**sST 2 AS A MARKER OF THE TREATMENT OF PATIENTS AFTER MYOCARDIAL INFARCTION WITH ACCOMPANYING ARTERIAL HYPERTENSION ON THE BACKGROUND OF TREATMENT WITH MELDONIUM AND FOLIC ACID**

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**Abstract.** Coronary artery disease (CAD) is one of the leading reason of mortality in Ukraine and all over the world. Arterial hypertension (AH) is the most common manageable factor in cardiovascular morbidity. Every third Ukrainian suffers from this disease. The presence of AH in a patient often becomes the reason for the further development of stable coronary artery disease (SCAD) due to the close pathogenetic connection of both pathologies. sST2 is a modern marker of cardiac fibrosis, which can help to evaluate the effectiveness of the underlying treatment for the patients with SCAD and concomitant AH.

**The aim.** To study the possibility of using sST2 as a marker of the effectiveness of treatment of patients after a myocardial infarction with accompanying arterial hypertension on the background of treatment with meldonium and folic acid.

**Materials and methods.** During our study we observed 40 patients with SCAD FC II-III and concomitant AH stage III, who had an acute myocardial infarction and underwent percutaneous coronary intervention with balloon angioplasty and stenting. All examined were divided into 2 groups of 20 patients each. The first group received standard treatment. The second group in addition to standard treatment, received a combination of folic acid and meldonium. In the course of the work, a detailed analysis of the results of general clinical, laboratory and instrumental examination methods was carried out. Laboratory study of sST2 levels in blood plasma was carried out by quantitative enzyme immunoassay.

**Results.** We observed improvement of all Echocardiography parameters in patients of both groups. Somewhat more significant changes were recorded in the analysis of end systolic diameter of left ventricle. So, if in the first group the decrease in this indicator occurred gradually and amounted to an average of 7.8% after 6 months of treatment, then in the group of combined application of meldonium and folic acid against the background of traditional therapy, a significant reduction in ESD by 10.5% was recorded. The indicator decreased from 4.2 cm to 3.8 cm (p<0.05). Also there was a different trend regarding the dynamics of thickness of the posterior wall during systole. In the first group the reduction of this indicator at the end of the study was 5.7% (p>0.05). In the second group this indicator decreased from 1.13 cm to 1.11 cm after 1 month of treatment and to 0.89 cm after 6 months. That is, the decrease in the first stage was only 1.8% (p>0.05), and then 26.9% (p<0.05). In the course of the study, an increase in LVEF was found among patients with SCAD and concomitant AH. The increase in this indicator after 6 months was 3-4% among all the examined, regardless of the applied drug therapy.

We observed the decrease in the concentration of sST2 in both groups of patients. However, it was reliable only among patients to whom, in addition to standard treatment, we added a combination of meldonium and folic acid. In the group of patients on SCAD with concomitant hypertension, a weak direct correlation between the level of ST2 and LVMI was established. The correlation coefficient in this case was r=0.1033 (p>0.05).

**Conclusions.** In the course of our study, the feasibility of using sST2 as a marker of the effectiveness of treatment of patients after a myocardial infarction with accompanying AH against the background of treatment with meldonium and folic acid was established. Application of myocardial cytoprotectors reliably reduced the concentration of a sST2, which makes their use in the complex treatment of patients after MI with concomitant AH reasonable.

**Keywords:** stable coronary artery disease, arterial hypertension, sST2, meldonium, folic acid.

**Introduction.** Diseases of the cardiovascular system remain the most common cause of mortality in the population. Coronary artery disease (CAD), in particular previous myocardial infarction (MI), occupies a prominent place among the widespread causes of disability among Ukrainians [1]. The pathogenetic basis of this remains a violation of the coronary blood flow with the development of heart failure (HF). The presence of concomitant arterial
hypertension (AH) in patients significantly worsens the course of the underlying disease due to the close mechanism of development and progression of both pathologies. The formation of a zone of necrosis with the subsequent development of focal cardioclesis forms a "weak spot" in the tissue of the myocardium, which reduces its contractile capacity and leads to the progression of characteristic clinical manifestations – shortness of breath, chest pain, rhythm and conduction disturbances [2].

In addition to the traditional instrumental and laboratory methods of diagnosing the specified pathology (ECG, echocardiography, coronary angiography, troponin test), the question of finding new methods of monitoring the effectiveness of treatment, forecasting and evaluating the progression of pathological remodeling of the left ventricle in the post-infarction period remains open. One of these markers is the soluble form of ST2 protein, which is also called a marker of myocardial fibrosis [3].

The ST2 protein is a member of the interleukin 1 (IL-1) receptor family. It was first described in 1989, but for many years it remained an orphan receptor, mainly associated with immune and inflammatory diseases [4]. In 2005, it was first reported that ST2 is expressed in cardiac cells in response to myocardial stress, and interleukin 33 (IL-33) is a ligand for ST2. Since then, its role in the development of cardiovascular diseases, in particular myocardial fibrosis, has been of great interest in the scientific community [5].

One of the mechanisms of the development and progression of fibrosis of the heart muscle after a MI is an imbalance and insufficient supply of oxygen and nutrients, even after revascularization of a heart attack-related vessel (No-Reflow syndrome). Adding of myocardial cytoprotectors (meldonium and folic acid) to the list of standardized treatment is appropriate in the complex solution of the indicated problem. Studying the dynamics of changes in the concentration of soluble ST2 can be one of the potential markers of the effectiveness of such treatment.

Research rationale. Cardiac fibrosis is a major global health problem associated with late recovery in almost all forms of heart disease [6]. Scar tissue is the final response of cells and tissues to pathophysiological stress, during which the heart undergoes late remodeling to compensate for both the loss of dead cells and the hypertrophic remodeling of surviving cardiomyocytes [7]. In pathological conditions such as hypertension, coronary occlusion, valvular dysfunction, and myocardial infarction, the left ventricle (LV) undergoes a series of biomechanical, molecular, cellular, and extracellular matrix changes that alter LV chamber geometry and physiology. The wall of the ventricle becomes stiffer and over time this leads to the development of diastolic dysfunctions and changes in the propagation of the heart impulse through the myocardium, which contributes to the appearance of rhythm and conduction disorders [8]. Structural rearrangements are accompanied by inflammatory edema and scarring around the perivascular areas, slowing the flow of oxygen and nutrients to the cardiomyocytes and triggering a chain of pain that supports myocardial remodeling [9].

One of the ways to reduce the speed or even prevent the development of such a cascade of events is to restore the supply of oxygen and nutrients to the affected area in time. In the case of occlusion of the main coronary arteries (CA), the "gold standard" of treatment remains revascularization of the CA with implantation of a stent in the infarct-related vessel. However, in practice, the question of normalization of nutrition of affected areas in the presence of microcirculatory occlusion and No-Reflow syndrome remains unresolved.

Application of myocardial cytoprotectors, such as meldonium and folic acid, is one of the promising ways to improve the situation. The mechanism of action of meldonium is based on reducing the intensity of lipid peroxidation with the activation of endogenous antioxidants. This contributes to the stabilization of the function of the endothelium with the gradual normalization of vascular tone. Meldonium additionally reduces the peripheral resistance of blood vessels, reduces the activity of vasoconstriction caused by the action of catecholamines. Its use optimizes the assimilation of oxygen in cells by stimulating the oxidation of glucose and stabilizes the use of ATP molecules [10].

Folic acid is a water-soluble vitamin, the effectiveness of which in the treatment of cardiovascular pathologies has not been sufficiently studied. Nevertheless, its intake improves the function of the endothelium in hypercholesterolemia [11]. Folic acid in combination with vitamins B6 and B12 reduces the rate of restenosis after coronary stenting, which allows it to be considered a useful addition to established standards of treatment for patients with heart disease.

The relationship between sST2 and coronary artery disease, one of the most common causes of heart failure, is still under investigation. Most modern studies of sST2 in the field of coronary heart disease study the combination of atherosclerosis, prediction of the No-Reflow phenomenon, assessment of LV myocardial remodeling and selection of optimal treatment for such patients [12]. Application of myocardial cytoprotectors can be one of the "keys" to solving this problem.

Zhang et al. found that levels of sST2 in plasma were much higher in patients from acute coronary syndrome (ACS) with difficult lesions than in patients from simple lesions that indicated that sST2 may be a new marker to evaluate stability and complexity atherosclerotic plaques [13]. However given above research also showed that it was not correlations between level sST in plasma and severity of stenosis measured by quant wine vessels and Hensini ball.

As in patients with STEMI, prognostic role of sST2 in patients with a stable coronary artery disease (SCAD) remains controversial. The results of research KAROLA for 13 years testify that levels sST2 can be an independent predictor of mortality patients from SCAD, but do not provide non-fatal cardiovascular events [14]. Similarly results also showed Ludwigshafen Risk and Cardiovascular Health Study where equal increase of sST2 is an independent predictor of long-term mortality from of all causes in patients from SCAD [15]. However there is opposite conclusion, stating that sST2 was not connected with mortality patients from SCAD, despite being strong communication with mortality patients with STEMI [16]. Despite the fact that many research confirmed that sST2 has strong prognostic effect on the prognosis of cardiac deficiencies, quantity of research of sST2 and the prognosis of CAD, both with ACS and with chronic coronary syndrome (CHS), is limited, and their conclusions are contradictory.
So in the future more needs to be done research for the future study prognostic effect sST2 on CAD.

**The aim of the study.** To study the possibility of using sST2 as a marker of the effectiveness of treatment of patients after a myocardial infarction with accompanying arterial hypertension on the background of treatment with meldonium and folic acid.

**Materials and methods.** 40 patients with SCAD FC II–III and concomitant hypertension stage III were examined, who had an acute myocardial infarction no earlier than 12 months before the time of inclusion in the study, and for which they underwent percutaneous coronary intervention with balloon angioplasty and stenting of the infarct-related vessel in acute period. The diagnosis was established on the basis of complaints, anamnesis, data of an objective physical examination and data of general clinical, laboratory, biochemical and instrumental methods of examination (ECG, echocardiography, coronary angiography).

The criteria for inclusion in the study were: the presence of patients with stable coronary artery disease (FC II–III), arterial hypertension of the III stage, the absence of contraindications to treatment with the studied drugs, age up to 80 years.

Exclusion criteria were: acute coronary syndrome, acute cerebrovascular disorders, chronic kidney disease IV-V stage, liver failure, blood diseases, oncological diseases, pregnancy and breastfeeding, acute and chronic inflammatory diseases of the heart and its lining (endocarditis, myocarditis, pericarditis), atrial/ventricular fibrillation/flutter, II–III degree AV block, neuropsychiatric pathology, severe coronary artery disease complicated by cardiogenic shock, severe heart failure with HF <40%.

All examined were divided into 2 groups of 20 patients each:

1. patients who received standard treatment according to the "Unified Clinical Protocol" and "Adapted Clinical Guidelines";
2. patients who, in addition to standard treatment, received a combination of folic acid and meldonium.

The work was carried out on the basis of ethical principles for research involving humans (Declaration of Helsinki) and was conducted as an open, controlled, comparative study in parallel groups. Informed consent was signed by all study participants.

In the course of the study, a detailed analysis of the results of general clinical, laboratory and instrumental examination methods was carried out.

Laboratory study of ST2 levels in blood plasma was carried out by quantitative enzyme immunoassay. Presage® ST2 Assay EIA Test kits were used to determine ST2 Kit REF#BC-1065E, manufactured by CRITICAL DIAGNOSTICS 3030 Bunker Hill St. Suite 117A San Diego to determine the concentration of ST2 in blood serum according to the attached instructions.

Indicators of cardiac hemodynamics were determined by the echocardiography. This technique made it possible to obtain information about the state of the heart and its structure (valves, sizes and volumes of heart chambers, myocardium mass, presence of bulges, condition of the pericardial sac) and functional characteristics (systolic and diastolic functions of the ventricles, contractility of the entire left ventricle and its individual parts, valve function, pressure in the pulmonary artery system) using a GE Voluson E6 Ultrasonograf echocardiograph with 2.5 and 3.5 MHz sector sensors in M- and B-modes according to standard techniques.

LV systolic function was assessed by determining the ejection fraction (EF) according to a standard method. Remodeling indicators, LV end-diastolic diameter (EDD), LV end-diastolic volume (EDV) were evaluated. The end-systolic volume and diameter (ESV, ESD, respectively) of the LV, the thickness of the interventricular septum and the thickness of the posterior wall of the LV in systole and diastole were also evaluated. LV myocardial mass (LVM) was determined according to the formula recommended by the American Society of Echocardiography (ASE).

Statistical processing of the obtained results was carried out using the STATISTICA-10 computer program and a package of statistical functions of the Microsoft-Excel program on a personal computer, using the variational statistical method of analysis. The quantitative indicators obtained in the study were first checked for the type of their distribution according to the method of A. M. Kolmogorov – M. V. Smirnov and H. Lilliefors (AN Kolmogorov – NV Smirnov & H. Lilliefors test for normality) and SS Shapiro - M. Wilk’s W test (SS Shapiro - M. Wilk's W test). Since all of them did not correspond to the law of normal distribution, to present measures of central tendency (Measures of Central Tendency) chose the median value (Me) and the interquartile range (LQ - UQ). Accordingly, to test the null hypothesis, the non-parametric test of the HB Mann-DR Whitney U test was used, values p<0.05 were considered probable.

**The results.** In order to evaluate the features of the remodeling of the left ventricle and the changes in its geometry, the patients underwent echocardiography during the treatment.

Among patients who received only basic medical treatment, the EDV from 142.2 (127.0-154.0) ml decreased to 137.7 (123.0-152.0) ml after 1 month and to 132.9 (121.5-139.0) ml at the end of the study. ESV in this group was 78.6 (66.0-79.0) ml, 72.2 (65.0-80.0) ml and 71.8 (61.0-72.5) ml, respectively (table 1).

Similar dynamics regarding the levels of EDV and ESV were observed in the group where the combination of meldonium with folic acid was added to the standard treatment.

Somewhat more significant changes were recorded in the analysis of ESD. So, if in the first group the decrease in this indicator occurred gradually and amounted to an average of 7-8% after 6 months of treatment, then in the group of combined application of meldonium and folic acid against the background of traditional therapy, a significant reduction in ESD by 10.5% was recorded at the time of the completion of the examination. The indicator decreased from 4.2 (3.8-4.6) cm to 3.8 (3.5-4.2) cm (p<0.05).
In both groups of patients, despite the medications used, thickness of the interventricular septum during systole and diastole gradually decreased by 6-7% by the end of the study (p>0.05).

There was a different trend regarding the dynamics of thickness of the posterior wall during systole. Thus, in the group of standard treatment, it was 1.12 (0.97-1.27) cm before the start of therapy, 1.11 (0.96-1.26) cm after 1 month and 1.06 (1.00-1.17) cm after 6 months of medication use. The reduction of thickness of the posterior wall at the end of the study was 5.7% (p >0.05).

In the group of combined use of meldonium and

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Basic therapy (n=20) Me (LQ-UQ)</th>
<th>Basic therapy + folic acid + meldonium (n=20) Me (LQ-UQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>1 month</td>
</tr>
<tr>
<td>EDV, ml</td>
<td>142.2 (127.0-154.0)</td>
<td>137.7 (123.0-152.0)</td>
</tr>
<tr>
<td>ESV, ml</td>
<td>78.6 (66.0-79.0)</td>
<td>72.7 (65.0-80.0)</td>
</tr>
<tr>
<td>EDD, cm</td>
<td>5.6 (5.3-5.8)</td>
<td>5.6 (5.2-5.7)</td>
</tr>
<tr>
<td>ESD, cm</td>
<td>4.2 (3.9-4.2)</td>
<td>4.1 (3.8-4.1)</td>
</tr>
<tr>
<td>Thickness of the interventricular septum (systole), cm</td>
<td>1.07 (1.00-1.12)</td>
<td>1.06 (0.98-1.20)</td>
</tr>
<tr>
<td>Thickness of the interventricular septum (diastole), cm</td>
<td>1.02 (0.92-1.10)</td>
<td>1.00 (0.90-1.09)</td>
</tr>
<tr>
<td>Thickness of the posterior wall (diastole), cm</td>
<td>1.12 (0.97-1.27)</td>
<td>1.11 (0.96-1.26)</td>
</tr>
<tr>
<td>Thickness of the posterior wall (systole), cm</td>
<td>1.04 (0.92-1.14)</td>
<td>1.02 (0.92-1.14)</td>
</tr>
<tr>
<td>EF, %</td>
<td>49.3 (48.0-52.0)</td>
<td>50.1 (48.7-52.8)</td>
</tr>
<tr>
<td>Pressure in pulmonary artery, mm Hg.</td>
<td>31.6 (27.0-33.8)</td>
<td>30.7 (26.1-32.7)</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>113.6 (99.7-126.2)</td>
<td>109.3 (95.8-121.4)</td>
</tr>
<tr>
<td>LVM, g</td>
<td>230.9 (204.3-242.1)</td>
<td>222.1 (196.5-232.9)</td>
</tr>
</tbody>
</table>

Notes: 1. The percentage of the total number of people in the group is indicated in parentheses. 2. p is the probability of the difference of the indicator according to the indicator before treatment.

Table 1

Dynamics of echocardiography indicators in patients with SCAD with concomitant hypertension
folic acid among the examined patients, to some extent, unexpected changes in thickness of the posterior wall during systole were recorded. Thus, this indicator decreased from 1.13 (1.00-1.20) cm to 1.11 (0.98-1.17) cm after 1 month of treatment and to 0.89 (0.80-1.02 ) cm after 6 months. That is, the decrease in the first stage was only 1.8% (p>0.05), and then 26.9% (p<0.05).

Thickness of the posterior wall during diastole among patients receiving standard therapy decreased from 1.04 (0.92-1.14) cm at the beginning of therapy to 1.02 (0.92-1.14) cm at the end of the study (∆-1.9 %).

In the group of combined use of both studied medications, the reduction of thickness of the posterior wall during diastole from the beginning of therapy to the moment of its completion amounted to 17.9% (p<0.05), respectively.

In the course of the study, an increase in LVEF was found among patients with SCAD with concomitant hypertension. The increase in this indicator after 6 months was 3-4% among all the examined, regardless of the applied drug therapy.

![Fig. 1. Dynamics of LVMI in patients with SCAD with concomitant hypertension under the influence of various treatment methods.](image)

**Note.** Probability of difference p - compared to the indicators before treatment, * - p<0.05, ** - p>0.05.

In the course of our study, we recorded positive dynamics regarding the geometry of the heart among both groups of patients, however, the use of basic therapy in combination with cytoprotectors provided better results.

We obtained the same results regarding the decrease in the concentration of sST2 in both groups of patients (Fig.2). However, it was reliable only among patients to whom, in addition to standard treatment, we added a combination of meldonium and folic acid.

![Fig. 2. The dynamics of the sST2 index in patients with SCAD with concomitant hypertension under the influence of various treatment methods.](image)

**Note.** Probability of difference p - compared to the indicators before treatment, * - p<0.05, ** - p>0.05.
We considered that the decrease in the concentration of sST2 in the blood of patients as one of the markers of the effectiveness of the treatment, along with the improvement of the geometry of the heart and the decrease in LVMI. To confirm this fact, we determined the relationship between the concentration of a biomarker of myocardial fibrosis in the blood of patients and LVMI.

In the group of patients on SCAD with concomitant hypertension, a weak direct correlation between the level of ST2 and LVMI was established. The correlation coefficient in this case was $r=0.1033$ ($p>0.05$) (Fig. 3).

![Fig. 3. Correlation between ST2 concentration and LVMI in patients with stable CAD with accompanying hypertension.](image)

The obtained results allow us to assert the expediency of evaluating the results of echocardiogram and sST2 concentration during the treatment of patients with stable coronary artery disease and concomitant hypertension. We consider the gradual improvement of indicators as confirmation of the effectiveness of the selected therapeutic scheme. It should be noted that the additional use of cytoprotectors (meldonium and folic acid) contributed to the achievement of better results.

**Conclusions.** In the course of our study, the feasibility of using sST2 as a marker of the effectiveness of treatment of patients after a myocardial infarction with accompanying arterial hypertension against the background of treatment with meldonium and folic acid was established.

Application of myocardial cytoprotectors reliably reduced the concentration of a biomarker of myocardial fibrosis, which makes their use in the complex treatment of patients after MI with concomitant hypertension reasonable.

**Prospects for further research.** The relationship between the dynamics of echocardiogram indicators and the concentration of sST2 in the blood expands the possibilities of their comprehensive study to assess the effectiveness of treatment of patients months and years after an MI with concomitant hypertension.

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sST2 як маркер ефективності лікування маркер ефективності лікування пацієнтів після перенесеного інфаркту міокарда із супутньою артеріальною гіпертензією на фоні лікування мельдонієм і фолієвою кислотою

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Резюме. Ішемічна хвороба серця (ІХС) є одним з основних причин смертності в Україні та в усьому світі. Артеріальна гіпертензія (АГ) є найбільш поширенням елементом серцево-судинної захворюваності. sST2 — це сучасний маркер кардіофіброзу, який може допомогти оцінити ефективність основного лікування пацієнтів з ІХС та супутньою АГ.

Мета. Вивчити можливість застосування sST2 як маркера ефективності лікування пацієнтів після перенесеного інфаркту міокарда із супутньою артеріальною гіпертензією на фоні лікування мельдонієм і фолієвою кислотою.

Матеріали та методи. Обстежено 40 пацієнтів із СІХС ФК ІІ-III та супутньою АГ III стадії після госп- трового інфаркту міокарда та ургентного стентування. Хворих було поділено на 2 групи по 20 пацієнтів: ті, які отримували стандартне лікування, і ті, які отримували комбінацію фолієвої кислоти та мельдонію. У процесі дослідження ми провели аналіз результатів загальноклінічних, лабораторних та інструментальних методів обстеження. Лабораторне дослідження рівнів сST2 у плазмі крові проводили шляхом кількісного імуноферментного аналізу. Показники середньої гемодинаміки визначали методом EhoKГ.

Результати. Спостерігалося покращення всіх показників EhoKГ у пацієнтів обох груп. Більш суттєві зміни зафіксовано стосовно КСР лівого шлуночка. Також спостерігалася інша тенденція щодо динаміки товщених задньої стінки ЛШ у систолу. У 1-й групи зниження цього показника становила 5.7% (p<0.05), а в 2-й групі - 26.9% (p<0.05). Виявлено підвищення ФВ ЛШ у хворих на стабільну ІХС із супутньою АГ. При- ріст цього показника становив 3-4% серед усіх обстежених. Зафіксовано зниження sST2 в обох групах пацієнтів. Проте він був достовірним лише у пацієнтів 2-ї групи. Встановлено слабкий прямий кореляційний зв’язок між рівнем sST2 та ІМЛІШ.

Висновки. Встановлено доцільність викорис- тання sST2 як маркера ефективності лікування хворих після інфаркту міокарда із супутньою АГ на фоні лікування мельдонієм і фолієвою кислотою. Застосування цитопротекторів достовірно знижало концентрацію sST2, що робить доцільним їх використання у комплексному лікуванні хворих після перенесеного ІМ із супутньою АГ.

Ключові слова: стабільна ішемічна хвороба серця, артеріальна гіпертензія, sST2, мельдоній, фолієва кислота.