Title: Impact of intrinsic coagulation pathway factors activity and hemostatic markers of endothelial dysfunction on thrombotic complications in patients with atherosclerotic peripheral arterial disease

Authors: R.E. Kalinin, I.A. Suchkov, N.D. Mzhavanadze, O.N. Zhurina, E.A. Klimentova

Affiliation: Ryazan State Medical University, Ryazan, Russia

A short title (running head): Hemostatic markers of endothelial dysfunction

Category: original article

Authors and affiliations:

Roman E. Kalinin, MD, PhD, DSc, head of the department of cardiovascular, endovascular, operative surgery, and topographic anatomy, Ryazan State Medical University, Russia. 390026 Vysokovoltnaya, 9, Ryazan, Russia. kalinin-re@yandex.ru

Igor A. Suchkov, MD, PhD, DSc, professor in the department of cardiovascular, endovascular, operative surgery, and topographic anatomy, Ryazan State Medical University, Russia. 390026 Vysokovoltnaya, 9, Ryazan, Russia. suchkov-_med@mail.ru

Nina D. Mzhavanadze MD, PhD, associate professor in the department of cardiovascular, endovascular, operative surgery, and topographic anatomy, Ryazan State Medical University, Russia. 390026 Vysokovoltnaya, 9, Ryazan, Russia. nina_mzhavanadze@mail.ru

Olga N. Zhurina, MD, head of the clinical laboratory in the research center for hematology, oncology and immunology, Ryazan State Medical University, Russia. 390029 Stroiteley, 5B, Ryazan, Russia. zavlab@hemacenter.org

Emma A. Klimentova, MD, postgraduate student in the department of cardiovascular, endovascular, operative surgery, and topographic anatomy, Ryazan State Medical University, Russia. 390026 Vysokovoltnaya, 9, Ryazan Russia. klimentowa.emma@yandex.ru

Corresponding author: Nina D. Mzhavanadze. Address: 390026 Vysokovoltnaya, 9, Ryazan State Medical University, Ryazan, Russia. Phone: +74912460801 E-mail: nina_mzhavanadze@mail.ru

Funding sources. European Society for Vascular Surgery Research Grant 2016.

Conflict of interest: none.

Number of pages – 18; **number of tables** – 4.

Number of words: 4000.

Brief statement: the article presents results of the study on the impact of intrinsic coagulation pathway factors (VIII, IX, XI) activity and hemostatic markers of endothelial dysfunction (von Willebrand factor, soluble endothelial protein C receptors, plasminogen activator inhibitor – 1) on thrombotic complications in patients with atherosclerotic peripheral arterial disease.

Abstract

Objective. To evaluate the impact of activity of intrinsic coagulation pathway factors and hemostatic markers of endothelial dysfunction on thrombotic complications in patients with peripheral atherosclerosis.

Design. Prospective cohort study.

Material. 120 patients with atherosclerotic lower limb ischemia, stage 2b-3 Fontaine were divided into three groups, 40 subjects each: group A - polytetrafluorethylene (PTFE) graft bypass surgery; group B - endovascular angioplasty and stenting; group C - conservative treatment.

Methods. Peripheral venous blood samples were collected to assess the activity of intrinsic coagulation factors (VIII, IX, XI) and hemostatic endothelial dysfunction markers (von Willebrand factor (vWF), soluble endothelial protein C receptor (sEPCR), plasminogen activator inhibitor-1 (PAI-1)), and nitric oxide (NO) metabolites as integral endothelial dysfunction parameter. Vascular duplex scanning of lower extremities was performed at baseline, at 3, 6, and 12 months.

Results. In groups A and B at baseline activity of vWF, factors VIII, IX, XI, levels of PAI-I and sEPCR were increased as compared to normal values and subjects in group C; NO metabolites levels were decreased. At 3 months after PTFE grafting activity of factor VIII increased (p=.0002) and NO metabolites decreased (p=.012). At 3 months after endovascular treatment activity of factors VIII (p=.012), IX (p=.01), and XI (p=.011) increased, NO metabolites level decreased (p=.007). Six subjects in group A with increasing factor VIII activity (p=.01) developed graft thrombosis. Four subjects in group B and three patients in group C with increased activity of vWF developed myocardial infarction by 6 months (p=.049).

Conclusions. Atherosclerotic peripheral arterial disease was associated with increased activity of vWF, factors VIII, IX, XI, elevated levels of PAI-1 and sEPCR. Invasive treatment promoted hypercoagulation. Increased activity of

factor VIII was associated with PTFE graft thrombosis. Increased activity of vWF was associated with development of myocardial infarction.
Key words: hemostasis, endothelial dysfunction, thrombosis, restenosis.

Introduction

Post-procedural patency rates after reconstructive procedures in subjects with atherosclerotic peripheral arterial disease (PAD) may vary due to the development of thrombotic complications, restenosis, and progression of disease. While peripheral procedures involving autologous venous grafts have rather satisfactory results, prosthetic polytetrafluoroethylene (PTFE) grafts occlude within the 1st year in up to 20% in above-knee procedures and 75% of cases of below-knee interventions [1]. Thrombotic rates reach 12.5% within one year after peripheral procedures involving endovascular stents [2].

Shear stress, coagulation factors and hemostatic molecules expressed by endothelium (soluble endothelial protein C receptor (sEPCR), von Willebrand factor (vWF), plasminogen activator inhibitor-1 (PAI-1)), adhesion molecules, proinflammatory cytokines, and chemokines play an important biological role in both hemostasis and vascular remodeling [3, 4].

Historically intrinsic cascade has been regarded as less physiologically important as compared to the extrinsic one. Nowadays intrinsic pathway is regarded as a key player in thrombogenesis, immune system, and inflammation [5, 6]. The main factors of intrinsic coagulation pathway are VIII, IX, XI, and XII. Along with these 4 factors, vWF, an adhesive glycoprotein, which binds with factor VIII and protects it from inactivation through proteolysis by activated protein C, plays an important role [7]. Factor VIII is bound to vWF; the latter has long been regarded as an important marker of endothelial dysfunction, while the role and the origin of its binding agent - factor VIII remained understudied. It has been recently discovered that factor VIII is produced not only in sinusoid endothelial liver cells but also by extrahepatic endothelium elsewhere [8]. Coagulation proteases not only regulate hemostasis and thrombosis but also contribute to the hemostatic cellular responses: thrombin affects the detachment of factor VIII from vWF complex and thus activates factor XIa [9]. Additional quantity of factor IXa is formed under the action of factor XIa; a tenase complex

are activated factor VIII bound to factor IX on the surface of platelets [10]. Polish researchers investigated the influence of different hemostatic parameters on restenosis and thrombosis and made a conclusion that the main association was with tissue factor level: by binding factor VIIa, tissue factor-VIIa complex activates the coagulation factors IX and X, which leads to fibrin formation. [11]. Dutch researchers showed that decreased concentration of factors VIII and IX was associated with an 80% reduced mortality due to coronary artery disease [12]. Increased activity of factor XI was associated with higher risks for ischemic stroke. Factor XII becomes active on a charged surface via contact activation, which then launches activation of both factors IX and XI. However, factor XII was not associated with either myocardial infarction or ischemic stroke risk [13].

Assessment of atherothrombotic pathogenesis involving endothelial dysfunction markers and intrinsic coagulation pathway may reveal new predictors of thrombotic complications in patients with PAD and give insight into the future possible application of alternative antithrombotic therapies.

Objective: to evaluate impact of intrinsic coagulation pathway factors activity and hemostatic markers of endothelial dysfunction on thrombotic complications in patients with atherosclerotic peripheral arterial disease (PAD).

Material.

The work was funded by the European Society for Vascular Surgery Research Grant and approved by the Local ethical committee of the Ryazan State Medical University. All subjects gave informed consent to the work. The study was performed in the department of cardiovascular, endovascular, operative surgery, and topographic anatomy at Ryazan State Medical University, Russia from December 2016 to July 2018.

A prospective study enrolled 120 patients with chronic lower limb ischemia due to atherosclerotic PAD, stage 2b-3 Fontaine (Rutherford category 3-4). The subjects of similar age, sex, and ethnicity were divided into three groups. Group

A: 40 patients who underwent PTFE bypass surgery on aorto-femoral or above-knee femoropopliteal segment; group B: 40 patients who underwent peripheral endovascular angioplasty and stenting; group C (control): 40 patients who underwent conservative treatment alone. Treatment was assigned according to TransAntlantic Inter-Society Consensus II and generally accepted clinical guidelines. Decision on revascularization or conservative treatment was made by a team of vascular specialists and depended on severity of claudication, previous treatment, anatomy, possible need for repeat procedures in the future, and patient's preferences. Stage III disease was predominant in groups A and B due to the need for more aggressive treatment options in subjects with ischemic rest pain. Description of subjects and procedures is given in table 1.

Table 1

Description of subjects and procedures (M±σ)

Parameter	Group A	Group B	Group C
Age, years	63.4 ± 7.9	63.9 ± 7.9	59.8 ± 8,3
Males, n (%)	33 (82.5%)	35 (87.5%)	36 (90%)
Females, n (%)	7 (17.5%)	5 (12.5%)	4 (10%)
Stage of ischemia (Fontaine)			
IIB, n (%)	11 (27.5%)	13 (32.5%)	32 (80%)
III, n (%)	29 (72.5%)	27 (67.5%)	8 (20%)
Concomitant pathology			
Ischemic heart disease, n (%)	16 (40%)	19 (47.5%)	15 (37.5%)
Arterial hypertension, n (%)	15 (37.5%)	17 (42.5%)	20 (50%)
History of myocardial infarction, n (%)	9 (22.5%)	8 (20%)	8 (20%)
Localization of atherosclerotic lesion			

Aortofemoral segment, n (%)	13 (32.5%)	17 (42.5%)	13 (32.5%)
Femoropopliteal segment, n (%)	27 (67.5%)	23 (57.5%)	27 (67.5%)

Reconstructive procedures in group A patients	
Type of procedure	Number, n (%)
Aortobifemoral bypass grafting	9 (22.5%)
Femorofemoral crossover bypass grafting	4 (10%)
Above-knee femoropopliteal bypass grafiting	27 (67.5%)

Reconstructive procedures in group B patients			
Localization of atherosclerotic lesion	Number of procedures N (%)	Angioplasty	Stenting
aortofemoral	17 (42.5%)	3 (7.5%)	14 (35%)
femoropopliteal	23 (57.5%)	20 (50%)	3 (7.5%)

Methods.

Peripheral venous blood samples were collected from patients in groups A and B before and at 3 months after operative or endovascular treatment; from patients in group C – once at baseline. The following parameters were analyzed: activity of intrinsic pathway coagulation factors VIII, IX, XI; hemostatic endothelial dysfunction markers (soluble endothelial protein C receptor (sEPCR), von Willebrand factor and its antigen, plasminogen activator inhibitor-1 (PAI-1) using ELISA, and nitric oxide II level as integral endothelial parameter). Ankle-brachial index measurement (ABI), duplex ultrasound (DUS) of lower extremity vessels were performed at baseline in all patients. Patients in groups A and B underwent angiography at baseline, repeat physical examination, ABI measurement and DUS testing at 3, 6, and 12 months after reconstructive procedures in order to determine the rates of complications. Patients in groups C

underwent repeat vascular testing at 12 months. Design of the work let us additionally study graft patency in terms of restenosis and disease progression.

Subjects in group A underwent reconstructive bypass procedures with PTFE grafts while subjects in group B underwent endovascular treatment involving angioplasty and placement of bare metal stents. All subjects received dual antiplatelet treatment for at least 6 months after the start of the study.

Statistical analysis was performed using a Mann-Whitney U test as a non-parametric alternative test to the independent sample t-test; Wilcoxon test for paired samples; Spearman rank correlation was used to test the association between two ranked variables. A threshold probability value of $p \leq .05$ was used to indicate statistical significance.

Results.

In group A patients at baseline activity of vWF, factors VIII, IX, XI, levels of PAI-I, and sEPCR were increased as compared to normal values; vWF antigen level was normal; NO metabolites level was decreased as compared to healthy volunteers. At 3 months after PTFE grafting such trend remained (table 2). Statistically significant results were obtained for factor VIII (p=.0002) and NO metabolites level (p=.012). As compared to group C subjects (control) statistically significant results were obtained for vWF (p=.001), vWF antigen (p=.00009), factor VIII (p=.0002), factor IX (p=.045), factor XI (p=.000002), NO metabolites level (p=.028), and sEPCR level (p=.0001) as presented in table 2.

Table 2

Intrinsic coagulation pathway factor and hemostatic markers of endothelial dysfunction in group A patients

Time	Value	vWF	vWF antigen	Factor VIII	Factor IX	Factor XI	PAI-I	sEPCR	NO
	Normal value	70-150%	0.5-1.5 U/ml	70-150%	70-150%	70-130%	7- 43 ng/ml	2- 43 ng/ml	76-80 mcM
Baseline	Median	600	1.1	175	222	189	76	67	60

	Lower quartile	300	0.96	145	151	141	90.5	61.2	37
	Upper quartile	1200	1.2	226	275	270	65.3	75.3	81
3months	Median	1200	1.0	233	246	208	78.1	65	43
	Lower quartile	300	0.78	179	158	118	56.5	58	34
	Upper quartile	1200	1.16	294	284	287	98.3	68	67.7
	p	.103	.109	.0002	.394	.878	.909	.153	.012

Note: von Willebrand factor (vWF), von Willebrand factor antigen (vWF antigen), plasminogen activator inhibitor type 1 (PAI-1), soluble endothelial protein C receptor (sEPCR), nitric oxide (II) metabolites level (NO).

In group B patients at baseline activity of vWF, factors VIII, IX, XI, levels of PAI-I and sEPCR were increased as compared to normal values; vWF antigen level was normal; NO metabolites level was decreased as compared to healthy volunteers. At 3 months after endovascular treatment activity of vWF, factors VIII, IX, and XI increased while PAI-1 and sEPCR levels remained elevated; vWF antigen level remained normal, and NO metabolites level continued to decrease (table 3). Statistically significant results were obtained for factors VIII (p=.012), IX (p=.01), XI (p=.011), and NO metabolites level (p=.027). As compared to group C subjects (control) statistically significant results were obtained for vWF (p=.006), factor VIII (p=.01), NO metabolites level (p=.046), and sEPCR level (p=.0002) as presented in table 3.

Table 3

Intrinsic coagulation pathway factor and hemostatic markers of endothelial dysfunction in group B patients

Time	Value	vWF	vWF antigen	Factor VIII	Factor IX	Factor XI	PAI-I	sEPCR	NO
	Normal value	70-150%	0.5-1.5 U/ml	70-150%	70-150%	70-130%	7- 43 ng/ml	2- 43 ng/ml	76-80 mcM

Baseline	Median	600	0.92	157	180	156	78	57	65
	Lower quartile	300	0.82	128	134	92	47	43	48
	Upper quartile	1200	1.0	210	237	195	110	87	72
3 months	Median	660	0.9	184	218	181	97	57	52
	Lower quartile	300	0.7	138	156	119	48	44	35
	Upper quartile	800	1.08	271	297	226	119	100	69
	p	.703	.949	.012	.010	.011	.909	.182	.027

Subjects in group C had moderately increased activity of vWF, factors IX, XI, PAI-1, and sEPCR; activity of factor VIII, levels of vWF antigen and NO metabolites were normal as presented in table 4.

Table 4

Intrinsic coagulation pathway factor and hemostatic markers of endothelial dysfunction in group C patients

Parameter	vWF	vWF antigen	Factor VIII	Factor IX	Factor XI	PAI-I	sEPCR	NO
Normal value	70-150%	0.5-1.5 U/ml	70-150%	70-150%	70-130%	7- 43 ng/ml	2- 43 ng/ml	76-80 mcM
Median	300	0.9	134	202	132	77	49	72
Lower quartile	160	0.83	96.6	122	101	43	39	50
Upper quartile	400	1.0	156.9	255	159	133	52	95

Higher activity of intrinsic coagulation factors and hemostatic markers of endothelial dysfunction in subjects in groups A and B were associated with a higher proportion of patients with more advanced stage of ischemia (stage III disease Fontaine in 72.5 and 67.5% of subjects, respectively) as compared to

milder ischemia in group C patients (stage III in 20% of patients).

The following correlations were found at baseline in all study groups: between the activity of vWF and factor VIII (r=+0.475), PAI-I level and activity of factor XI (r=+0.390), sEPCR and PAI-I levels (r= +.439). The strongest correlations were found between the activity of factors VIII and IX (r=+.603), VIII and XI (r=+.609), IX and XI (r=+.603).

At 3 months after open revascularization in group A subjects the following correlations were found: between vWF activity and NO metabolites level (r=-0.395), factor XI and NO metabolites level (r=-.387), factor VIII and NO metabolites level (r=-.413), vWF antigen and PAI-1 levels (r=+.383). Stronger correlations were found between the activity of factors VIII and IX (r=+0.530), vWF and factor VIII (r=+.698), vWF and factor IX (r=+.508), vWF and factor XI (r=+.558), factors VIII and XI (r=+.733), factors IX and XI (r=+.631).

At 3 months after endovascular treatment in group B subjects the following correlations were found: factors VIII and IX (r=+.457), factor IX and PAI-I level (r=+.410), factor IX and sEPCR level (r=+.395), factor XI and sEPCR level (r=+.423), sEPCR and PAI-I levels (r= +.367); stronger correlations were found between factors VIII and XI (r=+.657), factors IX and XI (r=+.595), vWF and NO metabolites level (r= -.517).

Six subjects in group A with increased activity of factor VIII (p=0.01) developed thrombosis in early post-operative period, possibly, due to the overestimation of distal runoff in 4 subjects and technical difficulties while performing distal anastomosis in 2 patients. Repeat revascularizations in those subjects were not effective and required transfemoral amputation. At baseline and three months after revascularization there was an increased activity of coagulation factors and hemostatic markers of endothelial dysfunction in absolute values, although statistically significant results were not obtained. Five subjects in group A with increased activity of vWF (p=.027) and decreased level of NO metabolites (p=.014) were diagnosed with progression of the disease at 12 months according to the results of DUS. These subjects had increased activity of vWF, factors VIII,

IX, XI, elevated levels of sEPCR and PAI-1, low level of NO metabolites at baseline.

One subject in group B with increased activity of both coagulation factors and hemostatic markers of endothelial dysfunction in absolute values developed thrombosis at 3 months and underwent unsuccessful thrombolytic therapy resulting in above-knee amputation. Four patients in group B with increased activity of vWF (p=0.049) patients developed myocardial infarction at a 6-month follow—up period and underwent percutaneous coronary interventions. Restenosis occurred in four subjects in group B at 6 months after the initial endovascular treatment, which necessitated repeat procedures with satisfactory results. The subjects had increased activity of vWF (p=0.023) and decreased NO metabolites level (p=0.003). At baseline those subjects had increased activity of vWF, factors VIII, IX and XI while levels of PAI-I and sEPCR were normal; NO metabolites level was initially decreased. At 3 months activity of vWF increased (p=.014) while NO metabolites level lowered (p=.006).

Three patients in group C (control) with increased activity of vWF (p=0.019) developed myocardial infarction at 6 months after the start of the study and underwent percutaneous coronary interventions. These subjects had increased activity of of vWF, factors VIII, IX and XI, elevated levels of sEPCR and PAI-1, decreased level of NO metabolites in absolute values as compared to other patients in group C. Three subjects in group C with increased activity of PAI-1 (p=.028) developed progression of peripheral atherosclerosis at 12 months.

Discussion.

We found that open or endovascular reconstructive procedures may promote hypercoagulation and endothelial dysfunction, which is reflected in increased activity of vWF, PAI-1, elevated levels of sEPCR and low levels of NO metabolites. Our previous works have shown that NO metabolites levels decreased in accordance with progression of the ischemia in subjects with peripheral atherosclerosis [14].

Increased activity of vWF and low levels of NO may be predictors of restenosis and progression of the disease. We found that at three months after open revascularization subjects in group A had decreased level of NO metabolites, while activity of vWF, factors VIII, IX, XI increased. At three months after endovascular treatment in group B subjects there was a negative correlation between the activity of vWF and NO metabolites level, which corresponds to the previously data that NO had a negative impact on vWF secretion. Classical effects of NO are mediated via cGMP signaling pathway and cGMP-dependent proteinkinase-1; its activation leads to the inhibition of agonist-induced mobilization of calcium ions and thus secretion of vWF [15]. We have previously shown that in PTFE grafting the lack of NO lead to the excessive adhesive properties of endothelium, monocyte migration into the subendothelial structures, platelet activation, hypercoagulation, and enhanced proliferation of smooth muscle cells [13].

The role of vWF as a predictor of the development of thrombotic complications including myocardial infarction may be explained by its biological function: adhesion of platelets to endothelium and protection of factor VIII from proteolysis by protein C, which determines both platelet and fibrin components of intraarterial thrombosis. Costa C.E. et al. (2014) have shown an association between the factor VIII and acute myocardial infarction [16].

Lazarenko V.A. et al (2017) found higher levels of PAI-1 in both systemic and local blood samples in subjects with atherosclerotic PAD [17]. Possible influence of PAI-1 on restenosis and progression of the disease may be due to its role in regulating migration of smooth muscle cells in vascular wall [18]. Correlation between PAI-1 and factor XI may be explained by the fact that factor XI activates thrombin activated fibrinolysis inhibitor (TAFI), thus inhibiting fibrinolytic activity; at the same time PAI-1 inhibits plasminogen and thus limits fibrinolysis. Correlation between sEPCR and PAI-I levels may be interpreted by the fact that sEPCR may inhibit anticoagulant activity of protein C, which limits its neutralizing effects on PAI-1 [19].

Conclusion.

1. Atherosclerotic peripheral arterial disease was associated with increased activity of vWF, coagulation factors VIII, IX, XI, elevated levels of PAI-1 and sEPCR.
2. PTFE bypass grafting was associated with the tendency for increased activity of factor VIII and decreased level of NO metabolites at 3 months after revascularization; endovascular procedures were associated with the tendency for increased activity of factors VIII, IX, XI and decreased level of NO metabolites.
3. PTFE graft thrombosis was associated with increased activity of factor VIII. Development of myocardial infarction in subjects with peripheral atherosclerosis was associated with increased activity of vWF.
4. Additionally, restenosis after endovascular procedures and progression of disease after PTFE grafting was associated with increased activity of vWF and decreased level of NO metabolites. Progression of disease in patients with conservative management was associated with increased activity of PAI-1.

Acknowledgements

We thank our colleagues from Ryazan Regional Clinical Cardiological Dispensary, Ryazan, Russia for help throughout the study.

References:

1. Singh P, Harper Y, Oliphant CS, et al. Peripheral interventions and antiplatelet therapy: Role in current practice. World J Cardiol. 2017;9;7:583-593. DOI: 10.4330/wjc.v9.i7.583

2. Katsanos K, Al-Lamki SA, Parthipun A, et al. Peripheral Stent Thrombosis Leading to Acute Limb Ischemia and Major Amputation: Incidence and Risk Factors in the Aortoiliac and Femoropopliteal Arteries. Cardiovasc Intervent Radiol. 2016;40;3:351-359. DOI: 10.1007/s00270-016-1513-0

3. Sana TR, Janatpour MJ, Sathe M. Microarray analysis of primary endothelial cells challenged with different inflammatory and immune cytokines. Cytokine. 2005;29;6:256-69. DOI: 10.1016/j.cyto.2004.11.003

4. Mohan Rao LV, Esmon CT, Pendurthi UR. Endothelial cell protein C receptor: a multiliganded and multifunctional receptor. Blood. 2014;124:10:1553-62. DOI: 10.1182/blood-2014-05-578328

5. Delvaeye M, Conway EM. Coagulation and innate immune responses: can we view them separately? Blood. 2009;114;12:2367-74. DOI: 10.1182/blood-2009-05-199208

6. Doolittle RF. Coagulation in vertebrates with a focus on evolution and inflammation. J Innate Immun. 2011;3;1:9-16. DOI: 10.1159/000321005

7. Sanders YV, Eikenboom J, De Wee ME. et al. Reduced prevalence of arterial thrombosis in von Willebrand disease. J ThrombHaem. 2013; 11:845-54. DOI: 10.1111/jth.12194

8. Zanolini D, Merlin S, Feola M. Extrahepatic sources of factor VIII potentially contribute to the coagulation cascade correcting the bleeding phenotype of mice with hemophilia A. Haematologica. 2015;100;7:881-92. DOI: 10.3324/haematol.2014.123117

9. Hoffman M., Pawlinski R. Hemostasis: old system, new players, new directions. Thromb Res. Thromb Res. 2014;133:Suppl 1:S1-2. DOI: 10.1016/j.thromres.2014.03.001

10. Dougald M. Monroe, Hoffman M. What Does It Take to Make the Perfect Clot? Arterioscler Thromb Vasc Biol. 2006; 26:41-48. DOI: 10.1161/01.ATV.0000193624.28251.83

11. Kotschy D, Kotschy M, Socha P. Tissue factor and other hemostatic parameters in patients with advanced peripheral artery disease after endovascular revascularization - search for hemostatic factors which indicate restenosis. Adv Clin Exp Med. 2015;24;1:93-8. DOI: 10.17219/acem/38160

12. Srámek A, Kriek M, Rosendaal FR. Decreased mortality of ischaemic heart disease among carriers of haemophilia. Lancet. 2003;362(9381):351-4.

13. Johansson K, Jansson J-H, Johansson L et al. Factor XII as a Risk Marker for Hemorrhagic Stroke: A Prospective Cohort Study. Cerebrovasc Dis Extra 2017;7:84-94. doi: 10.1159/000468994

14. Kalinin RE. Endothelial dysfunction: role in surgery of atherosclerotic peripheral arterial disease. LAP Lambert Academic Publishing. 2011. 248pp. EAN 9783845417172

15. Vischer UM. von Willebrand factor, endothelial dysfunction, and cardiovascular disease. Journal of Thrombosis and Haemostasis. 2006; 4:1186-1193. DOI: 10.1111/j.1538-7836.2006.01949.x

16. Costa C, Alves M, Durao D. Elevated factor VIII in a patient with acute coronary syndrome. RevPortCardiol. 2014; 33:3:181-84. DOI: 10.1016/j.repc.2013.09.009

17. Lazarenko VA, Bobrovkaya EA, Khruslov MV, Yukhanova IYu. Assessment of fibrinolytic activity in patients with peripheral arterial disease before and after reconstructive procedures. Thrombosis, hemostasis and rheology. 2017;69:5559. (In Russ.) DOI: 616.137.83/87-004.6-007.271:612.115.1

18. Yildiz SY, Kuru P, Oner ET, Agirbasli M. Functional stability of plasminogen activator inhibitor-1. The scientific world journal. 2014; 858293. DOI: 10.1155/2014/858293

19. Zhalyalov A.S., Balandina A.N., Kuprash A.D., Srivastava A., Shibeko A.M. The overview of fibrinolysis system contemporary concepts and of its

disorders diagnostic methods. Pediatric Hematology/Oncology and Immunopathology. 2017;16(1):69-82. (In Russ.)