ABSTRACT: Neuropathy is a common complication of end-stage kidney disease (ESKD), typically presenting as a distal symmetrical process with greater lower-limb than upper-limb involvement. The condition is of insidious onset, progressing over months, and has been estimated to be present in 60%–100% of patients on dialysis. Neuropathy generally only develops at glomerular filtration rates of less than 12 ml/min. The most frequent clinical features reflect large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, muscle wasting, and weakness. Nerve conduction studies demonstrate findings consistent with a generalized neuropathy of the axonal type. Patients may also develop autonomic features, with postural hypotension, impaired sweating, diarrhea, constipation, or impotence. The development of uremic neuropathy has been related previously to the retention of neurotoxic molecules in the middle molecular range, although this hypothesis lacked formal proof. Studies utilizing novel axonal excitability techniques have recently shed further light on the pathophysiology of this condition. Nerves of uremic patients have been shown to exist in a chronically depolarized state prior to dialysis, with subsequent improvement and normalization of resting membrane potential after dialysis. The degree of depolarization correlates with serum K\(^+\), suggesting that chronic hyperkalemic depolarization plays an important role in the development of nerve dysfunction in ESKD. These recent findings suggest that maintenance of serum K\(^+\) within normal limits between periods of dialysis, rather than simple avoidance of hyperkalemia, is likely to reduce the incidence and severity of uremic neuropathy.


UREMIC NEUROPATHY: CLINICAL FEATURES AND NEW PATHOPHYSIOLOGICAL INSIGHTS

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Accepted 24 October 2006

End-stage kidney disease (ESKD) occurs when nephrons are irretrievably impaired to the extent that the retention of metabolic waste products, salt, and water becomes potentially fatal.\(^{128}\) ESKD may occur due to either a primary renal disorder or as a complication of a multisystem disorder. The common causes of ESKD remain diabetes, glomerulonephritis, and hypertension.\(^{136}\) When renal function reaches critically low levels, renal replacement therapy either in the form of dialysis or transplantation is required in order to remove waste products and excess fluid.

Uremic neuropathy has for many decades been recognized as a common complication of ESKD.\(^{7,72,145}\) Although the advent of dialysis and transplant programs has led to reductions in the rate of severe neuropathy, the prevalence of this condition remains high.\(^{113}\) This review covers the clinical and electrophysiological features of uremic neuropathy, with a focus on advances in understanding the pathophysiology of this condition.

HISTORICAL ASPECTS

The possibility of peripheral neuropathy in patients treated with hemodialysis was first raised shortly after the introduction of the first formal hemodialysis program.\(^{172}\) The first clinical documentation of neuropathy was provided in 1961 in two young male patients with hereditary interstitial nephritis and deafness.\(^{209}\) The development of neuropathy in these cases, how-
ever, was attributed to the underlying hereditary disorder, rather than viewed as a complication of ESKD.

Following this report, Asbury et al. provided extensive clinical and pathological findings in four men who developed neuropathy as a consequence of ESKD of varying etiologies. All four patients had clinical features of renal disease for many years before the development of neuropathy, which manifested as a symmetrical length-dependent sensorimotor neuropathy. Nerve biopsies established axonal degeneration, maximal distally, with sparing of proximal nerve segments and nerve roots. Moreover, there was no evidence to suggest nerve compression, inflammation, or the superimposition of a systemic disease process, such as diabetes or amyloid, leading to the conclusion that the development of neuropathy was a consequence of the underlying renal disorder.

Early clinical neurophysiological investigations in ESKD patients demonstrated reductions in motor nerve conduction velocity in symptomatic and asymptomatic patients. Jebsen et al., studying the natural history of uremic neuropathy, compared clinical and nerve conduction findings in patients treated conservatively to those receiving dialysis therapy. Whereas the development of neuropathy in the conservatively treated group was related to deteriorating renal function, those patients treated with long-term dialysis manifested improvement in both clinical and neurophysiological parameters. Following these early reports and in light of the increasing use of dialysis and renal transplantation therapies, greater attention has been focused on uremic neuropathy, with numerous studies reporting high rates of neuropathy in ESKD patients, generally relating the development of neuropathy to the severity of renal failure. Of particular note, studies by Nielsen and Bolton et al. in the 1970s demonstrated nerve conduction slowing in clinically unaffected nerve segments, with correlation between the extent of renal impairment and degree of conduction slowing, as well as improvement in neurophysiological parameters following renal transplantation. These studies provided clinical evidence to suggest that a uremic toxin was responsible for the development of neuropathy in ESKD patients, a hypothesis that was to become a major focus of future neurophysiological research in this condition.

**INCIDENCE AND CLINICAL FEATURES**

Peripheral neuropathy in ESKD generally presents as a distal symmetrical polyneuropathy with greater lower-limb than upper-limb involvement. The condition is of insidious onset, progressing over months, and has been noted to have a male predominance. It generally only develops at glomerular filtration rates of less than 12 ml/min. The most frequent clinical features are those of large-fiber involvement, with paresthesias, reduction in deep tendon reflexes, impaired vibration sense, weakness, and muscle wasting (Fig. 1). In the 1970s, Nielsen demonstrated the presence of neuropathic symptoms in over 50% of patients with ESKD. Other studies have demonstrated prevalence rates varying from 60% to 100%, depending on the diagnostic criteria applied. Laaksonen et al. staged the clinical severity of uremic neuropathy in 21 ESKD patients, using a modified version of the neuropathy symptom score (NSS) developed by Dyck et al., and combined...
this assessment with results of nerve conduction studies. The NSS quantified symptoms that were grouped into three categories to reflect alteration in motor, sensory, and autonomic systems. Within each group, further subsets were used to group symptoms according to the region affected and the presence of positive or negative symptoms. Using the NSS and the staging procedure previously used in studies of diabetic patients,\textsuperscript{57,58} 81\% of ESKD patients received a diagnosis of neuropathy. Stage 1 neuropathy (asymptomatic neuropathy) was diagnosed in 19\%, stage 2 neuropathy (symptoms nondisabling) was present in 48\%, and stage 3 neuropathy (disabling symptoms) was noted in 14\%. In a more recent study,\textsuperscript{113} 93\% of ESKD patients had neuropathic symptoms on NSS testing, with 72\% diagnosed with stage 2 neuropathy and 21\% with stage 3 neuropathy, despite all patients meeting currently accepted guidelines of dialysis adequacy.\textsuperscript{143}

CLINICAL AND NEUROPHYSIOLOGICAL FINDINGS IN GENERALIZED UREMIC NEUROPATHY

Early studies of uremic neuropathy utilizing nerve biopsy techniques revealed prominent axonal degeneration, most severe in the distal parts of nerve trunks. Although initial studies suggested that demyelination was a significant feature of uremic neuropathy,\textsuperscript{5,54} subsequent reviews demonstrated that demyelination was secondary to axonal loss and that proximal segments of the nerves were relatively spared.\textsuperscript{3,55,67,187} These findings supported the concept that uremic neuropathy was a dying-back neuropathy, with metabolic failure of the neuron causing distal axonal degeneration.\textsuperscript{25}

Numerous neurophysiological series have been undertaken in patients with uremic neuropathy and have demonstrated findings consistent with a generalized neuropathy of the axonal type.\textsuperscript{1,4,15,20,41,46,49,68,80,107,113,121,130,148,155,156,179,183,185,191}

Early studies focused on motor nerve conduction parameters and demonstrated slowing of conduction velocity in patients prior to the development of clinical neuropathy.\textsuperscript{25,158} Subsequent studies demonstrated abnormalities of nerve conduction\textsuperscript{148} with generalized slowing in both sensory and motor nerves, accompanied by reduction in sensory response amplitudes. Motor response amplitudes tend to remain relatively preserved, although abnormalities in lower-limb motor nerves were noted in some patients, accompanied by neurogenic changes in distal lower-limb muscles on electromyography.\textsuperscript{148,149} In a recent study, amplitude of the sural sensory nerve action potential was found to be the most sensitive indicator of uremic neuropathy, being reduced in 50\% of ESKD patients.\textsuperscript{113} Other groups have confirmed similar findings, demonstrating reductions in sensory and motor response amplitudes in addition to abnormalities of late responses.\textsuperscript{1,4,49,122,130,157,157,191} Reduction in peroneal nerve motor conduction velocity\textsuperscript{46,157,148} and prolongation of tibial F-wave minimum latencies\textsuperscript{122} have been established as sensitive indicators of neuropathy in ESKD patients. Prolongation of soleus H reflexes has also been demonstrated in patients without clinical evidence of neuropathy, suggesting that this parameter may be more sensitive in detecting early neuropathy.\textsuperscript{68,191}

Studies of quantitative sensory testing in ESKD patients have demonstrated increased vibratory perception thresholds, most marked in the lower limbs,\textsuperscript{147} whereas somatosensory-evoked potentials in ESKD patients demonstrate abnormalities of conduction along both the distal and proximal segments of peripheral somesthetic pathways, but less commonly along intracranial sensory pathways.\textsuperscript{25,155,166}

A study of single-fiber electromyography demonstrated normal fiber densities in motor units of ESKD patients.\textsuperscript{186} This finding suggested that reinnervation, characterized by increased fiber density, had failed to occur. However, this was accompanied by increased jitter, possibly reflecting peripheral demyelination in the setting of axonal degeneration. A further single-fiber EMG study established that jitter abnormalities improved following a year of dialysis.\textsuperscript{106}

Early studies of nerve excitability, utilizing a limited range of excitability parameters, demonstrated an elevated threshold for excitation even when nerve conduction values were normal, in addition to demonstrating prolongation of absolute and relative refractory periods.\textsuperscript{25,125,182,208} As a consequence, it was concluded that the safety factor for neural transmission at the nodes of Ranvier would be lowered. Unexpectedly, uremic nerves retained vibratory perception and their sensory response amplitudes for a longer period than control nerves when rendered ischemic.\textsuperscript{45} Uremic nerves also behaved differently when temperature was lowered, with a less rapid rise in response amplitude compared to controls.\textsuperscript{24,25}

In addition to the slowly progressive sensorimotor axonal neuropathy, a more rapidly progressive motor neuropathy has been described. A small number of ESKD patients with diabetes have also been shown to develop a subacute neuropathy progressing over a few months, with severe muscle weakness. In this group of patients, nerve conduction studies may demonstrate features of either a demyelinating
or axonal neuropathy.\textsuperscript{26,27,165} Although the presence of diabetes complicates assessment of nerve conduction data, the absence of preexisting neuropathic symptoms and the clinical improvement noted following dialysis or renal transplantation suggest a metabolic basis for the neuropathy, related to the underlying ESKD. Analysis of cerebrospinal fluid (CSF) is rarely helpful, as CSF protein concentration is frequently elevated in ESKD patients and may simulate the albuminocytologic dissociation that is characteristic of Guillain–Barré syndrome.\textsuperscript{25}

Small-fiber neuropathy may develop as a clinical entity in ESKD patients. Lindblom and Tegner\textsuperscript{124} demonstrated abnormalities of thermal sensation in 30% of ESKD patients and concluded that small-fiber neuropathy may exist as a distinct entity in these patients. These results, however, differed from those of other groups who demonstrated minimal impairment of thermal sensation in ESKD.\textsuperscript{56,188} In a study of 20 ESKD patients, abnormalities in standard nerve conduction studies were demonstrated in 16 patients,\textsuperscript{4} whereas abnormal thermal thresholds were found in only 6 patients and, when present, did not correlate with clinical evidence of polyneuropathy.\textsuperscript{4} Such findings are consistent with those of pathological studies that demonstrated greater vulnerability of larger-diameter fibers in ESKD patients.\textsuperscript{55}

**MONONEUROPATHIES IN ESKD**

Mononeuropathies are a frequent clinical complication in ESKD patients and most typically occur in the median, ulnar, and femoral nerves.\textsuperscript{39}

Carpal tunnel syndrome (CTS) is the most common mononeuropathy in ESKD, with prevalence rates varying from 6% to 31%.\textsuperscript{15,17,52,66,67,76,81,170} $\beta_2$-Microglobulin amyloidosis is a major factor underlying the development of CTS in ESKD patients,\textsuperscript{63} a complication noted in patients on long-term hemodialysis. Amyloid deposits have been identified in synovial specimens from dialysis patients with CTS\textsuperscript{63} and an increase in the rate of CTS has been demonstrated with increasing hemodialysis duration.\textsuperscript{65} Strategies geared at reducing the levels of $\beta_2$-microglobulin, such as the use of high-flux biocompatible membranes and $\beta_2$-microglobulin adsorption columns, have resulted in reduced rates of CTS development and ultimately improvement in symptoms.\textsuperscript{63,118,192}

Other factors that may contribute to the increased incidence of CTS in ESKD patients include uremic tumoral calcinosis\textsuperscript{17,203} and the placement of arteriovenous fistulas (Fig. 2), inducing a “steal” of blood from the distal limb.\textsuperscript{66,70,105,119,131,141,201} The placement of Brescia–Cimino arteriovenous fistulas between the radial artery and cephalic vein has been associated with the development of both the clinical features of CTS and subclinical neurophysiological abnormalities in median or ulnar nerve territories.\textsuperscript{70,105} A recent study demonstrated CTS in 30.5% of limbs with fistulas compared to 12.2% on the contralateral side.\textsuperscript{66} Although the site of the fistula had no effect on the development of CTS, a significant correlation was noted between the age of the fistula and the presence of CTS.

With regard to treatment of CTS in ESKD, the outcome of median nerve decompression appears inferior in this group compared to patients with idiopathic CTS.\textsuperscript{76,102,175} In addition, recurrence rates are higher. In ESKD patients with recurrent CTS, an endoscopic approach may prove to be effective in relieving persistent symptoms.\textsuperscript{211}

Ulnar neuropathy is also a common occurrence in ESKD, affecting up to 51% of patients undergoing hemodialysis.\textsuperscript{142} Causes include external compres-
sion at the elbow during prolonged dialysis therapy and other risk factors as outlined for CTS, particularly arteriovenous fistulas and uremic tumoral calcinosis.

In addition to their possible contributions to the development of CTS and ulnar neuropathy, upper-limb arteriovenous fistulas may be associated with an acute-onset neuropathy, first described by Bolton et al. and later termed ischemic monomelic neuropathy. In this condition, acute limb ischemia develops due to shunting of arterial blood away from the distal parts of the limb. The severity of ischemia typically affects nerves, without causing changes in other tissues such as muscle, that possess a higher threshold for ischemic injury. Diabetic patients are particularly vulnerable, especially those with preexisting peripheral vascular disease or neuropathy. The symptoms are those of multiple upper-limb mononeuropathies, with distal sensory loss and weakness in the muscles of the forearm and hand. Electromyography demonstrates neurogenic abnormalities in distal limb muscles with sparing of proximal musculature. There may be predilection for median nerve involvement and the presence of conduction block in this nerve has been described as a sign of reversible injury. Early ligation or revision of the fistula frequently leads to significant clinical and electrophysiological improvement.

Femoral neuropathy in ESKD patients is a well-recognized complication of renal transplantation, with an incidence of around 2%. Prolonged use of self-retaining retractors in the region of the femoral nerve during renal transplantation may cause nerve compression and neuropraxic injury. Rapid recovery is expected in cases of neuropraxia but prolonged ischemia may lead to axonal loss. The prognosis is generally favorable, with most patients achieving complete recovery, although residual deficits may be present when significant axonal loss has occurred.

AUTONOMIC NEUROPATHY IN ESKD

Autonomic neuropathy may develop in ESKD patients, manifesting as postural hypotension, impaired sweating, diarrhea, constipation, or impotence. In a study of 36 ESKD patients, gastrointestinal autonomic symptoms were evident in 42% and impotence in 45%. Although postural hypotension was an uncommon clinical finding, 36% complained of episodes of postural dizziness, which was most prominent in elderly ESKD patients. Some studies have suggested that autonomic neuropathy occurs as a manifestation of generalized polyneuropathy, but others have shown no correlation between autonomic dysfunction and peripheral nervous system abnormalities. The mechanisms underlying the development of uremic autonomic neuropathy remain unknown, although an association with hyperparathyroidism has been suggested.

Studies utilizing objective measures of autonomic function, including R–R interval variation as a measure of parasympathetic function and sustained handgrip and sympathetic skin response as measures of sympathetic function, have established abnormalities in up to 62% of ESKD patients on dialysis treatment. However, these abnormalities frequently occur in the absence of clinical symptoms of autonomic dysfunction. Parasympathetic dysfunction has been shown to occur with greater frequency than sympathetic dysfunction, which is generally more common in diabetic ESKD patients.

The contribution of autonomic dysfunction to the development of intradialytic hypotension remains a matter of ongoing debate, with some studies suggesting a possible association and others suggesting no significant relationship. A recent review of the literature on the use of the oral alpha-1-adrenoceptor agonist midodrine in the treatment of intradialytic hypotension suggested a beneficial effect, although the authors drew attention to the fact that most studies were not randomized and had small sample sizes.

EFFECTS OF DIALYSIS AND TRANSPLANTATION ON UREMIC NEUROPATHY

Early reports investigating the effects of hemodialysis on uremic neuropathy suggested that some patients with mild neuropathy recovered completely with adequate dialysis. In fact, failure to improve was considered to be an indicator of insufficient dialysis. These reports, however, did emphasize that the extent of improvement was likely to be related to the severity of neuropathy and that patients with severe neuropathy were unlikely to experience any significant recovery.

More recent studies, however, have demonstrated that improvement in neuropathy with dialysis is an uncommon event. Although these studies suggest that dialysis retards the progression of neuropathy in most patients, in some cases a gradual deterioration of neuropathy may occur. A comparison of hemodialysis and peritoneal dialysis with regard to neuropathy pro-
gress has demonstrated no significant difference between the two dialysis forms.184

Renal transplantation remains the only known cure for uremic neuropathy,20,21 with clinical improvement in sensory and, to a lesser extent, motor function occurring within a few days of transplantation.80 Serial nerve conduction studies following transplantation demonstrated a correlation between the improvement in nerve conduction and biochemical parameters, suggesting that metabolic phenomena may underlie the rapid improvement.156 Even with severe neuropathy, improvement in symptoms and signs may occur within 1 month of transplantation, although in some patients the recovery is prolonged or remains incomplete.21,152,183

Dialysis and transplantation are less beneficial for patients with autonomic neuropathy compared to large-fiber neuropathy. An early study suggested that autonomic function may be improved with dialysis,74 but a more recent report failed to show any significant benefit.198 Although renal transplantation may lead to improvement or normalization of autonomic function,127,164 the time course of such improvement is often slow and may be incomplete, with significant changes often occurring after 4–8 years.177,199

Recent evidence suggests that treatment with erythropoietin (EPO) may prove beneficial in ESKD patients with neuropathy71,174 as well as for patients with neuropathy due to other etiologies.91,189 Treatment with EPO improved motor nerve conduction velocity in ESKD patients, but had no effect on sensory indices. In vitro studies have shown that EPO receptors are present on Schwann cells and in dorsal root ganglion neurons.79,90 Upregulation of EPO receptors occurs after axonal injury, mediated by release of nitric oxide, and administration of exogenous EPO is associated with reduction in limb weakness and neuropathic pain behavior.90

DIALYZABLE TOXINS AND THE MIDDLE MOLECULE HYPOTHESIS

Hegstrom et al.72 postulated that uremic neuropathy occurred due to accumulation of a dialyzable substance on the basis of their observational studies that demonstrated improvement in neuropathy in two subjects with long-standing ESKD following commencement of dialysis therapy. Later studies demonstrated that patients treated with peritoneal dialysis had lower rates of uremic neuropathy despite the fact that these patients frequently had higher blood urea and creatinine concentrations.10 The lower neuropathy rate in the peritoneal dialysis group was thought to indicate that the substance responsible for neuropathy was better dialyzed by the peritoneum than by the cellophane membranes used in hemodialysis. On this basis, the most likely group of substances was thought to be the “middle molecules,” substances with a molecular weight of 300–12,000 Da,193 given that such substances were known to be poorly cleared by hemodialysis membranes.

Marked elevations in the concentrations of middle molecules have been demonstrated in ESKD patients, a finding not observed in healthy controls.60,61 Examples of such molecules include parathyroid hormone (PTH) and β-2-microglobulin (β-2M), the levels of which are elevated in patients with ESKD.193 Further studies demonstrated that the use of thinner dialysis membranes and longer dialysis times, strategies that would have greater benefits for the clearance of middle molecules compared to small molecules, led to significant reductions in the rates of severe neuropathy.74,64 A study using a hemodialysis membrane highly permeable to middle molecules also demonstrated a dramatic reduction in the development of neuropathy.129

These early studies, however, were hampered by a number of difficulties, not least of which was the inability to measure middle molecule levels.10 Another major shortcoming of the hypothesis has been the lack of conclusive evidence that any single molecule in the middle molecular range is actually neurotoxic.104,198 In a study of nerve conduction velocity following renal transplantation, correlation was noted between the postoperative concentration of myoinositol, a middle molecule, and median nerve sensory conduction velocity.156 Although myoinositol levels are elevated in ESKD patients, there is little convincing evidence for a neurotoxic effect.193,207

The only middle molecule for which some evidence of neurotoxicity exists is PTH, with some studies suggesting a link between PTH and the neurological complications of ESKD.132,176 PTH has been shown to prolong motor nerve conduction velocities in animal studies,55 although human studies of the effect of PTH on peripheral nerves have yielded conflicting results, with variable changes in motor nerve conduction velocity in patients with ESKD.8,53,169

Despite the shortcomings of the middle molecule hypothesis, the hypothesis that a dialyzable toxin may be involved in the pathophysiology of this condition remains prevalent. More recently, it has been suggested that the following criteria should be met in order for a substance to be truly regarded as a uremic neurotoxin: (1) it must be an identifiable chemical; (2) it should be elevated in the blood of uremic patients; (3) there should be a direct positive relationship between blood level and neurological
dysfunction; (4) it should cause neurological dysfunction in animals at appropriate blood levels; and (5) its removal from the blood should abolish the dysfunction. The middle molecule hypothesis fails to satisfy a number of these criteria, most importantly criterion 3, as there is very little evidence to suggest that such molecules are actually neurotoxic.

Despite the evidence that a dialyzable toxin may underlie the development of uremic neuropathy, the mechanism of this neurotoxicity remained unclear. The possibility that the neurotoxic effect may be due to alteration in membrane excitability was first proposed by Nielsen who, drawing on evidence from in vitro studies of muscle and red blood cells in ESKD patients, proposed that one or more of these toxins may cause neuropathy by inhibiting activity of the axonal Na⁺/K⁺ pump. This energy-dependent pump is electrogenic, with three Na⁺ ions being pumped out for every two K⁺ ions pumped into the axon, leading to a net deficit of positive charge on the inner aspect of the axonal membrane. Paralysis of the Na⁺/K⁺ pump abolishes the direct contribution of the hyperpolarizing pump current to the membrane potential and leads to an accumulation of extracellular K⁺ that causes further depolarization. The Na⁺/K⁺ pump is therefore of critical importance in maintaining normal ionic gradients, which are essential for axonal survival. Disruption of these gradients may cause reverse operation of the Na⁺/Ca²⁺ exchanger, leading to increased levels of intracellular Ca²⁺ and axonal loss.

Although it is not possible to measure membrane potential directly in human axons in vivo, indirect information regarding membrane potential and axonal ion function may be gained from nerve excitability studies. Axonal excitability can be investigated using threshold tracking, where “threshold” indicates the stimulus current required to produce a target potential that can be adjusted online by computer (i.e., tracked) to assess excitability. The recent development of automated protocols has facilitated the use of excitability techniques in the clinical setting. Rather than relying on a single parameter, excitability techniques provide information regarding alterations in membrane potential and axonal ion channel function based on coherent changes in a number of different indices. Nerve excitability measures have been used to study peripheral nerves in patients with neuropathy and have provided information about disease pathophysiology. Prior to discussing the changes in axonal excitability that develop in patients with ESKD, a general understanding of nerve physiology is critical for the further discussion related to the pathophysiological mechanisms involved in the development of neuropathy.

**MOLECULAR STRUCTURE OF THE AXON AND SALTATORY CONDUCTION**

Transmission of impulses in myelinated axons occurs by means of saltatory conduction (Fig. 3), with action potentials advancing between successive nodes of Ranvier:

"Like a kangaroo travelling at speed, the action potential advances at near-uniform velocity, but it..."
is powered by discrete kicks of inward membrane current at nodes of Ranvier.753

The chief role of the axon is that of impulse conduction, which depends on the electrical cable structure and voltage-dependent ion channels of the axonal membrane. Much of the knowledge about axonal membrane structure and ion channel function comes from studies in nonmammalian axons (squids, vertebrates). Only over the last few decades have techniques such as patch-clamping allowed investigation of mammalian axons, and only over more recent years have human axons been studied in vivo.

In myelinated axons from peripheral nerve, voltage-sensitive Na⁺ channels are clustered at high densities (up to 1,000/μm²) in the nodal axon, compared to the internodal region (25/μm²).202 The high density of Na⁺ channels at the node reflects the need of saltatory conduction for a large inward current at the node (Fig. 3). When the nodal membrane is depolarized, an inward current is established, carried by Na⁺ ions. The Na⁺ conductance is voltage sensitive and regenerative: it increases with depolarization, and this in turn leads to greater depolarization as well as depolarization of the next node.75 This explosive process would end with the whole axon depolarized, were it not that the Na⁺ channels immediately started closing again, due to Na⁺ channel inactivation.

Na⁺ channels are membrane-spanning protein molecules, containing a pore unit (α-subunit) through which Na⁺ ions can diffuse almost freely in the open state.171 The fast activation process (from resting closed to open state) and the slower inactivation process (from open to inactivated state) consist of conformational changes by the channel protein, both driven by the changes in voltage gradient across it. A variety of toxins and drugs bind to the α-subunits of Na⁺ channels. Most toxins bind to sites that are involved in activation and inactivation, except for tetrodotoxin and its derivatives that occlude the outer pore of the Na⁺ channel.100,154 Some of these binding sites are also the target of mutation in hereditary Na⁺ channelopathies.101

**ASSESSMENT OF NERVE EXCITABILITY IN A CLINICAL SETTING**

Assessment of nerve excitability using automated protocols (Fig. 4) includes assessment of both nodal and internodal axonal properties. The activity of nodal persistent Na⁺ conductances may be assessed by measurement of the strength–duration time constant and rheobase. The strength–duration time constant (τ_SD) refers to the rate at which the threshold current for a target potential declines as the stimulus duration is increased.28,138,139,204 Calculation of τ_SD in human subjects may be performed using the ratio between the stimulus–response curves for two different stimulus durations using Weiss’ formula.204 shown below for threshold currents for stimuli of 0.2 ms (I_0.2) and 1.0 ms (I_1.0) duration:

\[
\tau_{SD} = 0.2(I_{0.2} - I_{1.0})/[I_{1.0} - (0.2 \times I_{0.2})]
\]

Both strength–duration time constant and rheobase (the threshold for a stimulus of infinitely long duration) are properties of the nodal membrane, dependent on passive membrane properties and a local response mediated by persistent Na⁺ channels.36 Alterations in membrane potential will affect both parameters, with depolarization leading to prolongation of strength–duration time constant and reduced rheobase; and hyperpolarization causing a shorter strength–duration time constant and increased rheobase. When measured in isolation, strength–duration time constant, however, is of limited utility as a marker of membrane potential, as it is also affected by other factors including demyelination and discrete changes in nodal Na⁺ conductances.28,100

Threshold electrotonus is the only clinical technique available to assess alterations in both nodal and internodal conductances. This method measures the threshold changes produced by long-duration depolarizing and hyperpolarizing currents.30,37 These conditioning polarizing currents are set to defined percentages of the unconditioned threshold current, but importantly remain subthreshold in that they do not trigger an action potential.37 The response of the threshold current to the subthreshold conditioning currents is tested at varying conditioning–test intervals before, during, and after the conditioning currents. By convention, threshold changes are plotted as threshold reductions (see Figs. 5, 6), such that depolarizing responses are plotted in an upward direction and hyperpolarizing responses in a downward direction. In addition to providing information regarding internodal conductances, threshold electrotonus is also sensitive to changes in axonal membrane potential.11,92 with membrane depolarization causing a “fanning-in” appearance of threshold electrotonus,36 whereas hyperpolarization leads to a “fanning-out” (Fig. 5).

Information regarding axonal ion channel function may also be gained through assessment of recovery cycle parameters. Following conduction of a single impulse, myelinated axons go through a stereotypical series of excitability changes known as the
recovery cycle (Figs. 5, 6). For a period of 0.5–1.0 ms after an impulse, axons are completely inexcitable and cannot generate another impulse regardless of the strength of the depolarizing stimulus. This period is known as the absolute refractory period. The axon then enters a period of relative refractoriness that can be measured either as the increase in current required to produce a potential of a specified size, known as refractoriness, or as the duration of the relative refractory period until threshold has returned to baseline, usually 3–4 ms.

This period of refractoriness is followed by a period of superexcitability (or supernormality), during which there is a reduction in threshold occurring over a 10–15-ms interval. Finally, there is a late phase of raised threshold known as late subexcitability, ending around 100 ms. These changes in threshold are associated with changes in latency, which is increased during the refractory period, decreased during superexcitability, and increased during late subexcitability.16,181

The relative refractory period results from inactivation of nodal transient Na⁺ channels. It is prolonged by membrane depolarization and reduced by hyperpolarization. Refractoriness may therefore be used a measure of membrane potential, although it is essential to take into account the effect of temperature, given that cooling leads to an increase in refractoriness.94 Furthermore, measures of refractoriness may be unreliable in situations of impaired distal transmission, as may occur with axonal demyelination, neuromuscular junction abnormalities, muscle disease, or any other factor that reduces the security of impulse
Alteration in refractoriness may also occur secondary to changes in nodal Na⁺ conductances. Reductions in refractoriness have been demonstrated in diabetic and toxic neuropathies, consistent with a reduction in the nodal Na⁺ conductances. In a recent study, an increase in refractoriness was demonstrated in patients treated with the chemotherapeutic agent oxaliplatin, in the absence of significant changes in other excitability parameters, suggesting that...
the neurotoxicity of this agent may be mediated by blockage of nodal transient Na\(^+\) channels.\(^{110}\)

Superexcitability is due to a depolarizing afterpotential that results from the capacitative charging of the internode by the action potential\(^{12}\) and subsequently discharges through high resistance pathways under or through the myelin sheath.\(^{40,99}\) Recent studies have also suggested that activation of nodal Na\(^+\) conductances may be a further contributing factor.\(^{133}\) As for refractoriness, superexcitability also varies with membrane potential, with depolarization leading to a reduction in superexcitability and hyperpolarization causing an increase. Late subexcitability is determined by activation of nodal slow K\(^+\) channels and the difference between membrane potential (\(E_m\)) and the K\(^+\) equilibrium potential (\(E_k\)) and increases with depolarization if extracellular K\(^+\) is unchanged. It may therefore be used to differentiate between pure depolarization and depolarization secondary to nerve ischemia in which there is no significant change in late subexcitability due to compensatory changes in extracellular K\(^+\) ions.\(^{92}\)

**NERVE EXCITABILITY STUDIES IN ESKD**

Nerve excitability studies in ESKD patients (Fig. 4) have recently demonstrated significant alterations in membrane potential prior to hemodialysis, with recovery in the postdialysis period.\(^{97,113,115–117}\) Prior to dialysis, measures of nerve excitability were significantly abnormal in ESKD patients compared to control data.\(^{93,95,108}\) Stimulus–response curves were shifted to the right, indicating that axons were of high threshold. This was accompanied by a fan-
Potassium satisfies criteria that have been suggested for a substance to be accepted as a uremic neurotoxin. It is an identifiable chemical that is elevated in the serum of ESKD patients and causes neurological dysfunction in both humans and animals. It is also a critical determinant of axonal resting membrane potential. Moreover, a direct relationship exists between serum levels of K⁺ and neurophysiological parameters, and its removal leads to considerable improvement in these indices. The resting potentials of both nerve and muscle membranes are largely determined by K⁺, with relative changes in K⁺ capable of depolarizing membranes.

It may be argued that the abnormalities of serum K⁺ noted in excitability studies are the consequence of a transient homeostatic disturbance, rapidly corrected by dialysis, and therefore unlikely to play a major role in the development of chronic irreversible neuropathy. Against such an argument, prolonged exposure to hyperkalemia in ESKD patients seems likely, given that postdialysis rebound of K⁺ is a well-recognized phenomenon with hyperkalemia typically recurring within 6 h of a dialysis session due to reequilibration between intracellular and extracellular fluid compartments. Such prolonged hyperkalemia may cause disruption of normal ionic gradients and activate damaging Ca⁺⁺-mediated processes, leading to axonal loss. Furthermore, given the importance of K⁺ in mediating these abnormalities, current measures of dialysis adequacy, which are based solely on blood urea concentrations, may be inappropriate for determining the adequacy of a dialysis regimen to prevent neurotoxicity. A better indication of adequate dialysis might be the maintenance of serum K⁺ within normal limits between periods of dialysis, which may require more attention to dietary restriction of K⁺ intake in some patients.

**AXONAL Na⁺/K⁺ PUMP FUNCTION IN ESKD PATIENTS**

Inhibition of the Na⁺/K⁺ pump by uremic neurotoxins, previously proposed as the mechanism underlying the development of uremic neuropathy, may induce membrane depolarization. Of further relevance, previous studies have demonstrated that alterations in membrane potential and intracellular K⁺ concentration have a direct effect on Na⁺/K⁺ pump function. Vagg et
al.190 showed that the activity-dependent hyperpolarization (ADH) of motor axons induced by voluntary activity causes threshold changes that can be used to assess Na\(^+\)/K\(^+\) pump function. Assessment of activity-dependent excitability changes prior to hemodialysis in 10 ESKD patients demonstrated quantitatively similar changes in ESKD patients and controls, arguing against any significant reduction in the axonal Na\(^+\)/K\(^+\) pump in ESKD (Fig. 8).115

A further study also assessed Na\(^+\)/K\(^+\) pump function in six ESKD patients prior to dialysis by monitoring the excitability changes that occurred before, during, and after 13 min of nerve ischemia.116 With the onset of ischemia, a short-lived threshold reduction was followed by a rapid increase in threshold (Fig. 9). Whereas normal controls manifested a postischemic threshold increase due to increased activity of the Na\(^+\)/K\(^+\) pump and consequent membrane hyperpolarization,\(^{112}\) a paradoxical reduction in threshold was noted in ESKD patients. This pattern suggested that the axonal Na\(^+\)/K\(^+\) pump had a stabilizing effect on the axon and was attempting to return membrane potential toward baseline from the highly depolarized levels of the ischemic period. Importantly, however, the rapid return of threshold to baseline levels in the postischemic period confirmed that the Na\(^+\)/K\(^+\) pump was functioning well in ESKD.

**CONCLUSION**

Neuropathy is a common complication of ESKD, occurring in the majority of patients undergoing dialysis. At present, renal transplantation remains the only known cure for uremic neuropathy.\(^{20,21}\) Recent nerve excitability studies have suggested that hyperkalemia may underlie the development of neuropathy and have argued against any dysfunction of the axonal Na\(^+\)/K\(^+\) pump in the development of this condition. Excess K\(^+\) fits the profile of the neurotoxin responsible for uremic neuropathy better than middle molecules, parathyroid hormone, or any other organic substance that has been previously linked to the development of uremic neuropathy. Recent findings from nerve excitability studies in ESKD patients suggest that maintenance of serum
K⁺ within normal limits between periods of dialysis, rather than simple avoidance of hyperkalemia, is likely to reduce the incidence and severity of uremic neuropathy.

Grant support was received from the Australian Brain Foundation, Sylvia and Charles Viertel Charitable Foundation, National Health and Medical Research Council of Australia and the Australian Association of Neurologists. We thank Hugh Bostock and David Burke for help in the development of the excitability studies, and Bruce Pussell and John Charlesworth for assistance in studies in uremic patients.

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