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Immune System Activation Follows Inflammation in Unstable Angina: Pathogenetic Implications

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Objectives. **The aim of this study was to assess the relations between inflammation, specific immune response and clinical course in unstable angina (UA).**

Background. **Several studies suggest that either inflammation and/or T-cell activation might have a pathogenetic role in UA, but neither their potential reciprocal connection nor their relation to the clinical course is known.**

Methods. **Serum levels of C-reactive protein (CRP) (inflammation), IgG, IgA, IgM, C3, C4 (humoral immunity), IL-2 and the percentage of CD4+, CD8+ and CD3+/DR+ T-cells (cell-mediated immunity) were measured in 35 patients with UA and 35 patients with chronic stable angina (CSA) during a period of 6 months.**

Results. **The CRP levels and the main specific immune markers (CD4+ and CD3+/DR+ cells, IL-2 and IgM) were higher in unstable than in stable angina. In UA, the serum levels of IgM and IL-2 and the percentage of double positive CD3+/DR+ significantly increased at 7 to 15 days, and returned to baseline at 6 months. The increment of circulating activated T cells (CD3+/DR+) in UA was inversely related to the admission levels of CRP ($r = -0.63$, $p = 0.003$) and associated with a better outcome.**

Conclusions. **Our data suggest that the inflammatory component systemically detectable in UA may be antigen-related and that the magnitude of the immune response correlates with the clinical outcome of instability.**

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Systemic levels of inflammatory markers are frequently elevated and associated with a worse prognosis in unstable angina (UA) (1–3). Similarly, inflammatory cells are frequently activated in UA (4,5) and are especially abundant in the shoulder region of coronary plaques (6) where they can play a key role in plaque disruption (7) and thrombosis (8,9). Although these findings strongly suggest that inflammation may have an important role in the pathogenesis of UA, the possible triggers of this inflammatory response remain unclear. Recently, we have demonstrated that neither clot system activation (10) nor ischemia-reperfusion injury (11) are sufficient to elicit the acute phase response observed in UA patients. Interestingly, activated T lymphocytes are frequently found in peripheral blood (12,13) and in the coronary plaques (8,9,14) of patients with acute coronary syndromes. Thus, we reasoned that antigenic inflammatory stimuli might trigger both inflammation and activation of the immune system in UA. To this end, we correlated the time course of inflammatory markers and immune system activation with disease progression in 35 patients with UA, either in the acute phase and during a 6-month follow-up after stabilization of symptoms, by measuring serum levels of C-reactive protein (CRP) (as a marker of inflammation), IgG, IgA, IgM, C3 and C4 (as markers of humoral immunity) and the prevalence of circulating CD3+/DR+ cells (i.e., activated T lymphocytes) and serum levels of interleukin (IL)-2 (as markers of cell-mediated immunity). The same protocol was also applied to 35 patients with CSA serving as control.

Methods

Patient population. *Group A.* Only patients with documented severe UA (15) of recent onset (<10 days before admission) were admitted to the study as UA (n = 35). All patients had at least two episodes of rest angina or one episode lasting more than 20 mins, during the last 24 h, accompanied by transient ischemic ST-segment changes and no detectable rise in creatine kinase-MB levels or troponin T levels (to exclude micronecrosis, only patients with less than 0.2 μg/L were included in the study). Full medical therapy, including beta-adrenergic blocking agents and/or calcium antagonists, low-dose aspirin and continuous i.v. infusion of nitrates and heparin, was introduced on admission, and continuous electrocardiogram (ECG) telemetry monitoring was applied to all patients during their stay in our coronary care unit. Patients with less than one further ischemic episode after 48 h of full

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Abbreviations and Acronyms

Cp = *Chlamydia pneumoniae*
CRP = C-reactive protein
CSA = chronic stable angina
IL = interleukin
UA = unstable angina

medical therapy were assigned to group A1 (n = 19) while patients with more than two unstable ischemic episodes (either symptomatic or asymptomatic), after 48 h of full medical therapy were assigned to group A2 (n = 16, Braunwald class 3, high risk).

Group B. As controls we studied 35 patients with exclusively effort-related angina, stable for at least 12 months, with a positive exercise stress test and at least one coronary stenosis detected at angiography (>75% reduction of lumen diameter). All patients were on low-dose aspirin and various combinations of nitrates, beta-blockers and/or calcium antagonists. This group also was subsequently split in two, according to the clinical outcome. Group B1 included 20 patients with angina Canadian Class I and II, who were discharged on medical treatment only, while group B2 included 15 patients with angina Canadian class III, who underwent elective coronary revascularization.

Exclusion criteria. The exclusion criteria included evidence of recent infectious disease, erythrocyte sedimentation rate >20 mm/h, fever, immunosuppressive drug therapy, immunologic disorders, known or suspected neoplastic diseases, congestive heart failure, valvular heart disease, evidence of left ventricular aneurysm, recent (<3 months) major trauma, surgery, myocardial infarction or coronary revascularization (coronary angioplasty or bypass surgery). All patients gave their written informed consent to participate in the study, which was approved by the Ethics Committee of our institution.

Sampling protocol. During an antigen-directed immune response, the immune markers show a transient increase starting from day 5, reach a plateau at day 7 through day 15 and then gradually decrease, returning to baseline at day 28 (16). The time course of immunologic and inflammatory markers shows a transient reduction of the former and an increase of the latter during the first 48 h after a surgical procedure, with complete normalization at 7 days (17). Thus, in patients with UA, blood samples were taken: 1) as close as possible to the onset of the unstable phase and within 24 h of an episode of rest angina (sample 1); 2) between 7 and 15 days

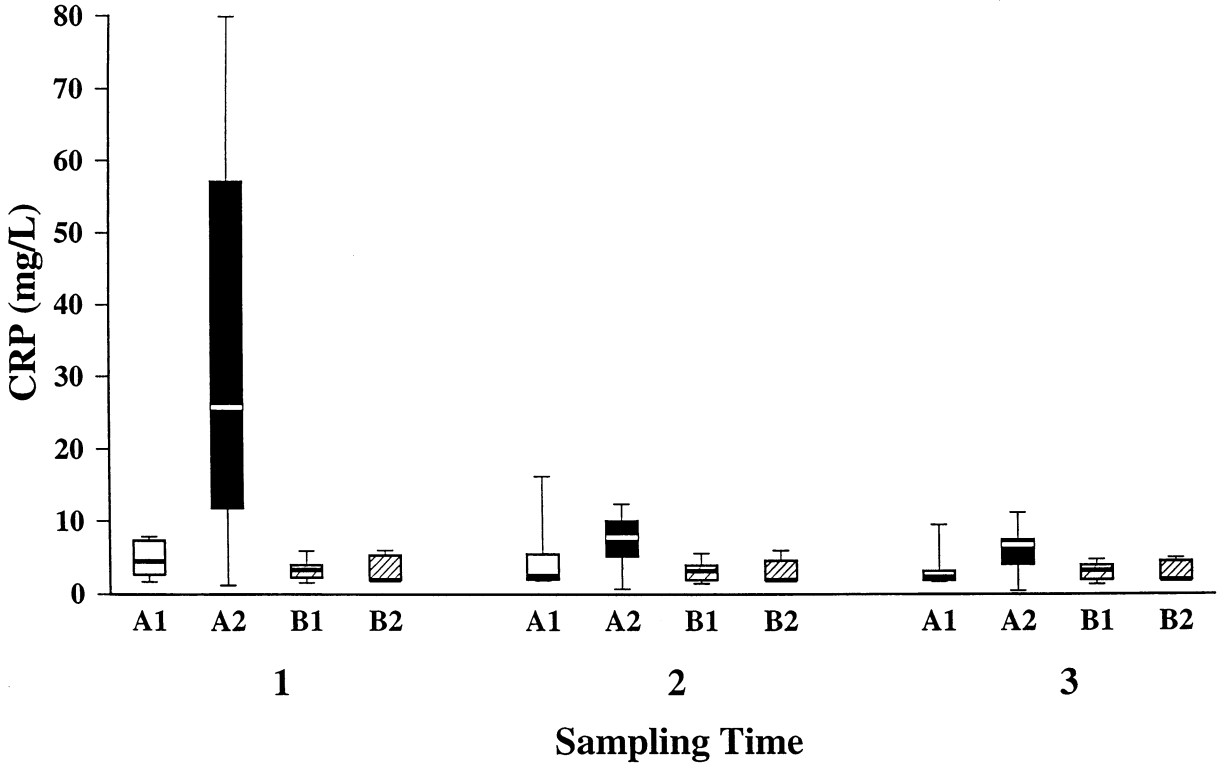


Figure 1. CRP levels were significantly higher on admission in group A2 (25 mg/L, $p < 0.0001$) than in group A1 (4.5 mg/L) and groups B1 and B2 (3.3 and 2 mg/L respectively). The high CRP levels significantly decreased in group A2 to 7.8, 0.2 to 32.2 mg/l in sample 2 and to 6.8, 0.2 to 26.5 mg/l in sample 3 ($p < 0.0001$ vs. sample 1). In control groups B1 and B2, CRP levels were lower than in unstable angina groups (A1 and A2, $p < 0.0001$) and did not change during the study. The x-axis represents the time of sampling: **1** = admission; **2** = after 7 to 15 days; **3** = after 6 months; **A1** = resolving UA, n = 19; **A2** = refractory UA, n = 16; **B1** = stable angina, Canadian class I to II, n = 20; **B2** = stable angina, Canadian class III to IV, n = 15.

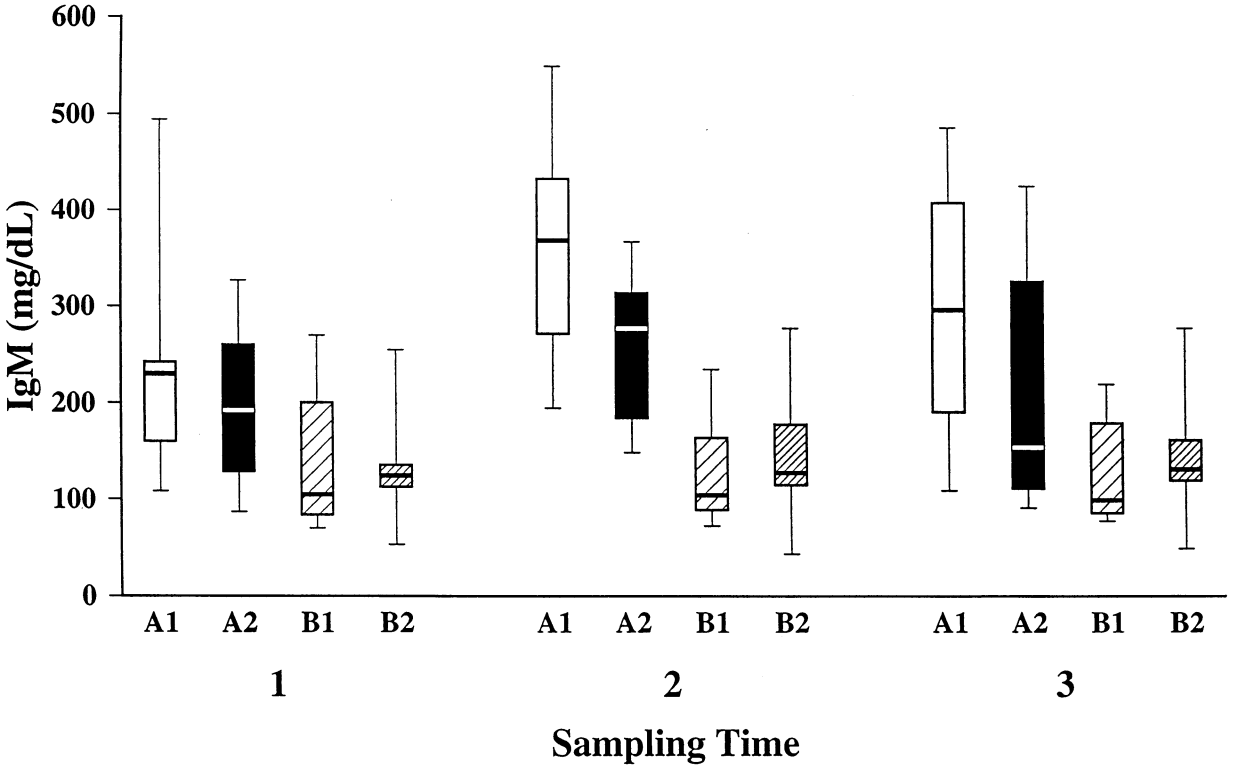


Figure 2. Total IgM serum levels were higher in unstable groups A1 and A2 than in stable angina groups B1 and B2 ($p < 0.0001$) and showed a transient increase at sample 2 ($p < 0.001$ vs. sample 1 and $p < 0.05$ vs. sample 3) that was not detectable in the controls. The increment of IgM was significantly greater in group A1 (favorable outcome) than in group A2 ($p < 0.05$).

after the last ischemic episode and/or coronary revascularization (sample 2); and 3) at 6 months follow-up (sample 3). In patients with chronic stable angina (CSA) blood samples were taken 1) on admission (sample 1); 2) between days 7 and 15 after the first sample and/or coronary revascularization (sample 2); and 3) at 6 months (sample 3). Each sample consisted of 10 ml of blood obtained from a peripheral vein; an aliquot of 3.5 ml was collected in tubes containing EDTA (1.5 ml) and immediately analyzed by flow-cytofluorimetry. The remaining blood was collected in plain plastic tubes and allowed to coagulate for 1 h at room temperature. After clot formation, the serum was collected in 200 μl aliquots and stored at −70°C until analysis.

Sample analysis. *Serum.* C-reactive protein was measured by an automated monoclonal antibody solid phase sandwich enzyme immunoassay on the Abbott IMx instrument (Abbott Laboratories, Chicago, Illinois). Immunoglobulins and complement fractions were measured by nephelometry. Specific IgG and IgM titres for *Chlamydia pneumoniae* (Cp) were assessed by microimmunofluorescence assay, as previously described (18). Interleukin-2 levels were measured by a double-antibody sandwich technique (ELISA, CABRU, Milan, Italy). Lymphocyte subpopulations were assessed by staining fresh whole blood (EDTA) with the following fluorescein isothyocianate (FITC) or phycoerythrin (PE) conjugated monoclonal antibodies: anti-Leu-4 (CD3), anti-Leu-3a (CD4), anti-Leu-2a (CD8), anti-Leu 12 (CD19) and anti-HLA-DR. Leuco GATE-TM (CD45/CD14) was used to assess purity and recovery inside the lymphocyte gate; FITC conjugated IgG1 and PE conjugated IgG2a were used to detect nonspecific antibody binding (Becton Dickinson, California). The stained samples were then treated with a lysing solution (Ortho-immune Lysing Reagent, Ortho Diagnostic Systems, Raritan, New Jersey) to lyse erythrocytes and washed prior to flow cytometric analysis. The percentage of fluorescent positive cell was determined using a FACscan flow-cytometer. As CD3+/DR+ double positive cells represent a very small proportion of all leukocytes, in all experiments a minimum of 20,000 events was acquired in the lymphocyte gate. Analysis was performed using a commercially available software (LysYs II, Becton Dickinson).

Statistical analysis. Data were analyzed by two-factor (group and time) analysis of variance using the Statview 4.1 software (Abacus Concept Inc., Berkeley, California). Sheffe's test was used to identify significant differences between means (group and/or time). Correlation between variables were assessed by Spearman's rank correlation. Prevalence of specific Cp antibody titres in the study population was analyzed using the Chi-squared test. A p value <0.05 was considered statistically significant. In the box plot charts (Figs. 1 through 5), the top, bottom and line through the middle of the box correspond to the 75th percentile (top quartile), 25th percentile (bottom quartile) and 50th percentile (median) respectively. The whis-

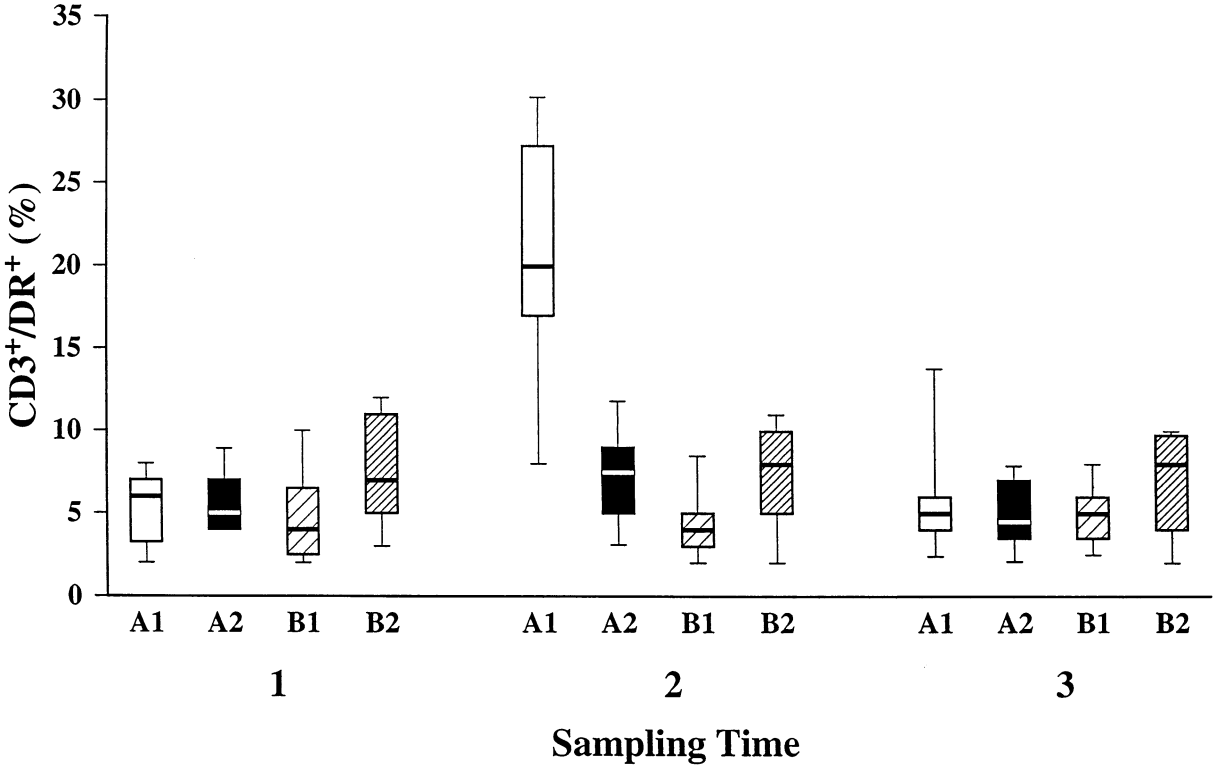
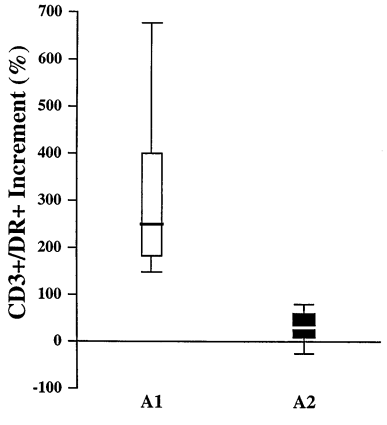


Figure 3. The proportion of activated T cells ($CD3^+/DR^+$) was similar in unstable and stable angina groups on admission (sample 1), but was transiently and significantly increased at sample 2 in group A and not in group B ($p < 0.0001$). Group A1 (favorable outcome) showed a more dramatic transient increase in activated T cells than group A2 (less favorable outcome): they were 6 (2 to 8) % in sample 1, increased up to 20 (7 to 31) % at sample 2 ($p < 0.0001$) and returned to 5 (2 to 15) % at sample 3 ($p < 0.0001$ vs. sample 2, p = NS vs. sample 1). No time variation was detectable in controls. The x-axis represents the time of sampling: **1** = admission; **2** = after 7 to 15 days; **3** = after 6 months; **A1** = resolving UA, n = 19; **A2** = refractory UA, n = 16; **B1** = stable angina, Canadian class I to II, n = 20; **B2** = stable angina, Canadian class III to IV, n = 15.

Figure 4. The increment in $CD3^+/DR^+$ (activated T) cells was significantly greater in case of favorable outcome (group A1, median increase 250%) than in case of medical therapy failure in UA (group A2, median increase 30%, $p < 0.0001$).

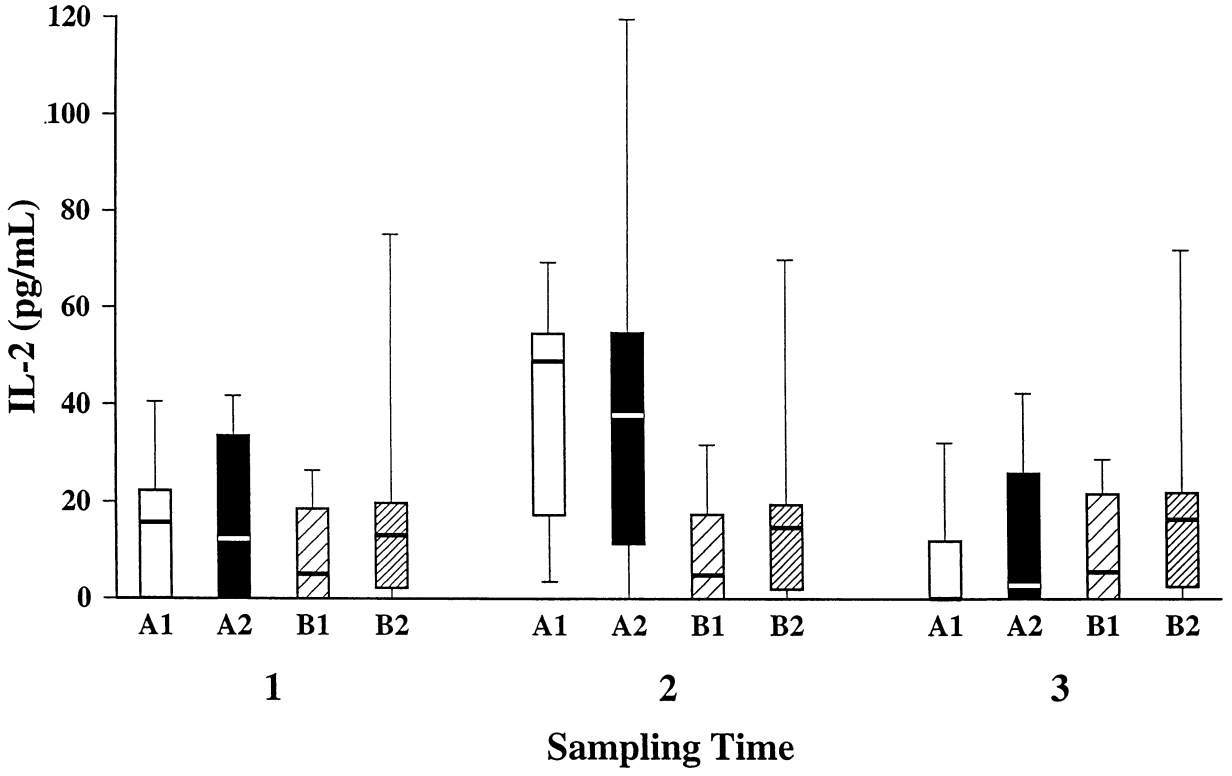


kers extend from the 10th percentile (bottom decile) to the 90th percentile (top decile).

Results

White blood cell count, percentages of total, CD19, CD3 and DR single positive lymphocytes, neutrophils, monocytes, basophils and eosinophils, and serum protein levels did not differ in any of the four subgroups throughout the study (data not shown). The number of diseased coronary vessels, blood cholesterol levels, blood pressure, cigarette smoking, diabetes and familiarity for ischemic heart disease were all similar in the four subgroups (data not shown).

Inflammation and immune system activation in acute UA as compared with CSA. Data (median and range) are shown in Table 1. Group A (UA) had significant higher admission CRP serum levels and percentage of circulating T-helper (CD4+) cells than group B (CSA, $p < 0.0001$ and $p < 0.01$, respectively) and had also less circulating T-suppressor (CD8+) cells than group B ($p < 0.0001$). Although being similar on admission, the time course of IgM ($p < 0.001$), IL-2 ($p < 0.0001$) and CD3+/DR+ ($p < 0.0001$) values showed a significant and transient increase at sample 2 only in group A. Conversely, CRP levels decreased in the follow-up ($p < 0.0001$). In group B, none of the inflammatory/immune markers showed any variation during the study period. Specific IgM titres for Cp were below the detectable limit in all patients. Specific IgG for Cp were found in more than 60% in both groups A and B (Table 2) and were stable over time (data not



shown). Of interest, the highest titres were detected in group B even though seropositive patients tended to be more frequently found in group A ($p = 0.09$).

Relation between grade of inflammatory/immune responses and the clinical outcome in UA and CSA. Data (median and range) are shown in Table 3. Patients with persistent, severe UA (group A2) had significantly higher CRP levels than patients with treatment-responsive UA (group A1, $p < 0.0001$ vs. A2, Fig. 1). Conversely, the IgM levels increase was higher in group A1 ($p < 0.05$, Fig. 2) and the percentage of activated T cells (CD3+/DR+) dramatically increased at sample 2 only in group A1 ($p < 0.0001$ in sample 2 vs. samples 1 and 3, Fig. 3). Accordingly, highest titres of specific IgG for Cp were significantly more frequent in group A1 than in A2 ($p < 0.0001$, Table 2).

The levels of IL-2 were also transiently increased in UA as compared to CSA ($p < 0.0001$, Table 1), but the increment was similar in groups A1 and A2 (Fig. 5) and also the percentage of CD4+ and CD8+ cells, in spite of being different in unstable as compared to stable angina, did not show any relation neither to the onset nor to the clinical evolution of instability and remained unchanged during the study in both groups A1 and A2. Interestingly, in group A the increment in the percentage of CD3+/DR+ cells was inversely related to the waxing UA phase levels of CRP (Spearman's rank correlation, $r = -0.63$, $p = 0.0003$, Fig. 6). A more severe disease in CSA (group B2) was associated with higher percentage of circulating CD3+/DR+ cells ($p < 0.05$ vs. group B1) but, at variance with group A1, activated T cells did not show any further variation during the study period in group B2 (Fig. 3).

Figure 5. IL-2 levels were similar in unstable and stable angina on admission, but showed a significant and transient increase at sample 2 only in group A ($p < 0.001$ vs. samples 1 and 3). Such a time variation was absent in groups B. The x-axis represents the time of sampling: **1** = admission; **2** = after 7 to 15 days; **3** = after 6 months; **A1** = resolving UA, n = 19; **A2** = refractory UA, n = 16; **B1** = stable angina, Canadian class I to II, n = 20; **B2** = stable angina, Canadian class III to IV, n = 15.

Discussion

Our findings show that in UA a transient specific immune response actually follows by 7 to 15 days the signs of inflammation detected by CRP elevation and that an increase in circulating activated T cells and IgM is associated with a more favorable short-term clinical outcome of UA.

Inflammation in UA. C-reactive protein (3) and IL-6 (2) are markers of poor short-term clinical outcome in UA. The present study demonstrates that after the acute phase of instability, CRP levels decline rapidly, paralleling the resolution of clinical symptoms but remain elevated in case of an unfavorable outcome, thus strengthening the hypothesis that an inflammatory process is associated with the unstable phase of angina.

Signs of inflammation can be detected both locally in the culprit lesions and systemically in the circulating blood of UA patients. The local activation of inflammatory cells could be due to plaque complication or may, in turn, facilitate plaque disruption (7,9,19). The systemic inflammatory response may also be either cause or consequence of endothelial activation with increased expression of procoagulant and vasoconstrictor

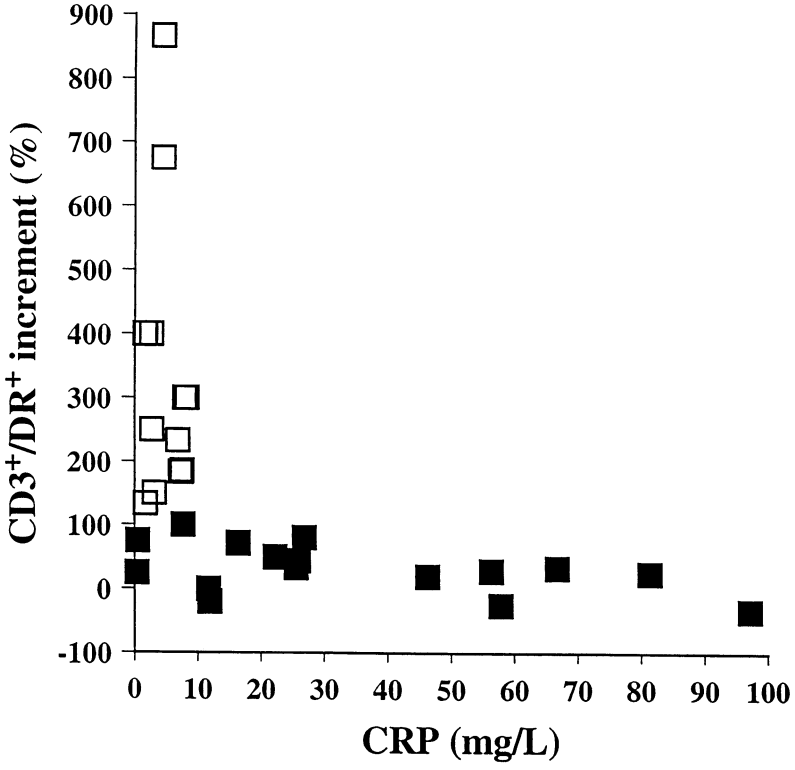


Figure 6. Scatter plot shows the relation between CRP acute levels (at sample 1) and the percentage increment in $CD3^+/DR^+$ (at sample 2 compared to sample 1 in each patient) in UA (group A). Serum levels of CRP in the acute phase of UA were inversely related to the percentage increment of $CD3^+/DR^+$ lymphocytes at 7 to 15 days (Spearman's rank correlation: r = 0.63, p = 0.0003). Patients with a more favorable outcome (group A1, **open squares**) had lower CRP levels and a higher $CD3^+/DR^+$ increment as compared with patients with a less favorable outcome of UA (group A2, **solid squares**).

substances (20–22). Reperfusion damage following severe, prolonged ischemia (23) and clot system activation (24,25) may lead to cytokine release and to an increase in levels of acute phase reactants. Yet we found that neither ischemia-reperfusion injury (11) nor activation of the clot-system (10) by themselves elicit the acute phase response in UA, and indeed CRP and IL-6 values often remain elevated up to 3 months after hospital discharge. Thus, inflammation in UA does not appear to be a consequence of ischemia-reperfusion or thrombosis but its trigger is still unclear.

Table 1. Inflammatory and Immune Markers in UA vs. CSA

Group	A			B		
Time	1	2	3	1	2	3
CRP	7.5	5.5	3.2	3.2	2.4	2.1
(mg/l)	(0.4–97.2)	(0.2–32.2)	(0.2–26.5)	(0.4–6.1)	(0.4–10.0)	(0.4–5.0)
IgG	1,130	1,342	1,320	1,310	12,050	1,230
(mg/dl)	(902–1,860)	(960–2,620)	(965–2,100)	(925–1,740)	(938–1,870)	(965–1,620)
IgA	341	430	399	346	342	360
(mg/dl)	(88–569)	(152–725)	(165–659)	(222–621)	(199–632)	(200–642)
IgM	202	312	198	113	115	120
(mg/dl)	(69–618)	(112–615)	(85–527)	(53–613)	(43–710)	(49–699)
C3	98.7	101.0	103.0	97.9	93.2	99.0
(mg/dl)	(59.5–145.0)	(80.0–159.0)	(76.0–166.0)	(55.2–162.0)	(54.0–172.3)	(52.0–178.0)
C4	39.8	42.0	42.5	42.3	40.3	39.8
(mg/dl)	(14.9–89.0)	(18.5–89.6)	(17.2–93.0)	(18.2–94.7)	(22.0–100.0)	(20.3–99.6)
$CD4^+$	52	50	45	42	42	42
(%)	(28–65)	(24–64)	(25–65)	(31–54)	(29–53)	(35–52)
$CD8^+$	29	35	32	35	34	32
(%)	(13–56)	(16–52)	(20–53)	(25–62)	(25–60)	(25–58)
IL-2	13.6	44.0	0.1	8.7	7.9	10.0
(pg/ml)	(0.0–51.1)	(0.0–154.4)	(0.0–65.9)	(0.0–75.2)	(0.0–70.0)	(0.0–72.0)
$CD3^+/DR^+$	5	10	5	5	5	5
(%)	(2–9)	(3–31)	(2–15)	(1–16)	(2–11)	(2–10)

Data are expressed as median (range).

Table 2. Specific IgG titre for Cp

	Cp Titre		
	Negative	1/8–1/32	> 1/64
A1	16.7	66.6	16.7
A2	30.7	53.8	7.8
B1	41.7	33.3	25
B2	30.8	46.2	23

Data are expressed as percentage.

Immune system activation in UA. An intriguing hypothesis is that the inflammatory response observed in UA 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 (8,9). Our study is the first to assess the time course of systemically detectable inflammatory markers of the immunologic response during waxing and waning phases of UA. The initial unstable phase of UA is associated with an acute phase response, indicated by increased levels of CRP, and waning of the instability is followed by a transient activation of the immune system, indicated by increased levels of both humoral (IgM) and cellular (IL-2, CD3+/DR+) immunologic markers. This suggests that the nature of the inflammatory component in UA may be antigenic. Interestingly, we found that a favorable outcome is associated with a greater increment of IgM titre and CD3+/DR+ cells and with a lower inflammatory response.

A dynamic view of immune factors is essential to establish the biologic association with clinical events. In the study by Neri Serneri et al. (13) as well as in our own, the percentage of circulating CD3+/DR+ lymphocytes was transiently increased, 7 days after admission, in most UA patients with favorable outcome. Considering the statistical association of the immune response with a better outcome, it is tempting to speculate that the immune response, in some cases, might actually favor the waning of instability. Conversely, in our study population and in previous observations (26,27), the admission levels of activated T cells were not related to the clinical outcome at variance with the report by Neri Serneri et al. (13). This may not be surprising because T-cell activation is a complex phenomenon not easily interpretable in clinical studies. The regulation of inflammation and antibody production are under the control of different subsets of immunocompetent cells. Most disease-inducing T cells are of the Th1 phenotype (28) and experimental studies suggest that atherosclerosis may be accelerated by a Th1 immune response (29). But in several experimental models, induction of a Th2-type immune response is protective (30–35). Possibly, the activated T cells observed in UA patients with better outcome are of the Th2 "protective" phenotype, although this aspect was not assessed in the present study.

Putative causes of immune system activation. Transient activation of T lymphocytes as well as transient production of IgM antibodies imply a recent antigenic stimulation, but the culprit antigen(s) in patients with UA are not known. Such antigen(s) may be either self-modified proteins or infectious agents. Several autoantigens expressed in atherosclerotic plaque, including oxidized low-density lipoproteins (36,37) and heat shock proteins (38), can elicit an immune response. It has also been reported that infectious agents such as Cp (18,39,40), cytomegalovirus (41) and *Helicobacter pylori* (42,43) may be associated with the risk of ischemic heart disease. Cytomegalovirus and *H. pylori* do not appear to be related to instability of angina (44,45), while viable Cp has recently been found in active coronary atherosclerotic lesions (46) and thus this microorganism might be the target for activated lymphocytes in the unstable plaques. Nevertheless, the total IgM increase observed in UA patients in the present study cannot be ascribed to active Cp infection, considering that no specific IgM for Cp could be detected in these patients. The specific IgG for Cp were detectable in more the 60% of both UA and CSA patients, although UA patients tended to be more frequently seropositive than CSA patients. Suprisingly, the highest levels of specific antibodies (titre >1/64) were more frequently detected in group B and in the subgroup A1 (favorable outcome) of the UA group. However, none of the patients in the study showed any significant increase of the specific IgG anti-Cp during the study period. Hence, other antigens have to be considered as the trigger for the transient immune response in UA. Indeed, the rise in the total antibody levels in our study as well as the polyclonal origin of plaque T cells (47) and the many nonspecific clinical infections that have been associated with ischemic heart disease (40,48) suggest that different antigenic stimuli might play a role in different patients or even in the same patient over time.

Immune system activation in CSA. Evidence for T-cell activation has been found also in the circulating blood of CSA patients (49), implying that the inflammatory/immune response in UA might be generically related to the atherosclerotic background (50,51). Therefore, we choose to compare the time course of immune parameters in UA in comparison with a group of patients with similar coronary atherosclerotic background (CSA patients). We found that severe effort angina (group B2) is associated with higher percentage of CD3+/DR+, supporting the hypothesis that the immune system is associated with the chronic atherosclerotic background. But, of note, in stable patients the time course of this marker did not vary over the study period. This observation suggests that the acute and transient immune system activation observed in UA cannot be explained by the chronic atherosclerotic background.

Limitations of the study. Surgical trauma may influence both the acute phase and immune system responses. Ethical reasons prevented us from delaying revascularization in cases of refractory angina. However, the immune and inflammatory effects of surgery last only 24 h (17) while sample 2 was taken always >7 days after the revascularization. Moreover, in CSA elective coronary revascularization did not affect the time course of any inflammatory marker.

Table 3. Inflammatory and Immune Markers in the 4 Programs' Subgroups

Subgroup	A1			A2			B1			B2		
Time	1	2	3	1	2	3	1	2	3	1	2	3
CRP	4.5	2.6	2.4	25.8	7.8	6.8	3.3	3.2	3.3	2	2	2
(mg/l)	(1.6–8.1)	(1.8–22.3)	(1.6–11.9)	(0.4–97.2)	(0.2–32.2)	(0.2–26.5)	(0.4–6.1)	(0.4–10)	(0.4–5)	(2–6)	(2–6)	(1.9–5)
IgG	1,040	1,210	1,230	1,130	1,390	1,350	1,230	1,230	1,210	1,470	1,350	1,250
(mg/dl)	(980–1,860)	(1,030–2,620)	(1,050–2,100)	(900–1,480)	(960–1,950)	(960–1,820)	(920–1,740)	(1,000–1,650)	(960–1,560)	(920–1,740)	(930–1,870)	(960–1,620)
IgA	320	430	320	352	453	422	400	395	420	288	280	320
(mg/dl)	(88–569)	(152–599)	(165–635)	(183–542)	(188–725)	(190–659)	(222–564)	(210–554)	(220–560)	(233–621)	(199–632)	(200–642)
IgM	230	369	297	192	278	154	105	104	99	125	128	132
(mg/dl)	(101–618)	(170–615)	(102–527)	(69–339)	(112–530)	(85–436)	(70–613)	(62–710)	(72–699)	(53–613)	(43–710)	(49–699)
C3	86	98	100	106	106	117	98	97	100	101	87	99
(mg/dl)	(59–127)	(142–80)	(76–166)	(77–145)	(81–159)	(96–141)	(55–162)	(54–172)	(52–178)	(74–120)	(68–146)	(75–123)
C4	42	40	42	40	46	44	42	41	39	39	36	40
(mg/dl)	(133–867)	(32–58)	(29–93)	(32–89)	(18–89)	(17–86)	(18–95)	(22–100)	(20–100)	(18–98)	(22–100)	(23–100)
$CD4^+$	54	54	45	49	50	45	42	42	42	46	45	45
(%)	(28–65)	(39–61)	(41–59)	(36–64)	(24–64)	(25–65)	(36–51)	(29–51)	(35–50)	(31–54)	(29–53)	(36–52)
$CD8^+$	27	35	31	32	36	35	33	33	28	37	40	39
(%)	(13–42)	(16–42)	(20–44)	(19–56)	(19–52)	(20–53)	(25–48)	(25–44)	(25–46)	(25–62)	(27–60)	(26–58)
IL-2	16	49	0	12	38	3	5	5	6	13	15	16
(pg/ml)	(0–51)	(0–72)	(0–45)	(0–46)	(0–154)	(0–65)	(0–58)	(0–46)	(0–49)	(0–75)	(0–70)	(0–72)
$CD3^+/DR^+$	6	20	5	5	7	4	4	4	5	7	8	8
(%)	(2–8)	(7–31)	(2–15)	(2–9)	(3–13)	(2–9)	(1–16)	(2–9)	(2–8)	(1–16)	(2–11)	(2–10)

Data are expressed as median (range).

Conclusions. Although evidence of inflammation and of specific immune activation are found both in CSA and UA patients (52), we have observed that a "dynamic" immune response is only detectable in UA patients and is associated with a favorable outcome. The possibility of a causal role for the immune system in the pathogenesis and/or in the clinical outcome of UA, if confirmed, would open novel therapeutic approaches for this syndrome.

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