The Prognostic Value of IL-8 for Cardiac Events and Restenosis in Patients with Coronary Heart Diseases After Percutaneous Coronary Intervention

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SUMMARY

The objective of the present study was to investigate the prognostic value of plasma interleukin-8 (IL-8) for adverse cardiac events and restenosis in patients with percutaneous coronary intervention (PCI). The pre- and post-procedural peak plasma levels of IL-8 and serum C-reactive protein (CRP) were examined by immunoassay, while adverse cardiac events and restenosis within one year follow-up were observed in 134 consecutive patients who underwent PCI. Angiography revealed that 23.88% (32/134) of the patients had adverse cardiac events and 29.41% (35/119) of the patients had restenosis. Preprocedural levels of IL-8 and CRP and post-procedural peak levels of IL-8 in patients with adverse cardiac events were higher than those without adverse cardiac events (all $P < 0.05$). The incidence of adverse cardiac events increased from 6.67% in the bottom tertile to 31.82% in the top tertile of IL-8 levels ($P = 0.001$); a similar trend was observed for restenosis from 10% in low tertile to 51.28% in high tertile of IL-8 levels to 51.8% ($P = 0.012$). The preprocedural levels of IL-8 ($RR = 5.539$, $CI = 1.720-17.887$, $P = 0.001$) and CRP ($RR = 2.031$, $CI = 1.132-2.049$, $P = 0.003$) were the only independent predictors of adverse cardiac events. The post-procedure peak level of IL-8 ($RR = 3.766$, $CI = 2.990-5.904$, $P = 0.002$) and stent length ($RR = 1.468$, $CI = 1.161-2.022$, $P = 0.021$) were the independent predictors of restenosis. The results demonstrate that the release of IL-8 after PCI is a powerful prognostic factor for cardiac events and restenosis. The higher the peak level of post-procedure IL-8, the lower the event-free survival observed. (*Jpn Heart J* 2003; 44: 623-632)

Key words: PCI, IL-8, Cardiac events, Restenosis

PERCUTANEOUS coronary intervention (PCI) is an established myocardial revascularization procedure. However, the high initial success rate is compromised by the risk of cardiac events and restenosis ranges from 30% to 60%. Recent experimental and clinical studies have shown that inflammatory cytokines and inflammatory responses can be provoked following PCI in patients with coronary heart disease, and there are accumulations of inflammatory cells around the

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Received for publication November 29, 2002.

Revised and accepted March 10, 2003.

stent after PCI by the pathologic study of coronary plaques.¹⁾ Angioi, *et al* reported that the increased plasma level of C-reactive protein (CRP) before PCI has a predictive value for early complications and reverse cardiac events.^{2,3)} The increase in preprocedural CRP levels appears to be a powerful predictor of restenosis.²⁾ Our previous studies revealed that there were changes in plasma IL-8 levels and the predictive value of early complications in patients undergoing PCI.^{3,4)} These observations suggested that inflammatory responses play an important role in the prognosis in patients with PCI. Therefore, we prospectively investigated the predictive value of periprocedural levels of IL-8 on the one-year angiographic and clinical outcomes of cardiovascular events and restenosis in consecutive patients undergoing coronary stent implantation.

METHODS

Patients: The study group was comprised of 134 of 261 consecutive patients who underwent PCI on a single nontotal occlusive coronary stenosis, 65 patients with stable angina, and 69 patients with unstable angina. An indication for PCI was based on a history of angina lasting 20 minutes within 24 hours with ST segment changes for unstable patients, and/or a positive exercise stress test in the presence of a significant (> 75%) residual stenosis for stable angina. Exclusion criteria were a myocardial infarction within three months (19 patients), only percutaneous coronary angioplasty (8 patients), direct stenting (20 patients), total occlusion (10 patients), multilesion PCI (31 patients), left ventricular ejection fraction < 30% (12 patients), left bundle branch block (4 patients), and patients with interfering noncardiac diseases such as inflammatory disorders, malignancy, or infection were not eligible for either study group (13 patients). Ten other patients (4 patients lost, 2 patients whose data was unavailable, 2 patients with noninfarction related infarction, and 2 patients with nontarget vessel stenosis) were also excluded during a one-year follow-up. The regular medications of the patients were not altered for the study; none of the patients was on any anti-inflammatory agent except aspirin (150 mg/day). Forty angiographically normal patients served as controls. The hospital ethics committee for human subjects approved the study. Written informed consent was obtained from all patients.

Blood sampling: Peripheral blood samples were taken immediately before and 30 minutes, 4, 12, 24, 48, and 72 hours, and 7 days after balloon angioplasty.³⁾ Coded samples were stored at -80°C and analyzed in a single batch at the end of the study. Thus, patient management was independent of these results. Blood samples of 40 angiographically normal patients were obtained before and 12, 24, and 48 hours after the procedure.

Laboratory assays: Plasma levels of IL-8 and serum CRP were assayed by an automated monoclonal antibody solid phase sandwich-type enzyme immunoassay on an Abbott 311S instrument (Abbott Laboratories, North Chicago, Illinois). The minimum measuring sensitivity was 16 pg/mL, with intra- and interassay variations less than 10% at different levels of IL-8. The measuring range was 0.1 to 24 mg/L, with intra-assay variation coefficients ranging from 0.6% to 1.5% and interassay variations from 1.4% to 6.5% at different levels of CRP.

Coronary angioplasty: Coronary angiography was performed with Judkin's catheters via the right femoral artery using a digital angiographic system. Angiography, coronary angioplasty, and stent implantation (BX, Cordis; AVE, Medtronic) were performed by experienced investigators only. All patients received heparin

Table I. Clinical Features of Patients With or Without Cardiac Events After PCI.

	Noncardiac events (<i>n</i> = 102)	Cardiac events (<i>n</i> = 32)	<i>P</i>
Age, years	64.0 ± 6.5	64.5 ± 6.0	0.924
Sex, M/F	83/19	25/7	0.685
Diabetes, <i>n</i> (%)	28 (27)	15 (47)	0.040
Hypertension, <i>n</i> (%)	49 (48)	15 (47)	0.908
Smoking, <i>n</i> (%)	61 (60)	25 (78)	0.059
MI, <i>n</i> (%)	35 (34)	11 (34)	0.626
Body index	26.2 ± 3.24	26.4 ± 3.30	0.826
TC (mmol/L)	3.82 ± 0.14	3.85 ± 0.12	0.383
LDL-C (mmol/L)	1.67 ± 0.93	1.78 ± 0.90	0.612
HDL-C (mmol/L)	2.38 ± 0.19	2.40 ± 0.16	0.735
Ejection fraction (%)	61.05 ± 7.68	58.54 ± 8.03	0.152
PTCA coronary artery, (<i>n</i>)	102	32	
LAD, <i>n</i> (%)	63 (62)	20 (63)	0.940
LCX, <i>n</i> (%)	17 (17)	5 (16)	0.890
RAC, <i>n</i> (%)	22 (22)	7 (22)	0.971
A/B/C Types*	39/37/26	10/10/12	0.419
Small vessel (< 3.0 mm), <i>n</i> (%)	51 (50)	17 (53)	0.758
Dilation pressure, atm	6.6 ± 4.1	7.2 ± 3.9	0.457
Inflation time, s	90 ± 12	88 ± 14	0.463
Balloon/vessel ratio	1.2 ± 0.4	1.1 ± 0.5	0.211
Stenosis after PTCA, %	30 ± 5	31 ± 4	0.343
Minimal lumen diameter, mm	2.2 ± 0.29	2.1 ± 0.32	0.102
Stent length (mm)	22 ± 10	21 ± 12	0.612
Stents/lesion	1.6 ± 0.9	1.5 ± 1	0.598
Acute gain (mm)	2.0 ± 0.6	2.1 ± 0.5	0.416
Late loss (mm)	0.82 ± 0.4	0.90 ± 0.6	0.328
Ultravist 370 (mL)	113 ± 27	115 ± 26	0.968

* ACC/AHA

at the dose required to maintain the activated clotting time above 300 seconds throughout the procedure. Catheter-related parameters are presented in Table I.

Qualitative and quantitative assessment: Two expert angiographers who were unaware of the clinical and analytic data of the patients independently reviewed an end-diastolic frame of the vessel segment. Angiographic lesion morphology before coronary angioplasty was categorized according to the scheme of the American College of Cardiology/American Heart Association Task Force classification.⁵⁾ Minimal luminal diameter, percent of diameter stenosis, acute gain, and balloon/vessel ratios were assessed by computerized quantitative angiography. Procedural angiograms were also analyzed for Thrombolysis in Myocardial Infarction (TIMI) flow grade,⁶⁾ coronary angioplasty was considered successful if the final percent diameter stenosis was less than 30% with TIMI 3 flow in the absence of death, recurrent ischemia, MI (creatinine kinase increase to more than twice the upper limit of normal with or without evidence of new Q waves), or urgent coronary artery bypass graft (CABG) during the hospital period.

Definition of cardiac events: The following clinical events occurring within 3-12 months after the procedure were considered to be cardiac events:

1) Acute myocardial infarction diagnosed based on continuous chest pain lasting more than 30 minutes and new Q wave recurrence $\geq$ two ECG leads plus an increase in creatine kinase $\geq$ twice the upper limit of normal with a concomitant rise in the MB isoenzyme or a positive troponin T test, 2) cardiac sudden death, and 3) target vessel revascularization (TVR).

Definition of restenosis: Either of the following occurred, 1) recurrence of ischemia (angina with ST segment reversible changes $\geq$ 0.1 mv in at least two contiguous ECG leads in the area of a PCI related vessel or 2) luminal diameter loss of target vessel $\geq$ 50% of the acute minimal lumen diameter by angiography.

Follow up: After the procedure, creatine kinase was measured every 24 hours and electrocardiograms (ECG) were recorded daily for 7 days. All patients were given ticlopidine (250 mg to 500 mg per day) and aspirin (150 mg/day) for four weeks. Repeat coronary angiography was conducted in 88.8% (119/134) of the patients (patients with clinical evidence of restenosis, otherwise, all patients at one year after PCI).

Statistical analysis: Data are expressed as the mean $\pm$ standard deviation for continuous variables and were compared using Student's *t* test. IL-8 and CRP exhibited a nonnormal distribution and are presented as median and tertile. The data were compared using the Mann-Whitney *U* test. Categorical variables were compared by the Fisher exact test or chi-square statistics. Logistic regression analysis was performed to determine predictors of early complications. The chi-square model was used to test the significance of the coefficients for all the terms in the model. To verify whether the model fit the data well, the Hosmer-Lemeshow

Goodness-of-Fit statistics were computed. Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS 10.0 for Windows, SPSS Inc, Illinois). A P value < 0.05 was considered statistically significant.

RESULTS

The baseline clinical characteristics, angiographic findings, and procedural variables in both the cardiac events group and noncardiac events group are summarized in Table I.

Cardiac events and restenosis: Cardiac events were observed in 32 of the 134 study group patients (23.88%), and the cardiac event rate was similar in patients with stable or unstable angina (14/65, 21.53% vs 18/69, 26.09%, $P = 0.340$). After coronary angioplasty, the plasma IL-8 level had increased at 4 hours, reached a peak (150.24 ± 36.12 pg/mL) at 12 hours, and then tended to decrease to the preprocedural level by 24 hours. The preprocedural concentrations, peak levels, and follow-up levels of plasma IL-8 in the cardiac event group were significantly higher than those in the noncardiac event group. The serum level of CRP increased to a peak level of 9.24 ± 3.17 mg/L at 48 hours after PCI. A trend similar to that of IL-8 was observed for serum CRP (Table II). An increasing incidence of cardiac events was observed from 6.67% (3/45) in tertile I to 31.82% (14/44) in tertile III of IL-8 in the 3-6 month follow-up period. During 6-12 months follow-up, all patients with a myocardial infarction and TVR were in the higher level of IL-8 group (Table III).

The incidence of restenosis determined by angiography was 29.41% (35/119) and only 65.71% (23/35) of them had clinical symptoms of ischemia. The restenosis rate was 10%, 27.5%, and 51.28%, respectively, in three tertiles of pre-procedure levels of IL-8 ($P = 0.012$). A similar trend was observed for percent of

Table II. Parameters of Pre-PCI, Peak Level and Follow-up at 6-Month in Patients With or Without Cardiac Events After PCI.

	Noncardiac events ($n = 102$)	Cardiac events ($n = 32$)	P
IL-8 (pg/mL)			
Pre-PCI	65.13 ± 41.02	90.81 ± 20.30	0.002
Peak level	134.42 ± 35.92	200.06 ± 32.14	0.026
6-Months follow-up	68.11 ± 32.56	112.98 ± 30.21	0.001
CRP (mg/L)			
Pre-PCI	2.71 ± 2.78	5.04 ± 3.86	0.001
Peak level	8.16 ± 2.67	12.64 ± 3.52	0.001
6-Months follow-up	3.42 ± 2.62	8.41 ± 2.94	0.002

Table III. Cardiac Events at 6-12 Month Follow-up in Patients According to Tertile of IL-8

	IL-8 (<152.86) (<i>n</i> = 45)	IL-8 (152.86-234.89) (<i>n</i> = 45)	IL-8 (> 234.89) (<i>n</i> = 44)	<i>P</i>
3-6 months follow-up				
Myocardial infarction, <i>n</i> (%)	1	1	3	0.001
Target vessel revascularization, <i>n</i> (%)	2	5	10	
Sudden cardiac death, <i>n</i> (%)	0	0	0	
Total, <i>n</i> (%)	3 (6.67)	6 (13.33)	14 (31.82)	
6-12 months follow-up				
Myocardial infarction, <i>n</i> (%)	0	0	1	0.001
Target vessel revascularization, <i>n</i> (%)	0	1	6	
Sudden cardiac death, <i>n</i> (%)	0	0	1	
Total, <i>n</i> (%)	0	1 (2.22)	8 (18.18)	

Table IV. Follow-up Quantitative Angiographic Analyses

Follow-up (<i>n</i> = 119)	IL-8 (< 155.2) (<i>n</i> = 40)	IL-8 (155.2-235.15) (<i>n</i> = 40)	IL-8 (> 235.15) (<i>n</i> = 39)	<i>P</i>
Reference diameter (mm)	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	0.500
Minimal lumen diameter (mm)	1.96 ± 0.7	1.74 ± 0.6	1.68 ± 0.7	0.613
Percent stenosis (%)	33 ± 20	44 ± 21	44 ± 25	0.032
Late loss (mm)	0.45 ± 0.6	0.82 ± 0.7	1.21 ± 0.7	0.014
Restenosis rate (%)	4 (10)	11 (27.5)	20 (51.28)	0.012

stenosis and later lumen diameter loss during the angiographic follow-up (Table IV).

Predictors of cardiac events and restenosis: The preprocedural level, peak levels of IL-8 and CRP, hypertension, diabetes, high TC and LDL-c levels, and length of the stent were found to be associated with a higher risk of cardiac events by univariate regression analysis. However, the preprocedural levels of IL-8 ($RR = 5.539$, $CI = 1.720-17.887$, $P = 0.001$) and CRP ($RR = 2.031$, $CI = 1.132-2.049$, $P = 0.003$) were the only independent predictors of cardiac events in the multivariate regression analysis (Table V). The risk predicted by our logistic regression model was closely correlated with cardiac events (correct classification in 80%; Hosmer-Lemeshow Goodness-of-Fit, $P = 0.892$).

The preprocedural and peak levels of IL-8, preprocedural level of CRP, cigarette smoking, diabetes, type C lesion, and stent length were found to be associated with a higher risk of restenosis by univariate regression analysis. However, the peak levels of IL-8 ($RR = 3.766$, $CI = 2.990-5.904$, $P = 0.002$) and stent length ($RR = 1.468$, $CI = 1.161-2.022$, $P = 0.021$) were the only independent predictors of restenosis in the multivariate regression analysis (Table VI). The risk predicted

Table V. Logistic Regression Analysis for Cardiac Events

	Univariate Relative Risk (95% CI)	<i>P</i>	Multivariate Relative Risk (95% CI)	<i>P</i>
Age	0.924 (0.276-2.338)	0.425		
Female gender	0.811 (0.548-0.953)	0.512		
Diabetes	0.448 (0.167-1.174)	0.041		
Hypertension	1.132 (0.460-2.689)	0.017		
Cigarette smoking	1.643 (0.682-4.010)	0.269		
UAP	0.756 (0.310-1.875)	0.549		
Type A lesion	1.598 (0.489-5.208)	0.438		
Type B lesion	1.919 (0.569-6.445)	0.304		
Type C lesion	1.970 (1.379-2.448)	0.939		
TC	0.979 (0.935-1.064)	0.043		
LDL-C	0.459 (0.308-1.121)	0.020		
Stent length	1.099 (1.008-1.216)	0.019		
IL-8 (peak level)	3.025 (3.016-3.038)	0.001	5.539 (1.720-17.887)	0.001
CRP (peak level)	1.362 (1.165-1.534)	0.033		
IL-8 (pre-PCI)	1.528 (1.110-2.237)	0.048		
CRP (pre-PCI)	1.669 (1.240-2.271)	0.001	2.031 (1.132-2.049)	0.003

Table VI. Logistic Regression Analyses for Restenosis

	Univariate Relative Risk (95% CI)	<i>P</i>	Multivariate Relative Risk (95% CI)	<i>P</i>
Age	1.010 (0.929-1.083)	0.939		
Female gender	1.278 (0.449-4.252)	0.602		
Diabetes	9.573 (3.052-29.587)	0.001		
Hypertension	0.711 (0.190-1.879)	0.502		
Cigarette smoking	15.388 (3.301-71.903)	0.001		
UAP	1.236 (0.474-3.305)	0.675		
Type A lesion	1.669 (1.228-2.202)	0.363		
Type B lesion	1.529 (1.132-2.420)	0.422		
Type C lesion	38.031 (8.288-173.4)	0.001		
Stent length	1.382 (1.209-1.567)	0.001	1.468 (1.161-2.022)	0.021
Reference diameter	0.323 (0.124-0.883)	0.030		
TC	1.008 (0.952-1.061)	0.577		
LDL-C	0.964 (0.931-1.032)	0.359		
IL-8 (peak level)	3.047 (3.034-3.081)	0.001	3.766 (2.990-5.904)	0.002
CRP (peak level)	1.022 (0.906-1.136)	0.791		
IL-8 (pre-PCI)	1.975 (1.209-3.162)	0.003		
CRP (pre-PCI)	1.937 (1.528-2.761)	0.041		

with our logistic regression model correlated well with restenosis (correct classification in 80%; Hosmer-Lemeshow Goodness-of-Fit, $P = 0.883$).

The Cox proportional-hazard model was used to evaluate the timing of cardiac events and restenosis at follow-up; IL-8 was the most powerful independent predictor of restenosis and cardiac events at 12-months follow-up (Figure).

Figure. Event-free survival from major adverse cardiac events (panel A) and from clinical restenosis (panel B) at one year by peak levels of IL-8 after procedure (multivariate Cox regression analysis). Among all clinical, angiographic, and clinical procedural variables considered, elevated IL-8 levels were the most powerful independent predictor of major adverse cardiac events ($RR = 3.031$, $CI = 3.018$ - 3.044 , $P = 0.002$) and of clinical restenosis ($RR = 2.587$, $CI = 2.465$ - 3.323 , $P = 0.003$). I tertile (*), II tertile (▲) and III tertile (●) of IL-8 peak levels.

DISCUSSION

The results of this study extend our previous observations and further reveal that elevated preprocedural levels and high peak levels of IL-8 are associated with enhanced restenosis development after coronary stent implantation. Most importantly, the increased restenosis and cardiac event rate with high levels of IL-8 are accompanied by a worse event-free survival.

The novel findings of the present study were that the plasma levels of CRP have been shown to be a powerful predictor of early and late clinical outcome.⁷⁾ In addition, in patients with stable angina and one-vessel disease, normalization of CRP plasma levels after coronary stenting identified patients who do not develop cardiovascular events. In line with a previous study in patients undergoing PCI,⁸⁾ in our population, high preprocedural levels of CRP were found to indicate a low risk for cardiac events and restenosis by logistic multivariate regression analysis. CRP, as a result of system inflammatory responses, produced by liver cells, cannot play a role in the inflammatory responses of a local lesion related to the coronary vessels; therefore it has a low predictive value for cardiac events and restenosis after PCI.

One of our previous studies³⁾ revealed that IL-8 concentrations showed a remarkable increase in the unstable angina group pre- and post-PCI. A sizable cardiac release of IL-8, however, occurs after recanalization of the stenosis vessel even in patients with stable angina who had a normal level of IL-8 before PCI. It demonstrated that the occurrence of early complications correlated with the high

plasma levels of IL-8, and the incidence of early complications increased with the tertiles of IL-8, it was strongly suggested that there was a powerful relation between early complications and inflammatory responses existed in the target vessels. This study further demonstrates that patients with elevated preprocedural IL-8 levels are associated with a high incidence of cardiac events and restenosis. The higher the peak levels of IL-8 after PCI, the more enhanced was the occurrence of the restenosis and cardiac events. This study further reveals that the inflammatory responses present in the atherosclerosis plaque may be a primary factor, which were further evoked by the PCI procedure, and that the level of IL-8 may play a pivotal role in the progress of inflammation in patients with cardiac events and restenosis after PCI.⁹⁾ This possibility is supported by experimental and clinical studies showing that the release of IL-8 results in an interaction of endothelium cells and neutrophils and platelets.¹⁰⁾ Meanwhile, IL-8 evokes an increased surface expression of CD11b/CD18 on neutrophils, which directly activate coagulation factor X and switch on the cascade of the coagulation system.¹¹⁾ On the other hand, it has been shown that endothelium cell injury by inflammatory cell infiltration after PCI provokes the proliferation of endothelium cells.^{12,13)}

Study limitations: The negative predictive value of preprocedural levels of plasma IL-8 in this study need to be considered cautiously due to the relatively small number of patients divided into the subgroup with cardiac events and restenosis. Thus, the prognostic value of the marker, if confirmed in larger clinical studies, could contribute to optimizing therapeutic resources in the complex scenario of restenosis following PCI. Furthermore, since plasma levels of IL-8 in peripheral blood but not in the coronary circulation were examined, the specificity of the factor on restenosis needs to be further studied. However, as discussed above, we and others have demonstrated the importance of these values for evaluating the contribution of inflammatory changes in patients following PCI.^{3,4,14)}

Conclusions: Our study shows that preprocedure plasma levels and peak levels of IL-8 provide a more powerful predictor of cardiac events and restenosis than other factors considered thus far in patients with PCI. Low preprocedural IL-8 levels may help identify patients with a good outcome who did not require additional treatment after PCI. Therefore, for better resource administration in interventional cardiology and until specific causes of restenosis are identified, complex and expensive therapeutic tools, such as drug-eluting stents, may be reserved for patients with high levels of IL-8 who are at the highest risk of restenosis.

ACKNOWLEDGMENT

The study was supported by a grant from Hebei Provincial Natural Science Foundation (No 301417).

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