Increased Arterial Wall Stiffness Limits Flow Volume in the Lower Extremities in Type 2 Diabetic Patients

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OBJECTIVE — To document an association between arterial wall stiffness and reduced flow volume in the lower-extremity arteries of diabetic patients.

RESEARCH DESIGN AND METHODS — We recruited 60 consecutive type 2 diabetic patients who had no history or symptoms of peripheral arterial disease (PAD) in the lower extremities and normal ankle/brachial systolic blood pressure index at the time of the study (non-PAD group) and 20 age-matched nondiabetic subjects (control group). We used an automatic device to measure pulse wave velocity (PWV) in the lower extremities as an index of arterial wall stiffness. At the popliteal artery, we evaluated flow volume and the resistive index as an index of arterial resistance to blood flow using gated two-dimensional cine-mode phase-contrast magnetic resonance imaging.

RESULTS — Consistent with previous reports, we confirmed that the non-PAD group had an abnormally higher PWV compared with that of the control group ($P < 0.001$). To further demonstrate decreased flow volume and abnormal flow pattern at the popliteal artery in patients with a higher degree of arterial wall stiffness, we assigned the 60 non-PAD patients to tertiles based on their levels of PWV. In the highest group, magnetic resonance angiograms of the calf and foot arteries showed decreased intravascular signal intensity, indicating the decreased arterial inflow in those arteries. The highest group was also characterized by the lowest late diastolic and total flow volumes as well as the highest resistive index among the groups. From stepwise multiple regression analysis, PWV and autonomic function were identified as independent determinants for late diastolic flow volume ($r^2 = 0.300$; $P < 0.001$).

CONCLUSIONS — Arterial wall stiffness was associated with reduced arterial flow volume in the lower extremities of diabetic patients.

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I t has been reported that macrovascular diseases in the lower extremities caused by either occlusive arterial disease (1,2) or increased arterial resistance to blood flow (3) in diabetic patients may lead to foot lesions. Contrast angiography has been used to evaluate the severity of morphologic changes in peripheral arteries but is frequently limited for several reasons, including possible nephrotoxity from contrast medium (4). Other reasons include the invasiveness of the procedure itself, associated risks, and costs (4). Therefore, it is important to innovate noninvasive vascular assessment of the lower extremities for the prevention of macrovascular events. To help identify high-risk patients with occlusive arterial disease in the lower extremities, the ankle/brachial blood pressure index (ABI) is generally used (5). Although a negative ABI does not exclude peripheral vascular disease (PAD) (6), the presence of an abnormal ABI is extremely useful and has been shown in multiple studies to predict cardiovascular disease. To evaluate structural and functional vessel wall properties, the thickness of the intima-media complex (7,8), medial arterial calcification (6), vascular resistance to blood flow (9), and arterial wall stiffness (10) are beneficial. Arterial wall stiffness can be noninvasively assessed by either direct or indirect methods (10). Direct techniques involve the measurement of the relative change in arterial diameter and pressure during the cardiac cycle (11). Indirect measurements are also used, including pulse wave velocity (PWV) (12,13) and augmentation of the central arterial pressure due to early pulse wave reflection (14). The PWV is calculated from measurements of pulse transit time and the distance traveled by the pulse between two recording sites (12,13). The diabetic patients with chronic hyperglycemia are known to have stiffer arteries (15,16) and abnormal PWV (17). In general, increased aortic PWV is associated with increased cardiovascular risk factors and events (18). Other noninvasive tests, such as measurement of transcutaneous oxygen tension, have been proposed to evaluate PAD (19).

The present study was designed to clarify whether arterial wall stiffness was associated with reduced flow volume in the lower-extremity arteries in diabetic patients, using gated two-dimensional (2D) cine-mode phase-contrast magnetic resonance imaging and an automatic device for PWV measurement.

RESEARCH DESIGN AND METHODS

Diabetic patients and control subjects. A total of 60 type 2 diabetic patients ranging in age from 50 to 69 years and 20 age-matched nondiabetic subjects (control group) were admitted consecutively to our hospital between November 1999 and October 2000. All 60 diabetic patients were admitted for strict glycemic control or assessment of diabetic complications. These patients had no history or symptoms of PAD and normal ankle/brachial blood pressure index (ABI) values at the time of the study (non-PAD group) (5). The nondiabetic subjects were defined according to World Health Organization criteria (20) and had neither a personal history of hypertension nor dyslipidemia at the time of the study. Patients who had foot edema caused by apparent heart failure, liver cirrhosis, or severe nephropathy (serum creatinine >133 μmol/l); alcohol abuse; nondiabetic neurological disorders; or acute illness were excluded from the study. No subjects showed signs of subclavian stenoses. Subjects with a brachial systolic blood pressure (sBP) >140 or <110 mmHg were excluded from the study, so that the range of brachial systolic and diastolic blood pressures (dBPs) were similar between the groups. 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 hospital stay.

Clinical evaluations. Neurological assessments were done by motor nerve conduction velocity (MCV) of the posterior tibial nerve and sensory nerve conduction velocity (SCV) of the sural nerve using electromyography (Medelec MS-25; Sanei, Tokyo). Autonomic function was evaluated by measurement of the coefficient of variation of the R-R interval ($CV_{R\text{-}R}$) during deep breathing monitored on an electrocardiogram (Cardimax FX-3301; Fukuda Denshi, Kyoto, Japan). A trained ophthalmologist carried out fundus ophthalmoscopies and defined diabetic patients as either without retinopathy or as having simple retinopathy corresponding to levels 21–53 or proliferative retinopathy corresponding to levels 60–80 of the modified Airlie House System (21). Furthermore, diabetic patients with normoalbuminuria, microalbuminuria, or overt proteinuria were defined as having a urinary albumin excretion rate of <15, 15–199, and >200 μg/min, respectively, by 24-h urine collection in our university hospital. These patients were also defined by their smoking habits as being a current smoker or nonsmoker.

Pulse wave velocity. Occlusion and monitoring cuffs were placed snugly around both sides of the upper and lower extremities in patients in the supine position. Then, pressure waveforms of the brachial and tibial arteries were recorded after 15 min of bed rest using an automatic waveform analyzer (BP-203RPE; Colin, Komaki, Japan). Electrocardiogram monitoring was performed with electrodes placed on both wrists, and arrhythmia was evaluated. Heart sounds S1 and S2 were detected by a microphone set on the left edge of the sternum at the fourth intercostal space. The pressure waveforms obtained at two different sites were simultaneously recorded to determine the time interval between the initial rise in the brachial and tibial pressure waveforms (ΔTa). The path length from the suprasternal notch to the elbow (ΔDa) was obtained from superficial measurements and was expressed using the following equation: ΔDa = 0.2195 × H − 2.0734, where H (in centimeters) is the height of the patient. The path length from the suprasternal notch to the femur to the ankle (ΔDb) was calculated as follows: ΔDb = (0.5643 × H − 18.381) + (0.2486 × H + 30.709). The following equation was used as a surrogate index of PWV in the lower extremity: (ΔDb − ΔDa)/ΔTa.

Magnetic resonance equipment. A magnetic resonance imaging scanner (1.5-Tesla, Signa Horizon-LX; GE Medical Systems, Milwaukee, WI) was used for the following experimental protocols. All patients were at rest in the supine position during examinations, which were done in a temperature-controlled room at 25°C.

Vasculatures in the calf and foot and flow analysis at the popliteal artery. To set up the individual flow analysis, the popliteal artery was depicted by 2D time-of-flight (TOF) magnetic resonance angiography (3,22). A single slice was oriented perpendicular to the flow direction, and flow data were obtained using 2D cine-mode phase-contrast (2D-cine-PC) magnetic resonance imaging with 80 cm/s velocity encoding triggered by peripheral gating (3,23). Flow data were analyzed with the Flow Analysis version 5.8 software package (GE Medical Systems) to determine direction, velocity, and volume. The instantaneous flow volume at 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 velocities or flow volumes allowed assessment of flow variations in pulsatility and hemodynamics during the cardiac cycle. The control group had a typically triphasic waveform of the popliteal artery that could clearly be separated into systolic, early diastolic, and late diastolic phases (3). Flow volumes of the systolic, early diastolic, and late diastolic phases of the cardiac cycle were calculated from the integration of the waveform. A resistive index, which allows quantitative analysis of the waveform and associates with arterial resistance to blood flow, has been defined as (A-B)/A, where A is the systolic peak velocity and B is the end-diastolic velocity (9). To assess the morphologic findings of foot arteries, three-dimensional–PC (3D-PC) magnetic resonance angiography with no contrast medium was performed with 5-cm/s velocity encoding (3,24).

Statistical analysis. Statistical evaluation was performed using StatView-J version 5.0 software (SAS Institute, Cary, NC) on a Macintosh computer. Normality of distribution of any variable was assessed with the Kolmogorov-Smirnov test. Comparison between the diabetic patients and their respective control group were done using the unpaired Student's t test. A multiple comparison of significant differences among the three groups was analyzed by one-way analysis of variance followed by Scheffe's F test. The χ^2 test for 2 × 2 or Bonferroni test for 2 × 3 contingency tables was used to compare the frequencies between two groups or among three groups. Pearson's correlation coefficient was applied to assess the relation between normally distributed variables. Stepwise multiple regression analysis was used to evaluate the association among late diastolic flow volume at the popliteal artery and various clinical characteristics of the subjects. Diabetic retinopathy and nephropathy were classified 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. We considered P values <0.05 to be statistically significant.

Table 1—*Clinical characteristics of the non-PAD group classified into tertiles based on the levels of PWV in lower extremity*

	Lowest group (1,316 ± 152 cm/s)	Intermediate group (1,629 ± 46 cm/s)	Highest group (2,105 ± 277 cm/s)
n	20	20	20
M/F	10/10	10/10	10/10
Age (years)	57.9 ± 6.7	62.2 ± 5.9	65.5 ± 3.5*
Height (cm)	161 ± 7	159 ± 9	160 ± 7
BMI (kg/m^2)	23.5 ± 3.3	24.4 ± 4.0	23.6 ± 3.0
Duration of diabetes (years)	7.3 ± 5.0	14.0 ± 7.3†	16.9 ± 9.6*
Treatment (D/OHD/I)	8/8/4	2/10/8	2/13/5
FPG (mmol/l)	7.83 ± 1.81	7.32 ± 2.13	7.97 ± 1.91
HbA$_{1c}$ (%)	8.9 ± 1.7	8.7 ± 1.4	8.2 ± 1.6
TC (mmol/l)	4.81 ± 0.82	5.05 ± 0.83	5.13 ± 0.61
HDL cholesterol (mmol/l)	1.13 ± 0.35	1.30 ± 0.28	1.31 ± 0.32
TGs (mmol/l)	1.43 ± 0.63	1.22 ± 0.42	1.52 ± 0.55
Smokers (%)	12 (60)	10 (50)	6 (30)
MCV (m/s)	42.6 ± 4.7	40.8 ± 5.3	36.6 ± 6.6‡
SCV (m/s)	43.6 ± 4.9	38.0 ± 5.8‡	37.3 ± 5.7‡
CV$_{R-R}$ (%)	2.67 ± 1.04	1.73 ± 0.97†	1.88 ± 0.97†
Retinopathy (%)	7 (35)	13 (65)	11 (55)
Nephropathy (%)	1 (5)	7 (35)	3 (15)

Data are n, means ± SD, or n (%). D, diet; I, insulin; OHD; oral hypoglycemic drugs. *$P < 0.001$, †$P < 0.05$, and ‡$P < 0.01$ vs. the lowest group.

RESULTS

Clinical characteristics in all subjects. The 60 diabetic patients with no apparent PAD by traditional criteria (non-PAD group) and the 20 nondiabetic subjects (control group) were comparable with respect to age (61.9 ± 6.3 vs. 61.3 ± 6.4 years), sex (30 men and 30 women vs. 10 men and 10 women), height (160 ± 8 vs. 160 ± 10 cm), total cholesterol (TC; 4.99 ± 0.76 vs. 4.74 ± 0.67 mmol/l), HDL cholesterol (1.25 ± 0.32 vs. 1.29 ± 0.44 mmol/l), triglycerides (TGs; 1.39 ± 0.55 vs. 1.15 ± 0.27 mmol/l), frequency of smoking habit (47 vs. 45%), sBP (128 ± 10 vs. 124 ± 8 mmHg), and dBP (74 ± 9 vs. 75 ± 8 mmHg) at the brachial artery. Total flow volume at the popliteal artery (88.3 ± 31.3 vs. 90.5 ± 20.8 ml/min) and ABI (1.21 ± 0.14 vs. 1.15 ± 0.08) were similar between the groups. However, the non-PAD patients had a higher PWV (1,683 ± 374 vs. 1,274 ± 111 cm/s; $P < 0.001$), which was consistent with previous findings, and a higher resistive index (1.01 ± 0.04 vs. 0.96 ± 0.03; $P < 0.001$) than that of the control group.

Three representative cases associated with arterial wall stiffness. To further demonstrate decreased flow volume and abnormal flow pattern at the popliteal artery in patients with a higher degree of arterial wall stiffness, we assigned the 60 non-PAD patients to tertiles based on their levels of PWV, although this parameter was used as a continuous variable and was normally distributed. The clinical characteristics of these groups are summarized in Tables 1 and 2. There were significant differences in age, duration of diabetes, MCV, SCV, and CV$_{R-R}$ without any difference in height, BMI, fasting plasma glucose (FPG), HbA$_{1c}$, TC, HDL cholesterol, TGs, frequency of smoking habit, retinopathy, and nephropathy among the groups (Table 1). The highest group had higher brachial and ankle sBP than those of the lowest group (Table 2). The popliteal, anterior tibial, posterior tibial, and peroneal arteries in one patient in the lowest group (Fig. 1*a*) were clearly depicted using 2D-TOF magnetic resonance angiography. However, those arteries in a subject from the highest group (Fig. 1*c*) showed abnormal vasculature and decreased intravascular signal intensity, indicating the decreased arterial inflow to these arteries. 3D-PC magnetic resonance angiography reflected the flow velocities >5 cm/s. Foot vasculatures, such as dorsalis pedis, medial and lateral plantar arteries, and plantar arch, in a patient of the lowest group (Fig. 1*d*) were clearly depicted. However, these arteries in a subject from the highest group (Fig. 1*f*) showed a decreased intravascular signal intensity, indicating decreased flow velocities in these arteries. To evaluate these vascular abnormalities, flow analysis at the popliteal artery in these groups was studied using gated 2D-cine-PC magnetic resonance imaging. Instantaneous flow volumes at 16 equally spaced time

Table 2—*Peripheral circulation in the non-PAD group classified into tertiles based on levels of PWV in lower extremity*

	Lowest group (1,316 ± 152 cm/s)	Intermediate group (1,629 ± 46 cm/s)	Highest group (2,105 ± 277 cm/s)
n	20	20	20
Brachial BP (mmHg)			
Systolic	119 ± 8	132 ± 9*	133 ± 7*
Diastolic	74 ± 8	76 ± 10	73 ± 10
Ankle BP (mmHg)			
Systolic	142 ± 23	165 ± 27†	165 ± 24†
Diastolic	74 ± 10	82 ± 12	81 ± 12
ABI	1.18 ± 0.14	1.23 ± 0.14	1.20 ± 0.14
Heart rate (bpm)	67 ± 9	69 ± 10	71 ± 12
Flow volume (ml/min)			
Total	98.0 ± 33.1	92.2 ± 25.1	73.8 ± 30.3†
Systolic	91.1 ± 21.4	91.5 ± 16.9	84.1 ± 29.6
Early diastolic	−12.4 ± 9.2	−12.5 ± 11.6	−13.3 ± 8.7
Late diastolic	19.2 ± 12.8	13.2 ± 9.5	3.0 ± 6.3*‡
Resistive index	0.99 ± 0.04	1.00 ± 0.04	1.04 ± 0.03*§

Data are means ± SD. *$P < 0.001$ and †$P < 0.05$ vs. the lowest group; ‡$P < 0.01$ and §$P < 0.05$ vs. the intermediate group.
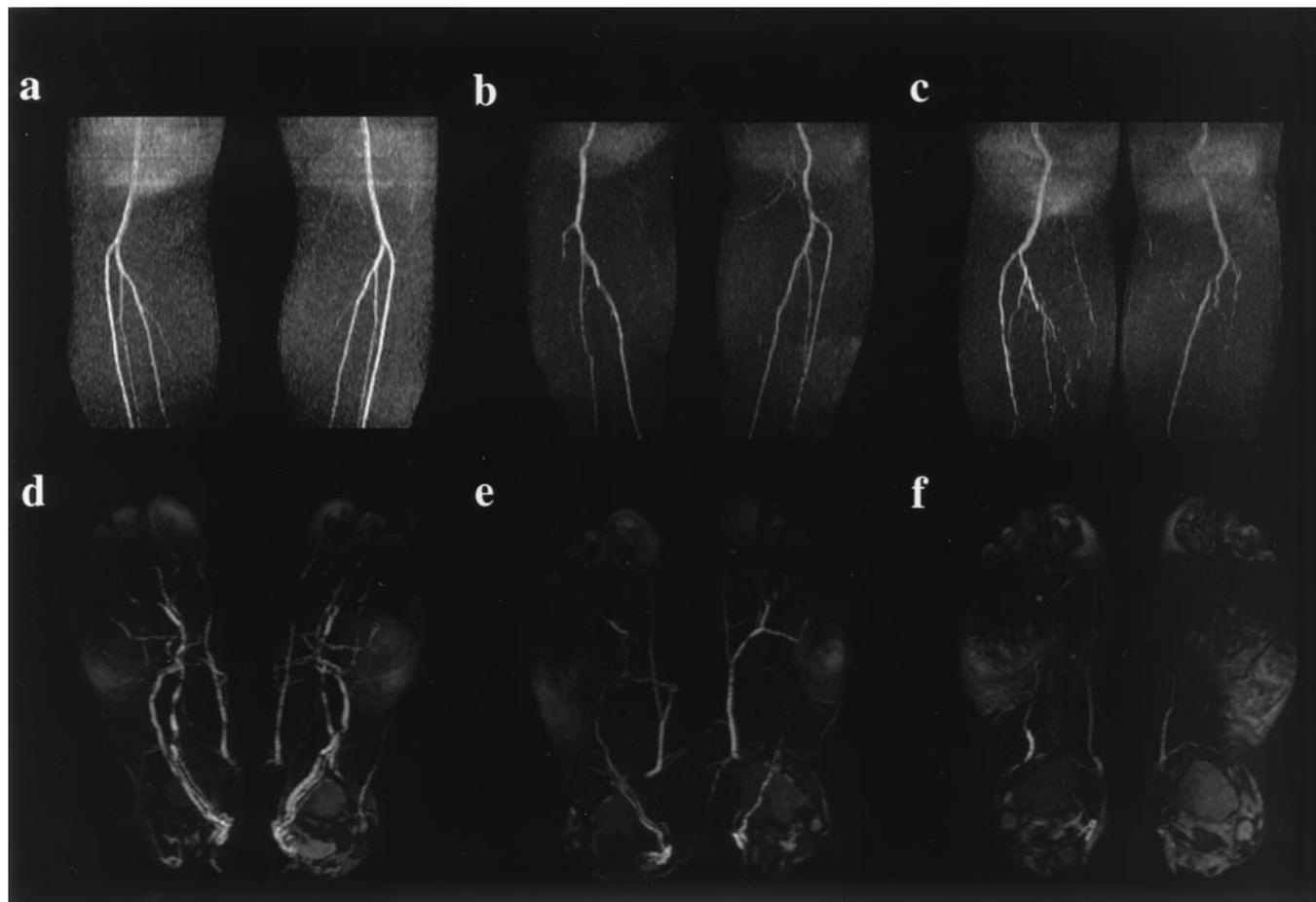
Figure 1—*Three case subjects with vasculatures in the calf using 2D-TOF magnetic resonance angiography* (a, b, *and* c) *or with vasculatures in the feet using 3D-PC magnetic resonance angiography* (d, e, *and* f), *with no contrast medium in each of the lowest* (a *and* d), *intermediate* (b *and* e), *and highest* (c *and* f) *groups. We placed 60 non-PAD patients into tertiles based on their levels of PWV in the lower extremities.*

points through the cardiac cycle were reconstructed. The lowest group (Fig. 2*A*) had a normal triphasic waveform at the popliteal artery. However, the highest group (Fig. 2*C*) was characterized by a lower amplitude in the late diastolic component compared with that of the lowest group. Flow analysis at the popliteal artery showed that the highest group was characterized by lower values for late diastolic and total flow volumes as well as a higher resistive index compared with the lowest group (Table 2).

Analysis of arterial wall stiffness. To clarify factors affecting abnormal PWV and the threshold for normal PWV in diabetic patients, we classified the patients as follows: 15 patients with PWV values comparable to the normal range in the control group (means $\pm$ 2 SD; range 1,052–1,496 ms) were classified as the normal PWV group; the remaining 45 patients with abnormal PWV ($>$1,497 ms)

were classified as the abnormal PWV group. In the abnormal PWV group, age (63.7 $\pm$ 5.1 vs. 56.2 $\pm$ 6.3 years; $P <$ 0.001), duration of diabetes (14.8 $\pm$ 8.3 vs. 6.5 $\pm$ 5.1 years; $P <$ 0.001), and brachial sBP (131 $\pm$ 8 vs. 118 $\pm$ 8 mmHg; $P <$ 0.001) and ankle sBP (164 $\pm$ 25 vs. 139 $\pm$ 22 mmHg; $P <$ 0.01) were higher, and MCV (38.8 $\pm$ 6.1 vs. 43.6 $\pm$ 4.3 m/s; $P <$ 0.01), SCV (38.2 $\pm$ 5.9 vs. 44.2 $\pm$ 4.4 m/s; $P <$ 0.001), and CV_{R-R} (1.86 $\pm$ 0.96 vs. 2.79 $\pm$ 1.07%; $P <$ 0.05) were lower compared with those of the normal PWV group. The normal PWV group had lower age (56.2 $\pm$ 6.3 vs. 61.3 $\pm$ 6.4 years; $P <$ 0.05) and a higher resistive index (0.99 $\pm$ 0.04 vs. 0.96 $\pm$ 0.03; $P <$ 0.05) than those of the control group, despite similar PWV (1247 $\pm$ 105 vs. 1,274 $\pm$ 111 cm/s) between them.

To characterize clinical variables for determining PWV in the non-PAD group, we did stepwise multiple regression anal-

ysis of the relationship between this parameter and 10 possible risk factors for atherosclerosis (age, duration of diabetes, FPG, HbA_{1c}, TC, HDL cholesterol, TGs, ankle sBP and dBP, and percentage of smokers), three neurological factors (MCV, SCV, and CV_{R-R}), and two factors of diabetic microangiopathy (retinopathy and nephropathy). Age (β-value = 0.47; F value = 31.08), duration of diabetes (β-value = 0.34; F value = 14.01), ankle dBP (β-value = 0.44; F value = 28.10), and MCV (β-value = $-$0.26; F value = 8.49) were identified as significant independent variables for determining PWV (r^2 = 0.652; $P <$ 0.001). Furthermore, PWV was positively correlated with the resistive index at the popliteal artery (r = 0.474; $P <$ 0.001).

Analysis of flow volume. To characterize clinical variables for determining the late diastolic flow volume at the popliteal artery in the non-PAD group, we did step-
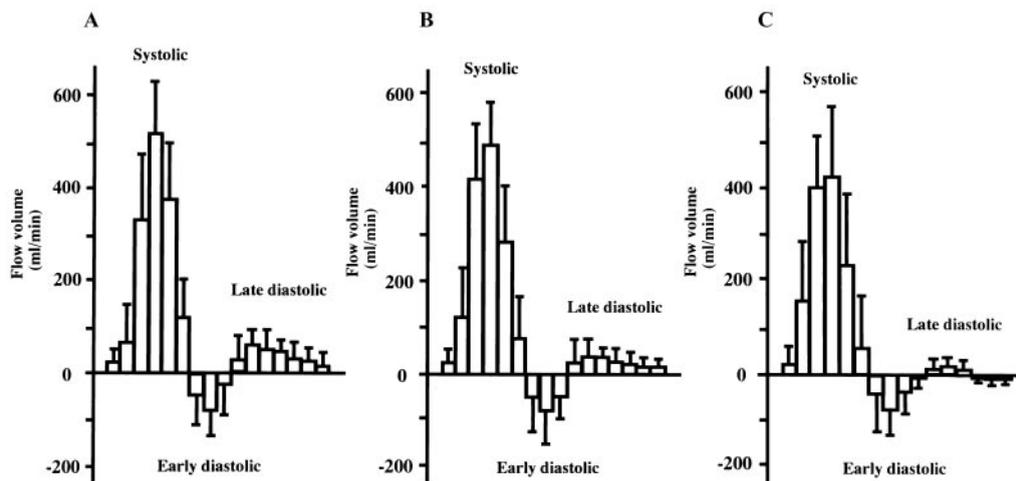
Figure 2—*Waveform analysis of the popliteal artery in 60 non-PAD patients. These patients were put into categories of the lowest (A), intermediate (B), and highest (C) groups based on their levels of PWV in the lower extremities. Instantaneous flow volume at 16 equally spaced time points through the cardiac cycle were reconstructed. Data are means ± SD.*

wise multiple regression analysis of the relation between this parameter and 15 possible risk factors (age, duration of diabetes, FPG, HbA_{1c}, TC, HDL cholesterol, TGs, ankle sBP and dBP, percentage of smokers, MCV, SCV, CV_{R-R}, retinopathy, and nephropathy) and PWV. Both PWV (β-value = −0.01; F value = 14.94) and CV_{R-R} (β-value = 3.01; F value = 5.69) were identified as significant independent variables for determining late diastolic flow volume at the popliteal artery (r^2 = 0.300; $P < 0.001$).

CONCLUSIONS — To clarify whether arterial wall stiffness was associated with reduced flow volume in the lower extremity arteries in diabetic patients, we evaluated PWV in the lower extremities and flow volume at the popliteal artery. The patients who had no apparent peripheral arterial disease by traditional criteria (the non-PAD group) had a higher PWV than the control subjects. We assigned the 60 non-PAD patients to tertiles based on their levels of PWV. Magnetic resonance angiography in the calf and foot showed abnormal vasculature and lower intravascular signal intensity in the highest group compared with the lowest group. The late diastolic flow volume was of a much lower amplitude compared with the systolic component in the arterial waveform and was more easily affected by arterial wall stiffness. The flow analysis at the popliteal artery showed that the highest group was characterized by lower late

diastolic and total flow volumes as well as by a higher resistive index compared with the lowest group. These findings indicated that arterial wall stiffness in the lower extremities was associated with an increased arterial resistance to blood flow, resulting in decreased arterial inflow to the popliteal artery and decreased flow velocity in the foot arteries.

PWV is widely used as an indirect index of arterial distensibility (12,13). Findings from necropsy studies in animal models (25) and human subjects (26) before death support the accuracy of this method. In the present study, the time interval between the initial rise in the brachial and tibial pressure waveforms (ΔTa) and the path length from the suprasternal notch to the elbow (ΔDa) or from suprasternal notch to the femur to the ankle (ΔDb) were obtained using an automatic device for PWV measurement. The equation (ΔDb − ΔDa)/ΔTa included the stiffness of the brachial artery and the stiffness from the aorta to the tibial artery. However, the PWV from the heart to the brachial artery was similar between the control subjects and diabetic patients (557 ± 68 vs. 589 ± 108 cm/s). Thus, we defined (ΔDb − ΔDa)/ΔTa as a surrogate index of PWV in the lower extremities, although this parameter included the stiffness of the aorta. Not only the abnormal vasculature in the calf and foot arteries but also the reduced flow volume and increased resistive index at the popliteal artery in patients with higher PWV support the usefulness of this parameter in clinical practice.

Noninvasive magnetic resonance angiography using either TOF (22) or PC (24) has been implemented to define both the morphologic and physiologic changes in the vessels. Furthermore, a velocity-encoded cine-PC magnetic resonance image was used to measure flow velocity or flow volume throughout the cardiac cycle. The accuracy and reproducibility of cine-PC magnetic resonance imaging to measure flow volume for the triphasic waveform created from a pulsatile pump have been reported (23). When the feasibility of cine-PC imaging was compared with color-coded Doppler sonography, the velocity waveform in the popliteal artery acquired using both methods correlated well (22). A resistive index allows quantitative flow analysis and associates with vascular resistance to blood flow (9).

Diabetic patients with chronic hyperglycemia are known to have stiffer arteries (15–17). The biomechanical properties of aortic samples taken from diabetic patients at postmortem examination showed a marked increase in stiffness and a marked reduction in extensibility, as determined using a materials testing machine (15). The nonenzymatic glycosylation of matrix proteins caused by chronic hyperglycemia (27), increased intima-media thickness (IMT), (7,8) or medial arterial calcification (MAC) (6) may be responsible for the pathogenesis of vascular rigidity. The evaluation of IMT provides

information about structural changes in the vessel wall and correlates with vessel wall distensibility in diabetic patients (7,8). The vascular rigidity assessed by carotid-to-femoral PWV before coronary artery bypass surgery showed that the diabetic patients with coronary arterial disease had stiffer aortas than nondiabetic subjects (27). Furthermore, tissue specimens of the ascending aorta taken from these patients during the coronary arterial bypass surgery showed a positive correlation between vascular rigidity and collagen-linked fluorescence advanced glycosylation end products (27). The prevalence of MAC, which was defined as parallel tramline calcification using a radiographic analysis, has been reported to be more frequent in the feet of diabetic patients compared with nondiabetic subjects (6). However, the relation between the presence of MAC and clinically important peripheral vascular disease is disputed.

To clarify factors affecting abnormal PWV and the threshold for normal PWV in diabetic patients with no apparent PAD, we divided the group into 15 patients with PWV comparable to the control group (normal PWV group) and 45 patients with abnormal PWV (abnormal PWV group). Age, duration of diabetes, blood pressure, and neurological factors were significantly different between the groups. The normal PWV patients had stiffer arteries at a younger age and higher arterial resistance to blood flow than the nondiabetic subjects, despite similar PWV between the groups. This result indicates that the threshold for normal PWV in the diabetic patients may be set to lower values than that of the nondiabetic subjects.

Aging (28) and hypertension (29) are known to be associated with decreased elasticity of the large arteries. In the present study, when the non-PAD group was classified into tertiles based on their PWV levels in the lower extremities, the highest group had similar ages and brachial and ankle blood pressures compared with those of the intermediate group. However, magnetic resonance angiograms in the highest group showed lower arterial inflow in the calf and foot arteries compared with those of the intermediate group. Furthermore, the highest group had a lower late diastolic flow volume and a higher resistive index at the popliteal artery than those of the intermediate group. These findings suggest that

the increased rigidity of the vessel wall, indicated by higher PWV, may contribute not only to increased arterial resistance to blood flow but also to decreased flow volume of the popliteal artery, despite similar ages and blood pressures between the groups.

The 16 diabetic patients with lower-extremity occlusive arterial disease (arteriosclerosis obliterans [ASO]) had lower ABI (0.74 ± 0.09 vs. 1.15 ± 0.09; *P* < 0.001) and similar PWV in the lower extremity (1,364 ± 373 vs. 1,274 ± 111 ms) compared with 20 nondiabetic subjects. A lower ankle blood pressure in the ASO patients may be responsible for the decreased PWV in the lower extremity. Thus, we excluded the ASO patients from the present study. Further studies are necessary to clarify whether arterial wall stiffness may associate with the development of ASO in diabetic patients.

In the present study, statistical analysis demonstrated that arterial wall stiffness and autonomic function were independent risk factors for determining the late diastolic flow volume. In terms of autonomic function, two possible major causes are considered. First, the autonomic denervation is believed to develop MAC (30) and could be biologically

linked to arterial wall stiffness. Second, however, sympathetic failure affects microvascular blood flow by continuously opening arteriovenous shunts and increasing flow volume (31). It may be important that a concomitant abnormality, such as basement membrane thickness, regulates vascular resistance to blood flow, although there was no explanation for microangiopathy as a determinant factor of flow volume in the present study (32). In conclusion, we clarified that arterial wall stiffness was associated with reduced flow volume in the lower extremity arteries in diabetic patients.

APPENDIX

Appendix 1—*Clinical characteristics in the non-PAD patients with PWV comparable to the control group (normal PWV group) or with abnormal PWV (abnormal PWV group) and the nondiabetic subjects (control group)*

	Control group (1,274 ± 111 cm/s)	Normal PWV group (1,247 ± 105 cm/s)	Abnormal PWV group (1,829 ± 312 cm/s)
n	20	15	45
M/F	10/10	6/9	24/21
Age (years)	61.3 ± 6.4	56.2 ± 6.3*	63.7 ± 5.1†
Height (cm)	160 ± 10	161 ± 7	160 ± 8
BMI (kg/m²)	23.0 ± 2.3	23.3 ± 3.5	24.0 ± 3.4
Duration of diabetes (years)	—	6.5 ± 5.1	14.8 ± 8.3†
Treatment (D/OHD/I)	—	7/4/4	5/27/13
FPG (mmol/l)	5.26 ± 0.43	7.70 ± 1.88‡	7.71 ± 1.99‡
HbA_{1c} (%)	4.6 ± 0.5	8.9 ± 1.7‡	8.5 ± 1.5‡
TC (mmol/l)	4.74 ± 0.67	4.78 ± 0.89	5.06 ± 0.71
HDL-cholesterol (mmol/l)	1.29 ± 0.44	1.13 ± 0.38	1.29 ± 0.30
TGs (mmol/l)	1.15 ± 0.27	1.36 ± 0.69	1.40 ± 0.50
Smokers (%)	6 (30)	10 (67)	18 (40)
MCV (m/s)	44.8 ± 1.9	43.6 ± 4.3	38.8 ± 6.1‡§
SCV (m/s)	44.7 ± 1.3	44.2 ± 4.4	38.2 ± 5.9†‡
CV_{R-R} (%)	3.44 ± 1.21	2.79 ± 1.07	1.86 ± 0.96‡‖
Retinopathy (%)	—	4 (27)	27 (60)
Nephropathy (%)	—	3 (20)	21 (47)

Data are means ± SD. D, diet, I, insulin, OHD, oral hypoglycemic drugs. *P < 0.05 and ‡P < 0.001 vs. the control group; †P < 0.001, §P < 0.01, and ‖P < 0.05 vs. the normal PWV group.

Appendix 2—*Peripheral circulation in the non-PAD patients with PWV comparable to the control group (normal PWV group) or with abnormal PWV (abnormal PWV group) and the nondiabetic subjects (control group)*

	Control group (1,274 ± 111 cm/s)	Normal PWV group (1,247 ± 105 cm/s)	Abnormal PWV group (1,829 ± 312 cm/s)
n	20	15	45
Brachial BP (mmHg)			
Systolic	124 ± 8	118 ± 8	131 ± 8*†
Diastolic	75 ± 8	72 ± 8	75 ± 10
Ankle BP (mmHg)			
Systolic	142 ± 11	139 ± 22	164 ± 25*‡
Diastolic	73 ± 8	73 ± 10	81 ± 12§
ABI	1.15 ± 0.08	1.16 ± 0.12	1.24 ± 0.14§
Heart rate (bpm)	74 ± 9	68 ± 10	70 ± 11
Flow volume (ml/min)			
Total	90.5 ± 20.8	93.1 ± 31.5	86.7 ± 31.5
Systolic	82.4 ± 16.2	88.8 ± 21.1	88.7 ± 23.8
Early diastolic	−8.1 ± 6.0	−13.6 ± 9.9	−12.4 ± 9.8
Late diastolic	16.3 ± 7.8	17.8 ± 12.7	10.3 ± 12.1
Resistive index	0.96 ± 0.03	0.99 ± 0.04§	1.01 ± 0.04‖

Data are means ± SD. *$P < 0.01$, §$P < 0.05$, and ‖$P < 0.001$ vs. the control group; †$P < 0.001$ and ‡$P < 0.01$ vs. the normal PWV group.

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