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Фактор фон Виллебранда при выполнении инвазивных вмешательств у больных с периферическим атеросклерозом

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АННОТАЦИЯ

Обоснование. Эндотелиальные клетки (ЭК) продуцируют как анти-, так и прокоагулянтные факторы, в частности фактор фон Виллебранда (vWF). vWF приводит к активации тромбоцитов и запускает их агрегацию, а также имеет важное значение в регуляции сосудистого воспаления.

Цель. Изучить уровень и активность vWF у больных с периферическим атеросклерозом при выполнении эндоваскулярных или открытых операций на артериях нижних конечностей.

Материалы и методы. В исследование включено 115 пациентов с хронической ишемией нижних конечностей IIб–IV стадий заболевания по А.В. Покровскому–Фонтейну. 55 больным выполнены эндоваскулярные вмешательства на артериях нижних конечностей, 60 — открытые шунтирующие. Всем пациентам до и через 3 месяца после проведенного лечения выполнен забор периферической крови для оценки уровня — антигена (АГ) vWF и активности vWF. В течение года больные наблюдались каждые 3 мес. для оценки развития неблагоприятных исходов, включая прогрессирование заболевания, рестеноз, тромбоз зоны реконструкции, онкологическое заболевание, инфаркт миокарда (ИМ), потерю конечности, инсульт и летальные исходы.

Результаты. У пациентов группы эндоваскулярных операций максимальное значение АГ vWF выявлено при многоуровневом типе поражении — 1,25 мкг/мл (vs 0,2 мкг/мл, 95% доверительный интервал (ДИ) 0,72–3,21 мкг/мл, p = 0,019); в срок 3 мес. схожая тенденция сохранялась. В группе эндоваскулярных вмешательств АГ vWF был статистически значимо выше у больных с развившимся впоследствии ИМ (1,15 мкг/мл, 95% ДИ 1,05–1,18 мкг/мл) по сравнению с лицами без инфаркта (0,9 мкг/мл, 95% ДИ 0,78–1,01 мкг/мл, p = 0,015). Кроме того, АГ vWF в срок 3 мес. был повышен у лиц с летальным исходом в течение года, составив 1,06 мкг/мл (95% ДИ 0,96–1,18 мкг/мл, p = 0,031). Активность vWF среди лиц, у которых в течение года после эндоваскулярного лечения развился ИМ, была в 4 раза выше по сравнению с лицами без ИМ (p = 0,022); схожая тенденция отмечалась и в отношении развития летальных исходов (p = 0,009). У больных группы открытых операций в срок 3 мес. максимально высокая активность vWF отмечалась при проксимальном характере поражения артериального русла в виде подвздошно-бедренной окклюзии (1200%, 95% ДИ 640–1200%) и IV стадии заболевания (770%, 95% ДИ 320–1200%, p < 0,05). ROC-анализ показал, что при активности vWF равной или выше 620% у пациентов группы эндоваскулярных операций прогнозировался летальный исход; чувствительность и специфичность метода составили 83,3 и 75,5%, соответственно.

Выводы. Для пациентов с периферическим атеросклерозом характерны повышенные антиген и активность vWF с максимальными значениями при многоуровневом поражении артериального русла и критической ишемии. Повышенные антиген и активность vWF характеризовались развитием ИМ и летальных исходов в течение года наблюдения у больных после эндоваскулярных операций на артериях нижних конечностей.

Ключевые слова: *фактор фон Виллебранда; vWF; периферический атеросклероз; тромбоз; инфаркт миокарда*

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Von Willebrand factor in patients with peripheral artery disease who undergo invasive treatment

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ABSTRACT

BACKGROUND: Endothelial cells (ECs) produce both anti- and procoagulant factors, in particular von Willebrand factor (vWF). vWF leads to platelet activation following platelet aggregation, as well as is actively involved in vascular inflammation.

AIM: To evaluate the level and activity of (vWF) in patients with peripheral artery disease (PAD) who underwent endovascular or open bypass grafting.

MATERIAL AND METHODS: The study included 115 patients with chronic lower limb ischemia due to PAD, stage IIb–IV according to A.V. Pokrovsky–Fontaine. Fifty-five participants underwent endovascular treatment, while sixty underwent open bypass procedures using synthetic grafts. Peripheral blood samples were collected from all patients at baseline and three months after invasive treatment to determine the vWF antigen and activity. All patients were monitored every three months for a year to detect the development of unfavorable outcomes including disease progression, restenosis, graft thrombosis, oncology, myocardial infarction (MI), limb loss, stroke, and lethal outcomes.

RESULTS: The highest values of vWF antigen in patients who underwent endovascular treatment were detected in patients with multilevel lesions — 1.25 μg/mL (vs 0.2 μg/mL, 95% confidence interval (CI) 0.72–3.21 mcg/mL p = 0.019); with a similar trend observed after a 3–month follow-up. Baseline vWF antigen was higher in endovascular group patients who developed myocardial infarction (MI) within a year following the procedures as compared to those without MI: 1.15 mcg/mL (95% CI 1.05–1.175 mcg/mL) and 0.9 mcg/mL (95% CI 0.78–1.01 mcg/mL), respectively (p = 0.015). Moreover, vWF antigen was increased at the 3-month follow-up in patients with lethal outcomes–1.06 mcg/mL (95% CI 0.96–1.18 mcg/mL, p = 0.031). vWF activity in endovascular group patients with developed MI was four times higher than those without MI (p = 0.022); a similar trend was detected in the development of lethal outcomes (p = 0.009). Those who underwent open bypass grafting presented with high activity of vWF with maximum values detected in participants with proximal iliofemoral lesions (1200%, 95% CI 640%–1200%) and stage IV disease (770%, 95% CI 320%–1200%, p < 0.05). ROC analysis revealed that vWF activity at least 6.2 times higher in patients who underwent endovascular treatment associated with the development of lethal outcomes within one year after invasive treatments; sensitivity and specificity of the method were 83.3% and 75.5%, accordingly.

CONCLUSION: Patients with PAD presented with increased vWF antigen and activity with maximum values detected in patients with multilevel lesions and critical lower limb ischemia. Increased vWF antigen and activity was associated with development of MI and lethal outcomes within one year following endovascular procedures on lower extremity arteries.

Keywords: *von Willebrand factor; vWF; peripheral artery disease; thrombosis; myocardial infarction*

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ECO•VECTOR

BACKGROUND

Endothelial dysfunction plays an important role in the pathogenesis of several pathologies such as atherosclerosis, arterial hypertension, diabetes, autoimmune, inflammatory, infectious, and oncological diseases. Endothelial cells (ECs) produce both anti- and procoagulant factors, which makes endothelium a key element in hemostasis. Active substances with procoagulant properties derived from endothelium are plasminogen activator inhibitor-1, protease activated receptors, platelet activating factor, adenosine diphosphate, thromboxane, thrombospondin, collagen and elastin, fibronectin, as well as von Willebrand factor (vWF) [1].

vWF, a multidomain adhesive glycoprotein, is synthesized in ECs and megakaryocytes and is accumulated as ultra-large multimers in Weibel-Palade bodies inside ECs or alpha-granules of platelets [2–4]. vWF binds to glycoproteins Ibα and αIIbβ3 on platelets and subendothelial collagen, which leads to platelet activation following platelet aggregation. Along with its key role in hemostasis, vWF is actively involved in vascular inflammation. vWF and its molecular regulator, ADAMTS13, are linked with immunothrombosis, activation and migration of leukocytes, vascular permeability, ischemia and reperfusion, complement activation, and netosis [5].

Aim — this study aimed to evaluate the level and activity of vWF in patients with peripheral artery disease (PAD) who underwent endovascular or open bypass grafting procedures.

MATERIALS AND METHODS

This prospective cohort study was approved by the Local Ethical Committee of the Ryazan State Medical University and was registered on the clinicaltrials.gov website with identification number NCT04391374. The project involved 115 patients with chronic lower limb ischemia stage IIb–IV according to Pokrovsky-Fontaine due to peripheral atherosclerosis. The patients were divided into two groups according to the type of invasive treatment performed on the lower extremity arteries.

The endovascular group comprised 55 patients 57–69 years of age, 48 (87.3%) of which were males; 19 patients (34.6%) underwent angioplasty and stenting using nitinol stents, and 36 (65.5%) patients underwent angioplasty alone.

The open bypass grafting group consisted of 60 patients 60–67 years of age, of which 51 (85.0%) were male; 40 (66.6%) patients underwent femoropopliteal bypass grafting, 13 (21.7%) underwent aortobifemoral bypass grafting, 5 (83.3%) underwent crossover femorofemoral bypass grafting, and 2 (3.3%) underwent aortopopliteal bypass grafting, all using synthetic grafts.

The type of atherosclerotic lesion, stage of chronic ischemia, and concomitant pathology are listed in Table 1.

Table 1. Clinical characteristics of patients in the studied groups (n = 115)

Parameters	Endovascular treatment group, n = 55	Open bypass grafting group, n = 60
Type of atherosclerotic lesion		
Occlusion of femoropopliteal arterial segment, n (%)	34 (61.8)	32 (53.3)
Occlusion of iliofemoral arterial segment, n (%)	14 (25.5)	9 (15.0)
Occlusion of popliteal artery, n (%)	1 (1.8)	0
Multilevel lesions (iliac, femoral, popliteal), n (%)	6 (10.9)	11 (18.3)
Leriche syndrome, n (%)	0	8 (13.3)
Stage of the disease		
IIb, n (%)	8 (14.6)	6 (10.0)
III, n (%)	33 (60.0)	39 (65.0)
IV, n (%)	14 (25.5)	15 (25.0)
Concomitant pathology		
Prior reconstructive procedures on lower extremity arteries, n (%)	6 (10.9)	3 (5.0)
Prior myocardial infarction, n (%)	18 (32.7)	10 (16.7)
Ischemia heart disease, n (%)	27 (49.1)	17 (28.3)
Type 2 diabetes mellitus, n (%)	18 (32.7)	2 (3.3)
Arterial hypertension, n (%)	37 (67.3)	44 (73.3)

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At baseline and 3 months after invasive treatment, peripheral blood samples were collected to assess vWF antigen activity using vacuum containers S-Monovette (Sarstedt, Germany). vWF antigen in blood plasma was detected with Technozym vWF:Ag ELISA kits (Diapharma Group Inc., USA) using ELISA analyzer Lazurit (Dynex, USA). vWF activity was determined in blood plasma using the manual method of platelet agglutination in the presence of vWF and ristocetin A with von Willebrand Reagent (Siemens Healthcare Diagnostics Products GmbH, Germany).

All patients received optimal medical treatment according to the clinical guidelines [6]. Within one year after invasive treatment, the participants underwent physical and instrumental examination every 3 months to detect unfavorable outcomes, including disease progression, restenosis, graft thrombosis, oncology, myocardial infarction (MI), limb loss (amputation), stroke, and death.

RESULTS

The outcomes in both endovascular treatment and open bypass grafting groups within 1 year are listed in Table 2.

Table 2. Unfavorable outcomes within 1 year after invasive treatment in the studied groups (n = 115)

Type of outcome	Endovascular treatment group, n = 55	Open bypass grafting group, n = 60
Disease progression, n (%)	11 (20.0)	3 (5.9)
Restenosis, n (%)	13 (23.6)	6 (11.8)
Graft thrombosis, n (%)	1 (1.8)	10 (19.6)
Oncology, n (%)	5 (9.1)	5 (9.8)
Myocardial infarction, n (%)	4 (7.3)	2 (3.9)
Limb loss (amputation), n (%)	1 (1.8)	5 (9.8)
Stroke, n (%)	1 (1.8)	1 (2.0)
Lethal outcome, n (%)	6 (10.9)	2 (3.9)

Six patients (10.9%) died in the endovascular treatment group, of which two cases were caused by MI, the other two were caused by oncology, and the cause of the remaining two deaths was unknown. Meanwhile, two died (3.9%) in the open bypass grafting group, of which one case was caused by the oncology, and the cause of the remaining one was unknown.

vWF antigen values in both endovascular treatment and open bypass grafting groups at baseline and 3 months after invasive treatments are presented on Figure 1.

vWF antigen was lower in patients in the endovascular treatment group [0.90 mcg/mL (0.20); 95% confidence interval (CI): 0.83–0.97] than in the open bypass grafting group [1.04 mcg/mL (0.22); 95% CI: 0.98–1.12; $p < 0.001$]. Baseline vWF antigen in patients in the endovascular treatment group differed according to the type of atherosclerotic lesion: occlusion of femoropopliteal arterial segment [0.87 mcg/mL (0.20; 95% CI: 0.78–0.95)] and multilevel lesion [1.25 mcg/mL (0.20; 95% CI: 0.72–3.21), $p = 0.019$]; occlusion of iliofemoral arterial segment [0.90 mcg/mL (0.15; 95% CI: 0.79–1.01)] and multilevel lesion ($p = 0.021$). At 3 months, vWF antigen in patients with multilevel lesion was higher than in those with iliofemoral lesion [1.18 and 0.87 mcg/mL (95% CI: 1.15–1.21 vs. 0.79–1.08, respectively]; $p = 0.04$], which reflects a more severe hemostatic endothelial dysfunction in patients with severe atherosclerotic lesions in the lower extremity arteries.

vWF antigen at 3 months in patients who underwent endovascular treatment was higher in participants who developed MI within 1 year after the procedures compared with those without infarction [1.15 and 0.90 mcg/mL (95% CI: 1.05–1.18 vs. 0.78–1.01, respectively); $p = 0.015$]. Moreover, vWF antigen at 3 months after endovascular treatment was higher in participants who died compared with surviving patients [0.90 and 1.06 mcg/mL (96% CI: 0.78–1.08 vs. 0.96–1.18, respectively); $p = 0.031$].

Performance of open bypass grafting procedures was characterized by the decrease of vWF antigen from baseline to 3 months, from 1.1 to 0.91 mcg/mL (95% CI: 0.96–1.21 vs. 0.71–1.10), respectively ($p = 0.005$). However, there was no association between the vWF antigen and unfavorable outcomes in the open bypass grafting group.

vWF activity in both endovascular treatment and open bypass grafting groups at baseline and 3 months after invasive treatment are presented in Figure 2.

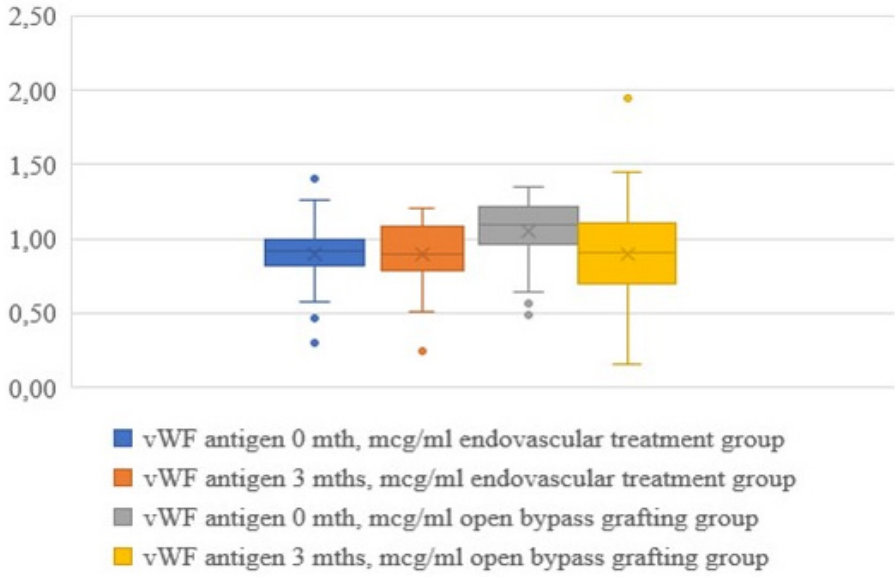

Fig. 1. von Willebrand factor antigen before and after invasive treatment in the studied groups (n = 115).

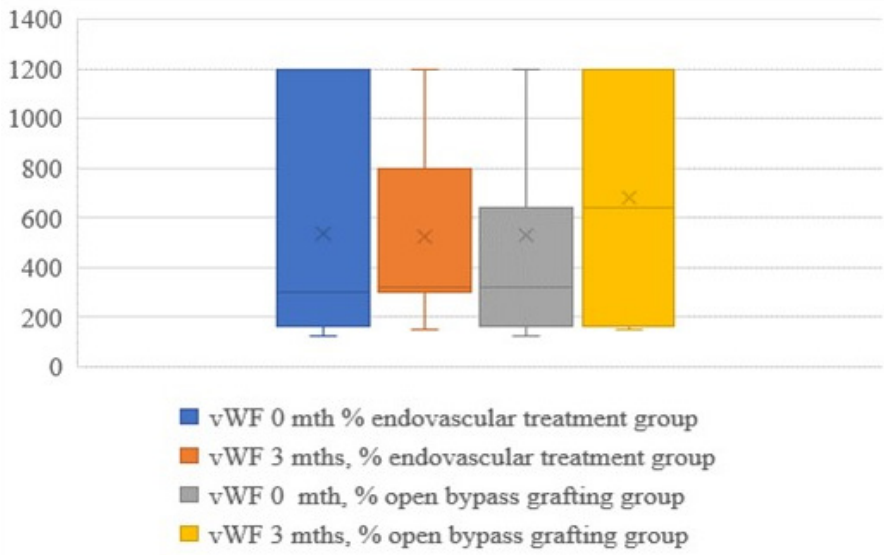

Fig. 2. von Willebrand factor activity before and after invasive treatment in the studied groups (n = 115).

Baseline activity of vWF in the endovascular treatment group who developed MI within 1 year after the procedure was four-fold higher than in those without MI [1200% and 300% (95% CI: 900–1200 vs. 160–800, respectively); p = 0.022]. Increased baseline vWF activity in the endovascular group was also detected in participants who died within 1 year compared with surviving participants [1200% and 300% (95% CI: 640–1200 vs. 160–600, respectively); p = 0.009].

vWF activity at 3 months in the open bypass grafting group was higher in subjects with iliofemoral lesions compared with those with femoropopliteal lesions [1200% and 600% (95% CI: 640–1200 vs. 160–1200, respectively); p = 0.045]. Although vWF activity decreased

after open surgery, it remained significantly higher than the normal values (70%–150%, Figure 2). vWF activity at 3 months in the open bypass grafting group correlated to the severity of the ischemia, with 160% (95% CI: 150–320) in stage IIb ischemia, 640% (95% CI: 300–1200) in stage III, and 770% (95% CI: 320–1200) in stage IV ischemia ($p < 0.05$).

ROC analysis was performed to build prognostic models of the relationship between the vWF antigen activity and development of unfavorable outcomes. Analysis of vWF activity and lethal outcomes in patients who underwent endovascular treatment showed an area under ROC curve equal to 0.827 ± 0.064 with a 95% CI of 0.701–0.952 (Figure 3).

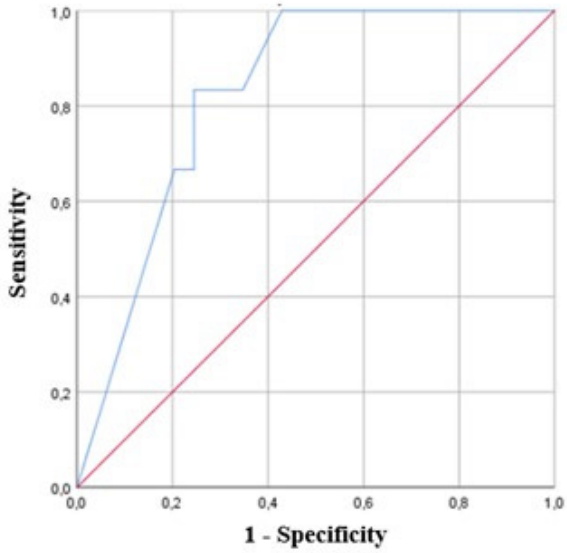

Fig. 3. ROC curve in the prognostic model of the relationship between the von Willebrand factor activity and development of lethal outcomes in endovascular treatment group.

The significance of the model was $p = 0.01$. vWF activity cutoff value was 620%. Therefore, lethal outcome was expected when vWF activity was ≥620%. The sensitivity and specificity of the method were 83.3% and 75.5%, respectively.

DISCUSSION

Thus, we found that the antigen activity of vWF increased in patients with PAD. The more severe atherosclerotic lesion and chronic ischemia, the higher the values of the studied parameters. Moreover, increased vWF activity was noted in patients in the endovascular treatment group who developed myocardial infarction or lethal outcomes within 1 year after invasive procedures.

Previous studies have mentioned an important role of vWF in patients with atherosclerosis. Nowakowski et al. (2019) described elevated vWF levels in patients with PAD. Although neither our study nor any previous ones could confirm vWF as a strong potential prognostic marker of restenosis, Nowakowski et al. showed that elevated vWF levels reflected the severity of endothelial dysfunction and may have influenced the development of restenosis [7].

Our results regarding increased vWF antigen activity in patients with PAD who developed MI and lethal outcomes after endovascular procedures agree with the results of previous studies that considered vWF a prognostic marker of major cardiovascular events, which, according to our study, is also fair for patients with PAD [8]. The prognostic role of vWF in the development of MI can be explained by its biological properties and effects, in which vWF promotes adhesion of platelets to the endothelium and protects coagulation factor VIII from protein C proteolysis, thereby defining both platelet and fibrin components of thrombosis. Therefore, vWF reflects the severity of PAD and plays an important role in the pathogenesis of ischemic heart disease, particularly myocardial infarction. vWF may become a potential therapeutical target influencing the treatment of patients with multifocal atherosclerosis [9-11].

CONCLUSIONS

1. von Willebrand factor antigen activity are increased in patients with PAD. The degree of their increase corresponded to the extent of atherosclerotic lesions of the lower extremity arteries and severity of chronic ischemia with maximum values detected in participants with multilevel lesions and stage IV lower limb ischemia.

2. High von Willebrand factor antigen activity in patients with PAD was associated with the development of myocardial infarction and lethal outcomes within 1 year after endovascular treatment performed on the lower extremity arteries.

ADDITIONAL INFORMATION

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