Serum VEGF Predicts Worse Clinical Outcome of Patients with Coronary Heart Disease After Percutaneous Coronary Intervention Therapy

Background:
Percutaneous coronary intervention (PCI) is an effective treatment for coronary heart disease (CHD) patients. However, patients after PCI treatment often have ischemic events that result in poor prognosis. Our study aimed to investigate the effects of vascular endothelial growth factor (VEGF) level on the prognosis of CHD patients.

Material/Methods:
We enrolled 114 CHD patients in the study. Serum VEGF level was measured by enzyme-linked immunosorbent assay (ELISA). Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and Hs-CRP were also tested in patients. The patients were divided into 2 groups according to the level of VEGF. Kaplan-Meier curve was used to observe the differences in survival situation of patients of the 2 groups. Cox regression analysis was conducted to judge whether VEGF was an independent biomarker for prognosis in CHD.

Results:
We included 104 patients for survival analysis. VEGF level in CHD patients was significantly lower than that of healthy individuals (P<0.05). In the analysis of basic information, we found differences in sex distribution and hypertension between groups (P<0.05 for both). Kaplan-Meier curve indicated that patients with low expression of VEGF presented with poor prognosis. The mortality rate of the low-expression group was 37.71%, higher than that of the high-expression group (14.3%). Cox analysis suggested that VEGF could serve as a biomarker for prognosis in CHD (HR: 3.014, P: 0.019).

Conclusions:
Low level of VEGF may predict poor clinical outcome of CHD patients after PCI treatment.

MeSH Keywords:
Coronary Disease • Percutaneous Coronary Intervention • Prognosis • Vascular Endothelial Growth Factor A

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Background

Coronary heart disease (CHD) is a complex cardiovascular disease. Both genetic and environmental factors are involved in its pathogenesis. The prognosis of most CHD patients is favorable; however, cardiovascular events and death often occur. Identification of biomarkers that could predict the clinical outcome of CHD patients will help in improving the survival of patients.

The genetic biomarkers for CHD prognosis have been extensively studied. PF-4var/CXCL4L1 levels were reported to be associated with poor prognosis of patients with stable CHD [1]. Li et al. concluded that miR-4513 rs2168518 and miR-499 rs3746444 had strong relationship with event-free survival (EFS) in CHD [2]. Another gene, FSAP was demonstrated to be related with clinical outcome in acute coronary syndrome (ACS) [3]. Breitling et al. found that methylation of F2RL3 was strongly correlated with mortality among patients with stable CHD [4].

Percutaneous coronary intervention (PCI) is an effective treatment for CHD patients, which could greatly improve the prognosis of patients; however, the occurrence of cardiovascular events, such as myocardial infarction (MI) and coronary restenosis after PCI, still is 20–40% [5]; therefore, it is crucial to investigate the clinical outcome of CHD patients after PCI therapy. Zhang et al. reported that F2R rs168753 minor allele could predict ischemic events in CHD patients after PCI therapy [6]. A recent study showed that VEGF expression was related with major adverse cardiac events (MACE) in CHD patients treated by PCI, which suggests that VEGF expression might be important in CHD prognosis [7].

In our study, the expression of VEGF in CHD patients and healthy controls were investigated. We used Kaplan-Meier curve and Cox analysis to evaluate the significance of VEGF in prognosis of CHD patients.

Material and Methods

Subjects

We enrolled 114 patients with coronary heart disease (CHD) from Laiwu People’s Hospital. The diagnosis of each patient was performed by 2 experienced physicians. Patients were scheduled for percutaneous coronary intervention (PCI) therapy for acute myocardial infarction (MI) (n=58), unstable angina pectoris (SAP) (n=35) or ischemic cardiomyopathy (ICM) (n=21). Patients with artery diseases, infectious diseases, tumor and inflammatory diseases were excluded from the study. We also included 56 healthy controls to test the serum level of VEGF. In the present study, we tested levels of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and Hs-CRP.

After PCI, the survival of patients was investigated for up to 5 years by telephone contact. We defined “Endpoints” as cardiovascular death, recurrent acute coronary syndromes (ACS) for re-admission, and acute heart failure. Because 10 patients could not be contacted in follow-up, 104 patients were included for further analysis. Written consent was obtained from each subject before the study and the study was approved by the Institutional Review Board (IRB) of the hospital.

Serum VEGF level

Peripheral blood collected from each patient and healthy control was centrifuged at 2500 rpm for 10 min. Serum was obtained and stored at –80°C. VEGF level in serum was measured by enzyme-linked immunosorbent assay (ELISA). The test was performed in duplicate and the average value was used for analysis.

Statistical analysis

The patients were classified into 2 groups according to the level of VEGF: low expression and high expression. The differences in average age, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and Hs-CRP of the 2 groups were compared using the independent-samples t test. The variations in sex, diabetes, smoking, CHD in family, and medication treatment between groups were evaluated with the chi-squared test. The survival was recorded and association between VEGF levels with clinical outcome was analyzed with Kaplan-Meier curve. The log-rank test was used for evaluating the significance in survival situation of the 2 groups. Cox regression analysis was performed to determine if VEGF could serve as an independent prognostic biomarker of CHD patients after PCI therapy. All analyses were conducted in SPSS 18.0. The diagram was completed in GraphPad Prism 5.

Results

Basic information of CHD patients

CHD patients were divided into VEGF high-expression and VEGF low-expression groups (Table 1). The average age in the high-expression group was 66.74 years and in the low-expression group it was 67.87 years. There were no significant differences in age. In the high-expression group, there was 25 females, a significantly higher ratio than in the low-expression group (56.0% vs. 33.9%, P<0.05). There were also differences in hypertension ratio between the 2 groups (P<0.05). However, we found no differences in diabetes, smoking, CHD in family, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, medication treatment, or Hs-CRP level (P>0.05 for all).
We used ELISA technology to test serum level of VEGF. As shown in Figure 1, VEGF level in CHD patients was lower than that in healthy controls (18.88 pg/ml vs. 389.25 pg/ml, P<0.05).

In the 5-year follow-up, we found there were 24 deaths in the low-expression group (38.71%), significantly higher than in the high-expression group (6 deaths, 14.3%) (Figure 2). The patients with low expression of VEGF showed worse prognosis compared to those with high expression of VEGF (P<0.05). Further analysis indicated that VEGF could serve as a prognostic biomarker in CHD (HR: 3.014, P: 0.019, Table 2).

As a type of cardiovascular disease, ischemic heart disease is the primary cause of mortality in the world, especially in developing countries [8,9]. Much effort has been made to improve the treatments of cardiac diseases. Double infusion of bone marrow mesenchymal stem cells and 5-azacytidine was reported to improve the treatment efficacy on dilated cardiomyopathy [10]. Coronary artery bypass graft (CABG) surgery and PCI are effective treatments for CHD, both of which could greatly reduce the mortality rate of patients. PCI is now the most common technology used in myocardial revascularization [11].

PCI, also known as coronary angioplasty or simply angioplasty,
is a non-surgical procedure used to treat the stenotic coronary arteries of the heart in CHD patients. CABG serves as another alternative treatment for CHD, which bypasses stenotic arteries via grafting vessels from elsewhere. However, CABG treatment may increase the risk of stroke [12]. Compared to CABG, PCI has been proven to be as effective and less costly in CHD patients [13,14]. As regard to the clinical outcome, CABG is better long-term outcome and patients after PCI therapy showed relatively worse outcomes [15–17].

Great efforts have been made to prevent or treat adverse events after PCI to increase the survival time of CHD patients. One study demonstrated that Tong-xin-luo can prevent restenosis and recurrence of cardiovascular events in CHD patients after PCI [18]. Jones et al. found no relationship between manual thrombus aspiration and reduced mortality of patients treated by PCI [19]. Some studies tried to resolve the problem through theoretical evidence for choosing PCI or CABG in clinical practice. The present study provides evidence for a potential treatment target for CHD after PCI to improve clinical outcome. However, we did not investigate the effects of VEGF level on potential adverse events caused by PCI, which may provide details of the association between VEGF and prognosis. Moreover, studies with larger sample sizes are needed to compare differences in effects of VEGF between PCI and CABG treatments, providing theoretical evidence for choosing PCI or CABG in clinical practice.

Conclusions

A low level of VEGF predicts worse clinical outcome of CHD patients receiving PCI treatment.

Table 2. Cox regression.

| Index                     | HR  | 95% CI          | P value |
|---------------------------|-----|-----------------|---------|
| Sex (male vs. female)     | 1.337 | 0.618–2.984   | 0.461   |
| Hypertension (yes vs. no) | 1.920 | 0.758–4.863   | 0.169   |
| VEGF (low vs. high)       | 3.014 | 1.197–7.589   | 0.019   |
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