HDL-C and Plaque Calcification are Associated with Microcirculatory Damage after Percutaneous Coronary Intervention

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Abstract: *Aims*: Microvascular disturbance followed by percutaneous coronary intervention (PCI) was sometimes occurred. There were no report of the quantitative evaluation about microvascular disturbance after PCI. The aim of this study was to quantitate microcirculatory injury caused by elective PCI using index of microcirculatory resistance (IMR), and to clarify preprocedural predictors of microvascular damage.

Methods: Fifty patients with stable angina and planned PCI for single vessel disease were enrolled in this study. IMR was measured after PCI. Plaque components were analyzed by integrated backscatter intravascular ultrasound.

Results: Post-PCI IMR tended to correlate with high-density lipoprotein cholesterol levels ($r = –0.298$, $p = 0.078$) and plaque calcification ($r = -0.22$, $p = 0.058$) in the univariate analysis. Multivariate logistic analysis adjusted for these covariates revealed that the high-density lipoprotein cholesterol levels and plaque calcification were inversely associated with higher post-PCI IMR (odds ratio = 0.919, $p = 0.049$; and odds ratio = 0.546, $p = 0.049$, respectively).

Conclusion: Low levels of high-density lipoprotein cholesterol and plaque calcification independently predict higher post-PCI IMR. Based on these results, Serum lipid and plaque calcification profiles might be important for predicting and preventing periprocedural myocardial damage during elective PCI.

Keywords: Index of microcirculatory resistance.

1. INTRODUCTION

Reduced coronary antegrade flow in the coronary artery, such as that during the angiographic no-reflow phenomenon, sometimes occurs after percutaneous coronary intervention (PCI) [1]. This is speculated to be caused by fibrin, platelet, and neutrophil plugging; endothelial damage; tissue edema; or microvascular spasms of the target arteries, and has been demonstrated to be associated with, and to strongly predict, adverse long-term outcomes [2,3]. However, angiographic findings provide only qualitative information.

Recently, the index of microcirculatory resistance (IMR), a new quantitative method for evaluating microcirculatory function, has been validated in clinical practice [4,5]. IMR is derived from the distal coronary pressure and hyperemic mean transit time, and IMR after PCI can be used to evaluate microcirculatory dysfunction if no significant myocardial disorder, such as previous myocardial infarction or cardiomyopathy, was present at baseline. Accordingly, the aim of this study was to quantitate PCI-induced microcirculatory injury using IMR, and to identify any independent predictors of microvascular damage.

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2. MATERIALS AND METHODS

2.1. Patients

A total of 50 patients admitted to Shinshu University Hospital to undergo elective PCI for significant coronary stenosis between July 2010 and December 2011 were included in the study. Significant coronary stenosis was defined as luminal stenosis over 50% by quantitative coronary arteriography, with a fractional flow reserve (FFR) of<0.80. The indication of revascularization was determined using the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization [6]. Exclusion criteria was the cases with preexisted microvascular disorder or severe complex lesion or higher wedge pressure. For example, acute coronary syndrome; in-stent restenosis; severe stenosis >99%); chronic total occlusion; severe calcification; left main trunk, ostial, or coronary artery bypass graft lesions; history of previous myocardial infarction at the target vessel; low ejection fraction (<30%); low systolic blood pressure (<90 mmHg); allergy to adenosine; bronchial asthma or chronic obstructive pulmonary disease; and patients not providing informed consent.

Medical information was obtained from interviews with each patient. Hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg on admission, or a history of

E-ISSN: 2311-052X/15

treatment for hypertension. Patients who had smoked cigarettes in the past or were currently smoking at least one cigarette per day were defined as "smokers'. Basic examinations, including blood tests and cardiac ultrasonography, were performed on admission. The levels of cardiac enzymes such as aspartate aminotransferase, lactate dehydrogenase, creatinine kinase, creatinine kinase-MB, and troponin-T were measured before and 18 h after PCI, which is the time when peak troponin-T levels were observed.

This study was approved by the Shinshu University Ethics Committee and carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and informed consent for study participation was obtained from all patients before PCI.

2.2. PCI Procedure

Before admission, all patients were administered oral aspirin (100mg) and clopidogrel (75mg) daily. Immediately prior to PCI, intravenous bolus heparin (100 IU/kg) and nitroglycerin (500μg) were administered. A guiding catheter was engaged at the coronary artery, and a guide wire was passed through the target lesions. Intravascular ultrasound (IVUS; View it, Terumo, Tokyo) was performed to determine the vessel size and to characterize the coronary plaque, followed by balloon dilatation and stent placement. At the discretion of each cardiologist, either a bare metal stent (BMS) or drug-eluting stent (DES) was deployed.

2.3. Coronary Physiological Measurement

An intracoronary pressure and temperature sensor-tipped 0.014-inch wire (Certus, St. Jude Medical, Minneapolis, MN, USA) was passed through a 6F- or 7F-guiding catheter. The sensor near the wire tip measured the distal pressure and temperature, whereas the shaft of the pressure wire detected proximal temperature. Stable hyperemia was attained by continuous intravenous adenosine triphosphate infusion (140-180μg/kg/min) through a 4F sheath *via* the brachial vein. FFR was measured before and after PCI without engagement of the guiding catheter.

IMR was measured after PCI. For measurement of IMR, a brisk injection of room temperature saline (3 mL) to the target coronary artery was performed three times through the guiding catheter; this timing indicated the hyperemic mean transit time, and IMR was calculated by multiplying the distal pressure at 3cm from the floppy tip and the mean transit time [4,5,7]. The interval between each injection was approximately 10 s. Finally, pulling back of the pressure wire was performed to reveal the position of the FFR step up, which was the target of revascularization.

2.4. IVUS Measurement

IVUS examination was performed before and after PCI, as previously reported by our group [8]. Conventional IVUS images were obtained by a 40MHz intravascular catheter (View it, Terumo, Japan). Prior to the IVUS measurement, 0.5mg nitroglycerine was administered into the target vessel. The IVUS catheter was advanced not more than 10mm distal from the lesion and was then automatically pulled to the proximal portion of the target vessel at 0.5mm/s. Echo plaque 2 (Indec Systems, Mountain View, CA, USA) was used for IVUS analysis. The range for analysis was 20mm around the site at minimum lumen. The vessel and plaque areas were measured by tracing the leading edge of the external elastic membrane and lumen at every 0.5mm slice (approximately 40 slices in total) in accordance with the American College of Cardiology clinical expert consensus[9]. The plaque area and plaque burden were calculated by subtracting the lumen area from the area inside of the extra elastic membrane. Each volume was calculated by the integral of the area. Volumetric parameters were corrected for a longitudinal length for 20mm because of some differences of the measured length. The minimum stent area and stent volume were also measured after PCI.

Integrated backscatter-IVUS automatically provided information for coronary tissue characterization, which was categorized by integrated backscatter-values (e.g. red for calcification, blue for lipid pools, and green for fibrosis). The volumes of each component were calculated with correction for lesion length (mm^3/20mm).

2.5. Statistical Analysis

All data are presented as mean±standard deviation for continuous variables and as numbers and percentages for categorical variables. For comparisons between groups, the non-paired t-test and the Mann-Whitney test were performed for normal and non-normal distributions, respectively. Categorical variables were compared using the chi-square test. To determine the crude and adjusted correlations between IMR and different variables, univariate and multivariate logistic regression analyses, respectively, were performed. Parameters that were significantly associated with IMR

in the univariate analysis were included in the multivariate logistic regression analysis. IMR showed log-normal distribution, and log transformation was hence performed. All statistical tests were 2-tailed, and p-values < 0.05 were considered statistically significant. All statistical analyses were performed with PASW Statistics v. 18 (IBM, Somers, NY, USA).

3. RESULTS

The patient characteristics are summarized in Table **1**. Most of the patients were male (82.0%), had hypertension (74.0%), a history of smoking (66.0%), and had received statin therapy (82.0%). The mean high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) levels were 47.6±10.7mg/dL and94.7±29.4mg/dL, respectively, and the ratio of LDL-C to HDL-C was 2.1±0.7.The number of left anterior descending artery, left circumflex artery, and right coronary artery lesions was 28 (56.0%),9 (18.0%), and 13 (26.0%), respectively. All target lesions were clinically stable, and the type of coronary stenosis was A or B1 in all cases.

All cases attained procedure success. Upon angiography, the coronary flow after revascularization was not reduced. The number of patients treated with BMS and DES was 16 (32.0%) and 31 (62.0%), respectively (Table **2**). The mean number of placed stents was 1.1±0.4, and the mean stent diameter and length were3.3mm and 18.3mm, respectively. Plain balloon angioplasty was performed in 3 patients because of small vessels, which were deemed

Table 1: Clinical Characteristics

	Total n = 50
Age	71.1 ± 7.0
Sex, male	41(82.0%)
BMI (kg/m^2)	23.9 ± 2.6
Hypertension	37(74.0%)
Smoking	33(66.0%)
HbA1c (%)	6.1 ± 1.0
LDL-C (mg/dL)	94.7 ± 29.4
HDL-C (mg/dL)	47.6 ± 10.7
L/H	2.1 ± 0.7
TG (mg/dL)	159.8 ± 85.1
EPA/AA	0.50 ± 0.23
Cr (mg/dL)	1.01 ± 0.71
eGFR (mL/min/1.73 m^2)	61.9 ± 16.9
BNP (pg/mL)	94.4 ± 118.1
FDP-DD (μg/mL)	1.4 ± 1.9
Statin	41(82.0%)
LAD	28(56.0%)
LCX	9(18.0%)
RCA	13(26.0%)
LMT	0(0%)

Data are presented as mean ± standard deviation or n (%).
Hypertension was defined as systolic blood pressure at rest of <140 mm Hg and/or diastolic pressure at rest >90 mm Hg on admission, or current treatment with an antihypertensive agent.
BMI, body mass index; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C to HDL-C ratio; TG, triglyceride; EPA/AA, eicosapentaenoic acid to arachidonic acid ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; FDP-DD, fibrin/fibrinogen degradation products-D dimer; LAD, left anterior decending artery; LCX, left circumflex artery; RCA, right coronary artery; LMT, left main trunk artery.

Table 2: Interventional Characteristics

	Total n = 50
PCI	
BMS	16(32.0%)
DES	31(62.0%)
POBA	3(6.0%)
Pre dilatation	43(86.0%)
Post dilatation	45(95.7%)
Stent number	1.1 ± 0.4
Stent diameter (mm)	18.3 ± 5.2
QCA	
MLD (mm)	1.1 ± 0.4
% Stenosis (%)	55.0 ± 11.6
Lesion length (mm)	9.2 ± 4.3
IVUS (per 20 mm)	
Vessel volume (mm^3)	248 ± 80.6
Plaque volume (mm^3)	135.1 ± 54.1
Lumen volume (mm^3)	90.4 ± 57.3
Plaque burden (%)	55.1 ± 9.3
Calcification (%, mm^3)	1.8 ± 1.6 (2.3 ± 1.9)
Dense fibrosis (%, mm^3)	6.0 ± 3.6 (7.8 ± 4.2)
Fibrosis (%, mm^3)	42.8 ± 11.1 (57.4 ± 20.3)
Lipid (%, mm^3)	49.3 ± 14.8 (77.3 ± 38.2)
FFR	
Pre	0.77 ± 0.14
Post	0.92 ± 0.08
IMR	
Post	29.53 ± 25.66
Blood test	
Pre troponin T (ng/ml)	0.05 ± 0.03
Post troponin (ng/ml)	0.12 ± 0.17
D Troponin T>0.1	7(15.9%)
Pre CK-MB (ng/ml)	9.47 ± 2.89
Post CK-MB (ng/ml)	13.80 ± 9.62
D CK-MB > 16	2(4.5%)

Data are presented as mean ± standard deviation or n (%).
PCI, percutaneous coronary intervention; BMS, bare metal stent; DES, drug eluting stent; POBA, plain old balloon angioplasty; QCA, quantitative coronary angiography; MLD, minimal lesion diameter; IVUS, intravascular ultrasound; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; CK-MB, creatinine kinase MB.

inappropriate for stent implantation. Quantitative coronary angiography revealed that the minimal lesion diameter was 1.1±0.4mm, and the ratio of luminal stenosis was 55.0±11.6%. The mean lesion length was relatively short (9.2±4.3mm). Conventional IVUS revealed that the mean volumes of the lesion vessels and plaques per 20mm were 248.6±80.6 and 135.1±54.1mm^3, respectively. The plaque burden was 55.1±9.3%. By integrated backscatter-IVUS characterization of the coronary tissue, the prevalence of calcification, dense fibrosis, fibrosis, and lipid pools was determined to be 1.8±1.6%, 6.0±3.6%, 42.8±11.1%, and 49.3±14.8%, respectively. By pressure and thermo dilution studies, the mean FFR, measured before and after revascularization, was determined to be 0.77±0.14 and 0.92±0.08, respectively. The mean post-PCI IMR was 29.53±25.66.

Table **3** shows the results of the univariate analysis. Post-PCI IMR tended to have negative associations with HDL-C (p=0.078), calcification at the target lesion (p=0.058), and hypertension (p=0.071; non-paired t tests). The receiver operating characteristics curve confirmed that the HDL-C level and calcification rate were significant predictors of high IMR (p=0.026, area under the curve=0.721 and p=0.023, area under the curve=0.719, respectively), and the cutoffs for the HDL-C level and calcification rate to predict high IMR were determined to be 42.5 mg/dL and 1.975%, respectively (sensitivity 82.4%, specificity 61.1% and sensitivity 57.9%, specificity 88.9%, respectively). No significant cutoff value was found for hypertension.

Subsequently, the patients were divided into 2 groups according to the levels of HDL-C (HDL-C > 42.5 mg/dL [high HDL-C] and HDL-C < 42.5 mg/dL [low HDL-C] and calcification (calcification > 1.975% [high calc] and calcification < 1.975% [low calc]).We found that post-PCI IMR was significantly lower in the high HDL-C group compared to in the low HDL-C group (p=0.016), and that it tended to be lower in the high calcification ratio group compared to in the low calcification rate group (p=0.066) (Figure **1**).

Table **4** shows the results of the multivariate logistic regression analysis. Independent variables were selected according to the results of the univariate analysis. HDL-C and calcification ratio were found to be independent predictors of high IMR (odds ratio [OR], 0.919; 95% confidence interval [CI], 0.845-1.000, p=0.049; and OR, 0.546; 95% CI, 0.298-0.998, p=0.049, respectively), whereas hypertension was not independently associated with high IMR (p=0.054).

Table 3: Univariate Analysis for Post-IMR

	Post-IMR	
	r	p
Age	-0.156	0.348
Sex, male		0.399
BMI (kg/m^2)	-0.029	0.862
Hypertension		0.071
Smoking		0.631
HbA1c (%)	-0.061	0.722
LDL-C (mg/dL)	-0.146	0.395
HDL-C (mg/dL)	-0.298	0.078
L/H	0.118	0.492
TG (mg/dL)	0.2	0.242
EPA/AA	-0.035	0.841
Cr (mg/dL)	0.066	0.692
eGFR (mL/min/1.73 m^2)	0.029	0.86
BNP (pg/mL)	-0.148	0.389
FDP-DD (μg/mL)	-0.203	0.222
D Troponin-T positive (>0.1 ng/ml)		0.852
DCK-MB (IU/l)	0.067	0.701
Vessel volume (mm^3)	0.2	0.234
Plaque volume (mm^3)	0.148	0.382
Lumen volume (mm^3)	0.216	0.2
Calcification (%)	-0.22	0.058
Dense fibrosis (%)	-0.141	0.223
Fibrosis (%)	-0.138	0.417
Lipid (%)	0.212	0.208
Pre FFR	-0.139	0.226

Delta troponin-T positive was defined as elevation more than 0.1 ng/ml.
Spearman's rank correlation test was performed for continuous variables because post IMR was not normally distributed.
Categorized variables were analyzed with the Mann-Whitney test.
BMI, body mass index; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; L/H, LDL-C to HDL-C ratio; TG, triglyceride; EPA/AA, eicosapentaenoic acid to arachidonic acid ratio; Cr, creatinine; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide; FDP-DD, fibrin/fibrinogen degradation products-D dimer; CK-MB, creatinine kinase MB; FFR, fractional flow reserve.

Moreover, the multivariate regression analysis (Table **5**) revealed a significant association between post-PCI IMR and HDL-C levels (β =-0.464, p=0.005; Figure **2a**), whereas the calcification ratio did not show a significant association with IMR (p=0.406, Figure **2b**).

4. DISCUSSION

In this study, we found that microvascular injury after PCI was inversely associated with preprocedural HDL-C levels and plaque calcification.

Microvascular resistance increases occasionally after elective PCI, and has been speculated to mainly

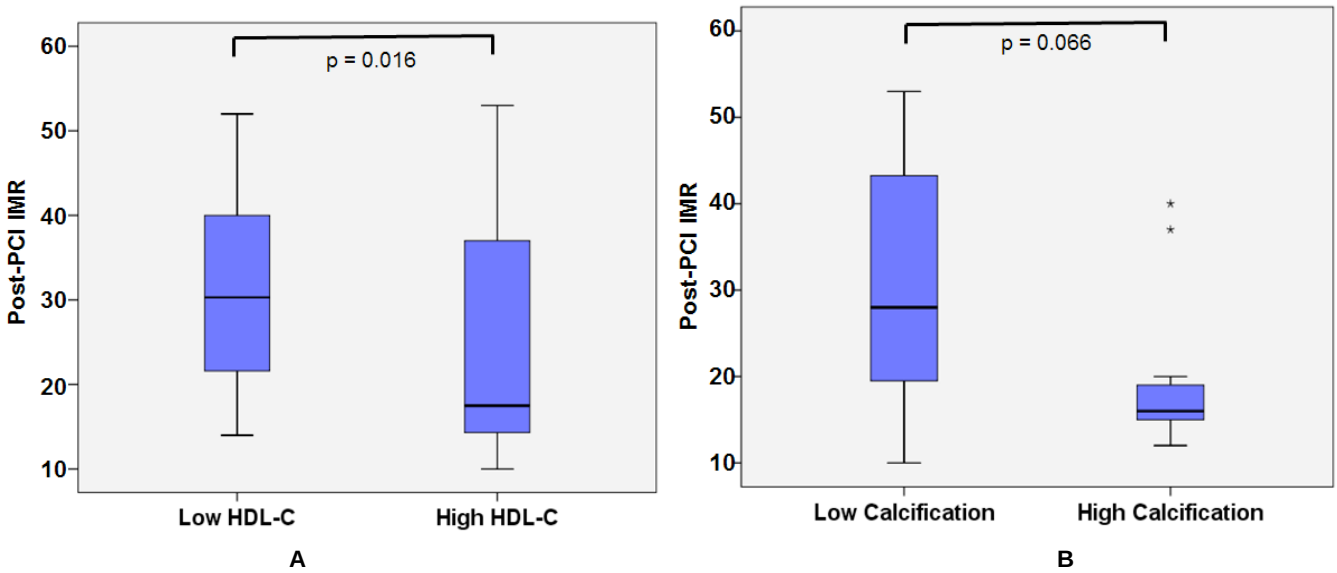

Figure 1: (**A**) Post-percutaneous coronary intervention (PCI) index of microcirculatory resistance (IMR) levels in the high and low serum high density lipoprotein cholesterol (HDL-C) groups. The patients were divided into two groups by HDL-C 42.5mg/ dL. Because each group had non-normal distribution, Mann-Whitney-tests were performed. The high HDL-C group had significantly lower Post-PCI IMR levels than the low HDL-C group (p=0.016).

(**B**) Post-percutaneous coronary intervention (PCI) index of microcirculatory resistance (IMR) levels in the high and low coronary calcification groups. The patients were divided into two groups by coronary calcification 1.9750 %. Because each group had non-normal distribution, Mann-Whitney-tests were performed. The Post-PCI IMR tended to be lower in the high calcification group than in the low calcification group (p=0.066).

Table 4: Multiple Logistic Regression Analysis for High IMR

	High IMR		
	OR	**95% CI**	**p**
HDL-C	0.919	0.845-1.000	0.049
Calcification %	0.546	0.298-0.998	0.049
Hypertension			0.054

Multiple logistic regression analysis was performed to predict the high IMR group.
Independent variables were selected according to the univariate analysis.
IMR, index of microcirculatory resistance; OR, odds ratio; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol.

Table 5: Multiple Logistic Regression Analysis for Post-IMR

	IMR		
	R2	**b**	**p**
HDL-C	0.192	-0.464	0.005
Calcification %			0.406

Multiple regression analysis was performed to predict post-IMR.
Independent variables were selected according to the univariate analysis.
IMR, index of microcirculatory resistance; R2, adjusted R2; b; standard partial regression coefficient; HDL-C, high-density lipoprotein cholesterol.

result from distal embolisms and increased susceptibility of the coronary microcirculation. Distal embolism is a common issue during PCI; balloon expansion and stent implantations can lead to vascular stress, and coronary plaques composed of components such as lipid pools, fibrosis, and calcification may be injured during these procedures. In turn, injury to these components can result in small particles breaking loose and causing occlusion of the coronary capillaries, known as microvascular injury [10]. When over 50% of the coronary capillaries are obstructed, the myocardial blood flow is considered to be reduced irreversibly [11].

The no-reflow phenomenon has been reported to occur both during elective and emergency PCI (in 2-5% and 30% of cases, respectively) [12]. Katayama *et al*.

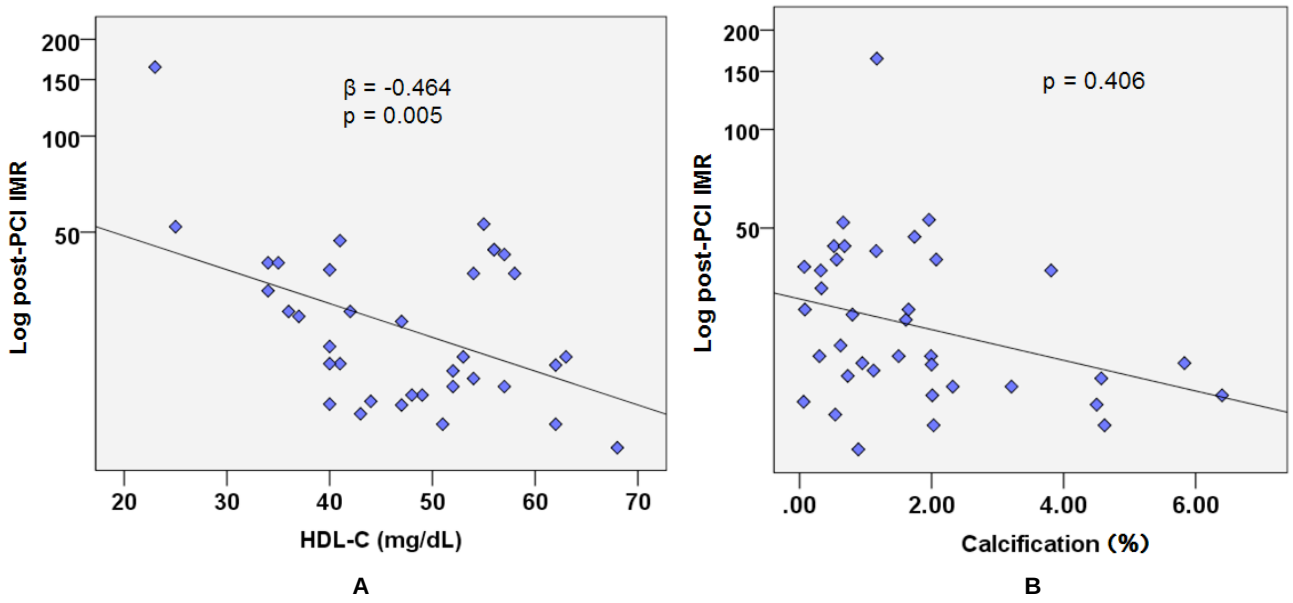

Figure 2: (**A**) The relationship between high-density lipoprotein cholesterol (HDL-C) and logarithm index of microcirculatory resistance (IMR). According to the multivariate regression analysis, HDL-C was an independent predictor of post-percutaneous coronary intervention (PCI) IMR (β=-0.464, p=0.005).

(**B**) The relationship between calcification ratio and logarithm IMR. The calcification ratio was not associated with logarithm post-PCI IMR (p=0.406).

reported in their study that high atherothrombotic burden and decreased plaque volume during stent implantation in patients with acute myocardial infarctionare potential risk factors for the development of the angiographic no-reflow phenomenon [13]. Similarly, Ohshima *et al*. reported that the presence of fibrofatty-rich components with necrotic cores or dense calcium are closely related to an increased risk of the angiographic no-reflow phenomenon following PCI in patients with acute myocardial infarction [14]. Bose *et al*. reported that patients with large necrotic cores in culprit lesions experienced higher in creases in serum cardiac markers during elective PCI than in patients without these [15]; and Hong *et al*. reported that post-PCI cardiac Troponin-I elevation occurs more frequently in lesions with a large necrotic core area [16]. In this study, we found that the calcium component in the plaque, rather than the lipid or fibrotic component, was more highly associated with microvascular damage, as assessed by IMR. In accordance with these findings, Kodama *et al*. also reported that calcification surrounded by plaque detected with computed tomographic angiography predicted no-reflow phenomenon [17].

In addition to distal embolism, susceptibility of the microcirculation has also been demonstrated to berelated with the elevation of microcirculatory resistance; and baseline inflammation markers, such as C-reactive protein, have been hypothesized to indicate infarct sizes associated with the no-reflow phenomenon [18]. Moreover, it has been reported that dyslipidemia worsens reperfusion injury by oxidative stress in an animal model [19].

Lipid therapy with statin or nutraceuticals lead to reduction of risk for atherosclerotic events [20,21]. Lee *et al*. showed that the therapy of flubastatin which reduced LDL-C and increased HDL-C levels produced significant improvement in major cardiac events (MACE) after PCI [22]. Conversion from vulnerable to fibrotic plaque might indicate more reduction of distal embolism which caused increase of microvascular disorder. Mangiacapra *et al*. reported that IMR before revascularization correlated with total cholesterol and LDL-C levels, and that LDL-C was an independent predictor of IMR [23]. In this study, we found that HDL-C, but not LDL-C, was significantly associated with IMR after elective PCI.

The importance of HDL-Chas been the focus of numerous recent research efforts, and several studies have indicated that HDL-C levels are inversely associated with the presence of coronary artery disease [24,25]. Arsenault *et al*. reported that major cardiovascular events, defined as coronary artery disease death, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal strokes, correlated with LDL-C,

triglyceride, and HDL-C levels in patients treated with statin in whom the serum LDL-C levels were maintained at <70mg/dL [26]. Peters *et al*. reported that the occurrence of echolucent carotid plaques related to cardiovascular events was inversely associated with HDL-C, and that high levels of HDL-C resulted incarotid plaques becoming more echogenic, and there by more stable [27]. Recent reports suggest that HDL-C exerts potent antioxidant effects [28] and has anti-inflammatory properties [27]. Furthermore, platelet aggregation is inversely correlated with HDL-C levels in humans, suggesting that HDL-C has antiplatelet actions. Indeed, HDL-C acts indirectly on platelet activation *via* effects on endothelial cells, such as enhanced prostacyclin synthesis and reduced von Willebrand factor levels [21]. It was reported that anti-proliferating drug coated to coronary stent for usual clinical use might indicate microvascular endothelial dysfunction [29]. Direct approach of anti-proliferative drug to vascular smooth muscle cells with microRNA prevented endothelial damage. Like this method, antioxidant and antithrombotic effects of HDL-C might contribute to the reduced microvascular damage during PCI. In addition, local effects of HDL-C on macrophage cholesterol efflux and cholesterol disposition have been reported [28], which may also be related to the stabilization of coronary plaques and prevention of the no-reflow phenomenon during PCI.

5. STUDY LIMITATIONS

There were a number of limitations associated with this study. First, this study was not a prospective study, and selection bias hence existed. There was no follow-up data. Second, the study population in this study was relatively small. Third, the difference in IMR between before and after PCI may reflectreal myocardial damage. However, to measure pre-PCI IMR, it is necessary to adjust the IMR according to the presence of epicardialartery stenosis [30], and pre-PCI MR was not measured in this study. Reproducibility of value of IMR was sometimes unstable. In this study, we measured IMR several times and averaged these value.

6. CONCLUSION

Low levels of serum HDL-C and plaque calcification independently predict higher post-PCI IMR. Serum lipid and plaque calcification profiles might be important for predicting and preventing periprocedural myocardial damage during elective PCI.

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Received on 03-04-2015 Accepted on 20-04-2015 Published on 29-04-2015

DOI: http://dx.doi.org/10.12970/2311-052X.2015.03.01.3