PERIÓDICO TCHÊ QUÍMICA
ARTIGO ORIGINAL

ANÁLISE PROSPECTIVA DE PARÂMETROS DE ESPECTRO LÍPIDO E MARCADORES INFLAMATÓRIOS VASCULARES COMO VARIANTE DE UMA ABORDAGEM PERSONALIZADA AO PROGNÓSTICO DE EVENTOS CORONÁRIOS INDESEJÁVEIS EM PACIENTES COM DOENÇA CARDÍACA CORONÁRIA APÓS ANGIOPLASTIA

PROSPECTIVE ANALYSIS OF LIPID SPECTRUM PARAMETERS AND VASCULAR INFLAMMATORY MARKERS AS A VARIANT OF A PERSONIFIED APPROACH TO PROGNOSIS OF UNDESIRABLE CORONARY EVENTS IN PATIENTS WITH CORONARY HEART DISEASE AFTER ANGIOPLASTY

ПРОСПЕКТИВНЫЙ АНАЛИЗ ПАРАМЕТРОВ ЛИПИДНОГО СПЕКТРА И МАРКЕРОВ СОСУДИСТОГО ВОСПАЛЕНИЯ КАК ВАРИАНТ ПЕРСОНИФИЦИРОВАННОГО ПОДХОДА К ПРОГНОЗУ НЕЖЕЛАТЕЛЬНЫХ КОРОНАРНЫХ СОБЫТИЙ У ПАЦИЕНТОВ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА ПОСЛЕ АНГИОПЛАСТИКИ

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RESUMO

A relevância do estudo se deve ao fato de que o papel ambíguo dos mediadores bioquímicos no desenvolvimento de complicações da angioplastia com colocação de stent e a falta de consenso quanto ao tempo dos parâmetros laboratoriais são determinados para esclarecer abordagens ao estudo de parâmetros bioquímicos que indicam a natureza do curso da doença arterial coronariana e o desenvolvimento de possíveis complicações indesejáveis após intervenção coronária percutânea. O objetivo deste artigo foi analisar os parâmetros do espectro lipídico e marcadores da resposta inflamatória vascular em pacientes com doença arterial coronariana em grupos com angina de peito estável e angina de peito instável após angioplastia com colocação de stent para monitorar a dinâmica de parâmetros bioquímicos e identificar preditores de vasos coronários indesejados. Pacientes com doença arterial coronariana com estenose arterial coronariana significativa (n=95) revelados após angiografia coronária no ponto de aumento máximo no nível de marcadores de reação inflamatória (três meses após angioplastia) foram divididos em 2 grupos – pacientes com angina de peito estável e persistente (n=77) até o final do estudo, e pacientes com um episódio pós-revascularização desenvolvido de angina instável (n=18) após angioplastia com colocação de stent. Foi estabelecido que pacientes com angina instável no estágio inicial apresentaram um risco significativamente maior de desenvolver instabilidade do fluxo sanguíneo coronariano no período pós-revascularização devido aos níveis inicialmente elevados de homocisteína e proteína C reativa altamente sensível. Os resultados obtidos são muito importantes para a implementação de um programa ideal para o monitoramento de pacientes com doença arterial coronariana, melhorando medidas para aumentar a adesão à terapia no estágio ambulatorial do tratamento.

Palavras-chave: *angina de peito, angioplastia, colocação de stent, espectro lipídico, marcadores de inflamação.*

ABSTRACT

The relevance of the study is due to the fact that the ambiguous role of biochemical mediators in the development of angioplasty complications with stenting and the lack of consensus on the timing of laboratory indicators determine to specify the approaches to the study of biochemical parameters that indicate the nature of the course of coronary heart disease (CHD) and the development of possible undesirable complications after

percutaneous coronary intervention. This article aims to analyze the parameters of lipid spectrum and markers of vascular inflammatory reaction in patients with CHD, in groups with stable angina and unstable angina episode after angioplasty with stenting, to trace the dynamics of biochemical parameters and to reveal the predictors of undesirable coronary events. Patients with CHD with significant coronary artery stenosis (CKS, n=95) revealed after coronary angiography (CAG) at the point of maximum increase in the markers of the inflammatory response (3 months after angioplasty) are divided into 2 groups – patients with stable angina pectoris (AP, n=77) until the end of the study and patients with a developed post-revascularization episode of unstable angina (UA, n=18) after angioplasty with stenting. It was established that patients with UA at the initial stage have a significantly higher risk of developing coronary blood flow instability in the post-revascularization period due to initially elevated levels of homocysteine and rf-CRP. The results obtained are very important for the implementation of an optimal program for monitoring patients with coronary artery disease, improving measures to increase adherence to therapy at the outpatient stage of treatment.

Keywords: *angina pectoris, angioplasty, stenting, lipid spectrum, markers of inflammation*.

АННОТАЦИЯ

Актуальность исследования обусловлена тем, что существует неоднозначное отношение к роли биохимических медиаторов в развитии осложнений после ангиопластики со стентированием и отсутствует консенсус по срокам проведения лабораторных исследований, которые отражают характер течения ИБС и временные точки для развития возможных нежелательных осложнений. Целью данной статьи является анализ параметров липидного спектра и маркеров сосудистой воспалительной реакции у пациентов с ИБС в группах со стабильной стенокардией и нестабильным приступом стенокардии после ангиопластики со стентированием, для отслеживания динамики биохимических показателей и выявления предикторов нежелательных коронарных сосудов. Пациенты с ишемической болезнью сердца (ИБС) с выявленным значимым коронарным стенозом артерий (ЗКС, n=95) после проведенной коронароангиографии (КАГ) в точке максимального повышения уровня маркеров воспалительной реакции (3 месяца после ангиопластики) разделены на 2 группы – пациенты с сохраняющейся стабильной стенокардией (СС, n=77) до конца исследования и пациенты с развившимся постреваскуляризационным эпизодом нестабильной стенокардии (НС, n=18) после ангиопластики со стентированием. Установлено, что пациенты с НС на исходном этапе имеют достоверно более высокий риск развития нестабильности коронарного кровотока в постреваскуляризационом периоде за счет исходно повышенных уровней гомоцистеина и вч-СРБ. Полученные результаты очень важны для осуществления оптимальной программы по наблюдению за пациентами с ИБС, улучшению мер по повышению приверженности к терапии на амбулаторном этапе лечения.

Keywords: *стенокардия, ангиопластика, стентирование, липидный спектр, маркеры воспаления.*

1. INTRODUCTION

Cardiovascular diseases (CVD) remain the main cause of disability and mortality in developed countries, of which more than half of cases are atherothrombotic diseases, in particular, coronary artery disease (CAD) (Karpov *et al.,* 2010). A characteristic feature of CAD are unpredictable acute coronary events (ACE), the main pathogenetic factor of which is a breach in the integrity of the unstable atherosclerotic plaque, causing the formation of a blood clot in the coronary artery lumen. Currently, there is an active search for biochemical markers that can predict the development of acute atherothrombotic events. These include serum lipid spectrum parameters and markers of systemic and local activity of vascular inflammation, the most studied of which are C-reactive protein (CRP), interleukins-6,8 (IL), matrex metalloproteinases (MMP-2 and 9), CD40 receptor–CD40 ligand signaling system and others (Zykov *et al.,* 2011; Gusev *et al.,* 2012; Afanasieva *et al.,* 2016; Ezhov *et al.,* 2017; Mironova and Mironov, 2018).

Coronary stenting is one of the most common methods for treating patients with various forms of CAD, characterized by an effective restoration of coronary circulation and stabilization of a patient's condition. The prognosis in patients after percutaneous coronary intervention (PCI) depends on many factors (Schiele *et al.,* 2018; Solow *et al.,* 2018; Tanaskovic *et al.,* 2018). Clinical prognostic parameters, such as gender, age and presence of diabetes mellitus (DM) were studied as predictors of poor prognosis (Golukhova and Kuznetsova, 2016; Golukhova *et al.,* 2016; Tomilova *et al.,* 2017; Muhsin and Ibrahim, 2018; Sergienko and Ansheles, 2018). However, while

the clinical and angiographic parameters of coronary complications of angioplasty are well known, changes in laboratory data that contribute to their development are presented insufficiently. According to published data, CRP, levels of plasminogen activator inhibitor-1, von Willebrant factor activity, erythrocyte sedimentation rate, levels of eosinophils and myeloperoxidase are predictors of poor prognosis after PCI with stenting and implantation of drug-eluting stents, but the results are often inconsistent (Ndrepepa *et al.,* 2014; Getz and Reardon, 2014; Bibek *et al.,* 2015; Moon *et al.,* 2016; Petelina *et al.,* 2017; Mukherjee *et al.*, 2018). An ambiguous role of biochemical mediators in the development of complications after angioplasty with stenting and a lack of consensus regarding timing of determination require specification of their importance for the course of post-revascularization CAD and the development of possible coronary adverse events (Velibey *et al.,* 2016; Parsa *et al.,* 2018; Czubaszewski *et al.,* 2018; Fracassi *et al.,* 2018; Kosaki *et al.,* 2018; Manati *et al.,* 2018; Sihag *et al.,* 2018; Trasca *et al.,* 2018; Le Gall *et al.,* 2018).

Patients with CAD and significant coronary stenosis of the arteries (SCS, n = 95) (SCS, n=95) after coronary angiography, at the point of maximum increase in the level of markers of the inflammatory reaction (3 months after angioplasty) are divided into 2 groups – patients with persistent stable angina pectoris (SA, n=77) until the end of the study and patients with post-revascularization episodes of unstable angina (UA, n=18).

Changes in biochemical parameters showed a prolonged nature of the vascular inflammatory response with a tendency to decrease in the parameters after 6 months in the SA group and after 12 months of follow-up in the group with post-revascularization UA episodes. In the group of patients with SCS, an increase in low density lipoproteins by 1 mmol/L increased the probability of post-revascularization unstable angina 7.387 times. It was found that patients with UA at baseline had a significantly higher risk of coronary circulation instability in post-revascularization period due to initially elevated levels of homocysteine and hsCRP.

The initial increase in the levels of atherogenic lipid fractions and systemic prolonged nature of the vascular inflammatory reaction after angioplasty with stenting are prognostic factors for the development of coronary adverse events (Tenekecioglu *et al.,* 2016; Sirtori *et al.,* 2017).

This article aims to analyze the parameters of lipid spectrum and markers of vascular inflammatory reaction in patients with CHD, in groups with stable angina and unstable angina episode after angioplasty with stenting, to trace the dynamics of biochemical parameters and to reveal the predictors of undesirable coronary events.

2. MATERIALS AND METHODS

The study was conducted at the emergency cardiology department of the Tyumen Cardiology Research Center and Tomsk National Research Medical Center of the Russian Academy of Sciences. The study involved 143 patients with coronary artery disease. The distribution of the patients was based on the following parameter - severity of coronary stenosis defined as ≥75% narrowing of the artery lumen diameter. After selective CAG, the groups of patients with significant coronary stenosis, SCS (n = 95), initially stable angina (SA, n = 53) and unstable angina (UA, n = 42) were identified.

The study parameters were evaluated at baseline, when the patient was admitted to the hospital, before CAG and 3, 6 and 12 months after angioplasty with drug-eluting stent implantation during standard therapy (ACE inhibitors, β-adrenergic blockers, disaggregants – clopidogrel and/or acetylsalicylic acid, statins). The mean follow-up was 12±1.4 months.

The study protocol is approved by the Institutional Ethics Committee. Before inclusion in the study, each study participant gave a written informed consent to the use of study results for scientific purposes.

The diagnosis of CAD, criteria for stable and unstable angina pectoris, dyslipidemia, severity of hypertension, CHF and obesity were verified according to the modern national and international clinical guidelines for diagnosis and treatment developed by the expert committee of the Russian Society of Cardiology, World Health Organization, American Heart Association and European Society of Cardiology, respectively.

Venous blood was collected in disposable tubes of the Vacuette system (Japan) on an empty stomach and the blood was centrifuged for 15 minutes at 2500 rpm in a Sigma centrifuge (Germany). Patients' blood serum was aliquoted for further freezing (at -70 °C).

The parameters of lipid metabolism were studied using the Cobas Integra 400 plus biochemical automatic analyser (Switzerland).

Total cholesterol (TC), triglycerides (TG), HDL and LDL were determined using a direct enzymatic colorimetric method; concentrations of apolipoproteins A-I (Apo A-I), apolipoproteins B (Apo-B) and lipoproteins a (Lp (a)) were determined using immunoturbidimetry using analytical kits and control materials by Roche Diagnostics Gmb (Germany).

The following biochemical markers of inflammation were determined: highly sensitive C-reactive protein (hsCRP, reference values 0-3.0 mg/L) – using an immunoturbidimetric method with the C-reactive protein hs analytical kit (BioSystem, Spain) on a Clima MC-15 open type analyser (Spain); interleukin-1β (IL-1β, reference values 0-5.0 pg/mL), interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor-α (TNF-α, reference values 0-8.11 pg/mL) – "sandwich" and homocysteine (HYC, reference values 5.0–15.0 μmol/L) – by competitive methods (solid-phase chemiluminescent enzyme immunoassay) on the IMMULITE 1000 analyser (Siemens Diagnostics, USA); soluble CD40 – ligand (sCD40 L) by the method of "sandwich immunoassay" using the Human sCD40L Elisa kits on the Bender MedSystems analyser, Austria; CD40 receptor and matrix metalloproteinase-9 (MMP-9, reference values 20.3-77.2 ng/mL) – Bender MedSystems and eBioscience company, Austria; tissue inhibitor of metalloproteinase-1 (TIMP-1, reference values 92-116 ng/mL)) – Human TIMP-1 Elisa K.t Invitrogen, USA on the Personal Lab analyser, Italy.

Parameters of endothelial functional activity in blood serum: levels of nitrites (reference value 3.77±0.87 nmol/L) were determined on the Humalyzer 2000 Human biochemical analyser (Germany, 1995) and endothelin-1-21 (reference values 0.2-0.7 fmol/L) – on the Dynatech enzyme immunoassay analyser (Germany, 1989).

A comprehensive assessment of the vasculature condition was carried out using a high-tech method – selective CAG using the Diagnost ARC A, Poly diagnost C, Integris Allura (Phillips, Holland) angiographic units according to the standard Judkins method of femoral access. Percutaneous coronary intervention was performed using transluminal balloon coronary angioplasty (TBCA) with stenting.

Statistical methods. Statistical data processing was performed using the Statistica application software package (SPSS Inc, version 11.5). To assess the normality of distribution, the Kolmogorov – Smirnov criterion was used. The Student's t-test was used to detect differences between the groups in quantitative variables of normal distribution; the non-parametric Mann-Whitney test was used to compare qualitative and quantitative values that were not normal. The groups were compared using the Wilcoxon test for paired measurements. Data is presented as mean values with standard deviations (M±SD). Significance of differences was detected at $p<0.05$. The relationship between signs was evaluated using the Pearson and Spearman rank correlation coefficients for quantitative and qualitative values, respectively. To identify predictors among the total number of parameters studied, the binary logistic regression was used.

3. RESULTS AND DISCUSSION:

According to the previously obtained results of a prospective observation in general groups of patients who underwent angioplasty with stenting, the signs of correction of initially elevated levels of atherogenic lipid fractions, parameters of vascular inflammatory response and endothelial dysfunction were observed within 12 months. A significant decrease in atherogenic fractions of TC, LDL, HDL and TG was observed after 6 months with baseline SA and after 12 months with baseline UA. A prolonged response of systemic highly sensitive C-reactive protein (hs-CRP) and local inflammatory reactions (TNF-α, homocysteine, IL-1β, MMP-9) were observed with a maximum after 3 months and a decrease with a tendency to target levels after 6 months in SA and after 12 months in UA after angioplasty with stenting.

Parallel unidirectional growth of the parameters of vascular inflammatory response at "3 months" point after angioplasty, together with persisting hypercholesterolemia, identifies patients with SCS, regardless of the clinical manifestation of CAD, as patients at very high risk of early restenosis and the process of prolonged indolent inflammatory reaction up to the end point of follow-up does not exclude late atherothrombotic complications.

Over the last years, as the frequency of percutaneous coronary interventions with stenting has increased, more and more attention has been focused on solving problems associated with atherothrombosis and restenosis inside stents, which are detected in approximately 10–40% and 0.87–2.2% of cases during the first year after stent placement, respectively (Cassese *et al.,* 2014; Chen *et al.,* 2014; Darvishpour *et al.,* 2016; Palur Ramakrishnan *et al.,* 2017; Persic *et*

al., 2018).

As a starting point for the development of restenosis, a combined involvement is considered – mechanical damage to the intima and media of the arteries with aggravated local inflammatory reaction, as well as hypersensitivity to stent materials, involving eosinophilic granulocytes in the reaction process (Gabbasov *et al.,* 2010; DeSart *et al.,* 2016; Lee *et al.,* 2016).

Taking into account the peak of inflammatory response activation after 3 months of follow-up, we analysed changes in the markers of the lipid profile and vascular inflammatory response in patients with persistent SA and patients with episodes of UA in post-revascularization period. It was established that in the patients with SCS after angioplasty with stenting (n=95), stable condition in the patients from the initial groups was maintained over the period of further analysed follow-up in 81.1% of cases (n=77); development of post-revascularization UA episodes was observed in 18.9% of cases (n=18). It was found that post-revascularization episodes of UA in 72.2% of cases (n=13) were significantly (p=0.02) more often in the patients with initial instability of the coronary circulation at the initial stage of the study, and only in 27.8% of cases (n=5) – in patients with SA at baseline. In the patients with post-revascularization episodes of UA after diagnostic CAG, restenosis of the operated coronary vessel was detected in 4 cases (1.3%).

Comparative characteristics of clinical and historical parameters in patients after angioplasty with stenting according to the clinical course of CAD, reported during the observation, are presented in Tables 1-2.

According to Table 1, patients with SA and post-revascularization episodes of UA were comparable for incidence and history of tobacco smoking, family history of CAD, history of MI, and presence and history of CAD, type 2 diabetes.

In accordance with the data presented in Table 2, patients in both groups did not significantly differ in a number of parameters considered as possible risk factors for adverse coronary events. The majority of patients were men with single vessel SCS, CAD mainly associated with exertional angina (EA) II FC in combination with grade 3 hypertension, CHF II FC (NYHA) and grade I obesity.

Comparative characteristics of lipid spectrum parameters in patients with SA and with post-revascularization episode of UA are presented in Table 3. The point of maximum increase of the studied parameters and the end point of the study are presented.

As can be seen from Table 3, no significant differences were revealed in the comparative description of the level of atherogenic fractions between groups of patients with SA and post-vascularization episode of UA at the point of 3 and 12 months of angioplasty with stenting.

A significant decrease in TC and LDL ($p<0.05$) was found while the level of parameters above the reference values was maintained during a prospective analysis of the lipid spectrum parameters in patients with SA. The constancy of high values of TG and LP (a) levels was revealed. A significant decrease in VLDL and Apo B/Apo A-I parameters was registered, their target level after 12 months was observed. The statistically significant increase in Apo A-I can be traced in the reference values. A prospective analysis of lipid spectrum parameters in patients with a post-revascularization UA episode did not reveal a significant decrease in elevated levels of total cholesterol, LDL, TG and LP (a). A significant decrease in the level of VLDL reaches the limits of the reference interval after 12 months. No significant change in the content of the antiatherogenic fraction represented by HDL and Apo A-I was detected in the initial and prospective stages.

According to the data presented in Table 4, patients with SA and post-revascularization UA episode did not significantly differ in the degree of activation of systemic and local inflammatory responses represented by hyperproduction of hsCRP and TNF-α, MMP-9, homocysteine, respectively, and endothelial dysfunction in the form of elevated plasma endothelin-1 concentrations and reduced nitrite levels.

A prospective analysis of inflammatory markers in patients with SA revealed a significant decrease in elevated levels of hsCRP, TNF-α, and homocysteine with the achievement of a standard interval of values 12 months after angioplasty with stenting. Despite a significant decrease in the concentration of MMP-9 following 12 months after angioplasty, the target marker level was not observed. A statistically significant decrease in the values of the cytokine cascade (IL-1β, IL-6, IL-8), CD 40, sCD 40L and an increase in TIMP-1 were detected within the reference range. Endothelial dysfunction showed hyperproduction of plasma endothelin-1 and a significant increase in the level of nitrites 12 months after angioplasty. A prospective analysis

of inflammatory markers in the group of patients with a post-vascularization UA episode revealed an increased content of hsCRP, TNF-α and homocysteine after 3 months and a significant decrease in the above values up to the reference range following 12 months after angioplasty with stenting. Despite a significant decrease in the level of MMP-9, an increased concentration of the marker was observed after 12 months. Constant endothelin-1 hyperproduction and a tendency to increased nitrite following 12 months after angioplasty with stenting are observed.

Direct correlations of prolonged activation of vascular inflammatory response and endothelial dysfunction markers with clinical and historical parameters were characteristic during the analysed observation period. Thus, in the group of SA patients, VLDL and LP (a) were positively correlated with homocysteine (p=0.02, r=0.3; p=0.01, r=0.4, respectively), homocysteine with the fact of smoking and HF functional class (p=0.01, r=0.4; p=0.01, r=0.4, respectively), hsCRP with HF functional class and compliance with therapy (p=0.02, r=0.4; p=0.001, r=0.8, respectively), TNF-α with HF functional class (p=0.03, r=0.4), and endothelin-1 with hypertension grade (p=0.02, r=0.4).

In the group of patients with a post-revascularization UA episode, TNF-α is positively correlated with body mass index, CHF FC (NYHA), family history of CAD (p=0.02, r=0.4; p=0.02, r=0.4; p=0.01, r=0.8; respectively), hsCRP with CHF FC (NYHA), the multi-vascular nature of the significant damage in the coronary bed, the number of angina episodes (p=0.01, r=0.3, p=0.03, r=0.4; p=0.03, r=0.4, respectively), homocysteine level with the presence of type 2 diabetes (p=0.03, r=0.4), endothelin-1 level with a history of myocardial infarction (MI) (p=0.01, r=0.6).

The identified correlation coincides with studies that indicate a close relationship between clinical and laboratory parameters (Moon *et al.,* 2016; Getz and Reardon, 2014; Cassese *et al.,* 2014; Chen *et al.,* 2014). According to the goal of our work, a multivariate analysis (binary logistic regression) was used to identify the main predictors that determine the maximum development of UA in the post-revascularization period in patients with SCS after stenting. The initial set of variables included: lipid profile parameters and markers of vascular inflammation. The final model included: low density lipoproteins, triglycerides, total cholesterol and endothelin-1. As a result of the analysis of variables, the most essential parameters were selected and a model with three variables was created. The encoding of the values of essential parameters is presented in Table 5. The technical result was expressed using the formula of the obtained linear function (Equation 1).

In order to classify the entire set into subgroups using the obtained linear function, a logit-transformation with the calculation of the separation point is applied (Equation 2). Where P is the probability that an event of interest will occur – unstable angina: e is a mathematical constant equal to 2.718; F is the value of the regression equation.

Exp (B) for logistic regression coefficients specifies the degree of change in the relative risk of an event of interest for a particular variable B. For example, increase in low-density lipoproteins increases the probability of an event of interest 7.387 times compared to the baseline risk (relative risk of outcome).

The specificity of this model was 70.1%; sensitivity was 75.0%; on average, 71.1% of the initial grouped observations are correctly classified. An indicator of the prediction accuracy for an episode of post-revascularization unstable angina is the area under the ROC curve – for our model it was 0.715 (P<0.001), which corresponds to the good quality of the model, Figure 1.

Therefore, in the general group of patients with SCS, an increase in low-density lipoproteins by 1 mmol/L increased the risk of post-revascularization unstable angina 7.387 times compared to baseline risk (OR=1.76; 95% CI 1.95 – 27.8353; p=0.027). Our data is indirectly consistent with the data of Mihaylova B. et al., who showed that the reduction of LDL cholesterol by 1 mmol/L reduced the risk of cardiovascular complications by 20% (Mihaylova *et al.,* 2012).

It should be mentioned that, based on clinical and historical data, the binary logistic regression method showed that the risk of SCS increased 2.8 times in men (OR=2.761; 95% CI: 1.41 – 5.39; p=0.003); when LDL levels in men increased by 1 mmol/L, the risk of SCS further increased 1.8 times (OR=1.76; 95% CI 1.23 – 2.53; p=0.002).

In addition, the same method showed that in the patients with UA episodes at the initial stage of the study, the risk of unstable coronary circulation in post-vascularization period increased 4.1 times (OR=4.07; 95% CI 1.32-12.59; p=0.02).

All cases of recurrent UA episodes (n = 13) in the group with baseline UA were recorded with

hyperhomocysteinemia (>15 μmol/L) detected at the initial stage of the study with mean homocysteine level of 16.52 μmol/L, or 10.1% higher than the upper limit of normal.

Hyperhomocysteinemia correlated both with a repeated episode of UA (p=0.04 and r=0.4) and hyperproduction of hs-CRP (p=0.02 and r=0.5), indicating a vicious circle of interaction between local inflammation in atherosclerotic plaque, repeated coronary adverse event and activation of systemic inflammatory response, which is consistent with literature data (Bibek *et al.,* 2015; Ndrepepa *et al.,* 2014; Moon *et al.,* 2016).

Therefore, a summary of available data of laboratory blood tests allows determination of biochemical markers that can reliably predict significant coronary stenosis and adverse events in post-revascularization period for different clinical variants of the course of CAD at the initial stage of examination, when patients are admitted to the hospital, prior to angioplasty with stenting – these are male gender, elevated levels of LDL, and hyperhomocysteinemia. The established set of parameters can be considered as a variant of a personified approach to prognosis of coronary adverse events in patients with CAD after angioplasty with stenting and can determine the choice of rational tactics of drug therapy.

4. CONCLUSIONS:

From a practical point of view, it is important for a physician who works with patients to know what time points after a transcutaneous intervention are most dangerous for the development of coronary complications. Our data suggests that almost the entire postoperative year can be dangerous in terms of the development of complications. Elevated levels of atherogenic lipid parameters and markers of vascular inflammation, i.e. hs-CRP, TNF-α, homocysteine, endothelin-1 and MMP-9, from the beginning of follow-up to the maximum rise at the point of "3 months" after angioplasty, may indicate a risk of the development of early coronary complications, such as early restenosis and atherothrombosis, and the failure to achieve the target levels of the studied parameters at the final stage of follow-up (endothelin-1, nitrite, MMP-9) may indicate of a systemic slow vascular inflammatory response in patients with CAD with a probability of late atherothrombotic complications.

The implementation of an optimal program to increase patients' adherence to therapy, in particular, with statins and antiplatelet agents, which maintain the target levels of LDL cholesterol and reduce the risk of thrombosis, together with dynamic monitoring of laboratory markers, are two main directions that can protect a patient from coronary events in postoperative period.

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$$F = 0.927 + 2.000 \times LDL + 1.355 \times TG - 2.288 \times TC \quad \text{(Eq. 1)}$$

$$P = 1/(1+e^{(-F)}) \quad \text{(Eq. 2)}$$

Table 1. *Characterization of risk factors in patients with stable angina and with a post-vascularization episode of unstable angina (M±SD)*

Parameter	Patients with SA (n=77)	Patients with UA episode (n=18)
Fact of smoking	29.9% (n=23)	22.2% (n=4)
Family history of CAD	24.4% (n=19)	11.1% (n=2)
CAD without hypertension	10.4% (n=8)	27.8% (n=5)
History of MI	44.2% (n=34)	44.4% (n=8)
Dyslipidemia	94.8% (n=73)	94.4% (n=17)
Type 2 diabetes	33.8% (n=26)	27.8% (n=5)
CAD duration, years	6.95±5.87	9.26±7.43
Smoking history, years	10.43±1.19	9.75±2.3
DM 2 type duration, years	4.67±2.46	5.44±2.61

Note: n – number of patients, % – percentage of the total subjects in the group

Table 2. *Characteristics of clinical and historical parameters of patients with stable angina and with a post-revascularization episode of unstable angina (M±SD)*

Parameter	Patients with SA (n=77)	Patients with UA episode (n=18)
Men	68.8% (n=53)	83.3% (n=15)
Single vessel SCS	57.1% (n=44)	61.1% (n=11)
Multi-vessel SCS (≥2 CA)	42.9% (n=33)	38.9% (n=7)
Exertional angina, FC		
I	6.5% (n=5)	5.6% (n=1)
II	62.3% (n=48)	72.2% (n=13)
III	31.2% (n=24)	22.2% (n=4)
Hypertension, grade		
1	6.5% (n=5)	11.1% (n=2)
2	14.3% (n=11)	16.7% (n=3)
3	68.8% (n=53)	44.4% (n=8)
CHF (NYHA) FC		
I	5.2% (n=4)	5.6% (n=1)
II	79.2% (n=61)	66.7% (n=12)
III	15.6% (n=12)	27.8% (n=5)
Dyslipidaemia	94.8% (n=73)	94.4% (n=17)
Obesity		
0	32.5% (n=25)	16.7% (n=3)
I	46.8% (n=36)	50.0% (n=9)
II	15.6% (n=12)	22.2% (n=4)
III	5.2% (n=4)	11.1% (n=2)
Age, years	60.47±9.54	57.17±10.11

Note: n – number of patients, % – percentage of the total subjects in the group

Table 3. *Comparative characteristics of lipid spectrum parameters in patients with stable angina and with post-vascularization episode of unstable angina (M±SD)*

Parameter	Patients with SA (n=77)		Patients with UA episode (n=18)	
	after 3 months	after 12 months	after 3 months	after 12 months
TC (mmol/L)	4.9±0.88	4.64±0.85*	4.71±1.22	4.7±1.15
HDL (mmol/L)	1.13±0.26	1.18±0.28	1.03±0.2	1.08±0.21
LDL (mmol/L)	2.82±0.78	2.46±0.81*	2.77±1.02	2.6±0.96
VLDL (mmol/L)	0.69±0.23	0.63±0.25*	0.77±0.19	0.55±0.23*
TG (mmol/L)	1.87±0.65	1.74±0.45	1.95±0.54	1.76±0.5
Apo B (mg/dl)	102.94±27.72	94.23±24.6*	95.52±18.8	97.73±22.9
Apo A-I (mg/dl)	142.15±30.32	151.47±26.5*	135.67±31.92	147.08±16.9
Apo B/Apo A-I	0.74±0.3	0.66±0.32*	0.7±0.2	0.65±0.19
LP (a) (mg/dl)	35.33±22.01	27.01±10.61	25.58±20.6	24.46±17.55

Note: n – number of patients; significance of differences in groups of patients with SA and with an UA episode 3 and 12 months after angioplasty with stenting: * $p<0.05$

Table 4. *Comparative characteristics of inflammatory markers and endothelial dysfunction parameters in patients with stable angina and with a post-revascularization episode of unstable angina (M±SD)*

Parameter	Patients with SA (n=77)		Patients with UA episode (n=18)	
	after 3 months	after 12 months	after 3 months	after 12 months
CD 40 (ng/mL)	104.42±38.2	90.81±28.42*	86.53±21.9	77.98±21.65
sCD40L (ng/mL)	3.64±0.83	3.24±0.72	3.35±0.72	2.99±0.91
CD 40/sCD 40L	29.25±8.76	29.15±8.73	24.85±7.06	26.53±9.11
TIMP-1(ng/mL)	96.59±19.98	106.44±28.0*	97.88±23.3	105.48±23.5
MMP-9 (ng/mL)	115.68±29.0	88.19±31.12*	129.8±16.6	85.72±28*
IL-1β (pg/mL)	5.07±1.77	4.47±1.85*	4.43±1.74	4.1±1.2
IL-6 (pg/mL)	3.89±2.32	3.18±1.5*	4.27±2.95	3.4±1.89
IL-8 (pg/mL)	23.52±20.48	17.92±14.64*	19.65±13.0	15.32±9.45
TNF-α (pg/mL)	11.26±4.81	6.99±3.19*	11.41±4.69	7.02±2.67*
hsCRP (mg/L)	3.47±0.81	2.78±0.94*	3.4±0.94	2.52±0.93*
homocysteine (μmol/L)	17.94±5.99	10.77±5.44*	16.72±4.95	10.42±3.6*
nitrites (nmol/ml)	2.59±1.06	3.29±0.98*	2.67±1.12	3.07±0.91
endothelin-1 (fmol/l)	1.07±0.5	1.05±0.55	0.95±0.51	1.05±0.41

Note: n – number of patients; significance of differences in the groups of patients with SA and UA episode 3 and 12 months after pangioplasty with stenting: * $p<0.05$

Table 5. *Encoding values of essential features*

Parameter	Variable	Type	Unit of measurement
Low density lipoprotein	LDL	Quantitative	mmol/L
Triglycerides	TG	Quantitative	mmol/L
Total cholesterol	TC	Quantitative	mmol/L

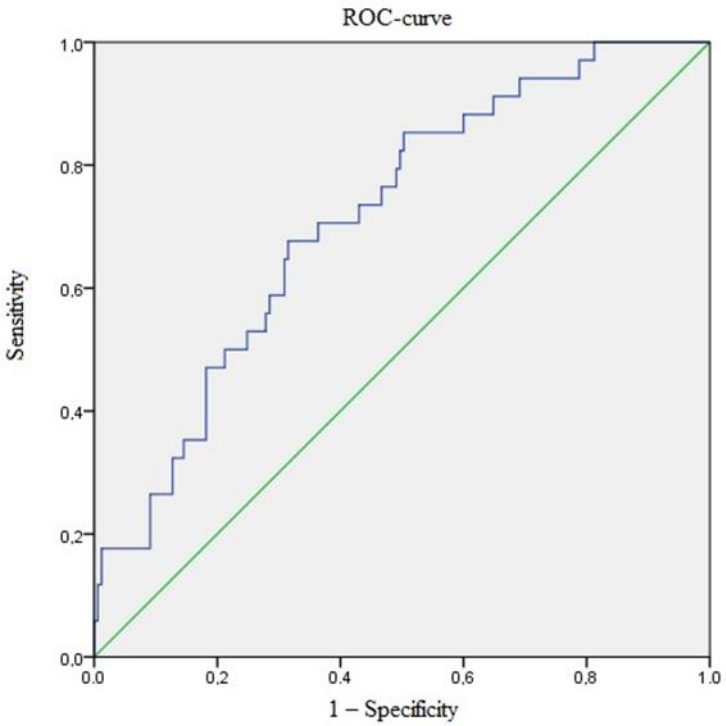

Figure 1. *ROC-curve: area under the ROC-curve is 0.715 (P<0.001)*