Delayed recovery of nerve conduction and vibratory sensibility after ischaemic block in patients with diabetes mellitus

P Lindström, U Lindblom, T Brismar

Abstract

Objectives—To determine if the recovery of nerve function after ischaemic block is impaired in patients with diabetes mellitus relative to healthy controls.

Methods—Median nerve impulse conduction and vibratory thresholds in the same innervation territory were studied in patients with diabetes mellitus (n = 16) and age-matched controls (n = 10) during and after 30 minutes of cuffing of the forearm. Results—Cuffing caused a 50% reduction of the compound nerve action potential (CNAP) after 21.9 (SEM 1.6) minutes in patients with diabetes mellitus and after 10.6 (0.7) minutes in controls. After release of the cuff the half life for CNAP recovery was 5.13 (0.45) minutes in patients with diabetes mellitus and < 1 minute in controls. At seven minutes after release of the cuff CNAP was fully restored in the controls whereas in patients with diabetes mellitus CNAP had only reached 75.1 (4.1)% of its original amplitude. After onset of ischaemia it took 14.6 (1.9) minutes in patients with diabetes mellitus before the vibratory threshold was doubled, whereas this took 5.8 (0.8) minutes in controls. After release of the cuff half time for recovery of vibratory threshold was 8.8 (1.0) minutes in patients with diabetes mellitus and 2.6 (0.3) minutes in controls. Ten minutes after the cuff was released the threshold was still raised (2.0 (0.3)-fold) in the diabetes mellitus group, whereas it was normalised in controls. Among patients with diabetes mellitus the impaired recovery correlated with older age, higher HbA1c, and signs of neuropathy, but not with blood glucose.

Conclusion—After ischaemia there is a delayed recovery of nerve conduction and the vibratory sensibility in patients with diabetes mellitus. Impaired recovery after ischaemic insults may contribute to the high frequency of entrapment neuropathy in patients with diabetes mellitus.

Keywords: diabetes mellitus; neuropathy; ischaemia

Peripheral nerves of patients with diabetes mellitus exhibit a paradoxical contrast between their resistance to ischaemia and their susceptibility to ischaemic lesions as suggested by the higher incidence of entrapment neuropathies in diabetic patients than in the general population. The mechanism underlying the resistance to acute ischaemic conduction block in the diabetic nerve remains unclear. The phenomenon may be attenuated by improved glycaemic control and correlates with HbA1c rather than with the plasma glucose concentration indicating a metabolic abnormality related to medium term hyperglycaemia.

The postischaemic recovery phase has been less studied. High glucose concentration induces resistance to ischaemia and depresses the postischaemic recovery in isolated normal nerves from the rat. In a previous study in isolated diabetic mammalian nerve we have shown that anoxic conduction block is followed by a delayed and incomplete recovery of the nerve potential. It was suggested that a delayed postischaemic recovery (DPIR) may contribute to a greater susceptibility to chronic ischaemia or hypoxia which—if present also in diabetic patients—may explain a higher incidence of entrapment neuropathies in relation to diabetes. The purpose of the present study was therefore to analyse the time course and recovery of the ischaemic conduction block and change in vibratory threshold in patients with diabetes mellitus with and without evidence of polyneuropathy.

Subjects and methods

SUBJECTS

Sixteen patients with diabetes mellitus and 10 age-matched healthy controls were investigated. The mean age of the patients with diabetes mellitus was 52.5 (4.1) years and it was 52.5 (5.5) years in the controls. The table gives the clinical and laboratory data of the patients. The patients were classified as two groups: with (A) and without (B) signs of neuropathy (see below). In group A two patients were insulin dependent (type 1) and six were insulin treated non-insulin dependent (type 2). In group B five were of type 1 and three were of type 2. Patients in group A were older than those in group B (P < 0.01), and had a longer duration of diabetes (P < 0.05), and higher HbA1c (P < 0.001). Plasma glucose and years of insulin treatment were not significantly different between the two groups.

CLINICAL AND LABORATORY EXAMINATION

A clinical examination was made according to a fixed protocol testing muscle power, tendon reflexes, sensation of touch, pin prick, tempera-
Delayed recovery of nerve conduction and laboratory findings

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (y)</th>
<th>Duration of diabetes (y)</th>
<th>Insulin treatment (y)</th>
<th>HbA1c (%)</th>
<th>Plasma glucose (mmol/l)</th>
<th>Clinical sign (score 0-24)</th>
<th>Vibrametry (score 0-4)</th>
<th>Temperature sensibility (score 0-4)</th>
<th>Electro-neurography (score 0-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With neuropathy (n=8)</td>
<td>62.9 (2.4)</td>
<td>17.5 (1.8)</td>
<td>8.3 (2.3)</td>
<td>7.7 (0.3)</td>
<td>9.9 (1.1)</td>
<td>6.1 (1.5)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
<td>2.0 (0.4)</td>
</tr>
<tr>
<td>Without neuropathy (n=8)</td>
<td>42.1 (6.0)</td>
<td>10.9 (2.3)</td>
<td>10.0 (2.5)</td>
<td>5.7 (0.3)</td>
<td>8.4 (1.1)</td>
<td>0</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.006</td>
<td>0.039</td>
<td>0.61</td>
<td>0.0002</td>
<td>0.34</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>All patients</td>
<td>52.5 (4.1)</td>
<td>14.2 (1.6)</td>
<td>9.1 (1.6)</td>
<td>6.7 (0.3)</td>
<td>9.1 (0.8)</td>
<td>6.1 (1.5)</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
<td>2.0 (0.4)</td>
</tr>
</tbody>
</table>

VIBRAMETRY
Vibratory thresholds were determined with a hand held vibrometer in which an accelerometer recorded the movement of the stimulator head (Somedic AB, Sweden). The technique has been described in detail including the normal values for each age group. Measurements were made on the dorsum of the second metacarpal bone, on the proximal part of the tibia, and dorsomedially on the first metatarsal bone. Three measurements were made bilaterally on each location and the respective mean values were taken as the thresholds. A graded classification of the vibratory thresholds was made using a scale from 0-3 representing impairment in increasing severity.

ISCHAEMIC TESTS
The action of ischaemia and subsequent recovery were studied in diabetic patients and controls. The median nerve was made ischaemic by a sphygmomanometer cuff positioned below the elbow and inflated to a pressure of 60-80 mm Hg above the systolic blood pressure. The nerve was stimulated every second minute supramaximally with surface electrodes at the wrist distally to the cuff and the amplitude of the compound (motor and sensory) nerve action potential (CNAP) was recorded with surface electrodes over the median nerve at the elbow proximally to the cuff. After 30 minutes the cuff was removed and the recordings were continued during 10 minutes of reperfusion. At a later occasion the effect of ischaemia was tested in a similar way measuring vibratory thresholds from the dorsum of the second metacarpal bone. After 30 minutes of ischaemia the cuff was removed and the recovery of the thresholds was studied during 12 minutes. Informed consent was obtained from each patient. The study was approved by the ethics committee of the Karlinska Hospital.

STATISTICAL ANALYSIS
Statistical analysis was performed using Student’s t test or analysis of variance (ANOVA). Results are expressed as mean (SEM).

Results
Nerve conduction and vibratory thresholds were studied in the forearm during and after a period of ischaemia in patients with diabetes mellitus and age matched controls. Concentrations of HbA1c ranged from 4.7 to 8.7%. The table gives the clinical, sensorimetric, and neurographic scores of the diabetic patients. The neurological examination following a fixed protocol disclosed abnormalities indicating the
existence of neuropathy in eight (group A) of the 16 patients. Six patients showed an impaired thermal sensibility. Five patients had pathologically raised vibratory thresholds. In seven patients the electroneurography score was raised because of a slowing in sensory and motor conduction velocity. An increasing discomfort in the forearm was experienced by patients and controls toward the end of the ischaemic phase. Paraesthesiae in the hand experienced during the first minutes of the postischaemic period were more pronounced among controls than in the patients. This has been described earlier.23 Figure 1 shows the time course of the ischaemic conduction block and the recovery in the median nerve in diabetic patients and controls. The cuff was placed around the forearm, the nerve was stimulated supramaximally at the wrist, and the nerve signal was recorded at the elbow. A 50% reduction occurred after 21.9 (1.6) minutes in the diabetic patients and after 10.6 (0.7) minutes in the controls (P < 0.0001). At the end of the ischaemic period 30.2 (2.9)% of the CNAP remained in the diabetic patients, whereas the block was virtually complete already after 20 minutes in the controls. After release of the cuff the recovery of CNAP was slower in the patients than in the control group. The half time of CNAP recovery was 5.13 (0.45) minutes in the diabetic group, whereas in the control group the half time was < one minute, as CNAP had increased from 0% to 60.9 (3.8)% already at the first test one minute after release of the cuff. At seven minutes after release of the cuff CNAP was fully restored in the control group whereas in the diabetic group it had only reached 75.1 (4.1)% of its original amplitude (P < 0.0001). A similar difference between diabetic patients and controls was found in the action of ischaemia on the vibratory thresholds. Figures 2A and B show the time course of this effect in each patient. Figure 2A shows a large individual variability in the effect of ischaemia among patients with diabetes mellitus. After the onset of ischaemia it took 14.6 (1.9) minutes in the diabetic patients before the threshold was doubled, and 4.9 (0.7) minutes in controls (P < 0.0001). After 30 minutes the threshold was raised 7.9 (1.8)-fold in the diabetic patients and 28.0 (5.0)-fold in the controls (P < 0.0001). The recovery of the vibration perception (reduction of vibratory threshold) was delayed in diabetic patients compared with controls. It took 7.9 (0.87) minutes before the vibratory threshold was reduced to half its value in the diabetic group, whereas in the controls this took < two minutes as the threshold was already reduced to less than half (41 (7%)) at the first test two minutes after release of the cuff. Ten minutes after the cuff was released the threshold was still significantly raised (2.02 (0.29) times, P = 0.0002) compared with the level before initiation of ischaemia in the diabetic group, whereas it was normalised (1.06 (0.09), NS) in controls. The possible correlation between diabetic neuropathy and an abnormal reaction to ischaemia was studied. Comparison (Student’s t test) of eight patients with signs of neuropathy and those without such signs showed that the half time of CNAP reduction during ischaemia was 24.1 (1.4) and 19.6 (2.6) minutes, respectively (NS) and the half time of CNAP recovery was 5.25 (0.45) and 5.0 (0.93) minutes respectively (NS). The time for a doubling in vibratory threshold was 18.5 (2.5) in patients with neuropathy and 10.6 (2.2) in patients without neuropathy (P = 0.032), and the half time for recovery of vibratory threshold was 11.0 (0.78) and 7.6 (0.78) minutes respectively (P = 0.0084). This showed that both the abnormal resistance to ischaemia and the impaired recovery were significantly more pronounced in diabetic patients with peripheral neuropathy. Analysis of variance (ANOVA) showed a correlation between the time for doubling in vibratory threshold and old age (P = 0.002) and high HbA1c (P = 0.026), and a correlation between the half time for recovery of vibratory threshold and old age (P = 0.011), years of insulin treatment (P = 0.048), and high HbA1c (P = 0.010). There was, however, no correlation between resistance to ischaemia or half times for recovery with blood glucose.

Figure 2 Vibratory thresholds measured from the dorsum of the second metacarpal bone during and after 30 minutes of ischaemia in (A) 16 patients with diabetes mellitus and (B) 10 healthy controls.
Delayed recovery of nerve conduction

Discussion

The present study shows that the recovery after ischaemic conduction block is delayed in diabetic patients relative to healthy controls. This effect was noted both as a delay in the recovery of CNAP in the median nerve and as a slower normalisation of the sensory threshold to vibratory stimulation. The onset of conduction block was also delayed in diabetic patients compared with controls, which is in agreement with previous findings. The presence of delayed postischaemic recovery has not been described previously in diabetic patients. Nerves isolated from diabetic (BB-Wistar) rats similarly showed both a delay in the onset of hypoxic conduction block and an impaired recovery. The cause is uncertain and there is evidence in support of several alternative mechanisms or different components in the mechanism:

(1) Diabetic nerve may be adapted to chronic hypoxia by modification of cytoplasmic metabolic enzymes or their regulation so that anerobic glycolysis is able to maintain energy metabolite levels for longer periods of acute hypoxia. This hypothesis is supported by the finding that resistance to acute ischaemic conduction block in non-diabetic subjects is strongly influenced by endoneurial oxygenation. Vasodilators increasing nerve blood flow have also been shown to attenuate the development of resistance to acute ischaemic conduction block in streptozotocin induced diabetic rats.

(2) In diabetic rats resistance to acute ischaemic conduction block is a consequence of increased energy sources for anerobic glycolysis in the nerve and can be reversed in about two hours by restoration of normoglycaemia using insulin. Incubation of isolated normal rat nerves for three hours in high (25 mM) glucose similarly induces resistance to acute ischaemic conduction block and a delayed recovery of the nerve potential after the hypoxic period. However, in diabetic patients the degree of resistance correlated closely with HbA1c but not with coinced blood glucose concentration.

(3) Some studies have indicated that treatment with an aldose reductase inhibitor (ARI) prevents resistance to acute ischaemic conduction block in diabetic rats and humans implying a role for hyperglycaemia induced exaggerated flux through the polyol pathway. Accumulation of the polyol pathway products sorbitol and fructose in diabetic nerve was attenuated by insulin treatment but there was no normalisation of nerve myoinositol as has been found in a previous study. Treatment of diabetic rats with myoinositol did not prevent the development of resistance to acute ischaemic conduction block.

(4) Resistance to acute ischaemic conduction block is due to a reduced energy requirement in diabetic nerve because of a diminished Na,K-ATPase activity in normal rat nerves with ouabain resulted in resistance and also in delayed postischaemic recovery. In the present patients there was a high correlation between the presence of neuropathy and medium term poor metabolic control (high HbA1c), which is in agreement with previous studies (see Hyllienmark et al). Furthermore, the degree of resistance to acute ischaemic conduction block and delayed postischaemic recovery were highly correlated, both when measured with vibrametry and CNAP. Resistance to acute ischaemic conduction block and delayed postischaemic recovery also showed a high correlation with presence of neuropathy and high HbA1c when measured with vibrametry. Both resistance to acute ischaemic conduction block and delayed postischaemic recovery measured from the effect on CNAP was not significantly different between the two groups of diabetic patients, although there was a tendency towards an increased resistance in the patients with neuropathy. However, neither resistance to acute ischaemic conduction block nor delayed postischaemic recovery was correlated with the blood glucose concentration measured in connection with the ischaemic test. This is in agreement with the findings of Price et al that acute ischaemic conduction block is correlated with HbA1c rather than with blood glucose in patients with diabetes mellitus.

In conclusion, this study has shown that after ischaemia there is a delayed recovery of nerve conduction and vibratory sensitivity in patients with diabetes mellitus. These findings are in agreement with a previous study on nerves isolated from diabetic rats. Impaired recovery after ischaemic insults may contribute to the high frequency of entrapment neuropathy in patients with diabetes mellitus.

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12 Goldberg JM, Lindblom U. Standardised method of determining vibratory perception thresholds for diagnosis.
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