Stiffness and Impaired Blood Flow in Lower-Leg Arteries Are Associated With Severity of Coronary Artery Calcification Among Asymptomatic Type 2 Diabetic Patients

Masanobu Tsuchiya, md[1]
Eiji Suzuki, md[1]
Katsuya Egawa, md[1]
Yoshihiko Nishio, md[1]
Hiroshi Maegawa, md[1]

Shinji Inoue, md[1]
Kenichi Mitsunami, md[1]
Shigehiro Morikawa, md[2]
Toshiro Inubushi, phd[2]
Atsunori Kashiwagi, md[1]

OBJECTIVE — To clarify whether stiffness and impaired blood flow in lower-leg arteries are associated with severity of coronary artery calcification among asymptomatic diabetic patients.

RESEARCH DESIGN AND METHODS — We enrolled 102 asymptomatic type 2 diabetic patients with no history of cardiovascular complications consecutively admitted to our hospital. Agatston coronary artery calcium (CAC) score, as a marker of coronary artery calcification, was obtained using electron-beam computed tomography. Total flow volume and resistive index, as an index of vascular resistance, at the popliteal artery were evaluated using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging. Brachial-ankle pulse-wave velocity (PWV), as an index of distensibility in the lower-extremity arteries, was also measured using an automatic device.

RESULTS — When the patients were grouped according to CAC scores of 0–10 ($n = 54$), 11–100 ($n = 25$), and >100 ($n = 23$), those with the highest scores, which is considered to show possible coronary artery disease, showed the highest brachial-ankle PWV ($P < 0.001$) and resistive index ($P < 0.001$) and the lowest total flow volume ($P < 0.001$) among the groups. Simple linear regression analyses showed that both brachial-ankle PWV ($r = 0.508$, $P < 0.001$) and resistive index ($r = 0.500$, $P < 0.001$) were positively correlated and total flow volume ($r = -0.528$, $P < 0.001$) was negatively correlated with the log-transformed CAC score. Receiver operator characteristic curve analyses indicated that 1,800 cm/s for brachial-ankle PWV, 1.03 for resistive index, and 70 ml/min for total flow volume were diagnostic values for identifying patients with the highest scores.

CONCLUSIONS — Quantitatively assessed stiffness and impaired blood flow in lower-leg arteries may help identify diabetic patients with possible coronary artery disease.

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Atherosclerotic coronary artery disease (CAD) is a major cause of mortality and morbidity among diabetic patients (1). It is desirable to identify subjects with coronary atherosclerosis before the onset of angina pectoris or myocardial infarction. When atherosclerotic plaques are at an advanced stage, calcified deposits in the coronary arteries are found more frequently and in greater amounts (2). A number of studies (3) have documented the usefulness of electron-beam computed tomography (EBCT) for the detection and evaluation of the extent of coronary calcified atherosclerotic lesions in asymptomatic patients before the development of life-threatening cardiac complications. The reliability of EBCT in the detection of calcified deposits in coronary arteries has been confirmed by histomorphometric analysis of dissected coronary vessels from autopsied hearts (4). Moreover, diabetic patients show twofold prevalence of extensive coronary artery calcification compared with nondiabetic subjects as evaluated by EBCT (5). Calcified lesions of arterial walls can be classified as either intimal atherosclerotic calcification or medial arterial calcification according to the site of development. It has been reported (6) that these forms of calcium deposition in the coronary vessel wall arise by different mechanisms. Postmortem examination revealed that calcium deposits predominantly accumulate in the intimal layer rather than in the medial wall of coronary arteries (7). Coronary artery calcification, as detected by EBCT, has been strongly correlated with clinical CAD in diabetic patients (8,9).

Diabetic patients are likely to develop stroke and myocardial infarction as well as obstructive arterial disease in the lower extremities, resulting in a low ankle-brachial index (ABI) (10). These cardiovascular complications frequently coexist (11). Therefore, the ABI is generally used

as a predictive marker of CAD (12). On the other hand, radiologically detectable medial artery calcification has been reported to occur more frequently in the feet of diabetic patients compared with nondiabetic subjects (13). Although it may not be directly related to occlusive arterial disease, this lesion is considered the most severe form of reduced arterial elasticity (14). Therefore, medial artery calcification in the lower extremities is regarded as a powerful predictive marker of cardiovascular mortality (14). Stiffer arteries result in increased vascular resistance and reduced total flow volume in the lower extremities, even in diabetic patients with a normal ABI (15). The prevalence of these patients is comparable with that of patients with intermittent claudication, suggesting that increased vascular resistance may be a major cause of lower-extremity arterial disease (16). However, it is unclear whether quantitatively assessed distensibility measures in the lower-leg arteries can help identify diabetic patients with possible CAD in clinical practice.

We attempted to clarify the association of quantitatively assessed measures of distensibility in the lower-leg arteries and severity of coronary artery calcification among asymptomatic diabetic patients by using the new techniques of EBCT and gated two-dimensional cine-mode phase-contrast magnetic resonance imaging.

RESEARCH DESIGN AND METHODS

We enrolled 139 type 2 diabetic patients ranging in age from 50 to 69 years who had been consecutively admitted to our hospital between October 2001 and November 2003. All patients were admitted for strict glycemic control or assessment of long-term complications of diabetes, including renal, eye, neurological, and circulatory disorders. No patients had life-threatening short-term complications of diabetes, including ketoacidosis, hyperosmolarity, and coma. No patients had alcohol abuse or acute illness. Thirty-seven patients with a history of cardiovascular disease and foot edema caused by liver cirrhosis or severe nephropathy (serum creatinine >133 μmol/l) were excluded from the study; thus, 102 asymptomatic patients were studied. Patients were considered to have cerebrovascular disease if they had a history of sudden focal neurological deficit.

The diagnosis of CAD was made if the patients had a history of angina pectoris or myocardial infarction or showed abnormal electrocardiographic findings. Lower-extremity arterial disease was diagnosed if the patient had a history of intermittent claudication or low ABI (<0.9) (10). The study was approved by the ethics committee of our institution, and informed consent was obtained from all patients before the examinations, which were done during their stay in the hospital.

Clinical assessment
The ABI was examined using a handheld ultrasound Doppler device (ES-1000SP; Nihon Kohden, Tokyo, Japan) to assess lower-extremity arterial disease (10). As an alternative to radiological detection of vessel wall calcification in the lower legs, an automatic device (BP-203RPE; Colin, Komaki, Japan) can be easily applied in diabetic populations to measure brachial-ankle pulse-wave velocity (PWV) by an oscillometric method (17). The accuracy and reproducibility of this methodology have been reported (17). Because the PWV from the heart to the brachial artery in diabetic patients is similar to that in control subjects, brachial-ankle PWV is regarded as a quantitative measure of arterial distensibility from the aorta to the tibial artery (15). Autonomic function was evaluated by the measurement of the coefficient of variation of the R-R interval (CV_{R-R}) during deep breathing monitored on an electrocardiogram (Cardimax FX-3301; Fukuda Denshi, Kyoto, Japan). A highly trained ophthalmologist carried out fundus ophthalmoscopies and classified the diabetic patients as without retinopathy or as having either simple retinopathy, corresponding to levels 21–53 of the modified Airlie House System, or proliferative retinopathy, corresponding to levels 60–80 (18). The diabetic patients were classified as having normoalbuminuria, microalbuminuria, or overt proteinuria when the urinary albumin excretion rate was 15, 15–199, or ≥200 μg/min, respectively, based on 24-h urine collection in our university hospital. These patients were also classified as current smokers or nonsmokers.

EBCT studies
Twenty contiguous slices of 3-mm thickness of the proximal coronary arteries were obtained during a single breath hold using an electron-beam scanner (C-100;

Imatron, South San Francisco, CA) at a scan time of 100 ms per slice. These scans are electrocardiographically triggered at 80% of the R-R interval, near the end of diastole and before atrial contraction, to minimize the effect of cardiac motion. A calcified deposit was considered present if there were contiguous pixels with a threshold computed tomography number >130 Hounsfield units, with an area >1.02 mm^2. This imaging technique does not recognize different sites of calcification within the vessel wall. Therefore, the Agatston coronary artery calcium (CAC) score, including both intimal and medial calcification in the four major coronary arteries (i.e., left main, left anterior descending, circumflex, and right coronary arteries), was obtained as a quantitative marker of coronary artery calcification (19). We also used a recently proposed risk stratification based on the CAC score ranges 0–10, 11–100, and ≥101 (20).

Magnetic resonance studies
An MRI scanner operating at 1.5 Tesla (Signa Horizon-LX; GE Medical Systems, Milwaukee, WI) was used for the following experimental protocols as previously described (15,16). Briefly, after at least 15 min of rest, all patients were evaluated in the supine position in a temperature-controlled 25°C room. To set up the individual flow analysis, the popliteal artery was depicted by two-dimensional time-of-flight magnetic resonance angiography (2D-TOF MRA). A single slice with 5-mm thickness was oriented perpendicular to the flow direction, and flow data were obtained using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging with 80-cm/s velocity encoding triggered by peripheral gating (21). Flow data were analyzed on an Advantage Windows version 3.1 workstation (GE Medical Systems, Milwaukee, WI) to determine the direction and velocity through the cardiac cycle. The instantaneous flow volume at each of 16 equally spaced time points through the cardiac cycle was calculated from the individual velocity images by integrating the velocity across the area of the vessel. The resultant 16 flow volumes allowed assessment of flow variations in pulsatility and hemodynamics during the cardiac cycle. Total flow volume was calculated from the integration of the waveform. A resistive index, which associates with vascular resistance, has been defined as $(A - B)/A$,

Table 1—*Clinical characteristics of asymptomatic diabetic patients classified according to Agatston CAC score*

	Range of CAC score		
	0–10	11–100	>100
n	54	25	23
CAC score	0 (0–9)	43 (13–100)	300 (119–1,837)
Sex (male/female)	29/25	15/10	15/8
Age (years)	58.4 ± 5.8	61.7 ± 5.7	62.5 ± 5.3*
BMI (kg/m^2)	24.7 ± 3.7	23.5 ± 2.9	22.9 ± 3.3
Duration of diabetes (years)	8.5 ± 7.5	16.1 ± 9.0†	16.7 ± 9.0‡
Treatment (diet/OHA/insulin)	5/20/29	1/9/15	3/9/11
Fasting plasma glucose (mmol/l)	6.56 ± 1.68	6.98 ± 1.91	7.26 ± 2.35
HbA$_{1c}$ (%)	8.2 ± 1.5	8.2 ± 1.4	8.5 ± 1.5
Total cholesterol (mmol/l)	4.74 ± 0.72	4.63 ± 0.75	4.87 ± 1.18
HDL cholesterol (mmol/l)	1.18 ± 0.38	1.20 ± 0.25	1.17 ± 0.35
Triglycerides (mmol/l)	1.30 ± 0.45	1.22 ± 0.40	1.48 ± 0.71
Blood pressure (mmHg)			
Systolic	115 ± 12	121 ± 10	131 ± 13‡§
Diastolic	69 ± 7	68 ± 8	74 ± 8*
Smokers	26 (48)	13 (52)	14 (61)
CV$_{R-R}$ (%)	2.48 ± 0.88	2.53 ± 1.05	2.25 ± 0.93
Retinopathy	13 (24)	10 (40)	14 (61)*
Nephropathy	17 (31)	8 (32)	11 (48)
ABI	1.11 ± 0.08	1.14 ± 0.09	1.12 ± 0.08
Brachial-ankle PWV (cm/s)	1,526 ± 264	1,726 ± 360*	1,993 ± 296‡‖

Data are median (range), means ± SD, or n (%). *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$ vs. the lowest group; §$P < 0.05$; ‖$P < 0.01$ vs. the intermediate group. OHA, oral hypoglycemic agent.

where A is the systolic peak velocity and B is the end-diastolic velocity (22).

Statistical analysis

Statistical evaluation was performed using StatView-J 5.0 software (SAS Institute, Cary, NC) on a Macintosh computer. A multiple comparison of significant differences among the three groups was carried out by one-way ANOVA followed by Scheffe's F test. The Bonferroni test for two-by-three contingency tables was used to compare the frequencies among the three groups. Because the distribution of the CAC scores was highly skewed, the common log-transformed CAC score [log(CAC score + 1)] was used for linear regression analysis. Receiver operator characteristic (ROC) curve analysis was done to determine the diagnostic value for identifying patients with a CAC score >100. To assess the discriminatory power of a test, area under the ROC curve (AUC) was calculated using the trapezoid rule (23). An AUC of 0.5 represents a worthless test, whereas an AUC of 1.0 corresponds to a perfect test. Therefore, the accuracy of a diagnostic test is roughly classified into failed (0.50–0.59), poor (0.60–0.69), fair (0.70–0.79), good (0.80–0.89), and excellent (0.90–1.0) according to the AUC (23). Stepwise multiple regression analysis was performed to evaluate the association of the log-transformed CAC score with 10 or 13 possible risk factors. Diabetic retinopathy and nephropathy were graded into three groups based on the severity. The F value was set at 4.0 at each step. Values were expressed as the means ± SD or as median with range where the distribution was skewed. We considered P values <0.05 to be statistically significant.

RESULTS — The 102 asymptomatic diabetic patients were classified into groups having CAC scores of 0–10 ($n = 54$), 11–100 ($n = 25$), and >100 ($n = 23$) using a recently proposed risk stratification (20), in which a score <10 is regarded as normal and one >100 indicates possible CAD (24). The clinical characteristics of these groups are shown in Table 1. There were no significant differences among the groups for prevalence of male sex, BMI, fasting plasma glucose, HbA$_{1c}$, total cholesterol, HDL cholesterol, triglycerides, smoking status, CV$_{R-R}$, and frequency of nephropathy. However, the patients with the highest CAC scores were older ($P < 0.05$) and had longer duration of diabetes ($P < 0.001$), higher brachial systolic blood pressure ($P < 0.001$) and diastolic blood pressure ($P < 0.05$), and more frequent retinopathy ($P < 0.05$) than those with the lowest scores. These patients also showed the fastest brachial-ankle PWV ($P < 0.001$), whereas the ABIs were similar among the three groups.

EBCT and magnetic resonance studies

Figure 1 shows the vasculature in the coronary arteries depicted using EBCT (*A–C*) and the vasculature in the calf depicted using 2D-TOF MRA in three subjects. The patient with a low CAC score showed a normal scan without any calcium deposits (Fig. 1*A*), whereas the patients with intermediate (Fig. 1*B*) and high (Fig. 1*C*) scores showed spotty and extensive amounts of calcification in the left main and left anterior descending coronary arteries, respectively. The popliteal, anterior tibial, posterior tibial, and peroneal arteries were clearly depicted in the patient with the low score (Fig. 1*D*). However, in the patient with the high score (Fig. 1*F*), these arteries showed abnormal vasculature and decreased intravascular signal intensity, indicating decreased arterial inflow to these arteries. The analysis of waveforms recorded at the popliteal artery in patients in each subgroup is shown in Fig. 2. The instantaneous flow volume at each of 16 equally spaced time points through the cardiac cycle was reconstructed. The group with the lowest CAC scores (Fig. 2*A*) had a normal triphasic waveform, which could clearly be separated into systolic, early diastolic, and late diastolic phases. However, the waveform for the group with the highest scores (Fig. 2*C*) was characterized by an abnormal late diastolic flow component, indicating an increased vascular resistance. Heart rates (68 ± 10, 68 ± 8, and 69 ± 9 bpm, respectively) were similar among the three groups. Compared with the other two groups, the group with a high CAC score had higher resistive index (0.993 ± 0.033 vs. 1.011 ± 0.029 vs. 1.036 ± 0.020, respectively, $P < 0.001$) and lower total (92.2 ± 20.6 vs. 79.6 ± 19.2 vs. 61.1 ± 16.3 ml/min, respectively, $P < 0.001$), systolic (90.9 ± 17.6 vs. 86.0 ± 18.1 vs. 73.3 ± 13.9 ml/min, respectively, $P < 0.001$), and late diastolic
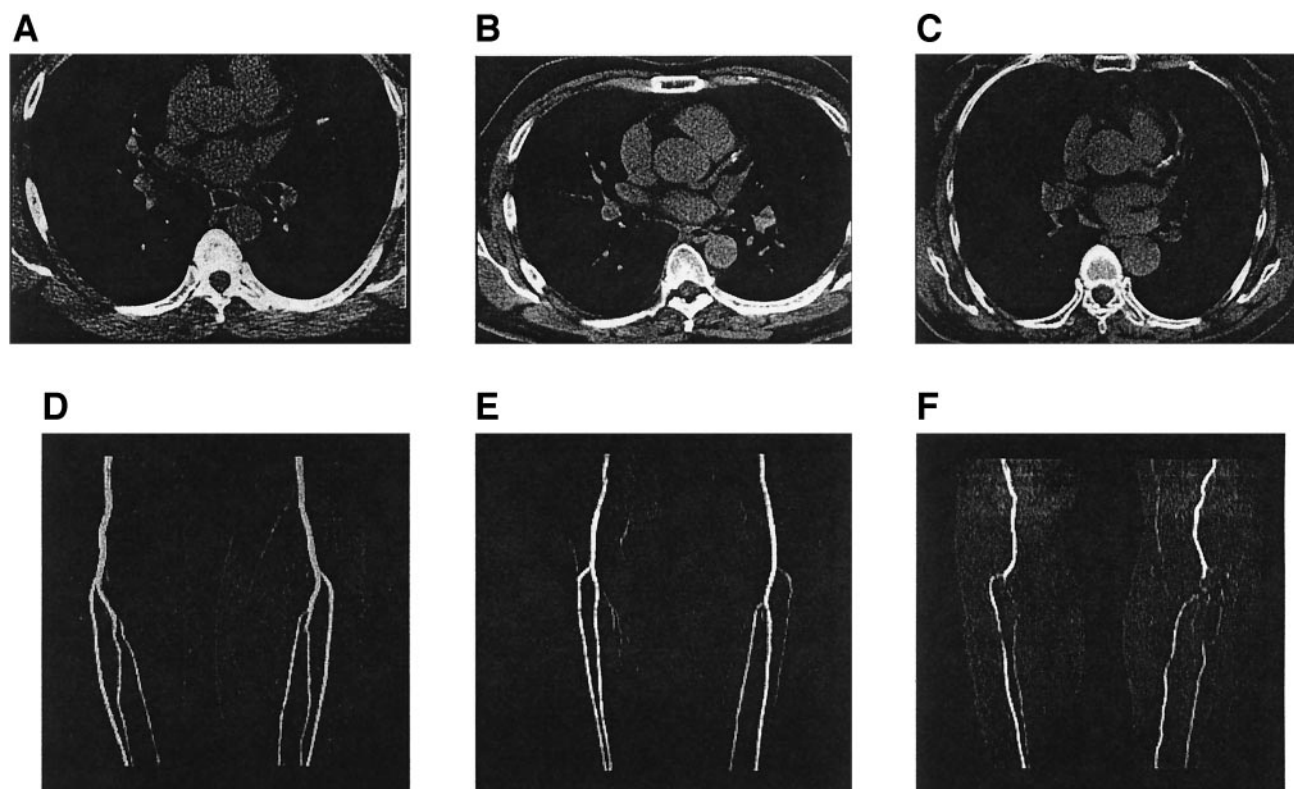
Figure 1—*The vasculature in the left main and left anterior descending coronary arteries, scanned at the level of the origin of the left main coronary artery, visualized by EBCT in three subjects (A–C), and the vasculature in the calf visualized using 2D-TOF MRA in the same subjects (D–F). The three patients had low (A and D), intermediate (B and E), and high (C and F) CAC scores.*

$(14.4 \pm 8.9$ vs. 8.6 ± 7.5 vs. 2.3 ± 5.3 ml/min, respectively, $P < 0.001$) flow volumes, whereas the early diastolic flow volumes $(-13.1 \pm 9.3$ vs. -15.0 ± 7.8 vs. -14.5 ± 8.1 ml/min, respectively) were similar among the groups.

Association of distensibility measures and coronary artery calcification

To clarify the association of quantitatively assessed distensibility measures in the lower-leg arteries and severity of coronary artery calcification, simple linear regression analyses were performed. Both brachial-ankle PWV ($r = 0.508$, $P < 0.001$) (Fig. 3A) and resistive index ($r = 0.500$, $P < 0.001$) (Fig. 3B) were positively correlated and total flow volume ($r = -0.528$, $P < 0.001$) (Fig. 3C) was negatively correlated with log-transformed CAC score, suggesting that diabetes may actively promote parallel development of atherosclerosis in the lower-leg and coronary arteries. To define the diagnostic value of those parameters for identifying patients with a CAC score >100, an ROC curve analysis was performed. The diag-

nostic values were 1,800 cm/s for brachial-ankle PWV (sensitivity 74%, specificity 72%), 1.03 for resistive index (sensitivity 70%, specificity 79%), and 70 ml/min for total flow volume (sensitivity 70%, specificity 79%). The AUC, which is a measure of discriminatory power of the test (20), was 0.80 for brachial-ankle PWV, 0.83 for resistive index, and 0.91 for total flow volume, indicating that these measures are applicable to identify patients with CAC score >100.

Major risk factors associated with CAC score

Stepwise multiple regression analysis was performed to examine the relation between the log-transformed CAC score and 10 possible risk factors for atherosclerosis (age, duration of diabetes, fasting plasma glucose, HbA_{1c}, total cholesterol, HDL cholesterol, triglycerides, systolic and diastolic blood pressure, and prevalence of smokers) or 13 possible risk factors that included the three distensibility measures (brachial-ankle PWV, resistive index, and total flow volume). Systolic blood pressure ($\beta = 0.027$; $F = 17.802$), duration of

diabetes ($\beta = 0.033$; $F = 12.797$), and age ($\beta = 0.031$; $F = 4.803$) were identified among the 10 possible risk factors ($r^2 = 0.343$, $P < 0.001$), and duration of diabetes ($\beta = 0.029$; $F = 11.550$), systolic blood pressure ($\beta = 0.018$; $F = 8.532$), resistive index ($\beta = 7.372$; $F = 7.652$), and total flow volume ($\beta = -0.010$; $F = 6.606$) were identified among the 13 possible risk factors ($r^2 = 0.469$, $P < 0.001$) as significant independent variables correlated with the log-transformed CAC score.

CONCLUSIONS

CAC scores in nondiabetic subjects and diabetic patients in our institution

During the present study, a total of 139 type 2 diabetic patients were consecutively admitted to our hospital. Compared with 105 age- and sex-matched nondiabetic subjects evaluated in our institution by EBCT, these diabetic patients showed increased value of CAC score (median [range], 32 [0–1,051] vs. 49 [0–2,559], $P < 0.05$) and increased prevalence of
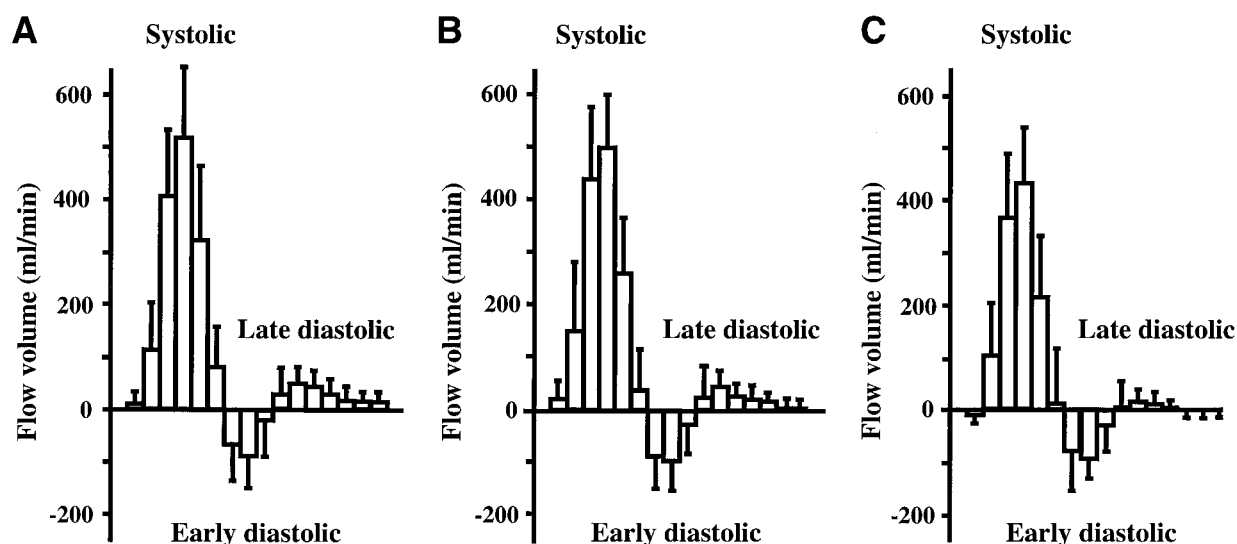
Figure 2—*Waveform analysis at the popliteal artery in 102 asymptomatic diabetic patients classified as having low (0–10) (n = 54) (A), intermediate (11–100) (n = 25) (B), and high (>100) (n = 23) (C) CAC scores. Instantaneous flow volumes at 16 equally spaced time points through the cardiac cycle were reconstructed. Data are means ± SD.*

CAC score >400 (12% [*n* = 13] vs. 24% [*n* = 34], *P* < 0.05]), which is considered extensive atherosclerotic plaque burden and high likelihood (≥90%) of at least one significant coronary stenosis (≥70% diameter stenosis) (20). Although ABI is generally used as a predictive marker of CAD (12), 25 of the 34 (74%) diabetic patients with a CAC score >400 had a normal ABI. Therefore, we assessed the association of quantitatively assessed distensibility measures in lower-leg arteries and severity of coronary artery calcification among 102 asymptomatic patients, after excluding 37 patients with cardio-

vascular disease and/or severe nephropathy (serum creatinine >133 μmol/l).

Association of distensibility measures and coronary artery calcification
In the present study, simple linear regression analyses showed that quantitatively assessed distensibility measures in lower-leg arteries associate with severity of coronary artery calcification, suggesting that diabetes may actively promote parallel development of atherosclerosis in the lower-leg and coronary arteries. Therefore, diabetic patients with coronary ar-

tery calcification may be identified by using indexes of arterial wall stiffness in the lower legs. At the different stages of atherosclerosis in diabetes, nonenzymatic glycosylation of matrix proteins (25), increased intima-media thickness (26,27), or radiologically detectable calcified deposits in the vessel walls (13,14) are seen, and these are considered to be responsible for the pathogenesis of vascular rigidity.

Diagnostic value and discriminatory power of distensibility measures
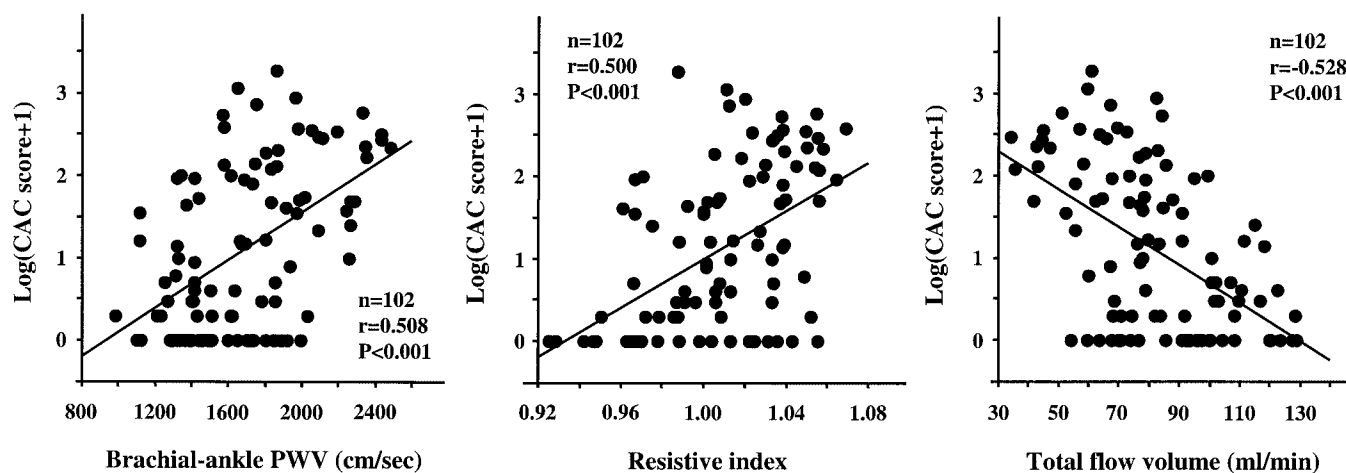Although the presence of CAC deposits detected by EBCT does not indicate the

Figure 3—*Simple linear regression analyses of the relationship between brachial-ankle PWV (A), resistive index (B), and total flow volume (C) at the popliteal artery and log-transformed Agatston CAC score for all 102 asymptomatic diabetic patients.*

location or severity of atherosclerotic lesions, this imaging procedure can be used as a risk stratification based on the CAC score ranges 0–10, 11–100, and ≥101 (20). Exercise single-photon emission computed tomography in asymptomatic subjects revealed that all subjects with CAC score <100 showed a normal perfusion pattern. However, 11% of subjects with CAC score from 100 to 400 ($P <$ 0.001) and 40% of those with CAC score >400 ($P < 0.001$) showed underlying myocardial ischemia (24). Therefore, to define the diagnostic value of distensibility measures for identifying diabetic patients with CAC score >100, an ROC curve analysis was performed (23). Diagnostic values were 1,800 cm/s for brachial-ankle PWV, 1.03 for resistive index, and 70 ml/min for total flow volume, indicating that those distensibility measures may help identify patients with possible CAD.

Major risk factors associated with CAC deposition

In the present study, patients with CAC scores >100 were older and showed longer duration of diabetes, higher brachial systolic and diastolic blood pressures, and greater frequency of retinopathy compared with patients with CAC scores <10, whereas the prevalence of male sex and serum lipid levels were similar in the two groups. Stepwise multiple regression analysis showed that the major risk factors associated with CAC score were hypertension, duration of diabetes, and age. Recent EBCT studies on the coronary arteries have revealed that diabetes (5,8,9), aging (28), male sex (28), hypercholesterolemia (29), and hypertension (30), which are all well recognized as risk factors for coronary atherosclerosis, contribute to the progression of calcification and the abundance of calcium deposits. The prevalence of calcium deposits in the coronary arteries increases with age in both men and women (28). However, prevalence in women was reported to be one-half that in men up to the age of 60 years (28). Lipid-lowering medications can reduce the LDL cholesterol level and reduce the volume of calcified plaques in the coronary arteries (29). Hypertension may contribute to the atherogenic process through arterial wall trauma induced by the elevated blood pressure and coexistent shearing conditions (31).

In conclusion, quantitatively assessed distensibility measures in the lower-leg arteries may help identify diabetic patients with possible CAD.

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