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**Heterogeneous effect of increasing spinal cord perfusion pressure on sensory evoked potentials recorded from acutely injured human spinal cord**

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**ABSTRACT**

**Purpose**

To investigate the effect of increasing spinal cord perfusion pressure (SCPP) on sensory evoked potentials (SEPs) and injury site metabolism in patients with severe traumatic spinal cord injury TSCI.

**Materials and Methods**

In 12 TSCI patients we placed a pressure probe, a microdialysis catheter and a strip electrode with 8 contacts on the surface of the injured cord. We monitored SCPP, lactate-to-pyruvate ratio (LPR) and SEPs (after median or posterior tibial nerve stimulation).

**Results**

Increase in SCPP by ~20 mmHg produced a heterogeneous response in SEPs and injury site metabolism. In some patients, SEP amplitudes increased and the LPR decreased indicating improved tissue metabolism. In others, SEP amplitudes decreased and the LPR increased indicating more impaired metabolism. Compared with patients who did not improve at follow-up, those who improved had significantly more electrode contacts with SEP amplitude increase in response to increasing SCPP.

**Conclusions**

Increasing SCPP after acute, severe TSCI may be beneficial (if associated with increase in SEP amplitude) or detrimental (if associated with decrease in SEP amplitude).Our findings support individualized management of patients with acute, severe TSCI guided by monitoring from the injury site rather than applying universal blood pressure targets as is current clinical practice.

**Keywords**

Blood pressure; Critical care; Microdialysis; Monitoring; Somatosensory evoked potential; Subdural electrode; Spinal cord injury

**ABBREVIATIONS**

AIS, American spinal injuries association Impairment Scale

BASIC score, Brain and Spinal Injury Center score

CSF, cerebrospinal fluid

ISCoPE, Injured Spinal Cord Pressure Evaluation study

ISP, intraspinal pressure

LPR, lactate-to-pyruvate ratio

MAP, mean arterial pressure

MD, microdialysis

NICU, neuro-intensive care unit

SCBF, spinal cord blood flow

SCPP, spinal cord perfusion pressure

SCPPopt, optimum spinal cord perfusion pressure

SEP, spinal somatosensory evoked potential

sPRx, spinal pressure reactivity index

TSCI, traumatic spinal cord injury

**1. INTRODUCTION**

Traumatic spinal cord injury (TSCI) is a catastrophic event; most patients remain disabled and <1 % leave the hospital neurologically intact [1]. Currently, there is no treatment proven to improve neurological outcome after TSCI [2]. The medical management of acute TSCI varies widely [3, 4]. In contrast to traumatic brain injury [5], injury site monitoring is not used in neuro-intensive care units (NICUs) to guide TSCI management. Thus, the effect on injury site physiology and metabolism of medical interventions, e.g. increasing blood pressure, is unclear.

Current guidelines [6] recommend maintaining mean arterial pressure (MAP) at 85 – 90 mmHg for the first week after a TSCI, based on animal studies and human case series with little understanding of the impact of MAP on the physiology of the injured cord. To rationalize NICU management, we developed injury site monitoring of intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP) and metabolism [7, 8]. A key finding is that the optimum SCPP (SCPPopt) varies temporally and between patients, which suggests individualized management [9, 10]. To date, our monitoring studies have focussed on the effect of changing SCPP on injury site autoregulation (quantified using the spinal pressure reactivity index, sPRx) [10], metabolism (determined by microdialysis, MD) [7, 11] and spinal cord blood flow (SCBF, assessed with laser speckle contrast imaging) [12]; little is known about the effect of altering SCPP on the electrical activity of the injured cord, e.g. sensory evoked potentials (SEPs).

SEPs are typically elicited by stimulating a peripheral nerve and recording from skin electrodes placed cranially to assess the functional integrity of the dorsal columns. Depending on the severity of TSCI, SEPs may be absent or the signal amplitude decreases [13-16]. Experimental studies in animal models reveal a correlation between severity of spinal cord compression and SEP abnormalities [17, 18]. Previous studies have also demonstrated the prognostic value of SEP in predicting the functional outcome in the context of TSCI [19, 20]. Here, we placed a subdural electrode strip to record spinal SEPs directly from contacts along the injury site in patients with acute, severe TSCI. We investigated the effect of increasing SCPP on SEP amplitude and how this effect relates to changes in injury site metabolism.

**2. MATERIALS AND METHODS**

**2.1. Institutional approvals.** Patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) study. Approvals for ISCoPE including the patient information sheet and consent form were obtained from the St George’s, University of London Joint Research Office and the National Research Ethics Service London–St Giles Committee (No. 10/H0807/23). The study is registered at ClinicalTrials.gov as NCT02721615.

**2.2. Patient recruitment.** Patients were recruited between September 2016 and June 2018. Inclusion criteria are: 1. Severe TSCI (American spinal injuries association Impairment Scale (AIS) grade A – C); 2. Age 18 – 70 years; 3. Surgery within 72 hours of TSCI. Exclusion criteria are: 1. Major concurrent injury or co-morbidity; 2. Penetrating TSCI; 3. Failure to consent. We only included awake, self-ventilating patients who were safe to transfer from the NICU to the neurophysiology department.

**2.3. Clinical assessments.** A neurological AIS examination was performed on admission, at 4 – 8 weeks after injury and at 6 – 12 months. The exam was performed by a neurosurgery research fellow trained in AIS. CT and MRI scans of the whole spine were performed on admission. Post-operative CT was done at 24 – 48 hours after surgery and MRI after probe removal.

**2.4. Surgery.** Surgical decompression was laminectomy +/- corpectomy with spinal instrumentation based on surgeon preference. Posterior fixation was with lateral mass screws for the cervical spine and pedicle screws for the thoracic spine. Anterior cervical fixation was with vertebral body plate and screws.

**2.5. Intraspinal pressure probe, microdialysis and subdural electrodes.** An ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK), a MD catheter (CMA 61, CMA microdialysis AB, Sweden) and a flexible subdural strip with eight platinum electrode contacts (AD Tech, Oak Creek, USA) were tunnelled through the skin into the wound [7, 8, 21]. Under the operating microscope, the dura and arachnoid were opened one level below the injury. The ISP probe, MD catheter and electrode strip were inserted through the durotomy and advanced on the cord surface until the ISP probe tip was at the site of maximal cord swelling and the strip electrode straddled the injury site (Figs. 1A-B). The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). The probes were sutured to the skin.

**2.6. ISP and SCPP monitoring.** The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.8 (AD Instruments, Oxford, UK). Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) in turn connected to the PowerLab system. The ISP and arterial blood pressure signals were sampled at 1 kHz. LabChart was used to analyse the signals and compute SCPP (mean arterial pressure minus ISP). ISP is different from intrathecal pressure measured above or below the injury because the swollen, injured cord is compressed against the dura thus compartmentalising the intrathecal space [8, 21, 22].

**2.7. Microdialysis.** CNS perfusion fluid (CMA Microdialysis AB, Sweden) was perfused at 0.3 µL/min using a CMA106 pump (CMA Microdialysis AB, Sweden). MD vials were changed hourly, stored at 4 °C, and batch analysed up to 24 hours later using ISCUS Flex (CMA Microdialysis AB, Sweden). The first two samples from each patient were discarded. All samples were analysed for glucose, lactate, pyruvate, glycerol, glutamate and lactate-to-pyruvate ratio (LPR). 100-fold changes in metabolite concentration, and 10-fold changes in LPR, compared with the preceding hour, were excluded from analysis. This MD method measures injury-site surface metabolism, which correlates with intraparenchymal metabolism, but is different from metabolites measured from lumbar cerebrospinal fluid (CSF) [7, 11, 23].

**2.8. Spinal cord SEPs.** SEPs were recorded by a highly specialized clinical neurophysiologist, supervised by a consultant neurophysiologist using a XLTEK Protektor 32 system with a bipolar stimulating bar electrode (Natus Neuro, Middleton, WI, USA). Sampling rate was 30 kHz, downsampled to 7,538 Hz for analysis, with bandpass filter 30 – 1.5 kHz. For the upper limbs, we stimulated the median nerve (wrist) and for the lower limbs the posterior tibial nerve (ankle). In each patient, optimal stimulation was determined by observing repetitive muscle contraction of the abductor pollicis brevis or flexor hallucis brevis; subsequent runs were performed at the same intensity at 1.9 Hz. As control, we obtained surface recordings using Ag/AgCl cup electrodes (Unimed, Surrey, UK) filled with Ten20 conductive paste (Weaver & Co, Colorado, USA) with Nuprep skin preparation gel (Weaver & Co, Colorado, USA). Impedances were <5 kΩ. We also obtained control responses from peripheral nerves using electrodes placed at Erb’s point and popliteal fossa with the ground electrode at Fz. SEPs were recorded from the subdural electrode strip with a reference electrode placed on the neck. Each run was the averaged of 300 accepted sweeps with at least two runs obtained for each limb. Responses were recorded after lower limb stimulation for thoracic injuries and after upper then lower limb stimulation for cervical injuries at MAP 65 – 70 mmHg; then, MAP was increased using intravenous norepinephrine by ~20 mmHg and kept constant for 10 minutes before the SEPs were repeated.

**2.9. SEP signal analysis.** For each of the eight electrode contacts and each run, two neurophysiology staff independently and blindly assessed if SEP was present. Both assessors had to agree for the SEP to be termed active. We used Labchart v.8 (AD Instruments, Oxford, UK) to compute SEP amplitude (µV, maximum positive peak to maximum negative peak) and latency (ms, stimulus to maximum positive peak). In response to SCPP increase, overall BETTER SEP was defined as 25 % amplitude increase in >50 % of active contacts and overall WORSE SEP as 25 % amplitude increase in ≤50 % of active contacts. MIXED SEP was BETTER SEP with one side stimulated, but WORSE SEP with the other side stimulated. Because the change in latency in response to SCPP increase was small (-5 – 5 % in ~95 % electrodes), latencies were not analyzed.

**2.10. MRI/CT analysis.** A post-operative CT was obtained before SEP recording to determine the anatomical position of each electrode contact (Fig. 1C). These positions were transcribed onto the pre-operative T2 MRI to obtain, for each electrode contact, an axial BASIC (Brain and Spinal Injury Center) score as follows [24]: 0 = No signal change, 1 = Hyper intensity confined to grey matter, 2 = Hyper intensity beyond grey matter but not all white matter, 3 = Hyper intensity involves whole axial cord, 4 = Hypo intensity indicative of hemorrhage.

**2.11. Statistical analysis.** Analyses were done with XLStat Biomed (v.18.07; Addinsoft, NY, USA). SEP assessor agreement was tested with Cohen’s . LPR *versus* SCPP and *versus* [glucose] for the two groups (BETTER SEP, WORSE SEP) was tested with two-way ANOVA and *post hoc* Fisher’s least significant difference test. AIS grade improvement *versus* active contacts and *versus* amplitude increase was tested by two tailed t test. Significance was at *P* < 0.05.

**3. RESULTS**

**3.1. Patient characteristics.** We recruited and tested 12 patients with severe TSCI. Patients were young (mean age 40 years), 67 % were male, 58 % had cervical TSCI and 67 % had incomplete injuries. The mean interval between TSCI and surgery was <2 days and between TSCI and SEP testing 6 – 7 days. All patients were normothermic and off intravenous sedation and analgesic infusions for SEP testing. At follow up (mean 9.9 months), 42 % patients improved by one AIS grade and one patient deteriorated one AIS grade. Table 1 and the Supplement provide details.

**3.2. Injury site monitoring is safe.** There were no major probe-related complications (Table 2). Three patients had CSF leak from the skin probe sites, successfully managed with purse string sutures around these sites. To minimize the risks of CSF leak and infection, we tunnelled the probes >5 cm and covered the operative and probe skin sites with a large iodine impregnated drape. Compared with before surgery, 1 – 2 weeks after probe removal there was no intradural hematoma on MRI and no deterioration in AIS grade, in line with published safety data [21].

**3.3. Overall SEP analysis.** Of the 96 electrode contacts (12 patients × 8), four did not contact the cord according to the CT thus having no SEP. Overall, two independent and blinded assessors agreed 86 % of the time regarding the presence / absence of SEPs ( = 0.72, *P* <0.0005). SEP signals had a wide range of amplitudes and latencies from 1.0 – 112.7 V, 8.2 – 16.6 ms (upper limb stimulation) and 0.3 – 29.5 V, 17.9 – 30.6 ms (lower limb stimulation). Electrode contacts cranial to the site of maximal MRI injury (BASIC score 3 or 4) were ~50 % less likely to have detectable SEP signals than contacts with the same BASIC score, but caudal to the injury site (Fig. 2). Also, AIS grade inversely correlated with the probability of SEP detection cranial to the injury: 13 % AIS A patients had SEPs cranial to the injury, compared with 45 % AIS C patients. Thus, monitoring SEPs from the injured cord may be used to assess the severity of injury.

**3.4. Increasing SCPP produces heterogeneous SEP amplitude changes.** We then investigated whether increasing SCPP increases SEP amplitudes. Three patient groups were identified (Fig. 3A): BETTER SEP i.e. increasing SCPP improved overall SEP amplitudes in six (50 %) patients (AIS grades: 1 A, 5 C) bilaterally, WORSE SEP i.e. worsened overall SEP amplitudes in five (42 %) patients (AIS: 2 A, 1 B, 2 C) bilaterally, and MIXED RESPONSE i.e. improved SEP amplitudes when stimulating one side but worsened SEP amplitudes when stimulating the other side in one (8 %) patient (AIS A). Such heterogeneous amplitude changes in response to increasing SCPP were seen with upper and lower limb stimulations as well as cervical and thoracic injuries (Fig. 3B). For detectable SEP signals, intervention to increase SCPP had little effect on SEP latency and thus latencies were not analyzed further; with upper limb stimulation latency changed by -2.0 – 6.2 % (in 39/41 electrodes latency change was -5 – 5 %) and with lower limb stimulation by -5.4 – 3.8 % (in 34/36 electrodes latency change was -5 – 5 %).

**3.5. Injury site LPR correlates with SEP amplitude change in response to SCPP increase.** To understand why a patient’s SEP improves or worsens when SCPP is increased, we compared injury site metabolic profiles of the BETTER SEP and WORSE SEP groups (Fig. 4). In the BETTER SEP group, when SCPP is increased LPR decreases, indicating improved (more aerobic) injury site metabolism. In the WORSE SEP group, when SCPP is increased LPR increases, indicating more impaired (more anaerobic) injury site metabolism. In the BETTER SEP group, as injury site [glucose] is increased, LPR remains static suggesting that injury site metabolism is independent of tissue [glucose]. In the WORSE SEP group, LPR decreases as injury site [glucose] increases, indicating improved, i.e. more aerobic, injury site metabolism.

**3.6. SEPs correlate with neurological outcome.** SEPs significantly correlated with neurological outcome. In response to increased SCPP, the patients who improved an AIS grade had a greater increase in total active contacts (all limbs combined) than those that did not improve (22.7 % increase *versus* 0.4 % increase, *P* < 0.0001). Furthermore, with all limbs combined, the number of active contacts with amplitude increase when SCPP increased was higher in patients who improved an AIS grade compared to those that did not (75.1 % *versus* 47.1 %, *P* < 0.0001).

**4. DISCUSSION**

We showed that it is feasible and safe to record SEPs from the acutely injured human spinal cord by placing a subdural electrode strip, in addition to simultaneously monitoring injury site SCPP and metabolism. The data show that increasing the SCPP may have beneficial or detrimental effects on spinal cord electrical activity and metabolism.

**4.1. SEPs correlate with severity of injury.** Injury severity, quantified as AIS grade, correlated with the likelihood of SEP signal detection: AIS grade A patients had fewer active electrodes than AIS grade C patients. We also showed that spinal cord segments with BASIC scores 3 or 4 were more likely to block SEP conduction than cord segments with BASIC scores 0, 1 or 2, thus supporting BASIC [24] as a grading system of spinal cord tissue damage.

**4.2. Heterogeneous SEP response to SCPP increase.** We found heterogeneous SEP amplitude responses when SCPP increased: In 50 % patients, SEP amplitudes increased overall with left and right limb stimulations, suggesting that the SCPP increase was beneficial. In 42 % patients SEP amplitudes decreased overall with left and right limb stimulations, i.e. increasing SCPP appeared detrimental. These findings support our concept that too high and too low SCPPs are detrimental, i.e. there is an intermediate SCPPopt. SCPPopt which is individualistic [25] and varies temporally [9]. Our data suggest that universal MAP targets [9] or intervention to increase the MAP without monitoring SCPP and without computing a target SCPPopt may damage the injured cord.

**4.3. SEP response to SCPP increase correlates with injury site metabolism.** We found profound differences in the metabolism of the injured cord between patients who had BETTER SEPs compared with WORSE SEPs in response to increasing the SCPP. In patients with BETTER SEPs, increasing the SCPP reduced the LPR i.e. improved tissue metabolism, with no change in the LPR when injury site [glucose] increased. We hypothesize that O2, but not glucose, supply to the injury site is the limiting factor here. In these patients, increasing the SCPP may increase SCBF at the injury site thus reducing injury site hypoxia, in turn increasing SEP amplitudes. In contrast, in patients with WORSE SEP amplitudes, increasing the SCPP increased the LPR, i.e. worsened metabolism, and there was decrease in the LPR when injury site [glucose] increased. Increasing the SCPP in these patients may produce local steal at the injury site [12] thus increasing the LPR, and worsening the SEP. Glucose supply may be a limiting factor here thus explaining why increase in tissue [glucose] improves injury site metabolism (decreases LPR).

**4.4. Potential role of injury site penumbra.** Rodent studies suggest that changes in amplitude and latency correlate with the severity of cord injury, but reduction in amplitude is more sensitive than increase in latency for assessing the degree of injury [17]. In our study, patients with an increase in the number of active contacts and SEP amplitude when SCPP increased, were more likely to improve their AIS grade. This finding may indicate the presence of salvageable penumbral tissue, which is non-functional at low SCPP, but becomes functional when SCBF is increased. In patients without salvageable penumbra, increasing the SCPP will not increase the number of active contacts or SEP amplitude when SCPP is increased. These ideas are supported by measurements of SCBF showing a SCPP-sensitive penumbra only in some TSCI patients [12].

**4.5. Limitations of the study.** Though no significant complications were encountered, placement of subdural electrodes is invasive potentially exposing the cord to risks of damage. The data were obtained from a small number of patients (12 in total with only four AIS grade A), because of the requirement that patients self-ventilate; nevertheless, the large number of repeated measurements performed to obtain the final SEPs gives the results significance. The stability of SEP latencies shows that the amplitude changes were not secondary to other patient factors, whereas the correlation of SEPs with injury severity, injury site metabolism and neurological outcome support our conclusions. However, the small patient number precludes detailed analysis of correlations between SEPs and neurological outcomes.

**4.6. Clinical significance.** The heterogeneous SEP responses observed here when SCPP was increased, and previous findings that increasing the SCPP has a profound and heterogeneous effect on sensory and motor function [8, 26], injury site autoregulation [9] and metabolism [7] suggest individualized management for TSCI patients rather than the current practice of universal blood pressure guidelines [6]. Debates regarding timing of surgical management and novel drug therapies [27] may be difficult to address until individualized medical management has been introduced.

**5. CONCLUSIONS**

Intervention to increase the SCPP may be beneficial in some patients (increased SEP amplitudes, reduced LPR), but detrimental in others (reduced SEP amplitudes, increased LPR). Our findings support individualized management of TSCI patients, guided by injury site monitoring, rather than universal MAP targets.

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**FIGURE LEGENDS**

**Fig. 1. Setup for recording SEP, ISP and MD from injury site. A.** ADTech Medical 8-contact electrode strip. **B.** Schematic showing subdural position of electrode array (EA), ISP probe and MD catheter on cord surface, sutured dural opening and fibrin glue. **C.** Pre-operative MRI, post-operative CT and post-operative MRI of a 22-year-old male T9 AIS grade A TSCI. ISP (pressure probe), MD (microdialysis catheter), EA (electrode array).

**Fig. 2. SEP signal depends on injury severity. A.** SEPs from two patients: (*left*) 28-year-old C5 AIS A, and (*right*) 32-year-old C4 AIS C. Green electrodes (signal recordable), black electrodes (no detectable signal), ‘off’ (electrode not in contact with cord). BASIC score corresponding to each electrode is coded yellow-purple. **B.**Plot of % electrodes with detectable SEP in relation to the BASIC score of the cord under each electrode. Electrodes were termed caudal or cranial depending on whether the SEP signal was travelling toward or away from the region of maximum cord damage i.e. BASIC score 3/4. If maximum cord injury was BASIC 2, then all electrodes were classed caudal. ‘Off’ electrodes omitted. Mean +/- standard error. Trendline R = -0.88.

**Fig. 3. Effect of increasing SCPP on SEP amplitude. A.** SEPs in three patients at low (pink) and high (black) SCPP: (*top*) 19-year-old C5 AIS A (*middle*), 53-year-old C5 AIS A (*bottom*), 63-year-old C5 AIS C. (*left*) SEPs at low and high SCPP, (*middle*). % change in SEP amplitude in response to SCPP increase coded blue-white-red. Grey electrode (no recordable SEP), grey electrode + cross (electrode off cord surface). SCPP change in mmHg shown above each array. (*right*) corresponding vertebral levels. **B.** Plot of % increase in SEP amplitude in response to rise in SCPP *vs.* % of electrodes. Black (lower limb stimulation), white (upper limb stimulation). **C.** Effect of increasing SCPP on overall SEP amplitudes from each side (left *vs.* right) *vs.* % of patients. Higher higher (both sides increased), higher lower (one side increased, other decreased), lower lower (both sides decreased).

**Fig. 4. Effect of increasing SCPP on injury site metabolism. A.** Plot of injury site LPR *vs.* SCPP recorded for eight hours before SEPs. **B.** Plot of injury site LPR *vs.* injury site glucose recorded for eight hours before SEPs. Patients whose SEP amplitude increases (blue circles, Better SEP) or decreases (red squares, Worse SEP) with increase in SCPP. Mean +/- standard error. *P* < 0.05\*, 0.01\*\*, 0.005# for corresponding points, NS = not significant.