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Evidence for a causal relationship between hyperkalaemia and axonal dysfunction in end-stage kidney disease

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HIGHLIGHTS

- Potassium has a causal role in the development of axonal dysfunction in end-stage kidney disease (ESKD).
- Axonal dysfunction is not influenced by middle molecule concentrations.
- Achievement of normokalaemia may help restore nerve function in ESKD.

ABSTRACT

Objective: Potassium (K^+) has been implicated as a factor in the development of uraemic neuropathy. This study was undertaken to investigate whether hyperkalaemia plays a causal role in axonal dysfunction in end-stage kidney disease (ESKD).
Methods: Median motor nerve excitability studies were undertaken in four haemodialysis patients during a modified dialysis session. The serum K^+ level was "clamped" (fixed) for the first 3 h of dialysis, whilst allowing all other solutes to be removed, this was followed by dialysis against low dialysate K^+ for a further 4 h. Blood chemistry and nerve excitability studies were undertaken prior to, during and following dialysis. Results were compared to results from the same patients during routine dialysis sessions.
Results: All patients demonstrated significant nerve excitability abnormalities reflective of nerve membrane depolarization in pre-dialysis recordings ($p < 0.01$). After the 3 h clamp period, serum K^+ remained elevated (5.0 mmol/L) and nerve excitability remained highly abnormal, despite the significant clearance of other uraemic toxins. In contrast, studies undertaken during routine dialysis sessions demonstrated significant improvement in both serum K^+ and nerve function after 3 h.
Conclusions: The current study has established a causal relationship between serum K^+ and axonal membrane depolarization in haemodialysis patients.
Significance: From a clinical perspective, strict K^+ control may help improve nerve function in ESKD.

1. Introduction

Peripheral neuropathy is the most prevalent neurological complication of end-stage kidney disease (ESKD), affecting 70–90% of dialysis patients (Hojs-Fabjan and Hojs, 2006; Stosovic et al., 2008; Tilki et al., 2009). Clinical features of neuropathy include sensory loss and weakness, which contribute to physical limitations and patient morbidity. Since the initial clinical description of uraemic peripheral neuropathy by Marin and Tyler (1961), middle molecules, such as β-2 microglobulin and parathyroid hormone, have claimed much of the pathophysiological focus (Babb et al., 1973, 1981; Milutinovic et al., 1978). Despite these early hypotheses, more recent studies have cast doubt on the role of middle molecules in mediating neurotoxicity (Bostock et al., 2004; Kiernan et al., 2002; Krishnan et al., 2005, 2006). Additionally, criteria for the identification of uraemic neurotoxins have been developed (Bolton and Young, 1990), and these include the

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need for a direct positive relationship between serum levels of the toxin and nerve dysfunction, a criterion that middle molecules fail to satisfy.

Recent studies have suggested that small solutes, specifically potassium (K^+), may mediate neurological dysfunction in ESKD and contribute to the development of neuropathy (Kiernan et al., 2002; Krishnan et al., 2005, 2006). These insights have been provided through the use of nerve excitability techniques which provide information on axonal ion channel function and membrane potential, in addition to measurement of standard parameters such as action potential amplitude and latency (Kiernan et al., 2000). Moreover, these techniques are highly sensitive to pharmacological and therapeutic interventions (Lin et al., 2011; Park et al., 2009). Previous studies of excitability undertaken in ESKD patients prior to dialysis have demonstrated prominent excitability abnormalities consistent with axonal depolarization, with improvements noted during and at the conclusion of dialysis (Kiernan et al., 2002, Kiernan et al., 2002; Krishnan et al., 2005, 2006). These studies also noted correlations between pre-dialysis measures of axonal depolarization and serum K^+ concentration. Similar findings have also been demonstrated in studies of muscle excitability in ESKD (Z'Graggen et al., 2010). Despite these data, a causative role for K^+ in mediating neurological dysfunction has not been established. Furthermore given the complex milieu of uraemic toxins known to accumulate in ESKD, the role of K^+, independent of other factors, remains unknown.

As such, the aim of the present study was to assess whether hyperkalaemia has a causal role in mediating nerve dysfunction in haemodialysis patients. To establish causality the present study utilized a modified dialysis session that maintained an elevated serum K^+ for the first 3 h of dialysis whilst allowing all other solutes to be removed. This protocol was designed to investigate the effects of serum K^+ on nerve function independent of other uraemic metabolites. Additionally, to assess whether the changes in nerve excitability seen in ESKD patients were comparable to normal axons with elevated K^+, mathematical modeling of nerve excitability was undertaken.

2. Subjects and methods

This study was undertaken as a prospective interventional investigation. Subjects recruited to the study were ESKD patients receiving haemodialysis at the Kidney Care Centre, Prince of Wales Hospital. The studies were approved by the South East Sydney Area Health Service Human Research Ethics Committee (Northern Section) and the Human Research Ethics Committee of the University of New South Wales. Participants gave informed consent to the procedures in accordance with the Declaration of Helsinki. Baseline 'unclamped' studies were conducted in all patients prior to 'clamped' recordings (pre-dialysis K^+ range 4.5–6.0 mmol/L). Inclusion criteria for the clamped phase of the protocol were: ability to give informed consent; stable haemodialysis for at least 6 months; absence of arrhythmia on 12-lead electrocardiogram prior to study; habitually elevated pre-dialysis serum K^+ of 5.0 mmol/L but not greater than 5.5 mmol/L over the 3 months prior to enrolment. Exclusion criteria were: history of recent coronary artery disease; severe left ventricular failure as determined by transthoracic echocardiography and diabetes. The K^+ clamp protocol required the patient pre-dialysis serum K^+ to be >5.0 mmol/L. Patients underwent 12-lead ECG analysis to ensure that there were no signs of baseline arrhythmia.

Four ESKD patients (3M:1F) receiving 4–6 h, thrice-weekly haemodialysis were recruited to the study. The causes of ESKD include interstitial nephritis, glomerulonephritis (2 patients) and amyloidosis. The subject with amyloidosis had AA amyloidosis, which causes renal and gastrointestinal dysfunction but without peripheral nerve involvement (Perfetto et al., 2010; Reilly and Staunton, 1996). Median motor nerve excitability studies were obtained from the non-fistula arm of the patients prior to dialysis (time zero), at the end of the K^+ clamp (~3 h), and at the cessation of the dialysis session (7 h) (Fig. 1). Compound muscle action potentials were recorded from the abductor pollicis brevis muscle following median nerve stimulation using previously published protocols (Kiernan et al., 2000, 2002; Krishnan et al., 2005). Multiple nerve excitability parameters were recorded, including threshold electrotonus (TE) and the current-threshold relationship (I/V) which provide

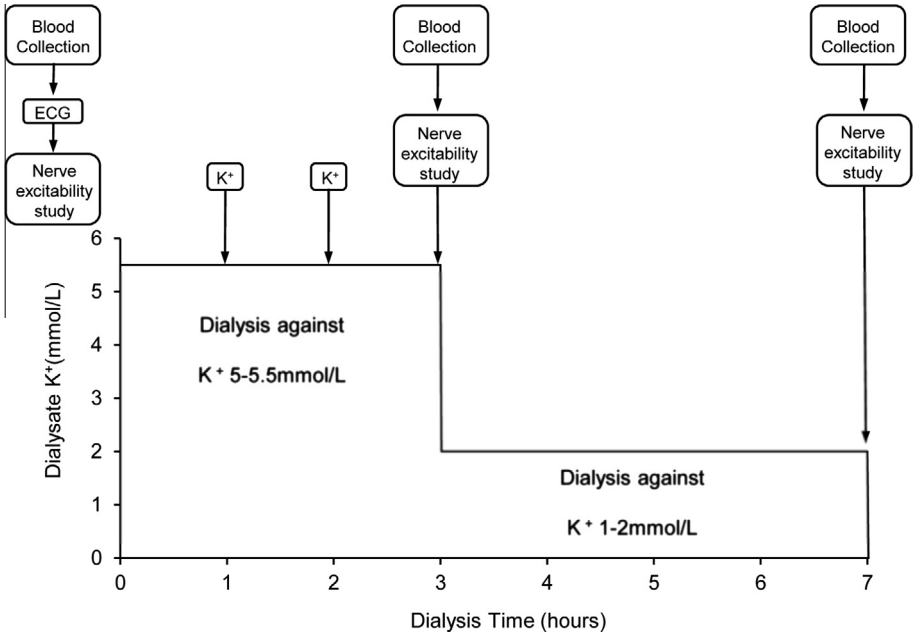

Fig. 1. Diagrammatic representation of the K^+ clamp protocol. Blood collection, ECG and nerve excitability were conducted prior to dialysis. If patients were eligible, they then commenced dialysis with the dialysate concentration of 5–5.5 mmol/L for 3 h, following this K^+ clamped period, the dialysate K^+ concentration was normalized (2 mmol/L) for a further 4 h to allow its removal and ensure dialysis adequacy. Full serum chemistry and nerve excitability studies were obtained prior to, during the clamped period (at ~3 h) and again at the cessation of dialysis. Additionally venous blood K^+ was measured hourly during the clamped period.