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Full Length Research Paper

Interleukin-6 but not soluble adhesion molecules has short-term prognostic value on mortality in patients with acute ST-segment elevation myocardial infarction

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Inflammatory responses represent an important element in all phases of the atherosclerotic process. This recognition has stimulated the evaluation of different inflammatory markers as potential predictors of cardiovascular risk. This study was designed to simultaneously measure serum levels of interleukin-6 (IL-6), soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), and soluble P-selectin (sP-selectin) in patients with acute ST-segment elevation myocardial infarction (STEMI) and to evaluate their ability to predict short-term prognosis. We recruited 263 consecutive patients admitted to our institute within 6 h of symptoms onset with the diagnosis of first STEMI. Clinical data were recorded and serum admission levels of IL-6, sICAM-1, sVCAM-1 and sP-selectin were measured. The patients were then followed prospectively for the occurrence of cardiovascular mortality for 4 weeks. Nineteen (7.2%) patients died during the 4 weeks. The admission levels of IL-6 were significantly higher in patients who died from cardiovascular causes, whereas sICAM-1, sVCAM-1, and sP-selectin were not. Kaplan–Meier plots demonstrated a significant increase in cardiovascular mortality with increasing IL-6 levels (P = 0.0060). Logistic regression analysis revealed that IL-6 was an independent predictor for cardiovascular mortality. The present study indicates that elevated admission level of IL-6 but not soluble adhesion molecules could provide valuable information for short-term risk stratification in patients with STEMI.

Key words: Acute ST-segment elevation myocardial infarction, interleukin-6, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble P-selectin, cardiovascular mortality.

INTRODUCTION

There is an extensive literature supporting the role of inflammation in Coronary Artery Disease (CAD). Inflammatory cells, inflammatory proteins, and inflammatory responses from vascular cells play a pivotal role in the pathogenesis of various stages of atherosclerosis, including the initiation and progression of atheroma, plaque instability and rupture (Ross, 1999; Libby, 2002). Recent research paid much attention to sensitive specific serum biomarkers for vulnerable plaques. The new markers do not only serve as diagnostic tools for the identification of patients with Acute Coronary Syndrome (ACS) but also help us to identify high-risk patients. Among the circulating markers of inflammation, interleukin-6 (IL-6) is the major stimulus for production of most acute phase proteins and appears to play an essential role as a mediator of inflammation (Yudkin et al., 2000). Circulating levels of serum IL-6 has been shown to be predictors of adverse outcome in patients with CAD (Lindmark et al., 2001; Fisman et al., 2006). However, the role of cellular adhesion molecules (CAMs) in risk stratification in patients with CAD is not established as the results on

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Abbreviations: IL-6, Interleukin-6; **CAMs,** cellular adhesion molecules; **sICAM-1,** soluble intercellular adhesion molecule-1; **sVCAM-1,** soluble vascular cell adhesion molecule-1; **sP-selectin,** soluble P-selectin; **CAD,** coronary artery disease; **ACS,** acute coronary syndrome; **ECG,** electro-cardiogram; **BMI,** body mass index; **LVEF,** left ventricular ejection fraction; **ELISA,** enzyme-linked immunosorbent assay; **CRP,** C-reactive protein; **LPL,** lipoprotein lipase; **HPA,** hypothalamic–pituitary–adrenal.

predicting cardiovascular risk are rather confusing (Blankenberg et al., 2001; Rallidis et al., 2003; Doo et al., 2005; Hillis et al., 2001). In the present study, we evaluated the association between the circulating serum levels of the inflammatory markers IL-6, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble P-selectin (sP-selectin) and cardiovascular mortality during the 4-week follow-up period in patients with acute ST-segment elevation myocardial infarction (STEMI).

MATERIALS AND METHODS

Patients

We enrolled 263 consecutive patients (203 men and 60 women) with STEMI who were admitted to our institute within 6 h of symptoms onset and fulfilled all of the following criteria (Alpert et al., 2000): (1) Typical, prolonged (>30 min) chest pain at rest; (2) ST-segment elevation ≥0.2 mV; at the J point in two or more contiguous precordial leads or ≥0.2 mV in two or more adjacent limb leads on the standard 12-lead electro-cardiogram (ECG); and (3) presentation in the first 6 h since the onset of chest pain. Diagnosis of acute myocardial infarction was confirmed by increased serial serum markers of myocardial damage (>2-fold increase over the upper normal range required for creatinekinase and troponin I). Patients with equivocal or uninterpretable ECGs (that is, left bundle branch block, paced rhythm, or persistent ST-segment elevation after a previous myocardial infarction) were not included in the study.

The present study did not include patients with a history of hematological, neoplastic, renal, liver, or thyroid disease, or patients receiving treatment with anti-inflammatory drugs. Patients with acute or chronic infections, autoimmune disease were also excluded from the study. The study protocol was approved by the ethics committee of our institution, and written informed consent was obtained from all participating patients.

Clinical data collection

A special questionnaire was used to collect information on demographic and clinical information, including age, gender, smoking, hypertension, hyperlipidemia, diabetes mellitus, and current mediations (use of aspirin, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, lipid-lowing agents) were also recorded. Diabetes mellitus was defined as a previous diagnosis, use of diet or antidiabetic medicines, or fasting venous blood glucose level ≥126 mg/dl on two occasions in previously untreated patients. Patients who received medications for hypertension or those with seated systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least three separate clinic visits were classified as having hypertension. Patients who used cholesterol-lowering medicines or had a total serum cholesterol level ≥200 mg/dl were classified as having hypercholesterolemia. Patients who reported smoking at least one cigarette per day for at least 1 year were defined as current smokers, and ex-smokers were defined as abstainers for at least 1 year. Height, weight, and waist circumference were measured, and body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. The presence and degree of heart failure on admission were assessed following the Killip classification: Killip I: Absence of clinical heart failure; Killip II: mild heart failure with rales involving less half of the lung fields, an S3 gallop; Killip III: acute pulmonary edema; Killip IV: cardiogenic shock. Left ventricular ejection fraction (LVEF) was measured by echocardiography (HP 7500, Hewlett-Packard Development Company, L.P. Palo Alto, CA, USA) after admission using the Simpson method.

Patients were followed-up for 4 weeks after admission using a standardized protocol that included outpatient visits, telephone contacts, and the recording of recurrent cardiovascular event. A death was classified as cardiovascular if the predominant and immediate cause was related to myocardial infarction or ischemia, arrhythmia, refractory congestive heart failure, sudden death, stroke, or peripheral artery disease.

Laboratory assays

In every subject, peripheral venous blood was drawn right after admission. Sample after clotting were centrifuged at 2500 rpm for 10 min, and the serum was frozen and stored at -70℃ until analysis. Sandwich enzyme-linked immunosorbent assay (ELISA) was performed for measuring concentrations of serum IL-6, sICAM-1, sVCAM-1, and sP-selectin, using Quantikine (R and D Systems, Minneapolis, MN, USA) commercial kits. The lower detection limits were 0.7 pg/ml for IL-6, 0.35 ng/ml for sICAM-1, 0.6 ng/ml for sVCAM-1, and 0.095 ng/ml for sP-selectin. The average inter- and intra-assay coefficients of variation were <10% for all assays. Biochemical measurements were carried out by our biochemistry department using standard laboratory methods.

Statistical analysis

Data are expressed as mean ± SD or median and interquartile ranges, as appropriate. Unpaired Student's t-test and nonparametric equivalent (Mann–Whitney U statistic test) were used to evaluate differences in continuous variables between the two groups. Qualitative data are presented as numbers (percentages) and Chi-square tests were performed for categorical variables. The Kaplan–Meier method was used for cumulative event-free survival analysis, and the log-rank test for assessing the statistical differences between the curves. Logistic regression was used to analyze the relationship between these variables and clinical outcome. A value of $P < 0.05$ was considered statistically significant. All calculations were performed using SPSS statistical software for Windows (version 12.0).

RESULTS

Clinical characteristics

During the 4-week follow-up period, 19 (7.2%) cardiovascular deaths occurred out of 263 patients, including 18 cardiac deaths and 1 cerebrovascular death. Baseline demographic, clinical and treatment data are presented in Table 1. Patients who died from cardiovascular causes were associated with older age, a higher proportion of females, hypertensive and diabetes mellitus patients, Current and ex-smokers, higher heart rate, poor cardiac function, and smaller proportion of b-blocker, ACE-I, and statin use.

Admission levels of inflammatory markers

The admission levels of IL-6 were significantly higher in patients who died from cardiovascular causes, whereas

Table 1. Baseline characteristics of the study population according to the occurrence of cardiovascular death during a 4-week follow-up period.

Variable	Cardiovascular death (n = 19)	No cardiovascular death (n = 244)	P value
Sex (female)	9 (47.4%)	51 (20.9%)	0.008
Age (years)	70.5 ± 11.6	60.4 ± 12.2	<0.001
BMI (kg/m^2)	23.8 ± 2.7	25.4 ± 3.3	0.064
Waist circumference (cm)	86.6 ± 11.4	90.7 ± 11.3	0.156
Hypertension	14 (73.3%)	104 (42.6%)	0.009
Hypercholesterolemia	3 (15.8%)	47 (19.3%)	0.268
Diabetes mellitus	9 (47.4%)	50 (20.5%)	0.007
Current and ex-smokers	8 (42.1%)	183 (75.0%)	0.002
Heart rate (beats/min)	97.7 ± 30.8	76.8 ± 16.5	<0.001
SBP (mmHg)	127.4 ± 33.6	138.5 ± 29.5	0.120
DBP (mmHg)	72.8 ± 17.2	80.6 ± 16.4	0.074
Killip's class ≥II	14 (73.7%)	58 (23.8)	<0.001
LVEF <50%	6 (31.6%)	21 (8.6%)	0.014
Antiplatelet agents	17 (89.5%)	233 (95.5%)	0.244
β-Blocker use	8 (42.1%)	199 (81.6%)	<0.001
ACE-I use	10 (52.6%)	225 (92.2%)	<0.001
Statin use	12 (66.7%)	224 (91.8%)	<0.001
Reperfusion therapy	10 (52.6%)	174 (71.3%)	0.087
Peak CK (U/l)	2341.0 (1048.5–5076.0)	1296.0 (477.0–2551.3)	0.051
Peak CK-MB (U/l)	201.5 (85.3–418.0)	104.0 (45.0–191.3)	0.054
Peak Tn-I (mg/l)	76.9 (32.0–225.4)	29.1 (10.3–99.3)	0.097

Age, BMI, waist circumference, SBP and DBP are presented as mean ± standard deviation; peak CK, CK-MB, and Tn-I are presented as medians (25 to 75th percentile); categorical variables are presented as number (%). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LVEF: left ventricular ejection fraction; ACE-I: angiotensin-converting enzyme inhibitors; Tn-I: Troponin I; CK: creatine kinase; CK-MB: creatine kinase-myocardial fraction.

Table 2. Admission levels of IL-6, sICAM-1, sVCAM-1, and sP-selectin of the study population according to the occurrence of cardiovascular death during a 4-week follow-up period.

Variable	Cardiovascular death (n = 19)	No cardiovascular death (n = 244)	P value
IL-6 (pg/ml)	10.15 (6.14 -142.31)	5.41 (4.29 - 8.02)	<0.001
sICAM-1(ng/ml)	372.0 (300.5 - 532.5)	318.5 (235.0 - 440.0)	0.145
sVCAM-1(ng/ml)	1050.0(719.0 - 1475.0)	887(670.0 - 1120.0)	0.156
sP-Selectin(ng/ml)	116.0 (56.7 - 214.5)	99.0 (57.6 -166.0)	0.654

Data are presented as medians (25 to 75th percentile), IL-6, sICAM-1, sVCAM-1, sP-selectin.

sICAM-1, sVCAM-1, and sP-selectin were not (Table 2).

Inflammation and cardiovascular prognosis

To determine the factors which influence the cardiovascular prognosis, the significant different variables between the two groups were selected and analyzed using logistic regression analysis. Only Killip's class ≥II, age ≥75 years, less use of ACE-I, and admission level of IL-6 were independent predictors for cardiovascular mortality during a 4-week follow-up in patients with STEMI (Table 3).

Using the median of admission IL-6 level as cutoff point, Kaplan–Meier curves were derived for the entire cohort of patients with IL-6 values of ≥5.57 and <5.57 pg/ml. Kaplan–Meier plots demonstrated a significant increase in cardiovascular mortality with increasing IL-6 levels (χ^2 =7.56, P = 0.0060 by log-rank test) (Figure 1).

DISCUSSION

The present study showed a significant increase in

Table 3. Multivariate analysis for cardiovascular mortality at 4 weeks in the entire cohort.

Parameter	β	Wald	*P value*	OR	95%CI
Killip's class ≥II	1.856	6.715	0.010	6.401	1.572 - 26.064
age ≥75y	1.683	5.065	0.024	5.380	1.243 - 23.292
ACE-I use	–2.112	7.947	0.005	0.121	0.028 - 0.525
IL-6	1.512	4.567	0.033	4.538	1.134 - 18.167

ACE-I, Angiotensin-converting enzyme inhibitors; IL-6, interleukin-6; OR, odds ratio; CI, confidence interval.

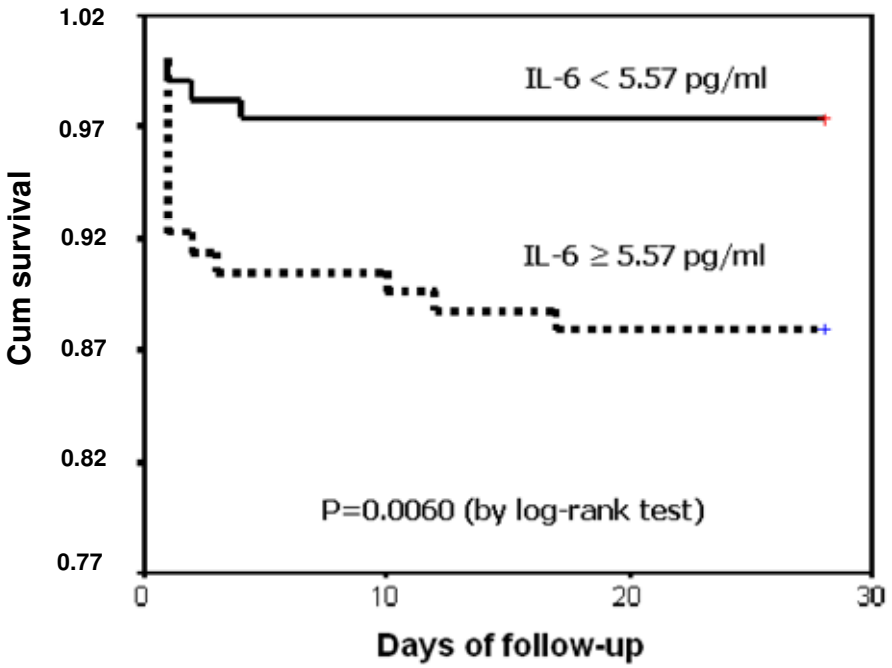

Figure 1. Kaplan-Meier survival curve. IL-6, interleukin-6.

cardiovascular mortality with increasing IL-6 levels, and logistic regression analysis revealed that IL-6 was an independent predictor for cardiovascular mortality during 4 weeks of follow-up in patients with STEMI. These findings suggested that an elevated admission level of IL-6 but not of sICAM-1, sVCAM-1, or sP-selectin could provide prognostic value for short term cardiovascular mortality, and IL-6 may be an attractive risk marker for clinical use in patients with STEMI.

Cell adhesion molecules and their counter receptors of the β2-integrin family, mainly Mac-1, play a pivotal role in the interactions between leucocytes, platelets, and vascular endothelium. Adherence of circulating leukocytes to the endothelium and their transmigration into the arterial wall is an early step of atherosclerosis (Nakashima et al., 1998). Soluble CAMs (sCAMs: sICAM-1, sVCAM-1 and E- and P-selectins) are shed from cell surfaces and reflect cellular activation (Blankenberg et al., 2003). Several studies have evaluated the association between soluble CAMs levels and risk of future acute coronary events in patients with ACS but the results are rather conflicting. Postadzhiyan et al. (2008) reported that sICAM-1 could identify patients with ACS that are at highest risk for ischemic events. In a prospective observational study, among patients presenting acutely with ACS (unstable angina and non-Q MI) raised concentrations of sVCAM-1 but not sICAM-1, E-selectin, and P-selectin was predictive of an increased major cardiovascular event within 6 months after presentation (Mulvihill et al., 2001). Hillis et al. (2002) studied 126 consecutive patients presenting with clinical myocardial ischemia. In this study, only P-selectin and cardiac troponin I but not sICAM-1, sVCAM-1, or E-selectin were significantly higher among patients who had a serious cardiac event during the index admission or the subsequent 3 months, and remained independently predictive in a multivariable regression equation. In the present study, we failed to detect serum sICAM-1, sVCAM-1, or sP-selectin at the early phase of acute STEMI to be associated with poor clinical outcome. The utility of CAMs in predicting the outcome of patients with STEMI seems to be limited.

Among inflammatory biomarkers, the proinflammatory

cytokine IL-6 has been widely studied. Yudkin et al. (2000) summarized a key role for the IL-6 with several detrimental effects that contribute to the development of coronary heart disease. Interleukin-6 is the main effector of the hepatic acute-phase response. Ferroni et al. (2007) confirmed significant correlation of IL-6 and hs-C-reactive protein (CRP) or fibrinogen, most likely reflecting the role of IL-6 as a key mediator of inflammatory reactions including hepatic synthesis and release of CRP and fibrinogen. The acute-phase reaction is associated with elevated levels of fibrinogen, a strong risk factor for coronary heart disease, with autocrine and paracrine activation of monocytes by IL-6 in the vessel wall contributing to the deposition of fibrinogen. The acute-phase response is associated with increased blood viscosity, platelet number, and activity. Furthermore, IL-6 decreases lipoprotein lipase (LPL) activity and monomeric LPL levels in plasma, which increases macrophage uptake of lipids. Circulating IL-6 also stimulates the hypothalamic–pituitary–adrenal (HPA) axis, activation of which is associated with central obesity, hypertension, and insulin resistance.

Over the past few years, several studies have suggested that IL-6 is a valuable inflammatory marker to identify those patients at high risk of a cardiac event. Ridker et al. (2000) have demonstrated that apparently healthy men in the highest quartile of IL-6 had a risk ratio 2.3 times higher than those in the lowest quartile of IL-6 over a 6-year follow-up period, which supports a role for cytokine-mediated inflammation in the early stages of atherogenesis. In another study, increased IL-6 plasma levels were independent predictors for future cardiac events and mortality in a population with stable coronary artery disease during a 6.3-year follow-up, and each increase of 1 pg/ml in IL-6 was associated with a 1.70 increased relative odds of subsequent myocardial infarctt-ion or sudden death (Fisman et al., 2006). Koukkunen et al. (2001) reported that both IL-6 and CRP are independent predictors of the risk of coronary death and major coronary events (coronary death or nonfatal myocardial infarction) in patients with unstable angina pectoris. Circulating IL-6 not only was a strong independent marker of increased mortality in unstable coronary artery disease, but was also able to identify patients who benefit most from a strategy of early invasive management (Lindmark et al., 2001). In patients with reperfused myocardial infarction, circulating IL-6 levels are correlated closely with left ventricular geometric changes during the remodeling process (Ohtsuka et al., 2004). Funayama et al. (2006) found that the regional IL-6 levels in the culprit coronary artery after percutaneous coronary intervention were strongly associated with the future restenosis of the recanaled coronary artery in acute myocardial infarction.

However, there is controversy regarding the significant independent association between IL-6 concentration and atherosclerosis burden. Sukhija et al. (2007) found no association of serum levels of IL-6 with coronary atherosclerotic burden or major adverse cardiac events at 6 months after adjustment for traditional coronary artery disease risk factors inpatients hospitalized with chest pain.

The limitations of this study need to be addressed. Blood samples to measure levels of inflammatory factors were drawn within the first 6 h of symptoms' onset, which does not elucidate the dynamics of serum CAMs levels after the initial symptoms of acute STEMI.

Conclusion

The main finding of this study supports that IL-6 but not soluble adhesion molecules may behave as a prognostic tool to assist in the risk assessment of patients with STEMI within the first 6 h of symptoms onset.

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