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Original article

Relationship between vascular endothelial growth factor and left ventricular dimension in patients with acute myocardial infarction

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ABSTRACT

Background: Although vascular endothelial growth factor (VEGF) is elevated in patients with acute myocardial infarction (AMI), the clinical significance of its elevation remains unclear. The present study was designed to determine the relationship between VEGF and left ventricular dimension in patients with AMI.

Methods and results: Plasma VEGF levels were examined by enzyme-linked immunosorbent assay daily for one week and then weekly for four weeks in 38 patients with AMI (65.4 ± 1.7 years). Left ventriculography was performed at 14 days, 6 months, and 2 years after the onset of AMI. Plasma VEGF levels were significantly elevated and reached a peak on day 6. Peak plasma VEGF levels positively correlated with both end-diastolic and end-systolic volume indices at 14 days after the onset of AMI. When patients with AMI were divided into two groups according to plasma VEGF levels on admission, left ventricular volume indices were higher in the high VEGF group than in the low VEGF group at the subacute phase of AMI (14 days). These differences were no longer present in the chronic phase of AMI.

Conclusion: Plasma VEGF levels were increased in patients with AMI, and peak levels were associated with left ventricular volume indices in the subacute phase, suggesting an important role of endogenous VEGF in the left ventricular dimension in patients with AMI.

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Introduction

Vascular endothelial growth factor (VEGF) [1] is an important endothelial cell-specific mitogen. VEGF enhances vascular permeability [2,3], accelerates collateral formation in ischemic myocardium [4–6], and promotes tissue repair after wound healing [7]. Several reports have demonstrated that patients with acute myocardial infarction (AMI) have elevated circulating VEGF levels as compared with healthy subjects [8–12]. Treatment with exogenous VEGF promoted vessel formation in ischemic myocardium and improved ventricular function in patients with ischemic heart diseases [13,14]. On the other hand, granulocyte colony stimulating factor upregulated VEGF and improved survival by accelerating neovascularization in a rabbit model of myocardial ischemia [15]. However, the clinical significance of endogenous VEGF in patients with AMI has not been fully understood.

The relationship between plasma VEGF levels and subsequent cardiac dimension in patients with AMI is controversial. Soeki et al. defined the remodeling group as having an increase in left ventricular end-diastolic volume index (LVEDVI) more than 5 ml/m^2 at 3 months after the onset of AMI. They found no changes in VEGF levels between the remodeling group and the non-remodeling group [11]. On the other hand, Suzuki et al. defined the remodeling group as showing an increase in LVEDVI at one month after the onset of AMI and demonstrated that peak VEGF levels were significantly higher in the remodeling group than in the non-remodeling group

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[12]. However, there are no reports investigating the relationship between peak VEGF levels and left ventricular volume indices at the more chronic phase of AMI, such as 6 months or 2 years after the onset of AMI. Therefore, the aim of the present study was to examine the time course of plasma VEGF levels in patients with AMI, and to investigate the correlation between plasma VEGF levels and left ventricular dimension in the early and chronic phase of AMI.

Methods

Patient characteristics

The present study included 38 patients (27 males and 11 females, mean age 65.4 ± 1.7 years) with AMI who were admitted to the National Hospital Organization Kagoshima Medical Center within 12 hours after the onset of symptoms and had successful reperfusion therapy with percutaneous coronary intervention from August 2001 to July 2002. The clinical characteristics and medication in all patients with AMI are shown in Tables 1 and 2, respectively. The diagnosis of AMI was based on the findings of severe prolonged chest pain for at least 30 min, ST-segment elevation of at least two continuous leads by a standard 12-lead electrocardiogram, and elevation of serum creatine kinase (CK)-MB isozyme to more than twice the upper limit of normal range. Patients with AMI more than 12 h from the onset and those with AMI who had already received heparin treatment before admission to our hospital were excluded in the present study. Patients with preexisting heart diseases including previous myocardial infarction, valvular heart disease, and cardiomyopathy were also excluded. Other exclusion criteria were renal dysfunction requiring dialysis and evidence of malignant and inflammatory diseases. All patients were monitored in our intensive care unit and entered into the cardiac rehabilitation programs in our hospital. Age-matched 22 subjects (13 men and 9 women, mean age 63.7 ± 1.5 years) having atypical chest pain with angiographically normal coronary arteries and a normal left ventriculogram served as control subjects. The investigation conforms to the principles outlined in the Declaration of Helsinki, and it was approved by the Institutional Review Board in our hospital. Written informed consent was obtained from each patient with AMI and also from the control subjects.

Blood sampling

Peripheral blood samples were obtained immediately before administration of heparin at the time of admission, daily for one week, and then weekly for four weeks in patients with AMI. B-type natriuretic peptide (BNP) was also examined.

Measurement of VEGF levels

Plasma samples for the measurement of VEGF were placed in ethylenediaminetetraacetic acid-coated tubes containing 500 IU/ml of aprotinine, centrifuged immediately at 3000 rpm for 10 min at 4 °C, and stored at −80 °C until analysis. Plasma VEGF levels were determined using a specific enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, USA) according to the manufacturer's instructions. The minimal detection limit of this ELISA was 31.2 pg/ml. VEGF levels were defined as zero if the values were less than the minimal detection limit. VEGF assay was performed by an investigator blinded to the sources of the samples. Intra-assay and inter-assay variations were 5.6% and 9.8%, respectively.

Ultrasound cardiography

Standard two-dimensional and Doppler echocardiographic examinations were performed at admission, at 28 days, 6 months, and 2 years after the onset of AMI. Left ventricular end-diastolic diameter (LVDd) and left ventricular end-systolic diameter (LVDs) were measured by two-dimensional and M-mode echocardiography. Ejection fraction (EF, Simpson method) was calculated according to the standard formula.

Table 1
Patient characteristics in high VEGF group and low VEGF group.

	Total (n = 38)	High (n = 12)	Low (n = 26)	p-Value
Age (years)	65.4 ± 1.7	69.8 ± 3.5	63.3 ± 1.8	NS
Sex (%)				
Male	27 (71.0)	10 (83.3)	17 (65.4)	NS
Female	11 (29.0)	2 (16.7)	9 (34.6)	NS
BMI (kg/m^2)	24.4 ± 0.5	25.3 ± 1.0	24.0 ± 0.5	NS
Risk factors				
Hypertension (%)	24 (63.2)	5 (41.7)	9 (34.6)	NS
Hyperlipidemia (%)	17 (44.7)	4 (33.3)	13 (50)	NS
Diabetes mellitus (%)	16 (42.1)	4 (33.3)	12 (46.2)	NS
Smoking (%)	12 (31.6)	6 (50.0)	6 (23.1)	NS
Killip classification				
I	30 (78.9)	8 (66.7)	22 (84.6)	NS
II	8 (21.1)	4 (33.3)	4 (15.3)	NS
Time to reperfusion (h)	3.9 ± 0.4	3.3 ± 0.4	4.1 ± 0.6	NS
Diseased vessels				
Single-vessel disease	24 (63.2)	5 (41.7)	19 (73.1)	NS
Multivessel disease	14 (36.8)	7 (58.3)	7 (26.9)	NS
Rentrop collateral grade				
0/1	23 (60.5)	6 (50.0)	17 (65.4)	NS
2/3	15 (39.5)	6 (50.0)	9 (34.6)	NS
CI (L/min/m^2)	3.59 ± 0.2	3.2 ± 0.19	3.8 ± 0.2	NS
PCWP (mmHg)	13.7 ± 1.1	15.9 ± 2.8	12.8 ± 1.1	NS
LVEF (UCG) (%)	58.2 ± 1.9	52.7 ± 3.7	60.9 ± 1.9	NS
Peak CK (IU/L)	3029 ± 320	3614 ± 661	2759 ± 352	NS
Peak BNP (pg/ml)	240 ± 31	260 ± 75	229 ± 37	NS

Values are expressed as number (percentage) of patients or mean value ± SE. VEGF, vascular endothelial growth factor; NS, not significant; BMI, body mass index; CI, cardiac index; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; UCG, ultrasound cardiography; CK, creatine kinase; BNP, B-type natriuretic peptide.

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