UDC 616.127–005.8–053.7–059: [616.12–02: 616.151.5] –07: 616.12–018.74
DOI: 10.21668/health.risk/2020.2.13.eng

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ASSESSING ENDOTHELIUM RESISTANCE TO THROMBUS FORMATION AS A POTENTIAL RISK FACTOR CAUSING RECURRENT CARDIOVASCULAR EVENTS IN YOUNG PATIENTS AFTER CARDIAC INFARCTION

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Cardiac infarction is considered a disease more common for elderly people; despite that, up to 10 % of all cardiac infarctions occur at a young age. Cardiac infarction has grave consequences both for mental health and future working capability of patients who had it. Approximately 15 % patients who have had cardiac infarction have to face a recurrent cardiovascular event based on thrombus formation in spite of therapy. Our research goal was to assess endothelium homeostasis in patients after cardiac infarction being treated with double anti-thrombocyte therapy during out-patient rehabilitation and to reveal potential risks that could cause recurrent cardiovascular diseases. Overall, we examined 25 people aged from 18 to 45 who had cardiac infarction and were treated with invasive therapy aimed at eliminating ischemic heart disease. The therapy was emergency percutaneous coronary intervention and coronary artery stenting performed at Perm Clinical Cardiologic Clinic during a period from September 2018 to March 2019. Endothelial homeostasis was examined in 12 months after cardiac infarction.

We detected that, together with conventional risk factors, young patients after cardiac infarction had apparent changes in coagulation homeostasis (shorter activated partial thromboplastin time, shorter prothrombin time, an increase in fibrinogen concentration; greater aggregative activity of thrombocytes with adenosine-diphosphate; depressed Hageman-factor-dependent fibrinolysis. Nevertheless, there was no significant difference in aggregative activity of thrombosytes with ristocetin between the test and control groups. Therefore, in 12 months after cardiac infarction, young patients still ran high risks of recurrent cardiovascular events; those risks were caused both by significant prevalence of conventional risk factors and by high thrombogenic risk that persisted in spite of relevant anti-thrombus therapy.

Key words: *cardiac infarction, young patients, recurrent cardiovascular events, risk factors, endothelial homeostasis, hyper-coagulation, thrombosis.*

Cardiovascular diseases remain the leading cause of death all over the world. The forecasts state that by 2030 ischemic heart disease (IHD) will still hold the first place among 15 main reasons for population mortality [1]. Cardiac infarction (CI) is one of the gravest IHD outcomes; it can result in sudden cardiac death.

Up to 10 % of all the infarctions occur at young age even though CI is considered to be more typical for elderly people [2, 3]. When a young patient has CI, it usually leads to grave outcomes both for his or her mental health and for working ability in the future. Mortality risk grows by 74 times in comparison with healthy young people [4].

Over the last years serious progress has been made in treating patients with CI. A considerable decrease in mortality caused by this

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pathology has been achieved due to widely implemented percutaneous coronary interventions (PCI) and secondary prevention activities that include double anti-thrombocyte therapy. Nevertheless, patients with CI in their case history run 6 times higher risks of recurrent cardiovascular events than patients without it [5]. Approximately 15 % of patients with CI in their case history suffer a recurrent cardiovascular disease that happens due to thrombus formation in spite of anti-thrombocyte treatment [6].

Probability of an acute thrombotic event depends on a balance between susceptibility to thrombus formation and efficiency of endogenous thrombolytic processes. Thus, any disorder in fibrinolysis leads to elevated thrombosis risks [7]. And vice versa, if the fibrinolytic system counterbalances impacts exerted by thrombogenic factors, then a thrombus may not occur at all or, at least, may not result in long-term vessel occlusion [8].

Large vessels endothelium when being in its normal state inhibits adhesion and thrombocytes activation due to various mechanisms, either directly or indirectly via degradation of thrombocytes receptors antagonists. Endotheliocytes produce substances with anti-thrombotic potential such as nitrogen oxide (NO), thrombomodulin, prostanoids, and adenosine. When endothelium doesn't function properly, namely loses its anti-aggregation potential, it makes for atherosclerotic process development [9–12].

Nowadays, a lot of attention is being paid to how thrombocytes interact with intact endothelial surfaces and participate in atherosclerosis development. Thrombocytes may become involved into atherogenesis due to hydrodynamic stress exerting its influence on endothelium cells [13]. A classical way of thrombocytes involvement into blood stasis is interaction between GPIb/IX/V thrombocyte receptor complex components and active A1-domain of von Willebrand factor [14]. Von Willebrand factor is a large multi-dimensional glycoprotein that is synthesized by endothelium cells, sub-endothelial connective tissues, and by thrombocytes themselves though in smaller quantities [15, 16]. After being synthesized large quantities of von Willebrand factor are stored in Weibel-Palade bodies and are released from them after an endothelial cell is stimulated, in particular, as a response to damage, and it can be a sign that endothelial dysfunction has already occurred [17]. Von Willebrand factor production increases under hypoxia and impacts exerted on endothelium by anti-inflammation cytokines [18, 19]. Having bound themselves to von Willebrand factor, thrombocytes activate and a cascade of reaction occurs in them; this cascade ultimately results in thromboxane A2 synthesis and adenosine diphosphate (ADP) release. Thromboxane A2 and ADP initiate talin and αIIbβ3 polymerization thus causing thrombocytes aggregation [20, 21]. Therefore, von Willebrand factor is a key component in blood stasis. Thrombocytes aggregation with ristocetin, a co-factor of von Willebrand factor, indirectly reflects von Willebrand factor quantity in blood plasma.

Endogenous fibrinolysis activation is a function performed by an endothelium cell that prevents local thrombus formation. Fibrinolytic activity violation leads to greater risks of thrombosis in patients suffering from cardiovascular diseases [22]. Research data indicate that patients with early cardiovascular events in their family case histories have denser fibrin clots that are more resistant to lysis [23].

Hageman factor (factor XII) is a glycoprotein that circulates in blood plasma as zymogen; it is activated due to a contact with a negatively charged surface. Hageman factor is structurally similar to other proteins with fibrinolytic activity such as plasminogen, tissue (t-PA) and urokinase (u-PA) plasminogen activator [24]. XII factor activates prekallikrein and thus induces fibrinolysis; prekallikrein in its turn decomposes single-stranded u-PA into active double-stranded u-PA. Kallikrein that occurs in the process releases bradykinin out of high-molecular kininogen. Kallikrein and bradykinin promote t-PA re-

lease [25]. XII factor also can directly activate plasminogen [7]. Disorders in Hageman-dependent fibrinolysis make for thrombotic events development.

Therefore, thrombus formation assessment requires determining thrombocytes reactivity, endothelial function, and activity of endogenous thrombolytic processes.

Endothelium resistance to thrombus in long-term period in young patients with CI in their case history has not been given as much attention in the literature as traditional risk factors. Most research works concentrate on assessing blood stasis parameters only in an acute CI phase. Nevertheless, an attempt to determine individual risks of thrombotic events seems quite promising for treating such patients as it will allow optimizing therapy via targeted selection of medications and treatment duration.

Our research goal was to assess endothelial blood stasis parameters in patients who had CI and were treated with double anti-thrombocyte therapy at an out-patient department; another goal was to reveal potential risks of recurrent cardiovascular events.

Data and methods. We included 25 people aged from 18 to 45 into our research; they all had suffered CI and had been treated against IHD with emergency percutaneous coronary intervention and coronary arteries stenting at Perm Clinical Cardiologic Clinic over a period from September 2018 to March 2019. All the patients were prescribed relevant anti-thrombocyte therapy. Criteria for a patient being excluded from our research were as follows: systemic diseases, grave functional disorders in the liver and kidneys, acute conditions of any concomitant disease, heart rhythm disorders, pancreatic diabetes, thrombocytes concentration being lower than $100 \cdot 10^9$/l, and diagnosed disorders in thrombocytes functioning. Our reference group was made up of 15 practically healthy volunteers aged from 18 to 45.

Initial profiles of research participants are given in Table 1.

The reference group was comparable with the test group as per age and sex. Men prevailed among young patients who had suffered CI. 40 % patients in the test group had overweight and 8 % suffered from obesity; only 26.7 % had overweight in the reference group. It should be noted that smokers accounted for a rather big share among patients with CI, higher than 75 % (whereas it was only 25 % in the reference group); arterial hypertension and burden heredity as per early cardiovascular diseases were also more widely spread among patients with CI.

Table 1

Clinical and demographic profiles of participants in the research

Parameter	Young patients with CI (n = 25)	Reference group (n = 15)
Average age	37.5±7.1	36.3±7.1
Sex	men 84.0 % women 16.0 %	men 80.0 % women 20.0 %
Height, m	1.73±0.08	1.75±0.1
Weight, kg	76.6±14.3	72.4±10.0
Body mass index, kg/m²	25.5±3.3	23.6±1.8
Smoking status	76.0 %	26.7 %
Arterial hypertension	60.0 %	20.0 %
Burdened heredity	72.0 %	33.3 %
Total cholesterol, mmol/l	3.6±0.8	4.5±0.6
LDLP, mmol/l	2.0±0.6	2.4±0.7

16 % out of all the patients had already had CI, and 8 % among them had had even two CIs. Antero-lateral and posterior CIs were the most prevailing in terms of CI localization (Figure 1). CI with ST elevation accounted for 70 % of all cases; CI without ST elevation, 30 %.

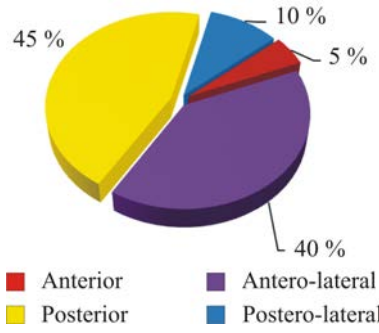

Figure 1. Cardiac infarction localizations

All the patients underwent primary percutaneous coronary intervention; the procedure allowed revealing that 69 % patients had two or more coronary arteries with stenosis exceeding 50 % (Figure 2). Either the anterior inter-ventricular artery or the right coronary artery was symptom-dependent in most patients; those arteries are the largest among all coronary ones.

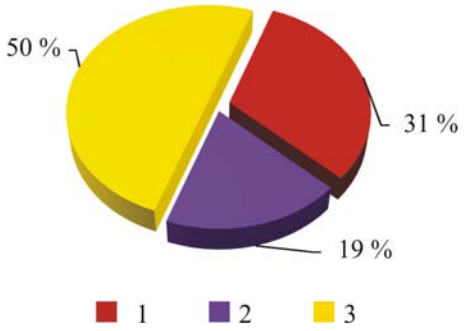

Figure 2. Number of damaged coronary arteries

71.4 % patients also had stenting procedure; in 40 % cases stents covered with a medication were applied. According to some research works, peculiarities of stenting, in particular such parameters as stent diameter and overall length, exert their influence on risks of thrombosis in future [26]. In our research each third patient had a stent with its diameter being less than 3 mm and overall length of applied stents was more than 18 mm practically in all cases.

After being released from hospital, patients were recommended to take medications according to the latest clinical recommendations on treating patients with CI. Thus, angiotensin-converting enzyme (ACE) inhibitors / sartan drugs were prescribed to 80 % patients; beta-blockers, to 88 %; statins in maximum doses and double anti-thrombocyte therapy including acetylsalicylic acid and P2Y12-thrombocyte receptors blocker, to all patients (Table 2).

Perindopril was the most frequently prescribed among all ACE inhibitors / sartans due to its great affinity with tissue ACE and it predetermined additional organ-protective properties of the drug [27]. The greatest share among prescribed beta-blockers belonged to cardioselective Bisoprosol; among P2Y12-thrombocyte receptors blockers, to Clopidogrel; among statins, to Atorvastatin. Commitment to therapy was close to 100 % in our research. Therefore, all the patients were prescribed relevant therapy aimed at improving prognosis for the disease.

Table 2

Принимаемые лекарственные препараты

Medications group	Active ingredient	A share of prescription
ACE inhibitors / sartan drugs	Perindopril	70.0 %
	Ramipril	10.0 %
	Losartan	10.0 %
	Valsartan	5.0 %
	Telmisartan	5.0 %
Beta-blockers	Bisoprosol	59.2 %
	Metoprolol succinate	31.8 %
	Carvediol	4.5 %
	Nebivolol	4.5 %
Acetylsalicylic acid	Acetylsalicylic acid	100.0 %
P2Y12-thrombocytes receptors blocker	Clopidogrel	72.0 %
	Ticagrelor	24.0 %
	Prasugrel	4.0 %
Statins	Atorvastatin	84.0 %
	Rosuvastatin	16.0 %

The research protocol was approved by the Local Ethical Committee at E.A, Vagners' Perm State Medical University of the RF Public Healthcare Ministry according to Helsinki Declaration (2008). All the patients included into the research gave their written voluntary informed consent to take part in it.

CI was diagnosed as per «Fourth Universal Definition of Myocardial Infarction» [28]. According to the WHO classification, age under 45 was considered young. Endothelial blood stasis was estimated 12 months after CI. Blood was taken from a patient on an empty stomach out of a peripheral vein into vacuum systems containing 3.2 % solution of waterless sodium nitrate in ratio 1: 10. To determine aggregation of thrombocytes with ristocetin, we

centrifuged blood samples at 200g for 7 minutes and them collected plasma enriched with thrombocytes. Thrombocytes aggregation was examined as per Born method with «Biola» ALA-T2 laser thrombocytes aggregation analyzer. We determined blood fibrinolytic activity with Hageman-dependent fibrinolysis as per a procedure described by G.F. Eryomin and A.G. Arkhipov (1981, 1982). 12 months after CI frequency of a combined ultimate point was estimated; that point included cardiovascular death, recurrent CI, and unstable stenocardia development.

All the data were statistically processed with Microsoft Excel and Stat Soft Statistica 13.0 applied statistical software. Quantitative parameters are given as simple mean ± standard deviation; qualitative parameters are frequencies given in %. Disprecpancies were considered statistically significant at $p \leq 0.05$.

Results and discussion. Table 3 contains the results obtained in laboratory assessment of blood stasis 12 months after CI.

Table 3

Blood stasis parameters in research participants

Parameter	Young patients with CI ($n = 25$)	Reference group ($n = 15$)	p
APTT, sec	28.5±2.8	33.3±0.7	<0.05
PTT, sec	13.7±0.7	15.07±0.1	<0.05
TT, sec	16.0±1.2	18.53±1.0	<0.05
Fibrinogen, g/l	3.2±0.6	2.94±0.1	<0.05
Aggregation of thrombocytes with ADP, sec	10.3±0.4	14.9±0.2	<0.05
Aggregation of thrombocytes with ristocetin, %	66.2±2.3	64.3±3.1	>0.05
HDF, min	12.0±3.6	9.6±0.4	<0.05

Patients with CI in their case history had more apparent changes in coagulation blood stasis system such as shorter activated partial thromboplastine time (APTT), shorter prothrombin time (PTT), shorter thrombin time (TT), and higher fibrinogen concentration.

Blood stasis disorders are a significant factor that influences rehabilitation after CI. Thus, it was shown in several research works that increased coagulation activity after PCI was related to higher risks of recurrent cardiovascular events such as re-stenosis or recurrent CI [29–31].

We examined aggregation function of thrombocytes with ADP and revealed a significant increase in their activity in patients who had suffered CI against healthy people (OR 4.4; 95 % CI 1.5–12.0; $p < 0.05$). Several prospective studies detected a relation between thrombocytes aggregation activity and cardiovascular event development in patients with diagnosed IHD [32, 33]. TRITON TIMI 38 and PLATO studied revealed that effective ADP-receptors inhibition improved a long-term prognosis for patients' survival rate [34, 35]. A recent ADAPT-DES study showed that high residual thrombocytes reactivity against relevant therapy that included antagonists of P2Y12-thrombocytes receptors resulted in elevated risks of stent thrombosis, recurrent CI, and mortality due to cardiovascular reasons [36].

We didn't reveal any significant differences between two groups regarding aggregation activity of thrombocytes with ristocetin in our research (OR 1.9; 95 % CI 0.2–20.2; $p > 0.05$). Some research works showed that patients with CI had elevated von Willebrand factor concentration. Austrian scientists concluded that elevated von Willebrand factor concentration in patients with CI led to elevated risks of recurrent ischemic events [37]. A. Sambola et al. revealed a correlation between elevated von Willebrand factor concentration in blood plasma and thrombus resistance to fibrinolysis in patients with CI with ST elevation [38]. K. Ozawa et al., in their turn, revealed that an increase in endothelium-associated von Willebrand factor concentration slowed down blood flow in the microcirculatory channel after CI [39]. Chinese researchers performed substantial meta-analysis aimed at estimating von Willebrand factor kinetics af-

ter CI. It was detected that the highest von Willebrand factor concentration occurred during the 1st week after CI and then it decreased gradually. It was detected that high von Willebrand factor concentration had prognostic significance and could be applied to estimate short-term prognosis [37].

Patients who had suffered CI had depressed Hageman-dependent fibrinolysis system. The discrepancy in this parameter was statistically authentic (OR 6.6; 95 % CI 1.1–14.7; $p < 0.05$). Recent works consider weaker endogenous fibrinolysis to be an unfavorable prognostic marker in case there is acute coronary syndrome [40, 41]. M. Farag et al. showed that patients who ran high cardiovascular risks still had functional disorders in their endogenous fibrinolysis 30 days after CI; there was an assumption that endogenous fibrinolysis assessment after CI could help revealing patients who still ran high cardiovascular risks in spite of PCI and double anti-thrombocytes therapy [42]. Researchers from Perm also mention in their works that poorer fibrinolysis parameters in patients after CI have unfavorable prognostic significance [43]. Endogenous fibrinolysis is assumed to become a new target for medication therapy prescribed to patients with high cardiovascular risks [41].

Conclusions. 12 months after CI young patients still run high risks of recurrent cardiovascular events. In addition to traditional risk factors such as smoking, dyslipidemia, overweight, and family case history with early cardiovascular diseases, there is also high thrombogenic risk caused by grave damage to coronary lumen, stenting procedure peculiarities as well as apparent changes in blood stasis. Indirect assessment of von Willebrand factor concentration in patients receiving relevant double anti-thrombocyte therapy allows considering this parameter to become normal during rehabilitation after CI. Nevertheless, there is still a functional disorder in thrombocytes activity, proneness to hyper-coagulation, and endogenous fibrinolysis deterioration.

Funding. The research was not granted any sponsor support.

Conflict of interests. Authors state there is no any conflict of interests.

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Received: 06.04.2020
Accepted: 03.06.2020
Published: 30.06.2020