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Serum Interleukin-6 on Admission Predicts Expansion of the Left Ventricle in Patients with Successfully Reperfused Acute Myocardial Infarction

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ABSTRACT

We tested the hypothesis that left ventricle (LV) expansion continues after the onset of acute myocardial infarction (AMI) and that serum levels of interleukin (IL)-6, the most important proinflammatory cytokine, before reperfusion predict LV expansion. For this purpose, we measured serum levels of IL-6 and performed left ventriculography at admission (acute phase) and before discharge (subacute phase) in 36 consecutive patients with first AMI successfully reperfused within 12 hours of onset. LV expansion in the subacute phase was defined as (1) an increase in the ratio of LV end-diastolic volume of more than a 10% compared with that in the acute phase or (2) an increase in the LV end-diastolic volume index of more than 70 ml/m². Serum levels of IL-6 at admission were significantly higher in patients with LV expansion (8.95 ± 2.12 pg/ml, $n = 13$) than in patients without LV expansion (5.05 ± 0.68 pg/ml, $n = 23$; $p < 0.05$), although the difference in the subacute phase was not significant. Twenty-three variables concerning prescribed medications and the baseline, clinical, angiographic, and percutaneous coronary intervention did not differ significantly between the groups. Thus, elevated serum IL-6 levels at admission predict continued LV expansion after AMI. (Jikeikai Med J 2006 ; 53 : 63-7)

Key words : interleukin-6, acute myocardial infarction, expansion, remodeling

INTRODUCTION

Infarcted myocardial tissue is replaced by fibrous tissue after 2 weeks[1,2]. The 70% of infarcted myocardium that is replaced is assumed to expand the infarcted myocardium through wall thinning, left ventricular (LV) dilatation, and the resulting progression of left ventricular (LV) remodeling[3]. Remodeling determines the prognosis of patients with acute myocardial infarction (AMI)[4]. Therefore, it is important to examine the causes of infarct expansion in the subacute phase which may lead to cardiac remodeling.

The inflammatory reaction system, which is initiated by AMI through cytokine production, has received much attention recently as a mechanism of infarct expansion and remodeling[5-7]. In particular, interleukin (IL)-6, which is produced during the AMI acute phase, is thought to be a crucial cytokine that controls the survival of cardiomyocytes in the infarcted lesion[5,6].

In this study, we examined the relationship between the IL-6 produced during the acute phase and LV function during the subacute phase, when expansion begins. For this purpose, we examined the rela-

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tion of serum IL-6 levels before a reperfusion procedure, particularly on admission, with the presence of LV expansion diagnosed with left ventriculography (LVG) performed after a patient's first AMI, with successful reperfusion within 12 hours of onset, and in the following subacute phase.

METHODS

1. *Subjects*

The subjects were 36 patients with a first AMI who were admitted to the Saitama Cardiovascular and Respiratory Center or The Jikei University Hospital from January 2002 through December 2003 and underwent succession reperfusion by means of primary percutaneous coronary intervention (PCI) within 12 hours of onset. The diagnostic criteria for AMI were sustained chest discomfort, ST elevation confirmed by two or more adjacent leads on electrocardiography, and serum creatine kinase (CK) and serum CK-MB fractions that exceeded twice the normal levels in serological examinations.

Reperfusion was considered successful when residual stenosis of the coronary arteries was less than 25% with a Thrombolysis in Myocardial Infarction flow of grade 3[8]. Exclusion criteria were severe valvular heart disease, atrial fibrillation, left main trunk lesion, and cardiogenic shock that required mechanical circulatory support. Moreover, in patients with congestive heart failure (CHF) and an LV end-diastolic pressure greater than 25 mmHg, the timing of LVG after successful PCI was left to the operator's discretion so as not to exacerbate CHF.

All subjects were admitted directly to the coronary care unit. After levels of CK had peaked, patients were transferred to the general ward and cardiac rehabilitation was started. Heparin (10,000 IU/day) was given intravenously and continuously for 48 hours after the PCI. Oral administration of a beta-blocker, angiotensin-converting enzyme inhibitor, or an angiotensin II receptor antagonist was started several days after the onset of AMI. After cardiac rehabilitation had been completed, cardiac catheterization including LVG was performed again during the subacute phase (hospital day 8 to 49 ; 15.5 hospital days on average). Written informed consent was obtained from each patient.

2. *Protocol*

Except when not possible because of the above-mentioned reasons, LVG was performed during the acute phase immediately after successful PCI and was repeated after cardiac rehabilitation had been completed.

LVG was performed 30° to the right anterior oblique, and the LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), and LV ejection fraction were measured using the area-length method. To correct for variances between cases, the LVEDV index LVEDVI (ml/m²) and the LVESV index (LVESVI) (ml/m²) were calculated by dividing the LVEDV and LVESV by the body surface area calculated from the height and weight of the patient.

Blood samples for measuring serum IL-6 levels were collected during the acute phase immediately after admission and again before discharge (on the 15.5 th hospital day on average). The samples were stored at −80°C, and serum IL-6 levels were measured within 1 month. The samples were collected every 3 hours from the onset of AMI (at 3, 6, 9, 12, 15, or 18 hours), and the peak CK values were measured in the central laboratory at each hospital.

3. *Definition of LV expansion*

Patients who were able to undergo LVG in both the acute and subacute phases and patients in whom LVEDV in the subacute phase was more than 10% greater than that in the acute phase were placed in the expansion group. Patients in whom LVEDV in the subacute phase increased by less than 10% were placed in the nonexpansion group. Six of the 36 patients who were unable to undergo LVG in the acute phase because of one of the causes described above or who had an LVEDVI of 70 ml/m² or more during the subacute phase were also placed in the expansion group.

4. *Statistical analysis*

The measured values are shown as means±SD. Differences were assessed with the unpaired t-test,

were considered significant at $p<0.05$.

Results

1. *Comparing individual factors between the expansion and nonexpansion groups*

Of the 23 factors examined (including patient characteristics, clinical course, LVG and coronary angiographic findings, PCI course, and prescribed medications), none except LVEDVI differed significantly between the expansion group (13 patients) and the nonexpansion group (23 patients). Subacute LVEDVI was 75.3±9.9 ml/m² in the expansion group and 32.7±22.2 ml/m² in the nonexpansion group.

2. *Comparing IL-6 levels between the expansion and nonexpansion groups*

The IL-6 levels during the acute and subacute

Table. Comparison of variables between Expansion and Nonexpansion Group

	Expansion group (n=13)	Nonexpansion group (n=23)	
Age (years)	60±7.5	61±8.9	n.s.
Male Sex (%)	92.3	91.3	n.s.
Coronary risk factor			
Hypertension (%)	46	56	n.s.
Hyperlipidemia (%)	92	87	n.s.
Diabetes mellitus (%)	31	39	n.s.
Current smoker (%)	69	70	n.s.
Clinical course			
Elapsed time (hours)	3.0±2.3	2.51±1.69	n.s.
Prodromal angina (%)	38	30	n.s.
Killip's classification (mean)	1.23±0.6	1.13±0.34	n.s.
Peak CK (IU/l) (mean)	4,634±903	3,385±461	n.s.
Duration between subacute LVG (mean days)	15.7±6.3	15.5±9.2	n.s.
Ventriculography			
Subacute LVEF (%)	53.6±2.9	56.4±2.4	n.s.
Subacute LVEDVI (ml/m²)	75.3±9.9	32.7±22.2	−
Angiographic finding & PCI course			
Culprit vessel			
LAD/LCX/RCA	8/1/4	12/2/9	n.s.
Diseased vessel			
1/2/3 vessel	10/3/0	16/5/2	n.s.
First TIMI grade (mean)	0.62±0.92	1.03±1.56	n.s.
Rentrop (mean)	0.38±0.26	0.50±0.43	n.s.
Recanalization time (hours)	4.62±2.43	4.06±1.90	n.s.
Reperfusion phenomenon (%)	23	13	n.s.
Intervention			
Stenting (%)	46	43	n.s.
Thrombectomy (%)	23	26	n.s.
Distal protection device (%)	31	30	n.s.
Prescribed medicine			
β blocker (%)	54	65	n.s.
ACEI or ARB (%)	92	91	n.s.

Results are the means±SD.
LAD indicates the left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers.
Killip's classification[13] and Rentrop[14] refers to the original work.

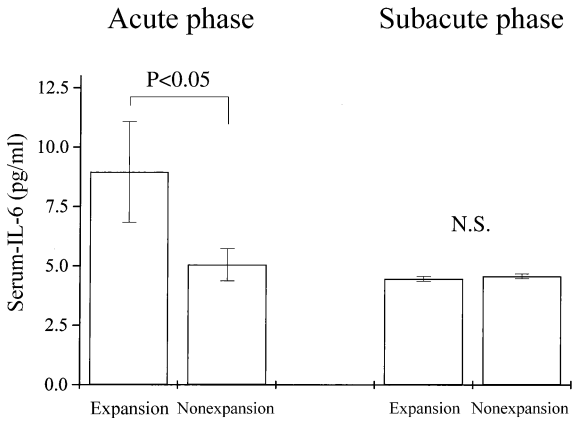

Fig. 1. Serum of IL-6 levels during the acute and subacute phases in the expansion and nonexpansion groups
During the acute phase (left side), mean serum IL-6 levels were significantly higher in the expansion group than in the nonexpansion group ($p < 0.05$). However, during the subacute phase (right side), mean serum IL-6 levels did not differ significantly between the groups.

phases in both groups are shown in Fig. 1. The IL-6 levels during the acute phase were significantly higher in the expansion group (8.95±2.12 pg/ml) than in the nonexpansion group (5.05±0.68 pg/ml, $p < 0.05$). On the other hand, IL-6 values in the subacute phase did not differ between the expansion and nonexpansion groups (4.46±0.10 pg/ml and 4.75±0.10 pg/ml, respectively).

DISCUSSION

This study examined the relationship between LV expansion in the subacute phase of AMI and IL-6 levels before reperfusion. Other recent studies suggest that the induction of monocytes and macrophages during the acute phase produces and induces IL-6, which plays a key role in LV remodeling[5,6], but the significance of IL-6 levels before reperfusion remain unclear.

That IL-6 levels begin to increase during the acute phase[6,9] suggests that factors that determine LV expansion or remodeling might be present before reperfusion therapy. We have attempted to test this hypothesis. We found LV expansion in the subacute phase in patients who showed elevated serum IL-6 levels before reperfusion therapy. This finding suggests that LV expansion, reflecting an elevation of serum IL-6 levels at admission, had already developed. To our knowledge, the present study is the first to report such a finding.

The dynamics of serum IL-6 after AMI and its participation in LV expansion are as follows. Studies in rats show that mRNA of IL-6 is expressed in the ischemic lesion surrounding the infarcted myocardium 3 hours after the onset of AMI[6,9,10]. Monocytes and macrophages, which strongly affect IL-6 production, migrate and further amplify IL-6 activation[5,11]. Moreover, after the onset of AMI, cytokines, such as IL-6, express matrix metalloproteinases, which cause dysfunction and defects in the extracellular matrix[12]. This series of inflammatory reactions, an index of which is the elevation in IL-6 levels after AMI, may promote the formation of collagen, resulting in scarring and expansion of the infarcted myocardium.

The IL-6 levels during the subacute phase did not differ significantly between the expansion and nonexpansion groups. After the initial increase in expression of the IL-6 gene in the infarcted region, IL-6 normally begins to decrease toward baseline levels after 1 week[5,7]. However, if the infarct is large or if other myocardial stresses continue, IL-6 gene expression may remain significantly elevated or may increase again as a second wave of cytokine activation, particularly in the noninfarcted myocardium away from the original site of injury[5,7]. In the present study the mean ejection fraction was greater than 50% in both groups. Therefore, in the subacute phase IL-6 levels may remain decreased. To prove this hypothesis, however, we would need to perform LVG in chronic phase.

This study is limited by the division of the definition of expansion into two items. As described in the methods, we could not perform LVG in the acute phase for the following reasons: to prevent CHF exacerbation in patients with AMI, to prevent LV end-diastolic pressure from increasing, and to prevent renal function from deteriorating. For these reasons, the clinical course leading to LVG in the expansion group has yet to be clarified during the subacute phase. Therefore, the IL-6 activity described above

could not be correlated with the presence of expansion. This study was limited cases of only two hospitals. A larger prospective multicenter investigation is necessary.

Conclusion

An increase in IL-6 during the acute phase of AMI is an important factor for predicting LV expansion.

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