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Relationship of Carotid Intima-Media Thickness, Pulse Wave Velocity, and Ankle Brachial Index to the Severity of Coronary Artery Atherosclerosis

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Summary

Background: Carotid intima-media thickness (IMT), pulse wave velocity (PWV), and the ankle brachial index (ABI) are widely used noninvasive modalities for evaluating atherosclerosis.

Hypothesis: The aim of this study was to determine the relationship of carotid IMT, PWV, and ABI with the severity of coronary artery disease (CAD), expressed as the Gensini score, and the presence of coronary risk factors.

Methods: We examined 205 consecutive patients (mean age 65 ± 12 years) who were clinically suspected of having CAD and were scheduled to undergo coronary angiography. Carotid intima-media thickness, brachial-ankle PWV (baPWV), and ABI were measured in all subjects before they underwent coronary angiography.

Results: Of the 205 patients, 124 patients were diagnosed as having CAD based on the presence of > 50% stenosis in a major coronary artery; the remaining 81 patients did not have CAD. A relatively good correlation was obtained between carotid IMT and the Gensini score ($R = 0.411$, $p < 0.0001$), whereas baPWV correlated only weakly with the Gensini score ($R = 0.203$, $p = 0.0035$), and ABI did not correlate with it. A multiple regression analysis revealed that the Gensini score correlated significantly and independently with age, male gender, and carotid IMT.

Conclusions: Of the three noninvasive methods, carotid IMT may be more useful for determining coronary artery atherosclerosis than baPWV or ABI.

Key words: atherosclerosis, intima-media thickness, pulse wave velocity, ankle-brachial index, coronary artery disease

Introduction

The development of atherosclerosis consists of structural and functional changes. High-resolution B-mode ultrasound has facilitated the noninvasive assessment of structural changes in the arterial wall, measured as the intima-media thickness (IMT).[1] The IMT of the carotid artery correlates strongly with the presence and extent of coronary artery disease (CAD).[2, 3] In addition, the carotid IMT is reportedly associated with cardiovascular and cerebrovascular events.[4] Aortic stiffness is also an important aspect of atherosclerosis related to vessel function that can be evaluated noninvasively by measuring the pulse wave velocity (PWV), which is reportedly associated with the severity of vascular damage[5] and the prognosis of cardiovascular disease in hypertensive patients.[6] Recently, brachial-ankle PWV (baPWV) measurements have become possible;[7, 8] these measurements are easier to obtain than the conventional carotid-femoral PWV. The baPWV has also been reported to be a marker of atherosclerotic vascular damage and cardiovascular risk.[9] The ankle brachial index (ABI) is another noninvasive method used to assess the presence of peripheral occlusive arterial disease; this measure also correlates with the prevalence of CAD and cardiovascular events.[10] Recently, the Rotterdam study reported that IMT and ABI were strong predictors of myocardial infarction.[11] However, these three noninvasive markers have not been compared in the same group of subjects, nor has their relationship with the severity of coronary atherosclerosis been investigated. The aim of this study was to determine the

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relationship of carotid IMT, PWV, and ABI with the severity of CAD and with the presence of coronary risk factors.

Materials and Methods

We examined 205 consecutive patients (mean age 65 ± 12 years) who were clinically suspected of having CAD and were scheduled to undergo coronary angiography in our department. Exclusion criteria were acute myocardial infarction, unstable angina, and history of coronary angioplasty or coronary bypass surgery. Written informed consent was obtained from every enrolled patient. The study protocol was approved by our institutional ethical committee. Overall, 124 patients were diagnosed as having CAD based on the presence of > 50% stenosis in a major coronary artery. Fasting blood samples were obtained from all patients before cardiac catheterization. Body mass index (BMI), blood pressure, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, uric acid (UA), glycohemoglobin (hemoglobinA1c), carotid IMT, baPWV, and ABI were evaluated in these subjects. Smokers were defined as subjects who had smoked regularly for more than 1 year. Hypertension was defined as ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic blood pressure, or current use of antihypertensive agents. Hypercholesterolemia was defined as a plasma LDL-cholesterol level of > 3.38 mmol/l or the use of cholesterol-lowering drugs. Diabetes was defined as the use of insulin, oral hypoglycemic agents, or a plasma hemoglobinA1c level of > 6.5%.

Pulse Wave Velocity and Ankle Brachial Index Measurements

The baPWV and ABI were measured using a volume-plesthymographic apparatus (Form PWV/ABI; Colin, Co., Ltd., Komaki, Japan). The method of baPWV measurement has been reported previously.[7,8] Briefly, the subject was examined in supine position, with occlusion and monitoring cuffs wrapped around both sides of the upper and lower extremities, and pressure waveforms of the brachial and tibial arteries were recorded. Heart sounds S1 and S2 were detected by a microphone placed on the left edge of the sternum at the fourth intercostal space. The time interval between the brachium and ankle (ΔT_{ba}) was defined as the time interval between the wave front of the brachial waveform and that of the ankle waveform. The sampling time was 10 s with automatic gain analysis and quality adjustment. The distance between sampling points of baPWV was calculated automatically according to the height of the subjects. The path length from the suprasternal notch to the brachium (L_b) and ankle (L_a) was expressed using the following equation: $L_b = 0.2195 \times$ height of the patient (cm) -2.0734, $L_a = 0.8129 \times$ height of the patient (cm) + 12.328. The following equation was used to calculate the baPWV: baPWV= $(L_b - L_a)/\Delta T_{ba}$(cm/s). The mean baPWV was calculated from the average of the right and left baPWV results. The left and right ABI were measured and the lower value of the ABI was used for data analysis.

Carotid Ultrasonographic Measurements

Ultrasonographical B-mode imaging of the carotid artery was performed using high-resolution 7.5 MHz transducer (Power Vision 8000; Toshiba Medical Co., Ltd., Tokyo). The carotid IMT examinations were recorded using digital video. The examiner chose the best images of bilateral carotid arteries within 20 mm of the edge detection border; IMT measurements were automatically performed using computer software (Intima Scope; Soft Medical, Co., Ltd., Tokyo). We selected the far wall of common carotid artery and bifurcation to detect the edge of the intima more clearly compared with other potions (e.g., near wall of bifurcation or internal carotid artery) for evaluation by the automated software, which was optimized for assessing those portions. The diagram of the carotid circulation and transducer position is shown in Figure 1. The mean maximum IMT (mean max IMT) was calculated from the average of the right and left maximum IMT.

Evaluation of Coronary Angiography Results

All subjects underwent coronary angiography. Coronary angiography was conducted using either the standard Judkins femoral or the Sones brachial or radial method. Two examiners blinded to the carotid IMT, ABI, and baPWV results evaluated the results of the coronary angiography examination. Gensini score[12] was calculated to give a measure of the severity of CAD.

Statistical Analysis

All data were expressed as mean ± standard deviation (SD). Pearson correlation analysis was performed to determine whether the IMT, baPWV or ABI results correlated with the examined risk factors of CAD. Possible correlations between IMT, baPWV, or ABI and Gensini score were assessed by linear regression analysis. Potential predictors of the Gensini score were tested using multiple regression analysis. The opti-

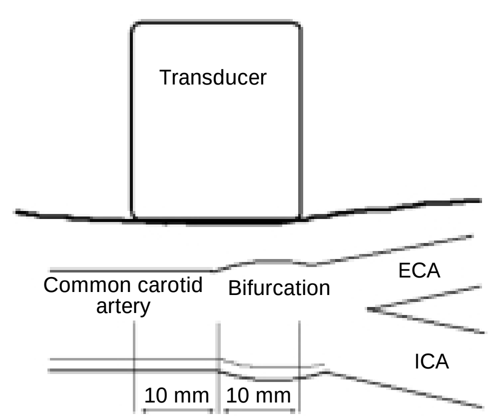

FIG. 1 The carotid circulation and transducer position. ICA = internal carotid artery, ECA = external carotid artery.

TABLE I Clinical characteristics of the study population (n = 205)

Variable	
Age (years)	65 ± 12
Male gender (%)	130 (63)
Smoking (%)	75 (37)
Hypertension (%)	130 (63)
Hypercholesterolemia (%)	89 (43)
Diabetes (%)	46 (22)
Systolic blood pressure (mmHg)	128 ± 23
Diastolic blood pressure (mmHg)	71 ± 13
Body mass index (kg/m^2)	23.0 ± 3.6
Total cholesterol (mmol/l)	5.01 ± 0.93
Triglyceride (mmol/l)	1.35 ± 0.74
HDL-cholesterol (mmol/l)	1.31 ± 0.44
LDL-cholesterol (mmol/l)	2.95 ± 0.77
Uric acid (mmol/l)	0.37 ± 0.10
Hemoglobin A1c (%)	5.8 ± 1.0

mal cutoff point of the carotid IMT was determined by receiver-operating characteristic (ROC) analysis. A p value of < 0.05 was considered to be statistically significant.

Results

The clinical characteristics of the patients in this study are summarized in Table I. Overall, 63% of the subjects had hypertension, 43% had hypercholesterolemia, 22% had diabetes, and 37% were smokers. Of patients with hypertension, 85% had been taking antihypertensive agents; 63% of patients with hypercholesterolemia had been taking cholesterol-lowering drugs, and 48% of patients with diabetes had been taking insulin or hyperglycemic agents.

TABLE II Vascular characteristics of the study population

Variable	
Mean max IMT (mm)	1.23 ± 0.45
Mean baPWV (cm/s)	1637 ± 362
ABI	1.06 ± 0.17
Gensini score	35.5 ± 41.3

Abbreviations: IMT = intima media thickness, baPWV = brachial ankle pulse wave velocity, ABI = ankle brachial index.

The vascular characteristics obtained using the three noninvasive diagnostic methods for atherosclerosis evaluated in this study are shown in Table II. The mean max IMT and the mean baPWV were relatively high, and the ABI was within the normal limits.

The results of the Pearson correlation analysis comparing IMT, PWV, and ABI with the risk factors of CAD are listed in Table III. The mean max IMT correlated positively with age and hemoglobinA1c and negatively with HDL cholesterol. The mean baPWV showed a positive correlation with age and systolic blood pressure and a negative correlation with BMI. The ABI showed a positive correlation with HDL cholesterol and a negative correlation with UA.

TABLE III Pearson correlation of carotid IMT, baPWV, and ABI with risk factors of coronary artery disease

Risk factors	Mean max IMT	Mean baPWV	ABI
Age	r = 0.350	r = 0.543	r = −0.089
	p < 0.0001	p < 0.0001	NS
Body mass index	r = 0.017	r = -0.137	r = 0.044
	NS	p = 0.049	NS
Systolic blood pressure	r = 0.133	r = 0.336	r = −0.071
	NS	p < 0.0001	NS
Diastolic blood pressure	r = −0.065	r = 0.128	r = 0.068
	NS	NS	NS
Total cholesterol	r = −0.044	r = −0.06	r = 0.010
	NS	NS	NS
Triglyceride	r = 0.069	r = −0.007	r = −0.121
	NS	NS	NS
HDL cholesterol	r = −0.234	r = −0.067	r = 0.165
	p = 0.0007	NS	p = 0.021
LDL cholesterol	r = 0.035	r = −0.042	r = −0.096
	NS	NS	NS
Hemoglobin A1c	r = 0.281	r = 0.143	r = 0.068
	p = 0.0005	NS	NS
Uric acid	r = 0.063	r = −0.059	r = −0.183
	NS	NS	p = 0.01

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, NS = not significant. Other abbreviations as in Table II.

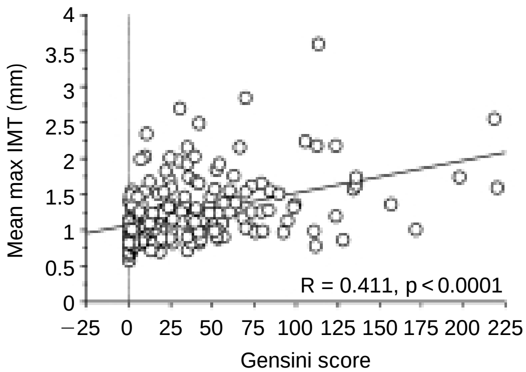

FIG. 2 The relationship between mean max intima-media thickness (IMT) and the Gensini score.

The mean max IMT correlated significantly with the Gensini score (Fig. 2), as did the mean baPWV, but this correlation was relatively weak (Fig. 3). On the other hand, the ABI was not related to the Gensini score (Fig. 4).

Multiple regression analysis revealed that, among the coronary risk factors evaluated in this study, the Gensini score correlated significantly and independently with age and male gender. Of the three noninvasive methods used to evaluate atherosclerosis, only the mean max IMT correlated significantly and independently with the Gensini score (Table IV).

According to ROC analysis, the cutoff point for carotid IMT indicating the presence of CAD was 1.1 mm (Fig. 5). Using this cutoff point, the sensitivity and specificity were 0.70 and 0.69, respectively.

Discussion

An increased IMT has been shown to be associated with the presence and extent of CAD.[2, 3, 13] However, Adams *et al.*[14] showed a poor correlation between IMT and CAD, although only the common carotid artery was examined in their study. Other researchers have demonstrated that the IMT in the carotid artery bulb was associated with the extent of CAD,[13] cardiovascular risk factors, and the prevalence of ischemic heart disease.[15] We also demonstrated that the carotid IMT correlated significantly and relatively well with the severity of coronary atherosclerosis. Our IMT data may be more accurate and reliable than those previously reported because we used an automated edge-detection system to measure the IMT and assessed a relatively long region of the carotid artery, including the carotid bifurcation. Bots *et al.*[16] described in detail various issues and difficulties with the evaluation of carotid IMT, and they recommended the use of the mean max IMT rather than the mean common IMT. We also confirmed that the mean max IMT had a better correlation with the Gensini score than the mean common IMT ($R = 0.411$, $p < 0.0001$ vs. $R = 0.376$, $p < 0.0001$, respectively). Thus, we used the mean max IMT for data analysis.

Pulse wave velocity is also a marker of atherosclerosis that is known to reflect arterial stiffness.[17] Yamashina *et al.*[7] showed that baPWV was significantly higher in patients with than in those without CAD. However, Megnien *et al.*[18] reported that aortic stiffness does not predict the presence of coronary atherosclerosis in asymptomatic men. We demonstrated that baPWV correlated significantly with the severity of coronary atherosclerosis, although a multiple regression analysis showed that baPWV was not a determinant for coronary atherosclerosis. These data suggest that baPWV may not be a strong marker of CAD.

The ABI is also a noninvasive marker used to evaluate peripheral occlusive arterial disease. Papamichael *et al.*[10] reported that the ABI was related to the extent of CAD and was an independent predictor of coronary atherosclerosis. We found no association between ABI and the Gensini score. The patients in their study had higher LDL cholesterol (3.85 ± 1.28 mg/dl) and a lower ABI (0.93 ± 0.16) than the patients in our study (2.95 ± 0.77 mg/dl; 1.06 ± 0.17, respectively). Therefore, the ABI may be a more useful measure of CAD in patients with severe peripheral atherosclerosis.

Previous studies have shown that many factors, including coronary risk factors, are related to the IMT, PWV, and ABI.[9, 15, 19] The present study revealed that IMT correlated

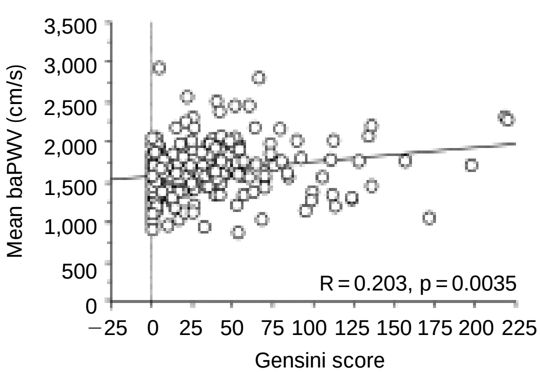

FIG. 3 The relationship between mean brachial-ankle pulse wave velocity (baPWV) and the Gensini score.

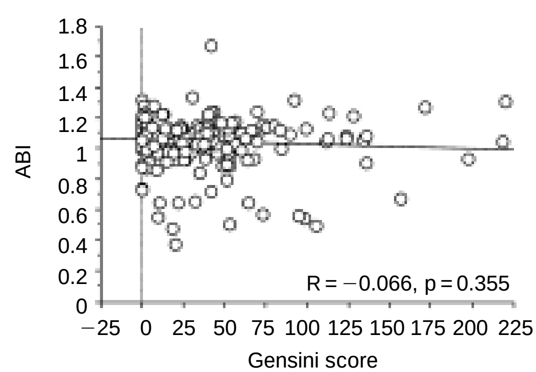

FIG. 4 The relationship between ankle brachial index (ABI) and the Gensini score.

TABLE IV Multiple regression analysis for determinants of the Gensini score

Variable	Partial regression coefficient	Standard regression coefficient	p Value
Age	1.02	0.23	0.027
Male gender	25.25	0.26	0.0085
Smoking	−7.29	−0.08	NS
Body mass index	0.31	0.02	NS
Systolic blood pressure	−0.24	−0.12	NS
Diastolic blood pressure	−0.13	−0.04	NS
Total cholesterol	−0.001	−0.001	NS
Triglyceride	−0.01	−0.08	NS
HDL cholesterol	−0.14	−0.05	NS
LDL cholesterol	0.096	−0.06	NS
Hemoglobin A1c	5.02	0.10	NS
Uric acid	−1.68	−0.07	NS
Mean max IMT	28.92	0.30	0.0009
Mean baPWV	0.0002	0.001	NS
ABI	−0.27	−0.001	NS

Multiple r value = 0.56, $r^2 = 0.32$.
Abbreviations as in Tables II and III.

positively with age and hemoglobinA1c and negatively with HDL cholesterol. Although PWV also had a positive association with age and systolic blood pressure, it was not related to any of the blood sample data. These results suggest that IMT is more strongly influenced by metabolic disorders than PWV. The ABI had a positive correlation with HDL cholesterol and a negative correlation with UA. Thus, the ABI is also influenced by metabolic disorders, although the mechanism seems to differ from that of IMT.

With regard to multiple regression analysis, none of the dyslipidemic data were found to be relevant; however, previous data have shown that dyslipidemia is one of the most important risk factors for CAD.[20] In the present study, the LDL cholesterol level was lower than that in previous studies on the relation between noninvasive methods and CAD, although the other data and characteristics were almost the same as those in previous reports.[9, 10] Recently, antihyperlipidemic agents, such as hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, have become more popular for the treatment of patients, especially those with CAD. This trend may explain why we found no correlation between these noninvasive atherosclerotic measures and LDL cholesterol.

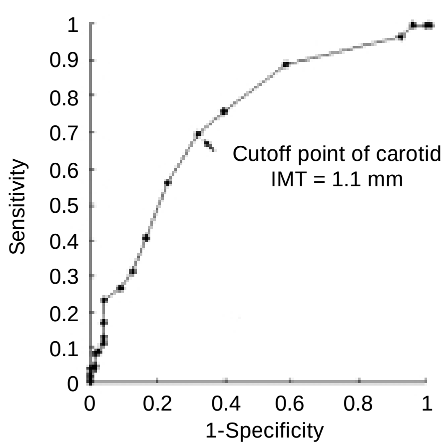

FIG. 5 Receiver-operating characteristic analysis to determine the cutoff point for carotid intima-media thickness (IMT) indicating the presence of coronary artery disease.

By ROC analysis, we showed that a cutoff point for carotid IMT was 1.1 mm to predict the presence of CAD, with a sensitivity of 0.70 and a specificity of 0.69. The previous studies also demonstrated that its sensitivity and specificity ranged from about 0.6 to 0.8.[14, 21] Sensitivity and specificity in both previous and the present studies may not be high enough to predict the presence of CAD accurately. Sakaguchi *et al.*[21] showed that the mean maximal IMT in the common carotid artery, carotid bulb, and internal carotid artery could be better indices than only common carotid artery IMT to predict CAD. The measured portion of the carotid artery seems to be one of the most important factors to improve its sensitivity and specificity.

Conclusions

We evaluated carotid IMT, baPWV, and ABI in the same group of subjects and investigated the relationship between these three markers and the severity of CAD. A relatively strong correlation was found between carotid IMT and the Gensini score, whereas baPWV correlated only weakly with it, and the ABI did not correlate with it. According to a multiple regression analysis, age, male gender, and carotid IMT were determinants of the Gensini score; on the other hand, baPWV and the ABI were not. The carotid IMT may be more useful for predicting coronary artery atherosclerosis than baPWV or ABI.

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