

The participation of myocardial hormonal systems, which are directly related to cardiac influences and hemodynamic manifestations of chronic heart failure (CHF) and, in general, to the pathogenesis of heart failure, is manifested by increased levels of norepinephrine (NA) [5], aldosterone (A) [2], and brain natriuretic peptide (MNUP) [4]. Their source is largely myocardial tissue, and the level of these hormones is an important determinant of diagnostic and therapeutic interventions [5, 8], since their influence largely determines the inotropic properties of the myocardium and can be one of the diagnostic tests for the severity of CHF[10].

The aim of this study was to study the state of neurohumoral regulation of the activity of the cardiovascular system in terms of the content of NA, A and BNP, depending on the nature and severity of systolic and diastolic myocardial dysfunction in patients with CHF caused by postinfarction cardiosclerosis

Materials And Research Methods

We examined 115 patients with myocardial infarction (MI) 4 months ago, aged 37 to 88 years (mean age 56.6±10.8 years). Among the examined were 100 men (86.9%) and 15 women (13.1%). Anterior localization of MI was registered in 82 patients (71.3%), lower in 26 (22.6%), lateral in 7 (6.1%). Q - MI was determined in 59 patients (51.4%), MI without Q wave was registered in 56 patients (48.6%). Randomization of patients was carried out by random sampling of every fourth patient who was treated in the cardiology department of the regional clinical hospital of the Republican Scientific Center for Medical Emergencies of the Bukhara branch.

Of all included in the study, in 90 patients (78.2%) - MI occurred for the first time, in 16 (13.9%) - again, 9 patients (7.8%) suffered more than 2 myocardial infarctions. In the clinical picture of 32 patients (27.8%), MI was preceded

by unstable angina. The systolic function of the left ventricle (LV) was determined by the value of the ejection fraction (EF), a decrease in EF of less than 40% was detected in 51 patients (43.5%). The mean values of LV EF in all examined were 47±14%. To determine the functional class (FC) of CHF, the classification of the New York Heart Association (NYHA) was used. CHF I FC was determined in 19 patients (16.5%), II FC - in 48 (41.8%), III FC - in 40 (34.7%) and IV FC - in 8 (6.9%) patients . Among the risk factors for coronary artery disease, 73 patients (63.5%) were diagnosed with hypertension, 53 patients (46.1%) smoked at the time of the examination, hypercholesterolemia with a total cholesterol level > 6.2 mmol/l was found in 62 patients (53, 9%). 11 persons (9.6%) suffered from diabetes mellitus, 11 (9.6%) were obese. The control group (21 people) consisted of persons who did not have a history of diseases of the cardiovascular system, according to instrumental methods of research, who did not differ from the main one in age. During the follow-up, patients took acetylsalicylic acid (aspirin-cardio, Bayer, Germany) 100 mg per day, carvedilol (Koriol, KRKA, Slovenia) 25-50 mg per day, enalapril maleate (Enap, KRKA, Slovenia) 20 mg per day . The study did not include patients with concomitant acute inflammatory, infectious, oncological, immunocomplex diseases and chronic diseases in the acute stage. FC CHF was determined using a 6-minute walk test. Echocardiography (EchoCG) was performed using Philips En Visor C (USA, 2005) with a 3.5 MHz electronic probe and Vivid-7 (USA, 2004) with a multifrequency probe. One-dimensional (M-mode), two-dimensional (B-mode) and Doppler echocardiography were used according to the generally accepted technique [2]. The following indicators were assessed: end-diastolic volume (EDV, cm3), end-systolic volume (ESV, cm3), thickness of the posterior wall of the left ventricle in diastole (TZSLVD, cm), contractility indicators: stroke volume (SV, cm3), ejection fraction (EF,%), the rate of circular shortening of the fibers (CCS, approx. s-1). Diastolic function was assessed by pulse Doppler echocardiography according to the standard method using the SIM 5000 plus device. The following indicators were determined: the maximum rate of late diastolic filling (A, cm s-1), the maximum rate of early diastolic filling (E, cm s-1), the E / A ratio - the ratio between the amplitudes of the rates E and A, isovolumic relaxation time (IVRT , ms) is the period from the closure of the aortic valve to the opening of the mitral valve. Determination of norepinephrine in plasma of peripheral venous blood was carried out in accordance with the instructions for Noradrenalin ELISA (BL Hamburg), aldosterone and brain natriuretic peptide by enzyme immunoassay (Aldosterone EIA, BNP, Diagnostic Systems Laboratories, inc. USA, Peninsula Laboratories), respectively. Statistical processing of the obtained data was carried out on a personal computer by the methods of variational statistics using the software package "Microsoft Excel", "Statistica" using Student's criterion. Data are presented as M SD. Differences were considered significant at $p<0.05$ [1].

RESULTS AND DISCUSSION An analysis of the content of cardiac hormones was carried out depending on the state of myocardial systolic function (Table 1) in groups of patients with EF more than 50%, 40–50% and less than 40%. In patients with EF more than 50%, the level of norepinephrine was 59% higher than in the control group ($p<0.01$). With EF in the range of 40-50%, the level of norepinephrine was 30% higher than in healthy individuals ($p<0.01$), and in patients with EF less than 40% - by 40% ($p<0.05$). Consequently, norepinephrine levels were most significantly elevated in patients with an EF greater than 50%. The content of aldosterone in the blood of patients with different indicators of EF: more than 50%, 40–50% and less than 40% was increased almost to the same extent compared with the control and in patients with EF was more than 50% - 201.7 ± 47.2 pg /ml, with EF 40-50% - 176.0±52.9 pg/ml and EF less than 40% - 199.0±70.8, which exceeds the level of aldosterone in the blood plasma of healthy individuals by 40.2%, 23 .9% and 41.5%, respectively ($p<0.05$). The most significant dependence on the value of FI was

found in relation to the content of BNUP. In patients with an EF of more than 50%, the content of BNP in the blood plasma was 8.5±5.9 pg/ml, which did not differ significantly from the level of healthy individuals. Deterioration of the propulsive capacity of the heart and a decrease in EF to 40–50% is characterized by an increase in the content of BNP in the blood to 18.2±6.4 pg/ml, which is 73.3% (p<0.01) higher compared to the control and patients with an EF of more than 50%.

Table 1

The content of cardiac hormones in the peripheral venous blood of patients depending on the value of the ejection fraction (M ± SD)

Indicators	Control group n=21	Ejection fraction (%)		
		<40% 40-50% >50%	<40% 40-50% >50%	<40% 40-50% >50%
norepinephrine, pg/ml	458,0±40,2	738,6±162,8* N=12	600,2±150,5 N=14	780,7±192,6* N=21
Aldosterone, pg/ml	142,6±32,5	199,0±70,8* N=11	176,0±52,9* N=17	201,7±47,2* N=24
BNP, pg/ml	10,5±1,8	59,3±19,1 ** N=12	18,2±6,4** N=15	8,5±5,9 N=21

Note: * - p<0.05 compared with the control group; ** - p<0.01 compared with the previous group of patients.

A particularly significant increase in the content of BNP in the blood occurs in patients with EF less than 40%. The level of BNP in this group of patients was 59.1±19.1 pg/ml, which is significantly (p<0.001) higher than in other groups of patients. At the same time, the EF value significantly negatively correlated with the content of BNP in the blood (r=-0.62; p=0.033). Based on the characteristics of the transmitral diastolic blood flow, two types of LV myocardial dysfunction were identified in the examined patients - isolated diastolic (IDD) and a combination of systolic and diastolic dysfunction (SSDD). In patients with myocardial infarction and SSDD, the level of NA in the blood was significantly (p<0.01) increased by 62% compared to the control and averaged 741.9±90.5 pg/ml, and 715.5±90.5 pg/ml, respectively, which was 56.2% higher than in the control group (p<0.05). The content of aldosterone in the blood was increased in both groups, and in patients with IDD it was 193.7±9.7 pg/ml, and in SSDD - 185.2±13.5 pg/ml, i.e. 29.9% higher (p<0.01) compared with the control group (p>0.1). The change in blood concentration of BNP was largely dependent on the variant of heart failure.

The level of BNP in the blood plasma of patients with IDD was 9.3±2.0 pg/ml, which did not differ significantly from the content of BNP in the control group. Accession of LV systolic dysfunction to diastolic one was characterized by a significant increase in the content of BNP in the blood, amounting to 56.1±18.4 pg/ml (p<0.01) compared with the control group and patients with LV diastolic dysfunction. Our data indicate that the change in the level of NA and aldosterone in patients with postinfarction cardiosclerosis depends little on the value of EF and the nature of myocardial dysfunction. As for the content of BNP in the blood, it increases with a decrease in EF and the progression of CHF. In the latter case, the level of BNP can be a diagnostic test for low EF and the presence of systolic myocardial dysfunction [6, 8]. Activation of the endocrine myocardial system is one of the mechanisms for implementing the adaptive mechanisms of myocardial adaptation to new hemodynamic conditions, and is determined by the adequacy of the load on the myocardium [3, 7, 9]. It is believed that this applies to all cardiac neurohormones: norepinephrine, aldosterone and brain natriuretic peptide. Pharmacodynamic effects of

enhancing the functioning of the tissue RAAS and sympathoadrenal system, as evidenced by an increased level of NA and A, occur in the early stages of CHF development. Elevated blood levels of NA and especially A are an early sign of neurohormonal changes in postinfarction patients. In our opinion, an increase in the content of A in the blood is due not so much to hemodynamic, but rather to reparative processes in the myocardium [11], which is characteristic of the early stage of the formation of atherosclerotic cardiosclerosis. Elevated blood levels of NA in postinfarction patients complicated by heart failure precede the development of clinically significant symptoms of congestive heart failure, are due to a decrease in the inotropic properties of the myocardium, and are also combined with an increased risk of death due to arrhythmic complications [4, 8]. The content of NA in plasma increases to some extent due to the release of NA from nerve endings, and in general, sympathoadrenal activity directly correlates with the level of norepinephrine in the blood [12]. Therefore, an increase in the level of NA may reflect the activation of the sympathoadrenal system in patients with CHF in general. An increase in the content of NA in the blood plasma is not associated with the nature of myocardial dysfunction and occurs with preserved EF. In our opinion, an increase in the content of NA in patients with postinfarction cardiosclerosis is primarily associated with the processes of healing of the zone of myocardial infarction [5, 10]. Taking into account the fact that A enhances myocardial fibrosis in ischemic and dilated cardiomyopathy [5], the stimulus for increasing tissue synthesis of aldosterone may be the processes of post-infarction fibrosis formation even during the healing of the myocardial infarction site. As regards NA metabolism, suppression of NA uptake by the myocardium [10] and an increase in the level of NA in the blood is one of the mechanisms of synergistic action of neurohormones: angiotensin II and NA. The change in the content of BNP in the blood is associated with the mechanisms and features of the development of CHF and is determined by the nature of myocardial dysfunction. There is a clear dependence of changes in the content of BNP in the blood on the nature of chronic heart failure: an increase in its content with the addition of systolic heart failure.

A decrease in EF in patients less than 50% is accompanied by an increase in the content of BNP by 2.5 times. A particularly significant increase in the content of BNP occurs in patients with EF less than 40%. This is confirmed by the presence of an inverse correlation between the level of BNP and the value of EF ($r=-0.62$; $p=0.033$) and the rate of shortening of the size of the left ventricle of the heart ($r=-0.40$; $p=0.008$). The main stimulus for increased BNP formation in the myocardium is the tension of the left ventricular wall [9]. An increase in the content of BNP in the blood occurs due to both an increase in the secretion of BNP and an increase in the gene expression of the formation of this hormone [7]. In addition to myocardial wall tension, other endocrine, paracrine, and autocrine factors that are activated in CHF, such as norepinephrine, RAAS, ET-1, and cytokines, affect the secretion and increase in gene expression of BNP synthesis [4].

This effect is mediated by changes in cardiodynamics during myocardial remodeling [7], which explains the increase in the content of BNP with the appearance of systolic myocardial dysfunction. At the same time, its influence is aimed at reducing the negative effects of the sympathoadrenal and renin-angiotensin-aldosterone systems. The end result of counteracting the RAAS and the natriuretic peptide system is a decrease in peripheral vascular resistance and blood pressure [6], as well as a decrease in the tone of the sympathoadrenal system and inhibition of its peripheral and central influences [7]: a decrease in preload, as well as a decrease in hypertrophy of muscle vascular cells [8] and suppression of renal mechanisms of CHF progression [5]. Based on the characteristics of the pathophysiological effects of BNP, its activation leads to positive effects in the form of vasodilation, natriuresis, suppression of the activity of the sympatho-adrenal and renin-angiotensin-aldosterone

systems, and the action of growth factors. From this point of view, the level of circulating hormones is an important aspect of diagnostic and therapeutic interventions in patients with CHF. Based on the research done, the following conclusions can be drawn.

Literature

1. Пулатова Ш. Х. Особенности тромболитической терапии у больных острым инфарктом миокарда //Вестник экстренной медицины. – 2019. – Т. 12. – №. 6. – С. 88-91.
2. Кенжаев М.Л., ЛА Ахмедов, ШХ Пулатова Выбор тромболитиков при лечении инфаркта миокарда // Вестник экстренной медицины.- 2017.- Т. 3. – С. 93-96
3. Akhmedov L.A., Poulatova Sh.H. Optimization of hemodynamic diagnostics of acute left ventricular failure // Materials of the 7th Eurasian Congress of Cardiology. In J. Cardiology of Uzbekistan. 2019, C. 255.
4. Kenjaev ML, Ahmedov LA, Povlatova SH, Boboeva MM The course of myocardial infarction in patients of young age // Bulletin of Physicians. Tashkent, 2017.- No.4 - P.44.
5. Kenjaev ML, Ahmedov LA, Pulatova SH, Boboeva MM. Cardiogenic shock bilan asoratlangan útkir myocardial infarcti davosida vasopressor therapy takomillashtirish // Bulletin of therapists. Tashkent, 2017.- No.1 - P.31
6. Pulatova, Sh. H. (2012). Founders: Institute of Immunology of the Academy of Sciences of the Republic of Uzbekistan. THEORETICAL AND CLINICAL MEDICINE
7. Pulatova, Sh. H. (2012). Founders: Institute of Immunology, Academy of Sciences of the Republic of Uzbekistan. THEORETICAL AND CLINICAL MEDICINE Founders: Institute of Immunology, Academy of Sciences of the Republic of Uzbekistan ISSN: 2091-5853
8. Khamroev, E. E., Nurboev, F. E., & Pulatova, S. K. (2022). CHRONIC HEART FAILURE: FEATURES CLINICAL MANIFESTATIONS IN THE ELDERLY. British Medical Journal, 2(2).
9. Pulatova Sh.H. Method of improving vasopressor therapy for acute myocardial infarction complied with cardiogenetic shock // American Journal Of Medicine And Medical Sciences. 2020.– Vol. 10 (11). – – P. 911-913
10. Pulatova Sh.H. Improvement of treatment of patients with acute heart failure, a comparative evaluation of the effectiveness of dobutamine and levosimendan// World Journal Of Pharmaceutical Research. 2020. Vol 9 (6). –P. 2283-2288
11. Khamroev, E. E., F. E. Nurboev, and Sh Kh Pulatova. "CHRONIC HEART FAILURE: FEATURES CLINICAL MANIFESTATIONS IN THE ELDERLY." British Medical Journal 2, no. 2 (2022).
12. Турдиев, У. М. "UNSTABLE PROGRESSIVE ANGINA." УЗБЕКСКИЙ МЕДИЦИНСКИЙ ЖУРНАЛ 3.3 (2022).