Peripheral Autonomic Impairment in Patients Newly Diagnosed With Type II Diabetes

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OBJECTIVE — To measure both peripheral and central autonomic function in patients newly diagnosed with type II diabetes.

RESEARCH DESIGN AND METHODS — Measurements were made on 49 diabetic patients (8 with long-standing diabetes and neuropathic complications, 41 with newly diagnosed type II diabetes) and on 49 healthy, age- and sex-matched, control subjects. Five of the 41 newly diagnosed type II diabetic patients had retinopathy, and 4 had clinical evidence of neuropathy. No patient or control subject had significant vascular disease. Cardiac autonomic function was investigated by using standard cardiovascular reflex tests. The digital vasoconstrictor responses to deep breathing and body cooling were measured using venous occlusion plethysmography.

RESULTS — The vasoconstrictor responses to a deep breath and body cooling were significantly reduced ($P < 0.001$) in the fingers and toes of the neuropathic patients compared with their matched control subjects, as were the heart rate responses ($P < 0.02$). The vasoconstrictor responses were significantly reduced in the toes ($P < 0.001$) and fingers ($P < 0.05$, $P < 0.01$) of the newly diagnosed patients compared with the corresponding responses in the control subjects. There was no significant difference in the heart rate or blood pressure responses of these patients and control subjects during standard tests of cardiac autonomic function.

CONCLUSIONS — Patients with type II diabetes may have impaired peripheral autonomic function at diagnosis.

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BP, blood pressure; CV, coefficient of variation; sBP, systolic blood pressure.

Diabetes is a common cause of neuropathy that involves motor, sensory, and autonomic nerve fibers. Involvement of the latter may alter function in the cardiovascular system, where autonomic regulation of both the heart and peripheral circulation may be affected. Cardiac autonomic neuropathy has been reported to be associated with an increasing mortality rate (1), and deaths may be sudden and unexplained (2,3). However, other studies suggest a more favorable prognosis (4). Cardiac autonomic neuropathy and its severity can be identified using standard tests of heart rate variability and blood pressure (BP) responses to stimuli, such as deep breathing, the Valsalva maneuver, and the move from lying to standing (5).

In the lower limbs, diabetic autonomic neuropathy is associated with foot ulceration (6–8), although other factors, such as impaired sensation and musculoskeletal abnormalities, will also contribute. Foot ulceration is a major cause of morbidity associated with diabetes and sometimes may be the first indication of neuropathy or type II diabetes. Most patients with long-standing diabetes complicated by autonomic neuropathy show both cardiac and peripheral autonomic involvement, but some may have peripheral autonomic involvement with normal cardiac function (9). Peripheral autonomic function can be assessed by the reflex vasoconstrictor responses to a deep breath and to body cooling, both of which are mediated by sympathetic nerves (10,11).

At the time type II diabetes is diagnosed, patients may already have macrovascular or neuropathic complications (12). Abnormalities in cardiac autonomic function have also been observed soon after diagnosis in patients with type II diabetes (13,14). The aim of this investigation was to measure both peripheral and central autonomic function in patients newly diagnosed with type II diabetes.

RESEARCH DESIGN AND METHODS

Pilot study

Measurements were made in eight men with long-standing diabetes (5–22 years since initial diagnosis), whose ages ranged from 46 to 69 years. All had a clinical diagnosis of severe neuropathy with greatly diminished sensation in their feet, absent ankle reflexes, and impairment of motor and sensory nerve conduction velocities. Five had a history of foot ulceration.

Main study

Measurements were made in 41 patients newly diagnosed with type II diabetes (13 women, 28 men). The age range was 33–85 years (mean 61 years), and weights ranged from 53.6 to 102.6 kg (mean 79.6 kg). They were studied within 3 months of diagnosis and were on dietary treatment only. HbA_1 values ranged from 6.1 to 15.5% (mean 10.1%) and height from 148 to 180 cm (mean 167 cm). All new type II diabetic patients seen at the outpatient clinic who agreed to participate were considered for the study. Clinical evidence of peripheral somatic neuropathy, using a scoring system based on both symptoms and signs (15), was found in four patients. Five patients had evidence of retinopathy, defined as the presence of at least one microaneurysm in either eye.

For both studies, patients with any evidence of significant peripheral vascular disease (history of claudication or ankle/brachial pressure index ≤ 0.9) were excluded. Patients were also excluded if they had Raynaud's syndrome or were taking medication with a significant cardiovascular action. These exclusion criteria may result in an underestimate of the prevalence of autonomic dysfunction in type II diabetic patients at the time of diagnosis.

Forty-nine healthy control subjects were measured under identical conditions, were subject to the same exclusion criteria as the patients, and were individually matched to the patients for age and sex. The study had the approval of the Northern Ireland Ethical Committee, and the subjects gave informed consent.

All measurements were carried out in a laboratory maintained at 23 ± 1°C, and the protocol was identical for all patients and control subjects. Subjects wore only underclothing and light cotton surgical suits and lay supine on an examination couch that had an approximate head elevation of 30°C. They lay between two water blankets (Blanketrol Model 2, Hawksley & Sons) that were perfused with water at a rate of 1.2 l/min at 34°C. This temperature was maintained by a Churchill Chiller Thermo Circulater 05/CTC VM. The bottom blanket extended from the shoulders to the ankles. The top blanket was positioned to leave the feet and arms uncovered. The participants' arms were positioned on arm rests that were elevated slightly above the level of the heart. The upper water blanket was covered by a blanket to minimize heat loss. The inlet and outlet temperatures of the water blankets were continuously monitored.

Peripheral blood flow was measured by venous occlusion plethysmography using indium/gallium strain gauges (Medasonics PMS Inst. S.G.6). These were placed on the middle phalanges of the middle finger of each hand and around the distal phalanges of the great toes. Collecting cuffs were positioned on the proximal phalanges of each finger and toe.

The electrocardiogram was recorded from three chest electrodes, and heart rate data were obtained using a Hewlett Packard heart rate module and Apple IIe microcomputer.

After a 15-min equilibration period, resting heart rate was recorded for 512 beats. The mean was calculated, and variability was expressed as the coefficient of variation (CV) where CV = (SD × 100) ÷ mean. When the subjects had been lying between the perfused blankets for 30 min, finger and toe blood flow were recorded continuously for the 2 min before, during, and after a deep breath. Following a 2-min recovery period, the deep breath sequence was repeated at least twice. Since responses vary with the depth of inspiration, values cited in the results section refer to the maximum deep breath response in each patient. This was calculated as the difference between the flow value immediately following the deep breath and the mean value for the 2-min control period.

Resting finger and toe blood flows were then recorded continuously for 5 min, and the mean and CV values were calculated as described earlier. After a further 2-min control period, body cooling was induced by reducing the temperature of the water perfusing the blankets as quickly as possible to 21°C (normally, 9 ± 1 min). The blankets were then rewarmed. If shivering occurred, rewarming was started immediately. The blood flow response to cooling was calculated as the difference between the mean flow during the 1-min period immediately preceding cooling and the mean value during the last minute of cooling.

The heart rate responses to deep breathing, Valsalva maneuver, and standing and the systolic blood pressure (sBP) response to standing were assessed following the method described by Ewing and Clarke (5). The R-R intervals were recorded continuously during these procedures using a computerized system (16).

Statistical analysis

All the experimental records were evaluated blindly to avoid any bias due to subjective interpretation. The data were not normally distributed, and because in both the pilot and main studies a number of variables were being compared in two study groups, analysis of the results was carried out using the Wilcoxon's signed-rank test.

RESULTS

Pilot study

Table 1 shows the digital blood flow results for the eight diabetic neuropathic

Table 1—*Blood flow measurements in the fingers and toes of eight diabetic patients with clinically severe neuropathy and eight matched control subjects*

		Diabetic neuropathic patients	Control subjects
Resting flow ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$)	Toe	7.0 ± 1.1*	11.4 ± 1.1
	Finger	28.1 ± 2.9	38.9 ± 5.1
CV	Toe	6.7 ± 0.6†	18.7 ± 1.6
	Finger	13.4 ± 1.4‡	21.6 ± 2.7
% Vasoconstriction after deep breath	Toe	14.1 ± 1.6†	48.7 ± 1.7
	Finger	28.2 ± 5.7†	79.5 ± 2.5
% Vasoconstriction after cooling	Toe	−6.4 ± 4.5†	53.9 ± 2.3
	Finger	26.1 ± 5.3†	78.0 ± 2.9

Data are means ± SE. * $P < 0.05$; † $P < 0.001$; and ‡$P < 0.02$ for diabetic patients compared with control subjects.

patients and their matched control subjects. The values have been calculated using measurements from both toes and both fingers of each patient and control subject. Baseline flows did not vary significantly throughout an experimental run. There were four control periods during an experiment (three for deep breaths and two for body cooling). The average variation between the mean control values in a particular diabetic patient was 0.7 $ml \cdot 100\ ml^{-1} \cdot min^{-1}$ (range 0.4–1.0). Resting toe blood flow, its variability, and the vasoconstrictor responses in the toes to a deep breath and body cooling were all greatly reduced in the diabetic neuropathic patients. The fingers of these patients also exhibited significant reductions in flow variability and vasoconstrictor responses, although resting finger blood flow was not significantly different from that in the control subjects.

The measurements of heart rate variability in the eight neuropathic diabetic patients and their matched control subjects are shown in Table 2. Resting heart rate and the beat-to-beat variation were not significantly different. However, there were significant reductions ($P < 0.02$) in heart rate variation during deep breathing, Valsalva maneuver, and standing in the neuropathic patients. The sBP changes following standing were similar in the two groups.

Table 2—*Heart rate responses in eight diabetic patients with clinically severe neuropathy and eight matched control subjects*

	Diabetic neuropathic patients	Matched control subjects
n	8	8
Resting heart rate (beats/min)	74 ± 3.8	73 ± 5.5
CV	4.7	5.9
Variation during deep breathing (beats/min)	5.7 ± 1.6*	18.0 ± 2.0
Valsalva maneuver	1.19 ± 0.05*	1.58 ± 0.11
30:15 ratio on standing	0.92 ± 0.13*	1.14 ± 0.04
sBP fall on standing (mmHg)	6.4 ± 1.8	6.9 ± 3.1

Data are mean ± SE. * $P < 0.02$, diabetic patients compared with control subjects.

Main study

There was no significant difference in resting blood flow or flow variability in the toes or fingers of the 41 newly diagnosed patients and their matched control subjects (Table 3). The mean results shown were calculated using the values from both fingers and both toes of the patients and the control subjects. The vasoconstrictor responses to a deep breath and body cooling were significantly reduced in both the toes ($P < 0.001$) and the fingers ($P < 0.05$, $P < 0.01$) of the diabetic patients compared with the corresponding responses in the control subjects.

Figure 1 shows the percentage vasoconstriction following a deep breath and body cooling in the toes of all the patients and control subjects. The range of mean response with 2 SDs is shown for the control subjects. It can be seen that 28 and 37 of the patient responses fall below this range for deep breathing and for body cooling, respectively.

There were no significant differences between the values obtained for the diabetic patients and their matched control subjects in any of the heart rate responses or BP measurements (Table 4).

CONCLUSIONS — Abnormalities in cardiac autonomic function have been observed in some patients with type II diabetes soon after diagnosis (13,14). In the present study, both central and peripheral autonomic function were measured in patients newly diagnosed with type II diabetes. The tests used to assess cardiac autonomic function were originally described by Ewing and Clarke (5) and are widely used for this purpose. However, there is no generally accepted, independent gold standard of autonomic reflex function in the peripheries. Various peripheral vascular measurements (17–19) or sudomotor responses (20,21) have been used in previous work.

In our present investigation, venous occlusion plethysmography was used for the measurement of digital blood flow responses since it is a well-estab-

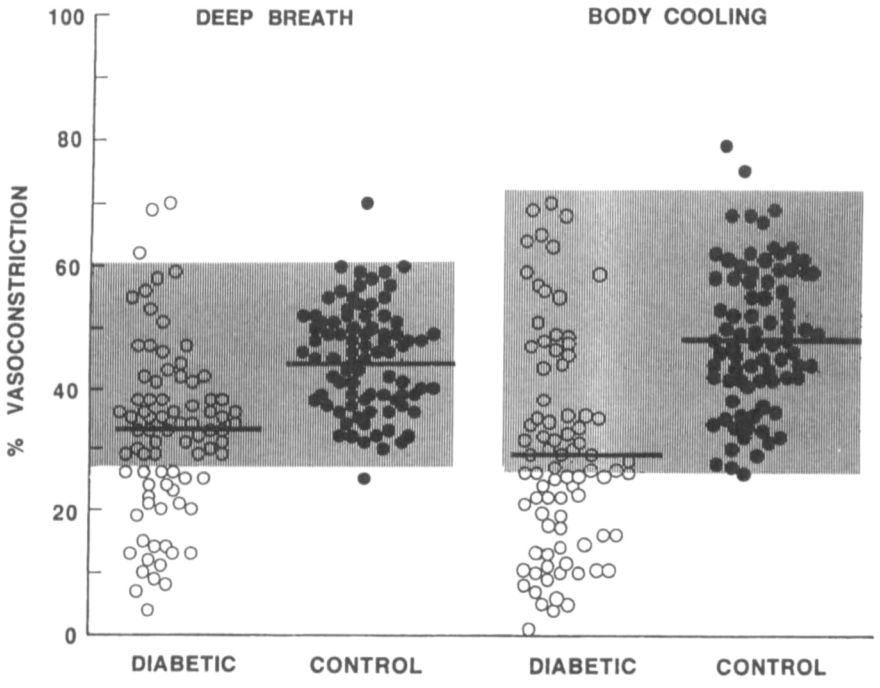

Figure 1—*The percentage vasoconstriction in the toes of 41 patients newly diagnosed with type II diabetes and their matched control subjects following a deep breath and body cooling. The black bars represent the mean value for each group of responses. The shaded area represents the mean control response ± 2 SDs for the particular stimulus.*

lished and reliable technique. Interpretation of recordings can be difficult in the digits because of high blood flow and limited capacity during venous occlusion. Accordingly, the thermal environment of the patients was set to be just comfortable to avoid excessively high digital blood flows.

An attempt was made to establish the sensitivity and specificity of the measurements in the pilot study. Measurements of blood flow and vasoconstrictor responses in eight patients with a clear-cut clinical diagnosis of neuropathy were compared with measurements in healthy control subjects with no clinical evidence of autonomic or vascular impairment. None of the eight neuropathic patients appeared to have significant large vessel disease as judged by the absence of relevant symptoms and a normal ankle-brachial sBP index. In a previous study (9), all had exhibited a >60% reduction in foot blood flow during exposure to a local foot temperature of 16°C. This was not significantly different to the responses in matched control subjects, suggesting that any depression of vasoconstrictor responses in the present study was due to impairment of neural mechanisms rather than to alteration in the mechanical properties of the blood vessel wall. All the neuropathic patients had greatly diminished vasoconstrictor responses in both fingers and toes compared with their matched control subjects, indicating that this type of measurement will detect autonomic impairment.

In the main study, there was no significant difference in cardiac autonomic function in the type II diabetic patients and their matched control subjects. The mean values for heart rate variation during deep breathing were in the borderline range in both groups, but all other cardiac responses were in the normal range (5). The reason for the slight depression in the deep breathing response in both patients and control subjects is not immediately obvious. Obesity has been reported to be associated with impaired autonomic function in healthy subjects and in patients with type II diabetes (22,23). However, in the present study, there was no correlation between patient weight and cardiac autonomic responses even when men and women were considered separately.

In contrast, our present study did show a significant decline of sympathetic function in the fingers and toes of patients with type II diabetes within 3 months of diagnosis. This was detectable in the absence of related symptoms in the majority of the affected patients. To our knowledge, similar findings have not previously

Table 3—***Blood flow measurements in the fingers and toes of 41 patients newly diagnosed with type II diabetes and 41 matched control subjects***

		Diabetic patients	Control subjects
Resting flow ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$)	Toe	8.9 ± 0.7	8.9 ± 0.6
	Finger	39.9 ± 3.1	34.1 ± 2.9
CV	Toe	16.1 ± 0.8	18.2 ± 0.8
	Finger	20.6 ± 1.0	22.2 ± 1.5
% Vasoconstriction after deep breath	Toe	32.6 ± 1.6*	44.5 ± 1.0
	Finger	59.6 ± 2.1†	64.6 ± 1.8
% Vasoconstriction after cooling	Toe	29.8 ± 1.9*	49.3 ± 1.3
	Finger	65.1 ± 2.1‡	74.6 ± 1.9

Data are mean ± SE. * $P < 0.001$, † $P < 0.05$, ‡ $P < 0.01$, for diabetic patients compared with control subjects.

Table 4—*Heart rate responses in 41 patients with type II diabetes and their matched healthy control subjects*

	Diabetic patients	Control subjects
n	41	41
Resting heart rate (beats/min)	70.0 ± 1.7	75.0 ± 2.0
CV	5.8	5.3
Variation during deep breathing (beats/min)	11.2 ± 1.1	12.5 ± 1.0
Valsalva ratio	1.43 ± 0.05	1.38 ± 0.06
30:15 ratio on standing	1.14 ± 0.02	1.10 ± 0.02
sBP fall on standing (mmHg)	4.3 ± 1.2	6.7 ± 1.3

Data are mean ± SE.

been described. There was no correlation between diminished sympathetic function in the digits and cardiac autonomic function. However, most of the cardiac function tests used assess vagal function (5). Of the tests that we performed, only the fall in sBP on standing is thought to assess sympathetic integrity. This is a relatively insensitive indicator (24), so that abnormal values are only found late in the course of autonomic neuropathy.

The present findings would appear to contradict the theory that vagal impairment occurs early and precedes sympathetic involvement in diabetic autonomic neuropathy (5). They are, however, in agreement with an earlier study on the feet of patients with long-standing diabetes. This showed that while many of the patients had both cardiac (vagal) and peripheral (sympathetic) autonomic impairment, some had peripheral impairment with normal cardiac function, suggesting that vagal involvement is not always the earliest feature (9). Discrepancies in the literature may be related to the sensitivity of the methods used for the detection of abnormality. For example, reduced peripheral sympathetic vasoconstrictor responses have been found to be more sensitive than postural hypotension in detecting sympathetic impairment in patients with diabetes (9).

The results of the present study confirm that diabetic autonomic neuropathy is not confined to the lower limbs but also occurs in the upper limbs. The absence, in the latter, of a clinical syndrome comparable to that of foot ulceration may result from the absence of other contributory factors, such as dependency and musculoskeletal abnormalities.

At diagnosis, five patients were found to have microvascular complications (retinopathy), and four had clinical evidence of neuropathy. There was no relationship between the presence of retinopathy and the presence or absence of autonomic neuropathy. All those who had clinical evidence of somatic neuropathy had evidence of autonomic impairment.

Testing revealed that many more patients newly diagnosed with type II diabetes had evidence of sympathetic impairment than might have been expected from the clinical evidence of somatic neuropathy. Furthermore, these patients did not exhibit abnormal cardiac autonomic function tests when compared with age-matched control subjects. Thus, it would seem that neither somatic neuropathy nor cardiac function are sufficiently accurate markers for autonomic neuropathy in the lower limbs of diabetic patients. Therefore, it may be important to directly assess autonomic function in the lower limbs of these patients in view of the known association with development of foot ulceration (6–8).

The time relationship between this early laboratory detection of autonomic impairment in the lower limbs and subsequent development of clinical signs and symptoms is, as yet, unknown. Reassessment of the patients' autonomic status is required after a period of good glycemic control, since this, in itself, may promote an improvement in autonomic function (25). Further studies are in progress to follow any progression to the stage of clinical impairment of function.

In conclusion, peripheral vascular measurements in the digits appear to be a sensitive method of detecting early autonomic impairment in diabetic patients before there is clinical or cardiac evidence of diminished function.

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