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Original Article

The expressions of HGF, PDGF, VEGF and Angl in peripheral arterial blood and coronary artery blood of patients with acute coronary syndromes and the relationship with disease severity

Feng Lin[1], Xiangqian Ren[2], Weizu Wang[2], Suihao Zhang[1], Bin Yuan[2]

[1]*Department of Cardiology, The Second Clinical Medical College of Jinan University, Shenzhen People's Hospital, Shenzhen, Guangdong, China;* [2]*Department of Cardiology, Anning Branch of The 940th Hospital of The People's Liberation Army, Lanzhou, Gansu, China*

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Abstract: Objective: Our study aims to investigate the expressions of hepatocyte growth factor (HGF), platelets derived growth factor (PDGF), vascular endothelial growth factor (VEGF), angiopoietin I (Angl) in peripheral arterial blood and coronary artery blood of patients with acute coronary syndromes (ACS), and to determine their relationship with disease severity. Methods: In total 148 ACS patients were enrolled. Additionally, there were 50 volunteers with normal CAG regarded as the control group. The levels of HGF, PDGF, VEGF and Ang-1 in peripheral arterial blood were detected, the correlation of which with the disease severity was analyzed. Results: The levels of HGF and PDGF in the coronary artery blood of ACS patients were significantly higher than those in the peripheral arterial blood ($P < 0.05$). However, the contents of VEGF and Angl in the coronary artery blood of ACS patients were statistically lower than those in the peripheral arterial blood ($P < 0.05$). Additionally, the levels of HGF, PDGF and VEGF in the peripheral arterial blood of ACS patients were significantly increased compared to those in the control volunteers ($P < 0.05$). Besides, the Gensini score of ACS patients was (36.93 ± 1.47), which was statistically higher than that of the control group (5.48 ± 0.62) ($P < 0.05$). Correlation analysis showed that the Gensini score was positively associated with levels of HGF, PDGF, VEGF ($P < 0.05$). Conclusion: The levels of HGF, PDGF, and VEGF in the peripheral arterial blood and coronary artery blood of patients with acute coronary syndromes were significantly changed compared to that in normal individuals, and were positively correlated with the Gensini score of ACS, which provides basis for the further diagnosis of ACS.

Keywords: Osteoporosis acute coronary syndromes, coronary artery blood, Gensini score, hepatocyte growth factor, platelet derived growth factor

Introduction

Acute coronary syndromes (ACS) represents a type of severe coronary heart disease (CHD) and refers to complete or incomplete vessel occlusion caused by the secondary rupture of the coronary artery by atherosclerotic plaque. However, the specific pathogenesis remains unknown. Recent studies indicate that the mortality rate of ACS is high, followed by instability angina pectoris (UA), ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) [1, 2]. At present, common therapies for CHD in clinic include conservative drug treatment, percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [3]. However, due to the severity and complication of ACS, current treatment of CHD is still unsatisfactory. Therefore, it is imperative to explore the pathogenesis of ACS and develop new treatment strategies. Therapeutic angiogenesis emerges as a new treatment direction for ACS. As hepatocyte growth factor (HGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and angiopoietin I (Angl) all play important roles in angiogenesis, their involvement in the pathogenesis of ACS remains poorly understood. This study aims to investigate the expression profiles of HGF, PDGF, VEGF and

Table 1. General clinical data analysis of patients

Group	Cases (case)	BMI (kg/m^2)	Average age (years)	Gender (case)		Diabetes history (n, %)	Hypertension history (n, %)	Smoking history (n, %)
				Male	Female			
Control group	50	21.67 ± 4.17	62.86 ± 7.35	28	22	9 (18.0)	13 (26.0)	13 (37.14)
ACS group	148	22.45 ± 2.39	61.99 ± 8.02	81	67	31 (20.95)	49 (33.11)	61 (41.22)

AngI in peripheral arterial blood and coronary artery blood of patients with acute coronary syndromes (ACS), as well as determine their relationship with disease severity.

Patients and methods

Clinic data

In this study, 148 ACS patients who were treated by coronary angiography (CAG) in our hospital from July 2016 to June 2017 were enrolled, including 81 male patients and 67 female patients with an average age of 62.86 ± 7.35 years old ranging from 44 to 81 years old. They included 52 UA patients, 51 STEMI patients and 45 NSTEMI patients. According to the CAG examination in our hospital, there were no abnormal results. Fifty patients with negative examinations of myocardial enzyme and cardiac troponin were included in this study as the control group. Gensini score was adopted to evaluate disease stages. Age, gender, body mass index (BMI), diabetes history, hypertension history and smoking history of both groups were basically comparable between the two groups ($P > 0.05$) (**Table 1**). This study was approved by the ethics committee in our hospital and all the subjects provided informed consent.

Inclusion criteria

(1) The patients was diagnosed with ACS through evaluation by CAG, clinic symptoms and auxiliary examination; (2) The patients and their family members signed informed consent.

Exclusion criteria

(1) Patients didn't meet the above inclusion criteria; (2) The patients had severe disturbance of consciousness, hypertensive crisis, or acute heart failure before treatment; (3) The patients had severe combined impairment of liver and kidney function; (4) The patients had severe blood system diseases or hemorrhagic disease; (5) The patients had malignant tumor.

Main instruments and reagents

A GTR16-2 type high-speed desktop refrigerated centrifuge was used (Beijing Times Beili Centrifuge Co., Ltd., Beijing, China). A US ELX-808 type fully-automatic quantitative drawing microplate reader was used (Shanghai Maisha Biotechnology Co., Ltd., Shanghai, China). HGF, PDGF, VEGF, AngI ELISA kits were purchased from BD (San Jose, CA, USA).

Coronary angiography (CAG)

Patients were injected at 2 cm of the processus styloideus radii, with an injection of 3000 U-6000 U heparin through a sheathing canal. All-round X-ray examination for left and right coronary arteries was performed while DSA image processing system for quantitative analysis of the degree of coronary artery stenosis was adopted. Gensini scoring system was used for evaluation: 1 score, stenosis < 25%; 2 score, 25%-50% stenosis; 4 score: 51%-75% stenosis; 8 score: 76%-90% stenosis; 16 score: 91%-99% stenosis; 32 score, 100% stenosis. Coefficient of each section of the coronary artery: left main coronary artery × 5; proximal segment, meddle segment and distal segment of anterior descending branch × 2.5, × 1.5, × 1, respectively. The first and second diagonal branches were × 1, × 0.5, respectively; proximal segment, meddle segment and distal segment of circumflex branch were × 2.5, × 1.5, × 1, respectively. The proximal segment, meddle segment and distal segment of the right coronary artery, posterior descending branch and posterior branch of left ventricle were × 1, respectively. All disease scores were summed as final total scores.

In order to detect indicators related to angiogenesis, 5 ml blood from the coronary artery blood of the ACS patients was extracted. When all subjects were processing CAG, 5 ml blood of the radial artery or peripheral blood of the femoral artery was collected. Blood samples were centrifuged at 1500 g at room temperature and

Table 2. Comparison of examination results of subjects of both groups at admission (mean ± SD)

Group	PLT (× 10^9/L)	PFG (mmol/l)	HbAlc (%)	TG (mmol/l)	TC (mmol/l)	HDL (mmol/l)	LDL (mmol/l)
Control group	176.95 ± 69.37	5.41 ± 1.48	6.33 ± 1.56	1.23 ± 1.24	4.11 ± 1.65	1.26 ± 0.17	2.52 ± 0.21
ACS group	217.43 ± 81.62*	6.58 ± 1.28*	6.24 ± 0.97	1.05 ± 1.33	3.98 ± 1.44	1.26 ± 0.34	2.57 ± 0.16

Note: *Compared with control group, P < 0.05.

Table 3. Comparison of HGF, PDGF, VEGF and angi levels of peripheral arterial blood and coronary artery blood of ACS patients (mean ± SD)

ACS	HGF (ng/ml)	PDGF (ng/ml)	VEGF (pg/ml)	Angl (ng/ml)
Coronary artery	39.05 ± 8.33	3.87 ± 1.04	1.36 ± 0.38	7.57 ± 2.16
Peripheral arterial blood	7.42 ± 1.08*	1.02 ± 0.36*	91.24 ± 26.42*	32.69 ± 10.22*

Note: *Compared with blood content of coronary artery of ACS patients, P < 0.05.

Table 4. Comparison of HGF, PDGF, VEGF and angi levels of peripheral arterial blood and gensini score of subjects of both groups (mean ± SD)

Group	HGF (ng/ml)	PDGF (ng/ml)	VEGF (pg/ml)	Angl (ng/ml)	Gensini Score
Control group	1.27 ± 0.18	0.26 ± 0.02	19.83 ± 7.49	29.76 ± 9.15	5.48 ± 0.62
ACS group	7.42 ± 1.08*	1.02 ± 0.36*	91.24 ± 26.42*	32.69 ± 10.22	36.93 ± 1.47*

Note: *Compared with control group P < 0.05.

the supernatant was collected and stored at -80°C.

According to the ELISA levels, HGF, PDGF, VEGF and Angl in serum were detected. A fully-automatic quantitative microplate reader was used to measure the OD value at the wavelength of 450 nm.

Statistical treatment

SPSS 21.0 software was used for statistical analysis. Data were presented as means ± standard deviation (SD). Those samples that fitted a normal distribution were compared by two-sample independent *t*-test. One-way ANOVA, with the Tukey's post hoc test was performed for the analysis on data from multiple groups. Pearson examination or Spearman examination was adopted for correlation analysis. P < 0.05 indicated statistical significance.

Results

Preoperative examination

Blood biochemical indexes in both groups were examined and the result showed that, platelet count (PLT) and fasting blood-glucose content of ACS patients were significantly higher than those of the control group (*P* < 0.05). However, other indexes including glycosylated hemoglobin (HbAlc), triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) presented no statistical differences (P > 0.05) (**Table 2**).

HGF, PDGF, VEGF and Angl levels in peripheral arterial blood and coronary artery blood

HGF, PDGF, VEGF and Angl contents in the peripheral arterial blood and the coronary artery blood of ACS patients were then detected in our study and we found that the values of HGF and PDGF from the coronary artery of ACS patients were significantly higher than those from the peripheral arterial blood, but VEGF and Angl levels were statistically lower than those from the peripheral arterial blood (P < 0.05) (**Table 3**).

We further compared the HGF, PDGF, VEGF and Angl contents from the peripheral arterial blood of ACS patients with those in the control group. Interestingly, levels of HGF, PDGF and VEGF from the peripheral arterial blood of ACS patients were significantly higher than those of the control group (P < 0.05). However, Angl levels from the peripheral arterial blood showed no statistical difference with that of the control group (P > 0.05). In addition, the Gensini score of the ACS patients (36.93 ± 1.47) was significantly higher than that of the control group (5.48 ± 0.62) (P < 0.05) (**Table 4**).

Table 5. Correlation analysis of gensini score and expression of HGF, PDGF, VEGF and AngI

Variable	r	*P*
HGF	0.419	0.012
PDGF	0.731	0.003
VEGF	0.486	0.010
AngI	0.119	0.078

Correlation analysis of HGF, PDGF, VEGF, AngI and Gensini score

Pearson analysis was performed for correlation analysis. Our data indicated that the Gensini score was positively correlated with the levels of HGF, PDGF and VEGF of the ACS patients ($P < 0.05$) without significant association with the level of AngI ($P > 0.05$) (**Table 5** and **Figure 1**).

Discussion

Coronary heart disease is one of the cardiovascular and cerebrovascular diseases that severely impairs human health, and it can give rise to remarkably high mortality rates and disability rates. In recent years, the age of onset presents towards a younger trend. It also causes a great economic burden to the family of patients, but the pathogenesis remains poorly understood [4, 5]. ACS is the most severe coronary heart disease [6]. Increasing studies have confirmed that, coronary endothelial dysfunction, plaque rupture, platelet aggregation, inflammation and other aspects are closely related to the development and progression of ACS [3, 7]. In particular, endothelia injury inflammation theory is proposed and increasingly recognized as the cause of arterial intimal injury [8].

HGF, PDGF, VEGF and AngI belong to a multitiude of cell factors and are closely related to the generation of the inflammatory reaction, angiogenesis, apoptosis and other physiological and pathological processes [9]. HGF is derived from Leydig cells and specifically combines with C-met receptor. It can activate multiple signaling pathways, participate in angiogenesis and inhibit apoptosis. Meanwhile, it is also involved in the repair and proliferation of endothelial cells to protect ischemic myocardial cells [10, 11]. In this study, levels of HGF, PDGF, VEGF and AngI from the coronary artery of ACS patients were apparently changed compared to those from peripheral arterial blood, indicating the potential role of these molecules in the pathogenesis of ACS. Similar to HGF, PDGF also exerts various physiological effects on vasoconstriction by inhibiting the synthesis of endothelium-derived relaxing factor. After endothelial injury occurs in ACS patients, platelets are activated, which promotes the release of PDGF and AngI, as well as further induces migration of smooth muscle cells into the intima to form thrombus [12]. Recent research utilized PDGF as a candidate gene to predict long term outcome in patients with acute myocardial infarction [13]. VEGF secreted from vascular endothelial cells is necessary for growth and differentiation of endothelial cells [14]. AngI also can strengthen angiogenesis of VEGF, induce endothelial cell aggregation to promote vascular damage and endothelialization [15].

It is suggested that HGF and PDGF are expressed in various organs through the endocrine pathway [16]. The levels of HGF and PDGF from the coronary artery blood of ACS patients are higher than those from the peripheral arterial blood, which was consistent with the findings in our study. Generally, VEGF in the body is maintained at a low level. In response to ischemia and anoxia, a large amount of VEGF can be secreted for compensation and repair of ischemic tissues [17]. In this scenario, the content of VEGF from the peripheral arterial blood is higher than that of the coronary artery blood.

In addition, we also found that levels of HGF, PDGF and VEGF in the peripheral arterial blood of ACS patients were higher than those of the control group. VEGF has effects on new vessels, promotes connection of endothelial cells and with the extracellular matrix [18]. Intriguingly, our result exhibited that AngI levels in the peripheral arterial blood of patients was not significantly different from that of controls. Presumably, AngI mainly plays a role in vascular remodeling and maturation during the late angiogenesis period and is closely related to VEGF [19]. Whereas Pearson correlation analysis showed no statistical relation was found between the Gensini score and AngI. The exact effect of AngI, as well as HGF, PDGF, VEGF, also requires further investigation within a large group of samples in order to comprehensively evaluate the prognostic values [20, 21].

Conclusion

Our data demonstrate that HGF, PDGF, VEGF and AngI are closely related to the development

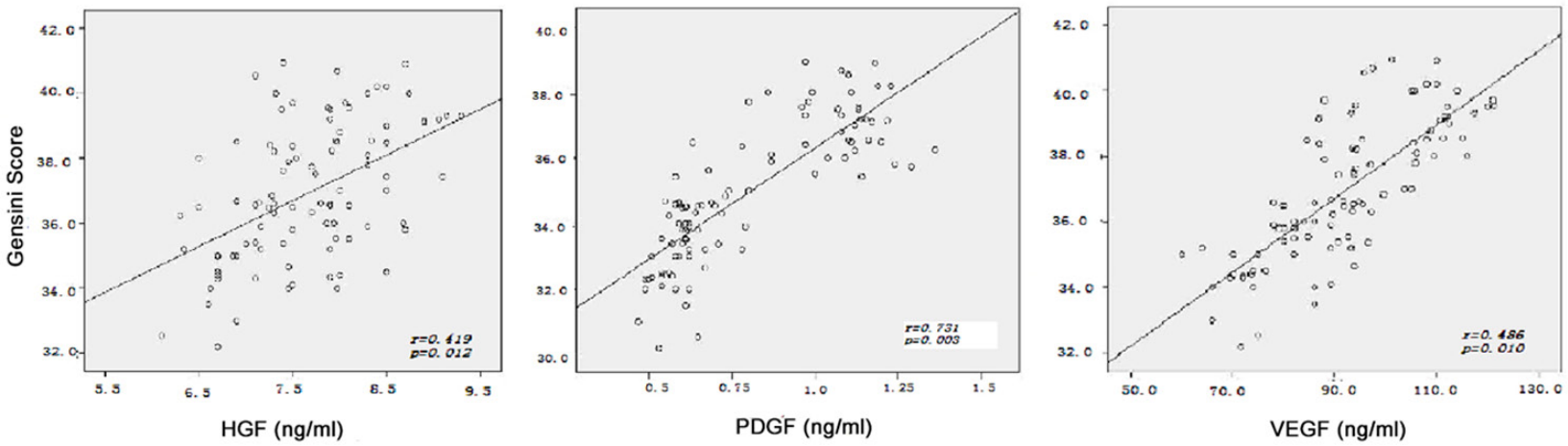

Figure 1. Correlation analysis of gensini score and expression of HGF, PDGF and VEGF.

of ACS and can serve as potential molecular markers, which provides new insights for future ACS diagnosis and disease severity prediction.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bin Yuan, Department of Cardiology, Anning Branch of The 940th Hospital of The People's Liberation Army, 1026 Anning East Road, Lanzhou 730070, Gansu, China. Tel: +86-15117209956; Fax: +86-931-2583999; E-mail: hongliangliu8yj@163.com

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