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Original Article

The relationship between levels of tumor necrosis factor-alpha, interleukin-6, and C-reactive protein in the serum of elderly and acute myocardial infarction

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Abstract

This study aimed to explore the relationship between the serum levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and hypersensitive C-reactive protein (hs-CRP) and the prognosis of acute myocardial infarction (AMI) patients after percutaneous coronary intervention (PCI) treatment. A total of 118 early-onset AMI patients who successfully received PCI (in the PCI group, blood samples were collected before PCI, 12, 24, 48 h after PCI, and 90 d follow-up period) and 52 AMI patients who received only cardioangiography (CAG) (in the CAG group, blood samples were collected before CAG, 12, 24, 48 h after CAG, and 90 d follow-up period). The serum levels of IL-6, hs-CRP and TNF-α were detected, and the incidence of major adverse cardiac events (MACE) in the PCI group during follow-up was observed. The basic levels of IL-6, hs-CRP, and TNF-α between the PCI group and the CAG group were not statistically different (P>0.05); there was no statistically significant difference in changes of serum IL-6, hs-CRP, and TNF-α in the CAG group before and after CAG (P>0.05); IL-6, hs-CRP, and TNF-α in the PCI group were significantly higher than those before treatment (P<0.01); in the PCI group, the levels of IL-6, hs-CRP and TNF-α between the MACE group and the MACE-free group were statistically different (P<0.05). Serum IL-6, hs-CRP and TNF-α levels in AMI patients after PCI significantly increased in the short term, and PCI may induce an inflammatory response; the high levels of inflammatory cytokines, IL-6, hs-CRP, and TNF-α, in peripheral blood may have an important reference value for MACE and short-term prognosis in early-onset AMI patients after PCI.

Keywords: Acute myocardial infarction, C-reactive protein, Interleukin-6, Tumor necrosis factor-α.

1. Introduction

Myocardial infarction (MI), occurs when the blood flow in a part of the heart is reduced or stopped, causing damage to the heart muscle. The most common symptom is chest pain or discomfort that may radiate to the shoulder, arm, back, neck, or jaw. It usually occurs in the center or left side of the chest and lasts more than a few minutes. Discomfort can sometimes feel like a stomach ache. Other symptoms may include shortness of breath, nausea, feeling weak, cold sweats, or feeling tired. About 30% of people have unusual symptoms. In women, sometimes chest pain does not appear and instead, they have neck pain, arm pain or feel tired. Among people over age 75, about 5% of people who have had a stroke had few or no symptoms. A heart attack may cause heart failure, irregular heartbeat, cardiac shock, or cardiac arrest [1, 2].

Acute myocardial infarction (AMI) is a dangerous and critical illness that endangers people's lives and health. Clinical studies have shown that the inflammatory response is the pathological basis for the occurrence and development of coronary heart disease, and is an important mechanism for the occurrence and development of coronary atherosclerosis. Even if the stent is implanted in the infarcted myocardium, it persists after the operation, and the inflammatory response to restenosis after stent surgery is one of the important mechanisms [1, 2]. Inflammatory cytokines are the regulation and participation cytokines of inflammatory response, indicating that inflammatory cytokines also play important roles in the process of coronary heart disease. Hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6, etc., can promote the ischemia-reperfusion injury of myocardial cells, leading to poor clinical prognosis of AMI [3-5]. This study explored the changes of IL-6, hs-CRP, and TNF-α and other inflammatory cytokines, and revealed their intrinsic relationship and the association with the severity of AMI.

2. Materials and methods

2.1. General data

A total of 170 early-onset AMI patients from January 2019 to January 2021 were continuously enrolled in our hospital. Among them, the PCI group: The 118 patients who successfully received direct PCI treatment within 12 h of the onset of symptoms, 66 males and 52 females, aged 41~72 (61.70 ± 10.53) years. All patients successfully received PCI, and cardioangiography (CAG) blood flow classification (TIMI classification) reached level III. The patients' general clinical conditions, CAG and PCI data, etc., were recorded in detail. The CAG group: The

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patients were diagnosed with myocardial infarction (MI) by CAG, but did not continue interventional treatment due to the following reasons: 1) The patients or family members were afraid of interventional risks or required drug treatment due to economic reasons; 2) the CAG detected a multivessel disease, or the location of the disease was not suitable for interventional treatment; 3) the patients experienced discomfort during the operation and could not tolerate further interventional treatment; there were a total of 52 cases, the patients and their families were fully communicated with and signed relevant informed consent forms, and the records were kept. The diagnosis of AMI adopted the American College of Cardiology (ACC)/American Heart Association (AHA) diagnostic criteria in 2007 [6], which met at least four of the following: 1) Typical ischemic chest pain symptoms lasting more than 30 minutes; 2) characteristic dynamic evolution of ECG; 3) the biochemical markers of myocardial necrosis consistent with the characteristic changes of MI; 4) the CAG showed that the anatomy of the infarct-related arteries can be performed with PCI. All selected patients signed informed consent and were approved by the ethics committee of the hospital.

Exclusion criteria: 1) Past MI history; 2) used to receive percutaneous coronary angioplasty or stent implantation; 3) severe cardiac insufficiency, and ejection fraction < 30%; 4) excluding autoimmune diseases and abnormal liver function; 5) excluding patients with acute and chronic infections, hematological diseases, malignant tumors, and chronic kidney disease; 6) excluding patients with trauma, surgery, and severe infections within 3 months; 7) patients who had recently taken glucocorticoids or immunosuppressants. At the same time, 100 normal healthy individuals were selected as the control group. There were no significant differences in age, gender and body mass index (BMI) between the two groups (P>0.05), as shown in Table 1.

2.2. Treatment methods

CAG and PCI were performed according to conventional methods. According to the standard Judkins method, the femoral artery or radial artery approach was chosen for CAG to confirm the infarct-related arteries. PCI success criteria: After stent implantation, the vascular lumen of the diseased site was significantly enlarged, the residual vascular stenosis was less than 20%, and there was no surgery and clinical complications (such as death, MI, emergency target lesion vascular reconstruction, etc.). Before the operation, antiplatelet drugs were orally taken according to the conventional method, and aspirin 300 mg and clopidogrel 300 mg were prescribed; 100-150 U/kg unfractionated heparin was used during the operation to maintain the intraoperative activated coagulation time >300 s. After the operation, a maintenance dose of aspirin 300 mg/d was followed, and after 1 month, it was changed to 100 mg/d for life, and clopidogrel was orally taken at 75 mg/d for at least 1 year. AMI patients were routinely given low-molecular-weight heparin for 5-7 days during the perioperative period. The treatment of coronary artery expansion, heart strengthening, blood pressure reduction, lipid regulation, and blood sugar reduction were all performed according to conventional methods.

2.3. Sample collection

All AMI patients were drawn 3-5 ml of venous blood within 6-12 h (before PCI) of the onset of AMI and 12, 24, 48 h, and 90 days after operation, injected into the test tube pre-added with EDTA and aprotinin, immediately placed on ice and centrifuged at 3000 r/min for 15 min in a high-speed refrigerated centrifuge. The serum was separated and placed in a refrigerator at -70°C for testing. Repeated freezing and thawing needed to be avoided. ELISA method was used to determine the serum levels of IL-6, hs-CRP and TNF-α in 118 patients in PCI group and 52 patients in CAG group. The kit was purchased from German IBL company, and the detection was carried out by professional test technicians in strict accordance with the operating instructions. The detection instrument was a microplate reader MODEL550 produced by Bio-Rad Company, USA.

2.4. The occurrence of MACR

Patients in the PCI group were followed up to observe the occurrence of MACE within 90 days after surgery, including angina pectoris, non-fatal reinfarction, revascularization of infarction-related blood vessels, heart failure and cardiogenic death [7]. The outpatient or telephone follow-up was used. The observation period was 90 days. According to whether MACE occurred within 90 days, they were divided into the MACE group and the MACE-free group.

2.5. Statistical analysis

SPSS 21.0 software was used for analysis, measurement data was expressed as x ± s, measurement data comparison between groups was performed by two independent sample t-tests, and classification data was analyzed by Fisher exact probability method or x test. The paired t-test was used for the comparison before and after diagnostic CAG and before and after PCI. Repeated measures analy-

Table 1. General data of patients in the two groups.

Index	CAG group (52)	PCI group (118)	P	t/χ^2
Age (year)	61.70 ± 8.65	62.53 ± 9.97	0.6037	0.5200
Gender (male/female)	30/22	67/51	0.9118	0.01227
BMI (kg/m^2, x ± s)	24.55 ± 1.87	24.72 ± 1.92	0.5786	0.5565
Hypertension [n (%)]	24 (46.1)	69 (58.5)	0.1370	2.2110
Diabetes [n (%)]	19 (36.5)	53 (44.9)	0.3084	1.0370
Smoking [n (%)]	22 (42.3)	63 (53.4)	0.1830	1.7730
Mono-vessel pain [n (%)]	23 (44.2)	47 (39.8)	0.5912	0.2885
Multi-vessel pain [n (%)]	29 (55.8)	71 (60.2)	0.5912	0.2885
Receiving anticoagulant and antiplatelet drug treatment [n (%)]	43 (2.6)	95 (80.5)	0.7371	0.1127
Total cholesterol (mmol/L, x ± s)	4.82 ± 0.43	4.91 ± 0.85	0.4707	0.7230

sis of variance was applied between different time points of PCI. Spearman-grade correlation analysis was performed for different lesions of PCI. Univariate Logistic regression analysis was used for preliminary screening of risk factors, and multivariate Logistic regression analysis was used to further reveal the effect of different factors on dependent variables. After PCI, the odds ratio (OR) was used to describe the relationship between variables and outcomes to reveal the effect of IL-6, hs-CRP, and TNF-α on the occurrence of MACE in AMI patients.

3. Results

3.1. Comparison of general data between the two groups

There were no statistically significant differences in age, gender, and BMI distribution between the PCI group and the control group (P>0.05), suggesting that the PCI group and the CAG group were comparable, as shown in Table 1.

3.2. Comparison of changes in serum levels of inflammatory cytokines between the two groups

The levels of inflammatory cytokines in the two groups are shown in Tables 2 and 3. There were no significant differences in the basic serum levels of IL-6, hs-CRP, and TNF-α between the two groups (P>0.05). There were no statistically significant differences in the changes of various indicators at each time point before and after operation in the control group (F = 2.498, P>0.05). The levels of IL-6, hs-CRP, and TNF-α in the PCI group were significantly higher 12, 24, and 48 h after operation than those before operation, and successively reached the peak during this period, and then began to decrease, and the differences were statistically significant (F = 4.173, P<0.05); the serum concentration of each indicator 90 days after operation returned to the preoperative level (P>0.05), and compared with the level 48 h after the onset, there was a significant decrease (P<0.05).

3.3. The relationship between the serum levels of IL-6, hs-CRP and TNF-α and MACE

The patients in the PCI group were followed up for 90 days after the onset of the disease. A total of 42 patients had MACE, including 4 cases of recurring myocardial infarction, 21 cases of angina pectoris, 12 cases of heart failure, 5 cases of revascularization, and 0 cases of cardiogenic death. According to the occurrence of MACE, it was divided into two subgroups of the MACE group (42 cases) and the MACE-free group (76 cases). The t-test was used to compare the differences in the levels of IL-6, hs-CRP, and TNF-α at 3 d of onset between the two subgroups, as shown in Table 4. The levels of IL-6, hs-CRP and TNF-α

Table 2. The serum levels of IL-6, hs-CRP, and TNF-α before and after CAG in the CAG group (x ± s).

Time point	IL-6 (pg/ml)	hs-CRP (mg/L)	TNF-a (ng/L)
Before operation	41.39 ± 6.96	5.95 ± 1.13	11.97 ± 3.09
12 h after operation	43.17 ± 7.12	6.10 ± 1.07	12.31 ± 2.43
24 h after operation	44.23 ± 8.93	6.02 ± 1.02	13.03 ± 3.87
48 h after operation	42.35 ± 6.98	6.13 ± 1.21	12.54 ± 3.65
90 d after operation <1	41.09 ± 7.99	5.76 ± 1.18	11.89 ± 2.49

Table 3. The serum levels of IL-6, hs-CRP and TNF-α before and after operation in the PCI group (x ± s).

Time point	IL-6 (pg/ml)	hs-CRP (mg/L)	TNF-a(ng/L)
Before operation	44.17 ± 7.23	6.23 ± 1.27	12.92 ± 3.14
12 h after operation	59.71 ± 8.25*	24.25 ± 4.13*	17.28 ± 4.37*
24 h after operation	84.23 ± 11.93$^{\#}$	30.76 ± 6.66$^{\#}$	31.97 ± 7.15$^{\#}$
48 h after operation	62.35 ± 9.98^{a}	35.32 ± 8.71^{a}	21.32 ± 6.03^{a}
90 d after operation <1	43.29 ± 8.03^{b}	6.37 ± 1.32^{b}	13.14 ± 4.01^{b}

Note: Versus preoperative: *P<0.05; versus 12 h after operation: $^{\#}$P<0.05; versus 24 h after operation: ^{a}P<0.05; versus 48 h after operation: ^{b}P<0.05.

Table 4. The levels of IL-6, hs-CRP and TNF-α in the MACE-free group and the MACE group after PCI.

Index	MACE-free group (n=76)	MACE group (n=42)	P	t/χ^2
Age (year)	61.63 ± 9.87	63.75 ± 19.79	0.2009	1.120
Gender (male/female)	43/33	24/18	0.9528	0.003
BMI (kg/m^2)	24.75 ±1.93	25.09 ± 2.01	0.3685	0.903
Hypertension [n (%)]	39 (51.3)	30 (71.4)	0.0338	4.507
Diabetes [n (%)]	29 (38.2)	24 (57.1)	0.0471	3.941
Smoking [n (%)]	37 (48.7)	26 (62.0)	0.1681	1.900
Total cholesterol (mmol/L)	4.82 ± 0.73	5.09 ± 0.82	0.0683	1.840
Triacylglycerol (mmol/L)	1.95 ± 0.85	2.23 ± 0.78	0.0805	1.763
Low-density lipoprotein (mmol/L)	3.95 ± 0.79	4.25 ± 0.91	0.0000	1.870
High-density lipoprotein (mmol/L)	1.06 ± 0.37	1.15 ± 0.46	0.2491	1.158
Fibrinogen (g/L)	4.66 ± 0.69	4.95 ± 0.92	0.0553	1.936
IL-6 (pg/ml)	42.01 ± 7.83	45.32 ± 18.21	0.0328	1161
hs-CRP (mg/L)	6.17 ± 11.27	6.75 ± 11.51	0.0285	1219
TNF-a (ng/L)	12.40 ± 4.56	14.49 ± 4.75	0.0205	2.349

Table 5. Multivariate stepwise Logistic regression analysis of early complications.

Item	Regression coefficient	Standard error	P	OR (95 % CI)
Hypertension	0.921	0.460	0.0411	2.513 (1.127-12.475)
Diabetes	0.860	0.394	0.0352	2.363 (1.247-10.384)
IL-6	1.416	0.343	0.0252	4.122 (2.351-15. 159)
hs-CRP	0.762	0.291	0.0219	3.987 (2.031-14.853)
TNF-a	1.431	0.319	0.0136	4.185 (2.071-17.661)

in the MACE group were significantly higher than those in the MACE-free group (P<0.05).

3.4. The serum levels of IL-6, hs-CRP and TNF-α and related parameters after PCI predict short-term complications

Using the recent complications as dependent variables, and the age, gender, BMI, hypertension, diabetes, smoking, total cholesterol, triacylglycerol, low-density lipoprotein, high-density lipoprotein, fibrinogen, IL-6, hs-CRP and TNF-α as independent variables, univariate Logistic regression analysis first showed that the levels of IL-6, hs-CRP and TNF-α, hypertension, diabetes, and fibrinogen after PCI all had a high predictive value for early complications after PCI. Using early complications as the dependent variable and P<0.01 as the independent variable, further multivariate stepwise Logistic regression analysis was performed. Hypertension (OR = 2.513, 95% CI: 1.127-12.475), diabetes (OR =2.363, CI: 1.247-10.384), and the levels of IL-6 (OR = 4.122, CI: 2.351-15.159), hs-CRP (OR = 2.143, CI: 1.317-13.572), and TNF-α after PCI (OR = 4. 185, CI: 2. 071-7. 661) were more significant, as shown in Table 5.

4. Discussion

In recent years, the role of inflammation in the occurrence, development, and outcome of coronary atherosclerotic lesions and coronary stent restenosis has received increasing attention [8, 9]. PCI can open infarct-related blood vessels early, quickly, adequately, and effectively, and restore forward blood flow, thereby effectively reducing mortality. At the same time, the inflammatory responses and adverse cardiovascular events caused by this have also received increasing attention. Stone et al. have believed that the mechanisms of PCI triggering inflammatory response roughly include mechanical damage and ischemia-reperfusion, and PCI leads to plaque rupture, arterial wall destruction, vascular endothelial damage, and the release of inflammatory cytokines and chemokines, promoting the entry of white blood cells into the tissue [7]. In addition, the balloon dilation repeatedly blocks the coronary arteries during PCI, causing myocardial ischemia, and the reperfusion of ischemic myocardium triggers a series of adverse events, leading to more serious myocardial injury than ischemic injury. At present, there is still not much predictive value of inflammatory cytokines in the prognosis of AMI patients undergoing direct PCI, and it is not comprehensive enough [10, 11].

IL-6 is a cytokine with multiple biological activities. Wassmann et al have found that IL-6 promotes the synthesis of low-density lipoprotein receptors on the surface of macrophages and the uptake of low-density lipoproteins by macrophages, accelerating lipid deposition, thus, IL-6 is closely related to unstable plaque. hs-CRP is an acute-phase protein synthesized by the liver. It is synthesized by the liver which is stimulated by cytokines produced by the activated inflammatory cells, which can activate the complement system and participate in the inflammatory response. Ridker et al. believe that hs-CRP is the new independent predictor of coronary heart disease with the strongest predictive effect among the 12 cardiovascular disease markers [12]. TNF-α is an inflammatory cytokine with multiple functions in the body, which can cause inflammation, cell necrosis and the formation of new blood vessels, and promote the production of endothelin, which leads to the damage of blood vessel walls, thus exerting the role of promoting atherosclerosis [13].

This study showed that the serum levels of IL-6, hs-CRP, and TNF-α in AMI patients undergoing PCI were significantly higher than those before surgery, while there were no significant changes in the postoperative serum levels of IL-6, hs-CRP, and TNF-α in AMI patients undergoing CAG alone compared with those before surgery, suggesting that PCI may trigger and aggravate this inflammatory response of coronary arteries in a short term.

At the same time, in this study, AMI patients carried out a 90-day follow-up after successful PCI, and the occurrence of major MACE events was recorded. This study showed that the serum levels of IL-6, hs-CRP, and TNF-α after PCI were closely related to the patients' short-term prognosis. The MACE event survey results of AMI patients 90 days after PCI showed that the serum levels of IL-6, hs-CRP, and TNF-α in the MACE group were significantly higher than those in the MACE-free group; univariate and multiple stepwise Logistic regression analysis demonstrated that the serum levels of IL-6, hs-CRP and TNF-α, blood pressure and blood glucose after PCI have a significant predictive value for early complications after PCI, confirming that the serum levels of IL-6, hs-CRP, and TNF-α can be directly used to judge the short-term prognosis of patients undergoing PCI. This research has an important reference value for early clinical identification of high-risk patients, clinical guidance of early anti-inflammation treatment for AMI patients after PCI and providing new ideas and theoretical basis for postoperative targeted intervention.

Informed consent

The authors report no conflict of interest.

Availability of data and material

We declared that we embedded all data in the manuscript.

Authors' contributions

MJ conducted the experiments and wrote the paper; DT conceived, designed the study and revised the manuscript.

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