Low Carotid Artery Wall Shear Stress is Associated with Significant Coronary Artery Disease in Patients with Chest Pain

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Aim: To investigate the relationships among carotid wall shear stress (WSS), carotid intima-media thickness (IMT), and total plaque area (TPA) using ultrasound (US) in the common carotid artery (CCA) in patients with suspected coronary artery disease (CAD).

Methods: Carotid artery US was performed in 950 patients with suspected CAD, and mean IMT, TPA, and hemodynamic parameters of CCA, including peak and mean WSS, were measured. We analyzed the carotid parameters according to the presence of CAD and the predictive values of WSS and TPA for the presence of significant CAD.

Results: Compared with patients without CAD \(n = 667\), patients with CAD \(n = 283\) demonstrated significantly higher mean IMT (0.66 vs. 0.74 mm, \(p < 0.001\)), TPA (0.13 vs. 0.20 cm², \(p = 0.002\)), and beta stiffness index (5.12 vs. 5.60, \(p = 0.045\)) and lower mean WSS (2.59 vs. 2.23 dyne/cm², \(p < 0.001\)). Mean WSS revealed significant negative correlations with the beta stiffness index \(r = -0.116, p < 0.001\), mean IMT \(r = -0.193, p = 0.007\), and TPA \(r = -0.296, p < 0.001\). Mean WSS, mean IMT and TPA revealed significant difference with respect to CAD severity (for all \(p < 0.001\)). Age \([OR, 1.038 (95\% CI, 1.010–1.066), p = 0.007\], diabetes mellitus \([1.606 (1.194–1.807), p = 0.011\], smoking \([1.758 (1.564–1.966), p < 0.001\), carotid TPA \([2.615 (1.320–5.183), p = 0.006\], and mean WSS \([0.554 (0.371–0.838), p = 0.005\] were significant CAD predictors.

Conclusions: In patients with chest pain, low local shear stress and high plaque burden in the carotid arteries were significant CAD predictors. These findings indicate that carotid WSS has a role as an index of atherosclerosis and serves as a predictor of significant coronary atherosclerosis.

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Key words: Atherosclerosis, Carotid artery, Wall shear stress, Coronary artery disease

Introduction

Atherosclerosis is the leading cause of death in developed countries, and screening for subclinical atherosclerosis has been endorsed to assist with prevention¹. Carotid ultrasound (US) is a noninvasive and effective screening tool for carotid atherosclerosis. Carotid intima-media thickness (IMT) is widely considered to be an early index of atherosclerosis and has been related to cardiovascular risk factors and the severity of coronary atherosclerosis and thus can be used to predict cardiovascular events¹ ³. Recently, US assessment of carotid total plaque area (TPA) has been reported to be more sensitive than IMT for detecting temporal changes in atherosclerosis³ ⁴, which may be related to the foam cell formation or thrombosis. These observations indicate the importance of an integrated approach in assessing the severity of atherosclerosis. Although atherosclerosis is associated with systemic coronary heart disease (CHD) risk factors, such as arterial hypertension, hyperlipidemia, diabetes mellitus (DM), and smoking status, there are also local hemodynamic factors that participate in the physiopa-
thology of atherogenesis, accounting for the focal nature of this disease process). The principal local hemodynamic factor is wall shear stress (WSS), and the parallel frictional drag force of shear stress is an important blood flow-induced mechanical stress acting on the vessel wall. The effect of WSS on the endothelium depends on its magnitude and direction as well as on the local vessel geometry and blood flow characteristics. WSS is an important determinant of endothelial function, and lower WSS is associated with the development of atherosclerotic plaques. Recently, Sameshima et al. reported that an increased value of WSS closely correlated with the onset of plaque erosion in areas of smooth muscle cell-rich plaque. Although it is well known that WSS influences the atherosclerotic process, its exact role is not yet defined. Systemic CHD risk factors and reduced WSS may interact to cause increased damage to the arterial wall. Therefore, we hypothesized that if lower carotid WSS is associated with a higher plaque burden in the carotid arteries, carotid WSS may play a role as an early index of atherosclerosis and a predictor of significant coronary atherosclerosis. Therefore, we aimed to investigate the relationships between carotid WSS and the parameters of carotid atherosclerosis in the common carotid artery (CCA) in patients with suspected coronary artery disease (CAD). Furthermore, we investigated the predictive values of carotid WSS and systemic CHD risk factors for the presence of significant CAD.

Methods

Study Population

The study population included 950 consecutive eligible patients who were admitted to the hospital and suspected of having CAD and thus underwent coronary angiography between January 2013 and October 2014 at the Kosin University Gospel Hospital. Assessment of CHD risk factors included the presence or absence of medically diagnosed hypertension, DM, dyslipidemia, and current cigarette smoking status. Blood pressure (BP) was measured with a standard mercury manometer, and hypertension was defined as systolic BP (SBP) >140 mmHg and/or diastolic BP (DBP) >90 mmHg and/or use of antihypertensive drugs. The American Diabetes Association criteria were used to define DM, and we considered a patient to have DM if the fasting plasma was >126 mg/dl on two consecutive assessments, hemoglobin A1c was >6.5%, or if he/she was on the treatment for DM. The presence of dyslipidemia was defined as total cholesterol >220 mg/dl, low-density lipoprotein (LDL) cholesterol level >130 mg/dl, high-density lipoprotein (HDL) cholesterol level <40 mg/dl, triglyceride >200 mg/dl, or administration of lipid-lowering drugs. Patients reported to be current smokers or non-smokers. Body mass index (BMI) was calculated as the ratio of body weight in kilograms to height squared (in square meters), and obesity was defined as a BMI >25 kg/m². Patients with typical chest pain or angina equivalents, such as dyspnea on exertion or arm pain with exertion, and known or suspected ischemic heart disease were diagnosed with stable angina. Acute coronary syndrome (ACS) was assumed if patients were diagnosed with myocardial infarction or unstable angina. Patients with anemia, infections, immunological disorders, or chronic kidney disease were excluded. This study complied with the Declaration of Helsinki with regard to investigations in humans. This study was approved by the local Institutional Review Board, and all patients provided written informed consent for US quantification of carotid arteries.

Laboratory Measurements

Venous blood was drawn in the morning after an overnight fast. Complete blood cell counts, serum electrolytes, and thyroid function tests were found to be within normal ranges. The following parameters were obtained with standard techniques on the day of examination: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, high sensitivity C-reactive protein, and fibrinogen. Height and weight were measured, and BMI values were calculated.

Carotid Ultrasound Examination

All patients rested for at least 10 min in the supine position prior to carotid US examination, and a normal sinus rhythm with a rate of 60–100 beats/min was required on resting electrocardiogram prior to examination. The examination was performed on the bilateral CCA, carotid bifurcations, and origins of the internal carotid arteries in longitudinal and transverse planes using a 14-MHz transducer (Philips iE33, Philips Medical Systems, Bothwell, WA, USA). The reader was the same throughout the study and was blinded to the subject being investigated. All participants were examined in the supine position with their necks extended and their chins facing the contralateral side. The offline measurement of carotid parameters was performed by two cardiologists (HS Kim and KI Cho) who were unaware of the clinical data. The measurement of carotid parameters was undergone at least twice to improve reliability.
Carotid IMT Measurement

Two observers, blinded to the participants' demographic data and cardiovascular risk, measured the combined thickness of the intima and media of the bilateral CCA. After selecting a region of interest in the far wall of CCA, mean IMT was estimated in an atherosclerotic plaque-free region using an automatic tracking system. Mean IMT was computed from 80 to 120 measurements over a 10-mm span that ended 5-mm proximal to the transition between CCA and the bulb regions. An increased IMT was defined as ≥0.9 mm in either or both carotid arteries. Intra- and inter-operator coefficients of variation were 2.9 and 3.0%, respectively, and intra- and inter-operator intra-class correlations were both 0.96.

TPA Measurement

Atherosclerotic plaque was defined as a focal structure that encroached into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or demonstrated a thickness >1.5 mm as measured from the media–adventitial interface to the intima–lumen interface. The measurement plane was determined by scanning to identify the largest plaque extension on the longitudinal views of each plaque in the bilateral common, internal, and external carotid arteries. The image was then frozen and magnified, and the plaque was measured by tracing the perimeter with the cursor. Measurement of the plaque area was acquired by tracing the plaque border, which was previously defined. The process was repeated until all plaques on both sides were measured. TPA was the sum of the areas of all plaques between the clavicle and angle of the jaw. Intra- and inter-operator intra-class correlations were 0.95 and 0.87, respectively.

WSS Measurement

Several moving 5-s image clips of CCA that were 1–2 cm proximal to the carotid artery bifurcation were acquired and stored in digital format for subsequent offline analysis. From the clip images, the best quality of cardiac cycle was selected. Blood flow velocity was detected with the sample volume placed in the CCA center. Peak systolic (Vpeak), end diastolic, and mean velocities (Vmean) were recorded for at least three cardiac cycles. The systolic internal diameter of CCA (SD) and the diastolic CCA diameter (DD) were acquired at the peak T and R waves for calculating the carotid hemodynamic parameters. WSS was calculated using the Poiseuillian parabolic model of velocity distribution across the arterial lumen on the basis of the assumption of laminar blood flow according to the following formulas:

\[ 1) \text{Peak WSS} = 8 \times \mu \times \frac{V_{\text{peak}}}{\text{SD}} \]
\[ 2) \text{Mean WSS} = 8 \times \mu \times \frac{V_{\text{mean}}}{\text{DD}} \]

where \( \mu \) is blood viscosity and is assumed to be 0.035 dyn/s/cm² in patients with hematocrit level within a normal range. The inter-observer coefficients of variation for peak and mean WSS were between 6% and 8%, which were similar to a previous study.

Carotid Elasticity

Carotid elasticity of an artery segment is a reflection of the mechanical stress affecting the arterial wall during a cardiac cycle. Stress was defined as the difference in SBP and DBP; strain was defined as the systemic artery response. Ultrasound and concomitant brachial BP measurements with an automated sphygmomanometer (Omron M4, Omron Matsusaka Co., Ltd, Japan) were used to calculate the following indices of arterial elasticity, which we previously reported:

1) Strain as the amount of deformation that is relative to the unstressed state and is expressed as percent change in the arterial diameter: strain = \( \frac{(\text{SD} - \text{DD})}{\text{DD}} \)

2) Stiffness (\( \beta \)) as stress (SBP-DBP)-to-strain ratio: \( \ln (\text{SBP/DBP})/\text{strain} \)

Coronary Angiography

An INTEGRIS BV 5000 (Philips Medical System, Best, Netherlands) was utilized to visualize the coronary artery stenosis. Quantitative measurements were performed using a workstation with dedicated software (WIN 32 version 3.3). Patients with at least one lesion of >50% within the main branches of the coronary arteries were considered to have significant CAD. Patients with minimal atherosclerotic lesions (≤50% in diameter stenosis) in the coronary arteries were not included. The associations of mean IMT, TPA, and WSS with CAD severity were assessed using SYNTAX score by one expert (JH Heo).

Statistical Analysis

Statistical analyses were performed with SPSS 18.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to evaluate variable distribution. Parametrically distributed data were presented as mean ± standard deviation (SD) or number (percentage). The difference between the categorical variables was determined using the \( \chi^2 \)-test. Student's 2-tailed unpaired \( t \)-test was used for comparison of means between subjects with and without CAD. A simple linear regression analysis was performed to test the association between WSS and IMT/TPA. Multiple
stepwise logistic and linear regression analyses were used to test the associations between systemic and local risk factors and to detect the predictors of the presence of CAD. Covariates that entered into the regression model were age, obesity, hypertension, dyslipidemia, DM, and current smoking. A \( p \) value < 0.05 was considered statistically significant.

**Results**

**Baseline Clinical Characteristics**

Clinical characteristics were analyzed according to the presence or absence of CAD and are presented in Table 1. The mean age of the patients was 59.7 ± 13.1 years; 56.4% were male. Compared with patients without CAD \( (n=667) \), patients with CAD \( (n=283) \) were significantly older and had more cardiovascular risk factors, such as male gender, current smoker, hypertension, dyslipidemia, and DM (Table 1).

The parameters of carotid atherosclerosis, arterial stiffness, and WSS are presented in Table 2. Compared with patients without CAD, patients with CAD demonstrated significantly higher mean IMT \( (0.66 \pm 0.15 \text{ vs. } 0.74 \pm 0.27 \text{ mm, } p<0.001) \), TPA \( (0.13 \pm 0.24 \text{ vs. } 0.20 \pm 0.42 \text{ cm}^2, p=0.002) \), and beta stiffness index \( (5.12 \pm 3.11 \text{ vs. } 5.60 \pm 2.66, p=0.045) \). Compared with patients without CAD, the peak \( (3.65 \pm 1.22 \text{ vs. } 3.13 \pm 1.25 \text{ dyne/cm}^2, p<0.001) \) and mean WSS \( (2.59 \pm 0.82 \text{ vs. } 2.23 \pm 0.90 \text{ dyne/cm}^2, p<0.001) \) were significantly lower in patients with CAD mainly because of an enlarged luminal diameter and slower blood flow velocity (Table 2). Furthermore, when the parameters of both carotid arteries were analyzed according to the carotid artery status, carotid arteries with plaque formation demonstrated the lowest peak and mean WSS among the three groups (normal carotid arteries, 3.59 ± 1.63 and 2.56 ± 1.09; carotid arteries with increased IMT, 3.40 ± 1.26 and 2.39 ± 0.92; and carotid arteries

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**Table 1.** Baseline clinical characteristics according to the presence of coronary artery disease

| Patients without CAD \( (n=667) \) | Patients with CAD \( (n=283) \) | \( P \) value |
|---------------------------------|---------------------------------|-------------|
| Age, years                      | 57.9 ± 13.4                     | 64.2 ± 10.7 | <0.001    |
| Male, n (%)                     | 353 (52.9%)                     | 183 (64.7%) | 0.001     |
| Systolic blood pressure, mmHg   | 127.7 ± 18.2                    | 127.4 ± 19.7| 0.827     |
| Diastolic blood pressure, mmHg  | 75.2 ± 13.1                     | 76.7 ± 13.0 | 0.055     |
| Heart rate/min                  | 73.9 ± 13.8                     | 71.4 ± 12.9 | 0.018     |
| BMI, kg/m²                      | 25.2 ± 12.6                     | 24.6 ± 3.20 | 0.290     |
| Obesity, n (%)                  | 292 (43.8%)                     | 126 (44.5%) | 0.444     |
| Hypertension, n (%)             | 323 (48.4%)                     | 158 (55.8%) | 0.022     |
| Diabetes mellitus, n (%)        | 115 (17.2%)                     | 97 (34.3%)  | <0.001    |
| Current smoker, n (%)           | 105 (15.7%)                     | 106 (37.5%) | <0.001    |
| Dyslipidemia, n (%)             | 448 (67.2%)                     | 212 (74.9%) | 0.010     |
| Previous medication             |                                 |             |           |
| RAS blockade, n (%)             | 185 (27.7%)                     | 99 (35.1%)  | 0.021     |
| Beta blocker, n (%)             | 77 (11.6%)                      | 95 (33.6%)  | <0.001    |
| Calcium channel blocker, n (%)  | 118 (17.7%)                     | 82 (28.9%)  | 0.015     |
| Diuretics, n (%)                | 48 (7.2%)                       | 41 (14.4%)  | 0.030     |
| Statin, n (%)                   | 357 (53.5%)                     | 185 (65.2%) | 0.002     |
| Oral hypoglycemic agents, n (%) | 100 (15.0%)                     | 92 (32.4%)  | <0.001    |
| Acute coronary syndrome, n (%)  | 0                               | 103 (36.4%) | <0.001    |
| Total cholesterol, mg/dl        | 152.8 ± 41.7                    | 168.6 ± 41.6| <0.001    |
| Estimated GFR, mL/min/1.73 m²   | 73.5 ± 23.6                     | 74.4 ± 21.7 | 0.635     |
| hs-CRP, mmol/L                  | 6.73 ± 28.3                     | 6.79 ± 20.4 | 0.974     |
| Free T4, pmol/L                 | 1.19 ± 0.46                     | 1.11 ± 0.19 | 0.016     |
| TSH, mIU/L                      | 2.61 ± 6.65                     | 2.12 ± 2.54 | 0.152     |
| Fasting glucose, mg/dl          | 101.7 ± 29.5                    | 118.4 ± 64.6| 0.001     |
| Hemoglobin A1c, %               | 6.68 ± 1.87                     | 7.49 ± 1.70 | 0.001     |

All values are presented as mean ± SD. CAD, coronary artery disease; BMI, body mass index; RAS, rennin angiotensin system; GFR, glomerular filtration rate; hs-CRP, high sensitivity C-reactive protein; TSH, thyroid stimulating hormone.
with plaque formation, 3.37 ± 1.25 and 2.37 ± 0.90; for all, \( p < 0.05 \).

**Correlations Among Carotid IMT, TPA, and WSS**

Mean WSS revealed significant negative correlations with the beta stiffness index \( r = -0.116, p < 0.001 \), mean IMT \( r = -0.193, p = 0.007 \), and TPA \( r = -0.296, p < 0.001 \) (Table 3). Linear regression analysis revealed that mean WSS had significant effects on the beta stiffness index (Fig. 1A), mean IMT (Fig. 1B), and TPA (Fig. 1C). In contrast, TPA significantly affected the beta stiffness index (Fig. 1D) and mean WSS (Fig. 1C) and did not affect the mean IMT (Fig. 1E). Multivariate linear regression was performed to examine the independent factors that affected carotid TPA and WSS (Table 4). SBP, hemoglobin A1c, and mean WSS were significant contributors to TPA; age, BMI, and TPA were independent determinants of mean WSS (for all \( p < 0.05 \)).

**Associations Among Mean WSS, Mean IMT, TPA, and Coronary Artery Disease**

Table 5 shows comparisons of the mean carotid IMT, TPA, and mean WSS according to the number...
Fig. 1. Linear regression analysis showing the associations among mean wall shear stress (WSS) and beta stiffness index (A), mean common carotid artery intima-media thickness (IMT) (B), and total plaque area (TPA) (C). Linear regression analysis showing the association between TPA and beta stiffness index (D) and mean IMT (E).

Mean WSS significantly affected beta stiffness index, mean IMT, and TPA. In contrast, TPA significantly affected beta stiffness index and mean WSS but not mean IMT.
Table 4. Multiple linear regression analysis of carotid total plaque area and wall shear stress

|                     | Coefficient (β) | 95% CI         | P   | Coefficient (β) | 95% CI    | P   |
|---------------------|-----------------|----------------|-----|----------------|-----------|-----|
| **Univariate analysis** |                 |                |     | **Multivariate analysis** |           |     |
| Age                 | 0.088           | 0.001 to 0.003 | 0.002 | 0.006           | 0.000 to 0.000 | 0.918 |
| Systolic blood pressure | 0.067           | 0.000 to 0.003 | 0.041 | 0.140           | 0.000 to 0.002 | 0.049 |
| Diastolic blood pressure | 0.085           | 0.001 to 0.005 | 0.009 | -0.009          | -0.003 to 0.001 | 0.191 |
| Body mass index     | 0.011           | -0.002 to 0.003 | 0.706 | 0.083           | -0.001 to 0.009 | 0.706 |
| LDL-cholesterol     | 0.033           | 0.000 to 0.001 | 0.317 | 0.081           | 0.000 to 0.001 | 0.135 |
| HDL-cholesterol     | -0.081          | 0.002 to 0.000 | 0.013 | -0.027          | -0.002 to 0.001 | 0.631 |
| hs-CRP              | -0.026          | -0.014 to 0.006 | 0.436 | -0.011          | -0.005 to 0.004 | 0.833 |
| Hemoglobin A1C      | 0.099           | 0.000 to 0.019 | 0.047 | 0.211           | 0.010 to 0.029 | <0.001 |
| Carotid mean WSS    | -0.128          | -0.050 to -0.017 | <0.001 | -0.469          | -0.188 to -0.007 | 0.036 |
| Carotid beta stiffness index | 0.242 | 0.024 to 0.041 | <0.001 | 0.043           | -0.003 to 0.007 | 0.437 |

TPA (R²=0.121, adjusted R²=0.099 in multivariate analysis)

Mean WSS (R²=0.070, adjusted R²=0.058 in multivariate analysis)

Table 5. Comparison of the mean carotid intima-media thickness, total plaque area, and mean wall shear stress according to the severity of coronary artery disease

|         | Normal (n=667) | 1 Vessel CAD (n=171) | 2 Vessel CAD (n=78) | 3 Vessel CAD (n=34) | P value |
|---------|----------------|----------------------|---------------------|---------------------|---------|
| Mean WSS, dyne/cm² | 2.59±0.82 | 2.20±0.83 * | 2.36±1.11 | 2.17±0.74 * | <0.001 |
| CCA mean IMT, mm   | 0.66±0.15 | 0.73±0.21 * | 0.74±0.18 * | 0.72±0.13 * | <0.001 |
| TPA, cm²           | 0.13±0.24 | 0.26±0.58 * | 0.34±0.58 * | 0.53±1.04 * | <0.001 |

Data are presented as mean ± standard deviation. Statistical significance was tested by one-way analysis of variance. CCA, common carotid artery; CAD, coronary artery disease; IMT, intima-media thickness; WSS, wall shear stress; TPA, total plaque area.

*p<0.05 compared with the normal coronary artery. *p<0.05 compared with 1 vessel CAD.

of atherosclerotic coronary arteries and the angiographically normal coronary arteries, one-, two-, and three-vessel CAD. Mean WSS, mean IMT, and TPA demonstrated significant difference with the multi-vessel involvement, and patients with three-vessel CAD revealed the lowest WSS and the highest TPA (for all p<0.05). Moreover, when we dichotomized patients with CAD according to the presence of ACS, patients with ACS demonstrated a higher beta stiffness index and lower peak/mean WSS with comparable mean IMT and TPA (supplementary Table 1). Although mean IMT (r=0.109, p=0.126) and TPA (r=0.065, p=0.372) revealed no statistically significant correlation between the SYNTAX score, the score was significantly correlated with the beta stiffness index (r=0.205, p=0.007) and mean WSS (r=-0.142, p=0.048).
Binary logistic regression analysis revealed that age [odds ratio (OR), 1.038; 95% confidence interval (CI), 1.010–1.066], presence of DM (OR, 1.606; 95% CI, 1.045–2.111), current smoker (OR, 1.758; 95% CI, 1.194–1.866), carotid TPA (OR, 2.615; CI 1.320–5.183), and mean WSS (OR, 0.554; CI, 0.371–0.838) were significant predictors of significant CAD (Table 6). When the predictive values of TPA, mean IMT, and WSS were analyzed for the presence of significant CAD using the receiver operating characteristics curve, TPA of 0.71 cm² (sensitivity, 14.2%; specificity, 96.4%; \( p = 0.009 \)), mean IMT of 0.8 mm (sensitivity, 63.2%; specificity, 55.7%; \( p < 0.001 \)), and mean WSS of 1.67 dyne/cm² (sensitivity, 31.4%; specificity, 97%; \( p < 0.001 \)) were useful for the prediction of significant CAD. Mean WSS demonstrated the highest area under the curve (AUC=0.630) (Fig. 2).

### Discussion

The major finding of this study was that patients with CAD exhibited reduced carotid WSS and increased carotid artery stiffness and carotid atherosclerosis in CCA compared with those without CAD. In addition, lower carotid WSS was associated with a higher plaque burden in the carotid arteries, and both carotid WSS and TPA were significant CAD predictors. These findings indicate that local shear stress, such as carotid WSS, has a role as an index of atherosclerosis and serves as a new predictor of significant coronary atherosclerosis.

The evaluation of structural and functional changes in arteries may be helpful in identifying individuals at a risk for developing clinical cardiovascular disease. Decreased carotid elasticity represents early functional atherosclerosis and has been implicated as an independent predictor for cardiovascular mortality in high-risk individuals. The measurement of IMT as a surrogate marker for structural atherosclerosis is common in clinical practice, and carotid plaque formation has been recently shown to be more closely related to the presence of CAD and to predict coronary events more accurately than IMT. This is likely because of carotid plaques representing a later stage of atherogenesis related to inflammation, endothelial dysfunction, oxidative stress, and smooth muscle cell proliferation. For quantitative plaque measurements, we previously attempted to measure plaque burden as TPA according to a validated method in patients with well-established cardiovascular risk factors. In this study with a larger cohort, the \( r \) value between IMT and TPA was relatively low (\( r = 0.187, p = 0.007 \)), indicating that a large plaque is not always associated with increased IMT. Moreover, our study demonstrated that mean WSS has a significant effect on mean IMT, but TPA did not affect mean IMT. This implies that IMT is not a pure atherosclerotic index being substantially affected by age and hemodynamic factors, including BP and vessel WSS.

Although atherosclerosis is a systemic and multifactorial disease related to systemic CHD risk factors, it is also a focal disease that predominantly occurs in the predisposed areas. Previous study findings support the hypothesis of an interaction between systemic and local risk factors that have an influence on atherogene-
events. To date, no carotid artery segment (i.e., comparison among the various segments) has clearly demonstrated a more significant association with cardiovascular disease. Some reports suggest that CCA may have a marginally higher adjusted relative risk (RR) for stroke prediction, whereas ICA may have a marginally higher RR for CHD risk prediction\textsuperscript{1). Considering that carotid plaques predominantly occur at sites of non-laminar turbulent flow, such as in the carotid bulb and the proximal ICA, but rarely in CCA except in advanced atherosclerotic disease\textsuperscript{2,5), the roles of low WSS in CCA for plaque burden and CHD risk prediction in our results can be explained. The mechanisms by which low WSS can cause arterial damage are well known, and WSS is an important determinant of endothelial cell function by inhibiting the proliferation, thrombosis, and inflammation of the vessel wall\textsuperscript{7). WSS is known to be atheroprotective and is lower in carotid arteries with plaques than in contralateral plaque-free arteries\textsuperscript{8). There is increasing evidence suggesting that low WSS expresses an atherogenic endothelial gene profile\textsuperscript{6, 7, 26). Moreover, WSS regulates the arterial diameter by modifying the release of vasoactive mediators from endothelial cells\textsuperscript{7, 27).
Therefore, mechanical shear stress plays an important role in atherosclerosis both directly and indirectly via the release of bioactive molecules\(^\text{28}\). Because of the lack of techniques to assess WSS \textit{in vivo}, WSS has been calculated according to Poiseuille’s law using recorded velocity profiles and whole-blood viscosity in large arteries\(^\text{10}\). Our previous study suggested that local shear stress measured by US was associated with carotid vascular deformation, which could be an underlying mechanism for the progression of atherosclerosis\(^\text{29}\). Because high WSS is atheroprotective and low WSS may be atherogenic, the atheroprotective effect may be maximal above a given value, and classic risk factors would be required to cause arterial damage in these cases. However, this hypothesis needs to be tested, and our data do not currently allow us to define such a threshold value.

We recognize that our study is limited by some factors, including a unique study cohort from which our findings may not be generalized to other groups of patients. In addition, because it was difficult to define plaque border in cases with diffuse plaques connected by increased IMT, there are some technical limitations to plaque measurement. However, we measured such plaque borders by defining the plaque as suggested by Spence \textit{et al.}\(^\text{3, 13}\). Second, WSS measurement was based only on Poiseuille’s law, which is a common approximation of WSS\(^\text{8, 30}\). However, when assuming a parabolic velocity profile, the underestimation of WSS may potentially lead to inaccuracy. However, even actual measurements of viscosity may not determine the real values of shear stress\(^\text{31}\), and the use of an arbitrary value of blood viscosity would not change the statistical significance of the results\(^\text{32}\). Genetic factors and other CHD risk factors, such as fibrinogen level, alcohol use, low physical activity, and homocysteine level, were not investigated in this study but may also play a role. In addition, the manner in which risk factors were classified and defined may be inaccurate. Low-level, long-term risk factors may be more deleterious than high-level, short-term risk factors because most patients included in this study were under treatment for hypertension, dyslipidemia, and DM. Furthermore, the associations of WSS and/or TPA with future CAD events were not investigated, which may provide more insight into the clinical significance of these parameters. Despite these limitations, we believe that our data disclose interesting new perspectives. The finding that carotid WSS and TPA were independent predictors of significant CAD in individuals with chest pain may be of help in clinical practice, suggesting the requirement for a more or less intensive treatment in these patients. A trial to evaluate factors that influence the level of WSS may provide a more comprehensive approach in understanding the atherosclerotic process.

**Conclusion**

Our study revealed that in subjects with chest pain, there was a significant association between IMT/TPA of the carotid arteries and WSS, implicating that low local shear stress and high plaque burden in the carotid arteries were significant predictors of significant CAD. These findings indicate that carotid WSS has a role as an early index of atherosclerosis and serves as a predictor of significant coronary atherosclerosis. A strategy of measuring CCA mean IMT in concert with plaque formation and hemodynamic factors, such as WSS, may improve CHD risk prediction.

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None.

**Conflicts of Interest**

All of the authors have no conflicts of interest to declare.

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**Supplementary Table 1.**
Comparison of the mean carotid intima-media thickness, total plaque area, mean wall shear stress between stable angina and acute coronary syndrome

|                        | Patients with stable angina (n=180) | Patients with ACS (n=103) | P value |
|------------------------|-------------------------------------|---------------------------|---------|
| CCA mean IMT, mm       | 0.72 ± 0.23                         | 0.76 ± 0.36               | 0.326   |
| Peak WSS, dyne/cm²     | 3.05 ± 1.25                         | 3.33 ± 1.26               | 0.046   |
| Mean WSS, dyne/cm²     | 2.16 ± 0.88                         | 2.39 ± 0.94               | 0.031   |
| Beta stiffness index    | 5.17 ± 2.52                         | 6.02 ± 3.57               | 0.048   |
| Plaque number           | 1.75 ± 2.41                         | 1.84 ± 3.18               | 0.816   |
| TPA, cm²               | 0.28 ± 0.49                         | 0.33 ± 0.72               | 0.492   |

Data are presented as mean ± standard deviation. CCA, common carotid artery; CAD, coronary artery disease; IMT, intima-media thickness; WSS, wall shear stress; TPA, total plaque area.