Impaired Endothelium-Dependent Vascular Responses of Retinal and Intrarenal Arteries in Patients With Type 2 Diabetes

Takahiko Kawagishi, Miyoko Matsuyoshi, Masanori Emoto, Hiromichi Taniwaki, Hiroyuki Kanda, Yasuhisa Okuno, Masaaki Inaba, Eiji Ishimura, Yoshiki Nishizawa, Hirotoshi Morii

Abstract—Endothelial dysfunction has been implicated in the pathogenesis of diabetic microangiopathies such as retinopathy and nephropathy as well as macrovascular diseases. The aim of the current study was to determine whether endothelial function in the retinal and renal arteries is impaired in type 2 diabetes mellitus. We examined the effects of an intravenous infusion of L-arginine and a sublingual administration of nitroglycerin on the brachial, retinal, and interlobar arterial hemodynamics in 20 type 2 diabetic patients (10 with normoalbuminuria and 10 with microalbuminuria) and 10 aged-matched control subjects. Despite no difference in the nitroglycerin-induced vascular response of the brachial or retinal artery among the 3 groups, the L-arginine–induced vascular response of each artery was significantly lower in both the normoalbuminuric and microalbuminuric patients than in the control subjects and the microalbuminuric patients showed the lowest value among the 3 groups (P<0.01, each artery, respectively). The L-arginine–induced vascular response of each artery was significantly correlated with HbA1c levels (brachial artery, r=0.617, P=0.0003; retinal artery, r=0.599, P=0.0005; interlobar artery, r=0.636, P=0.0002). In addition, stepwise multiple regression analysis of all subjects showed that HbA1c level was an independent determinant for the L-arginine–induced vascular response of each artery. The results showed that the endothelium-dependent vascular responses of the retinal and intrarenal arteries as well as the brachial artery were impaired in diabetic patients before the clinical manifestation of diabetic nephropathy, and suggest that endothelial dysfunction in these arteries is associated with hyperglycemia in these patients. (Arterioscler Thromb Vasc Biol. 1999;19:2509-2516.)

Key Words: L-arginine ■ diabetes mellitus ■ endothelium-dependent vasodilation ■ kidney ■ retina

Reciently, the role of the L-arginine/nitric oxide (NO) pathway in the regulation of vascular smooth muscle tone has attracted increasing interest. NO is synthesized from the physiological precursor L-arginine by the stereospecific enzyme NO synthase.1 NO induces relaxation of the smooth muscle by activating soluble guanylate cyclase to increase cyclic 3′, 5′-guanosine monophosphate (cGMP) levels. There is evidence from in vitro and in vivo studies that NO-mediated vasodilation may be impaired in type 1 and type 2 diabetes.2-4 Endothelium-derived NO has also been shown to regulate renal and ocular blood flow.5-7 In isolated ophthalmic arteries, NO is an important modulator of vascular tone,8 and systemic NO-synthase inhibition decreases choroidal blood flow in animals9 and humans.10 By using L-arginine analogues as probes for the renal NO pathway, several studies have demonstrated that NO acts as a potent vasodilator in the kidney.11,12 In addition, endothelial dysfunction, as estimated by the plasma von Willebrand factor concentration, precedes and may predict the development of microalbuminuria in type 1 diabetic patients.13 Although endothelial dysfunction is assumed to contribute to altered ophthalmic and intrarenal circulation and the development of diabetic retinopathy and nephropathy,7,14 there has been little research regarding endothelial function in both the retinal and renal arteries of type 2 diabetic patients.

On the basis of these observations, we hypothesized that either local NO synthesis/release or local sensitivity to exogenous NO might be impaired in patients with diabetes mellitus and that this may contribute to the development of diabetic retinopathy and nephropathy. Vascular responses after the intravenous administration of L-arginine were recently demonstrated to be a likely consequence of an increase in the endothelial production of NO.15 Accordingly, we compared the effects of L-arginine and NO donation with nitroglycerin on systemic, retinal, and renal hemodynamics in patients with and those without microalbuminuria.

Methods

Subjects
We evaluated 20 Japanese type 2 diabetic patients. Ten patients were normoalbuminuric and 10 patients were microalbuminuric. The
diagnosis of diabetes was based on a history of diabetes or criteria according to the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. All patients were admitted to Osaka City University Hospital for an educational course on diabetes. As a control group, 10 age- and sex-matched healthy subjects were examined. No subjects were taking medication known to affect the retinal, renal, or systemic circulation. Control subjects were receiving no regular medication and had no evidence of macrovascular, renal, or retinal vascular disease as well as diabetes or hypertension. Patients with hypertension or a history of ischemic heart disease, those with advanced diabetic complications (macular degeneration or proliferative retinopathy), and those treated with insulin were excluded from the study. Subjects with nondiabetic or obstructive kidney diseases and smokers were also excluded from this study. Eleven of the diabetic patients had mild nonproliferative diabetic retinopathy. Each subject gave informed consent to participate in the study. The study methodology was approved by the Ethics Committee on Clinical Investigation of the Osaka City University Medical School.

### Vascular Responses of Retinal and Intrarenal Arteries to L-Arginine and Nitroglycerin

Ultrasound examinations of the central retinal and interlobar arteries were performed simultaneously during the study of the brachial artery by 2 examiners (one examined the retinal artery and the other examined the interlobar artery). Images were obtained with a duplex Doppler apparatus (Aloka SSD 2000, Aloka Co Ltd) with a 5-MHz convex array probe.

### Duplex Doppler Sonography of the Central Retinal Artery

In the control subjects and the diabetic patients without retinopathy, the right eye was studied. In the patients with retinopathy, the eye with more advanced retinopathy was studied. The color Doppler mode, which shows arterial and venous flows in different colors, was used to identify the appropriate position of the central retinal artery for the pulsed Doppler recordings. The pulsed Doppler mode was used to obtain quantitative measurements of velocity. The sample volume was adjusted to a pulse length of 1.0 mm and was positioned so that its center was ~3.0 mm behind the disk surface. The sample volume was estimated by use of the angle-correction menu of the apparatus and by placing a cursor along the course of the central retinal artery as previously reported.

### Duplex Doppler Sonography of the Intrarenal Artery (Interlobar Artery)

The ultrasound probe was positioned gently on the right flank in an oblique projection, and the right kidney was visualized as a longitudinal image. Sample volumes were obtained to position the cursor of the pulsed Doppler mode at the mid-portion of the interlobar arteries, which flow along the renal pyramid. The pulsed Doppler mode was used to obtain quantitative measurements of velocity by placement of a cursor along the course of the interlobar arteries. The sample volume was adjusted to a pulse length of 1.0 mm and was estimated by use of the angle correction menu of the apparatus. The pulsed Doppler recordings for the waveform analysis were obtained in the same position as the interlobar artery during the ultrasonographic examination in each subject, as previously reported.

### Flow Wave Analysis of the Pulsed Doppler Image

The peak systolic flow velocity (PSV), the end-diastolic flow velocity (EDV), and the time-averaged flow velocity (TAV) were automatically calculated by the ultrasound apparatus. Flow velocities were determined from signals that were stable for at least 5 seconds. Measurements represent the average of 3 complete waveforms of the arteries. The resistance index (RI) was determined as \[\text{RI} = \frac{\text{PSV} - \text{EDV}}{\text{PSV}}\].

All measurements were performed by the same examiners, who were unaware of subject characteristics. The ultrasound studies of both the retinal and interlobar arteries were performed simultaneously when the brachial artery was assessed.

For both the retinal and interlobar arteries, the changes in the RI caused by the L-arginine and nitroglycerin administrations were expressed as the percent change relative to that at the initial resting scan. The responses of each artery to the L-arginine and nitroglycerin administrations were expressed as the area under the cumulative response curve (AUC) during each study period.

### Reproducibility of the Ultrasound Study

Eight diabetic patients and 8 control subjects were examined on 2 different occasions separated by 7 days to estimate the intraobserver...
variability of the values of nitroglycerin-induced vasodilation of the brachial artery diameter by the same examiner, who was unaware of the values from the first examination. The coefficient of variance for the RI values in the central retinal artery and the interlobar artery are highly reproducible, as in our previous reports. The coefficient of variation for the RI values was 3.6% for the retinal artery and 3.3% for the interlobar artery.

Biochemical Analysis
In each diabetic patient, the level of 24-hour urinary albumin excretion (UAE) was the mean value from 3 consecutive days. Normoalbuminuria was defined as UAE <20 μg/min and microalbuminuria was defined as UAE ≥20 μg/min and <200 μg/min. The plasma glucose and HbA1c levels were measured as previously described. The plasma insulin levels were measured with the use of a double-antibody radioimmunometric assay (Insulin RIABEAD II, Dianabo Co, Ltd). Serum total cholesterol, triglycerides, HDL cholesterol, and creatinine levels were measured with the autoanalyzer. Urinary albumin was measured by use of immunoturbidimetry (TIA MicroAlb Kit, Nittobo). As an insulin sensitivity index, we used the homeostasis model assessment insulin resistance (HOMA-IR): HOMA-IR=Fasting plasma insulin (μU/mL) · Fasting plasma glucose (mmol/L)/22.5.

Statistical Analysis
The AUC for the vascular response of each artery was calculated by use of the trapezoidal rule. For l-arginine study, the AUC was calculated as the incremental or decremental values from the baseline obtained during the 50 minutes (from time 0 to 50 minutes after l-arginine administration). For nitroglycerin study, the AUC was calculated as the incremental or decremental values from the baseline obtained during the 5 minutes (from time 0 to 5 minutes after nitroglycerin administration). The AUC was expressed in arbitrary units. Data are expressed as mean±SE unless otherwise indicated. Differences in variables among the groups were analyzed by one-way ANOVA with a Scheffé-type or Mann-Whitney U test. The relations between the vascular parameters and biochemical variables were examined by linear regression analysis. Subsequently, variables whose correlation with the vascular responses achieved near statistical significance (P<0.1) were entered into a stepwise regression model to assess the magnitude of their individual effects on the vascular responses. These procedures were performed on a Macintosh computer with the StatView IV Statistical System. A value of P<0.05 was accepted as statistically significant.

Results
All subjects tolerated the study well, and there were no adverse events. The clinical and biochemical characteristics of the control and diabetic subjects within each group are summarized in Table 1. Fasting plasma glucose and HbA1c levels were significantly higher in both the normoalbuminuric and microalbuminuric patients than in the control subjects (P<0.05 and P<0.01, respectively). The serum triglyceride level was significantly higher in the microalbuminuric patients than in the control subjects (P<0.01). There was no significant difference in the age, sex, body mass index (BMI), blood pressures, serum total cholesterol, HDL cholesterol, and baseline hemodynamic parameters of each artery among the 3 groups.

Effects of L-Arginine and Nitroglycerin Administrations on Blood Pressures and Heart Rate
The systolic, diastolic, and mean blood pressures decreased significantly after the infusion of l-arginine compared with the baseline values in the normoalbuminuric and microalbu-
The percent AUC for the L-arginine–induced vasodilation was significantly lower in both the normoalbuminuric (186 ± 4) and microalbuminuric (139 ± 21) patients compared with the control subjects (475 ± 78) (P<0.05 and P<0.01, respectively). Additionally, the percent AUC of the L-arginine–induced vasodilation showed the lowest value in the microalbuminuric patients among the 3 groups (P<0.01). On the other hand, there was no significant difference in the percent change in the nitroglycerin-induced vasodilation of the brachial artery at 3 or 5 minutes or in the percent AUC among the normoalbuminuric and microalbuminuric patients and the control groups (Figure 2b).

Central Retinal Artery
The percent change in the L-arginine–induced reduction in the retinal arterial RI at 15 minutes was significantly lower in the microalbuminuric patients than in the control subjects (P<0.05) (Figure 2a). The percent changes in the L-arginine–induced reduction in the retinal arterial RI at 30 and 50 minutes were significantly lower in both the normoalbuminuric (P<0.05) and microalbuminuric (P<0.01) patients than in the control subjects. The percent AUC for the response of the RI to L-arginine was significantly lower in both the normoalbuminuric (103 ± 57) and microalbuminuric patients (41 ± 17) than in the control subjects (378 ± 91) (P<0.05 and P<0.01, respectively). Additionally, the percent AUC for the response of the RI to L-arginine showed the lowest value in the microalbuminuric patients among the 3 groups (P<0.01). The percent AUC for the response of the RI to L-arginine showed no significant difference between the patients with and those without retinopathy. On the other hand, there was no significant difference in the percent change in the nitroglycerin-induced reductions in the retinal arterial RI at 3 minutes or 5 minutes or in the percent AUC among the normoalbuminuric and microalbuminuric patients and control groups (Figure 2b).

Intrarenal Artery (Interlobar Artery)
The percent change in the L-arginine–induced reduction in the interlobar arterial RI at 15 minutes was significantly lower in the microalbuminuric patients than in the control subjects (P<0.01) (Figure 3a). The percent changes in the L-arginine–induced reduction in the interlobar arterial RI at 30 and 50 minutes were significantly lower in both the normoalbuminuric and microalbuminuric patients than in the control

### Table 2. Effects of L-Arginine Infusion on Blood Pressures and Heart Rate

<table>
<thead>
<tr>
<th>Hemodynamic Parameters</th>
<th>0 min</th>
<th>15 min</th>
<th>30 min</th>
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<tr>
<td><strong>Systolic blood pressure, mm Hg</strong></td>
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<td></td>
<td></td>
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<td>109±2†</td>
<td>110±3†</td>
<td>109±3†</td>
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<td>105±4*</td>
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<td>113±4*</td>
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<td>69±2*</td>
<td>67±2†</td>
<td>69±2*</td>
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<tr>
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<td></td>
<td></td>
</tr>
<tr>
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<tr>
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<td>77±2‡</td>
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<td>81±2†</td>
<td>83±3*</td>
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<tr>
<td>Control subjects</td>
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<td>67±2</td>
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</tbody>
</table>

Values are mean±SE of 10 control subjects, 10 normoalbuminuric patients, and 10 microalbuminuric patients.

*P<0.05 and †P<0.01 vs baseline value (0 min).

### Table 3. Effects of Nitroglycerin Administration on Blood Pressures and Heart Rate

<table>
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<th>5 min</th>
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<td>Control subjects</td>
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<td>111±3†</td>
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<td>Normoalbuminuria</td>
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<td>102±3†</td>
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<td>Microalbuminuria</td>
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<td>108±4†</td>
<td>106±3†</td>
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<tr>
<td><strong>Diastolic blood pressure, mm Hg</strong></td>
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<td></td>
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<tr>
<td>Control subjects</td>
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<td>74±3</td>
</tr>
<tr>
<td>Normoalbuminuria</td>
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<td>66±3†</td>
<td>66±3†</td>
</tr>
<tr>
<td>Microalbuminuria</td>
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<td>69±3</td>
<td>68±3*</td>
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<tr>
<td><strong>Mean blood pressure, mm Hg</strong></td>
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<td></td>
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<tr>
<td>Control subjects</td>
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<td>84±2†</td>
<td>86±2†</td>
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<td>78±3†</td>
<td>78±3†</td>
</tr>
<tr>
<td>Microalbuminuria</td>
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<td>82±3†</td>
<td>81±2†</td>
</tr>
<tr>
<td><strong>Heart rate, min⁻¹</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Control subjects</td>
<td>61±2</td>
<td>70±2†</td>
<td>66±2†</td>
</tr>
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<td>Normoalbuminuria</td>
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<td>59±3†</td>
<td>59±4†</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>67±4</td>
<td>72±4†</td>
<td>72±4†</td>
</tr>
</tbody>
</table>

Values are mean±SE of 10 control subjects, 10 normoalbuminuric patients, and 10 microalbuminuric patients.

*P<0.05 and †P<0.01 vs baseline value (0 min).
subjects \((P<0.01\), respectively\). The percent AUC for the response of the RI to L-arginine was significantly lower in both the normoalbuminuric \((124\pm53)\) and microalbuminuric patients \((64\pm25)\) compared with the control subjects \((369\pm29)\) \((P<0.01\), respectively\). Additionally, the percent AUC for the response of the RI to L-arginine showed the lowest value in the microalbuminuric patients among the 3 groups \((P<0.01)\). On the other hand, the percent changes in the nitroglycerin-induced reduction in the interlobar arterial RI at 3 and 5 minutes were significantly lower in the microalbuminuric patients than in the control subjects \((P<0.01)\). However, there was no significant difference in the percent changes in the nitroglycerin-induced reduction in this artery at 3 or 5 minutes or in the percent AUC between the normoalbuminuric and microalbuminuric patients (Figure 3b).

**Effects of L-Arginine Infusion on Plasma Concentrations of Glucose and Insulin**

The plasma concentrations of glucose and insulin increased significantly at 15 and 30 minutes compared with baseline in each group \((P<0.01\), respectively\). Although the plasma concentrations of glucose at all 3 time points were significantly high in both the normoalbuminuric and microalbuminuric patients compared with the control subjects \((P<0.01\), respectively\), there was no significant difference in the plasma concentrations of insulin among the 3 groups (Table 4).

**Relation Between Clinical Characteristics and Vascular Responses**

The percent AUC for the L-arginine–induced vasodilation in the brachial artery of all subjects was significantly correlated with fasting plasma glucose \((r=0.531, P=0.0025)\) and HbA1c \((r=0.617, P=0.0003)\) (Table 5). The percent AUC for the response of the RI to L-arginine in the retinal artery of all subjects was significantly correlated with HbA1c \((r=0.599, P=0.0005)\). The percent AUC for the response of the RI to L-arginine in the interlobar artery of all subjects was significantly correlated with fasting plasma glucose \((r=0.571, P=0.001)\), HbA1c \((r=0.636, P=0.0002)\), and HOMA index \((r=0.377, P=0.0398)\). The nitroglycerin-induced vascular response of the retinal artery was significantly correlated with plasma fasting insulin \((r=0.398, P=0.0294)\), and that of the interlobar artery was significantly correlated with HbA1c \((r=0.452, P=0.0122)\).

In multiple stepwise regression analysis of factors affecting the vascular responses, HbA1c level, BMI, and fasting plasma glucose were independently associated with the vascular response of the brachial artery \((R^2=0.558, P<0.0001)\); HbA1c was independently associated with the vascular response of the retinal artery \((R^2=0.359, P=0.0005)\); HbA1c and diastolic...
blood pressure were independently associated with the vascular response of the intrarenal artery ($R^2=0.522$, $P=0.0001$) (Table 6).

Effects of 300-mL Saline Infusion on Hemodynamic Parameters

The systolic, diastolic, and mean blood pressures and vascular responses of each artery did not show any significant change between before and after the saline infusion in 5 healthy subjects (data not shown).

Discussion

We have demonstrated for the first time that not only the brachial artery but also retinal and intrarenal hemodynamic responses to an intravenous infusion of L-arginine are impaired in type 2 diabetic patients. Despite no significant difference in the vascular responses of the retinal and brachial arteries after the nitroglycerin administration between the patient and control groups, there were significant differences in the vascular responses of these arteries in both the normoalbuminuric and microalbuminuric patients compared with the control subjects after the L-arginine infusion, suggesting that the endothelium-dependent vascular responses in the retinal and brachial arteries are impaired but that the responsiveness of the smooth muscle to exogenous NO is not impaired in diabetic patients. On the other hand, the reduction in vascular resistance of the interlobar artery after the nitroglycerin administration was significantly lower in the microalbuminuric patients than in the control subjects, suggesting that the responsiveness of the smooth muscle to

![Figure 3. a, Effect of an intravenous infusion of L-arginine (1 g/min) on the RI of the interlobar artery in control subjects (open columns), normoalbuminuric patients (shaded columns), and microalbuminuric patients (closed columns). b, Effect of a sublingual administration of nitroglycerin (300 μg) on the RI of the interlobar artery in control subjects (open columns), normoalbuminuric patients (shaded columns), and microalbuminuric patients (closed columns). *$P<0.01$ vs control subjects. Data are expressed as described in Figure 1.]

![TABLE 4. Effects of L-Arginine Infusion on Plasma Concentrations of Glucose and Insulin](http://atvb.ahajournals.org/)

![TABLE 5. Correlation Between Glycemic Control or Insulin Sensitivity and AUC for Vascular Response to L-Arginine and Nitroglycerin in All Subjects (n=30)](http://atvb.ahajournals.org/)
flow is increased in patients with early stages of diabetic arteries of diabetic patients are controversial. Retinal blood may be impaired in type 2 diabetic patients.

estimates the vascular resistance of the retinal artery RI measured with the use of Doppler sonography in our study compared with healthy subjects. These findings suggest that type 1 diabetic patients but not in type 2 diabetic patients recent study showed that endothelial function was preserved in we studied the vascular responses in type 2 diabetic patients. A diabetic patients compared with the control subjects. In addition, vascular compliance. Indeed, the RI of the retinal and renal arteries decreased significantly after L-arginine and nitroglycerin patients with microalbuminuria.

vascular responses of these arteries to NO may not be involved in diabetic patients without microalbuminuria. It must be determined whether the impaired vascular response to L-arginine is the cause or the effect of diabetic retinopathy and nephropathy. Since the vascular responses of these arteries to L-arginine were impaired even in the diabetic patients without retinopathy or nephropathy, it is unlikely that the impaired vascular responses to L-arginine are resultant phenomena. Therefore we suggest that endothelial dysfunction in these arteries precedes the clinical manifestations of diabetic microangiopathy in diabetic patients.

Recently, Giugliano et al demonstrated that the vascular effects of L-arginine are mediated partly by endogenously released insulin. In the current study, the insulin response to L-arginine was lower (but not significantly) in the diabetic patients compared with the control subjects, and therefore it is possible that the decrease in endogenous released insulin contributed in part to the impaired vascular responses to L-arginine in the diabetic patients. Additionally, it must be mentioned that a physiological link between insulin resistance and endothelial dysfunction has been shown in insulin resistance syndromes such as essential hypertension and obesity. Insulin sensitivity index correlated with the vascular response to L-arginine in the intrarenal artery in all subjects. This finding suggests that insulin resistance in this artery may in part contribute to the impaired vascular response to L-arginine in diabetic patients. However, because HOMA index is a rough method for estimating insulin resistance, further examination is required to determine the association between endothelial function and insulin resistance.

Sulfonylurea can impair dilation mediated by NO-mediated, ATP-sensitive K⁺ channel activation. However, no significant difference in the vascular responses observed between the diabetic patients treated with diet alone and those treated with sulfonylurea in the current study (data not shown) is consistent with the study by McVeigh et al.

Another important factor contributing to endothelial dysfunction in diabetes mellitus is reported to be hyperglycemia in vivo. In the current study, both plasma glucose and Hba1c levels were significantly higher in the diabetic patients than in the control subjects. The L-arginine–induced vascular responses in these arteries were correlated with...
plasma glucose and/or HbA1c levels, whereas multiple regression analysis showed the independent association between the vascular response to L-arginine in each artery and HbA1c rather than plasma glucose, suggesting that long-term hyperglycemia may contribute to impairment of the vascular responses in these arteries. These data are consistent with the findings that chronic hyperglycemia is associated with impaired vascular endothelial function in diabetic patients.36

In conclusion, the results showed that vascular endothelial function was impaired in retinal and intrarenal arteries as well as the brachial artery in the type 2 diabetic patients with and those without microalbuminuria and therefore suggest that the endothelial dysfunction in these arteries may precede the clinical manifestations of diabetic microangiopathies. The endothelial dysfunction thus may be associated with poor glyemic control and may contribute to the development of microangiopathy and macrovascular diseases in type 2 diabetic patients.

References
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doi: 10.1161/01.ATV.19.10.2509

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