Increased concentrations of inflammatory mediators in unstable angina: correlation with serum troponin T

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Abstract

Objective—To measure plasma interferon γ , monocyte chemotactic protein-1 (MCP-1), and interleukin 6 and to assess their correlation with cardiac troponin T in unstable angina.

Design—Blood sampling in patients undergoing coronary arteriography for known or suspected ischaemic heart disease.

Patients—76 patients divided in three groups: 29 with unstable angina (group 1), 28 with stable angina (group 2), and 19 without ischaemic heart disease and with angiographically normal coronary arteries (group 3).

Main outcome measures—Plasma interleukin 6, interferon γ , MCP-1, and troponin T in the three groups of patients.

Results—Interleukin 6 was increased in group 1 (median 2.19 (range 0.53–50.84) pg/ml) compared with the control group (1.62 (0.79–3.98) pg/ml) ($p < 0.005$), whereas interferon γ was higher in group 1 (range 0–5.51 pg/ml) than in the other two groups (range 0–0.74 pg/ml and 0–0.37 pg/ml; $p < 0.005$ and $p < 0.001$, respectively). Patients with unstable angina (group 1) and positive troponin T had higher concentrations of interferon γ than those with negative troponin T (0–5.51 pg/ml *v* 0–0.60 pg/ml, $p < 0.001$). Plasma MCP-1 was also higher in group 1 (median 267 (range 6–8670) pg/ml) than in the other two groups (134 (19–890) pg/ml and 84.5 (5–325) pg/ml; $p < 0.005$ and $p < 0.001$, respectively), and among group 1 patients with a positive troponin T assay than in those with normal troponin T (531 (14.5–8670) pg/ml *v* 69 (6–3333) pg/ml; $p < 0.01$). There was no difference in plasma interleukin 6 in group 1 patients between those with and without raised troponin T.

Conclusions—The inflammatory cytokines interferon γ and MCP-1 are increased in patients with unstable angina, particularly in those with raised concentrations of troponin T, suggesting that they are probably related to myocardial cell damage or to plaque rupture and thrombus formation.

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Over the past two decades many experimental and human studies have examined the role of cytokines, chemoattractants, and adhesives molecules in the initiation, progression, and clinical emergence of the atherosclerotic plaque.^{1–9} These observations suggest that, whatever the initial stimuli (mechanical, chemical, infectious, or immunological), a continuous ongoing inflammatory process plays a role in the evolution of an uncomplicated atheromatous plaque into complex and vulnerable atheroma. Hallmarks of this evolving immune process are monocyte–macrophage and lymphocyte cells, initially found in the fatty streaks and then playing a major role in plaque rupture and superimposed thrombosis.^{1–10} In acute coronary syndromes an increase in circulating activated lymphocytes, as well as of activated neutrophils, their inflammatory markers, and monocyte adhesion molecules, has been described.^{4–5 11–15}

Increased concentrations of interleukin 6 have been detected in patients with severe unstable angina and have been shown to be potent predictors of a poor short term outcome.¹⁶ However, the relation of interleukin 6 concentrations to troponin T in unstable angina has not

yet been investigated. It is known that, independently of and in combination with increases in troponin T and troponin I, interleukin 6 is the major determinant of the liver production of C reactive protein—an acute phase protein which, when raised in unstable angina, predicts a worse early outcome.^{17–20} It has also been found that C reactive protein is predictive of long term cardiovascular morbidity and mortality in patients with stable angina as well as in asymptomatic patients at risk of coronary artery disease.^{21 22}

Activated T lymphocytes secrete interferon γ , a cytokine which interferes with the stability of the collagenous framework of the plaque's fibrous cap.¹⁰ On the one hand interferon γ greatly decreases the synthesis of the interstitial forms of collagen from smooth muscle cells, while on the other hand it stimulates the formation and activation of macrophages, which accelerate the breakdown of both collagen and elastin. Moreover, this cytokine stimulates revascularisation and in situ thrombosis and impairs the ability of the endothelium to generate nitric oxide.¹⁰ Taken together, these processes are likely to affect the evolution of unstable coronary syndromes.¹⁰

Table 1 Baseline clinical and angiographic characteristics

	Group 1 (n=29)	Group 2 (n=28)	Group 3 (n=19)
Age (years) (mean (SD))	54 (10.5)	50 (8.6)	59 (8.7)
Sex (M/F)	24/5	19/9	10/9
Diabetes	4 (13.8%)	2 (7%)	0
Hypertension	12 (41.3%)	7 (25%)	7 (36.8%)
Hypercholesterolaemia	12 (41.3%)	5 (17.8%)	0
Current smokers	10 (34.5%)	6 (21%)	8 (42%)
Previous MI	11 (37.9%)	6 (21%)	0
Drug treatment			
Aspirin	24 (82.7%)	24 (85.7%)	0
IV nitrates	14 (48.3%)	0	0
β Blockers	13 (44.8%)	25 (89.3%)	0
IV heparin	10 (34.5%)	0	0
Calcium antagonists	19 (65.5%)	10 (35.7%)	0
Coronary angiography			
Single vessel disease	8 (27.5%)	18 (64%)	0
Multiple vessel disease	21 (72%)	10 (36%)	0

Values are n (%) unless stated.

Group 1, unstable angina; group 2, stable angina; group 3, control; IV, intravenous; MI, myocardial infarction.

Monocyte chemotactic protein-1 (MCP-1) is a chemokine that is implicated in the adhesiveness and transmigration of monocytes and T lymphocytes into the vessel wall. Several lines of evidence indicate that this chemotactic protein is one of the key factors initiating the inflammatory process of atherogenesis. The expression and release of MCP-1 from the endothelium is induced by multiple chemical stimuli (lipopolysaccharides, cytokines, oxidised low density lipoprotein (LDL)) or by interaction between activated neutrophils, platelets, and endothelial cells. Finally, this chemokine may also activate or increase the expression of adhesion molecules to facilitate monocyte adhesion.²³⁻²⁵

As no study has evaluated the role of interferon γ and MCP-1 in unstable coronary syndromes, we undertook to measure plasma concentrations of interleukin 6, interferon γ , and MCP-1 and to correlate them with troponin T concentrations in patients with both stable and unstable angina.

Methods

PATIENTS

The study population included 76 patients admitted to our clinic for cardiac evaluation. Group 1 was composed of 29 patients with unstable angina, admitted to the coronary care unit because of chest pain at rest associated with transient ST segment changes but without enzymatic evidence of ongoing myocardial infarction (classes B and C of the Braunwald classification).²⁶ All patients were given full medical treatment, including intravenous heparin and glyceryl trinitrate. Nine of these patients were secondary referrals to our centre. Group 2 included 28 patients with stable exercise induced angina, confirmed by a positive exercise test result (the development of horizontal or downward ST segment depression of ≥ 1 mm). Group 3 was formed of 19 control subjects with angiographically normal coronary arteries who underwent cardiac catheterisation for reasons other than cardiac ischaemia. The final diagnosis in these patients was mitral or aortic valve disease in 17 and dilated cardiomyopathy in two.

Figure 1 Interleukin 6 (IL-6) concentrations were higher in unstable angina (UA) than in controls. There was no difference between unstable angina and stable angina (SA). Data are means, error bars = SEM.

In all three groups of patients, blood samples were taken at the time of coronary angiography, before injection of the contrast medium. Cardioactive drugs—including nitrates, β blocking agents, and aspirin—were not discontinued at the time of the study. However, patients with intercurrent inflammatory conditions and those taking non-steroidal anti-inflammatory drugs or steroids were excluded.

CORONARY ANGIOGRAPHY

All patients underwent coronary angiography by the Judkins technique. Left ventricular angiography was performed in the 30° right anterior oblique projection. End systolic and end diastolic ventricular volumes and left ventricular ejection fraction were calculated by the standard area-length method. Significant coronary artery disease was defined as lumen diameter narrowing of more than 50% in at least one major epicardial coronary artery. Among the patients with unstable angina, four were studied within 48 hours of admission, while the other 25 had coronary arteriography at a mean of 5.1 days after admission (range 3–9 days).

LABORATORY INVESTIGATION

Aliquots of blood from each patient were collected in test tubes containing EDTA. Plasma was separated by centrifugation and then frozen at -80°C .

Quantitative measurements of interleukin 6 and interferon γ were performed using an enzyme linked immunosorbent assay (ELISA) with a microtitre plate precoated with the specific monoclonal antibody (Bender MedSystem, Vienna, Austria). Tests were performed according to the supplier's instructions. Samples and standards were assayed simultaneously in duplicate. The sample volume used for interleukin 6 and interferon γ was 50 μl . None of the samples was diluted. The standard curve range for interleukin 6 was 1.6–100 pg/ml and for interferon γ , 1.5–100 pg/ml. The sensitivity of the assay was 0.6 pg/ml for interleukin 6 and 0.30 pg/ml for interferon γ . The overall intra-assay coefficient of variation was 3.4% for interleukin 6 and 5.7% for interferon γ ; the overall interassay coefficients of variation were 5.2% and 5.7%.

Quantitative measurement of MCP-1 was performed by ELISA, using a DuoSet kit (R&D System, Edinburgh, UK) with monoclonal antibodies for capture and detection. Samples and

Figure 2 Interferon γ (IFN- γ) concentrations were higher in unstable angina (UA) than in stable angina (SA) or controls. There was no difference between stable angina and controls. Data means, error bars = SEM.

Figure 3 Among patients with unstable angina, those with positive cardiac troponin T (cTnT+) had significantly higher concentrations of interferon γ (IFN- γ) than those with negative troponin T (cTnT-). Data means, error bars = SEM.

standards were assayed simultaneously in duplicate. The sample volume used was 50 μ l. None of the samples was diluted. The standard curve range was 15.6–1000 pg/ml. The sensitivity of the assay was 3.4 pg/ml. The overall intra-assay and interassay coefficients of variation were 2.9% and 4.8%, respectively.

Serum troponin T was measured by an electrochemiluminescence immunoassay (ECLIA), using the EleSYS 2010 system (Roche Diagnostic, Basel, Switzerland). The intra-assay coefficient of variation was 5% and the interassay variability 7%. The lower limit of detection was 0.01 ng/ml and the diagnostic cut-off point was 0.1 ng/ml.

The study was approved by the institutional ethics committee for human subjects. Informed consent was obtained from all patients.

STATISTICAL ANALYSIS

Results are expressed as median and range. The non-parametric one way Kruskal–Wallis test was used to investigate differences among the three groups of patients at each time point. The Mann–Whitney test for unpaired data was used for comparison of data between patients with unstable angina and those with stable angina. Two tailed probability values of $p < 0.05$ were considered significant.

Results

Clinical and angiographic characteristics of the patients are given in table 1. Interleukin 6 was increased in group 1 (unstable angina) compared with group 3 (control): group 1, mean

Figure 4 Monocyte chemoattractant protein-1 (MCP-1) concentrations were higher in unstable angina (UA) than in stable angina (SA) or controls. There was no difference between stable angina and controls. Data means, error bars = SEM.

Figure 5 Monocyte chemoattractant protein-1 (MCP-1) concentrations were higher in unstable angina (UA) patients with positive cardiac troponin T (cTnT+) than in those with negative troponin T (cTnT-). Data means, error bars = SEM.

2.19 (range 0.53–50.84) pg/ml; group 2, 1.81 (0.66–48.93) pg/ml; group 3, 1.62 (0.79–3.98) pg/ml; $p < 0.005$ group 1 *v* group 3 (fig 1).

Interferon γ was higher in the group 1 than in the other two groups: group 1, 0 (0–5.51) pg/ml; group 2, 0 (0–0.74) pg/ml; group 3, 0 (0–0.37) pg/ml; $p < 0.005$ and $p < 0.001$, respectively (fig 2). Among the 29 patients with unstable angina, 11 with raised troponin T concentrations had significantly higher plasma interferon γ than the 18 without a raised troponin T: 0 (0–5.51) pg/ml *v* 0 (0–0.60) pg/ml ($p < 0.001$) (fig 3). On the other hand, no difference was found in plasma interleukin 6 concentrations in patients with unstable angina between those with raised and those with normal plasma troponin T: 2.89 (1.04 to 13.56) *v* 1.90 (0.53 to 15.84) pg/ml.

Plasma MCP-1 concentrations were also higher in the patients with unstable angina than in those with stable angina or in the controls: group 1, 267 (6–8670) pg/ml; group 2, 134 (19–89) pg/ml; group 3, 84.5 (5–325) pg/ml; $p < 0.005$ and $p < 0.001$, respectively (fig 4). Patients with unstable angina and a raised plasma troponin T had higher plasma MCP-1 concentrations than those with no increase in troponin T: 53 (14.5–8670) pg/ml *v* 69 (6–3333) pg/ml; $p < 0.01$ (fig 5).

In the patients with unstable angina differences were found in interleukin 6, interferon γ , and MCP-1 values depending on whether or

Table 2 Interleukin 6 (IL-6), interferon γ (IFN- γ), and monocyte chemoattractant protein-1 (MCP-1) values in patients with unstable angina who did or did not have chest pain in the 48 hours preceding coronary arteriography

	Chest pain within 48 hours (n=10)	No chest pain within 48 hours (n=19)
IL-6 (pg/ml)	2.83 (2.19–4.23)	2.16 (0.53–50.84)
IFN- γ (pg/ml)	0 (0–0.47)	0 (0–5.51)
MCP-1 (pg/ml)	257 (44–1746)	196 (6–8670)

Values are median (range).

not they had had chest pain in the 48 hours preceding coronary arteriography (table 2).

Discussion

Inflammation is well recognised as a pathogenic component of unstable angina.^{2–10} Inflammatory mediators as well adhesion molecules of neutrophils and monocytes have been shown to be increased in the plasma of patients presenting with acute coronary syndromes.

INTERLEUKIN 6, INTERFERON γ , AND MCP-1 IN UNSTABLE ANGINA

Interleukin 6, a proinflammatory cytokine with stimulatory effects on T and B lymphocytes, induces the synthesis of acute phase proteins such as C reactive protein and fibrinogen. Biasucci and colleagues found that interleukin 6 was increased in 61% of patients with unstable angina, compared with 21% of patients with stable angina.¹⁶ Increasing concentrations of interleukin 6 were also found to be associated with a complicated clinical course in unstable angina.

Interleukin 6 is the major determinant of the liver production of acute phase proteins through direct stimulation of hepatocytes.¹⁶ Raised concentrations of C reactive protein, a prototypical acute phase reactant, are also associated with an unfavourable outcome.¹⁷ In the TIMI (thrombolysis in myocardial infarction) 11A substudy,¹⁸ the relation between C reactive protein concentrations and the qualitative result of a rapid troponin T assay was determined in 437 patients with unstable angina and non-Q wave myocardial infarction. The probability of a positive rapid troponin T rose significantly with increasing C reactive protein concentrations. However, 20% of patients with a negative rapid troponin T assay had raised C reactive protein. Our data show that interleukin 6 was increased in patients with unstable angina in comparison with a control group of patients without coronary artery disease. Although patients with unstable angina had higher values than those with stable angina, the difference between these two groups was not significant. Moreover, in patients with unstable angina no correlation was found between interleukin 6 concentrations and increased troponin T values.

MCP-1, a major chemotactic molecule secreted in the vessel wall, is predominantly found in macrophage-rich areas of atherosclerotic lesions. Gawatz and colleagues studied the secretion of MCP-1 by human umbilical endothelial cells incubated with non-stimulated or ADP activated platelets for six hours.²⁷ They found that activated platelets

induced endothelial secretion of MCP-1, whereas significantly less secretion occurred in the presence of non-stimulated platelets, implying that an activation dependent release of platelet derived products stimulates MCP-1 production, favouring the migration and entrapment of monocytes—an early step in the atherogenesis and restenosis process. In a preliminary report, Nakamura and colleagues measured MCP-1 concentrations in 15 patients with acute myocardial infarction, 30 with stable angina, and 19 controls.²⁸ These investigators found increased concentrations of this chemotactic protein in patients with acute myocardial infarction compared with the other two groups. As particularly high MCP-1 concentrations were found in patients with preinfarction angina, they concluded that monocytes may play an important role in plaque rupture. In our study, we observed much higher concentrations of MCP-1 in patients with unstable angina than in the other two groups, and a significant correlation with a positive troponin T.

Similarly, interferon γ concentrations were also significantly higher in patients with unstable angina than in the other two groups. Moreover, in the unstable angina group, patients with a positive troponin T assay had higher interferon γ values than those with a negative troponin T. Interferon γ is a potent immunostimulatory cytokine secreted by T lymphocytes, which promotes atherosclerosis through local effects in the arterial wall as well as through a systemic effect on plasma lipoproteins. Moreover, this cytokine greatly decreases the ability of human smooth muscle cells to express the interstitial collagen genes and can also contribute to activating the apoptosis programme in human vascular smooth muscle cells. Inhibition of interstitial collagen synthesis and impaired muscle cell growth in the fibrous cap of the atherosclerotic lesion may destabilise vulnerable regions of the plaque, rendering them weak and prone to rupture.

CORRELATION BETWEEN INFLAMMATORY MARKERS AND TROPONIN T

The correlation of high concentrations of MCP-1 and interferon γ with a positive troponin T assay is intriguing. About 20–40% of patients with unstable angina are reported to have detectable troponin T in the serum. Circulating troponin T is a marker of minor myocardial injury and is associated with an increased risk of serious cardiac events in this condition. This marker of myocardial injury may be raised in the absence of other signs of myocardial infarction. It is controversial whether this reflects microinfarcts or reversible myocardial damage.²⁰ It has been hypothesised that high serum concentrations of troponin T or I reflect an active thrombotic process with distal embolisation of platelet thrombi originating from the culprit lesion.²⁹ Recent data from the CAPTURE trial (c7E3 Fab antiplatelet therapy in unstable refractory angina) show that antithrombotic treatment with high doses of glycoprotein IIb/IIIa receptor blockers

significantly reduces the rate of myocardial infarction before as well as during coronary angioplasty in patients with refractory unstable angina and raised troponin T concentrations.²⁹ It has also been shown that enhanced activation of coagulation is present in patients with troponin T positive unstable angina. Terres and colleagues studied 22 patients with angiographically documented coronary heart disease and unstable angina at rest³⁰: in nine patients with increased maximum serum troponin T value, the maximum concentrations of fibrin monomers during the first 48 hours were higher than in patients with persistently normal troponin T. The investigators concluded that enhanced activation of coagulation in patients with troponin T positive unstable angina may contribute to the adverse outcome associated with this condition.

It is possible that the greatly raised concentrations of MCP-1 and interferon γ observed in patients with unstable angina and positive troponin T are secondary to myocardial cell damage. Alternatively, it is conceivable that the increased concentrations of MCP-1 and interferon γ are related to the mechanism of plaque rupture and thrombus formation.

CONCLUSIONS

MCP-1 and interferon γ concentrations are specifically increased in patients with unstable angina, particularly in those with a positive troponin T assay, suggesting a probable relation to myocardial cell damage or plaque rupture with thrombus formation. Further studies should clarify the time course of MCP-1 and interferon γ concentrations in unstable angina and their prognostic value.

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