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**Monitoring Spinal Cord Tissue Oxygen in Patients with Acute, Severe Traumatic Spinal Cord Injuries**

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Microdialysis; Licox; monitoring; perfusion pressure; spinal cord injury; tissue oxygen

**ABSTRACT**

**OBJECTIVE:** To determine the feasibility of monitoring tissue oxygen tension from the injury site (psctO2) in patients with acute, severe traumatic spinal cord injuries.

**DESIGN:** We inserted at the injury site a pressure probe, a microdialysis catheter and an oxygen electrode to monitor for up to a week intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), tissue glucose, lactate/pyruvate ratio (LPR) and psctO2. We analysed 2,213 hours of such data. Follow-up was 6–28 months post-injury.

**SETTING:** Single-center Neurosurgical and Neurocritical Care units.

**SUBJECTS:** 26 patients with traumatic spinal cord injuries, American spinal injury association Impairment Scale A–C. Probes were inserted within 72 hours of injury.

**INTERVENTIONS:** Insertion of subarachnoid oxygen electrode (Licox), pressure probe and microdialysis catheter.

**MEASUREMENTS AND MAIN RESULTS:** psctO2 was significantly influenced by ISP (psctO2 26.7+0.3mmHg at ISP>10mmHg *versus* psctO2 34.7+0.8mmHg at ISP<10mmHg), SCPP (psctO2 26.8+0.3mmHg at SCPP<90mmHg *versus* psctO2 32.1+0.7mmHg at SCPP>90mmHg), tissue glucose (psctO2 26.8+0.4mmHg at glucose<6mM *versus* 32.9+0.5mmHg at glucose>6mM), tissue LPR (psctO2 25.3+0.4mmHg at LPR>30 *versus* psctO2 31.3+0.3mmHg at LPR<30) and fever (psctO2 28.8+0.5mmHg at cord temperature 37–38oC *versus* psctO2 28.7+0.8mmHg at cord temperature >39oC). Tissue hypoxia also occurred independent of these factors. Increasing the fraction of inspired oxygen by 0.44 increases psctO2 by 71.8% above baseline within 8.4 minutes. In patients with motor-incomplete injuries, fluctuations in psctO2 correlated with fluctuations in limb motor score. The injured cord spent 11% (39%) hours at psctO2 <5mmHg (<20mmHg) in patients with motor-complete outcomes, compared with 1% (30%) hours at psctO2 <5mmHg (<20mmHg) in patients with motor-incomplete outcomes. Complications were cerebrospinal fluid leak (5/26) and wound infection (1/26).

**CONCLUSION:** This study lays the foundation for measuring and altering spinal cord oxygen at the injury site. Future studies are required to investigate whether this is an effective new therapy.

**INTRODUCTION**

Traumatic spinal cord injury is a catastrophic event that affects 0.7–0.8 million new cases annually worldwide (1) and causes disability (paralysis, sensory loss, incontinence, loss of sexual function, hypotension, poikilothermia) (2), morbidity (renal failure, decubitus ulcers, pneumonia, urosepsis) (2) and psychological distress (anxiety, depression, chronic pain) (3). Unlike the management of acute, severe traumatic brain injury, which focuses on reducing secondary damage by monitoring and optimizing intracranial pressure and cerebral perfusion pressure (4), the management of acute, severe traumatic spinal cord injury is limited (5), lacking monitoring techniques to provide physiological information about the injury site.

 To facilitate the management of spinal cord injury in the Neurocritical Care Unit, we place a pressure probe intradurally at the injury site to record intraspinal pressure and spinal cord perfusion pressure, analogous to intracranial pressure and cerebral perfusion pressure for traumatic brain injury (6). We use the Codman ICP microsensor that has little (2 mmHg) drift in 108 hours (7). Intraspinal pressure and spinal cord perfusion pressure are clinically important parameters that correlate with injury site metabolism (8) and long-term outcome (9). Interventions to increase spinal cord perfusion pressure improve somatosensory (10) and motor-evoked (11) responses at the injury site, increase limb motor score (11, 12), lower the sensory level (13) and improve urinary (14) and anal sphincter (15) functions.

After traumatic brain injury, some units also monitor brain tissue oxygen. Factors other than high intracranial pressure and low cerebral perfusion pressure reduce brain tissue oxygen, e.g. low arterial oxygen, anemia, fever, dysglycemia, hypovolemia, vasospasm and patient transfer (16, 17). The benefit of brain tissue oxygen monitoring in brain injured patients is currently being investigated in three randomized trials (BOOST-III (18), OXYTC (19), BONANZA (20)). Unfortunately, the enthusiasm to establish brain tissue oxygen-guided interventions for brain injury has not been mirrored in spinal cord injury where there are no techniques to monitor spinal cord tissue oxygen. Here we used the Licox oxygen probe, which has no significant drift for at least 5 days (21). We demonstrate the feasibility of monitoring spinal cord tissue oxygen, identify treatable factors associated with cord hypoxia and explore the relation between cord tissue oxygen and neurological outcome.

**MATERIALS AND METHODS**

**Institutional Research Board Approvals.** Patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) study ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) NCT02721615) at St George’s Hospital. Approvals were from the St George’s, University of London Joint Research and Enterprise Service and the National Research Ethics Service London–St Giles Committee (10/H0807/23). The study has been performed in accordance with ethical standards, laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants.

**Inclusion/exclusion criteria.** We included all traumatic spinal cord injury patients recruited into ISCoPE between September 2016 and December 2020. Inclusion criteria are: i) severe traumatic spinal cord injury (American spinal injury association Impairment Scale grade A–C); ii) age 18–70 years; iii) timing between injury and surgery within 72 h. Exclusion criteria are: i) patient unable to consent; ii) other major comorbidities; iii) penetrating injury.

**Probe placement.** During posterior surgery, a pressure probe (Codman Microsensor Transducer®: Depuy Synthes, Leeds, UK), a microdialysis catheter (CMA61: CMA microdialysis AB, Solna, Sweden) and an oxygen electrode (Licox - CC1P1: Integra, Sophia-Antipolis, France) were inserted under the operating microscope between cord and arachnoid at the site of maximal cord swelling and were secured to the skin using sutures (Fig. 1). For patient management see S-Methods.

**Intraspinal pressure and spinal cord perfusion pressure.** The pressure probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab data acquisition hardware device, in turn linked to a laptop running the data acquisition and analysis software LabChart v.8 (ADInstruments, Oxford, UK). Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitor and then to the PowerLab system. Intraspinal pressure and blood pressure signals were sampled at 1 kHz. Spinal cord perfusion pressure was computed as mean arterial pressure minus intraspinal pressure. Intraspinal pressure is the same as intraparenchymal cord pressure at the injury site (22), which differs from cerebrospinal fluid pressure above or below because the swollen cord is compressed against dura thus compartmentalizing the intrathecal space (11, 22–24).

**Microdialysis.** Microdialysis was started postoperatively in the Neurocritical Care Unit as described (8, 25, 26). Central nervous system fluid (CMA microdialysis AB) was perfused at 0.3 μL/min using the CMA106 pump (CMA microdialysis AB). Microdialysis vials were changed hourly and analysed using ISCUS Flex (CMA microdialysis AB) for glucose, lactate, and pyruvate. The first two samples from each patient were discarded to allow priming of the microdialysis catheter and stabilization of the metabolite concentrations. 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from analysis. Our method measures spinal cord surface metabolism at the injury site, which correlates with intraparenchymal injury site metabolism, but differs from metabolites measured from lumbar cerebrospinal fluid (8, 25, 26).

**Tissue oxygen.** The Licox oxygen electrode was connected to a tissue oxygen Monitor (Integra, Integra, Sophia-Antipolis, France), in turn linked to a Philips Intellivue MX800 bedside monitor (Philips, Guildford, UK), which was connected to the PowerLab system. The signal was sampled at 1 kHz. In two patients, a second oxygen electrode was inserted intradurally about 2 cm below the injury site.

**Cord tissue oxygen changes.** For each >5 mmHg change in cord tissue oxygen, the preceding hour was assessed for the following possible causes: change in intraspinal pressure or spinal cord perfusion pressure, spinal cord metabolism, fraction of inspired oxygen, spinal cord temperature or sedation. We assessed whether the change in the putative causative factor could explain the change in cord tissue oxygen.

**Cerebrospinal fluid drainage.** A lumbar catheter was placed in11/26 patients at the time of surgery and about 10 mL cerebrospinal fluid was drained on several occasions to evaluate the effect on tissue oxygen. No more than 30 mL of cerebrospinal fluid was drained in a 24-hour period (27).

**Limb Motor Score.** Patients underwent regular AIS motor limb assessments with the patient off sedation or during sedation hold. Motor scores were compared to cord tissue oxygen values in the hour preceding the neurological assessment.

**Statistics.** Fourier analysis of the tissue oxygen signal was done using Weka v.3.8.5 (Waikato, New Zealand). [www.mycurvefit.com](http://www.mycurvefit.com) was used to fit linear, quadratic, exponential, sigmoid and Michaelis-Menten curves with *R2* and *P* values. The effects of temperature and cerebrospinal fluid drainage on tissue oxygen were evaluated with Student’s t-test. The % hours with tissue oxygen <5 mmHg for different outcomes were compared using 2. Data are mean + standard error. Statistical tests are noted as not significant (*NS*) or *P* < 0.05\*, 0.005\*\*, 0.0005†, 5 × 10-6#. Figs. 1C, 2 (A, B, D) and S-Figs. 1, 2, 4 use 1 kHz data. Figs. 2C, 3, 4 and S-Fig. 3 use averaged hourly values.

**RESULTS**

**Participants.** We recruited 26 patients (Table 1). Most (21/26) are males and most (22/26) are younger than 60 years. There are 14/26 cervical, 10/26 thoracic and 2/26 conus injuries. On admission, 15/26 had grade A, 3/26 grade B and 8/26 grade C injury severity (American spinal injury association Impairment Scale). 22/26 had posterior surgery only, and 4/26 had combined anterior-posterior approach. We analyzed 2,213 hours of monitoring data; on average, each patient was monitored for 85.0 hours (range 3.0–149.0). Patients were followed up at least 6 months (mean 12.9, range 6.0–28.0).

**Complications.** 5/26 patients had cerebrospinal fluid leak from the probe exit site successfully managed by placing extra skin sutures at the bedside, and 1/26 had wound infection successfully managed with wound washout (S-Table 1). We had no spinal cord damage, hematoma, or meningitis. Non-probe related complications were pneumonia (11/26), urosepsis (2/26), pressure ulcers (3/26), pulmonary embolus (1/26) and dysphagia (1/26).

**Cord tissue oxygen signal.** The cord tissue oxygen signal has major cardiac and minor respiratory frequency components (S-Fig. 1). Altering the fraction of inspired oxygen influences cord tissue oxygen (Fig. 2A). On average, increasing the fraction of inspired oxygen by 0.48 causes sigmoid rise in cord tissue oxygen to 71.8 % above baseline within 8.4 minutes. Decreasing the fraction of inspired oxygen by 0.44 causes exponential fall in cord tissue oxygen to 79.0 % below baseline within 6.0 minutes. Increasing the arterial oxygen partial pressure significantly correlated with increase in cord tissue oxygen in a Michaelis-Menten saturation curve relation (Fig. 2C). Increasing the fraction of inspired oxygen also correlated exponentially with increase in cord tissue oxygen. The injury site had lower tissue oxygen than the cord below, with no correlation between the two (Fig. 2D).

**Cord tissue oxygen correlates with injury site physiology and metabolism.** We observed significant sigmoid correlations between intraspinal pressure, spinal cord perfusion pressure, tissue glucose and tissue lactate/pyruvate ratio *versus* cord tissue oxygen (Fig. 3): As intraspinal pressure rises >5–10 mmHg, cord tissue oxygen falls reaching a minimum at intraspinal pressure 15–20 mmHg. As spinal cord perfusion pressure rises >80–90 mmHg, cord tissue oxygen suddenly rises reaching a maximum at spinal cord perfusion pressure 90–100 mmHg. As tissue glucose increases >4–6 mM/L, cord tissue oxygen progressively rises to a maximum at tissue glucose 8–10 mM. As tissue lactate/pyruvate ratio increases >10–20, cord tissue oxygen progressively falls to a minimum at tissue lactate/pyruvate ratio 40–50. Fever is associated with lower cord tissue oxygen compared with normothermia. Blood transfusion is also associated with significant rise in cord tissue oxygen (6.1+3.2 mmHg, mean+standard error), but without significant change in cord metabolism (tissue glucose -0.7+0.3 mmol/L, tissue lactate/pyruvate ratio -0.6+2.8) (S-Fig. 2).

**Causes of changes in cord tissue oxygen.** Rise in intraspinal pressure or drop in spinal cord perfusion pressure was often accompanied by drop in tissue oxygen. We also observed changes in tissue oxygen that are independent of changes in intraspinal pressure and spinal cord perfusion pressure. Examples are shown in S-Fig. 3. Factors that may cause change in tissue oxygen by >5 mmHg, ranked in decreasing frequency, are change in cord metabolism, change in intraspinal pressure or spinal cord perfusion pressure, change in the fraction of inspired oxygen, change in sedation, and change in cord temperature (S-Table 2). In more than a third of cases, the cause of tissue oxygen change is unknown.

**Effect of lumbar cerebrospinal fluid drainage on cord tissue oxygen.** Cerebrospinal fluid drainage had a variable effect on tissue oxygen, ranging from increase by 14.4 mmHg to decrease by -20.8 mmHg (S-Fig. 4). On average, cerebrospinal fluid caused no change in tissue oxygen in 9/11 patients, and caused a significant, but modest, reduction in tissue oxygen in 2/11 patients.

**Cord tissue oxygen correlates with neurological status.** The injured cord spends significantly more hours at low tissue oxygen values in patients with motor-complete compared with patients with motor-incomplete outcome at follow-up (Fig. 4A). For example, in patients with motor-complete outcome at follow-up, the cord spends 7–21 % hours daily at tissue oxygen <5 mmHg (cord infarction), compared with 0–2 % hours in patients with motor-incomplete outcome. In the eight motor-incomplete patients at presentation, we observed an inverted U-shaped relationship between the limb motor score *versus* the average psctO2 in the hour preceding each motor examination (Fig. 4B).

**DISCUSSION**

We showed that, after spinal cord injury, it is feasible to monitor tissue oxygen from the injury site, analogous to brain tissue oxygen monitoring in brain injury (20, 29). Cord tissue oxygen is a key physiological parameter that correlates with injury site physiology, metabolism, and neurological outcome. In our spinal cord injury patients, time spent below tissue oxygen thresholds was associated with long-term outcome, as reported for brain injury (29). The observation that, in patients with motor-incomplete injuries, fluctuations in cord tissue oxygen were accompanied by fluctuations in limb power suggests that cord tissue oxygen may influence spinal cord function. The inverted U-shaped relationship between motor score and cord tissue oxygen suggests that not only hypoxia, but also hyperoxia, may impair motor function. We have also identified factors that influence cord tissue oxygen that may be modified to improve outcome, e.g. increasing the fraction of inspired oxygen or increasing spinal cord perfusion pressure. These appear analogous to brain injury, where increasing the fraction of inspired oxygen (30, 31) or cerebral perfusion pressure (32) augments low brain tissue oxygen.

The Licox oxygen probe tip comprises a cylindrical polyethylene membrane ~18 mm2 that contains two polarographic electrodes and an electrolyte solution (S-Fig. 5A). Oxygen diffuses through this membrane to reach the electrodes where it is electrolytically reduced using revoxode technology, that is the chemical reaction at the electrode tips is reversible. This means that there is no calibration ‘drift’ with time, ensuring accurate measurement over days. We did not place the oxygen electrode intraparenchymally to avoid causing further spinal cord damage. Studies of other organs indicate that monitoring surface tissue oxygen provides accurate information about tissue perfusion and viability. Such studies include intraoperative monitoring of surface tissue oxygen from human brain during clipping of a middle cerebral artery aneurysm (33), in various brain tumors, in edematous brain and in arteriovenous malformations (34). Intraoperative surface tissue oxygen monitoring also detects changes in tissue perfusion in liver before and after portacaval shunting, in kidney during nephrectomy, in normal versus gangrenous bowel (33) and in graded ischemic regions of bowel (35). In our study, the injured cord is swollen and compressed against the dura with the oxygen probe sandwiched between cord and dura. Because the dura is largely metabolically inactive, the electrodes primarily detect oxygen that diffuses into the probe from the adjacent cord (S-Fig. 5B). If the cord is surrounded by cerebrospinal fluid, the oxygen electrode will detect oxygen that diffuses into the probe from the adjacent cord and cerebrospinal fluid (S-Fig. 5C). Therefore, the surface probe is always sensitive to cord tissue oxygen tension, but less sensitive when the cord is not compressed against dura.

Our study aimed to establish the technique of monitoring psctO2 from the injury site and investigate whether the measurements are meaningful and likely to help clinical management. This is by no means the definitive trial in the field. Though we did intervene for short periods, e.g. by increasing FiO2 to determine its effect on psctO2, we did not set out to compare neurological outcome in an interventional arm *versus* a control arm. Our study provides the basis for future research to determine whether intervention to alter psctO2 is an effective new therapy. Such studies will require multivariable analysis to define whether any benefit of increasing psctO2 is independent of other prognostic factors such as severity of injury (36), patient age (37), co-morbidities (38), fever burden (26), timing of surgery (39) and spinal cord perfusion pressure (9).

 Current management guidelines recommend maintaining mean arterial pressure 85–90 mmHg for the first week after spinal cord injury (5). However, two patients with the same mean arterial pressure, but different intraspinal pressures, will have different spinal cord perfusion pressures. Also, two patients with the same spinal cord perfusion pressure may have different cord tissue oxygen. Multi-modality monitoring overcomes these problems by allowing individualized management (8, 11) that may ultimately yield management guidelines for spinal cord injury analogous to brain injury protocols that incorporate both pressure and tissue oxygen monitoring (40, 41). Multi-modality monitoring may also be employed to evaluate the impact of therapeutic interventions on the injury site. For example, treating fever in spinal cord injury improves injury site metabolism (assessed using microdialysis) (26) and cord tissue oxygen (shown here), whereas blood transfusion increases tissue oxygen, but without improving metabolism, in spinal cord (shown here) and brain injury (42).

 A limitation of our study is the small numbers of patients (n = 26), though our conclusions are supported by a large dataset (2,213 hours of monitoring, 165 motor examinations) and long follow-up (>6 months). As shown here, and in an earlier study (43), the main complication of injury site monitoring is cerebrospinal fluid leak through the probe skin exit sites. The insertion procedure requires surgery, which is another limitation. An alternative is to insert probes into the lumbar cerebrospinal fluid, which is technically easy and does not require surgery (44, 45). However, there is lack of correlation between intraspinal pressure, spinal cord perfusion pressure and microdialysis values measured at the injury site compared with the lumbar cerebrospinal fluid (27). Draining lumbar cerebrospinal fluid has been proposed as a therapeutic maneuver in spinal cord injury (44, 45), but it does not effectively reduce intraspinal pressure (27) or improve cord tissue oxygen (shown here) at the injury site probably because the swollen cord is compressed against the dura (11, 22–24). The effect of durotomy on cord tissue oxygen has not been investigated; however, a randomized, controlled trial termed DISCUS (Duroplasty for Injured cervical Spinal Cord with Uncontrolled Swelling) is underway to evaluate the effect of expansion duroplasty on neurological outcome after spinal cord injury. [https://fundingawards.nihr.ac.uk/award/NIHR130048].

**CONCLUSIONS**

After spinal cord injury, tissue oxygen monitoring is feasible and allows prompt detection and treatment of injury site hypoxia. Further studies are needed to investigate whether such intervention improves neurological outcome.

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**FIGURE LEGENDS**

**Fig. 1. Monitoring technique.** 23-year-old male, C5 American spinal injury association grade A (patient no. 89). **A.** Intraoperative photo of exposed dorsal dura at injury site. **B.** Surgical site after wound closure. Drain, wound drain; ISP, intraspinal pressure probe; MD, microdialysis catheter; psctO2, oxygen probes (at injury site + below); suction, suction tubing. **C.** Multi-modality monitoring from injury site: ISP (intraspinal pressure), SCPP (spinal cord perfusion pressure), psctO2 (cord tissue oxygen), tissue glucose, LPR (lactate/pyruvate ratio).

**Fig. 2. Fraction of inspired oxygen and arterial oxygen *versus* cord tissue oxygen. A.** Effect of oxygen challenge on intraspinal pressure, spinal cord perfusion pressure and cord tissue oxygen in 23-year-old male, C5 American spinal injury association grade A (patient no. 89). **B.** Summary of oxygen challenge data. (*top*) Cord tissue oxygen (psctO2) *versus* time after increasing the fraction of inspired oxygen **(**FiO2) from 0.38 + 0.04 to 0.82 + 0.09 (9 repeats, 4 patients) and (*bottom*) decreasing the fraction of inspired oxygen from 0.89 + 0.07 to 0.41 + 0.04 (8 repeats, 3 patients). **C.** Cord tissue oxygen (psctO2) *versus* arterial oxygen (paO2). *Inset:* paO2 *versus* FiO2. **D.** Cord tissue oxygen (psctO2) *versus* time. 23-year-old male, C5 American spinal injury association Impairment Scale grade A (patient no. 89). Green, Cord tissue oxygen (psctO2) at injury site; Black, Cord tissue oxygen (psctO2) of spinal cord below injury site. *Inset*: psctO2 at injury site *versus* psctO2 below. B, C and D-inset show mean + standard error. Regression lines: B-top (sigmoid, *R2* = 1.00), B-bottom (exponential decay, *R2* = 0.99), C (Michaelis-Menten, *R2* = 0.83), C-inset (exponential, *R2* = 0.98), D-inset (linear, *R2* = 0.02). *NS*, Not significant; *P* < 0.005\*\*, 0.0005†, 5×10-6#.

**Fig. 3. Injury site parameters** ***versus* cord tissue oxygen. A.** Cord tissue oxygen (psctO2) *versus* intraspinal pressure (ISP), *R2* = 0.94. **B.** psctO2 *versus* spinal cord perfusion pressure (SCPP), *R2* = 0.94. **C.** psctO2 *versus* tissue glucose, *R2* = 0.95. **D.** psctO2 *versus* tissue lactate/pyruvate ratio (LPR), *R2* = 1.00. Data (A-D) are hourly values, mean+standard error fitted with sigmoid regression. **E.** psctO2 readings at spinal cord temperatures 37–38 0C and >39 0C. Individual data points (circles), means (lines). *P* < 0.05\*, 5×10-6#.

**Fig. 4. Cord tissue oxygen (psctO2) correlates with neurological status. A.** % of hours with cord tissue oxygen (psctO2) below threshold *versus* psctO2 threshold, for American spinal injury association Impairment Scale (AIS) grade at follow-up (A, B *versus* C, D) fitted with sigmoid regressions (*R2* = 1.00 for both) *Inset*: % of hours with psctO2 <5 mmHg *versus* days after injury for AIS at follow-up (A, B *versus* C, D). **B.** Motor score *versus* average psctO2 (mmHg) in the hour preceding the motor exam in motor-incomplete patients (AIS grade C) patients. Quadratic regression, *R2* = 0.97. Mean + standard error. *P* < 0.05\*, 0.0005†, 5×10-6#.