Short report

Resistance to ischaemic conduction failure in chronic hypoxaemia and diabetes

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SUMMARY  Median nerve function was studied in twelve diabetic subjects, six subjects with chronic hypoxaemia and ten control subjects. Resistance to ischaemic conduction failure (RICF), a characteristic electrophysiological feature of diabetic neuropathy, was assessed by measuring the decline in median nerve action potential amplitude at minute intervals for up to 20 minutes while the arm was rendered ischaemic. Initial nerve conduction velocity and action potential amplitude was similar in all three groups. Following the onset of ischaemia the time to a 50% reduction in action potential amplitude was prolonged in both diabetic subjects and hypoxaemic subjects compared with controls. After 20 minutes of ischaemia no control subject had persisting nerve function, while function remained in 5 (80%) of hypoxaemic subjects and 10 (83%) of diabetic subjects. The time to a 50% reduction in action potential amplitude during ischaemia correlated with the blood oxygen saturation among the hypoxic subjects and haemoglobin A1c among diabetic subjects. These results are consistent with the hypothesis that hypoxia has a role in the pathogenesis of resistance to ischaemic conduction failure in diabetes.

Diabetic nerves continue to function longer after the onset of ischaemia than normal nerves.1 This resistance to ischaemic conduction failure (RICF) precedes the onset of clinical neuropathy and is normalised by good metabolic control.2 RICF also occurs in uraemia, chronic liver disease and hypercalcaemia. The mechanism of RICF is unclear but increased anaerobic metabolism secondary to endoneurial hypoxia has been proposed as being of primary importance.3 Endoneurial oxygen tension is reduced in both human diabetic subjects4 and rats with experimental diabetes.5 Alternatively, the increased levels of sorbitol, glucose and fructose which occur in diabetic nerves6 may act as increased energy substrates. If the metabolic adaptation to hypoxia is the cause of RICF other situations which cause endoneurial hypoxia alone might also cause RICF. The aim of this study was to compare peripheral nerve function in diabetic patients without symptomatic neuropathy, chronically hypoxaemic non-diabetic subjects and control subjects. Patients with hypoxaemia due to cyanotic heart disease were studied rather than patients with hypoxaemia due to chronic airways disease because the aetiology of airways disease is often due to smoking and hence likely to be associated with co-existent vascular disease.

Materials and methods

The subjects studied were: A) six non-diabetic subjects with chronic hypoxaemia (four had Eisenmenger Complex secondary to a ventricular septal defect and two pulmonary hypertension), B) twelve diabetic subjects (three non-insulin dependent, nine insulin treated) who had been treated for at least one year but did not exhibit clinical signs or symptoms of diabetic neuropathy and C) ten age matched control subjects. The protocol was approved by the Leeds Western District Research Ethics Committee.

Median nerve conduction studies were performed in the right forearm with the subject supine. Skin temperature was measured using a Comark 1624 electronic thermometer (Comark Ltd, Littlehampton, Sussex, England) and was maintained at 32-34°C in all subjects. Both stimulation and recording were carried out using a Medelec MS92a neurophysiology unit (Medelec Ltd, Old Woking, Surrey, England). The nerve was stimulated at the wrist supramaximally with square wave pulses of 0·1 ms duration. The recording electrode was placed over the median nerve in the antecubital fossa and conduction velocity was calculated from the distance between the electrodes. The mean of three
recordings was calculated. To render the arm ischaemic a sphygmomanometer cuff was inflated to 200 mmHg around the upper arm. Recordings were made at one minute intervals for 20 minutes or until no electrical activity was discernable. Venous blood was taken for estimation of blood glucose and haemoglobin Alc (HbAlc). An arterialized venous sample was taken from the left arm into a heparinised syringe for estimation of oxygen saturation. Plasma glucose was measured using a glucose analyser (Yellow Springs Instruments, Yellow Springs, Ohio). HbAlc was measured by iso-electric focusing. Blood oxygen saturation was measured with a Corning 178 blood gas analyser (Corning Ltd, Halstead, Essex, England). Results are expressed as mean, SEM. Statistical analysis was carried out using the Fisher exact probability test, the Mann-Whitney U test and the Spearman rank correlation coefficient.

Results

The results are shown in the table. Initial median nerve conduction velocities and amplitudes were similar in all three groups. The time taken to a 50% fall in amplitude during ischaemia (T50) was greater in diabetic subjects (p < 0.01) and hypoxic subjects (p < 0.001) compared with controls. In no control subject was there persisting median nerve conduction after 20 minutes of ischaemia, compared with 5 (80%) hypoxic subjects (p < 0.002) and 10 (83%) of the diabetic subjects (p < 0.001) who continued to have median nerve conduction. The magnitude of persisting activity (expressed as a percentage of initial amplitude) was greater in diabetic subjects (42.6%) than hypoxic subjects (16%) (p < 0.05). There was a negative correlation in hypoxic subjects between blood oxygen saturation and T50 (rs = -0.64). There was a correlation in diabetic subjects between HbAlc and T50 (rs = 0.77).

Table Median nerve function in hypoxic, control and diabetic subjects.

<table>
<thead>
<tr>
<th></th>
<th>Hypoxic Subjects</th>
<th>Diabetic Subjects</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Sex</td>
<td>4F : 2M</td>
<td>4F : 8M</td>
<td>7F : 3M</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.5, (6-0)</td>
<td>42.6, (3-0)</td>
<td>50-9, (4-7)</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>4-0, (0-3)</td>
<td>8-8, (1-0)</td>
<td>4-4, (0-6)</td>
</tr>
<tr>
<td>O2 saturation (%)</td>
<td>66-8, (3-4)</td>
<td></td>
<td>91-2, (0-68)</td>
</tr>
<tr>
<td>Initial median nerve conduction velocity (m/s)</td>
<td>64-4, (3-1)</td>
<td>60-5, (1-8)</td>
<td>63-9, (1-8)</td>
</tr>
<tr>
<td>Initial median nerve action potential amplitude (uV)</td>
<td>18-3, (3-7)</td>
<td>21-5, (4-0)</td>
<td>21-3, (2-9)</td>
</tr>
<tr>
<td>Time to a 50% fall in amplitude (mins)</td>
<td>16-3, (0-67)**</td>
<td>17-3, (1-1)*</td>
<td>11-4, (0-5)</td>
</tr>
<tr>
<td>Number of subjects with persisting nerve function after 20 mins ischaemia</td>
<td>5**</td>
<td>10**</td>
<td>0</td>
</tr>
<tr>
<td>Amplitude (% initial value) after 20 mins ischaemia</td>
<td>16-0, (4-1)*</td>
<td>42-6, (7-0)**</td>
<td>0</td>
</tr>
</tbody>
</table>

Results expressed as mean, (SEM).

Discussion

The results of this study demonstrate that RICF, comparable to that found in diabetes mellitus, occurs in chronic hypoxaemia in humans. Since this work was completed, Masson et al have reported that RICF occurs in hypoxic subjects with chronic obstructive airways disease. However, most of these patients have vascular disease and the observed neurophysiological changes may have been due to nerve ischaemia as well as hypoxia.

Human and experimental diabetes cause many metabolic abnormalities that have been implicated in the pathogenesis of diabetic neuropathy such as sorbitol accumulation, reduced nerve free myoinositol and reduced nerve Na-K-ATPase activity. However, it is unlikely that these metabolic abnormalities are present in subjects with cyanotic heart disease. Thus RICF in diabetes is probably not due solely to the fact that increased nerve polyol and sugar concentrations act as increased energy stores. There is evidence that hypoxia has a role in the pathogenesis of RICF in animal models. Rats maintained in a hypoxic environment develop RICF in the absence of hyperglycaemia, nerve sorbitol accumulation or myoinositol reduction, and RICF in diabetic rats is partly prevented by maintaining them in an oxygen enriched environment. RICF may be secondary to metabolic adaptations to ischaemia within the nerves which enable them to function at a lower metabolic cost. It is known that diabetic nerves depend more on anaerobic pathways than normal nerves. The cause of RICF in uraemic and hypercalcaemia is also unknown. It is unlikely that it be secondary to the presence of increased energy substrates in the nerve but, like diabetic nerves, may be due to metabolic adaptations to hypoxia.

The correlation between blood oxygen saturation and RICF may indicate that RICF reflects the degree of endoneurial hypoxia; in hypoxaemic subjects being proportionate to the severity of the cardiovascular defect. In the diabetic subjects this may be related to reduced nerve blood flow and reduced tissue oxygen delivery due to abnormalities such as endoneurial oedema and increased inter-capillary distances.

In all three groups of subjects initial median nerve conduction velocity and amplitude, the conventional parameters of nerve function, were similar. Both diabetic and hypoxaemic subjects clearly demonstrated RICF. This may indicate that RICF is a more sensitive test of nerve function than slowing of nerve conduction velocity. However, neither is specific for diabetes and the relationship between RICF and nerve conduction slowing and the development of clinical neuropathy is not clear.

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References


