Preinterventional Peak Monocyte Count and in-Stent Intimal Hyperplasia after Coronary Stent Implantation in Human Coronary Arteries

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Summary

Background: The mechanism of restenosis after stent implantation principally is neointimal hyperplasia. There is evidence that monocytes play a important role in in-stent restenosis (ISR) after stent implantation.

Hypothesis: This study assessed the relationship between preinterventional peak monocyte count and neointimal growth after successful stent implantation.

Methods: We performed coronary stent implantation in 85 patients (85 de novo lesions). Peripheral blood sample was obtained in all patients every 12 h before coronary angiography for measurement of peripheral monocytes. All patients received angiographic and intravascular ultrasound (IVUS) follow-up at 6 months after stenting.

Results: The preinterventional circulating monocyte count was significantly higher in the ISR group than that in the group without ISR (654 ± 62 vs. $461 \pm 222/\text{mm}^3$, $p < 0.001$) and was significantly higher in the reintervention group than that in the no-reintervention group (660 ± 72 vs. $470 \pm 216/\text{mm}^3$, $p < 0.001$). The incidence of ISR and repeat intervention associated with preinterventional monocyte count was highest among the patients in the highest tertile, who were at a 2.64-fold increased risk of ISR and 3.22-fold increased risk of repeat intervention compared with the patients in the lowest tertile. A significant positive correlation was found between preinterventional peak monocyte count and preinterventional plaque

and media cross-sectional area and follow-up neointima area ($r = 0.311$, $p = 0.007$, $r = 0.465$, $p < 0.001$, respectively). The neointima area associated with preinterventional monocyte count was largest among the patients in the highest tertile, that is, 2-fold larger than that of the patients in the lowest tertile ($p < 0.001$) and 1.44-fold larger than that of the patients in the middle tertile ($p = 0.001$).

Conclusion: Our results suggest that circulating preinterventional monocytes play a principal role in the process of in-stent neointimal growth after successful stent implantation.

Key words: stents, coronary artery disease, restenosis, inflammation

Introduction

Stent implantation is now established therapeutic strategy for coronary artery disease (CAD).^{1,2} However, in-stent restenosis (ISR) is a main limitation of coronary stent implantation,³ and this ISR is mainly developed by neointimal hyperplasia.^{4,5}

Inflammation plays an important role in the pathogenesis of atherosclerosis,^{6,7} and restenosis.⁸ There is an increasing evidence from several experimental studies that white blood cells, especially monocytes, play a central role in restenosis after balloon angioplasty and stent implantation.^{9–12} Activated monocytes may contribute to neointimal thickening¹² by generating reactive oxygen species through the production of growth and chemotactic factors,¹³ binding to a broad repertoire of ligands,¹⁴ or by matrix metalloproteinase production capable of degrading matrix constituents and consequently facilitating cell migration.¹⁵ Monocytes/macrophages have been demonstrated to be one of the components of the neointima.¹²

So far, many investigators have focused on local inflammatory response after stenting as a great contributor of restenosis. However, the vascular injury from stent implantation itself may induce platelet activation, thrombosis, and inflammation within the vessel wall. In addition, to the best of our knowledge, few in vivo studies have dealt with the relation between preinterventional monocyte count and neointimal growth in patients with CAD. We tried to exclude the effect of inflam-

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matory response induced by vascular injury from stent implantation itself and to evaluate the relationship between the pure inflammatory reaction induced by CAD itself and neointimal hyperplasia.

Therefore, the aim of this study was to investigate the relationship between preinterventional peak monocyte count and in-stent neointimal growth, as observed under intravascular ultrasound (IVUS), after successful stent implantation.

Methods

Study Population

Our patient population comprised 85 patients (85 lesions) who received successful IVUS-guided single stent implantation. The patients were scheduled to undergo elective stent implantation for single de novo lesions in native coronary arteries with a diameter of 2.5–4.0 mm. Patients with acute ST-elevation myocardial infarction within 24 h before admission, left main disease, bifurcation lesions, graft stenosis, and left ventricular dysfunction were excluded. At the time of stenting, all patients were scheduled for a 6-month follow-up angiogram and IVUS. All patients gave their written informed consent.

Measurement of White Blood Cell Count

Peripheral blood was obtained from all patients every 12 h before coronary angiography. Blood sampling was performed carefully and gently to avoid hemolysis. Total white blood cells and each fraction were measured with a Coulter® Gen S™ (Beckman Coulter, Fullerton, Calif., USA) automated hematology analyzer.

Stent Implantation Procedure

Stent implantation was performed as previously described.¹⁶ All implanted stents were bare metallic stents. All patients received aspirin (300 mg at least 12 h prior to stent implantation and 100–200 mg daily, indefinitely) and ticlopidine (500 mg at least 6 h prior to stent implantation and 250 mg daily continued for 30 days), or clopidogrel (300 mg at least 6 h prior to stent implantation and 75 mg daily continued for 30 days). A coronary angiogram was performed through the femoral or radial arteries. Dalteparin was administered 120 U per kg of body weight intravenously every 12 h or unfractionated heparin as an intravenous bolus (usually 5000 units) followed by a continuous infusion at a dose adjusted according to the activated partial thromboplastin time. All stenotic lesions were predilated and stents were deployed at 10 to 18 atm. Each angiogram or IVUS sequence was preceded by 200 to 300 µg of intracoronary nitroglycerin.

Quantitative Coronary Angiography

Angiograms were analyzed with a validated quantitative coronary angiography system (Philips H5000™ [Philips Medical Systems, Andover, Mass., USA] or Allura DCI™ [Philips]

program). Minimal luminal diameter, reference diameter, and percent diameter stenosis were measured in identical views before percutaneous balloon angioplasty and immediately after stent implantation. Angiographic restenosis was defined as percent diameter stenosis > 50% at follow-up.

Analysis of Intravascular Ultrasound Images

We used the EndoSonics (EndoSonics Corp., Pleasanton, Calif., USA) IVUS system, which allows digital storage of pullback sequences. Automated pullbacks at 1 mm/s were performed before intervention and repeated after stenting. The IVUS measurements were performed at the tightest segment within the stent and the proximal and distal reference segments (defined as the location with the least amount of disease within 10 mm of the stent border without intervening branches). Trained catheterization laboratory personnel performed IVUS measurements according to previously described methods.¹⁷ Preinterventional lesion and proximal and distal reference segment external elastic membrane (EEM), lumen, plaque and media cross-sectional areas (CSA), and plaque burden (plaque and media/EEM) were measured. The lesion was the site with the smallest lumen CSA; in multiple image slices with the same minimum lumen CSA, the slice with the largest EEM and plaque and media was measured. Preinterventional arterial remodeling was assessed by comparing the lesion site EEM to the proximal and distal reference EEM CSA: positive remodeling (lesion > proximal reference), intermediate remodeling (distal reference < lesion < proximal reference), and negative remodeling (lesion < distal reference). Remodeling index was defined as follows: the target lesion EEM CSA divided by the average of the proximal and distal reference EEM CSA. Postinterventional and follow-up stent, lumen, and neointimal hyperplasia (stent minus lumen CSA) areas were measured.

Statistical Analysis

Statistical analysis was performed with the aid of commercially available software (Statistical Package for Social Sciences Version 11—SPSS Inc., Chicago, Ill, USA). For statistical analyses, the unpaired *t*-test, chi-square tests, and linear correlation analysis were performed and the results were designated as the mean value ± standard deviation (SD) or number (%) of patients. A *p* value of < 0.05 was considered as significant.

Results

Patient Characteristics

Baseline patient characteristics are shown in Table I. At follow-up angiogram, ISR occurred in 22 patients and no ISR was observed in 63 patients. Of the 22 patients with ISR, 19 underwent repeat intervention. Plain old balloon angioplasty was performed for 8 patients with ISR and drug-eluting stent was deployed in another 11. The ISR occurred more frequent-

TABLE I Baseline clinical characteristics

	In-stent restenosis (n = 22)	No in-stent restenosis (n = 63)	p Value
Age (years)	56 ± 12	56 ± 10	NS
Men (%)	22 (100.0)	47 (74.6)	0.009
Diabetes mellitus (%)	5 (22.7)	10 (15.9)	NS
Hypertension (%)	12 (54.5)	32 (50.8)	NS
Dyslipidemia (%)	7 (31.8)	18 (28.6)	NS
Smoking (%)	17 (77.3)	27 (42.9)	0.005
Clinical presentation (%)			0.020
Stable angina pectoris	0 (0.0)	7 (11.1)	
Unstable angina pectoris	11 (50.0)	41 (65.1)	
Non-ST-segment elevation myocardial infarction	1 (4.5)	2 (3.2)	
ST-segment elevation myocardial infarction	10 (45.5)	9 (14.3)	
Old myocardial infarction	0 (0.0)	4 (6.3)	
Peak monocyte count (/mm ³)	654 ± 62	461 ± 222	<0.001
C-reactive protein (mg/dl)	1.18 ± 0.56	0.55 ± 0.48	0.026
Fibrinogen (mg/dl)	267 ± 53	258 ± 26	NS
Low-density lipoprotein cholesterol (mg/dl)	136 ± 55	105 ± 47	NS
Lipoprotein (a) (mg/dl)	36 ± 28	30 ± 24	NS
Left ventricular ejection fraction (%)	63 ± 10	63 ± 9	NS

ly in men and current smokers. The acute coronary syndromes were observed more frequently in the ISR group. The peak monocyte count was significantly higher in the ISR group and the reintervention group than that in the groups with no ISR and no reintervention (654 ± 62 vs. $461 \pm 222/\text{mm}^3$, 660 ± 72 vs. $470 \pm 216/\text{mm}^3$, $p < 0.001$, $p < 0.001$, respectively, Table I, Fig. 1). The baseline C-reactive protein level was significantly higher in the ISR group than in that with no ISR (1.18 ± 0.56 vs. 0.55 ± 0.48 mg/dl, $p = 0.026$, Table I).

Angiographic Characteristics and Procedural Results

Angiographic characteristics and procedural results are shown in Table II. There were no significant differences in diseased vessel number and target vessel between the groups. Type B₂ lesion was observed more frequently in the ISR group than in that with no ISR. The stent size was significantly smaller in the ISR group than in that with no ISR.

In-Stent Restenosis and Repeat Intervention According to the Tertile of Preinterventional Peak Monocyte Count

The increase in the incidence of ISR and repeat intervention associated with preinterventional peak monocyte count was primarily seen among the patients in the highest tertile, who were at a 2.64-fold increased risk of ISR and 3.22-fold increased risk of repeat intervention compared with the patients in the lowest tertile (Fig. 2).

Intravascular Ultrasound Measurements

Preinterventional and follow-up IVUS data are shown in Table III. At preintervention, the lumen area at lesion site was

significantly smaller in the ISR group than in that with no ISR (3.8 ± 0.5 vs. 4.2 ± 1.0 mm², $p = 0.017$); plaque and media CSA at lesion site was significantly larger in the ISR group than in that with no ISR (10.6 ± 3.9 vs. 9.5 ± 3.4 mm², $p =$

FIG. 1 Preinterventional peak monocyte count in patients with in-stent restenosis (A) and in those who underwent repeat intervention (B).

TABLE II Baseline angiographic characteristics and procedural results

	In-stent restenosis (n = 22)	No in-stent restenosis (n = 63)	p Value
Narrowed coronary arteries (%)			NS
1	19 (86.4)	57 (90.5)	
2	3 (13.6)	6 (9.5)	
3	0 (0.0)	0 (0.0)	
Target coronary arteries (%)			NS
Left anterior descending artery	14 (63.6)	47 (74.6)	
Left circumflex artery	6 (27.3)	7 (11.1)	
Right coronary artery	2 (9.1)	9 (14.3)	
ACC/AHA type (%)			0.003
B ₁	16 (72.7)	60 (95.2)	
B ₂	6 (27.3)	3 (4.8)	
Stent size (mm)	3.2 ± 0.2	3.4 ± 0.3	0.003
Stent length (mm)	18.4 ± 3.5	17.3 ± 1.8	NS
Reference vessel diameter (mm)	3.3 ± 0.3	3.3 ± 0.4	NS
Minimal lumen diameter (mm)			
Preintervention	1.0 ± 0.5	1.0 ± 0.6	NS
Postintervention	2.7 ± 0.4	2.8 ± 0.5	NS
Diameter stenosis (%)			
Preintervention	70 ± 14	70 ± 16	NS
Postintervention	18 ± 7	15 ± 6	NS

Abbreviation: ACC/AHA = American College of Cardiology/American Heart Association.

FIG. 2 The incidence of in-stent restenosis (A) and repeat intervention (B) according to the tertile of preinterventional peak monocyte count. NS = not significant.

0.026); and the preinterventional remodeling index was significantly higher in the ISR group than in that with no ISR (1.02 ± 0.13 vs. 0.94 ± 0.13 , $p = 0.012$). At 6-month follow-up IVUS examination, the intrastent neointima area was significantly larger in the ISR group than in that with no ISR (3.5 ± 1.5 vs. $2.0 \pm 1.5 \text{ mm}^2$, $p < 0.001$). Significant positive correlations were found between preinterventional peak monocyte count and preinterventional plaque and media CSA and plaque burden ($r = 0.311$, 0.360 ; $p = 0.007$, 0.002 , respectively, Fig. 3), as well as between preinterventional peak monocyte count and follow-up neointima area ($r = 0.465$, $p < 0.001$, Fig. 4A). The neointimal hyperplasia area associated with preinterventional monocyte count was largest among the patients in the highest tertile, that is, 2-fold larger than that of the patients in the lowest tertile ($p = 0.001$) and 1.44-fold larger than that of the patients in the middle tertile ($p < 0.001$, Fig. 4B). However, preinterventional peak total white blood cell count and preinterventional peak neutrophil count had no significant correlation with in-stent neointima hyperplasia (Fig. 5).

Discussion

Based on the experience derived from experimental models, cell culture, and human pathologic evidence, as well as angiographic, angioscopic, and IVUS observations, the sequence of events that take place in the artery after stent implantation and that characterize the restenotic process consists of thrombosis, recruitment of inflammatory cells, and proliferation/remodeling.^{18,19} The important role of white blood cells,

TABLE III Intravascular ultrasound measurements

	In-stent restenosis (n = 22)	No in-stent restenosis (n = 63)	p Value
Preintervention			
Proximal reference external elastic membrane cross-sectional area (mm ²)	14.9 ± 3.0	15.7 ± 3.5	NS
Lesion site external elastic membrane cross-sectional area (mm ²)	14.4 ± 4.1	13.7 ± 3.8	NS
Lesion site lumen area (mm ²)	3.8 ± 0.5	4.2 ± 1.0	0.017
Lesion site plaque plus media cross-sectional area (mm ²)	10.6 ± 3.9	9.5 ± 3.4	0.026
Lesion site plaque burden (%)	71.9 ± 7.4	67.9 ± 7.7	0.040
Distal reference external elastic membrane cross-sectional area (mm ²)	13.0 ± 3.1	13.3 ± 3.5	NS
Preintervention remodeling index	1.02 ± 0.13	0.94 ± 0.13	0.012
Postintervention stent cross-sectional area (mm ²)	7.0 ± 1.2	7.7 ± 2.0	NS
Follow-up			
Proximal reference external elastic membrane cross-sectional area (mm ²)	15.1 ± 2.9	15.5 ± 3.4	NS
Lesion site external elastic membrane cross-sectional area (mm ²)	14.2 ± 3.9	13.7 ± 3.7	NS
Stent cross-sectional area (mm ²)	7.0 ± 1.3	7.5 ± 1.9	NS
Intrastent lumen area (mm ²)	3.5 ± 0.4	5.6 ± 1.3	<0.001
Intrastent neointimal hyperplasia area (mm ²)	3.5 ± 1.5	2.0 ± 1.5	<0.001
Distal reference external elastic membrane cross-sectional area (mm ²)	13.2 ± 3.4	13.4 ± 3.4	NS
Serial (after intervention to follow-up) comparison			
Δ Stent cross-sectional area (mm ²)	0.0 ± 1.1	-0.2 ± 1.2	NS
Δ Intrastent lumen area (mm ²)	-3.5 ± 1.6	-2.2 ± 1.8	<0.001
Δ Intrastent neointimal hyperplasia area (mm ²)	3.5 ± 1.5	2.0 ± 1.5	<0.001

FIG. 3 Correlation between preinterventional peak monocyte count and preinterventional plaque and media (A) and between preinterventional peak monocyte count and preinterventional plaque burden (B).

FIG. 4 Follow-up neointimal hyperplasia according to preinterventional peak monocyte count (A) and the tertile of preinterventional peak monocyte count (B).

FIG. 5 Follow-up neointimal hyperplasia according to preinterventional peak total white blood cell count (A) and peak neutrophil count (B). NS = not significant.

especially monocytes, in in-stent neointimal proliferation has been demonstrated previously.¹² So far, many investigators have focused on local inflammatory response following percutaneous coronary intervention as a great contributor of restenosis. However, very few *in vivo* studies have addressed the relationship between preinterventional peak monocyte count and neointimal hyperplasia by IVUS study. Our study showed the strong positive correlation between preinterventional peak monocyte count and in-stent neointima area in human stented lesions.

Stent implantation for CAD is now established as a therapeutic strategy of great benefit;^{1, 2} however, ISR, which is a main limitation of coronary stent implantation, remains unresolved. Excessive in-stent neointimal hyperplasia is the main contributing factor to ISR.^{4, 5} Experimental and clinical studies have suggested that inflammation plays an important role in the pathogenesis of intimal hyperplasia after arterial injury.^{20, 21} Other animal studies have demonstrated that after stenting a particularly brisk early inflammatory response is induced with abundant surface adherent monocytes and granulocytes.²² Several days and weeks later, macrophages invade the forming neointima and are observed clustering around stent struts.²² Systemic inflammatory reaction may play a pivotal role in neointima formation within stent struts in addition to the local vessel wall injury, with the subsequent release of chemotactic and growth factors.^{8, 23} Fukuda *et al.*²⁴ reported that the circulating monocyte count increased and reached its peak 2 days after stent implantation and that the maximum monocyte count after stent implantation showed a positive correlation with in-stent neointimal volume at 6-month follow-up. They concluded that circulating monocytes after stent implantation play a role in the process of in-stent neointimal hyperplasia.

However, vascular injury from stent implantation itself may induce platelet activation, thrombosis, and inflammation within the vessel wall. No data are available to show whether preinterventional inflammatory reaction is associated with neointimal growth after stent implantation. Recent clinical and his-

topathologic data suggest that inflammation plays a key role in coronary artery plaque instability and subsequent occlusive thrombosis.^{25–27} Inflammation in acute coronary syndromes is suggested by numerous clinical studies showing increased acute-phase reactants in the serum of patients with unstable angina and those at risk of future myocardial infarction.^{28, 29}

In the present study, the preinterventional peak monocyte count was significantly higher in the ISR group and the re-intervention group than in that with no ISR and with no re-intervention. Furthermore, significant positive correlations were found between preinterventional peak monocyte count and plaque, media CSA, and plaque burden, and between preinterventional peak monocyte count and follow-up neointima area. Therefore, our results show that preinterventional monocyte count appears to predict in-stent restenosis, supporting the role of preinterventional inflammatory reaction in neointima hyperplasia; our results may contribute to stratifying lesions at high-risk for in-stent restenosis in patients who undergo stent implantation.

Study Limitations

The study has several limitations. First, the group sizes were relatively small; second, because preinterventional IVUS imaging was performed based on each surgeon's decision, lesion selection may be biased; third, functional analysis of monocytes was not performed. Finally, to analyze each white blood cell fraction count, we only performed automated measurements in this study.

Conclusions

Our results suggest that preinterventional monocyte count may predict ISR and preinterventional circulating monocytes play a principal role in the process of in-stent neointimal growth after successful stent implantation. Measurement of

preinterventional monocyte counts could provide a rationale for risk stratification before stent implantation in CAD, thus offering a useful tool for targeting aggressive anti-inflammatory therapy in patients who are exposed to the highest risk for ischemic complications or restenosis development after coronary stent implantation.

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