The Correlation between Post-Procedural Plasma Fractalkine and Lipid Plaque Volume in Target Lesion after Coronary Stent Implantation

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Abstract
Several reports suggest that fractalkine (FKN) and its cognate receptor, CX3CR1, play a role in atherogenesis. Recent data showed that plasma FKN is elevated in patients with unstable angina pectoris and is more elevated with patients with plaque rupture. We assessed the hypothesis that plasma FKN might be elevated after stent implantation and related to the plaque-characteristics. First of all we tested the time course of plasma FKN level 30-min., 3-hour, 6-hour and 12-hour after coronary stenting. Their levels are elevated at 30 min. after percutaneous coronary intervention (PCI) and maintained the level until 12-hour after PCI. Then we examined the plasma levels of FKN, IL-8 and IL-6 in 50 consecutive patients before and 12-hour after coronary stenting following in integrated backscatter-intravascular ultrasound (IB-IVUS) analysis. The plasma IL-8 did not change 12-hour after stenting. Those of FKN and IL-6, however, were significantly elevated 12-hour after stenting (FKN: from 656 ± 122 pg/mL to 811 ± 177 pg/mL, p<0.0001, IL-6: from 3.15 ± 3.42 pg/mL to 16.0 ± 15.0 pg/mL, p<0.0001). In IB-IVUS analysis the lipid volume and volume fraction were correlated with post-procedural FKN level (R2=0.29, p<0.0001; R2=0.22, p<0.0001), while they were not related with post-procedural IL-6 level. In conclusion, a local release of FKN and IL-6 occurs shortly after PCI, which is possibly related to plaque rupture and/or endothelial traumatism following stent-implantation. We have further shown that local release of FKN is evoked proportionally to the volume of the lipid-rich plaques which are prone to be ruptured. These suggested that anti-FKN treatment could be of benefit to decrease the amount of lipid-rich plaque.

Keywords: Inflammatory cytokine; Fractalkine; Percutaneous coronary intervention; Integrated backscatter-intravascular ultrasound; Lipid-rich plaque

Introduction
The leukocyte recruitment at all stages of atherosclerotic progression is a crucial feature, besides lipid deposition and vascular smooth muscle cell proliferation [1,2]. The chemokine families are thought to contribute significantly to the pathogenesis of atherosclerosis. Fractalkine (FKN) is the unique member of the CX3C chemokine subfamily because of its chemotactic and adhesive properties in the vessel-wall [3,4].

Previous studies have revealed that the rapture of plaques might play a critical role in the acute coronary syndrome (ACS), where the lipid-rich plaques affect the plaque vulnerability [5,6]. Recently the integrated backscatter intravascular ultrasound (IB-IVUS) system, which provides two-dimensional color-coded maps for the tissue characterization of coronary plaques, has been widely used [6,7]. A good correlation between the maps obtained by IB-IVUS and histological findings was recognized. It was also revealed that IB-IVUS could differentiate vulnerable plaques and predict acute coronary syndrome (ACS) [6-8].

A previous report suggested that the level of FKN/CX3CR1 is enhanced in coronary artery disease (CAD) patients and is more in unstable angina pectoris (AP) patients [9]. While it is believed that local inflammatory response after percutaneous coronary intervention (PCI) is triggered by atherosclerotic plaque rupture and PCI-associated vessel injury leading to smooth muscle cell migration and proliferation [10,11]. However there was no previous study which clarifies the relationship between quantitative analysis of target lesion and the local release of inflammatory cytokines including FKN. The purpose of this study, therefore, was to investigate the correlation between plaque morphology obtained by IB-IVUS and plasma level of inflammatory cytokines after PCI.

Methods
Patient population
In this study we prospectively included 50 consecutive patients with stable AP or inducible myocardial ischemia of a single coronary vessel who underwent elective coronary stent implantations following IB-IVUS examination of target lesion. Target lesions were identified by the association of ECG signs of ischemia and angiographic findings of the lesion. Patients were not eligible for enrollment if they had a clinical history of recent myocardial infarction or thrombotic treatment within the previous 6 weeks, severe concomitant disease (e.g. infections, connective tissue disease, or malignancies), congestive heart failure, and the use of medications other than aspirin with known anti-inflammatory effects.

Percutaneous coronary intervention procedure
All patients received treatment with at least 2 anti-platelet agents (aspirin 100 mg plus clopidogrel 75 mg or ticlopidine 200 mg) 48 hour before the procedure and then daily for 3 to 9 months. Furthermore, 1000 IU of heparin was administered before stenting and an additional

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bolus 1000-2000 IU was given every hour if the procedure lasted more than one hour. The operator decided the position and length of the angioplasty and stent implantation according to angiography and IVUS findings. Successful PCI, defined as less than 50% residual stenosis with no occlusion of the large branch and final grade 3 flow in the Thrombolysis in the Myocardial Infarction Trial (TIMI) grading system, was achieved in all enrolled patients. The study was approved by the University Ethics Committee and done in accordance with the Declaration of Helsinki. All participants gave written informed consent.

**Coronary angiographic analysis**

Quantitative angiographic analysis (QCA) was performed using an offline QCA system (CAAS QCA for Research 2.0, Pie Medical Imaging BV, The Netherlands). The minimal luminal diameter of treated coronary segments, reference diameter, percent diameter stenosis, and lesion length on baseline angiogram were determined in the view that demonstrated the lesion to be the most severe and not foreshortened. Then, minimal lumen diameter, percent diameter stenosis, and acute gain were measured on final angiogram.

**IVUS analysis**

Intravascular ultrasound assessment was performed using the 40-MHz IVUS catheter (Boston Scientific/Scimed, Natick, MA). All IVUS procedures were performed after intracoronary administration of isosorbide dinitrate 1-2 mg. The IVUS catheter was advanced distally to lesion/stent whenever possible, and imaging was performed retrograde back to the proximal reference at an automatic transducer pullback speed of 0.5 mm/s. Studies were recorded on compact disc for offline analysis using Echopaque 2 (INDEC Systems, Inc., Mountain View, CA, USA). The following five representative points were measured for the lesion slices of analysis: the proximal and distal reference segments, the proximal and distal stent edge segments, and culprit lesion segment. The proximal and distal reference segments were the most normal-looking cross within 5 mm proximal or distal to the lesion but before any side branch. The average of the proximal and distal reference segments lumen cross-sectional area (when both were available) was used for reference vessel measurements.

Target lesion segment means minimum lumen cross-sectional area in IVUS assessment before intervention. Percent stent expansion was defined as stent cross-sectional area/reference lumen cross-sectional area. This parameter was measured at the proximal and distal stent edge segments and culprit lesion segment. Stent under-expansion was defined according to criteria of the Multicenter Ultrasound Stenting in Coronaries (MUSIC) study as a minimal stent cross-sectional area that was 90% of the average reference lumen area [12]. If reference lumen cross-sectional area was >9 mm², stent under-expansion was defined as a minimal stent cross-sectional area that was <80% of the average reference lumen area. Radial stent symmetry index was defined as minimum/maximum stent diameter. This parameter was also measured at the proximal and distal stent edge segments as well as culprit lesion segment. Axial stent symmetry was minimum/maximum stent cross-sectional area.

**IB-IVUS analysis**

A personal computer (Windows XP Professional, CPU 3.4 GHz) equipped with custom software (IB-IVUS, YD Co., Ltd, Nara, Japan) was connected to the IVUS imaging system (Galaxy, Boston Scientific, Natick, MA, USA) in order to obtain radio frequency signal output, signal trigger output, and video image output. Ultrasound backscattered signals were acquired using a 40 MHz mechanically rotating IVUS catheter in order to be digitalized and subjected for spectral analysis. Integrated backscatter (IB) values for each tissue component were calculated as an average power using a fast Fourier transform, measured in decibels, of the frequency component of the backscattered signal from a small volume of tissue. We applied the manufacturer’s default setting on the basis of previous data to define a range of IB value for each plaque component (lipid, fibrous, dense fibrous, and calcified) [6,7]. A total of 256 vector lines per image (1.4 grade/line) and a set of 20 regions of interests (ROIs) for each 100 µm depth on each vector line (total 5120 ROIs/image) were used for IB analysis. Polar coordinates were transformed into Cartesian coordinates (64 x 64 pixels) using computer software [6]. We then manually excluded the vessel lumen and area outside of the intima in the two-dimensional IB-IVUS images. Color-coded maps were constructed for each 1 mm slice to illustrate the tissue characteristics in the target lesions. Three-dimensional analysis of IB-IVUS images was performed to calculate lipid, fibrous, dense fibrous and calcified volumes from the sum of lipid, fibrous, dense fibrous and calcified areas in each CSA at 1 mm axial intervals for the IB-IVUS images of the target lesion, respectively.

**Blood sampling and analysis**

For time-course assay peripheral blood samples were drawn from 10 patients before and 30 min., 3 hour, 6 hour, and 12 hour after PCI. Then all patients’ blood samples were drawn before and 12 hour after PCI. Plasma samples were collected in EDTA 2Na anticoagulant tubes and stored at -40°C until assay. Plasma levels of FKN, interleukin-6 (IL-6), and interleukin-8 (IL-8) were determined by enzyme immunoassays (EIA; R&D Systems, Minneapolis, MN, USA). hsCRP was measured using testing kit (N-Latex CRP II, Dade Behring, Marburg, Germany).

**Clinical parameters**

The clinical parameters assessed age, sex, and coronary risk factors (smoking, hypertension, diabetes mellitus, hyperlipidemia, and obesity). The diagnostic criteria for coronary risk factors as follows: hypertension defined as blood pressure ≥ 140/90 mmHg, and/or a history of antihypertensive drug use; diabetes mellitus defined as fasting blood glucose of ≥ 126 mg/dl or casual plasma glucose ≥ 200 mg/dl, or diabetes as shown by an oral glucose tolerance test; hyperlipidemia defined as serum low-density cholesterol (LDL) level ≥ 140 mg/dl or serum triglyceride level ≥ 150 mg/dl; obesity defined as body mass index ≥ 25 kg/m² [13].

**Statistics**

Continuous variables were presented as mean ± 1 SD values. A comparison of continuous variables was achieved with the unpaired Student’s t-test and of categorical variables using χ² analysis or Fisher’s exact probability test. For comparison within the same individuals, the Wilcoxon matched-pairs test was used. No adjustment was made to the significance level owing to the exploratory nature of the study. Linear regression analysis was performed to assess the association between quantitative plaque characteristics, as assessed using IB-IVUS, and an increase in plasma chemokine. To identify predictors of lipid plaque volume, simple regression analyses were performed. All statistical analyses were performed using Stat View 5.0 (SAS Institute, Cary, NC, USA). Differences were considered significant at P < 0.05.

**Results**

**Baseline clinical, lesion, and procedural characteristics**

Clinical variables for this study population are given in table 1. In
this population 40 patients (80%) have hyperlipidemia, but their levels of low-density lipoprotein (LDL) were controlled with mean level of 151.9 ± 39.6 mg/dl. The numbers of patients who have a history of myocardial infarction are small (14%). There are few patients whose LVEF are less than 50% (16%). Angiography (quantitative coronary angiography, QCA) and IVUS measurements shows that target lesions were not long or complicated (Table 2). Most of culprit lesions were type A/B1 which means they were easy to treat with PCI (Table 3).

**Time course of plasma chemokine level after stenting**

First of all we checked plasma level of FKN, IL-6, and IL-8 30-min., 3-hour, 6-hour, 12-hour and 24-hour after PCI in 10 of 50 patients. Their IL-6 levels are gradually increased within an observation period and plateaued 12-hour after PCI. And their IL-8 levels did not change significantly (Figures 1A and 1B). While their FKN levels elevated at 30 min. after PCI with 1.3 fold increases and maintained the level until 12-hour after PCI (Figure 1C). The time course of plasma FKN concentration was almost identical among these patients.

**Plasma chemokine levels after PCI**

We examined the plasma levels of high-sensitivity C-reactive protein (hsCRP), FKN, IL-8 and IL-6 in fifty consecutive patients before and 12-hour after coronary stenting. The plasma levels of hsCRP did not change 12-hour after stenting, nor change those of IL-8 (Figures 2A and 2B). Those of FKN and IL-6, however, were significantly elevated 12-hour after stenting (FKN: from 656 ± 122 pg/mL to 811 ± 177 pg/mL, p<0.0001, IL-6: from 3.15 ± 3.42 pg/mL to 16.0 ± 15.0 pg/mL, p<0.0001 in the simple regression analysis) (Figures 2C and 2D).

**Table 1:** Baseline patient characteristics.

| Age (years) | 69.1 ± 9.3 |
|-------------|------------|
| Males       | 33 (66)    |
| Diabetes    | 29 (58)    |
| Hypertension| 29 (58)    |
| Hyperlipidaemia | 40 (80) |
| BMI         | 24.3 ± 3.3 |
| Current smoker | 22 (44) |
| Previous MI | 7 (14)     |
| LVEF<50%    | 7 (14)     |
| β-blocker   | 17 (34)    |
| ARB/ACEI    | 30 (60)    |
| Statins     | 41 (82)    |
| LDL cholesterol | 151.9 ± 39.6 (mg/dl) |
| Hemodialysis| 6 (12)     |

Values are given in mean ± SD or n (%). BMI: Body Mass Index; MI: Myocardial Infarction; LVEF: Left Ventricular Ejection Fraction; ARB: Angiotensin Receptor Blocker; ACEI: Angiotensin Converting Enzyme Inhibitor; LDL: Low Density Lipoprotein

**Table 2:** Baseline angiographic characteristics of the patients.

| Lesion location | LAD | RCA | LCX |
|-----------------|-----|-----|-----|
| Number of stents| 1.21 ± 0.44 | 33 (66) | 3 (6) |
| Total stent length | 21.2 ± 6.2 | 18.4 ± 2.2 (atm) | 140.5 ± 68.2 (s) |

Values are given in n (%) or mean ± SD. LAD: Left Anterior Descending Coronary Artery; RCA: Right Coronary Artery; LCX: Left Circumflex coronary artery; Type B2/C, American Heart Association College of Cardiology classification type B2 or type C

**Table 3:** Lesion and plaque characteristics by IVUS and IB-IVUS analysis.

| Lesion and plaque characteristics by IVUS and IB-IVUS. |
|------------------------------------------------------|
| Values are given in mean ± SD, IVUS, intravascular ultrasound; IB-IVUS, integrated backscatter intravascular ultrasound; EEM, external elastic membrane |

**Table 4:** Simple regression analysis of coronary risk factors with lipid plaque volume.

| R²  | P-value |
|-----|---------|
| Diabetes | 0.03   | 0.56   |
| Hypertension | 0.00 | 0.89   |
| Hyperlipidaemia | 0.00 | 0.88   |
| BMI | 0.00 | 0.68   |
| Current smoker | 0.00 | 0.92   |
| LDL cholesterol | 0.05 | 0.13   |
| Hemodialysis | 0.03 | 0.12   |

A total of 50 lesions were measured of plaque volume which was composed of 4 different contents: lipid, fibrous, dense fibrous and calcification plaque. First of all, we analyzed the relationship between lipid plaque and coronary risk factors. However, lipid plaque volume was not correlated with any coronary risk factors (Table 4). Then the simple regression analysis revealed that lipid plaque volume was significantly correlated positively only with post-procedural plasma FKN level (R²=0.29, p<0.0001) (Figure 3). Although plasma IL-6 level elevated after coronary stenting as well as that of FKN, it was not correlated with lipid plaque volume (R²=0.09, p=0.05) (Figure 3).

**Discussion**

Vascular interventions, such as percutaneous coronary interventions (PCI), lead to endothelial damage and cause an inflammatory response. Following tissue injury, several chemokines are released into a local environment by several cell types, including monocytes, platelets, neutrophils, and T lymphocytes, where it evokes its activity on a number of target cells. Chemokines are inflammatory cytokines characterized by their ability to cause directed migration of leukocytes into inflamed tissue, and raised levels are found in atherosclerosis, both systemically and within the atherosclerotic plaques. Fractalkine is an atypical chemokine that exists in either a membrane-bound form or as a cleaved soluble chemokine that functions as a chemo-attractant for monocytes and T cells [3,4]. This study is the first study that shows that plasma FKN level elevates immediately after PCI and its level is correlated positively with lipid plaque volume.
As far as we know there are two studies that reported of plasma FKN levels of CAD patients. Damas et al. [9] suggested that those are elevated in CAD patients, especially in ACS patients and Ikejima et al. [14] suggested that those are related to plaque rupture [14]. However there are no studies that investigate the interval change of plasma FKN after coronary stent-implantation. Our findings that both FKN and IL-6 levels elevated 30-min after stent-implantation suggests that this was not due to a systemic response which requires more longer time to occur. We can be hypothesized that FKN might originate from cells infiltrating plaque itself. Few reports revealed that local release of pro-inflammatory cytokines occurs shortly after coronary stent-implantation related plaque rapture and/or endothelial injury following the procedure [15-17]. The relevance of the results obtained from our data is the demonstration that a significant release of powerful pro-inflammatory cytokines occurs very rapidly after stent-implantation. Although in 66% of all patients we used drug-eluting stent which release substances possessing anti-inflammatory effect, our data indicate the lack of an inhibitory effect in the very first moments of stent-implantation.

We used IB-IVUS for detection of tissue characteristics of coronary plaques. This system uses a conventional IVUS instrument, a digital analog converter, and computer software to identify and quantitate various plaque characteristics. Several histological studies validated that IB measurements accurately reflect the tissue characteristics of human coronary plaques [18,19]. Angioscopic studies showed that lipid-rich plaques were identified in patients with ACS and in 50-70% of patients with stable angina pectoris (SAP) [20,21]. In another words, lipid-rich
plagues itself is inflamed tissue which is prone to be ruptured. The fact that inflammation in atherosclerotic lesions seems to be present with local preference suggests that plaque inflammation is locally affected. Evidence for local immunologic activation has been provided by the demonstration of activated T lymphocytes and macrophages in the atherosclerotic plaque [22]. Enhanced FKN levels evoke CX3CR1-expressing monocytes, T lymphocytes, and NK cells to activate, leading to plaque rupture. Taken together, FKN/CX3CR1 system might exist mainly in lipid-rich plaques.

**Conclusion**

A local release of pro-inflammatory cytokines is evoked shortly after PCI, which is possibly related to plaque rupture and/or endothelial traumatism following stent implementation. Several studies have found FKN/CX3CR1 pathway affects coronary plaque rupture. We have further shown that local release of FKN is evoked proportionally to the volume of the lipid-rich plaques which are prone to be ruptured. These findings suggested that anti-FKN treatment could be of benefit to decrease the amount of lipid-rich plaque.

**Study Limitations**

First, this study was conducted at a single center with a small sample size. Larger cohort study will be necessary to confirm our findings. Second, our study was observational and dose not provides a sample size. Larger cohort study will be necessary to confirm our findings. Third, our definition of lipid in IB value may contain a certain amount of thrombus because thrombus and lipid-rich plaque tissues had similar IB values and it is difficult to differentiate between these tissues components by IB-IVUS [7]. However, there were no emergency cases in our study and the incidence of thrombus formation in the target lesion may therefore be relatively small.

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