Circulating Intercellular Adhesion Molecule-1 and E-Selectin in Patients With Acute Coronary Syndrome*

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To characterize the role of circulating intercellular adhesion molecule-1 (ICAM-1) and E-selectin in patients with acute coronary syndrome, serum levels of ICAM-1 and E-selectin were measured by enzyme-linked immunosorbent assay (ELISA). Group 1 comprised 17 patients with acute myocardial infarction; group 2 included 17 patients with unstable angina; and group 3 included 19 control subjects. These 53 patients all had prolonged chest pain within 24 h and all underwent coronary angiography. Group 1 and 2 patients had significant coronary artery disease, while group 3 had normal coronary arteries. Blood samples were collected at the emergency department before antiplatelet agents were given. Serum levels of ICAM-1 were higher in group 1 and 2 (383±27 and 337±11 ng/mL, respectively) as compared with group 3 (282±18 ng/mL) (group 1 vs 3, p<0.01; group 2 vs 3, p<0.05). The serum levels of ICAM-1 were not significantly different between group 1 and 2. Serum levels of E-selectin in group 1, 2, and 3 were 58±8, 51±4, and 58±5 ng/mL, respectively. The serum levels of E-selectin showed no significant difference among the three groups. In conclusion, serum levels of ICAM-1 were elevated in patients with acute coronary syndrome within 24 h, while the E-selectin levels did not change significantly. This finding suggests that adhesion molecule may play an important role in the postrolling process of leukocyte-endothelial cell interaction in acute coronary syndrome.

Key words: acute coronary syndrome; adhesion molecule; enzyme-linked immunosorbent assay

Abbreviations: ELISA=enzyme-linked immunosorbent assay; ICAM-1=intercellular adhesion molecule-1

Atherosclerosis has always been regarded as an important component of the pathogenesis of acute coronary syndrome. Cell adhesion molecules facilitate the adherence of platelets and leukocytes in the blood to the vascular endothelium. Recent experimental studies demonstrated massive leukocyte extravasation at sites of myocardial ischemia and reperfusion. Leukocytes are now considered to potentiate ischemic myocyte damage by microvascular obstruction and generation of cytotoxic metabolites. Inhibition of neutrophil adhesion was shown to reduce myocardial infarct size.

Intercellular adherence is necessary for leukocyte accumulation at sites of inflammation. E-selectin and intercellular adhesion molecule-1 (ICAM-1) are located primarily at surfaces of activated endothelial cells and bind leukocytes. E-selectin is needed for the initial accumulation of neutrophil at the inflammatory site, whereas ICAM-1 is needed for optimal migration of neutrophils out of the blood vessels and for adhesion of neutrophils to myocytes. Recent studies have demonstrated expression of ICAM-1 on human atherosclerotic plaques. Treatment of anti-ICAM-1 monoclonal antibody resulted in a significant reduction of infarct size in animal experiments. These studies indicated that adhesion molecules might play a role in the development of ischemic myocyte damage. Soluble isoforms of these adhesion molecules thought to be shed from the surfaces of activated cells can now be quantified in peripheral blood. Increased serum concentrations have been observed in a variety of diseases. Circulating adhesion molecules in acute coronary syndrome have been found to be elevated in the acute phase and to correlate with the extent of plaque rupture and the severity of the syndrome. These findings suggest that adhesion molecules may play a role in the pathogenesis of acute coronary syndrome.
coronary syndrome are rarely reported. The aim of this study was to measure the serum ICAM-1 and E-selectin in patients with acute myocardial infarction and unstable angina in comparison to those in patients with normal coronary arteries who have prolonged chest pain.

**Materials and Methods**

**Patients**

Patients evaluated in the Emergency Department of Shin Kong Wu Ho-Su Memorial Hospital for chest pain occurring at rest during the preceding 24 h and lasting at least 30 min were eligible for enrollment. Exclusion criteria for patients were presence of infections, other inflammatory or malignant diseases, and renal disease. All patients were admitted to the coronary care unit or intermediate care unit; coronary angiography using the Judkin technique was performed during the hospitalization. Criteria used to diagnose acute myocardial infarction were (1) chest pain persisting more than 30 min and not relieved by sublingual nitroglycerin and (2) ST segment elevation more than 0.1 mV on at least two adjacent ECG leads. The type of infarction (Q-wave or non-Q-wave) was determined from the ECG.13

Group 1 comprised 17 consecutive patients with acute myocardial infarction. The group included 11 men and 6 women, with a mean (±SD) age of 60±17 years. In all the patients with myocardial infarction, serial blood samples were obtained over a period of 48 h to analyze the creatine kinase level and its isoenzyme. All the group 1 patients had significant coronary artery disease (>50% coronary narrowing in at least 1 major coronary vessel). Group 2 comprised 17 patients with unstable angina. This group included 10 men and 7 women, with a mean age of 66±16 years. The ECGR in these patients all showed ST-segment deviations that were diagnostic of myocardial ischemia during angina attacks and coronary angiography showed more than 50% stenosis in at least 1 major coronary artery in all patients. The creatine kinase MB isoenzyme values in this group were all 14 U/L or less in 2 or more sequential blood samples obtained 6 to 12 h apart.

Group 3 comprised 19 patients with prolonged chest pain and normal coronary arteries proved by coronary angiography. There were 10 men and 9 women, with a mean age of 62±11 years.

A detailed history of potential vascular factors and conditions assumed to be associated with coronary atherosclerosis were obtained from each patient and from the medical records. Chest radiograph, complete blood cell count, and blood biochemistry studies were performed routinely.

**Measurement of ICAM-1 and E-Selectin**

Venous blood samples from patients were collected in syringes by needle aspiration from an antecubital vein at the emergency department before antiplatelet agents were given. All patients gave informed consent. Blood was allowed to clot at 4°C for 1 h, and was centrifuged at 3,000 rpm for 10 min. Serum was frozen at −80°C until it was used. Serum ICAM-1 and E-selectin were measured by enzyme-linked immunosorbent assay (ELISA). The assay was performed in duplicate for each sample. The ICAM-1 ELISA kit was purchased from one company (T Cell Diagnostics Inc; Cambridge, Mass) and the E-selectin was purchased from another (British Bio-technology Products Ltd; Abingdon, UK). The lower limits of detection of serum ICAM-1 and E-selectin were 0.3 ng/mL and 1.6 ng/mL, respectively.

**Statistics**

Categoric variables were analyzed with the Fisher’s Exact Test. Continuous variables were analyzed by paired Student’s t test or by analysis of variance with Scheffé posteriori comparison where appropriate. A p<0.05 was considered statistically significant.

**Results**

**Patient Characteristics**

There were 10 Q-wave and 7 non-Q-wave myocardial infarctions in the group 1 patients. Of these 17 patients, coronary angiography showed 3-vessel disease in 3, 2-vessel disease in 6, and 1-vessel disease in 8. According to the Killip classification, there were 15 Killip I, 1 Killip II, and 1 Killip III in the myocardial infarction patients. Thrombolytic therapy was given to four patients and direct percutaneous coronary angioplasty was also performed in four patients. The peak creatine kinase level in this group of patients was 1,620±1,570 (mean±SD) U/L. In the group 2 patients, coronary angiography showed 3-vessel disease in 2, 2-vessel disease in 9, and 1-vessel disease in 6. Coronary angiography showed patent coronary arteries in all group 3 patients. The risk factors, including diabetes mellitus, hypertension, smoking, and hyperlipidemia were not significantly different among the three groups of patients (Table 1).

**Hematologic Parameters**

Hematologic values for the groups are shown in Table 2. The total leukocyte count was significantly higher in the acute myocardial infarction group than in group 2.
the unstable angina or control group. There was no significant difference among the groups for hemoglobin, platelet count, or monocyte cell count.

**Serum Levels of Adhesion Molecules**

The mean (±SE) ICAM-1 levels in group 1, group 2, and group 3 patients were 383±27 ng/mL, 337±11 ng/mL, and 282±18 mg/mL, respectively. The serum levels of ICAM-1 were significantly higher in group 1 and 2 patients than in group 3 patients (group 1 vs group 3, p<0.01; group 2 vs group 3, p<0.05). There was no significant difference of serum ICAM-1 between group 1 and group 2 patients, although the group 1 patients had higher serum ICAM-1. We also measured the serum ICAM-1 in 15 patients with stable angina (10 men, 5 women; mean age, 62±13 years). Mean ICAM-1 levels in these patients was 352±27 ng/mL. The ICAM-1 level was higher in patients with stable angina (p<0.05) as compared with control subjects. There was no difference in ICAM-1 levels among patients with stable angina, unstable angina, or acute myocardial infarction. The serum levels of ICAM-1 in patients with Q-wave and non-Q-wave myocardial infarction were 372±23 (SE) ng/mL and 395±61 ng/mL, respectively, which showed no significant difference. The serum ICAM-1 levels in patients (n=8) undergoing direct angioplasty or receiving thrombolytic therapy decreased from 357±21 ng/mL to 296±17 ng/mL (p<0.05) after reperfusion at the second day of hospitalization. Serum levels of E-selectin in group 1, group 2, and group 3 patients were 58±8, 51±4, and 58±5 ng/mL (mean±SE), respectively. The serum levels of E-selectin showed no significant difference among the three groups.

**Assay Variation**

The intra-assay coefficients of variation for serum ICAM-1 and E-selectin were 4.8% and 5.6%, respectively. The interassay coefficients of variation were 6.2% and 7.2%, respectively.

**DISCUSSION**

In this study, we found a significantly higher level of serum ICAM-1 in patients with acute coronary syndrome, while the serum E-selectin level was not elevated in these patients compared with normal control subjects.

Serum levels of ICAM-1 have been reported to be elevated in patients with inflammation, infection, cancers, and renal and heart transplants. ICAM-1 is expressed on vascular endothelium and other cells. This adhesion molecule is a ligand for the integrins, CD11 and CD11b, which are expressed in the leukocyte and are necessary for leukocyte migration. The expression of leukocyte CD11b/CD18 adhesion receptor was increased in patients with unstable angina. Immunohistochemical studies indicated that human atherosclerotic plaques contain smooth muscle cells that express ICAM-1. Soluble isoform of the ICAM-1 may be shed from the surface of the activated cells on the endothelium. Thus, serum ICAM-1 level could be increased in patients with unstable angina. Actually, serum ICAM-1 level was elevated in patients with acute myocardial infarction and unstable angina, as reported by our study and other studies.

Selectins interact with carbohydrate ligands and mediate the initial rolling of leukocytes on the endothelium. E-selectin is expressed only by activated endothelial cells and not by other cell types. The demonstration of soluble E-selectin in the blood would be taken as conclusive evidence of endothelial activation. The role of E-selectin in patients with acute coronary syndrome is not known and to our knowledge, the serum level of E-selectin in patients with acute coronary syndrome has not been reported yet. In this study, the serum E-selectin level was not elevated in patients with acute coronary syndrome. We did not show that serum E-selectin levels could have prognostic utility in patients with acute myocardial infarction or unstable angina. This finding could be explained by the absence of expression of E-selectin on human aorta smooth muscle cells. Actually, E-selectin is probably not a primary mediator of the pathophysiologic state of ischemia-reperfusion injury.

The binding of leukocytes to endothelial cells is a prerequisite for tissue injury. Leukocyte-endothelial cell interaction required at least three sequential events. E-selectin is responsible for the rolling process, while ICAM-1 is responsible for the activation-dependent adhesion. Leukocyte activation and leukocyte count were significantly higher in patients with acute myocardial infarction, as shown by Chang et al and our study. ICAM-1 is known to be a major ligand on endothelial cells for adherence of activated leukocytes and subsequent passage of the leukocytes into the myocardium. Serum ICAM-1 level, but not the E-selectin level, was elevated in patients with acute coronary syndrome, suggesting that postrolling events play an important role in the acute coronary syndrome.

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