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Interleukin-1 Receptor Antagonist Levels Correlate with Extent of Myocardial Loss in Patients with Acute Myocardial Infarction

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Summary

Background: Interleukin-1 receptor antagonist (IL-1Ra) levels are elevated early in patients with acute myocardial infarction (MI) and often precede release of markers of necrosis; however, IL-1Ra levels did not correlate previously with infarct size and prognosis in such patients.

Hypothesis: The goal of our study was to evaluate prospectively the correlation between IL-1Ra levels upon emergency department (ED) presentation and the extent of myocardial necrosis and prognosis in patients with ST-segment elevation MI.

Methods: Levels of IL-1Ra were measured upon ED presentation in 44 consecutive patients (40 men, aged 55 ± 10 years). Peak values of creatine kinase (CK) and CK-MB were determined during hospitalization, and left ventricular ejection fraction (LVEF) was evaluated by echocardiography before discharge. All patients were followed prospectively and underwent clinical and echocardiographic assessment at 42 ± 3 months after the infarction.

Results: Levels of IL-1Ra upon ED presentation correlated directly with CK ($p = 0.002$) and CK-MB ($p = 0.01$) peak levels and correlated inversely with LVEF before discharge ($p = 0.009$). Patients with in-hospital adverse events had significantly higher IL-1Ra levels upon ED admission (n = 10, 2620 ± 4706 pg/ml) than those without events (n = 34, 598 ± 457 pg/ml) ($p = 0.015$).

Conclusions: In patients with MI, levels of IL-1Ra upon ED presentation correlated significantly with the extent of myocardial necrosis, as measured by cardiac enzymes peak and reduction of LVEF, and are predictive of in-hospital events. Results of this study may influence early therapeutic approach in patients with acute MI.

Key words: inflammation, interleukins, myocardial infarction, prognosis

Introduction

Inflammation plays a key role in the pathogenesis of unstable coronary syndromes.[1] Recent studies found that interleukin-1 receptor antagonist (IL-1Ra), a competitive inhibitor of the proinflammatory cytokine IL-1, is a sensitive diagnostic and prognostic marker in patients with unstable angina[2, 3] and may be helpful in identifying high-risk patients after coronary stenting.[4, 5] Interleukin-1Ra may also represent a useful diagnostic tool in patients with acute myocardial infarction (MI), since its levels rise early and precede release of markers of myocardial necrosis;[6] moreover, patients with acute MI and hemodynamic instability have also significantly higher IL-1Ra peak levels during their stay in the coronary care unit than those without severe ventricular dysfunction.[7] However, no previous study has evaluated the prognostic value of early IL-1Ra determination on infarct size and prognosis in patients with acute MI. The goal of our study was to evaluate prospectively the correlation between IL-1Ra levels upon emergency department presentation in patients with ST-segment elevation acute MI and extent of myocardial loss and early in-hospital and long-term prognosis.

Methods

The study population consists of 44 consecutive patients with first acute myocardial infarction admitted to the emergency department (ED) within the first 12 h after symptoms onset.

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Myocardial infarction was defined as (1) chest pain lasting > 30 min; (2) ST-segment elevation ≥ 0.2 mV in ≥ 2 contiguous leads, persisting after nitrates administration; (3) rise in serum creatine kinase (CK) and CK-MB above diagnostic levels (reference range 5–195 and 5–25 IU/l, respectively) during hospitalization. Upon ED admission, venous blood was drawn to measure levels of markers for myocardial necrosis (CK and CK-MB), and in the same samples determination of IL-1Ra and C-reactive protein was performed. Also obtained during coronary care unit stay were serial CK and CK-MB levels by measurements every 6 h for 24 h, every 12 h for 48 h, and every 24 h until transfer into the cardiology section. No patient had clinical or laboratory evidence of malignancy, infections, inflammatory disease, or recent (< 2 months) surgery or trauma. All patients developed Q-wave MI. Echocardiographic left ventricular ejection fraction (LVEF) was assessed by the Simpson method during hospital stay. Major in-hospital cardiac events included death, new MI, and need for urgent coronary revascularization. All patients underwent prospective follow-up assessment by office visits every 6 months, including occurrence of major adverse events (angina, reinfarction, cardiac death, coronary revascularization) and LVEF determination at echocardiography. Each patient gave informed consent to the study.

Laboratory Assays

Venous blood samples for IL-1Ra determination were centrifuged at 2000xg at 4°C for 30 min. The plasma was frozen at −80°C until it was assayed. Interleukin-1Ra kits were purchased from R&D Systems (Minneapolis, Minn., USA), and the assays employed the quantitative sandwich enzyme immunoassay technique. The microplate reader was LP400 from Sanofi-Diagnostics Pasteur (Milan, Italy). The lower level of detection was 49 pg/ml; IL-1Ra levels in healthy individuals are ≤ 230 pg/ml.

Statistical Analysis

Values are expressed as mean ± standard deviation. The U-Mann Whitney test was used to compare continuous variables; correlations were done by Spearman's rank test. Associations were also assessed using logistic regression analysis. P values < 0.05 were considered significant.

Results

Patients Characteristics

Demographic and clinical characteristics of the 44 patients are described in Table I. Mean duration of chest pain prior to ED presentation was 228 ± 170 min. Thirty-nine patients (89%) received intravenous thrombolysis with front-loaded recombinant tissue plasminogen activator (rt-PA); the remaining patients did not receive thrombolysis because of contraindications (2 patients) or arrival > 6 hours after chest pain onset (3 patients). In-hospital mortality was 7% (3/44): one patient died of primary ventricular fibrillation and two of cardiogenic shock 3 days after admission; three patients were treated successfully with angioplasty during the first 72 h, and four further patients had in-hospital postinfarction angina and underwent early coronary angioplasty with stenting. Thus, in-hospital cardiac events occurred in 10 patients (23%).

Twenty-nine patients underwent elective coronary angiography after discharge (mean 32 ± 11 days) for residual inducible postinfarction myocardial ischemia: 21 patients were treated with stent implantation (single-vessel intervention in 16 patients, multivessel in 5); 3 underwent elective by-pass surgery; and 5 were treated medically.

On long-term follow-up (mean 42 ± 3 months, range 39–48), two other major adverse events occurred: one patient died of cardiac arrest 3 months after surgical revascularization and one patient, treated with stenting of the infarct-related artery, had a new MI after 12 months and repeat coronary angiography showed total occlusion of a nontarget vessel.

Interleukin-1 Receptor Antagonist Data

Upon ED presentation, IL-1Ra levels (mean 1057 ± 2351 pg/ml) correlated directly with CK (mean 2173 ± 3235 IU/l, Fig. 1A) ($p = 0.002$) and CK-MB peak levels (mean 181.6 ± 116.7 IU/l, Fig. 1B) ($p = 0.01$) during hospitalization. The IL-1Ra levels also correlated inversely with LVEF measured during hospital stay (Fig. 2, $p = 0.009$); patients with in-hospital LVEF ≤ 40% had significantly higher IL-1Ra levels upon ED admission (n = 7, 3518 ± 5465 pg/ml) than those with

TABLE I Patients' characteristics

Variable	Number of patients
Number	44
Males (%)	40 (91)
Age (years) (range)	55 ± 10 (32–71)
Risk factors	
Diabetes (%)	11 (25)
Hypertension (%)	25 (57)
Dyslipidemia (%)	26 (59)
Smoking (%)	33 (75)
Previous myocardial infarction (%)	1 (2)
Site of infarction	
Anterior (%)	16 (36)
Inferior (%)	25 (57)
Lateral (%)	3 (7)
Time from symptoms onset (min) (range)	228 ± 170 (30–720)
Mean left ventricular ejection fraction (%)	53 ± 9
Patients with left ventricular ejection fraction ≤ 40% (%)	7 (16)
Severity of coronary disease	
Single-vessel disease (%)	20 (46)
Multivessel disease (%)	12 (27)
Nonsignificant disease (%)	1 (2)

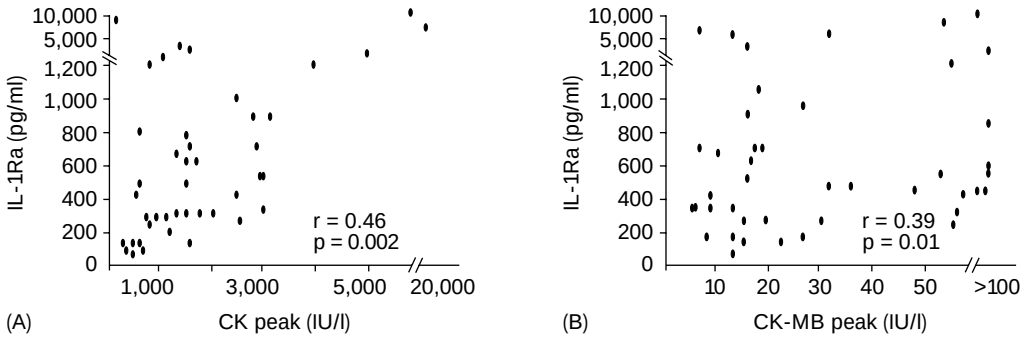

FIG. 1 Correlations of interleukin-1 receptor antagonist (IL-1Ra) levels upon emergency department admission with creatine kinase (CK) (A) and CK-MB (B) peak levels during hospitalization.

LVEF > 40% (n = 37, 591 ± 477 pg/ml, p = 0.038) (Fig. 3). Likewise, patients with in-hospital major cardiac events had higher IL-1Ra levels (n = 10, 2620 ± 4706 pg/ml) than those without events (n = 34, 598 ± 457 pg/ml, p = 0.015) (Fig. 3). There was a nonsignificant trend between IL-1Ra levels and number of vessels with significant stenoses at coronary angiography (p = 0.09). C-reactive protein levels upon ED presentation did not correlate with CK and CK-MB peak values nor with LVEF during hospitalization (p ≥ 0.8).

Logistic regression analysis confirmed the association between in-hospital events and LVEF > 40%, CK peak < 1495 IU/l (median value), and baseline IL-1Ra < 456 pg/ml (median value). Occurrence of adverse events was negatively associated with LVEF > 40% (odds ratio [OR] 0.35, 95% confidence interval [CI] 0.16–0.74) and IL-1Ra < 456 pg/ml (OR 0.18, CI 0.05–0.57); an almost significant association was also found with CK peak < 1495 IU/l (OR 0.22, CI 0.05–1.03).

At 42 ± 3 months mean follow-up, mean LVEF was significantly improved compared with baseline (57 ± 5 vs. 53 ± 9%, p = 0.02), especially in patients who underwent coronary revascularization (60 ± 5 vs. 53 ± 5%, p = 0.01); however, late LVEF by echocardiography or major adverse cardiac events were not related to initial IL-1Ra levels (p ≥ 0.2).

Discussion

The present study indicates that IL-1Ra levels upon ED presentation are related to the extent of myocardial necrosis and in-hospital prognosis in patients with acute MI.

Interleukin-1 is a cytokine involved in tissue inflammation, ischemia/reperfusion injury, and coronary atherosclerosis.[8,9] Interleukin-1Ra is a competitive inhibitor of the IL-1 membrane receptor without agonistic effects and is locally released by activated cells (i.e., monocytes) or produced by hepatocytes as acute phase reactant;[8,9] IL-1Ra secretion occurs simultaneously with activation of IL-1 receptor to modulate proinflammatory effects of IL-1, and IL-1Ra values correlate well with grade of inflammation.[8–10] Elevation of IL-1Ra occurs early in patients with acute MI, often preceding the rise of markers for necrosis.[6] In a previous study of patients with acute MI,[7] elevated IL-1Ra peak levels during coronary care unit stay were associated with hemodynamic impairment, but

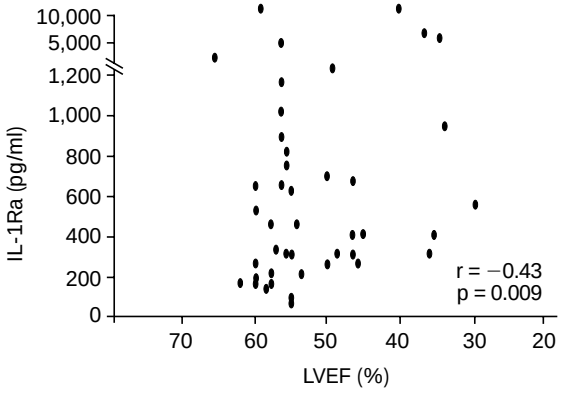

FIG. 2 Correlation between interleukin-1 receptor antagonist (IL-1Ra) levels upon emergency department admission and left ventricular ejection fraction (LVEF) before discharge.

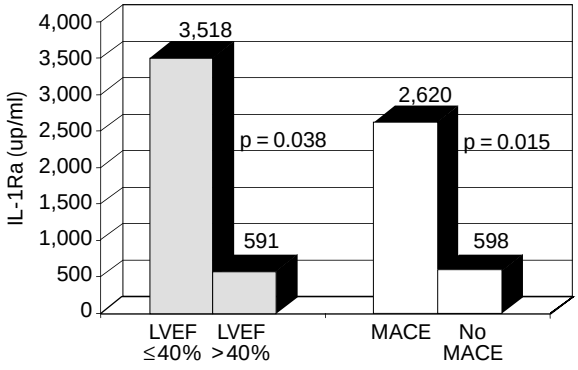

FIG. 3 Interleukin-1 receptor antagonist (IL-1Ra) levels upon emergency department admission in patients with predischarge left ventricular ejection fraction (LVEF) ≤ 40% or > 40% and in patients with or without in-hospital major adverse cardiac events (MACE).

did not correlate with peak CK values. In contrast, in the present study IL-1Ra levels correlated directly with peak CK and CK-MB values, depression of LVEF, and in-hospital adverse events. This correlation was not observed with C-reactive protein, likely because of the long half-life of this acute phase marker and the slow production kinetics (peak levels usually occur > 18 h after activation of the inflammatory pathways). Our findings suggest that copious amounts of IL-1 (determining subsequent marked release of IL-1Ra) may be produced by ischemic myocardium in evolving MI. This is supported by previous experimental data showing that IL-1 is released by ischemic myocytes during the first hours of MI[11] and may be involved in the initiation of wound healing of the necrotic area.[12] Thus, early detection in the ED of elevated IL-1Ra levels (> 2600 pg/ml) may be useful for better identification of patients who will develop more extensive necrosis, ventricular dysfunction, and in-hospital cardiac complications (death, need for rescue angioplasty, or postinfarction angina). Thus, our study suggests that a single determination of IL-1Ra levels in patients with acute MI upon presentation may be helpful in identifying a higher-risk group in need of closer monitoring, more aggressive medical treatment, and possibly early coronary revascularization.

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