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Clinical Investigations

Relation of Circulating Interleukin-6 to Left Ventricular Remodeling in Patients with Reperfused Anterior Myocardial Infarction

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Summary

Background: During the remodeling process after myocardial infarction (MI), the expression of proinflammatory cytokines is enhanced in the myocardium. However, only a few clinical studies have been conducted on cytokine involvement in left ventricular (LV) remodeling after MI.

Hypothesis: Circulating proinflammatory cytokines may be involved in LV remodeling in patients with reperfused MI.

Methods: We studied 25 patients with acute anterior MI who had undergone coronary reperfusion therapy, and 10 normal control subjects with no cardiac disease. In all patients, LV ejection fraction, end-diastolic volume index (EDVI), and end-systolic volume index (ESVI) were determined using left ventriculography at the acute phase and 6 months after onset. The Δ EDVI and Δ ESVI were calculated as the value of LV volume reduction, suggesting LV reverse remodeling. Serum levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha were measured using enzyme-linked immunosorbent assay.

Results: Serum levels of IL-6 and TNF-alpha at the acute phase were significantly higher in patients with MI than in control subjects (both $p < 0.05$). The IL-6 levels correlated well negatively with Δ EDVI ($r = 0.779$, $p = 0.039$), whereas no correlation was found for TNF-alpha. According to multivariate analysis, IL-6 at the acute phase was a significant independent predictor for LV remodeling after reperfused MI ($p = 0.007$).

Conclusions: Circulating IL-6 levels correlated closely with LV geometric changes during the remodeling process in patients with reperfused MI. Our study addresses the usefulness of another marker for LV remodeling after MI.

Key words: cytokines, left ventricular remodeling, myocardial infarction

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Introduction

Left ventricular (LV) remodeling after myocardial infarction (MI) is commonly referred to as progressive structural and geometric changes in the left ventricle.[1,2] The remodeling process is believed to serve initially as a compensatory mechanism for maintaining cardiac output. However, progressive remodeling of the myocardium leads to global LV enlargement, which results in congestive heart failure and subacute cardiac rupture.[3,4] There is a general consensus that large infarct size, wall stress, and overexpression of the renin-angiotensin-aldosteronesystem promote structural LV remodeling after MI, and thus, postinfarct remodeling is a complex process.

Reperfusion of the ischemic myocardium is associated with a dramatic inflammatory response.[5–7] Several studies have reported that a marked elevation of serum C-reactive protein (CRP) level and peripheral monocytosis are closely related to the process of infarct healing and structural LV remodeling in patients with acute myocardial infarction (AMI).[8–10] The expression of proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6, is enhanced in the myocardium during the remodeling process after reperfused MI.[11,12] In addition, clinical studies have demonstrated the presence of increased circulating levels of proinflammatory cytokines in patients with AMI.[13,14] These cytokines can stimulate fibroblast proliferation and collagen deposition and may be involved in apoptosis, which is proposed as an important mechanism in postinfarct remodeling.[15,16] In view of these results, it is apparent that proinflammatory cytokines play an important role in the reperfused myocardium during the remodeling process. However, clinical studies of the involvement of cytokines in LV remodeling after MI are few. Accordingly, the present study tested the hypothesis that circulating

proinflammatory cytokines may be involved in LV remodeling in patients with reperfused MI.

Materials and Methods

Subjects

Between January 1998 and December 2000, we studied consecutive patients with a first Q-wave acute anterior MI. All patients underwent primary percutaneous coronary intervention of their culprit lesions within 12 h of onset. Successful reperfusion was defined as restoration of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the left anterior descending artery. In addition, patients received other therapies, including aspirin, angiotensin-converting enzyme (ACE) inhibitors, and beta-adrenergic blockers. Patients who had restenosis or reocclusion of an infarct-related coronary artery 6 months after onset were excluded from this study. Patients who had clinical or laboratory evidence of neoplasms or autoimmune disease or liver or renal dysfunction were also excluded. Finally, 25 patients were included in this study. Ten age-matched subjects, whose cardiac catheterization findings had exhibited no significant coronary stenosis and no cardiac dysfunction, were selected as normal controls. All subjects participated in this study after giving their informed consent, and the protocol was approved by the Human Investigations Committee of our institution.

Blood Sampling and Immunoassays

After bed rest for at least 30 min, peripheral venous blood samples were collected into chilled tubes, immediately centrifuged at 4° C, and stored at −80° C until assay. Blood samples from patients for the measurement of cytokine levels were collected within 24 h and 6 months after the onset of infarction. Serum levels of IL-6 and TNF-alpha were measured by enzyme-linked immunosorbent assays with commercial kits (Immunotech Co., Marseille, France) as previously reported.[17] The average inter- and intra-assay coefficients of variation were <10% for all assays. Blood samples for the measurement of creatine kinase (CK) activity were drawn every 6 h until it reached peak value and every 12 h in the following 48 h. Plasma CK levels were measured using a standardized automated enzyme analyzer.

Analysis of Left Ventriculography

In all patients, left ventriculography was performed according to the Judkins technique on admission and 6 months after onset. The volume of contrast medium and treatments at the time of first and second ventriculography were similar. Left ventriculograms were analyzed independently by two different observers blinded to the clinical features. Left ventricular ejection fraction (LVEF) was calculated by a center-line method. Left ventricular volumes were estimated from the right anterior oblique projection by an automated system, and LV end-diastolic and end-systolic volume indices (EDVI and ESVI) were calculated as the LV volume/body surface area. Since all patients showed a reduction of EDVI and ESVI 6 months after onset, changes in them (Δ EDVI and Δ ESVI) were obtained by subtracting the respective values 6 months after onset from the values on admission. These values were considered indicators of the extent of reduction in LV volume, suggesting LV reverse remodeling as previously reported.[18] Left ventricular end-diastolic pressure (LVEDP) was also measured using a 5F pig-tail catheter.

Statistical Analysis

All values are expressed as means ± standard deviation (SD). Differences between patients and control subjects were compared with the Mann-Whitney *U* rank-sum test for unpaired data. Clinical variables and serum levels of cytokines in patients were compared at the acute phase and 6 months after onset using the Wilcoxon's paired sign rank test. Correlation coefficients for relationships between serum levels of cytokines and clinical variables were tested using the Spearman rank test. To evaluate the independent predictors of LV remodeling (Δ EDVI), six variables, including age, peak CK levels, LVEDP, LVEF, and serum levels of IL-6 and TNF-alpha at the acute phase, were analyzed using univariate and multivariate analyses in patients. A p value <0.05 was considered statistically significant.

Results

Patient Characteristics

The mean age of the study population (6 women, 19 men) was 64 ± 10 years (range 44–76). Twenty (80%) patients were in Killip class I and five (20%) were in class II. The mean peak plasma CK level was 3182 ± 835 IU/l. In all patients, the treatment with ACE inhibitors and aspirin was started within 24 h of onset. Seven patients (28%) were treated with beta blockers in addition to ACE inhibitors.

Serum Cytokine Levels at the Acute Phase

Figure 1 shows serum levels of IL-6 and TNF-alpha in patients with MI at the acute phase and in control subjects. Serum levels of IL-6 and TNF-alpha were significantly higher in patients with MI than in control subjects.

Changes in Left Ventricular Function and Volume and Cytokine Levels in Patients with Myocardial Infarction

Table I shows the changes in LV function and volume in patients with MI. Left ventricular end-diastolic pressure was significantly decreased, and LVEF was significantly improved 6 months after onset. In addition, both EDVI

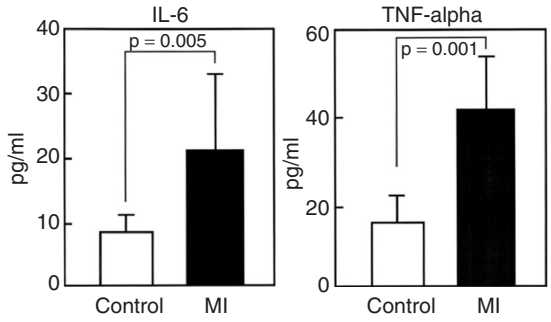

FIG. 1 Graphs showing serum levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha in 10 age-matched control subjects and in 25 patients with myocardial infarction (MI) at the acute phase.

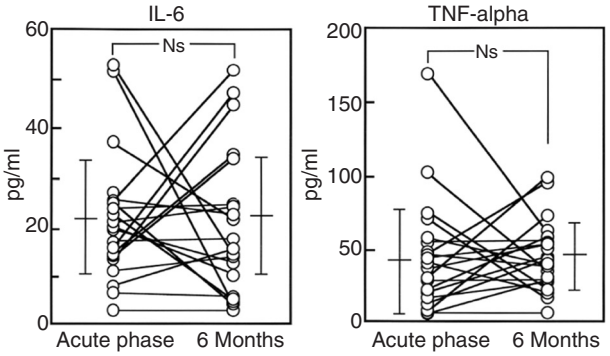

FIG. 2 Comparisons of serum levels of interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha in 25 patients with myocardial infarction at the acute phase and 6 months after onset. NS = not significant.

and ESVI were significantly reduced. Figure 2 shows the changes in IL-6 and TNF-alpha levels in patients with MI. There were no significant differences in both serum levels at the acute phase and 6 months after onset.

Relationships between Cytokine Levels and Left Ventricular Function and Remodeling in Patients with Myocardial Infarction

In patients with MI, there were no significant correlations between serum levels of IL-6 and TNF-alpha and LVEDP and LVEF at the acute phase. In addition, both IL-6 and TNF-alpha levels did not significantly correlate with LV volume and peak CK levels. On univariate analysis of six factors affecting LV remodeling (Δ EDVI), age and IL-6 levels at acute phase were significant predictors of LV remodeling ($r = -0.509$, $p = 0.044$ and $r = -0.779$, $p = 0.039$, respectively) (Fig. 3). According to multivariate analysis (Table II), age and IL-6 at the acute phase were significant independent predictors of LV remodeling after reperfused MI with IL-6 the strongest indicator in patients with MI.

TABLE I Changes in left ventricular (LV) function and volume in patients with myocardial infarction

	Acute phase	6 Months after
LV end-diastolic pressure (mmHg)	18.2±6.4	12.6±5.1[a]
LV ejection fraction (%)	46.3±13.2	56.1±11.2[b]
LV end-diastolic volume index (ml/m^2)	80.9±17.3	68.7±17.0[a]
LV end-systolic volume index (ml/m^2)	45.2±18.9	32.1±15.3[a]

Data are presented as the mean values ± standard deviation.
[a] $p < 0.0001$.
[b] $p < 0.01$ versus values at acute phase.

Discussion

The present study indicates that circulating IL-6 levels are closely related to LV geometric changes during the remodeling process in patients with reperfused MI. It was interesting to note that multivariate analyses demonstrated that circulating IL-6 at the acute phase was a powerful inde-

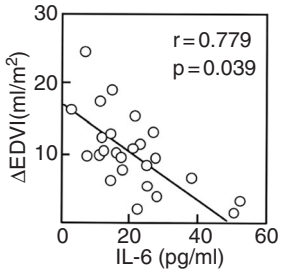

FIG. 3 Correlation between interleukin (IL)-6 at the acute phase and Δ end-diastolic volume index (EDVI) in 25 patients with myocardial infarction.

TABLE II Multivariate analysis of predictors of left ventricular remodeling after myocardial infarction

	Standard coefficient (β)	p Value
Age	−0.515	0.032
Peak CK	0.091	0.615
LVEDP (acute phase)	−0.407	0.400
LVEF (acute phase)	0.179	0.639
IL-6 (acute phase)	−0.629	0.007
TNF-alpha (acute phase)	−0.330	0.143

Abbreviations: CK = creatine kinase, IL = interleukin, LVEDP = left ventricular end-diatolic pressure, LVEF = left ventricular ejection fraction, TNF = tumor necrosis factor.

pendent predictor of LV remodeling after reperfused MI. Thus, IL-6 may have a more important role in inflammation during post-infarct remodeling in comparison with other inflammatory cytokines.

Healing after MI involves inflammatory cell infiltrations followed by fibroblast proliferation, collagen deposition, and remodeling in the infarct myocardium.[2] In addition, reperfusion of the ischemic myocardium has been shown to trigger the release of cytokines and other mediators of inflammation.[6,7] Previous clinical studies have indicated the presence of activated circulating leukocytes and inflammatory cytokines, as well as acute-phase reactants such as CRP in patients with AMI.[13,14,19] In particular, it has been shown that elevated CRP levels and monocytosis are associated with LV enlargement and aneurysm after reperfused MI, suggesting an important role of inflammatory response in post-infarct remodeling.[8,9] The monocyte-related cytokines, such as IL-6, stimulate liver cells to produce CRP and lead to peripheral monocytosis. In fact, a previous study demonstrated that circulating IL-6 levels correlated well with serum CRP level in patients with AMI.[20] In the present study, we demonstrated the presence of increased circulating levels of IL-6 and TNF-alpha in patients with AMI, and that patients with a higher IL-6 level showed lesser reduction in LV volume in spite of successful early reperfusion or other drug interventions. These findings indicate that circulating IL-6 levels are closely related to LV geometric changes associated with reverse remodeling after MI. Several investigators suggested the distinct roles and unique aspects of IL-6, as opposed to TNF-alpha and IL-1β, in the process of LV remodeling after MI.[12,21] One of these studies has shown that, whereas the time courses of gene expression of TNF-alpha and IL-1β parallel each other, peaking early (1 h) after reperfusion, IL-6 expression remains elevated for 6 h, an effect attributable to its differences in transcriptional regulation in the postischemic reperfused myocardium.[21] Therefore, IL-6 may contribute to structural LV remodeling after reperfused MI, unlike other inflammatory cytokines.

One limitation of our study is the small number of patients, which may impact our results. However, previous investigators clarified the close relationships between inflammatory mediators and LV remodeling in patients with MI, and thus we believe that circulating IL-6, which is a mediator of inflammation, can predict LV remodeling after reperfused MI. To confirm this, however, further studies will be needed on a larger patient sample.

Conclusions

We clarified that a higher circulating IL-6 involved LV geometric changes during the remodeling process in patients with reperfused MI, and that circulating IL-6 can predict LV remodeling after reperfused MI. Therefore, our study addresses the usefulness of another marker affecting LV remodeling of outcome after MI.

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