Original Article
Correlation of CD4+ and CD8+ T lymphocytes and Th17 with acute coronary syndrome

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Abstract: We studied CD4+ and CD8+ levels in peripheral blood from patients with acute coronary syndrome (ACS) before and after treatment. We also examined the percentage of Th17 among CD4+ T lymphocytes to determine whether its trend changes and to evaluate the clinical significance of such changes. We studied 100 patients, dividing them into the following 4 groups: (1) an acute myocardial infarction (AMI) group (n=30), (2) an unstable angina pectoris (UAP) group (n=30), (3) stable angina pectoris (SAP) group (n=20) and (4) control group (n=20). The percentage of peripheral blood mononuclear cells (PBMCs) from each group was measured by flow cytometry. The differences among the groups were evaluated, and their correlations with the severity of coronary atherosclerosis (Gensini score) were analyzed. In this study, the proportions of CD8+ lymphocytes in the UAP and AMI groups before treatment were significantly lower than in the normal control group. After treatment, the CD4+/CD8+ ratio in the ACS group increased, as the proportion of CD8+ T lymphocytes significantly decreased. Before treatment, the proportions of peripheral blood Th17 cells among CD4+ T cells in the UAP and AMI groups were significantly higher than in the SAP and normal control groups. We also found that the percentage of Th17 cells among CD4+ T cells decreased significantly after treatment. Therefore, the levels of CD4+ and CD8+ T lymphocytes correlate with the severity of coronary atherosclerosis. Th17 cells also play a role in forming unstable atherosclerotic plaques in coronary heart disease.

Keywords: Inflammatory reaction, acute coronary syndrome, T lymphocyte, CD4+, CD8+, Th17

Introduction

Coronary atherosclerotic heart disease (CHD) is one of the most rapidly rising causes of death and one of the most severe diseases that threaten public health among Chinese residents. Current work suggests that inflammation enhances immune cell infiltration and promotes platelet adhesion and aggregation, leading to plaque rupture, complete or incomplete occlusion of the lumen, and subsequent acute coronary syndrome (ACS). Therefore, inflammatory cells and factors involved in immunity play important roles in the occurrence and development of ACS [1, 2]. Studies have shown that CD8+ T cells can secrete a large number of inflammatory cytokines after activation and that the activation of macrophages releases a variety of cytokines that initiate an immune cascade effect and promote atherosclerosis (AS) [3, 4].

Based on their secretion of different cytokines, CD4+ T lymphocytes can be divided into many functional subgroups, such as Th1, Th2, Th17 and regulatory T cells (Tregs) [5, 6]. Th17, a newly identified subgroup of CD4+ Th cells, represents a specific effector T cell subpopulation that is characterized by the secretion of interleukin-17 (IL-17A). Th17 cells can act on different target cells to induce the production of other cytokines and are involved in the regulation of cytokine networks that trigger the release of inflammatory mediators; they thus elicit a variety of biological effects. A number of studies have confirmed the role of Th17 cells in a variety of chronic inflammatory diseases, including AS [7, 8]. In this study, flow cytometry analysis was used to detect CD4+, CD8+ T lymphocytes and Th17 cells in peripheral blood from ACS patients before and after treatment and to understand their abundance trends and clinical significance.

Materials and methods

Subjects and groups

We selected 100 patients who were hospitalized at the Department of Cardiology from June 2014 to August 2015 at the First Affiliated Hospital of Shihezi University Medical College. All of the selected patients underwent coronary angiography (CAG). CHD diagnosis was made according to the World Health Organization diagnostic criteria for CHD [9]. CAG was used to confirm that at least one coronary arterydisplayed inner diameter stenosis of greater than 50%. Patients were divided into 4 groups based on diagnostic criteria. The first group was the normal control and case group, which included 20 patients who had unexplained chest discomfort and displayed no abnormalities after routine examination. Coronary artery disease was excluded after CAG. The stable angina pectoris (SAP) group included 20 patients with fatigue angina pectoristhat did not changeover 2 months. The exercise test was positive, and CAG was used for diagnosis as CHD. The unstable angina pectoris (UAP) group included 30 patients who were diagnosed with CHD and met the following conditions: (1) Resting angina with duration >20 min; (2) Severe initial angina or worsening angina; (3) When angina attacked, ST segmentsfrom the electrocardiogram changed quickly and returned to normal or near normal; And (4) cardiac troponin T (cTnT) was negative, excluding angina after infarction. Finally, the acute myocardial infarction (AMI) group also included 30 patients. According to clinical symptoms, ECG changes and dynamic evolution, simple right ventricular infarction was excluded, and CAG was used for the diagnosisas CHD.

Cases were removedbased on the following exclusion criteria: (1) Patients with combined stroke, severe liver and kidney dysfunction; (2) Patients who experienced myocardial infarction in the past 6 months; (3) Patients with pain in the precordial area more than 12 hours after admission to the hospital; (4) Patients with peripheral vascular disease or peripheral vascular thrombotic disease; And (5) patients with malignant tumors and rheumatic diseases. Patients with infectious diseases, such as sepsis, severe upper respiratory tract infection, pulmonary or biliary tract infection or hyper-thermia, and patients who used anti-inflammatory drugs, such as non-steroidal anti-inflammatory drugs, steroids and opiates, were also excluded.

Specimen collection and research methods

Blood samples were taken 3 times from each AMI patient. Five milliliters of venous blood were extracted from the middle of the elbow under aseptic conditions when thrombolysis was not performed: (1) Within 24 hours of AMI onset or before percutaneous coronary intervention (PCI); (2) Within 24 hours of surgery completion; and (3) on the morning of the discharge day with an empty stomach. Five milliliters of venous blood were taken 3 times from each UAP patient. The blood collection times were 2 days after admission, within 24 hours of surgery and on the morning of the discharge day with an empty stomach. Five milliliters of fasting venous blood were collected from patients in the control and SAP groups on the morning of the second admission day. Heparin sodium anticoagulation and peripheral blood mononuclear cell (PBMC) separation were used for flow cytometry.

PBMCs were isolated by density gradient centrifugation after dilution with phosphate-buffered saline (PBS). The cell concentration was adjusted to 2×10^6 cells/ ml in RPMI1640 supplemented with phorbol myristate acetate (PMA, 50 µg/L), 1 µmol/L ionomyc in and 50 µg/L protein transfer inhibitor monensin (PMA) in 24-well plates. The plates were mixed and placed in a 37°C and 5% CO_2 incubator for 4 hours (the main reagents were purchased from Alexis Biochemicals, San Diego, CA). The collected cells were divided into experimental tubes and isotype control tubes according to cell counting. Fluorescein isothiocyanate (FITC) or phycoerythrin (PE) labeled anti-human CD4 or CD8 monoclonal antibody (4 µl) was added to the cells according to the design group; The cells were then incubated at 4°C for 30 min. Next, the cells were washed twice with PBS; Centrifuged to separate the supernatant, which was then removed; And fixed at room temperature in the dark for 20 min. For Th17 analysis, the cells were then washed 2 more times with PBS before 1 ml of rupture agent was added to each tube for cell drilling, which enhanced cytokine monoclonal antibody permeation into the

Table 1. Clinical data from patients in the different groups (mean ± SD)

Characteristics	AMI	UAP	SAP	Control	F/X^2	P
	n=30	n=30	n=20	n=20		
Sex (male)	26 (86.7%)	25 (83.3%)	7 (35%)	14 (70.0%)	2.232	0.337
Age (years)	52.17±11.94	55.6±10.27	52.6±10.27	50.55±9.49	1.576	0.215
Smoking	17 (56.7%)	16 (53.3%)	9 (45.0%)	8 (40.0%)	1.418	0.492
Hypertension	18 (60.0%)	14 (46.6%)	8 (40.0%)	9 (45.0%)	1.484	0.476
Diabetes mellitus	5 (16.67%)	5 (16.67%)	2 (10.0%)	2 (10.0%)	0.524	0.848
Urea nitrogen	6.057±2.46	5.88±1.29	5.8±1.50	5.78±1.92	0.811	0.449
Creatinine	88.68±30.71	83.43±19.77	82.41±20.12	81.90±22.05	3.452	0.178
TG (mmol/L)	1.83±0.68	1.57±0.66	1.63±0.61	1.65±0.69	0.873	0.423
LDL (mmol/L)	2.60±0.74	2.48±0.95	2.45±0.87	2.50±0.83	0.422	0.658
HDL (mmol/L)	0.91±0.28	0.94±0.24	0.94±0.15	0.94±0.17	0.125	0.883
TC (mmol/L)	4.8±0.97[a]	4.08±0.87[a]	4.04±1.05[a]	4.03±1.06	3.962	0.024

Values are expressed as the mean ± SD or as a number. AMI, acute myocardial infarction; UA, unstable angina; SA, stable angina; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol. Note: [a]P<0.05 compared with the normal control group.

cells. After the cells were centrifuged and the supernatant was discarded, intracellular cytokine staining was performed. PE anti-human IL-17A (4 µl) for Th17 detection after fixation and permeabilization was added to the experimental tube and the corresponding control tube, and the tubes were incubated for 30 min at 4°C in the dark, washed twice with PBS and analyzed by flow cytometry (main reagents were purchased from the eBioscience, San Diego, CA). The lymphocyte populations served as the gates, and the corresponding isotype IgG-stained cells served as a negative control for the FL1 and FL2 channels when utilizing the FACS AriaIII-type flow cytometry assay with the appropriate forward and lateral scattered light. After calibrating the fluorescence compensation between each channel, CD4+, CD8+ and Th17 cells were detected.

Coronary angiography and evaluation

All of the patients underwent CAG using the Judkins method. The angiography results were analyzed by 2 experienced physicians. CAG was performed through the femoral or radial artery, and the degree of stenosis was expressed by the diameter method. Coronary artery stenosis in the epicardial main blood vessels of greater than 50% was regarded as a meaningful lesion. Coronary stenosis of less than 50% was normal (control group). The Gensini criteria [10] were used to integrate any stenosis in the left main coronary artery, left anterior descending artery,

left circumflex artery and right coronary artery with the following grading system: (1) ≤25% is 1.0 point, (2) 26% to 49% is 1.5 point, (3) 50% is 2.0 points, (4) 51% to 74% is 3.0 points, (5) 75% is 4.0 points, (6) 76% to 89% is 12.0 points and (7) 100% is 32.0 points. Different segments of the coronary artery were scored according to this standard, and the final determination of the degree of coronary artery disease was the sum of the points from each branch.

Statistical analysis

The data were processed and analyzed with SPSS17.0 software (SPSS, USA). The data were expressed as the mean ± standard deviation. The t test was used to compare pairs of groups, and samples among groups were compared by ANOVA. The LSD test was used to compare any 2 groups. The paired t test was used to measure the data before and after treatment. Pearson correlation analysis was used to analyze the correlation between 2 variables. The chi-square test was used to compare the count data. P<0.05 was considered statistically significant.

Results

Demographic and perioperative baseline data

There were no significant differences in the sex ratio, age distribution, presence of hypertension, proportion of patients with diabetes mel-
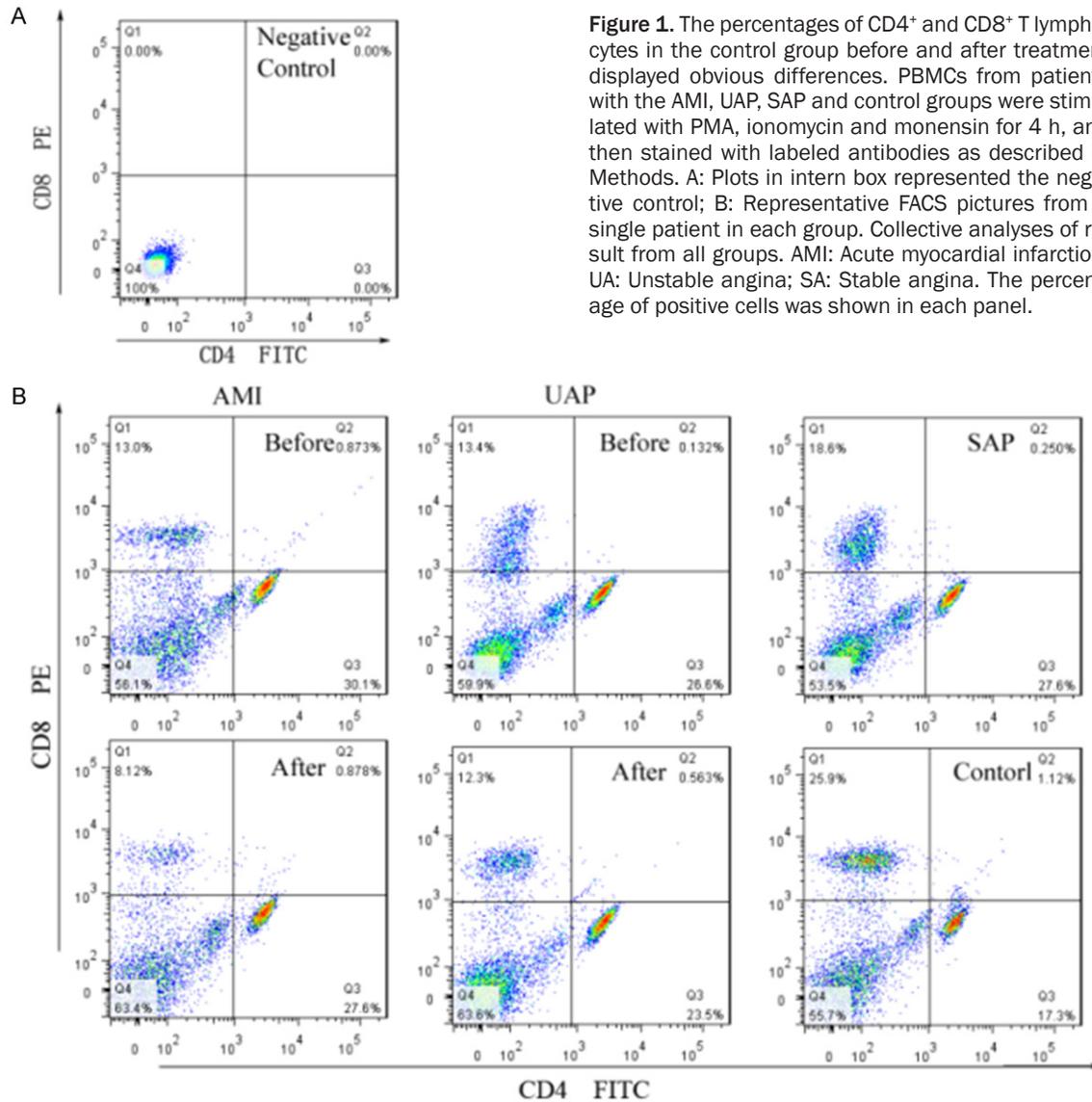
Figure 1. The percentages of CD4$^+$ and CD8$^+$ T lymphocytes in the control group before and after treatment displayed obvious differences. PBMCs from patients with the AMI, UAP, SAP and control groups were stimulated with PMA, ionomycin and monensin for 4 h, and then stained with labeled antibodies as described in Methods. A: Plots in intern box represented the negative control; B: Representative FACS pictures from a single patient in each group. Collective analyses of result from all groups. AMI: Acute myocardial infarction; UA: Unstable angina; SA: Stable angina. The percentage of positive cells was shown in each panel.

litusor triglyceride (TG) levels among the groups (P>0.05). The serum total cholesterol (TC) in the AMI group was significantly different from that in the other 3 groups (P<0.05). The differences among the latter 3 groups displayed no statistical significance (P>0.05). There were significant differences among the coronary artery Gensini scores in the 4 groups (P<0.01 for all 4 groups; **Table 1**).

Percentages of peripheral blood T lymphocyte subsets in patient groups before treatment

The percentages of CD4$^+$ and CD8$^+$ T lymphocytes in the control group before treatment (**Figure 1** and **Table 2**) displayed obvious differences when compared to the other 3 groups.

The CD4$^+$ cell levels in the control (18.25± 6.20%), SAP (23.16±7.22%), UAP (27.53±8.28%) and AMI (30.01±13.77%) groups showed a progressively increasing trend. The percentages of CD4$^+$ T lymphocytes in the UAP and AMI groups were both significantly higher than in the control group (P<0.05), although there were no significant differences between the AMI and UAP groups or between the SAP and control groups (P>0.01). The level of CD8$^+$ cells in the control (22.75±6.25%), SAP (19.0±7.11%), UAP (15.50 ±5.93%) and AMI (12.34±6.48%) groups before treatment showed a gradually decreasing trend (P<0.01). The percentages of CD8$^+$ T lymphocytes in the UAP and AMI groups were significantly lower than in the control group (P<0.05).

Table 2. Peripheral blood T cell subset proportions from each group of patients before conventional therapy (%, mean ± SD)

Peripheral Blood Cells (%, mean ± SD)	AMI n=30	UAP n=30	SAP n=20	Control n=20	F/X^2	P
CD4$^+$	30.01±13.77$^\Delta$	27.53±8.28$^\Delta$	23.16±7.22	18.25±6.20	19.37	<0.01
CD8$^+$	12.34±6.48$^{\Delta,*}$	15.50±5.93$^\Delta$	19.0±7.11	22.75±6.52	20.08	<0.01
Th17	4.30±3.91$^{\Delta,*}$	3.60±3.46$^\Delta$	1.61±0.81	1.20±0.76	24.95	<0.01

Values are expressed as the mean ± SD. AMI, acute myocardial infarction; UA, unstable angina; SA, stable angina. $^\Delta P<0.01$ vs. The control group and $^*P<0.01$ vs. the SAP group.
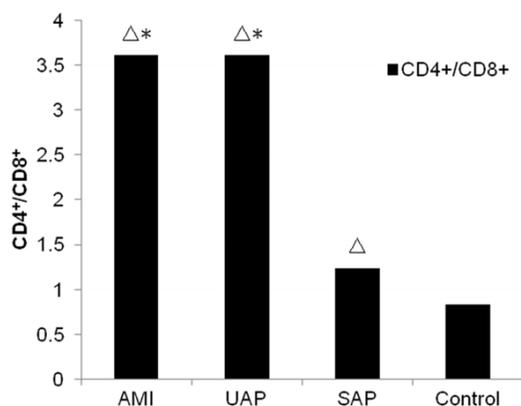

Figure 2. CD4$^+$/CD8$^+$ level comparison (mean ± SD). $^\Delta P<0.01$ vs. The control group and $^*P<0.01$ vs. the SAP group.

The difference in the CD8$^+$ cell levels between the UAP and AMI groups was not significant ($P>0.05$), though the level of CD8$^+$ cells was higher in the AMI group. The difference in the CD4$^+$/CD8$^+$ ratios (**Figure 2**) of the AMI and UAP groups and that of the SAP and control groupswas statistically significant ($P<0.01$).

The percentages of peripheral blood Th17 cells among the CD4$^+$ T lymphocytes from patients in the AMI and UAP groups before treatment (**Figure 3** and **Table 2**) were (4.60±3.91%) and (1.60±3.46%), respectively, which were significantly higher than in the SAP (1.61±0.81%) and control (1.20±0.76%) groups ($P<0.01$). However, there were no significant differences between the SAP and control groups ($P>0.05$). Before treatment, the proportions of peripheral blood Th17 cells among CD4$^+$ T cells in the UAP and AMI groups were significantly higher than in the SAP and normal control groups.

Percentages of peripheral blood T lymphocyte subsets in patient groups after treatment

The proportion of CD8$^+$ T lymphocytes decreased significantly in ACS patients 3-5 days after PCI (**Figure 1** and **Table 3**). The percentage of Th17 cells among the CD4$^+$ T cells was also significantly lower in ACS patients within 24 hours of PCI (both statistically significant, $P<0.01$).

Analysis of the correlation between the percentage of peripheral T lymphocyte subsets and the degree of coronary artery disease in all patient groups before treatment.

The proportions of CD4$^+$, CD8$^+$ and Th17 cells among the CD4$^+$ T lymphocytes were compared to the Gensini scoresusing Pearson correlation (**Figure 4**). The following results were determined from this analysis: (1) The levels of CD4$^+$ T cells in peripheral blood were positively correlated with the Gensini score (r=0.621, $P<0.01$); (2) The levels of CD8$^+$ T cells and the Gensini scores were significantly negatively correlated (r=-0.61, $P<0.01$); (3) The CD4$^+$/CD8$^+$ ratio in peripheral blood was positively correlated with the Gensini score, although the correlation was not significant (r=0.421, $P<0.01$); And (4) the levels of Th17 cells and Gensini scores showed a significant positive correlation (r=0.58, $P<0.01$).

Discussion

The experiments in this study show that immune dysfunction may be indirectly or directly involved in AMI by causing infarction area expansion or complications. Clinically detected T lymphocyte subsets can reflect the immune function of the body.The balance in immune function can typically be expressed as the percentage of CD4$^+$ and CD8$^+$ cells, both of which are involved in regulating immune responses [11]. In this study, we observed that the percentages of CD8$^+$ cells in ACS patients before treatment significantly decreased compared with those in the SAP and control groups and that the percentages of CD4$^+$ cells in the SAP and control groups were significantly lower than

Figure 3. Circulating Th17 frequencies increased in ACS patients within 24 hours of PCI. We also found that the percentage of Th17 cells among CD4+ T cells decreased significantly after treatment. A: The negative control. B: Representative Th17 expression in CD4+ T subsets from each group was shown. AMI: Acute myocardial infarction; UA: Unstable angina; SA: Stable angina. The percentage of positive cells was shown in each panel.
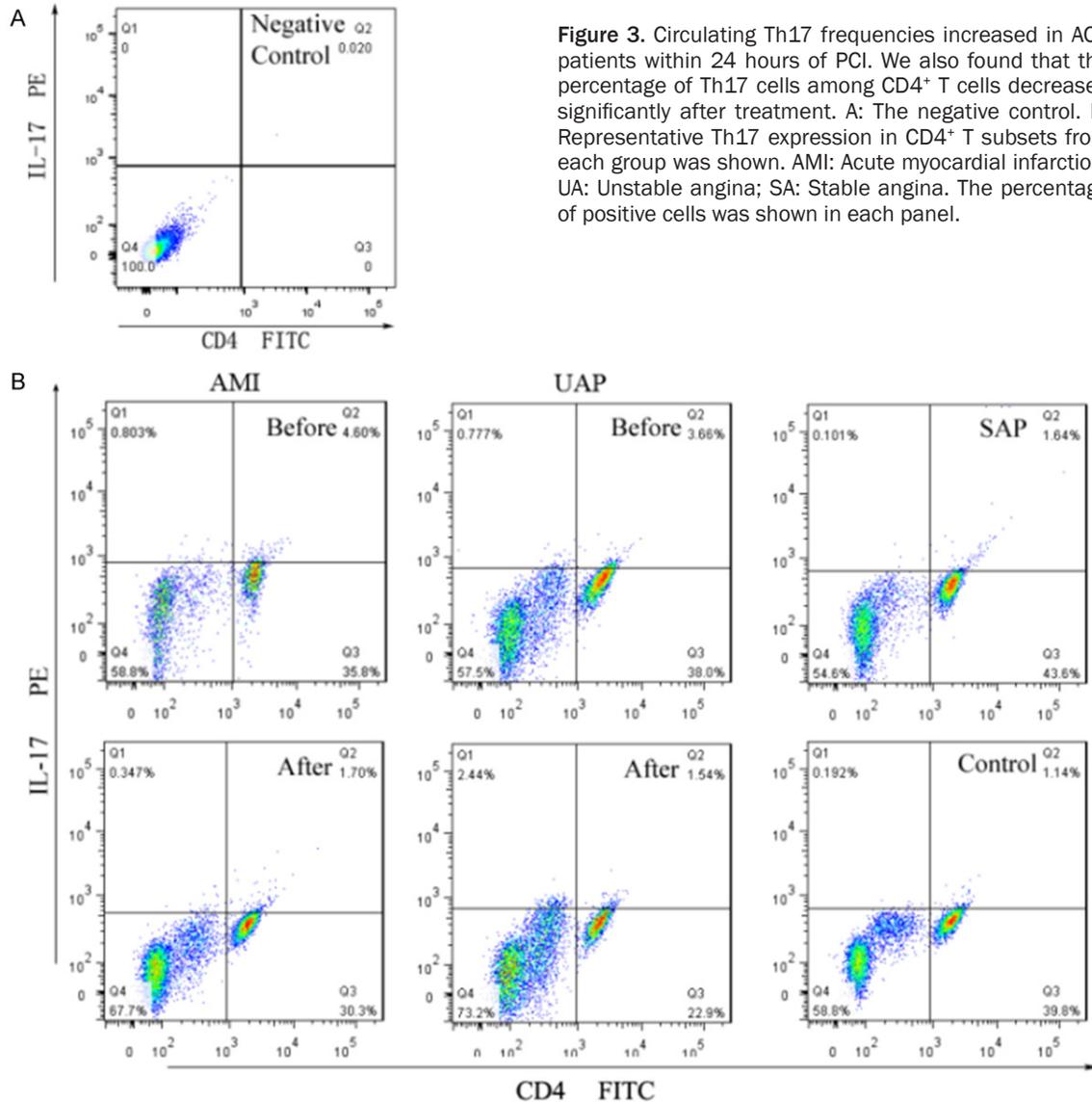
Table 3. Peripheral blood T cell subset proportions from ACS patients before and after conventional therapy (%, mean ± SD)

Peripheral Blood	AMI		UAP	
Cells (%, mean ± SD)	Before	After	Before	After
CD4+	30.01±13.77	28.20±12.92	27.53±8.28	26.03±8.37
CD8+	12.34±6.48$^\Delta$	9.20±5.53	15.50±5.93$^\Delta$	11.37±4.02
%CD4+/%CD8+	3.61±3.28	4.96±4.93	3.61±3.28	2.72±1.67
Th17	4.30±3.91$^\Delta$	1.73±1.07	3.60±3.46$^\Delta$	1.53±1.36

Values are expressed as the mean ± SD. AMI, acute myocardial infarction; UA, unstable angina; SA, stable angina. $^\Delta P<0.01$ vs. The after-treatment groups.

in the AMI and UAP groups, contrasting with the CD8+ cell result. The present study confirmed that growing coronary atherosclerotic lesions activated the immune inflammatory response and that the percentage of CD4+ cells increaseddas the percentage of CD8+ cells decreased.
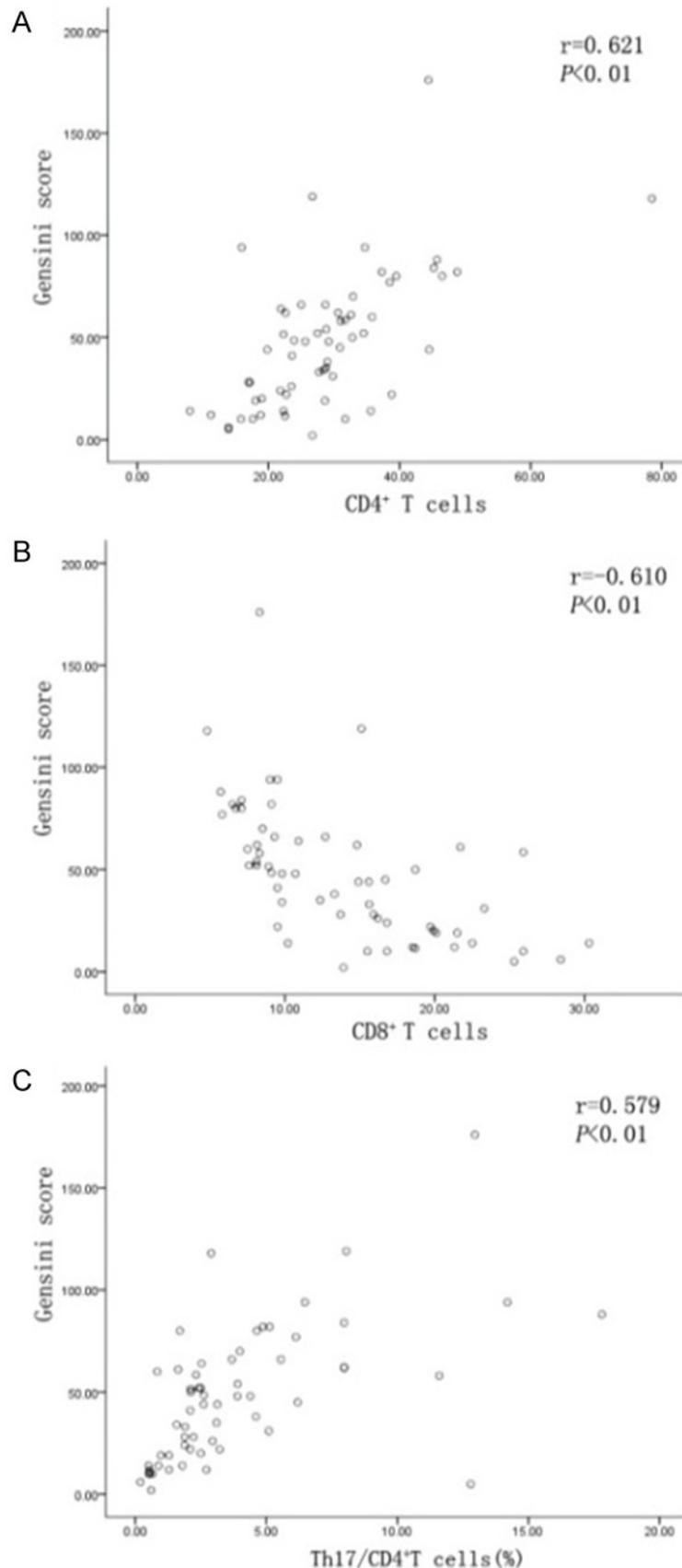
Figure 4. The proportions of CD4+, CD8+ and Th17 cells among the CD4+ T lymphocytes were compared to the Gensini scores using Pearson correlation.

Furthermore, the CD4+/CD8+ ratio increased significantly, in agreement with previous studies [12, 13]. This finding suggests that immune inflammation in patients with acute coronary syndromes before treatment causes the body to be in a state of immune dysfunction, which is characterized by imbalanced T lymphocyte subset proportions. Such imbalances inhibit or damage the immune system and eventually lead to increased atherosclerotic plaque instability. According to previous studies [14], CD8+ T cell activation is associated with the pathogenesis of coronary artery spasms, especially because damage to myocardial cells caused by activated CD8+ T cells may be regarded as the development of AMI. Coronary artery Gensini scoresfrom the CAG, which are based on the number of coronary artery stenoses, and stenosis scores can more objectively reflect the degree of coronary artery disease. This study confirmed that the severity of coronary AS and coronary Gensini scores concomitantly increased and that the proportions of CD4+ and CD8+ cells and the CD4+/CD8+ ratio can be used as indicators to measure coronary plaque instability.

We observed that the percentage of Th17 cells among CD4+ T lymphocytes in the SAP group did not increase relative to the control group. However, the percentage of Th17 cells among CD4+ T lym-

phocytes in the UAP and AMI groups were significantly increased relative to the control. The proportion of Th17 cells in peripheral blood from patients with acute coronary syndromes was significantly higher than in the SAP and control groups, in accord with the studies by Cheng et al. [15, 16]; This finding suggests that Th17 plays an important role in AS. Furthermore, Th17 cells were elevated in the peripheral blood of patients with stable angina, even in the absence of an acute inflammatory process associated with unstable plaques, suggesting that Th17 also plays a role in the development of AS. At the same time, myocardial necrosis is associated with AMI and may be a source for peripheral-blood Th17 cells and IL-17 [17, 18]; this may be one reason why the peripheral blood level of Th17 cells was significantly higher than in the other groups. We also observed a significant reduction in Th17 cells among CD4⁺ T lymphocytes within 24 hours of PCI in patients with ACS. We hypothesize that an acute inflammatory response to a dominant cellular immune response may lead to atherosclerotic plaque rupture, thereby causing ACS onset. However, the decrease in Th17 cells among CD4⁺ T lymphocytes a short time after operation suggests that there is a close relationship between Th17 cells and coronary atherosclerotic plaque instability. Th17 may be an accurate indicator of the inflammatory status of AS. We hypothesize that Th17, a newly discovered pathologic effector T cell, may aggravate the body's pathological immune responses, possibly via the proinflammatory effects of IL-17, and may participate in and promote atherosclerotic plaque instability and the occurrence and development of ACS. There have been many studies and much progress towards determining the molecular mechanisms of cell differentiation, including Th17 cell differentiation, but many aspects of differentiation remain uncertain [19]. The IL-17 and Th17 metabolic pathways in rodents and humans do not appear to be identical [20]. Additionally, there is still much discordance between basic and clinical studies, which makes it more important to study IL-17 and Th17 cells in the human body. Initial results have been achieved for antibody therapies against IL-17 in such autoimmune diseases as rheumatoid arthritis [21, 22], but anti-inflammatory therapies for AS are currently only in the experimental phase.

In summary, this study suggests that CD4⁺ and CD8⁺ cell levels and the severity of coronary AS are related, and that the detection of these cell-levels will help determine clinical conditions and will have a certain value for the prognosis of CHD. The percentage of Th17 cells in the peripheral blood of patients with ACS increased significantly before treatment and clearly decreased in the 24 hours after PCI, suggesting that the proportion of Th17 cells may play important roles in the formation and progression of atherosclerotic plaques and in the development of unstable coronary artery disease. However, the specific mechanisms require further elucidation.

Disclosure of conflict of interest

None.

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