Adaptation of motor function after spinal cord injury: novel insights into spinal shock

Robert A. Boland,1 Cindy S.-Y. Lin,2 Stella Engel3 and Matthew C. Kiernan1,4

1 Spinal Injuries Research Centre, Neuroscience Research Australia, Sydney, NSW 2031, Australia
2 University of New South Wales, School of Medical Sciences, Sydney, NSW 2031, Australia
3 Department of Spinal Medicine, Prince of Wales Hospital, Sydney, NSW 2031, Australia
4 Prince of Wales Clinical School, University of New South Wales, Sydney, NSW 2031, Australia

Correspondence to: Prof. Matthew C. Kiernan,
Neuroscience Research Australia,
Barker St, Randwick, NSW 2031,
Sydney, Australia
E-mail: m.kiernan@unsw.edu.au

The mechanisms underlying spinal shock have not been clearly defined. At present, clinical assessment remains the mainstay to describe progression through spinal shock following traumatic spinal cord injury. However, nerve excitability studies in combination with conventional nerve conduction and clinical assessments have the potential to investigate spinal shock at the level of the peripheral axon. Therefore, peripheral motor axon excitability was prospectively and systematically evaluated in more than 400 studies of 11 patients admitted to hospital after traumatic spinal cord injury, with cord lesions above T9 (nine cervical, two thoracic). Recordings commenced within 15 days of admission from the median nerve to abductor pollicis brevis in the upper limb and the common peroneal nerve to tibialis anterior in both lower limbs, and were continued until patient discharge from hospital. Excitability was assessed using threshold tracking techniques and recordings were compared with data from healthy controls. In addition, concurrent clinical measures of strength, serum electrolytes and nerve conduction were collected. High threshold stimulus–response relationships were apparent from the early phase of spinal shock that coincided with depolarization-like features that reached a peak on Day 16.9 (±2.7 standard error) for the common peroneal nerve and Day 11.8 (±2.0 standard error) for the median nerve. Overall, changes in the common peroneal nerve were of greater magnitude than for the median nerve. For both nerves, the most significant changes were in threshold electrotonus, which was ‘fanned in’, and during the recovery cycle superexcitability was reduced (P<0.001). However, refractoriness was increased only for the common peroneal nerve (P<0.05). Changes in the spinal injured cohort could not be explained on the basis of an isolated common peroneal nerve palsy. By the time patients with spinal injury were discharged from hospital between Days 68 and 215, excitability for upper and lower limbs had returned towards normative values, but not for all parameters. Electrolyte levels and results for nerve conduction studies remained within normal limits throughout the period of admission. Contrary to prevailing opinion, these data demonstrate that significant changes in peripheral motor axonal excitability occur early during spinal shock, with subsequent further deterioration in axonal function, before recovery ensues.

Keywords: spinal cord injury; plasticity; nerve injury; excitability

Abbreviations: APB = abductor pollicis brevis; ASIA = American Spinal Injury Association; CMAP = compound motor action potential; CPN = common peroneal nerve
Introduction

The mechanisms underlying spinal shock following spinal cord injury have not been clearly established. Consequently, spinal shock is described by clinical features such as flaccidity, loss of voluntary movement and reduced tendon reflexes (DiTunno et al., 2004). This presentation has traditionally been interpreted to reflect processes intrinsically related to disconnection from central axons and reduced excitability of the motor neuron pool. Neurophysiological parameters that support this concept include reduced amplitudes of compound motor action potentials (CMAPS) and difficulty eliciting H-reflexes (Hiersenzenel et al., 2000; Schindler-Ivens et al., 2000). However, abnormalities of the peripheral axon have not yet been identified, and specific therapies for peripheral nerve involvement in acute spinal cord injury have not yet been considered.

During later spinal shock, except in circumstances such as distal cord infarction (Horowitz et al., 2003), increased excitability occurs that is clinically associated with the development of brisk deep tendon reflexes, increased resistance to muscle stretch, muscle spasms and clonus. Neurophysiological correlates include prominent accentuation of H-reflexes (Schindler-Ivens et al., 2000). Again, the sequence of clinical motor changes following spinal cord injury has traditionally been attributed to altered descending excitatory and inhibitory inputs to peripheral motor neuron pools, with the features of spinal shock attributed to altered central inputs to anterior horn cells or axons, with little consideration of contributions from peripheral processes. As a consequence, while it has been recognized that trophic inputs to the anterior horn cell may be compromised by spinal axon dysfunction (Kirshblum et al., 2001), the prevailing view has remained that lower motor neurons remain functionally unaffected by spinal cord injury.

Against such a concept, a recent cross-sectional investigation of 24 patients with spinal cord injury provided evidence to challenge an isolated spinal perspective of cord injury. In these studies, threshold tracking techniques sensitive to axonal membrane properties were applied to upper and lower limb axons of patients with sub-acute and chronic spinal cord injury (Lin et al., 2007). These studies identified altered excitability properties and intrinsic dys-excitability of peripheral motor axons in patients with lesions at cervical and thoracic levels that were attributed to a combination of decentralization and inactivity. In a subsequent longitudinal study, altered excitability of distal limb motor axons was observed as early as Day 6 after traumatic C6 spinal cord injury in a patient eventually discharged ambulant from hospital on Day 68 (Boland et al., 2009). While these data suggested a significant superimposed peripheral contribution to spinal cord injury, it was not possible to dissect the relative contributions of the nature of the original injury, stage of recovery, reductions in activity levels and vascular and metabolic influences secondary to factors such as organ dysfunction and sepsis after injury.

The implications of altered peripheral nerve function for management of spinal cord injury are potentially profound, particularly for rehabilitation interventions and length of hospital admission. Consequently, the aim of the present series of studies was to establish the onset and progression of peripheral axonal changes across a cohort of patients with traumatic spinal cord injury in a precise fashion, utilizing a novel approach combining clinical assessment, conventional nerve conduction studies and nerve excitability techniques. Prospective longitudinal data were systematically collected, commencing during the acute phase of spinal shock and continuing until patients were discharged from hospital.

Materials and methods

Eligibility criteria

Patients admitted to hospital with acute (first-time) traumatic spinal cord injury were eligible to participate in the present study and were enrolled on a consecutive basis. Patients were eligible if classified according to the American Spinal Injury Association (ASIA) as between ‘A’ and ‘D’ (Marino et al., 2003) and whether tetraplegic or paraplegic. A specialist multidisciplinary team involving spinal, neurosurgical and neurological physicians confirmed the diagnosis of spinal cord injury and assessments of ASIA scores and levels were undertaken by spinal rehabilitation physicians and physical therapists not involved in data collection. Patients were excluded if they could not commence testing within 15 days of injury or had lesions that directly affected lower motor neuron function in the lower limbs. Other exclusion criteria included injuries arising from self-harm, co-existent head injury, diagnosis of renal dysfunction or disease, open wounds or fractures in the regions of electrode placement or deep venous thromboses in the lower limbs in the first 15 days after injury. The Human Research Ethics Committees of the South-Eastern Sydney Area Health Service and the University of New South Wales approved the study and all patients or their guardians gave informed, written consent to participate prior to the commencement of testing.

Initial clinical assessments and research investigations were undertaken in an intensive care setting, with subsequent longitudinal studies undertaken in the spinal rehabilitation wards, continuing until patients were discharged from hospital. Clinical data recorded throughout the period of patient admission included routine neurological assessments of functional grading, structural imaging and laboratory investigations, such as haemodynamic measures and oxygen saturation. Investigations for co-existent diagnoses, such as inflammatory or critical illness neuropathies, were undertaken on the basis of diagnostic and clinical need as determined by the medical management team consisting of neurologists, intensive care, trauma and spinal rehabilitation specialists throughout the duration of the patient’s hospitalization.

Neurophysiological studies

Baseline nerve conduction study were undertaken with a Medelec Synergy Teca machine (Oxford Instruments, UK) using standard techniques (Kimura, 2001) to determine acute effects on terminal motor latency, conduction velocity, CMAP amplitude and F-wave persistence. Recordings were obtained from (i) the common peroneal nerve (CPN) from both lower limbs in response to supramaximal stimulation at the level of the head of fibula, with the resultant CMAPs recorded from tibialis anterior; and (ii) the median nerve in response to stimulation at the wrist with the resultant CMAP recorded from abductor pollicis brevis (APB). Bipolar surface recording electrodes were used with an inter-electrode distance of 4 cm (Eduardo and Burke, 1988). Motor stimulation was delivered to distal and proximal sites at 1 Hz using...
square-wave pulses of 0.1 ms duration with filter settings of 20 Hz–2 kHz. Electromyographic screening was undertaken using concentric needles to monitor acute denervation and any re-innervation prior to hospital discharge. Skin temperature was monitored throughout recordings that were obtained at resting temperature to avoid the risk of burns associated with warming at sites of testing below the neurological level of injury.

Nerve excitability recordings (Bostock et al., 1998; Burke et al., 2001; Krishnan et al., 2009) were assessed in a longitudinal fashion from both CPNs and the median nerve using QTRAC software (© Institute of Neurology, UK). Responses were amplified (ICP511 AC amplifier, Grass Product Group, Warwick, USA), digitized with an analogue/digital board (DT2812, Data Translation Inc., Marlboro, 97 Mass., USA) and imported to a personal computer. Stimulus–response curves were recorded using a stimulus duration of 1.0 ms, and strength duration time constant using four stimulus durations of 0.2, 0.4, 0.8 and 1.0 ms.

Threshold electrotonus, which records changes in threshold representing the nodal and intermodal axolemma, was assessed using prolonged (100 ms) subthreshold currents set to +40% (depolarizing) or −40% (hyperpolarizing) of the control threshold. The resultant changes in threshold were measured using a 1 ms test stimulus at various time intervals before, during and after the conditioning polarizing currents. A current–threshold relationship, an indicator of the rectifying properties of nodal and internodal axolemma, was then obtained by tracking changes in response to 1 ms test stimuli following 200 ms subthreshold polarizing currents in 15 steps from +50% to −100% of threshold. The recovery cycle of excitability was recorded by tracking changes in threshold for 1 ms duration test stimuli as the conditioning test interval was increased from 2 to 200 ms in 17 steps (Kiernan et al., 2000) to determine the absolute and relative refractory periods, superexcitability and late subexcitability. Reproducibility of motor recordings had been previously established (Kiernan et al., 2001), including for test–retest data from healthy control subjects for the median nerve and CPN collected at intervals of 2–3 days (Boland et al., 2009).

Clinical variables

Spinal rehabilitation physicians and physiotherapists naïve to the results of neurophysiological assessments performed standard clinical strength assessments for upper and lower limb muscles using the ASIA scale, with 0 indicating total paralysis and 5 indicating active movement against full resistance throughout range (Marino et al., 2003). In addition, APB strength (not usually collected for assessment of ASIA scores) was assessed according to the same scale.

Analyses

Admission data for muscle grading of APB and tibialis anterior power were analysed for similarity between sides using the Wilcoxon signed-rank test. Having established that there were no differences between sides, data were then pooled into single data sets for each muscle to increase the power associated with subsequent analyses. Manual assessments of power for each muscle, recorded on admission and discharge, were then compared for differences using a t-test for related samples.

Excitability data for 32 parameters were analysed. Initial CPN data were again compared for similarity between sides, before data from both sides were pooled into single data sets that represented data for admission (Occasion 1) and discharge (Occasion 3). Since the time course of excitability changes was shown to vary between participants, data for each patient were examined and a third data set (Occasion 2) was created for each nerve that corresponded to the test occasion over the course of admission that demonstrated the greatest deviation from the normative mean for superexcitability (taken from the recovery cycle of excitability).

Data for median nerve and pooled lower limb data for CPN were then compared: (i) to normative data for CPN stimulation (Krishnan et al., 2004) and median nerve stimulation (Kiernan et al., 2000), respectively, using t-tests for independent samples to assess for effects of injury; and (ii) between-occasions using repeated measures ANOVA with post hoc comparisons to assess for effects of recovery. Correlations between changes in excitability parameters and changes in muscle strength were determined using Pearson’s correlation co-efficients, or using Spearman’s rho when data sets were too small for Pearson’s calculations. Specifically, parameters that demonstrated significant changes over the course of hospitalization were identified from the post hoc analyses and then correlated against changes in strength of tibialis anterior and APB over the course of hospitalization. All data were corrected for temperature using normative data for the lower limb (Krishnan et al., 2004) and upper limb (Kiernan et al., 2000).

All data are expressed [± standard error (SE)] unless otherwise indicated. Data for CMAP amplitudes, distal motor latencies and conduction velocities were compared for each limb. Since abnormal electrolyte levels (particularly serum K+) may alter axonal excitability (Kiernan et al., 2002b), serum electrolyte levels were compared for the corresponding nerve excitability measurement.

Results

Sample characteristics

During the study period, 74 patients were admitted with spinal cord injury. The most common reasons for ineligibility related to admission for chronic spinal cord injury, or when patients with acute injury had been medically stabilized at another satellite hospital and transferred after 15 days from the date of injury. From the 14 patients identified as eligible to participate, one patient declined participation and another two did not provide consent within 15 days of injury, resulting in 11 participants who enrolled in the trial (mean age ± SD of 28 ± 10 years).

Patient characteristics are detailed in Table 1. All were males, with a high proportion of traumatic spinal cord injury associated with motor vehicle accidents (45%), followed by swimming injuries (27%) and high-speed cycling trauma (11%). Overall, 73% suffered cervical lesions, 18% thoracic lesions and the remaining patient suffering a combination of cervical and thoracic lesions. Discharge recordings were obtained between Days 68 and 215.

In terms of data not included in the results, one subject admitted as ASIA D C4 incomplete and subsequently discharged ambulant, withdrew for personal reasons on Day 13. Only his admission data were included. For another participant with a T7 lesion, tibialis anterior became inexcitable in response to stimulation of the CPN or direct stimulation over the muscle motor point at a stimulus intensity of 100 mA, after Day 13. No recovery in CPN excitability over repeated testing was observed, up to discharge 7 months later. However, upper limb studies that
patients demonstrated no recovery, while 45% recovered to normal for both lower limbs by discharge. Data from admission through to discharge are described in Table 1.

Similar variability in recovery outcomes was observed for APB, although this may reflect the level of lesion. For instance, three patients with cervical lesions demonstrated no recovery, remaining at grade 0/5 for both upper limbs until discharge, while two patients with thoracic lesions retained normal APB power throughout the inpatient period. Specific details for patients with respect to site of lesion and ASIA scores are described in Table 1.

### Nerve conduction studies

Initial motor nerve conduction data for the lower limbs were within normal limits with relative symmetry for tibialis anterior: CMAP (right = 2.2 ± 1.2 mV; left = 2.5 ± 1.2 mV); terminal motor latency (right = 3.6 ± 0.5 ms; left = 3.8 ± 0.3 ms); conduction velocity (right = 48.7 ± 2.3 m/s; left = 46.7 ± 2.9 m/s). In the upper limbs, the CMAP for APB was reduced after cervical spinal cord injury (4.6 ± 1.3 mV) compared with control data (8.4 ± 1.1 mV; P = 0.002), but terminal motor latency (3.6 ± 0.2 ms) and conduction velocity (52.1 ± 1.2 m/s) were within normal limits (Kiernan et al., 2000). F-waves were generally unobtainable from either nerve during the acute phase, consistent with the effects of acute spinal shock (Hiersenzenzel et al., 2000).

### Longitudinal nerve conduction studies and electromyography

Analyses of repeated nerve conduction study demonstrated no significant differences for CMAP or terminal latency for APB (F = 0.32, P = 0.74; F = 0.51, P = 0.62; respectively) and tibialis anterior (F = 2.31, P = 0.11; F = 1.01, P = 0.37). As such, there was no neurophysiological evidence to suggest delayed onset of normal for both lower limbs by discharge. Data from admission through to discharge are described in Table 1.

### Clinical assessment and outcome

Sensory ASIA scores were assessed according to a maximum of 224 and motor scores from a maximum of 100. Impairments on admission ranged from ASIA A complete to D incomplete. Three subjects (27%) remained ASIA A complete throughout the period of admission and another remained D incomplete. Three patients improved by one level (e.g. from A complete to B incomplete) and another three improved by two levels on the ASIA scale. One patient regressed from ASIA B incomplete to ASIA A complete (Table 1).

### Manual power grading

On admission, there was no difference between sides for manual assessments of power for either APB (P = 0.11) or tibialis anterior (P = 0.785). For the period between admission and discharge, power for APB improved from 1.6 (± 0.4) to 2.6 (± 0.4; P = 0.001) and tibialis anterior improved from 0.9 (± 0.3) to 2.5 (± 0.5; P = 0.002). Over the total inpatient period, 45% of patients demonstrated no recovery, while 45% recovered to normal for both lower limbs by discharge. Data from admission through to discharge are described in Table 1.

### Table 1 Demographic and clinical findings of the cohort of patients with spinal cord injury from the time of admission to hospital through to discharge

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>ASIA sensory score</th>
<th>ASIA motor score</th>
<th>Motor level</th>
<th>Sensory level</th>
<th>ASIA classification admission</th>
<th>ASIA classification discharge</th>
<th>APB power admission (side)</th>
<th>APB power discharge (side)</th>
<th>TA power admission (side)</th>
<th>TA power discharge (side)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>32</td>
<td>10</td>
<td>C5</td>
<td>C5</td>
<td>A complete</td>
<td>A complete</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>18</td>
<td>19</td>
<td>C5</td>
<td>C5</td>
<td>A complete</td>
<td>A complete</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
<td>L: 0 R: 0</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>114</td>
<td>50</td>
<td>T7</td>
<td>T7</td>
<td>B incomplete</td>
<td>A complete</td>
<td>5 L: 5 R: 5</td>
<td>5 L: 5 R: 5</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>4</td>
<td>37</td>
<td>154</td>
<td>48</td>
<td>C4</td>
<td>C4</td>
<td>C incomplete</td>
<td>D incomplete</td>
<td>5 L: 1 R: 1</td>
<td>5 L: 1 R: 1</td>
<td>4 L: 1 R: 5</td>
<td>5 L: 5 R: 5</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>44</td>
<td>8</td>
<td>C5</td>
<td>C5</td>
<td>A complete</td>
<td>B complete</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>146</td>
<td>33</td>
<td>C7</td>
<td>C8</td>
<td>B incomplete</td>
<td>D incomplete</td>
<td>1 L: 0 R: 0</td>
<td>3 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>32</td>
<td>27</td>
<td>C5</td>
<td>C5</td>
<td>B incomplete</td>
<td>D incomplete</td>
<td>0 L: 0 R: 0</td>
<td>3 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>116</td>
<td>50</td>
<td>T7</td>
<td>T7</td>
<td>A complete</td>
<td>A complete</td>
<td>5 L: 5 R: 0</td>
<td>5 L: 5 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>181</td>
<td>25</td>
<td>C6</td>
<td>C4</td>
<td>B incomplete</td>
<td>D incomplete</td>
<td>0 L: 0 R: 0</td>
<td>3 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
<td>0 L: 0 R: 0</td>
</tr>
<tr>
<td>10</td>
<td>23</td>
<td>103</td>
<td>86</td>
<td>C4</td>
<td>C4</td>
<td>D incomplete</td>
<td>D incomplete</td>
<td>3 L: 3 R: 3</td>
<td>4 L: 4 R: 4</td>
<td>4 L: 4 R: 5</td>
<td>5 L: 5 R: 5</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>112</td>
<td>60</td>
<td>C4</td>
<td>C8</td>
<td>C incomplete</td>
<td>D incomplete</td>
<td>2 L: 1 R: 2</td>
<td>4 L: 2 R: 1</td>
<td>3 L: 1 R: 3</td>
<td>1 L: 3 R: 1</td>
</tr>
</tbody>
</table>

Classification for each of the patients and assessments of clinical power were according to the American Spinal Injury Association classification and muscle grading scale, respectively (Marino et al., 2003).

a Patient sustained concurrent burst fracture at T4.

L = left; R = right; TA = tibialis anterior.

Demonstrated normal median motor axon function continued throughout his hospitalization. The combination of nerve conduction study, EMG and clinical assessment confirmed a diagnosis of infarction of the spinal cord below the level of injury and the patient was discharged with ongoing lower limb flaccidity and sensory deficit below T7. As such, the patient’s lower limb excitability data were not included in analyses because of the high likelihood of direct, though delayed, lower motor neuron effects. Therefore, a complete series of lower limb excitability data from admission through to discharge was collected from nine patients with spinal cord injury.
conduction deficits secondary to bed rest pressures over the CPN at the level of the fibular head, or the development of carpal tunnel syndrome during rehabilitation (Nogajski et al., 2006). Similarly, EMG sampling undertaken in the upper and lower limbs at the time of patient discharge from hospital confirmed that there was no evidence of denervation or development of neurogenic abnormalities.

Results of systemic investigations

None of the patients from the present series required prolonged admission to the intensive care unit or non-routine investigations, such as for cerebrospinal fluid or somatosensory evoked potentials. Furthermore, none suffered any complication known to adversely affect electrolyte levels. Routine electrolytes were collected on 31 occasions that coincided with nerve excitability testing. Serum electrolyte levels remained within normal laboratory ranges ($Na^+ = 137.5 \pm 0.5$ mmol/l; $K^+ = 4.0 \pm 0.06$ mmol/l; $Cl^- = 103.5 \pm 0.5$ mmol/l; $HCO_3^- = 24.8 \pm 0.4$ mmol/l; urea $= 5.8 \pm 0.4$ mmol/l). These data reflected the generally young and healthy pre-morbid characteristics of the present spinal cord injury sample. The absence of electrolyte imbalance would tend to support the argument that the following prominent excitability changes recorded from the spinal cord injury patient sample were not metabolic in origin.

Axonal excitability on admission

Overall, 403 excitability recordings were obtained during the study period from participants. Initial data were collected 1–15 days after injury ($6.2 \pm 1.2$ days). Given that there were no between-side differences for any excitability parameter for CPN on admission (Wilcoxon Signed Rank Test: range for $P=0.10–1.00$), lower limb excitability data were pooled for subsequent analyses. Compared with healthy control subjects, CPN axons from patients with spinal cord injury were uniformly of high threshold, with a significant shift to the right of the stimulus–response curve (Fig. 1A) and increased current required to generate a CMAP 50% of maximum, using 1 ms stimulation (spinal cord injury $7.2 \pm 1.1$ mA; controls $5.4 \pm 1.1$ mA; $P=0.01$; Fig. 1A). There were no differences for peak amplitudes or for the slope of the stimulus–response curves. Strength–duration time constant, derived from the rate at which threshold current reduced as stimulus duration was increased and reflecting the behaviour of persistent $Na^+$ conductances active near threshold, was similar between groups (spinal cord injury $0.44 \pm 0.06$ ms; controls $0.43 \pm 0.01$ ms; $P=0.81$).

![Figure 1](http://brain.oxfordjournals.org/)

**Figure 1** Initial excitability data (mean $\pm$ SE) as recorded between Days 1 and 14 from tibialis anterior after CPN stimulation for patients with spinal cord injury (SCI: filled circle) compared with responses from healthy controls (HC: open circle) (Krishnan et al., 2004) for the stimulus–response curves [1 ms stimulus: (A)], the current–threshold relationship (B), threshold electrotonus (C) and recovery cycle (D). The threshold for a CMAP 50% of maximum with 95% confidence limits are indicated for each curve in (A). Patient data were pooled from both lower limbs.
The current–threshold relationship reflects the rectifying properties of nodal and paranodal axolemma (Fig. 1B). By convention, an increase in threshold is demonstrated by shift of the curve to the left and threshold reduction by shift to the right. The slope of the current–threshold relationship also provides an estimate of the threshold analogue of input conductance. For CPN recordings, the current–threshold curve for spinal cord injury was shifted to the right (Fig. 1B) and the slope of the curve in the hyperpolarizing direction confirmed a smaller change in threshold (spinal cord injury 0.34 ± 0.04; controls 0.25 ± 0.01; P = 0.01). Similar abnormal responses to prolonged hyperpolarizing currents were evident throughout threshold electrotonus at durations of 10–20 ms, 20–40 ms and 90–100 ms (P < 0.001) and for responses to prolonged depolarizing currents (P < 0.001), resulting in a ‘fanned in’ appearance of patients with spinal cord injury (P = 0.001; Fig. 1C). Such changes observed during threshold electrotonus were consistent with those during the recovery cycle of excitability (Fig. 1D), which demonstrated a comparatively flatter appearance, with reduced superexcitability (spinal cord injury—8.6 ± 2.3%; controls —18.8 ± 1.3%; P < 0.001). Refractoriness, taken to reflect the recovery of transient Na⁺ conductances from their inactivated state, was increased (spinal cord injury 54.5 ± 8.5%; controls 37.1 ± 3.8%; P < 0.05).

In the upper limb, median axons were of high threshold compared with control data, indicated by a shift to the right of the stimulus–response curve for 1 ms stimuli (Fig. 2A). Peak amplitude for APB after spinal cord injury (Fig. 2A) was relatively reduced (P = 0.008), perhaps reflecting direct effects of the initial injury on nerve roots. Removing data from the two subjects with T7 lesions and preserved median CMAPs resulted in further reductions in the CMAPs recorded from the remaining patients with cervical lesions to 50% of that for controls, supporting the hypothesis that direct injury damaged median nerve roots. Threshold required to generate a CMAP 50% of maximum was increased (spinal cord injury 7.7 ± 1.2 mA; controls 4.5 ± 1.1 mA; P < 0.001; Fig. 2A). There was no difference between groups in the slope of the stimulus–response curve (P = 0.94) or in strength–duration time constant (P = 0.79).

In contrast with recordings from CPN, no differences were evident in median nerve recordings between controls and patients with spinal cord injury for current–threshold relationships (P = 0.27; Fig. 2B). However, ‘fanning in’ was evident during threshold electrotonus (Fig. 2C) for responses from patients with spinal cord injury to both hyperpolarizing (P < 0.05) and depolarizing currents (P = 0.05). During the recovery cycle of excitability (Fig. 2D), there was a trend towards a flattened appearance, indicated by reductions in both superexcitability (spinal cord injury —17.5 ± 1.7%; controls —25.4 ± 1.05%; P < 0.001) and subexcitability (spinal cord injury —10.7 ± 1.9%; controls —14.7 ± 0.7%; P = 0.02). Taken in total, changes in median nerve motor axons

![Figure 2](image-url)

**Figure 2** Initial excitability data (mean ± SE) recorded between Days 1 and 14 from APB after median nerve stimulation for patients with spinal cord injury (SCI: filled circle) compared with responses from healthy controls (HC: open circle) (Kiernan et al., 2000) for the stimulus–response relationships (1 ms stimulus: A), current–threshold relationship (B), threshold electrotonus (C) and recovery cycle (D). The threshold for a CMAP 50% of maximum with 95% confidence limits are indicated for each curve in (A).
were generally of lower magnitude than those recorded from CPN axons.

Comparison of spinal cord injury data to compression neuropathy

To investigate the possibility that lower limb excitability changes arose secondary to a focal nerve injury or conduction block, although these were not evident either clinically or on the basis of neurophysiology testing, further excitability data were collected from a patient with a unilateral CPN lesion. The nerve palsy had occurred while the patient had been hospitalized for a non-spinal cord condition, from which he fully recovered. Diagnosis was confirmed by clinical assessment and standard neurophysiological techniques. Comparison data from the unaffected side were within normal limits.

After identifying the site of the lesion as the head of the fibula on the affected side using standard neurophysiological techniques, excitability studies were undertaken at the level of the lesion and slightly distal to it. Data for the recovery cycle of excitability, current–threshold relationships (Fig. 3A) and threshold electrotonus (Fig. 3B) were in stark contrast with spinal cord injury data that were markedly ‘fanned in’ and shifted to the right, respectively. Taken in total, the pattern of changes around the site of focal nerve palsy involving the peroneal nerve were similar to those described previously for conduction block (Kiernan et al., 2002a) and were in marked contrast to data obtained from the spinal cord injury cohort.

Progressive abnormalities in axonal excitability

Data for admission (Occasion 1), discharge (Occasion 3) and the occasion of testing when excitability parameters demonstrated the greatest deviation from normative means (Occasion 2) were compared with control data and between-occasion for CPN (Fig. 4) and median nerve (Fig. 5), respectively. Over the 2 weeks following Occasion 1 readings, excitability underwent further deterioration for both nerves (Occasion 2), before recovery by the time of discharge (Occasion 3). Recordings for Occasion 2 were taken on average 16.9 (±2.8) days after injury for CPN and 11.8 (±2.0) days after injury for APB.

Repeated measures and post hoc analyses for CPN for the three occasions of testing established significant longitudinal differences (P < 0.05) during the period of hospitalization for 15 parameters combined from stimulus–response curves, the recovery cycle of excitability, superexcitability, late subexcitability and threshold electrotonus (for both hyperpolarizing and depolarizing currents). Conversely, median nerve excitability demonstrated relative stability over the three occasions of testing. These findings confirmed that excitability changes after spinal cord injury were of lower magnitude for median nerve than for CPN.

Thus, the overall pattern of change for CPN appeared to coincide with transition of patients with spinal cord injury through the period of spinal shock (Fig. 6). This was evident when excitability measures for Occasions 1–3 for patients with spinal cord injury were compared to control data (Fig. 6A). All excitability data demonstrated similar patterns of deterioration and then recovery as patients moved from the period of spinal shock, as demonstrated using the example of changes in superexcitability, throughout the inpatient period (Fig. 6B). Perhaps in further support of such a hypothesis, no significant correlations were evident between changes in tibialis anterior strength and excitability parameters recorded for CPN throughout the inpatient period.

Discussion

Using a novel combination of traditional clinical assessment, nerve conduction study and nerve excitability techniques, the present study has identified significant changes in the responses of peripheral motor axons following traumatic spinal cord injury. Specifically, the present study has established that: (i) peripheral axons undergo significant functional changes in the acute phase

**Figure 3** Data from the CPN of a patient without spinal cord injury and diagnosed with a unilateral focal CPN lesion at the head of the fibula and confirmed by standard neurophysiological techniques. Data were collected at the site of the lesion (filled circle) and below the lesion (open circle) and compared with 95% confidence limits (broken line) for healthy controls (Krishnan et al., 2004) for the current–threshold relationship (A) and threshold electrotonus (B).
after spinal cord injury that are of greater magnitude for lower limb axons than for the upper limb; and (ii) both upper and lower limb axons undergo recovery of excitability independent of surgical stabilization. Perhaps more significantly, the period of acute axonal changes coincided with the clinical onset of hyperreflexia during the later period of spinal shock (Ditunno et al., 2004), with recovery of axonal excitability seeming to manifest from this period (Fig. 6).

The development of longitudinal changes in lower limb motor axonal excitability developed while compound amplitudes and other measures from conventional nerve conduction study remained normal. Conversely, in the upper limbs, significant reductions in compound amplitudes developed. Such findings may be attributed to different mechanisms underlying upper and lower limb responses to spinal shock. For instance, reductions in upper limb potentials may reflect the direct traumatic effects of injury on the cervical nerve roots and anterior horn cells. Further evidence for this hypothesis was suggested when CMAP data from the two subjects with T7 lesions (and preserved upper limb compound potentials) were excluded, with the result that CMAP amplitude for the remaining cervical injured patients was ~50% of that for controls.

In the absence of direct traumatic effects on lower limb peripheral axons, it may be reasonably suggested that lower limb changes reflect involvement of transynaptic processes. Metabolic effects cannot have accounted for the observed changes in excitability given that electrolyte levels consistently remained normal throughout the hospitalization period. Similarly, there was no clinical evidence for development of inflammatory or critical illness neuropathy during hospitalization for any of the spinal cord injury cohort. Furthermore, the relative differences for CPN compared with median nerve would also argue against a systemic or metabolic cause, as does the subsequent recovery of excitability responses in the setting of stable electrolyte levels. The marked differences in excitability changes between the patient with focal compressive nerve palsy and the cohort of patients with spinal

**Figure 4** Excitability data (mean ± SE) recorded from tibialis anterior after CPN stimulation for patients with spinal cord injury. Data were recorded on admission (filled circle), between Days 1 and 14 (open circle), on the occasion that superexcitability (in percentage) showed the greatest deviation from the mean for healthy controls (open square) and at discharge (open diamond). Data include the current–threshold relationship (A), threshold electrotonus (B) and recovery cycle of excitability (C). Patient data are pooled from both legs.

**Figure 5** Excitability data (mean ± SE) recorded from APB after median nerve stimulation for patients with spinal cord injury. Data were recorded on admission (filled circle), between Days 1 and 14 (open circle), on the occasion that superexcitability (in percentage) showed the greatest deviation from the mean for healthy controls (open square) and at discharge (open diamond). Data again include the current–threshold relationship (A), threshold electrotonus (B) and recovery cycle (C).
cord injury would also support the conclusion that a focal nerve lesion cannot account for the excitability changes recorded from patients with spinal cord injury.

What underlies the acute excitability changes during spinal shock?

Superficially, the initial pattern of excitability changes in upper and lower limbs may appear consistent with depolarization (Kiernan and Bostock, 2000). Recordings from the lower limbs (Fig. 1) demonstrated a shift to the right of the current–threshold relationship (Fig. 1B), ‘fanning in’ of threshold electrotonus (Fig. 1C) in association with an increased relative refractory period and reduced superexcitability from the recovery cycle (Fig. 1D). However, late subexcitability was reduced in CPN following spinal cord injury (Fig. 1D), in contrast with the increase that occurs in response to depolarization (Kiernan and Bostock, 2000). Furthermore, changes in the strength–duration time constant were not observed and the thresholds required to generate a compound potential were increased for both upper and lower limb axons. Initial upper limb excitability responses demonstrated a similar pattern to those observed in the lower limbs (Fig. 2B–D), although with changes of smaller magnitude. Thus, differences between the upper and lower limb CMAP responses and recovery cycle parameters suggested potentially different initial effects on upper and lower limbs, with ‘depolarization-like’ changes for some parameters but not others. Overall, such features may infer that complex mechanisms were responsible for the longitudinal changes recorded during hospitalization.

Longitudinal recordings obtained from the lower limbs in patients with spinal cord injury demonstrated significant deterioration compared to concurrent recordings from the upper limbs in those patients that demonstrated recovery. Perhaps most significantly, an increase in the refractory period recorded during the recovery cycle was associated with abolished superexcitability, while late superexcitability remained relatively stable. Such a pattern of change was reminiscent of the axonal response to generalized ischaemia (Kiernan and Bostock, 2000). However, ischaemic changes secondary to the effects of local nerve compression, perhaps associated with bed rest compression or mattress palsy (Nogajski et al., 2006), were considered unlikely based on the following: (i) direct trauma to the CPN as a cause for the prominent excitability abnormalities was not evident on conventional nerve conduction study; (ii) stability of motor latencies and amplitudes that remained within normal limits for the duration of all studies suggested that subsequent bed rest-related focal neuropathy had not occurred during the period of hospitalization for the spinal cord injury cohort; and (iii) excitability studies in the presence of focal conduction block were markedly dissimilar to excitability changes recorded in response to cuff-induced ischaemia from healthy control subjects (Kiernan and Bostock, 2000), when threshold electrotonus was ‘fanned in’, the current–threshold relationship was shifted to the right, and during the recovery cycle, superexcitability was abolished by increased refractoriness. Overall, such findings support the conclusion that a focal lesion cannot account for lower limb changes observed in the spinal cord injury cohort.
A number of pathophysiological mechanisms have been identified at the site of spinal cord injury, including direct mechanical effects on the upper motor neuron, secondary metabolic effects from processes such as cord inflammation and cord ischaemia from disrupted vasculature and secondary inflammation. In turn, it remains conceivable that such processes may have potentiated the peripheral axonal changes observed in the current series by release of inflammatory or metabolic products that may have directly affected ion channel function in peripheral axons. Perhaps of relevance, immunological activation has been reported in patients with chronic spinal cord injury, with increased levels of pro-inflammatory cytokines and anti-GM1 antibodies (Hayes et al., 2002). The combined effects of these by-products have previously been shown to unsharpen K+ channels in the paranodal region of peripheral axons in rat models and promote formation of antibody-complement complexes that may potentially block Na+ channels to thereby disrupt the node of Ranvier (Takigawa et al., 1995). However, the differences between upper and lower limb excitability changes in the current spinal cord injury series may argue against a systemic process.

An alternative and plausible explanation is that the lower limb axonal dysfunction that developed during spinal shock resulted from interruption to homeostatic processes at the level of the axonal membrane. For instance, it is known that ischaemia has inhibitory effects on the energy-dependent axonal Na+/K+ pump (Kiernan and Bostock, 2000). Previous electrical and mathematical simulation of lower limb recordings from a patient after cervical spinal cord injury using a model of the human axon (Boland et al., 2009) were found to best fit recordings from normal subjects exposed to limb ischaemia (Kiernan and Bostock, 2000). Such an energy crisis may also have been responsible for the ischaemia-like changes in lower limb motor axons from the present spinal cord injury cohort. While the precise axonal transport mechanism remains unknown, the current data could also support the hypothesis that disrupted upstream regulation may have influenced homeostasis of energy-dependent processes to account for the abnormalities in peripheral motor axonal excitability.

Further adding to the complexity of axonal responses after spinal cord injury, measures of lower limb excitability recovered towards normative values by the time patients were discharged from hospital. However, significant abnormalities remained for many markers of axonal membrane function, including the refractory period. Similarly, upper limb excitability parameters returned towards normative values but recovery was more complete. Therefore, there remains the paradox that a cervical cord lesion has greater effects on excitability properties of distant peripheral axons, with more pronounced changes in lower limb motor axons than for upper limb axons, despite direct traumatic effects on upper limb axons.

**Correlations between clinical and excitability findings**

While recovery of axonal excitability towards normal was subsequently observed in patients with spinal cord injury that corresponded to recovery of strength in some patients, there was no significant overall correlation between the recovery of excitability and changes in power. This finding may not be surprising given that the most significant factor causing reduced strength after spinal cord injury is reduced cortical drive, secondary to axonal discontinuity at the site of cord injury. Such a conclusion would be supported by the current findings of preserved lower limb compound motor amplitudes in the presence of ongoing reduced muscle power, with concurrent recovery of excitability over the duration of hospitalization. In the presence of recovery of corticospinal transmission, other factors may contribute in a complex manner to strength recovery, including changes in cross-sectional area of the muscle (Jones et al., 2008), learning effects associated with rehabilitation (Farthing et al., 2007) and re-inervation (Bromberg et al., 1993; Bromberg and Larson, 1996).

**Time course of excitability changes**

It has been proposed that the third of a four-phase model of spinal shock includes the onset of hyporeflexia within 4 weeks following spinal cord injury (Ditunno et al., 2004). Recovery of lower limb excitability in the current studies appeared to coincide with the onset and development of hyporeflexia, as determined clinically. Classical teaching has related hyporeflexia during the early phases of spinal shock as a secondary process that develops due to disconnection of peripheral from corticospinal axons, and reduction of corticospinal transmission and excitatory inputs to peripheral axons, with the result that lumbar neurons become hyperpolarized (Ditunno et al., 2004). Thus, the current data add a further layer of complexity to the interpretation of spinal shock.

**Clinical implications**

The current data challenge the classic view that spinal cord injury spares the peripheral nerves or that peripheral axons remain in a ‘state of hibernation’ from the time of injury. Rather, changes in lower limb axonal excitability, especially after cervical spinal cord injury, support a conclusion of adverse downstream effects on axonal processes that likely incorporate trans-synaptic processes, commencing during the early phases of spinal shock. The development of significant lower limb changes supports a distance-dependent effect, although differences between upper and lower limbs may reflect the complex organization of corticospinal pathways, whereby neurons corresponding to the upper and lower limbs are segregated (Nathan et al., 1990; Nathan, 1994). Furthermore, recovery of excitability relatively independently of muscle power may support the argument that recovery of activity levels is not solely responsible for changes in peripheral motor excitability. Instead, lower limb recovery may reflect recovery of fibres in the opposite lateral corticospinal tract that contribute to a re-inervation process (Nathan et al., 1990; Bromberg et al., 1993; Nathan, 1994; Bromberg and Larson, 1996). As such, a directed clinical trial would seem warranted to establish whether the transitory deterioration in peripheral excitability may be ameliorated, with consequent beneficial effects on function and better rehabilitation outcomes.
Acknowledgements

The authors acknowledge the assistance of Ms Danielle Burton RN for her assistance with collection of clinical data.

Funding

New South Wales Office for Science and Medical Research; Spinal Cord and Related Neurological Conditions Program.

References


