Redistribution of Sudomotor Responses Is an Early Sign of Sympathetic Dysfunction in Type 1 Diabetes

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Patients with diabetic neuropathy typically have decreased sweating in the feet but excessive sweating in the upper body. Previous studies of sudomotor function in diabetes have included patients with longstanding disease. The present study was designed to test for the early presence of sudomotor dysfunction and to characterize its relation to glycemic control and other aspects of peripheral nerve function. A total of 37 patients (10 males, 27 females) enrolled in a longitudinal study, in which autonomic function was evaluated annually for 3 years. Patients enrolled 2–22 months after the diagnosis of type 1 diabetes. Forty-one age- and sex-matched healthy control subjects were also studied. Sweat production in response to acetylcholine stimulation was dramatically increased in the forearm at the time of the first evaluation (1.67 ± 0.24 µl/cm^2 in the diabetic patients vs. 1.04 ± 0.14 µl/cm^2 in the control subjects, $P < 0.05$). Likewise, the ratio of sweating in the forearm to sweating below the waist was higher in the diabetic patients (0.553 ± 0.07 µl/cm^2) than in the control subjects (0.385 ± 0.04 µl/cm^2, $P < 0.05$). Forearm sweat was negatively associated with the renin-to-prorenin ratio and vanillylmandelic acid (VMA) excretion ($P < 0.025$), tests of sympathetic nerve function. The ratio of sweating in the forearm to sweating in the foot was likewise increased in diabetic patients with poor glycemic control. We interpret this redistribution of sudomotor responses to be indicative of sympathetic nerve injury and conclude *1*) that the sympathetic nervous system is especially vulnerable to the adverse effects of chronic hyperglycemia and *2*) that sympathetic dysfunction can be detected very early in type 1 diabetes. *Diabetes* 50:436–443, 2001

It is widely recognized that sympathetic denervation leads to decreased sudomotor responses, atrophy of sweat glands, and eventually anhidrosis (1,2). Paradoxically however, sympathetic nerve injury can also cause hyperhidrosis, which is a common complication of sympathectomy (3,4). Hyperhidrosis in patients with sympathetic dysfunction may occur adjacent to an anhidrotic lesion or at a remote location. Decreased sweating in the feet of patients with diabetic neuropathy is typically associated with excessive sweating elsewhere, most often in the face or neck (1). Although it seems as if the remaining sweat glands are excessively active to compensate for those that have been denervated or atrophied, this theory has been difficult to test, and the pathophysiology of compensatory hyperhidrosis remains obscure.

Previous studies of sudomotor function in diabetes have been performed on patients with longstanding disease, many of whom had overt neuropathy and sudomotor dysfunction. The early natural history of sudomotor function, particularly its relation to other aspects of autonomic function and glycemic control, has not yet been described.

The purpose of the present research was to determine whether sudomotor dysfunction could be detected early in type 1 diabetes in patients with intact somatosensory and cardiovascular autonomic nerve function. Patients were recruited <2 years after the onset of diabetes and studied longitudinally for 3 years. Patients had a comprehensive annual evaluation of cardiovascular autonomic and sudomotor function. We were also interested in comparing sudomotor function, a cholinergic sympathetic activity, with adrenergic sympathetic events known to be affected by diabetes. Because the adrenergic nervous system is the major site of norepinephrine synthesis, we measured vanillylmandelic acid (VMA) excretion, which is an index of norepinephrine production and known to be decreased in patients with autonomic neuropathy (5,6). The sympathetic nervous system also promotes the processing of prorenin and the synthesis and secretion of renin; therefore, we measured the plasma renin-to-prorenin ratio, which is known to be diminished in diabetic autonomic neuropathy (7,8).

RESEARCH DESIGN AND METHODS

Patients. A total of 37 patients (10 males, 27 females) with type 1 diabetes enrolled 2–22 months after diagnosis in a longitudinal study of autonomic nerve function (Table 1). Patients with symptoms of neuropathy, other systemic illnesses, or excessive alcohol consumption (an average of more than two drinks per day) were excluded from the study. All patients were taught to monitor their glucose levels at home and to adjust their insulin doses as necessary to maintain optimal glycemic control. HbA_1 was measured one to four times a year for 3 years. A total of 36 patients underwent three annual evaluations, and 1 patient withdrew after the second year. None of the patients complained of decreased sweating or hyperhidrosis.

The diabetic patients were admitted to beds designated for research at West Virginia University Hospital to control their dietary intake, activity, and glucose before and during the annual autonomic function testing. Glucose was monitored before each meal and snack and at 3:00 A.M., and insulin adjustments were made as needed. Patients were administered a weight-maintaining diet containing 130 mEq sodium daily. Caffeine, aspirin, and cigarettes were not allowed on the morning of the tests because of possible effects on autonomic function.

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QSART, quantitative sudomotor axon reflex test; VMA, vanillylmandelic acid.

TABLE 1
Clinical characteristics of patients

	Diabetic patients	Healthy control subjects
n (M/F)	37 (10/27)	41 (14/27)
Age at diagnosis (years)	20.3 (10–40)	21.0 (10–42)
Disease duration at initial evaluation (months)	10.4 (2–22)	—

Autonomic function tests were also performed in 41 age- and sex-matched healthy control subjects to provide a basis of comparison with the diabetic patients. The control subjects were also admitted to the hospital, administered the same diet, and subjected to the same restrictions.

The research protocol was approved by the Institutional Review Board of West Virginia University Hospital, and informed consent was obtained from the participants.

Cardiovascular autonomic function

Beat-to-beat variation with deep breathing. Patients were studied in the supine posture after relaxing comfortably for at least 10 min. Heart rate was monitored electrocardiographically while they breathed slowly (5 s inspiration/5 s expiration), as deeply as possible, for 5 min. The difference between the maximum and minimum instantaneous heart rates reflects the integrity of the parasympathetic innervation of the heart (9). In addition, vector analysis of the instantaneous heart rate was performed, and mean circular resultant was determined. This alternative index of heart rate variability minimizes error introduced by variation in intrinsic heart rate or ectopic cardiac beats (10).

Heart rate response to the Valsalva maneuver. Heart rate was monitored electrocardiographically while patients were supine and instructed to expire into a sphygmomanometer until a pressure of 40 mmHg was maintained for 20 s. The Valsalva ratio was calculated by dividing the maximal instantaneous heart rate during the maneuver by the minimal heart rate observed after release (11). The test was performed twice and the average result calculated. A normal response (ratio >1.15) indicates that the baroreceptor reflex and the efferent limb of the sympathetic nervous system are intact.

Small fiber somatosensory function. Quantitative sensory testing was used to assess small and thinly myelinated A delta fibers, which convey cold sensation, and C fibers, which convey heat. The hot and cold stimuli were applied to the dorsal aspect of the feet and the wrist, and participants were asked to distinguish between progressively small thermal stimuli until they were no longer able to detect the change in temperature (12). Specific thermal thresholds were then determined by a microprocessor-controlled forced-choice technique (Neurolink, East Lyme, CT). Thresholds were determined on two separate days, and the average performance was calculated for each of the four parameters of interest (heat-threshold feet, cold feet, heat wrist, and cold wrist).

Sudomotor function. Sudomotor function was assessed with the quantitative sudomotor axon reflex test (QSART) (13). Sweat production was quantitated in a circular sweat cell connected to the sudorometer (Abrams Instrument, Okemos, MI). The sweat cell was applied to the skin; an inner air chamber was connected to a dry nitrogen gas (2–5% absolute humidity); and acetylcholine (10%) was placed in an outer chamber from which it was applied to the skin by iontoelectrophoresis using a constant-current (1 mA for 5 min) generator (World Precision Instruments, Sarasota, FL). Sweating was quantitated by measuring the change in relative humidity of the nitrogen flowing through the inner chamber. Chart recordings proportional to relative humidity were integrated with respect to time, using a HiPad digitizer (Houston Instruments, Austin, Tx) and a Bioquant II Computer Analysis Program (R and M Biometrics, Nashville, TN). Four sweat capsules were used. One was placed on the left forearm, 25% of the distance from the pisiform bone to the ulnar epicondyle; one was placed over the anterior surface of the distal left leg; one over the proximal left leg; and one over the proximal left foot, over the extensor digitorum brevis muscle. Total sweat was calculated by taking the sum of sweat produced in the four sites.

Biochemical measurements

HbA_1. HbA_1 was measured by agar gel electrophoresis (14). The reference range for the nondiabetic population was 4.7–7.3%.

Renin and prorenin. Active renin was measured as the rate of conversion of renin substrate to angiotensin I by plasma collected in EDTA (15). Total renin (active plus inactive) was prepared in a separate 1-ml aliquot of plasma by preincubating the latter for 1 h with 10 µg trypsin from porcine pancreas (Sigma, St. Louis, MO). Total and active renin were then assayed by determining angiotensin I by radioimmunoassay using ^{125}I-labeled angiotensin I (INCStar, Stillwater, MN). Prorenin was calculated as the difference between total and active renin (16). To avoid the confounding effect of ovarian prorenin, blood sampling was rescheduled for women who were menstruating at the time of their annual evaluation (17).

Vanillylmandelic acid. Urinary VMA was measured by high–performance liquid chromatography and coulometric detection using isoVMA as an internal standard (18).

Statistical analysis. Analysis of variance was used to test differences between diabetic patients and control subjects and differences between years in the longitudinal study (19). Association between biochemical parameters and sudomotor function was assessed using regression analysis (20).

RESULTS

None of the diabetic patients developed signs or symptoms of neuropathy, microvascular disease, or other diabetic complications during the course of this study. One patient developed hypertension. Of the 37 patients, 20 maintained their HbA_1 concentrations within American Diabetes Association guidelines (<1% above the upper limit of normal for patients without diabetes). Patients with good control had the same age and sex distribution as those with poor control.

Cardiovascular autonomic function in the diabetic patients was similar to that in the control subjects. Heart rate variability with deep breathing was slightly greater in the diabetic patients than in the control subjects during the first and second evaluations (Table 2). At the time of the third evaluation, the post-Valsalva R-R interval was 1.83 ± 0.07, significantly lower ($P < 0.05$) than that of control subjects (2.02 ± 0.06).

The renin-to-prorenin ratio of the diabetic patients was ~50% that of the control subjects at each evaluation ($P < 0.01$ each year) (Table 2). Urinary sodium had a negative correlation with plasma renin, a positive correlation with prorenin, but no correlation with the renin-to-prorenin ratio. VMA excretion was decreased in the diabetic patients only at the third evaluation (2.43 ± 0.17 vs. 3.01 ± 0.19 mg/g creatinine, $P < 0.05$).

Sweat production in response to acetylcholine iontophoresis was dramatically increased in the forearms of the diabetic patients at the first evaluation (1.67 ± 0.24 vs. 1.04 ± 0.14 µl/cm^2 in the control subjects, $P < 0.05$) (Table 3). Smaller increases at other sites during the first patient evaluation were not significant, but total sweat was increased (5.09 ± 0.54 µl/cm^2 in the diabetic patients vs. 3.90 ± 0.41 in the control subjects, $P < 0.05$). Forearm and total sweat were normal in the diabetic patients during subsequent evaluations. Sweating in the feet and sweating below the waist were not different in the diabetic versus the nondiabetic patients. However, the ratio of sweating in the forearm to sweating below the waist was dramatically increased at the time of the first evaluation (0.553 ± 0.07 vs. 0.385 ± 0.04 µl/cm^2, $P < 0.05$).

Sweat production tended to be greater in the males than in the females for both the control subjects and the diabetic patients, but the effect of sex was not statistically significant (Table 4). The female diabetic patients produced sweat at rates equal to or greater than that of the nondiabetic males. Age had no effect on sweat production.

To assess the effect of glycemic control on sweat production, we divided patients according to whether their average HbA_1 was above or below the median for all patients. The average HbA_1 for those in the low HbA_1 group (14 female, 6 male) was 7.66 ± 0.16%, whereas the average HbA_1 for those in the high HbA_1 group (13 female, 4 male) was 10.0 ± 0.28%.

TABLE 2
Biochemical changes, small-fiber somatosensory and cardiovascular autonomic function

	Control subjects	Diabetic patients		
		First evaluation	Second evaluation	Third evaluation
HbA_1 (%)	—	8.20 ± 0.32	9.05 ± 0.29	8.93 ± 0.29
Beat-to-beat variation with deep breathing (max-min)	19.0 ± 1.1	22.8 ± 1.3*	22.1 ± 1.3	20.9 ± 1.2
Mean circular resultant	42.0 ± 3.3	53.2 ± 4.6*	54.1 ± 3.2*	47.3 ± 3.8
Post-Valsalva R-R interval	2.02 ± 0.06	1.89 ± 0.07	1.90 ± 0.06	1.83 ± 0.07*
Thermal thresholds (°C)				
Heat feet	1.16 ± 0.13	0.866 ± 0.14	0.973 ± 0.12	0.897 ± 0.13
Cold feet	0.368 ± 0.05	0.416 ± 0.10	0.417 ± 0.07	0.366 ± 0.05
Heat wrist	0.133 ± 0.02	0.138 ± 0.017	0.159 ± 0.019	0.135 ± 0.018
Cold wrist	0.131 ± 0.02	0.115 ± 0.008[I]	0.152 ± 0.015	0.151 ± 0.016
Renin-to-prorenin ratio	0.475 ± 0.08	0.260 ± 0.03[H]	0.236 ± 0.05[H]	0.227 ± 0.05[H]
VMA (mg/g creatinine)	3.01 ± 0.19	2.72 ± 0.13	3.06 ± 0.14	2.43 ± 0.17*

Data are means ± SE. *Different from control subjects, $P < 0.05$; †different from second and third evaluation, $P < 0.025$; ‡different from control subjects, $P < 0.01$.

The excessive forearm and total sweat production at the time of the first patient evaluation was more pronounced in those with poor control. In the forearm, sweat production in the poorly controlled diabetic patients was 2.10 ± 0.41 µl/cm^2, greater than that of the well–controlled diabetic patients (1.30 ± 0.26 µl/cm^2, $P < 0.01$) and greater than that of the control subjects (1.04 ± 0.14 µl/cm^2, $P < 0.001$) (Fig. 1). In the feet, however, the opposite pattern was seen. At the second evaluation, sweat production in the feet of the diabetic patients with good versus poor control was 1.05 ± 0.18 vs. 0.676 ± 0.13 µl/cm^2, respectively ($P < 0.05$) (Table 5). At the third evaluation, sweat production was 1.36 ± 0.29 µl/cm^2 in those with good control and 0.86 ± 0.18 µl/cm^2 in those with poor control ($P < 0.025$). However, sweating in the feet of the poorly controlled diabetic patients was not different from that of the control subjects at any time point. The ratio of forearm sweat to foot sweat was greater ($P < 0.01$) in patients with poor control than in patients with good control throughout the study (Table 5). At the time of the first evaluation, the ratio of forearm sweating to below-the-waist sweating was 0.703 ± 0.14 µl/cm^2 in the diabetic patients with poor control, significantly different from those with good control (0.426 ± 0.07 µl/cm^2) and the control subjects (0.385 ± 0.04 µl/cm^2) ($P < 0.01$). The ratio of forearm to below-the-waist sweat was significantly greater ($P < 0.01$) in patients with poor control than in patients with good control throughout the study (Fig. 1). Analysis of the forearm sweat to total sweat and HbA_1 as continuous variables confirmed an association, although it was only of borderline significance ($P < 0.06$).

Sweat production was negatively associated with heart rate variability with deep breathing. The average total sweat production for each patient during the 3-year study was inversely correlated with their average beat-to-beat variation with deep breathing ($P < 0.05$) (Fig. 2). Weak negative associations with heart rate variability were noted for sweat production in the forearm ($P < 0.1$), the foot ($P < 0.05$), and below the waist ($P < 0.1$). Similar weak negative associations were noted for the heart-rate response to the Valsalva maneuver and sweat production, but these were significant only in the foot ($P < 0.05$).

Thermal threshold detection did not differ between the diabetic patients and the control subjects (Table 2). There was no correlation between sudomotor function and thermal threshold detection in the upper extremities. In the feet, thermal thresholds for cold correlated with sweating at the time of the second evaluation ($P < 0.025$). At the third evaluation, the association approached significance ($P = 0.065$). The average thermal threshold for cold in the feet over the entire study was negatively correlated with the average sweat production in the foot ($P < 0.05$) (Fig. 3).

TABLE 3
Sweat production

	Control subjects	Diabetic patients		
		First evaluation	Second evaluation	Third evaluation
Forearm	1.04 ± 0.14	1.67 ± 0.24*	1.01 ± 0.14†	0.984 ± 0.10†
Proximal leg	1.07 ± 0.16	1.13 ± 0.13	1.01 ± 0.18	1.13 ± 0.15
Distal leg	1.02 ± 0.12	1.27 ± 0.16	1.18 ± 0.19	1.22 ± 0.15
Foot	0.816 ± 0.11	1.02 ± 0.13	0.876 ± 0.11	1.13 ± 0.18
Total sweat	3.90 ± 0.41	5.09 ± 0.54*	4.07 ± 0.46‡	4.44 ± 0.44
Above waist/below waist	0.385 ± 0.04	0.553 ± 0.07*	0.404 ± 0.07‡	0.409 ± 0.06‡

Data are means ± SE of sweat produced (µl/cm^2). *Different from control subjects, $P < 0.05$; †different from first evaluation, $P < 0.01$; ‡different from first evaluation, $P < 0.05$.

TABLE 4
Sweat production in males versus females

	Control subjects	Diabetic patients
Forearm sweat		
Females	0.986 ± 0.29	1.56 ± 29*
Males	1.27 ± 0.32	1.96 ± 0.47
Total sweat		
Females	3.65 ± 0.65	4.84 ± 0.65
Males	4.45 ± 1.05	5.45 ± 1.0

Data are means ± SE of sweat produced (μl/cm^2) for control subjects and diabetic patients at the time of their first evaluations. *Different from women control subjects, $P < 0.05$.

The renin-to-prorenin ratio was inversely correlated with sweat production. Forearm sweat production showed a significant negative association with the renin-to-prorenin ratio for years 1 ($P < 0.025$) (Fig. 4) and 3 ($P < 0.05$) and for the average of years 1, 2, and 3 ($P < 0.01$). Total sweat production showed a significant negative association with the renin-to-prorenin ratio for years 1 ($P < 0.01$) (Fig. 4) and 3 ($P < 0.05$) and for the average of years 1, 2, and 3 ($P < 0.05$).

VMA excretion was also inversely associated with sweat production. Forearm sweat was negatively associated with VMA excretion for year 1 ($P < 0.025$) (Fig. 5). Total sweat was negatively associated with VMA for years 1 ($P < 0.01$) (Fig. 5) and 2 ($P < 0.025$) and for the average of years 1, 2, and 3 ($P < 0.05$).

The renin-to-prorenin ratio was decreased in the well-controlled diabetic patients as well as in the poorly controlled diabetic patients, but the changes were more pronounced in the poorly controlled diabetic patients (Table 6). VMA excretion was decreased only in the poorly controlled diabetic patients at the third evaluation (Table 6). The post-Valsalva R-R interval ratios were lower in the poorly controlled diabetic patients than in the well-controlled diabetic patients or in the control subjects (Table 6).

DISCUSSION

This study was designed to test for the presence of sympathetic neuropathy in early type 1 diabetes. In experimental diabetes, sympathetic dysfunction develops rapidly (21), and studies of pupillary light reflexes in humans have suggested that this also occurs in clinical diabetes (22). In the present study, we observed a redistribution of sympathetic sudomotor responses at the time of the first patient evaluation, which was within the first 2 years after diagnosis. Increased sweating was observed in the forearm, and the ratio of forearm sweating to the sum of sweating in three sites below the waist was increased (Table 3) (Fig. 1). A similar redistribution pattern was observed at the second and third evaluations, although the ratios of sweating in the forearm to sweating below the waist or sweating in the feet in poorly controlled diabetic patients were not different from the ratios in control subjects. Nevertheless, the ratio of sweating in the forearm to sweating in the foot was higher in the poorly controlled versus the well-controlled diabetic patients throughout the study (Table 5). At the second and third evaluations, the ratio was increased in the poorly versus the well-controlled diabetic patients because the hyperglycemic group had less sweat production in the feet than the well-controlled diabetic patients. Because it is well documented that patients with overt neuropathy have decreased sweating in the lower extremities and increased sweating in the upper trunk, head, and neck (1,2), we interpret the presently observed redistribution of sudomotor responses as evidence of sympathetic dysfunction. It is unlikely that the excessive forearm sweating should be interpreted to mean that sudomotor function is paradoxically healthier in the

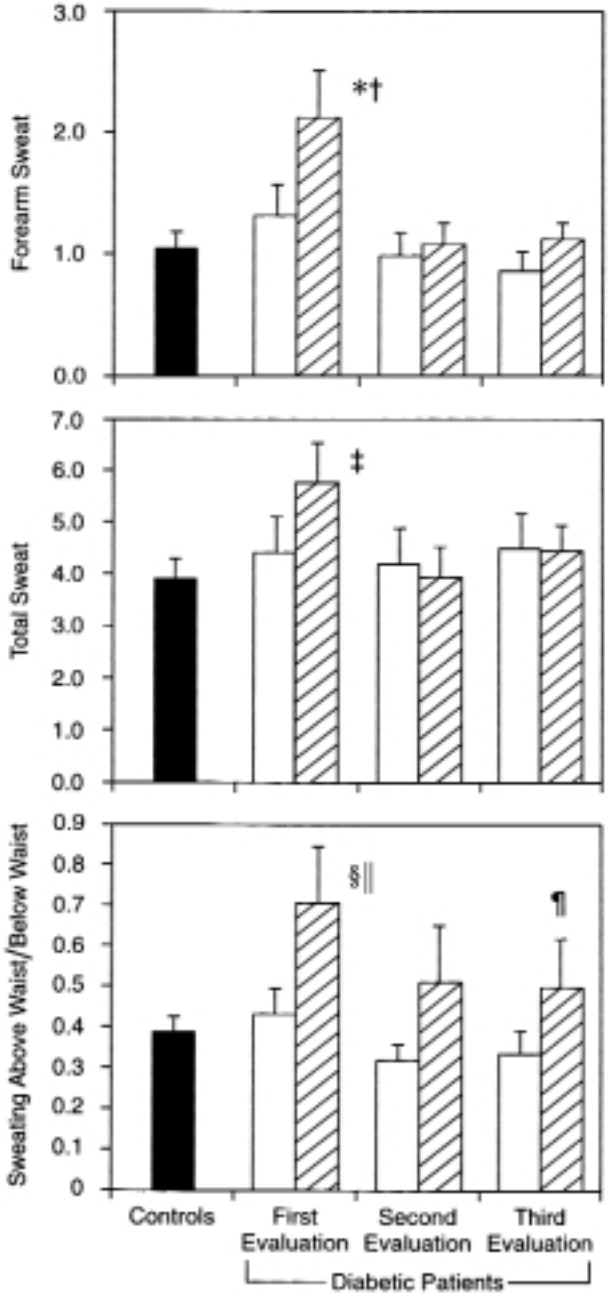

FIG. 1. Effect of glycemic control on forearm sweat, total sweat, and ratio of sweating above the waist to sweating below the waist. Mean results for patients whose HbA_1 values were below (□) or above (▨), respectively, the median for the group, versus that of the control subjects (■). Forearm sweat is expressed as microliters per square centimeter, whereas total sweat is expressed as microliters per 4 cm^2. *Different from controls, $P < 0.001$; †different from diabetic patients with low HbA_1, $P < 0.01$; ‡different from controls, $P < 0.005$; §different from controls, $P < 0.01$; ‖different from diabetic patients with low HbA_1, $P < 0.01$; and ¶diabetic patients with high versus low HbA_1 across all years were different ($P < 0.01$).

TABLE 5
Redistribution of sudomotor responses

		Diabetic patients					
		First evaluation		Second evaluation		Third evaluation	
	Control subjects	Low HbA_1	High HbA_1	Low HbA_1	High HbA_1	Low HbA_1	High HbA_1
Forearm	1.04 ± 0.14	1.30 ± 0.27	2.10 ± 0.41*	0.970 ± 0.19	1.06 ± 0.23	0.889 ± 0.17	1.10 ± 0.14
Foot	0.816 ± 0.11	1.01 ± 0.18	1.08 ± 0.20	1.05 ± 0.18†	0.676 ± 0.13	1.36 ± 0.29†	0.860 ± 0.18‡
Sweating below waist	2.92 ± 0.37	3.13 ± 0.52	3.57 ± 0.52	3.24 ± 0.53	2.85 ± 0.51	3.57 ± 0.62	3.33 ± 0.42
Forearm/below waist	0.385 ± 0.04	0.426 ± 0.07	0.703 ± 0.14*	0.316 ± 0.04	0.508 ± 0.14	0.331 ± 0.06	0.496 ± 0.12§
Forearm/foot	2.03 ± 0.38	1.32 ± 0.20	2.67 ± 0.49	1.65 ± 0.46	2.19 ± 0.53	1.25 ± 0.28	3.32 ± 0.92§

Data are means ± SE of sweat produced (μl/cm^2). *Different from controls and different from diabetic patients with low HbA_1, $P < 0.01$; †different from diabetic patients with high HbA_1 at the third evaluation, $P < 0.05$; ‡diabetic patients with high versus low HbA_1 across all years were different, $P < 0.05$; §diabetic patients with high versus low HbA_1 across all years were different, $P < 0.01$.

diabetic patients than in the control subjects. The redistribution of sudomotor responses was seen primarily in the diabetic patients with poor glycemic control (Fig. 1) (Table 5), and the latter is known to damage the autonomic nervous system (23). Accordingly, Cardone and Dyck (21) observed that the early development of sudomotor dysfunction was evident only in poorly controlled diabetic rats. In addition, the negative associations between forearm sweating and biochemical measures of the integrity of the sympathetic nervous system, VMA excretion and the plasma renin-to-prorenin ratio, also suggest that excessive sweating at the time of the first evaluation was indicative of sympathetic nerve injury (Figs. 4 and 5). Moreover, excessive sweating was associated with worse heart-rate variability with deep breathing, suggesting that the pathological process taking place in the sympathetic nervous system was also showing early effects on parasympathetic function (Fig. 2).

We also tested the function of small somatosensory nerves by measuring thermal threshold detection. Performance of the diabetic patients was not different from that of the control subjects on this test. Thus, it appears that sympathetic nerves are more vulnerable to the adverse effects of chronic hyperglycemia than other small nerves. Generally, there was little or no correlation between thermal threshold detection and sudomotor responses. However, high cold thresholds in the feet were associated with decreased sweating in the feet (Fig. 3). This indicates that the decreased sudomotor function in the feet previously described in patients with chronic diabetes and overt neuropathy begins to develop early in the disease.

Although decreased sweating in the feet is the anticipated response to sympathetic dysfunction, the excessive sweating in the forearm is not as easily explained. Excessive sudomotor responses to acetylcholine have also been observed in individual diabetic patients, raising the question of denervation hypersensitivity (24). There is no evidence, however, that a damaged sympathetic nerve is hypersensitive to administered acetylcholine or that the sweat gland is hypersensitive to the acetylcholine released by the neuron (13,21,25,26). In

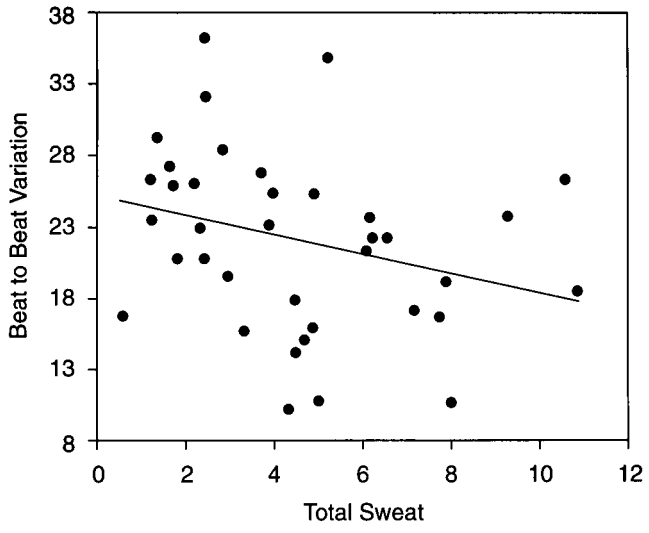

FIG. 2. Average heart rate variability with deep breathing versus average total sweat production. The beat-to-beat variation is expressed as the maximum heart rate during deep breathing minus the minimum heart rate during deep breathing. Total sweat is expressed as microliters per 4 cm^2 of skin. The average heart-rate variability with deep breathing for each patient during the 3-year study was inversely associated with their average total sweat production ($P < 0.05$).

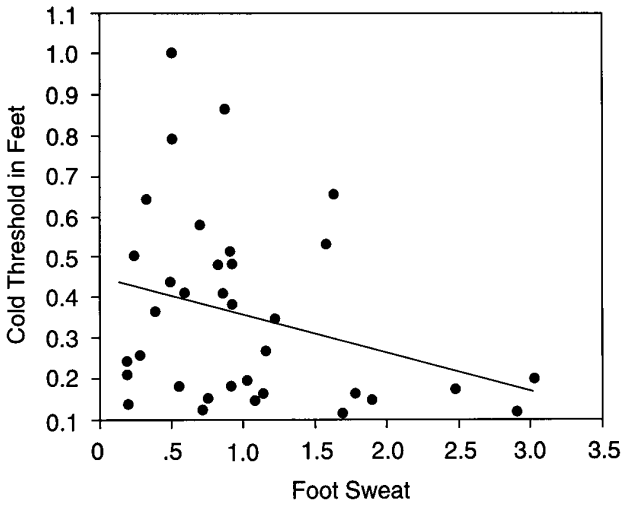

FIG. 3. Average thermal threshold for cold in the feet versus average sweat production in the foot. The cold threshold is expressed in degrees centigrade. Sweat production is expressed as microliters per square centimeter. The average cold threshold for each patient during the 3-year study was inversely associated with average sweat production in the foot ($P < 0.05$).

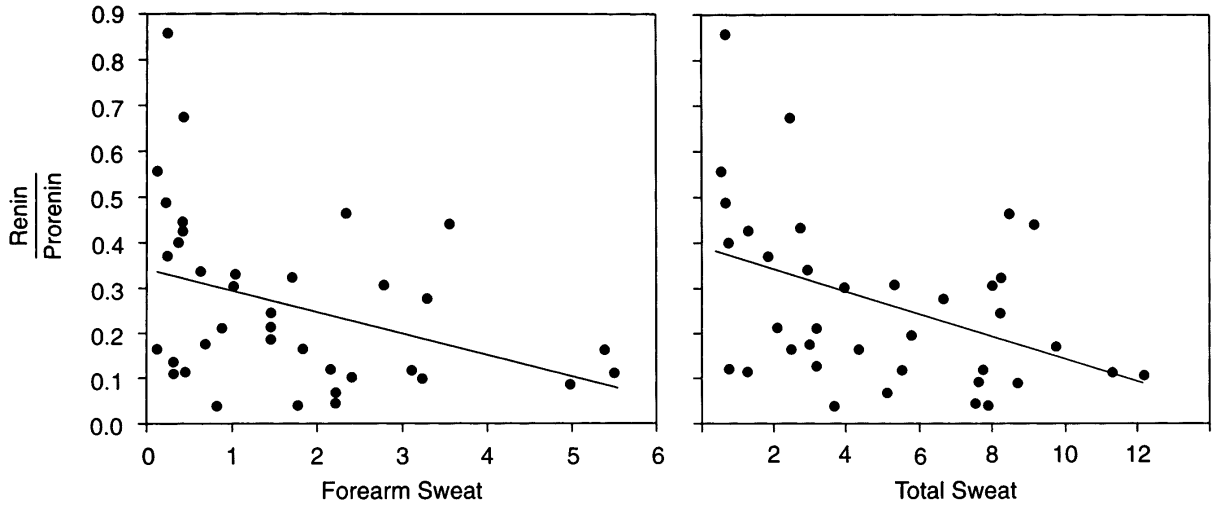

FIG. 4. Plasma renin-to-prorenin ratio versus forearm sweat and total sweat at the first evaluation. Plasma renin and prorenin are both expressed as nanograms of angiotensin I formed per milliliter of plasma per hour. Forearm sweat is expressed as microliters per 4 cm^2. Forearm and total sweat were negatively associated with the renin-to-prorenin ratio ($P < 0.025$ for both measures of sweat).

fact, the opposite has been observed; namely, that sympathetic nerve damage decreases its response to acetylcholine stimulation, and decreased sweating is the usual consequence (13). Thus, we feel it is unlikely that the increased sweating in the forearm in early diabetes is indicative of denervation hypersensitivity.

Could the increased sweating in the forearm in early diabetes reflect a compensatory response to sympathetic nerve injury elsewhere in the body (1)? The phenomenon of compensatory hyperhidrosis is a well-documented consequence of regional sympathectomy (3,4,27). Moreover, there are other instances in which decreased sympathetic activity in one part of the body is associated with excessive activity elsewhere in the body. Nondiabetic patients with orthostatic tachycardia have decreased autonomic surface potentials and other evidence of sympathetic dysfunction in the feet, yet they have increased increments in plasma norepinephrine (a large fraction of which derives from forearm sympathetic neurons) when they undergo orthostatic stress (28). Finally, diabetic patients with overt sympathetic neuropathy in the lower extremities may have increased sweating in upper body and face, typically after eating (29). Thus, it is reasonable to postulate that increased sweating in the forearm reflects sympathetic hyperactivity, which in turn is a compensatory response to sympathetic nerve injury elsewhere in the body. However, there are problems with this interpretation of our data. Because there was no sign of decreased sweating below the waist at the time of the first patient evaluation, it is necessary to postulate that any compensatory increase in sweating in the forearm was the result of sympathetic injury suffered by neurons we did not test. The decreased renin-to-prorenin ratios at the time of the first patient evaluation, especially in the poorly controlled diabetic patients (Table 6), provides indirect evidence for the early onset of sympathetic injury that may have been missed at the time of the first evaluation by the QSART, which was only performed on a very small fraction (4 cm^2) of the total surface area of the body. Sweating in the feet, the renin-to-prorenin ratios, and the post-Valsalva R-R interval ratios were all decreased in the poorly controlled versus the well-controlled diabetic patients at the time of the second and third evaluations.

An alternative explanation of our findings is that compensatory hyperhidrosis may be a local process, whereby partially denervated sweat glands are reinnervated by multiple regenerating neurons (30), which transiently leads to an exaggerated response to cholinergic stimulation. Kennedy et al. (30) have documented in rodents that denervated sweat glands are

TABLE 6
Sympathetic function and glycemic control

		Diabetic patients					
		Year 1		Year 2		Year 3	
	Control subjects	Low HbA_1	High HbA_1	Low HbA_1	High HbA_1	Low HbA_1	High HbA_1
Renin/prorenin	0.475 ± 0.08	0.296 ± 0.05*	0.218 ± 0.03†	0.284 ± 0.08*	0.180 ± 0.04†	0.301 ± 0.08*	0.134 ± 0.03†‡
VMA (mg/g creatinine)	3.01 ± 0.19	2.67 ± 0.22	2.78 ± 0.24	2.97 ± 0.23	3.15 ± 0.25	2.60 ± 0.22	2.22 ± 0.25†
Post-Valsalva R-R interval	2.02 ± 0.06	2.07 ± 0.1	1.73 ± 0.1*‡	2.02 ± 0.09	1.79 ± 0.09*‡	1.94 ± 0.09	1.74 ± 0.11*§

*Different from control subjects, $P < 0.05$; †different from control subjects, $P < 0.01$; ‡different from patients with low HbA_1, $P < 0.05$; §diabetic patients with high versus low HbA_1 across all years were different, $P < 0.025$.

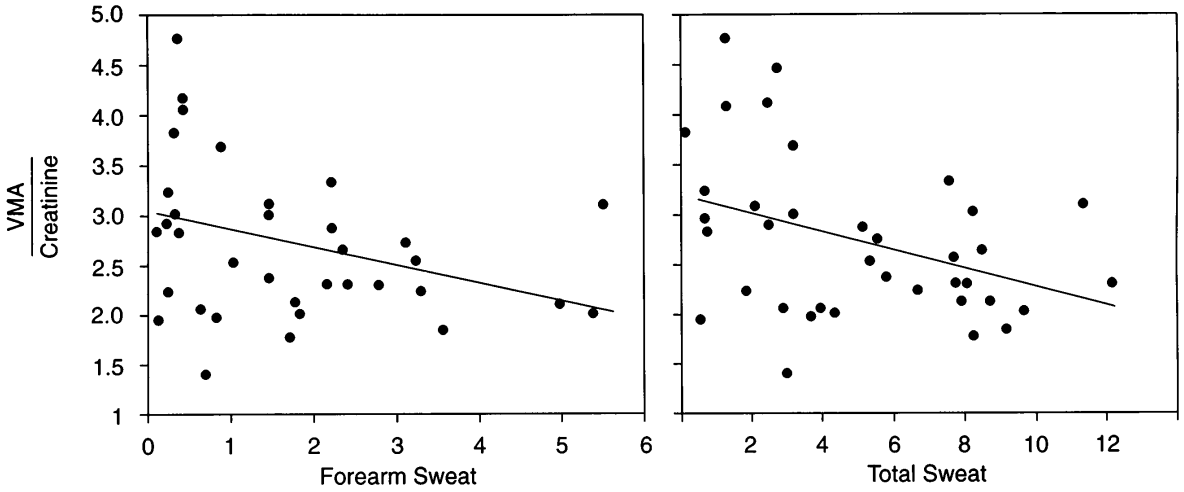

FIG. 5. VMA excretion versus forearm sweat and total sweat at the first evaluation. VMA is expressed as milligrams per gram creatinine. Forearm sweat is expressed as microliters per square centimeter and total sweat as microliters per 4 cm^2. Forearm sweat and total sweat were negatively associated with VMA excretion ($P < 0.05$ and $P < 0.01$, respectively).

quickly reinnervated by regenerating sympathetic neurons, and it is possible that this occurs clinically early in diabetes and caused the transient increase in the acetylcholine–induced forearm sweating and total sweating that we observed. However, the excessive sweating was seen only at the first evaluation, presumably because persistent hyperglycemia continues to damage both new and preexisting sympathetic neurons.

Although we are unable to prove the validity of the above mechanistic speculations, our results are nevertheless consistent with the large body of literature that indicates that diabetes-related sudomotor disturbances reflect sympathetic nerve injury (1–4,28–30). These studies support the broad interpretation of our current data, namely that redistribution of sudomotor responses in diabetic patients is an adverse consequence of chronic hyperglycemia and is definitely pathological. In this regard, our results provide a new perspective of the natural history of diabetic autonomic neuropathy. Although it is a common belief that parasympathetic abnormalities develop early in diabetes and that sympathetic dysfunction develops late (31), this dogma may be invalid because it is based on comparisons of sensitive tests of parasympathetic function, such as the heart rate variability with deep breathing, and insensitive tests of sympathetic function, such as the hemodynamic response to orthostatic stress or isometric hand grip. However, the QSART, a much more sensitive test of postganglionic sympathetic neurons than older methods (32,33), has made it possible to demonstrate that sympathetic involvement occurs very early in poorly controlled type 1 diabetes and may be the first detectable feature of peripheral neuropathy.

In summary, we observed a relative increase in forearm sweating and a relative decrease in sweating below the waist, especially in the feet, early in poorly controlled type 1 diabetes. Increased sweating in the forearm at the time of the first evaluation showed a negative association with plasma renin-to-prorenin ratio and VMA excretion, two independent measures of the integrity of the sympathetic nervous system. The renin-to-prorenin ratio was decreased throughout the study in the diabetic patients, and VMA excretion was decreased at the time of the third evaluation; both parameters were more significantly affected in the poorly controlled diabetic patients. Thus, multiple lines of evidence indicate sympathetic nerve dysfunction in our patients. Because small-fiber somatosensory function and cardiac parasympathetic function were normal during the first few years of diabetes, our results indicate that the sympathetic nervous system is especially vulnerable to the adverse effects of chronic hyperglycemia.

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REFERENCES

1. Goodman JI: Diabetic anhidrosis. *Am J Med* 41:831–835, 1966
2. Fealey RD, Low PA, Thomas JE: Thermoregulatory sweating abnormalities in diabetes mellitus. *Mayo Clin Proc* 64:617–628, 1989
3. Shelley WB, Florence R: Compensatory hyperhidrosis after sympathectomy. *N Engl J Med* 263:1056–1058, 1960
4. Moran KT, Brady MP: Surgical management of primary hyperhidrosis. *Br J Surg* 78:279–283, 1991
5. Kopin IJ, Polinsky RJ, Oliver JA, Oddershede IR, Ebert MH: Urinary catecholamine metabolites distinguish different types of sympathetic neuronal dysfunction in patients with orthostatic hypotension. *J Clin Endocrinol Metab* 57:632–637, 1983
6. Hoeldtke RD, Cilmi KM: Norepinephrine secretion and production in diabetic autonomic neuropathy. *J Clin Endocrinol Metab* 59:246–252, 1984
7. Keeton TK, Campbell WB: The pharmacological alteration of renin release. *Pharmacol Rev* 31:81–277, 1981
8. Hoeldtke RD, Bryner KD, Komanduri P, Christie I, Ganser G, Hobbs GR: Decreased prorenin processing develops before autonomic dysfunction in type 1 diabetes. *J Clin Endocrinol Metab* 85:585–589, 2000
9. Ewing DJ, Cambell IW, Clarke BF: Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Int Med* 92:308–311, 1980
10. Genovely H, Pfeifer MA: R-R–variation B: the test of choice in diabetes. *Diabetes Metab Rev* 4:255–271, 1988
11. Baldwa VS, Ewing DJ: Heart rate response to Valsalva manoeuvre: reproducibility in normals, and relation to variation in resting heart rate in diabetics. *Br Heart J* 39:641–644, 1977
12. Jamal GA, Hanser S, Weir AL, Ballatyne JP: The neurophysiologic investigation of small fiber neuropathies. *Muscle Nerve* 10:537–545, 1987
13. Low PA, Caskey PE, Tuck RR, Fealey RD, Dyck PJ: Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Ann Neurol* 14:573–580,

1983
14. Menard LA, Dempsey MD, Blankstein LA: Agar gel electrophoresis determination of glycosylated hemoglobin: effect of variant hemoglobins, hyperlipidemia, and temperature. *Clin Chem* 27:472, 1981
15. Sealey JE, Atlas SA, Laragh JH, Oza NB, Ryan JW: Activation of a proreninlike substance in human plasma by trypsin and urinary kallikrein. *Hypertension* 1:179–189, 1979
16. Kotchen TA, Guyenne TT, Corvol P, Menard J: Enzymatic activation of renin in plasma in normal and uraemic subjects. *Clin Sci* 67:365–368, 1984
17. Blankestijn PJ, Derkx FH, Van Geelen JA, De Jong FH, Schalekamp MA: Increase in plasma prorenin during the menstrual cycle of a bilaterally nephrectomized woman. *Br J Obstet Gynaecol* 97:1038–1042, 1990
18. Matson WR, Langlais P, Volicer L, Gamache PH, Bird E, Mark KA: N-electrode three-dimensional liquid chromatography with electro-chemical detection for determination of neurotransmitters. *Clin Chem* 30:1477–1488, 1984
19. Winer BJ: Multifactor experiments having repeated measures on the same elements. In *Statistical Principles in Experimental Design*. 2nd ed. NY, McGraw-Hill, 1979, p. 514–603
20. Snedecor GW, Cochran WG: *Statistical methods*. 6th ed. Ames, IA, Iowa University Press, 1967, p. 172–195
21. Cardone C, Dyck PJ: A neuropathic deficit, decreased sweating, is prevented and ameliorated by euglycemia in streptozocin diabetes in rats. *J Clin Invest* 86:248–253, 1990.
22. Hreidarsson AB: Acute reversible autonomic nervous system abnormalities in juvenile insulin dependent diabetes. *Diabetologica* 20:477–481, 1981
23. The DCCT Research Group: The effect of intensive therapy on the development and progression of neuropathy. *Ann Int Med* 122:561–569, 1995
24. Levy DM, Reid G, Abraham RR, Rowley DA: Assessment of basal and stimulated sweating in diabetes using a direct-reading computerized sudorometer. *Diabet Med* 8:S78–S81, 1991
25. Hayashi H, Nakagawa T: Functional activity of the sweat glands of the albino rat. *J Invest Dermatol* 41:365–367, 1963
26. Janowitz HD, Grossman MI: The response of the sweat glands to some locally acting agents in human subjects. *J Invest Dermatol* 14:453–458, 1950
27. Voris HC: Symposium on techniques and procedures in surgery: thoracolumbar sympathectomy for hypertension. *S Clin North Am* 35:255–264, 1955
28. Hoeldtke RD, Dworkin GE, Gaspar SR, Israel BC: Sympathotonic orthostatic hypotension: report of four cases. *Neurology* 39:34–40, 1989
29. Odel HM, Roth GM, Keating FR: Autonomic neuropathy simulating the effects of sympathectomy as a complication of diabetes mellitus. *Diabetes* 4:92–97, 1955
30. Kennedy WR, Navarro X, Kamei H: Reinnervation of sweat glands in the mouse: axonal regeneration versus collateral sprouting. *Muscle Nerve* 11:603–609, 1988
31. Bennett T, Hosking DJ, Hampton JR: Cardiovascular control in diabetes mellitus. *Br Med J* 2:585–587, 1975
32. Low PA, Zimmerman BR, Dyck PJ: Comparison of distal sympathetic with vagal function in diabetic neuropathy. *Muscle Nerve* 9:592–596, 1986
33. Riedel A, Braunee S, Kerum G, Schulte-Monting J, Lucking CH: Quantitative sudomotor axon reflex test (QSART): a new approach for testing distal sites. *Muscle Nerve* 22:1257–1264, 1999