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Transient rise in serum interleukin-8 concentration during acute myocardial infarction

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Abstract

***Objective*—To determine whether interleukin-8 (IL-8, a potent activator of neutrophils) is involved in tissue injury during ischaemia and reperfusion in patients with acute myocardial infarction.**

***Setting*—Teaching hospital.**

***Subjects*—Five consecutive patients with acute Q-wave myocardial infarction, two patients with stable angina who underwent elective percutaneous transluminal coronary angioplasty, and 10 normal controls.**

***Main outcome measure*—Serum IL-8 concentration measured by enzyme linked immunosorbent assay (ELISA) over time (every four, eight or 12 hours for 36–72 hours).**

***Results*—All five patients with acute myocardial infarction had a transient but significant rise in serum IL-8 concentration (13-1100 ng/l) within 22 hours after the onset of symptoms, whereas IL-8 was not detected in any of the samples from patients with angina pectoris or normal controls. One patient who died of pump failure and two patients who had mild congestive heart failure showed the highest values (1100, 920, and 190 ng/l respectively).**

***Conclusions*—Serum IL-8 concentration showed a transient rise during the very early phase of acute myocardial infarction. In combination with several recent lines of evidence indicating the importance of injurious activities of neutrophils as a cause of tissue damage in acute myocardial infarction and the potent stimulation of neutrophils by IL-8, these results strongly suggest that IL-8 is important in the development of myocardial injury in acute myocardial infarction.**

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Substantial and convincing evidence from recent investigations indicates that tissue injury after ischaemia and reperfusion in acute myocardial infarction is not a consequence of simple tissue anoxia but of a sequence of cellular interactions involving several agents including leucocytes,[1 2] oxygen free radicals,[3–5] and calcium ions.[6] Among these, neutrophils are believed to be one of the most important cell types causing damage to myocardial tissues by generating and releasing reactive oxygen metabolites,[7] proteolytic enzymes,[5 8] and arachidonate derivatives.[9] Therefore, it is very important to elucidate the mechanisms of neutrophil recruitment from the bloodstream to the myocardium during and after ischaemia and reperfusion.

Interleukin-8 (IL-8) is a cytokine and a potent chemoattractant for neutrophils.[10 11] In addition, this cytokine is currently considered to have regulatory and activating effects on neutrophils.[12–14]

We measured the serum concentration of IL-8 to examine whether this cytokine affects the mobilisation and activation of neutrophils during the development of tissue damage in acute myocardial infarction.

Patients and methods

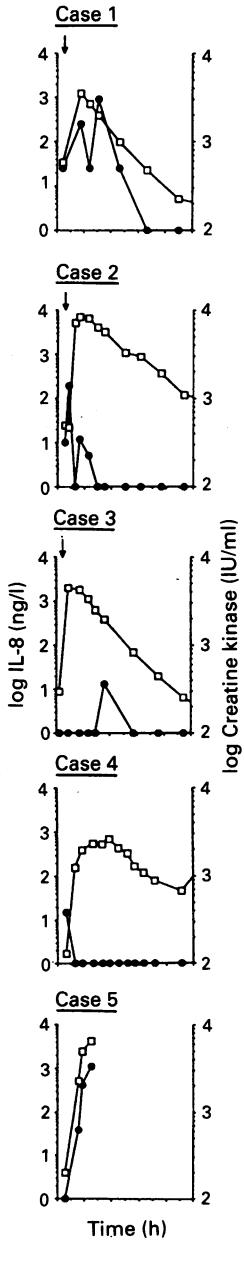
We studied five consecutive patients with acute Q-wave myocardial infarction who were admitted to this medical centre within four hours of the onset of symptoms, two patients with stable angina who underwent percutaneous transluminal coronary angioplasty, and 10 healthy controls. The table shows the clinical features of the five patients. All the patients underwent coronary angiography immediately after admission and received intracoronary thrombolysis with recombinant tissue plasminogen activator and coronary angioplasty if the thrombolytic treatment failed. Heparin (10 000–20 000 U/day) was administered intravenously during the study period. Blood samples were drawn from the patients every four, eight, or 12 hours for at least three days, except in one patient who died. Serum was separated immediately by centrifugation and stored at −20°C until use. Blood was also drawn every four hours from two patients with angina pectoris who underwent elective coronary angioplasty immediately before and after the procedure for 36 hours. Blood samples from 10 healthy volunteers were included as normal controls and were treated and stored identically.

Serum IL-8 concentration was measured by enzyme linked immunosorbent assay (ELISA) using a fluorescent substrate, 4-methylumbelliferyl phosphate, which was developed by one of us.[15] The assay was performed in duplicate for each sample. Serum creatine kinase concentration was also measured as a marker of myocardial infarction.

Clinical characteristics of five patients with myocardial infarction

	Case No				
	1	*2*	*3*	*4*	*5*
Age (years)	64	42	67	69	64
Sex	Male	Male	Female	Male	Male
Time before admission	2 h 35 min	3 h 40 min	1 h 20 min	4 h	3 h 30 min
Reperfusion:					
Present	Yes	Yes	Yes	No	No
Mode	Rescue PTCA	Rescue PTCA	Rescue PTCA	—	—
Delay	3 h 20 min	4 h 25 min	4 h 30 min	—	—
Thrombolytic agents	t-PA	t-PA	t-PA	t-PA	t-PA
Heparin (U/day)	10 000	12 000	20 000	20 000	10 000*
Coronary stenosis (%)	LAD(99), RCA(90)	LAD(100), LCX(100)	LAD(100)	RCA(99), LAD(100)	RCA(100), LAD(100), LCX(75)
Congestive heart failure	Killip II, Forrester III	Killip II, Forrester II	Killip I, Forrester I	Killip II, Forrester II	Killip IV, Forrester IV
Maximum creatine kinase (IU/ml)	3509	8060	4459	2606	6465

*Total no of units.
PTCA = percutaneous transluminal coronary angioplasty; t-PA = tissue plasminogen activator; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery.



Serum concentrations of IL-8 (-●-) and creatine kinase (-□-) in patients with acute myocardial infarction (↓ shows the time of reperfusion).

Results

The detection limit of IL-8 by our ELISA was consistently less than 5 ng/l. With this assay IL-8 was detected in at least one of the samples obtained serially from all five patients, whereas none of the samples from patients with angina pectoris who underwent coronary angioplasty or the healthy subjects showed any detectable concentration of IL-8. The highest concentration of the cytokine during the observation period in each patient varied from 13 ng/l to 1100 ng/l. In all patients with acute myocardial infarction IL-8 was detected in the serum within 22 hours after the onset of symptoms and disappeared rapidly thereafter. The patient who showed the highest concentration (1100 ng/l; case 5) died of cardiogenic shock two hours after the peak IL-8 concentration was evident (figure). The two patients who suffered mild congestive heart failure (cases 1 and 2) also had high values (920 ng/l and 190 ng/l respectively).

The numbers of neutrophils in peripheral blood increased in all patients on admission except in the patient who died, and they returned to normal range within three days after the onset of the symptoms in all patients. We found, however, no apparent correlation between neutrophil counts and peak serum IL-8 concentration.

Discussion

Previous reports have indicated that depletion of leucocytes[16] and administration of anti-inflammatory drugs[17 18] or monoclonal antibodies against leucocyte integrins[19] all reduce the infarct size in experimental myocardial infarction in dogs. These findings strongly suggest that tissue damage mediated by leucocytes is one of the most important determinants of the extent of infarction and subsequent residual myocardial function. The next questions are what recruits leucocytes from the bloodstream into the site of myocardial infarction and what activates them. IL-8 is a recently identified cytokine believed to have a key role in the accumulation of neutrophils in inflamed tissue. IL-8 upregulates complement receptor type 1[20] and leucocyte adhesion molecule Mac-1 (CD11b, CD18)[12] and stimulates neutrophil adhesion to endothelial cells, as well as exerting potent chemoattractant activity for neutrophils,[10 11] basophils, and T lymphocytes.[21 22] It also stimulates neutrophils to generate and release lysosomal enzymes,[23] toxic oxygen metabolites,[13] and arachidonate derivatives.[14] Our results show that IL-8 was released and appeared in the systemic circulation in the very early phase of acute myocardial infarction. This transient rise in IL-8 concentration is not attributable to angiography or angioplasty because IL-8 was not detectable in patients with angina pectoris who underwent the same procedure. In combination with recent lines of evidence, our preliminary results suggest that this cytokine could contribute to leucocyte mobilisation and leucocyte mediated tissue damage in acute myocardial infarction.

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