Enhanced Inflammatory Response in Patients With Preinfarction Unstable Angina

Giovanna Liuzzo, MD,* Luigi M. Biasucci, MD, FACC,* J. Ruth Gallimore, BSc,† Giuseppina Caligiuri, MD,* Antonino Buffon, MD,* Antonio G. Rebuzzi, MD,* Mark B. Pepys, MD,† Attilio Maseri, MD, FACC*

Rome, Italy and London, United Kingdom

OBJECTIVES
We assessed the extent and the time course of the acute phase response following myocardial cell necrosis and its relationship with the presence of preinfarction unstable angina (UA).

BACKGROUND
Elevated levels of acute phase proteins have been reported in patients with UA and in patients with acute myocardial infarction (MI).

METHODS
C-Reactive Protein (CRP), serum amyloid A protein (SAA) and interleukin-6 (IL-6) were measured in 36 patients with MI admitted within 3 h from symptoms onset. All patients had normal levels of creatine kinase and of troponin T on admission, rising above diagnostic levels within 6 to 12 h. Blood samples for CRP, SAA and IL-6 measurements were taken on admission, at 6, 24, 48, 72 h and at discharge.

RESULTS
Twenty of the 36 patients studied presented an unheralded MI (Group 1); the remaining 16 patients had symptoms of unstable angina in the preceding 7 days (Group 2). Group 2 patients have much higher levels of CRP and SAA on admission (median values 8.8 vs. 3 mg/L and 28 vs. 3.4 mg/L, respectively, all p < 0.001). Following the necrotic insult, despite similar infarct size and clinical signs of reperfusion, Group 2 patients had strikingly higher peaks of IL-6 (median values 85.2 vs. 19 pg/ml, p < 0.05), CRP (50 vs. 31.4 mg/L, p < 0.05) and SAA (228 vs. 45 mg/L, p < 0.001).

CONCLUSIONS
Our data demonstrated that the acute phase response is greatly enhanced in patients with preinfarction UA compared with those presenting with an unheralded MI. The significant differences in acute phase response observed in these two clinical presentations of MI indicate a major difference in their underlying pathogenetic components.

Recently, the observation of inflammatory infiltrates in unstable coronary plaques (1–3) and the presence of activated circulating neutrophils (4–6), lymphocytes (7,8) and monocytes (9,10) have suggested that inflammatory stimuli may contribute to the pathogenesis of acute coronary syndromes. Furthermore, increased concentrations of C-reactive protein (CRP) and serum amyloid A protein (SAA), highly sensitive acute phase reactants and interleukin-6 (IL-6), a proinflammatory cytokine which is the major determinant of acute phase protein production, have been reported in patients with unstable angina (UA) (11–14) and in patients with acute myocardial infarction (MI) at the time of hospital admission (12,15).

However, the triggers of the acute persistent thrombotic occlusion responsible for (MI) may be multiple. In a previous study we have found that a substantial proportion of patients presenting with totally unheralded MI had normal CRP and SAA levels, in striking contrast with patients with preinfarction UA (12).

Thus, in this study we measured plasma levels of CRP, SAA and IL-6 in 36 patients with documented MI admitted within 3 h from symptom onset. Our findings demonstrate that the acute phase response on admission and following MI is significantly greater in patients with preinfarction UA than in those with unheralded MI, suggesting that these two clinical presentations of MI might be associated with different pathogenetic components of acute coronary occlusion.

METHODS

Patient population. Thirty-six of the 158 consecutive patients admitted to our coronary care unit between October 1993 and October 1994 with a diagnosis of possible
Abbreviations and Acronyms

- CAD = coronary artery disease
- CI = confidence interval
- CK = creatine kinase
- CRP = C-reactive protein
- EF = ejection fraction
- IL-6 = interleukin-6
- MI = myocardial infarction
- SAA = serum amyloid A protein
- SK = streptokinase
- UA = unstable angina
- WM = wall motion score

acute MI were included into the study (27 men; mean age 61 ± 10 yr).

Inclusion criteria were: typical chest pain lasting >30 min; ST-segment elevation ≥0.2 mV in ≥2 contiguous leads of the standard 12-lead ECG, resistant to a 2 to 4 mg intravenous bolus of isosorbide dinitrate; admission within 3 h from onset of prolonged chest pain and normal serum creatine kinase (CK) (reference range 30 to 230 IU per liter) and troponin T (<0.1 μg/l) on admission rising above diagnostic levels (i.e. two times the upper limit of normal and >0.5 μg/l, respectively) within 6 to 12 h. Exclusion criteria were: admission more than 3 h from onset of symptoms (48 patients, in 29 of whom CK was already elevated), a previous myocardial MI within 6 months (18 patients), contraindications to thrombotic therapy (16 patients), left bundle branch block or atrial fibrillation (15 patients), chronic dissecting aortic aneurysm (5 patients), inflammatory conditions likely to be associated with an acute phase response (12 patients), and neoplastic disease (8 patients).

All patients received intravenous thrombolytic agents, streptokinase (SK) 1.5 million units as a continuous infusion over 60 min (26 patients) or rt-PA 15 mg as bolus followed by 50 mg as a continuous infusion over 30 min and 35 mg in 60 min (10 patients), according to the physician’s judgment. An intravenous infusion of isosorbide dinitrate was started at a rate of 1 to 10 mg/h, titrated against systolic blood pressure and continued for 24 to 48 h as clinically required. All patients also received oral aspirin (100 mg/day); 30 patients received an intravenous infusion of heparin over the first 24 h adjusted four-hourly to achieve an activated partial thromboplastin time between two and three times the control value; and 18 patients were also treated with oral calcium-channel blockers and 12 with oral beta-adrenergic blocking agents. Coronary angiography was performed in 26 patients within five to seven days from admission.

Within 24 h from admission, the patients were classified as having either an unheralded MI or UA in the week preceding their MI. Unheralded MI was defined as a single episode of prolonged chest pain in patients without previous history of ischemic heart disease or in patients with previous history of chronic stable angina, but no acute events or worsening of symptoms in the last 6 months. Preinfarction UA was defined as ≥2 episodes of angina at rest lasting <30 min in the seven days preceding the MI, documented ST-segment shift diagnostic for myocardial ischemia during the angina attacks, the last episode of chest pain in the last 48 h.

The Ethics Committee of the Catholic University of Rome approved the protocol; all patients gave informed consent.

Study protocol. Blood sampling. Blood samples were taken from an antecubital vein as soon as possible after the Coronary Care Unit admission, before the intravenous administration of drugs, and subsequently, at 6, 24, 48, 72 h and at discharge. Coded plasma samples were stored at −70° C and analyzed for CRP, SAA and IL-6 in a single batch at the end of the study; all categorization and management of patients were independent of these results. In addition, six-hourly blood samples for the plasma determination of total CK were collected during the first 24 h from admission and at 48 h. Finally, troponin T, a specific marker of myocardial necrosis, was measured on admission and 6 and 12 h later.

Estimation of infarct size and noninvasive assessment of reperfusion. Infarct size was estimated from peak CK level, from the area under the 48-h CK time-concentration curve and from the predischARGE evaluation of left ventricular ejection fraction (EF) and global wall motion score (WMS) assessed by echocardiography. The success of the thrombolytic treatment was assessed using noninvasive markers of reperfusion: the time to peak CK level and a reduction greater than 50% in the sum of ST elevation (in the leads showing >1 mm ST elevation) at 4 h from the start of the thrombolysis (16).

Laboratory assays. C-reactive protein and SAA were assayed by an automated monoclonal antibody solid phase sandwich-type enzyme immunoassay on the Abbott IMX instrument (Abbott Laboratories, Chicago, Illinois), as previously described (12). The median normal value for CRP is 0.8 mg/L, with 90% of normal values <3 mg/L. C-reactive protein levels begin to rise 6 h after an acute stimulus and peak after 24–48 h; the half-life of CRP in the circulation is 19 h (17). The median (range) normal SAA concentration is 3 (0.7 to 26.4), with 82% less than 5 mg/L. Circulating concentrations of SAA can increase from normal, about 5 mg/L, to >1,000 mg/L within 24 to 48 h of an acute stimulus (17).

Interleukin-6 was measured with a commercial assay kit (Quantikine human IL-6 R&D System, Minneapolis, Minnesota). Interleukin-6 measurements were performed in duplicate, and the intra- and interassays variability was less than 10%. The range of values detected by the assay is 3 to 300 pg/ml. Interleukin-6 levels begin to rise 45 to 60 min after endotoxin injection in healthy volunteers and peak after 2 to 4 h (18). Interleukin-6 half-life in the circulation was calculated to be around 4 h (19).

Troponin T was measured with a commercial enzyme immunoassay kit (Boehringer Mannheim, Mannheim, Germany).
Statistics. Because CRP, SAA and IL-6 values do not follow a normal distribution, comparisons between groups were carried out using the Mann-Whitney U test. Comparisons within groups were carried out using the Friedman test; for a p value of <0.05, pairwise comparisons were carried out using the Wilcoxon test with the Bonferroni correction. Correlations were determined using Spearman’s rank correlation test. The remaining continuous variables were compared using t tests for paired and unpaired variables, as appropriate. Proportions were compared using the chi-square test. C-reactive protein, SAA and IL-6 values are expressed as median and range, the remaining variables are expressed as mean ± standard deviation; p values <0.05 (two-tailed) were considered statistically significant.

RESULTS

Of the 36 patients enrolled, 20 had a totally unheralded MI; in 15 MI was the very first manifestation of coronary artery disease, 5 of them had a history of chronic stable angina but without worsening of symptoms before the acute event (Group 1). The remaining 16 patients had symptoms of severe UA (Braunwald class IIIB) in the preceding 7 days (Group 2).

In Group 2, symptoms of UA started 2 to 18 days before MI, on average 9.8 ± 5 days. There were 79 episodes of angina at rest before the MI, which accounted for a mean of 5.3 ± 2 angina episodes per patient (range 2 to 9). The time interval between the last episode and the onset of MI was 19 ± 10 h (range 2 to 36 h). In 11 patients of this group, UA was the first manifestation of coronary artery disease.

The two groups did not otherwise differ significantly in baseline characteristics (Table 1).

Infarct size. At the time of Coronary Care Unit admission, troponin T and CK were normal in all samples. During the subsequent 6 to 24 h, the cardiac enzymes reached a diagnostic level for myocardial cell necrosis in all patients.

The three indexes used for the estimation of infarct size (peak total CK, predischarge left ventricular EF and global WMS assessed by echocardiography) were similar in the two groups of patients (Table 1, Fig. 1). The success of the thrombolytic treatment, assessed using time to peak CK level and a reduction greater than 50% in the sum of ST

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>59 ± 9</td>
<td>65 ± 10</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>14/6</td>
<td>13/3</td>
<td>0.7</td>
</tr>
<tr>
<td>Risk factors; n. of patients (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Family history of CAD</td>
<td>10 (50)</td>
<td>4 (25)</td>
<td>0.24</td>
</tr>
<tr>
<td>- Hypercholesterolemia</td>
<td>7 (35)</td>
<td>4 (25)</td>
<td>0.78</td>
</tr>
<tr>
<td>- Diabetes</td>
<td>7 (35)</td>
<td>1 (6)</td>
<td>0.1</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>5 (20)</td>
<td>7 (44)</td>
<td>0.47</td>
</tr>
<tr>
<td>- Smoking</td>
<td>15 (75)</td>
<td>12 (75)</td>
<td>0.7</td>
</tr>
<tr>
<td>Previous history; n. of patients (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Chronic stable angina</td>
<td>5 (25)</td>
<td>1 (6)</td>
<td>0.29</td>
</tr>
<tr>
<td>- Previous MI (&gt;6 months)</td>
<td>2 (10)</td>
<td>4 (25)</td>
<td>0.45</td>
</tr>
<tr>
<td>Interval between onset of symptoms and admission (min)</td>
<td>132 ± 47</td>
<td>106 ± 63</td>
<td>0.16</td>
</tr>
<tr>
<td>Thrombolytic therapy; n. of patients (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- SK</td>
<td>16 (80)</td>
<td>10 (63)</td>
<td>0.43</td>
</tr>
<tr>
<td>- rtPA</td>
<td>4 (20)</td>
<td>6 (37)</td>
<td>0.43</td>
</tr>
<tr>
<td>Infarct site; n. of patients (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anterior</td>
<td>6 (30)</td>
<td>9 (56)</td>
<td>0.21</td>
</tr>
<tr>
<td>- Inferior</td>
<td>12 (60)</td>
<td>7 (44)</td>
<td>0.53</td>
</tr>
<tr>
<td>- Lateral</td>
<td>2 (10)</td>
<td>0</td>
<td>0.57</td>
</tr>
<tr>
<td>Infarct size:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Peak CK level (IU/L)</td>
<td>1,932 ± 1,496</td>
<td>1,654 ± 967</td>
<td>0.52</td>
</tr>
<tr>
<td>- Predischarge EF (%) (Echo)</td>
<td>46 ± 9</td>
<td>44 ± 7</td>
<td>0.39</td>
</tr>
<tr>
<td>- Predischarge WM score (Echo)</td>
<td>8 ± 6</td>
<td>7.4 ± 5</td>
<td>0.73</td>
</tr>
<tr>
<td>Noninvasive markers of reperfusion:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Time to peak CK level (h)</td>
<td>16 ± 6.5</td>
<td>11.6 ± 6.4</td>
<td>0.057</td>
</tr>
<tr>
<td>- Patients with a reduction in ST sum elevation ≥50% at 4 h (%)</td>
<td>11 (55)</td>
<td>13 (81)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease; CK = creatine kinase; EF = ejection fraction; MI = myocardial infarction; SK = streptokinase; WM score = wall motion score.
Inflammatory response to myocardial cell necrosis. Unheralded MI. On admission, plasma levels of IL-6 were detectable only in 9/20 (45%) patients, all of whom also had elevated levels of CRP and five also had elevated levels of SAA. Plasma concentrations of CRP and SAA were normal (<3 mg/L and <5 mg/L, respectively) in 11 patients (55%). Median CRP and SAA values were 3 and 3.4 mg/L, respectively (Table 2, Fig. 2). No difference was found in baseline CRP and SAA levels between the 15 patients of Group 1 in whom MI was the very first manifestation of coronary artery disease (CAD) and the five patients with previous history of chronic stable angina. In response to myocardial cell necrosis, IL-6 median levels in Group 1 showed a slight but not significant increase (p = 0.16) (Table 2, Fig. 3); the median levels of CRP and SAA significantly increased with a peak at 48 h and 72 h, respectively (all p < 0.01) (Table 2, Fig. 4).

Preinfarction unstable angina. On admission, IL-6 levels were detectable in 14/16 patients (88%, p = 0.014 vs. Group 1) and CRP or SAA were elevated in all patients (p = 0.002 vs. Group 1); CRP was 8.8 mg/L and SAA was 28 mg/L (all p < 0.001 vs. Group 1) (Table 2, Fig. 2). No correlation was found between the number and the mean duration of ischemic episodes in the week preceding the MI and baseline levels of acute phase reactants. The serum concentration of IL-6 significantly increased 6 h later (p = 0.010) and reached the peak value at 24 h (p = 0.005 vs. baseline, p = 0.36 vs. 6 h) (Table 2, Fig. 3). Also CRP and SAA showed a marked increase, with a peak value at 48 h (all p < 0.001) (Table 2, Fig. 4). There was a significant correlation between the peak values of IL-6 and those of CRP and SAA (r = 0.48, 95% confidence interval (CI) = 0.12 to 0.71, p < 0.001 and r = 0.68, p < 0.001, 95% CI = 0.40 to 0.84, respectively).

Thus, Group 2 patients showed a strikingly higher acute phase response during the study period than Group 1 patients. Interleuken-6 levels were significantly higher in Group 2 than in Group 1 at 6 and 24 h, CRP at 6, 24 and 48 h and SAA at 6, 24, 48 and 72 h (Table 2).

Correlation between baseline and peak levels of CRP and SAA after myocardial cell necrosis. In order to investigate whether the inflammatory response observed after MI was related to the baseline levels of CRP and SAA, we correlated baseline and peak levels of CRP and SAA using the Spearman’s rank correlation test. In the overall population of 36 patients, there was a significant, close correlation between the baseline levels of CRP and SAA and the respective increases after MI (r = 0.55 and r = 0.65, respectively; all p < 0.001) (Fig. 5).

When the increase of CRP and SAA was normalized for the peak level of CK, Group 2 patients still showed a significantly higher acute phase response than Group 1 patients. C-reactive protein increase normalized for CK peak level [(peak CRP/peak CK) × 100] was 2.6 (0.3 to 13.6) in Group 1 and 5 (2.4 to 19.7) in Group 2 (p = 0.03); SAA increase normalized for CK peak level [(peak SAA/peak CK) × 100] was 6.4 (0.5 to 53.7) in Group 1 and 14.8 (8.1 to 73.4) in Group 2 (p = 0.019).

Table 2. Plasma Levels of CRP and SAA and Serum Levels of IL-6 During the Study Period

<table>
<thead>
<tr>
<th>Entry</th>
<th>6 h</th>
<th>24 h</th>
<th>48 h</th>
<th>72 h</th>
<th>Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>GROUP 1</td>
<td>3 (2.4–8.9)</td>
<td>4.2 (2.4–14.3)*</td>
<td>27.2 (2.8–161)*</td>
<td>31.4 (6.7–125)*</td>
<td>21.9 (4.8–65.3)*</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>8.8 (4.4–69.8)§</td>
<td>17.7 (7.6–75.4)†§</td>
<td>46.2 (7.7–256)†‡</td>
<td>50 (13.7–158)†‡</td>
<td>34.7 (10–116)*</td>
</tr>
<tr>
<td>SAA (mg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP 1</td>
<td>3.4 (0.7–7.9)</td>
<td>5.4 (1.3–203)*</td>
<td>30.5 (3.4–249.9)*</td>
<td>37.7 (5.7–295)*</td>
<td>45 (4.7–312)*</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>28 (3.2–282.4)§</td>
<td>38.3 (58–968)§</td>
<td>191 (29.2–992)†§</td>
<td>228 (4.2–597)§</td>
<td>207 (3.7–386.9)§</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GROUP 1</td>
<td>3.9 (0–34.2)</td>
<td>12.8 (0–37.5)</td>
<td>19.1 (0–100)</td>
<td>10.2 (0–78.9)</td>
<td>5.9 (0–53.3)</td>
</tr>
<tr>
<td>GROUP 2</td>
<td>12.5 (0–74.4)</td>
<td>44.6 (12.5–172)‡</td>
<td>85.2 (9–393.3)‡</td>
<td>18.2 (3–296.5)</td>
<td>12.9 (0–138.3)</td>
</tr>
</tbody>
</table>

Data are presented as median (range). CRP = C-reactive protein; IL-6 = interleukin-6; SAA = serum amyloid A protein. Group 1 = 20 patients with unheralded myocardial infarction; Group 2 = 16 patients with preinfarction unstable angina. *p < 0.05 vs. entry; †p < 0.001 vs. entry; ‡p < 0.05 vs. Group 1; §p < 0.001 vs. Group 1.
DISCUSSION

Our findings demonstrate that the acute phase response is greatly enhanced in patients with preinfarction UA compared with those presenting with a totally unheralded MI. They had much higher levels of CRP and SAA before the event and also strikingly higher peaks of IL-6, CRP and SAA following the necrotic insult, despite similar infarct size and clinical signs of reperfusion. The consistently elevated levels of CRP and SAA in all patients with preinfarction UA, but only in 45% of patients with unheralded MI, confirm previous data from our group (12), and the observation that monocytes activation was observed at the time of hospital admission in UA but not in acute MI (10). These conspicuous differences in acute phase response observed in these two subgroups suggest that the different clinical presentation, i.e. unheralded MI and UA may be related to different pathogenetic components.

Preinfarction acute phase response. The elevation of baseline levels of acute phase proteins in patients with UA cannot be attributed to the severity of atherosclerosis, as there is no correlation between the degree of atherosclerosis and the acute phase response in patients with chronic stable angina or peripheral vascular disease, in spite of much more extensive atherosclerotic and thrombotic involvement (12). It cannot be attributed to episodic activation of the hemostatic system because the systemic elevation of markers of thrombin production is not followed by further elevation of acute phase proteins (20), nor can it be attributed to ischemia-reperfusion injury, as circulating neutrophils were not activated and CRP levels were not increased in patients with variant angina (6,21). Indeed, about 45% of patients with Braunwald’s class IIIb UA have CRP levels above the normal range 3 months after hospital discharge, and the risk of recurrent episodes of instability and of MI within 1 year is greatly increased in such patients (22). This observation is in line with the long-term prognostic value of elevated CRP levels in patients with known ischemic heart disease (13) and in apparently healthy subjects with (23,24) or without (25) high levels of risk factors.

Several autoantigens expressed in the atherosclerotic plaque are able to elicit an inflammatory response, including oxidized LDL and heat shock proteins (26,27). Infectious agents have been detected in advanced coronary atherosclerotic lesions and associated to the risk of ischemic heart disease in several epidemiological studies and could be responsible for the acute phase response (28).

The observation that no elevation of IL-6, CRP or SAA was detectable in about one half of the cases presenting with a totally unheralded MI suggests that MI can develop also in the absence of any detectable acute phase response. On the other hand, some cases of unheralded MI could have been preceded by undetected or silent UA.

Postinfarction acute phase response. Myocardial cell necrosis is well recognized as a powerful proinflammatory stimulus (29,30). Experimental studies have shown that periods of ischemia as short as 15 min followed by reperfusion elicit a cascade of proinflammatory reactions that include production of oxygen-derived free radicals (31),

Figure 2. Plasma levels of CRP (Panel A) and SAA (Panel B) at the time of hospital admission. On admission, within 3 h from onset of prolonged chest pain, patients with preinfarction UA had significantly higher levels of CRP and SAA than patients with unheralded MI (all p < 0.001). CRP = C-reactive protein; MI = myocardial infarction; SAA = serum amyloid A protein; UA = unstable angina.
activation of the complement system, adhesion molecule expression, adherence of neutrophils to the coronary endothelium and cardiac myocytes (32), leukocyte-mediated injury of the myocardial cells (33) and production of cytokines (34), including IL-6 and IL-1, which are the major determinants of acute phase protein production (35,36). In patients, neutrophil activation with signs of endothelial injury and release of proinflammatory cytokines has been demonstrated in acute MI (29,30) and after coronary angioplasty (37).

Several studies investigated the acute phase response and the kinetics of proinflammatory cytokines in patients after acute MI (38–41). The magnitude of the acute phase response was found directly correlated with short- and long-term prognosis after MI (12,42–44). However, in many of these studies, particularly in patients treated with early thrombolysis, no correlation was found between infarct size and extent of the acute phase response (12,15,42,43). Thus, the mechanisms that may relate the blood level of acute phase proteins to acute coronary syndromes are still only partially known.

In our study, we observed a typical acute phase response of CRP and SAA following myocardial cell necrosis with an early peak of IL-6 followed by CRP and SAA peaks. However, the acute phase response was strikingly greater in patients with preinfarction UA than in those with totally unheralded MI. As the two groups did not differ significantly in estimated infarct size and clinical signs of reperfusion, we can hypothesize that the nature and intensity of the stimuli provoked by myocardial cell necrosis and by reperfusion were similar in the two groups of patients. Thus, patients with preinfarction UA may be more responsive than patients with unheralded MI to the inflammatory stimuli caused by myocardial necrosis and reperfusion, and elevated baseline levels of acute phase reactants may be markers of such hyper responsiveness. A genetically determined variability of response was reported for cytokine production by human monocytes following endotoxin stimulation in vitro (45) and for inflammatory responses to oxidized lipoproteins in inbred mouse strains (46). Alternatively, monocytes and granulocytes of patients with preinfarction UA and elevated levels of IL-6, CRP and SAA may be “primed” to produce more cytokines and reactive oxygen species in response to subliminal stimuli (47–49). The
hypothesis of an enhanced individual acute phase responsiveness is supported by two observations. First, when the increase of CRP and SAA was normalized for the peak level of CK, Group 2 patients still showed a significantly higher acute phase response than Group 1 patients. Second, we found a positive correlation between baseline and peak values of acute phase reactants not only following MI, but also following percutaneous transluminal coronary angioplasty and following uncomplicated cardiac catheterization and coronary angiography (50).

This interpretation is consistent with our recent observation that monocytes of unstable patients are hyper-responsive to lipopolysaccharide challenges in vitro (51).

The acute phase hyper responsiveness, if confirmed, may contribute to explaining the strong positive correlation between baseline CRP values within the normal range and the incidence of MI over an eight-year follow-up in the Physician’s Health Study (25) and the long-term prognostic value of elevated CRP levels in patients with known ischemic heart disease (13,22) and with high levels of risk factors (23,24). Thus, individuals with an enhanced acute phase response to low-grade stimulation by chronic infection, oxidized LDL and to other inflammatory stimuli may be at increased risk of UA and of its evolution towards MI in the short- or long-term (12,22).

It may look surprising that patients with preinfarction UA have high levels of CRP at baseline and a strikingly higher increase of CRP after MI. As in other studies preinfarction angina was associated with better outcomes (52,53) and CRP was almost uniformly associated with worse outcomes (12,13,22–25,42–44). However, the question we addressed in our study was neither the prognostic importance of CRP (although it is evident in our study, as indeed patients with baseline high levels of CRP and UA develop an acute MI) nor the protective effect of having preinfarction angina. We found an increased acute phase response following necrotic insult in patients with preinfarction UA and high CRP levels at baseline as compared with those with totally unheralded MI (the 55% of whom had normal baseline levels of CRP). This is in agreement with our recent observation that patients with UA and raised levels of CRP have an enhanced acute phase response following percutaneous transluminal coronary angioplasty as compared not only with stable angina patients but also with patients with UA and normal levels of CRP (50). These observations are not in contrast with the possibility that patients with preinfarction UA and low CRP, although in our experience rarer, might have low CRP after the MI and a better clinical outcome.

Conclusion. Our findings suggest that the causes responsible for the progression from UA to infarction may differ from those triggering unheralded infarction. This possibility may have clinical implications, as different precipitating causes may not equally benefit from the same therapeutic and preventive approach nowadays applied indiscriminately to all patients with acute MI (54).

Reprint requests and correspondence: Dr. Giovanna Liuzzo, Department of Cardiology, Catholic University, Largo A. Gemelli, N. 8-00168 Rome, Italy.

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