Journal of Neurology, Neurosurgery, and Psychiatry 1987;**50**:1671–1673

Short report

The relationship between peripheral nerve resistance to ischaemia and diabetic control

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SUMMARY The cause of the abnormal resistance to ischaemia of peripheral nerve function in diabetes is unknown. Median nerve function was more resistant to ischaemia in diabetic patients than in control subjects. In diabetic patients the degree of resistance to ischaemia correlated closely with HbA1c but not with the coincident blood glucose level, the duration of diabetes, the vibration perception threshold at the thumb or the initial median nerve action potential amplitude. Thus in diabetes the resistance of peripheral nerve function to ischaemia is dependent on medium term metabolic control and is not directly related to the presence or absence of neuropathy.

Peripheral nerves continue to function longer after the onset of ischaemia in diabetic patients than in control subjects.[1-3] The cause of this abnormal "resistance" to ischaemia in diabetes is unknown. It occurs, in the absence of clinical neuropathy, soon after the onset of diabetes and is normalised by good glycaemic control.[4] This phenomenon also occurs in uraemia,[5,6] chronic liver disease[7,8] and hypercalcaemia[9] suggesting a metabolic cause rather than hyperglycaemia alone. The aim of this study was to examine the relationship of the resistance to ischaemia of peripheral nerve function in diabetes to short and medium term blood glucose control as well as to the duration of diabetes and to the presence or absence of clinical evidence of neuropathy, by examining the effect of forearm ischaemia on median nerve action potential amplitude in diabetic patients and control subjects.

Patients and methods

Thirty four diabetic patients (23M, 11F; aged 20–67 years) were selected from the Diabetic Clinic for the study which was approved by the Hospital Ethics Committee. There were 28 insulin dependent and six non-insulin dependent diabetic patients. Initially a neurological examination was performed. Vibration perception threshold was measured at the right thumb (average of three readings) using a biothesiometer (Biomedical Instruments, Newbury, Ohio). Venous blood was taken from each subject for measurement of whole blood glucose level using a glucose analyser (Yellow Springs Instruments, Yellow Springs, Ohio, USA) and HbA1c level measured by an iso-electric focusing method.[10] Peak-to-peak median mixed nerve action potential amplitude (MNAP) (averaged over five responses) was measured by surface electrodes at the elbow 1·5 cm apart, in response to supramaximal stimulation at the right wrist with square wave pulses of 0·1 ms duration at 1 per second using a Medelec MS92a EMG system (Medelec Ltd, Old Woking, Surrey). A sphygmomanometer cuff was then inflated around the upper arm to 80 mm Hg above systolic pressure for 20 minutes and the measurements repeated. Twenty two non-diabetic control subjects (14M, 8F; aged 19–52) were also studied. All subjects tolerated 20 minutes forearm ischaemia without adverse reaction.

Statistical analysis

Median mixed nerve action potential amplitudes after ischaemia are expressed as a percentage of their initial value. Vibration perception threshold is expressed in arbitrary units. Results are expressed as median (range) and comparisons of initial MNAP and vibration perception threshold were made using the Mann–Whitney test and correlations with the Spearman rank correlation coefficient (rs).

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Received 13 March 1987 and in revised form 24 June 1987.
Accepted 26 June 1987

Table *HbA1c, vibration perception threshold (VPT) and median mixed nerve action potentials (MNAP) before and after 20 minutes forearm ischaemia in control subjects and diabetic patients. Group 1: no clinical or neurophysiological evidence of neuropathy. Group 2: no clinical evidence of neuropathy but subnormal initial MNAP. Group 3: clinical neuropathy*

	n	*HbA1c (%)*	*VPT*	*Initial MNAP (μV)*	*% MNAP after ischaemia*
Diabetics					
group 1	11	8·7 (6·0–11·3)	4·0 (3·7–6·0)	38·7 (21·1–66·8)	21·3 (0–68·5)
group 2	9	10·2 (9·1–10·7)	4·3 (3·3–8·0)	16·4 (12·5–19·5)	47·6 (18·8–88·5)
group 3	14	10·8 (7·8–14·4)	7·0 (5·0–10·0)	8·9 (4·7–25·8)	70·3 (22·5–118)
all diabetics	34	10·1 (6·0–14·4)	5 (3·3–10)*	16·1 (4·7–66·8)†	46·1 (0–118)
Controls	22	—	3·9 (2·3–8)	24·8 (14·1–57·0)	0 (0–24·7)

*p < 0·05; †p < 0·01 vs controls.

Results

Fourteen diabetic patients (group 1) had no neuropathy detected clinically and had an initial MNAP within our normal range for control subjects (16·5–60 μV). Six diabetic patients (group 2) had no clinical evidence of neuropathy but had an initial MNAP below the normal range. Fourteen diabetic patients (group 3) had clinical evidence of neuropathy: seven had neuropathic symptoms such as pain and parathesiae and seven were asymptomatic but had absent ankle jerks. One diabetic patient with absent ankle jerks (M, aged 58) had normal MNAP (25·8 μV). One normal subject (M, aged 27) was found to have high MNAP remaining after ischaemia (24·8%) and a high HbA1c of 7·4% (normal range 5·5–7·2%). A glucose tolerance test showed impaired glucose tolerance. Four months later a repeat glucose tolerance test showed frank diabetes. His results are not included in these data.

The initial MNAP, vibration perception threshold, HbA1c and percentage MNAP remaining after ischaemia in diabetic patients and control subjects are shown in the table. Vibration perception threshold was higher ($p < 0·05$), and MNAP lower ($p < 0·01$), in diabetic patients than control subjects. Among diabetic patients there was a negative correlation between initial MNAP and vibration perception threshold ($rs = -0·52$, $p < 0·01$). Median nerve function was more resistant to ischaemia in diabetic patients than in control subjects (fig). This appeared to be dependent on medium term metabolic control; there was a strong correlation between percentage median nerve action potential remaining after ischaemia and HbA1c level ($rs = 0·80$, $p < 0·0001$), but there was no significant correlation with coincident blood glucose level ($rs = 0·34$), the duration of diabetes ($rs = 0·19$), the initial MNAP ($rs = 0·48$) or vibration perception threshold ($rs = -0·11$).

Discussion

The results of this study suggest that in diabetes the phenomenon of resistance to ischaemia of peripheral nerve function, as judged by mixed median nerve action potential amplitude, is related to medium term blood glucose control. Action potential amplitude and vibration perception threshold, like many tests of peripheral nerve function, are relatively crude measures of neuropathy. However, taken with the clinical findings, these results strongly suggest that the resistance to ischaemia of peripheral nerve function in diabetes is not directly related to the degree of neuropathy.

The cause of the resistance of peripheral nerve function to ischaemia in diabetes is unknown. Our results would suggest that this phenomenon is not related to the permanent structural changes that

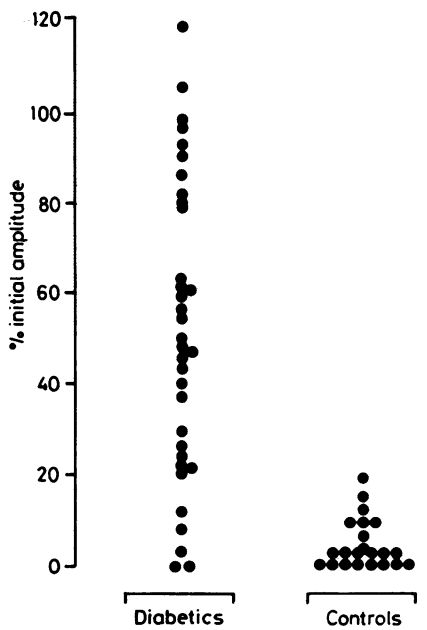

Fig *Percentage median nerve action potentials remaining after 20 minutes forearm ischaemia in diabetic patients and control subjects.*

occur in diabetic neuropathy, such as axonal loss and small vessel occlusion.[11] The strong correlation between the resistance of median nerve function to ischaemia and HbA1c level suggests that the intraneural changes responsible develop over approximately the same time course as the glycosylation of haemoglobin, that is, about 6 to 8 weeks.[12]

Several metabolic abnormalities are known to occur in diabetic nerves which might be the cause of the resistance to ischaemia, such as accumulation of glucose, sorbitol and fructose.[11] These might represent increased energy substrate stores enabling the nerve to continue functioning longer after the onset of ischaemia. It has also been reported that nerves of diabetic animals can maintain a higher level of anaerobic metabolism for a longer time than normal nerves.[13] The resistance phenomenon has been reproduced in rats fed a diet enriched with galactose, which accumulate high intraneural levels of galactitol (a polyol with similar properties to sorbitol) whilst maintaining normal glucose levels.[14] However, Jaramillo *et al* reported that the resistance to ischaemia of the tail nerves of streptozotocin-diabetic rats was unaltered by aldose reductase inhibition,[15] which has been shown to restore nerve sorbitol, fructose and myo-inositol levels towards normal,[16] and was reproduced in control rats by oral glucose loading. They suggested that the resistance of peripheral nerve function to ischaemia in diabetic rats is due to increased glucose concentrations rather than abnormal polyol concentrations in the nerve. However, the resistance phenomenon cannot be reproduced in normal human subjects by glucose loading[4] and we have shown it does not correlate with prevailing blood glucose levels and since in vivo tissue glucose concentrations normally reflect plasma glucose levels[17 18] it seems unlikely that the resistance to ischaemia of peripheral nerve function in diabetic patients is solely due to increased intraneural glucose concentrations. Low *et al* reported that the resistance phenomenon could be reproduced in rats maintained under hypoxic conditions[19] and suggested this may be due to reduced energy requirements and increased efficiency of anaerobic glycolysis secondary to hypoxia. As the nerves of human diabetic subjects have been shown to be hypoxic[20] these metabolic changes may have a role in the aetiology of resistance to ischaemic conduction block in diabetes.

We thank Mrs KM Ely and Mrs ME Smith for typing the manuscript.

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