Inflammation and Immune System Response against Unstable Angina and Its Relationship with Coronary Angiographic Findings

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SUMMARY

The aim of this study was to assess the relations between inflammation, immune response, and coronary angiographic findings in patients with unstable angina pectoris (UAP).

Recent studies suggest a role for inflammation in the pathophysiology of UAP. Although activation of neutrophils, monocytes and lymphocytes has been shown in UAP, no studies have correlated the activation findings with clinical and angiographic features of patients with UAP.

Seventy-three patients undergoing coronary angiography were classified according to their ischaemic syndrome; stable angina pectoris (SAP) (*n*=25) and UAP (*n*=48). Patients with UAP were classified using the Braunwald classification; UAP class I (*n*=15), UAP class II (*n*=15), and UAP class III (*n*=18). Patients with UAP were also classified into a progression to myocardial infarction (MI(+)) group (*n*=15) and a non-progression to myocardial infarction (MI(-)) group (*n*=33). Venous blood samples were taken from all patients. Cell surface receptors (CD4, CD8, CD3, CD14, CD45, CD56+16, and HLA-DR) were detected by flow cytometry using monoclonal antibodies tagged with fluorescent markers and serum levels of C-reactive protein (CRP) were measured.

The serum levels of CRP and the percentages of HLA-DR, CD14, and CD16+56 were higher in UAP than SAP. The serum levels of CRP and percentages of HLA-DR, CD14, and CD16+56 were higher in UAP class II than UAP class I. The serum levels of CRP and percentages of HLA-DR, CD14, and CD16+56 were higher in UAP class III than UAP class II and UAP class I. The serum levels of CRP and percentages of CD16+56 were higher in the MI(+) group than the MI(-) group. The CRP levels in serum and the percentages of cell surface antigens had no correlation with extent of coronary artery disease (no differences among one, two or three vessels) but Type C lesion had significantly higher percentages of HLA-DR, CD14, CD16+56 and the serum levels of CRP than Type A and Type B lesions.

This investigation shows that inflammatory and immunologial components may be detectable in UAP and were correlated with the clinical severity, progression to myocar-

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dial infarction, and lesion morphology, but were not correlated with the extent of coronary artery disease. (Jpn Heart J 2002; 43: 593-605)

Key words: Immune system activation, Unstable angina pectoris, Coronary angiography

CORONARY artery disease (CAD) is characterized by long periods of clinical stability with a few, occassional abrupt changes that lead to acute coronary syndromes.[1] Inflammatory cells accumulate in the coronary lesions, possibly causing plaque instability.[2] Systemic levels of inflammatory markers are frequently elevated and associated with a worse prognosis in unstable angina pectoris (UAP) and are especially abundant in the shoulder region of coronary plaque disruption and thrombosis.[3-7] Although these findings strongly suggest that inflammation may have an important role in the pathogenesis of UAP, the possible triggers of this inflammatory response remain unclear.[8,9] Activated T-lymphocytes are frequently found in peripheral blood and in the coronary plaques of patients with acute coronary syndromes.[10-12] Patients with UAP have increased expression of granulocytes and monocyte CD11b/CD18 adhesion receptors, indicating that an inflammatory reaction takes place within the coronary tree.[13]

The objectives of the present study were to investigate (1) T-lymphocyte activation and involvement in stable and unstable angina pectoris, (2) the relationship between possible lymphocyte activation and the clinical presentation of angina and (3) the relationship between lymphocyte activation and the coronary angiographic findings and (4) the inflammation and immune response differences between progression to acute myocardial infarction (MI(+)) and non-progression to acute myocardial infarction (MI(-)) in unstable angina pectoris.

METHODS

Study Population: Twenty-five patients with stable angina pectoris (SAP) (Group A) (17 men and 8 women; mean age, 57.35±8.57) and 48 patients with UAP (35 men and 13 women; mean age, 54.24±10.21) were admitted to hospital and underwent diagnostic coronary angiographic examinations between June 1999 and January 2000 at the Department of Cardiology of the Faculty of Medicine at Karadeniz Technical University.

Patients with UAP were classified according to Braunwald's classification[14] as Group B1 which included 15 patients with UAP Braunwald class I (new onset, severe or accelerated angina, no rest pain in the last 2 months), as Group B2 which included 15 patients with UAP Braunwald class II (Angina at rest. Subacute. Patients with one or more episodes of angina at rest during the preceding

month but not within the preceding 48 hours), and as Group B3 which included 18 patients with UAP Braunwald class III (Angina at rest. Acute. Patients with one or more episodes at rest within the preceding 48 hours). Patients with UAP were also classified according to whether or not they progressed to acute myocardial infarction.

Stable angina pectoris patients had no acute events or worsening of symptoms during the previous 6 months. This group determined clinical history and positive exercise stress test.

Unstable angina pectoris patients had no elevation in serum creatinine kinase on admission or during the first 24 hours of hospitalization.

Myocardial infarction was diagnosed if any two of the following criteria were fulfilled :

- Cardiac chest pain lasting at least 30 minutes ;
- ST elevation of ≥0.1 mV in at least one standard lead or ≥0.2 mV in two or more contiguous chest leads ;
- Creatine kinase ≥400 IU/L (upper limit of reference range 200 IU/L).

Exclusion criteria: The exclusion criteria included evidence of recent infectious disease, an erythrocyte sedimentation rate >20 mm/h, fever, immunosuppressive drug therapy, an immunologic disorder, a known or suspected neoplastic disease, congestive heart failure, valvular heart disease, evidence of left ventricular aneurysm, or recent (<3 months) major trauma or surgery.

Blood: Peripheral blood samples were taken from an antecubital vein as soon as possible after admission to the coronary care unit and before intravenous drug administration, such as nitroglycerin infusion.

Flow cytometry: Two mililiter blood samples were taken from each patient in EDTA containing counter blood cell (CBC) tubes in order to perform flow-cytometric analysis of peripheral blood. One hundred microliters of these blood samples was added to 15 μL double coloured monoclonal antibody containing marked test tubes. Monoclonal antibody pairs were selected as CD4 ±ITC/CD8 PE, CD3FITC/CD19PE, CD45±ITC/CD14 PE, CD3±ITC/CD16±56PE, CD3±ITC/HLA-DRPE. After an incubation period of 20 minutes, the samples were treated with a Multi Q prep device by means of immunoprep A, B, and C solutions in order to perform erythrocyte lysis during another incubation period. Approximately 5000 cells were counted by flow-cytometry for each patient.The percent positivity was calculated for each selected monoclonal antibody as CD4 (T-helper), CD8 (T-suppressor), CD3 (T-lympocytes), CD19 (B-lymphocytes), CD45 (total monoclonal cell), CD14 (monocytes), CD16+56 (natural killer cell), and HLA-DR (active T lymphocytes) using a Coulter EPICS ELITE ESP flow cytometer.

Counter blood cell (CBC) was also measured in peripheral blood of the patients using a flowcytometric method. C-reactive protein was measured from the serum samples of the patients using a nephelometric method. Creatine kinase was measured in serum samples of the patients using an enzymatic kinetic ultraviolet (UV) test and a Roche/Hitachi analyzer.

Coronary angiography: Coronary angiography was performed by the Judkins technique three days after the patient was admitted to hospital. The presence and severity of coronary angiographic lesions were evaluated from at least three projections. We determined the presence and severity of coronary arterial stenosis in the 15 segments of the artery designated by the American Heart Association.[15] CAD was considered to be present if 1 or more lesions narrowed the lumen of any of the 15 segments by >75%. Patients with such lesions were considered to have CAD, whereas those without narrowings or with <25% narrowing of the lumen were considered to have normal coronary arteries.[16] Coronary angiographic lesions were classified according to both extent of coronary artery disease (one vessel, two vessels, and three vessels) and morphology (Type A, Type B, and Type C).[17]

Statistical analysis: Unless otherwise indicated, the results are given as the median and range. Because all values followed a normal distrubution, comparisons between the groups were carried out using Student's *t* test, ANOVA, and the chi square test. For correlation analysis, Spearman's rank correlation coefficient was used. All probability values reported are two-tailed, with values of $P<0.05$ considered statistically significant.

RESULTS

Clinical characteristics: The clinical features of the patients with SAP and UAP are listed in Table I. The UAP and SAP patients did not differ with respect to their demographic characteristics. A comparison of the coronary angiographic findings in group A (SAP) and group B (UAP) patients is summarized in Table I. There were no differences between the SAP and UAP patients from the point of view of severity or extent of the angiographic lesions ($P>0.05$).

The comparison of coronary angiographic findings among the subgroup UAP (groups B1, B2 and B3) patients is summarized in Table II. There were no differences in the subgroup UA patients with respect to the severity or extent of angiographic lesions ($P>0.05$).

A comparison of the immune system activation findings and CRP levels in serum among normal, one two and three vessels are summarized in Table III. In the three vessels group, CRP levels and the percentages of HLA-DR, CD14, and

Table I. Demographic Features of the Patients

	Group A (*n*: 25)	Group B (*n*: 48)	*P*
Age	57.35±8.57	54.24±10.21	NS
Sex	17 men/8 women	35 men/13 women	NS
Diabetes mellitus	8/25	14/48	NS
Hypertension	12/25	29/48	NS
Hypercholesterolemia	11/25	22/48	NS
Family history of CAD	5/25	19/48	NS
Smokers	13/25	27/48	NS
Normal vessel	6/25	10/48	NS
One vessel disease	9/25	21/48	NS
Two vessel disease	6/25	10/48	NS
Three vessel disease	4/25	7/48	NS

CAD=coronary artery disease, NS=not significant.

Table II. Angiographic Features of Group B Subgroups

	Group B1 (*n*: 15)	Group B2 (*n*: 15)	Group B3 (*n*:18)
Normal vessel	4/15	3/15	3/18
One vessel disease	7/15	8/15	6/18
Two vessel disease	2/15	2/15	6/18
Three vessel disease	2/15	2/15	3/18

CD4 were higher than the other groups however there were no significant differences between the three vessels group and the other groups ($P>0.05$).

The inflammation and immune system activation findings in Type A, Type B and Type C are listed in Table IV. The percentages of CD14, CD16+56, HLA-DR, and CRP serum levels and WBC in Type C lesion were significantly higher than those in Type A and Type B lesion ($P<0.05$). In the immune system activation findings,there were not significant differences between Type A and Type B lesion, although the serum levels of CRP in Type B lesion were higher than in Type A lesion (0.87±0.25 vs 1.61±0.32) ($P<0.05$).

The inflammation and immune system activation markers in UAP and SAP are presented in Table V. The percentages of CD4, CD8, CD3, CD19, and CD45 did not differ between groups A and group B ($P>0.05$). The percentages of CD14, CD16+56, HLA-DR and CRP levels in serum and WBC in group B were significantly higher than those in group A (1.54±0.20 vs 2.83±0.17 ($P<0.05$), 8.39±3.31 vs 19.92±4.23 ($P<0.05$), 6.26±1.01 vs 10.7±1.2 ($P<0.05$), 0.38±0.27 vs 1.95±0.41 ($P<0.05$)).

Table III. Immunologic and Inflammatory Findings Among Normal Vessel, One Vessel, Two Vessels and Three Vessels Diseases

Variable	Normal vessel	One vessel	Two vessels	Three vessels	*P*
CD4	31.74±8.3	32.77±10.3	33.43±9.8	34.2±14.7	NS
CD8	19.61±5.4	18.11±5.4	21.17±7.8	19.73±6.5	NS
CD3	54.86±11	50.13±17	57.6±17.8	57.05±17.1	NS
CD19	15.47±5.9	13.64±10.6	15.37±6.0	15.28±4.6	NS
CD45	88.71±10	82.16±12	89.86±12	91.42±9.8	NS
CD14	1.94±0.24	1.76±0.34	1.74±0.4	2.34±0.76	NS
CD16+56	10.97±4.83	10.91±5.83	13.97±3.75	15.76±8.39	NS
HLA-DR	7.74±1.34	7.86±1.86	8.58±3.33	8.17±2.05	NS
CRP	0.94±0.71	0.91±0.80	1.22±0.69	1.74±0.72	NS
WBC	9460±4440	9700±4800	9810±4600	9650±4515	NS

Table IV. Immunologic and Inflammatory Findings in Type A, Type B, and Type C Iesions

Variable	Type A (*n*=23)	Type B (*n*=18)	Type C (*n*=16)
CD4	32.14±12.64	34.51±12.32	35.45±13.45
CD8	19.35±6.64	20.41±5.87	23.11±5.86
CD3	48.75±15.62	53.54±12.41	56.88±18.52
CD19	11.54±7.61	12.13±9.09	14.52±9.72
CD45	84.98±14.8	90.87±10.42	92.5±9.36
CD14	1.75±0.38	1.76±0.42	2.88±0.12** #
CD16+56	8.54±3.46	10.72±3.62	18.50±5.65**#
HLA-DR	6.3±1.05	7.16±1.79	9.95±1.95**#
CRP	0.57±0.46	1.61±0.32*	2.27±0.19**#
WBC	8970±3930	9210±4090	10270±4230**#

* Statistically significant difference between Type A and Type B ($P<0.05$), ** statistically significant difference between Type A and Type C ($P<0.05$), # statistically significant difference between Type B and Type C ($P<0.05$).

Table V. Immunologic and Inflammatory Findings in Group A and Group B

Variable	Group A	Group B
CD4	32.83±13.33	35.34±13.56
CD8	18.11±5.40	21.72±7.25
CD3	51.91±18.87	57.13±18.27
CD19	14.37±11.33	16.72±7.52
CD45	84.59±14.43	90.0±11.86
CD14	1.54±0.20	2.83±0.17*
CD16+56	8.39±3.31	19.92±4.23*
HLA-DR	6.26±1.01	10.70±1.2*
CRP	0.38±0.27	1.95±0.41*
WBC	8830±3930	9950±4550*

* Statistically significant difference between group A and group B ($P<0.05$)

The inflammation and immune system activation markers in groups B1, B2, and B3 are shown in Table VI. Group B3 had significantly higher WBC, percentages of CD14, CD16+56, HLA-DR, and serum levels of CRP than group B1 ($P<0.05$). Group B3 also had significantly higher WBC and serum levels of CRP than those of group B2 ($P<0.05$). There were no differences in the inflammation and immune system activation markers between groups B2 and B1 ($P> 0.05$).

A comparison of the immunologic and inflammatory findings between group A and the subgroups of group B are listed in Table VII. Group B1 had significantly higher percentages of CD 16+56, HLA-DR, and CRP serum levels than group A (16.11±0.42 vs 8.39±3.31, 9.70±0.20 vs 6.26±1.01, 1.66±0.12 vs 0.38±0.27) ($P<0.05$) (Table VII). Group B2 had significantly higher CRP serum levels and percentages of CD16+56, and HLA-DR than those of group A ($P<0.05$) (Table VII). Group B3 had significantly higher WBC, CRP serum levels, and percentages of CD14, CD16+56, and HLA-DR than group A ($P<0.05$). Group B3 had significantly higher WBC, CRP serum levels, and percentages of CD16+56 and HLA-DR than those of group B1 ($P<0.05$) and group B3 also had significantly higher CRP serum levels than group B2 (Table VII). The inflammation and immune system activation findings for MI(+) and MI(-) are shown in Table VIII. The MI (+) group had significantly higher WBC, CK, CRP serum levels and percentages of CD16+56 than the MI (-) group (2.1±0.26 vs 1.76+0.22, 22.15±2.0 vs 18.98±3.29) ($P<0.05$) (Table VIII).

DISCUSSION

Table VI. Immunologic and Inflammatory Findings in Group B Subgroups

Variable	Group B1	Group B2	Group B3
CD4	33.31±11.53	35.39±10.84	36.69±12.21
CD8	20.96±6.49	21.65±6.45	22.02±6.95
CD3	50.33±11.46	55.76±9.89	60.37±15.03
CD19	13.63±4.43	15.24±5.07	18.68±5.56
CD45	94.85±6.71	95.54±5.39	97.47±3.39
CD14	2.77±0.11	2.81±0.13	2.95±0.05*
CD16+56	16.11±0.42	18.18±2.31	22.21±1.94*
HLA-DR	9.70±0.20	9.81±0.30	11.71±0.18*
CRP	1.66±0.12	1.68±0.11	2.24±0.12*#
WBC	8850±3950	9410±3750	11300±4200*#

* Statistically significant difference between group B1 and group B3 ($P<0.05$), # statistically significant difference between group B2 and group B3 ($P<0.05$).

Table VII. Comparison of Immunologic and Inflammatory Findings between Group A and Group B Subgroups

Variable	Group A	Group B1	Group B2	Group B3
CD4	32.83±13.33	33.31±11.53	35.39±10.84	36.69±12.21
CD8	18.11±5.40	20.96±6.49	21.65±6.45	22.02±6.95
CD3	51.91±18.87	50.33±11.46	55.76±9.89	60.37±15.03
CD19	14.37±11.33	13.63±4.43	15.24±5.07	18.68±5.56
CD45	84.59±14.43	94.85±6.71	95.54±5.39	97.47±3.39
CD14	1.54±0.20	2.77±0.11	2.81±0.13	2.95±0.05β**
CD16+56	8.39±3.31	16.11±0.42#	18.18±2.31*	22.21±1.94β**
HLA-DR	6.26±1.01	9.70±0.20#	9.81±0.30*	11.71±0.18β**
CRP	0.38±0.27	1.66±0.12#	1.68±0.11*	2.24±0.12β**δ
WBC	8830±3930	8850±3950	9410±3750	11300±4200 β**δ

Statistically significant difference between group B1 and group A (P<0.05), * group B2 and group A (P<0.05), ** group B3 and group A (P<0.05), β group B3 and group B1 (P<0.05), and δ group B3 and group B2 (P<0.05).

Table VIII. Immunologic and Inflammatory Findings in MI(+) and MI(-) in Unstable Angina Pectoris

Variable	MI(-) (n=33)	MI(+) (n=15)
CD4	32.15±10.4	36.56±12.34
CD8	17.43±2.96	23.71±5.26
CD3	51.75±12.89	56.64±18.76
CD19	14.21±5.01	18.35±5.89
CD45	92.46±4.32	96.21±5.65
CD14	2.71±0.05	2.97±0.03
CD16+56	18.98±3.29	22.15±2.0*
HLA-DR	10.92±1.42	11.08±0.82
CRP	1.76±0.22	2.1±0.26*
WBC	9250±3780	11400±3100*
CK	122±42	632±145*

* Statistically significant difference between group A and group B (P<0.05).

Coronary plaque disruption with consequent thrombus formation and/or platelet aggregation, often with the contribution of dynamic changes of vascular tone, are considered to be the most important mechanism being responsible for the occurrence of acute coronary syndromes, including unstable angina and myocardial infarction.[1,2,18] Recent studies have provided evidence for an additional role of inflammation in the pathophysiology of unstable angina and myocardial infarction.[7,10,18-20] Evidence for an intermittent increase in T-cell activation has been found in the circulating blood of UAP patients.[10] The present results were

seen to be consistent with the hypothesis that inflammation and T cell activation play important roles in the pathophysiology of UAP.

Inflammation in UAP: Experimental studies have shown that periods of ischemia as short as 15 minutes followed by reperfusion elicit a cascade of proinflammatory reactions that include production of oxygen-derived free radicals, activation of the complement system, adherence of neutrophils to the coronary endothelium, leukocyte-mediated injury of the myocardial cells, and the production of cytokines, and these are the major determinants of acute-phase protein production.[21-25)]

Increased concentrations of CRP, a sensitive marker of inflammation, have been reported in patients with UAP.[3,26)] CRP is also a marker of poor short term clinical outcome in UAP.[5)]

In this study we have demonstrated that serum levels of CRP are correlated with the severity and prognosis of UAP. Patients with UAP had higher serum levels of CRP than patients with SAP. The serum levels of CRP in group B3 were higher than in groups B1 and B2. The serum levels of CRP in groups B3, B2, and B1 were higher than group A. Group B2 had higher serum levels of CRP than group B1 and group A.The MI (+) group had higher serum levels of CRP than the MI (-) group.

In the coronary angiographic findings, the serum levels of CRP had no correlation with extent of coronary artery disease (no differences among one, two or three vessels) but they were correlated with lesion morphology. Type C lesion had the highest serum levels of CRP of all lesions and Type B lesion had the serum levels of CRP higher than Type A lesions.

We have confirmed and demonstrated that the elevation of CRP serum levels in UAP was related to myocardial cell necrosis (MI (+) group), as creatine kinase and troponin T levels were higher than normal limits.

Plasma levels of CRP start to rise about 6 hours after an acute stimulus, reaching a peak within 48 hours, and with abrupt cessation of the stimulus, the values decrease exponentially at a rate close to the measured plasma half-life of CRP of about 19 hours. Thus, if ischemia-reperfusion does trigger an acute-phase response, the peak values of CRP should exhibit a persistent increase in CRP in patients with crescendo or refractory angina.[27,28)] Liuzzo, *et al*[29)] showed that episodes of ischemia-reperfusion are not by themselves a sufficient cause of the acute phase response in UAP. We showed the elevation of CRP serum levels in UAP, and the elevation of CRP serum levels was correlated with the severity and prognosis of UA. If so, the elevation of CRP serum levels may assist in deciding upon the kind of treatment or prognosis of UAP.

Lymphocyte and monocyte activation: An important hypothesis of the inflammatory response observed in UAP may be part of an immune, that is, antigen-

directed process. Histologic studies have consistently demonstrated an abundance of T lymphocytes within atherosclerotic lesions, especially at sites of complicated coronary plaques[6,7,30] and circulating blood of UAP patients.[8]

Evidence for T-cell activation has also been found in the circulating blood of SAP patients,[31] implying that the inflammatory/immune response in UAP might usually be related to the atherosclerotic background.[32,33] Caliguiri, *et al*[8] found that severe effort angina is associated with a higher percentage of CD3+/DR+. However, we observed that neither the percentage of CD3 nor the percentage of HLA-DR increased in SAP patients, which does not support the hypothesis that the immune system was associated with the chronic atherosclerotic background. Caliguiri, *et al*[8] also observed acute and transient immune system activation in UAP which cannot be explained by the chronic atherosclerotic background. Choi, *et al*[34] found that CD14, CD11b increased significantly in patients with UAP compared to patients with SAP. Our finding in VAP were similarly those of in that previoys study.

We showed that the percentages of HLA -DR, CD16+56 and CD14 in UAP patients were higher than in SAP patients. These findings suggest acute activation of the immune system in UAP. We also showed that group B3 patients had the highest percentages of CD16+56, CD14, and HLA DR of all UAP patients. The more the percentages of CD16+56, CD14, and HLA DR increased, the greater the severity of UAP increased and the prognosis of UAP worsened. This finding may suggest that higher percentages of CD16+56, CD14, and HLA-DR are associated with the severity of UAP.

Blum, *et al*[31] showed that T lymphocytes are activated and involved in atherosclerosis in at least half of the patients with SAP. However we did not observe any T- lymphocyte activation in SAP patients. Caliguiri, *et al*[8] showed that CD4+ and CD3+/DR+ cells, and IL-2 and IgM were higher in UAP than in SAP. We found that HLA-DR, CD14, and CD16+56 were higher in UAP than SAP, which is similar to their findings. Serneri, *et al*[11] observed that CD4+ and CD8+ circulating lymphocytes are activated in patients with UAP, and their activation state lasts 6 to 8 weeks, and the activation of lymphocytes is not a consequence of myocardial ischemia.

We found that immune system activation was not correlated with the number of sickly coronary artery vessels but correlated with lesion morphology. Type C lesions had the highest immune system activation of all the lesions. These results may explain why Type C lesions had a low success rate or higher restenosis rate in percutaneous transluminal coronary angioplasty.

In some previous studies the distribution of peripheral blood CD 16+56 was analyzed in order to correlate with disease activity and prognosis[35,36] but there are no studies related to coronary artery disease activity and prognosis. In our study,

the percentage of CD16+56, which indicates natural killer cell activity, was first used in patients with UAP and was found to be higher than in patients with SAP. Type C lesions and the MI (+) group had higher percentages of CD16+56 than the others.

The presence of activated T-lymphocytes in UAP patients implies antigenic stimulation, but the nature of such antigen(s) remain to be investigated. The fact that circulating activated T-lymphocytes are detectable only for a few weeks suggest an acute formation of antigen(s) being able to cause a transient activation.

Many possible candidate antigens may be put forward.[37] LDLs undergo oxidative modification *in vivo*,[38,39] and they have been found to be capable of activating the lymphocyte coculture *in vitro*,[40] Some autoantigens expressed in atherosclerotic plaque, such as heat shock proteins, could elicit an immune response.[41] It has also been reported that infectious agents such as Chlamydia pneumonia (Cp),[42] Cytomegalovirus (CMV)[43] and Helicobacter pylori (Hp)[44] might be associated with a risk of ischemic heart disease. CMV and Hp do not appear to be related to angina instability[45,46] while viable Cp has recently been found in active coronary atherosclerotic lesion[47] and thus this microorganism might be the target for activated lymphocytes in the unstable plaques.

These results suggest that activation of the immune system is altered in patients with UAP, independently extent of coronary artery disease. Changes in peripheral blood lymphocytes in UAP patients could be useful as predictive markers of an unfavorable outcome and clinical severity.

However, precisely designed studies are needed to investigate the mechanism(s) responsible for lymphocyte activation.

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