

INFLAMMATORY RESPONSE TO ACUTE MYOCARDIAL INFARCTION COMPLICATED BY CARADIOGENIC SHOCK

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Summary: We report a case of a 60-year-old man with acute myocardial infarction (AMI) treated using thrombolysis, and complicated by cardiogenic shock (CS). Plasma interleukin (IL) 1 β , IL 6, IL 8, tumor necrosis factor alpha (TNF α), and soluble adhesion molecule (sICAM 1, sE-selectin) levels were measured at 3-h intervals. This observation showed the effect of AMI and CS on the plasma interleukin levels. Remarkable changes were found in the plasma TNF α level, which reached two significant peaks. The peak of the first elevation caused by AMI (80.11 pg/ml, vs. normal value 4.35 pg/ml, SD 21.3 pg/ml) was seen 6 h after the onset of the symptoms. After the period of significant decrease, TNF α level was increasing until the end of the observation period because of CS (the last TNF α level was 204.1 pg/ml). The plasma IL 1 β level was continually increased during the period of observation (maximal IL 1 β level 32.1 pg/ml, normal value <10 pg/ml). The plasma IL 6 level reached the first peak caused by AMI nine hours after the onset of the symptoms (362.85 pg/ml, normal value 10 pg/ml). Because of CS, after the short period of decrease, the plasma IL 6 level was increasing until the end of the observation period (the last IL 6 level was 859.61 pg/ml). The plasma IL 8 level was also elevated throughout the time of observation (max. value 1652 pg/ml, vs. normal value <30pg/ml). The soluble adhesion molecule levels (sE-selectin and sICAM 1) were elevated throughout the period of observation without any significant peak.

Key words: *Acute myocardial infarction; Cardiogenic shock; Interleukins; Soluble adhesion molecules*

Introduction

Cardiogenic shock (CS) is one of the most serious complications of acute myocardial infarction (AMI). In spite of great progress in its therapy (early revascularisation, use of intra-aortic balloon contra-pulsation etc.), there are some questions concerning its pathophysiology which remain to be elucidated. One of them is immune system activation and its role in the myocardial ischemia-reperfusion process in the course of AMI complicated with cardiogenic shock.

The activated neutrophils and their interaction with endothelial cells and myocytes are believed to play the key role in the pathophysiology of the ischemia and reperfusion process by producing free oxygen radicals, arachidonic acid derivatives and proteolytic enzymes (5,6,8). Entman et al. (5) showed that cytokines and adhesion molecules are involved in this process. In his hypothesis the injured myocardial cells initially release the products that promote chemotaxis, neutrophil shape change, enhanced neutrophil surface expression of CD11/CD 18 adhesion heterodimers, and upon adherence, release of granular contents and production of oxygen free radicals. The secretory and migratory functions of neutrophils require adherence of CD11/CD18 to the intercellular adhesion molecule 1 (ICAM 1). At least one additional ligand (E-selectin, CD

62E) is suggested to be involved in this process. E-selectin is expressed on the cell surface over a period of 2-6 h after stimulation of the endothelial cells with interleukin 1 and TNF α . Once neutrophils are bound to the endothelium in the capillary venules, they can migrate into the extracellular space. Previous studies have shown that the effect of neutrophil on the cardiac myocyte also requires expression of the adherence complex of CD11/CD18 and ICAM 1, and that these processes are mediated by cytokines (12). We have shown the elevation of plasma interleukin and adhesion molecules levels in the course of AMI in our previous studies (9,10). Furthermore, the negative haemodynamic effects of cytokines, IL 1 β and TNF α , have been described in previous studies in patients with chronic heart failure. But little is known about the impact of CS on the plasma cytokine and adhesion molecule levels in the course of AMI.

The aim of this observation is to evaluate the plasma interleukin and adhesion molecule levels in the patient with AMI, complicated by fatal cardiogenic shock.

Report of a Case

A 60 year old man with no previous history of coronary artery disease was admitted for typical chest pain 3 h after onset of the symptoms. Physical examination revealed dys-

nea, tachycardia, and signs of the lung congestion. Blood pressure was 105/60 mmHg, pulse 98/min. and regular. Laboratory examination: Hb of 139g/l, leukocyte count 9800 per μ l with normal differential cell and platelet counts. Electrolytes, urea, and creatine concentrations were within normal limits. The ECG showed sinus rhythm with acute ST segment elevations in the chest leads (V1-V5). The thrombolysing treatment (1.500000 IU of Streptokinase) and other therapy was given to the patient. ST segment resolution showed the effect of thrombolysis. Hypokinesia of the antero-septal and lateral segments with an ejection fraction of 30% was diagnosed by echocardiography. Laboratory markers of myocardial damage were positive at 6 h after the admission. Lung edema with progression into cardiogenic shock developed on the following day. Despite the therapy (nitrates, ASA, diuretic drugs, sympatomimetic amines), the patient died 45 hours after the onset of the symptoms.

Methods

Plasma cytokine (IL 1 β , IL 6, IL 8 and TNF α) levels were measured by use of the commercially available enzyme-linked immunosorbant assay (ELISA) developed by RD Quantikine, Minneapolis, MN, USA. The plasma TNF α level was measured by using a commercial ELISA set purchased from Immunotech, Marseilles, France.

Blood samples were taken at 3-hour intervals. The blood was immediately centrifuged, aliquots of plasma were stored at -20°C overnight, and then until the assessment of the immune parameters the plasma samples were stored at -70°C.

The patient was enrolled into the study after obtaining of informed consent according to ethical standards of our institution.

Results

The plasma TNF α level reached two significant peaks, the first increase at 6 h after onset of the symptoms (80.11 pg/ml, vs. normal value 4,35 pg/ml, SD 21,3 pg/ml), and it was caused by AMI. After this period of significant decrease, the TNF α level was increasing until the end of the observation because of cardiogenic shock (the last TNF α level was 204.1 pg/ml) - Fig. 1.

The plasma IL 1 β level was continually increasing during the observation period and reached a maximal level 32.1 pg/ml (normal value <10 pg/ml) - Fig. 1.

The plasma IL 6 level reached the first peak caused by AMI (362.85 pg/ml, normal value <10pg/ml) nine h after the onset of the symptoms. Because of CS, after the short period of decrease, the plasma IL 6 level was increasing until the end of the observation (the last IL 6 level was 859.61pg/ml) - Fig. 2.

The plasma IL 8 level was elevated throughout the time of observation. Its rapid increase was caused by progression of CS (max. value 1652 pg/ml, vs. normal value <30pg/ml) - Fig. 2.

The soluble adhesion molecule levels (E-selectin and ICAM 1) were elevated throughout the period of observation without any significant peak - Fig. 3.

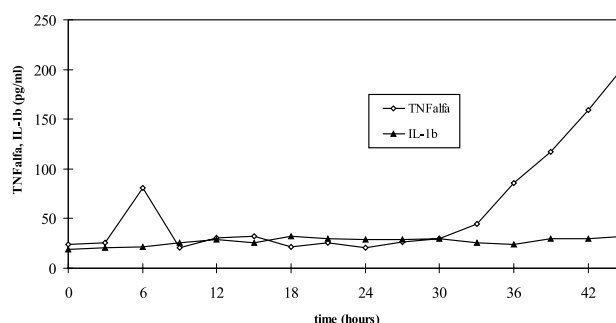


Fig. 1: Plasma TNF α and IL 1 β levels in cardiogenic shock (Normal values: TNF α 4.35 pg/ml, IL 1 β <10 pg/ml).

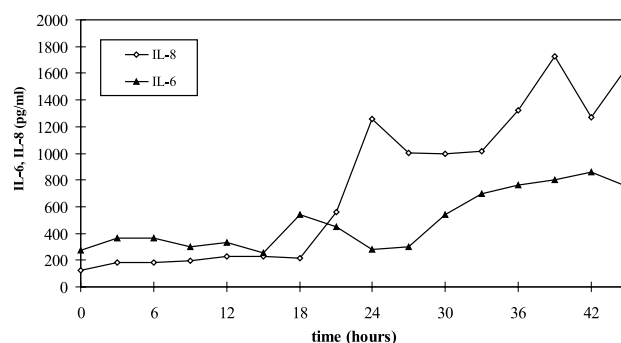


Fig. 2: Plasma IL 6 and IL 8 levels in cardiogenic shock (normal value of IL 6 <10 pg/ml, normal value of IL 8 <30 pg/ml).

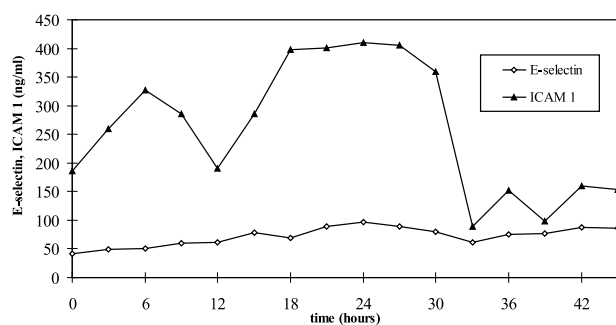


Fig. 3: Plasma ICAM 1 and E-selectin levels in cardiogenic shock (normal value of ICAM 1 189.05 ng/ml, SD 42.32 ng/ml, E-selectin 29.1-63.4 ng/ml).

Discussion

Recent studies (4-6,8,9,10,12) have shown that immune system activation, and the accumulation of activated neutrophils at the site of infarction are regulated by cytokines, and that neutrophil-endothelium, and neutrophil-myocyte

interactions require the expression of adhesion molecules (ICAM 1, E-selectin etc.).

Our observation showed the elevation of pro-inflammatory cytokines during the course of AMI, and, after a short period of decrease, the second elevation of TNF α , IL 6 and IL 8, which is very likely to be caused by CS. Two peaks of TNF α plasma concentration were noticed. The first elevation was caused by AMI and the second one was caused by cardiogenic shock. Although TNF α cytokine has a pleiotropic effect, it is also known to have cardio-depressant properties. The mechanism of TNF α elevation is not yet clear, but Brunkhorst et al. (3) showed, that exposure to bacterial endotoxin, perhaps due to bowel congestion or ischaemia and altered gut permeability, which may result in immune activation that is characteristic for patients with severe heart failure. Also Anker et al. (1,2) hypothesized that in patients with heart failure mesenteric venous congestion leads to increased bowel permeability, bacterial translocation, and thereby endotoxin release, which is responsible for immune system activation and increased TNF α production. However, these observations have been found in groups of patients with chronic heart failure. The study of Riemsdijk et al. (11) showed local myocardial production of these cytokines by myocytes and endothelium (7), and that the TNF α system is deregulated in the course of acute left ventricular failure. A positive correlation is found between the severity of heart failure and TNF α levels in patients with chronic heart failure.

In contrast to these observations, our results could support the hypothesis that elevated plasma TNF α level could be a marker of acute left ventricular dysfunction and cardiogenic shock.

Conclusion

This study confirms the excessive overproduction of interleukins with a predominantly negative effect on the cardiovascular system in the course of CS.

This observation also reveals a possible target for future therapeutic interventions with the aim of improving the survival of patients with cardiogenic shock.

Acknowledgments

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