Close Association of Regional Interleukin-6 Levels in the Infarct-Related Culprit Coronary Artery With Restenosis in Acute Myocardial Infarction

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Background The involvement of interleukin (IL)-6 in restenosis of the recanalized coronary artery after the percutaneous coronary intervention (PCI) was examined.

Methods and Results There were 40 patients enrolled in the study who had acute myocardial infarction and whose infarct-related coronary arteries were treated by new thrombectomy devices and stenting. Blood samples were collected from the culprit coronary artery before and immediately after the maneuver of the PCI. Restenosis was defined as residual stenosis because it accounted for more than 50% at the follow-up coronary angiography. Plasma IL-6 levels in the infarct-related coronary artery were 12.8 and 13.2 pg/ml before and after the initial maneuver of the PCI, respectively, values that were significantly greater than that of 7.2 pg/ml in the peripheral vein ($p < 0.0001$). The levels of IL-6 in the pre- and the post-stage of PCI were significantly greater in the patients with restenosis than those without restenosis. The plasma IL-6 levels in the post-stage of PCI had significant correlations with late loss and loss index.

Conclusions The present study findings indicate that plasma IL-6 levels in the culprit coronary artery at the post-stage of PCI are closely associated with the future restenosis of the revascularized coronary artery in acute myocardial infarction. (Circ J 2006; 70: 426–429)

Key Words: Acute myocardial infarction; Interleukin-6; Restenosis

Vulnerable fibrous caps of atherosclerotic plaque are suggested to be involved in an acute occlusion of the coronary artery in acute myocardial infarction.^{1–4} The in vivo studies in experimental animals with atherosclerotic plaques indicate that interleukin (IL)-1 β , IL-6 and tumor necrosis factor- α may be released from the vulnerable plaques.^{5–6} We demonstrated an increase in regional IL-6 levels in the infarct-related coronary artery in patients with acute myocardial infarction.⁷ Recent development of the percutaneous coronary intervention (PCI) technique enables us to rescue patients from acute coronary occlusion.^{8–10} However, one of the residual problems is restenosis of the coronary artery, which was recanalized by PCI. If regional cytokines would deteriorate the restenosis, the measurement of IL-6 level in the infarct-related coronary artery might be a useful tool for the risk of restenosis after PCI.

In the present study, we determined the IL-6 levels in the infarct-related coronary artery, and furthermore investigated whether the IL-6 level is associated with the recurrence of stenosis 6 months after the treatment of PCI in patients with acute myocardial infarction.

Methods

Subjects

Forty patients with acute myocardial infarction and who

were who were admitted to the Emergency Units of Jichi Medical School Omiya Medical Center were enrolled between April 2001 and March 2002. There were 34 males and 6 females whose ages ranged from 37 to 76 years (59.8 ± 9.8 years, mean $\pm$ SD). The diagnosis of acute myocardial infarction was determined by the findings of continuous chest pain more than 30 min, ST-segment elevation greater than 2.0 mm on at least 2 successive ECG leads, and more than a 2-fold increase in serum creatine kinase (CK) levels. In all patients, cardiac catheterization was carried out within 24 h after the onsets of myocardial infarction and a follow-up angiography was performed 6 months after the initial catheterization. Criteria for the patient enrolment were as follows: (1) within 24 h after the onset; (2) single vessel disease; and (3) a proximal lesion of the coronary artery. Anterior myocardial infarction was found in 25 patients, lateral myocardial infarction was in 4 patients, and inferior myocardial infarction was found in 11 patients. Coronary risk factors were obtained in a majority of patients; that is, 23 patients had diabetes mellitus, 28 patients had hypertension, 24 patients had hyperlipidemia, 23 patients had obesity, and 20 patients were current smokers. We excluded the patients with cardiogenic shock, those with chronic renal failure on hemodialysis, those with an apparent infectious disease, those with bypass failure, those with prior use of thrombolytic therapy, and those with an inability to cross the target lesion with a thrombectomy catheter because of excessive proximal vessel tortuosity from the study. Maximal levels of serum CK ranged from 262.0 to 8,648.0 mU/ml ($3,099.6 \pm 20,145.8$ mU/ml, mean $\pm$ SD).

Study Protocol

Blood samples were collected from the peripheral vein

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Table 1 Clinical, Angiographic and Procedural Characteristics in Patients With Acute Myocardial Infarction

	No restenosis (n=26)	Restenosis (n=14)	p value
Age, years	59.5±2.1	60.5±2.3	0.75
M/F	21/5	13/1	0.31
Coronary risk factors			
Hypertension (n)	19	9	0.56
Diabetes mellitus (n)	15	8	0.97
Hyperlipidemia (n)	17	7	0.34
Current smoker (n)	20	5	0.39
Time until the procedure of PCI (h)	6.5±0.8	8.4±1.3	0.19
Peak CK (IU/ml)	3,626.6±472.1	2,766.4±439.3	0.13
Ejection fraction at admission (%)	53.0±2.1	47.9±2.9	0.89
Culprit vessel (LAD/LCX/RCA) (n)	16/3/7	9/1/4	0.91
Type of stent (NIR/Multi-link/S670)	5/14/7	5/6/3	0.52
Stent length (mm)	16.65±0.60	15.00±0.89	0.12
Maximal inflation pressure (atm)	12.4±0.5	13.6±0.8	0.15
Duration of inflation (s)	51.0±1.5	56.8±6.4	0.26
Reference diameter (mm)	3.09±0.08	3.12±0.14	0.81
After PCI			
MLD (mm)	2.62±0.07	2.51±0.15	0.45
Residual stenosis (%)	14.8±1.5	19.8±3.6	0.14
Follow-up angiography			
MLD (mm)	2.56±0.41	0.99±0.15	<0.01
Residual stenosis (%)	29.7±2.4	66.8±4.8	<0.0001
Late loss (mm)	0.45±0.07	1.41±0.12	<0.0001
Loss index	0.18±0.03	0.56±0.05	<0.0001
Medications			
Statin at admission (n)	4	3	0.63
Statin at follow up (n)	20	11	0.91
ACEI at follow up (n)	22	12	0.93

Values are expressed as mean±SEM or number of patients.

PCI, percutaneous coronary intervention; CK, creatine kinase; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; MLD, minimum lumen diameter; ACEI, angiotensin-converting enzyme inhibitor.

and the occluded coronary vessel before and immediately after the maneuver of PCI by the thrombectomy catheter to measure plasma IL-6. Briefly, heparin (10,000 IU) was administered intravenously, and 162 mg of aspirin was given orally. A coronary angiography was performed using a catheter via the femoral approach. A thrombectomy catheter (RESCUE thrombectomy catheter, SciMED/BSC, Inc, Maple Grove, MN, USA) was introduced through the guiding catheter.⁸⁻¹⁰ After thrombectomy, direct stenting was carried out. Blood samples were collected by gentle sucking from the occluded site of the culprit coronary artery again immediately after the maneuver of the PCI. After PCI, the patients were treated with 81 mg/day aspirin and 200 mg/day ticlopidine for 1 month.

A follow-up coronary angiography was carried out 6 months after PCI to determine the recurrence of stenosis. Restenosis is defined as residual stenosis being more than 50% at the follow-up coronary angiography stage.¹¹ If restenosis was diagnosed, coronary intervention was conducted. The patients were divided into 2 groups; with and without restenosis. The present study was approved by the Ethical Committee of Jichi Medical School. We obtained written informed consent from all the patients before coronary angiography was performed.

Measurements

Blood was collected in chilled tubes containing EDTA-Na₂ (1 mg/ml blood) and centrifuged at 3,000 rpm at 4°C for 15 min. The supernatants were decanted and frozen at -80°C until the time of assay for plasma IL-6. Plasma IL-6 was determined by an ELISA using Quantikine human IL-6 assay kits (R&D system, Minneapolis, MN, USA).¹¹ The

minimal detectable concentration of IL-6 was 0.70 pg/ml. Intra- and interassay coefficients of variation were 2.6 and 4.5%, respectively.

Quantitative Coronary Angiography Analysis

A computer-based quantitative coronary angiography analysis software designed by GE Medical System (Milwaukee, WI, USA) was used. The measurements were performed on the end-diastolic frames by a single investigator who was blinded to the study results. A reference diameter, lesion length, and minimum lumen diameter (MLD) were measured before and after the angioplasty and at the time of the follow-up angiography. We determined the acute gain (MLD after the angioplasty minus MLD before the angioplasty), the late loss (MLD after the angioplasty minus MLD at follow-up angiography), and the late loss index (the average ratio of late loss to acute gain). A value of 0 mm was assigned for MLD in the case of total occlusion at base line.

Statistical Analysis

All values were expressed as mean±SEM. Comparisons between the 2 groups were analyzed by using the unpaired Student's t-test. Differences in the distribution of variables were analyzed by using the chi-square test. Simple linear regression analysis was performed to calculate correlations. A p value less than 0.05 was considered significant.

Results

Table 1 summarizes the clinical characteristics of patients with acute myocardial infarction. The patients were

Fig 1. Plasma interleukin (IL)-6 levels in culprit coronary artery before (A) or after (B) the maneuver of percutaneous coronary intervention in patients with acute myocardial infarction in the presence and absence of restenosis. Open circles indicated mean $\pm$ SEM values.

divided into 2 groups; with and without restenosis, by determining recanalization 6 months after the PCI. There were no differences in age, sex, coronary risk factors and lesion characteristics between the 2 groups. During the initial maneuver of PCI, residual stenosis was $19.8 \pm 3.6\%$ and $14.8 \pm 1.5\%$ in patients with and without restenosis, respectively. A follow-up angiography clearly showed that the residual stenosis was $66.8 \pm 4.8\%$ in the patients with restenosis; a value significantly greater than that of $29.7 \pm 2.4\%$ in those without restenosis ($p < 0.0001$). Both the late loss and loss indexes were significantly greater in patients with restenosis than those without restenosis.

Plasma IL-6 levels in the infarct-related coronary artery were 12.8 ± 1.4 and 13.2 ± 1.4 pg/ml before and after the initial maneuver of PCI, respectively, which was significantly higher than that of 7.2 ± 1.0 pg/ml in the peripheral vein ($p < 0.0001$). The regional IL-6 levels after PCI in the infarct-related coronary artery positively correlated with those before the PCI ($r = 0.61$, $p < 0.0001$). When plasma IL-6 levels were compared between the presence and absence of restenosis, the difference in plasma IL-6 levels in the culprit coronary artery was evident; that is, plasma IL-6 levels before and after the PCI were significantly greater in patients with restenosis than those without restenosis (Fig 1). The higher significance ($p < 0.0001$) was obtained with the values after PCI. In addition, it is evident that in those patients without restenosis, the plasma IL-6 levels in the infarct-related coronary artery were 10.5 ± 1.2 and 9.1 ± 1.1 pg/ml before and after PCI, respectively; values that were still greater than that of 6.6 ± 1.0 pg/ml found in the peripheral vein ($p < 0.05$). There was no difference in

Fig 2. Relationship between plasma interleukin (IL)-6 levels in the infarct-related coronary artery (CA) after percutaneous coronary intervention (PCI) with late loss (A) and late loss index (B) in the patients with acute myocardial infarction.

plasma IL-6 levels in the peripheral vein between patients with and without restenosis (8.3 ± 2.2 vs 6.5 ± 1.0 pg/ml, $p = 0.42$). Plasma IL-6 levels in the peripheral vein did not correlate with the maximal level of CK ($r = 0.28$, $p = 0.09$) and ejection fraction ($r = -0.16$, $p = 0.36$) (data not shown).

As shown in Fig 2, late loss had a positive correlation with plasma IL-6 levels in the culprit coronary artery after PCI in patients with myocardial infarction ($r = 0.57$, $p < 0.0001$). A similar result was obtained between the late loss index and plasma IL-6 levels in the culprit coronary artery after PCI ($r = 0.60$, $p < 0.0001$).

Discussion

The present study demonstrated an increase in regional IL-6 levels in the infarct-related coronary artery before and after PCI in patients with acute myocardial infarction. In particular, restenosis was found to be prominent in patients whose regional IL-6 levels after PCI were elevated.

In our previous study, the inflammatory cytokine IL-6 is increased in the infarct-related coronary artery in the patients with acute myocardial infarction.⁷ IL-6 could be synthesized by activated macrophages and with vascular smooth muscle cells infiltrating into the atherosclerotic plaque.¹²⁻¹⁶ Mechanical stretch, vascular injury and hypoxia may be involved in causing IL-6 release in the coronary circulation after PCI. The increase in regional IL-6 levels may facilitate the process of breakdown of the vulnerable

region of atherosclerotic plaque by activating macrophages. Macrophages secrete proteolytic enzymes such as metalloproteinases, which can break down both collagen and elastin to peptides and eventually amino acids.¹⁷⁻²⁰ The regional IL-6 levels are associated with the size of the fragile plaque itself. The present study did not evaluate the quality of plaque, but instead evaluated the fibrous plaque, which should be fragile.

We found that the regional IL-6 levels after PCI in the infarct-related coronary artery positively correlated with those before PCI. Furthermore, the regional IL-6 levels after PCI were strongly associated with restenosis of the recanalized coronary artery. In contrast, there was no difference in plasma IL-6 levels in the peripheral vein between the patients with and without restenosis. Recently, Suzuki et al found that in patients with stable angina pectoris, plasma IL-6 levels in the peripheral vein were significantly greater 1 and 6 h after the maneuver of PCI in the group with restenosis compared with the group without restenosis.²¹ Also, there was a significant correlation between changes in IL-6 levels in the coronary circulation after PCI and the degree of angiographic restenosis in the patients with stable angina pectoris.²² In the present study, we enrolled the patients with acute myocardial infarction. Plasma IL-6 levels in the patients' peripheral vein could be linked to total systemic inflammation, which is not only related to the culprit coronary artery, but also with necrosis of the myocardium.

An enhanced expression of cytokines is suggested to be involved in acute and chronic complications of PCI by causing the release of vasoactive substances and other growth factors, and thereby establishing a positive autocrine and paracrine feedback loop—a "cascade mechanism."²³ IL-6 is a multifunctional cytokine, regulating humoral and cellular responses and it plays a central role in inflammation and tissue injury. IL-6 has procoagulant properties²⁴⁻²⁶ and mitogenic activity for smooth muscle cells.²⁷ The alteration in regional IL-6 does not only include the present inflammation of the recanalized artery, but also the size and fragility of fibrous atherosclerotic plaque.

In conclusion, the measurement of plasma IL-6 in the infarct-related coronary artery at PCI is associated with future restenosis in patients with acute myocardial infarction. In particular, the regional IL-6 level after PCI is an excellent indicator for restenosis.

Study Limitations

The present study did not include any patients with stable angina pectoris, and our findings are only related to patients with acute myocardial infarction. The patient population was relatively small and further studies with larger numbers of patients are required to prove our hypothesis.

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