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

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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 χ^2 test. Patient 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).

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Table 1. Patients information.

Index	Total, n=104	VEGF		*P* value
		High expression, n=42	Low expression, n=62	
Age, years	67.41±1.24	66.74±1.33	67.87±1.12	0.516
Sex (female)	56 (53.8)	25 (56.0)	21 (33.9)	0.010
Diabetes, %	48 (46.2)	18 (42.8)	30 (47.4)	0.579
Smoking, %	44 (42.3)	15 (35.7)	29 (46.8)	0.263
Hypertension, %	61 (58.6)	19 (45.2)	42 (67.7)	0.022
CHD in family	55 (52.9)	21 (50.0)	34 (54.8)	0.628
Total cholesterol, mg/dl	201.77±2.41	200.52±1.98	202.61±2.83	0.546
LDL cholesterol, mg/dl	106.10±2.36	105.86±1.59	106.27±2.74	0.895
HDL cholesterol, mg/dl	47.02±1.72	46.07±1.24	47.66±2.06	0.511
Triglycerides, mg/dl	148.71±3.14	149.10±2.14	148.45±3.86	0.884
Medication treatment, %				
ACE inhibitor	67 (64.4)	25 (59.5)	42 (67.7)	0.390
Statin	65 (62.5)	23 (54.8)	42 (67.7)	0.180
Clopidogrel	58 (55.8)	19 (45.2)	37 (59.7)	0.147
ASS	55 (52.9)	20 (47.6)	35 (56.4)	0.376
β-blocker	61 (58.7)	21 (50.0)	40 (64.5)	0.140
Hs-CRP, mg/L	19.14±1.21	18.52±1.32	19.56±1.14	0.512

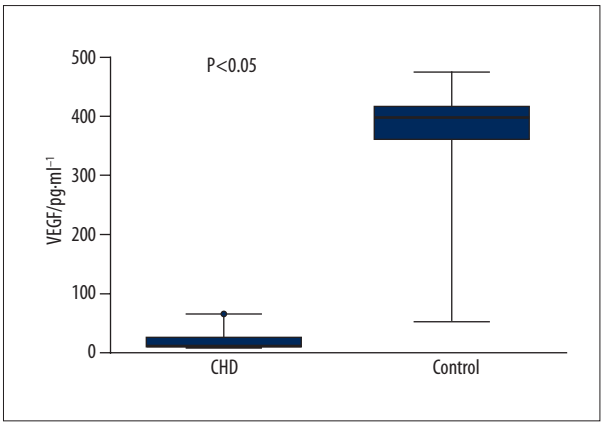

Figure 1. Serum level of *VEGF* in CHD patients and healthy controls. *VEGF* level was significantly downregulated in CHD patients (*P*<0.05).

VEGF level in CHD patients and healthy controls

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).

Kaplan-Meier curve and Cox analysis

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).

Discussion

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,

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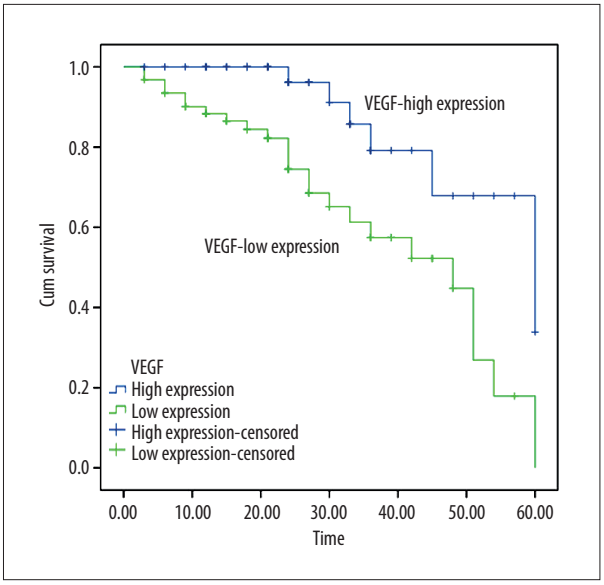

Figure 2. Kaplan-Meier curve. Patients with a low level of *VEGF* showed worse prognosis compared to those with higher levels ($P<0.05$).

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 has 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 investigating the situation of individuals. Zhang et al. reported that smoking was related with poor clinical outcomes after PCI or CABG therapy of CHD patients [20]. Further analysis indicated that non-access site-related bleeding complications were correlated with worse prognosis of patients after PCI therapy [21]. Another study suggested that serum apelin level could predict cardiac events in CHD patients receiving PCI therapy and that it was related with survival of patients [22]. Konishi et al. concluded that high levels of lipoprotein were associated with poor prognosis of patients after PCI [23]. *VEGF* was demonstrated to be related with MACE in CHD patients after PCI [7]. Based on the above reports, we decided to investigate whether *VEGF* is related with prognosis of CHD patients receiving PCI therapy, which will help improve survival of CHD patients.

Our study firstly analyzed the serum level of *VEGF* in CHD patients and healthy controls. The results indicated that *VEGF* level was significantly lower in CHD patients compared to controls. The outcome was consistent with previous studies [7,24,25]. However, Kazmierczak et al. found increased levels of *VEGF* in patients with chronic stable angina pectoris [26,27]. These inconsistent results may result from the variations in severity of CHD, onset period, pathogenesis, and population composition. The patients were divided into 2 groups according to *VEGF* levels. Further analysis showed that sex distribution and hypertension situation were related with *VEGF* expression level. Then, Kaplan-Meier curve indicated that *VEGF* level exerted strong effects on the survival of CHD patients. Patients with low-level *VEGF* were more likely to have poor prognosis. Cox regression results suggested that *VEGF* could serve as a promising prognostic biomarker in CHD.

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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