Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Cardiovascular Intervention

High Plasma Interleukin-6 Is Associated With Drug-Eluting Stent Thrombosis

– Possible Role of Inflammatory Cytokines in the Development of Stent Thrombosis From the Korea Stent Thrombosis Registry –

Seok-Jae Hwang, MD, PhD; Kyung Woo Park, MD, PhD; Dong-A Kwon, MD; Hyun-Jae Kang, MD, PhD; Bon-Kwon Koo, MD, PhD; In-Ho Chae, MD, PhD; Hyeon-Cheol Gwon, MD, PhD; Seung-Jung Park, MD, PhD; Ki Bae Seung, MD, PhD; Taehoon Ahn, MD, PhD; Jung-Han Yoon, MD, PhD; Yang-Soo Jang, MD, PhD; Myung-Ho Jeong, MD, PhD; Seung-Jea Tahk, MD, PhD; Hyo-Soo Kim, MD, PhD
on behalf of the Korea Stent Thrombosis Investigators

Background: Inflammation might contribute to the development of stent thrombosis (ST). The association between inflammatory cytokine concentrations and drug-eluting ST were evaluated.

Methods and Results: Among the 123 ST patients enrolled in the multicenter Korea Stent Thrombosis registry, plasma samples were available in 41 patients. The patients' clinical characteristics and plasma concentrations of monocyte chemoattractant protein-1, tumor necrosis factor-alpha, and interleukin (IL)-6 were compared with 81 matched controls. Although the concentrations of 3 cytokines were higher in the ST group, they did not have significant differences. When divided into quartiles, the proportion of patients with the highest quartile of IL-6 was higher in the ST group than in the control group (44% vs. 16%, P=0.001), and the highest IL-6 quartile was an independent predictor of ST for both early (adjusted hazard ratio [HR] 6.96; 95% confidence interval [CI] 1.75–27.66) and late ST (adjusted HR 4.71; 95%CI 1.06–20.92). In addition, the highest IL-6 quartile was an independent predictor of ST in those on clopidogrel (adjusted HR 7.70; 95%CI 1.97–30.13) but not in those who were off clopidogrel.

Conclusions: Highest IL-6 quartile was associated with ST, especially in clopidogrel users regardless of the time of ST, suggesting the involvement of inflammatory cytokines in ST. (*Circ J* 2011; **75:** 1350–1357)

Key Words: Drug-eluting stent (DES); Interleukins; Thrombosis

Stent thrombosis (ST) is one of the most serious complications of percutaneous coronary intervention (PCI). Although the equivocal short- and mid-term safety of drug-eluting stents (DES) compared with bare metal stents has been shown in several studies,[1–4] long-term safety concerns regarding DES are yet to be completely resolved, considering the steady annual occurrence rate of DES thrombosis, which has been reported to be 0.4–0.6% per year up to 4 years.[5] Some clinical predictors of DES thrombosis have been reported, including acute coronary syndrome, diabetes, decreased left ventricular systolic function, and early termination of antiplatelet agents.[6] However, the association of biochemical markers with ST has not been previously studied. Accumulating literature points to the role of chemokines and cytokines, normally involved in inflammation, in thrombogenesis.[7] Tumor necrosis factor (TNF)-α is capable of inducing tissue factor (TF) expression in monocytes, endothelial cells, and vascular smooth muscle cells.[8] Interleukin (IL)-6 and monocyte chemoattractant protein (MCP)-1 have been reported to be independent predictors of long-term risk of

Received June 6, 2010; revised manuscript received December 22, 2010; accepted January 24, 2011; released online April 18, 2011
Time for primary review: 15 days

Cardiovascular Center, Seoul National University Main Hospital, Seoul (S.-J.H., K.W.P., D.-A.K., H.-J.K., B.-K.K., H.-S.K.); Bundang Hospital, Sungnam (I.-H.C.); Gyeongsang National University Hospital, Jinjoo (S.-J.H.); Samsung Medical Center, Seoul (H.-C.G.); Asan Medical Center, Seoul (S.-J.P.); The Catholic University St. Mary's Hospital, Seoul (K.B.S.); Gachon University Gil Medical Center, Incheon (T.A.); Wonju Christian Hospital, Wonju (J.-H.Y.); Yonsei University Severance Hospital, Seoul (Y.-S.J.); Chonnam National University Hospital, Gwangju (M.-H.J.); and Ajou University Medical Center, Suwon (S.-J.T.), Korea
The first two authors contributed equally (S.-J.H., K.W.P.).
Mailing address: Hyo-Soo Kim, MD, PhD, Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, 28 Yongon-dong Chongno-gu, Seoul 110-744, Korea. E-mail: hyosoo@snu.ac.kr

ISSN-1346-9843 doi:10.1253/circj.CJ-10-0488

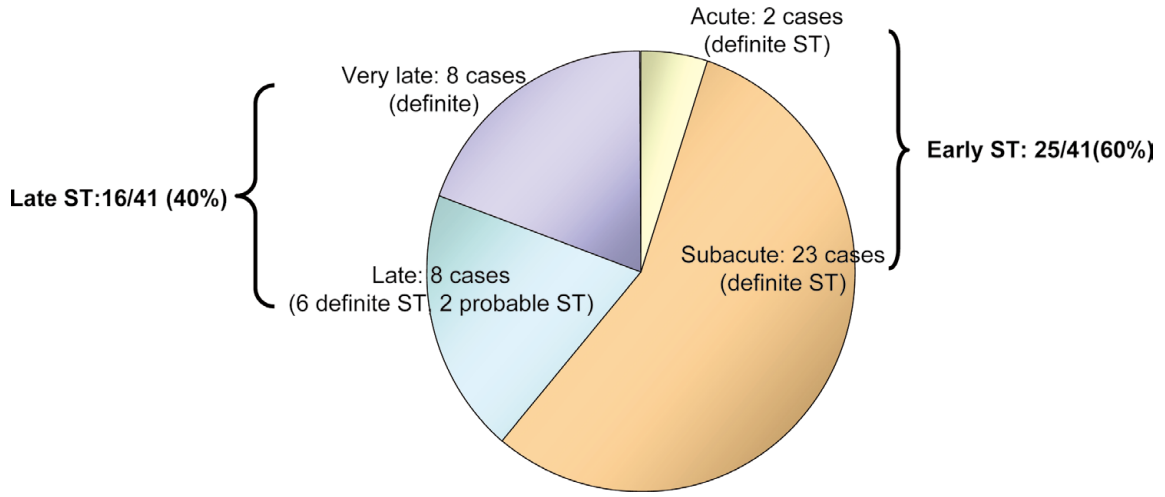

Figure 1. Category of stent thrombosis (ST) according to the time period and Academic Research Consortium (ARC) definition. Among the 41 ST cases analyzed in the present study, 60% (25 cases) were early ST cases and 40% (16 cases) were delayed ST cases. Eight cases of delayed ST were very late ST and 2 cases of late ST were probable ST.

death or heart failure in acute coronary syndrome.[9] In the present study we sought to evaluate the possible association between plasma concentrations of inflammatory cytokines and the development of DES thrombosis.

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Methods

Study Population: Patients With ST vs. the Matched Control

The Korean Stent Thrombosis (KoST) registry was a multicenter effort of 10 cardiovascular centers in Korea, where we collected the data of consecutive ST patients who underwent DES implantation from May 2003 to May 2007. The Academic Research Consortium (ARC) definition of ST was used,[10] and the ARC definite, probable, and possible ST were considered as ST. Acute and subacute ST cases were categorized as early ST, while those that occurred 30 days or more after stent implantation were categorized as delayed ST. A total of 124 ST cases that occurred in 123 patients were enrolled in the registry. Of these patients, plasma samples were available in 41 patients. All information was sent to a core center and the clinical, angiographic, and procedural characteristics of the ST patients were compared with the control group of 81 patients who had a clinical follow-up period of at least 6 months without ST and were matched for the following variables: age, sex, initial clinical manifestation of coronary artery disease, and stent type. Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg or diastolic BP ≥90 mmHg, or current use of antihypertensive treatment. Dyslipidemia was defined as serum total cholesterol ≥6.2 mmol/L or current use of lipid-lowering drugs. The Institutional Review Board of each participating center approved the study protocol, and the patients provided written informed consent for participation.

Blood Sample Collection

To elucidate whether the underlying condition of certain elevated biomarkers related to inflammation might be associated with the development of ST and to avoid conditions that might interfere with the baseline concentrations of biomarkers, blood samples were collected when the patients were in a stable condition in both groups, at least 3 months after the index procedure in the control group, and at least 3 months after development of ST in the ST group. Venous blood samples were obtained and immediately centrifuged at 3,000 g for 20 min at 4°C. The plasma component was then separated and sent on dry ice to the core lab (Cardiovascular Laboratory, Seoul National University Hospital) where samples were stored at –70°C in small aliquots.

Plasma Cytokine Analysis by Luminex Technology

The Luminex 100 system (Luminex Corp, Austin, TX, USA) along with the Lincoplex Kit (Linco Research, St Charles, MO, USA) was used to evaluate the serum concentration of IL-6, MCP-1, and TNF-α from a total of 41 ST patients (25 early ST and 16 late ST) and 81 non-ST patients. The assays were performed in duplicate. Briefly, 25 μl of diluent and 25 μl of serum were added to each well. Mixed micro-beads (25 μl) were then added. The plate was incubated and agitated for 1 h, washed and re-incubated with 25 μl of detection antibody for 30 min. The plate was washed again and incubated with 25 μl of Streptavidin-Phycoerythrin for 30 min. The plate was then washed twice and the beads were re-suspended in the plate with 100 μl sheath fluid and analyzed using the Luminex 100 system. The readout for the concentration of each cytokine was detected as the mean fluorescence intensity (MFI) by the instrument. These values were subsequently converted to pg/ml of cytokine based on the MFI values from a set of standards that were run simultaneously in the assay.

Statistical Analysis

All analyses were performed with the SPSS 12.0 software (Chicago, IL, USA). Because the IL-6, TNF-α, and MCP-1 concentrations were not normally distributed, comparisons between groups were carried out with the non-parametric Mann–Whitney tests. Univariate comparisons for equality

Table 1. Baseline Characteristics of the Study Population

	ST patients group (n=41)	Control patients group (n=81)	P value
Age (years)	57±10	57±10	1.000
Male gender	34 (83%)	68 (84%)	1.000
Hypertension	15 (37%)	41 (51%)	0.179
Diabetes	11 (27%)	19 (24%)	0.824
Current smoking	30 (73%)	55 (68%)	0.677
Hypercholesterolemia	10 (24%)	27 (33%)	0.405
GFR	86.27±32.19	81.48±18.21	0.381
Stable angina	8 (20%)	20 (24%)	0.650
Unstable angina	14 (34%)	24 (30%)	0.680
AMI	19 (46%)	37 (46%)	1.000
LV ejection fraction (%)	52±14	55±11	0.185
Total cholesterol (mg/dl)	184±55	184±41	0.984
ARB	8 (19.5%)	22 (27.2%)	0.384
Statin	28 (68.3%)	46 (56.1%)	0.169
Target vessel			
Left anterior descending artery	24 (59%)	34 (42%)	0.322
Left circumflex artery	9 (22%)	20 (25%)	
Right coronary artery	6 (15%)	22 (27%)	
Left main artery	2 (5%)	5 (6%)	
Multivessel disease	20 (49%)	44 (54%)	0.572
BMS ISR lesion	3 (7%)	4 (5%)	0.686
AHA/ACC lesion type B2/C	29 (71%)	56 (69%)	1.000
Total number of stents per patient	1.34±0.66	1.22±0.47	0.305
Stent diameter (mm)	2.97±0.33	3.03±0.34	0.327
Total stent length (mm)	37.1±21.8	32.5±14.8	0.232
Bifurcation intervention	4 (10%)	4 (5%)	0.440
Paclitaxel eluting stent	20 (49%)	30 (37%)	0.245

ST, stent thrombosis; GFR, estimated glomeular filtration rate by MDRD (Modification of Diet in Renal Disease) formula; AMI, acute myocardial infarction; LV, left ventricular; ARB, angiotensin type I receptor blocker; BMS ISR lesion, bare metal stent instent restenosis lesion.

of proportions were tested using the chi-square test. Binary logistic regression was used to adjust for baseline variables known to be associated with ST, including age, gender, hypertension, diabetes, renal insufficiency (serum creatinine >1.4 mg/dl), index diagnosis of acute myocardial infarction, stent length, stent diameter, and bare metal stent restenosis lesion. All P-values were 2-sided and values <0.05 were considered statistically significant.

Results

Baseline Characteristics

Among the 41 ST cases analyzed in the present study, 60% (25 cases) were early ST cases and 40% (16 cases) were delayed ST cases (Figure 1). Eight cases of delayed ST were very late ST and 2 cases of late ST were probable ST. Table 1 shows the baseline characteristics of the study populations, 41 ST patients vs. the control group of 81 patients who had a clinical follow-up period of at least 6 months without ST and were matched for the following variables: age, sex, initial clinical manifestation of coronary artery disease, and stent type. The 2 groups were mostly comparable regarding the baseline characteristics. Clinical characteristics including age, sex, major coronary risk factors including diabetes and the proportion of acute myocardial infarction and renal insufficiency were not different between the 2 groups. The use of medications known to decrease inflammatory activity, such as angiotension receptor blockers and statins, were not different between the 2 groups. There were also no significant differences in lesion and procedural characteristics.

Plasma Concentrations of Inflammatory Cytokines and DES Thrombosis

Because the MCP-1, TNF-α, and IL-6 concentrations were not normally distributed, comparisons between groups were carried out with the non-parametric Mann–Whitney test. The measurements of MCP-1, TNF-α, and IL-6 are shown in Figures 2A–C, and the relative distribution of ST and control patients according to the quartile of each cytokine is shown in Figures 2D–F. Due to the wide variability in values and the small samples size, the differences in mean values did not reach statistical significance. However, the concentrations in all 3 cytokines were higher in the ST group, and IL-6 showed a rather large difference between the 2 groups. To analyze whether there was a difference in the distribution of patients with high concentrations of the pro-inflammatory cytokines, we divided the patients according to the quartiles of the measured cytokines from the entire study population and calculated the percentage of patients from the 2 groups in each quartile (Figures 2D–F). In contrast to MCP-1 and TNF-α, where there were no significant differences in the distribution of patients from the 2 groups in each quartile, there was a difference in distribution in IL-6. In the ST group, the proportion of patients in the highest IL-6 quartile was

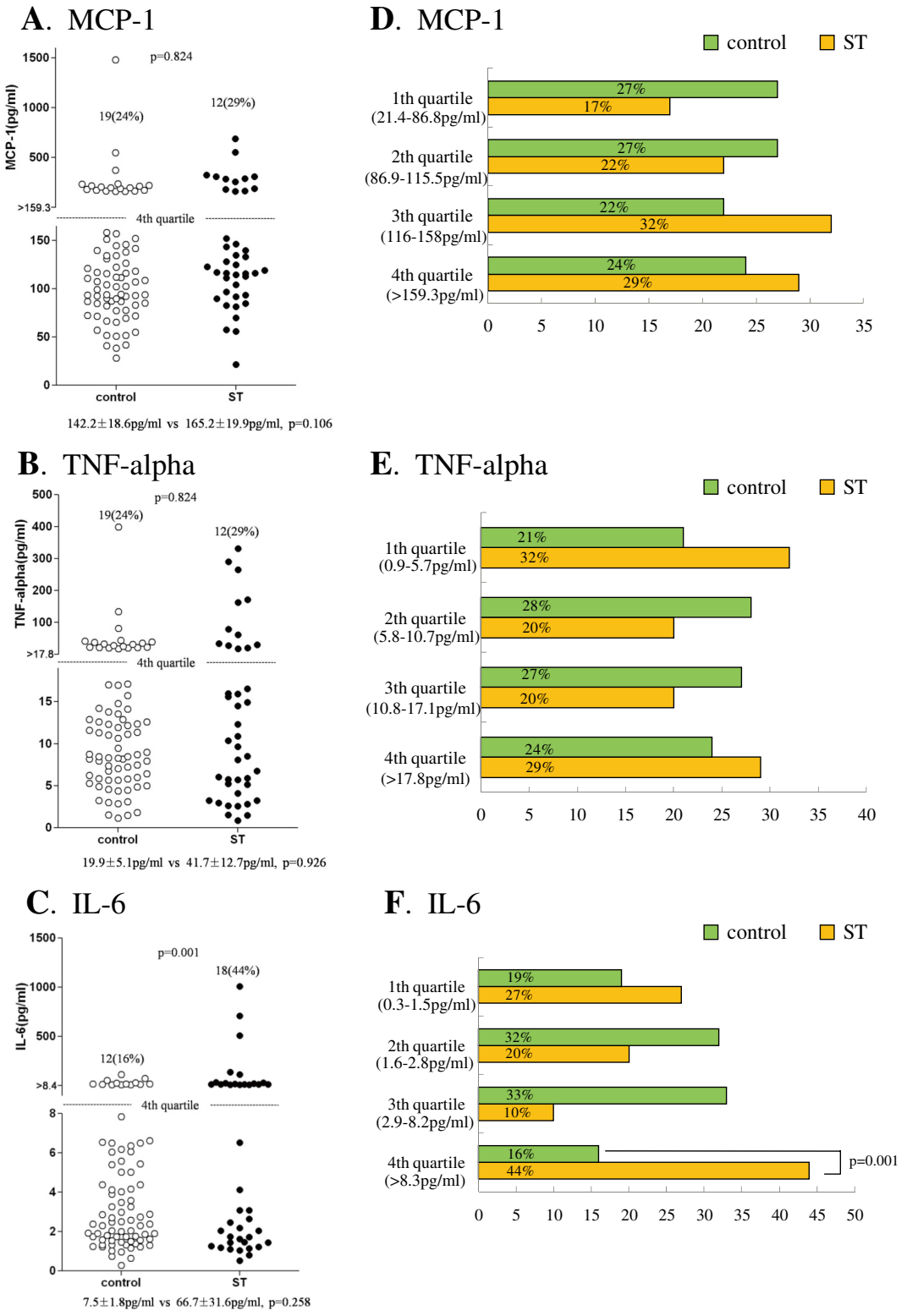

Figure 2. Inflammatory cytokine concentrations in stent thrombosis (ST) and control patients. **A**–**C** show the distribution of inflammatory cytokine concentrations of individual patients with the mean value. The differences in the mean concentrations of all 3 inflammatory cytokines were not significant, although the levels were numerically higher in the ST group. However, the difference between the 2 groups was rather large in the levels of interleukin (IL)-6. **D**–**F** show the relative quartile distribution of patients in the ST and control groups. The proportion of patients with the highest monocyte chemoattractant protein (MCP)-1 or tumor necrosis factor (TNF)-α quartile was not significantly different between the ST and the controls. However, the proportion of patients with the highest IL-6 quartile was significantly greater in the ST group compared with the controls (44% vs. 16%, P=0.001).

Table 2. Independent Predictors of ST in the Entire Study Population

	Total ST
Age (per 1 year increase)	0.98 (0.93–1.02)
Male	1.27 (0.38–4.29)
AMI	0.99 (0.41–2.43)
Hypertension	0.50 (0.21–1.21)
Diabetes	0.99 (0.34–2.87)
Renal insufficiency	2.55 (0.39–16.49)
BMS ISR	1.96 (0.33–11.51)
Stent length (per 1 mm increase)	1.02 (0.99–1.04)
Stent diameter (per 1 mm decrease)	2.78 (0.64–12.50)
IL-6 quartile 4	5.92 (2.22–15.7)

IL, interleukin. Other abbreviations see in Table 1.

significantly higher than in the control group (44% vs. 16%, P=0.001). In a multivariate analysis adjusted for conventional risk factors of ST (age, male gender, hypertension, diabetes, renal insufficiency [serum creatinine >1.4 mg/dl], index diagnosis of acute myocardial infarction, stent length, stent diameter and bare metal stent restenosis lesion), the highest quartile of IL-6 was an independent predictor of DES thrombosis (hazard ratio 5.92; 95% confidence interval [CI] 2.22–15.7, P<0.001) (Table 2). In addition, it showed the highest hazard ratio of all of the variables analyzed.

Highest Quartile of IL-6 as a Risk Factor for DES Thrombosis According to Timing of ST or Use of Clopidogrel

To find out whether the highest quartile of IL-6 could act as an independent predictor of ST in both early and delayed ST, we analyzed the association between ST and IL-6 quartile 4 according to the time period of ST. We found that it was a predictor of ST regardless of the time of presentation (Figure 3, Table 3). Because premature discontinuation of clopidogrel therapy is a profound risk factor for the development of ST, we investigated whether the highest quartile of IL-6 was associated with ST regardless of clopidogrel use. Among the ST patients who were on clopidogrel at the time of ST development, the proportion of ST patients in the highest IL-6 quartile was significantly higher than in the control patients (44% vs. 13%, adjusted hazard ratio 7.70; 95%CI 1.97–30.13, P=0.003) (Figure 4, Table 4). However, among the ST patients who were off clopidogrel at the time of ST, the proportion of patients with the highest quartile of IL-6 was slightly higher in the ST vs. non-ST group, but this did not reach statistical significance (43% vs. 18%, adjusted hazard ratio 4.22; 95%CI 0.86–20.79, P=0.077).

Discussion

This is the first study to show a positive association between elevated concentrations of IL-6, a marker of inflammation, and DES thrombosis. There was a strong preponderance for patients with the highest quartile of IL-6 to experience ST

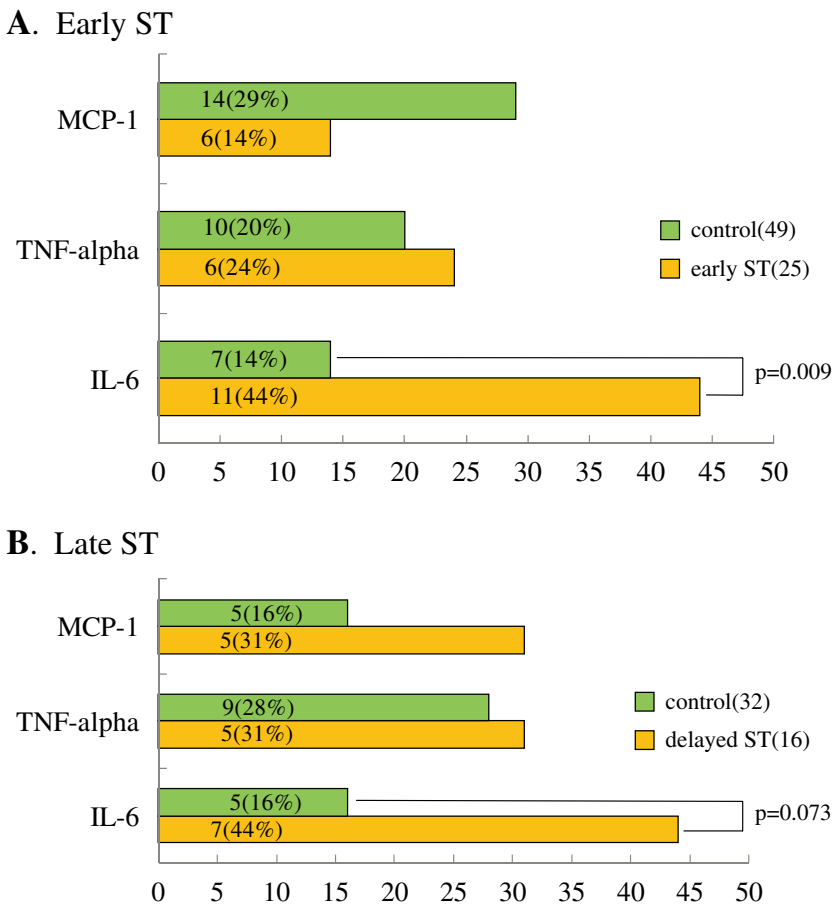

Figure 3. The proportion of patients with the highest quartile of each biomarker according to early or delayed stent thrombosis (ST). (**A**) The proportion of early ST patients in the highest interleukin (IL)-6 quartile was greater than that of the control (44% vs. 14%, P=0.009). (**B**) The proportion of delayed ST patients in the highest IL-6 quartile was marginally greater than that of the control patients. MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor.

Table 3. Independent Predictors of ST According to the Timing of Occurrence

	Early ST	Late ST
Age (per 1 year increase)	0.97 (0.90–1.04)	0.97 (0.90–1.06)
Male	1.94 (0.40–9.54)	0.73 (0.07–7.49)
AMI	0.77 (0.37–3.73)	1.09 (0.22–5.44)
Hypertension	0.40 (0.18–1.98)	0.72 (0.14–3.84)
Diabetes	0.46 (0.42–6.91)	0.56 (0.08–3.72)
Renal insufficiency	9.17 (0.44–190.84)	1.26 (0.06–26.99)
BMS ISR	1.25 (0.08–20.75)	2.58 (0.18–36.85)
Stent length (per 1 mm increase)	1.00 (0.97–1.04)	1.03 (0.99–1.08)
Stent diameter (per 1 mm decrease)	2.33 (0.36–14.29)	4.00 (0.29–50)
IL-6 quartile 4	6.96 (1.75–27.66)	4.71 (1.06–20.92)

Abbreviations see in Tables 1,2.

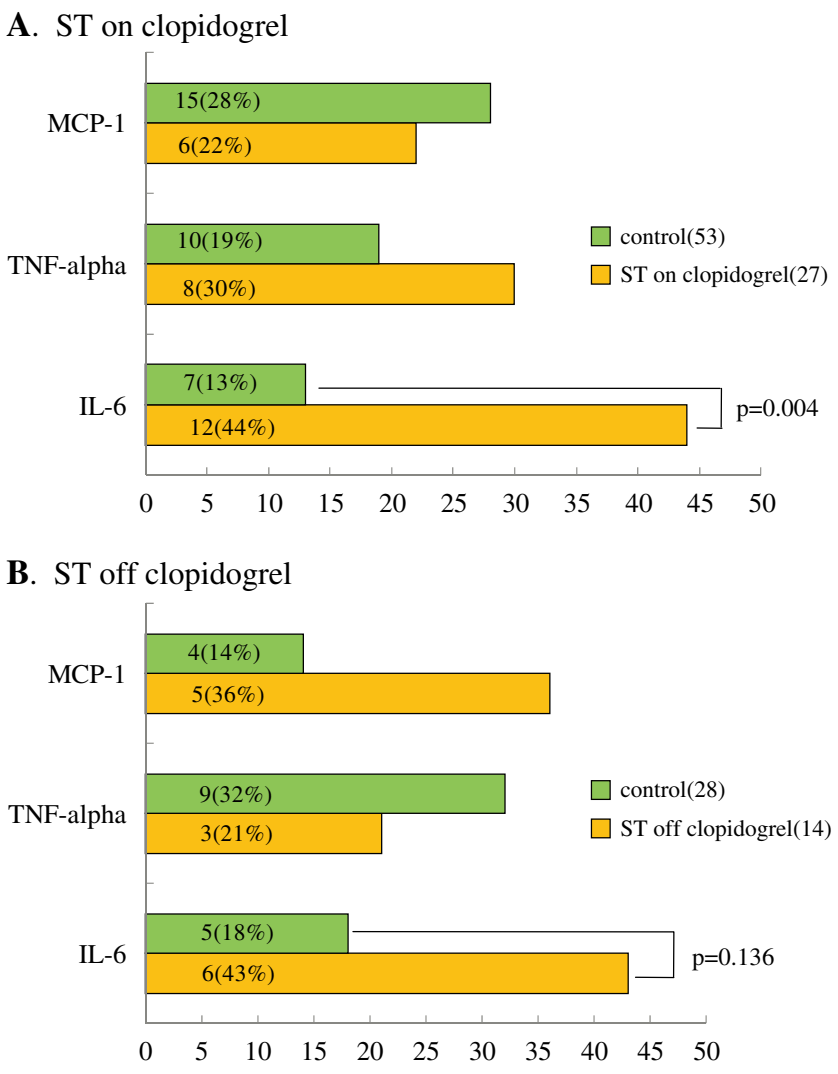

Figure 4. The proportion of patients with the highest quartile of each biomarker according to clopidogrel coverage. (**A**) The proportion of stent thrombosis (ST) patients who were on clopidogrel in the highest interleukin (IL)-6 quartile was greater than that of the control patients. (**B**) The proportion of ST patients off clopidogrel in the highest quartile of IL-6 was not significantly greater than that of the control group. MCP, monocyte chemoattractant protein; TNF, tumor necrosis factor.

and the highest quartile of IL-6 was an independent predictor of ST. Such association between high IL-6 and ST was stronger in users of clopidogrel than in non-users of clopidogrel at the time of ST occurrence. These results suggest that an increased level of inflammation could play a crucial role in the development of ST, even in patients on potent antiplatelet agents such as clopidogrel.

Pro-Inflammatory Status as a Potential Milieu for ST

The precise pathophysiology of DES thrombosis has not been clearly explained. Some aspects inherent to DES, such as delayed re-endothelialization,[11–14] marked endothelial dys-

Table 4. Independent Predictors of ST According to the Use of Clopidogrel at Occurrence

	ST with clopidogrel	ST without clopidogrel
Age (per 1 year increase)	0.97 (0.90–1.04)	0.98 (0.90–1.06)
Male	3.60 (0.35–37.20)	1.13 (0.10–12.79)
AMI	1.25 (0.40–3.90)	0.68 (0.13–3.61)
Hypertension	0.78 (0.25–2.48)	0.32 (0.05–2.20)
Diabetes	1.77 (0.44–7.10)	0.61 (0.09–4.12)
Renal insufficiency	14.61 (0.61–347.44)	1.51 (0.06–37.77)
BMS ISR	2.92 (0.30–28.91)	1.06 (0.05–24.01)
Stent length (per 1 mm increase)	1.00 (0.97–1.04)	1.02 (0.98–1.07)
Stent diameter (per 1 mm decrease)	2.22 (0.36–12.5)	4.00 (0.23–100)
IL-6 quartile 4	7.70 (1.97–30.13)	4.22 (0.86–20.79)

Abbreviations see in Tables 1,2.

function,[15] and increased TF expression by rapamycin or paclitaxel have been postulated as possible causes of ST.[16,17] Although the strongest patient-related predictor of ST is the premature discontinuation of clopidogrel,[6] 30% of late ST occur despite the use of dual antiplatelet therapy,[5] suggesting that factors other than the use of clopidogrel might impact the susceptibility to ST. The development of ST in these patients could be partially explained by factors related to complex lesion morphologies and complex procedures such as thrombus-containing lesions, bifurcation stenting, and insufficient acute gain. However, again these factors are insufficient in explaining all cases of ST because most of the patients with such complexities do not develop ST. Therefore, we focused on other factors that might contribute to the development of ST and thus should be considered as novel predictors of ST. Recently, Park et al reported that pre-procedural high-sensitivity C-reactive protein could predict a major cardiac event including death and Q-wave myocardial infarction in patients treated with DES.[18] Several studies also highlight the predictive value of MCP-1 or IL-6 for death or heart failure in patients with acute coronary syndrome.[9] These data support the theory that underlying pro-inflammatory status of patients might precipitate adverse events in high-risk patients treated with DES. It has been reported that an increased concentration of inflammatory cytokines including IL-6 could be detected immediately after stenting whether it is a bare metal stent or DES,[19,20] suggesting that the elevation of inflammatory cytokines is related to the procedure. The elevated concentrations of inflammatory cytokines normalized within a couple of weeks,[21–23] and its impact on the clinical outcome is yet to be determined. Furthermore, the significance of inflammatory cytokines time points beyond the peri-procedural period, which is different according to individual basal inflammation, is virtually unknown. We hypothesized that the underlying chronic inflammatory of a patient's status would be a predisposing condition for ST. Blood samples obtained too soon after the ST event would not be able to represent the patient's underlying chronic inflammatory status, because these levels can be affected temporarily by several factors such as myocardial infarction, procedural issues, and medications used in the treatment of ST. Therefore, a time point that would not be affected by the ST event and treatment for the ST event was chosen, and could more appropriately represent the underlying chronic inflammatory status of the patients.

Biological Sequence of IL-6 to Thrombogenecity and ST

Many inflammatory mediators are capable of inducing TF expression in monocytes, macrophages, endothelial cells, and vascular smooth muscle cells.[24] Not surprisingly, experimental evidence has revealed an important contribution of TF to the pathogenesis of subacute ST and restenosis after balloon angioplasty or stent deployment.[24] IL-6 also promotes TF expression from endothelial cells and circulating monocytes,[25–27] which is responsible for the thrombogenecity of the atherosclerotic plaque.[28] Recently, it has been reported that IL-6 is positively correlated with kinetic parameters of thrombin formation in the ACS patients, while no such associations were found for CRP.[29] Thus, it could be speculated that elevated IL-6 concentrations, which are known to be an upstream regulator of CRP, might precipitate thrombotic events, independently of CRP, in patients treated with DES. This might explain the selective occurrence of ST in patients with complex lesions and treated with complex procedures as shown in the present study.

High IL-6 as a Potential Risk Factor for Clinical Resistance Against Clopidogrel

In this study, the association between the highest IL-6 quartile and ST was more pronounced in early ST compared with late ST. Because stent re-endothelialization is not sufficiently achieved during the early period after stent implantation, and because the acute inflammatory condition that occurs during acute coronary syndrome is not fully stabilized in this period, we hypothesize that IL-6 could be elevated and the pro-inflammatory effect of IL-6 with other elevated inflammatory cytokines might contribute to the development of ST in susceptible individuals. Another finding was that the highest IL-6 quartile was an independent predictor of ST especially in patients who were on clopidogrel at the time of the ST. This suggests that in conditions where the antiplatelet effect is not sufficient, the lack of the antiplatelet effect might be the major determinant of ST development. However, in situations where the antiplatelet effect is sufficient (in patients who are on clopidogrel) subtle differences in susceptibility to inflammation might have a profound effect on the development of ST. This susceptibility to inflammation might also explain the higher occurrence of ST in patients receiving PCI for complicated lesion morphologies who are treated using complex techniques, which are bound to increased post-PCI inflammation. However, the elevated concentrations of IL-6 were only weakly associated with late ST and other mechanisms such as late stent malapposition[30–32] or poor re-endothelialization[13,14] could play a bigger role in late ST rather than systemic inflammation.

Study Limitations

There are several limitations in the present study. First, blood samples were not collected prospectively. The best method for studying the association of elevated baseline inflammatory status and ST would be to collect the blood samples at baseline before index PCI in a huge cohort and then to follow these patients prospectively for the occurrence of ST. Therefore, we have only shown a modest association, at best, between inflammatory cytokines and ST, and the results of the present study should be interpreted as hypothesis generating. Second, only a portion of the patients who developed ST had their serum sampled and were included in the study. Therefore, it is difficult to say that the patients and cases enrolled in the present analyses represent the general group of patients who develop ST, because some patients present with sudden death and these patients could not be included in the final analysis.

In conclusion, we show for the first time that elevated IL-6 concentrations might be associated with the development of DES thrombosis, suggesting the possible involvement of inflammatory cytokines in the pathophysiology of ST.

Acknowledgments

This study was supported by a grant from the Innovative Research Institute for Cell Therapy (IRICT: A062260) and Clinical Research Center for Ischemic Heart Disease (0412-CR02-0704-0001) sponsored by the Ministry of Health and Welfare, Republic of Korea.

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