Sympathetic Vasomotor Response of the Radial Artery in Patients With Diabetic Foot Syndrome

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OBJECTIVE — Neurophysiological assessment of the peripheral autonomic system is characterized by various limitations. An alternative approach to laser Doppler and venous plethysmography is the assessment of the sympathetic vasomotor response of the radial artery obtained by continuous wave Doppler sonography. Nomogram data have been established and demonstrate the temporary disappearance of diastolic flow after coughing or deep inspiration.

RESEARCH DESIGN AND METHODS — We assessed the sympathetic vasomotor response in 25 patients (mean age 64 years, range 43–76) with diabetic foot syndrome. The Doppler data were correlated with nerve conduction studies of the median and peroneal nerve, the extent of radiologically diagnosed media sclerosis, and compared with nomogram values ($n = 41$).

RESULTS — Although similar mean flow velocities were found under baseline conditions, the flow pattern was characterized by higher pulsatility in the diabetic group (resistance index [RI] 1.1 vs. 0.7). No significant difference in RI was observed after coughing. The latency of onset of the response was prolonged (2.1 vs. 1.5 s), while the duration of the response did not differ (18 vs. 15 s). Only the nerve conduction velocity of the peroneal nerve correlated inversely with the RI. The extent of radiologically proven calcification tended to correlate with the pulsatility of the baseline signal and the response latencies.

CONCLUSIONS — The data obtained by this study suggest the concurrent existence of reduced vessel elasticity due to media sclerosis and dysfunction of the autonomic vasomotor system.

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Autonomic neuropathy is a frequent complication in diabetes and one of the major causes of cardiovascular death. Mortality rates vary from a 60% 5-year mortality (1) to a 10% 10-year mortality (2) and are about three times as high as in patients with neuropathy without clinical evidence of autonomic involvement (3). While extensive tests for cardiovascular autonomic functions are readily available (4,5), they may be of little help in the diagnosis of peripheral autonomic dysfunction (6). To date, laser Doppler flowmetry, which enables assessment of the capillary and arteriovenous blood flow, represents the most reliable test for the diagnosis of peripheral autonomic dysfunction (7–9). This technique can be applied under conditions at rest and during sympathetic stimulation by means of a deep inspiratory gasp (10) or an electric stimulus (9). Alternatively, venous plethysmography (6) and duplex Doppler sonography (11) have been used. These studies have confirmed the hypothesis of a hyperperfusion state in the lower extremities at an arteriovenous shunt volume that was increased up to threefold due to opening of the sympathetically controlled resistance vessels (7,10). Furthermore, other workers reported a reduction in the response to sympathetic stimulation (10,11). In ~50% of a cohort of diabetic patients, an abnormal skin blood flow has been observed at the index finger and a nondiscernible decrease or abnormal latencies after stimulation was reported (9).

Continuous wave Doppler sonography represents an alternative approach available at all angiologic and neurological vascular laboratories, which offers easy access to the major blood supplying vessels of the extremities. In contrast to laser Doppler flowmetry, continuous wave Doppler measurements are not based on arbitrary units but on kilohertz frequency shifts. The sympathetic vasomotor response can be tested reliably in the radial artery. After 1.5 s of stimulation (electric, acoustic, or cough), an age-independent increase in pulsatility is observed under physiological conditions. This flow pattern continues for ~18 s (12–14) (Fig. 1*A*).

The aim of this study was to monitor flow velocities in the radial artery of diabetic patients with autonomic dysfunction, both under baseline conditions and after sympathetic stimulation. The data obtained were compared with those of a previously published nomogram trial (13). The clinical diagnosis and the severity of diabetic polyneuropathy are commonly supported by nerve conduction

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Abbreviations: RI, resistance index.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

abnormalities. However, this method is inadequate in the assessment of autonomic neuropathy, due to the fact that slow-conducting Aδ and C-fibers, which account for ~80% of all fibers, cannot not be measured by conventional conduction measurements. We compared the continuous wave Doppler results with results obtained by nerve conduction studies of the median and peroneal nerve to evaluate potential correlations between the autonomic and somatosensory system.

RESEARCH DESIGN AND METHODS

— We investigated 25 patients (mean age 64 years, range 43–76) with diabetes and diabetic foot syndrome (22 type 2 and 3 type 1 diabetic patients). Two of the patients presented with a deep ulcer, 19 patients had a deep ulcer combined with an abscess and/or osteomyelitis, and 4 patients had additional necrosis limited to the forefoot or the calcaneus. Mean duration of diabetes was 19.4 ± 9.1 years (range 5–37), and mean HbA_{1c} was 6.4 ± 1.4% (range 4.4–10.8). Patients were admitted to the hospital in order to optimize insulin treatment and stabilize dystrophic ulcers of the feet.

Recent biplanar plain radiographs of the feet were available in 23 diabetic patients. The presence of media sclerosis of the interdigital arteries was described semiquantitatively based on the cumulative length of visibly calcified vessels. Patients with grade I mediasclerosis ($n = 8$) had radiologically proven calcifications ≤1 cm, patients with grade II mediasclerosis ($n = 8$) had radiological evidence of calcification >1 and ≤5 cm, and patients with grade III mediasclerosis ($n = 7$) showed calcifications >5 cm. The extent of media sclerosis correlated with the duration of diabetes (degree 0 or I 15, II 15.5, and III 23 years).

The control group included 41 neurologically healthy volunteers (23 female, 18 male), aged 16–82 years (mean 52) (nondiabetic group).

The radial artery at the distal forearm was insonated noninvasively with a 4 MHz continuous wave Doppler probe (Multidop T; DWL, Sipplingen, Germany). The angle of insonation was ~45°. The Doppler signal was monitored for at least 1 min before stimulation to allow the establishment of diastolic flow. For sympathetic stimulation, volunteers and patients were asked to cough without moving the arm. The Doppler signal was monitored continuously, and the duration of the response was recorded. We calculated the latencies between the stimulus (cough) and the onset of response, as well as the latency between onset and the maximum extent of the reaction indicated by the flow velocity minimum. Flow velocities were recorded in kilohertz frequency shift. Because information concerning the accurate angle of insonation with continuous wave Doppler was lacking, conversions to centimeters per second were abandoned. Mean temporal flow velocity data were calculated according to equation 1, and the RI (or "Pourcelot" index), as an indicator of the peripheral (arteriolar) vasoconstriction, was calculated according to equation 2. Doppler measurements were repeated three times, allowing sufficient time intervals of at least 2 min to avoid attenuation of the responses. The shortest latency and the most pronounced reaction of the three measurements were further analyzed.

Nerve conduction studies of the median (motor and sensory) and peroneal (motor) nerve were obtained with the Medelec Sapphire system (Oxford Medical, Tubney Woods, U.K.). The antidrome sensory nerve conduction studies of the median nerve were performed by averaging a minimum of eight signals at a repetition frequency of 2 Hz. All measurements were taken at the bedside at room temperatures ranging from 22 to 25°C. To avoid cold skin temperatures, the patients rested in bed covered with a blanket for at least 30 min before onset of the study. Doppler data recorded in the diabetic group were correlated with the duration of diabetes, HbA_{1c}, and amplitudes and nerve conduction velocities of the peroneal and median nerve.

Informed consent was obtained from all patients. Statistical analysis included the comparison of Doppler parameters (absolute systolic, diastolic, mean flow velocity, and RI values) for the diabetic and the nondiabetic groups recorded at both baseline and the time of maximal reaction. The *t* test was used to compare the distribution of the parameters between the diabetic and the nondiabetic groups for normally distributed data, and the Wilcoxon test was applied in the presence of skewed data obtained in at least one group.

$$\text{Mean temporal velocity (kHz)} = \frac{2 \times \text{Velocity diastolic (kHz)} + 1 \times \text{Velocity systolic (kHz)}}{3} \quad (1)$$

$$\text{RI (Pourcelot)} = \frac{\text{Velocity systolic} - \text{Velocity diastolic}}{\text{Velocity systolic}} \quad (2)$$

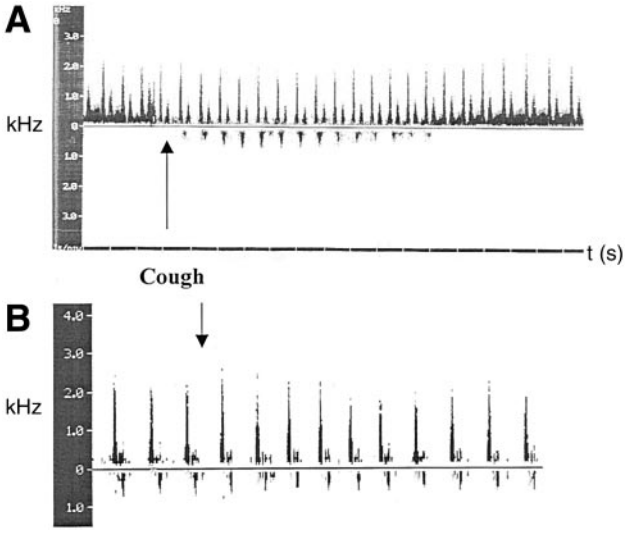

Figure 1—A*: Typical course of a normal sympathetic vasomotor response as recorded by continuous wave Doppler sonography. Note the reversed diastolic flow after the cough.* B*: Typical course of the vasomotor response in a diabetic patient. Note the increased pulsatility under baseline conditions and dampened response to the cough.*

Table 1—*Doppler baseline values and changes after stimulation*

	Control group	Diabetes group	Adjusted *P* value
Systolic flow (baseline) (kHz)	1.77 ± 0.27 (1.8)	2.63 ± 0.88 (2.55)	3.5×10^{-5} (W) sign
Change (kHz)	−0.30 ± 0.21 (0.3)	−0.28 ± 0.31 (0.3)	1.00 (t) NS
Diastolic flow (baseline) (kHz)	0.26 ± 0.48 (0.4)	−0.31 ± 0.39 (−0.3)	$3.8* 10^{-5}$ (t) sign
Change (kHz)	−0.60 ± 0.41 (−0.7)	−0.34 ± 0.31 (−0.2)	0.27 (W) NS
Mean flow (baseline) (kHz)	0.75 ± 0.33 (0.87)	0.67 ± 0.30 (0.6)	1.0 (t) NS
Change (kHz)	−0.50 ± 0.31 (−0.3)	−0.31 ± 0.27 (−0.3)	0.35 (W) NS
RI (baseline)	0.86 ± 0.28 (0.7)	1.11 ± 0.12 (1.1)	$6.8* 10^{-5}$ (t) sign
Change (kHz)	0.4 ± 0.28 (0.4)	0.18 ± 0.12 (0.15)	$4.98* 10^{-4}$ (t) sign
Duration of response (s)	14.5 ± 7.6 (15)	17.9 ± 5.5 (18.4)	0.48 (t) NS
Cough (onset of reaction) (s)	1.5 ± 0.6 (1.5)	2.3 ± 0.9 (2.05)	0.0022 (W) sign
Onset (maximum) (s)	3.1 ± 1.7 (3.5)	5.6 ± 3.1 (4.9)	0.012 (W) sign

Data are mean ± SD (median). t, *t* test; W, Wilcoxon test.

Spearman's correlation coefficient was used for the correlation of two continuous variables, and the Bonferroni correction was used to adjust for a multiplicity of tests (12 tests). Tests with an adjusted *P* value <5% are thus ensured to be significant at the multiple significance level of 5%.

RESULTS — All data in the text are presented as mean values; median values and SDs are shown in Table 1.

Baseline

A comparison with the nomogram data revealed a different flow profile in the radial artery with a significantly higher systolic (2.63 vs. 1.77 kHz; $P = 3.5 \times 10^{-5}$ Wilcoxon test) and lower diastolic (−0.31 vs. 0.26 kHz; $P = 3.8 \times 10^{-5}$, *t* test) flow (Figs. 1*B* and 2), which was further corroborated by a higher RI (1.11 vs. 0.86; $P = 6.8 \times 10^{-5}$, *t* test). A biphasic flow with flow reversal in early diastole was observed in 23 of 25 patients (92%), as compared with 10 of 42 volunteers (23%) in the control group. The mean temporal frequency shifts did not differ significantly (0.67 vs. 0.75 kHz). Although the systolic blood flow velocities increased in relationship to the severity of mediasclerosis (control group: 1.73 kHz; <1 cm: 2.36 kHz; 1–5 cm: 2.25 kHz; and >5 cm: 2.77 kHz) (Fig. 3), there was no rise in RI.

Nerve conduction of the peroneal nerve (Table 2) in the diabetic group showed an overall reduced conduction velocity (32.9 cm/s) in addition to a fall in amplitudes (1.8 mV). The distal motor latency of the median nerve was prolonged (5.1 ms), while the other nerve conduction parameters were unremarkable. Only the peroneal motor nerve conduction velocity correlated inversely with the RI ($r = -0.52$) (Fig. 4) and positively with the mean radial artery blood flow velocity ($r = 0.60$). None of the median nerve conduction parameters correlated with the Doppler results.

Stimulation

After coughing, similar Doppler curves were observed for the patients and the control group at identical RIs (1.3) (Table 1). However, in view of the different baseline value, the absolute change also varies (0.18 vs. 0.40; $P = 4.98 \times 10^{-4}$, *t* test). The drop in systolic flow did not differ significantly in regard to the absolute figures values (−0.3 vs. −0.28 kHz), although the relative change was less pronounced when considering the higher baseline value of the diabetic patients. The absolute drop in diastolic flow velocity was more pronounced in the control group (−0.34 vs. −0.6 kHz; $P = 0.27$, Wilcoxon test).

The latencies from coughing to the onset of the response were prolonged (2.3

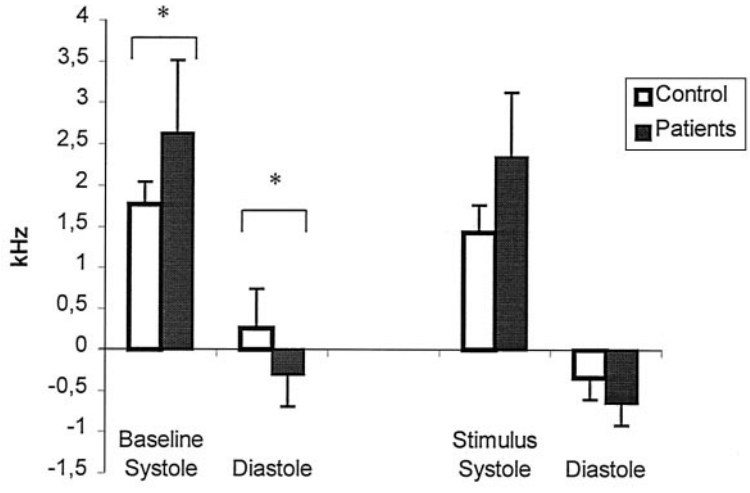

Figure 2—*Doppler frequency shifts (peak systolic and diastolic) in the diabetic and control groups before and after the cough (mean values ± SD).* *P < *0.00001.*

Table 2—*Nerve conduction studies in the diabetic group*

Peroneal	
n	19*
Motor CV (m/s)	32.9 ± 6.3 (33.1)
DML (ms)	5.8 ± 1.7 (4.9)
Amplitude (mV)	1.8 ± 2.2 (0.61)
Median	
n	25*
Motor CV (ms)	46.7 ± 6.5 (46.4)
DML (m/s)	5.1 ± 0.8 (5.2)
Amplitude (mV)	7.1 ± 3.7 (6.4)
Sensory CV	41.3 ± 6.7 (41.4)
Amplitude	11.9 ± 10.3 (8.4)

Data are mean ± SD (median). *All 25 patients were tested; patients with absent potentials were not analyzed further. CV, conduction velocity.

vs. 1.5 s, $P = 0.0022$, Wilcoxon test), as were the latencies from onset of the reaction to flow velocity minimum, indicating the maximum extent of the reaction period (5.6 vs. 3.1 s; $P = 0.012$, Wilcoxon test) (Table 1). The duration of the response was not significantly prolonged (17.9 vs. 14.5 s, $P = 0.48$, *t* test). Again, only the conduction velocities of the peroneal nerve correlated with the RI ($r = -0.54$) and mean flow velocity ($r = 0.40$) after coughing.

CONCLUSIONS — Data obtained by the present study show that flow velocity profiles in the radial artery of patients with diabetic foot syndrome differ considerably from flow profiles in the control group. The characteristic baseline flow profile in diabetic subjects reveals a high resistance flow at an increased systolic and decreased diastolic flow and an unchanged temporal mean flow velocity. One possible explanation for this finding is a reduction in the "Windkessel" function of the vascular system due to decreased elasticity (distensibility) of the vessel walls (15). Under physiological conditions, only proximal arteries of the upper extremities show a continuous bi- or triphasic flow profile. In more peripheral vessels this profile changes to a constant positive monophasic flow throughout systole and diastole. Similar mean flow velocities observed in both our patients and the control group, as well as the correlation between the severity of media sclerosis and the systolic flow velocities, further support this hypothesis. Arterial calcification of the media layer in diabetic subjects is a common phenomenon and can be diagnosed radiologically in 81% of the distal lower limb and 89% of the proximal lower limb arteries (16). This may lead to greater rigidity of the vessel, which can be diagnosed noninvasively clinically ("pseudohypertonia" of the lower limbs) and by Doppler ultrasound sonography (17).

Our results are in contrast to previously published data on flow profiles in diabetic subjects (18), which had shown a slightly lower systolic flow velocity in diabetic subjects compared with normal subjects. However, the presence of diabetes in the reported patient groups was of shorter duration than in our group (14 and 8 vs. 19 years). Autonomic changes were not reported in this cited study. The impact of the presence of autonomic changes is demonstrated by comparison of our data of severely affected patients with data from a second Doppler study with diabetic patients without clinical signs of polyneuropathy or autonomic dysfunction (12). Only a minority of 4 of 20 patients exhibited negative diastolic flow at baseline. In contrast, negative diastolic flow was present in our study in 23 of 25 patients. Our data are consistent with results of a thermal clearance study (19) and a laser Doppler flow study (20); both of these studies failed to show spontaneous variability of fingertip blood flow in patients with diabetic autonomic neuropathy. In the present study the high resistance flow profile remained unchanged over time, despite extended relaxation time.

In contrast to studies focusing on the hemodynamics of the diabetic foot (2,7,10), we found no hyperperfusion state in the arm. A hyperperfusion syndrome with up to threefold blood flow volume due to opening of arteriovenous anastomoses has been reported (21). Since the mean temporal flow in the radial artery was unchanged in our study, we found no evidence of extensive arteriovenous anastomoses in the upper extremity. This observation is supported by temperature measurements showing baseline hyperthermia at the ankle but not in the hands of diabetic patients (22).

Sympathetic vasomotor responses in the upper extremities have been demonstrated in normal volunteers using Doppler sonography of the radial artery (12–14), laser Doppler flowmetry (9,23), and thermal recovery after ice water exposition (24). The vasoconstrictive reaction is characterized by a decline in blood flow (laser Doppler) and a predominantly diastolic blood flow velocity reduction (radial artery Doppler). Our data in the diabetic group are consistent with data reported in the literature, showing a less pronounced or absent reaction diagnosed by laser Doppler (9,23). A thermography study showed the absence of a reaction in diabetic patients only in the presence of autonomic dysfunction (22). In a continuous wave Doppler study with diabetic patients without reported signs of autonomic dysfunction, 50% of the patients showed a normal reaction (12), defined as a diastolic flow reversal after stimulation, as compared with only two (8%) of our patients with a diabetic foot.

As the flow profile in the diabetic group of our study revealed the presence of already markedly increased pulsatility at baseline, changes in pulsatility due to

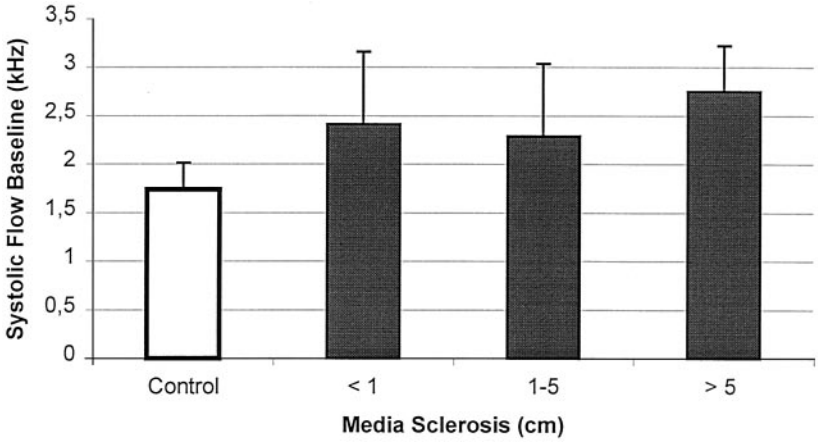

Figure 3—*Correlation of the extent of radiologically diagnosed media sclerosis and systolic baseline values of the radial artery (mean ± SD).*

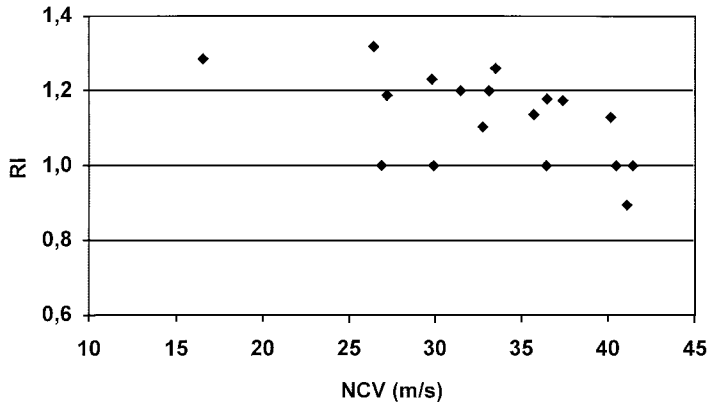

Figure 4—*Correlation of motor nerve conduction velocity (peroneal nerve) and RI. More pulsatile flow is noted in patients with slower nerve conduction velocites.*

the sympathetic reaction cannot be expected.

The significantly prolonged latencies from the stimulus to the onset of reaction (2.1 vs. 1.5 s), and from the onset to the maximum extent of the reaction period (4.9 vs. 3.5 s), are probably due to diabetes-induced dysfunction, caused by a demyelinating or axonal disorder of the sympathetic Aδ fibers. However, as continuous wave Doppler data of patients in a clinically critical condition due to other diseases have not been published, effects due to medication or clinical circumstances cannot be ruled out. Despite the coexistence of autonomic dysfunction and pathological nerve conduction studies, the correlation between the development of autonomic dysfunction in diabetic patients with polyneuropathy and the nerve conduction studies is poor (24). Furthermore, one of the most characteristic clinical features of somatosensory polyneuropathy, the deterioration of the vibration sense, is not correlated with autonomic dysfunction (25). Conversely, a pathological postural arteriolar vasoconstriction test was found in diabetic patients without clinical evidence of somatosensory polyneuropathy (9). For this reason it is not surprising that the only remarkable correlation established by any of the nerve conduction studies with the Doppler parameters was between the velocity of the peroneal nerve and the RI ($r = 0.54$). This study underlines the different mechanisms and topographic involvement of diabetes.

Continuous wave Doppler is a readily accessible tool for the evaluation of the peripheral arterial system. Functional changes in the vessel walls leading to reduced elasticity of major arteries and to the impairment of the autonomic nerve system are tested simultaneously. Monitoring of the radial artery offers an additional approach to the investigation of diabetic neuropathy and angiopathy.

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