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Concentration of vascular endothelial growth factor in patients with acute coronary syndrome

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ABSTRACT

Vascular endothelial growth factor (VEGF) is a regulator of vascular formation in physiological and pathological conditions. The aim of our study was to evaluate the value of VEGF as a surrogate marker of myocardial injury in acute ischemic conditions.

Materials and methods: In 104 consecutive patients with acute coronary syndrome (ACS) with and without ST segment elevation (STEMI and NSTEMI) the plasma and serum human VEGF (hVEGF) concentration was measured two times i.e. immediately after admission due to ACS and 24 h later. According to ECG findings and coronary angiography results, patients were divided into three groups. Group A represented major myocardial injury due to ST-segment elevation in precordial leads and/or in I and aVL leads and with left anterior descending (LAD) artery responsible for STEMI symptoms or additionally with significant atherosclerotic lesions (lumen vessel narrowed >50%) in other than LAD coronary arteries. Group B (medium myocardial injury) consisted of patients with ST-segment elevation in II, III and aVF leads and/or ST-segment depression in V2-V3 leads with one-vessel disease and the culprit artery was not LAD. Group C included patients with changes in ECG other than ST-segment elevation independently of the site of atherosclerotic lesions in coronary arteries.

Results: In all 104 patients with ACS the highest values of serum hVEGF were observed in second measurement (357.9 ± 346 pg/ml, $p < 0.01$). Although in the first measurement, plasma and serum hVEGF concentration did not differentiate groups, the difference between deltas for serum hVEGF was observed ($p < 0.05$). Increased number of neutrophils in the first measurement increased the OR of the high serum hVEGF concentration in the first measurement (OR = 1.155; 95%CI: 1.011; 1.32) ($p < 0.05$). The number of neutrophils in the second measurement also revealed significant relationship with high serum hVEGF in the first assessment (OR = 1.318, 95%CI: 1.097; 1.583) ($p < 0.01$). Increased values of triglycerides (exceeding the upper limit) were connected with decreased OR of high serum hVEGF concentrations in the first measurement (OR = 0.152, 95%CI: 0.033; 0.695, $p < 0.05$).

Conclusions: In acute coronary syndrome, serum VEGF concentrations are elevated and can serve as a surrogate marker of myocardial injury. The elevated number of neutrophils increases odds ratio of high VEGF concentrations in ACS. In patients with high concentrations of triglycerides, odds ratio of low level of hVEGF is expected.

1. Introduction

Vascular endothelial growth factor (VEGF) is a cytokine which plays a crucial role as a regulator of vascular formation in physiological and pathological conditions including embryogenesis, wound healing, tumor growth, ocular neovascular diseases, chronic inflammatory diseases and myocardial ischemia [1–8]. VEGF also regulates multiple endothelial cell functions including mitogenesis, permeability, vascular tone, and the production of vasoactive molecules [9–11]. The synthesis of VEGF is regulated by hypoxia-mediated control of gene transcription, alternative mRNA splicing and proteolytic processing [12].

The circulating VEGF in peripheral blood is mainly derived from platelets and granulocytes, in particular the neutrophils [13–19]. VEGF is produced in the megakaryocyte and is only partially released during maturation and platelet shedding but largely remains intra-cytoplasmic in the mature [20]. It has been shown that platelets transport VEGF and secrete VEGF upon activation with thrombin [16,17,20]. It was assumed that sera contain both free VEGF and that released from activated platelets, whereas in plasma the free fraction of the peptide is present [14]. In neutrophils VEGF is a pre-formed cytokine which is stored in the specific granule [21]. Release of VEGF from neutrophils typically occurs

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upon activation with proinflammatory cytokines such as tumor necrosis factor alpha (TNF alpha) [22].

Kusumanto et al. quantified the contribution of the various cell fractions to the total amount of circulating VEGF [15]. They found that in healthy volunteers the major part (58%) of the total circulating VEGF, is contained by neutrophils [15]. Platelets contain approximately 34% of total VEGF in healthy volunteers [15]. It was suggested that the finding of VEGF in neutrophils might indicate an important role for neutrophil derived VEGF in angiogenesis by controlling vessel permeability [11].

Neovascularization, which comprises angiogenesis and formation of collateral vessels, is a key process for the heart under ischemic stress to maintain its proper functioning and is also important for the prognosis in vascular disorders with acute tissue ischemia, such as myocardial infarction (MI) [23]. It has been shown that in ischemic conditions, VEGF promotes the development of coronary collateral vessels, in this way providing an adequate blood supply, preventing death of cardiomyocytes and heart remodeling [24]. In animal models, the application of recombinant VEGF to ischemic limbs induced angiogenesis and improved tissue perfusion. These findings suggest the use of recombinant VEGF as a treatment for ischemic diseases. In contrast to this, it was revealed that VEGF could also be related to the development of the endothelial damage, proliferative retinopathy, atherosclerosis and nephropathy in diabetic patients [13,25–28]. Blann et al. investigated plasma VEGF levels in patients with confirmed coronary artery disease and in healthy subjects and found that plasma VEGF levels increased in patients with CAD compared to healthy subjects [27]. Although their study included patients with acute coronary syndrome, they had no angiographic evaluation [27]. Alber et al. and Fleisch et al. found that there was no difference between plasma VEGF levels in patients with varying degrees of coronary artery lesions, while Kucukardali et al. revealed that increased plasma VEGF levels in patients with coronary artery disease may mean that coronary lesions were critical and increased VEGF in patients with established coronary artery disease (CAD) may be used as an indicator of the need for revascularization [29–31]. Seko et al. showed that circulating VEGF levels in patients with acute MI was elevated in comparison with normal subjects [32]. Hoyo et al. found that the extent of myocardial damage contributed to the elevation of serum VEGF levels in acute MI [33].

Although, in patients with acute coronary syndrome (ACS) routinely measured biomarkers as troponins, high-sensitivity C-reactive protein (hsCRP), brain natriuretic peptide (BNP) or N-terminal prohormone fragment (NT-proBNP) confirm ischemic myocardial injury and assess the prognosis they do not always reflect the extend of atherosclerotic lesions in coronary arteries. Biomarker which will help to estimate the stage of atherosclerotic lesions in coronary arteries probably, not only will confirm the acute myocardial injury but in additional way will assess prognosis in ACS patients especially under revascularization. The aim of our study was to evaluate the value of VEGF as a surrogate marker of myocardial injury in acute ischemic conditions. In patients with ACS platelets play a crucial role in the pathogenesis of this disease and their activation induced by a spontaneous or mechanical arterial injury leads to coagulation cascade initiation and intravascular thrombus formation within the first 24 h of ACS. For this reason we decided to measure VEGF in plasma for assessment the free fraction of peptide and in sera to establish additional effect of platelet activation on VEGF secretion upon acute myocardial ischemia.

2. Materials and methods

The study comprised a total of 104 patients admitted between January 2007 and September 2009 to the Intensive Cardiac Therapy Clinic at the Institute of Cardiology with the first episode of acute coronary syndrome in their lives, who were eligible for coronary angiography and, if necessary, for percutaneous coronary intervention. Each subject expressed their informed consent to participate in the study after being informed of its nature and purpose. Patients informed consent forms and the protocol of the study were approved by the Institutional Local Ethics Committee. The inclusion criteria were: (1) typical criteria of acute coronary syndrome according to the European Society of Cardiology guidelines, (2) indication for coronary angiography (with percutaneous coronary intervention, if necessary), (3) signing formal informed consent form. The exclusion criteria were: (1) known history of myocardial infarction, and (2) refusal to sign a formal informed consent form.

In order to obtain the aim of the study, it was necessary: (1) to establish the dynamic changes of plasma and serum VEGF concentrations in patients with acute coronary syndrome (ACS), (2) to assess the difference in VEGF concentrations in ACS with and without ST-segment elevation, (3) to reveal the relationships between plasma and serum VEGF levels and the number of lymphocytes, granulocytes and platelets, and (4) to show a potential risk for the elevation of VEGF concentration in blood with the presence of CAD risk factors in patients with ACS.

According to ECG findings and coronary angiography results, patients were divided into three groups. Group A comprised subjects with ST-segment elevation in precordial leads and/or in I and aVL leads and with left anterior descending (LAD) artery responsible for ACS symptoms or additionally with significant atherosclerotic lesions (lumen vessel narrowed >50%) in other than LAD coronary arteries. This Group comprised patients with anterior or antero-lateral myocardial infarction with one- or multi-vessel disease and representing major myocardial injury. Into Group B were included patients with ST-segment elevation in II, III and aVF leads and/or ST-segment depression in V2-V3 leads and with one-vessel disease and the culprit artery was not LAD. In Group B, there were patients with inferior or posterior myocardial infarction. This Group represented medium myocardial injury. Group C included patients with changes in ECG other than ST-segment elevation independently of the site of atherosclerotic lesions in coronary arteries. In Groups A and B, there were patients with ST-segment elevation myocardial infarction while in Group C there were subjects with nonST-segment elevation myocardial infarction (NSTEMI) and they represented minor myocardial injuries.

In all patients, we took blood samples for VEGF two times i.e. at admission and 24 h later. In all study patients we assessed cardiac troponin I (cTnI) which was a biomarker routinely measured in ACS patients in everyday clinical practice. Additionally NT-proBNP was measured. These measurements were performed twice i.e. at admission due to STEMI and 24 h later. The normal value for cTNI was <0.1 ng/ml and for NT-proBNP <125 pg/ml. The lipid profile was assessed routinely once at admission. The number of peripheral blood cells was measured twice as biomarkers of myocardial injury. All these measurements were performed in a standard diagnostic laboratory, while plasma and serum concentrations of VEGF were determined in the research laboratory of the Institute of Cardiology.

The quantitative determination of the human vascular endothelial growth factor (hVEGF) concentrations in either serum or plasma samples was performed with a sandwich enzyme immunoassay Quantikine ELISA kit from R&D Systems, Minneapolis, MN, USA. Mean plasma VEGF levels evaluated in EDTA using a Quantikine Elisa kit and presented in a manufacture brochure as a reference were upto 115 pg/ml while serum normal levels of VEGF were between 62 and 707 pg/ml.

3. Statistics

Assuming the fact that the mean plasma hVEGF level in the first measurement was within the normal range and the possible