Clinical Significance of Flow-Mediated Dilation, Brachial Intima-Media Thickness and Pulse Wave Velocity in Patients With and Without Coronary Artery Disease

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Background: Little is known about the interrelationships among brachial flow-mediated vasodilatation (bFMD), brachial-ankle pulse wave velocity (baPWV) and brachial intima-media thickness (bIMT) in patients with and without coronary artery disease (CAD).

Methods and Results: Two-hundred consecutive patients with stable angina pectoris (SAP) were enrolled as the CAD group and 50 age-, sex- and body mass index-matched patients without CAD were selected as the non-CAD group. bFMD, diastolic blood pressure (DBP) and high-density lipoprotein cholesterol (HDL-C) in the CAD group were significantly lower. The CAD group showed significantly higher levels of hemoglobin A_{1c} (HbA_{1c}) and low-density lipoprotein cholesterol (LDL-C), but not baPWV. CAD was independently associated with bFMD, DBP, HbA_{1c} and HDL-C. bFMD and HDL-C significantly decreased and LDL-C increased as the number of diseased vessels with significant stenosis increased. The number of diseased vessels was independently associated with bFMD and HDL-C. In addition, bFMD, bIMT, the time constant of the shear rate and the time constant of the flow rate as assessed by a new program, Trend Plus®, were associated with the presence of CAD. Among these parameters, the presence of CAD was independently associated with bIMT as well as bFMD.

Conclusions: bFMD was a better predictor of the severity of CAD than either baPWV or coronary risk factors in patients with SAP. In addition, bIMT may be a critical predictor of CAD. (*Circ J* 2012; **76**: 1469–1475)

Key Words: Atherosclerosis; Coronary artery disease; Endothelial function; Risk factors

Endothelial dysfunction is one of the initial pathological processes of atherosclerosis and has been associated with increased cardiovascular risk.¹ Measurement of flow-mediated vasodilatation (FMD) in the brachial artery, as determined by ultrasound techniques, has become more widely available, and enables non-invasive assessment of endothelial function.^{2,3} Brachial FMD (bFMD) has been shown to be an independent predictor of cardiovascular events,^{4,5} but not in all studies.^{6,7} Thus, the value of bFMD for predicting cardiovascular events is still not well established.

Non-invasive assessments of cardiovascular risk include brachial-ankle pulse wave velocity (baPWV)⁸ and carotid intima-media thickness (cIMT), in addition to bFMD. Several studies have demonstrated a significant correlation between PWV or FMD and cIMT.^{9,10} A previous report showed that FMD, cIMT and PWV are related to each other.¹¹ However, no association was observed in other studies.^{12,13} This difference regarding association may be related to differences in the patients' characteristics and the number of participants. Al-

though cIMT has also been associated with cardiovascular risk factors¹⁴ and with the morbidity and mortality of coronary artery disease (CAD),^{14,15} no reports have analyzed brachial (b)IMT. Therefore, bIMT in addition to various vasodilatation parameters of the brachial artery were analyzed using a new analysis program, Trend Plus®.

The aim of the present study was to evaluate the interrelationships among coronary risk factors, FMD and baPWV in patients with and without stable angina pectoris (SAP). We also evaluated the significance of bIMT and other vasodilatation parameters of the brachial artery using Trend Plus® for the prediction of CAD.

Methods

Study Population

SAP was defined as no changes in the frequency, duration, or intensity of symptoms for 4 weeks and as lumen diameter stenosis >50% in at least 1 major coronary artery as determined

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Table 1. Patients' Characteristics

	Non-CAD (n=50)	CAD (n=200)
Age, years	66±10	67±9
Male, n (%)	33 (66)	156 (78)
BMI, kg/m ²	23.4±3.2	23.8±3.4
HT, n (%)	28 (56)	172 (86)
SBP, mmHg	126±14	125±14
DBP, mmHg	72±10	69±10*
DL, n (%)	34 (68)	183 (92)
HDL-C, mg/dl	56±12	50±12*
LDL-C, mg/dl	110±27	97±28*
TG, mg/dl	122±60	136±79
DM, n (%)	15 (30)	95 (48)
Fasting glucose, mg/dl	105±35	112±40
HbA _{1c} , %	5.8±0.8	6.2±1.2*
HU, n (%)	40 (20)	10 (20)
UA, mg/dl	5.4±1.1	5.5±1.3
eGFR, ml·min ⁻¹ ·1.73 cm ⁻²	66±14	62±16
U-Alb/Cr, mg/L Cr	0.05±0.1	0.77±4.0
Smoking, n (%)	14 (28)	40 (20)
bFMD, %	6.1±3.4	4.5±2.3*
baPWV (mean), cm/s	1,725±325	1,775±410
Medication, n (%)		
ARB/ACEI	17 (36)	149 (82)*
CCB	21 (42)	110 (55)
α -blocker	0 (0)	3 (2)
β -blocker	5 (10)	42 (21)
Diuretics	7 (14)	33 (17)
Statin	20 (40)	175 (88)*
Ezetimibe	1 (2)	24 (12)
Insulin	0 (0)	15 (8)
Sulfonylurea	10 (20)	27 (14)
Pioglitazone	0 (0)	17 (9)

Continuous variables are expressed as mean±SD. *P<0.05 vs. non-CAD.

CAD, coronary artery disease; BMI, body mass index; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; HU, hyperuricemia; UA, uric acid; eGFR, estimated glomerular filtration rate; bFMD, brachial flow-mediated dilatation; U-Alb/Cr, urinary albumin/creatinine ratio; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker.

Table 2. Predictors for the Presence of CAD

Factor	OR (95%CI)	P value
bFMD	0.79 (0.69–0.90)	0.0002
HDL-C	0.96 (0.94–0.99)	0.010
LDL-C	0.99 (0.98–1.00)	0.108
DBP	0.96 (0.92–0.99)	0.015
HbA _{1c}	1.66 (1.07–2.60)	0.025

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

by coronary angiography (CAG). Patients with unstable angina or myocardial infarction (MI) within the previous 4 weeks, chronic renal disease with hemodialysis or peripheral artery disease were excluded. After exclusion, a total of 200 consecutive patients with SAP who underwent CAG between February 2008 and January 2009 (CAD group) were enrolled. In addition, 50 age-, sex- and body mass index (BMI)-matched patients without CAD [as diagnosed by 64-multidetector row computed tomography (MDCT)] were selected as a non-CAD group. baPWV and bFMD were assessed on the morning of the planned CAG or 64-MDCT. baPWV was measured before bFMD. The protocol of this study was approved by the Ethics Committee of Fukuoka University Hospital, and all subjects gave their informed consent to participate.

Evaluation of Cardiovascular Risk Factors

In all subjects, we measured BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), creatinine (Cr), uric acid (UA), fasting plasma glucose, and hemoglobin A_{1c} (HbA_{1c}) as metabolic factors, and determined the urinary albumin/Cr ratio (U-Alb/Cr), family history (MI, angina pectoris or sudden death) and history of smoking as cardiovascular risk factors. All blood samples were drawn in the morning after the patients had fasted overnight. Laboratory data were determined using enzymatic methods. BP was determined as the mean of 2 measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. Estimated glomerular filtration rate (eGFR) was determined using the abbreviated equation that the Japanese Society of Nephrology modified for Japanese based on the Modification of Diet in Renal Disease study: $194 \times [\text{age (years)}]^{-0.287} \times [\text{serum Cr (mg/dl)}]^{-1.094} \times [0.739 \text{ if female}]$.

The patients' characteristics with regard to history of hypertension (HT), dyslipidemia (DL), diabetes mellitus (DM), history of smoking, and medication use were obtained from medical records. Patients who had a current SBP/DBP $\geq 140/90$ mmHg or who were receiving antihypertensive therapy were considered to have HT. Patients with LDL-C ≥ 140 mg/dl, TG ≥ 150 mg/dl, and/or HDL-C < 40 mg/dl, or who were receiving lipid-lowering therapy, were considered to have DL. DM was defined using the American Diabetes Association criteria. BMI was calculated as weight (kg)/height (m)². Hyperuricemia was defined as a serum UA level ≥ 7.0 mg/dl or the use of UA-lowering drugs.

Measurement of bFMD

Endothelial function was noninvasively assessed by FMD, which is the change in the brachial artery diameter after regional ischemia. bFMD was measured, according to recent guidelines, by ultrasound (UNEXEF18G, Unex Co Ltd, Nagoya, Japan) using a 10-MHz linear-array transducer. bFMD was assessed by measuring, with the ultrasound unit's electronic calipers, the change in the brachial artery diameter after 120 s of reactive hyperemia compared with baseline measurements after the deflated to 50 mmHg greater than SBP for 5 min. Imaging was performed in a dark, quiet room at 25°C. All vasoactive medications were withheld for at least 12 h before each measurement. Patients rested supine for at least 5 min before the first scan and remained supine until the final recording was acquired. In addition, various vasodilatation parameters of the brachial artery (such as the resting diameter, time of maximum diameter, time constant of the shear rate, per-

centage increase in the shear rate, time constants of dilation, time constant of the flow rate and decay time constants of dilation), including bIMT, were also analyzed by Trend Plus® (Unex Co Ltd, Nagoya, Japan). We measured bIMT and bFMD at the same site of the (right) brachial artery.

Measurement of baPWV

baPWV was measured while each subject was supine, using a volume-plethysmographic device (PWV/ABI, Colin Co, Aichi, Japan) as described previously.¹⁶ The following equation was used to obtain baPWV: $\text{baPWV} = [\text{La (the path length from the suprasternal notch to the ankle)} - \text{Lb (the path length from the suprasternal notch to the brachium)}] / \Delta \text{Tba (the time interval between the brachium and ankle)}$. In all studies, baPWV was obtained after at least 5 min of rest.

Statistical Analysis

Statistical analysis was performed using the Excel 2003 (SSRI, Tokyo, Japan) and Stat View statistical software package (Stat View 5; SAS Institute Inc, Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Data are expressed as mean $\pm$ standard deviation. Categorical and continuous variables were compared between groups by chi-square analysis and Student's t-test, respectively. Multivariate analysis was performed using a logistic regression analysis for independent variables that were related to the severity of CAD and the presence or absence of

CAD. Receiver-operating characteristic (ROC) curve analysis was used to determine the cut-off value of bFMD that distinguished between the presence and absence of CAD at the highest possible sensitivity and specificity levels. A value of $P < 0.05$ was considered significant.

Results

Patient Characteristics

Table 1 shows the baseline clinical characteristics in the CAD and non-CAD groups. In the CAD group, the percentages of HT, DL and DM were 86%, 92% and 48%, respectively, which were higher than those in the non-CAD group. In addition, bFMD, DBP, LDL-C and HDL-C in the CAD group were significantly lower than in the non-CAD group. The CAD group showed significantly higher levels of HbA_{1c}, but not baPWV.

Next, we analyzed predictors of the presence of CAD using independent variables (bFMD, HDL-C, LDL-C, DBP and HbA_{1c}) by logistic regression analysis (**Table 2**). CAD was independently associated with bFMD ($P=0.0002$), DBP ($P=0.015$), HbA_{1c} ($P=0.025$) and HDL-C ($P=0.010$).

Correlation Between the Levels of bFMD, baPWV and Cardiovascular Risk Factors

As shown in **Figure 1**, bFMD was negatively associated with

age ($r=-0.197$, $P=0.002$), baPWV ($r=-0.289$, $P<0.0001$) and SBP ($r=-0.289$, $P<0.0001$), and positively correlated with eGFR ($r=0.227$, $P=0.0003$) in all subjects. bFMD in the CAD group was more negatively associated with age ($r=-0.242$, $P=0.0006$) and baPWV ($r=-0.316$, $P<0.0001$).

Association Between the Severity of CAD and bFMD, baPWV and Cardiovascular Risk Factors

The frequencies of 1-, 2- and 3-vessel disease in the CAD group were 37%, 39% and 24%, respectively. bFMD (P for trend <0.0001), eGFR (P for trend $=0.016$) and HDL-C (P for trend $=0.0001$) significantly decreased and LDL-C (P for trend $=0.005$) increased as the number of diseased vessels increased (Figure 2), but there was no relation to baPWV (P for trend $=0.671$).

Next, we analyzed the predictors for the number of diseased vessels using independent variables (bFMD, eGFR, HDL-C and LDL-C) by logistic regression analysis (Table 3). An increased number of diseased vessels was independently associated with bFMD ($P<0.0001$) and HDL-C ($P=0.001$).

Cut-Off Value of bFMD for Diagnosis of CAD

ROC curve analysis showed a higher area under the curve for bFMD (0.644) (Figure 3). The cut-off level of bFMD that had the greatest sensitivity and specificity for the diagnosis of CAD

was 5.3% (sensitivity 0.698, specificity 0.560).

Association Between the Presence of CAD and Various Vasodilatation Parameters of the Brachial Artery, Including bIMT

We analyzed the association between the presence of CAD and various vasodilatation parameters of the brachial artery, including bIMT, as assessed by Trend Plus® (Table 4). The time constant of the shear rate, the time constant of the flow rate and bFMD in the CAD group were significantly lower than in the non-CAD group. The CAD group showed a significantly thicker bIMT than the non-CAD group. Moreover, the measurement of bIMT was negatively correlated with bFMD ($r=-0.144$, $P=0.038$).

Among these parameters, the presence of CAD was independently associated with bIMT ($P=0.043$) as well as bFMD ($P=0.006$) in the logistic regression analysis (Table 5).

Discussion

In this cross-sectional study, we assessed the interrelationship between the presence or severity of CAD, non-invasive assessments (bFMD, baPWV and cIMT) and coronary risk factors in patients with and without CAD. bFMD was a better predictor of the presence and severity of CAD than either

Table 3. Predictors for the Number of Diseased Vessels With Significant Stenosis

Factors	OR (95% CI)	P value
bFMD	0.65 (0.53–0.79)	<0.0001
eGFR	0.99 (0.97–1.02)	0.668
HDL-C	0.94 (0.90–0.98)	0.001
LDL-C	0.99 (0.98–1.01)	0.279

Abbreviations as in Tables 1,2.

Figure 3. Receiver-operating characteristic (ROC) curve for bFMD levels for the diagnosis of CAD. bFMD, brachial flow-mediated vasodilatation; CAD, coronary artery disease.

baPWV or coronary risk factors in patients with SAP. The cut-off level of bFMD that the greatest sensitivity and specificity for the diagnosis of CAD was 5.3%. Moreover, bIMT may also be an independent predictor of CAD.

The predictive value of bFMD for cardiovascular events is still not well established. We found that the presence of CAD was most strongly associated with bFMD. There are 3 possible reasons why bFMD was a better predictor of CAD in this study. First, we judged the presence or absence of CAD as assessed by CAG or 64-MDCT. Second, we selected a non-CAG group that was matched to the CAD group with respect to age, sex and BMI. Earlier studies on the association between FMD and the incidence of CAD events were conducted in relatively young subjects^{6,7} and these studies did not show an association. In addition, age is a critical factor because it is an independent cardiovascular risk factor and is associated with diminished FMD.¹⁷ In fact, bFMD was negatively correlated with age in this study. Thus, it is important to select an age-matched control group.

The presence of CAD was independently associated with bFMD, DBP, HbA_{1c} and HDL-C. bFMD predicted CAD events independent of traditional cardiovascular risk factors in a previous study.⁵ That study included almost all the constituents of the Framingham risk score (FRS) except HDL-C in the Cox model. However, the authors were uncertain whether inclusion of the HDL level in the multivariable Cox model would affect the predictive value of FMD for the incidence of

Table 4. Various Vasodilation Parameters of the Brachial Artery Including bIMT Using Trend Plus®

Parameter	Non-CAD (n=48)	CAD (n=143)
bFMD, %	6.0±3.3	4.4±2.4*
Rest diameter, mm	4.1±0.6	4.1±0.6
Time of the maximum diameter, s	60±19	58±20
Time constant of the shear rate, s	64±178	25±28*
Increase ratio of the shear rate, times	3.2±4.6	3.1±2.7
Dilation start time, s	25±11	25±15
Maximum rate of the dilation, mm/s	0.02±0.01	0.02±0.01
Dilation time, s	35±19	33±18
Time constant of the dilation, sec	58±92	93±226
Time constants of the dilation (T1), s	18±15	17±22
Time constant of the flow rate, s	91±267	36±68*
AUC of the diameter expansion, mm/s	4.2±4.0	2.8±2.7
bIMT, mm	0.31±0.06	0.35±0.08*

*P<0.05 vs. non-CAD.

AUC, area under the curve; bIMT, brachial intima-media thickness. Other abbreviations as in Table 1.

Table 5. Predictors Including bIMT for the Presence of CAD

Factor	OR (95%CI)	P value
bIMT	1.77 (1.02–3.07)	0.043
Time constant of the shear rate	1.00 (0.99–1.00)	0.217
Time constant of the flow rate	1.00 (0.99–1.00)	0.373
bFMD	0.83 (0.73–0.95)	0.006

Abbreviations as in Tables 1,2,4.

cardiovascular events. Based on our results, the presence of CAD was independently associated with lower levels of HDL-C as well as bFMD, the association of HDL-C (P=0.010) was much weaker than that of bFMD (P=0.0002). Although the age-adjusted FRS was a better predictor of CAD than either FMD or baPWV in patients with SAP,¹⁸ FRS did not include Cr in its risk score formula. Chronic kidney disease is an important risk factor of CAD.^{19,20} In the present study, we evaluated eGFR and U-Alb/U-Cr as coronary risk factors. Because the average values of eGFR and U-Alb/U-Cr in the CAD group were 62±16 min and 0.77±4.0 mg/g Cr, and because CAD patients have only mild renal insufficiency, neither eGFR nor U-Alb/U-Cr may be associated with the presence of CAD based on our data.

In this study, lower DBP also predicted the presence of CAD. The DBP in the CAD group was 69±10 mmHg. With regard to BP-lowering, a J-curve phenomenon regarding the incidence of a primary outcome, such as all-cause death and non-fatal MI, is controversial.^{21–23} However, a lower DBP could compromise blood flow to target organs, thus impairing coronary perfusion and causing cardiac ischemia. Messerli et al reported that the DBP level at the bottom of the J-curve was 70–80 mmHg and was positively associated with the primary outcome, all-cause death, and total MI.²²

A higher number of diseased vessels was independently associated with lower levels of bFMD (P<0.0001) and HDL-C (P=0.001). Although many studies have analyzed the association

between the presence of CAD or CAD events and FMD,⁴⁻⁷ there have been no reports on the relation between the severity of CAD and FMD. bFMD is a valid physiological measure of endothelial dysfunction, and this dysfunction is one of the pathological steps in the progression of atherosclerotic CAD. bFMD may be greatly diminished in patients with advanced atherosclerosis. The present study showed that bFMD was most closely associated with the severity of CAD in a real clinical setting.

Many previous studies have revealed that the levels of LDL-C and HDL-C are major predictors of atherosclerotic CAD.^{24,25} In this study, the level of HDL-C, but not LDL-C, predicted the presence or severity of CAD. We previously reported that when the level of LDL-C is reduced to approximately 120 mg/dl by statin therapy, HDL-C may appear to become a stronger risk factor for CAD than LDL-C, because the HDL-C level in the CAD group was significantly lower than that in the non-CAD group.²⁶ Statin treatment may reduce the adverse effect of higher levels of LDL-C, and lower levels of HDL-C may become the strongest risk factor under statin treatment. In fact, 88% of patients in the present CAD group had been administered a statin and the average LDL-C level reached 97±28 mg/dl.

cIMT and baPWV are factors that predict cardiovascular events.^{27,28} Although baPWV was negatively associated with bFMD, it did not predict the presence of CAD in this study. Interestingly, a previous report indicated that bFMD is associated with cIMT.²⁹ No previous reports have analyzed the association between bIMT and bFMD. In the present study, there was a weak correlation between bIMT and bFMD, and bIMT in the CAD group was thicker than that in the non-CAD group. Among various vasodilatation parameters obtained using Trend Plus®, CAD was independently associated with bIMT as well as bFMD. In this study, we analyzed cIMT in 94 of 250 patients. Although bIMT was positively correlated with cIMT ($r=0.315$, $P=0.002$) (Figure S1), the association was relatively low. Moreover, among age, sex, BMI, cIMT and bIMT, the presence of CAD was independently associated with bIMT ($P=0.039$) in the logistic regression analysis (Table S1). Sorensen et al reported that the severity of atherosclerosis in a coronary artery was significantly correlated with both brachial and carotid arteries in their histopathologic study.³⁰ In addition, Weidinger et al reported that the wall thickness of the posterior brachial artery wall and wall index (wall thickness/vessel diameter×100) were greater in patients with than without CAD,³¹ although they did not analyze the usefulness of cIMT. Thus, the measurement of bIMT may be a strategy for predicting CAD. Although the brachial artery is a similar in size to the major epicardial coronary arteries, we do not know the mechanism of why bIMT was more closely associated with CAD than cIMT. Therefore, we can not conclude that bIMT is superior to cIMT for the prediction of CAD at this time.

In addition, the time constant of the shear rate and the flow rate in the CAD group were significantly lower than in the non-CAD group using Trend Plus®, although the presence of CAD was not independently associated with these parameters. Because atherosclerotic lesions develop mainly in areas of low shear stress,³² CAD patients may show lower levels of these parameters.

Study Limitations

First, the study was cross-sectional. Second, non-invasive measurements were performed after various treatments. Many of the patients were taking antihypertensive, antidiabetic

and/or antidiabetic medications that might modify the measurements of bFMD and baPWV. It is a matter of course that CAD patients were taking more medications than non-CAD patients. Third, we did not include the variables (age, sex and BMI, which are known important factors of CAD) by a logistic regression analysis in Table 2 and 3 because non-CAD group was age-, sex- and BMI-matched patients with CAD group. Prospective studies are needed to clarify these limitations.

Conclusions

Our findings are consistent with the fact that bFMD reveals stages of pathological atherosclerosis and CAD. bFMD was a better predictor of the presence and severity of CAD than either baPWV or coronary risk factors in patients with stable angina. In addition, bIMT may also be a critical predictor of the presence of CAD.

Disclosures

K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan.

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Supplemental Files

Supplemental File 1

Figure S1. Correlation between the levels of bIMT and cIMT in 94 of 250 patients.

Table S1. Predictors of the Presence of CAD

Please find supplemental file(s);
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