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Endothelial Dysfunction and Increased Carotid Intima-Media Thickness in the Patients with Slow Coronary Flow

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Flow mediated brachial dilatation (FMD) and carotid intima-media thickness (IMT) have been a surrogate for early atherosclerosis. Slow coronary flow in a normal coronary angiogram is not a rare condition, but its pathogenesis remains unclear. A total of 85 patients with angina were evaluated of their brachial artery FMD, carotid IMT and conventional coronary angiography. Coronary flow was quantified using the corrected thrombosis in myocardial infarction (TIMI) frame count method. Group I was a control with normal coronary angiography (n = 41, 56.1 ± 8.0 yr) and group II was no significant coronary stenosis with slow flow (n = 44, 56.3 ± 10.0 yr). Diabetes was rare but dyslipidemia and family history were frequent in group II. Heart rate was higher in group II than in group I. White blood cells, especially monocytes and homocysteine were higher in group II. The FMD was significantly lower in group II than in group I. Elevated heart rate, dyslipidemia and low FMD were independently related with slow coronary flow in regression analysis. Therefore, endothelial dysfunction may be an earlier vascular phenomenon than increased carotid IMT in the patients with slow coronary flow.

Key Words: Endothelium; Coronary Artery; Carotid Intima

INTRODUCTION

Coronary slow flow is not a rare finding which characterized by angiographically normal or near-normal coronary arteries with delayed progression of the contrast agent into distal vasculature. It is characterized by slow velocity flow of dye through the coronary artery in the absence of any evident obstructive lesion in it grossly. Since first description of this phenomenon in 1972, the mechanism of this phenomenon has not been extensively studied so far (1). On the basis of myocardial biopsy studies, it can be suggested that a combination of structural and functional obstruction exists in the coronary microcirculation (2, 3).

Previous studies have shown that impaired endothelial function plays an important role in this abnormal coronary vasoreactivity (4). Several surveys have investigated the relationship between coronary slow flow phenomenon and endothelial dysfunction as a probable etiology.

Among several atherosclerotic surrogate, increased carotid intima-media thickness (IMT) was positively related with coronary artery severity and cardiovascular event; therefore it regarded as an early indicator of overall atherosclerosis (5). In the present studies, the patients with obesity or ischemic heart disease proven coronary angiography were found to have increased IMT and impaired FMD compared to the healthy controls (6). However, the situation might not be same in patients with coronary slow flow. Therefore, we aimed to determine the relationship among the vascular risk factors, including endothelial dysfunction and carotid IMT in the patients with slow coronary flow.

MATERIALS AND METHODS

Study populations

The study population consisted of 150 patients with newly diagnosed stable angina. All of them were evaluated conventional coronary angiography, brachial artery FMD, and carotid IMT. We excluded subjects with significant narrowed coronary artery from coronary angiography (n = 65, 59.5 ± 8 yr). Eighty-five patients without significant coronary stenosis were divided into two groups according to the presence of coronary slow flow: Group I included patients without slow flow (n = 41, 56.1 ± 8.0 yr) and group II patients with slow flow (n = 44, 56.3 ± 10.0 yr). We evaluated the relationship of the vascular risk factors, includ-

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ing endothelial dysfunction and carotid IMT in the patients with slow coronary flow.

Definition of slow coronary flow

Determination of frame counts was carried out by the method described previously by Gibson et al. (7). According to corrected thrombolysis in myocardial infarction (TIMI) frame count, slow flow was defined as more than 2 standard deviations of frame count (TIMI 2) from the normal published range for that particular vessel (7). We corrected the TIMI frame count for the left anterior descending (LAD) to take account of the longer distance to the TIMI landmark. This ratio was obtained by dividing the mean TIMI frame count of the LAD by the mean TIMI frame count of the circumflex and the right coronary artery. More than two experienced cardiologists reviewed all the patients' angiography and calculated the frame count. Interobserver and intraobserver agreement (κ-value) were 0.73 and 0.78 for TIMI flow grade respectively. Interobserver and intraobserver coefficients of variation were 9.72% and 5.86% for corrected TIMI frame count. Normal coronary artery was defined as no significant stenosis even at < 50% of the diameter of the coronary artery.

Measurement of endothelial and vascular smooth muscle dysfunction

A Sequoia 512 ultrasound system (Siemens Corp, Upplands-Väsby, Sweden) was used with a 15L8 transducer for brachial artery and a 8L5 transducer for carotid artery studies. All investigations were digitally stored for analyses, which were performed by a single observer (EL, intraobserver variability r = 0.988) on a Sequoia 512. R-wave triggered end diastolic right brachial artery longitudinal images proximal to the antecubital fossa were recorded at baseline after 15 min of supine rest. Transducer position was carefully noted for subsequent investigations. For flow mediated dilatation (FMD), R-wave triggered images were stored for 90 sec following ischemia. The ischemia was induced using a cuff on the forearm inflated 20 mmHg above the systolic blood pressure for five minutes with additional lower arm muscular work by repetitively squeezing a small ball during the last minute of ischemia. Maximal brachial artery diameter was calculated for both conditions as a mean of three measurements (8). After 15 min of recovery to the baseline diameter, 400 μg sublingual nitroglycerine was administered and nitrogen mediated diameter (NMD) was assessed. FMD and NMD values were expressed as percentage change from baseline value. The reproducibility of this method was reliable level in this study (r = 0.997, $P < 0.001$).

Measurement of carotid artery intima-media thickness

Carotid artery studies were performed with the individual in the supine position with the neck extended and the chin turned away from the side being examined. The right and left common carotid artery proximal to the bulb was imaged in multiple longitudinal planes for the best resolution of the IMT of the far wall. The mean IMT was obtained manually tracing the intima-media in the far wall of the artery for a distance of approximately 10 mm (9). Measurements were performed on three end diastolic images and averaged.

Statistical analysis

All eligible patients enrolled in this study were included in the analysis. Standard statistics were used to describe the baseline clinical characteristics. Continuous variables are presented as mean ± standard deviations. Comparisons of means between the groups were done using a Student's t-test and analysis of variance (ANOVA) as appropriate. A P value < 0.05 was considered statistically significant. To find out optimal cutoff values, receiver operating characteristic (ROC) analysis was performed. Sensitivity, specificity were calculated using typical formulas. No missing value imputation was performed. All statistical analysis were performed with SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Ethics statement

The study protocol was reviewed and approved by the institutional review board of Chonnam National University Hospital (No. 2010-05-092). All subjects provided their informed, written consent before participation.

RESULTS

Baseline characteristics

As shown in Table 1, there were no significant differences in age and gender between two groups. Baseline heart rate was higher in group II than in group I. Dyslipidemia and family history of premature cardiovascular disease were significantly frequent in

Table 1. Baseline clinical characteristics

Parameters	Group I (n = 41)	Group II (n = 44)	*P* value
Age (yr)	56.1 ± 8	56.3 ± 10	0.942
Sex (male, %)	20 (48.7)	22 (50.0)	0.433
Height (cm)	163.1 ± 9.8	162.8 ± 8.9	0.864
Weight (kg)	66.2 ± 11.8	67.0 ± 8.2	0.787
AC (cm)	86.43 ± 10.6	90.23 ± 10.65	0.166
BMI (kg/m^2)	25.06 ± 3.1	25.21 ± 3.5	0.849
Systolic BP (mmHg)	126.97 ± 14.2	126.64 ± 15.3	0.919
Diastolic BP (mmHg)	80.5 ± 11.6	80.16 ± 11.0	0.879
HR (/min)	66.1 ± 7.3	72.09 ± 6.26	0.001
Hypertension (%)	12 (29.3)	15 (34.0)	0.404
Diabetes (%)	9 (20.4)	2 (4.5)	0.018
Dyslipidemia (%)	5 (12.2)	21 (47.7)	0.001
Smoking (%)	11 (26.8)	15 (34.1)	0.312
Family history (%)	1 (2.4)	7 (17.0)	0.036

Data are given as mean ± SD or No. (%). AC, abdominal circumference; BMI, body mass index; BP, blood pressure; HR, heart rate.

group II. The prevalence of diabetes was lower in groups II than in group I. The percentage of hypertension and smoking were not different between groups.

Laboratory findings in the patients with coronary slow flow

White blood cell count, especially monocytes was higher in group II than in group I. In spite of dyslipidemia was more frequent in group II, the level of lipid profile contained total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) and triglyceride was not significant different between groups. The level of homocysteine was higher in group II than in group I significantly. Other inflammatory marker such as high sensitivity C-reactive protein and fibrinogen were not significantly different between groups (Table 2).

The difference of endothelial and vascular smooth muscle function

The FMD showed normal distribution pattern; mean FMD was 7.22 ± 3.62 (minimum 1.79% to maximum 21.43%). The FMD was significantly lower in group II than in group I (5.52 ± 2.18 vs 9.03 ± 3.98, $P < 0.001$). NMD was not significantly different between two groups (Fig. 1). Avarage carotid IMT was 0.61 ± 0.15 in the patients of this study. Carotid IMT was tended to be higher in group II, without no statistical significance (Table 3).

The independent risk factors of slow coronary flow

In regression analysis, elevated heart rate, dyslipidemia and low FMD were independently related with slow coronary flow in regression analysis (Table 4). The cut off value of FMD for pre-

Table 2. Laboratory findings in the patients with slow coronary flow

Laboratory parameters	Group I (n = 41)	Group II (n = 44)	*P* value
WBC (/μL)	6,410 ± 1,705	7,536 ± 2,548	0.021
Monocytes (/μL)	430 ± 207	549 ± 200	0.010
Creatinine (mg/dL)	0.78 ± 0.24	0.81 ± 0.19	0.678
Total cholesterol (mg/dL)	159.60 ± 36.84	182.86 ± 39.29	0.128
LDL cholesterol (mg/dL)	131.22 ± 35.46	117.77 ± 38.10	0.097
HDL cholesterol (mg/dL)	52.69 ± 10.99	48.11 ± 14.31	0.104
Triglyceride (mg/dL)	100.63 ± 74.10	125. 78 ± 89.53	0.166
HbA1c (g/dL)	5.84 ± 0.85	5.88 ± 0.93	0.877
hs-CRP (mg/dL)	0.16 ± 0.18	0.57 ± 1.01	0.178
Homocysteine (μM/L)	7.34 ± 2.44	9.30 ± 4.89	0.031
Fibrinogen (μg/mL)	258.22 ± 59.12	277.49 ± 83.18	0.251

Data are given as mean ± SD. HDL, high density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; WBC, white blood cells.

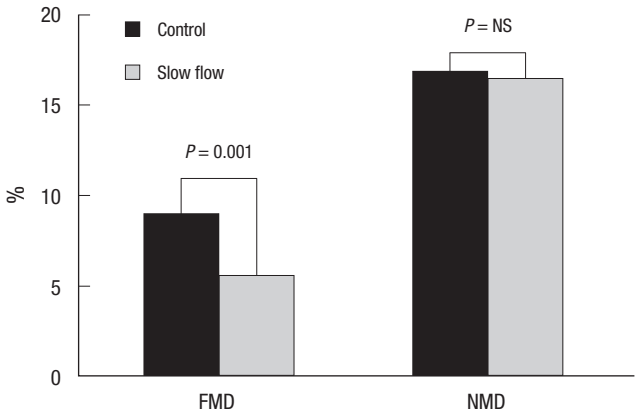

Fig. 1. Differences of endothelial and vascular smooth muscular function. FMD, flow mediated dilatation; NMD, nitrogen mediated dilatation.

Table 3. The difference of atherosclerotic surrogate in the patients with slow coronary flow

Parameters	Group I (n = 41)	Group II (n = 44)	*P* value
Pre FMD diameter (mm)	3.93 ± 0.67	4.09 ± 0.8	0.327
Post FMD diameter (mm)	4.27 ± 0.65	4.31 ± 0.81	0.783
FMD (%)	9.03 ± 3.93	5.52 ± 2.18	0.001
Pre NMD diameter (mm)	4.53 ± 0.27	4.12 ± 0.814	0.444
Post NMD diameter (mm)	4.69 ± 0.68	4.76 ± 0.81	0.660
NMD (%)	16.87 ± 18.4	16.37 ± 8.4	0.871
Left carotid IMT (mm)	0.55 ± 0.14	0.62 ± 0.17	0.095
Right carotid IMT (mm)	0.56 ± 0.13	0.60 ± 0.24	0.529

Data are given as mean ± SD. IMT, intima-media thickness; FMD, flow mediated dilatation; NMD, nitrogen mediated dilatation.

Table 4. Independent predictors of slow coronary flow

Predictors	Hazard ratio	Confidence interval	*P* value
Heart rate (> 70/min)	4.971	1.264-19.552	0.022
Dyslipidemia	13.050	1.739-97.910	0.012
Family history	5.229	0.091-302.080	0.424
WBCs	2.642	0.642-10.877	0.178
Monocytes	0.862	0.200-3.707	0.841
Homocysteine	1.468	0.370-5.830	0.585
FMD	17.228	3.006-98.774	0.001

CCA IMT, common carotid artery intima-media thickness; FMD, flow mediated dilatation.

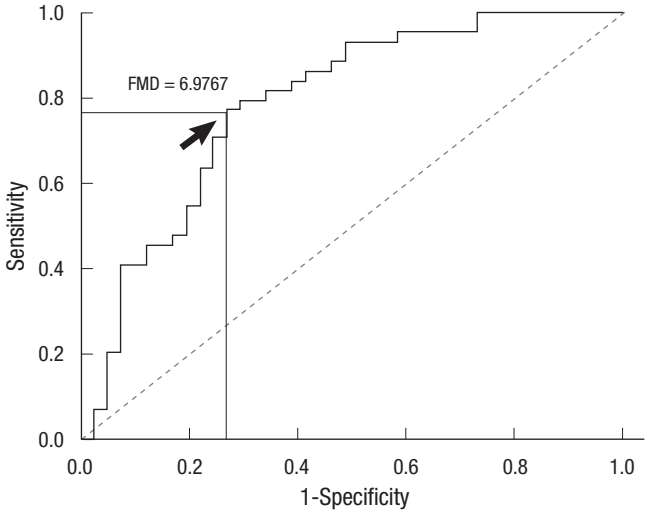

Fig. 2. Receiver operator characteristics curves of slow coronary flow. Arrow means cut off value of FMD (Area under the curve = 0.787, sensitivity = 0.773, specificity = 0.732).

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diction of slow flow was 6.97% (area under the curve = 0.787, sensitivity = 77.3%, specificity = 73.2%) (Fig. 2).

DISCUSSION

Slow coronary flow means the slow dye progression into distal vasculature of coronary arteries during coronary angiography. It was reported in approximately 1% of patients undergoing conventional coronary angiography (10). The exact mechanism was not clear until now; small vessel dysfunction may be involved in this phenomenon. Increased flow resistance, increased microvascular tone, platelet dysfunction (11), early demonstration of diffuse atherosclerosis (12), inflammation (13, 14), and an imbalance of vasoactive substances (15) have been suggested as underlying mechanisms.

In our study, baseline heart rate was higher in slow flow group and heart rate more than 70/min was the independent factor of slow flow. Increased sympathetic tone with elevated catecholamine levels may have direct effects on vessel or it may affect other factors promoting the progression of atherosclerosis. If we could measure the baseline catecholamine level, it would be more supportive presenting this phenomenon. This catecholamine may be a role for the difference of family history in this study due to emotional stress. In spite of insignificance of the level of lipid profile, dyslipidemia was also significantly frequent in slow flow group and an independent predictor of slow flow in this study. Fortunately, the patients with previous medicated statin were excluded in this study, because they contained the group of significant coronary stenosis. Hyperlipidemia has been associated with an increased blood viscosity, which causes an increase in capillary resistance (16). Although diabetes was frequent risk factor of cardiovascular disease increasing inflammation and vascular damage, diabetes was significantly more common in the control group than in slow flow group in this study. Because we analyzed the control and slow flow group after excluded the significant coronary artery lesion, it may be a result from analysis of the covariance for omission of the confounding factor. Vascular inflammatory marker was variety. In this study, we checked white blood cells with differential count, fibrinogen, hs-CRP and homocysteine. White blood cells, especially monocytes and homocysteine were elevated in the patient with slow flow. In a previous study, homocysteine levels increased but folate levels decreased in patients with slow coronary flow (17). Even though we did not check the folate levels, the possible disturbance in the metabolism of homocysteine in patients with coronary slow flow may have a role in the pathogenesis of this phenomenon associated with inflammation by causing generalized atherosclerosis.

Different theories have been postulated about the cause of small-vessel dysfunction, including microvascular tone alteration, small-vessel wall thickening (18), patchy fibrosis and impaired endothelial release of nitric oxide (NO) (19, 20). The endothelium plays a crucial role for initiation of atherosclerosis in early stage. Endothelial dysfunction was considered as early marker of atherosclerosis (21, 22). In this study, the FMD was significantly lower in slow flow group than in control and low FMD were independently related with slow coronary flow in regression analysis. The cut off value of FMD for prediction of slow flow was 6.97% from ROC curve. Vascular smooth muscle dysfunction from NMD was not affected in coronary slow flow. Collectively, it can be hypothesized that the impaired peripheral endothelial function (assessed by FMD of the brachial artery), not vascular smooth muscle, may also suggest the involvement of epicardial coronary arteries with slow flow. Another surrogate of early atherosclerosis is carotid IMT. Carotid arterial IMT correlates well with most cardiovascular risk factors and, in population studies, increasing carotid arterial wall thickness (IMT and plaques) has been associated with worsening coronary artery disease. Several studies have now demonstrated that carotid IMT is significantly increased in patients with slow coronary flow (23). However, our data showed carotid IMT was not significantly different between normal and slow coronary flow patients. Since FMD constitutes a physiologic assessment of endothelial dysfunction and carotid IMT is an anatomic structural measure of subclinical atherosclerosis, endothelial dysfunction is an earlier phenomenon than increased carotid IMT on the cascade of atherosclerosis in the patients with slow coronary artery.

This study had several limitations. There was a patient selection bias. Because this study was cross-sectional, baseline characteristics of this study could not be controlled, especially risk factors. Also, we did not consider about previous medication history. Although we measured FMD and carotid IMT in the state of holding drug during one day, previous duration of antianginal or antiplatelets might affect the results of frame count in coronary angiography cession. There had insufficient impact for endothelial dysfunction due to absence of laboratory markers. Finally, our study population was relatively small, and further large-scale clinical and experimental studies are warranted to detect precise pathogenesis and effective therapy for this systemic disorder.

Notwithstanding all these limitations, the data suggest that the slow coronary flow is not a simple, isolated change localized in epicardial coronary arteries, but may be a part of systemic vascular disturbance.

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