

Altered peripheral nerve function resulting from haemodialysis

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SUMMARY The amplitudes of muscle and nerve action potentials evoked by median nerve stimulation were recorded just before and immediately after haemodialysis. These revealed a growth of action potential amplitude during dialysis. It is suggested that some component of the defective peripheral nerve function that inevitably accompanies uraemia is temporarily improved during dialysis.

The advent of maintenance haemodialysis has brought into prominence the neuropathy associated with renal failure, in which there is axonal degeneration and segmental demyelination (Dayan *et al.*, 1970). However, much of the altered peripheral nerve function in this condition cannot be dependent upon such structural changes: after transplantation, the increase in conduction velocity occurs more rapidly than could be explained by recovery of segmental demyelination (Ibrahim *et al.*, 1974; Nielsen, 1974a,b; Bolton, 1976). The reduction in conduction velocity is more evident in proximal than distal segments in uraemic patients (Nielsen, 1973), in contrast to the findings in demyelinating neuropathies.

While rapid improvement in peripheral nerve function after transplantation is beyond dispute, the precise effect of haemodialysis is still unclear. It may arrest the progressive decrease in conduction velocity which accompanies renal failure (Nielsen, 1974c), yet the neuropathy may develop explosively only when haemodialysis has been started (Tenckhoff *et al.*, 1965). Does a single haemodialysis have any effect on peripheral nerve function? Studies just before and immediately after haemodialysis should answer this question. To date, these have been restricted to clinical observations and conduction velocity estimations where no significant change has been noted (Jebson *et al.*, 1967). We have, therefore, measured the evoked muscle and nerve action potential amplitude from exactly the same sites before and after haemodialysis in uraemic patients to show the effect of a single dialysis.

Methods

Studies were carried out on 10 occasions in six patients whose clinical and dialysis details are shown in Table 1. Patient 1 had a moderately severe sensory-motor peripheral neuropathy principally involving the lower extremities. Patients 2-6 had no clinical evidence of peripheral nerve dysfunction.

The median nerve was stimulated through surface electrodes at the wrist. The cathode was a silver-silver chloride coated disc of 1 cm diameter over the course of the nerve on the volar aspect. The anode was a silver-silver chloride coated strip 5 cm × 2 cm over the dorsal aspect. Supramaximal electric stimuli of 0.2 ms duration were delivered from a Devices digitimer through a gated pulse generator.

Evoked action potential recordings were made in turn from each of three sites (Fig. 1): (1) sensory potentials from the digital nerves of the middle finger (an antidromic impulse) through a pair of Disa Velcron tip surface ring electrodes; (2) potentials of the abductor pollicis brevis muscle recorded between surface disc electrodes of 1 cm diameter, one over the belly of the muscle and the other as a reference electrode at the tip of the thumb; (3) mixed (combined orthodromic sensory and antidromic motor) action potentials recorded from the median nerve at the elbow through Disa subcutaneous recording needle electrodes at the site where the nerve was most accessible, previously located by a searching percutaneous stimulating electrode. The active recording electrode was inserted over the course of the nerve and the reference electrode 1 cm lateral to it.

The evoked action potentials were amplified by a Medelec 2A3 parametric amplifier and displayed on a Tektronix 564B storage oscilloscope, nerve action

Table 1 Details of patients

Patient	Age (yr), sex	Dialysis details	Clinical condition
1	63 M	Ultra flow II dialyser RSP machine 6 h, three times per week	Proliferative GN* (crescent type) Anuric
2	18 M	Ultra flow II dialyser REDY machine 6 h, twice weekly	Membrane-proliferative GN Anuric
3	47 M	Ultra flow II dialyser REDY machine 6 h, twice weekly	Hypertensive renal failure Passing 500 ml urine daily at time of study
4	22 F	Ultra flow II dialyser REDY machine 6 h, once weekly	Chronic GN Still passing 2 l urine at time of study
5	40 M	Ultra flow II dialyser RSP machine 6 h, twice weekly	Membranous GN Passing 1 l urine daily at time of study
6	49 F	Ultra flow II dialyser RSP machine 6 h per week	Malignant hypertension and renal failure Passing 500 ml urine daily at time of study

*Glomerulonephritis.

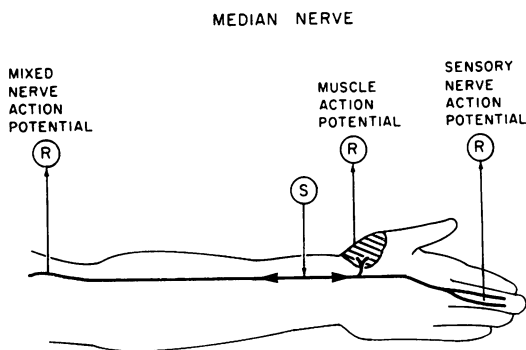


Fig. 1 Stimulating and recording sites (see text).

potentials being first fed through a Disa 14B15 input transformer.

Patients were first studied during the hour before starting dialysis. The exact positions of each of the stimulating and recording sites were marked with indelible pencil and, during the hour after completion of dialysis, the electrodes were reapplied at these sites and the procedure repeated. The ambient temperature was maintained at 20–22°C. The surface temperature at the base of the middle finger was recorded using a thermocouple during the predialysis recording. After dialysis, the limb was either cooled or warmed so that the temperature was the same during the latter recording.

In addition to the study of the responses evoked by supramaximal nerve stimulation, the excitability of the median nerve was compared before and after dialysis by noting the stimulus current required to

evoke a threshold (smallest recognisable) response, 50% of the maximal response, and the maximal response for each of three types of potential. Finally, the motor and sensory conduction velocity was estimated in the forearm segment of the median nerve and terminal latencies noted.

Results

Table 2 shows the increase in evoked action potential generally induced by dialysis. Amplitudes recorded from the same site on different days (patients 2 and 6) were different as neither the recording sites nor the temperature were identical on different days, although these were identical in each study before and after dialysis on the same day.

There were only two exceptions each to this rise in the muscle and sensory nerve recordings. There was growth of the mixed nerve action potential in all cases where a recognisable action potential could be seen before dialysis (eight out of ten occasions). Figure 2 indicates that this increase in mixed nerve action potential is proportionately greater than that of the muscle or sensory nerve action potentials.

Measurement of motor conduction velocity and of sensory velocity (six recordings) showed no significant difference before as compared with after dialysis (Fig. 3). Before dialysis, the mean motor conduction velocity was 45.9 m/s and the sensory was 46.6 m/s. After dialysis, the mean motor velocity was 45.5 m/s and the mean sensory velocity was 47.0 m/s. Motor and sensory terminal latencies were usually reduced after dialysis but these changes were not significantly different. Similarly, the excitability of the median nerve was not affected significantly since the stimulus current required to evoke the different types of action potential was the same before and after dialysis.

Discussion

Peripheral nerve function is defective in most, if not all, patients with chronic renal failure in that conduction velocities are reduced (Preswick and Jeremy, 1964) and segmental demyelination can be seen (Bolton, 1976). Furthermore, improvement in nerve function after transplantation is now well-documented (Ibrahim *et al.*, 1974; Nielsen, 1974a,b; Bolton, 1976). This study shows that haemodialysis also causes improvement, though this is only partial and transient. There are four possible explanations for this. Firstly, the metabolic and electrolyte changes consequent upon dialysis might alter electrical conductance between nerve and recording electrode. However, were this the case, a similar alteration would be expected between a stimulating

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Table 2 *Action potential amplitudes before and after dialysis*

Patient	Pre-dialysis amplitude			Post-dialysis amplitude			Increase in post-dialysis amplitude		
	Mixed nerve action potential μV	Muscle action potential mV	Sensory nerve action potential μV	Mixed nerve action potential μV	Muscle action potential mV	Sensory nerve action potential μV	Mixed nerve action potential μV	Muscle action potential mV	Sensory nerve action potential μV
1	10.5	16.0	26.0	13.0	20.0	37.0	2.5	4.0	11.0
2	15.5	20.0	30.5	27.0	26.5	48.0	11.5	6.5	17.5
	11.0	11.0	18.0	15.0	10.6	20.0	4.0	-0.4	2.0
3	15.5	6.7	48.0	24.5	10.0	49.0	9.0	3.3	1.0
4	10.4	16.0	130.0	13.0	19.5	130.0	2.6	3.5	0.0
	—	8.4	72.0	—	11.8	135.0	—	3.4	73.0
5	—	3.4	66.0	—	4.4	76.0	—	1.0	10.0
	4.0	12.0	38.0	5.2	11.2	57.0	1.2	-0.8	19.0
6	5.0	7.1	52.0	11.7	10.6	46.0	6.7	3.5	-6.0
	10.7	6.5	37.0	17.0	6.8	44.0	6.3	0.3	7.0
Mean	10.3	10.7	51.8	15.8	12.1	64.2	5.5	2.4	12.5
SD	4.2	5.3	32.3	7.1	6.4	38.7	3.6	2.3	19.4
							$t = 4.36$	3.33	2.03
							$df = 7$	9	9
							$P < 0.01$	$P < 0.01$	$P > 0.10$

P=probability of no change in amplitude.

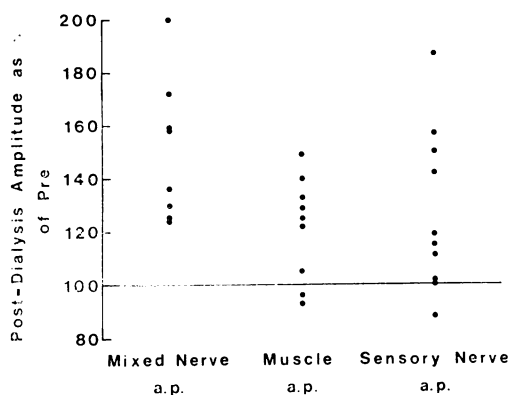


Fig. 2 *Effect of dialysis upon amplitude of evoked action potentials.*

electrode and nerve, leading to a change in excitability. In fact, excitability was not affected by dialysis.

Secondly, the rise in amplitude of the compound action potential after dialysis might be due to changes in conduction velocity leading to better synchronisation. This seems unlikely for the following reasons. No change in conduction velocity occurred in the forearm segment of the median nerve during dialysis. No consistent changes in terminal latency occurred. Dialysis resulted in no significant change in the duration of the action potentials. Finally, where better synchronisation is induced in peripheral nerves by cooling, any increase in action potential amplitude is accompanied by a reduction in conduction velocity and prolongation of terminal latency (Ritchie and Straub, 1956 and own observations). However, after

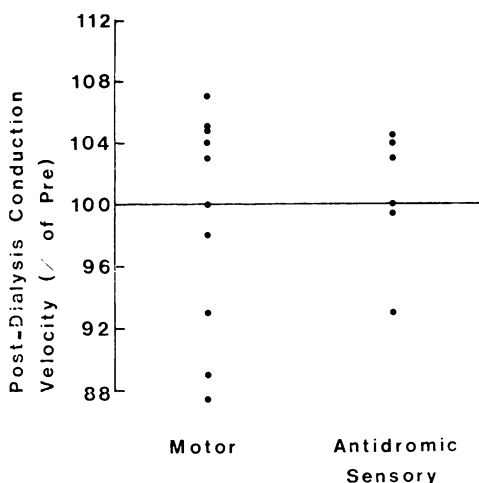


Fig. 3 *Effect of dialysis upon conduction velocity.*

dialysis velocities were not reduced nor were latencies prolonged.

Thirdly, the number of functioning fibres in the median nerve might be increased by dialysis. While function of a proportion of nerve fibres will be permanently depressed by uraemia and a further proportion may be functioning normally, the function in some fibres may be at a critical level whereby the changes in concentration of certain metabolites induced by dialysis might determine their capacity to generate an action potential.

Fourthly, the amplitude of individual muscle and nerve fibre action potentials might increase during dialysis. Since intracellular sodium concentration is in-

creased in uraemia, the resting membrane potential is reduced (Bolt *et al.*, 1963). Hence, if a dialysable humoral factor in uraemic serum is responsible for the toxic impairment of axon membrane function, a transient reduction in its concentration may allow such improvement to take place, perhaps through effects on sodium⁺-potassium⁺ activated ATPase (Welt *et al.*, 1964). We are not able at present to conclude which of the two latter possibilities is responsible for the rise in action potential amplitude. It is possible that both phenomena are occurring.

The nature of the metabolic or toxic defect responsible for the altered peripheral nerve function in uraemia must next be considered. In our studies, as in those of Nielsen and Winkel (1971), there was no correlation between peripheral nerve function and blood urea or creatinine levels. It is difficult to relate the changes in nerve function to these or to serum electrolyte levels, particularly since the twin coil type of dialysis, rapidly correcting defects of urea and electrolyte concentration, appears to be less effective in preventing peripheral nerve damage than the slow Kiil type of dialysis (Tenckhoff *et al.*, 1965).

A number of metabolic disorders in uraemia have been related to peripheral nerve dysfunction (Lonergan *et al.*, 1971; Clements *et al.*, 1973; London *et al.*, 1975). It is probable that the accumulation of intermediate molecular weight substances ('middle molecules') is responsible for the peripheral nerve damage (Babb *et al.*, 1971). Such molecules cross the dialysing membrane only slowly and are thus more effectively cleared when dialysis time is prolonged than when flow rate is increased. This may well explain the deterioration in peripheral nerve function that may occur despite apparently effective dialysis. Our findings would support the contention that the appearance of features of a peripheral neuropathy is an indication for an increase in the frequency and duration of dialysis, or the use of dialysing membranes with higher 'middle molecule' clearance rates.

It is not yet clear to what extent this disordered peripheral nerve function in uraemia is related to the appearance of the neuropathy: the reduction in conduction velocity noted by Nielsen (1973) is as marked in the upper limbs as in the lower, and is more evident in proximal segments of the nerve, yet clinical features of a neuropathy are first manifest in distal segments of the lower limbs. The abnormality we have shown is also greater at the proximal site, and is apparently unrelated to the clinical features of neuropathy.

Although conduction velocity measurement has been of value in showing altered peripheral nerve function in uraemia, the changes related to dialysis are revealed only by measurement of evoked action

potential amplitude. Scrutiny of this, and of such aspects of peripheral nerve function as excitability and refractory period, should provide more information about the peripheral nerve in metabolic disorders.

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