We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Promising Role of Vascular Endothelial Growth Factor-A in Risk Stratification after PCI

Olga V. Petyunina, Mykola P. Kopytsya, Iurii S. Rudyk and Ganna S. Isayeva

Abstract

Vascular endothelial growth factor-A (VEGF-A), dimeric glycoprotein, is a potent endothelial cell-specific mitogen which plays a key role in angiogenesis, especially in response to ischemia. Biomarkers reflect various pathophysiological faces of spherical LV transformation that related to myocardial stress due to persisted ischemia, fibrosis, and inflammation, and they may be helpful to improve risk stratification, more personalized medical approach for creating of individual medical care for HF preventing and adjusted treatment after STEMI. VEGF-A decrease ≤172.4 pg./ml on the 7th day of STEMI allows to prognose after infarction angina after 6-month observation (area under curve (AUC) 0.697, with sensitivity 88.9% and specificity 50.9%; 95% CI 0.567–0.807, P = 0.0515). Anxiety and depression 10–14 days before MI associated with VEGF-A level decrease (anxiety (Taylor): OR 0.834, 95% CI 0.726–0.959, P = 0.0107; depression (HADS): OR 0.741, 95% CI 0.535–1.027, P = 0.0519. Cut-off VEGF-A level ≤201.86 pg./ml on the 7th day of STEMI (AUC 0.711, sensitivity 85.7% and specificity 57.9%; 95% CI 0.513–0.908, P = 0.036) was effective for prognosis of dysadaptive left ventricular remodeling in STEMI patients after 6-month observation period. These findings may open new approach to stratify patients with successful coronary revascularization at risk of HF.

Keywords: vascular endothelial growth factor-A, STEMI, prognostication

1. Introduction

Vascular endothelial growth factor-A (VEGF-A) plays a key role in inducing angiogenesis. Angiogenesis is a multifunctional process of new vessels formation by gemmation or by cleavage of the already existing ones. There are the following successive stages of angiogenesis: (1) vasodilatation; (2) migration with adhesion and proliferation of endothelial cells; (3) formation of the vascular wall of a new three-layer vascular tube that develops as the circulation restores [1]. The VEGF was discovered in 1983 [2] as a factor raising vascular permeability, further evidence of a wider range of cytokine activity was obtained. There are 7 representatives of the VEGF family—VEGF-A, B, C, D, E, F, the growth factor of the placenta. The most common is VEGF-A, which is a homodimeric highly glycosylated protein with the molecular weight of 36–46 kDa. VEGF is registered in the heart, lungs, kidneys, adrenal glands, liver, spleen, stomach, and expression of the protein grows

under the pathology conditions. VEGF-A is represented by homodimeric isoforms consisting of 121, 145, 148, 165, 183, 189, 206 amino acid residues, among which the essential for the vascular system adequate development is VEGF-165 [3–6].

VEGF-A is produced by endothelial cells, smooth muscle vessels, macrophages, cardiac fibroblasts, lymphocytes, polymorphous nuclear cells, megakaryocytes, monocytes, platelets. Expression of VEGF-A depends on hypoxia, including hypoxia-induced factor, proangiogenic factors (HIF-1, EGF, PDGF, FGF, IL-1-beta), angiotensin II, endotoxin, high glucose level, IL-6, IL-8, IL-10, pH of the medium, oxygen concentration [4–6]. Its products are enhanced by aggregation of platelets, stretching of the left ventricle myocardium. VEGF is a proinflammatory cytokine, it inhibits the formation of dendritic cells, promotes the expression of monocytes, macrophages, leukocytes migration, stimulates adhesive molecules, and the activity of CD34 [7].

VEGF-A is a promoter of the collaterals formation in the ischemic myocardium, has a positive effect on revascularization through the following mechanisms: selective mitogenic effect on endothelial cells, stimulation of vascular endothelial cells expression, their proliferation, regeneration, vascular permeability increase, vasodilatation by activating NO synthase and prostacyclin, inhibition of apoptosis, matrix proteinase products. VEGF has antithrombotic properties due to the activation of serine proteases, urokinase, plasminogen activator, and the thrombolytic enzymes generation. However, VEGF induces the formation of the Willebrand factor and thrombogenesis [3, 4, 7].

In coronary artery disease (CAD), the double role of VEGF-A has been determined: under the conditions of acute or chronic myocardial ischemia, VEGF-A is a promoter of the coronary collaterals development, which promotes adequate blood circulation, oxygen saturation, cardiomyocyte loss prevention, heart remodeling improvement, and ultimately, a positive cardioprotective effect [8–11]. However, the negative component of the VEGF-A is its proatherogenic properties [12], which are implemented through the protein participation in the inflammatory infiltration of the atherosclerotic plaque, its neovascularization and destabilization. The VEGF expression promotes the process of monocytes migration with subsequent transformation into macrophages, the formation of foam cells and atherosclerotic tissues. The VEGF stimulates the matrix metalloprotease expression, which causes the extracellular matrix dissolution and the endothelium migration into a collagen gel with the endothelial tubes formation. The de novo formed vessels contribute to the plaque growth, its rupture, and destabilization of the clinical course in coronary artery disease [7, 13].

Information on changes in the VEGF-A level with stable CAD compared to the healthy group varied from its increase [14–16], to decrease [17] or lack of changes [18]. A number of studies have shown a direct correlation between the level of VEGF-A growth and the degree of damage to coronary vessels. Kucukardali et al. [16], examined the relationship in patients with proven CHD between the level of VEGF-A in blood plasma and the degree of coronary occlusion and the traditional risk factors. Groups with normal coronary angiogram (control), critical coronary injuries (with stenosis >70%) and non-critical changes (with stenosis of 40–70%) were selected. Logistic regression analysis showed that the VEGF-A level in patients with critical coronary sclerosis was significantly higher than in patients with normal coronary angiogram and non-critical stenosis. Higher levels of total cholesterol and LDL cholesterol in patients with critical stenosis were detected, VEGF-A negative correlation with hemoglobin and the positive correlation between VEGF-A and the age. No relationship was found between VEGF-A and other cardiac risk factors. The authors believe that the VEGF-A level growth in patients with coronary heart disease indicates critical coronary sclerosis [16]. Lin et al. [14], showed that the

VEGF-A level in patients with total coronary occlusion was higher than in patients with partial stenotic injuries, indicating the compensatory role of the VEGF-A in angiogenesis. Nakajama et al. [15], in patients with marked coronary atherosclerosis, detected increased levels of VEGF-A compared to moderate stenosis or its lack thereof. Alber et al. [18], however, did not find correlations between the concentration of VEGF-A in the blood plasma, the presence, severity and extent of coronary vessels injuries. The authors drew attention to the fact that in patients treated with statins, the level of VEGF-A was lower, this trend indicates the mechanisms of statins' antiangiogenic effect.

Ramos et al. [17], studied the dynamics of the VEGF-A level after PCI and its role as a predictor of major adverse cardiovascular events (MACE). Patients with ACS (STEMI, MI without ST segment elevation, unstable angina) and without ACS with stable angina pectoris were examined. The content of VEGF-A in the blood serum before PCI did not depend on the clinical form and was lower than that in the healthy group. The level of VEGF-A grew 1 month after revascularization and remained stable during 1 year of observation, reaching the control group's value. The results indicate the positive role of the VEGF-A level growth in the endothelium regeneration.

Angiogenesis and the coronary collaterals formation in AMI is of particular importance as an adaptation process in response to myocardial hypoxia. An increase in collateral circulation limits myocardial ischemia, prevents the spread of necrosis, improves the function of the myocardium [8]. The ability of VEGF-A to promote the development of collateral circulation has been demonstrated on the MI experimental models in animals. The use of VEGF for therapeutic angiogenesis in AMI in experimental animals was performed by intracardiac administration of VEGF-encoding genes, use of deproteinized isoforms of DNA (pVEGF 165), adenoviral vectors (Ad VEGF 121), etc. As a result, initially, in the perinecrotic zone, in remote areas, and then in the MI zone, there was an increase in the number of functioning capillaries, their bulk surface, anastomoses, activation of capillary collateral circulation [1, 9], improvement of cardiac micro vessels regeneration, cardiac function [10], fibrosis reduction and increasing of the myocardium contractile function [11], which ultimately reflects the cardioprotective effects of VEGF-A as a result of angiogenesis and endothelial cells proliferation.

In most clinical studies, an increase in the VEGF-A level in AMI compared to healthy persons, patients with stable or unstable angina [8, 19–24] was determined. At the same time, in works by Ramos et al. [17], the level of VEGF-A in patients with CAD was lower than in healthy persons, and its differences between clinical forms of coronary heart disease were not found.

The analysis of the factors influencing the VEGF level growth in AMI showed the following. The classic cardiovascular risk factors (gender, age, hypertension, overweight, diabetes mellitus, smoking, hypercholesterolemia) in patients with AMI did not correlate with the VEGF-A level [8, 17, 21, 25], although the VEGF-A level in patients with H, DM, high BMI, obesity, HF without MI were different from healthy ones.

Comparison of the VEGF-A level in patients with AMI with single- and multivascular coronary sclerosis revealed a lack of cytokine correlation with a heart attack-dependent coronary artery [8, 21, 26], simultaneously, Wojakovski et al. [24], determined higher values of VEGF-A in the blood serum in patients with MI with multi-vessel injuries compared to those with single-vessel ones. No relationship was found between the VEGF level and the heart attack localization [8]. Results of the connection between the VEGF and the size of the myocardial injury, which were determined by the level of CK, CK-MB cardiomarkers, were ambiguous. Kranz et al. [8], Shimokawahara et al. [21] did not find any connection between

VEGF-A and CK; Hojo et al. [20], Ogawa et al. [22], showed a positive correlation between VEGF-A and CK-MB and suggested an association between the prevalence of MI and the increase in the VEGF-A formation.

Several studies were devoted to the dynamics of VEGF-A in the acute phase of the MI and the subsequent post-infarction prognosis. The VEGF-A level in AMI after PCI peaked on the 7th–14th days [8, 20, 21, 27, 28] and returned to the norm for 6 months [28]. According to experimental data, administering of VEGF 124 before the coronary artery occlusion was accompanied by a pronounced activation of the angiogenesis process, collateral circulation in the perinecrotic zone and the distant regions of myocardium on the 7th day of the experiment [1]. It is possible to assume that a peak increase in the VEGF-A level for 7–10 days of AMI corresponds to the beginning of active angiogenesis. Mechanisms of VEGF-A endogenous expression activation in AMI are associated with response to hypoxia and acute myocardial ischemia and are implemented at the molecular level. A number of studies have provided additional information on the pathogenesis of VEGF-A expression enhancement in AMI. Thus, according to Hojo et al. [20], in patients with AMI, VEGF-A level was determined in the blood serum and in mononuclear cells of peripheral blood. Its blood serum levels peaked at the 14th day of AMI and correlated positively with the CK. There was a slight difference in the VEGF-A level in mononuclear cells: it was maximally elevated on the 7th day of AMI, did not correlate with CK, its reliably higher values were determined in patients with LVEF—≥40% compared to the VEGF group <40%. The authors believe that peripheral blood mononuclear cells are an important source of VEGF-A, and if they are mononuclear cells that infiltrate myocardium injured by infarction, VEGF-A, locally formed by mononuclear cells, promotes endothelial proliferation, the formation of microvessels, recovery of the damaged endothelium, healing of the infarcted myocardium, performing an important role in improving systolic function after MI [20].

Kranz et al. [8], observed a significant increase in the level of VEGF-A in the blood of AMI patients, which was maximally expressed on the 7th–10th days and reached the baseline value for 6 months, with unstable angina, the cytokine value did not reliably differ from the control. The absence of VEGF-A level differences in the blood serum and coronary sinus was detected unexpectedly, i.e. the infracted myocardium is not the main source of VEGF-A in the blood stream. The authors found a reliable growth in the number of platelets in the dynamics of MI. Platelets are an important source of VEGF-A, and the cytokine level growth in AMI can be explained by an increase in the number of platelets, and their aggregation enhancement, which leads to the secretion of growth factors from alpha granules.

Korybalska et al. [23], determined a significant increase in the level of VEGF-A in the blood serum of STEMI patients compared to healthy individuals. The number of platelets did not differ between patients with STEMI and healthy persons, however, in patients with STEMI, a direct reliable correlation between VEGF-A and platelets was found. The cytokine concentration increased immediately after retrosternal pain onset in patients with occlusive thrombi, which corresponded to the 3–4° by the TIMI scale. The authors believe that the VEGF-A level growth in patients with STEMI occurs not only due to ischemia and hypoxia of the myocardium, but can also be formed from activated platelets and characterize patients with increased intracoronary thrombosis [23].

Wojakovski et al. [24], studied the correlation between the levels of the VEGF, pro- and anti-inflammatory markers, traditional risk factors, the status of systolic function of the lungs, and the marker of inflammation—high sensitive CRP (hsCRP) in patients with AMI and stable angina. The authors found that the level of VEGF-A in patients with AMI was reliably higher than in those with stable angina, in AMI patients with a multi-vessel injury it was higher than in those with

mono-vascular injury, in group with EF <40% and Killip III–IV class in comparison with EF >40% and Killip I–II class, with a duration of pain syndrome >6 h compared to that of <6 h. Acute myocardial ischemia was associated with a reduction in the level of anti-inflammatory cytokine IL-10. Although the authors did not find correlation between VEGF-A and IL-10, they believe that changes of these cytokines concentration will help identify persons with high cardiovascular risk. The level of hsCRP, a marker, the importance of which was proven in inflammation, had a negative correlation with anti-inflammatory cytokine IL-10 and a positive one with VEGF-A, which indicates the VEGF-A participation in the immune response to AMI.

Eržen et al. [28], determined a reliable increase in the level of the VEGF in patients with MI, on average 20.5 months ago, compared to the control, a reliable positive correlation between the VEGF level and the pro-inflammatory IL-6 and IL-8 molecules, lack of correlation between VEGF and the atherosclerotic injury parameters, although dilatation of the right shoulder artery and the intima-media thickness of the common carotid artery in the examined patients were significantly weakened. The authors believe that the VEGF-A increase in the stable phase after the past MI is a part of inflammatory activity, since VEGF-A in these patients stimulates neovascularization, inflammation of the plaque and promotes its destabilization, its level increase may have a negative prognostic value.

An important component in raising the VEGF-A level, angiogenesis enhancing, cardiac blood flow, myocardial perfusion, oxygen transport, and the entry of energy substrates into cardiomyocytes is its effect on the structural and functional parameters of the myocardium, followed by adaptive or dysadaptive remodeling. Moreover, the VEGF-A expression and its receptors in cardiac fibroblasts and non-endothelial cells with properties of fibroblasts that perform tissue growth and regeneration assumes cytokine involvement in the process of myocardial remodeling in the ischemia and necrosis zones [29]. With experimental MI in rats, administration of VEGF-A-165 and VEGF-B-167 into the myocardium reduced myocardial fibrosis and improved its contractile function, viability, and remodeling of the left ventricle [11]. Administration of anti-P-selectin-conjugated liposomes containing the VEGF to experimental MI rats was accompanied by a 37% reduction in collagen deposition in the myocardium, a significant improvement in the pressure of the LV filling, with a significant improvement in the cardiac function 4 weeks after the MI: LV EDD reduction, growth of the fractional shortening, at the same time, the number of anatomical and perfused vessels increased [10, 30, 31]. Injection of the collagen-bound VEGF domain resulted in the infarction area reduction, improvement of the processes of LV remodeling within 3 months, and 12 months later, in the MI zone, mature vasculature and myocardium-like tissues were observed. Thus, the protection of cardiomyocytes from apoptosis and involvement of precursor cells in the infarction zone occurred [32].

The results of clinical studies on the correlation between VEGF-A and post-infarction remodeling are ambiguous. Thus, in the AMI patients, the indices of LV volumes, determined by ventriculography on the 14th day of AMI, were increased in the group with a high peak VEGF-A value compared to the low VEGF-A value group, the peak of the VEGF-A plasma level positively correlated with LV EDV and LV ESV. These differences were absent in the chronic phase of MI. The authors believe that endogenous VEGF-A plays an important role in the dilatation of LV in patients with AMI [21]. Soeki et al. [33], referred patients, in whom 3 months after the AMI an increase in the EDV-index was more than 5 ml/m^2, to the group with remodeling; the authors did not find changes in the VEGF level between patients with and without remodeling. However, patients with AMI and improvement of systolic function, compared to patients without such improvement, had higher VEGF-A levels in mononuclear cells of the peripheral blood; the authors believe that

VEGF-A, which is formed in mononuclear cells infiltrating the infarcted myocardium, plays an important role in angiogenesis, re-endothelialization, restoration of the LV systolic function after the AMI [20]. Devaux et al. [19], determined the LV remodeling according to the EDV dynamics in the period between the patient's hospitalization and 6 months after the MI; the first group consisted of patients with ΔEDV, which did not undergo significant changes or was decreasing; group 2 included patients whose ΔEDV was increasing. The level of VEGF-B was 69% higher in patients with $\Delta EDV \leq 0$ than in patients with $\Delta EDV > 0$. The authors believe that the low level of VEGF-B in blood with AMI is associated with a high risk of LV remodeling and is its predictor.

In accordance with the spectrum of the VEGF biological cardiovascular effects, a number of studies are devoted to the role of cytokine for the long-term prognosis in patients with MI. The contradictory results were obtained. Thus, Heeschen et al. [34], determined the level of VEGF-A in plasma of 1090 patients with ACS 8.7 h after the onset of the event. The frequency of major cardiovascular complications during the 6 months of observation was high in patients with the initially increased VEGF-A level. But other studies have obtained evidence that it is the decrease in the VEGF-A level which is an independent prognostic factor of recurrent cardiovascular events in other studies. Thus, Niu et al. [25], determined the VEGF-A level on the 7th day after MI, groups with low and high (less than or greater than 190 ng/ml) median VEGF-A levels. Repeated examinations were carried out every 2 months during the year; MACE, which included cardiovascular death, heart failure, severe arrhythmias, cardiogenic shock and post-infarction angina, were recorded. Within 6 months, the MACE frequency in the VEGF-A high-level group was significantly lower than in the low-cytokine group. Accordingly, the VEGF-A concentration in the group of patients without MACE was significantly higher than that in the MACE group.

Multivariant regression analysis showed that the decrease of the VEGF-A level is an independent MACE risk factor, its high value on the 7th day after AMI determines a positive long-term prognosis. Matsudaira et al. [27], examined 879 patients with AMI after successful PCI within the framework of a prospective, multicenter NAMIS study (Nagoya Acute Myocardial Infarction Study). According to VEGF-A level terciles, which was determined on the 7th day of AMI, 3 groups were formed, in which within 6 months of observation the major unfavorable cardiac and cerebral events were determined: cardiac death, repeated ACS, hospitalization for heart failure, strokes. Compared to the "medium" tercile, patients with the "low" tercile had a much higher risk of MACE. The authors believe that the low of VEGF-A level on the 7th day after AMI is associated with a significant increase in the MACE risk for 6 months.

Unlike the previous authors, Ramos et al. [17], determined that the level of VEGF-A in patients with AMI was lower than that of healthy individuals at admission, it was getting increased within 1 month term and remained steadily increased up to 1 year of observation. But in this study, it was shown that a decrease in the VEGF-A level < 40.8 pg./ml contributed to an increased risk of MACE for 5 years. The obtained results indicated the positive role of VEGF-A in the cardiovascular circulation restoration and confirmed its prognostic importance. In studies of Teplyakov et al. [35], the degree of ischemic genesis cardiac failure progression, most of the examined were postinfarction patients, there was a decrease in the VEGF-A level, and the initial low VEGF-A level characterized the unfavorable CHF course.

It is known that psychological stress is involved in the development and progression of cardiovascular disease. Thus, in an INTERHEART study performed in 52 world countries, anxiety and depression ranked third among the MI risk factors [36]. In Surtees et al. [37], within the 8.5 years period of observation, patients with a

"major" depression were by 2.7 times more likely to die from the coronary heart disease. Findings from this large prospective cohort study suggest that increased psychological distress is associated with elevated stroke risk. Episodic major depressive disorder was not associated with incident stroke in this study. Doering et al. [38], demonstrated that the presence of anxiety and depression was the predictor of the overall death-rate in patients with coronary artery disease. Versteeg et al. [39], showed that depression was independently associated with an increased risk of the overall death-rate for 5 years in patients with coronary artery disease. In the study by Beach et al. [40], the high level of depression by the Patient Health Questionaire-9 (PHQ-9) was reliably associated with re-hospitalization after 6 months in patients with acute coronary syndrome, heart failure, or arrhythmia.

Mechanisms to be associated with anxiety-depressive disorders (ADD) and cardiovascular diseases are complex and take into account both behavioral and physiological factors: smoking, lifestyle underactivity, obesity, as well as increased platelet aggregation, arterial pressure, reduced insulin sensitivity and disordered endothelial function [41, 42].

In recent years, the evidence base for participation of VEGF-A in the cerebrovascular disease pathogenesis, including ADD, is growing. VEGF-A is known to be involved in such processes in the central nervous system as the ontogenetic development of the nervous system, which includes the processes of migration, differentiation, synaptogenesis, myelination, neuroprotection, stimulation of neurogenesis in adulthood, post-ischemic restoration of cerebral and vessel tissues, stimulation of memory formation mechanisms. VEGF-A participates in all phases of neuro-and angiogenesis: formation of blood vessels de-novo from mesenchymal stem cells, formation of new capillaries, expansion of arteriolar anastomoses, and also demonstrates direct neurotrophic and neuroprotective properties. Thus, the role of VEGF in the pathogenesis of cerebrovascular pathology, including anxiety-depressive disorders, is to combine angiotropic and neurotropic activity [43].

An increase in the VEGF-A level in patients with major depression was observed [44–48]; the correlation between depression and VEGF-A is confirmed by the fact that cytokine stimulates neurogenesis caused by antidepressants [49, 50]. In patients with coronary heart disease, higher levels of VEGF-A, CRP, IL-6 gene expression and cortisol level reduction were detected, indicating an increase in immune-mediated activity [51].

It should be noted that in these works, patients with major depression were somatically healthy, or patients with coronary artery disease were with a stable course. However, in acute experimental ischemia, psychological stress was associated with a decrease in the VEGF-A and its signaling molecules (P44/P42, MAPK, Akt) expression, violation of neurovascularization at the macro- and microvascular levels, which the authors associate with the oxidative stress activation in the ischemic tissue [52].

The aim of our research was investigation of association between VEGF-A level in STEMI patients with TIMI III and development of repeated coronary events and adverse remodeling within 6-month follow-up and determination of the factors influencing this relationship.

2. Material and methods

2.1 Patients

Sixty-two patients with STEMI, 51 (82.3%) male and 11 (17.7%) female, at the average age (58.63 ± 8.90) years with acute STEMI during 2–12 h of symptoms onset

in a given period between 2016 and 2017. STEMI was diagnosed according to ECS Guidelines [53]. Inclusion criteria were: confirmed STEMI, age >18 years old, and lack of contraindication to PCI. Non-inclusion criteria were previous myocardial infarction, established chronic HFrEF, HFmrEF and HFpEF, known malignancy, severe comorbidities (anemia, chronic obstructive lung disease, bronchial asthma, liver cirrhosis, chronic kidney disease, valvular heart disease, bleeding), inability to understand of written informed consent. Control group consisted of 20 persons comparable of age and sex. Patients were hospitalized to the Department of prevention and treatment of emergency conditions of Government institution "L.T. Malaya Therapy National Institute of the National Academy of medical science of Ukraine" after selective coronaroangiography (SCAG) with stenting of infarct-related artery, were performed in the Institute of general and emergency surgery n.a. V.T. Zaitsev. Repeated observation performed after 6 month.

Research was performed due to Helsinki Declaration, the protocol was approved by local ethics committee of GI "National Institute of therapy n.a. L.T.Malaya NAMS Ukraine" (protocol No. 8, 29.08.2016). Informed consent was obtained from each patient.

Conventional coronary angiography was performed using Digital X-Ray system "Integris Allura" (Philips Healthcare, Best, The Netherlands) and managed by radial or femoral vascular access. Coronary arteries were visualized with two-to-three orthogonal projections. In this study the contrast "Ultravist-370" (Baier Pharma GmbH, Germany) and automatic contrast injector were used. Primary PCI with bare-metal stent (COMMANDER, "Alvimedica", Turkey) implantation was performed in 36 patients and 26 patients were previously treated with primary thrombolysis (tenecteplase, alteplase) before admission with followed PCI during 6–12 h after initial STEMI confirmation. Thrombolytic therapy performed by tenecteplase, which dosing was calculated depending on patients weight and was no more than 50 mg or alteplase, or tenecteplase—100 mg. All the patients intook medical therapy in accordance to existing recommendations.

Repeated coronary events (after infarction angina) during 6-month observation period were estimated and diagnosed in 9 (14.5%) patients. Left ventricular remodeling as an end point in 6 months after STEMI were assessed too: adverse remodeling was in 29 patients, adaptive—in 33.

2.2 Methods

SYNTAX score (SS) was used to assess the severity of coronary atherosclerotic lesions and was calculated for all PCI-patients by experienced interventional cardiologist. SS was determined for all coronary lesions >50% diameter stenosis in a vessel >1.5 mm based on SS calculator (www.syntaxscore.com). All the patients were divided by the SS level on 3 subgroups—high SS > 32–2 patients, average SS $22 < n \leq 32$–17, low SS ≤ 22–32.

Echo-CG was performed on "Aplio 500 TUS-A500", Toshiba, with usage of sensor with ultrasound frequency of 3.5 MHz during first 24 h from hospitalization. Left ventricular end diastolic volume (LV EDV), left ventricular end systolic volume (LV ESV), left ventricular end diastolic and end systolic diameters (LV EDD, LV ESD), left ventricular myocardial mass (LVMM), left ventricular ejection fraction (LVEF), diastolic dysfunction—maximal rate of early diastolic filling E (m/s), maximal rate of left atrium diastolic rate A (m/s), their ratio—E/A were estimated. Repeated observation was done after 6-month period. VEGF-A level was assessed on the 7th day of STEMI. Late adverse cardiac remodeling was defined as increased LVEDV (>10% from baseline) and/or LVESV (>10% from baseline) for 6 months after acute STEMI managed by PCI.

Hypercholesterolemia (HCE) was diagnosed if total cholesterol (TC) level was above 5.2 mmol/l, and/or low density lipoprotein cholesterol (LDL) level was above 3.0 mmol/l, and/or level of triglycerides (TG) was above 1.7 mmol/l according to with European Cardiology Society dyslipidemia guideline, 2016. Hypertension was diagnosed if systolic blood pressure (SBP) was >140 mm Hg, and/or diastolic blood pressure (DBP) >90 mm Hg according to European guideline on diagnostics and treatment of arterial hypertension, 2018. Type 2 diabetes mellitus determined according to new ADA statement [54].

The level of anxiety during 10–14 days before STEMI estimated due to Taylor questionnaire. High level of anxiety was consistent with less or equal 14 balls, high level—more than 14 balls. Together with Taylor questionnaire, Heart Anxiety and Depression Scale (HADS) was used to diagnose anxiety and depression: 0–7 balls—low level, 8–10—borderline, 11–21—high.

Troponin I (Tn I) level measuring performed with chemo luminescent immunoassay (Humalyzer 2000, Mannheim, Germany). The TnI level average was 0.5–50 ng/ml. Total creatine kinase (CK) and CK MB-fraction (CK-MB) were analyzed using immunoinhibition method on quantitative immunoassay analyzer Humalyzer 2000 (Mannheim, Germany) according to the manufacturers' recommendations. Total cholesterol (TC), low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides (TG) were measured direct enzymatic method (Roche P800 analyzer, Basel, Switzerland). The intra-assay and inter-assay coefficients of variation were <5%. Fasting glucose level was measured by a double-antibody sandwich immunoassay (Elecsys 1010 analyzer, F. Hoffmann-La Roche Diagnostics, Mannheim, Germany). The intra-assay and inter-assay coefficients of variation were <5%.

Blood research were done at baseline. VEGF-A level determined by enzyme-linked immunosorbent assay with reactives of IBL INTERNATIONAL GMBH, Germany (standard concentrations diapason 0.0–1000 pg./ml, serum control: low—100–200, high—600–1200 pg./ml) in the laboratory of immune-chemical and molecular-genetic researches of GI "National Institute of therapy n.a. L.T. Malaya NAMS Ukraine". Serum VEGF-A level measured in the 7th day of STEMI: in the main group it was equal 160.33 [83.82–299.62] pg./ml, in the control group—112.30 [75.45–164.65] pg./ml (P = 0.05).

2.3 Statistical analyses

Statistical data processing was performed with programs Statistica 8.0 (Stat Soft Inc., USA), median (Me) with upper (UQ) and low quartiles (LQ). Continuous variables are presented as mean ± standard deviation when normally distributed, or median and interquartile range if otherwise. Mann-Whitney U-criterion and Wald-Wolfowitz χ^2- criterion were used for intergroup differences. For all types of analysis, all differences were considered statistically significant with $P < 0.05$. Univariate and multivariate logistic statistical analyses were used. The group with repeated coronary events pointed as 1, without events—0, cut-off point with VEGF-A were found.

3. Results

The first group with repeated coronary events (after infarction angina) represented 9 patients (14.5%), the second group consisted from 53 patients without angina to 6 months after STEMI. Cardiovascular risk factors [sex, age, H, DM, HCE, complicated heredity, anxiety-depressive disorders (ADD)] showed the

absence of reliable differences between patients of group 1 and 2. VEGF-A level was significantly less in patients from group 1:83.82 [49.14–162.26] pg./ml versus 194.10 [102.54–327.30] pg./ml accordantly, P = 0.049.

ROC-analysis was performed to find VEGF-A level which prognoses repeated coronary events after 6-month observation after STEMI. Cut-off VEGF-A level ≤ 172.4 pg./ml on the 7th day of index event (area under curve (AUC) 0.697, with sensitivity 88.9% and specificity 50.9%; 95% CI 0.567–0.807, P = 0.0515) was effective for differentiation STEMI patients from those without and with unfavorable prognosis of repeated coronary event—after infarction angina (**Figure 1**).

To identify factors influenced on VEGF-A level, univariate and multivariate logistic analysis were performed. In patients with STEMI was revealed association between anxiety and depression levels increase and VEGF-A level decrease (anxiety (Taylor): OR 0.834, 95% CI 0.726–0.959, P = 0.0107; depression (HADS): OR 0.741, 95% CI 0.535–1.027, P = 0.0519.

ROC-analysis for prognostication of dysadaptive left ventricular remodeling was used. Cut-off VEGF-A level ≤ 201.86 pg./ml on the 7th day of STEMI (area under curve (AUC) 0.711, with sensitivity 85.7% and specificity 57.9%; 95% CI 0.513–0.908, P = 0.036) was effective for unfavorable prognosis of dysadaptive left ventricular remodeling of STEMI patients after 6-month observation period (**Figure 2**).

As a result of our research, we revealed than anxiety and depression 10–14 days before MI associated with VEGF-A level decrease (anxiety (Taylor): OR 0.834, 95% CI 0.726–0.959, P = 0.0107; depression (HADS): OR 0.741, 95% CI 0.535–1.027, P = 0.0519. VEGF-A decrease ≤172.4 pg./ml on the 7th day of STEMI allows to prognose

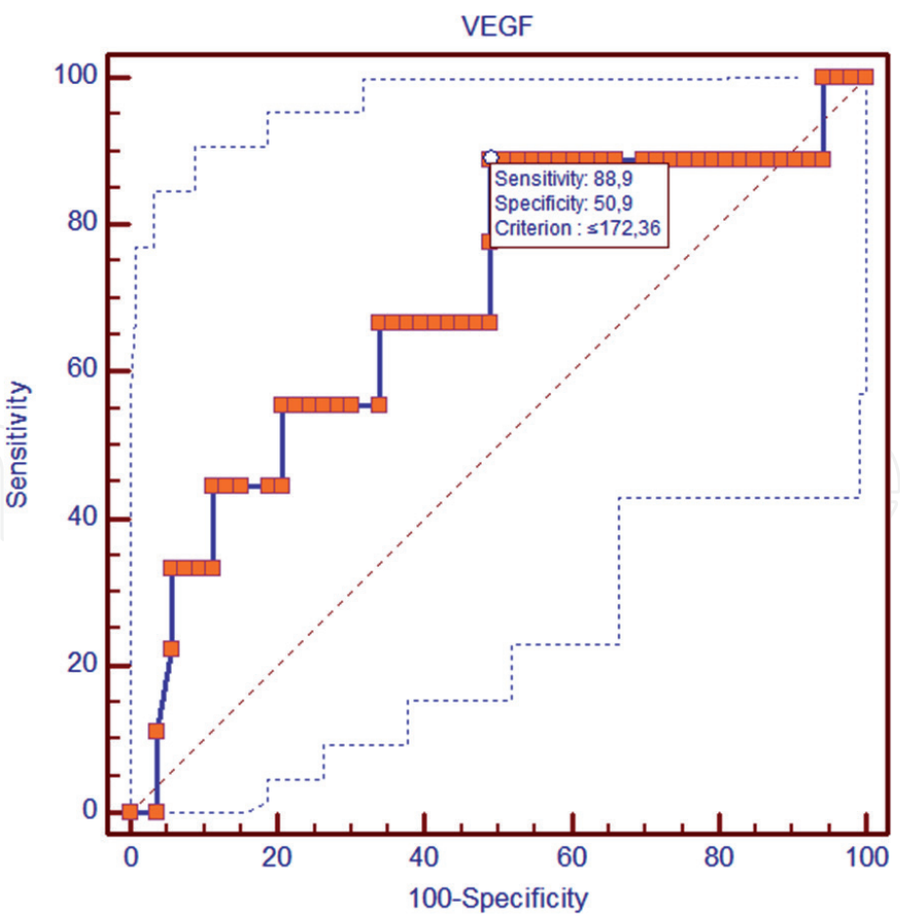


Figure 1.
Cut-off VEGF-A level ≤ 172.4 pg./ml on the 7th day of STEMI (area under curve (AUC) 0.697, with sensitivity 88.9% and specificity 50.9%; 95% CI 0.567–0.807, P = 0.0515) was effective for differentiation STEMI patients from those without and with unfavorable prognosis of repeated coronary event (after infarction angina after 6-month observation).

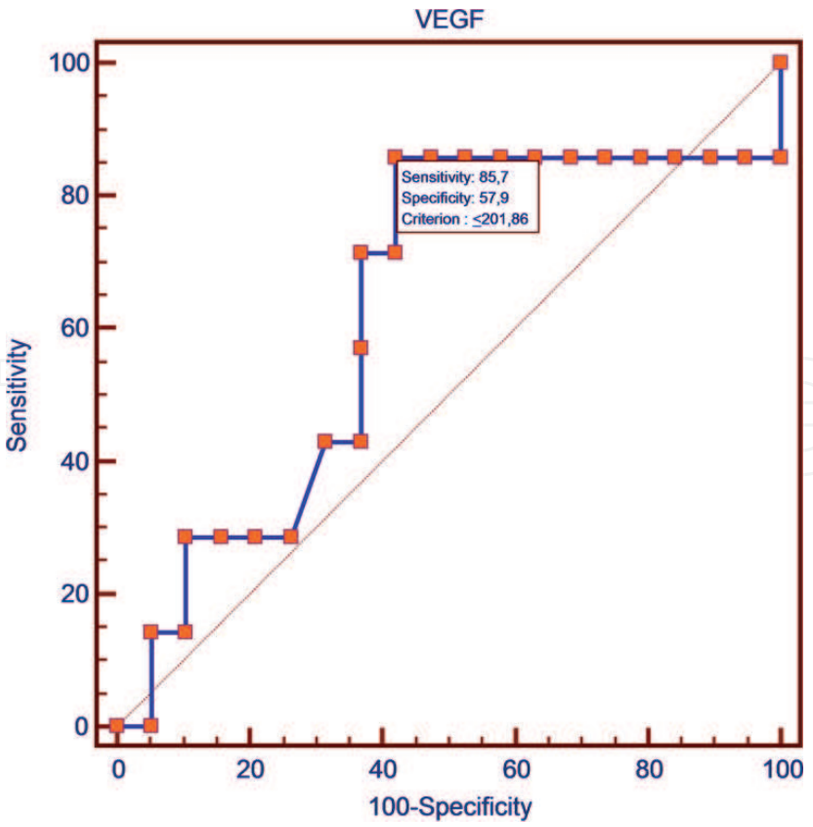


Figure 2.
Cut-off VEGF-A level ≤ 201.86 pg./ml on the 7th day of STEMI (area under curve (AUC) 0.711, with sensitivity 85.7% and specificity 57.9%; 95% CI 0.513–0.908, P = 0.036) was effective for unfavorable prognosis of dysadaptive left ventricular remodeling in STEMI patients after 6-month observation period.

repeated coronary events (after infarction angina) after 6-month observation with sensitivity of 88.9% and specificity 50.9%. Cut-off VEGF-A level ≤ 201.86 pg./ml on the 7th day of STEMI (area under curve (AUC) 0.711, with sensitivity 85.7% and specificity 57.9%; 95% CI 0.513–0.908, P = 0.036) was effective for prognosis of dysadaptive left ventricular remodeling in STEMI patients after 6-month observation period.

4. Conclusion

We have shown that the levels of VEGF-A measured in acute STEMI patients managed by PCI could predict late adverse LV remodeling and after infarction angina. These findings may open new approach to stratify patients with successful coronary revascularization at risk of HF.

Acknowledgements

There are no previous presentations of the information reported in the article. We thank Nataliia Tytarenko and Igor Polivenok for performing ultrasound examination and cardiac interventions respectively. Additionally, we thank, Galina Bugrimenko for her excellent technical assistance. Permission to acknowledge has been obtained.

Conflict of interest

There are no conflicts of interest.

Author contribution

Conception and design: Olga V. Petyunina; writing of the article Olga V. Petyunina, critical revision of the article for intellectual content Mykola P. Kopytsya, Iurii S. Rudyk, Ganna S. Isayeva.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Limitation of the study

This was a retrospective observational study and the number of patients was relatively small. A randomized controlled study based on a greater number of patients with a longer observational period is needed to confirm our results.

Founding

The study is a fragment of the research project: "To study the biochemical, genetic mechanisms of reperfusion damage of the myocardium and to assess the cardioprotective effect of antiplatelet therapy in acute myocardial infarction", State Registration No. 0117 U003028.

Author details

Olga V. Petyunina*, Mykola P. Kopytsya, Iurii S. Rudyk and Ganna S. Isayeva
Government Institution "L.T. Malaya Therapy National Institute of NAMS of Ukraine", Kharkiv, Ukraine

*Address all correspondence to: o_petyunina@ukr.net

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Sisakyan AS, Oganyan VA, Semerdzhyan AB, Petrosyan MV, Sisakyan SA, Gurevich MA. Vliyanie faktora angiogeneza na morfofunkcionalnoe sostoyanie miokarda u krys pri eksperimentalnom infarkte miokarda. Rossijskij kardiologicheskij zhurnal—Russian Cardiology journal. 2008;**2**:63-66 (in russ)

[2] Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. Endocrine Reviews. 1997;**18**:527-543

[3] Hoeben A, Landuyt B, Highley MS, et al. Vascular endothelial growth factor and angiogenesis. Pharmacological Reviews. 2004;**56**(4):549-580. DOI: 10.1124/pr.56.4.3

[4] Ferrara N. Binding to the extracellular matrix and proteolytic processing. Two key mechanisms regulating vascular endothelial growth factor action. Molecular Biology of the Cell. 2010;**21**(5):687-690. DOI: 10.1091/mbc.E09-07-0590

[5] Ferrara N. Vascular endothelial growth factor. Arteriosclerosis, Thrombosis, and Vascular Biology. 2009;**29**(6):789-791. DOI: 10.1161/ATVBAHA.108.179663

[6] Starostin IV, Talitskiy KA, Bulkina OS, Parfenova EV. Karpov YuA collateral blood flow in the myocardium: The role of endothelial growth factor. Kardiologiia—Cardiology. 2012;**11**:49-55 (in russ)

[7] Berezin AE. Predicitive role of circulating vascular endothelial growth factor-1 in patients with cardiovascular diseases. Journal of Disease Markers. 2014;**1**(3) id1013

[8] Kranz A, Rau C, Kochs M, et al. Elevation of vascular endothelial growth factor-A serum levels following acute myocardial infarction. Evidence for its origin and functional significance. Journal of Molecular and Cellular Cardiology. 2000;**32**(1):65-72. DOI: 10.1006/jmcc.1999.1062

[9] Sant'Anna RT, Kalil RAT, Moreno P, Anflor LCJ, Correa DLC, Ludwig R, et al. Gene therapy with VEGF 165 for angiogenesis in experimental acute myocardial infarction. Brazilian Journal of Cardiovascular Surgery. 2003. Print version ISSN 0102-7638; On-line version ISSN 1678-9741. DOI: 10.1590/S0102-76382003000200006

[10] Wang B, Cheheltani R, Rosano J, Crabbe DL, Kiani MF. Targeted delivery of VEGF to treat myocardial infarction. Advances in Experimental Medicine and Biology. 2013;**765**:307-314. DOI: 10.1007/978-1-4614-4989-8_43

[11] Zentilin L, Puligadda U, Lionetti V, Zacchigna S, Collesi C, et al. Cardiomyocyte VEGFR-1 activation by VEGF-B induces compensatory hypertrophy and preserves cardiac function after myocardial infarction. The FASEB Journal. 2010;**24**(5):1467-1478. DOI: 10.1096/fj.09-143180 (Epub Dec 17, 2009)

[12] Kimura K, Hashiguchi T, Deguchi T, et al. Serum VEGF—As a prognostic factor of atherosclerosis. Atherosclerosis. 2007;**194**(1):182-188. DOI: 10.1016/j.atherosclerosis.2006.07.025

[13] Moreno P, Purushothaman KR, Fuster V, Echeverri D, Truszczynska E, et al. Plaque neovascularization is increased in ruptured atherosclerotic lesions of human aorta. Circulation. 2004;**110**(14):2032-2038. DOI: 10.1161/01.CIR.0000143233.87854.23 (Epub Sep 2, 2004)

[14] Lin TH, Yen HW, Su HM, Chien WT, Lu YH, Voon WC, et al. Effects

of total coronary artery occlusion on vascular endothieial growth factor and transforming growth factor beta. The Kaohsiung Journal of Medical Sciences. 2005;**21**(10):460-465

[15] Nakajama K, Tabata S, Yamashita T, et al. Plasma vascular endothelial growth factor level is elevated in patients with multivessel coronary artery disease. Clinical Cardiology. 2004;**27**(5):281-286

[16] Kucukardali Y, Aydogly S, Ozmen N, Yonem A, Solmazgul E, Ozyurt M, et al. The relationship between severity of coronary artery disease and plasma level of vascular endothelial growth factor. Cardiovascular Revascularization Medicine. 2008;**9**:66-70. DOI: 10.1016/j.carrev.2007.11.005

[17] Ramos K, Napoleao P, Selas M, et al. Prognostic Value of VEGF in Patients Submitted to Percutaneous Coronary Intervention. Disease Markers. Hindawi Pub Corp; 2014;**2014**:7. Article ID: 135357. https://doi.org/10.1155/2014/135357

[18] Alber HF, Frick M, Dulak J, et al. Vascular endothelial growth factor (VEGF) plasma concentrations in coronary artery disease. Heart. 2005;**91**(3):365-366. DOI: 10.1136/hrt.2003.021311

[19] Devaux Y, Vausort M, Azuaje F, et al. Low levels of vascular endothelial growth factor B predict left ventricular remodeling after acute myocardial infarction. Journal of Cardiac Failure. 2012;**18**(4):330-337. DOI: 10.1016/j.cardfail.2012.01.010

[20] Hojo Y, Ikeda U, Zhu Y, et al. Expression of vascular endothelial growth factor in patients with acute myocardial infarction. Journal of the American College of Cardiology. 2000;**35**(4):968-973

[21] Shimokawahara H, Jougasaki M, Setoguchi M, et al. Relationsheep between vascular endothelial growth factor and left ventricular dimension in patients with acute myocardial infarction. Journal of Cardiology. 2014;**64**(5):360-365. DOI: 10.1016/j.jjcc.2014.02.017

[22] Ogawa H, Suefuji H, Soejma H, et al. Increased blood vascular endothelial growth factor levels in patients with acute myocardial infarction. Cardiology. 2000;**93**(1-2):93-99. DOI: 7008

[23] Korybalska K, Pyda M, Kawka E, et al. Interpretation of elevated serum VEGF concentration in patients with myocardial infarction. Cytokine. 2011;**54**(1):74-78. DOI: 10.1016/j.ijcard.2012.05.103

[24] Wojakovski W, Maslankiewicz K, Ochala A, et al. The pro- and anti-inflammatory markers in patients with acute myocardial infarction and chronic stable angina. International Journal of Molecular Medicine. 2004;**14**(2):317-322. DOI: 10.3892/ijmm.14.2.317

[25] Niu J, Han X, Qi H, et al. Correlation between vascular endothelial growth factor and long-term prognosis in patients with acute myocardial infarction. Experimental and Therapeutic Medicine. 2016;**12**(1):475-479. DOI: 10.3892/etm.2016.3286

[26] Chung NA, Lydakis C, Belgore F, Li-Saw-Hee FL, Blann AD, Lip GY. Angiogenesis, thrombogenesis, endothelial dysfunction and angiographic severity of coronary artery disease. Heart. 2003;**89**(12):1411-1415

[27] Matsudaira K, Maeda K, Okumura N, et al. Impact of low levels of vascular endothelial growth factor after myocardial infarction on 6-month outcome. Resuls from Nagoya Acute Myocardial Infarction Study. Circulation Journal. 2012;**76**:1509-1516. DOI: 10.1253/circj.CJ-11-1127

[28] Eržen B, Šilar M, Šabovic M. Stable phase post-MI patients

have elevated VEGF levels correlated with inflammation markers, but not with atherosclerotic burden. BMS Cardiovascular Disorders. 2014;**14**:166. DOI: 10.1186/1471-2261-14-166

[29] Chintalgattu V, Nair DM, Katwa LC. Cardiac myofibroblasts: A novel source of vascular endothelial growth factor (VEGF) and its receptors Flt-1 and KDR. Journal of Molecular and Cellular Cardiology. 2003;**35**(3):277-286

[30] Rosano JM, Cheheltani R, Wang B, et al. Targeted delivery of VEGF after a myocardial infarction reduces collagen deposition and improves cardiac feunction. Cardiovascular Engineering and Technology. 2012;**3**(2):237-247. DOI: 10.1007/s13239-012-0089-3

[31] Chelentani R, Rosano JM, Wang B, Kiani MF. Targeted VEGF therapy favorably alters collagen deposition and guality after myocardial infarction. The FASEB Journal. 2010;**24**(1). (Published online Apr 1, 2010) – abstract

[32] Shi C, Zhao Y, Yang Y, Chen C, Hou X, Shao J, et al. Collagen-binding VEGF targeting the cardiac extracellular matrix promotes recovery in porcine chronic myocardial infarction. Biomaterials Science. 2018;**6**(2):356-363. DOI: 10.1039/c7bm00891k

[33] Soeki T, Tamura Y, Shinohara H, Sakabe K, Onose Y, Fukuda N. Serum hepatocyte growth factor predicts ventricular remodeling following myocardial infarction. Circulation Journal. 2002;**66**:1003-1007

[34] Heeschen C, Dimmeler S, Hamm CW, et al. Prognostic significance of angiogenic growth factor serum levels in patients with acute coronary syndromes. Circulation. 2003;**107**(4):524-530. DOI: 10.1161/01/CIR/0000048183.37648.1A

[35] Teplyakov AT, Berezikova EN, Shilov SN, Grakova EV, Torim YY, Efremova AV. i soavt. Patogeneticheskaya i prognosticheskaya znachimost rostovyh faktorov v razvitii hronicheskoj serdechnoj nedostatochnosti. Kardiologiya—Cardiology. 2017;**57**(10):20-28. DOI: 10.18087/cardio.2017.10.10039 (in russ)

[36] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-conrol study. Lancet. 2004;**364**(9438):937-952. DOI: 10.1016/S0140-6736(04)17018-9

[37] Surtees PG, Wainwright NWJ, Luben RN, Wareham NJ, Bingham SA, Khaw K-T. Psychological distress, major depressive disorder, and risk of stroke. Neurology. Mar 2008;**70**(10):788-794. DOI: 10.1212/01.wnl.0000304109.18563.81

[38] Doering LV, Moser DK, Riegel B, et al. Persistent comorbid symptoms of depression and anxiety predict mortality in heart disease. International Journal of Cardiology. 2010;**145**(2):188-192. DOI: 10.1016/j.ijcard.2009.05.025

[39] Versteeg H, Hoogwegt MT, Hansen TB, et al. Depression, not anxiety, is independently associated with 5-year hospitalization and mortality in patients with ischemic heart disease. Journal of Psychosomatic Research. 2013;**75**(6):409-413. DOI: 10.1016/j.jpsychores.2013.10.005

[40] Beach SR, Januzzi JL, Mastromauro CA, Healy BC, Beale EE, Celano CM, Huffman JC. Patient Health Questionnaire-9 score and adverse cardiac outcomes in patients hospitalized for acute cardiac disease. Journal of Psychosomatic Research. 2013 Nov;**75**(5):409-413. DOI: 10.1016/j.jpsychores.2013.08.001. [Epub 2013 Aug 13]

[41] Sotelo JL, Nemeroff CB. Depression as a systemic disease. Personalozed Medicine in Psychiatry. 2017;**1-2**:11-25. DOI: 10.1016/j.pmip.2016.11.002

[42] Stepoe A, Kivimaki M. Stress and cardiovascular disease. Nature Reviews Cardiology. 2012;**9**(6):360-370. DOI: 10.1038/nrcardio.2012.45

[43] Roslavtseva VV, Salmina AB, Prokopenko SV, et al. The role of vascular endothelial growth factor in the regulation of development and functioning of the brain: New target molecules for pharmacotherapy. Biomedicinskaia Chimiia. 2016;**62**(2):124-133. DOI: 10.1809/PBMC20166202124

[44] Elfving B, Buttenschen HN, Foldager L, et al. Depression and BMI influences the serum vascular endothelial growth factor level. International Journal of Neuropsychopharmacology. 2014;**17**(9):1409-1417. DOI: 10.1017/S1461145714000273

[45] Lee BH, Kim YK. Increased plasma VEGF levels in major depressive or manic episodes inpatients with mood disorders. Journal of Affective Disorders. 2012;**136**:181-184. DOI: 10.1016/j.jad.2011.07.021

[46] Kahl KG, Bens S, Ziegler K, et al. Angiogenic factors in patients with current major depressive disorder comorbid with borderline personality disorder. Psychoendocrinology. 2009;**34**(3):353-357. DOI: 10.1016/j.psyneuen.2008.09.016

[47] Takebayashi M, Hashimoto R, Hisaoka K, et al. Plasma levels of vascular endothelial growth factor and fibroblast growth factor 2 in patients with major depressive disorders. Journal of Neural Transmission. 2010;**117**(9):1119-1122. DOI: 10.1007/s00702-010-0452-1

[48] Wallenstein J, Asberg M, Nygen A, et al. Possible biomarkers of chronic stress induced exhaustion—A longitudinal study. PLoS One. 2016;**11**(5):e0153924. DOI: 10.1371/journal.pone.0153924

[49] Segi-Nishida E, Wamer-Schmidt JL, Duman RS. et al, Electroconvulsive seizure and VEGF increase the proliferation of neural stem-like cells in rat hippocampus. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(32):11352-11357. DOI: 10.1073/pnas.07108581105

[50] Warner-Schmidt JL. Dumah RS VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proceedings of the National Academy of Sciences of the United States of America. 2007;**104**(11):4647-4652. DOI: 10.1073/pnas.0610282104

[51] Nikkheslat N, Zunszain PA, Horowitz MA, et al. Insufficient glucocorticoid signaling and elevated inflammation in coronary artery disease patients with comorbid depression. Brain, Behavior, and Immunity. 2015;**48**:8-18. DOI: 10.1016/j.bbi.2015.02.002

[52] Maingrette F, Dussault S, Dhahri W, et al. Psychological stress impairs ischemia-induced neovascularization: Protective effect of fluoxetine. Atherosclerosis. 2015;**241**(2):569-578. DOI: 10.1016/j.atherosclerosis.2016.06.010

[53] Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal. 2018;**39**(2):119-177

[54] Standards of medical care in diabetes 2017: Summary of revisions. Diabetes Care. 2017;**40**:S4-S5