PERIPHERAL VASCULAR AND SWEAT-GLAND REFLEXES IN DIABETIC NEUROPATHY

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(Received 6 March 1973)

SUMMARY

1. In two groups of diabetic patients, one with and one without signs of peripheral neuropathy, reflex short vasoconstrictor responses to such stimuli as a cough, a sharp inspiration or sudden noise were recorded from a finger and both big toes by volume plethysmography. Simultaneous electrodermal responses to the same stimuli were recorded from a hand and a foot. Vasodilator responses to body warming were also recorded.

2. Significant impairment of these vasomotor reflexes in diabetic patients with neuropathy indicates that the sympathetic vasomotor system can be involved in diabetic peripheral neuropathy.

3. Loss of the reflex electrodermal responses is also evidence of impairment of another sympathetic function in such patients.

4. Because stimuli vary in their effectiveness in causing responses in both groups of subjects, it is suggested that changes of central nervous conductivity also occur in diabetes.

Key words: vasoconstrictions, vasoconstrictor reflexes, electrodermal responses, diabetics, diabetic neuropathy, sympathetic.

It is known from previous studies that impaired function of the sympathetic nervous system in diabetic patients alters the responses of the skin to warming or cooling of the body (Martin, 1953; Barany & Cooper, 1956; Odell, Roth & Keating, 1955; Moorhouse, Carter & Doupe, 1966). Further, Sharpey Schafer & Taylor (1960) showed that diabetic patients with severe peripheral neuropathy frequently showed loss of baroreceptor reflexes in response to tilting or Valsalva's manoeuvre. These changes were attributed to changes in the fibres of the afferent baroreceptor reflex arc.

In the present study we have examined rapid vasoconstrictor and electrodermal reflexes.

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mediated by the sympathetic nervous system in patients with diabetes mellitus. The aim of the study was to gain further information on the level within the nervous system at which damage may occur in diabetic patients.

METHODS

Patients

The patients were out-patients attending the Diabetic Clinics of the Royal Free Hospital and of St Mary’s Hospital, Paddington, and in-patients of the Seaman’s Hospital and Greenwich Hospital. Of a total of twenty-eight patients, fourteen had clinical signs of neuropathy and fourteen formed the control group without neuropathy. The age distributions were: neuropathic group, 41–78, mean 58·0 years; control group, 42–70, mean 60·8 years. The clinical evidence of peripheral neuropathy in this series of cases was absence of at least three of the following: quadriceps or Achilles tendon reflex, perception of heat and cold, light touch, pin-prick and vibration. Other evidence in some of the fourteen subjects included postural dizziness or fainting (3 out of 14), weakness (1 out of 14), spontaneous limb pains (4 out of 14), paraesthesiae (2 out of 14), numbness (6 out of 14) and foot ulcers (3 out of 14). The mildest case had diminished touch, temperature and pin-prick sensation with loss of one Achilles tendon reflex; the most severe had complete loss of sensory responses and muscle jerks coupled with spontaneous pains and paraesthesiae and numbness in both legs.

All the subjects had volunteered for the studies, the nature and purpose of which were explained to each patient in seeking their co-operation. Out-patients came to the laboratory for investigations, a portable recording apparatus was taken to in-patients in hospital.

Responses studied

Three groups of responses were studied. The first were rapid vasoconstriction reflexes (VCR), which can be observed in the hands and toes and have a latent period of 0·1–0·2 s and a duration of 5–20 s. They are provoked by sudden psychological alarm-producing stimuli, such as a sudden loud noise, bright light, a sharp pain, or the threat of one (Hallion & Conte, 1894), or the disturbance of somebody walking into a room. VCR may also be stimulated by coughing, by a quick deep inspiration and by other physiological stimuli. All these VCR are mediated by the sympathetic nervous system (Bolton, Carmichael & Stürup, 1936).

Secondly, the reactivity of peripheral blood vessels has also been recorded as the slow dilatation in response to body warming and constriction in response to body cooling (Pickering, 1932); these slow reactions are also mediated by the sympathetic nervous system (Lewis & Pickering, 1931). The stimuli eliciting VCR also provoke other changes in the periphery. Vigoroux (1879) first demonstrated in normal subjects that there are differences of potential between different areas of skin and that these potential differences may vary with emotional stimuli. Faré (1888) found that the electrical resistance of the skin varies with emotional status. Goadby & Goadby (1936) showed that sympathectomy abolishes these electrical phenomena in the periphery. These constitute the third group of responses studied, and have been called the electrodermal response (EDR; Wang, 1964). The voltage changes of the electrodermal responses (EDR) indicate activity only of sweat glands (Lader & Montague, 1962).

VCR and EDR were elicited by a cough, a sharp inspiration, a sudden loud noise, or by stroking the subject’s forehead or face gently. An ice bag or a warm flannel placed on the arm or
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forehead elicited the same acute VCR as stroking the skin. Other stimuli, such as someone walking into the room or extraneous noises, also produced VCR and EDR and were recorded as responses to 'external stimuli'. Slow reflex vasodilator responses to body warming were stimulated either by applying hot-water bottles to the abdomen and then covering the subject with two blankets, or by placing a large electric radiant heat cradle over the naked trunk.

Methods

Out-patients were examined lying on a couch in a comfortably warm room. Volume changes in the left middle finger were recorded from a thin brass plethysmograph cup sealed on to the base of the finger by adhesive strapping. The volume changes from the two big toes were recorded from perspex plethysmograph cups which were made airtight over the toes with adhesive plaster or grease bandages. Alternatively the seal was made by the use of a thin rubber membrane with a small hole in the centre. This was fixed across the open end of the plethysmograph cup which was pushed down to bring the toe through the hole; the sleeve thus gripped the base of the toe making a quick and effective airtight joint while leaving the toe free inside the plethysmograph cup. Volume changes were transmitted by air conduction through polythene tubes to Grass PT3 low-pressure volume transducers and recorded by a Grass six-channel ink-writing polygraph. The sensitivity of the recorders was adjusted so that the normal pulsations of the digits gave a pen excursion of about 5 mm. At this sensitivity, calibration showed that a 5 mm excursion indicated a change of volume of about 0.01 ml. The quick volume changes of the VCR of the digits in response to sensory stimuli were of the order of 0.2-1.2% of the enclosed volume of the digit. Simultaneous voltage changes of the EDR were recorded in other channels of the polygraph from silver electrodes which were smeared with Cambridge electrode jelly and then fastened on to the dorsum and palm of the left hand, and the dorsum and sole of the left foot. When recording from patients in the wards a two-channel Devices polygraph was used with switches allowing simultaneous recordings from one plethysmograph cup and one EDR.

RESULTS

Figs. 1 and 2 show examples of VCR and EDR in the two groups of patients. Vasodilatation in the finger is shown by a decrease in digit volume and pulse amplitude. Similar changes are seen in the big toes after a slightly longer latency. The EDR also occurs in the hand before the foot. The duration of VCR varies with the amplitude of the response, returning to the baseline in 20-120 s. In the non-neuropathic subject VCR varies not only between individuals but also in the same subject. There is some positive correlation between the size of the response and the intensity of the stimulus, e.g. the violence of a cough or the loudness of a noise. Subjects vary considerably in their sensitivity and some stimuli are more predictably effective than others. Table 1 shows the number of subjects in each group who responded to the various stimulations and to body warming. The most certain stimulus, i.e. the one with least failures, was a quick deep inspiration: the least certain was stimulating the skin by a light stroke or the application of ice. Confirmed neuropathy in the legs is accompanied by increased incidence of failure of response to any stimulus and it is notable that this failure was seen not only in the toes but also sometimes in the fingers. The EDR also fail more often when neuropathy is present.

A possible cause of failure of the brief VCR would be rigidity of the small vessels making
FIG. 1. Polygraph recordings of vasoconstrictor (VCR) and electrodermal (EDR) responses in a diabetic patient aged 42 years without clinical symptoms or signs of peripheral neuropathy. Tracings from the top are: volume changes of the left middle finger, the left hallux, and the right hallux, and voltage changes across skin of the left hand, and the left foot. The vertical lines show the times of (A) cough, (B) quick inspiration; these caused a temporary shift of the volume baseline. Note the positive VCR and EDR in both limbs and the longer latency of the responses in the foot. Time marks are 10 s. The decrease of volume of the digit is shown by a downward movement of pen; amplitude of recording of digital pulsation is adjusted as described in the text (under "Methods"). Calibration bars for EDR = 1 mV.

them mechanically unable to respond to the nerve volleys. This was tested by body warming. The consequent vasodilation shows either as an increase in pulse amplitude alone or as an increase in digit volume as well. A tiny leak in the air transmission line can mask a slow change in digit volume while leaving the quicker pulsatile changes unaltered: particular care was taken to identify and eliminate such false responses. Apparent increases in digit volume can be caused by external warming of the plethysmograph cups or transmission lines: warming of the air in the cup can also be caused by the digits becoming warmer through vasodilation. Because
FIG. 2. Polygraph recordings of vasoconstrictor (VCR) and electrodermal (EDR) responses in a diabetic patient aged 51 years with clinical evidence of neuropathy in the legs. Tracings from the top are as described in Fig. 1. The vertical lines show times of (A) and (B) coughs, and (C) sharp inspiration. Volume recordings show interference by spontaneous jerkings of legs. Time marks are 10 s. Note the presence of VCR in the finger, but the absence in toes, with EDR present in both hand and foot. The clinical signs of neuropathy in this patient were diminution of temperature, touch and pin-prick perception in both legs and absent sense of vibration in the left leg. EDR calibration bars = 1 mV.

Table 1 summarizes the occurrence of responses of fingers and toes in the control and neuropathic subjects. The two groups show distinct differences in their failure rates. The latter were calculated from the values in Table 1 for 'all brief responses', expressing the total number of tests (n) minus the number of positive responses as a percentage of the total number of tests; for hallux the values for right and left were summed before calculation. Similar calculations were made of the failure rate to body warming. In the non-neuropathic group the failure rates were: for VCR in finger 7%, in hallux 23%; for EDR in hand 9%, in foot 9%; absence of vasodilation to body warming in finger 10%, in hallux, 47%. In the neuropathic group the
Table 1. Summary of occurrence of responses in all subjects tested. Columns marked +, show the number of patients giving positive responses. Columns marked n, show the number of patients tested. VCR were recorded from the left middle finger and both big toes; EDR from the left hand and left foot. Responses to heating the body were recorded as the increase in volume pulsation accompanying vasodilation.

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<td>Cough</td>
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<td>Quick inspiration</td>
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<td>All brief responses</td>
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<td>Body warming</td>
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failures were VCR 10% and 52%; EDR 18% and 32%; vasodilation 36% and 82% respectively. Significance of the difference in the number of positive responses in the two groups was tested by the chi-square test. There were significantly more toe VCR in the diabetic patients without clinical signs of neuropathy in the legs than there were in those with this complication ($P<0.05$); this difference was shown also in the fingers in the two groups. The incidence of toe VCR was not significantly different ($P<0.01$), but the incidence of finger VCR was significantly different between the groups ($P>0.05$). In respect to EDR, there was no difference in the two groups in the hand responses ($P>0.05$), but there was a strongly significant difference in the reactions in the feet ($P<0.01$). There was a significant difference in vasodilation in response to body warming between the two groups ($P<0.05$). These results indicate that both VCR and EDR are significantly more likely to be absent in the toes of diabetics who have clinical signs of peripheral neuropathy in their legs than of diabetics without this complication.

**DISCUSSION**

The evidence presented here shows that certain transient reflexes, i.e. vasoconstrictor and electrodermal responses, which are mediated by the sympathetic outflow, tend to be absent in the feet of diabetic patients with clinical evidence of peripheral neuropathy. These losses are significant in comparison with the group of diabetics without neuropathy. The reflexes may be absent occasionally in the hands of patients who have signs of neuropathy only in the feet, or in both hands and feet of patients who had no clinical signs of neuropathy. In all subjects the various stimuli used to elicit the reflexes were not equally effective, and the EDR was generally more easily obtained than the VCR.

These findings cause one to question whether the loss of nerve function in patients with diabetic neuropathy is necessarily wholly in the peripheral efferent pathway, or whether there is also alteration on the afferent side or in the central pathways of the reflex. Sharpey Schafer & Taylor (1960) considered that the baroreceptor reflexes were lost on the afferent side, but gave no evidence for this opinion. If the loss of these acute vasoconstrictor reflexes is on the sensory side then many afferent nervous pathways to the vasomotor centre would have to be affected, e.g. from the eye, the ear, the skin, the chest wall and from higher cortical areas. Failure of sensory input is the least likely of the possibilities. The significantly less frequent VCR in the toes of neuropathic diabetics could be partly due to rigidity of the vessels. Neuropathy does correlate with failure of vessels to dilate on general body warming. However, failure of VCR was found when peripheral arteries were easily palpable and pulses were good and responded to body warming.

There is another possibility, that of changes in the central pathways, which should be considered. Even when there are no clinical signs of neuropathy the effectiveness of sensory stimuli varies. Table 1 shows that the most effective stimuli are those which will activate a wide sensory area. It also shows that even these stimuli are less frequently effective when neuropathy is present. Alteration of the preganglionic neuron in the spinal cord would be another adequate explanation, since stronger sensory stimuli could activate more synaptic junctions on the cell through more interneuronal pathways. The relative ineffectiveness of the different stimuli to cause toe responses does not forecast the proportion of failures in the fingers, nor vice versa; also, a stimulus may evoke a response only occasionally, or one sort of stimulus may consistently fail whereas another succeeds. Such patterns of behaviour would be
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readily explained by variations of central activity altering neuron responsiveness to various afferent volleys. The increased failure rate associated with clinical neuropathy is coupled with the finding that some stimuli are more certain to cause responses than others. This could be explained by an additional depression of central conductivity, rather than a common peripheral fibre degeneration which would be expected to affect the incidence of responses to all stimuli. It is notable that Garland (1955) also postulated changes in the spinal cord in diabetic neuropathy.

The dissociation of the EDR from VCR, both of which are mediated by sympathetic pathways, is of interest. This dissociation, i.e. one reflex present and the other absent, may be found in normal subjects (Prout, 1967) or after neuro-effector blockade (Lader & Montague, 1962). The voltage and the resistance changes of the EDR can also be dissociated experimentally in normal individuals (Goadby & Goadby, 1936). In our non-neuropathic cases the following number of dissociations were found: in the hands, +VCR and -EDR once; -VCR and +EDR three times; in the feet, +VCR and -EDR once; -VCR and +EDR seventeen times. In the absence of signs of peripheral nerve degeneration it appears that in both hands and feet the pathway for the EDR is more easily activated than is the path for the VCR. When neuropathy is present the EDR failure rate is increased, but less so than for the VCR of the toe. The present findings confirm the independence of the two sympathetic reflex responses in the two groups of elderly patients. If the differential effectiveness is not fully explained by central pathway differences the neuropathic process must affect the peripheral vasoconstrictor fibres more than the sudomotor fibres. Attempts to test directly the excitability of vasoconstrictor and sudomotor fibres by stimulating them in the forearm of normal subjects were unsuccessful because of the excessive movement and pain.

ACKNOWLEDGMENTS

This investigation was supported by a grant from the British Diabetic Association to H.K.G. We are grateful to Dr C. A. Young of St Mary’s Hospital, Paddington, Dr A. G. Beckett of The Royal Free Hospital, Gray’s Inn Road, and the Physicians of the Seaman’s Hospital and of Greenwich Hospital, Greenwich, for permission to test their patients. Mr Melvyn Adams gave expert technical assistance at all times.

REFERENCES


