ORIGINAL ARTICLE

Cutaneous silent period in the assessment of small nerve fibers in patients on hemodialysis

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ABSTRACT

Aim In hemodialysis patients renal disease may cause an impairment of central and peripheral nervous system. In most cases of the peripheral nervous system polyneuropathy is reported. The aim of this study was to evaluate the function of small A-delta nerve fibres, whose function is often overlooked.

Methods The function of large diameter nerve fibers was performed by standard routine neurophysiological examination. Cutaneous silent period (CSP) was elicited by single electrical stimulations at the tip of digit II by the bipolar electrodes. The superficial electrodes were placed on the muscle belly of m. abductor pollicis brevis. The onset latency (L1) was recorded at the beginning of voluntary muscle activity suppression, the late latency (L2) at the start of new muscle activity. The difference between two latencies indicates the duration of CSP.

Results The study included 38 consecutive patients (male/female – 21/17, median age 56.6±10.9 years) treated with hemodialysis (one month to 30 years) and 35 healthy subjects (male/female 23/17, age 47.4±10.1 years). The results of the conduction study demonstrated a significant prolongation of F-waves of the median and ulnar nerves, decreased motor and sensory velocities of both nerves in patients on hemodialysis (p<0.001). In patients with A-V fistulas a significant prolongation of the onset CSP latency L1 was obtained (p<0.001), whereas duration of CSP was not changed.

Conclusion In hemodialysis patients the significant impairment of small nerve fibers was recorded. The evaluation of small nerve fibers contributes to the assessment of the whole peripheral nerve function.

Key words: uremic polyneuropathy, arteriovenous fistula, EMNG

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INTRODUCTION
Renal diseases cause diverse central nervous system disturbances - uremic encephalopathy, seizures, stroke, movement disorders, sleep alterations and peripheral nervous system involvement (1). Polyneuropathy is a frequent neurological complication in patients with renal failure. It occurs as uremic polyneuropathy (UP), mononeuropathies and monomelic neuropathy due to arteriovenous (A-V) fistulas. Prevalence rates of UP range from 50–80% (1-3). Clinically sensory symptoms often predominate while motor dysfunction usually develops later (4,5). Sensory loss mainly involves large-diameter nerve fibers resulting in paresthesia and occasionally pain and burning feet. Autonomic symptoms are usually subclinical. Few patients develop subacute or chronic motor – predominant neuropathy simulating polyradiculoneuritis Guillain-Barré or chronic inflammatory demyelinating polyneuropathy. In these cases more frequent dialysis or renal transplantation are required (6,7). Hemodialysis and peritoneal dialysis tend to diminish the progression of UP. The pathophysiological mechanism of UP is still unknown. The role of chronic hyperkalemic depolarisation is discussed. The maintenance of a strictly normal serum K⁺ level may be an effective strategy in the treatment of UP (8).

Neurophysiological nerve conduction study provides the function of large-diameter motor and sensory nerve fibers (9). To assess the function of small nerve fibers the routine electromyography is insufficient. Cutaneous silent period (CSP) obtained by nociceptive cutaneous stimulus applied to sensory fibers on a fingertip induces a transient and brief suppression of voluntary muscle activity. The CSP is a result of the activation of small A-delta nerve fibers and is considered as a spinal inhibitory reflex (10,11). The CSP measurement is used in the functional evaluation of different neurological diseases (12-14).

The primary endpoint of our study was to assess the function of small-diameter A-delta nerves fibers in uremic patients with A-V fistulas by using CSP. The secondary endpoint was to compare the sensitivity of large-diameter motor and sensory parameters of the median and ulnar nerves with CSP with the intention to evaluate nerve impairments in hands with A-V fistulas. To our knowledge a study of CSP on hands with A-V fistulas had not been performed previously.

PATIENTS AND METHODS
This study included 38 consecutive patients treated with hemodialysis at the Hemodialysis Department, Clinical Centre of Sarajevo University, Bosnia and Herzegovina (B&H) in the period 05.01.2012-30.12.2013. Neurophysiological evaluation was performed at Neurology Department of Sarajevo. The patients with diabetes, alcoholism, systemic inflammatory, malignant diseases and psychiatric disorders were excluded. The control group consisted of 35 healthy subjects (our co-workers, friends and relatives). Before starting the study the informed consent from testing patients and healthy subjects was obtained. The study has received an approval of the Ethics Committee of the Sarajevo University Clinical Centre.

The neurophysiological examination included the routine nerve conduction study (NCS) and CSP. Using the superficial electrodes (Care Fusion, Middleton, WI, USA) the motor parameters of the peripheral nerves were recorded: distal motor latencies (DML) of the median and ulnar nerves, motor responses (M-waves), F-waves and motor conduction velocities (MCV). The active electrode was placed on the muscle abductor pollicis brevis and the reference electrode over the muscle tendon. Stimulation was applied at the wrist 8 cm from the active electrode. Sensory conduction study of the median and ulnar nerves included sensory conduction velocities (SCV) and amplitudes of sensory nerve action potentials (SNAP). The SNAP were obtained by antidromic nerve stimulation over the skin of the lateral (median nerve) and medial part (ulnar nerve) of the ring finger using standard bipolar electrodes. The distance between the stimulating and the recording electrode was 14 cm. Standard electrophysiological machine settings were used (15).

The CSP was elicited by single electrical stimulations (0.5 ms duration and 80-100 mA intensity, sweeps 250 ms, filters 30 and 10 kH) at the tip of digit II by the bipolar electrodes. The superficial electrodes were placed on the muscle belly of m. abductor pollicis brevis. During near-maximum, an activated APB muscle electrical stimulus was delivered. At least 4 individual responses were superimposed. The onset latency (L1) was recorded at the beginning of voluntary muscle activity suppression and the second - late latency (L2) at the start.
of new muscle activity. The difference between two latencies indicates the duration of CSP.

Routine nerve conduction study and CSP were undertaken using a Medelec Synergy system (Oxford Instruments, High Wycombe, UK).

Parameters are expressed as mean values with standard deviation. Shapiro-Wilk tests of normality was used. Additionally, independent Student’s t-test, Spermann’s correlation coefficient and Mann-Whitney U test were performed. The level of significance was set at p=0.05.

RESULTS

The study enrolled 39 patients on hemodialysis. In only one patient CSP was not elicitable. This patient was excluded and in the further study parameters of 38 patients were evaluated. Out of 38 patients 21 were males and 17 were females. The duration of hemodialysis differs from 1 month to 30 years. The control group included 35 volunteers, 23 males and 12 females. Median age for patients was 56.6 ± 10.9 years and for controls 47.4 ± 10.1 years (Table 1).

<table>
<thead>
<tr>
<th>Table 1. Demographic data of hemodialysis patients and controls</th>
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<tr>
<td><strong>Number of patients</strong></td>
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<tr>
<td>38</td>
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<tr>
<td><strong>Age (median) (years)</strong></td>
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<tr>
<td><strong>Gender (Males/Females)</strong></td>
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<tr>
<td><strong>Duration of hemodialysis (median) (years)</strong></td>
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The results of motor conduction study demonstrated a significant prolongation of F-waves for the median and ulnar nerves as well as a decreased MCV in patients on hemodialysis (p<0.001) (Table 2). There was no statistical difference in DML of both groups.

<table>
<thead>
<tr>
<th>Table 2. Motor conduction of median and ulnar nerve in hemodialysis patients and controls</th>
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<tbody>
<tr>
<td><strong>Median nerve</strong></td>
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<td>(mean ± SD) (ms)</td>
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<tr>
<td><strong>DML</strong></td>
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<tr>
<td>Patients</td>
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<td>Controls</td>
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A significant amplitude decrease and a slowed SCV of the median and the ulnar sensory SNAP—compared to healthy subjects were recorded (p<0.001) (Table 3).

<table>
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<th>Table 3. Sensory conduction of median and ulnar nerve in hemodialysis patients and controls</th>
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<tr>
<td><strong>Median nerve</strong></td>
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<tr>
<td>(mean ± SD) (mV)</td>
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<tr>
<td><strong>Amplitude (mV)</strong></td>
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<td>Patients</td>
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<td>Controls</td>
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<td><strong>p</strong></td>
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SCV, sensory conduction velocities

In patients on hemodialysis and A-V fistulas a significant prolongation of the onset CSP latency L1 was obtained (p<0.001). There was no important difference in the CSP duration of suppression of voluntary muscle activity (Table 4).

<table>
<thead>
<tr>
<th>Table 4. Cutaneous silent period of nervus medianus in hemodialysis patients and controls</th>
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<tr>
<td><strong>CSP L1</strong></td>
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<tr>
<td>(mean ± SD) (ms)</td>
</tr>
<tr>
<td>Patients</td>
</tr>
<tr>
<td>Controls</td>
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<td><strong>p</strong></td>
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CSP, cutaneous silent period; CSP L1, the onset latency;

There was no correlation between either motor or sensory nerve parameters and the onset CSP L1 latencies in the patients group.

The evident prolongation of the onset CSP L1 latency inpatients with A-V fistulas was found (Figure 1).

DISCUSSION

Neurological complications in patients with renal disease are quite common (1-4). The progressive renal failure may lead to the development of neurological disorders. In a few cases ischemic monomelic neuropathy was reported (16). In our patients no acute neuropathies were observed due to A-V fistulas. To rule out the impairment of peripheral nervous system the neurophysiological evaluation plays a very important role. Most of electrophysi-
ological studies are focused on the evaluation of nerves of the lower limbs (4,5,17). The damage is more prominent on the peripheral nerves of lower limbs than on the upper limbs due to the length-dependent factor of the nerves (1,8,11). The evaluation of large-diameter nerve fibers in different neuropathies is well established in routine praxis (8,9,11). The role of thin unmyelinated nerve fibers in most studies is underestimated (3,4,16). The CSP is a simple method and provides a new feasibility in detecting the function of small nerve fibers. Small nerve fibers are very susceptible and often precede the damage of large fibers in patients with metabolic polyneuropathy (17). In this study we intended to assess the impairment of small nerve fibers on the hands with A-V fistulas and their relationship to conventional electromyography. In the previous study the it was described the onset latency L1 of CSP of 66 ms (range 49-73) in females, 69 ms (range 42-79) in males, late latency L2 of 121 ms (range 109-131) in females and 124 ms (range 116-136) in males, where as the duration of suppression was 55.0 ms (range 45-74) in females and 59.0 ms (range 52-67) in males (18). There is a small number of electrophysiological methods which enable the quantitative assessment of these types of nerve fibers (quantitative sensory testing) (19), or analysis of heart rate variability and sudomotor axon reflexes (20). For this purposes a nerve biopsy is rarely performed.

In our study we recruited 38 patients on hemodialysis and 35 healthy subjects. In only one patient CSP was not obtained. In this case DML of the median nerve was very prolonged and sensory parameters were not elicitable. Similar results in a small group of patients with carpal tunnel syndrome were described previously (21). In our patients motor conduction study showed normal DMLs but prolonged F-wave latencies and decreased MCV; sensory conduction revealed significant abnormalities of sensory parameters, amplitude and SCV. Additionally, in the patients with A-F fistulas significantly prolonged onset CSP latencies L1 were recorded. This finding definitely indicates the impairment of small nerve fibers of the median nerves. The delay of the onset CSP latencies L1 cannot be related to the beginning carpal tunnel syndrome because concomitant abnormalities of ulnar sensory parameters were observed. This supports the impairment of small nerve fibers rather than arthritis focal entrapment neuropathy (11,22). An important step in the development of the prolongation of the onset CSP latency L1 may be the ischemic factor due to A-V fistula (22,23). Some authors suggest the occurrence of severe carpal tunnel syndrome with accompanying polyneuropathy in hemodialysis patients (24). In only one of our patients (duration of hemodialysis 19 years) a severe entrapment syndrome with absent motor and sensory parameters including CSP was observed. There is a great likelihood that the small unmyelinated nerve fibers are more sensitive to ischemia than the large myelinated fibers. Most of our patients were complaining of paresthesia and pain. These symptoms correlate with the involvement of small nerve fibers (23). The duration of voluntary muscle activity suppression (CSP) was not changed in the patient group. We assume that the reason for a prolonged onset CSP latency L1 was most probably due to decreased number of small nerve fibers. The reduced number of the small nerve fibers reduced the impulse volley on interneurons in the spinal cord. The deficient afferent impulse volley through the pathway to spinal interneurons has the consequence of a delayed onset CSP L1 latency. Simultaneously, the decreased number of large-diameter A-alpha and A-beta fibers diminish the activity of the interneurons (9,11,17). Our finding demonstrated an early dysfunction of small nerve fibers in patients with A-V fistulas. It seems that vascular ischemic component due to A-V fistulas contributes to the involvement of the thin nerve fibers resulting in abnormalities of CSP (5,8).

In hemodialysis patients the routine electromyography and CSP were recorded. Wite both neurophysiological techniques large and small-diameter nerve fibers were evaluated. Motor and sensory conduction revealed significant changes of motor and sensory parameters of the median and ulnar nerves, except DML. The significantly prolonged CSP latency L1 indicates the impairment of small nerve fibers. It seems that the measurement of small nerve fibers in hemodialysis patient is recommended.

FUNDING

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TRANSPARENCY DECLARATION

Competing interest: none to declare.
REFERENCES