Refractory period, sensory conduction velocity and visual evoked potentials before and after haemodialysis

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Summary In 18 patients suffering from chronic renal failure (being haemodialysed three times weekly for 22.2±27.9 months), sensory conduction velocity and relative refractory period of the sural nerve were estimated immediately before and after dialysis. Before haemodialysis all but one patient had conduction velocities within the normal range (x ±2 SD), but 50% had prolonged refractory periods. After dialysis the refractory period decreased to become normal in all but one patient. Visual evoked potential latencies showed no systematic alterations. A membrane abnormality due to uraemic poisoning is assumed to cause the reversible prolongation of the refractory period.

Peripheral neuropathy was known to be a rare neurologic disorder in renal failure1-4 before long-term haemodialysis and renal transplantation programmes were developed for the treatment of terminal uraemia.5-8 In the following studies, uraemic neuropathy was found in between 40% and 65% of patients prior to or shortly after starting dialysis,5-10 but declined to 10-20% during chronic haemodialysis11-13 and after successful transplantation.14-15 Despite intensive research the pathogenesis of uraemic neuropathy is still unclear.16-17 and neurophysiological findings seem to correlate poorly with clinical and laboratory data.10 16-19 In evaluating the adequacy of haemodialysis, the reliability of neurophysiological parameters is disputed. Whereas some authors have observed long-term improvement of motor conduction velocity,20 others were unable to find any significant correlation between clinical, laboratory, and neurophysiological data during short and long haemodialysis treatment schedules.21-22

These conflicting findings cannot be explained by the histopathological abnormalities reported in uraemic nerves, which comprise mainly axonal degeneration with secondary demyelination.23 24

A more generalised and reversible impairment of the axon membrane function probably affecting the resting membrane potential,10 17 also is likely to be present. We have investigated the sural nerve in chronically uraemic patients immediately before and after haemodialysis, looking for alterations in the refractory period. In addition pattern-reversal visual potentials were recorded before and after haemodialysis, thus testing optic nerve function which is known to be impaired in primary and secondary demyelinating processes.25 26

Subjects

Patients Eighteen patients suffering from terminal renal failure in a hospital or home dialysis programme for 22.2±27.9 months were studied. They were aged between 19 and 67 years (42.4±13.7), and six were female. The residual creatinine clearance in all cases was below 5 ml/min. Dialysis was performed three times weekly for five to eight hours. Preparations of water soluble vitamins, iron, aluminum hydroxide, vitamin D and antihypertensive agents were prescribed. Neurophysiological investigations included the antidromic sensory conduction velocity and relative refractory period of the sural nerve. Subcutaneous temperature also was measured, and tendon reflexes and vibratory perception were studied one hour before and two hours after haemodialysis the same day. In
two patients a repeated trial of the whole test battery was performed three times at weekly intervals. In these patients visual evoked potentials also were recorded at the same time intervals.

**Control group** Twenty-four healthy probands, matched for age (19-63 years), served as a control group.

**Methods**

**CLINICAL ASSESSMENT, VIBRATION, LABORATORY TESTS**

Before and after dialysis, subjective complaints, tendon reflexes, muscle force, sensation and vibratory perception measurement in the upper and lower extremities using a Bio-Thesiometer were recorded.

Laboratory serum tests such as electrolytes, creatinine and urea were performed immediately before and after haemodialysis. These tests could not be performed on the same day as the neurophysiological tests and were therefore performed before and after dialysis one week later corresponding to the times of neurophysiological investigation (table 1).

**CONDUCTION STUDIES, REFRACTORY PERIOD, TEMPERATURE**

Conduction velocity (Cv)

Cv was measured in the sural nerve by delivering supramaximal rectangular shocks percutaneously to the nerve trunk at the dorsal aspect of the calf below the gastrocnemius muscle. Compound action potentials were picked up by a thin steel needle inserted subcutaneously just distal to the lateral malleolus near the nerve branches with a second needle 3 cm away as reference (fig 1). Latency measurement was done to the first positive peak of the action potential; the duration of the action potential was measured from the first positive peak to the end of the negative main phase; and the amplitude was measured peak to peak.

Refractory period (Rp)

The procedure to determine the relative refractory period of the sural nerve was similar to that described for the ulnar nerve in our earlier papers. Supramaximal double shocks of variable intervals were applied to the nerve percutaneously adjacent to the Achilles tendon (fig 1). For each interval the conduction time of the "test" potential (fig 1a) was compared to that of an unconditioned potential by switching off the conditioning stimulus S1 (fig 1b) and superimposing both sweeps (fig 1c). The shortest interval at which the second ("test") potential was conducted at "resting" velocity was labelled as "relative refractory period" (Rp).

**Temperature**

Because of the high temperature dependency of the refractory period, temperature was measured subcutaneously near the stimulation point by a digital thermometer type BAT-8 (Bailey Instr) with a sc probe MT-3S (0°C). The mean temperatures were about 30°C in controls and in the postdialytic group. Therefore we decided to standardise all figures given in this paper to 30°C using a conversion factor of 0.5 °C/s for the refractory period and 1.1 m/s/°C for the conduction velocity.

**VISUAL EVOKED POTENTIALS (VEP)**

Visual evoked potentials were recorded 5 cm above theinion elicited by checkerboard pattern-reversal for each eye separately.

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**Table 1** Tendon reflexes and vibratory perception scores (mean±1 SD) in 18 uraemic patients before and after haemodialysis compared with control subjects (n=24; age-matched)

<table>
<thead>
<tr>
<th>Group</th>
<th>Tendon reflexes</th>
<th>Vibratory perception</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arms</td>
<td>Legs</td>
</tr>
<tr>
<td>Controls</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before haemodialysis</td>
<td>0</td>
<td>1.28±2.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>After haemodialysis</td>
<td>0</td>
<td>0.94±1.7</td>
</tr>
</tbody>
</table>

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**Fig 1** Determination of the relative refractory period (rp) in the sural nerve. Stimulating surface electrodes in the distal aspect of the gastrocnemius muscle, recording electrodes (steel needles) behind the ankle. (a) Conditioning stimulus S1 and test stimulus S2 each evoke a nerve action potential. (b) Shows an unconditioned test potential (b). 1-3: different double-shock intervals for S1-S2: the successive delay of the conditioned test potential (1. positive peak marked ▲) can be observed.
Results

Clinical assessment  Subjective complaints such as restless legs, cramp, paraesthesia, burning feet and pain, mostly of mild or moderate degree were common (table 2), and did not decrease directly after dialysis. Sensory disturbances and muscle weakness of mild degree were found only in a few patients (table 2) and did not change after dialysis. Tendon reflexes were normal in the upper extremities, but were diminished moderately in the legs and tended to improve after dialysis (table 1; fig 2).

Vibratory perception  In controls vibratory perception threshold was slightly higher in the lower extremities than in the upper ones. In uraemic patients, however, it was strikingly elevated in the legs (table 1; fig 2). After dialysis there was only a slight tendency to improvement which did not reach statistical significance.

Laboratory findings  Within the three days interval before haemodialysis there was a slight decrease of serum sodium from 139±3-4 mmol/l immediately after to 237±2-8 and 139±4-3 mmol/l before the next haemodialysis (table 3, fig 3).

Table 3  Laboratory findings of 18 uraemic patients before and after haemodialysis compared with the control data (n=24)

<table>
<thead>
<tr>
<th>Group</th>
<th>$\text{Na}^+$ (mmol/l)</th>
<th>$\text{K}^+$ (mmol/l)</th>
<th>Creatinine (mg%)</th>
<th>Urea (mg%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>140±0±2-6</td>
<td>4.2±0-4</td>
<td>1.05±0.2</td>
<td>34±1.8±2-1</td>
</tr>
<tr>
<td>Before haemodialysis</td>
<td>138±4±4.4</td>
<td>5.2±0.9</td>
<td>10±3.1</td>
<td>128±45±0</td>
</tr>
<tr>
<td></td>
<td>${\text{NS}}$</td>
<td>${\text{NS}}$</td>
<td>${\text{NS}}$</td>
<td>${\text{NS}}$</td>
</tr>
<tr>
<td>After haemodialysis</td>
<td>139±6±3-4</td>
<td>4.3±0.7</td>
<td>6±1±7</td>
<td>6±28±0</td>
</tr>
</tbody>
</table>

This probably was due to the predialysis water excess. Potassium, creatinine, and urea increased to high concentrations before haemodialysis indicating azotaemia, but decreased after dialysis (p<0.0001) (table 3, fig 3).

Table 2  Clinical data of 18 patients suffering from terminal renal failure. Figures indicate the number of patients in each group

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restless lags</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Cramps</td>
<td>6</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Burning feet</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sensory disturbances</td>
<td>4</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

For statistical evaluation the Student $t$-test and regression analysis were used.
Table 4  Sensory conduction velocity (cond vel), amplitude and duration of the nerve action potential and relative refractory period (refr period) of the sural nerve in 18 uraemic patients before and after haemodialysis compared to the control group (n=24). Subcutaneous temperature at the side of stimulation in the last column. Values of cond vel and refr period are standardised to 30°C. All figures are mean values±1 SD

<table>
<thead>
<tr>
<th>Group</th>
<th>Sensory conduction velocity (ms)</th>
<th>Action potential amplitude (μV)</th>
<th>Action potential duration (ms)</th>
<th>Refractory period (ms)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>44.3±4.9</td>
<td>10.25±4.4</td>
<td>1.50±0.25</td>
<td>6.99±1.16</td>
<td>29.75±2.1</td>
</tr>
<tr>
<td>Before haemodialysis</td>
<td>39.6±3.9</td>
<td>4.7±2.4</td>
<td>1.67±0.38</td>
<td>11.83±6.56</td>
<td>29.23±1.9</td>
</tr>
<tr>
<td>After haemodialysis</td>
<td>42.0±5.0</td>
<td>5.4±2.6</td>
<td>1.47±0.23</td>
<td>5.86±1.92</td>
<td>30.27±2.2</td>
</tr>
</tbody>
</table>

NEUROPHYSIOLOGICAL FINDINGS

Conduction velocity, amplitude and duration of nerve action potential (nap)

Sensory conduction velocities of the sural nerve standardised to 30°C were slowed by about 10% compared with the normal group (p<0.002) while the amplitude of the compound nerve action potential was considerably reduced (p<0.0002), although its duration was not altered (table 4, fig 4). After dialysis conduction velocity (p<0.006) and duration (p<0.008) but not potential amplitude (p<0.04), tended to recover towards normal.

Refractory period, temperature

The relative refractory period of the sural nerve, standardised to 30°C, was prolonged in 50% of the patients (fig 4). After dialysis, however, all values decreased remarkably (p<0.0002) (table 4, fig 4).

The temperature measured subcutaneously near the stimulating point showed a slight increase of about 1°C on the average after dialysis (table 4). This might be due to the long-lasting haemodialysis procedure during which patients were at rest for some hours. To rule out temperature influences all conduction velocity and refractory period values before and after dialysis were standardised to 30°C.

Visual evoked potentials (VEP)

The P2-latencies, amplitudes and shapes of pattern-reversal VEPs in two chronically uraemic patients were within the normal range and did not alter systematically before and after haemodialysis when tested three times in each patient (table 5).

Fig 4  Histograms of the nerve action potential parameters, conduction velocities and refractory periods of the three groups (controls, patients before and after dialysis). Conduction velocity and refractory period were standardised to 30°C. Horizontal bars and dashed lines mean values ±2 SD.
Table 5 Pre and postdialysis values of three different investigations of two uraemic patients (A: LB, 38 yr, female; chronic glomerulonephritis, haemodialysis three times weekly, 6.5 h each, for 40 months; B: SO, 28 yr, male; chronic glomerulonephritis; haemodialysis three times weekly 5 hours each for 114 months). The left figure in each column is the value before dialysis, the right figure is after dialysis. Cr: creatinine. CV 30°: Conduction velocity and refractory period of the sural nerve standardised to 30°C. T: subcutaneous temperature near the nerve. VEP: P2-latency of the pattern-reversal-evoked-visual potential of the left (LE) and the right (RE) eye.

<table>
<thead>
<tr>
<th>Investigation no</th>
<th>Na⁺ (mmol/l)</th>
<th>K⁺ (mmol/l)</th>
<th>Cr (mg%)</th>
<th>Urea (mg%)</th>
<th>Cr 30° (m/s)</th>
<th>rp 30° (ms)</th>
<th>T (°C)</th>
<th>VEP (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case A 1</td>
<td>145/140</td>
<td>5.5/3.7</td>
<td>12.0/4.3</td>
<td>189/58</td>
<td>38.1/40.9</td>
<td>6.9/5.5</td>
<td>30/63/4</td>
<td>104/100</td>
</tr>
<tr>
<td>2</td>
<td>140/144</td>
<td>5.3/3.9</td>
<td>10.1/4.2</td>
<td>144/43</td>
<td>37.1/36.7</td>
<td>6.6/5.3</td>
<td>31/4/31.0</td>
<td>110/107</td>
</tr>
<tr>
<td>3</td>
<td>141/139</td>
<td>5.5/4.3</td>
<td>11.7/4.4</td>
<td>199/58</td>
<td>40.2/42.3</td>
<td>6.9/4.4</td>
<td>29/0/31.2</td>
<td>109/106</td>
</tr>
<tr>
<td>Case B 1</td>
<td>140/140</td>
<td>6.6/3.7</td>
<td>15.3/5.7</td>
<td>165/49</td>
<td>37.2/37.3</td>
<td>10/1/5.4</td>
<td>31/3/37</td>
<td>108/110</td>
</tr>
<tr>
<td>2</td>
<td>143/142</td>
<td>6.2/3.4</td>
<td>16.5/6.1</td>
<td>186/56</td>
<td>41.3/45</td>
<td>9/7.5/6</td>
<td>30/3/32.8</td>
<td>108/108</td>
</tr>
<tr>
<td>3</td>
<td>140/140</td>
<td>5.8/6.3</td>
<td>14.8/6.3</td>
<td>148/49</td>
<td>41.2/35.2</td>
<td>9/1.5/8</td>
<td>31/3/33.7</td>
<td>110/109</td>
</tr>
</tbody>
</table>

Follow-up investigation

Two uraemic patients were investigated three times each at weekly intervals (table 5). Refractory periods declined rapidly and consistently. On the other hand, the VEPs were normal in latency, amplitude and shape in all investigations, and no systematic alteration of VEPs before and after dialysis could be observed.

Discussion

The relationship between nerve action potential parameters and refractory period is contradictory to the accepted concepts. From our investigations in neuropathies, as well as from experimental studies in animals, it is known that the refractory period is prolonged mainly by demyelinating processes. In contrast, early axonal degenerations diminish the amplitude of the action potential without slowing conduction velocity and prolonging refractory period. However, if secondary segmental demyelination takes place the refractory period is prolonged, followed later on by slowing of conduction velocity. In early primary segmental demyelination the refractory period, and with it the ability for impulse transmission, is impaired due to a diminished safety factor. At this stage, however, conduction velocity may still be normal because only a few internodal segments are involved and saltatory conduction can continue.

The present results do not fit with any of these concepts. The different course of conduction velocity and refractory period during haemodialysis is demonstrated in fig 5 in which pre-dialysis and postdialysis values of each patient are shown. Before dialysis refractory periods were commenced in 50% of cases in contrast to con-duction velocity which was borderline in only one case. After dialysis all refractory periods decreased, and all but one became normal. On the other hand, conduction velocity increased moderately in 13 cases, and decreased or were unchanged in five cases. These findings were supported by the follow-up studies in two patients (fig 6): conduction velocity increased three times, decreased rapidly once and was unchanged twice. The refractory period, however, declined rapidly in all six investigations. Creatinine and urea showed a very similar course indicating the steady state of uraemia in these two patients. Temperature influences were ruled out by standardising the values to 30°C.

Fig 5 Pre- and postdialysis values of conduction velocity and refractory period, standardised to 30°C. Filled circles: predialysis, open circles: postdialysis values. Stippled area: normal range of controls (±2 SD) for refractory period. Vertical lines: 95% area for conduction velocity.
optic nerve lesions, especially in demyelinating processes, showed no alterations indicating uninterrupted impulse conduction in the optic nerves. In contrast, the refractory period clearly decreased in all cases after dialysis, and reproducibly three times in a follow up study of two uremic patients. The underlying cause of the prolonged refractory process probably is of functional origin such as a reversible membrane abnormality due to poisoning by several known and unknown uraemic substances. Because of the close relationship between the refractory period and the membrane repolarisation processes, a decreased resting membrane potential may be one of the main causes for the prolongation of the refractory period. Recently, Nielsen reviewed the biophysical data, including in vivo measurements of muscle membrane potentials, in uraemic patients, and also studies on ouabain-sensitive Na-K-ATPase activity in relation to intracellular Na concentration after renal transplantation. We were able to demonstrate a marked shortening of the refractory period in patients with chronic hypokalaemia, probably as a result of the increased resting membrane potential.

In uraemia the elevated K+-level may cause the prolongation of the refractory period, and we found a positive correlation between the duration of the action potential and of the refractory period to the K+-level (r = -0.44/0.44; p<0.05). Slowing of conduction velocity and the decrease of action potential amplitude correlated poorly with Na+ depletion (r = -0.4; p>0.05). On the other hand the duration of the action potential and of the refractory period correlated at the 1% level with blood urea and creatinine (r = 0.54), which are indicators of the severity of the uraemia. However, these findings do not prove the direct dependence of the refractory period and K+-level in uraemia. No significant correlation was found by regression analysis between the changing refractory period and the decrease of K+ after dialysis (42±20% and 23±14%; r = -0.03). Surprisingly,

Table 6 Statistical correlations (regression analysis) between improvement of neurophysiological parameters after dialysis and some laboratory findings. Figures in brackets indicate the mean ±1 SD of the change after dialysis as a % of the predialysis value; figures in the table represent the correlation factor r

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Na+</th>
<th>K+</th>
<th>Creat.</th>
<th>Urea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduction velocity (7.5±6.3)</td>
<td>-0.03</td>
<td>-0.38</td>
<td>0.09</td>
<td>0.22</td>
</tr>
<tr>
<td>Amplitude (26.0±25.2)</td>
<td>0.28</td>
<td>-0.26</td>
<td>-0.20</td>
<td>-0.25</td>
</tr>
<tr>
<td>Duration (12.0±11.4)</td>
<td>0.21</td>
<td>0.48*</td>
<td>-0.17</td>
<td>-0.07</td>
</tr>
<tr>
<td>Refractory period (42.0±20.0)</td>
<td>-0.01</td>
<td>-0.03</td>
<td>0.28</td>
<td>0.47*</td>
</tr>
</tbody>
</table>

*p < 0.025.
a positive relationship was found between action potential duration and K⁺ (r=0.48; p<0.025), for which we have no interpretation. Whereas no direct correlation between the refractory period and K⁺-levels could be established, remarkably different correlations between refractory period decay and the decrease in creatinine and urea were seen (table 6). Possibly urea represents a group of “uraemic substances” affecting the membrane resting potential more than creatinine.

We conclude that in uraemia there are both moderate secondary lesions of the myelin sheath due to axonal degeneration and a reversible membrane abnormality due to uraemic poisoning which may result in a decreased resting membrane potential. The morphological alterations cause a slight slowing of conduction velocity poorly correlated to clinical and laboratory data. In contrast, the functional membrane disturbance resulting in a prolongation of repolarisation processes is responsible for the extension of the refractory period, and the impairment of repetitive impulse conduction.²⁹ ³⁸-³⁹ While the morphological lesions probably cause the chronic distal symmetrical neuropathy of uraemia (“dying-back-neuropathy”²² ²³), the reversible dysfunction of the membrane may be, however, responsible for subjective complaints such as pain, paraesthesia, restless legs, burning feet, flapping tremor. Moreover, the increase of the vibratory perception threshold also could be explained by this disturbance. Thus, the refractory period represents a useful neurophysiological parameter to study the condition of the axon membrane as well as the effect of haemodialysis on the peripheral nervous system.

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References

8 Tyler HR, Gottlieb AA. Uremic polyneuropathy. Excerpta med. 8th Internat Cong Neurol Proc 1965; 2:129.