Correlation between vascular endothelial growth factor and long-term prognosis in patients with acute myocardial infarction

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Abstract. The aim of the present study was to investigate the correlation between plasma the levels of vascular endothelial growth factor (VEGF) and major adverse cardiovascular events (MACE) in patients with acute myocardial infarction (AMI). A total of 124 patients with AMI undergoing emergency percutaneous coronary intervention (PCI) were selected, and plasma VEGF levels were measured 7 days after the onset of AMI using an enzyme-linked immunosorbent assay. The patients were divided into the L (≤190 pg/ml VEGF) and H (>190 pg/ml VEGF) groups, and were followed up every 2 months for an average of 12 months. MACE were recorded during follow-up. On the basis of these results, the patients were further divided into the MACE and non-MACE (N-MACE) groups, and the serum VEGF concentration was compared between the two groups. At the 6-month follow-up, the incidence of MACE in the H group was found to be significantly reduced compared with the L group. The serum VEGF concentration in the N-MACE group was significantly higher compared with the MACE group. Multinomial logistic regression revealed that reduced VEGF levels (β=1.243; 95% CI, 1.018-1.326; P=0.026) were independent risk factors for MACE. In conclusion, high plasma VEGF levels at 7 days after AMI onset facilitate the long-term prognosis in the same infarct zone in patients with AMI, while low plasma VEGF levels are independent risk factors for MACE.

Introduction

Vascular endothelial growth factor (VEGF) is a signal protein produced by endothelial cells, smooth muscle cells and macrophages, which is able to increase vascular permeability, stimulate the expression of vascular endothelial cells and induce angiogenesis (1). Independently of the physiological or pathological state, VEGF is crucially involved in vascular endothelial function repairing and vascular regeneration (2,3). Previous studies have demonstrated that plasma VEGF levels are significantly elevated in patients with acute myocardial infarction (AMI) compared with those in healthy individuals (4-7). Furthermore, studies involving AMI in animal models (8,9) have shown that VEGF promotes angiogenesis in infarct regions and reduces AMI area. Yin *et al* (10) and Hojo *et al* (11) observed that hypoxia and ischemia stimulate VEGF secretion in patients with AMI, and suggested that the marked increase in VEGF indicates a protective effect on patients as a result of angiogenesis and endothelial cell proliferation. According to its biological effects, VEGF may be able to improve the long-term prognosis of patients with AMI (11). However, the correlation between plasma VEGF levels and long-term prognosis in patients with AMI remains controversial. Matsudaira *et al* (12) observed that low plasma VEGF levels following the onset of AMI are associated with a significantly increased risk for MACE during 6 months of follow-up. In addition, Heeschen *et al* (13) indicated that high VEGF levels following the onset of acute coronary syndrome (ACS) are associated with a poor outcome. Therefore, in the present study, the correlation between plasma VEGF levels in the same infarct zone at 7 days after the onset of AMI following successful revascularization by percutaneous coronary intervention (PCI) and the long-term prognosis were evaluated in patients with AMI.

Materials and methods

Subjects. A total of 124 patients (76 females and 48 males; mean age, 59.1 years) with AMI were recruited from Laiwu People's Hospital (Laiwu, China) between June 2010 and February 2014. The present study was conducted in accordance with the declaration of Helsinki and was approved by the Ethics Committee of the Laiwu People's Hospital. Written informed consent was obtained from all participants.

Inclusion criteria. According to the standard diagnosis for AMI (14,15), patients were required to meet minimum two out of the three of the following criteria to be included in the study: i) Clinical history of ischemic chest pain; ii) dynamic electrocardiogram (ECG) changes; iii) dynamic changes in plasma levels of markers of myocardial necrosis. Furthermore, according to coronary artery segmentation (16), lesions involve

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segment 6 of left anterior descending (LAD) artery but not in left circumflex and right coronary arteries. In addition, PCI and stent implantation performed within 12 h from symptom onset to achieve a thrombolysis in MI (TIMI) flow grade 3.

Exclusion criteria. Patients were excluded if they had a history of any of the following: i) Angina following PCI; ii) previous MI indicated by past medical history, ECG or Color Doppler echocardiography; iii) prior PCI or coronary artery bypass grafting; iv) history of heart failure; v) left ventricular hypertrophy; vi) atrial fibrillation; vii) pacemaker implantation; viii) renal insufficiency; ix) digitalis administration; x) valvular heart disease; xi) severe lung disease; xii) acute or chronic infection; xiii) anemia; xiv) acute or chronic liver diseases, such as chronic hepatitis and liver cirrhosis; xv) cancer; xvi) organ or bone marrow transplantation.

Control subjects. A total of 30 subjects were recruited into the control group, over the same time period from the same hospital. Subjects in the control group were selected according to the following criteria: i) No hypertension or diabetes or other organic diseases; ii) normal blood routine, liver and kidney function test results, and normal abdomen and cardiac ultrasound, ECG and chest radiograph; and iii) no cancer or pregnancy.

Treatment. According to the guidelines for the management of patients with ST-elevation MI (14,15), all the patients received conventional drug therapy, and underwent PCI and stent implantation (EXCEL drug-eluting stent; JW Medical Systems Co., Weihai, China) within 12 h following symptom onset, to achieve thrombolysis in TIMI flow grade 3. The conventional drug therapy involved administration of aspirin enteric-coated tablets (100 mg orally, once a day; Bayer Health Care AG, Beijing, China), clopidogrel hydrogen sulphate tablets (75 mg orally, once a day; Sanofi Pharmaceuticals Co., Ltd., Hangzhou, China), rosuvastatin calcium tablets (10 mg orally, once a day; AstraZeneca Pharmaceutical Co., Ltd., Wuxi, China), metoprolol succinate sustained-release tablets (11.875 mg orally, once a day; AstraZeneca Pharmaceutical Co., Ltd.).

VEGF measurement. Fasting venous blood samples (2 ml) were obtained from patients 7 days after the onset of AMI and centrifuged at 3,000 rpm for 10 min. Plasma was isolated and stored at -20˚C for further analysis. VEGF levels were determined using VEGF-specific enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA), and measurements were performed according to the manufacturer's instructions. The antiserum containing the mouse anti-human monoclonal VEGF antibody (cat. no. MAB286; dilution, 1:100; R&D Systems) was adsorbed into the wells of a microtiter plate (BrandTech Scientific, Inc., Essex, CT, USA) and then washed three times with phosphate-buffered saline. Next, the blood sample was added, and binding occurred if the antiserum antibody matched the blood sample antigen. Subsequently, the excessive antibody was washed away, and the rabbit anti-mouse IgG secondary antibody (cat. no. G-202-C; dilution 1:400; R&D Systems) was added, which would specifically react with the test antigen to form the 'sandwich'. Tetramethyl benzidine (Sigma-Aldrich, St. Louis, MO,

USA) was then added and the production of colored enzymatic products indicated that the corresponding antigen was present on the well walls. The optical density of the end-product was measured using an F-7000 fluorescence spectrophotometer (Hitachi High-Technologies Corp., Tokyo, Japan).

Echocardiography. Echocardiography was performed to determine left ventricular ejection fraction (LVEF) and evaluate the cardiac systolic function in patients with AMI during hospital stay and follow-ups, as well as 1, 6 and 12 months after PCI. A Vivid E9 Doppler ultrasonic scanner (GE Healthcare Life Sciences, Shanghai, China) was used at a scanning speed of 50 mm/sec and frequency of 2.0-2.5 MHz. The left ventricular end systolic and diastolic volumes (LVESV and LVEDV, respectively) were measured according to the modified Simpson's rule using the apical two-chamber and four-chamber views recommended by the American Society of Echocardiography (17). LVEF = (LVEDV-LVESV)/LVEDV. An LVEF of <40% was diagnosed as heart failure.

Follow-up. All patients with AMI were followed up every 2 months for an average of 12 months. The endpoint of the study was the incidence of major adverse cardiovascular events (MACE) during hospitalization period or follow-up, including cardiac mortality, heart failure, severe arrhythmia, cardiac shock and post-infarction angina.

Statistical analysis. Statistical analysis was performed using SPSS software, version 19.0 (IBM SPSS, Armonk, NY, USA). Data were presented as mean ± standard deviation and were analyzed using the t-test and χ^2 test. VEGF was numerical variable following skewed distribution and presented as a median. The Wilcoxon rank-sum test was employed for the comparison of two independent samples. The comparison among multiple samples was performed using the χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

General patient data and VEGF levels. According to their plasma VEGF levels, the patients were divided into the L ($\leq$190 pg/ml) and H (>190 pg/ml) groups. General data and plasma VEGF levels of all groups are presented in Table I. No significant differences were identified in the general data of patients, including gender, age, systolic blood pressure (SBP), body mass index (BMI), presence of diabetes, smoking habits, and angiotensin-converting enzyme inhibitors (ACEI) and β-blocker administration among the control, H and L groups (P>0.05). By contrast, the concentrations of serum VEGF in the H and L groups was significantly different compared with control group (P<0.05).

Follow-up. At the 12-month follow-up, 18/124 patients with MI presented with MACE, including 2 cases of mortality, 7 cases of heart failure and 9 cases of recurrent angina or MI.

Correlation between VEGF levels and clinical outcomes. Based on the incidence of MACE, the 124 patients were divided into the MACE (n=18) and non-MACE (N-MACE; n=106) groups. The median plasma VEGF levels in the MACE group were

Table I. General data and plasma VEGF levels among the three groups.

Characteristic	Control group (n=30)	H group (n=62)	L group (n=62)	P-value
Males, n	18	25	23	0.100
Age, years	57.3±8.7	59.3±9.8	58.9±8.8	0.683
SBP, mmHg	145±21	156±18	150±20	0.248
Diabetes, n	4	13	19	0.156
Smoking, n	12	20	18	0.574
BMI	25.5±2.1	27.8±3.0	26.1±2.3	0.053
ACEI administration, n	10	18	16	0.751
β-blocker administration, n	5	10	8	0.843
Median VEGF, pg/ml	82.15	265.42	121.60	0.033

SBP, systolic blood pressure; VEGF, vascular endothelial growth factor; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitors; L group, ≤190 pg/ml VEGF plasma level; H group, >190 pg/ml VEGF plasma level; VEGF, vascular endothelial growth factor.

Table II. Incidence of major adverse cardiovascular events in the H and L groups (n=62 per group).

Time after AMI (months)	H group, % (n)	L group, % (n)	P-value
0	0.0 (0)	0.0 (0)	-
2	0.0 (0)	3.2 (2)	0.154
4	3.2 (2)	8.1 (5)	0.243
6	3.2 (2)	12.9 (8)	0.048
8	4.8 (3)	16.1 (10)	0.040
10	6.5 (4)	19.4 (12)	0.032
12	8.1 (5)	21.0 (13)	0.041

AMI, acute myocardial infarction; L group, ≤190 pg/ml VEGF plasma level; H group, >190 pg/ml VEGF plasma level; VEGF, vascular endothelial growth factor.
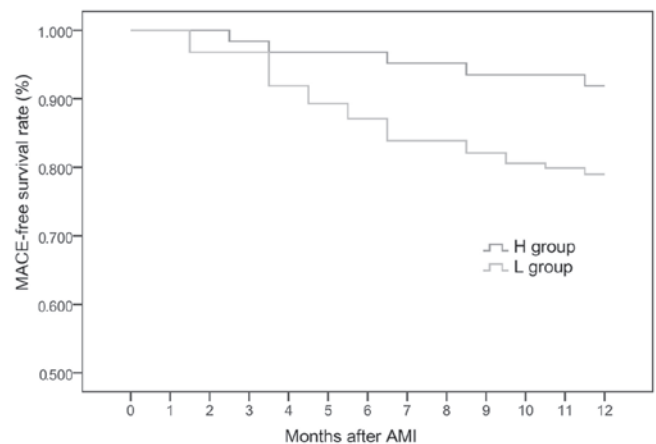

Figure 1. MACE-free survival rates among the two groups. The MACE-free survival rate of patients with acute myocardial infarction was significantly higher in the H group compared with that in the L group, when the follow-up was longer than 6 months. MACE, major adverse cardiovascular events; AMI, acute myocardial infarction; L group, ≤190 pg/ml VEGF plasma level; H group, >190 pg/ml VEGF plasma level; VEGF, vascular endothelial growth factor.

found to be significantly reduced (153.23 pg/ml) compared with those in the N-MACE group (208.05 pg/ml; P<0.001).

Incidence of MACE. At 6 months after the onset of AMI, the incidence of MACE was markedly higher in the L group compared with the H group; MACE-free survival rate was markedly higher in the H group compared with the L group (Table II and Fig. 1).

Logistic regression analysis. Logistic regression analysis was performed with MACE as the dependent variable (yes=1, no=0) and gender, age, SBP, diabetes, smoking, BMI, ACEI and β-blocker administration and VEGF levels as the independent variables. The results suggested that a low VEGF level (≤190 pg/ml) was an independent risk factor for MACE (β=1.243; 95% CI, 1.018-1.326; P=0.026).

Discussion

The present study involved 124 patients with AMI with single-vessel, proximal LAD disease, in which revascularization was performed within 12 h. Plasma VEGF levels were evaluated at 7 days after the onset of AMI. At the 12-month follow-up, the incidence of MACE in the patients, including cardiac mortality, heart failure, severe arrhythmia, cardiac shock and post-infarction angina was recorded. The results showed that the incidence of MACE in the H group was significantly higher compared with the L group at the 6-12-month follow-ups, and that the plasma VEGF levels were markedly elevated in the N-MACE group, as compared with those in the MACE group. The correlation between plasma VEGF levels and long-term prognosis in patients with AMI was investigated using logistic regression analysis, which revealed that a low VEGF level (β, 1.243; 95% CI, 1.018-1.326; P=0.026) was an independent risk factor for MACE, while high VEGF levels facilitated long-term prognosis in patients with AMI.

VEGF is a dimeric glycoprotein composed of two identical polypeptide chains, which is produced by endothelial cells, smooth muscle cells and macrophages. VEGF is able to promote

vascular endothelial cell mitosis, proliferation and migration, increase vascular permeability, stimulate the expression of vascular endothelial cells and induce angiogenesis (1). VEGF expression has been shown to be promoted by several factors, including hypoxia, angiotensin, advanced glycation end products, endotoxin and high glucose (18,19). VEGF is known to be crucially involved in the induction of vasculogenesis and angiogenesis, exerting a marked effect on angiogenesis by binding to kinase insert domain-containing receptor (20). Furthermore, VEGF may exert a positive effect in the revascularization of ischemic tissues, specifically through the promotion of vascular endothelial cell proliferation and neovascularization, increase of vascular permeability, and improvement of collateral circulation (20). Sluimer *et al* (21) performed carotid endarterectomy in patients with carotid atherosclerosis and observed an increase in the mRNA and protein expression of hypoxia-inducible factor 1 (HIF-1α), VEGF expression and microvessel density in the early stages of atherosclerosis. In addition, hypoxia correlated with thrombosis, angiogenesis, HIF-1α and VEGF expression; therefore, VEGF and HIF-1α were associated with atherosclerotic plaque instability and were considered to be an index indicating plaque instability in patients with ACS. Mao *et al* (22) used a rat model of myocardial ischemia and ligated the left descending coronary artery. After 3 h the VEGF expression in the ischemic myocardium had peaked, subsequently decreasing 6 h later. Thus, the VEGF expression level was able to assist in determining the degree of severity of ischemic injury. Wang *et al* (23) showed that short-term intermittent hypoxia has a cardioprotective effect, which may result from the upregulation of VEGF and HIF-1α expression in a rat model of ischemia/reperfusion injury. In 2003, Heeschen *et al* (13) measured the plasma VEGF levels of 1,090 patients with ACS at 8.7 h after the onset of MI, and observed that the incidence of MACE was increased in patients that exhibited significantly elevated plasma VEGF levels at the 6-month follow-up. In 2012, Matsudaira *et al* (12) detected the plasma VEGF levels in 873 patients with AMI 7 days after the onset of MI and found that the incidence of MACE was higher in patients with low plasma VEGF levels (≤190 pg/ml) at the 6-month follow-up. The present study included patients with AMI with single-vessel, proximal LAD disease, with a similar myocardial ischemia and injury area, in order to more accurately indicate the association between VEGF and MACE. In 2012, Devaux *et al* (24) recruited 290 patients with AMI and revealed that the risk of left ventricular remodeling was higher in patients with lower VEGF levels. Zentilin *et al* (25) reported that the long-term expression of VEGF-A165 and VEGF-B167 in the myocardium may reduce myocardial fibrosis and enhance myocardial contractility to protect the viable myocardium and improve ventricular remodeling. Furthermore, previous studies have indicated that the plasma VEGF levels in patients with AMI peaked on days 7-14 after the onset of AMI, and in patients that underwent successful percutaneous revascularization on day 7 (26-28). Collectively, the aforementioned and present results indicate that the increase in VEGF levels serves a crucial function in cardiovascular repair.

In addition, the results of the aforementioned studies suggest that due to the ischemia and hypoxia stimulation, patients with AMI may be expected to secrete increased quantities of VEGF to promote the angiogenesis and endothelial cell proliferation,

therefore promoting self-repair and cardiac remodeling, which indicates the cardioprotective effect of VEGF expression. In the present study, increased VEGF levels were shown to facilitate long-term prognosis in patients with AMI, while low VEGF levels were found to be independent risk factors for MACE, which is consistent with the results from the study by Matsudaira *et al* (12). By contrast, Shimokawahara *et al* (29) observed that in the acute period, the left ventricle volume index of the high-serum-VEGF-concentration group of patients with MI was significantly elevated compared with the low-serum-VEGF-concentration group, while the intergroup differences observed in the chronic period were not statistically significant. In conclusion, high plasma VEGF levels at 7 days after AMI onset facilitate the long-term prognosis in the same infarct zone in patients with AMI, while low plasma VEGF levels are independent risk factors for MACE. However, the correlation between plasma VEGF levels at different stages, genetic factors and prognosis in patients with AMI requires further investigation.

Acknowledgements

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