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A MULTI-MARKER MODEL FOR PREDICTING DECOMPENSATED HEART FAILURE IN PATIENTS WITH PRIOR ACUTE MYOCARDIAL INFARCTION

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Abstract

The aim of the study was to assess the prognostic value of determining the plasma concentration of NT-proBNP and ST2 in the patients with decompensated HF and prior acute myocardial infarction and their combination in this category of patients.

Materials and methods. There were examined 120 patients with acute myocardial infarction and stage II A-B decompensated chronic HF according to the classification proposed by Vasylenko V. Kh. and Strazhesko M.D., NYHA functional class (FC) III–IV. The patients with Q-QS wave MI (60 individuals) and non Q MI (60 individuals) were divided into 4 groups depending on the treatment methods.

Study groups were homogenous by age, gender, disease severity, duration of the post-infarction period, clinical signs of decompensation, which served as a basis for inclusion of the patients in the study.

All the patients underwent the six-minute walk test in a quiet 30–50-m long hospital corridor in the morning. N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) and ST-2 were analyzed in all patients.

Results. Promising biomarkers of HF decompensation in the post-infarction period were studied. In the patients with prior Q-QS MI and decompensated HF, NT-proBNP level was (950.38±3.15) pmol/l ($p<0.05$); in the patients with prior MI without signs of decompensated HF, it was (580.15±3.03) pmol/l ($p<0.05$); in apparently healthy individuals, the level of NT-proBNP was found to be (111.20±3.47) pmol/l.

ST2 level was (14.80±1.61) ng/ml, (36.00±1.43) ng/ml and (49.22±1.40) ng/ml in the patients of Group 1, Group 2 and Group 3, respectively ($p<0.05$).

Similar changes were found in patients with decompensated HF in postinfarction period after non Q MI.

Conclusions. The increase in plasma concentration of sST2 is associated with the activation of both neurohumoral and fibrous pathways and can help in detecting the patients with decompensated HF in the post-infarction period and predicting the risk of its development.

Our results confirmed the results of other multiple studies reporting ST2 in combination with NT-proBNP to be valuable tools for prognosing the development of decompensated HF in the patients with prior MI. ST2, alongside with NT-proBNP, is a promising biomarker to be included in the diagnostic panel for detecting acute HF and can provide additional information on risk stratification for such patients during hospitalization and at the time of discharge from the hospital.

Keywords: acute myocardial infarction, decompensated heart failure, biomarkers, NT-proBNP, ST2.

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1. Introduction

Heart failure (HF) is a syndrome affecting more than 5.7 million people annually and is the most frequent cause of hospitalization worldwide [1]. It is a major public health challenge. Both rapid and quality identification of the individuals at high risk of HF development in the post-infarction period and the determination of new therapeutic strategies should be considered [2]. However, the main recommendations for the prevention of cardiovascular diseases have not paid enough attention to HF prediction; the main mechanisms of its development in the post-infarction period have not been fully known [3]. Biomarker model for diagnosing HF has become an integral part of modern medicine; however, it needs further study and continuous improvement [4].

B-type brain natriuretic peptide (BNP) is a hormone synthesized and secreted by cardiomyocytes in response to ventricular pressure and volume overload [5]. These peptides are known to play a crucial role in maintaining homeostasis in the cardiovascular system and serve as counter-regulatory hormones for pressure and volume overload [6]. The Breathing not properly multinational study, conducted in 2002, was the first large study that evaluated the effectiveness of BNP as a cardiac marker [7]. Several factors can increase serum levels of natriuretic peptides. They include age, female sex and renal insufficiency [8]. Low levels of these peptides during the observation period indicated the reduction in the effects of HF, while elevated levels were associated with unfavorable prognosis for patients [9, 10].

ST2 is a member of the interleukin-1 (IL-1) superfamily. It is defined as a ligand for interleukin-33 (IL-33). ST2 has two main isoforms: transmembrane or cellular (ST2L) and soluble (ST2s) forms [11, 12]. ST2 is a member of the Toll-like/IL-1 receptor superfamily. The ST2 gene, found on human chromosome 2q12, is expressed in 4 isoforms; two of them contain transmembrane receptor (ST2 ligand or ST2L) and soluble serum circulating receptor (sST2) which can be detected in blood plasma [13–15]. All the forms are able to bind to IL-33; however, they have different effects. IL-33 is secreted in response to overstretching of certain cells that act as a barrier (e.g. endothelial cells, lung and intestinal epithelial cells, keratinocytes, fibroblasts and smooth muscle cells) and are regulated in case of inflammation [16, 17]. If it binds to ST2L, it functions as an alarm signal for the processes of protection against fibrosis and hypertrophy [18]. If sST2 binds to IL-33, it serves as a decoy receptor that prevents IL-33 signaling thereby inhibiting fibrosis and hypertrophy that occurs in case of elevated sST2 levels [19] by neutralizing the beneficial activity of circulating IL-33 [20, 21].

According to the latest research, ST2s is considered as a potential marker of inflammation and cardiac remodeling. In 2003, Weinberg et al. found that short-term changes in plasma sST2 levels were prognostically valuable for diagnosing mortality and heart transplantation in the patients with HF regardless of natriuretic peptide levels [22, 23].

According to the reasons mentioned above, novel biomarkers of HF prediction can improve the risk identification, as well as to provide an understanding of the pathophysiological mechanisms involved in this process [24]. New recommendations, being developed because of evidence-based clinical guidelines, are undoubtedly waiting for more data obtained from randomized multi-centered clinical trials to develop novel marker-associated system for detection and treatment of HF [25].

Two biomarkers, assessed in this study, are the parts of separate biological processes; therefore, they are able to provide independent and additional prognostic information on the occurrence of decompensated HF in the post-infarction period.

2. Materials and methods

There were examined 120 patients with Q-QS wave and non-Q wave myocardial infarction (MI), stage II A-B decompensated chronic HF according to the classification proposed by Vasilenko V. Kh. and Strazhesko M. D., NYHA functional class (FC) III-IV. The patients with Q-QS wave MI (60 individuals) were divided into 4 groups depending on the treatment methods: Group I comprised 15 patients who received basic therapy in accordance with the protocols of the Ministry of Health of Ukraine (lisinopril – 10 mg once a day; bisoprolol fumarate – 10 mg once a day; eplerenone – 50 mg once a day; valsartan – 40 mg twice a day; ivabradine – 5 mg twice a day).

day); Group 2 included 15 patients who, on the background of basic therapy, received a preparation of succinic acid according to the proposed scheme; Group 3 included 15 patients who, on the background of basic therapy, received arginine preparations according to the proposed scheme; Group 4 comprised 15 patients who, on the background of basic therapy, received succinic acid and arginine preparations according to the proposed scheme. The patients with non-Q wave MI (60 individuals) were divided into 4 analogous groups. All patients were examined and observed based on the Department of myocardial infarction No 2 of the Ivano-Frankivsk regional clinical cardiology center from 2016 to 2018.

Study groups were homogenous by age, gender, disease severity, duration of the post-infarction period, clinical signs of decompensation, which served as a basis for inclusion of the patients in the study. The mean age of patients in all groups averaged (56.67 ± 5.72) years, for men – (56.76 ± 5.71), women – (56.4 ± 5.75). The largest group was with patients aged 45–59, respectively 65.83 % (79).

The members of the Ethics Commission (extract from protocol No. 5 dated January 13, 2016) at the Ivano-Frankivsk National Medical University, decided that this study would not contradict the main provisions of the GCP, Convention Council of Europe on human rights and biomedicine, the Helsinki Declaration of the World Medical Association on ethical principles for the conduct of scientific medical research with the participation of man and the Law of Ukraine «On Medicines». All patients signed an informed consent to participate in a clinical trial.

All the patients underwent the six-minute walk test (6 MWT) in a quiet 30–50-m long hospital corridor in the morning. Blood samples were taken on an empty stomach after the patients had rested for at least 20 minutes. In 5 minutes, the samples were centrifuged for 10 minutes at 4°C and then, they were frozen at -70°C until analysed. N-terminal pro-B-type brain natriuretic peptide (NT-proBNP) was analyzed in the laboratory using clinically available enzyme-linked immunoassay (Roche Elecsys, Roche Diagnostics). ST2 was analysed using ST2 enzyme-linked immunosorbent assay (ELISA) (critical diagnostics) with the lower detection limit of 2 ng/ml, the upper detection limit of 200 ng/ml, the intra-assay coefficient of variation $<2.5\%$ and the inter-assay coefficient of variation $<4.6\%$. The results obtained were statistically processed on the personal computer by means of software package STATISTICA-7. During the work, the arithmetic mean M , the mean quadratic deviation δ , the mean error of the arithmetic mean m , the number of variant (n), the probability of the difference of the two arithmetic “ p ” were calculated, the values of $p < 0.05$ were estimated as probable.

3. Research results

During this study, promising biomarkers of HF decompensation in the post-infarction period were studied. For this purpose, there was analyzed the mean value of serum NT-proBNP and ST2 levels of the studied patients. The levels of biomarkers in the patients with prior MI depending on the presence of decompensated HF are presented in **Table 1**.

In the patients with prior Q-QS and non-Q MI with decompensated HF, NT-proBNP level was (950.38 ± 3.15) pmol/l ($p < 0.05$); in the patients with prior MI without signs of decompensated HF, it was (580.15 ± 3.03) pmol/l ($p < 0.05$); in apparently healthy individuals, the level of NT-proBNP was found to be (111.20 ± 3.47) pmol/l.

ST2 level was (14.80 ± 1.61) ng/ml, (36.00 ± 1.43) ng/ml and (49.22 ± 1.40) ng/ml in the patients of Group 1, Group 2 and Group 3, respectively ($p < 0.05$).

In the patients with decompensated HF signs after non Q and Q-QS MI, significantly higher serum NT-proBNP levels were observed. Moreover, in the patients of Group 3 with inadequate response to physical activity, the level of NT-proBNP increased significantly to (1048.06 ± 4.83) pg/ml; in the patients of Group 2 and healthy individuals, it was (619.03 ± 4.70) pg/ml and (116.20 ± 4.83) pg/ml, respectively ($p < 0.05$).

Considering the results of the 6 MWT and enzyme-linked immunoassay of serum NT-proBNP level in the patients with decompensated HF secondary to prior MI, there was conducted correlation analysis between the indicator of exercise tolerance, namely the distance walked over a span of 6 minute, and the concentration of this marker.

Table 1

Levels of biomarkers in the patients with prior myocardial infarction depending on the presence of decompensated heart failure

Indicator, units of measurement	Apparently healthy individuals (n=20)	Patients with prior MI without decompensated HF (n=40)	Patients with prior MI and decompensated HF (n=120)
NT-proBNP before physical activity, pg/ml	111.20±3.47	580.15±3.03 $p_1 < 0.05$	950.38±3.15 $p_1 < 0.05$ $p_2 < 0.05$
NT-proBNP after physical activity, pg/ml	116.20±4.83 $\Delta 49.4 \pm$	619.03±4.70 $p_1 < 0.05$	1048.06±4.83 $p_1 < 0.05$ $p_2 < 0.05$
ST2	14.80±1.61	36.00±1.43 $p_1 < 0.05$	49.22±1.40 $p_1 < 0.05$ $p_2 < 0.05$

Note: p_1 – statistically significant difference in the indicators as compared to apparently healthy individuals; p_2 – statistically significant difference in the indicators as compared to the patients with prior MI without decompensated HF

4. Discussion

The study allowed us to confirm that the patient's response to graded exercises and serum levels of NT-proBNP and ST2 play the most significant role in clinical and prognostic assessing the post-infarction period complicated by decompensated HF. It was earlier reported, that ST2 is an efficient marker of HF. The IL/ST2 pathway is correlated with the severity of HF clinical course and is a factor in the decline of cardiac function in HF patients [26]. It is thought to be a cardio-protective signalling pathway that is activated by cell damage and mechanical stress, through the release of IL-33 from cardiac cells. Activation of IL-33 prevents myocardial hypertrophy and fibrosis through interaction of IL-33 and transmembrane bound ST2L [27]. As noted, sST2 is a circulating form, which lacks the transmembrane and cytoplasmic domains [28].

For disease monitoring, serial test results proved to be specifically useful. Higher levels of sST2 are associated with more severe clinical symptoms and with other objective measures of HF severity, such as higher natriuretic peptide levels [29]. Although, levels of this enzymes have been used widely for the earlier diagnosis or exclusion of chronic HF in the outpatient setting, their use in the acute care settings has only partially been adopted, because their role has remained uncertain [30].

6 MWT is the simple walk test and particularly is applicable in the HF population due to the risk of acute cardiac events associated with the gold standard maximal exercise testing for assessing functional capacity [31] and determine functional capacity, which refers the ability of a person to perform activities of daily living and reflects the ability of the cardiac system to sustain aerobic metabolism.

Therefore, 6 MWT is used to determine the extent of myocardial contractility changes. High levels of NUP and ST2 indicate a poor prognosis. Therefore, an inadequate response to measured exercise and increased immunological parameters as quantitative HF markers may be useful not only for diagnosis but also for risk stratification, decision making on optimization of treatment of such contingent of patients and decision on discharge.

Study limitations. A limitation of the study is the fact, that in a course, that in most patients with HF, exercise tolerance reduces and the 6 MWT is used to determine the degree of changes in myocardial contractility, it was found high levels of natriuretic peptide and ST2 indicate an unfavorable prognosis. Therefore, an inadequate response to graded exercises and increase in the concentration of immunological indicators as quantitative markers of HF can be useful for diagnosis, as well as risk stratification, making decisions on optimizing the treatment of such patients and discharging them.

Prospective for the further research. Since the main limits of changes in NT-pro BNP and ST2 depending on the signs of decompensated HF secondary to acute MI have been deter-

mined, we plan to develop an algorithm for predicting the development of this syndrome in the post-infarction period under conditions of lower FC formation and assessing the quality of therapy, as well as determining the frequency and time periods of using these peptides for making therapeutic decisions.

5. Conclusions

Thus, we can conclude that the increase in plasma concentration of sST2 is associated with the activation of both neurohumoral and fibrous pathways, and can help in detecting the patients with decompensated HF in the post-infarction period and predicting the risk of its development. Our results confirmed the results of other multiple studies reporting ST2 in combination with NT-pro BNP to be valuable tools for prognosing the development of decompensated HF in the patients with prior MI. ST2, alongside with NT-pro BNP, is a promising biomarker to be included in the diagnostic panel for detecting acute HF and can provide additional information on risk stratification for such patients during hospitalization and at the time of discharge from the hospital.

Conflicts of interest

No conflict of interests.

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