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The predictive value of serum S1P and STIM1 levels after PCI for in-stent restenosis and their correlation with angiogenesis and inflammatory response

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ABSTRACT

Objective: To study the predictive value of serum S1P and STIM1 levels after percutaneous coronary intervention (PCI) for in-stent restenosis and their correlation with angiogenesis and inflammatory response. **Methods:** 130 patients who received PCI in our hospital between June 2013 and December 2016 were selected and divided into restenosis group and non-restenosis group according to the coronary angiography results 6-24 months after PCI. The serum levels of S1P, STIM1, angiogenesis molecules and inflammation molecules were detected 24 hours after PCI. **Results:** Serum S1P, NO, VEGF, Angptl2 and Angptl4 levels of restenosis group were significantly lower than those of non-restenosis group while STIM1, IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels were significantly higher than those of non-restenosis group; serum NO, VEGF, Angptl2 and Angptl4 levels of restenosis group with lower STIM1 were significantly higher those of restenosis group with normal STIM1; serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels of restenosis group with lower S1P were significantly higher than those of restenosis group with normal S1P. **Conclusion:** The decreased serum S1P and increased STIM1 after PCI have prediction value for in-stent restenosis and are closely related to the angiogenesis disorder and inflammation activation.

1. Introduction

Percutaneous coronary intervention (PCI) is an effective method for treatment of coronary heart disease, which can expand the coronary artery with stenosis and restore blood perfusion to the ischemic myocardium[1,2]. However, the occurrence of in-stent restenosis after PCI will affect the treatment effect, and the early predicting the risk of in-stent restenosis and implementing intervention can effectively improve the outcome after PCI. In-stent restenosis is considered to be local vascular self-repair after injury, and the reendothelialization dysfunction, platelet adhesion and aggregation, the activation of the inflammatory response, and the proliferation of smooth muscle cells are all closely related to the occurrence of restenosis[3,4]. Sphingosine-1-phosphate (S1P) and stromal interaction molecule 1 (STIM1) are the vasoactive molecules discovered in recent years, the former participates in regulation of angiogenesis process and is closely associated with reendothelialization after stenting, and the latter is involved in the regulation of inflammation process and closely related to the inflammation activation and the platelet aggregation after stenting[5,6]. In the following studies, the predictive value of serum S1P and STIM1 levels after PCI for in-stent restenosis and their correlation with angiogenesis and inflammatory response were analyzed.

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2. General information of PCI patients and methods of clinical research

2.1 General information of PCI patients

130 patients who received PCI in our hospital between June 2013 and December 2016 were selected as the research subjects, and all patients were with clear indications of PCI after coronary angiography, received drug-coated stent implantation, were with TIMI flow grade III and residual stenosis < 30% after PCI, and accepted the dual antiplatelet therapy and statins lipid-lowering therapy after surgery. The coronary angiography results 6-24 months after PCI were used to determine whether there was in-stent restenosis, in-stent restenosis more than 50% was judged as restenosis, and restenosis less than 50% or no restenosis was judged as non-restenosis. The patients with and without restenosis were included in restenosis group and non-restenosis group respectively. There were 58 cases in restenosis group, including 38 men and 20 women that were 46-62 years old; there were 72 cases in non-restenosis group, including 45 men and 27 women that were 43-63 years old. There was no significant difference in general information between the two groups of patients (P>0.05).

2.2 Clinical research methods

2.2.1 Serum sample collection methods

24 h after PCI, 5-8 mL of cubital venous blood was collected from patients, let stand at room temperature for 1 h for natural coagulation, and centrifuged for 10 min at a speed of 3 000 r/min, and the upper serum was isolated, moved into the new 1.5 mL EP tube and stored at -80 ℃.

2.2.2 Serum S1P and STIM1 detection and evaluation methods

Serum specimens were taken and dissolved at room temperature, enzyme-linked immunosorbent assay kit was used to detect the contents of S1P and STIM1, the median of S1P and STIM1 contents of restenosis group were calculated respectively, the restenosis patients with serum levels lower than the median were judged as restenosis patients with lower S1P and STIM1, and the restenosis patients with serum levels higher than the median were judged as restenosis patients with normal S1P and STIM1.

2.2.3 Serum angiogenesis molecule and inflammation molecule detection methods

Serum samples were taken and thawed at room temperature, and enzyme-linked immunosorbent assay kit was used to detect the contents of angiogenesis molecules NO, VEGF, Angptl2 and Angptl4 as well as the contents of inflammation molecules IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin.

2.3 Statistical processing

SPSS 19.0 software was used for data processing, analysis of above serum data between two groups was by t test and P<0.05 indicated statistical significance in differences.

3. Results

3.1 Serum S1P and STIM1 levels

Serum S1P and STIM1 levels of restenosis group were (83.41±10.24) ng/L and (12.15±1.47) U/L respectively; serum S1P and STIM1 levels of non-restenosis group were (129.36±16.76) ng/L and (7.38±0.93) U/L respectively. After t test, serum S1P level of restenosis group was significantly lower than that of non-restenosis group while STIM1 level was significantly higher than that of non-restenosis group, and differences in serum S1P and STIM1 levels were statistically significant between two groups of patients (P<0.05).

3.2 Serum angiogenesis molecule levels and their correlation with STIM1

Analysis of serum angiogenesis molecules NO (mol/L), VEGF (ng/L), Angptl2 (μg/L) and Angptl4 (μg/L) levels between restenosis group and non-restenosis group was as follows: serum NO, VEGF, Angptl2 and Angptl4 levels of restenosis group were significantly lower than those of non-restenosis group, and differences in serum NO, VEGF, Angptl2 and Angptl4 levels were statistically significant between two groups of patients (P<0.05), shown in Table 1.

Analysis of serum angiogenesis molecules NO, VEGF, Angptl2 and Angptl4 levels between restenosis group of patients with different STIM1 levels was as follows: serum NO, VEGF, Angptl2 and Angptl4 levels of restenosis group with lower STIM1 were significantly higher those of restenosis group with normal STIM1. Differences in serum NO, VEGF, Angptl2 and Angptl4 levels were statistically significant between between restenosis group of patients with different STIM1 levels (P<0.05), shown in Table 2.

Table 1.

Serum angiogenesis molecule levels in restenosis group and non-restenosis group.

Groups	n	NO	VEGF	Angptl2	Angptl4
Restenosis group	58	101.32±15.85	389.64±56.41	83.94±11.03	163.29±22.58
Non-restenosis group	72	176.49±22.36	594.64±75.82	147.59±19.46	293.48±36.27
T		8.298	8.918	7.589	8.038
P		<0.05	<0.05	<0.05	<0.05

Table 2.

Serum angiogenesis molecule levels in restenosis group of patients with different STIM1 levels.

STIM1 level	n	NO	VEGF	Angptl2	Angptl4
Lower	29	135.37±18.39	484.58±60.38	110.32±16.73	216.83±32.18
Normal	29	78.42±9.38	302.42±42.39	59.62±8.35	129.49±15.72
T		8.938	7.027	10.598	8.427
P		<0.05	<0.05	<0.05	<0.05

Table 3.

Serum inflammation molecule levels in restenosis group and non-restenosis group.

Groups	*n*	IFN-γ	IL-18	VCAM-1	P-selectin	L-selectin
Restenosis group	58	10.37±1.75	78.54±9.35	174.29±22.35	8.49±0.93	103.25±16.83
Non-restenosis group	72	4.57±0.55	45.28±6.28	94.21±10.25	3.58±055	45.68±6.48
T		12.018	8.308	9.118	15.287	11.495
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 4.

Serum inflammation molecule levels in restenosis group of patients with different S1P levels.

SIP level	*n*	IFN-γ	IL-18	VCAM-1	P-selectin	L-selectin
Lower	29	13.94±2.03	95.61±11.35	239.41±29.58	9.93±1.26	138.69±20.35
Normal	29	6.92±0.87	60.32±8.39	120.32±16.84	6.58±0.83	63.49±8.92
T		11.982	7.308	9.482	6.798	10.589
P		<0.05	<0.05	<0.05	<0.05	<0.05

3.3 Serum inflammation molecule levels and their correlation with S1P

Analysis of serum inflammation molecules IFN-γ (μg/L), IL-18 (ng/L), VCAM-1 (ng/L), P-selectin (μg/L) and L-selectin (ng/L) levels between restenosis group and non-restenosis group was as follows: serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels of restenosis group were significantly higher than those of non-restenosis group, and differences in serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels were statistically significant between two groups of patients (P<0.05), shown in Table 3.

Analysis of serum inflammation molecules IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels between restenosis group of patients with different S1P levels was as follows: serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels of restenosis group with lower S1P were significantly higher than those of restenosis group with normal S1P. Differences in serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels were statistically significant between between restenosis group of patients with different S1P levels (P<0.05), shown in Table 4.

4. Discussion

Reendothelialization is an important way to repair local stent area after PCI, and it can maintain the integrity of the endothelial barrier, and prevent the exposure of subendothelial collagen and the activation of thrombosis. STIM1 is a kind of calcium channel receptor that has regulatory effect on the calcium ion flow inside and outside of cells, and can affect the extracellular calcium distribution to regulate cell proliferation, migration and differentiation. STIM1 is involved in the control of endothelial progenitor cell biology in the progression of various cardiovascular diseases. The endothelial progenitor cell homing to the blood injured vessel is a way of partial restoration after stenting, which can promote the process of stent reendothelialization[7]. When STIM1 expression and secretion increase, the homing functions as well as the proliferation and migration process of endothelial progenitor cells are suppressed, which influence the local blood vessel damage repair by reendothelialization after stent implantation[8]. In the study, analysis of the relationship between serum STIM1 content 24 hours after PCI and in-stent restenosis 6-24 months after operation showed that serum STIM1 level of restenosis group was significantly higher than that of non-restenosis group. This suggests that the excessive STIM1 secretion in the serum after PCI will increase the risk of in-stent restenosis.

The process of angiogenesis is an important biological behavior for local stent area to complete reendothelialization, which is closely related to various cytokines. VEGF is the strongest cytokine that promotes angiogenesis, and it can promote the proliferation of endothelial cells and the formation of vascular structures[9]; NO is a gas signaling molecule with endothelial diastolic action, which can promote endothelial repair and angiogenesis[10]; Angptl2 and Angptl4 are important molecules that regulate the endothelial intercellular adhesion and junction, which can not only maintain the integrity of endothelial structure, but also promote the differentiation and growth of endothelial cells[11]. In the study, analysis of the relationship between serum angiogenesis molecules 24 h after PCI and in-stent restenosis 6-24 months after operation showed that serum NO, VEGF, Angptl2 and Angptl4 levels of restenosis group were significantly lower than those of non-restenosis group. This indicates that the insufficient secretion of angiogenesis factors and the disorder of stent reendothelialization after PCI are closely related to the occurrence of in-stent restenosis. Further analysis of the correlation between serum STIM1 and angiogenesis molecules in patients with restenosis showed that serum NO, VEGF, Angptl2 and Angptl4 levels of restenosis group with lower STIM1 were significantly higher those of restenosis group with normal STIM1. This means that the increased STIM1 secretion in serum after PCI will decrease the secretion of angiogenesis molecules and affect the angiogenesis process and stent reendothelialization process to increase the risk of in-stent restenosis.

Inflammation is the important pathological change throughout each

link of cardiovascular disease, the formation of atheromatous plaque, the reduced stability and rupture of plaque and the formation of blood clots are related to the excessive activation of the inflammatory response. In the occurrence of in-stent restenosis, the inflammatory response can mediate the platelet activation and thrombosis in local damaged blood vessels, and they are closely related to the lumen stenosis. S1P is the intermediate product of sphingomyelin metabolism in the body, the functions of both second messenger and ligand, and can not only regulate downstream inflammatory reaction within the cells through signaling pathways, but also be combined with membrane receptor S1PR to induce downstream Akt phosphorylation and inhibit inflammatory reaction[12]. Animal study has confirmed that S1P inhibits the accumulation of white blood cells and the apoptosis of myocardial cells in ischemic myocardial tissue[13]. In the study, analysis of the relationship between serum S1P content 24 h after PCI and in-stent restenosis 6-months after operation showed serum S1P level of restenosis group was significantly lower than that of non-restenosis group. This indicates that the insufficient secretion of S1P in serum after PCI will increase the risk of in-stent restenosis.

IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin are the cytokines closely associated with inflammatory response in atherosclerosis. IFN-γ and IL-18 are important pro-inflammatory cytokines that can mediate inflammatory response cascade activation; VCAM-1 can mediate the adhesion between inflammatory cells and vascular endothelial cells, and the P-selectin and L-selectin can mediate the adhesion between blood platelet and vascular endothelium, and promote the platelet aggregation and activation[14,15]. In the study, analysis of the relationship between serum inflammation molecules 24 h after PCI and in-stent restenosis 6-24 months after operation showed that serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels of restenosis group were significantly higher than those of non-restenosis group. This suggests that the excessive secretion of inflammation molecules and the activation of inflammatory response after PCI are closely related to the occurrence of in-stent restenosis. Further analysis of of the correlation between serum S1P and inflammation molecules in patients with restenosis showed that serum IFN-γ, IL-18, VCAM-1, P-selectin and L-selectin levels of restenosis group with lower S1P were significantly higher than those of restenosis group with normal S1P. This suggests that the deficiency of S1P secretion in serum after PCI will increase the inflammation molecule secretion and activate inflammatory response to increase the risk of in-stent restenosis.

The decreased S1P level and the increased STIM1 level in serum after PCI are closely related to the occurrence of in-stent restenosis, and have predictive value for the occurrence of restenosis; lower serum S1P content is closely related to the activation of inflammatory response, and higher serum STIM1 content is closely related to angiogenesis and reendothelialization dysfunction.

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