Short report

Quantitative sweat test in diabetics with neuropathic foot lesions

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SUMMARY The volume of sweat produced by axon reflex stimulation using acetylcholine was measured in one foot each of 35 control subjects and 52 feet of 37 diabetic patients (28 with neuropathic ulceration, 11 with Charcot arthropathy, nine with somatic neuropathy but no foot lesion and four with no evidence of somatic neuropathy). In controls, the volume of sweat was greater in males than females. A flare response was seen in 94% of control feet. In diabetics, the volume of sweat was within the control range in 17 feet, increased in one, reduced in seven, and absent in 27. Sweating was absent in 75% of feet with a neuropathic ulcer; a flare response was absent in 86% of them. Sweating was only absent in 36% of feet with Charcot arthropathy and was increased in one, whereas the flare response was absent in all. Autonomic cardiovascular reflexes were more frequently abnormal than the sweat test; sweating was absent in only one patient with normal cardiovascular reflexes.

In recent years measurement of cardiovascular reflexes has added much to our knowledge of the frequency and severity of autonomic neuropathy in diabetics.¹ Defects have been found to be more severe in the presence of somatic neuropathy² and in those with foot ulceration.³⁻⁵ Fewer measurements have been made of autonomic function in the limbs largely because of the greater technical complexity of obtaining quantitative data.

Alteration of sweating in diabetics with autonomic neuropathy was noted as early as 1893 by Pryce.⁶ Rundles⁷ stressed that anhidrosis was common in the lower limbs. Absent thermal sweating⁸ and abnormalities of galvanic skin resistance have been taken to indicate defective sudomotor function.⁹ The incidence of defective sweating is greater when neuropathic ulcers are present.³ Methods for more direct quantitation of the sweat output have been described recently. Kennedy *et al*¹⁰ demonstrated in diabetics a reduction of sweat output and the number of active

sweat glands in response to local electrophoresis of pilocarpine. They¹¹ found that the defect correlated better with loss of pain appreciation which, like sweating, is a function dependent on small nerve fibres, than large fibre function such as vibration perception and motor nerve conduction velocity.

Low *et al*¹² have described a quantitative method of measuring sweat output stimulated via an axon reflex in response to electrophoresis of acetylcholine into nearby skin. They found reduced or absent sweating in patients with peripheral neuropathy due to a variety of causes. We have used this technique in a series of diabetic patients with neuropathic ulcers of the feet and/or Charcot arthropathy to provide further information about the state of the autonomic nervous system in these conditions.

Patients and methods

Control measurements were made on one foot each of 35 volunteers from the hospital staff or in patients with no obvious neurological disease. All had normal appreciation of pin prick and vibration sensation, and ankle tendon reflexes were present. Twenty-three were males aged 26-75 years (mean 44 SD=13.8); 12 were females aged 20-53 years (mean 36 SD=12.6).

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volume when skin temperature was 30–31°C. Electrophoresis of normal saline did not stimulate sweating.

Following electrophoresis of acetylcholine a flare response occurred around the test area in 33 of 35 control subjects.

Diabetic subjects

Sweating was absent in 27 of the 52 feet tested, reduced in seven, within the control range in 17 and increased in one. The distribution in the different groups is shown in the fig and table. A flare response was absent in a high proportion of subjects in each of the diabetic groups (table).

Symmetrical results were obtained in 13 of the 15 patients in whom both feet were examined. In the other two, both of whom had bilateral ulcers, sweating was absent on one side and normal on the other.

In the ulcer group, both sweating and flare were absent in a high proportion, whereas in those with arthropathy flare was absent in all, but sweating only in one third (table).

In two patients with arthropathy sweat volume was at or above the upper limit of the control range. One patient with arthropathy gave an interesting history of excessive sweating of her feet several years previously, at the time she was developing arthropathy. For a few years prior to the sweat test she had had dry feet, even in hot weather; no axon reflex sweating could be induced.

Four patients in the ulcer group and six patients with arthropathy but no control subjects, had a resting foot skin temperature of 33°C or above, despite the absence of overt sepsis in any of the feet. The high foot temperature is a likely consequence of vasomotor denervation, but sweating was normal or increased in six.

Measurement of autonomic cardiovascular reflexes are available for comparison with the sweat test in 36 feet from 24 subjects. One or both cardiovascular reflexes were abnormal for 30 of them. Sweating was normal in seven of these and abnormal in 23. Where cardiovascular reflexes were normal, sweating was also normal in five feet and absent in only one. Thus, cardiovascular reflexes were more frequently abnormal than sweating.

Table Percentage of control subjects and diabetic patient with absent sweating or flare response

	n	Sweat absent	Flare absent
Control	23	0%	6%
No ulcer or arthropathy	13	15%	77%
Ulcer group	28	75%	86%
Arthropathy group	11	36%	100%

Discussion

The volume of sweat produced by axon reflex stimulation under standard conditions gives a good indication of the state of sudomotor innervation in the limb tested. The test has been shown to be highly reproducible in the same individual. Absent sweating is an indication of peripheral denervation. Denervated sweat glands do not respond to direct stimulation with acetylcholine,^{13 14} although in the test used here stimulation is via an axon reflex which obviously requires the integrity of sudomotor nerve fibres.

This study, showing a marked impairment of sweat production in response to reflex stimulation by acetylcholine in the great majority of patients with diabetic peripheral neuropathy, confirms the frequency of impairment of peripheral autonomic function in this condition. Of greater interest was the finding that one patient with severe arthropathy had an abnormally high sweat output and another produced a volume near the upper limit of the control range. These findings are particularly notable since it has been suggested that vasomotor denervation, resulting in arteriovenous shunting and increased blood flow through the foot, may be of aetiological importance in the development of arthropathy.¹⁵ It would be of interest to determine whether there is a dissociation of vasomotor and sudomotor function in these subjects. It is a recognised, but poorly documented, clinical observation that some diabetics have increased spontaneous sweating in their feet at some stage in their disease, as indeed did one of our patients and our observations provide quantitative confirmation of this phenomenon. They are in conformity with the observation of Ozeran *et al.*,⁹ who, on the basis of galvanic skin resistance measurements in the feet, demonstrated that both hyper- and hypoactivity of the autonomic system could occur in diabetics. It is of interest to note that two patients in the diabetic group, one with demonstrable somatic neuropathy, had a sweat output at the extreme upper end of the control range, suggesting that the phenomenon of autonomic hyperactivity may be more common than is generally realised, and that it may even be one of the earliest signs of neuropathy.

The cause of the phenomenon is not clear. Kennedy *et al.*¹⁶ have shown, in mice, that partial denervation is associated with extensive collateral sprouting of surviving autonomic nerves, resulting in each fibre innervating up to five times as many sweat glands as normal. Such a phenomenon occurring in the early stages of diabetic neuropathy could result in an increase in volume of sweat secretion via the axon reflex.

The flare response was first shown by Lewis¹⁷ to be an axon reflex and is thought to involve unmyelinated

afferent, probably nociceptive, nerve terminals.¹⁸ Such terminals are likely to be stimulated by electrophoresed acetylcholine and it is probable that the same nerves were involved in the present study as in the classical flare response to noxious stimulation and intradermal histamine. The high incidence of absent flare response in diabetics is not surprising in view of the predominant involvement of small nerve fibres in many patients with diabetic neuropathy.^{19 20}

The role of disturbed autonomic function as one important factor in the genesis of foot complications of diabetes has been stressed in recent years.²¹ Lack of sweating has been thought to contribute to the development of neuropathic ulcers and the incidence of this finding was high in the present series, as has been found by others.^{3 22} The absence of a flare response in all feet with arthropathy underlines the importance of degeneration of unmyelinated nociceptive afferent nerve fibres in the genesis of this condition.

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