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THE INFLUENCE OF ANXIETY AND DEPRESSIVE CONDITIONS ON AFTERINFARCTION REMODELING IN PATIENTS WITH STEMI

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Depression after AMI increases the frequency of re-hospitalization because of acute coronary syndrome, heart failure, MI, and is a risk factor for cardiac arrest and death. The objective of the study was to define the influence of anxiety-depressive disorders (ADD) on afterinfarction remodeling and the participation of sST2 fibrosis factor in this process. 100 STEMI patients were enrolled to the study, 81 (81 %) male and 29 (29 %) female, of average age of 58,94 ± 10,16 years. Examinations were performed twice: during 1–3 days after PCI with infarct-related artery stenting and included clinical-anamnesis data, blood analyses. The sST2 level was defined by immune-fermentative method with usage of «Presage ST2 Assay», Critical Diagnostics, USA. For ADD objectivization, HADS (Heart Anxiety and Depression Scale) and Teylor questionary were used. In 6 month 6-minute walk test and the volume fraction of interstitial collagen (VFIC) were done. Conclusion: ADD in patients with STEMI aggravates the course of postinfarction period and entails the progression of fibrotic-hypertrophic processes and corresponding remodeling of myocardium, decrease of physical tolerance.

KEY WORDS: anxiety-depressive disorders, STEMI patients, sST2, myocardial remodeling

ВПЛИВ ТРИВОЖНО-ДЕПРЕСИВНИХ СТАНІВ НА ПІСЛЯІНФАРКТНЕ РЕМОДЕЛЮВАННЯ У ПАЦІЄНТІВ З ІНФАРКТОМ МІОКАРДА З ПІДЙОМОМ СЕГМЕНТА ST

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Результати досліджень вказують на те, що тривожно-депресивні розлади погіршують перебіг післяінфарктного періоду. Мета роботи: дослідити у хворих на гострий інфаркт міокарда з підйомом ST вплив тривожно-депресивних розладів на післяінфарктне ремоделювання і участь в цьому процесі маркера фіброза sST2. Висновок: тривожно-депресивні розлади обтяжують перебіг післяінфарктного періоду та сприяють посиленню фіброзно-гіпертрофічних процесів.

КЛЮЧОВІ СЛОВА: тривожно-депресивні розлади, інфаркт міокарда з підйомом сегмента ST, sST2, післяінфарктне ремоделювання

ВЛИЯНИЕ ТРЕВОЖНО-ДЕПРЕССИВНЫХ СОСТОЯНИЙ НА ПОСТИНФАРКТНОЕ РЕМОДЕЛИРОВАНИЕ У ПАЦИЕНТОВ С ИНФАРКТОМ МИОКАРДА С ПОДЪЕМОМ СЕГМЕНТА ST

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Результаты исследований указывают на то, что тревожно-депрессивные расстройства ухудшают течение постинфарктного периода. Цель работы: определить у больных острым инфарктом миокарда с подъемом сегмента ST влияние тревожно-депрессивных расстройств на постинфарктное ремоделирование и участие в нем маркера фиброза sST2. Вывод: тревожно-депрессивные расстройства утяжеляют течение постинфарктного периода и влечет за собой усиление фиброзно-гипертрофических процессов.

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КЛЮЧЕВЫЕ СЛОВА: тревожно-депрессивные расстройства, инфаркт миокарда с подъемом сегмента ST, sST2, постинфарктное ремоделирование

INTRODUCTION

Acute myocardial infarction (AMI) is the main reason of mortality and morbidity in Ukraine and in all around the world. AMI mortality remains quite high and hospital mortality is 6–14 % [1–2], research of the factors, which contribute to AMI genesis and its pathogenesis is relevant. Depression and anxiety in European Society of Cardiologists due to cardiovascular prophylactics (2016) are considered as independent risk factors of Ischemic heart disease development. In the INTERHEART research, conducted in 52 countries, anxiety and depression hold the third place among myocardial infarction (MI)-associated risk factors [3]. The prevalence of depressive disorders during one year after AMI is 22,7 %–54 %, depression after AMI increases the frequency of re-hospitalization because of acute coronary syndrome, heart failure, MI, and is a risk factor for cardiac arrest and death [4–7]. The level of mortality in patients with MI with depression is 2–3 times higher than in patients without depression [8].

Multitude of regulatory systems, which are very sensitive to psychoemotional factors interact in the MI pathogenesis. Immuno-inflammatory reaction in AMI is integral component of response on damage of myocardium. It is involved in acute period in processes of survival of cardiomyocytes, apoptosis, myocardial contractility modulation, endothelium damage after ischemic event, reparation mechanisms, early and late remodeling. High level of inflammation markers (TNFα, IL6, IL1β, CRP, etc.), found in AMI, reflects expressed intensity of nonspecific immune-inflammation [9]. At the same time the proofs of relations of depression with activation of parameters of immune system – increase of generation of IL6, CRP, TNFα, MIF are present [4–5]. During experiment, acute stress was the starting point for the profibrotic processes in the myocardium [10]. Marker sST2, which is cytokine-related, draws special attention in this case, as a possible link between depression and postinfarction myocardial remodeling. ST2 (stimulating growth factor, expressed by the gene 2), belongs to the interleukin-1 receptors. IL-33 is a ligand for ST, sST2 blocks the cardioprotective effect of this cytokine, contributing to the development of myocardial fibrosis [11]. In single studies, the level of sST2 is increased in patients with myocardial infarction with elevation of ST segment (STEMI), high levels of this cytokine are predictors of cardiovascular death and heart failure after acute ischemic event [12–13]. We can assume the existence of connection between STEMI, anxiety-depressive disorders, sST2 level and after infarction remodeling process, though there are no available written paper works about it.

OBJECTIVE

To define the influence of anxiety-depressive disorders on postinfarction remodeling and the participation of sST2 fibrosis factor in this process, in patients with STEMI.

MATERIALS AND METHODS

100 STEMI patients were enrolled to the study, 81 (81 %) male and 29 (29 %) female, of average age of 58,94 ± 10,16 years. The patients were hospitalized to the intensive care unit of State Institution «National Institute of therapy n.a. L. T. Malaya of NAMS of Ukraine» during 72 hours of STEMI after PCI with stenting of infarction-dependent artery. Coronary intervention was performed in the catheter laboratory of Institute of general and emergency surgery n.a. V. T. Zaitsev. AMI was diagnosed based on clinical, electrocardiographic, biochemical researches data, according to European guidelines on diagnostics and treatment of STEMI (2012) and MOH Ukraine order №455 from 02 Jul 2014. The research was performed according to DoH regulations, the protocol of research was approved by LEC of GI «National Institute of therapy n.a. L. T. Malaya NAMS Ukraine». Re-examination was performed in 6 months after the index event.

The following clinical and biochemical indicators were defined: hemoglobin, blood glucose, creatinine and its clearance by Cockroft-Gault Equation; lipid metabolism markers: total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol

(HDLC) by fermentative method. The concentration of low-density lipoprotein cholesterol (LDLC) was calculated by the Friedwald equation, 2004г.

The sST2 level was defined by immune-fermentative method with usage of «Presage ST2 Assay», Critical Diagnostics, USA. Control group, which consisted of 20 practically healthy individuals, the sST2 level was (21,44 ± 8,68) ng/ml.

Echo-CG was performed on «Medison Sono Ace X6» device (Korea) with usage of sensor with ultrasound frequency of 3,5 MHz during first 24 hours from hospitalization. Left ventricular end diastolic volume (LV EDV), left ventricular end systolic volume (LV ESV), left ventricular end diastolic and end systolic diameters (LV EDD, LV ESD), left ventricular myocardial mass (LVMM), left ventricular ejection fraction (LVEF), diastolic dysfunction – maximal rate of early diastolic filling E (m/sec), maximal rate of left atrium diastolic rate A (m/sec), their ratio – E/A were estimated.

Six months later, another examination was performed. They included evaluation of severity of interstitial myocardial fibrosis by an indirect method – by calculating the volume fraction of interstitial collagen (VFIC) [14] and 6-minute walk test.

$$VFIC\ (\%)=\left(1-1{,}3\times\frac{total\quad voltage\ QRS(mm)\times height(m)}{MMLV(g)}\right)\times 100,$$

where 1,3 is coefficient of recalculation for MMLV.

VFIC in control group was 8,6 ± 2,1 %.

For anxiety-depressive disorders (ADD) objectivization, HADS (Heart Anxiety and Depression Scale) was used. According to it, there are 3 levels of anxiety and depression: 0–7 points – normal, 8–10 points – borderline case and 11–21 point – increased level, [15], in which 40–50 points corresponded very high anxiety level, 25–40 – high, 15–24 – average (with tendency to high level), 5–14 – average (with tendency to low level) and 0–4 – low. Testing of the subjects allowed defining two groups: 1 – with normal or borderline manifestations of anxiety and 2 – with its increased signs.

Statistical data processing was performed with programs Statistica 8.0 (StatSoft Inc, USA), Microsoft Office Excel 2003. Intergroup differences of qualitative signs were valued using Student's T-Test. For all types of analysis, all differences were considered statistically significant with $p < 0{,}05$.

RESULTS AND DISCUSSION

Table 1 contains the comparative data of clinical, clinical-laboratory and instrumental examination of patients with STEMI in dependence of ADD. The examination was performed on 48–72 hours of STEMI.

In STEMI patients with ADD (48 %) comparing to patients without ADD (51 %) reliable differences of the following parameters were found: gender, MI in anamnesis, complicated MI, HR, MMLV.

Among the examined patients with STEMI male patients (81 %) prevailed compared with female (19 %) patients. Among females, ADD was diagnosed in 31,2 % cases, absence of ADD – in 8 %, among males – 68,7 % and 92 % accordingly. The greater commitment of women with IHD to concomitant ADD is proved in literature: in INTERHEART research the influence of psychological factors and emotional stress on MI genesis and its course was especially expressed in women [16]. In VIRGO research, young women with AMI had higher level of depression and stress and lower level of physical and mental health than men [17]. Big frequency of co-morbid ADD in patients with STEMI in anamnesis (18,3 % и 1,6 % accordingly) corresponds to data about increased probability of development of new cardiovascular events, including re-infarction in patients with depression after MI [4–5, 18].

The HR in STEMI patients with ADD was increased compared to group without ADD ($P = 0{,}035$). Tachycardia as a sign of hyperactivity of sympathic-adrenal system is typical for AMI and is one of somatic syndromes of ADD. Cumulative effect of these reasons of hypersympathicotonia results in increased need of oxygen for myocardium consumption, and also to development of metabolic and dysfunctional disorders, which complicate the course of MI.

Table 1

Clinical characteristics of patients depending on anxiety and depressive conditions (M ± δ)

Data	Patients with ADD, (n=48)	Patients without ADD, (n=52)	T,χ^2 ,p
Age, years	60,75 ± 10,41	57,27 ± 9,72	0,07
Gender male/female	33(68,7 %) / 15(31,3 %)	48 (92,3) / 4(7,7 %)	9,00 p=0,003
Smoking	18 (37,5 %)	24 (46,2 %)	0,77 p=0,38
Diabetes mellitus	10 (20,8 %)	7 (13,5 %)	0,96 p=0,33
Body mass index	29,93 ± 5,19	29,61 ± 6,08	0,78
MI in anamnesis	9 (18,8 %)	1 (1,9 %)	6,09 p=0,01
Complicated MI	13 (27,1 %)	11 (21,2 %)	0,48 p=0,49
HR, per 1 min	81,14 ± 21,44	73,25 ± 15,12	0,035
SBP, mmHg	141,00 ± 14,21	140,10 ± 27,71	0,88
DBP, mmHg	82,83 ± 45,50	83,12 ± 12,18	0,91
Creatinine clearance, ml/min	77,17 ± 26,38	87,95 ± 28,13	0,047
Glucose, mmol/l in patients with DM	12,91 ± 5,44	11,02 ± 5,98	0,52
Glucose, mmol/l in patients without DM	7,26 ± 2,74	6,53 ± 1,71	0,15
Hemoglobin, g/l	133,43 ± 13,52	140,01 ± 18,19	0,04
Total cholesterol, mmol/l	4,77 ± 1,55	4,77 ± 1,30	0,99
LDL, mmol/l	3,02 ± 1,30	2,83 ± 1,23	0,49
CVHD, mmol/l	0,69 ± 0,47	0,81 ± 0,49	0,25
Triglycerides, mmol/l	1,54 ± 1,05	1,75 ± 1,01	0,35
HDL, mmol/l	1,06 ± 0,29	1,12 ± 0,39	0,43
ST2, ng/ml	76,75 ± 33,54 (n = 28)	76,44 ± 29,44 (n = 35)	0,96
LVEDD, sm	5,20 ± 0,53	5,20 ± 0,49	0,98
LVESD, sm	3,80 ± 0,67	3,78 ± 0,63	0,94
LVEF, %	51,70 ± 10,66	50,72 ± 9,57	0,65
E/A	1,13 ± 0,53	1,20 ± 0,49	0,65
LVMM, g	267,00 ± 79,61	231,27 ± 52,51	0,01

Reliable increase of LVMM in STEMI patients with ADD compared to patients without ADD (P = 0,01) is worth paying attention. This fact can be observed as manifestation, not connected with development of current MI, but caused by the pre-infarction period of left ventricular hypertrophy (LVH) formation. Hypertensive, ischemic lesions of myocardium, AMI in anamnesis and co-morbid ADD and neurochemical, neurohumoral and immunoinflammatory reactions, corresponding to it, take part in this multifactorial process.

In patients with STEMI with ADD the reliable decrease of creatinine clearance (P = 0,047) and hemoglobin level (P = 0,04) is defined, comparing to patients without ADD. Dysfunction of kidneys' functional abilities in AMI with ADD can be a consequence of summarized manifestations of severe cardiac status (re-infarction, complicated MI, diabetes mellitus (DM) with ADD symptoms, which negatively affects the glomerular apparatus of kidneys through multiple regulatory systems. The decrease of hemoglobin level in patients with STEMI and ADD was within the limits of normal values and requires further research and analysis.

Positive correlations between anxious states with female gender, (r = 0,47, P = 0,004), MI in anamnesis, (r = 0,47, P=0,005), systolic blood pressure (SBP), (r = 0,23, P = 0,081), diastolic blood pressure (DBP), (r = 0,31, P = 0,071) were found.

Tendency in differences between first and second groups of patients was found in the following indicators: smoking, DM, complicated infarction. In relation to connection of smoking and ADD in patients with STEMI, the following data was received: tendency of patients without ADD to smoke more (46,2 %), than with ADD (37,5 %), P = 0,38. The same data was retrieved by authors, who position smoking as a way to deal with stress [19]. Diabetes mellitus among patients with STEMI

and ADD was diagnosed in 20,8 % cases, without ADD – 13,5 %, P = 0,33. ADD in DM patients happens 10–20 % more frequent, than in general population, etiopathogenetic connection between affective disorders and DM is being implemented through the activation of hypothalamic-pituitary-adrenal system, resistance to insulin, cytokines [20]. That is why most frequency of ADD in STEMI patients and DM compared to patients without DM is totally reasonable. Complicated MI (acute decompensate heart failure, cardiac asthma, pulmonary edema, aneurism of heart, ventricular or supraventricular rhythm disorders) were observed in 27,1 % patients with co-morbid ADD and 21,2 % – without ADD. That's why the connection between ADD and factors, contributing to the complicated course of MI is quite possible.

There were no differences between 1 and 2 groups of STEMI in dependence of ADD on such parameters: age, BMI, SBP, DBP, blood glucose, lipid specter, level of sST2.

sST2 level in general group of patients STEMI was 76,58 ± 25,63, significally exceeding the value of the parameters of control group (P = 0,04), correlation between sST2 and complicated MI, (r = 0,39, p = 0,056), heart rate (HR), (r = 0,34, p = 0,094), LV EDD (r = 0,64, p = 0,01), LVEF, (r = -0,59, p = 0,02), LVMM, (r = 0,57, p = 0,042) were found. Depending on the presence of ADD, no differences in values of sST2 in acute period of STEMI were found.

After six months after index event, 46 patients with ADD and 51 – without it were examined. During this period, 3 patients died, 2 re-infarctions were diagnosed. In table 2 the structure and functional data of patients with STEMI depending on ADD presence are presented.

Table 2

Structure and functional data of patients in 6 month after STEMI depending on anxiety and depressive conditions (M ± δ)

Data	Patients with ADD N = 46	Patients without ADD N = 51	P
HR, per min	79,19 ± 16,14	71,18 ± 21,12	0,04
SBP, mm Hg	140,38 ± 44,54	134,62 ± 21,31	0,41
DBP, mm Hg	80,33 ± 38,50	78,43 ± 22,28	0,76
LV EDD, sm	5,58 ± 0,74	5,29 ± 0,67	0,045
LV ESD, sm	4,03 ± 1,04	3,96 ± 0,77	0,78
LVMM, g	274,72 ± 95,47	240,08 ± 70,27	0,043
LVEF, %	50,61 ± 38,50	53,93 ± 12,71	0,34
E/A	1,20 ± 0,62	1,31 ± 0,66	0,55
6-minute walk test, m	405,15 ± 105,29	480,30 ± 79,73	0,02
VFIC, %	28,06 ± 7,10	19,81 ± 6,80	0,042
sST2, ng/ml	35,58 ± 11,36	30,18 ± 9,79	0,047

After six months after index event, there was a difference between patients with ADD and patients with normal psychological status: significantly different HR (P = 0,09), LV EDD (P = 0,095), LVMM (P = 0,043), 6-minute walk test results (P = 0,02), VFIC (P = 0,042), sST2 level (P = 0,047).

In the literature you can find contradictory data about connection between ADD and structural and functional disorders of myocardium after endured AMI, the association between LVEF and ADD was the main topic [5, 18]. Significant increase of following markers, such as LV EDD, LVMM in patients with STEMI with ADD comparing to patients without ADD shows the influence of ADD on the process of post-infarction remodeling of myocardium (LVH), dimensions of the cavity of the left ventricle), also the values of LVEF and diastolic function of myocardium in compared groups had no differences. Negative influence of ADD on functional status of AMI eST patients is represented by 6-minute walk test results – in the first group, physical exercise tolerance corresponded II functional class(FC) of CHD, in the second – I FC (P = 0,02). These results are consistent with literature data about decreased physical exercise tolerance (by the results of 6-minute walk test) in IHD patients with ADD compared to comparable (in severity of IHD) group with normal psychological status [5,7].

Pathogenic mechanisms of negative ADD influence on post-infarction remodeling of myocardium are researched insufficiently. One of the markers of myocardium fibrosis is ST2, which is actively involved in the development of remodeling of myocardium and its function amongst with IL-33. ST2 is expressed from cardiomyocytes and fibroblasts as membrane-bound isoform (ST2L) and soluble isoform (sST2). Its ligand, IL-33, is expressed from cardiomyocytes and fibroblasts, and during increased pressure loading, interacting with ST2L, has a cardioprotective effect – decreases myocardial fibrosis, hypertrophy of cardiomyocytes, apoptosis, improves myocardial functions. In response to the stress and myocardial damage, sST2 is expressed in cardiomyocytes, fibroblasts, endothelium cells of microvascular system of myocardium, which works as a «bait-receptor» for IL-33 and decreases their cardioprotective effect by disrupting the system of interaction with ST2L. Increased genesis of sST2 leads to amplification of LVH, fibrosis, apoptosis, pathological remodeling of myocardium, decreased functional ability of myocardium and progression of the disease [11]. In some researches sST2 in STEMI, its increased level on hospitalization was associated with increased risk of death and heart failure, was risk factor of death in 30 days, had correlation with post-infarction remodeling [12].

The results of this study showed a significant increase of sST2 level in STEMI in both groups. It reflects the response on the stress damage of cardiomyocytes due to myocardial necrosis. In the acute period of STEMI, there were no differences in groups with or without ADD. In 6 months after the event, the patients with MI and ADD had sST2 level decreasing to a lesser extent, than without ADD (55 % and 61 % accordingly, P = 0,047). Combination of higher values of sST2 in group with ADD with increased dilatation and hypertrophy of left ventricle (LV EDD, LVMM), decrease of physical exercise tolerance (6-minute walk test) is an evidence of the existence of a bond between sST2, post-infarction remodeling and presence of ADD.

The comparison of the VFIC marker in myocardium in 6 months after STEMI discovered its significant increase compared to control in groups 1 and 2 (P = 0,03; P = 0,041), the level in ADD patients was higher than in patients without ADD (P = 0,042).

The positive correlation between sST2 during hospitalization and VFIC in six months after index event, (r = 0,51, P = 0,009), may evidence that its prognostic value for the development of fibrotic changes in myocardium and negative influence on the process of post-infarction remodeling and functional abilities of myocardium.

CONCLUSIONS

1. STEMI patients have ADD frequency of 48 %, positive relation between ADD and female sex, previously diagnosed myocardial infarction, heart rate, left ventricle myocardium mass, negative – with functional state of kidneys and hemoglobin level.

2. ADD in patients with STEMI aggravates the course of postinfarction period and entails the progression of fibrotic-hypertrophic processes and corresponding remodeling of myocardium, decrease of physical tolerance.

PERSPECTIVES OF FURTHER RESEARCH

Prospects for future studies is to estimate the prevalence of genetic polymorphism genes of RAAS – AT II R1 (A1166C), CYP11B2 (C344T) in investigated patients with STEMI, their connection with sST2 and association with phenotypic signs of MI and ADD.

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