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Evaluated plasma interleukin-18/interleukin-10 ratio is a risk factor for acute coronary syndromes in patients with stable angina pectoris

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Abstract

Background: *Studies suggested that interleukin-18 (IL-18)/interleukin-10 (IL-10) ratio is an independent predictor of adverse cardiovascular events in patients with acute coronary syndromes (ACS). In this study we aimed to evaluate the predictive significance of IL-18/IL-10 for the occurrence of ACS in patients with stable angina pectoris (SAP) over a 40-month follow-up.*

Methods: *The IL-18, IL-10 levels of 257 patients with SAP were determined by Enzyme-Linked Immunosorbent Assay (ELISA). Two hundred and fifty-two patients, 42 of whom had ACS and 210 were event-free, were divided into two groups according to the presence or absence of the occurrence of ACS during the 40-month follow-up.*

Results: *Plasma IL-18 and IL-18/IL-10 ratios were both significantly higher ($p = 0.001$ and $p = 0.044$, respectively) among patients with ACS, however, IL-10 level was lower ($p = 0.046$) compared to the patients without ACS. The elevation of plasma IL-18/IL-10 ratio and the number of coronary artery lesions made the advantage ratio of ACS in patients with SAP increase 4.242 times and 1.942 times ($p = 0.000$ and $p = 0.011$, respectively).*

Conclusions: *Plasma IL-18 and IL-10 levels in patients with SAP are closely related to the occurrence of ACS, elevated IL-18/IL-10 ratio has a positive predictive value for the occurrence of ACS in patients with SAP.* (Cardiol J 2014; 21, 1: 83–88)

Key words: stable angina pectoris, acute coronary syndromes, interleukin 18, interleukin 10

Introduction

The formation of complete or incomplete occlusive thrombus as a result of the erosion or rupture of vulnerable plaque is the pathological basis of acute coronary syndrome (ACS). Our long-term clinical practice suggests that although patients have different clinical manifestations, the underlying pathophysiological changes are very similar, that is the coronary atherosclerosis plaque transforms into vulnerable plaques, then ruptures and leads to the formation of thrombosis. Obviously, the rupture of coronary artery vulnerable plaque is one of the most important links in the occurrence of ACS. A number of studies [1–3] shows that inflammation plays an important role in the formation and rupture of vulnerable plaques.

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A variety of inflammatory cells and secreted pro--inflammatory cytokines make the fibrous cap of the plaque become thinner and the lipid core of the plaque become larger, leading to the formation of vulnerable plaque phenotype prone to rupture.

Interleukin-18 (IL-18) is a multi-performance pro-inflammatory cytokine, which plays an important role in inflammatory reaction [4]. IL-18 may accelerate the formation of vulnerable plaques [5] and is closely related to the occurrence and prognosis of ACS [6, 7]. Interleukin 10 (IL-10) is a kind of an anti-inflammatory cytokine which can reduce the formation of atherosclerosis and maintain the stability of atheromatous plaques, which play an important role in inhibiting the occurrence of ACS [8, 9]. Patients with ACS show an imbalance between serum levels of pro- and anti--inflammatory cytokines. Clinical data confirm that [6, 10, 11] IL-18 and IL-10 have predictive values for the prognosis of patients with ACS, however, it is not yet clear if they also have predictive values for the occurrence of ACS in patients with stable angina pectoris (SAP). In this study, we detected the plasma IL-18, IL-10 levels in patients with SAP and all patients were followed up. In order to investigate the correlation between IL-18/IL-10 ratio and the occurrence of ACS in patients with SAP, plasma IL-18/IL-10 ratio was determined as a correlative factor which may affect the prognosis of coronary heart disease (CHD).

Methods

Patient selection and follow-up

According to the definition of SAP from ACC/ /AHA CHD classification criteria, a total of 257 patients (175 male and 82 female, of average age 64.06 ± 10.46 years) with SAP were enrolled during the period of March 2007 and September 2008 in the Vasculocardiology Deparment of General Hospital of Guangzhou Military Command after obtaining the ethical approval and informed consent from all of them. All patients were confirmed by coronary angiography, having at least one major vascular stenosis ≥ 50% as the standard for vascular lesion and lesion number. Of the 257 patients, all were confirmed by medical history, physical examination, laboratory examination and assistant examination. Patients with myocarditis, severe cardiac dysfunction, peripheral vascular disease, severe liver and kidney diseases, autoimmune diseases, blood diseases, inflammation infection, other severe systemic diseases, or patients using inflammation inhibitor were excluded.

Patients' gender, age, body mass index (BMI), smoking history, history of diabetes, hypertension, and hyperlipidemia on admission were recorded, if not clearly, related examinations were conducted. Criteria for smokers are: current smokers (≥ 5 cigarettes/day) or having smoking history of more than 10 years but quitting less than 1 year before. According to the Chinese dyslipidemia prevention advice of 2006, hyperlipidemia diagnostic criteria are: hypercholesterolemia (total cholesterol ≥ 6.22 mmol/L and/or low-density lipoprotein cholesterol ≥ 4.14 mmol/L), hypertriglyceridemia (triglycerides ≥ 2.26 mmol/L) and combined hyperlipidemia. The above information, age and BMI were processed as data for measurement, all other data were processed as count data.

All patients without contraindications were given primary drug treatment of CHD (aspirin, beta receptor blocker and/or ACEI, nitrates, etc.). Patients with major vascular stenosis ≥ 70% were given percutaneous coronary intervention therapy, and low molecular weight heparin and/or platelet GP IIb/IIIa receptor antagonist, clopidogrel, etc., were given based on the primary drug treatment of CHD. Patients with diabetes received oral hypoglycemic or insulin hypoglycemic treatment. Patients who did not reach the standard of glycosylated hemoglobin ≥ 6.5% (Chinese Chronic Stable Angina Diagnosis and Treatment Guidelines of 2006), were closely followed up (1 time/month) and given more strengthening drugs. The glycosylated hemoglobin was closely monitored until it reached the standard. Patients with hypertension received oral hypertension treatment; aged patients (over the age of 60) who did not reach the standard, elderly systolic blood pressure ≥ 150 mm Hg and non--elderly blood pressure ≥ 130/80 mm Hg (Chinese Chronic Stable Angina Diagnosis and Treatment Guidelines of 2006), were closely followed up (1 time/month) and given more strengthening drugs. The blood pressure was closely monitored until it reached the standard. Unless contraindicated, patients with hyperlipidemia received statin treatment; patients who did not reach the standard, low density lipoprotein ≥ 2.6 mmol/L and/or total cholesterol ≥ 4.68 mmol/L (Chinese Dyslipidemia Control Suggestion of 2006), were closely followed up (1 time/month) and given more strengthening drugs. Lipidemia was closely monitored until it reached the standard. All smoking patients received patient education and smoking cessation guidance until they quit smoking successfully.

All patients were followed up once a month after being discharged by telephone contacts, letters,

Table 1. Patient characteristics with or without acute coronary syndromes.

Characteristic	Group A (n = 42)	Group B (n = 210)	χ^2/t	p
Gender (male)	28 (66.67%)	144 (63.57%)	$\chi^2 = 0.059$	0.809
Mean age [years]	64.62 ± 12.03	63.85 ± 10.13	t = 0.433	0.514
Smoking	18 (42.85%)	64 (30.48%)	$\chi^2 = 2.705$	0.100
History of diabetes	20 (47.62%)	68 (32.38%)	$\chi^2 = 3.576$	0.059
History of hypertension	22 (52.38%)	87 (41.43%)	$\chi^2 = 1.711$	0.191
History of hyperlipidemia	20 (47.62%)	76 (32.38%)	$\chi^2 = 1.938$	0.164
Lesion number: 1 branch	15	96	$\chi^2 = 10.562$	0.005
2 branches	15	51		
≥ 3 branches	8	26		
Mean BMI [kg/m^2]	25.30 ± 2.91	24.14 ± 3.03	t = 2.080	0.860
Main lesion stenosis [%]	74.88 ± 11.45	71.90 ± 12.69	t = 1.411	0.330
Treatment (stenting)	26 (61.90%)	117 (55.71%)	$\chi^2 = 1.921$	0.166

BMI — body mass index

or visit to collect medical records up to 40 months (March 2007 – February 2012). The end-point of the study was ACS (unstable angina pectoris, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction were included). Patients were divided into two groups according to the presence (group A) or absence (group B) of ACS during the 40 month follow-up.

IL-18 and IL-10 measurements

Fasting venous blood samples were drawn on the first morning after permission, 5 mL peripheral venous blood was placed into an ENTA-2Na anticoagulant tube, after centrifugation at 3000 rpm for 15 min, radius of 1 cm. One mL upper plasma was collected for biochemical examination of blood lipid, blood glucose and hepatorenal function. The residual upper plasma in EP tube was frozen in a –70°C refrigerator. The samples were applied by enzyme-linked immunosorbent assay (ELISA) kit (Rapidbio, Calabasas, CA, USA) and measured on a Biocell HT_2 ELISA microplate reader, operating strictly according to the kit instructions.

Statistical analysis

SPSS 17.0 was used to analyze the data. Continuous variables are presented as mean ± SD, and categorical data are presented as percentages. Independent-sample t-test was used to analyze the mean differences between the two groups in age, BMI, the degree of main lesion stenosis, the plasma IL-18, the plasma IL-10 and IL-18/IL-10 ratio. The fourfold table χ^2 test was used to compare the differences between the two groups in gender, smoking, diabetes, hypertension, and treatment methods. Logistic stepwise regression was used to analyze the linear relationship between IL-18/IL-10, smoking, age, gender, diabetes, hypertension, hyperlipidemia, BMI, the grade of main lesion stenosis, treatment methods, and occurrence of ACS. $P < 0.05$ was considered statistically significant.

Results

During the 40 month follow-up of 257 patients, 4 cases were lost (telephone number and address change), 1 case had a sudden death (died of a brain hemorrhage). Forty-two (18.01%) patients had ACS, 33 patients had unstable angina pectoris, 6 patients had ST-segment elevation myocardial infarction and 3 patients had non-ST-segment elevation myocardial infarction.

Table 1 shows that, during the follow-up, ACS group (group A) and non-ACS group (group B) had no significant differences (all $p > 0.05$) in age, gender, smoking, diabetes, hypertension, hyperlipidemia, BMI, the degree of main lesion stenosis, and treatment methods. They had significant difference in the number of coronary artery lesions ($p = 0.005$).

Table 2 shows the plasma IL-18 level. The IL-18/IL-10 ratio of group A was significantly higher than group B ($p = 0.001$ and $p = 0.044$, respectively). However, the IL-10 level of group B was higher than group A ($p = 0.046$).

The analyzed data took IL-18/IL-10 ratio, smoking, age, gender, diabetes, hypertension, hyperlipidemia, BMI, the grade of main lesion stenosis, and treatment methods as independent variables and the occurrence of ACS as dependent variable

Table 2. Plasma interleukin (IL)-18, IL-10, and IL-18/IL-10 levels in patients with or without acute coronary syndromes (mean ± SD).

	Group A (n = 42)	Group B (n = 210)	t	p
IL-18 [ng/L]	221.16 ± 78.30	170.27 ± 50.84	5.350	0.001
IL-10 [ng/L]	99.60 ± 35.17	117.76 ± 38.94	2.801	0.046
IL-18/IL-10	2.32 ± 0.73	1.57 ± 0.62	6.968	0.044

Table 3. Correlation factors analysis of the occurrence of acute coronary syndromes in patients with stable angina pectoris.

Correlative factors	P	OR	SE
IL-18/IL-10	0.000	4.242	0.279
Age	0.498	1.013	0.019
Gender	0.729	0.864	0.422
Smoking	0.224	1.635	0.404
Diabetes	0.270	1.565	0.406
Hypertension	0.526	1.291	0.402
Hyperlipidemia	0.764	1.132	0.412
Body mass index	0.214	1.090	0.086
Lesion number	0.011	1.942	0.664
Degree of MLS	0.156	1.037	0.037
Treatment	0.509	0.654	0.644

OR — odds ratio; SE — standard error of mean; MLS — main lesion stenosis

for logistic stepwise regression. From Table 3 we found that the elevation of plasma IL-18/IL-10 ratio and the number of coronary artery lesions made the advantage ratio of ACS in patients with SAP increase up to 4.242 ($p = 0.000$) and 1.942 ($p = 0.011$) times, respectively. Other factors were not significantly associated with the occurrence of ACS in patients with SAP (all $p > 0.05$).

Discussion

To our current knowledge, the main pathophysiological processes of ACS are the rupture, ulcers of vulnerable plaques and thus thrombus formation, leading to a series of clinical syndromes. Vulnerable plaque means all the atherosclerotic lesions which are prone to thrombosis, and may have a rapid progress to become a sin plaque. Inflammation not only promotes the occurrence of atherosclerosis and participates in the formation of vulnerable plaque [1–3], but also promotes the occurrence of ACS. As a pro-inflammatory cytokine, IL-18 plays a central role in the inflammatory reaction [4], accelerating atherosclerosis progress, promoting atherosclerotic plaque transforming into vulnerable plaque phenotype which would make the occurrence of ACS [12–14]. IL-10 is a major anti-inflammatory cytokine, which can inhibit the activity of inflammatory cells and down-regulate the expression and biological activity of inflammatory cytokines, thus inhibiting the occurrence and development of ACS [8, 14]. From our currently presented data, it is evident that, on one hand, IL-18/IL-10 ratio can reflect the body's inflammatory state, yet on the other hand, it is closely related to the occurrence of ACS. Clinical data showed that [10, 14] IL-18/IL-10 ratio had predictive value for the prognosis of ACS. In view of the role of IL-18 and IL-10 in the occurrence of ACS in patients with SAP, we speculate that the IL-18/IL-10 ratio should have a certain degree of clinical significance in prognosis of ACS in patients with SAP, however, the clinical data is of shortage. Here, in this study, IL-18 and IL-10 levels in patients with SAP were determined during a 40-month follow-up and were further included as the correlative factors that may indicate the prognosis of CHD.

The results showed that during the follow-up of 257 patients, ACS group and non-ACS group had no significant differences in age, gender, smoking, diabetes, hypertension, hyperlipidemia, BMI, the degree of main lesion stenosis, and treatment

methods. The results also showed that the above factors were not significantly associated with the occurrence of ACS in patients with SAP. However, the number of the coronary lesions is significantly higher in SAP patients with ACS than the SAP patients without ACS. Logistic regression analysis results also suggested that multivessel lesion elevated 1.942 times the risk of the occurrence of ACS in patients with SAP, which suggested that multivessel lesion was one of the risk factors for the occurrence of ACS in patients with SAP.

Compared to the patients without ACS, the plasma IL-18 level is significantly increased in patients with ACS. It suggests that IL-18 may promote the occurrence of ACS in patients with SAP, which is similar to Nishihira's findings [15]. The mechanism of vulnerable plaque formation promoted by IL-18 may be: (1) IL-18 stimulates the release of a variety of pro-inflammatory mediators (such as TNF, IL-1β, IL-6, and iNOS etc.). These inflammatory factors, promote the macrophage apoptosis in atherosclerotic plaque [16–18], increase the lipid core in plaque; (2) macrophages activated by IL-18 can secrete matrix metalloproteinase and collagen, which can make the fibrous cap become thinner [12]. The current results of this study showed that the plasma IL-10 level in patients with ACS was lower than in those without ACS, suggesting that IL-10 may suppress the occurrence of ACS. The mechanism may be related to its strong anti-inflammatory effect to maintain the stability of the atherosclerotic plaque.

Since IL-18 is the important pro-inflammatory cytokine and IL-10 is the pivotal anti-inflammatory cytokine conversely, the IL-18/IL-10 ratio can reflect the body's inflammatory activity state to a certain extent. Our results revealed that IL-18/ /IL-10 ratio was markedly higher in patients with ACS than those without ACS. Further logistic stepwise regression analysis showed that plasma IL-18/IL-10 ratio made the advantage ratio of the occurrence of ACS in patients with SAP increase 4.242 times; other factors, except for the number of coronary artery lesion, had no significant correlation with the occurrence of ACS in patients with SAP, suggesting that the enhanced body inflammatory activity and IL-18/IL-10 ratio as a predictive factor for the occurrence of ACS in patients with SAP. In recent years some studies have shown [9] IL-18/IL-10 ratio is an independent predictor of recurrent cardiovascular events in patients with ACS. Our study extends the view that IL-18 and IL-10 may play an important role in the occurrence and development of ACS.

Conclusions

In conclusion, plasma levels of IL-18, IL-10 in patients with SAP are closely related to the occurrence of ACS and IL-18/IL-10 ratio has some predictive value for the occurrence of ACS in patients with SAP. Therefore, in clinical practice, conventional detection of plasma levels of IL-18 and IL-10 in patients with SAP can be applied as a risk assessment method for the occurrence of ACS in patients with SAP. Moreover, the ratio has positive significance in the treatment of patients whom have increased IL-18/IL-10 ratio. This study may provide a new insight into the clinical treatment of ACS in patients with SAP.

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Conflict of interest: none declared

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