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**Improving neurological outcome in
patients with acute traumatic spinal cord
injury by monitoring from the injury site**

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BSc(Hons) MBBS MRCS(Eng)

Thesis submitted for the award of Doctor of Philosophy

January 2024

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Professor Marios C. Papadopoulos & Dr Argyro Zoumprouli

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Declaration

I certify that the intellectual content of this PhD thesis is the product of my own work, with guidance from my supervisors. All the assistance received in preparing this thesis and sources are acknowledged. I am solely responsible for the contents of this thesis, and there is no intentional misrepresentation of research results.

The studies in this thesis are either submitted for publication or published in peer-reviewed journals, and have been presented at national and international academic conferences. I confirm that this thesis has not been submitted for any other degree.

My PhD thesis is based on three research papers listed below, of which I am first author. My primary supervisor is Dr S. Saadoun PhD, and secondary supervisors are Prof. M.C. Papadopoulos MD FRCS and Dr Argyro Zoumprouli PhD. Dr Saadoun and Prof. Papadopoulos conceived the studies. Prof. Papadopoulos performed the surgery and inserted the research monitoring probes. The post-operative care was by Prof. Papadopoulos, Dr Zoumprouli and the neuro-intensive care unit staff at St George's University Hospitals NHS Foundation Trust, London, UK.

Contributions

I was responsible for patient recruitment, data collection, analysis and patient follow-up for all the studies. My predecessor research fellows helped collect oxygen (study 1) and fever (study 2) data. I established the monitoring setup for breathing function (study 3) with the help of Dr Saadoun, Dr Zoumprouli, Medical Physics & Engineering staff, and two Consultant Radiologists at St George's University Hospitals NHS Foundation Trust. Data analysis was performed by myself with Dr Saadoun. Together, Dr Saadoun and I prepared the text, tables and figures for each manuscript.

PhD Thesis Research Papers

- (i) Visagan R, Hogg F, Gallagher M, Kearney S, Zoumprouli A, Papadopoulos MC, Saadoun S. Monitoring spinal cord tissue oxygen in patients with acute, severe traumatic spinal cord injuries. *Crit Care Med* 2022; 50(5):e477-e486.
- (i) Visagan R, Kearney S, Blex C, Serdani-Neuhaus L, Kopp M, Schwab, JM, Zoumprouli A, Papadopoulos MC, Saadoun S. Adverse effect of neurogenic, infective and inflammatory fevers on acutely injured human spinal cord. *J Neurotrauma* 2023; 40(23-24):2680-2693.
- (ii) Visagan R, Boseta E, Zoumprouli A, Papadopoulos MC, Saadoun S. Correlation between breathing and spinal cord perfusion pressure in patients with acute, severe cervical traumatic spinal cord injury. *Crit Care* 2023; 27(1):362.



Visagan Ravindran

Date: 11/01/2024

Thesis Abstract

Introduction

Acute, severe traumatic spinal cord injury (TSCI) is a catastrophic event. No effective treatment exists for the primary neurological injury. Detecting and treating secondary neurological injury, however, is feasible, and may improve neurological outcome. This thesis contains three studies utilising injury site monitoring, translating to novel applications in the clinical management of TSCI.

Research Aims

- (i) To develop a novel technique to monitor tissue oxygen in TSCI
- (ii) To test the hypothesis that infective, inflammatory, and neurogenic fevers are detrimental
- (iii) To test the hypothesis that spinal cord perfusion pressure (SCPP) affects breathing function in patients with cervical TSCI

Methods

Patients sustaining acute, severe TSCI within 72 hours, underwent cervical decompression (posterior +/- metalwork fixation +/- anterior surgery). Simultaneously, microsurgical insertion of subdural pressure and microdialysis probes (+/- oxygen electrode +/- lumbar drain) was performed. Multimodality data were acquired from the injury site on neuro-intensive care for up to one week. Relevant clinical assessments were obtained during monitoring and follow-up.

Results

The key findings are, that following acute TSCI:

- (i) It is feasible to monitor spinal cord tissue oxygen ($p_{\text{sct}}\text{O}_2$) from the injury site. $p_{\text{sct}}\text{O}_2$ is a key parameter, associated with injury site physiology, metabolism, and neurologic outcome.
- (ii) Deranged injury site metabolism defines all three major types of fever (neurogenic, inflammatory and infective). Therefore, all are likely harmful. Specific clinical features of different fever types can be exploited to distinguish neurogenic from non-neurogenic fever.
- (iii) Monitoring breathing function using ultrasound and diaphragmatic EMG, is feasible and reproducible. SCPP correlates with breathing function, cord hypo-perfusion and hyper-perfusion being detrimental. SCPP 80 – 90 mmHg correlates with improved diaphragmatic and intercostal muscle contractility.

Conclusions

Multimodality monitoring following TSCI is feasible and safe. Improving injury site $p_{\text{sct}}\text{O}_2$, restoring normothermia and optimising breathing function, may minimise secondary neurological injury to enhance neurological recovery.

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Without the generous co-operation of our patients, this research would be impossible. Despite suffering a sudden life-changing trauma, their desire to selflessly support our research, represents the profound depth of human resilience. My research builds on a body of impactful scientific insights, defined by my predecessors (M. Werndle, I. Phang, M. Gallagher & F. Hogg). The high standards they achieved remained a source of inspiration during my research.

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Last but not least, this thesis is dedicated to my parents. Their support enabled the opportunities leading me to this stage. I am grateful to my partner Laura, for her understanding throughout the demands of this process.

List of Abbreviations

AANS	American association of neurological surgeons
ABP	Arterial blood pressure
AIS	ASIA impairment scale
ASIA	American spinal injuries association
ATLS	Advanced trauma life support
BTf	Brain Trauma Foundation
CNS	Congress of Neurological Surgeons
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
EDI	Diaphragm electromyography
EMG	Electromyography
LE	Life expectancy
ICP	Intracranial pressure
ICU	Intensive care unit
ISCoPE	Injured Spinal Cord Pressure Evaluation study
ISNCSI	International Standards for Neurological Classification of Spinal Cord Injury
ISP	Intraspinal pressure
LE	Life expectancy

LPR	Lactate-pyruvate ratio
MAP	Mean arterial pressure
MD	Microdialysis
MRI	Magnetic resonance imaging
NeuroICU	Neurological Intensive Care Unit
NLI	Neurological level of injury
PaCO₂	Partial pressure of carbon dioxide in arterial blood
PaO₂	Partial pressure of oxygen in arterial blood
PCT	Serum Procalcitonin
P_{set}O₂	Spinal cord tissue oxygen
PRx	Cerebral pressure reactivity index
RCT	Randomised Controlled Trial
RR	Respiratory rate
RTA	Road traffic accident
SCPP	Spinal cord perfusion pressure
sPRx	Spinal pressure reactivity index
SSEP	Somatosensory evoked potential
TBI	Traumatic brain injury
TSCI	Traumatic spinal cord injury
USS	Ultrasound scan
WCC	White cell count

Key Concepts & Definitions

Cytokine - Signalling proteins secreted by cells of the immune system

Excursion of diaphragm – maximal movement of the diaphragm during breathing

EDI min - Minimum EDI (diaphragm EMG signal) between breaths

EDI peak - Peak EDI (diaphragm EMG signal) per breath

Fever - Systemic temperature $> 38^{\circ}\text{C}$ (Chapter III) or Cord temperature $> 39^{\circ}\text{C}$

Intraspinal pressure (ISP) - Pressure wave transmitted from the spinal cord injury site, analogous to ICP

Microdialysis - Sampling technique measuring spinal cord surface metabolism at the injury site. It measures the hourly concentration of small molecules in the extracellular fluid (glucose, lactate, LPR, glutamate, glycerol)

Spinal cord perfusion pressure (SCPP) - Calculated as “*Mean Arterial Pressure (MAP) minus ISP*”, analogous to cerebral perfusion pressure ($CPP = MAP - ICP$)

Spinal cord tissue oxygen (P_{scfO_2}) - Surface oxygen tension of the spinal cord injury site

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Publications

Below are relevant peer-reviewed publications generated from the work presented in this thesis.

I - SPINAL CORD TISSUE OXYGEN MONITORING

Visagan R, Hogg F, Gallagher M, Kearney S, Zoumprouli A, Papadopoulos MC, Saadoun S. Monitoring spinal cord tissue oxygen in patients with acute, severe traumatic spinal cord injuries. *Crit Care Med* 2022; 50(5):e477-e486.

II - EFFECT OF FEVER ON INJURED SPINAL CORD

Visagan R, Kearney S, Blex C, Serdani-Neuhaus L, Kopp M, Schwab, JM, Zoumprouli A, Papadopoulos MC, Saadoun S. Adverse effect of neurogenic, infective and inflammatory fevers on acutely injured human spinal cord. *J Neurotrauma* 2023; 40(23-24):2680-2693.

III - EFFECT OF SPINAL CORD PERFUSION PRESSURE ON BREATHING

Visagan R, Boseta E, Zoumprouli A, Papadopoulos MC, Saadoun S. Spinal Cord perfusion pressure correlates with breathing function in patients with acute, severe traumatic spinal cord injuries. *Crit Care* 2023; 27(1):362.

Presentations

Monitoring spinal cord tissue oxygen in patients with acute, severe traumatic spinal cord injuries.

- Oral. Sep 2023. Society of British of Neurological Surgeons, Twickenham, London, UK. Prize-awarded.
- Oral. Mar 2023. Spine Summit – American Association of Neurological Surgeons / Congress of Neurological Surgeons (AANS/CNS), Miami, USA. Prize-awarded.

Correlation between breathing and spinal cord perfusion pressure in patients with acute, severe cervical traumatic spinal cord injury.

- Oral. Sep 2023. Society of British of Neurological Surgeons, Twickenham, London, UK.

Adverse effect of neurogenic, infective and inflammatory fevers on the acutely injured human spinal cord.

- Oral pre-recorded ‘iPresentation’. Mar 2023. AANS/CNS Spine summit, Miami, USA.

Spinal cord tissue oxygen guided treatment for patients with acute, severe traumatic spinal cord injuries.

- Accepted Oral, presented live virtually due to COVID-19 pandemic. Oct 2021. European Association of Neurosurgical Societies (EANS). Hamburg, Germany.
- Accepted Oral, presented live virtually due to COVID-19 pandemic. Sept 2021. International Spinal Cord Society (ISCoS). Vancouver, Canada.

Fellowships & Prizes

1. Campbell-Connolly Neurotrauma Prize, 2023

Awarding Body: Society of British Neurological Surgeons (SBNS)

Details: Nationally competitive neurosurgery prize for neurotrauma paper. Invited presenter for SBNS academic conference September 2023 to present paper.

2. Christopher Shaffrey International Travelling Fellow Award, 2023

Awarding Bodies: American Association of Neurological Surgeons / Congress of Neurological Surgeons (AANS/CNS)

Details: Globally competitive travelling fellowship for research in spine surgery.

3. Royal College of Surgeons of England - Research Fellowship, 2022-2023

Awarding Body: Royal College of Surgeons of England

Details: Nationally competitive research fellowship open to candidates from all surgical specialties in the UK. Awarded following application, presentation and viva voce.

1 INTRODUCTION

Traumatic spinal cord injury (TSCI) is a severely disabling, catastrophic event with no cure. Global incidence is reportedly 0.93 million (0.78–1.16 million) with the highest age-standardised incidence rates concentrated in the Middle East (Syria, Yemen, Iraq and Afghanistan), North America, Western Europe and high-income Asia-Pacific¹. Global prevalence in 2016 was estimated at 27 (25–30) million, an age-standardised rate of 268 (340– 409) per 100,000, being highest in western Europe (854 per 100,000)¹. The specific aetiology of TSCI is country-dependent and causes include falls, road traffic accidents (RTAs) and violence².

Survival and life-expectancy are associated with injury level and severity³. Severe C1-4 TSCI, American Spinal Injuries Association (ASIA) Impairment scale (AIS) grades A-C, have 64-69% of the mean life-expectancy versus 88-91% in T1-S5 injuries³. TSCI causes profound neurological impairment⁴ (paralysis, sensory loss, neurogenic bowel & bladder, sexual and autonomic dysfunction), systemic co-morbidities⁴ (decubitus ulcers, respiratory dysfunction, pneumonia, urosepsis and renal failure), and psychological distress (anxiety, depression and chronic pain)⁵. In sum, TSCI represents a significant health-economic burden to society², costing an average of £1.12 million per case (mean £0.47 million for AIS grade D – mean £1.87 million for tetraplegia AIS A-C)⁶.

Despite this, there is no effective treatment. This PhD thesis evaluates how specific novel monitoring techniques in acute, severe TSCI can translate to therapeutic targets to improve neurological outcome.

1.1 Current management of TSCI

Acute TSCI is a medical emergency, initially managed in the pre-hospital setting according to Advanced Trauma Life Support (ATLS®) principles in the UK^{7,8}. This prioritises airway maintenance with cervical-spine protection, using rigid cervical immobilisation for suspected TSCI⁹. Following breathing and circulatory stabilisation, patients should be transported to a major trauma centre for further evaluation⁸. Both UK & USA guidelines recommend obtaining computed tomography (CT) and magnetic resonance imaging (MRI) of the spine, and to classify the TSCI using an ASIA chart^{8,9}.

The ASIA classification⁹ is globally adopted, and predictive of neurological recovery¹⁰, compared to the clinical distinction of complete versus incomplete injury¹¹. However the prognostic accuracy of AIS grades B and C may be less consistent¹². The alternative, simpler Frankel scale does not incorporate neurological level, with subjectivity in grading motor function, and less sensitivity to subtle neurological improvement¹³.

Several controversies exist. For instance, medical management is variable in developed countries. Haemodynamic recommendations from the American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS), include maintaining a mean arterial pressure (MAP) of 85-90 mmHg for up to one week⁹. In the UK, the National Spinal Cord Injury Board advocate maintaining a MAP of 90–100 mmHg.¹⁴ However, in a national survey, 54% of neuroICU physicians reported aiming for a MAP target > 80mmHg¹⁵. MAP recommendations are not supported by robust trial evidence, limited to historic, uncontrolled and heterogenous cohort studies^{16–18}.

Surgical management aims to decompress neural elements, stabilise the spine to prevent further neurological injury¹⁹, facilitate early neuro-rehabilitation and

mobilisation²⁰. Timely intervention may mitigate medical complications such as infection and pressure sores²¹, which result in up to 30% of TSCI readmission rates¹⁹. However, there are no randomised trials evaluating surgery versus conservative management²². Despite a convincing biological rationale^{23–25} for early surgical decompression of the spinal cord, timing of surgery remains controversial²⁶. A landmark multi-centre prospective cohort study (STASCIS)²⁷ concluded the odds of achieving at least a 2 AIS grade improvement were significantly higher in patients undergoing surgery within 24 hours (OR 2.57, 95% CI 1.11-5.97). Methodological limitations (non-randomisation, time intervals and 30% loss to follow-up) downgraded its influence on AANS/CNS guidelines⁹. A subsequent pooled analysis concluded early (<24 hours post injury) versus late (>24 hours) surgery, amounted to greater sensorimotor and ASIA grade recovery at 1 year²⁸.

However, these findings are not ubiquitous. The OSCIS²⁹ study randomised 70 motor-incomplete cervical TSCI patients to early (<24 hours) versus late (> 2 weeks) surgery, concluding similar motor recovery at 1 year, despite faster recovery in the early group. Finally, a recent prospective multi-centre study (SCI-POEM) did not find statistically or clinically significant differences in lower extremity motor score at one year, between early (n=159 ≤ 12 hours post injury) versus late (n=135 >12 hours & < 14 days post-injury) surgery³⁰.

The reasons why several large studies have failed to define a robust relationship between surgical timing and neurological outcome, may be due to differences in the overall approach to managing the neurological injury in TSCI versus traumatic brain injury (TBI).

1.2 Comparison with acute traumatic brain injury (TBI) management

During a traumatic event, the initial mechanical insult evokes an irreversible primary neurological injury³¹. In contrast to the variable management of TSCI, modern TBI management is more systematised. Surgical mass lesions are promptly evacuated, and patients urgently transferred to ICU for physiological monitoring. Management includes detection of potentially treatable causes of secondary injury, such as hypotension, ischaemia and glycaemic derangement³². This approach differs substantially to acute TSCI, despite the primary and secondary injury to cranial and spinal neurological tissue being equivalent¹⁹. Multimodality monitoring provides prospective neurophysiological data and may detect secondary neurological injury.

1.2.1 Multimodality monitoring in TBI

The severe TBI patient on ICU commonly has an intracranial pressure (ICP) probe placed intraparenchymally and MAP monitored invasively. This permits the calculation and optimisation of cerebral perfusion pressure ($CPP = MAP - ICP$), a surrogate marker of cerebral blood flow. Other monitored parameters include vascular pressure reactivity index (PRx), optimum CPP (CPP_{opt}), microdialysis (MD), tissue oxygen (P_{btO_2}) and spreading depolarizations³³. PRx, a marker of autoregulation, is proposed as a guide to individualising CPP treatment in TBI³⁴. It represents the moving correlation coefficient between MAP and ICP over a 5-minute window. When plotted against CPP, it generates a U-shaped curve; the lowest point indicates the CPP at which pressure reactivity is optimal – termed CPP_{opt} ³⁴. Overall, medical and surgical interventions focus on reducing ICP and restoring CPP to reduce secondary neurological injury. These include surgery, to address mass lesions or critical herniation

and cerebrospinal fluid (CSF) drainage, and ICU management including osmotherapy, hypocapnia, inotropic support and barbiturate coma³⁵.

1.2.2 Physiology-driven management in TBI

Despite ICP-guided treatment previously shown not to be superior to imaging/clinical examination-based treatment in a historic randomised trial (BEST-TRIP)³⁶, fundamental criticisms limit the generalisability of the study findings³⁷. Routine ICP monitoring in TBI is now recommended by the Brain Trauma Foundation (BTF) Guidelines in “all salvageable patients with a TBI and abnormal CT scan”³⁸. It facilitates the tiered management of raised ICP and recent prospective data suggest ICP monitoring may predict (CENTRE-TBI study) and reduce mortality (SYNAPSE-ICU study)^{39–42}. Together with MAP, recording continuous ICP allows calculation of CPP as well as derived indices – PRx, CPP_{opt} and compensatory reserve (RAP).

CPP-guided treatment is advocated by the BTF for favourable outcomes and reduced 2-week mortality, recommending a target of 60-70 mmHg³⁸. Optimising CPP is theorised to preserve the ischaemic penumbra and limit secondary injury from free radicals, excitotoxic and inflammatory insults⁴³. This supported by beneficial effects on brain physiology (p_{bt}O₂^{44,45} and MD⁴⁶) and improved survival in large retrospective^{47,48} and small prospective^{49–51} series. However, the optimal CPP threshold is unclear and may not be universal to all TBI patients. To address this, the ongoing COGiTATE trial established feasibility of randomising patients to either BTF guideline endorsed CPP target range versus individualised autoregulation-guided CPP_{opt} therapy⁵².

However, ICP and CPP alone may not explain the whole picture. Ischaemia, evidenced by low P_{bt}O₂, may occur independently of changes in perfusion⁵³. In early studies, P_{bt}O₂ monitoring in TBI has been shown to correlate with outcome⁵⁴ and

mortality⁵⁵. Randomised phase 3 trial evidence is awaited from 3 large studies (OXY-TC⁵⁶, BOOST-III⁵⁷ & BONANZA⁵⁸). Therefore, currently guidelines endorse only level III evidence to guide and standardise $p_{bt}O_2$ guided-treatment (Seattle International Severe TBI Consensus Conference 2020)⁵⁹. In contrast, there are no established techniques to even monitor spinal cord oxygenation from the injury site.

1.2.3 Microdialysis evaluates metabolic stress

MD is an established technique for continuously monitoring metabolite concentrations in the extracellular interstitial fluid^{60,61}. Since its application in clinical TBI management over 30 years ago⁶², correlations with outcome have been shown – specifically low and high glucose, high lactate:pyruvate ratio (LPR), and prognostic association with glutamate³². By evaluating cellular substrate delivery and metabolism, MD can assess the effect of key metabolic stressors, such as fever, on neuronal metabolism^{63,64}. Fever has been shown to be strongly associated with poor outcome following neurological injury^{65,66}. Modern management favours normothermia, hypothesised to minimise secondary neurological injury⁶⁷. Intracranial MD allows the evaluation of metabolic insults such as fever and the effect of pharmacotherapeutic interventions on neuronal metabolism. This is not the case in TSCI despite fever being prevalent and detrimental to the injury site⁶⁸.

Overall, the lack of physiological monitoring in TSCI has limited our detection (and therefore treatment) of potentially reversible secondary insults.

1.3 The ISCoPE study

To address the lack of multimodality monitoring and, therefore, a physiology-targeted approach to TSCI, the Injured Spinal Cord Pressure Evaluation (ISCoPE) study⁶⁹ was established in 2010 at St George's Hospital. Patients aged 18-70 years with acute severe TSCI (AIS A–C) are recruited for surgery within 72 hours of injury. Concurrent comorbidities likely to influence outcome and penetrating injuries are excluded. During surgery to decompress and/or fix the spine with metalwork, subdural probes are placed under the microscope to monitor physiologic and metabolic parameters. The probes transmit data for up to one week after which they are removed on neuroICU. Full methodological details will be expanded in later sections. The initial objective of the study was to develop methods to measure cord pressure and metabolism from the injury site, trends in cord pressure and correlations with clinical outcomes. 98 patients have been recruited to date (01/07/23). From this cohort, several hypotheses have been tested, generating novel concepts in the field of TSCI, explored in subsequent sections.

1.4 TSCI monitoring techniques

Figure 1 shows the location of our TSCI monitoring probes, which are placed intradurally at the cord injury site during surgery. Currently, up to two probes are placed (i) a pressure probe recording intraspinal pressure, which we term ISP, and (ii) a microdialysis (MD) catheter evaluating spinal cord metabolism from the injury site.

The ISP measurement technique was defined in 2014⁷⁰, where Codman MicroSensor (DePuy Synthes, Leeds UK) probes were placed subdurally to monitor the pressure of the injured spinal cord. The MD measurement technique applied to TSCI was defined in 2016⁷¹. A subdural hepatic MD catheter (Solna, Sweden) placed at the

injury site allows hourly recording of spinal cord metabolites: glycerol, glutamate, glucose, lactate and pyruvate. The feasibility and low risk profile of both techniques has been established^{70,71}.

Both ISP and MD monitoring provide a focal measurement from the cord surface injury site versus diffuse measurement from the CSF. In TSCI the injured cord swells causing circumferential CSF space obliteration on MRI⁷². For ISP, comparability between subdural and intraparenchymal recordings has been demonstrated⁷², the implication being that cord swelling, propagates intraparenchymal pulsations to the probe. This comparability is analogous to subdural versus intraparenchymal ICP monitoring in the brains of animals⁷³ and humans⁷⁴. Extradural ISP⁷⁵ was shown to be an attenuated version of the subdural ISP signal and is thus not considered further.

Alternatively, lumbar CSF monitoring^{76,77} for pressure (CSF-P) guided management has appeal in TSCI, given the availability and ease of placement of lumbar catheters. However, our group showed previously that ISP and CSF-P are not consistently equivalent⁷². MRI revealed acute cord swelling against dural compression forms three distinct compartments: above, below and the injury site itself. The correlation between ISP and CSF-P was shown to be dynamic, varying with cord oedema extent and compression. Waveform analysis supported the idea that CSF-P assesses the CSF compartment whereas ISP assesses the solid ($\approx$ intraparenchymal) compartment. Therefore, subdural ISP monitoring is more accurate for cord pressure.

Similarly, MD catheters placed on the surface of the cord injury site yield greater deranged metabolite concentrations than below the injury⁶⁸. This may be secondary to cord swelling and dural compression, influencing metabolite levels. Injury site MD also correlated with intraparenchymal MD in this study, corroborated by porcine models of the beating heart⁷⁸, liver^{79,80} and small bowel⁸¹. Therefore, given the

greater accuracy of subdural ISP and MD monitoring compared to alternative placement, this method is adopted in my PhD experiments.

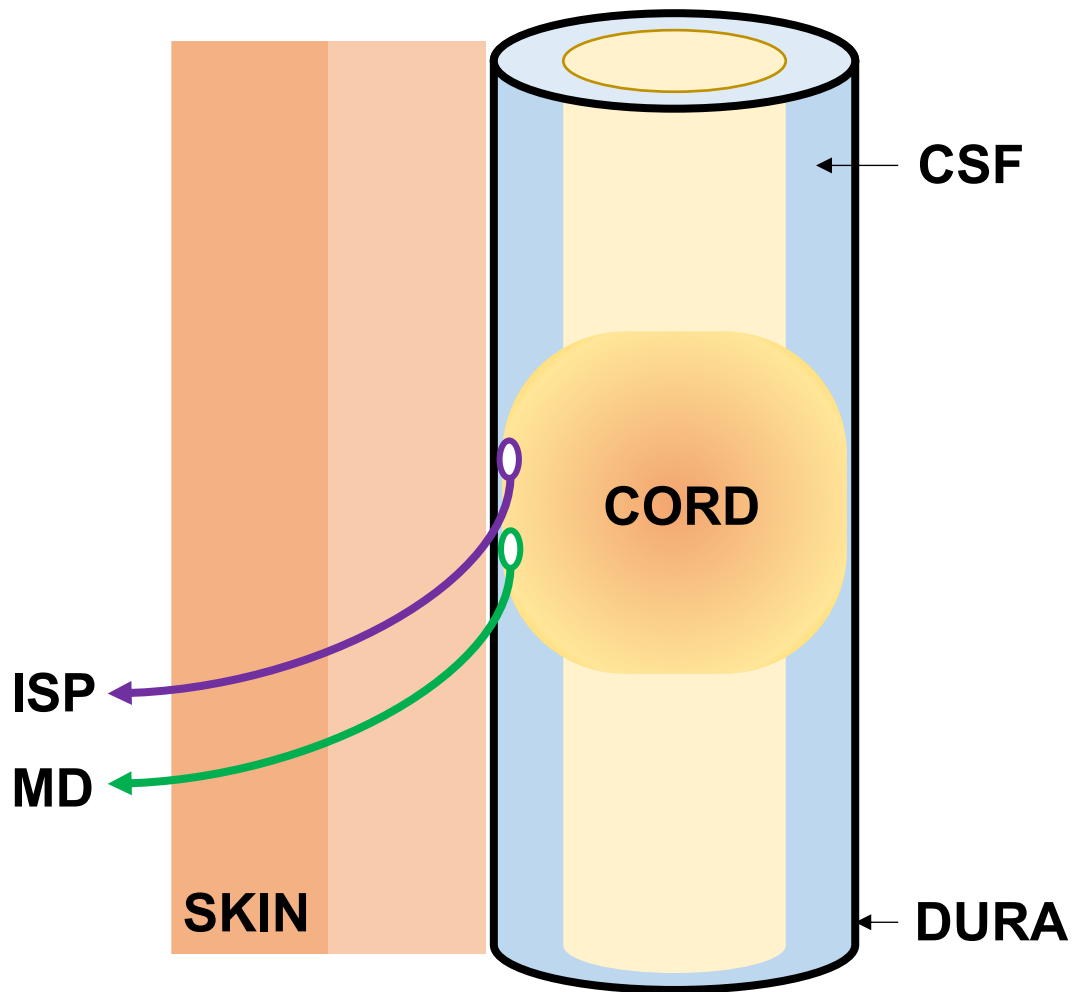


Fig. 1: The location of spinal cord injury monitoring probes

Schematic diagram showing the location of where the spinal cord injury site monitoring probes are placed intraoperatively. Currently up to 2 subdural probes are placed under the operative microscope, on the surface of the injury site, corresponding to the area of maximal spinal cord swelling. The probes are connected on neuroICU, providing continuous output of intraspinal pressure and microdialysis metabolites.

ISP = intraspinal pressure, MD = microdialysis.

1.5 Novel physiological concepts in acute TSCI

Since the establishment of ISP and MD monitoring techniques in TSCI, several novel concepts have been derived in the field of acute TSCI. They are summarised in Table 1 and compared with analogous concepts in TBI. The ISP wave is morphologically similar to the ICP wave with three classical P1-3 peaks. Spinal cord perfusion pressure (SCPP) is calculated as “MAP – ISP”, analogous to “CPP = MAP – ISP”, as a surrogate marker of spinal cord blood flow. Spinal pressure reactivity index⁷⁵ (sPRx), like PRx in the brain⁸², ranges from -1 to +1. In terms of autoregulation, sPRx ≤ 0 indicates intact vascular reactivity, whereas sPRx > 0 indicates impaired reactivity⁷⁰.

When plotted against SCPP, a U-shaped curve is produced. This defines optimum SCPP (SCPP_{opt}) as the SCPP that minimizes sPRx, analogous to CPP_{opt} in TBI (PRx versus CPP plot)⁸². There are currently no reliable clinical predictors of ISP and SCPP_{opt}, mandating invasive ISP monitoring for accurate calculation⁸³. Spinal reserve capacity index (sRAP) is a measure of spinal compensatory reserve⁷⁰ and similar to RAP in TBI⁸⁴. sRAP is a coefficient between ISP amplitude and mean ISP, ranging from 0 to 1. sRAP of 0 indicates adequate compensatory reserve but approaches 1 when there is poor compensatory reserve. Lastly, the metabolite parameters derived from MD monitoring in TSCI remain analogous to those obtained from in TBI: tissue glucose, lactate, pyruvate, glycerol and glutamate.

Table 1. Novel concepts in TSCI versus monitored physiological parameters in TBI

Summary of novel neurophysiological concepts derived from TSCI monitoring and their TBI counterparts.

Traumatic spinal cord injury (TSCI)		Traumatic brain injury (TBI)	
<i>Parameter</i>	<i>Definition</i>	<i>Parameter</i>	<i>Definition</i>
ISP	Intraspinal pressure	ICP	Intracranial pressure
SCPP	Spinal cord perfusion pressure	CPP	Cerebral perfusion pressure
sPRx	Spinal pressure reactivity index	PRx	Pressure reactivity index
sRAP	Spinal compensatory reserve	RAP	Compensatory reserve
SCPPopt	Optimum spinal cord perfusion pressure	CPPopt	Optimum cerebral perfusion pressure

1.6 Dural cord compression

Beyond describing the computation of novel physiological and autoregulatory concepts in TSCI, intervention to improve deranged parameters should be considered. In TBI, alleviating critically raised ICP, medically or surgically, is the cornerstone of treatment. Surgically, during a decompressive craniectomy procedure, after removing a portion of bone, the dura is widely opened⁸⁵. ICP may decrease a further 70% following dural opening after the bony decompression⁸⁶.

However, in TSCI, standard surgical treatment is to perform a bony decompression (laminectomy), without opening the dura. This addresses compression of the cord from fractured bony fragments, but fails to relieve ongoing compression from the dura against the swollen injured cord. Pre-clinical models highlight the injurious role of ongoing dural compression in TSCI^{87–89} consistent with MRI data in humans implicating the dura rather than bone as the major source of cord compression⁹⁰.

In surgery for TSCI, monitoring previously revealed persistently raised ISP following laminectomy and bony realignment alone⁷⁰. Dural decompression by fashioning an expansion duroplasty, lowered ISP by 10 mmHg, improved SCPP by 15 mmHg and lowered sPRx compared with laminectomy alone in 21 patients⁹¹. A multi-centre prospective RCT, DISCUS (Duroplasty for Injured Cervical Spinal Cord with Uncontrolled Swelling) is underway to evaluate expansion duroplasty versus conventional bony decompression⁹².

Addressing dural cord compression, followed by monitoring from the injury site to detect secondary injury and target SCPP_{opt}, represents a paradigm shift towards individualised treatment in TSCI.

1.7 Individualised Treatment in TSCI

The novel physiological concepts aforementioned can be applied to individualise TSCI management as follows. SCPP, a surrogate marker of spinal cord blood flow, varies with ISP even if the MAP remains constant. A further improvement beyond targeting SCPP could be to derive and target individualised SCPP_{opt} values (sPRx versus SCPP), where autoregulation is most efficient. The resultant U-shaped curve also implicates hypo- and hyperperfusion as injurious to the cord⁶⁸, defining an individualised optimal range of SCPP per patient. SCPP_{opt} may vary up to 60 mmHg between patients⁹³. Hence the need for monitoring to guide patient-specific treatment. TSCI is not physiologically homogenous, with significant patient differences (demographics, baseline MAP, mechanism severity, extent of secondary ischaemia and metabolic derangement)⁹⁴.

SCPP also varies with time, therefore the feasibility of real-time SCPP_{opt} calculation has been demonstrated⁹³. However, a range of SCPPs are required to define the U-shaped curve for SCPP_{opt}, with a future need to compute SCPP_{opt} in time windows shorter than 4 hours³³. For now, this technique enables patient-specific optimisation of spinal cord perfusion, and the detection of deranged parameters may guide therapeutic interventions.

1.8 SCPP is a key physiological variable

SCPP is a key physiological variable, demonstrated by its relationships with several important neurological and physiological parameters, as well as bladder, bowel and long-term outcomes.

Neurologically, intervening to increase SCPP increases the amplitude of motor-evoked potentials below the injury level in AIS grade C patients and just above in AIS

grade A patients⁷⁰. This is consistent with increased SCPP correlating with improved limb motor scores in some AIS grade C patients⁷⁰. Increasing SCPP improves sensory-evoked⁹⁵ potentials and lowers the sensory level in some patients^{70,96}.

Physiologically, increasing SCPP is associated with a favourable metabolic profile: increased tissue glucose, reduced glycerol, glutamate and LPR^{71,94}. Increasing SCPP is also associated with increased spinal cord blood flow⁷⁰ and enhanced autoregulatory parameters⁷⁵. Furthermore increasing SCPP was associated with improved urinary bladder sensitivity⁹⁷ and parameters of anal continence function⁹⁸.

In terms of outcome, at 9-12 month follow-up, the probability of AIS grade conversion after TSCI positively correlated with mean SCPP on admission and negatively correlated with mean ISP on admission⁹⁹. However, determination of cause and effect should be interrogated. One method is using causality analysis such as Granger causality^{100,101} which can evaluate multivariate physiological time series and information flow.

In summary, the management of neurological injury between TBI and TSCI varies in terms of setting, urgency, physiological monitoring and detection of secondary injury. Monitoring ISP and MD provide an array of physiological and metabolic parameters that provide the foundation for targeted, individualised care of TSCI patients.

The three experiments of the PhD thesis will each utilise multimodality monitoring to investigate the effects of injury to the human spinal cord and associations with physiological outcomes.

1.9 Aims of the PhD

1.9.4 Aim 1 – To develop a novel technique to monitor tissue oxygen in TSCI

- (i) To investigate whether it is feasible and safe to monitor spinal cord tissue oxygen from the injury site using a subdural oxygen probe
- (ii) To identify treatable factors associated with cord hypoxia including the effect of CSF drainage
- (iii) To explore the relationship between spinal cord tissue oxygen and neurological outcome

1.9.5 Aim 2 – To test the hypothesis that infective, inflammatory, and neurogenic fevers are detrimental

- (i) To investigate the effect of different fever types on injury site metabolism
- (ii) To investigate whether clinical (level of injury, temperature) and biochemical (serum leucocyte count, C-reactive protein and procalcitonin levels) parameters can distinguish neurogenic fever from other types of fever

1.9.6 Aim 3 – To test the hypothesis that SCPP affects breathing function in patients with cervical TSCI

- (i) To establish the feasibility of ultrasonographic and diaphragmatic EMG evaluation of breathing function in cervical TSCI patients
- (ii) To evaluate whether cervical SCPP correlates with breathing function

1.10 Common Methods

Presented in this section are the common methods across the 3 PhD experiments. Further specific methods are presented under each relevant chapter.

1.10.7 Institutional Research Board & Ethical Approvals

Patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) clinical study at St George's Hospital, London, UK (Appendix I). Approvals for ISCoPE, including consent form and patient information sheet (Appendix II) 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 was 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 included in the study or their family members. Patients were given adequate time to decide regarding participation including discussions with family members. ISCoPE is registered at www.clinicaltrials.gov and www.ichgcp.net as NCT02721615⁶⁹.

1.10.8 Inclusion and exclusion criteria

All TSCI patients recruited to ISCOPE with viable monitoring data were included.

Inclusion criteria were: (i) severe TSCI defined as AIS grade A, B, or C; (ii) age 18–70 years; (iii) timing between TSCI and surgery within 72 hours.

Exclusion criteria were: (i) patient unable to consent; (ii) other significant comorbidities; (iii) penetrating TSCI.

1.10.9 Neurosurgical management and probe placement

Following acute stabilisation in the emergency department, all patients were admitted to the neurosurgical unit at St. George's Hospital. Baseline preoperative CT, MRI spine and ASIA assessments by a trained neurosurgical resident were performed. After screening and recruitment to ISCoPE, surgery was performed by a neurosurgeon.

The type of surgery was based on clinical indication and surgeon preference: a posterior approach alone with lateral mass (cervical), pedicle screw (thoracic) and rod fixation (Stryker OASYS® for cervical and Stryker Xia 3® for thoracic) or a combined anterior approach (titanium cage +/- plate placement; Tritanium C®) (Stryker UK, Newbury, Berkshire, England). At induction the patients received cefuroxime 1.5g intravenously if no penicillin allergy and 48 hours of vancomycin and gentamicin postoperatively according to body weight. After decompressing the spinal cord and metalwork placement, a pressure probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) and MD catheter (CMA61: CMA microdialysis AB, Solna, Sweden) were inserted intradurally under the operating microscope. A needle durotomy was performed 1 level below the injury site with a 90°-angled needle to prevent cord damage. This was widened with a blunt hook. The probes were tunnelled from the skin, guided through the durotomy and placed on the site of maximal cord swelling, based on preoperative MRI, microscopic and in vivo ultrasonographic appearances. The ISP probe was calibrated to atmospheric pressure and a subfascial wound drain tunnelled and secured, kept on gravity for up to 7 days (Fig. 2).

CSF leak and infection risks were minimised by securing probes to the skin using silk sutures, applying Opsite spray (Farla Medical, London, UK) and an antimicrobial Ioban dressing (3M™, Bracknell, UK) covering the wound, probe and drain exit sites. A postoperative CT spine was obtained typically within 2 days, and postoperative MRI spine, typically within 1 week, after probe removal.

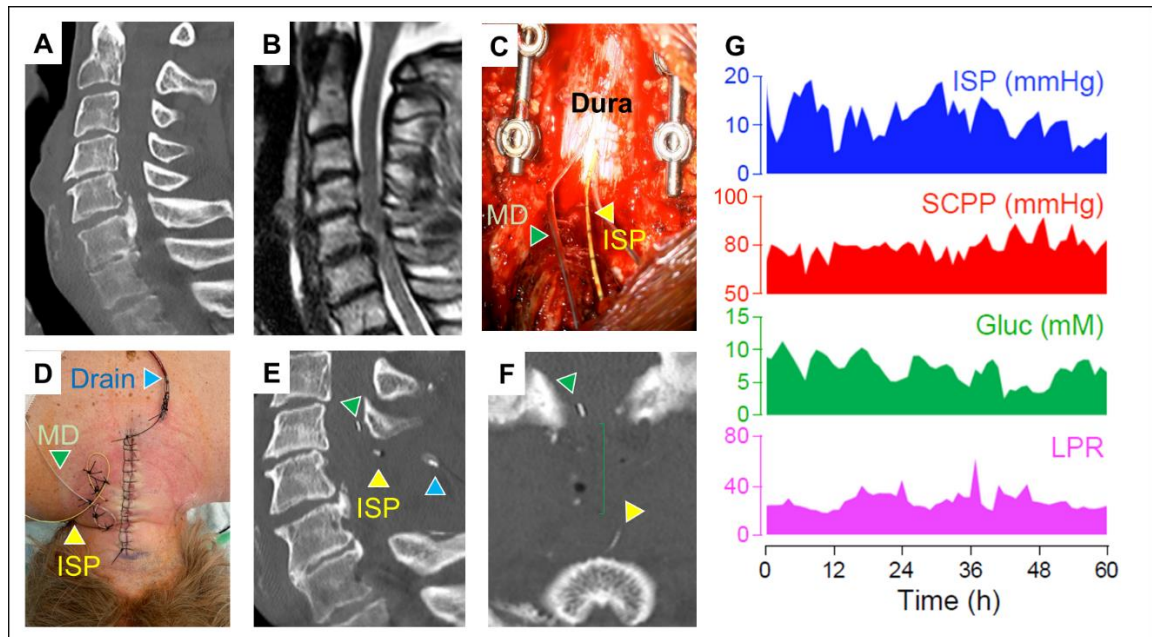


Fig. 2: TSCI patient multimodality monitoring set-up

A, Preoperative CT and **B**, MRI cervical spine scan showing bony compression of the spinal cord and TSCI. **C**, Intraoperative image showing location of the ISP and MD probes. **D**, Postoperative appearance showing tunnelled probes and wound drain. **E**, Sagittal and **F**, Coronal CT cervical spine showing location of monitoring probes and drain. Green triangle is radio-opaque gold MD tip and green bracket is length of dialysing membrane. **G**, Continuous signal output of physiological and metabolic parameters of interest.

ISP = intraspinal pressure, MD = microdialysis, SCPP = spinal cord perfusion pressure, Gluc = tissue glucose, LPR = lactate pyruvate ratio.

1.10.10 ISP and SCPP monitoring

The ISP probe was connected to a Codman ICP box and interfaced with a Philips Intellivue MX800 bedside monitor. Depending on the experiment, the ISP signal was recorded by data acquisition software on a research laptop in one of two ways. It was either transmitted to a ML221 amplifier to a PowerLab data acquisition hardware device and acquired by a laptop running LabChart v.8 software (ADInstruments, Oxford, UK) - experiments 1-2. Alternatively, to unify ventilatory signals for experiment 3, ISP was connected to a pressure module and directly interfaced with a Philips Intellivue MX800 bedside monitor and finally to the laptop running ICM+ recording software (Cambridge, UK). To facilitate this, I manually wired and configured the signal adaptor (Appendix 3)

Arterial blood pressure (ABP) was recorded from a radial artery catheter connected to a pressure module interfacing with the Philips Intellivue MX800 bedside monitor. MAP was subsequently derived from this signal and used to compute continuous SCPP as $MAP - ISP$.

1.10.11 Microdialysis monitoring

Following placement of the MD catheter, central nervous system fluid (CMA microdialysis AB) was perfused at 0.3 $\mu\text{L}/\text{min}$ using the CMA106 pump (CMA microdialysis AB). MD vials were changed hourly and analysed using ISCUS Flex (CMA microdialysis AB) for glucose, lactate, pyruvate, glycerol and glutamate. The LPR was calculated as $\text{lactate} \times 1000 / \text{pyruvate}$. The first two samples from each patient were discarded to allow priming of the MD catheter and stabilisation of the metabolite concentrations as recommended³². 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from the analysis.

1.10.12 NeuroICU management

Postoperatively, TSCI patients were admitted to NeuroICU, with daily review. Ventilation was supported as required, with corresponding sedation and timing of postoperative extubation dependent on the severity and neurological level of the TSCI (timely extubation postoperatively versus early tracheostomy). Vasopressors were administered at the discretion of neuroICU, typically adopting the guideline MAP target 85-90 mmHg. Intravenously administered norepinephrine via a central venous catheter was the preferred inotrope. In some patients, metaraminol was used initially.

The surgical wound was reviewed daily, a postoperative drain was kept on gravity for one week, and the patient was frequently turned in bed to avoid pressure ulcers. To prevent venous thromboembolism, we used Flowtrons® and started prophylactic low-molecular-weight heparin within 24 hours. NeuroICU physicians did not act on ISP, SCPP or MD values in line with the observational nature of the study. The ISP and MD probes were removed within a week, and the probe skin exit sites sutured with nylon to prevent CSF leak.

1.10.13 Patient assessments

Postoperatively, patients had a further ASIA examination at 2 weeks and 6 months. They underwent regular motor limb assessments on the NeuroICU. A CT spine was performed within 48 hours of surgery to assess the position of the probes, extent of bony decompression and position of metalwork. Arterial blood gases sampling was obtained at the discretion of the NeuroICU staff, typically 2-6 hourly depending on clinical need. Daily venous blood tests were obtained including a full blood count, electrolytes, renal and liver function, procalcitonin (PCT) and further specific tests based on clinical need (e.g. coagulation profile, imaging tests and microbiological cultures).

2 CHAPTER I - Spinal cord tissue oxygen monitoring

2.1 Introduction

To maximise neurological recovery in TSCI patients, ISP and SCPP are promising parameters. However, there are no clinical studies of spinal cord tissue oxygenation (p_{sctO_2}) despite hypoxia being a major cause of secondary neurological injury. In TBI, ICP alone may be a late indicator of secondary injury¹⁰² with both brain and spinal cord relying on an uninterrupted supply of oxygen and glucose to maintain cellular viability. Therefore, oxygen monitoring could be clinically significant in TSCI.

Following TBI, some centres routinely monitor p_{btO_2} . Brain tissue hypoxia ($p_{\text{btO}_2} < 20$ mmHg)^{103–105} may occur independently of changes in brain perfusion.⁵³ Brain hypoxia is associated with higher mortality^{102–111} independent of ICP, CPP and injury severity.¹¹² Other factors may reduce p_{btO_2} e.g. hypoxaemia, anaemia, fever, dysglycaemia, hypovolaemia, vasospasm, and patient transfer.^{53,113} p_{btO_2} monitoring in TBI is being evaluated in three RCTs (BOOST-III⁵⁷, OXY-TC,⁵⁶ and BONANZA).⁵⁸ BOOST-II was halted early, achieving its predetermined endpoint, demonstrating that p_{btO_2} -guided therapy in TBI is not futile, with a 9% reduction in mortality.⁵⁴ Currently the Seattle International Severe TBI Consensus Conference guidelines⁵⁹ endorse level III evidence for p_{btO_2} -guided treatment, while awaiting the results of the p_{btO_2} trials.

Unfortunately, the enthusiasm to establish p_{btO_2} -guided interventions for TBI has not been reflected in TSCI, with no techniques to monitor p_{sctO_2} . There are no human studies monitoring p_{sctO_2} from the injured spinal cord. Animal models reveal significant decreases in blood flow and oxygen levels after TSCI^{114,115}. This prompted experimental and clinical studies utilising hyperbaric oxygen therapy^{116,117}; however this is not utilised in practice. In this study, the Licox® oxygen probe (Integra®) is used to monitor spinal cord oxygenation from the injury site. The experiment demonstrates the feasibility of monitoring p_{sctO_2} , identifies treatable factors associated with cord hypoxia, and explores the relationship between p_{sctO_2} and neurologic outcome.

2.2 Methods

For Common Methods, please refer to Section 1.10. Below are study-specific methods:

2.2.1 Oxygen electrode insertion

The Licox® oxygen electrode (combined oxygen and temperature catheter [CC1P1], Integra LifeSciences) was chosen because it permits continuous recording of both spinal cord oxygenation and spinal cord temperature. Also, it does not exhibit significant signal drift for at least 5 days¹¹⁸. The oxygen electrode was stored in a refrigerator at 5°C preoperatively and opened on to the sterile operating table at the time of posterior surgery. The Licox® tissue oxygen monitor (Integra LifeSciences) was switched on intraoperatively to allow for sufficient calibration time, in line with the manufacturer's recommendations.

Three probes (an ISP probe, a MD catheter, and Licox® oxygen electrode) were tunnelled through the skin using a cannula. Following a miniature needle dural fenestration under the operating microscope, the oxygen electrode was positioned alongside the ISP pressure probe and microdialysis catheter. Specifically, the electrode was microsurgically placed between the pia and arachnoid of the spinal cord using forceps. The electrode tip rested on the surface of the injury site, localised based on the preoperative MRI and intraoperative appearances of maximal cord swelling. The electrode was finally secured to the skin using silk sutures and remained in situ for a maximum of 7 days. It was easily removed at the bedside on neuroICU under aseptic precautions, by cutting the holding sutures, gentle retraction of the probe and closing the probe exit site with a suture to prevent CSF leak.

2.2.2 Tissue Oxygen Signal Monitoring

The Licox® oxygen electrode was connected to the tissue oxygen monitor with its accompanying probe-specific monitor card. The signal from the monitor was then connected to a Philips Intellivue MX800 bedside monitor using a pressure module. This facilitated connection to the PowerLab system and recording laptop. The Licox® oxygen signal was sampled at 1 kHz. To compare $p_{\text{sct}}\text{O}_2$ values between injured versus uninjured sites, in two patients, a second oxygen electrode was inserted intradurally under the operating microscope, and positioned 2 centimetres below the injury site. A fast Fourier Transform analysis of the $p_{\text{sct}}\text{O}_2$ signal was performed to determine the contribution of cardiac, respiratory and other frequency components.

2.2.3 Relations Between Cord Tissue Oxygen, Physiology and Metabolism

The inter-relationships of $p_{\text{sct}}\text{O}_2$ with injury site physiology (ISP, SCPP) and metabolism (tissue glucose, lactate, pyruvate, LPR, glutamate, glycerol) were assessed. The effect of increasing the fraction of inspired oxygen (FiO_2) on the $p_{\text{sct}}\text{O}_2$ signal was evaluated, with a view to FiO_2 manipulation as a potentially novel therapy for TSCI. This was achieved by delivering a planned ventilator-driven “ O_2 boost” while concurrently time-stamping the continuous signal analysis. This provided a 10-minute FiO_2 increase of up to 100%. Additionally, the effects of spinal cord temperature and blood transfusion on the $p_{\text{sct}}\text{O}_2$ signal were assessed. Spinal cord temperature was continuously recorded by the combined oxygen electrode. The patient drug chart and neuroICU observation sheets documented timed incidences of blood transfusion. Thus, the $p_{\text{sct}}\text{O}_2$ signal, before, during and after transfusion, were interrogated. Restoring normothermia and optimised haemoglobin levels were hypothesised to improve cord oxygenation, as potentially additional novel therapeutic targets in acute TSCI.

2.2.4 Cord Tissue Oxygen Changes

Understanding the causes of a fall in $p_{\text{sct}}\text{O}_2$ may allow physicians to intervene and restore normoxia. Firstly, it was established whether a rise in ISP and/or fall in SCPP) were followed by a drop in $p_{\text{sct}}\text{O}_2$. Secondly, we investigated whether a drop in $p_{\text{sct}}\text{O}_2$ can occur independently of changes in ISP and SCPP. This approach mirrors management algorithms to treat sub-optimal $p_{\text{bt}}\text{O}_2$ thresholds in acute TBI⁵⁴.

Thirdly, for each greater than or equal to 5 mmHg change in cord tissue oxygen, the preceding hour was interrogated for the following potential causative factors: changes in (i) ISP or SCPP, (ii) spinal cord metabolism (tissue glucose, LPR) (iii) FiO_2 , (iii) spinal cord temperature, or (iv) sedation. We assessed whether the change in the putative causative factor could explain the change in spinal cord tissue oxygenation.

2.2.5 Effect of Cerebrospinal Fluid Drainage

Intracranial CSF drainage is widely applied in brain injuries secondary to trauma¹¹⁹ and subarachnoid haemorrhage¹²⁰ to reduce intracranial pressure, which may optimise brain perfusion. Lumbar CSF drainage has been used in an attempt to support spinal cord perfusion during surgery for descending thoracic +/- abdominal aortic aneurysms^{121,122}. To test the effect on $p_{\text{sct}}\text{O}_2$, a lumbar catheter was placed in 11 of 26 patients at the time of surgery. Under aseptic precautions on neuro-ICU, 10 mL cerebrospinal fluid was drained on a few occasions in subjects 66,67,69-78 to evaluate the effect on $p_{\text{sct}}\text{O}_2$. No more than 30 mL of CSF was drained in a 24-hour period¹²³. Given the compartmentalisation of CSF in TSCI⁷², and previous lack of relationship with ISP¹²³ the hypothesis was that CSF drainage in TSCI would not significantly alter injury site oxygenation.

2.2.6 Limb Motor Score & Follow-up

To assess the clinical impact of $p_{\text{sct}}\text{O}_2$ fluctuations, limb power was scored and evaluated. Limb motor scores recorded in TSCI assessment charts were used to calculate standardised limb motor scores for each patient. This was derived by subtracting the minimum postoperative motor score for each patient from all motor scores for that patient. Standardised motor scores were compared to the $p_{\text{sct}}\text{O}_2$ values averaged over the hour preceding the neurological assessment. Patients underwent a repeat ASIA examination and MRI spine at around 2-week postoperatively and at 6-month follow-up.

2.2.7 Statistics

Statistical analysis was performed in conjunction with Dr Saadoun. Fourier Transform analysis was performed using Weka Version 3.8.5 (Waikato, New Zealand) to determine the contribution of cardiac, respiratory and other frequency components to the $p_{\text{sct}}\text{O}_2$ signal. www.mycurvefit.com was used to fit linear, quadratic, exponential, sigmoid, and Michaelis-Menten curves with R^2 and P values. The effects of temperature and CSF drainage on $p_{\text{sct}}\text{O}_2$ were evaluated with Student t-test. The % hours with tissue oxygen less than 5 mmHg for different outcomes were compared using the Chi-square test. Data are presented as mean $\pm$ SE. Statistical tests are noted as not-significant (NS) or $p < 0.05^*$, 0.005^{**} , $0.0005^\dagger$, $5 \times 10^{-6}^\#$. Figures 3, 4B, 10, 11, and 13 use 1-kHz data. Figures 4A, 5, 6, 7, 8, 9 and 12 use averaged hourly values.

2.3 Results

2.3.8 Subjects

Twenty-six patients with viable $p_{\text{sc}}\text{O}_2$ monitoring were recruited (Table 2). Most were males (21/26) and most were younger than 60 years (22/26). Injury locations were 14 of 26 cervical, 10 of 26 thoracic, and two of 26 at the conus. On admission, 15 of 26 had grade A, three of 26 grade B, and eight of 26 grade C injury severities (AIS). Twenty-two of 26 cases had posterior surgery only, and four of 26 had a combined anterior-posterior approach. Overall, 2,213 hours of monitoring data was available for analysis. On average, each patient was monitored for 85.0 hours (range, 3.0 – 149.0 hrs). Patients were followed-up for at least 6 months (mean 12.9 months; range, 6.0–28.0 months).

2.3.9 Complications

Five of 26 patients had CSF leak from the probe exit site, successfully managed by placing extra skin sutures at the bedside. One of 26 had a wound infection, successfully managed with wound washout (Table 3). There were no instances of spinal cord damage, haematoma, 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).

Table 2. Patient Demographics. Abbreviations: Adm, admission; AIS, American spinal injuries association Impairment Scale; Ant, anterior; F, female; hrs, hours; m, months; M, male; Neuro, neurological; No, number; Post, posterior; y, years

Patient No	Age (y)	Sex	TSCI – surgery (hrs)	Neuro level	AIS (adm)	Surgery	Monitoring (hrs)	Follow -up (m)	AIS (follow -up)
48	29	M	58.0	C4	A	Post	3	25	B
59	22	M	58.0	T9	A	Post	16	7	A
62	36	F	47.0	T8	B	Post	129	13	C
63	60	M	72.0	T3	B	Post	130	28	C
64	28	F	40.0	C5	A	Post	139	11	A
66	67	M	38.0	C4	C	Post	99	11	C
67	32	M	38.0	C4	C	Post+Ant	147	9	D
68	37	F	23.0	L3	C	Post	87	20	C
69	39	M	39.0	T7	A	Post	114	14	B
70	35	M	39.0	C4	C	Post+Ant	60	11	A
71	27	M	41.0	L1	C	Post	95	6	D
72	50	M	22.0	C5	B	Post	137	19	B
73	47	M	22.0	T8	A	Post	79	12	B
74	57	M	35.0	C4	A	Post	149	8	A
75	66	M	40.0	C4	A	Post	117	7	A
76	46	M	18.0	T12	A	Post	33	19	C
78	26	M	39.0	C6	A	Post+Ant	34	12	B
80	55	M	45.0	T7	A	Post	79	23	C
81	54	M	69.0	C4	C	Post	149	17	D
83	51	M	49.5	T7	A	Post	50	17	A
84	22	M	70.0	C6	C	Post+Ant	67	17	D
85	54	F	38.0	C3	C	Post	58	8	C
86	54	F	45.0	C3	A	Post	15	7	C
87	44	M	24.0	T4	A	Post	43	7	A
88	61	M	48.0	T11	A	Post	54	6	A
89	23	M	15.5	C5	A	Post	130	6	B

Table 3. Complications of monitoring. Abbreviations: CSF, Cerebro Spinal Fluid; No., number. ICU, Intensive Care Unit; CKD, Chronic Kidney Disease; DM, diabetes mellitus; FEES, Fibre-optic endoscopic evaluation of swallowing; No, number; TSCI, traumatic spinal cord injury; PEG, percutaneous endoscopic gastrostomy

Complication	No of patients (/26)	Patients (%)	Comment
SURGICAL / PROBE RELATED			
CSF leak	5	19.2	Required bedside suture. No one returned to operating theatre
Haematoma / cord damage from probes	0	0.0	
Wound infection	1	3.8	Brittle DM with E.Coli urosepsis, positive E.Coli blood culture, positive E.Coli wound swab. Return to theatre for wound washout
Meningitis	0	0.0	
NON-SURGICAL			
Chest infection	11	42.3	One ICU readmission (immunocompromised, DM, stage IV CKD, obesity)
Urine infection	2	7.7	
Pulmonary Embolus	1	3.8	
Pressure Ulcer	3	11.5	Conservatively managed
Dysphagia	1	3.8	FEES confirmed; from TSCI; PEG insertion

2.3.10 Cord Tissue Oxygen Correlates with Inspired Oxygen (FiO₂)

Altering the FiO₂ influenced cord tissue oxygen (Fig. 3). On average, increasing the FiO₂ by 0.48 caused a sigmoid rise in p_{sct}O₂ to 71.8% above baseline within 8.4 minutes. Decreasing the FiO₂ by 0.44 caused an exponential fall in p_{sct}O₂ to 79.0% below baseline within 6.0 minutes. Increasing the arterial oxygen partial pressure (PaO₂) significantly correlated with increase in p_{sct}O₂ in a Michaelis-Menten saturation curve relation (Fig. 4A). Increasing the FiO₂ also correlated exponentially with increase in p_{sct}O₂. The injury site had a lower p_{sct}O₂ than the uninjured spinal cord below, with no correlation between the two p_{sct}O₂ readings (Fig. 4B).

2.3.11 Cord Tissue Oxygen Correlates with Injury Site Physiology and Metabolism

Several significant sigmoid correlations were observed between ISP, SCPP, tissue glucose, and tissue LPR versus p_{sct}O₂ (Fig. 4). As ISP rises greater than 5–10 mmHg, p_{sct}O₂ falls reaching a minimum at ISP 15–20 mmHg. As SCPP rises greater than 80–90 mmHg, p_{sct}O₂ suddenly rises reaching a maximum at spinal cord perfusion pressure 90–100 mmHg.

As tissue glucose increases greater than 4–6 mM/L, p_{sct}O₂ progressively rises to a maximum at tissue glucose 8–10 mM/L. As tissue LPR increases greater than 10–20, p_{sct}O₂ progressively falls to a minimum at tissue LPR 40–50. Fever is associated with lower p_{sct}O₂ compared with normothermia.

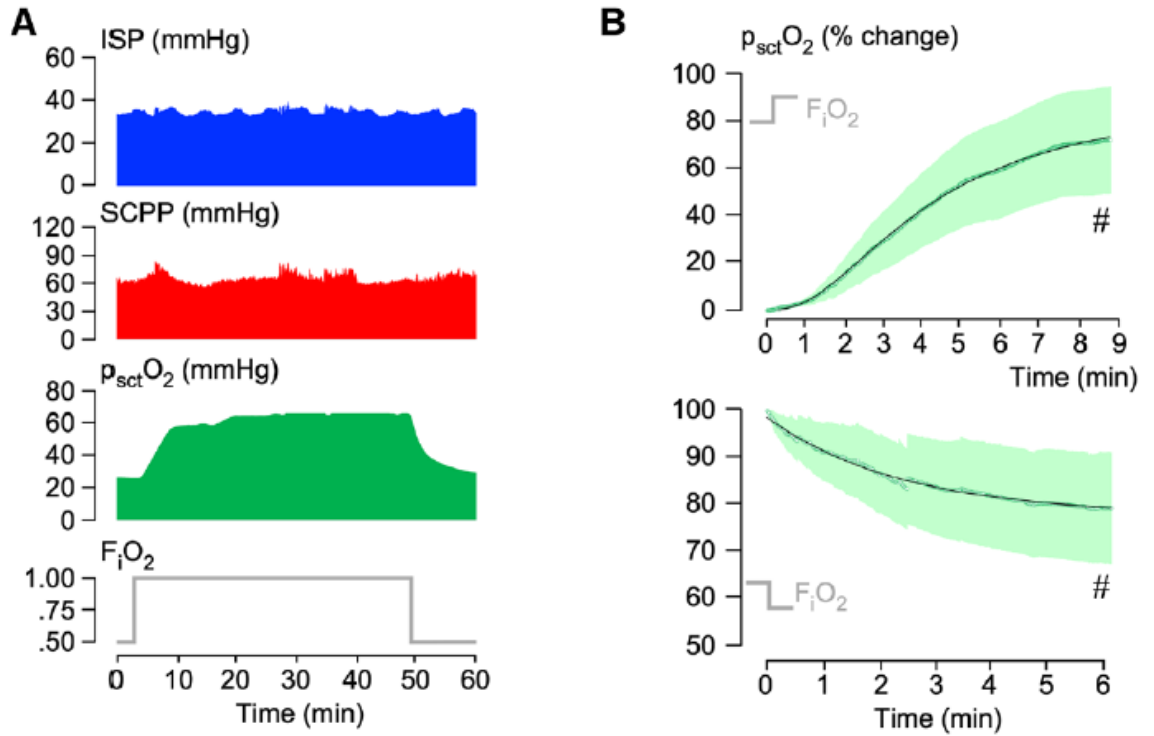


Fig. 3: The effect of oxygen challenge on ISP, SCPP, and $p_{sct}O_2$

A, Effect of oxygen challenge (F_{iO_2}) on intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), and $p_{sct}O_2$ in 23-yr-old male, C5 American spinal injury association Impairment Scale grade A (patient no. 89). **B**, Summary of oxygen challenge data. $p_{sct}O_2$ versus time after (top) increasing the F_{iO_2} from 0.38 ± 0.04 to 0.82 ± 0.09 (nine repeats and four patients) and (bottom) decreasing the F_{iO_2} from 0.89 ± 0.07 to 0.41 ± 0.04 (eight repeats and three patients). Mean $\pm$ SE. Regression lines: **B** (top) (sigmoid, $R^2 = 1.00$), **B** (bottom) (exponential decay, $R^2 = 0.99$). # $p < 5 \times 10^{-6}$.

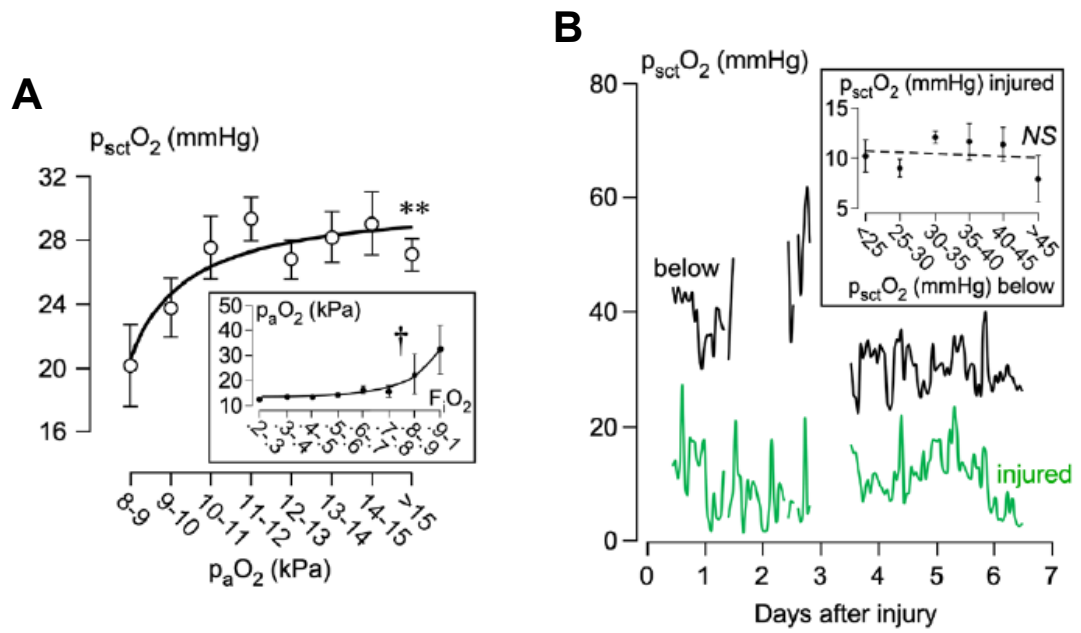


Fig. 4: The relationship of $p_{sct}O_2$ with PaO_2 and time

FiO_2 and arterial oxygenation (PaO_2) versus cord tissue oxygen ($p_{sct}O_2$). **A**, $p_{sct}O_2$ versus PaO_2 . Inset: PaO_2 versus FiO_2 . **B**, $p_{sct}O_2$ versus time. Twenty-three-year-old male, C5 ASIA AIS Grade A (patient no. 89). Green: $p_{sct}O_2$ at injury site. Black: $p_{sct}O_2$ of spinal cord below injury site. Inset: $p_{sct}O_2$ at injury site versus $p_{sct}O_2$ below. **A** (Michaelis-Menten, $R^2 = 0.83$), **A** (inset) (exponential, $R^2 = 0.98$), and **B** (inset) (linear, $R^2 = 0.02$). ** $p < 0.005$, †0.0005, NS = not significant.

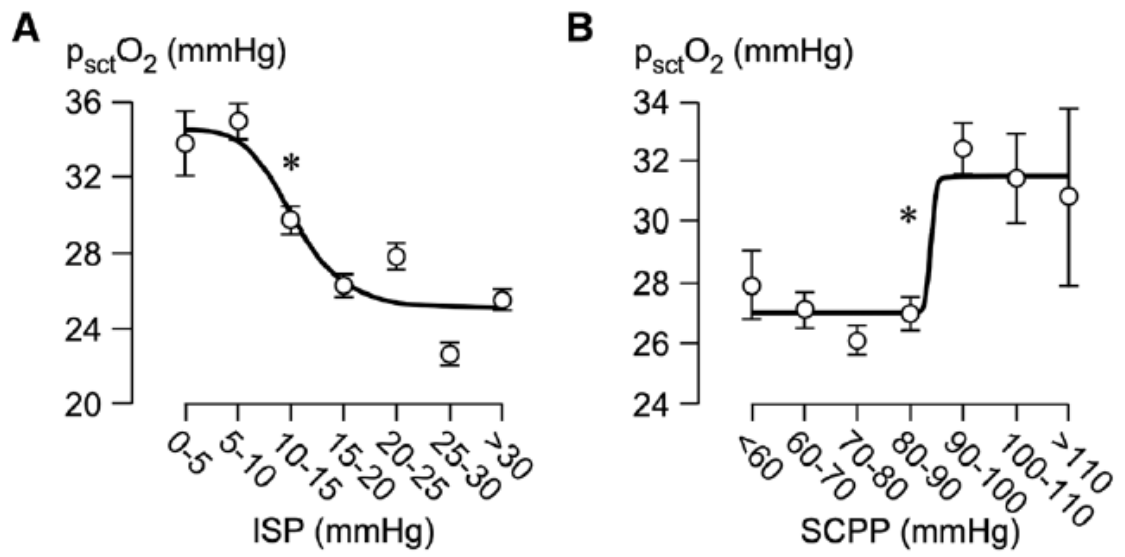


Fig. 5: $p_{\text{sct}}\text{O}_2$ versus ISP and SCPP

Injury site parameters versus cord tissue oxygen. **A**, Cord tissue oxygen ($p_{\text{sct}}\text{O}_2$) versus intraspinal pressure (ISP), $R^2 = 0.94$. **B**, $p_{\text{sct}}\text{O}_2$ versus spinal cord perfusion pressure (SCPP), $R^2 = 0.94$. $p < 0.05^*$.

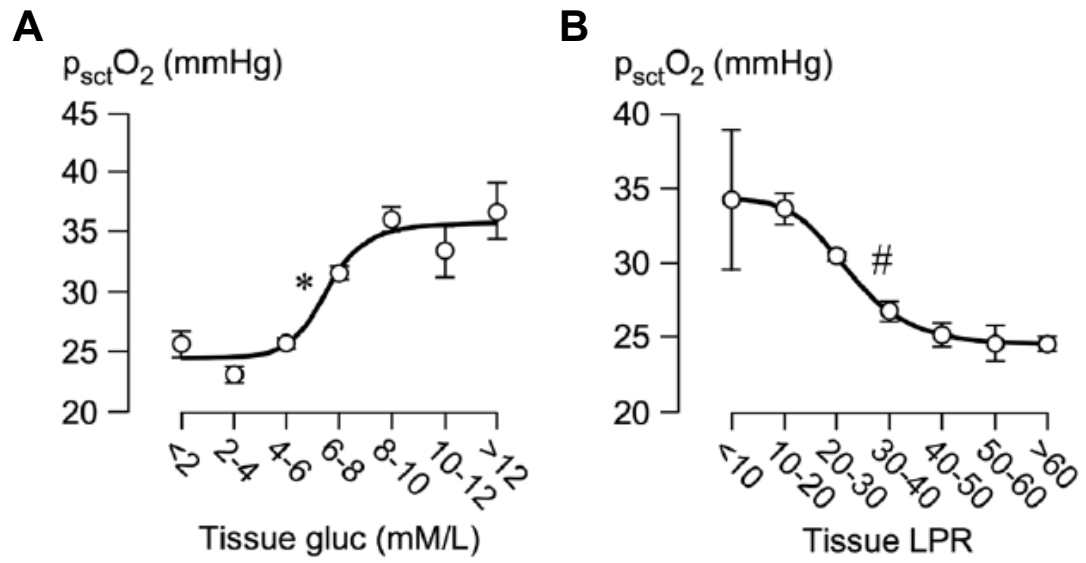


Fig. 6: $p_{sct}O_2$ versus tissue glucose and LPR

A, Spinal cord tissue oxygen ($p_{sct}O_2$) versus tissue glucose (gluc), $R^2 = 0.95$. **B**, $p_{sct}O_2$ versus tissue lactate/pyruvate ratio (LPR), $R^2 = 1.00$. $p < 0.05^*$, $5 \times 10^{-6} \#$.

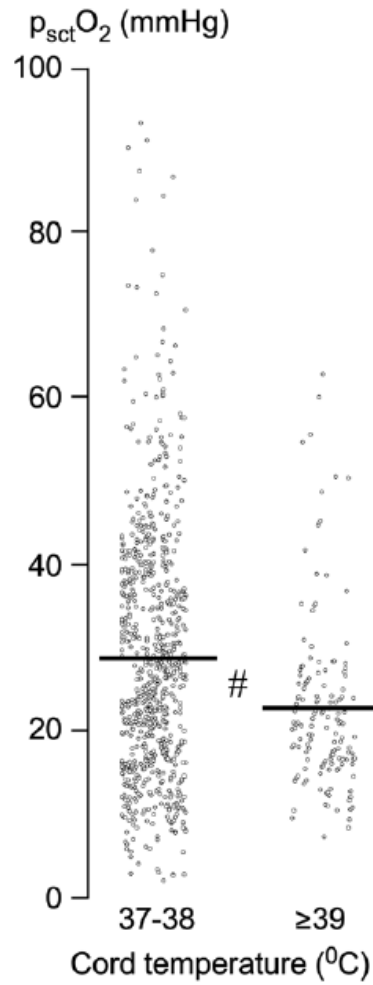


Fig. 7: p_{sct}O₂ versus spinal cord temperature

Spinal cord tissue oxygen (p_{sct}O₂) readings at spinal cord temperatures 37–38°C and greater than or equal to 39°C. Individual data points (circles) and means (lines). $p < 5 \times 10^{-6}$ #

2.3.12 Cord Tissue Oxygen Correlates With Neurologic Status

The injured spinal cord spends significantly more hours at low p_{sctO_2} values in patients with motor-complete compared with patients with motor-incomplete outcome at follow-up (Fig. 8). For example, in patients with motor-complete outcome at follow-up, the cord spends 7–21% hours daily at tissue oxygen less than 5 mmHg (compatible with cord infarction), compared with 0–2% hours in patients with motor-incomplete injuries. In the eight motor-incomplete patients at presentation, an inverted U-shaped relationship was observed between the limb motor score versus the average tissue oxygen tension from the injury site in the hour preceding each motor examination (Fig. 9).

2.3.13 Cord Tissue Oxygen Signal and Causes of Changes in p_{sctO_2}

The p_{sctO_2} signal was found to exhibit major cardiac and minor respiratory frequency components (Fig. 10). Several factors that may cause changes in p_{sctO_2} were observed. For example, blood transfusion was also associated with significant rise p_{sctO_2} (6.1 ± 3.2 mmHg, mean $\pm$ SE), but without significant change in cord metabolism (tissue glucose, -0.7 ± 0.3 mmol/L; tissue LPR, -0.6 ± 2.8) (Fig. 11). Rise in ISP or drop in SCPP was often accompanied by a drop in p_{sctO_2} . There were also observed changes in p_{sctO_2} that were independent of changes in ISP and SCPP. Examples are shown in Fig. 12. Factors that may cause changes in p_{sctO_2} by greater than or equal to 5 mmHg, ranked in decreasing frequency, were changes in: cord metabolism, ISP or SCPP, FiO_2 , sedation levels, and spinal cord temperature. (Table 4). In more than a third of cases, the cause of p_{sctO_2} change was unknown, unattributable to any obvious physiological or metabolic factors.

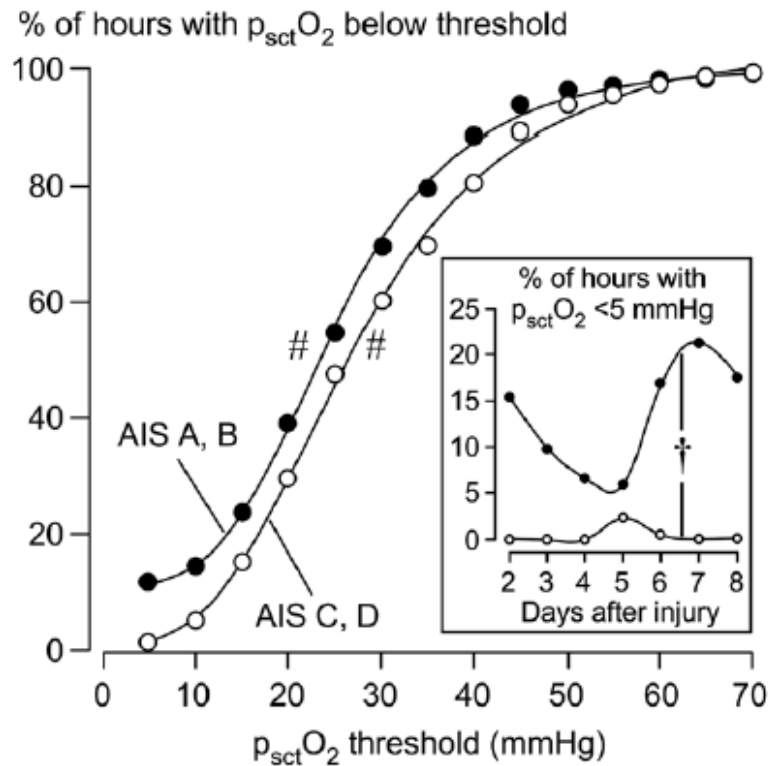


Fig. 8: Time spent below the $p_{sct}O_2$ threshold versus $p_{sct}O_2$ threshold, for AIS grade at follow-up

Spinal cord tissue oxygen ($p_{sct}O_2$) correlates with neurological status. Percentage of hours with $p_{sct}O_2$ below threshold (mmHg) versus $p_{sct}O_2$ threshold (mmHg), for AIS grade at follow-up (A and B versus C and D) fitted with sigmoid regressions ($R^2 = 1.00$ for both). Inset: Percentage of hours with $p_{sct}O_2$ less than 5 mmHg versus days after injury for AIS at follow-up (A and B versus C and D). # $p < 5 \times 10^{-6}$, † $p < 0.0005$.

AIS = American Spinal Injuries Association Impairment Scale.

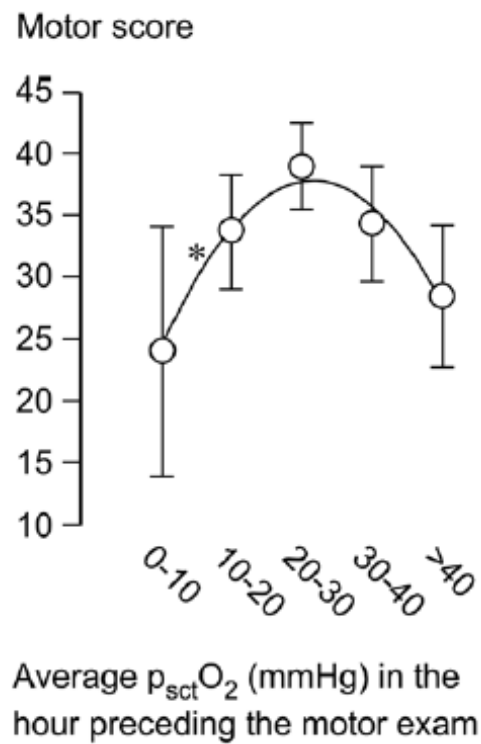


Fig. 9: Motor score versus average $p_{sct}O_2$ in the hour preceding motor examination in motor-incomplete patients

Motor score versus average spinal cord tissue oxygen ($p_{sct}O_2$) in the hour preceding the motor examination in motor-incomplete patients (AIS grade C). Quadratic regression, $R^2 = 0.97$. Mean $\pm$ SE. * $p < 0.05$.

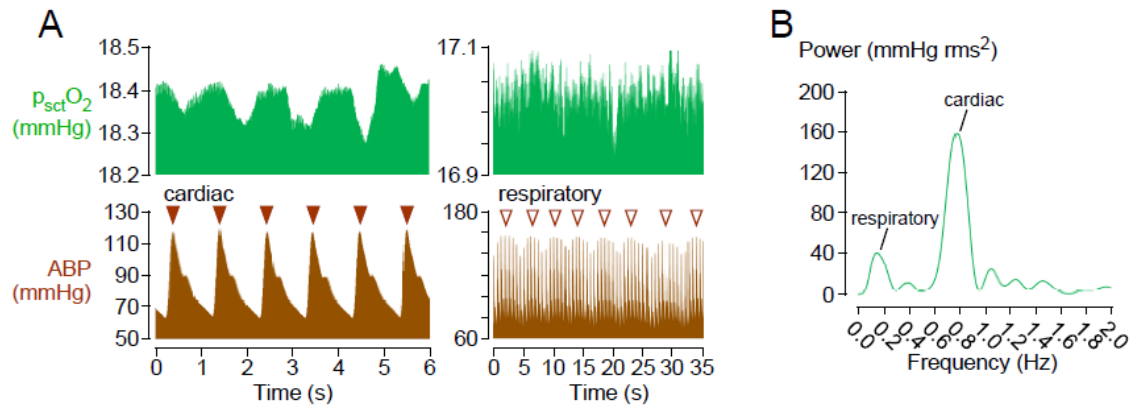


Fig. 10: Properties of the $p_{sct}O_2$ signal

A, (top, green) $p_{sct}O_2$ signal and (bottom, brown) corresponding blood pressure signal. Cardiac (closed arrowheads) and respiratory (open arrowheads) pulsations. **B**, Fast Fourier Transform (power vs. frequency) of $p_{sct}O_2$ signal with respiratory and cardiac peaks. Data from 50-year-old male, C5 AIS grade B injury (patient 72).

$p_{sct}O_2$ = spinal cord tissue oxygen, ABP = arterial blood pressure.

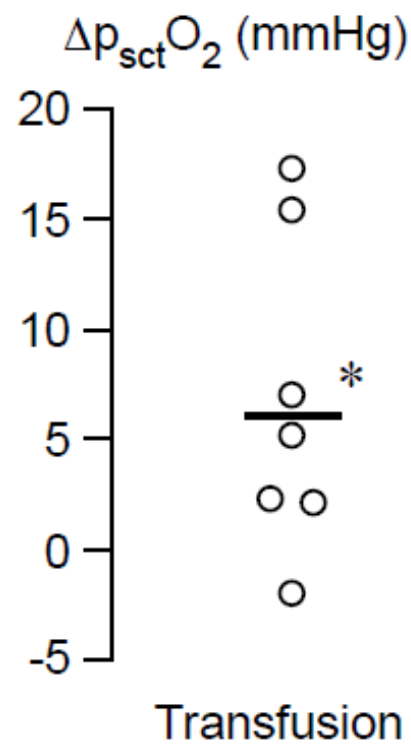


Fig. 11: Change in p_{sctO_2} versus blood transfusion

Change in spinal cord tissue oxygen (p_{sctO_2}) is associated with blood transfusion (mean of 2 hours after minus mean of 2 hours before transfusion). * $p < 0.05$

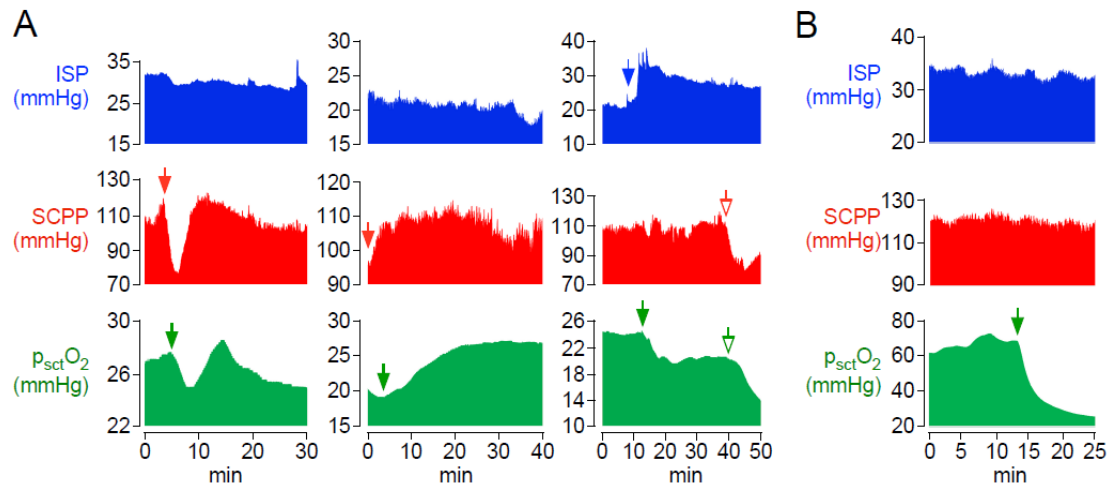


Fig. 12: Fluctuations in p_{sctO_2}

A, Changes in p_{sctO_2} (green) preceded by changes in ISP (blue) and/or in SCPP (red):
 (left) Fall in SCPP (onset at red arrow) followed by fall in p_{sctO_2} (onset at green arrow).
 (middle) Rise in SCPP (onset at red arrow) followed by rise in p_{sctO_2} (onset at green arrow). (right) Rise in ISP (onset at blue closed arrow) followed by fall in p_{sctO_2} (onset at green closed arrow); then, fall in SCPP (onset at red open arrow) followed by fall in p_{sctO_2} (onset at green open arrow). 36-year-old female, T8 AIS grade B injury (patient 62). **B**, Change in p_{sctO_2} (green) not associated with change in ISP (blue) or SCPP (red). Onset of drop in p_{sctO_2} at green arrow. Data from a 60-year-old male, T3 AIS grade B injury (patient 63).

ISP = intraspinal pressure, SCPP = spinal cord perfusion pressure, p_{sctO_2} = spinal cord tissue oxygen.

Table 4. Possible causes of changes in the cord tissue oxygen signal

Abbreviations: FiO₂, fraction of inspired oxygen; ISP, Intra Spinal Pressure, SCPP, Spinal Cord Perfusion Pressure

Possible cause	Number	%
Unknown	134	36.7
Change in cord metabolism	83	22.7
Change in ISP and/or SCPP	82	22.5
Change in FiO ₂	36	9.9
Change in sedation	18	4.9
Change in cord temperature	12	3.3
TOTAL	365	100

2.3.14 Effect of Lumbar Cerebrospinal Fluid Drainage on Cord Tissue

Oxygen

CSF drainage appeared to have a variable effect on $p_{\text{sct}}\text{O}_2$. Changes in spinal cord oxygenation ranged from an increase of 14.4 mmHg to a decrease of -20.8 mmHg (Fig. 13). On average, cerebrospinal fluid caused no significant change in $p_{\text{sct}}\text{O}_2$ in 9 of 11 patients and caused a significant, but modest, reduction in $p_{\text{sct}}\text{O}_2$ in 2 of 11 patients.

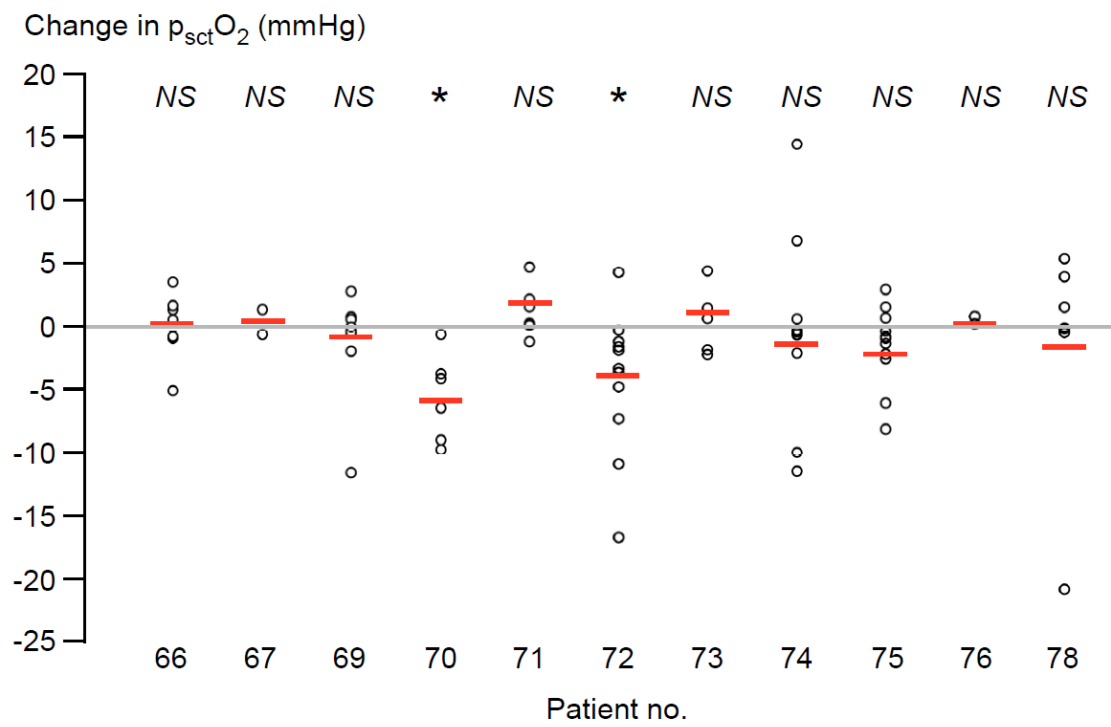


Fig. 13: The effect of cerebrospinal fluid drainage on p_{sctO_2}

Plot of the change in spinal cord tissue oxygen (p_{sctO_2}) after draining 10 mL lumbar CSF (circles are individual values and red lines are means) from 11/26 patients. $p < 0.05^*$; NS, not significant.

2.4 Discussion

This experiment demonstrates that, following spinal cord injury, it is feasible to monitor tissue oxygen from the injury site, analogous to brain tissue oxygen monitoring in brain injury¹²⁴. $p_{\text{sct}}\text{O}_2$ is a key physiologic parameter that correlates with injury site physiology, metabolism, and neurologic outcome. In our spinal cord injury patients, time spent below tissue oxygen thresholds was associated with long-term outcome, as reported for brain injury¹²⁵. The observation that, in patients with motor-incomplete injuries, fluctuations in $p_{\text{sct}}\text{O}_2$ were accompanied by fluctuations in limb power suggests that $p_{\text{sct}}\text{O}_2$ may influence spinal cord function. The inverted U-shaped relationship between motor score and $p_{\text{sct}}\text{O}_2$ suggests that not only hypoxia but also hyperoxia may impair motor function. Factors have been identified that influence $p_{\text{sct}}\text{O}_2$ and may be modified to improve outcome. For example, increasing the FiO_2 or increasing SCPP. These appear analogous to brain injury, where increasing the FiO_2 ^{126,127} or CPP augments low $p_{\text{bt}}\text{O}_2$ ¹²⁸. Additionally, given the relationship demonstrated between $p_{\text{a}}\text{O}_2$ and $p_{\text{sct}}\text{O}_2$ (Fig. 4), optimising PEEP to increase $p_{\text{a}}\text{O}_2$, may improve $p_{\text{sct}}\text{O}_2$ while avoiding potential hyperoxic toxicity from prolonged FiO_2 augmentation¹²⁹.

The Licox® oxygen probe tip comprises a cylindrical polyethylene membrane ~18 mm² that contains two polarographic electrodes and an electrolyte solution (Fig.14A). Oxygen diffuses through this membrane to reach the electrodes where it is electrolytically reduced using revoxide technology; that is, the chemical reaction at the electrode tips is reversible. This means that there is no significant calibration “drift” with time, ensuring accurate measurement up to 5 days. The oxygen electrode was not placed 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

aneurysm¹³⁰, in various brain tumours, in oedematous brain, and in arteriovenous malformations¹³¹. 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 bowel¹³⁰ and in graded ischemic regions of bowel¹³². In this study, the injured cord is swollen and compressed against the dura with the oxygen probe sandwiched between spinal cord and the dura. As dura is essentially metabolically inactive, the electrode primarily detects oxygen that diffuses into the probe from the adjacent cord (Fig. 14B). If the cord is surrounded by CSF, the electrode will detect oxygen that diffuses into the probe from the adjacent cord and CSF (Fig. 14C). Therefore, the surface probe is always sensitive to cord tissue oxygen tension but less sensitive when the cord is not compressed against the dura.

This study aimed to establish the technique of monitoring p_{sctO_2} 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, for example, by increasing FiO_2 to determine its effect on p_{sctO_2} , we did not set out to compare neurologic outcome in an interventional arm versus a control arm. The study provides the basis for future research to determine whether intervention to alter p_{sctO_2} is an effective new therapy. Such studies will require multivariable analysis to define whether any benefit of increasing p_{sctO_2} is independent of other prognostic factors such as severity of injury¹³³, patient age¹³⁴, comorbidities¹³⁵, fever burden⁶⁸, timing of surgery²⁸, and spinal cord perfusion pressure⁹⁹.

Current management guidelines recommend maintaining a MAP of 85–90 mmHg for the first week after spinal cord injury⁹. However, two patients with the same MAP but different ISP will have different SCPPs. In addition, two patients with the same SCPP may have different p_{sctO_2} values. Multimodality monitoring overcomes these problems by allowing individualised management^{70,71} that may ultimately yield

management guidelines for spinal cord injury analogous to brain injury protocols that incorporate both pressure and tissue oxygen monitoring^{59,136}. Multimodality 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)⁶⁸ and cord tissue oxygen (shown here), whereas blood transfusion increases tissue oxygen, but without improving metabolism, in spinal cord (shown here) and brain injury¹³⁷.

A study limitation is the small number of patients ($n = 26$), though the conclusions are supported by a large dataset (2,213 hr of monitoring, 165 motor examinations) and long follow-up (> 6 months). As shown here and in an earlier study¹³⁸, the main complication of injury site monitoring is CSF leak through the probe skin exit sites, which can be easily remedied with a bedside suture. Another limitation is that the electrode insertion procedure requires surgery. An alternative is to insert probes into the lumbar CSF, which is technically easier and does not require open surgery^{76,139}. However, there is lack of correlation between ISP, SCPP, and MD values measured at the injury site compared with lumbar CSF¹²³.

Though draining lumbar CSF has been proposed as a therapeutic manoeuvre in spinal cord injury^{76,139}, it does not effectively reduce ISP¹²³ or improve p_{sctO_2} (shown here) at the injury site probably because the swollen cord is compressed against the dura^{70,72,91,140}. The effect of durotomy on p_{sctO_2} has not been investigated. However, the DISCUS RCT⁹², currently underway, will evaluate the effect of expansion duroplasty on neurologic outcome after spinal cord injury.

In conclusion, following spinal cord injury, tissue oxygen monitoring is feasible. It allows the prompt detection and treatment of injury site hypoxia. Further randomised studies are warranted to investigate whether such intervention can improve neurological outcome.

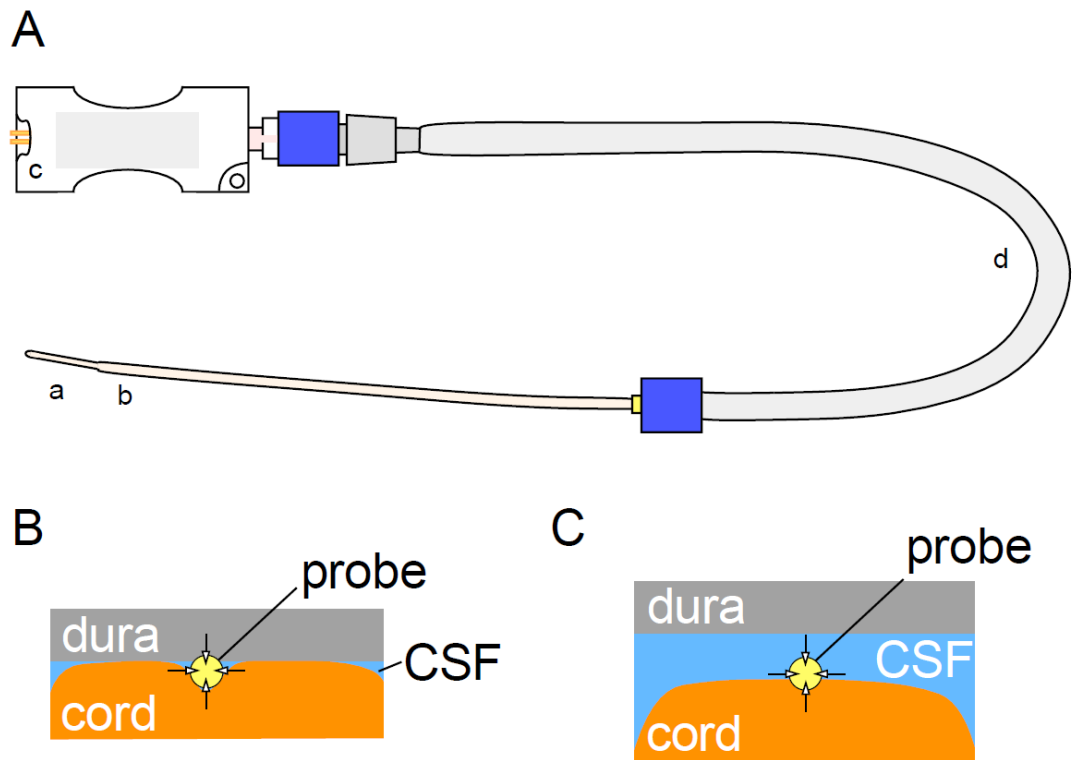


Fig. 14: The Licox® oxygen probe

A, the extension tube [d] serves to connect the probe to the bolt system. The probe is connected at the rear end [c] of its plug to the probe cable. At [a] the probe has its oxygen sensitive area of approximately 18 mm^2 ($\varnothing 0.65 \text{ mm}$). At [b] the probe has its temperature sensitive area of approximately 23 mm^2 ($\varnothing 1.3 \text{ mm}$). **B**, Cross-section of swollen spinal cord: probe on cord surface sandwiched between swollen cord and dura. **C**, Cross section of non-swollen spinal cord: probe between cord surface and cerebrospinal fluid (CSF). In **B** and **C**, arrows indicate oxygen diffusion to Licox® electrodes.

3 CHAPTER II - Effect of fever on injured spinal cord

3.1 Introduction

Fever is a key driver of metabolic stress, contributing to secondary neurological injury¹⁴¹. Previously, we identified that spinal cord fever ($>39^{\circ}\text{C}$) is associated with lower $p_{\text{scf}}\text{O}_2$, which in turn was associated with worse neurological outcome. Unlike in TSCI, in brain injury, fever detection and treatment is emphasised in clinical guidelines¹⁴² given its prevalence (up to 70%)⁶⁷ and harmful effects: it may worsen ischaemic injury¹⁴³, potentiate cerebral oedema¹⁴⁴, favour raised ICP¹⁴⁵, increase length of ICU stay, neurological morbidity¹⁴⁶ and mortality risk¹⁴⁷. Modern management favours targeted temperature control and maintenance of normothermia, not hypothermia⁶⁷. Despite theoretical rationale for therapeutic hypothermia, the multi-centre randomised EUROTHERM3235 trial for TBI was halted early due to safety concerns and worse neurological outcomes in the hypothermia group¹⁴⁸. Similarly, in acute TSCI, despite reduced inflammation following therapeutic hypothermia, subsequent rewarming increased cord swelling, inflammation and ischaemia¹⁴⁹.

Fever is equally common in TSCI patients, occurring in 71% in the first two weeks¹⁵⁰. It is associated with cord metabolic stress (low tissue glucose, high glutamate, high LPR) and impaired recovery⁶⁸. However, previous studies do not distinguish between different types of fever. Fever may be infective, inflammatory (peripheral trauma, surgery without infection, venous thrombosis and drug reactions) or neurogenic¹⁵¹. Misdiagnosis of different types of fever may result in overtreatment with antibiotics. Following TSCI, neurogenic fever is a distinctive and commonly encountered feature that has been poorly characterized. It may result from thermoregulatory dysfunction of the autonomic nervous system^{150,152}.

In this experiment, multimodality monitoring techniques were used to determine the effect of different types of fever on the injured spinal cord, and to identify clinical features that distinguish neurogenic from non-neurogenic fever.

3.2 Methods

For Common Methods, please refer to Section 1.10. Below are study-specific methods:

3.2.1 Temperature recordings and NeuroICU management

To measure spinal cord temperature, as per experiment 1, the Licox® oxygen electrode (combined oxygen and temperature catheter [CC1P1], Integra LifeSciences) was placed at the time of posterior surgery, intradurally on the injured spinal cord. The electrode placement methods are comprehensively described in Section 2.2.1.

Postoperatively on neuroICU, venous blood tests including white cell count (WCC, normal 4 – 11 cells/ μ L), C-reactive protein (CRP, normal 0 – 20 mg/L), and procalcitonin (PCT, normal <0.49 μ g/L) were performed daily. Arterial blood gas sampling was performed, initially 4 – 6 hourly, then at the discretion of the neuroICU staff according to clinical need.

Peripheral temperature was monitored by neuroICU staff every 1 – 4 hours, by placing a SureTemp Plus (WelchAllyn, Aston Abbotts, UK) thermometer in the axilla for 12 – 15 seconds. Temperature readings were paired with ISP and MAP readings for 30 minutes before and after the reading and with the chronologically nearest arterial or venous blood samples. Use of axillary temperature was a pragmatic choice because not all patients had monitoring of core temperature.

3.2.2 Fever definitions

Normothermia was defined as 36.5 – 37.4 °C, low fever as 37.5 – 37.9 °C, and high fever as ≥ 38 °C. Febrile episodes occurring during the multimodality period (up to 7 days) were recorded. Fever was classified as infective, inflammatory, or neurogenic as follows. Fever was considered infective if there was microbiological (culture positive,

confirmed micro-organism) plus biochemical evidence (raised WCC or CRP), with or without X-Ray/CT verification, of an infective source. Diagnosis of “Infection likely” was attributed to fever episodes with moderate clinical and biochemical suspicion without a concomitant positive culture or equivocal radiology, *at that specific time point*, precluding confident attribution to a systemic focus. Diagnosis of inflammatory fever (microbiology negative for infection) required raised inflammatory markers (WCC or CRP) and the presence of a cause, e.g. fever within 48 hours of surgery, or another inflammatory aetiology e.g. pulmonary/mediastinal injury, intra-abdominal injury, pelvic trauma, long-bone injuries, significant haematoma, or thrombosis. Inflammatory fever source was attributed as “Unknown” when criteria for other investigated causes were not met, and included drug fever. Neurogenic fever was a diagnosis of exclusion, when neither of the above sets of criteria were met, after comprehensive clinical and radiological work-up.

3.2.3 Cytokine/chemokine analysis.

The concentrations of cytokines/chemokines in the MD fluid collected from the injury site were measured. These molecules were selected because they have been implicated in the pathophysiology of TSCI, they are <30 kDa (i.e. cross the MD membrane) and are part of our multiplex electrochemiluminescence assay panel. For each patient, MD vials were collected during normothermia and during high fever. MD vials, each containing ~10 µL, were stored at –80 °C and analysed in a blinded fashion at Charité-Universitätsmedizin Berlin by multiplex electrochemiluminescence assays (Meso Scale Discovery, Rockville, MD, USA) using the following antibody sets from the U-PLEX Biomarker Group 1 Human Assays panel (K15067M): IL4, IL8, IL10, IP10, GRO α , MCP1, MIP1 α , MIP1 β . If necessary, the MD samples were diluted to the minimum required volume for a single determination (25 µl) or analysed directly

according to the manufacturer's protocol. 96-well plates including samples, blanks and recombinant standard concentrations were measured and unknown concentrations calculated, using the MESO QuickPlex SQ 120 Reader and the MSD DISCOVERY WORKBENCH software version 4.0 (Meso Scale Discovery, Rockville, MD, USA), respectively.

3.2.4 Serum procalcitonin (PCT) measurement

Serum PCT, a biomarker of bacterial sepsis, was measured preoperatively and daily, during the period of monitoring. PCT is an endogenous precursor to calcitonin involved in the regulation of phosphate homeostasis¹⁵³. The calcitonin 1 (CALC-1) gene in thyroid C-cells expresses PCT, which is cleaved to calcitonin before secretion. Due to cleavage, normal levels of PCT are low (<0.02 ng/mL)¹⁵³. Bacterial infection stimulates PCT production in non-neuroendocrine tissue, which lacks enzymic cleavage, both directly (lipopolysaccharides, bacterial toxins) and indirectly (IL-1 β , IL-6, TNF- α)¹⁵³. Therefore, after bacterial exposure, PCT levels rise quickly (3 – 6 hours), peak at 6 – 13.5 hours with a half-life of 22 – 36 hours¹⁵³.

Relying on CRP to track sepsis is limited by slower increase and faster recovery than PCT. A meta-analysis concluded superior diagnostic accuracy of PCT compared with CRP for bacterial infections¹⁵⁴. Furthermore PCT is a reliable biomarker of bacterial infection, tracking clinical resolution and de-escalation of antibiotics¹⁵³. In one study, a PCT-guided algorithm in 27 surgical Intensive Care Unit patients with severe sepsis resulted in 1.7 fewer antibiotic days, 17.8 % reduction in antibiotic costs and no difference in negative outcomes¹⁵⁵. A meta-analysis¹⁵⁶ concluded that the global odds ratio for diagnosing infection using PCT was 15.7 (95 % CI: 9.1 – 27.1) with superiority over CRP¹⁵⁶. A further meta-analysis¹⁵⁷ found longer antibiotic-free days (mean

difference 2.26 [1.40 – 3.12] and reduced short-term mortality (relative risk 0.87 [0.76 – 0.98]) with PCT-guided antimicrobial strategies.

Therefore, one aim was to evaluate PCT as a more specific biomarker of bacterial infection than CRP or WCC in acute TSCI. For the first 26 patients, PCT was measured using a portable analyser (Biopanda BR G800 PCT immunoassay, Belfast U.K.) In subsequent patients, PCT levels were measured at the St. George's Hospital biochemistry laboratory as part of daily blood tests obtained in the neuroICU.

3.2.5 NeuroICU response to fever

During a fever episode, blood, sputum, line, urinary catheter, and wound swabs were cultured. A chest radiograph was performed. There were daily neuroICU patient reviews by clinical microbiology physicians, who could request repeat cultures depending on the clinical picture and laboratory findings. Typical anti-pyretics administered were paracetamol 1 g four times a day and, either diclofenac infusion 150 mg daily, or ibuprofen orally 400 mg three times daily. On rare occasions when fever was refractory to pharmacotherapy, active surface cooling to normothermia was employed (Arctic Sun 5000, Medivance/Bard).

3.2.6 Statistical Analysis

Statistical analysis was performed in conjunction with Dr Saadoun. For each fever type, % hours at high fever *versus* temperature and *versus* day after TSCI were compared by two-way ANOVA. Number of cases of each fever type at or above T3 *versus* below T3 (the expected level of neurogenic temperature dysregulation) were compared by Fisher exact test. Change in the level of an injury site physiological variable (e.g. LPR) may precede the onset of fever or may be caused by an insult

unrelated to fever (e.g. drop in SCPP). Thus, to determine the effect of fever on each injury site physiological variable, we assessed trends related to episodes of normothermia then fever then normothermia, rather than plot the level of the injury site physiological variable during normothermia *vs.* fever.

The number of times that ISP, SCPP, tissue glucose, tissue LPR, and tissue $p_{\text{scf}}O_2$ increased, remained constant or decreased during fever *versus* normothermia, during short (1 hour) *versus* prolonged (>1 hour) fever, or during pre-fever *versus* normothermia were compared using Fisher exact test. Chemokine/cytokine levels during fever *versus* baseline were compared using the paired Mann-Whitney U-test. Statistical tests are two-tailed.

The data mining freeware Orange 3.34.0 was used to classify fever as neurogenic *versus* non-neurogenic using Tree, Stochastic gradient descent, Neural network, Logistic regression, and CN2 rule induction classifiers with leave-one-out cross-validation to compute Area Under Curve, Classification Accuracy, F1 score, Precision and Recall.

3.3 Results

3.3.8 Subjects

86 consecutive TSCI patients were recruited, who contributed a total of 5,591 hours of monitoring data. All subjects and family members approached agreed for the patients to participate. Table 5 shows patient characteristics. Most (80.2%) were males, and most (84.6%) were younger than 60 years. There were 59.3 % cervical, 34.8% thoracic and 5.8% conus injuries. On admission, 59.3% of the patients were AIS grade A, 16.3% B and 24.4% C. Most patients (82.6%) had posterior surgery only, and the rest (17.4%) had combined anterior and posterior surgery. AIS grade at follow-up (average 2.7 years) improved in 40.2%, stayed the same in 56.1% and deteriorated in 3.7%.

3.3.9 Complications

Table 6 lists the complications. Only fever episodes occurring in the postoperative, multimodality-monitoring period up to 7 days, were included in the analysis. A few delayed infections during the hospital episode i.e. beyond the multimodality monitoring period, are reported in Table 6. Furthermore, not all infections manifested in high grade fever (non-pyrogenic), therefore are also reported in Table 6, but not the high-grade fever analysis. This accounts for the discrepancy between reported fever episodes (Table 7) and reported infective complications.

11.6% of the patients had CSF leak from probe exit site(s), successfully managed by placing extra skin sutures at the bedside. 34.9% had non-compressive pseudomeningocele on the two-week postoperative MRI, all conservatively managed. Of these, 50% had MRI at 6 – 12 months, showing near-total or total resolution of the pseudomeningocele in 80%. 1.2% had positive wound swabs and drain fluid culture with neck stiffness, reported as a ‘serious adverse event’ successfully managed with

antibiotics for possible CNS infection. There was no probe-related haematoma or spinal cord damage based on neurological function and MRI. 4.7% had wound infections: the one patient requiring a wound washout had poorly controlled diabetes, primary E. coli urosepsis and subsequent wound infection.

Table 5. Patient characteristics

No. of patients monitored	Total	86
	ISP/SCPP	86
	MD	58
	p _{set} O ₂	33
Hours of monitoring	ISP/SCPP	2,864
	MD	1,887
	p _{set} O ₂	840
Age (years)	<20	5
	20 – 39	35
	40 – 59	29
	≥60	17
Sex	Male	69
	Female	17
Site of injury	Cervical	51
	Thoracic	30
	Conus	5
Surgical approach	Anterior	0
	Posterior	71
	360	15
No. of patients with admission AIS grade	A	51
	B	14
	C	21
No. of patients with follow-up AIS grade	A	38
	B	11
	C	17
	D	15
	E	1
	Unknown	4
No of patients with AIS change	-2	1
	-1	2
	0	46
	+1	22
	+2	8
	+3	3
	Unknown	4
Weeks of follow-up	Mean	138.0
	SEM	43.3

Table 6. Complications of monitoring

COMPLICATION	No. /86	%	COMMENT
PROBE RELATED			
CSF leak	10	11.6	Bedside management
Meningitis (?)	1	1.2	<i>E. coli</i> (wound swab + wound drain fluid). Wound healthy. <i>Enterococcus</i> (urine). Drowsy. Stiff neck. No CSF culture. Uncertain if meningitis. Vancomycin + meropenem. No sequelae.
Cord damage	0	0.0	
Pseudomeningocele	30	34.9	Non-compressive, conservatively managed
Retained probe	0	0.0	
SURGICAL			
Wound infection	4	4.7	3 superficial (antibiotics), 1 deep (wound washout)
Wound haematoma	1	1.2	Anterior wound required evacuation.
Further spinal surgery	1	1.2	Anterior stabilisation
NON-SURGICAL			
Chest infection	30	34.9	
Urine infection	6	7.5	
Line infection	5	5.8	
Pulmonary embolus	2	2.3	Delayed
Pressure ulcer	5	5.8	Delayed
Myositis ossificans	1	1.2	Delayed
Post-traumatic syrinx	4	4.7	Delayed. 3 drained, 1 conservatively managed.

3.3.10 Fever characteristics.

High fever (axillary temperature $\geq 38^{\circ}\text{C}$) was detected in 76.7 % of the patients and in 17.7% of the monitored hours (Table 7). Of all febrile hours, the type of fever was neurogenic in 25.7 % hours, inflammatory in 24.3% hours, and infective in 49.9 % hours. Of those with infective fever, 22.1% had risk factors (diabetes – 7 %, alcohol excess - 9.3%, chronic smoker - 5.8 %) No subject received acute or long-term steroids.

The three fever types have different characteristics: First, axillary temperatures are higher in neurogenic than inflammatory or infective fever (Fig. 15A); for example, 34.7 % of the time, neurogenic fever is $>39^{\circ}\text{C}$ compared with 10.8 % of the time for inflammatory and 18.9 % for infective fevers. Second, the time profiles are also different (Fig. 15B): neurogenic fever is infrequent in the first few days after TSCI, peaks at one week and subsides by 10 days; inflammatory fever, is most prevalent in the first 48 hours after the TSCI and subsides by 10 days; infective fever develops >48 hours after the TSCI and does not subside by 10 days. Third, neurogenic fever only occurs in TSCI above T4, whereas infective and inflammatory fevers occur with any level of TSCI (Fig. 15C).

Additionally, the incidence of different types of fever was different when stratified by admission injury severity, represented by AIS grade (Fig. 16). Infective fever was more prevalent in worse injury severities: AIS grade $A > B > C$ injuries. Whereas neurogenic fever appeared more prevalent with less severe injury severities: AIS grade $C > B > A$ injuries. Inflammatory fever had a relatively even distribution across AIS grades on admission.

Table 7. Incidence of high fever ($\geq 38^{\circ}\text{C}$)

TYPE OF FEVER	PATIENTS (/86)	HOURS (/3217 ^a)	LIKELY CAUSE	
All fevers	66	571		
Neurogenic	24	147		
Inflammatory	25	139	Surgery	84
			Lung injury	94
			Abdominal injury	4
			Pelvic injury	2
			Limb injury	8
			Haematoma	37
			DVT/PE	0
			Unknown*	11
Infective	40	285	Chest	149
			Urine	39
			Wound**	1
			Line	20
			Blood	9
			Infection likely***	64

^a Total number of hourly temperature recordings, of which 2,864 hours had accompanying monitoring data

*Inflammatory fever source attributed as “Unknown” when criteria not met for other causes

**Wound sepsis accounted for high fever in 1 patient; however, 4 cases presented in Table 2:

Complications because the remainder did not manifest with fever

***Moderate index of suspicion but no corresponding positive culture – see Methods.

NB: Figures represent fever episodes from pyrogenic infections. Non-pyrogenic infections and/or delayed infections outside the multimodality monitoring period in Table 6

DVT, deep venous thrombosis; PE, pulmonary embolism

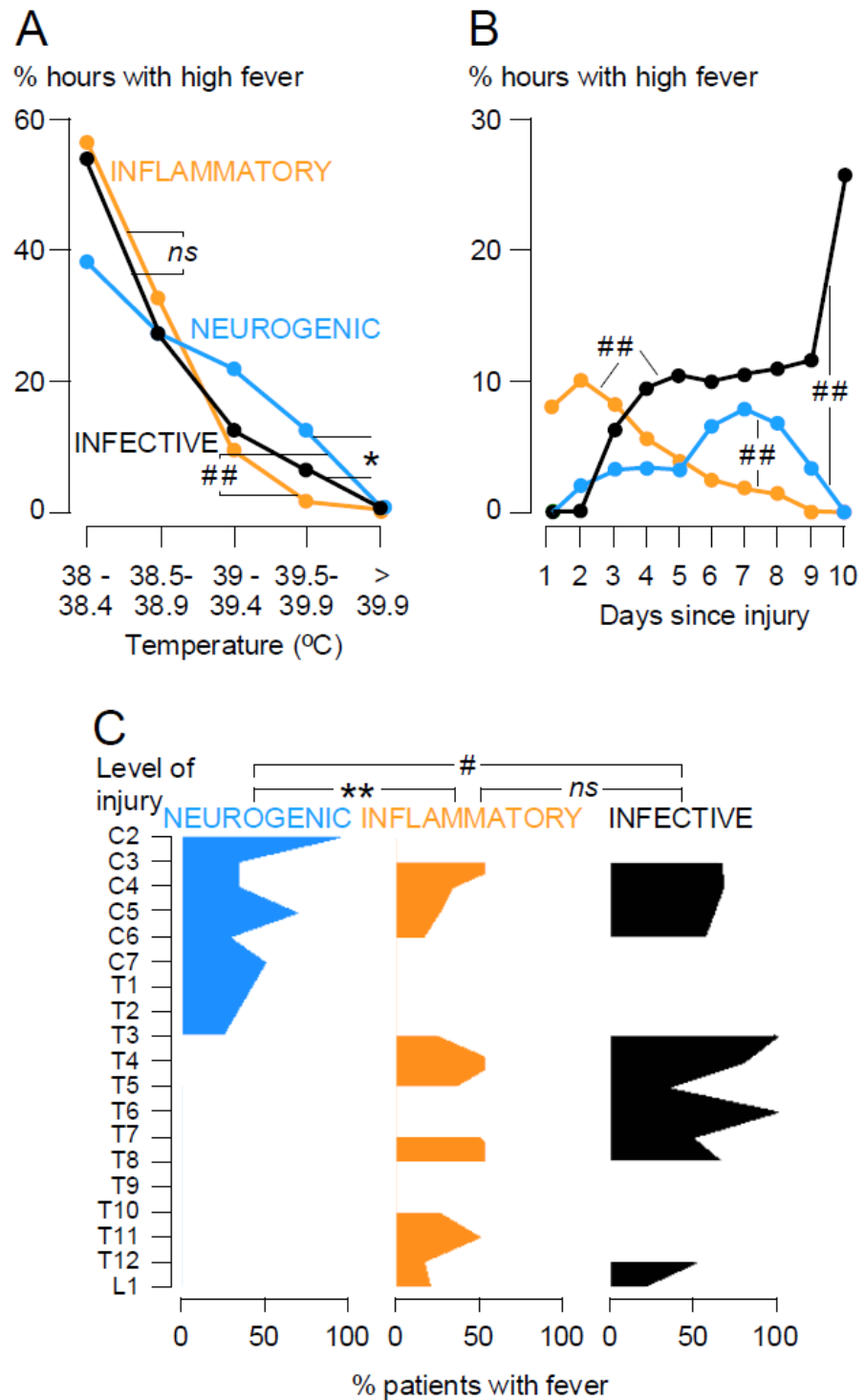


Fig. 15: Characteristics of different fevers

A, Temperature profiles of neurogenic (blue), inflammatory (orange), and infective (black) high fevers. **B**, % hours each day after TSCI with neurogenic, inflammatory, and infective high fever. **C**, Level of injury *versus* % of patients at each level who have high fever. *ns* not significant; $p < 0.05^*$, 0.01^{**} , $0.001^{\#}$, $0.0005^{##}$.

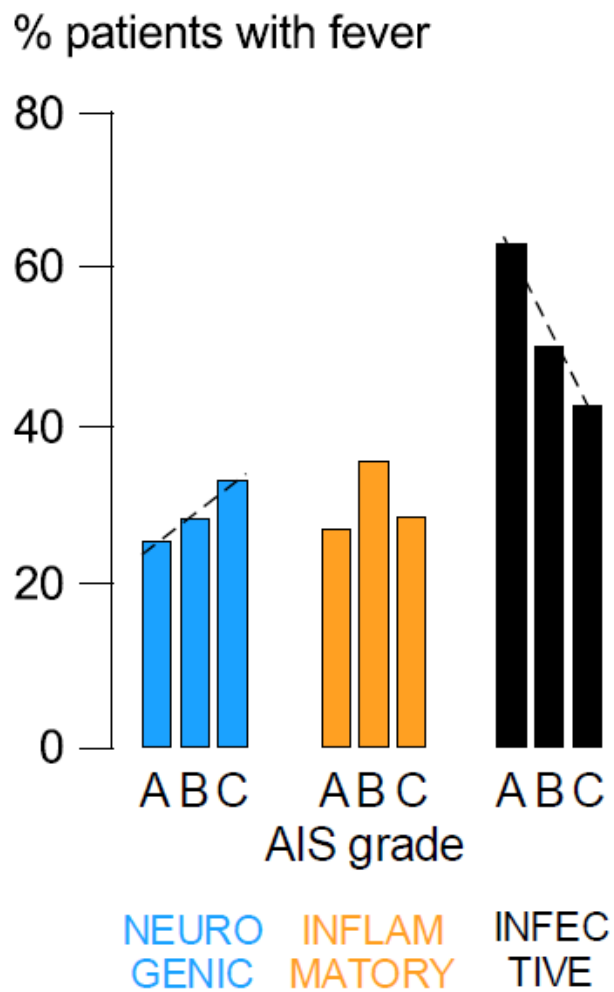


Fig. 16: Neurogenic, inflammatory, and infective fevers versus injury severity

% of patients who have high fever *versus* AIS grade on admission (neurogenic $R^2 = 0.98$, infective $R^2 = 0.97$).

AIS = American spinal injuries association Impairment Scale.

3.3.11 Effect of fever on injury site physiology and metabolism.

I tested whether each of the three types of fever were associated with metabolic stress at the injury site. Five parameters monitored from the injured cord were studied: ISP, SCPP, glucose, LPR, and p_{sctO_2} . I determined how often each parameter was increased, unchanged, or decreased during fever and compared this with the corresponding frequencies for normothermia (Fig. 17). None of the three fever types affected ISP or SCPP (not shown), but all three were associated with low glucose, high LPR, and low p_{sctO_2} . The changes in p_{sctO_2} did not reach significance for inflammatory fever. Therefore, in sum all three fever types were associated with metabolic stress at the injury site.

The next hypothesis was that prolonged (>1 hour) fever was associated with more metabolic stress at the injury site than brief (≤ 1 hour) fever. Fig. 18 shows that the duration of each of the three fever types had no impact on ISP or SCPP. However, compared with brief fever, prolonged fever was associated with lower tissue glucose (neurogenic fever), higher LPR (inflammatory and infective fevers), and lower p_{sctO_2} (neurogenic, inflammatory, and infective fevers). In sum, for all three fever types, prolonged fever was associated with more metabolic stress at the injury site than brief fever.

We then investigated whether the spinal cord metabolic derangement precedes the fever by examining the 5 hours before fever onset (Fig. 19). Changes in ISP, SCPP, glucose, LPR, and p_{sctO_2} before neurogenic or inflammatory fever were no different than during normothermia. However, a significant decrease in glucose, significant increase in LPR, and non-significant decrease in p_{sctO_2} occurred before the onset of infective fever. Therefore, spinal cord metabolic derangement preceded the onset of infective, but not neurogenic or inflammatory, fever by at least 4 hours.

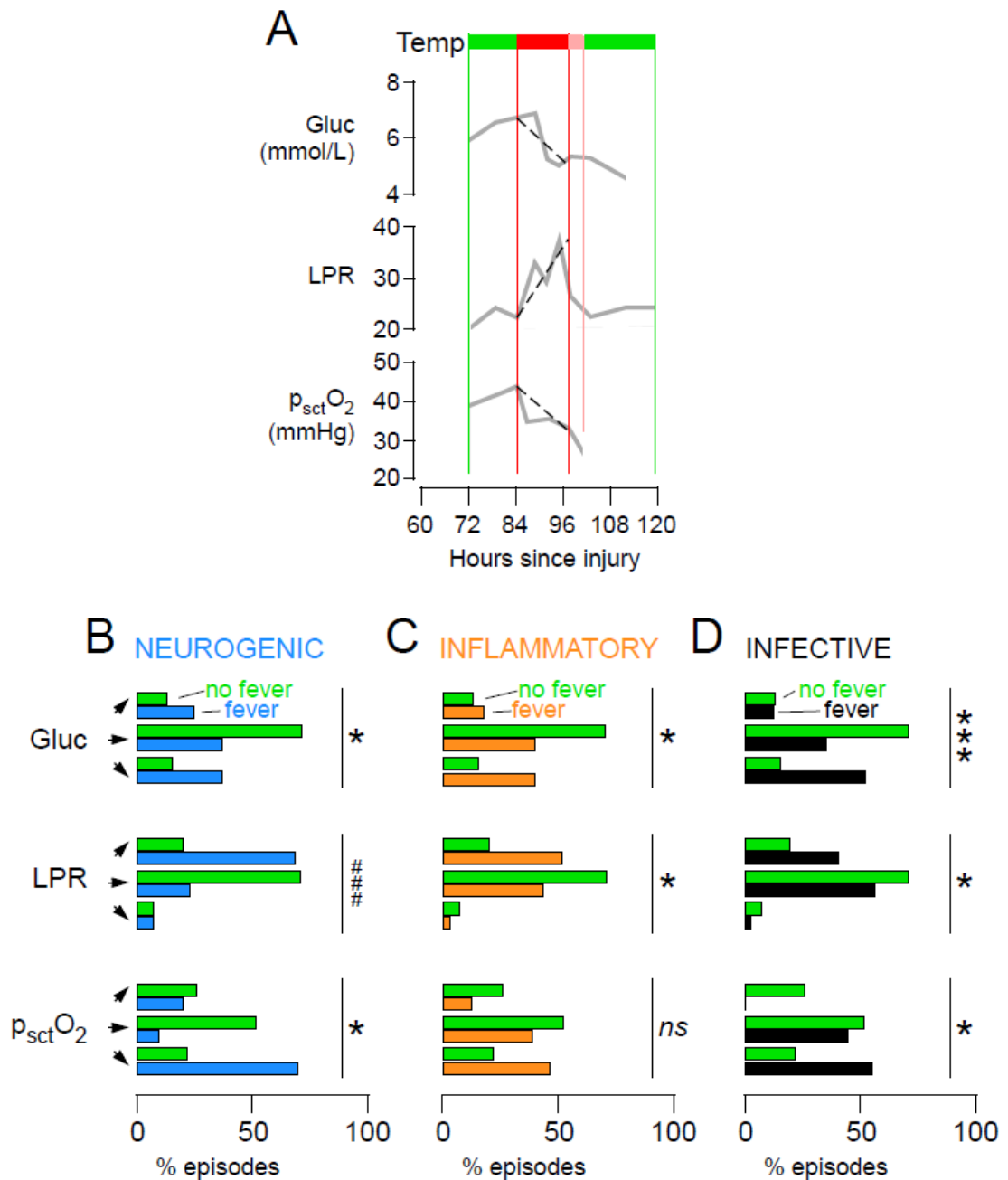


Fig. 17: Physiology and metabolism of injured cord during fever

A, Tissue glucose (gluc), lactate:pyruvate ratio (LPR), and oxygen (p_{sct}O₂) (grey lines) monitored from the injured cord of a patient with neurogenic fever (<37.5 green, 37.5 – 37.9 light red, ≥38.0 °C red). Dotted lines are trendlines during the fever. % episodes of no fever (green), **B**, *versus* neurogenic high fever (blue), or **C**, *versus* inflammatory high fever (orange), or **D**, *versus* infective high fever (black) associated with increase (↗), no change (→), or decrease (↘) in tissue glucose, tissue LPR, and tissue p_{sct}O₂. *ns* not significant; $p < 0.05^*$, 0.005^{***} , $0.0001^{####}$.

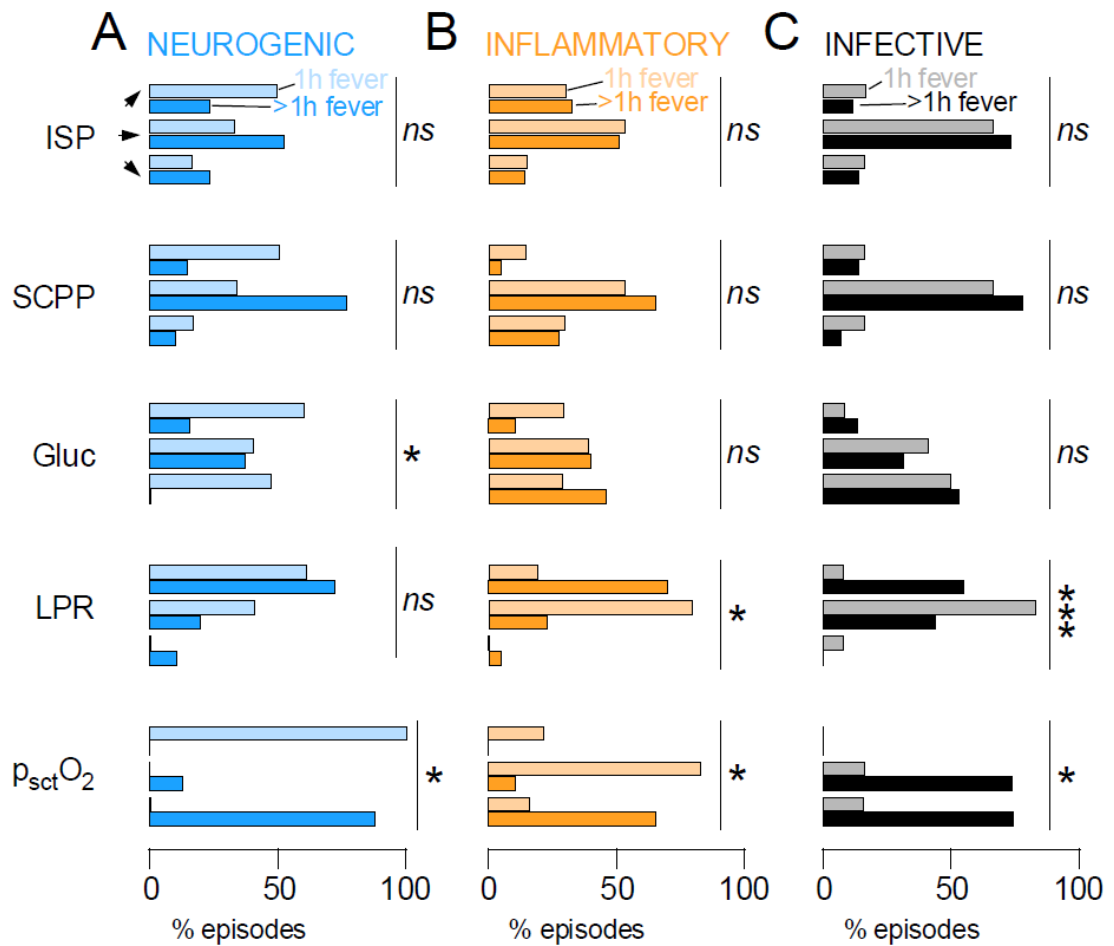


Fig. 18: Physiology and metabolism of injured spinal cord during brief *versus* prolonged neurogenic, inflammatory, and infective fevers

A, % episodes of neurogenic high fever lasting 1 hour (light blue) *versus* >1 hour (deeper blue), or **B**, % episodes of inflammatory high fever lasting 1 hour (light orange) *versus* >1 hour (deeper orange), or **C**, % episodes of infective high fever (black) lasting 1 hour *versus* >1 hour (grey), associated with increase (↗), no change (→), or decrease (↘) in ISP, SCPP, tissue glucose, tissue LPR, and tissue p_{sct}O₂. *ns* not significant; $p < 0.05^*$, 0.005^{***} .

ISP = intraspinal pressure, *SCPP* = spinal cord perfusion pressure, *Gluc* = tissue glucose, *LPR* = lactate:pyruvate ratio, *p_{sct}O₂* = spinal cord tissue oxygen.

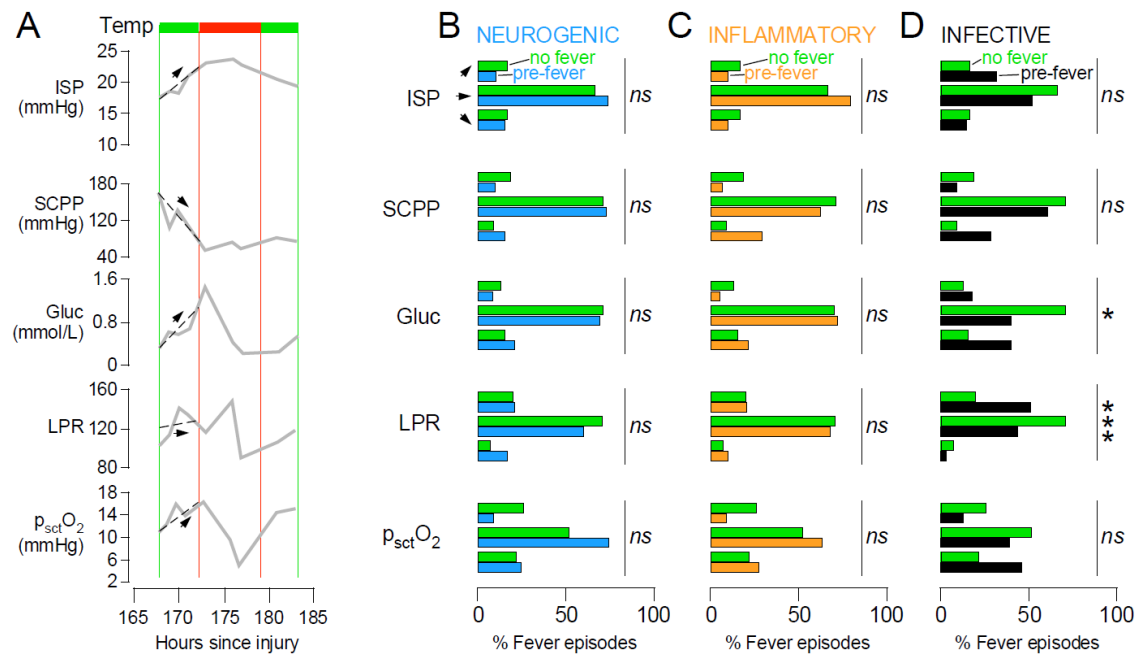


Fig. 19: Physiology and metabolism of injured spinal cord in the 5 hours preceding the onset of fever

A, ISP, SCPP, tissue glucose, tissue LPR, and tissue p_{sct}O₂ (grey lines) monitored from the injured cord of a patient with neurogenic fever (<37.5 °C green, >38.0 °C red). Dotted lines are trendlines during the fever. % episodes of no fever (green), **B**, versus neurogenic high fever (blue), or **C**, versus inflammatory high fever (orange), or **D**, versus infective high fever (black) associated with increase (↗), no change (→), or decrease (↘) in ISP, SCPP, tissue glucose, tissue LPR, and tissue p_{sct}O₂. *ns* not significant; $p < 0.05^*$, 0.005^{***} , $0.0001^{###}$.

ISP = intraspinal pressure, SCPP = spinal cord perfusion pressure, Gluc = tissue glucose, LPR = lactate:pyruvate ratio, p_{sct}O₂ = spinal cord tissue oxygen.

3.3.12 Injury site cytokines/chemokines

We asked whether fever is associated with increased cord inflammation, quantified as changes in the levels of cytokines/chemokines at the injury site during fever *versus* baseline. Fig. 20 shows that neurogenic and inflammatory fevers are not associated with significant changes in any assayed cytokines/chemokines, though wide variability between patients is observed. Infective fever is associated with significantly elevated levels of pro-inflammatory cytokines/chemokines (GRO α , IL8, IP10, MCP1, MIP1 β), but no significant change in the levels of anti-inflammatory cytokines/chemokines (IL4, IL10). These findings suggest that infective, but not neurogenic or inflammatory, fever is associated with increased injury site inflammation.

3.3.13 Neurogenic fever predictor

I hypothesised that it is possible to reliably distinguish neurogenic from non-neurogenic high fever by simple clinical tests. Patient characteristics (age, sex, level of injury, severity of injury) and daily fever characteristics (day from injury, maximum temperature, WCC, CRP, PCT) were entered into logistic regression, neural network, tree, stochastic gradient descent and CN2 rule induction algorithms with accuracy assessed by leave-one-out cross-validation (Fig. 21). All classifiers performed well in various evaluation metrics (Fig. 22). In general, the classifiers employed five key discriminating features, including level of injury, WCC, CRP, PCT and maximum daily temperature (Fig. 23). Five simple clinical rules, based on these characteristics, allow 59.3 % high fever episodes to be classified with 100 % accuracy, as neurogenic or non-neurogenic; the remaining 40.7 % high fever episodes cannot be reliably classified (Table 8). Applying the above, Fig. 24 shows a simple flow chart to distinguish neurogenic from non-neurogenic fever with examples of fever episodes in Fig. 25.

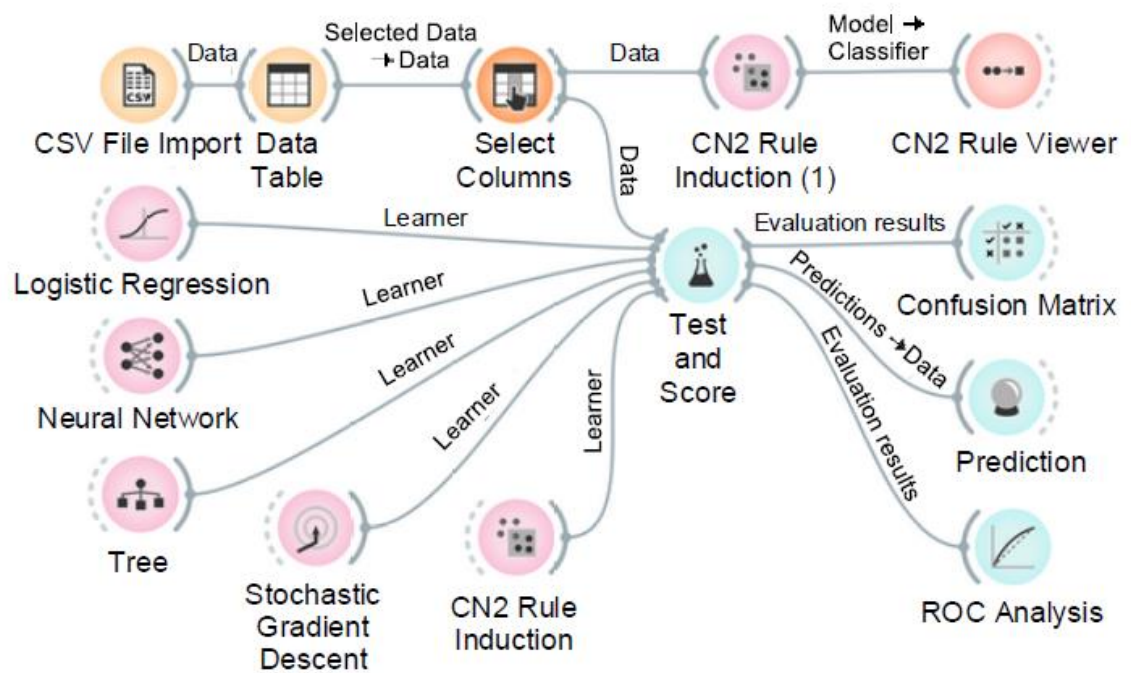


Fig. 21: Using algorithms to distinguish neurogenic from non-neurogenic fever

Interface workflow created by linking widgets in the data mining toolkit Orange. Patient and fever characteristics were entered into logistic regression, neural network, tree, stochastic gradient descent and CN2 rule induction algorithms.

CSV = comma-separated values, ROC = receiver operating characteristic.

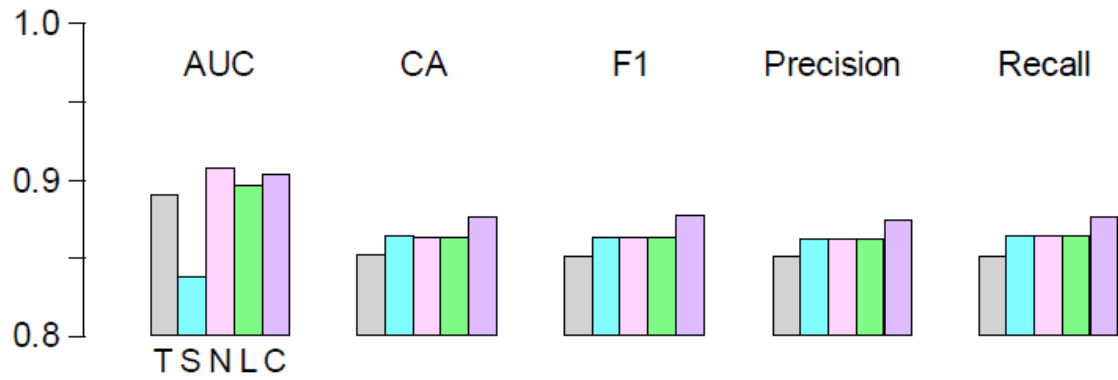


Fig. 22: Performance of algorithms to distinguish neurogenic from non-neurogenic fever

Performance of tree (T, grey), stochastic gradient descent (S, blue), neural network (N, pink), logistic regression (L, green), and CN2-rule induction (C, purple) algorithms.

Area Under Curve (AUC), Classification Accuracy (CA), F1 score, Precision and Recall are metrics evaluating the performance of classification machine learning models.

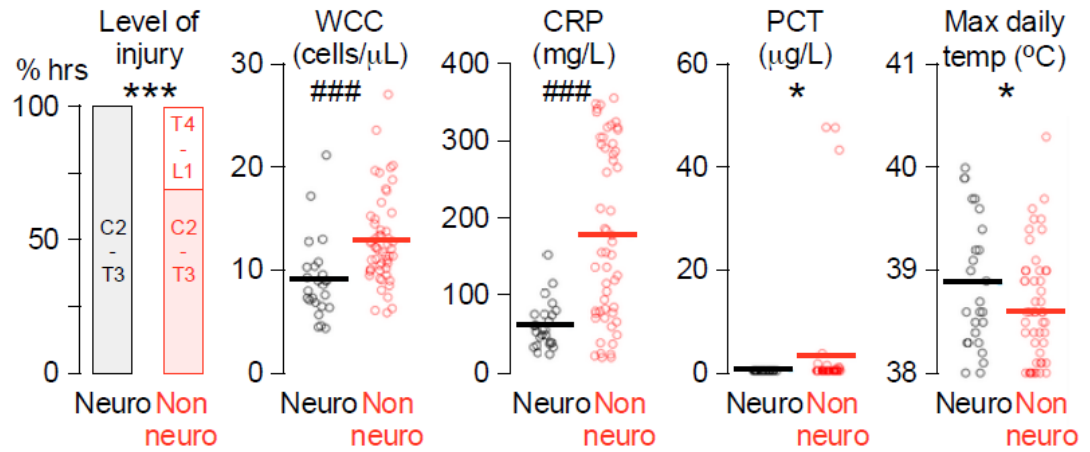


Fig. 23: Discriminating features to distinguish neurogenic from non-neurogenic fever

Classifiers employed 5 key discriminating features to distinguish neurogenic from non-neurogenic fever: Level of injury, White Cell Count (WCC), C-Reactive Protein (CRP), Procalcitonin (PCT), Maximum Daily Temperature for neurogenic (black) vs. non-neurogenic (red) fever. $p < 0.05^*$, 0.005^{***} , $0.0001^{###}$.

Table 8. Distinguishing neurogenic from non-neurogenic high fever

Clinical rule	Fever	High fever hours	
		No. / 81	%
Injury level below T3	Non-neurogenic	20	24.7
PCT >0.6 µg/L	Non-neurogenic	10	12.3
CRP >155 mg/L	Non-neurogenic	29	35.8
WCC >22 cells/µL	Non-neurogenic	2	2.5
WCC 4–11 cells/µL + CRP <100 mg/L + Temp >39 °C	Neurogenic	11	13.6
TOTAL*		48	59.3

CRP = C-reactive protein, PCT = procalcitonin, WCC = white cell count

**Not equal to the numerical sum because some high fever hours satisfy more than one rule*

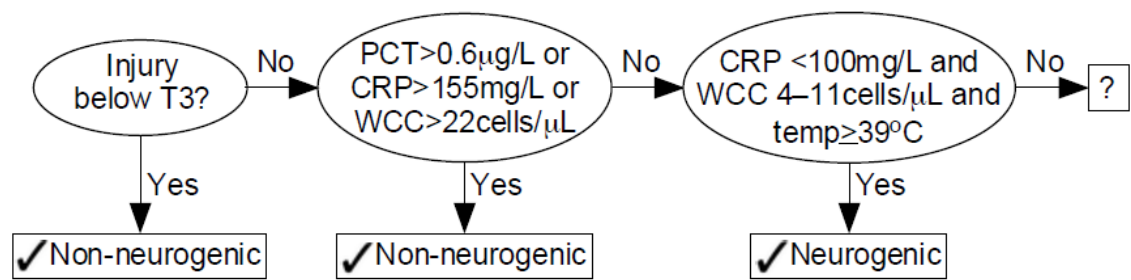


Fig. 24: Flow diagram distinguishing neurogenic from non-neurogenic fever

PCT = procalcitonin, CRP = C-reactive protein, WCC = white cell count, temp = temperature.

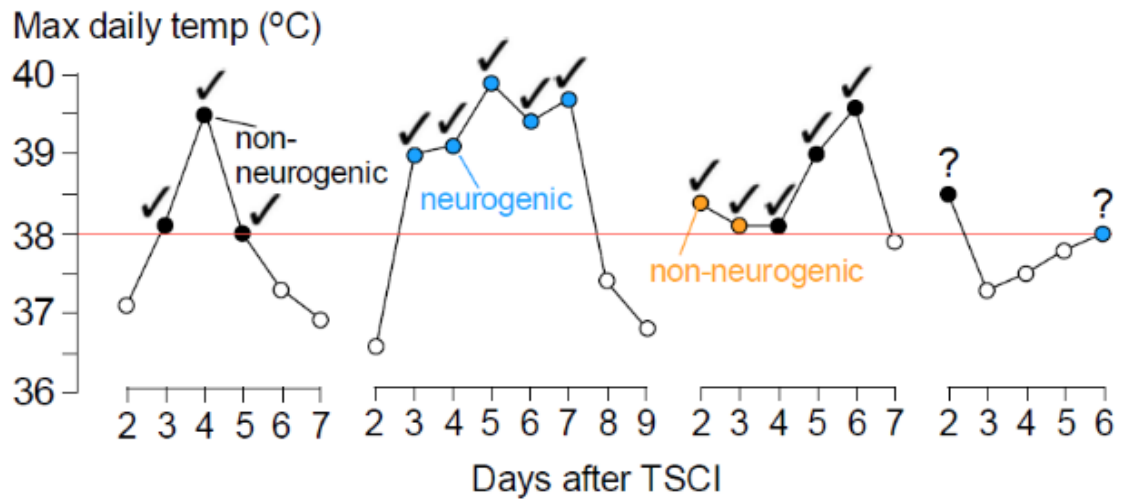


Fig. 25: Applying neurogenic vs. non-neurogenic fever distinction to fever episodes

Examples of fever episodes: Left infective (black), middle left neurogenic (blue), middle right inflammatory (orange) then infective (black), right infective (black), then neurogenic (blue).

CRP = C-reactive protein, PCT = procalcitonin, WCC = white cell count.

‘✓’ diagnosed correctly and ‘?’ cannot distinguish neurogenic versus non-neurogenic.

3.4 Discussion

Our group previously reported that following acute TSCI, fever (axillary temperature $\geq 38^{\circ}\text{C}$) is associated with cord metabolic stress and impaired neurological recovery⁶⁸. Here, the analysis has been refined to demonstrate that deranged injury site metabolism is a feature of all three major types of fever (neurogenic, inflammatory, infective) and, therefore, all three types of fever are probably harmful. Infective fever seems the most detrimental to the injured cord because it is also associated with elevated spinal cord levels of pro-inflammatory cytokines/chemokines. The three types of fever have different features that can be exploited to distinguish neurogenic from non-neurogenic fever with confidence.

The following mechanism may explain how fever causes metabolic stress at the injury site. Evidence from TSCI patients^{158–161}, rodents^{162,163}, and pigs^{164–166} suggests that the injured cord is ischaemic. By increasing the metabolic rate¹⁶⁷, fever increases glucose and oxygen consumption, which accounts for the reduction in tissue glucose and $p_{\text{scf}}\text{O}_2$ at the injury site that we detected during fever; these changes cannot be explained by reduced cord perfusion because fever does not affect SCPP or ISP. Tissue oxygen depletion during fever then exacerbates cord ischaemia evidenced by rising LPR at the injury site. It follows that more prolonged fever is associated with more metabolic stress at the injury site. This mechanism may apply to all types of fever and all central nervous system ischaemic pathologies, e.g. fever worsens outcome in TSCI patients^{168–172} TBI patients^{173,174}, and rodent TBI models^{144,175}. Fever also increases infarct size, mortality, and worsens outcome in stroke patients^{146,176}. Together, these findings suggest that prompt treatment of fever may improve outcome after TSCI.

Unlike other fevers, infective fever is linked to additional harmful effects. Infective fever is associated with elevated spinal cord levels of chemoattractants and activators of leukocytes including $\text{GRO}\alpha$ and IL8 (neutrophils)¹⁷⁷ as well as IP10,

MCP1, and MIP1 β (microglia^{178,179} and macrophages^{180–182}) without changes in IL4 or IL10, which are anti-inflammatory¹⁸³. Neutrophils, microglia, and macrophages are abundant in acutely injured human¹⁶¹ and rat^{184,185} spinal cord; their activation may cause further tissue damage¹⁸⁶. Our finding that cord metabolic stress precedes the onset of infective fever, suggests detrimental factors other than temperature, likely to be leukocytes. The clinical implication is that treating fever without addressing the leukocytes is unlikely to eliminate the detrimental effect of infective fever.

The three types of fever have different characteristics:

- (i) **Temperature:** Infective and inflammatory fevers may be mediated by prostaglandins^{151,187,188}, but neurogenic fever is caused by interruption of thermoregulatory spinal cord pathways¹⁵². Neurogenic fever is thus poorly responsive to cyclooxygenase inhibition by paracetamol/non-steroidal anti-inflammatory drugs¹⁸⁹. This may explain why neurogenic fever is higher than non-neurogenic fever.
- (ii) **Time course:** Neurogenic fever starts soon after TSCI and peaks at one week, likely related to evolving changes within the cord, e.g. cord oedema. Inflammatory fever is primarily from trauma to other organs/surgery and thus peaks early. Infection takes time to develop, which may explain why infective fever starts >48 hours after TSCI.
- (iii) **Level of injury:** Neurogenic fever is confined to injuries above T4. This coincides with the level for temperature dysregulation in chronic TSCI¹⁹⁰ and autonomic dysreflexia¹⁹¹. TSCI above T4 interrupts control of sympathetic supply to skin (trunk, legs) and internal organs thus disrupting vasoconstriction/dilation, which has a major impact on heat elimination. In contrast, inflammatory and infective fevers are not linked to the level of injury. It is unclear why neurogenic fever was more prevalent in less severe injuries.

(iv) **Peripheral inflammation.** Unlike neurogenic fever, infective and inflammatory fevers are associated with greater peripheral inflammation (higher WCC, CRP, PCT).

The three types of fever have differing management. Infective fever requires source identification, septic screening and treatment with antibiotics. However, may require additional measures, e.g. change of peripheral line or urinary catheter, chest physiotherapy, or surgical lavage^{171,192}. Inflammatory fever is multi-factorial, driven by systemic inflammatory response to polytrauma, surgery, venous thromboembolism, or blood transfusion; management is supportive^{193,194}. Neurogenic fever, a unique and prominent feature in acute TSCI, is non-inflammatory but difficult to diagnose because of concomitant peripheral inflammation^{195,196}. Therefore, neurogenic fever is often managed as infective with unnecessary septic screens and overuse of antibiotics.

We showed that neurogenic fever has simple distinguishing features: TSCI above T4, higher temperature and less peripheral inflammation (WCC, CRP, PCT). Using these, neurogenic fever can be confidently distinguished from non-neurogenic >50 % of the time. Early and accurate diagnosis of neurogenic fever may reduce over-investigation and over-treatment with antibiotics that may, in turn, limit the emergence of antibiotic resistance. There is no treatment for neurogenic fever after TSCI; bromocriptine merits investigation, based on reports of its effectiveness in eliminating neurogenic fever after TBI^{197,198}. Table 9 compares the pathological basis, diagnosis, and management of infective, inflammatory, and neurogenic fevers in patients with TSCI.

Our conclusions are supported by many hours of monitoring, but there are limitations. We show associations, not causality, and thus cannot prove that treating fever will improve outcome; a randomised, controlled trial is needed. It is also unclear if the cytokines/chemokines are produced locally or enter the cord from the circulation; simultaneous assays using serum and injury site MD may help resolve this. Finally, the

method of distinguishing neurogenic from non-neurogenic fever needs external validation. Our patient cohort is typical of the TSCI population with comparable demographics^{27,133,199}, fever^{150,168,200}, complications^{27,201}, and outcomes^{27,28,201}. We provide evidence that fever may cause secondary damage after acute TSCI and demonstrate how injury site monitoring can determine how the spinal cord responds to injury to guide patient management. Further studies are required to determine if treating fever improves neurological outcome.

Table 9. Comparison of the pathological basis, diagnosis, and management of infective, inflammatory, and neurogenic fevers in patients with TSCI

FEVER TYPE	NEUROGENIC	INFECTIVE	INFLAMMATORY
LIKELY PATHOLOGICAL BASIS			
Causes	Damaged sympathetic	Infection	Trauma, surgery, DVT
Mediator	Sympathetic	Prostaglandins	Prostaglandins
DIAGNOSIS (TYPICAL FEATURES)			
NLI	Above T4	Any	Any
Axillary temp. (°C)	≥39	<39	<39
Onset from TSCI (days)	>1	>2	0
Peak from TSCI (days)	7	No peak	2
End from TSCI (days)	10	No peak	10
WCC <22 cells/μL	✓		
CRP <155 mg/L	✓		
PCT <0.6 μg/L	✓		
LIKELY EFFECT ON TSCI			
Cord injury	↑	↑	↑
Cord metabolic demand	↑	↑	↑
Cord inflammation	→	↑	→
LIKELY EFFECTIVE MANAGEMENT			
Paracetamol, NSAIDs	×	✓	✓
Bromocriptine	? ✓	×	×
Active cooling	✓	✓	✓
Antibiotic	×	✓	×

CRP = C-Reactive Protein, DVT = Deep Venous Thrombosis, NLI = Neurological

Level of Injury, NSAID = Non-Steroidal Anti-Inflammatory Drug, PCT = Procalcitonin,

TSCI = Traumatic Spinal Cord Injury, WCC = white cell count.

4 CHAPTER III - Effect of spinal cord perfusion pressure on breathing

4.1 Introduction

To advance acute TSCI management, having identified spinal cord tissue oxygenation (Chapter II) and fever (Chapter III) as future therapeutic targets, the final study addresses respiratory dysfunction, the major source of morbidity and mortality following TSCI²⁰². It is the leading cause of death at 1 year (30.9%) and beyond one year (19.9%)²⁰². TSCI has profound detrimental effects on respiratory mechanics²⁰³. Inspiratory (diaphragm and external intercostals) and expiratory (internal intercostals and abdominal muscles) muscles become paralysed. Ventilatory pump failure occurs after 50% of respiratory muscle compromise²⁰³, causing acute respiratory failure and ventilatory dependence.

Cervical TSCI is more disabling than thoracic TSCI, because cervical TSCI weakens the upper limbs and impairs control of breathing, blood pressure and body temperature. Cervical TSCI causes diaphragmatic (nerve root supply C3 – C5) *and* intercostal (nerve root supply T1 – T11) muscle dysfunction, leading to reduced vital capacity from muscle fatigue, and secretion retention from impaired coughing²⁰⁴. Autonomic dysfunction further compounds secretion retention, causes bronchospasm and pulmonary oedema²⁰⁴. Consequences are pneumonia, failed extubation, tracheostomy, and prolonged neuroICU stay²⁰⁵. Therefore, intervention to enhance breathing in acute cervical TSCI in neuroICU would be a major advance.

The aim of this study was to determine whether SCPP affects the function of breathing muscles in acute cervical TSCI patients. Diaphragm weakness may result in intercostal muscles having a (suboptimal) compensatory role. Therefore, determining whether SCPP affects both muscle groups, may translate to clinical benefit. Hence, ultrasound scanning (USS) was used to evaluate both diaphragmatic and intercostal muscle function. Additionally, the electrical activity of the diaphragm (EDI) was evaluated using NAVA (neurally adjusted ventilatory assist) nasogastric tubes^{206,207}.

4.2 Methods

For Common Methods, please refer to Section 1.10. Below are study-specific methods:

4.2.1 Subjects

Data were collected from 21 subjects. We included all 13 cervical TSCI patients recruited to the ISCoPE study between September 2020 and January 2023 with viable ISP, SCPP, microdialysis (MD), and p_{setO_2} monitoring signals. Recordings of breathing function were made from patients when not attached to a ventilator or, if attached to a ventilator, patients initiated their own breaths with pressure support (PS) and positive end-expiratory pressure (PEEP) as chosen by the neuroICU team. We also included 8 controls (5 healthy subjects, 3 thoracolumbar spinal injuries) who consented to ultrasound examination to establish technique feasibility, reproducibility, and normal parameters in non-TSCI subjects. AIS classifications in the 3 thoracolumbar injuries were T8A, T9A and L1C. Lower intercostal function in the 2 thoracic injuries were excluded from final analysis.

4.2.2 Electrical activity of the diaphragm

EDI was captured by the modified NAVA nasogastric tube (MAQUET, Solna, Sweden) inserted by neuroICU staff for feeding and to monitor EDI. Optimal catheter position was verified by X-Ray and ventilator onscreen signal guidance during placement. The EDI catheter was connected to the SERVO-U ventilator (Getinge, Göteborg, Sweden) via a specific EDI module (Maquet, Solna, Sweden). The Philips Intellivue MX800 monitor (Philips, Guildford, UK) was configured to the EDI signal through a laptop with ICM+ recording software (Cambridge, U.K). Two parameters were used: EDI-peak (neural inspiratory effort responsible for the size and duration of

the breath) and EDI-min (tonic activity of the diaphragm that prevents de-recruitment of alveoli in expiration). Fig. 26 shows the setup.

4.2.3 Ultrasound scanning (USS)

Excursion of the left and right hemi-diaphragms was assessed with a 3.5 – 5.0 MHz probe set on M-mode via the anterior subcostal window (Fig. 27A). During inspiration, the diaphragm contracts and moves caudally towards the transducer, recorded as upward motion on the M-mode trace. Excursion is the maximum vertical height of the M-mode signal, from full expiration to inspiratory peak²⁰⁸. Diaphragmatic and intercostal muscle thickening was assessed bilaterally with a 10 – 15 MHz probe set on B-mode. Diaphragmatic thickness was measured as previously described^{209,210} at the zone of apposition, where the diaphragm is directly behind the inner aspect of the lower rib cage, with values obtained for quiet and deep breathing.

For intercostal USS the probe was oriented in the sagittal plane to record from the 2nd/3rd intercostals (Upper intercostals), 5th/6th intercostals (Middle intercostals), all measured in the mid-clavicular line, and from the 9th – 11th intercostals (Lower intercostals) measured in the anterior axillary line (Fig. 27B). Landmarks were marked on each subject's chest to enhance reproducibility of measurements. On each occasion, measurements were made for up to a minute, and the mean of each parameter (diaphragmatic excursion and thickness, intercostal thickness) was computed. Diaphragmatic or intercostal muscle thickening fraction during breathing was defined as: $(\text{thickness}_{\text{max}} - \text{thickness}_{\text{min}}) / \text{thickness}_{\text{min}} \times 100$. For each patient, I used the average of corresponding left and right measurements. This method of diaphragm ultrasound is in line with recent expert consensus²¹¹ and international guidelines²¹².

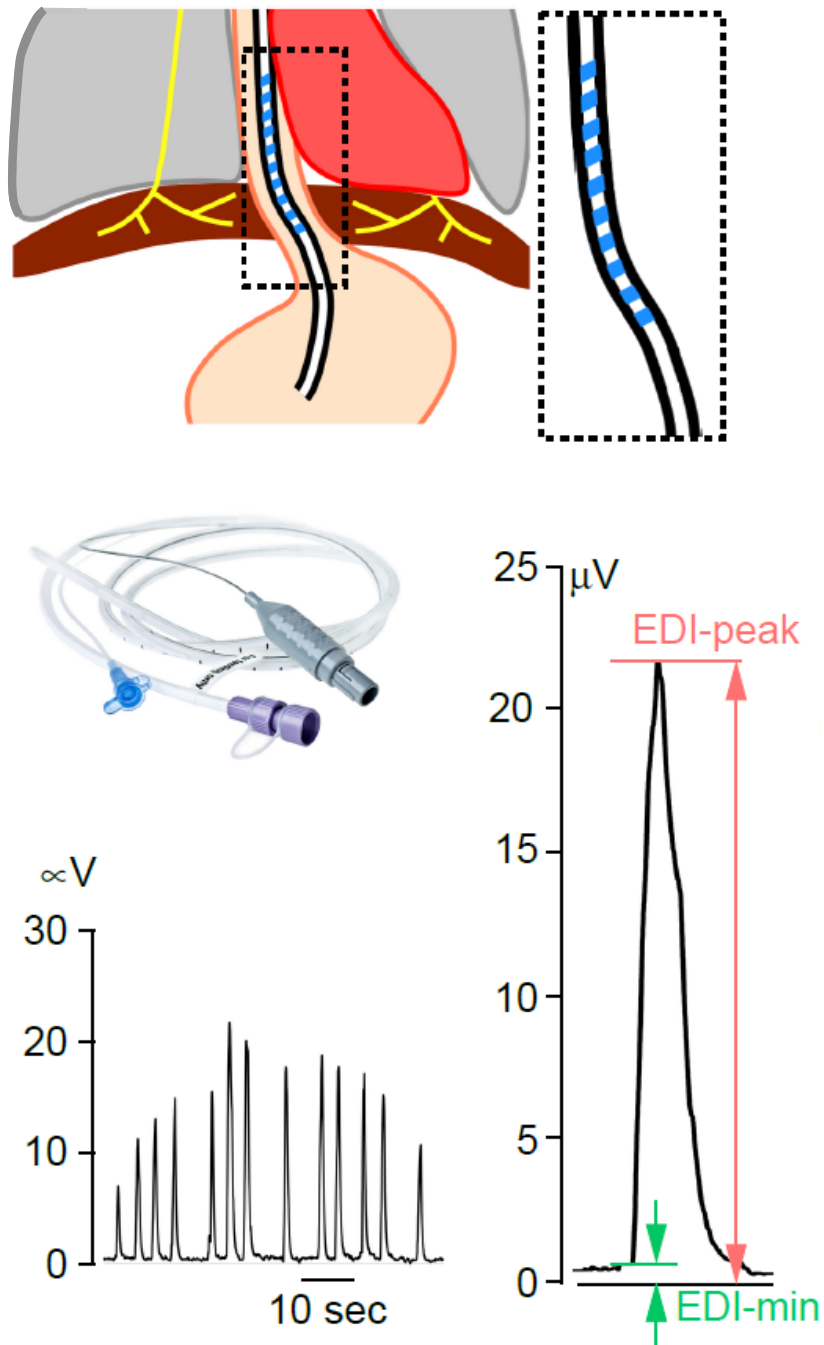


Fig. 26: Electrical activity of the diaphragm (EDI)

(*Top*) Schematic diagram of the nasogastric EDI catheter with electrode (blue stripes) in situ at the gastro-oesophageal junction. (*Middle*) Photograph of a real EDI nasogastric catheter. (*Bottom left*) EDI recordings from a C8A TSCI patient. (*Bottom right*) Magnified view of EDI signal showing EDI-min and EDI-peak.

Diaphragm excursion:



Intercostal thickness:



Fig. 27: Diaphragm excursion and intercostal muscle thickness measurement

A, Placement of ultrasound probe to record diaphragmatic excursion from (left) right hemidiaphragm, and (right) left hemidiaphragm. **B**, Placement of ultrasound probe to record intercostal muscular thickness from (left) right 2nd intercostal muscle, (middle) right 6th intercostal muscle, and (right) right 11th intercostal muscle.

4.2.4 Optimising assessments of breathing function

Following pilot studies in subjects without cervical TSCI (not shown), we eliminated the effect of patient position on EDI and USS parameters by performing all measurements with the patients sitting at 20 – 30 degrees in bed. Patients did not have active chest infection during the measurements. USS and EDI recordings were performed during spontaneous breathing to eliminate any confounding effects of mechanical ventilation. I performed all USS recordings to eliminate inter-assessor variability. I received training in respiratory USS by two consultant radiologists, who independently verified the method and measurement acquisition technique.

4.2.5 Statistical analysis.

Statistical analysis was performed in conjunction with Dr Saadoun. We used best fit linear, quadratic, and cubic polynomials for breathing function *vs.* SCPP monitoring data. The two noradrenaline groups (low *vs.* high dose) were compared using two-tailed t-tests.

4.3 Results

4.3.6 Subject characteristics

We recruited 13 cervical TSCI patients. All subjects and family members approached agreed for the patients to participate. Table 10 shows demographic information. Most (10/13) were males, and most (9/13) were younger than 60 years. On admission, 4/13 patients were AIS grade A, 7/13 grade B and 2/13 grade C. 10/13 patients had posterior surgery only, and 3/13 had combined anterior + posterior surgery. AIS grade at follow-up (on average 7.9 months) improved in 9, stayed the same in 3 and no one deteriorated. 1/13 patient was lost to follow-up, due to a non-surgical mortality from chest sepsis after discharge. In 8 control subjects (5 healthy and 3 thoracolumbar spinal injuries), we evaluated USS parameters in 38 exams. As in the TSCI group, most controls were male (7/8) and less than 60 years old (7/8), with mean age 41.1 years (range 27.0 – 63.9). No one had co-morbidities or chest injuries.

4.3.7 Patient complications

Table 11 lists complications in the cervical TSCI patients. There was no postoperative CSF leak, wound infection, haematoma, or cord damage from the monitoring probes. 11/13 patients (84.6%) had non-compressive pseudomeningocele on the two-week postoperative MRI, all conservatively managed. Non-surgical complications included chest infection in 7/13, urinary tract infection in 4/13 and delayed uncomplicated pressure ulcers successfully managed conservatively in 2/13.

Table 10. Demographic characteristics of cervical TSCI patients

No	Age	Sex	AIS admission	AIS follow-up	Follow-up (months)	Hours ISP monitoring
.	(years)	x				
1	23.0	M	C5A	C7B	12.04	151
2	35.0	M	C5A	C3A	6.90	158
3	24.0	M	C5C	C5D	10.01	122
4	21.0	M	C4B	C4B	6.25	160
5	61.0	F	C5B	Lost		93
6	62.0	M	C6B	C5C	6.85	159
7	50.4	M	C4B	C1D	8.05	106
8	71.4	F	C5B	C7D	10.55	116
9	37.0	M	C5B	C5B	8.71	113
10	54.3	F	C1C	C3D	7.72	98
11	20.1	M	C5B	C5C	6.25	56
12	70.6	M	C5A	C1C	6.51	14
13	44.5	M	C5A	C6A	4.74	112
					TOTAL	1,458

AIS = American spinal injury association Impairment Scale, F = female, ISP = Intra Spinal Pressure, M = male.

Table 11. Complications of cervical TSCI patients

Complication	No. of patients	%
<i>PROBE RELATED / SURGICAL</i>		
CSF leak	0	0.0
Wound infection	0	0.0
Meningitis	0	0.0
Cord damage from probes	0	0.0
Postoperative haematoma	0	0.0
Further surgery / return to theatre	0	0.0
Pseudomeningocele	*11	84.6
Post-traumatic syrinx	0	0.0
<i>NON-SURGICAL / DELAYED</i>		
Chest infection	7	53.8
Urine infection	4	30.8
Line/blood infection	1	7.7
Pulmonary embolus or DVT	0	0.0
Pressure ulcer	2	15.4
Delirium in NeuroICU	1	7.7
Mortality	**1	7.7

CSF = Cerebro-Spinal Fluid, DVT = Deep Vein Thrombosis.

** All non-compressive on postoperative MRI. 3/11 total resolution on 6 months MRI*

*** 1/11 non-surgical mortality from pulmonary sepsis several months after surgery*

4.3.8 Reproducibility and confounding factors

Based on 8 subjects without cervical TSCI, the coefficients of variation for the USS measurements were: diaphragmatic excursion 7.5 %, diaphragmatic thickening 5.3 % (right 4.7 %, left 5.8 %), and intercostal thickening 3.0 % (upper 3.7 %, middle 2.0 %, lower 3.3 %). The TSCI patients received noradrenaline infusion during 81.6 % of the USS and EDI measurements. To determine the effect of noradrenaline, we compared USS and EDI measurements made with TSCI patients on high ($>0.1 \mu\text{g/kg/min}$) vs. low ($\leq 0.1 \mu\text{g/kg/min}$) noradrenaline dose. High noradrenaline dose was associated with higher MAP (96.2 vs. 93.0 mmHg, $P < 0.005$), higher ISP (16.9 vs. 8.9 mmHg, $P < 0.001$), lower SCPP (79.9 vs. 85.1 mmHg, $P < 0.0005$) and lower % muscle thickening change during breathing for lower intercostals (-0.1 vs. 4.6 %, $P < 0.05$) with no effect on EDI-peak, EDI-min, diaphragmatic excursion (quiet + deep breathing), % diaphragmatic thickening change (quiet + deep breathing) or % muscle thickening change for upper and middle intercostals.

EDI and USS recordings were not performed in patients with cardiorespiratory instability, significant pre-existing lung disease, pulmonary contusions, pneumonia, or pulmonary embolus that may have influenced diaphragmatic or intercostal muscle function. PS support and PEEP may influence the USS and EDI parameters; therefore, in addition to analysing all breathing function recordings, we also analysed the subgroup related to patients not attached to a ventilator.

4.3.9 SCPP correlates with injury site metabolism.

We first determined whether SCPP correlates with injury site metabolism assessed using spinal cord tissue oxygen ($p_{\text{set}}\text{O}_2$) and microdialysis (MD) monitoring from the injury site. Details of the monitoring techniques are in Section 1.10 – Common

Methods. The relations between p_{setO_2} vs. SCPP and tissue glucose vs. SCPP are inverted-U shaped, with the maximum at SCPP 70 – 90 mmHg, whereas increasing SCPP is associated with decreasing LPR (Fig. 28). These findings suggest that low SCPP indicates ischaemia, and that both hypo- and hyper- perfusion may be detrimental to the injured spinal cord, with optimum SCPP at 70 – 90 mmHg.

4.3.10 SCPP correlates with diaphragmatic function

Figs. 29A and 29B show the relationship between SCPP and EDI. SCPP <60 mmHg is associated with low EDI-peak (diaphragmatic inspiratory effort) and EDI-min (diaphragmatic tonic activity). EDI-peak and EDI-min increase as SCPP increases >60 mmHg, plateau at SCPP 60 – 90 mmHg, and increase further at SCPP >90 mmHg. In non-ventilated patients, EDI varies with SCPP in a similar fashion. The diaphragmatic thickening fraction for quiet and deep breathing plotted vs. SCPP has inverted-U relationships, with maxima at SCPP 80 – 90 mmHg (Fig. 30).

During quiet breathing, there is no correlation between SCPP and diaphragmatic excursion, but during deep breathing, diaphragmatic excursion is low at SCPP <60 mmHg, increases as SCPP increases >60 mmHg, plateaus at SCPP 60 – 100 mmHg, and increases further at SCPP >100 mmHg (Fig. 31). Diaphragmatic excursion when PEEP = 0 and PS = 0 also does not correlate with SCPP for quiet breathing, but has inverse-U relationship with SCPP for deep breathing with peak at SCPP 80 – 90 mmHg. Figs. 30 and 31 also show that the diaphragmatic thickening fractions and the diaphragmatic excursions for quiet and deep breathing in the control subjects are generally low compared with the corresponding parameters in patients with cervical TSCI.

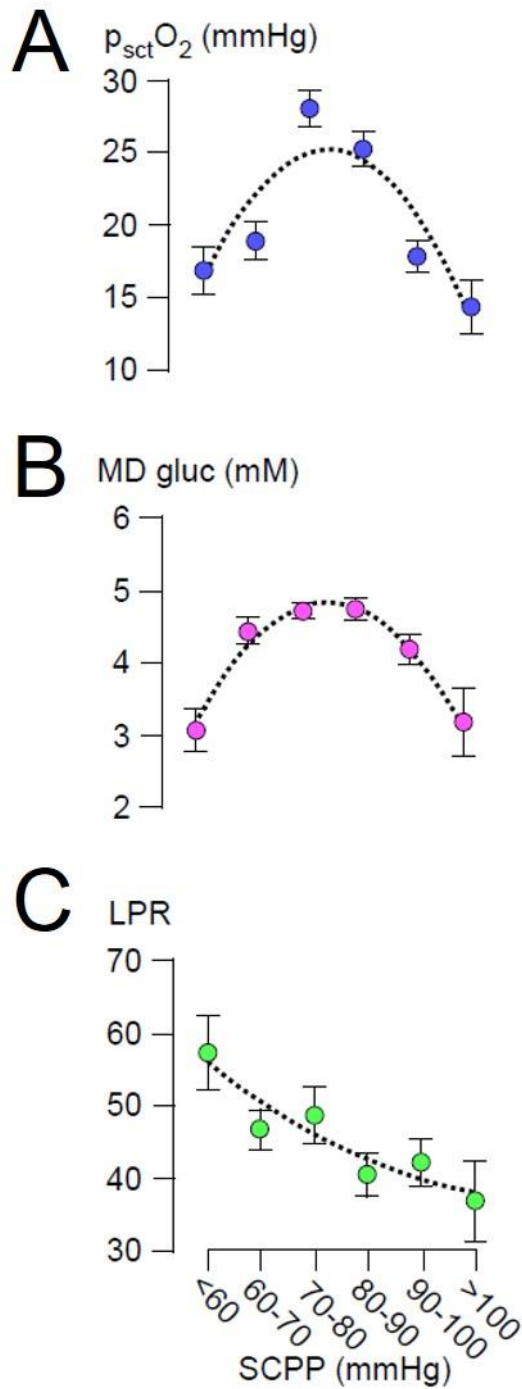


Fig. 28: Physiological importance of SCPP

Plots of **A**, $p_{\text{sct}}\text{O}_2$ vs. SCPP, **B**, tissue glucose vs. SCPP, and **C**, tissue LPR vs. SCPP.

Data from all 13 patients, mean $\pm$ standard error. Best fit quadratic (**A**, $r^2 = 0.78$; **B**, $r^2 = 0.98$), Michaelis-Menten (**C**, $r^2 = 0.82$).

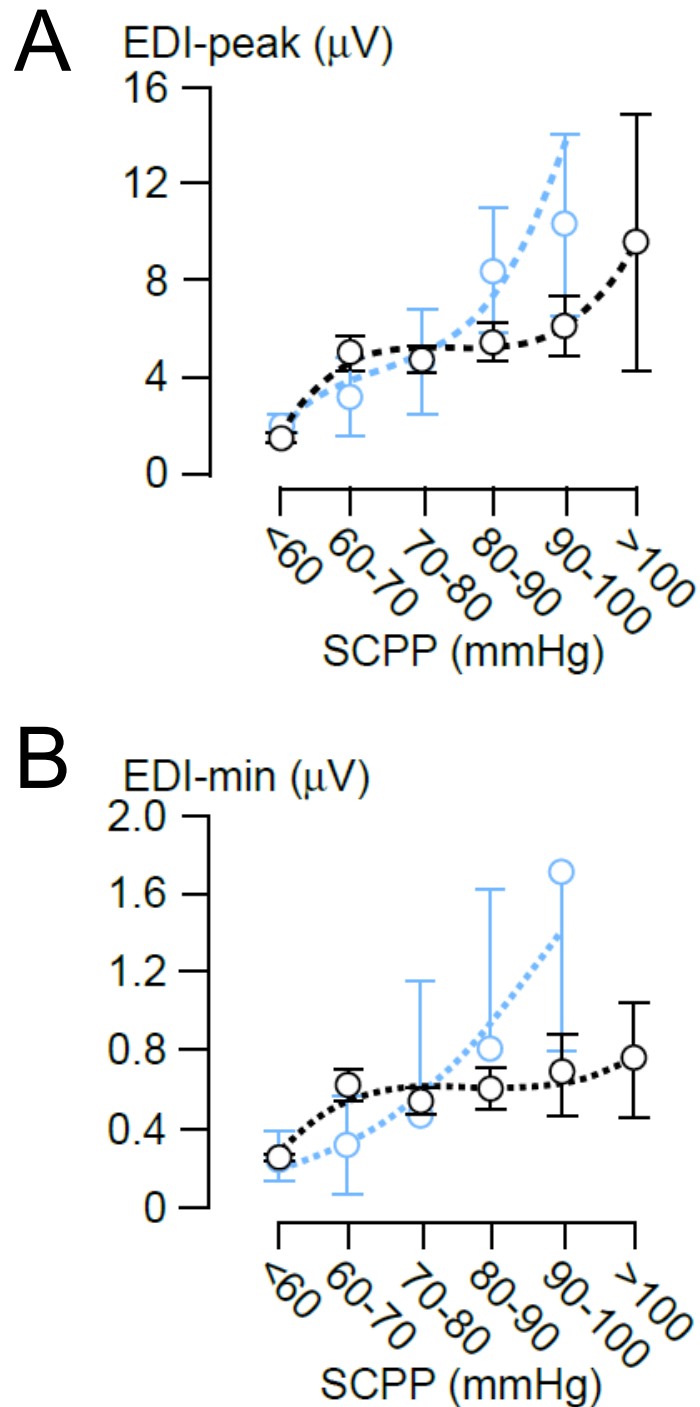


Fig. 29: Relationship of SCPP with electrical activity of the diaphragm (EDI)

Diaphragm EMG (EDI) vs. Spinal Cord Perfusion Pressure (SCPP) for **A**, EDI peak, and **B**, EDI-min. Black, all 198 recordings; blue, 73 recordings when PEEP = 0, PS = 0.

Mean $\pm$ standard error. Best-fit polynomial curves (**A** black, cubic: $r^2 = 0.90$, **A** blue cubic: $r^2 = 0.98$; **B** black, cubic: $r^2 = 0.98$; **B** blue, quadratic: $r^2 = 0.95$). PEEP =

Positive End-Expiratory Pressure, PS = Pressure Support.

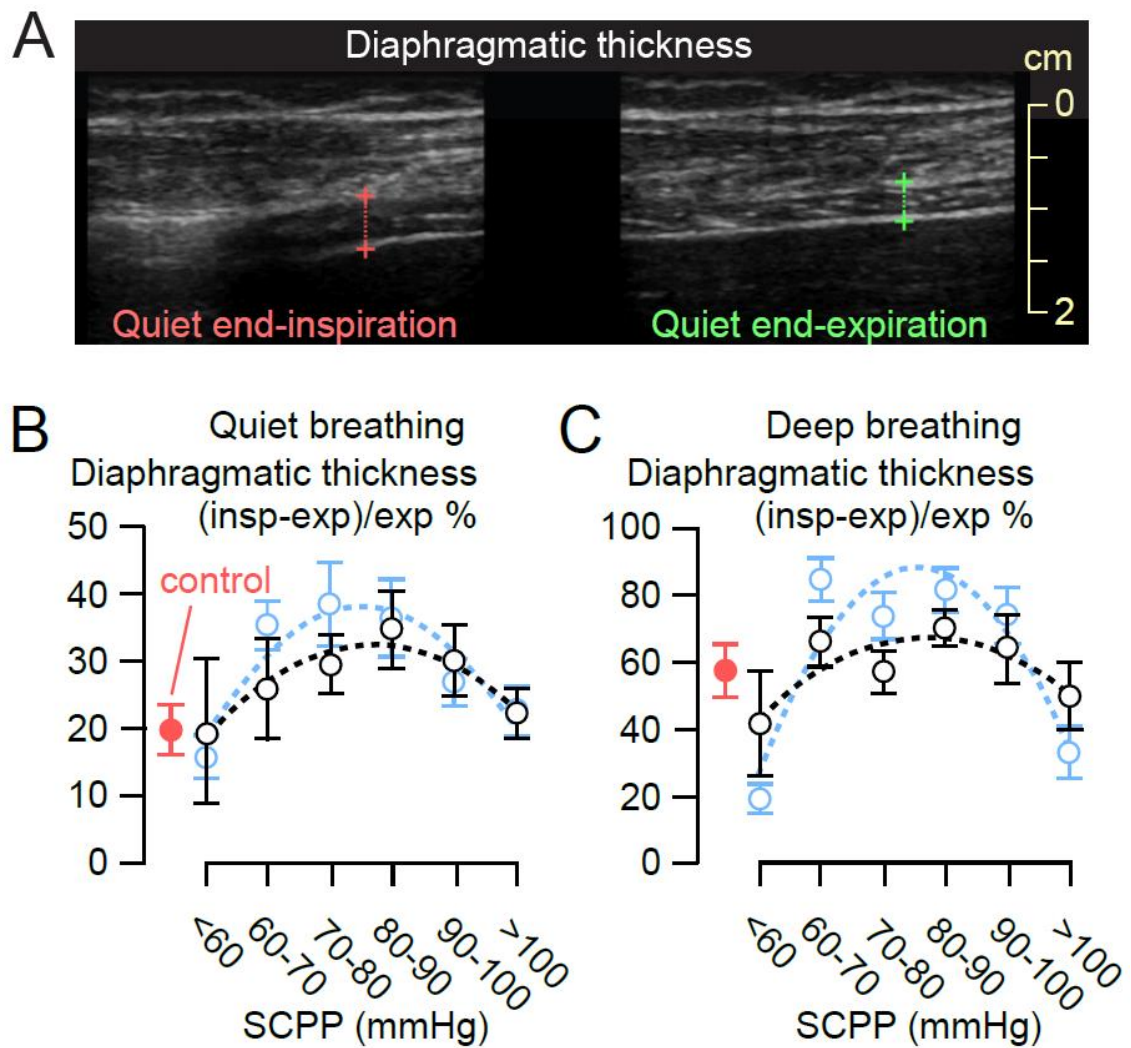


Fig. 30: Diaphragm thickening fraction

A, Photos of ultrasound exam of right hemi-diaphragmatic muscle thickening during quiet breathing, at end-inspiration and at end-expiration. % change in diaphragm thickness = (inspiration – expiration)/expiration plotted vs. SCPP. **B**, during quiet breathing, and **C**, during deep breathing. Black, all 103 recordings; blue, 52 recordings when PEEP = 0, PS = 0. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit quadratic (**B**, black: $r^2 = 0.92$; **B**, blue: $r^2 = 0.85$; **C**, black: $r^2 = 0.72$; **C**, blue: $r^2 = 0.84$).

insp = end-inspiration, *exp* = end-expiration, SCPP = Spinal Cord Perfusion Pressure, PEEP = Positive End-Expiratory Pressure, PS = Pressure Support.

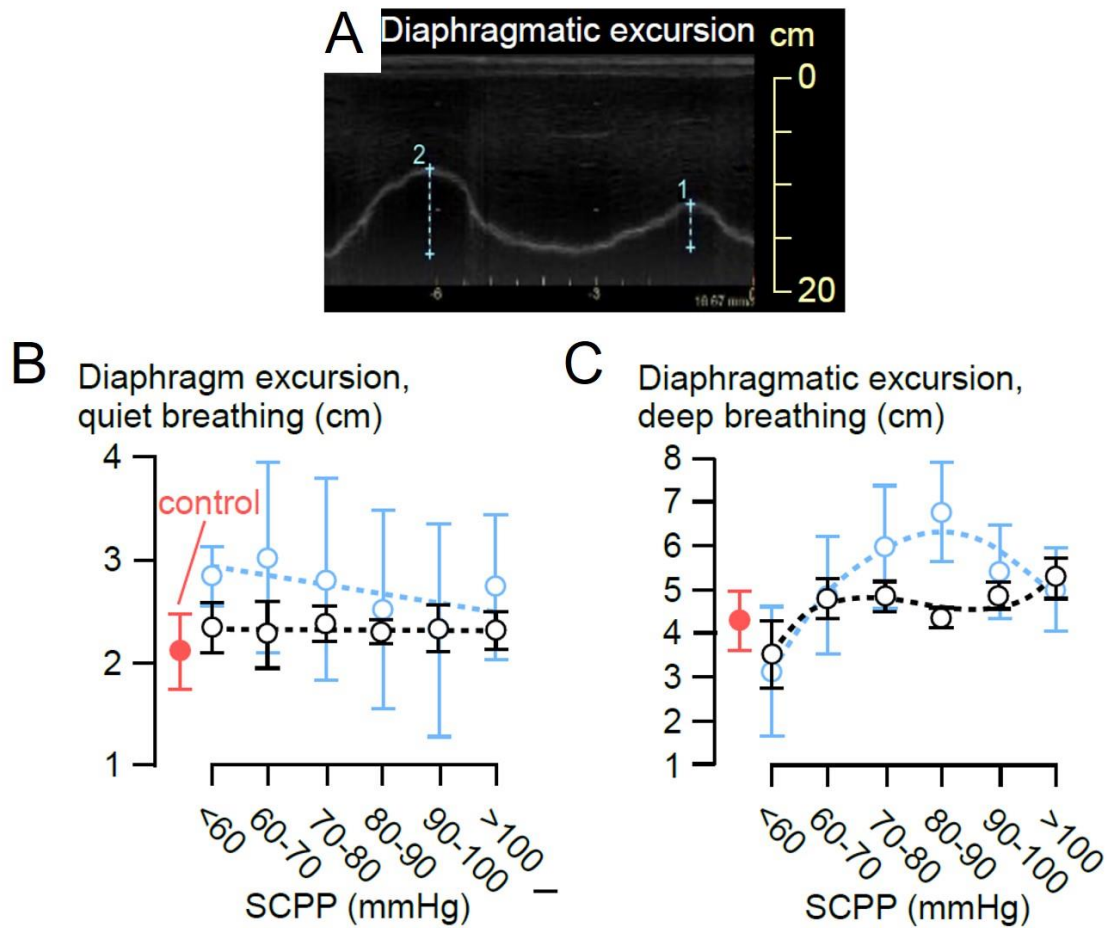


Fig. 31: Diaphragmatic excursion

A, Diaphragmatic excursion measurements in M-mode. Diaphragm excursion plotted vs. Spinal Cord Perfusion Pressure (SCPP) **B**, during quiet breathing, and **C**, during deep breathing. Black, all 103 recordings; blue, 52 recordings when PEEP = 0, PS = 0. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit curve (**B**, black, linear $r^2 = 0.00$; **B**, blue, linear $r^2 = 0.38$; **C**, black, cubic $r^2 = 0.79$; **C**, blue, quadratic $r^2 = 0.93$).

PEEP = Positive End-Expiratory Pressure, PS = Pressure Support.

4.3.11 SCPP correlates with intercostal muscle function

Fig. 32 shows the relationship between the thickening fractions of the upper, middle, and lower intercostal muscles plotted against SCPP. SCPP <70 mmHg (upper and lower intercostals), and <60 mmHg (middle intercostals) was associated with negative intercostal thickening fraction, suggesting failure of the muscles to contract during inspiration (likely passive stretching, diaphragmatic breathing).

For upper and middle intercostals, SCPP >100 mmHg was also associated with failure of the muscles to contract during inspiration. Overall, SCPP 80 – 100 mmHg was optimal for allowing upper, middle, and lower intercostal muscles to contract during inspiration. Intercostal thickening fractions when not attached to a ventilator, i.e. PEEP = 0 and PS = 0, correlate with SCPP in a similar fashion. Fig. 32 also shows that, in the control subjects, the upper, middle, and lower intercostals have positive thickening fractions, indicating intercostal muscle contraction during inspiration.

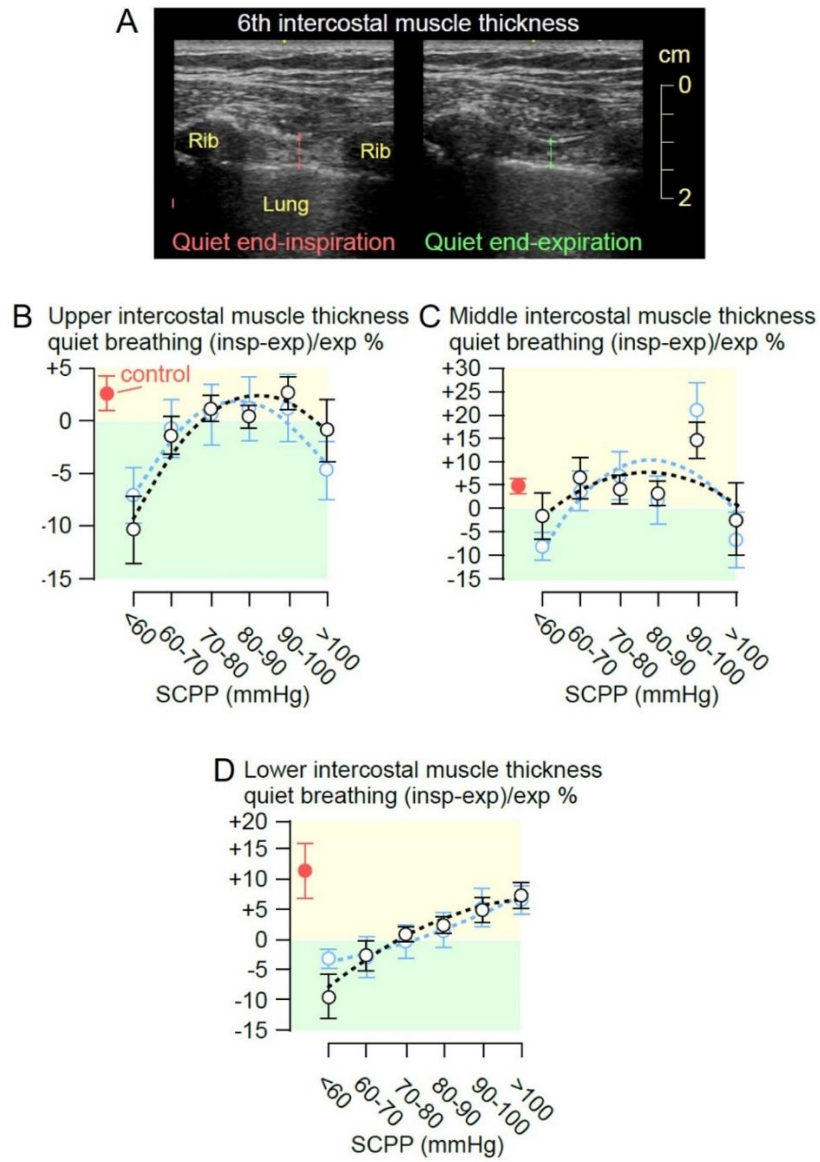


Fig. 32: Intercostal muscles thickening fraction

A, Ultrasound examination of right 6th intercostal muscle thickening during quiet breathing, at end-inspiration and at end-expiration. % change in intercostal muscle thickness during quiet breathing = (inspiration – expiration)/expiration, **B**, in upper intercostal muscles, **C**, in middle intercostal muscles, and **D**, in lower intercostal muscles. Black, all 103 recordings; blue, 52 recordings when PEEP & PS = 0. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit quadratic (**B**, black: $r^2 = 0.91$; **B**, blue: $r^2 = 0.94$; **C**, black: $r^2 = 0.35$; **C**, blue: $r^2 = 0.45$; **D**, black: $r^2 = 0.98$; **D**, blue: $r^2 = 0.97$). PEEP = Positive End-Expiratory Pressure, PS = Pressure Support.

4.4 Discussion

We showed that monitoring breathing function in critically ill patients with acute TSCI in neuroICU, using ultrasound and EDI, is feasible and reproducible. The key finding is that SCPP correlates with breathing: too low SCPP (cord hypo-perfusion) and too high SCPP (cord hyper-perfusion) are associated with more impaired breathing, whereas SCPP 80 – 90 mmHg correlates with improved diaphragmatic and intercostal muscle contractility. These findings are robust even when only data relating to patients not attached to a ventilator are considered, to eliminate the effects of PEEP and PS on the function of breathing muscles.

USS is a non-invasive, non-ionising technique that provides high-resolution images in real-time with good reproducibility²¹³. Disadvantages include the confounding effects of inotropic support, PEEP and PS on the measurements, whereas obesity, reduced compliance from the critically ill patients and technical factors (such as patient position, probe location and angulation) also affect the recordings²¹⁴. Subcostally scanning left hemi-diaphragmatic excursion is challenging because of the small splenic window and lung masking; we had a failure rate of 70.9 %, compared with subcostally scanning right hemi-diaphragmatic excursion. In the intensive care setting, diaphragmatic USS has been used to guide weaning from mechanical ventilation²⁰⁸, to evaluate diaphragmatic paralysis²¹⁵ and to quantify the work of breathing²⁰⁹. We recommend devoting time to optimise the technique before using the data for clinical decision making.

The key diaphragmatic USS parameters are thickening fraction and excursion. Thickening fraction is a measure of the force of contraction of the diaphragm during inspiration²¹⁶. Excursion is the up and down motion of the diaphragm that contributes to the lung inspiratory volume²¹⁷. Because of impaired intercostal muscle function, patients with severe cervical TSCI rely almost exclusively on diaphragmatic contraction

to increase lung volume during inspiration. By comparison, in normal subjects, diaphragmatic contraction is responsible for 70% of the tidal volume and the intercostal muscles for 30%²¹⁸. This may explain our observation that diaphragmatic thickening fraction and excursion are generally higher in patients with cervical TSCI than control subjects with intact intercostal muscle function. Our data show that, during quiet (tidal) breathing in patients with cervical TSCI, diaphragmatic excursion is independent of SCPP (i.e. the tidal volume is reached regardless of the SCPP). However, SCPP affects the force of diaphragmatic contraction, measured using the thickening fraction, with the strongest contraction at SCPP 80 – 90 mmHg. Deep breathing requires increased diaphragmatic effort to inflate and deflate the lungs to vital capacity; we found that, during deep breathing, SCPP has a major influence on diaphragmatic thickening fraction and excursion with optimum function at SCPP 80 – 90 mmHg.

Diaphragmatic function was further assessed using the EDI nasogastric tube, initially designed for NAVA ventilation^{206,207}. During quiet breathing, normal EDI-peak is 5 – 10 μ V, and normal EDI-min is up to 1 μ V. EDI-peak increases when the diaphragm has to contract more, e.g. during respiratory distress the EDI-peak may increase to 5 – 7 times above normal^{219,220}. Our data show that at SCPP <60 mmHg, the EDI-peak is too low and that SCPP 60 – 100 mmHg is required for EDI-peak to normalise. We also found that low SCPP (<60 mmHg) is associated with reduced EDI-min, which is a marker of diaphragmatic tone. Reduced diaphragmatic tone is detrimental by allowing the abdominal contents to displace the diaphragm cranially thus causing lung compression and atelectasis²²¹. We found that SCPP 60 – 100 mmHg increases EDI-min, which may, in turn, facilitate tonic diaphragmatic contraction.

We also assessed the thickening of intercostal muscles, which are easily accessible by USS. Normally, the contribution of intercostal muscles to breathing increases with intense respiratory effort²²². In our control group, the thickening fraction

was low ($\leq 5\%$ for upper and middle intercostal muscles, 10% for low intercostals). In the cervical TSCI patients, we found an inverted-U relationship between intercostal thickening fraction and SCPP for upper and middle intercostals with the maximum intercostal thickening fraction reaching normal level during quiet breathing at SCPP 80 – 90 mmHg. The thickening fraction of low intercostal muscles increased with increasing SCPP. Negative thickening fraction, seen during spinal cord hypo- and hyper-perfusion, likely indicates passive stretching of the intercostal muscles during inspiration that may occur with diaphragmatic (abdominal) breathing.

A limitation of the study is the small number of patients. However, the conclusions are supported by 1,458 hours of SCPP monitoring and 106 serial USS examinations (total 1,370 USS images/videos). The neuroICU setting with critically ill patients required to cooperate during the assessments was particularly challenging. Together, the findings raise the possibility that intervention to maintain SCPP 80 – 90 mmHg may improve breathing in patients with acute, severe cervical TSCI.

To conclude, acute severe cervical TSCI impairs breathing. Our study shows that SCPP 80 – 90 mmHg correlates with improved breathing function. Further studies are required to determine whether a SCPP-driven protocol affects clinical outcomes such as minimising failed extubation, avoiding tracheostomy, and reducing neuroICU length of stay.

5 CHAPTER IV - Overall Discussion

5.1 Summary of Findings

By utilising injury site monitoring, the three experiments presented in this thesis, have generated several novel and important findings, relevant to improving neurological outcome following acute TSCI.

First, spinal cord tissue oxygen, designated “ $p_{\text{sct}}\text{O}_2$ ”, has been defined as a novel parameter in spinal cord injury physiology. I showed that $p_{\text{sct}}\text{O}_2$ can be safely and accurately measured from the injured human spinal cord. $P_{\text{sct}}\text{O}_2$ correlates with injury site metabolism, physiology and, critically, is associated with neurological outcome. Having shown that hypoxia and hyperoxia may impair motor function, the next step is to define critical thresholds. Based on TBI studies, I hypothesise that <20 mmHg represents hypoxia^{102–105} and <5 mmHg, necrosis²²³. Overall, the findings support the monitoring of continuous oxygen data, directly from the injury site. This is important for tissue-oxygen guided optimisation, as a future treatment for acute TSCI.

Second, I defined different types of fever and their effects following TSCI. All types are likely harmful, increasing metabolic stress and exacerbating cord ischaemia. However infective fever is likely to be the most injurious by also exacerbating inflammation. Fig. 34 summarises the properties of the three different types, and their likely effects on the injured spinal cord. Fever is easily measured and treatable. Accurately ascertaining the aetiology of fever will guide appropriate treatment, and explains why anti-pyretics and anti-inflammatory agents are not always efficacious. The use of clinical and biochemical classifiers to distinguish neurogenic fever from infective and inflammatory is novel. Given the absence of treatment for neurogenic fever in TSCI, the novel application of bromocriptine in TSCI merits evaluation, given reports of its efficacy in TBI neurogenic fever. Timely and accurate diagnosis of fever may reduce over-investigation on ICU, thus economic burden. The commonly ascribed label of “pyrexia of unknown origin” may be reduced with our neurogenic fever flowchart.

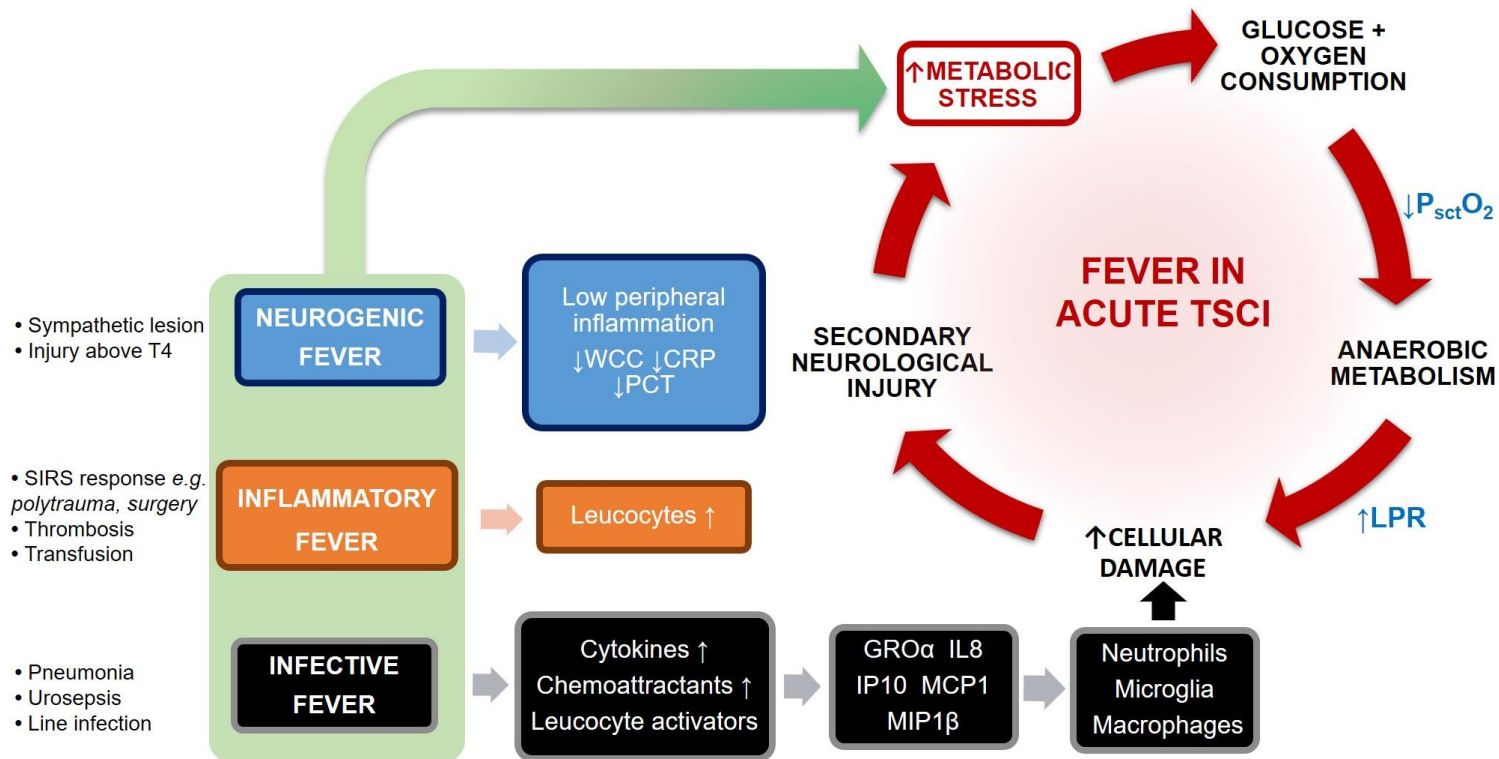


Fig. 33: The detrimental effects of fever following TSCI

All fever types (neurogenic, inflammatory, infective) potentiate metabolic stress, contributing to a vicious cycle of secondary neurological injury.

SIRS = Systemic Inflammatory Response Syndrome, WCC = White Cell Count, PCT = Procalcitonin, CRP = C-Reactive Protein, P_{sct}O₂ = Spinal Cord

Tissue Oxygen, LPR = Lactate Pyruvate Ratio; GROα, IL8, IP10, MCP1, MIP1β are all cytokine signalling molecules.

Third, I showed that following TSCI, breathing function correlates with SCPP. Specifically, spinal cord hypoperfusion and hyperperfusion were associated with impaired breathing. Whereas SCPP 80 – 90 mmHg correlated with optimal diaphragmatic and intercostal contractility. The findings were consistent across ventilated and non-ventilated patients, suggesting the scope for SCPP augmentation as a treatment for impaired breathing function. Fig. 35 shows the innervation of breathing muscles and how improving SCPP may optimise breathing function.

Despite previous evaluation of breathing in chronic TSCI cohorts^{224,225}, prospective quantification of breathing function (using EDI and ultrasonography) and the presented associations with spinal cord physiology in acute TSCI, are novel. The feasibility and reproducibility of EDI and ultrasound monitoring in acute TSCI have been established. Further study is warranted to elucidate EDI microvoltage and ultrasonographic thresholds across TSCI severities, for utility as an effective management adjunct. Furthermore, the current management of breathing dysfunction in acute TSCI focusses on reactive interventions (ventilation, secretion management and tracheostomy). The findings raise the prospect of targeting SCPP pro-actively, to minimise the need for tracheostomy, promote secretion clearance, prevent failed extubation and decrease neuroICU length of stay. Further evaluation of these outcomes in a larger cohort could lead to a reduction in the significant morbidity associated with respiratory dysfunction.

Multimodality monitoring in acute TSCI may now encompass tissue-oxygen monitoring, restoring normothermia specific to fever type, and optimisation of breathing function. The following sections expand on injury site monitoring as a paradigm, including the future, limitations, alternatives and further work to advance the field.

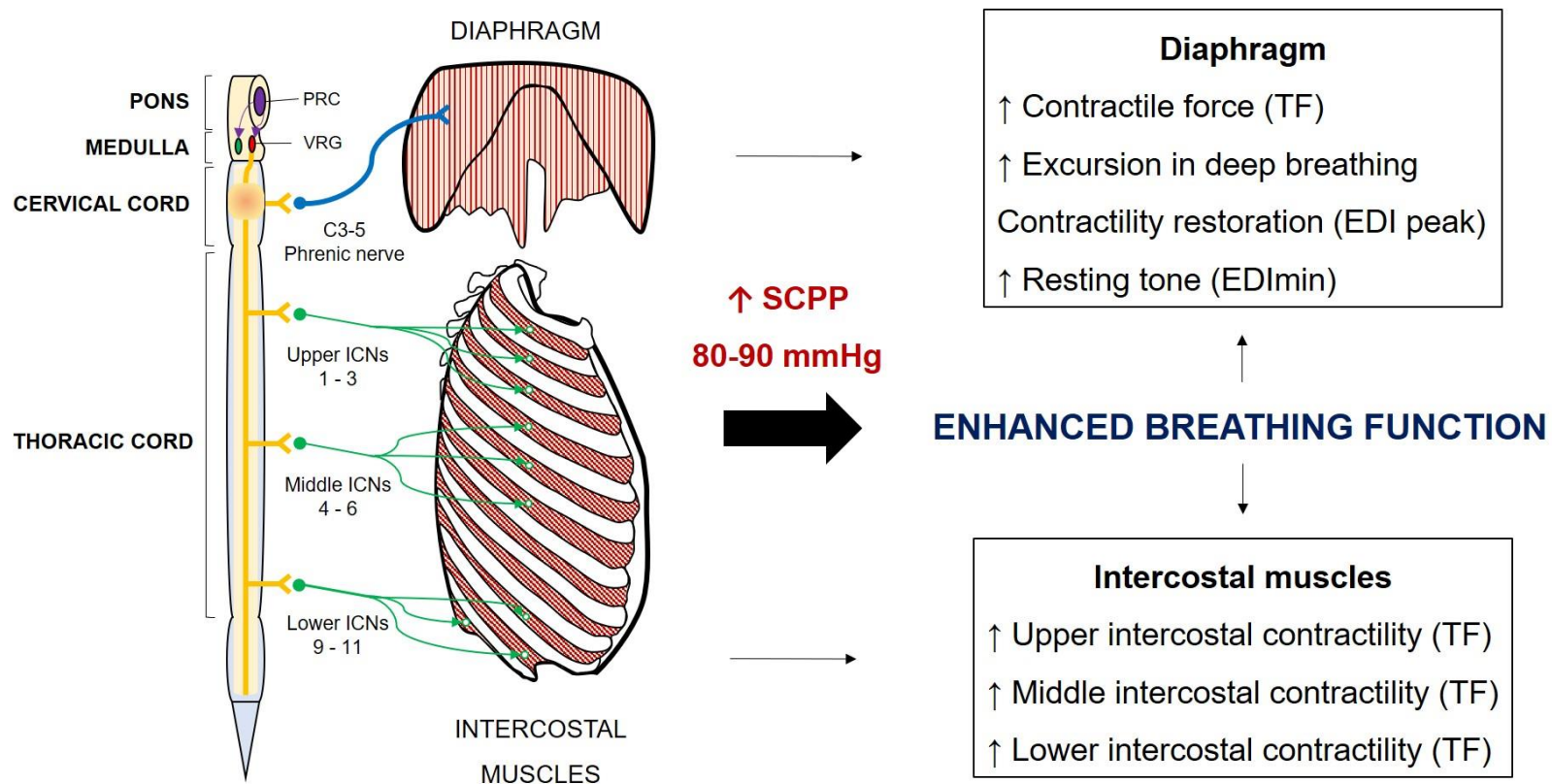


Fig. 34: The effects of optimising SCPP on breathing function

Schematic diagram showing (i) innervation of the diaphragm and intercostal muscles, and (ii) the effects of SCPP augmentation on breathing function.

PRC = pontine respiratory column, VRG = ventral respiratory group, ICN = intercostal nerve, SCPP = spinal cord perfusion pressure, TF =

thickness fraction, EDI = diaphragm electromyography signal, EDI peak = maximal force of contraction; EDI min = resting tone of diaphragm.

5.2 Is injury site monitoring the future of TSCI?

Monitoring from the injured spinal cord provides real-time, continuous information about cord physiology (ISP, SCPP, P_{scfO_2}), autoregulation (sPRx, sRAP) and metabolism (tissue glucose, LPR). The probes are placed at the time of surgery, not requiring additional intervention, with minimal risk. Monitoring may detect secondary neurological physiologic and metabolic insults, providing clinicians with the potential to intervene (e.g. inotropic augmentation of SCPP, FiO_2 boosting of p_{scfO_2}) and receive feedback from such interventions (e.g. treatment of fever). Monitoring allows quantitative feedback, therefore novel pharmacotherapeutic interventions, (e.g. AZD1236 MMP inhibitors²²⁶, minocycline^{227,228}, riluzole²²⁹) and novel surgical treatments (duroplasty⁹², experimental bio-scaffolding techniques^{230–232}) can be pre-clinically evaluated. First, to understand how they affect the injury site. Second, whether their effects can be potentiated by improving parameters detected by multimodality monitoring. For example, improving drug delivery by optimising spinal cord blood flow (SCPP). Such insights may support the research and development of future robust treatments for acute TSCI.

5.3 Limitations with injury site monitoring

There are limitations with monitoring. Currently it is invasive, requires specialist input, large volume data storage, and carries low but present risks including cord damage, CSF leak +/- infection and pseudomeningocele formation. Prospective detection of physiological stressors during the postoperative epoch, although the first step, may be behind the curve. For instance, calculating SCPPopt in 5-minute windows is a retrospective insight into autoregulation. Therefore, this approach may miss the therapeutic window before secondary neurological damage ensues.

5.4 Alternative to injury site monitoring

Lumbar CSF monitoring of both pressure (CSF-P) and metabolism is a documented technique, facilitated by placement of a lumbar catheter^{76,77}. Advantages include the availability and familiarity of the technique with relatively low risks of lumbar catheter placement, below the injury site. Disadvantages centre around the fundamental accuracy of the measured parameters. We previously showed that CSF-P and ISP from the injury site are not equivalent in terms of CSF-P vs. ISP⁷² as well as lumbar CSF metabolites vs. injury site MD⁶⁸. This is because each technique assesses different CSF compartments. Therefore, evaluating the spinal cord injury site swollen against the dura, may represent physiologic and metabolic parameters with greater accuracy. This favours multimodality injury site monitoring rather than lumbar CSF monitoring to accurately guide postoperative ICU management.

5.5 The future of multimodality monitoring

The future of injury site monitoring may relate to advances in probe factors, monitored parameters and data output.

5.5.1 Probe factors

The “ideal” monitoring probe should be minimally-invasive. This reduces the durotomy size minimising CSF leak and infection risk. Smaller probes could survey multiple foci, concentrically (contusion, peri-contusional) or cranio-caudally. Derived parameters would require validation against our spinal cord physiological measures before use. Alternatively, an extradural probe could be placed, without surgery / general anaesthetic e.g. fluoroscopic guidance in the lateral position. However, the need for technical precision, several anatomical layers to bypass and infection risk, render this challenging. Radio-opaque MRI compatible probes would allow early imaging

surveillance with probes in situ (vs. post-removal). Therefore, greater duration of monitoring but risk of signal drift and infection.

Finally, an intraoperatively placed, extradural micro-transmitter could relay near infrared spectroscopic (NIRS) ISP and $p_{\text{scf}}\text{O}_2$; translation of NIRS to ICP^{233–235} and $p_{\text{bt}}\text{O}_2$ ^{236–238} are described. For TSCI, a small implantable sensor (“MUSIC”) in development, promises neuromodulatory and ultrasonographic recording of autoregulation²³⁹. Neither technologies can provide microdialysate or the high-resolution data that we achieve with invasive monitoring.

5.5.2 Monitored Parameters and Data Output

Future development of a single combined probe capable of monitoring pressure, oxygenation, and electrical activity (e.g. D-wave amplitude for corticospinal tract integrity) would represent a major advance in probe technology. Multifocal parameter recording could evaluate the peri-contusional injury site profile, and potential salvageability with targeted perfusion therapy. Monitoring multiple SCPPs, short-window SCPPopts and sPRxs, could differentiate injury zones. Furthermore, continuous microdialysate data would be an advantage compared to hourly. Combined with other techniques such as cord tractography^{240,241}, prognostication of spinal cord injury could be improved, beyond the AIS grade designation.

Multimodality monitoring output delivers a continuous stream of physiologic and metabolic data to integrate with clinical management. Employing predictive data-modelling could quantitatively risk-stratify patients for cord hypoperfusion, hypoxia and metabolic derangement, allowing clinicians to intervene in a timely manner. This mandates rigorous validation and data safety measures before wider application.

5.5.3 Future work

On the basis of this thesis, future directions include: first, adopting the detection and treatment of cord hypoxia. A randomised trial comparing neurological outcomes in TSCI patients managed with a $p_{\text{sct}}\text{O}_2$ -targetted protocol versus standard management is warranted.

Second, enhanced classification of fever type including the use of neurogenic fever classifiers and normothermic restoration according to fever type, using anti-inflammatories, anti-pyretics, active cooling +/- D2 agonists, or appropriate antibiotics. A randomised trial is needed to compare neurological outcomes in TSCI patients with active normothermic restoration versus those without.

Third, the detection and mitigation of breathing dysfunction by augmentation of cervical spinal cord perfusion pressure. A randomised trial is needed to compare breathing functional outcomes (e.g. extubation failure, chest sepsis, mechanics, contractility) in cervical injuries with monitoring adjuncts (diaphragm EMG, ultrasound) and SCPP augmentation versus cervical TSCI patients without monitoring of breathing. There is a need to better define diaphragm EMG and ultrasound parameter thresholds, prior to clinical application.

5.5.4 Novel therapies

First, it is now possible to safely detect and improve $p_{\text{sct}}\text{O}_2$. This can be achieved by increasing FiO_2 concentration, improving $p_{\text{a}}\text{O}_2$ by increasing PEEP, clinically-indicated blood transfusion, and treating underlying causes of systemic hypoxia (e.g. chest sepsis and ventilatory failure). Second, the prompt recognition, classification and tiered management of fever episodes, to improve injury site metabolism. Currently anti-pyretics, non-steroidal anti-inflammatory drugs and active cooling are employed, the

latter with risks of thrombosis and infection. There is no effective drug for neurogenic fever, however the agent bromocriptine may have a role. It is a sympatholytic dopamine D2 receptor agonist²⁴² with a half-life of 5.4 hours, peak concentration - 1.5 hours, and a favourable side effect profile (transient cardiovascular/neuropsychiatric effects, systemic fibrosis only with chronic high-dose usage)²⁴².

Animal models of D2 receptor agonists report dose-dependent hypothermic effects^{243,244}, putatively by reducing sympathetic outflow. Evidence in humans for bromocriptine in neurogenic fever is limited to reports and heterogenic studies²⁴⁵. A randomised study is currently underway, comparing paracetamol versus paracetamol + 5 mg bromocriptine in acute TBI²⁴⁶. However, without injury site monitoring, such studies cannot determine effects on injured neurological tissue. With monitoring, we may define the local effects of drugs like bromocriptine, prior to robust evaluation in large, expensive clinical trials.

Third, diaphragm monitoring can be used to survey breathing dysfunction while augmenting cervical SCPP to optimise breathing function. Currently, the use of diaphragm EMG and chest ultrasound in TSCI is not routine. However, we have defined both as safe, quantifiable techniques, to profile the extent of breathing dysfunction, and therefore guide SCPP-driven management.

Multimodality monitoring has exposed the role of dural compression against the injured spinal cord. Persistently raised ISP is not adequately addressed by laminectomy and bony realignment alone⁷⁰. Expansion duroplasty can surgically address this by providing space for injured cord expansion. Preliminary data showed laminectomy and expansion duroplasty to lower ISP, improve SCPP and lower sPRx to a greater extent than laminectomy alone⁹¹. Currently, a multi-centre prospective RCT, DISCUS is underway to evaluate the technique⁹².

6 Conclusions

Acute traumatic spinal cord injury is a catastrophic event causing significant morbidity, however management should not be conceptualised as futile. Historically patients were prescribed bedrest and operated in a delayed fashion. In the future, physiological insights gained from multimodality monitoring, provides rationale for pro-active management. Prompt surgical decompression and adjunctive injury site monitoring may reduce early secondary injury. Addressing patients' individual physiological derangement using multimodality monitoring is feasible on neuroICU.

Optimising $p_{\text{set}}\text{O}_2$, restoring normothermia and supporting breathing function, may minimise secondary neurological injury to maximise neurological recovery. Randomised controlled trials are needed to verify and validate the findings from my experiments in larger TSCI cohorts. Crucially, even with optimal acute management for neurological outcomes, prompt transfer to specialised neuro-rehabilitative facilities with psychological support are critical, to achieving realistic functional outcomes in TSCI.

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8 Appendix I: Ethical Approvals

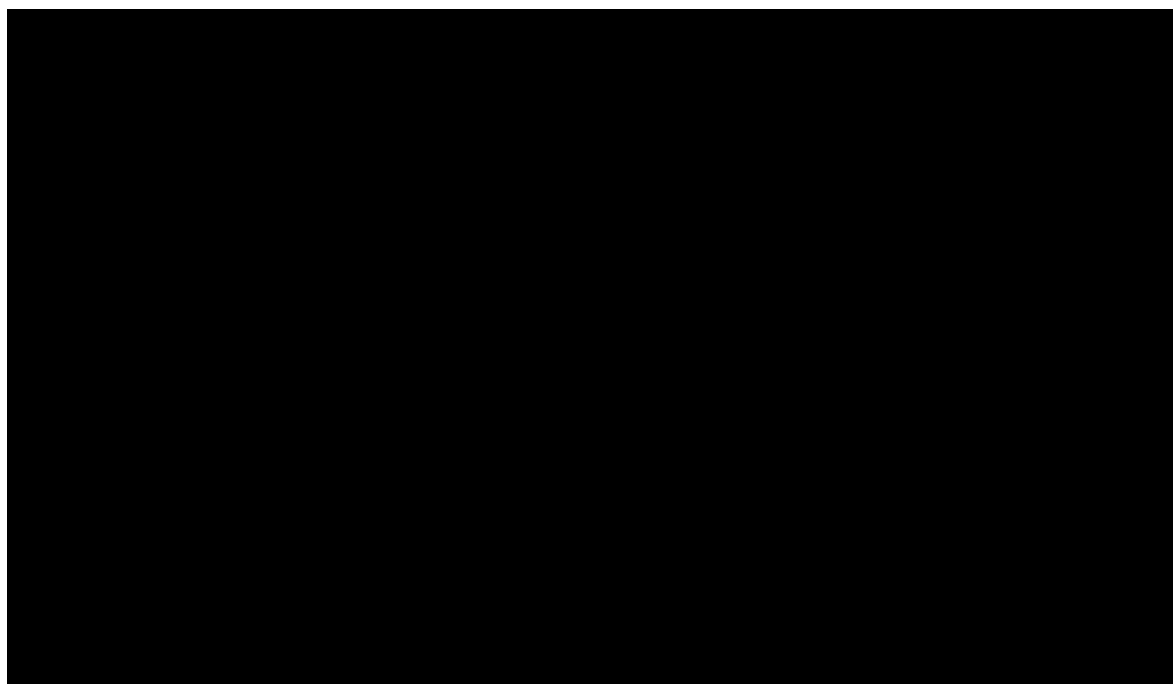


Date: 11th August 2020

Study title:	Evaluation of the potential adverse effect of pressure after spinal cord injury (ISCOPE)
REC reference:	10/110807/23
IRAS project ID:	38379
Sponsor:	St George's University of London

To whom it may concern,

This is a statement to confirm that the above referenced study was originally granted a favourable opinion by the *Camberwell St Giles* NHS Research Ethics Committee whereupon the study was opened to recruitment at St George's University Hospitals NHS Foundation Trust in July 2010.



London - Camberwell St Giles Research Ethics Committee

Ground Floor
Temple Quay House
2 The Square
Bristol
BS1 6PN

**Please note: This is the
favourable opinion of the REC
only and does not allow the
amendment to be implemented
at NHS sites in England until
the outcome of the HRA
assessment has been
confirmed.**

16 January 2023

Professor Marios Papadopoulos
Professor of Neurosurgery
St George's University Hospital NHS Foundation Trust & St. George's University London
Atkinson Morley Wing
Blackshaw Road
London
SW17 0QT

Dear Professor Papadopoulos

Study title:	Evaluation of the potential adverse effect of pressure after spinal cord injury
REC reference:	10/H0807/23
Amendment number:	Amendment 14
Amendment date:	28 September 2022
IRAS project ID:	38379

The above amendment was reviewed at the meeting of the Sub-Committee held in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Recommendations of the favourable opinion

Number	Recommendation
1	The Sub-Committee recommends that the following changes are made to the Personal Consultee Information Sheet: - The Second sentence in the first paragraph would benefit from a slight amendment to insert a comma after the fourth word ("you"). It is advised the letter 's' is deleted from the word "provides" and the word 'had' is inserted in the 3rd line so that the sentence reads: "Please note that you, as a consultee, provide advice whether in your opinion they should participate in this study and to state what the participants wishes and feelings would be had they had capacity; this is not consent." - In the paragraph titled "What do I have to do". It is noted that the second sentence would benefit from a slight change to add the word 'would' in the second sentence and the letter 's' is deleted from the word 'gives', so that the two sentences read: "if you advise that they would have no objection to taking part, you will be asked to sign the consultee declaration form. You as the consultee, give advice rather than consent". - It is recommended that the third sentence is removed.
2	The Sub-Committee recommends that the following changes are made to the Consultee Declaration Form: - It was recommended that the spaces for the name and signature of a witness and the related date should be deleted.
3	The Sub-Committee recommends that the following changes are made to the protocol: - It was recommended that the new text included to align with Section 33 is placed in a subsection relating to withdrawal of participants lacking capacity to consent who have been enrolled into the study. - It was noted that the word 'safeguarding' in the inserted text was in reference to the 'Additional safeguards' title of Section 33 of the MCA rather than its more specific usual meaning of protecting an individual's right to live in safety, free from abuse and neglect. Therefore it is recommended that words 'regarding safeguarding' are removed. - It was highlighted that there should be a comma rather than a full stop after the newly inserted word 'delay'. - It was noted that the protocol now states that after withdrawal of a participant who lacks capacity to consent follow-up will continue. It was recommended that a sub-section relating to withdrawal of participants lacking capacity to consent would be better suited.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Completed Amendment Tool [Locked amendment tool dated 28Sep2022]	v1.6	28 September 2022
Other [CRF V4 dated 28Nov2021]	4	28 July 2022
Other [DPIA signed 28Sep2022]	1	28 September 2022
Other [Response to further queries]	1	10 January 2023
Other [Consultee declaration]	1	10 January 2023
Participant consent form [ICF tracked]	6	10 January 2023
Participant consent form [ICF clean]	6	10 January 2023

Participant information sheet (PIS) [PIS after NOK V6 dated 28Jul2022_CLEAN]	6	28 July 2022
Participant information sheet (PIS) [PIS after NOK V6 dated 28Jul2022_TRACKED]	6	28 July 2022
Participant information sheet (PIS) [New PIS after consultee declaration]	1	13 December 2022
Participant information sheet (PIS) [NEW PIS for Consultee]	1	13 December 2022
Participant information sheet (PIS) [PIS After Consultee Declaration]	2	10 January 2023
Participant information sheet (PIS) [Personal Consultee information sheet tracked]	2	10 January 2023
Participant information sheet (PIS) [Personal Consultee information sheet CLEAN]	2	10 January 2023
Participant information sheet (PIS) [PIS sheet clean]	18	13 December 2022
Participant information sheet (PIS) [PIS sheet tracked]	18	13 December 2022
Research protocol or project proposal [ISCOPE protocol tracked]	19	10 January 2023
Research protocol or project proposal [ISCOPE protocol clean]	19	10 January 2023

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

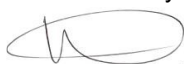
HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities— see details at: <https://www.hra.nhs.uk/planning-and-improving-research/learning/>

IRAS Project ID - 38379:

Please quote this number on all correspondence

Yours sincerely



Copy to: Debbie Rolfe, St George's, University of London and St George's Healthcare NHS Trust

Attendance at Sub-Committee of the REC meeting on 31 October 2022

<i>Name</i>	<i>Profession</i>	<i>Present</i>	<i>Notes</i>
Dr Hilary Anne Lavender	Retired General Medical Practitioner	Yes	
Mr Paul Riordan-Eva	Registered Medical Doctor	Yes	
Dr Mark Tanner	Consultant Psychiatrist	Yes	

Name	Position (or reason for attending)

9 Appendix II: Consent and Patient Information Sheets

Patient details: Name: _____
Date of Birth: _____
Hospital Number: _____
Patient Identification Number for this study: _____

INFORMED CONSENT

Title of study: **Injured Spinal Cord Pressure Evaluation (ISCoPE)**

Name of Chief investigator: Prof Marios Papadopoulos

Please initial box

1. I confirm that I have read and understood the information sheet dated (version) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from St George's University Hospitals NHS Foundation Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these people to have access to my medical records. ☐
4. I agree to take part in the above study. ☐
5. I agree to my General Practitioner being informed of my participation in this study ☐

_____ Name of Participant	_____ Date	_____ Signature of participant
_____ Name of Person taking consent	_____ Date	_____ Signature of person taking consent
_____ Name of Witness (If participant cannot sign) (but verbally consents)	_____ Date	_____ Signature of witness

N.B. 3 forms of written consent required: 1 form for Patient/Consultee; 1 to be kept as part of the study documentation in the site file with corresponding patient information sheet; 1 to be kept with medical notes (original) with corresponding patient/consultee information sheet

Patient details: Name: _____
 Date of Birth: _____
 Hospital Number: _____
 Patient Identification Number for this study: _____

CONSULTEE DECLARATION FORM

Title of study: **Injured Spinal Cord Pressure Evaluation (ISCoPE)**

Name of Chief investigator: Prof Marios Papadopoulos

Please initial box

1. I confirm that I have read and understood the information sheet dated (version) for the above study and have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that the patient's participation is voluntary and that I am free to advise withdrawal at any time, without giving any reason, without their medical care or legal rights being affected.
3. I understand that sections of any of their medical notes may be looked at by responsible individuals from St George's University Hospitals NHS Foundation Trust or from regulatory authorities where it is relevant to their taking part in research. I give permission for these people to have access to their medical records.
4. I agree as consultee for _____ to take part in the above study.
5. I agree to the patient's General Practitioner being informed of the patient's participation in this study

☐
☐
☐
☐
☐

Name of Participant

Date

Signature of participant

Name of Person taking consent

Date

Signature of person taking consent

Name of Consultee & Consultee Relationship to Patient

Date

Signature of Consultee

N.B. 3 forms of written consent required: 1 form for Patient/Consultee; 1 to be kept as part of the study documentation in the site file with corresponding patient information sheet; 1 to be kept with medical notes (original) with corresponding patient/consultee information sheet

Participant Information Sheet

Study Title: Injured Spinal Cord Pressure Evaluation (ISCoPE)

CI: Prof Marios Papadopoulos

IRAS ID: 38379

We invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it will involve for you. Please take time to read the following carefully and discuss it with others if you wish. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you detailed information about the conduct of the study. If you would like any further information or if anything is not clear, please ask us.

Part 1

What is the purpose of the study?

To find out what happens to the spinal cord during the early stages of its injury. This will include:

- Pressure monitoring*
- The electrical activities of the spinal cord*
- The spinal cord's oxygen consumption*
- The waste product produced by the spinal cord during injury*
- The effects of spinal injury on respiratory function*

Why have I been invited?

Because you have suffered a spinal cord injury. Initially, we aim to study about 110 patients.

Do I have to take part?

It is up to you to decide. If you do, you will be given this information sheet to keep and asked to sign a consent form. You are free to withdraw at any time without giving a reason. A decision to withdraw or not take part will not affect the standard of care you will receive.

What will happen to me if I take part?

*If you choose to take part, we will insert **probes** next to your spinal cord and attach them to a computer to measure **cord pressure**, cord oxygen, **various chemicals, blood flow and/or electrical waves** for up to a week. Measuring cord pressure is an experimental procedure not routinely done after a spinal cord injury.*

If your spinal cord is found to be swollen during the operation to fix your spine, we may perform one or more additional procedures: 1. a "duroplasty." This procedure is routinely performed in other spinal operations when the spinal cord is swollen and involves making a surgical incision in the spinal dura membrane to release the pressure.

After your surgery we would like to do some early tests to assess your respiratory function. This will involve monitoring your respiratory muscles using an ultrasound scanner, and the electrical activity of the diaphragm muscle using a routine feeding tube. This will help us to assess respiratory function during the early stages of recovery from the injury.

In all other respects, you will receive the care we normally provide for people with a spinal cord injury regardless of whether you decide to take part in this study.

*We will arrange one visit to examine your arms and legs between **6-12** months. This is to find out how strong your limbs are and how well they can feel.*

What do I have to do?

If you would like to take part in our study you need to sign the consent form. You have up to an hour to make up your mind.

What is being tested?

We are trying to find out if the pressure of your spinal cord is high, possibly for many days, even after surgery to fix the spine. We do not know if high cord pressure matters.

We are also trying to investigate changes in the spinal cord electrical activities, tissue oxygen, waste products produced and/or effect on respiratory function following spinal cord injury.

What are the risks of taking part?

The chance of being harmed by taking part is low, probably less than 1 in 100. We know this because we have already done such recordings from many patients without causing any damage. Nevertheless, there is a small chance that the catheter(s) causes damage to your spinal cord. The catheter might get infected and the infection might spread to the spinal fluid or metalwork used to stabilise the spine. After removing the catheter, there is a small risk of a spinal fluid leak. If this happens, you may need another operation to stop the leak. There is a small risk that performing the duroplasty will also cause a spinal fluid leak. 'Duroplasty' is a reconstructive operation that will close any openings in the dura membrane that surrounds the spinal cord. During the operation we may perform an additional test to check the blood supply to your spinal cord. This requires injection of a dye, routinely used in clinical practice. The risks of this are low and include rash and vomiting (1 in 500 people), or severe allergic reaction (1 in 2000 people). A separate dye, routinely used in clinical practice, may be used to assess the blood supply of the spinal cord. It may be injected at the time of an ultrasound scan during the operation. The risks are low and include nausea, flushing, rash, headache (less than 1 in 100 people), or a severe allergic reaction (less than 1 in 1000 people)

What are the possible benefits of taking part?

Your spinal cord pressure may be lowered by taking part. We do not know if lowering spinal cord pressure is beneficial in the long term.

It may help us improve treatment of future patients with spinal cord injury.

What happens when the research study stops?

We will let you know our findings.

What if there is a problem?

Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed. The detailed information is given in part 2

Will my taking part in the study be kept confidential?

Yes, all information about your participation will be confidential. The details are in part 2.

This completes Part 1. If the information in Part 1 interests you, please read the information in part 2 before making a decision.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about the procedure being studied. If this happens, we might consider withdrawing you from the study. We will explain the reasons and arrange for your care to continue. If the study is stopped for any reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with this study?

You can withdraw from the study at any time. You do not have to tell us why, however we would like to know for our records. . Withdrawal from the study would not affect the usual care or treatment that you would receive during or after the trial. As we would prefer to keep the data collected already we would ask for your permission to do so and would not collect any more.

What if there is a problem?

If you have a concern about any aspect of this study you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital.

If you are still not satisfied with the response you may contact the Joint Research and Enterprise Office at St George's: 020 8725 4986

St Georges, University of London, as the Sponsor, has appropriate insurance in place in the unlikely event that they suffer any harm as a direct consequence of their participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

Will my taking part in the study be kept confidential?

Yes. Yes. We are bound by legislation and the NHS confidentiality code of practice to safeguard confidentiality during and after the study.

It is possible that authorised persons from either the Sponsor organisation and/or the Regulatory authorities that monitor the quality of research such as this may require access to view your medical records for the purposes of audit or monitoring.

Data collected for this study may be retained on a secure database kept on NHS computers for up to a year following study closure whilst results are being analysed.

Once the study is closed following analysis study records may be kept for a further 10 years in a secure location. No information will be kept, which allows your identity to be revealed.

Once participation in this study is agreed we will notify your GP. We will provide a copy of this information sheet for them to enter onto the GP medical records.

If you decide to take part, you will be assigned a unique code so that your personal details are not revealed (anonymised). Any data collected will be stored under this code.

Where can you find out more about how your information is used?

You can find out more about how we use your information here:

*SGHFT Privacy link: <https://www.stgeorges.nhs.uk/about/privacy-notice/>
<https://www.stgeorges.nhs.uk/education-and-research/research/research-privacy-notice/>*

For general information on how the NHS uses research data please visit <https://www.hra.nhs.uk/information-about-patients/>

What will happen to any samples I give?

We may test spinal fluid and blood samples to help assess the metabolism of the injured spinal cord and your body's response to the injury. We will not store samples containing cells / human tissue / genetic material.

Will any genetic tests will be done?

No.

What will happen to the results of the research study?

We will try to publish the findings of our study in scientific journals and present them in scientific meetings. You will not be identified in any report or publication.

Who is organising and funding the research?

This research is funded by Wings for life spinal cord research foundation and the Neurosciences Research Foundation at St George's University of London. The study is organised by Marios Papadopoulos, a neurosurgeon at St. George's Hospital in London. St Georges University Hospitals NHS Foundation Trust is the Study Sponsor.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. This study was reviewed and given a favourable opinion by the London- Camberwell St Giles Research Ethics Committee.

Further Information and Contact Details

Please contact:

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

Personal Consultee Information Sheet

Study Title: Injured Spinal Cord Pressure Evaluation (ISCoPE)

CI: Prof Marios Papadopoulos

IRAS ID: 38379

We invite this patient to take part in a research study. We would like you, as a consultee for the patient, to advise whether the participant should be in the study. Please note that you as a consultee, provide advice whether in your opinion they should participate in this study and to state what the participants wishes and feelings would be had they had capacity; this is not consent. The participant will be asked to consent if and when they regain capacity. Before you decide you need to understand why the research is being done and what it will involve for them. Please take time to read the following carefully and discuss it with others if you wish. Part 1 tells you the purpose of this study and what will happen to them if they take part. Part 2 gives you detailed information about the conduct of the study. If you would like any further information or if anything is not clear, please ask us.

Part 1

What is the purpose of the study?

To find out what happens to the spinal cord during the early stages of its injury. This will include:

- *Pressure monitoring*
- *The electrical activities of the spinal cord*
- *The spinal cord's oxygen consumption*
- *The waste product produced by the spinal cord during injury*
- *The effects of spinal injury on respiratory function*

Why have they been invited?

Because they have suffered a spinal cord injury. Initially, we aim to study about 110 patients.

Do they have to take part?

No. It is up to you to advise us on their behalf. We feel your relative/friend is unable to decide currently whether to participate in this research. In such a circumstance, under current legislation (Mental Capacity Act 2005 (England) or Mental Capacity Act 2016 (NI)), a consultee can advise on their behalf. We ask your opinion to consider what you know of their wishes and feelings, and to consider their interests. Please let us know of any advance decisions they may have made about participating in research. These should take precedence. We will give you this participant information sheet, which we hope will help you decide. We are very happy to discuss this further if you have any questions or concerns. If your opinion is that they have no objection to taking part, you will be asked to sign a consultee declaration form. This form merely states your opinion and is not the same as consent. Your relative/friend is free to withdraw at any time without giving a reason. A decision to withdraw or not take part will not affect the standard of care they receive. If you are unsure about taking the role of consultee you may seek independent advice. We will understand if you do not want to take on this responsibility.

What will happen to them if they take part?

*They will receive the care normally provided for people with a spinal cord injury including the spinal operation that their surgeon considers to be the best for them regardless of whether they take part in this study. If you advise for them to take part, they may also have the following procedures during their spinal surgery. If you advise for them to take part, they may also have the following procedures: We may insert **probes** next to their spinal cord and attach them to a computer to measure **cord pressure, cord oxygen, various chemicals, blood flow and/or electrical waves** for up to a week. Measuring cord pressure is an experimental procedure not routinely done after a spinal cord injury.*

If your spinal cord is found to be swollen during the operation to fix your spine, we may perform one or more additional procedures: 1. A “duroplasty.” This procedure is routinely performed in other spinal operations when the spinal cord is swollen and involves making a surgical incision in the spinal dura membrane to release the pressure.

After their surgery we would like to do some early tests to assess the effects of their spinal injury on their respiratory function. This will involve monitoring their respiratory muscles using an ultrasound scanner, and the electrical activity of the diaphragm muscle using a routine feeding tube. This will help us to assess respiratory function during the early stages of recovery from the injury,

In all other respects, they will receive the care we normally provide for people with a spinal cord injury regardless of whether you decide for them to take part in this study.

*We will arrange one visit to examine their arms and legs between **6-12 months**. This is to find out how strong their limbs are and how well they can feel.*

What do I have to do?

After reading the study information, you should advise us on what the participant's wishes and feelings would be about taking part in the study. If you advise that they would have no objection to taking part, you will be asked to sign the consultee declaration form. You as the consultee, give advice rather than consent. You will have at least two hours to decide whether or not you advise for them to take part. We may also contact them to ask about their experiences of taking part in the study.

What is being tested?

We are trying to find out if the pressure of their spinal cord is high, possibly for many days, even after surgery to fix the spine. We do not know if high cord pressure matters. We are also trying to investigate changes in the spinal cord electrical activities, tissue oxygen, waste products produced and/or effect on respiratory function following spinal cord injury.

What are the risks of taking part?

The chance of your relative/friend being harmed by taking part is low, probably less than 1 in 100. We know this because we have already done such recordings from many patients without causing any damage. Nevertheless, there is a small chance that the catheter(s) may cause damage to their spinal cord. The catheter may get infected and the infection might spread to the spinal fluid or metalwork used to stabilise the spine. After removing the catheter, there is a small risk of a spinal fluid leak. If this happens, they may need another operation to stop the leak. There is a small risk that performing the duroplasty will also cause a spinal fluid leak. ‘Duroplasty’ is a reconstructive operation that will close any openings in the dura membrane that surrounds the spinal cord. During the operation we may perform an additional test to

check the blood supply to the spinal cord. This requires injection of a dye, routinely used in clinical practice. The risks of this are low and include rash and vomiting (1 in 500 people), or severe allergic reaction (1 in 2000 people). A separate dye, routinely used in clinical practice, may be used to assess the blood supply of the spinal cord. It may be injected at the time of an ultrasound scan during the operation. The risks are low and include nausea, flushing, rash, headache (less than 1 in 100 people), or a severe allergic reaction (less than 1 in 1000 people)

What are the possible benefits of taking part?

Their spinal cord pressure may be lowered by taking part. We do not know if lowering spinal cord pressure is beneficial in the long term.

It may help us improve treatment of future patients with spinal cord injury.

What happens when the research study stops?

We will let you know our findings.

What if there is a problem?

Any complaint about the way you or the patient have been dealt with or any possible harm they might suffer will be addressed. The detailed information is given in part 2

Will their taking part in the study be kept confidential?

Yes, all information about their participation will be confidential. The details are in part 2.

This completes Part 1. If the information in Part 1 interests you, please read the information in part 2 before making a decision.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about the procedure being studied. If this happens, we might consider withdrawing the patient from the study. We will explain the reasons and arrange for their care to continue. If the study is stopped for any reason, we will tell you and them and arrange continuing care.

What happens if I no longer wish for the patient to carry on with this study?

You can let us know if you have any concerns or you think your relative/friend should be withdrawn from the study at any time, without giving a reason. Withdrawal from the study would not affect their future care in any way. If you wish to withdraw them from study treatment, there will be no follow-up unless consent is obtained from the participant following capacity being regained.

What if there is a problem?

If you have a concern about any aspect of this study you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital.

If you are still not satisfied with the response you may contact the Joint Research and Enterprise Office at St George's: 020 8725 4986

St Georges, University of London, as the Sponsor, has appropriate insurance in place in the unlikely event that they suffer any harm as a direct consequence of their participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

Will their taking part in the study be kept confidential?

Yes. We are bound by legislation and the NHS confidentiality code of practice to safeguard confidentiality during and after the study.

It is possible that authorised persons from either the Sponsor organisation and/or the Regulatory authorities that monitor the quality of research such as this may require access to view the patient's medical records for the purposes of audit or monitoring.

Data collected for this study may be retained on a secure database kept on NHS computers for up to a year following study closure whilst results are being analysed.

Once the study is closed following analysis study records may be kept for a further 10 years in a secure location. No information will be kept, which allows the patient's identity to be revealed.

Once participation in this study is agreed we will notify the patient's GP. We will provide a copy of this information sheet for them to enter onto the GP medical records.

If you decide they should take part, the patient will be given a code so that their details are not revealed (anonymised). Any data collected from them will be stored under this code.

Where can you find out more about how your information is used?

You can find out more about how we use the patient's information here:

SGHFT Privacy link: <https://www.stgeorges.nhs.uk/about/privacy-notice/>
<https://www.stgeorges.nhs.uk/education-and-research/research/research-privacy-notice/>

For general information on how the NHS uses research data please visit <https://www.hra.nhs.uk/information-about-patients/>

What will happen to any samples the patient gives?

We may test spinal fluid and blood samples to help assess the metabolism of the injured spinal cord and the patient's body's response to the injury. We will not store samples containing cells / human tissue / genetic material.

Will any genetic tests will be done?

No.

What will happen to the results of the research study?

We will publish the findings of our study in scientific journals and present them in scientific meetings. The patient will not be identified in any report or publication.

Who is organising and funding the research?

This research is funded by Wings for Life-spinal cord research foundation and Neurosciences Research Foundation at St George's University of London. The study is organised by Marios Papadopoulos, a neurosurgeon at St. George's Hospital in London. St Georges University Hospitals NHS Foundation Trust is the Study Sponsor.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. This study was reviewed and given a favourable opinion by the London- Camberwell St Giles Research Ethics Committee.

Further Information and Contact Details

Please contact:

[REDACTED]

[REDACTED]

[REDACTED].

[REDACTED]

Participant Information Sheet following consultee declaration

Study Title: Injured Spinal Cord Pressure Evaluation (ISCoPE)

CI: Prof Marios Papadopoulos

IRAS ID: 38379

We requested advice from a consultee to include you in a research study:

Name of Consultee: _____ **Date of Consultation:** _____

We would like to obtain your permission now you are able to do so

Please take time to read the following carefully and discuss it with others if you wish.

Part 1 tells you the purpose of this study and what will happen/ may have happened to you if you take part/ continue to take part.

Part 2 gives you detailed information about the conduct of the study. If you would like any further information or if anything is not clear, please ask us.

Part 1

What is the purpose of the study?

To find out what happens to the spinal cord during the early stages of its injury. This will include:

- *Pressure monitoring*
- *The electrical activities of the spinal cord*
- *The spinal cord's oxygen consumption*
- *The waste product produced by the spinal cord during injury*
- *The effects of spinal injury on respiratory function*

Why you were/ have been invited?

Because you had suffered a spinal cord injury. Initially, we aim to study about 110 patients.

Do you have to take part / continue to take part?

No. It is up to you to decide.

When you were admitted you were unable to decide whether to be included in this study. Therefore, a consultee was asked to advise on your behalf in accordance with section 32(4) of the Mental Capacity Act 2005. We explained this study to your consultee and they advised that based on their opinion and considering your wishes, feelings and interests, you would have no objections to take part. Emergency treatment was undertaken and now we would like you to decide whether you wish to remain in the study. Now we would like you to decide and give your permission to remain in the study. If you do decide, you will be given this information sheet to keep and asked to sign a consent form.

You are still free to withdraw now or at any time without giving a reason. A decision to withdraw or not take part will not affect the standard of care you receive.

What has happened to me or will happen to me if I take part?

***Probes** will be inserted next to the spinal cord and they are attached to a computer to measure **cord pressure**, cord oxygen, **various chemicals**, **blood flow** and/or **electrical waves** for up to a week.*

Measuring cord pressure is an experimental procedure not routinely done after a spinal cord injury.

If your spinal cord is found to be swollen during the operation to fix your spine, we may perform one or more additional procedures: 1. a "duroplasty." This procedure is routinely performed in other spinal operations when the spinal cord is swollen and involves making a surgical incision in the spinal dura membrane to release the pressure.

After your surgery we would like to do some early tests to assess your respiratory function. This will involve monitoring your respiratory muscles using an ultrasound scanner, and the electrical activity of the diaphragm muscle using a routine feeding tube. This will help us to assess respiratory function during the early stages of recovery from the injury.

In all other respects, you will receive the care we normally provide for people with a spinal cord injury regardless of whether you decide to take part or continue to take part in this study.

We will arrange one visit to examine your arms and legs between 6-12 months. This is to find out how strong your limbs are and how well you can feel. We may also perform further urodynamic tests to assess your bladder function or request details of any recent urodynamic testing from the spinal rehabilitation unit that you attend if available.

What do I have to do?

Now that you are able to provide consent, if you would like to continue to take part in our study we will need you to sign the consent form.

What is being tested?

We are trying to find out if the pressure of your spinal cord is high, possibly for many days, even after surgery to fix the spine. We do not know if high cord pressure matters. We are also trying to investigate changes in the spinal cord electrical activities, tissue oxygen, waste products produced and/or effect on respiratory function following spinal cord injury.

What are the risks of taking part?

The chance of being harmed by taking part is low, probably less than 1 in 100. We know this because we have already done such recordings from many patients without causing any damage. Nevertheless, there is a small chance that the catheter(s) causes damage to the spinal cord. The catheter might get infected and the infection might spread to the spinal fluid or metalwork used to stabilise the spine. After removing the catheter, there is a small risk of a spinal fluid leak. If this happens, you may need another operation to stop the leak. There is a small risk that performing the duroplasty will also cause a spinal fluid leak. During the operation we may perform an additional test to check the blood supply to your spinal cord. This requires injection of a dye, routinely used in clinical practice. The risks of this are low and include rash and vomiting (1 in 500 people), or severe allergic reaction (1 in 2000 people). A separate dye, routinely used in clinical practice, may be used to assess the blood supply of the spinal cord. It may be injected at the time of an ultrasound scan during the operation. The risks are low and include nausea, flushing, rash, headache (less than 1 in 100 people), or a severe allergic reaction (less than 1 in 1000 people)

What are the possible benefits of taking part?

The spinal cord pressure may be lowered by taking part. We do not know if lowering spinal cord pressure is beneficial in the long term. It may help us improve treatment of future patients with spinal cord injury.

What happens when the research study stops?

We will let you know our findings.

What if there is a problem?

Any complaint about the way you have been dealt with or any possible harm you might suffer will be addressed. The detailed information is given in part 2

Will taking part in the study be kept confidential?

Yes, all information about participation will be confidential. The details are in part 2.

This completes Part 1. If the information in Part 1 interests you, please read the information in part 2 before making a decision.

Part 2

What if relevant new information becomes available?

Sometimes we get new information about the procedure being studied. If this happens, we might consider withdrawing you from the study. We will explain the reasons and arrange for your care to continue. If the study is stopped for any reason, we will tell you and arrange continuing care.

What will happen if I don't want to carry on with this study?

You can withdraw from the study at any time. You do not have to tell us why, however we would like to know for our records. Withdrawal from the study would not affect the usual care or treatment that you would receive during or after the trial. As we would prefer to keep the data collected already we would ask for your permission to do so and would not collect any more.

What if there is a problem?

If you have a concern about any aspect of this study you should ask to speak with the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally you can do this through the NHS Complaints Procedure. Details can be obtained from your hospital.

If you are still not satisfied with the response you may contact the Joint Research and Enterprise Office at St George's: 020 8725 4986

St Georges, University of London, as the Sponsor, has appropriate insurance in place in the unlikely event that they suffer any harm as a direct consequence of their participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

Will taking part in the study be kept confidential?

Yes. We are bound by legislation and the NHS confidentiality code of practice to safeguard your confidentiality during and after the study.

It is possible that authorised persons from either the Sponsor organisation and/or the Regulatory authorities that monitor the quality of research such as this may require access to view your medical records for the purposes of audit or monitoring.

Data collected for this study may be retained on a secure database kept on NHS computers for up to a year following study closure whilst results are being analysed.

Once the study is closed following analysis study records may be kept for a further 10 years in a secure location. No information will be kept, which allows your identity to be revealed.

Once participation in this study is agreed we will notify your GP. We will provide a copy of this information sheet for them to enter onto the GP medical records.

If you decide to take part, you will be given a code so that your personal details are not revealed (anonymised). Any data collected about you will be stored under this code.

Where can you find out more about how your information is used?

You can find out more about how we use your information here:

SGHFT Privacy link: <https://www.stgeorges.nhs.uk/about/privacy-notice/>
<https://www.stgeorges.nhs.uk/education-and-research/research/research-privacy-notice/>

For general information on how the NHS uses research data please visit <https://www.hra.nhs.uk/information-about-patients/>

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Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee to protect your interests. This study was reviewed and given a favourable opinion by the London- Camberwell St Giles Research Ethics Committee.

Further Information and Contact Details

Please contact:

[REDACTED]
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10 Appendix III: Data export for ICM+

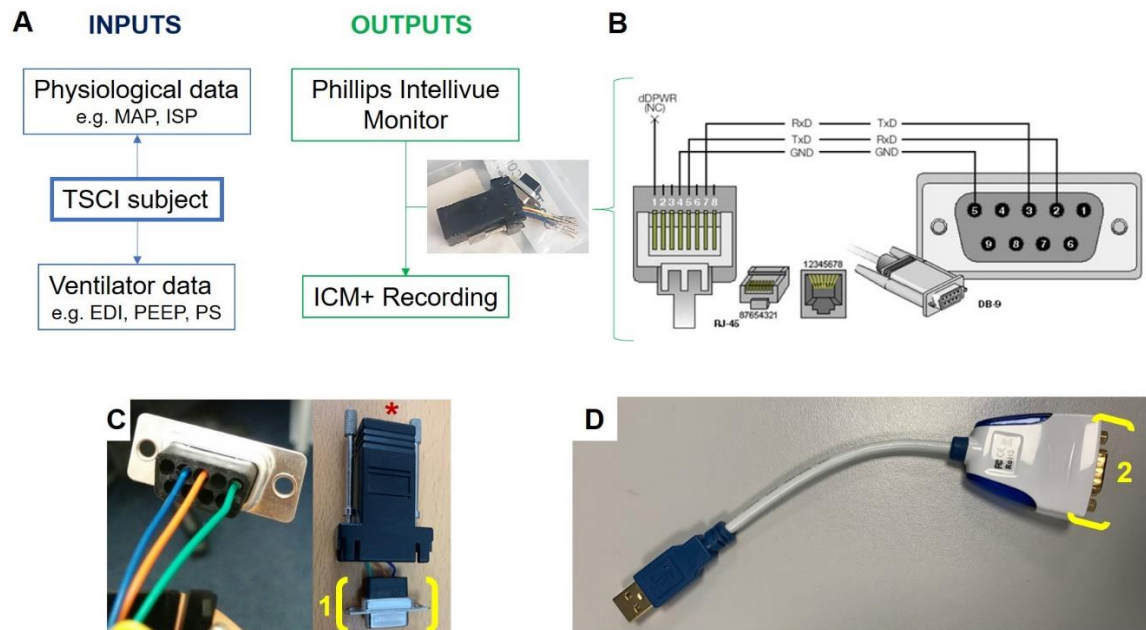


Fig. 35: Configuring the export of monitoring data to ICM+ in neuroICU

A, TSCI subject provides monitoring data (inputs) displayed on the Phillips Intellivue bedside monitor (outputs) and recorded by ICM+ (Cambridge, UK) software. **B**, Pin assignment of the “RJ45 female to 9-way D-sub modular adaptor” (RS, London); adapted with kind permission²⁴⁷. **C**, Final configuration of RJ45, prior to connecting (1) with (2). The opposite end (*) connects to a network cable (RJ45 connector at one end and male RS232 at other end) which then connects to the MIB/RS232 port on the Phillips monitor. **D**, USB to RS-232 adaptor. *MAP* = Mean Arterial Pressure, *ISP* = Intra Spinal Pressure, *TSCI* = Traumatic Spinal Cord Injury, *EDI* = diaphragm EMG, *PEEP* = Positive End-Expiratory Pressure, *PS* = Pressure Support, *RxD* = Receive Data, *TxD* = Transmit Data, *GND* = Signal Ground, *NC* = Not Connected.

11 Appendix IV: Manuscripts

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

OBJECTIVES: To determine the feasibility of monitoring tissue oxygen tension from the injury site ($p_{\text{sc}t}\text{O}_2$) 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 $p_{\text{sc}t}\text{O}_2$. We analyzed 2,213 hours of such data. Follow-up was 6–28 months postinjury.

SETTING: Single-center neurosurgical and neurocritical care units.

SUBJECTS: Twenty-six 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; Integra LifeSciences, Sophia-Antipolis, France), pressure probe, and microdialysis catheter.

MEASUREMENTS AND MAIN RESULTS: $p_{\text{sc}t}\text{O}_2$ was significantly influenced by ISP ($p_{\text{sc}t}\text{O}_2$ 26.7 ± 0.3 mm Hg at ISP > 10 mm Hg vs $p_{\text{sc}t}\text{O}_2$ 22.7 ± 0.8 mm Hg at ISP ≤ 10 mm Hg), SCPP ($p_{\text{sc}t}\text{O}_2$ 26.8 ± 0.3 mm Hg at SCPP < 90 mm Hg vs $p_{\text{sc}t}\text{O}_2$ 32.1 ± 0.7 mm Hg at SCPP ≥ 90 mm Hg), tissue glucose ($p_{\text{sc}t}\text{O}_2$ 26.8 ± 0.4 mm Hg at glucose < 6 mM vs 32.9 ± 0.5 mm Hg at glucose ≥ 6 mM), tissue LPR ($p_{\text{sc}t}\text{O}_2$ 25.3 ± 0.4 mm Hg at LPR > 30 vs $p_{\text{sc}t}\text{O}_2$ 31.3 ± 0.3 mm Hg at LPR ≤ 30), and fever ($p_{\text{sc}t}\text{O}_2$ 28.8 ± 0.5 mm Hg at cord temperature $37\text{--}38^\circ\text{C}$ vs $p_{\text{sc}t}\text{O}_2$ 28.7 ± 0.8 mm Hg at cord temperature $\geq 39^\circ\text{C}$). Tissue hypoxia also occurred independent of these factors. Increasing the FiO_2 by 0.48 increases $p_{\text{sc}t}\text{O}_2$ by 71.8% above baseline within 8.4 minutes. In patients with motor-incomplete injuries, fluctuations in $p_{\text{sc}t}\text{O}_2$ correlated with fluctuations in limb motor score. The injured cord spent 11% (39%) hours at $p_{\text{sc}t}\text{O}_2$ less than 5 mm Hg (< 20 mm Hg) in patients with motor-complete outcomes, compared with 1% (30%) hours at $p_{\text{sc}t}\text{O}_2$ less than 5 mm Hg (< 20 mm Hg) in patients with motor-incomplete outcomes. Complications were cerebrospinal fluid leak (5/26) and wound infection (1/26).

CONCLUSIONS: 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.

KEY WORDS: Licox, microdialysis, monitoring, perfusion pressure, spinal cord injury, tissue oxygen

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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, and poikilothermia) (2), morbidity (renal failure, decubitus ulcers, pneumonia, and urosepsis) (2), and psychologic distress (anxiety, depression, and 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

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spinal cord injury is limited (5), lacking monitoring techniques to provide physiologic 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 intracranial pressure (ICP) microsensor (Integra LifeSciences, Sophia-Antipolis, France) that has little (2 mm Hg) 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, for example, 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 (Brain Oxygen optimization in Severe Traumatic brain injury, Phase III [BOOST-III] [18], Comparison of strategies for monitoring and treating patients at the early phase of severe traumatic brain injury [OXY-TC] [19], and Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment [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 that 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 neurologic 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 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: 1) severe traumatic spinal cord injury (American spinal injury association Impairment Scale [AIS] grade A–C), 2) age 18–70 years, and 3) timing between injury and surgery within 72 hours. Exclusion criteria are: 1) patient unable to consent, 2) other major comorbidities, and 3) penetrating injury.

Probe Placement

During posterior surgery, a pressure probe (Codman Microsensor Transducer; Depuy Synthes, Leeds, United Kingdom), a microdialysis catheter (CMA61; clinical microdialysis analyzer [CMA] microdialysis AB, Solna, Sweden), and an oxygen electrode (Licox combined oxygen and temperature catheter [CC1P1; Integra LifeSciences) 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 **Supplemental Methods** (<http://links.lww.com/CCM/G947>).

Intraspinal Pressure and Spinal Cord Perfusion Pressure

The pressure probe was connected to a Codman ICP box linked via a bridge amplifier (ML221) to a PowerLab data acquisition hardware device (AD Instruments, Oxford, United Kingdom), in turn linked to a laptop running the data acquisition and analysis software LabChart Version 8 (AD Instruments). Blood pressure was recorded from a radial artery catheter connected to a Philips bedside monitor (Intellivue MX800; Philips, Guildford, United Kingdom) and then to the PowerLab system. Intraspinal pressure and blood pressure signals

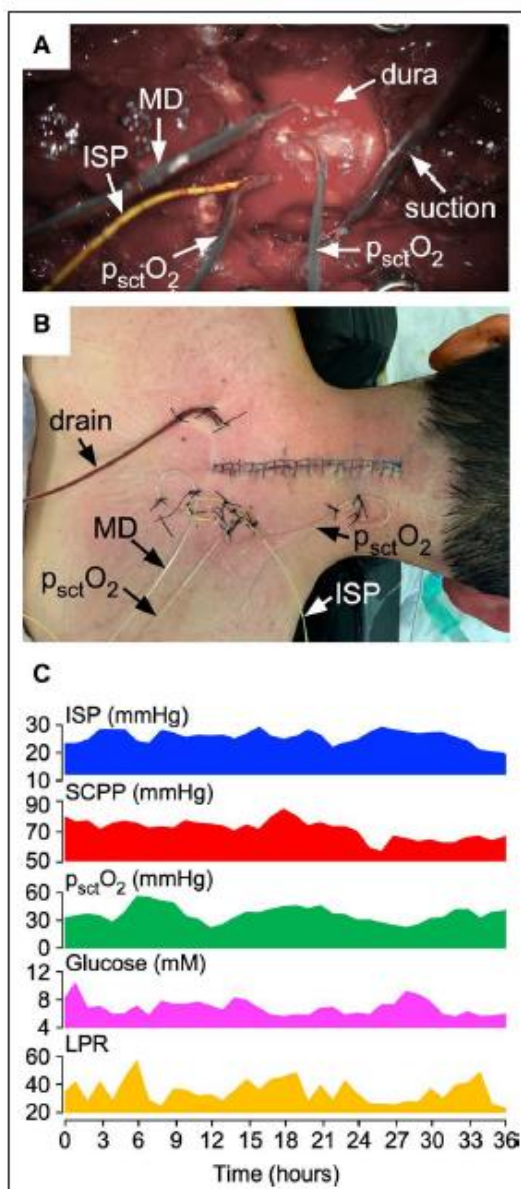


Figure 1. Monitoring technique. A 23-yr-old male, C5 American spinal injury association Impairment Scale grade A (patient no. 89). **A**, Intraoperative photo of exposed dorsal dura at injury site. **B**, Surgical site after wound closure. **C**, Multimodal monitoring from injury site: intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), cord tissue oxygen (p_{sctO_2}), tissue glucose, and LPR (lactate/pyruvate ratio). Drain = wound drain, MD = microdialysis catheter, suction = suction tubing.

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). CNS fluid (CMA microdialysis AB) was perfused at 0.3 μ L/min using the CMA106 pump (CMA microdialysis AB). Microdialysis vials were changed hourly and analyzed using ISCUSflex microdialysis analyzer (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. Hundred-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 LifeSciences), in turn linked to a Philips Intellivue MX800 bedside monitor, 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 greater than or equal to 5-mm Hg 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, F_{IO_2} , 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 in 11 of 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 with cord tissue oxygen values in the hour preceding the neurologic assessment.

Statistics

Fourier analysis of the tissue oxygen signal was done using Weka Version 3.8.5 (Waikato, New Zealand). www.mycurvefit.com was used to fit linear, quadratic, exponential, sigmoid, and Michaelis-Menten curves with R^2 and p values. The effects of temperature and cerebrospinal fluid drainage on tissue oxygen were evaluated with Student t test. The % hours with tissue oxygen less than 5 mm Hg for different outcomes were compared using chi-square test. Data are mean $\pm$ SE. Statistical tests are noted as not significant or $p < 0.05$, 0.005, 0.0005, 5×10^{-6} . **Figures 1C, 2A, B, and D, and S-Figures 1, 2, and 4** (<http://links.lww.com/CCM/G947>) use 1-kHz data. **Figures 2C, 3, and 4, and S-Figure 3** (<http://links.lww.com/CCM/G947>) use averaged hourly values.

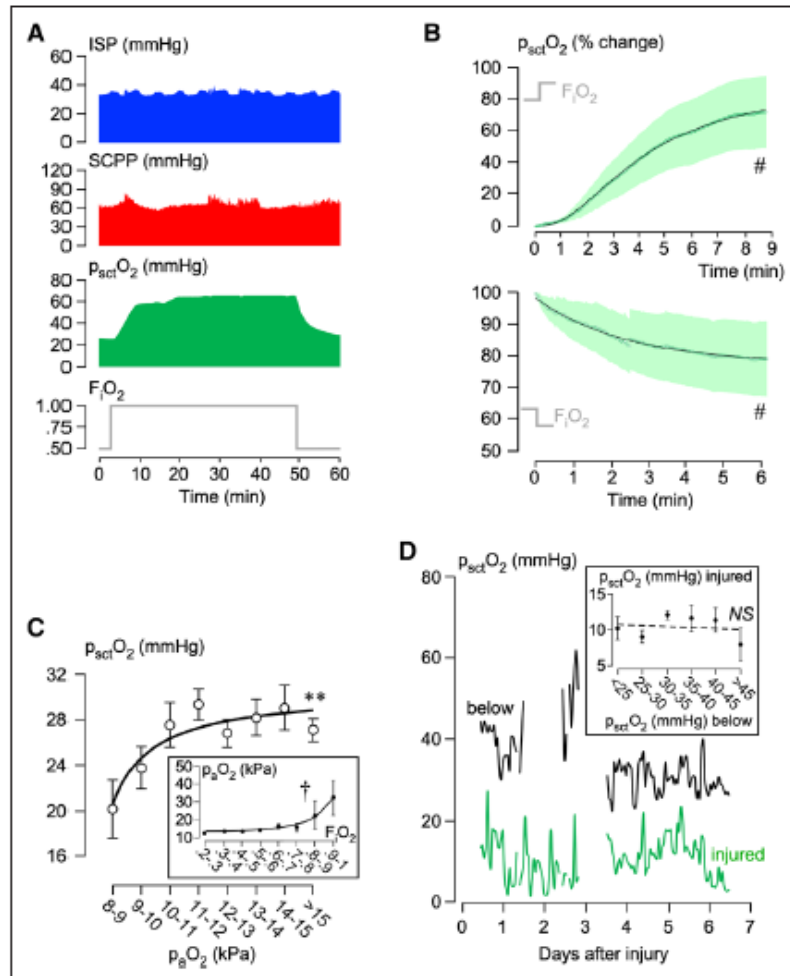


Figure 2. F_{iO_2} and P_{aO_2} versus cord tissue oxygen (p_{scO_2}). **A**, Effect of oxygen challenge on intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), and p_{scO_2} in 23-yr-old male, C5 American spinal injury association Impairment Scale grade A (patient no. 89). **B**, Summary of oxygen challenge data. p_{scO_2} versus time after (top) increasing the F_{iO_2} from 0.38 ± 0.04 to 0.82 ± 0.09 (nine repeats and four patients) and (bottom) decreasing the F_{iO_2} from 0.89 ± 0.07 to 0.41 ± 0.04 (eight repeats and three patients). **C**, p_{scO_2} versus P_{aO_2} . Inset: P_{aO_2} versus F_{iO_2} . **D**, p_{scO_2} versus time. Twenty-three-yr-old male, C5 American Spinal Injury Association Impairment Scale grade A (patient no. 89). Green: p_{scO_2} at injury site. Black: p_{scO_2} of spinal cord below injury site. Inset: p_{scO_2} at injury site versus p_{scO_2} below. **B–D** (inset): Mean $\pm$ SE. Regression lines: **B** (top) (sigmoid, $R^2 = 1.00$), **B** (bottom) (exponential decay, $R^2 = 0.99$), **C** (Michaelis-Menten, $R^2 = 0.83$), **C** (inset) (exponential, $R^2 = 0.98$), and **D** (inset) (linear, $R^2 = 0.02$). * $p < 0.005$, †0.0005, ‡ 5×10^{-6} . NS – not significant.

RESULTS

Participants

We recruited 26 patients (Table 1). Most are males (21/26) and most are younger than 60 years (22/26). There are 14 of 26 cervical, 10 of 26 thoracic, and two of 26 conus injuries. At admission, 15 of 26 had grade A, three of 26 grade B, and eight of 26 grade C injury severities (AIS). Twenty-two of 26 had posterior surgery only, and four of 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 hr). Patients were followed up at least 6 months (mean, 12.9 mo; range, 6.0–28.0 mo).

Complications

Five of 26 patients had cerebrospinal fluid leak from the probe exit site successfully managed by placing extra skin sutures at the bedside, and one of 26 had wound infection successfully managed with wound washout (S-Table 1, <http://links.lww.com/CCM/G947>). We had no spinal cord damage, hematoma, or meningitis. Nonprobe-related complications were pneumonia

TABLE 1.
Patient Details

Patient No.	Age (yr)	Sex	TSCI – Surgery (hr)	Neuro Level	AIS (Admission)	Surgery	Monitoring (hr)	Follow-Up (mo)	AIS (Follow-Up)
48	29	M	58.0	C4	A	Post	3	25	B
59	22	M	58.0	T9	A	Post	16	7	A
62	36	F	47.0	T8	B	Post	129	13	C
63	60	M	72.0	T3	B	Post	130	28	C
64	28	F	40.0	C5	A	Post	139	11	A
66	67	M	38.0	C4	C	Post	99	11	C
67	32	M	38.0	C4	C	Post + Ant	147	9	D
68	37	F	23.0	L3	C	Post	87	20	C
69	39	M	39.0	T7	A	Post	114	14	B
70	35	M	39.0	C4	C	Post + Ant	60	11	A
71	27	M	41.0	L1	C	Post	95	6	D
72	50	M	22.0	C5	B	Post	137	19	B
73	47	M	22.0	T8	A	Post	79	12	B
74	57	M	35.0	C4	A	Post	149	8	A
75	66	M	40.0	C4	A	Post	117	7	A
76	46	M	18.0	T12	A	Post	33	19	C
78	26	M	39.0	C6	A	Post + Ant	34	12	B
80	55	M	45.0	T7	A	Post	79	23	B
81	54	M	69.0	C4	C	Post	149	17	D
83	51	M	49.5	T7	A	Post	50	17	A
84	22	M	70.0	C6	C	Post + Ant	67	17	D
85	54	F	38.0	C3	C	Post	58	8	C
86	54	F	45.0	C3	A	Post	15	7	C
87	44	M	24.0	T4	A	Post	43	7	A
88	61	M	48.0	T11	A	Post	54	6	A
89	23	M	15.5	C5	A	Post	130	6	B

AIS – American spinal injuries association Impairment Scale, Ant – anterior, F – female, M – male, Neuro – neurological, Post – posterior.

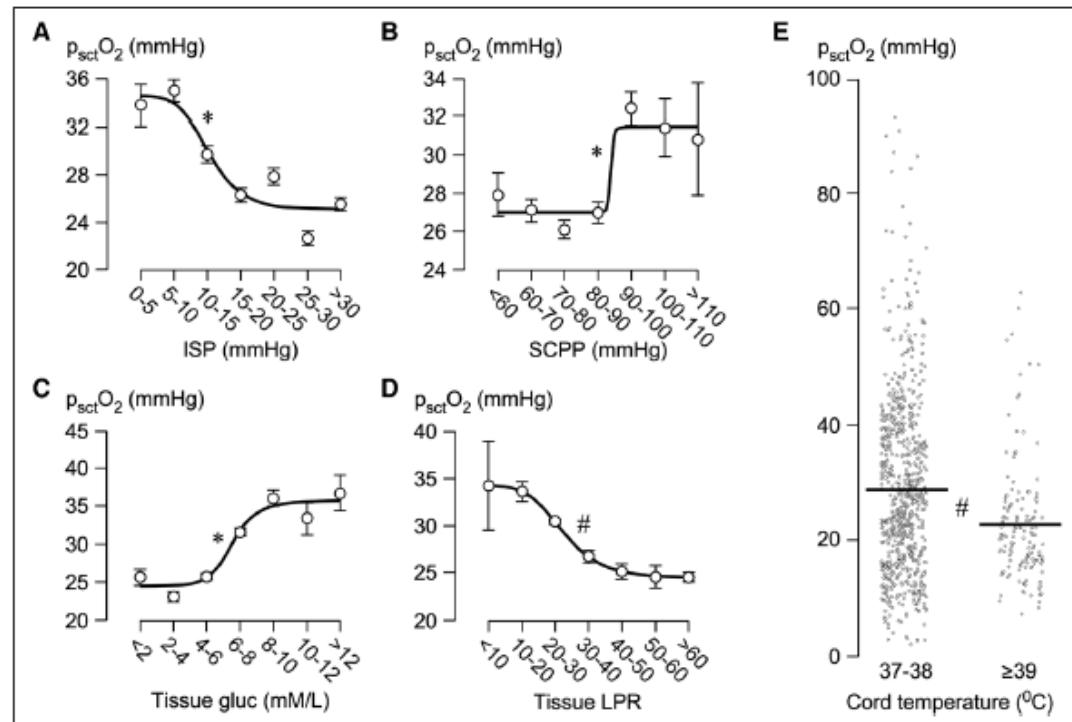


Figure 3. Injury site parameters versus cord tissue oxygen. **A**, Cord tissue oxygen (p_{sctO_2}) versus intraspinal pressure (ISP), $R^2 = 0.94$. **B**, p_{sctO_2} versus spinal cord perfusion pressure (SCPP), $R^2 = 0.94$. **C**, p_{sctO_2} versus tissue glucose, $R^2 = 0.95$. **D**, p_{sctO_2} versus tissue lactate/pyruvate ratio (LPR), $R^2 = 1.00$. Data (**A–D**) are hourly values, mean $\pm$ SE fitted with sigmoid regression. **E**, p_{sctO_2} readings at spinal cord temperatures 37–38°C and greater than or equal to 39°C. Individual data points (circles) and means (lines). $p < 0.05$, 5×10^{-6} .

(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, <http://links.lww.com/CCM/G947>). Altering the FiO_2 influences cord tissue oxygen (Fig. 2A). On average, increasing the FiO_2 by 0.48 causes sigmoid rise in cord tissue oxygen to 71.8% above baseline within 8.4 minutes. Decreasing the FiO_2 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 FiO_2 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 greater than 5–10 mm Hg, cord tissue oxygen falls reaching a minimum at intraspinal pressure 15–20 mm Hg. As spinal cord perfusion pressure rises greater than 80–90 mm Hg, cord tissue oxygen suddenly rises reaching a maximum at spinal cord perfusion pressure 90–100 mm Hg. As tissue glucose increases greater than 4–6 mM/L, cord tissue oxygen progressively rises to a maximum at tissue glucose 8–10 mM. As tissue

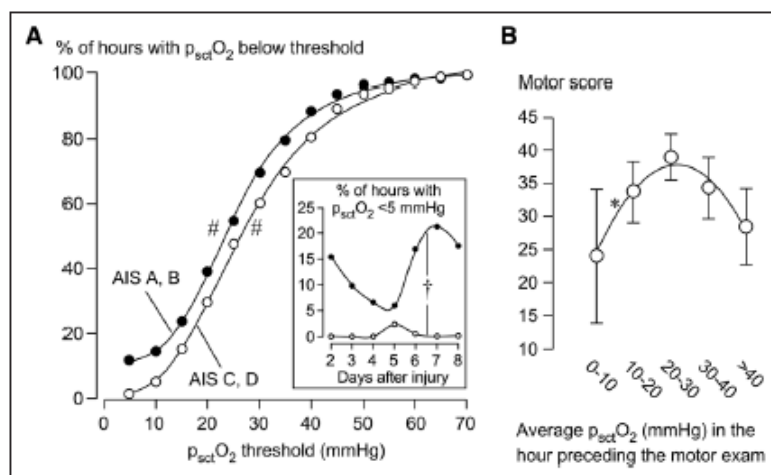


Figure 4. Cord tissue oxygen ($p_{sc}O_2$) correlates with neurologic status. **A**, Percentage of hours with $p_{sc}O_2$ below threshold versus $p_{sc}O_2$ threshold, for American spinal injury association Impairment Scale (AIS) grade at follow-up (**A** and **B** vs **C** and **D**) fitted with sigmoid regressions ($R^2 = 1.00$ for both). **Inset** Percentage of hours with $p_{sc}O_2$ less than 5 mm Hg versus days after injury for AIS at follow-up (**A** and **B** vs **C** and **D**). **B**, Motor score versus average $p_{sc}O_2$ (mm Hg) in the hour preceding the motor examination in motor-incomplete patients (AIS grade C) patients. Quadratic regression, $R^2 = 0.97$. Mean $\pm$ SE. * $p < 0.05$, † 0.0005 , ‡ 5×10^{-6} .

lactate/pyruvate ratio increases greater than 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 mm Hg, mean $\pm$ SE), 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, <http://links.lww.com/CCM/G947>).

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-Figure 3 (<http://links.lww.com/CCM/G947>). Factors that may cause change in tissue oxygen by greater than or equal to 5 mm Hg, ranked in decreasing frequency, are change in cord metabolism, change in intraspinal pressure or spinal cord perfusion pressure, change in the FiO_2 , change in sedation, and change in cord temperature

(S-Table 2, <http://links.lww.com/CCM/G947>). 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 mm Hg to decrease by -20.8 mm Hg (S-Fig. 4, <http://links.lww.com/CCM/G947>). On average, cerebrospinal fluid caused no change in tissue oxygen in nine of 11 patients and caused a significant, but modest, reduction in tissue oxygen in two of 11 patients.

Cord Tissue Oxygen Correlates With Neurologic 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 less than 5 mm Hg (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 tissue oxygen tension from the injury site ($p_{sc}O_2$) 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, 28). Cord tissue oxygen is a key physiologic parameter

that correlates with injury site physiology, metabolism, and neurologic outcome. In our spinal cord injury patients, time spent below tissue oxygen thresholds was associated with long-term outcome, as reported for brain injury (28). 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, for example, increasing the FiO_2 or increasing spinal cord perfusion pressure. These appear analogous to brain injury, where increasing the FiO_2 (29, 30) or cerebral perfusion pressure (31) augments low brain tissue oxygen.

The Licox oxygen probe tip comprises a cylindrical polyethylene membrane $\sim 18 \text{ mm}^2$ that contains two polarographic electrodes and an electrolyte solution (S-Fig. 5A, <http://links.lww.com/CCM/G947>). 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 (32), in various brain tumors, in edematous brain, and in arteriovenous malformations (33). 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 (32), and in graded ischemic regions of bowel (34). 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, <http://links.lww.com/CCM/G947>). 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, <http://links.lww.com/CCM/G947>). 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 $p_{\text{sc}}\text{O}_2$ 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, for example, by increasing FiO_2 to determine its effect on $p_{\text{sc}}\text{O}_2$, we did not set out to compare neurologic outcome in an interventional arm versus a control arm. Our study provides the basis for future research to determine whether intervention to alter $p_{\text{sc}}\text{O}_2$ is an effective new therapy. Such studies will require multivariable analysis to define whether any benefit of increasing $p_{\text{sc}}\text{O}_2$ is independent of other prognostic factors such as severity of injury (35), patient age (36), comorbidities (37), fever burden (26), timing of surgery (38), and spinal cord perfusion pressure (9).

Current management guidelines recommend maintaining mean arterial pressure 85–90 mm Hg 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. In addition, two patients with the same spinal cord perfusion pressure may have different cord tissue oxygen. Multimodality 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 (39, 40). Multimodality 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 (41).

A limitation of our study is the small numbers of patients ($n = 26$), though our conclusions are supported by a large dataset (2,213 hr of monitoring, 165 motor examinations) and long follow-up (> 6 mo). As

shown here and in an earlier study (42), 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 (43, 44). 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 (43, 44), 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 Duroplasty for Injured cervical Spinal Cord with Uncontrolled Swelling is underway to evaluate the effect of expansion duroplasty on neurologic 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 neurologic outcome.

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SUPPLEMENTARY METHODS

Neurosurgical management. Patients were admitted to the neurosurgical unit at St. George's Hospital and underwent International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessments by a trained neurosurgical resident, which was repeated at follow-up. Surgery was performed by a neurosurgeon. The type of surgery was based on surgeon preference and included posterior approach with lateral mass (cervical) or pedicle (thoracic) screw and rod fixation (Stryker Oasys for cervical, Stryker Xia for thoracic; Stryker, Newbury, Berkshire, England). Patients had CT + MRI of the spine before surgery, CT at 48 hours and MRI at 1 – 2 weeks postoperatively.

NeuroICU management. Post-operatively, patients were admitted to the Neuro Intensive Care Unit and were reviewed daily by the Neuro Intensive Care Unit and Neurosurgery teams. Ventilation was supported as appropriate, including timely extubation post-operatively or early tracheostomy. The wound drain was kept for the duration of monitoring 'on gravity'. Patients were turned in bed to avoid decubitus ulcers and given foot pumps and prophylactic low-molecular weight heparin (commenced at 24 after surgery) to reduce the risk of venous thromboembolism. Mean arterial Pressure management was at the discretion of the Neuro Intensive Care Unit consultant who was blinded to probe values. The probes were removed in the Neuro Intensive Care Unit.

SUPPLEMENTARY TABLES

S-TABLE 1. Complications of monitoring.

Complication	No. of patients (/26)	Patients (%)	Comment
SURGICAL / PROBE RELATED			
CSF leak	5	19.2	Required bedside suture. No one returned to operating theatre
Hematoma / cord damage from probes	0	0.0	
Wound infection	1	3.8	Brittle diabetes. E. Coli urosepsis, positive E. Coli blood culture, positive E. Coli wound swab. Return to operating theatre for wound washout
Meningitis	0	0.0	
NON-SURGICAL			
Chest infection	11	42.3	One ICU readmission (immunocompromised, DM, stage IV CKD, obesity)
Urine infection	2	7.7	
Pulmonary Embolus	1	3.8	Conservatively managed
Pressure Ulcer	3	11.5	
Dysphagia	1	3.8	
			FEES confirmed; from TSCI; PEG insertion

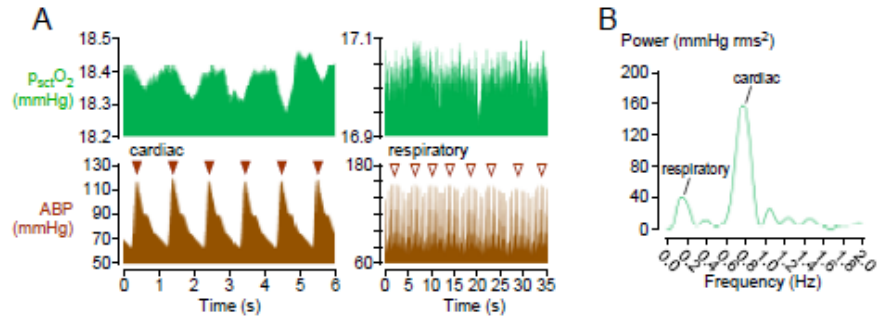
CSF, Cerebro Spinal Fluid; No., number. ICU, Intensive Care Unit; CKD, Chronic Kidney Disease; DM, diabetes mellitus; FEES, Fibre-optic Endoscopic Evaluation of Swallowing; No, number; TSCL, traumatic spinal cord injury; PEG, percutaneous endoscopic gastrostomy

S-TABLE 2. Possible causes of changes in the cord tissue oxygen signal.

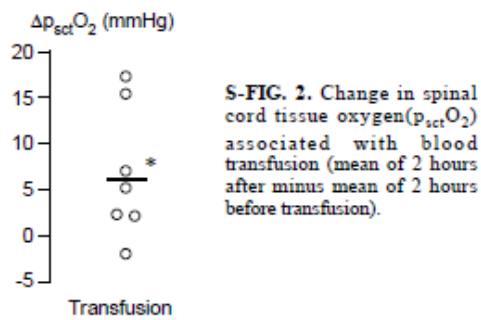
Possible cause	Number	%
Unknown	134	36.7
Change in cord metabolism	83	22.7
Change in ISP and/or SCPP	82	22.5
Change in F _i O ₂	36	9.9
Change in sedation	18	4.9
Change in cord temperature	12	3.3
TOTAL	365	100.0

F_iO₂, fraction of inspired oxygen; ISP, Intra Spinal Pressure, SCPP, Spinal Cord Perfusion Pressure

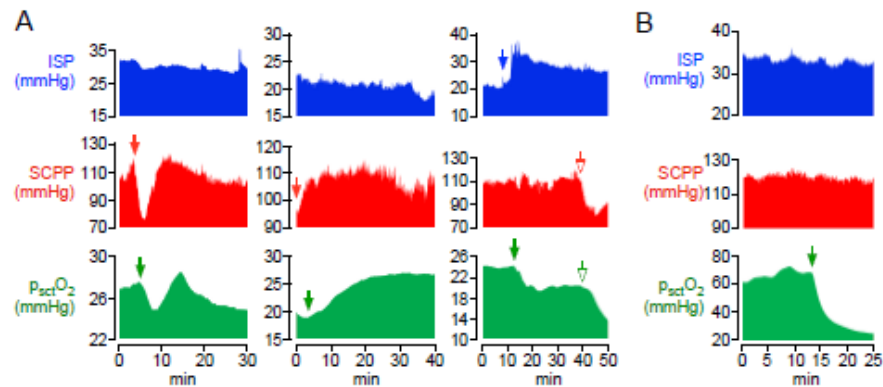
SUPPLEMENTARY FIGURES



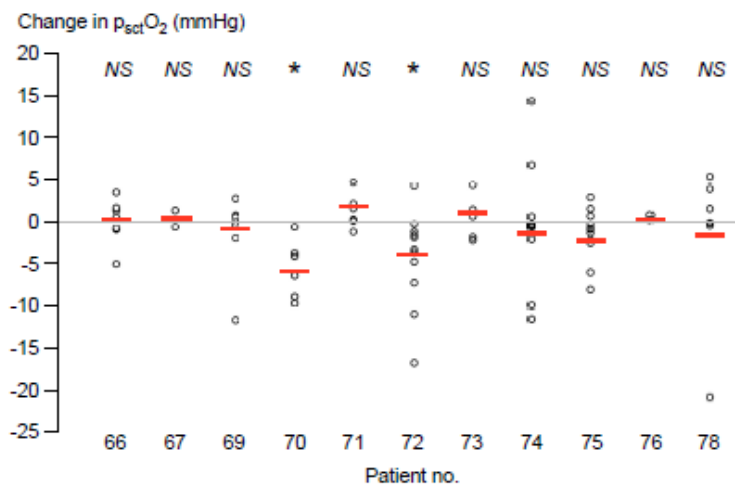
S-FIG. 1. Properties of $p_{sct}O_2$ signal. A. (top, green) $p_{sct}O_2$ signal and (bottom, brown) corresponding blood pressure signal. Cardiac (closed arrowheads) and respiratory (open arrowheads) pulsations. B. Fast Fourier Transform (power vs. frequency) of $p_{sct}O_2$ signal with respiratory and cardiac peaks. 50-year-old male, C5 AIS grade B injury (patient 72).



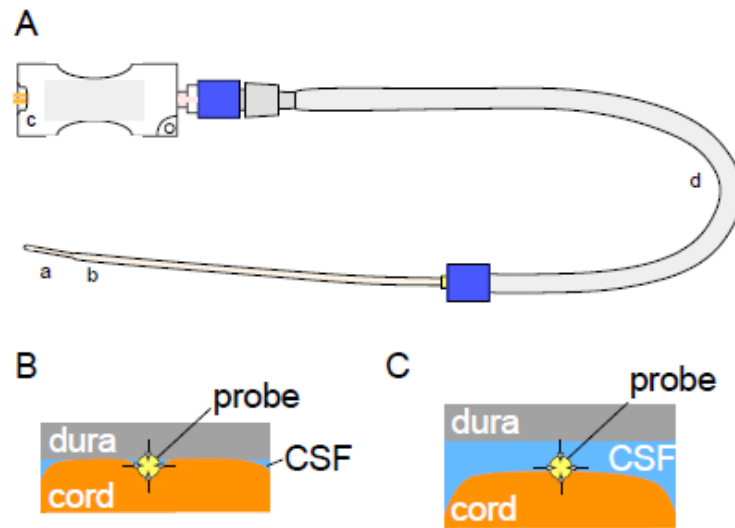
S-FIG. 2. Change in spinal cord tissue oxygen ($p_{sct}O_2$) associated with blood transfusion (mean of 2 hours after minus mean of 2 hours before transfusion).



S-FIG. 3. Fluctuations in p_{sctO_2} . A. Changes in p_{sctO_2} (green) preceded by changes in ISP (blue) and/or in SCPP (red): (*left*) Fall in SCPP (onset at red arrow) followed by fall in p_{sctO_2} (onset at green arrow). (*middle*) Rise in SCPP (onset at red arrow) followed by rise in p_{sctO_2} (onset at green arrow). (*right*) Rise in ISP (onset at blue closed arrow) followed by fall in p_{sctO_2} (onset at green closed arrow); then, fall in SCPP (onset at red open arrow) followed by fall in p_{sctO_2} (onset at green open arrow). 36-year-old female, T8 AIS grade B injury (patient 62). B. Change in p_{sctO_2} (green) not associated with change in ISP (blue) or SCPP (red). Onset of drop in p_{sctO_2} at green arrow. 60-year-old male, T3 AIS grade B injury (patient 63).



S-FIG. 4. Effect of cerebrospinal fluid drainage on cord tissue oxygen. Plot of change in cord tissue oxygen (p_{sctO_2}) from draining 10 mL lumbar cerebrospinal fluid (circles are individual values, red lines are means) from 11/26 patients. $P < 0.05^*$; NS, not significant.



S-FIG. 5. The Licor oxygen probe. A. The extension tube [d] serves to connect the probe to the bolt system. The probe is connected at the rear end [c] of its plug to the probe cable. At [a] the probe has its oxygen sensitive area of approximately 18 mm^2 ($\varnothing 0.65 \text{ mm}$). At [b] the probe has its temperature sensitive area of approximately 23 mm^2 ($\varnothing 1.3 \text{ mm}$). B. Cross section of swollen spinal cord: probe on cord surface sandwiched between swollen cord and dura. C. Cross section of non-swollen spinal cord: probe between cord surface and cerebrospinal fluid (CSF). In B. and C., arrows indicate oxygen diffusion to Licor electrodes.

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ORIGINAL ARTICLE

Adverse Effect of Neurogenic, Infective, and Inflammatory Fever on Acutely Injured Human Spinal Cord

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Abstract

This study aims to determine the effect of neurogenic, inflammatory, and infective fevers on acutely injured human spinal cord. In 86 patients with acute, severe traumatic spinal cord injuries (TSCIs; American Spinal Injury Association Impairment Scale (AIS), grades A–C) we monitored (starting within 72 h of injury, for up to 1 week) axillary temperature as well as injury site cord pressure, microdialysis (MD), and oxygen. High fever (temperature $\geq 38^{\circ}\text{C}$) was classified as neurogenic, infective, or inflammatory. The effect of these three fever types on injury-site physiology, metabolism, and inflammation was studied by analyzing 2864 h of intraspinal pressure (ISP), 1887 h of MD, and 840 h of tissue oxygen data. High fever occurred in 76.7% of the patients. The data show that temperature was higher in neurogenic than non-neurogenic fever. Neurogenic fever only occurred with injuries rostral to vertebral level T4. Compared with normothermia, fever was associated with reduced tissue glucose (all fevers), increased tissue lactate to pyruvate ratio (all fevers), reduced tissue oxygen (neurogenic + infective fevers), and elevated levels of pro-inflammatory cytokines/chemokines (infective fever). Spinal cord metabolic derangement preceded the onset of infective but not neurogenic or inflammatory fever. By considering five clinical characteristics (level of injury, axillary temperature, leukocyte count, C-reactive protein [CRP], and serum procalcitonin [PCT]), it was possible to confidently distinguish neurogenic from non-neurogenic high fever in 59.3% of cases. We conclude that neurogenic, infective, and inflammatory fevers occur commonly after acute, severe TSCI and are detrimental to the injured spinal cord with infective fever being the most injurious. Further studies are required to determine whether treating fever improves outcome. Accurately diagnosing neurogenic fever, as described, may reduce unnecessary septic screens and overuse of antibiotics in these patients.

Keywords: antipyretic; autonomic; critical care; management; monitoring; pyrexia

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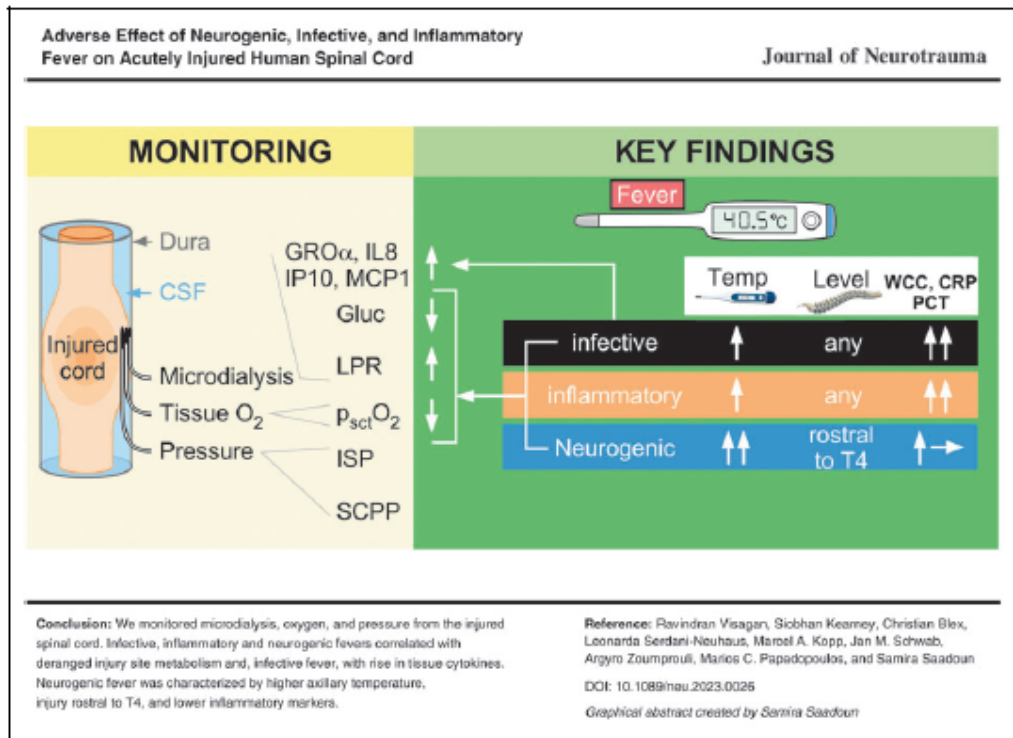
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Introduction

Traumatic spinal cord injury (TSCI) is a catastrophic event with global incidence of about 10.5/100,000 persons, resulting in 768,473 new cases annually worldwide.¹ TSCI causes substantial disability (paralysis, sensory loss, urinary/fecal incontinence, loss of sexual function, hypotension, and poikilothermia),² comorbidity (renal failure, decubitus ulcers, pneumonia, and urosepsis),² and distress (anxiety, depression, and chronic pain).³

The mechanisms of neuronal damage in TSCI are identical to those in traumatic brain injury (TBI); in addition to the primary injury, secondary damage is caused by edema, hypotension, hypoxia, metabolic insult, and inflammation.⁴ Despite such similarities, the managements of TBI and TSCI differ substantially; in severe TBI, we monitor intracranial pressure (ICP), cerebral perfusion pressure (CPP), and, in some neuro intensive care units (neuro ICUs), brain tissue oxygen ($p_{bt}O_2$) and tissue metabolism (by microdialysis [MD]) to mitigate secondary damage by detecting treatable deleterious factors, for example, high ICP, low CPP, and low $p_{bt}O_2$. Our group developed analogous injury-site monitoring after TSCI. After severe TSCI, we insert pressure, oxygen, and MD probes at the injury site to record intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), spinal cord tissue oxygen ($p_{sct}O_2$),⁵ and tissue metabolism.

ISP, SCPP, and $p_{sct}O_2$ are clinically important parameters that correlate with injury site metabolism⁵⁻⁷ and long-term outcome.⁸ Increasing SCPP improves somatosensory⁹ and motor-evoked responses¹⁰ at the injury site, increases limb power,^{6,10} lowers the sensory level,¹¹ improves urinary¹² and anal¹³ functions, and increases $p_{sct}O_2$.⁷ Monitoring is safe; risks are cerebrospinal fluid (CSF) leak and probe displacement.^{7,14,15}

In the first 2 weeks after TSCI, up to 71% of patients have fever,¹⁶ associated with cord metabolic stress (low tissue glucose, high glutamate, high lactate to pyruvate ratio [LPR]) and impaired recovery.¹⁷ Previous studies do not distinguish between different types of fever. Fever may be infective, inflammatory (peripheral trauma, surgery without infection, venous thrombosis, drug reaction) or neurogenic. After acute TSCI, neurogenic fever is a distinctive and commonly encountered feature that has been poorly characterized. Here, we used our monitoring techniques to determine the effect of these different types of fever on the injured spinal cord and to identify clinical features that distinguish neurogenic from non-neurogenic fever.

Methods

Institutional research board approvals

Patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCOPE) clinical study at

St. George's Hospital, London, UK. Approvals for ISCoPE, including consent form and patient information sheet, 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 was 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 included in the study or their family members. ISCoPE is registered at www.clinicaltrials.gov and www.ichgcp.net as NCT02721615.

Inclusion and exclusion criteria

We included all patients with TSCI recruited into ISCoPE between September 2016 and December 2021 with viable ISP, SCPP, MD, and $p_{\text{scf}}\text{O}_2$ monitoring signals. Inclusion criteria were: 1) severe TSCI defined as American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C; 2) age 18–70 years; and 3) timing between TSCI and surgery within 72 h. Exclusion criteria were: 1) patient unable to consent; 2) other significant comorbidities; and 3) penetrating TSCI.

Neurosurgical management and probe placement

All patients were admitted to the neurosurgical unit at St. George's Hospital and underwent International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessments by a trained neurosurgical resident, which were repeated prior to discharge to the rehabilitation unit (2–3 weeks post-TSCI) and at follow-up. Surgical decompression and spinal instrumentation were performed by a neurosurgeon. The type of surgery was based on clinical indication and surgeon preference and included posterior approach with lateral mass (cervical), pedicle screw (thoracic), and rod fixation (Stryker Oasys for cervical and Stryker Xia for thoracic; Stryker UK, Newbury, Berkshire, England).

At the end of posterior surgery to decompress the spinal cord and fix the spine, a pressure probe (Codman Microsensor Transducer[®], Depuy Synthes, Leeds, UK), an MD catheter (CMA61, CMA Microdialysis AB, Solna, Sweden), and an O_2 electrode (Licor CC1P1, Integra, Sophia-Antipolis, France) were inserted intradurally under the operating microscope, were positioned on the surface of the injured cord at the site of maximal cord swelling, and were secured to the skin using silk sutures. This setup allows multi-modality monitoring (ISP, SCPP, $p_{\text{scf}}\text{O}_2$, tissue glucose, tissue LPR) from the injury site (Fig. 1). The patients received antibiotics at induction (cefuroxime 1.5 g intravenously if no penicillin allergy) and 48 h of vancomycin and gentamicin post-operatively according to body weight as standard protocol. Pre-

operative computed tomography (CT) and magnetic resonance imaging (MRI) of the spine were performed, then post-operative CT of the spine, typically within 2 days, and post-operative MRI of the spine, typically within 1 week after probe removal.

Neuro ICU management

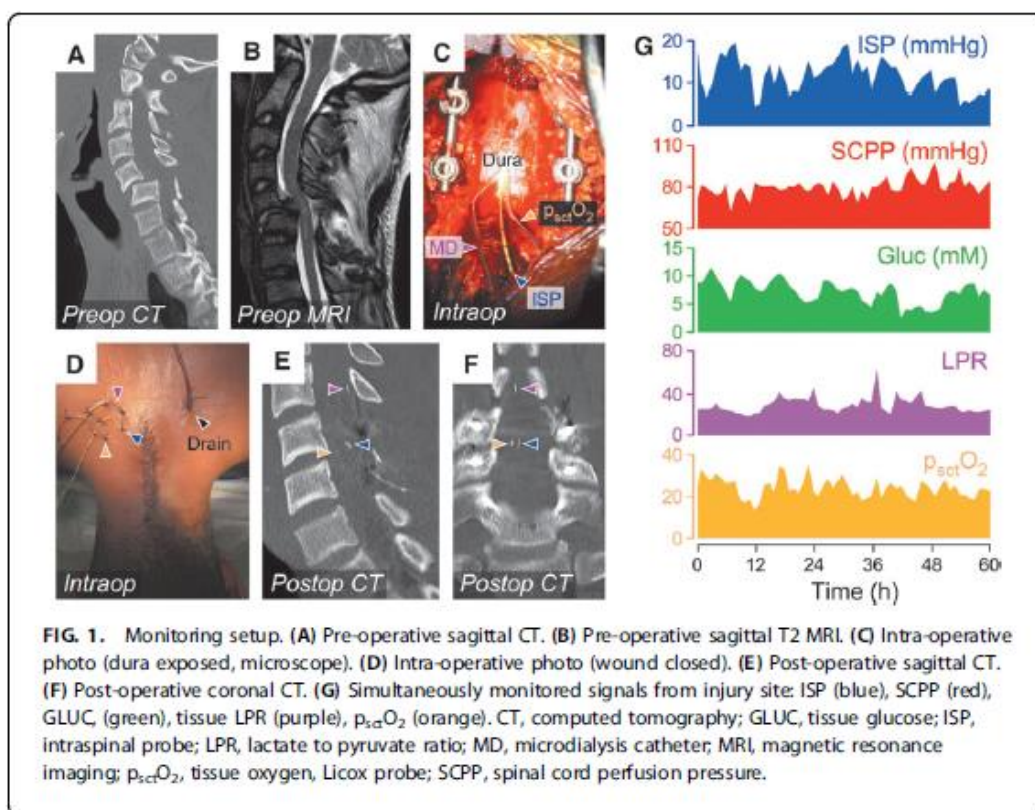
Post-operatively, all patients were admitted to the neuro ICU where they were reviewed daily by neuro ICU and neurosurgery teams. Each patient's ventilation was supported as appropriate with corresponding sedation, dependent on the level and severity of TSCI. This may have included timely extubation post-operatively or early tracheostomy. The surgical wound was reviewed daily, a post-operative drain was kept on gravity, and the patient was turned in bed to avoid pressure sores. To prevent venous thromboembolism, we used a standard protocol of Flowtrons[®] plus prophylactic low-molecular-weight heparin started at 48 h. To date, we have not observed post-operative hemorrhage in our patients with TSCI using this protocol.¹⁸ Vasopressor support (norepinephrine) was provided as required without set SCPP parameters. Neuro ICU physicians did not act on ISP, SCPP, $p_{\text{scf}}\text{O}_2$, or MD values in line with the observational nature of the study. The ISP, MD, and $p_{\text{scf}}\text{O}_2$ probes were removed within 1 week, and the probe skin exit sites were sutured using nylon.

ISP and SCPP monitoring

The ISP 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). Arterial blood pressure (ABP) was recorded from a radial artery catheter connected to a Philips Intellivue MX800 bedside monitor (Philips, Guildford, UK) and then to the PowerLab system or ICM+. The ISP and ABP signals were sampled at 1 kHz and used to compute SCPP as mean arterial pressure (MAP) – ISP. ISP is the same as intraparenchymal cord pressure at the injury site,¹⁹ which is different from CSF pressure measured above or below the injury because the swollen, injured cord is compressed against the dura, thus compartmentalizing the intrathecal space as described in earlier publications.^{10,14,20}

Microdialysis monitoring

MD was started post-operatively in the neuro ICU as described.^{15,17,21} Central nervous system fluid (CMA Microdialysis AB) was perfused at 0.3 $\mu\text{L}/\text{min}$ using the CMA106 pump (CMA Microdialysis AB). MD vials were changed hourly and analyzed using ISCUS Flex (CMA Microdialysis AB) for glucose, lactate, and pyruvate. The LPR was calculated. The first two samples



from each patient were discarded to allow priming of the MD catheter and stabilization of the metabolite concentrations. One-hundred-fold changes in metabolite concentration, compared with the preceding hour, were excluded from the analysis, assumed to be errors in measurement. Our MD method measures spinal cord surface metabolism at the injury site, which correlates with intraparenchymal injury site metabolism, but is different from metabolites measured from lumbar CSF.^{15,17,21}

Tissue oxygen monitoring

The O_2 electrode was connected to a Licox P_tO_2 Monitor (Integra), in turn linked to a Philips Intellivue MX800 bedside monitor (Philips), which was connected to the PowerLab system. The Licox signal was sampled at 1 kHz.

Patient assessments

Patients had an ISNCSCI examination on admission, at about 2 weeks post-operatively, and at 6-month follow-up. A pre-operative CT spine and MRI scan were performed. Following surgery, patients underwent regular motor limb assessments on the neuro ICU. A CT scan

of the spine was performed typically within 48 h of surgery. Post-operatively, arterial blood gases were measured, initially 4–6 hourly, then at the discretion of the neuro ICU staff. Venous blood tests including white cell count (WCC; normal 4–11 cells/ μ L), C-reactive protein (CRP; normal 0–20 mg/L), and procalcitonin (PCT; normal <0.49 μ g/L) were performed daily.

Temperature recordings

Our neuro ICU staff monitored peripheral temperature every 1–4 h by placing a SureTemp Plus (WelchAllyn, Aston Abbotts, UK) thermometer in the axilla for 12–15 sec. Temperature readings were paired with ISP and MAP readings for 30 min before and after the reading and with the chronologically nearest arterial or venous blood samples. Use of axillary temperature was a pragmatic choice because not all patients had monitoring of central temperature.

Fever definitions

We defined normothermia as 36.5–37.4°C, low fever as 37.5–37.9°C, and high fever as $\geq 38^\circ\text{C}$. Fever was

classified as infective, inflammatory, or neurogenic, and febrile episodes occurring during the multi-modality period (up to 7 days) were recorded. Fever is considered infective if there is microbiological (culture positive, confirmed micro-organism) plus biochemical (raised WCC or CRP) evidence, with or without X-ray/CT support, of an infective source. Diagnosis of "infection likely" was attributed to fever episodes with moderate clinical and biochemical suspicion without a concomitant positive culture or equivocal radiology, at that specific time-point, precluding confident attribution to a systemic focus. Diagnosis of inflammatory fever (microbiology negative for infection) requires raised inflammatory markers (WCC or CRP) and the presence of a cause, for example, fever within 48 h of surgery, or another inflammatory etiology, for example, pulmonary/mediastinal injury, intra-abdominal injury, pelvic trauma, long-bone injuries, significant hematoma, or thrombosis. Inflammatory fever source was attributed as "unknown" when criteria for other investigated causes were not met, and includes drug fever. Neurogenic fever was a diagnosis of exclusion, when neither of the above sets of criteria were met, after comprehensive clinical and radiological workup.

Only fever episodes occurring in the post-operative, multi-modality monitoring period (up to 7 days) were included in the analysis. A few delayed infections during the hospital episode are reported in the section Complications (see also Table 1). Further, not all infections mani-

fested in high grade fever, that is, non-pyrogenic, and so are reported in Table 1 but not the high-grade fever analysis. This accounts for the discrepancy between reported fever episodes and reported infective complications.

Cytokine/chemokine analysis

We measured the concentrations of cytokines/chemokines in the MD fluid collected from the injury site. These molecules were selected because they have been implicated in the pathophysiology of TSCI; they are <30 kDa (i.e., cross the MD membrane) and are part of our multi-plex electrochemiluminescence assay panel. For each patient, MD vials were collected during normothermia and during high fever. MD vials, each containing ~10 µL, were stored at -80°C and analyzed in a blinded fashion at Charité-Universitätsmedizin Berlin by multi-plex electrochemiluminescence assays (Meso Scale Discovery, Rockville, MD, USA) using the following antibody sets from the U-PLEX Biomarker Group 1 Human Assays panel (K15067M): interleukin (IL)-4, IL-8, IL-10, IP-10, GRO-α, MCP-1, MIP-1α, and MIP-1β. If necessary, the MD samples were diluted to the minimum required volume for a single determination (25 µL) or analyzed directly according to the manufacturer's protocol. Ninety-six-well plates including samples, blanks, and recombinant standard concentrations were measured and unknown concentrations calculated, using the MESO QuickPlex SQ 120 Reader and the MSD DISCOVERY WORKBENCH software version 4.0 (Meso Scale Discovery, Rockville, MD, USA), respectively.

Serum procalcitonin (PCT) measurement

PCT was measured pre-operatively and daily during the period of monitoring. For the first 26 patients, PCT was measured using a portable analyser (Biopanda BR G800 PCT immunoassay, Belfast, UK). In subsequent patients, we measured PCT levels at the St. George's Hospital biochemistry laboratory as part of the daily blood tests done in the neuro ICU.

Neuro ICU response to fever

During fever, blood, sputum, line, urinary catheter, and wound swabs were cultured. A chest radiograph was performed. There was daily neuro ICU review by clinical microbiology physicians who may request repeat cultures depending on the clinical picture and laboratory findings. Antipyretics administered were typically paracetamol 1 g 4 times a day and, either diclofenac infusion 150 mg daily, or ibuprofen orally 400 mg 3 times daily. On rare occasions when fever was refractory to pharmacotherapy, active surface cooling to normothermia was employed.

Vasopressors

Vasopressors were administered at the discretion of the neuro ICU. In general, a minimum MAP of 80 mmHg

Table 1. Complications of Monitoring

Complication	No./86	%	Comment
Probe-related			
CSF leak	10	11.6	Bedside management
Meningitis (?)	1	1.2	<i>Escherichia coli</i> (wound swab + wound drain fluid). Wound healthy. <i>Enterococcus</i> (urine). Drowsy. Stiff neck. No CSF culture. Uncertain if meningitis. Vancomycin + meropenem. No sequelae.
Cord damage	0	0.0	
Pseudomeningocele	30	34.9	Non-compressive, conservatively managed
Retained probe	0	0.0	
Surgical			
Wound infection	4	4.7	3 superficial (antibiotics), 1 deep (wound washout)
Wound hematoma	1	1.2	Anterior wound required evacuation
Further spinal surgery	1	1.2	Anterior stabilization
Non-surgical			
Chest infection	30	34.9	
Urine infection	6	7.5	
Line infection	5	5.8	
Pulmonary embolus	2	2.3	Delayed
Pressure ulcer	5	5.8	Delayed
Myositis ossificans	1	1.2	Delayed
Post-traumatic syrinx	4	4.7	Delayed. 3 drained, 1 conservatively managed

CSF, cerebrospinal fluid.

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was advised. The neuro ICU team were blinded to the ISP, SCPP, p_{actO_2} , and MD measurements. Intravenously administered norepinephrine (4 mg/50 mL, 5% dextrose) via a central venous catheter was the preferred inotrope. In some patients, metaraminol (10 mg/20 mL, 0.9% saline) was used initially. Vasopressor dose administered was recorded hourly by the neuro ICU nurses.

Statistical analysis

For each fever type, percentage of hours at high fever versus temperature and versus day after TSCI were compared by two-way analysis of variance (ANOVA). Number of cases of each fever type at or above vertebral level T3 versus below T3 (the expected level of neurogenic temperature dysregulation) were compared by Fisher's exact test. Change in the level of an injury site physiological variable (e.g., LPR) may precede the onset of fever or may be caused by an insult unrelated to fever (e.g., drop in SCPP). Thus, to determine the effect of fever on each injury site physiological variable, we assessed trends related to episodes of normothermia then fever then normothermia, rather than plotting the level of the injury site physiological variable during normothermia versus fever. The number of times that ISP, SCPP, tissue glucose, tissue LPR, and tissue p_{actO_2} increased, remained constant, or decreased during fever versus normothermia, during short (1 h) versus prolonged (>1 h) fever, or during pre-fever versus normothermia were compared using Fisher's exact test. Chemokine/cytokine levels during fever versus baseline were compared using the paired Mann-Whitney U test. Statistical tests are two-tailed. The data mining freeware Orange 3.34.0 was used to classify fever as neurogenic versus non-neurogenic using Tree, Stochastic gradient descent, Neural network, Logistic regression, and CN2 rule induction classifiers with leave-one-out cross-validation to compute Area Under Curve, Classification Accuracy, F1 score, Precision, and Recall.

Results

Participants

We recruited 86 consecutive patients with TSCI who contributed 5591 h of monitoring data in total. All subjects and family members approached agreed for the patients to participate. Table 2 shows demographic information. Most (80.2%) were males, and most (84.6%) were younger than age 60 years. There were 59.3% cervical, 34.8% thoracic, and 5.8% conus injuries. On admission, 59.3% of the patients were AIS grade A, 16.3% grade B, and 24.4% grade C. Most patients (82.6%) had posterior surgery only, and the rest (17.4%) had combined anterior + posterior. AIS grade at follow-up (on average 2.7 years) improved in 40.2%, stayed the same in 56.1%, and deteriorated in 3.7%.

Table 2. Patient Characteristics

No. of patients monitored	Total	86
	ISP/SCPP	86
	MD	58
	p_{actO_2}	33
Hours of monitoring	ISP/SCPP	2,864
	MD	1,887
	p_{actO_2}	840
Age (years)	< 20	5
	20–39	35
	40–59	29
	> 60	17
Sex	Male	69
	Female	17
Site of injury	Cervical	51
	Thoracic	30
	Conus	5
Surgical approach	Anterior	0
	Posterior	71
	360	15
No. of patients with admission AIS grade	A	51
	B	14
	C	21
No. of patients with follow-up AIS grade	A	38
	B	11
	C	17
	D	15
	E	1
	Unknown	4
No of patients with AIS change	-2	1
	-1	2
	0	46
	+1	22
	+2	8
	+3	3
	Unknown	4
Weeks of follow-up	Mean	138.0
	SEM	43.3

AIS, American Spinal Injury Association Impairment Scale; ISP, intra-spinal probe; MD, microdialysis; p_{actO_2} , tissue oxygen; SCPP, spinal cord perfusion pressure; SEM, standard error of the mean.

Complications

Table 1 lists complications. Of the patients, 11.6% had CSF leak from probe exit site(s), successfully managed by placing extra skin sutures at the bedside. On the 2-week post-operative MRI, 34.9% of patients had non-compressive pseudomeningocele, all conservatively managed. Of these, 50% had an MRI at 6–12 months, showing near-total or total resolution of the pseudomeningocele in 80%. Of the patients, 1.2% had positive wound swabs and drain fluid culture with neck stiffness reported as a "serious adverse event," successfully managed with antibiotics for possible central nervous system (CNS) infection. There was no probe-related hematoma or spinal cord damage based on neurological function and MRI. Of the patients, 4.7% had wound infections: the one patient requiring a wound washout had poorly controlled diabetes, primary *Escherichia coli* urosepsis and subsequent wound infection.

Fever characteristics

High fever (axillary temperature $\geq 38^\circ\text{C}$) was detected in 76.7% of the patients and in 17.7% of the monitored hours (Table 3). Of all febrile hours, the type of fever

Table 3. Incidence of High Fever ($\geq 38^{\circ}\text{C}$)

Type of fever	Patients (/86)	HOURS (/3217 ^a)	Likely cause
All fevers	66	571	
Neurogenic	24	147	
Inflammatory	25	139	Surgery 84 Lung injury 94 Abdominal injury 4 Pelvic injury 2 Limb injury 8 Hematoma 37 DVT/PE 0 Unknown ^b 11
Infective	40	285	Chest 149 Urine 39 Wound ^c 1 Line 20 Blood 9 Infection likely ^d 64

Figures represent fever episodes from pyrogenic infections. Non-pyrogenic infections and/or delayed infections outside the multi-modality monitoring period in Table 1.

^aTotal number of hourly temperature recordings, of which 2864 h had accompanying monitoring data.

^bInflammatory fever source attributed as "Unknown" when criteria not met for other causes.

^cWound sepsis accounted for high fever in 1 patient; however, four cases presented in Table 1: Complications because the remainder did not manifest with fever.

^dModerate index of suspicion but no corresponding positive culture; see the Methods section.

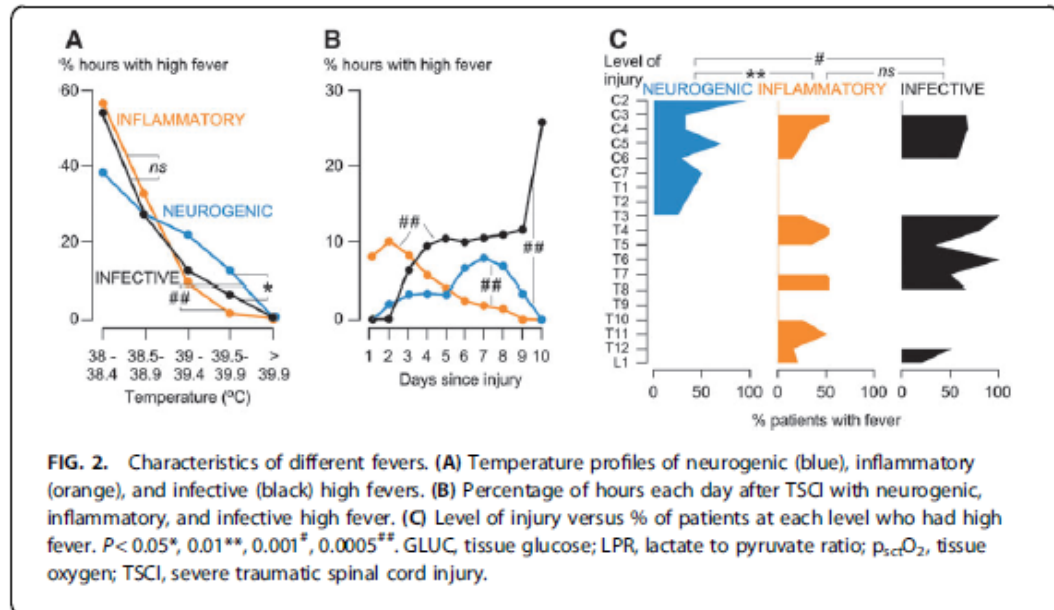
DVT, deep venous thrombosis; PE, pulmonary embolism.

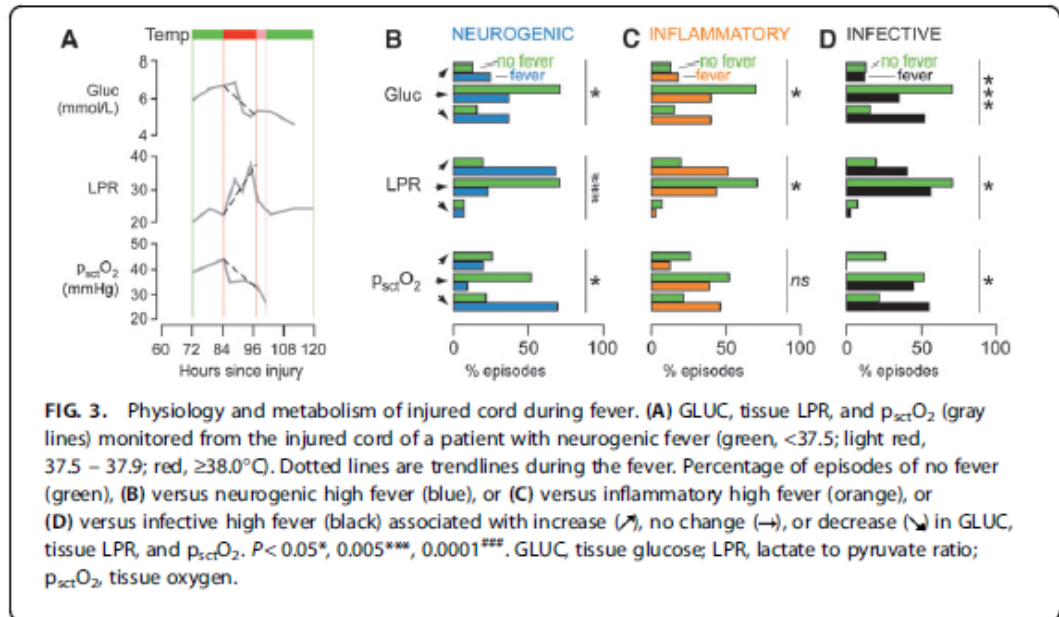
was neurogenic in 25.7% h, inflammatory in 24.3% h, and infective in 49.9% h. Of those with infective fever, 22.1% had risk factors (diabetes: 7 %, alcohol excess: 9.3%, chronic smoker: 5.8%) No one received acute or long-term steroids. The three fever types have differ-

ent characteristics: First, axillary temperatures are higher in neurogenic than inflammatory or infective fever (Fig. 2A); for example, 34.7% of the time, neurogenic fever is $>39^{\circ}\text{C}$ compared with 10.8% of the time for inflammatory and 18.9% for infective fevers. Second, the time profiles are also different (Fig. 2B): Neurogenic fever is infrequent in the first few days after TSCI, peaks at 1 week and subsides by 10 days; inflammatory fever is most prevalent in the first 48 h after the TSCI and subsides by 10 days; infective fever develops >48 h after the TSCI and does not subside by 10 days. Third, neurogenic fever only occurs in TSCI above vertebral level T4, whereas infective and inflammatory fevers occur with any level of TSCI (Fig. 2C). Supplementary Figure S1 shows additional characteristics of the three fever types.

Effect of fever on injury site physiology and metabolism

We asked if the three types of fever are associated with metabolic stress at the injury site. Five parameters monitored from the injured cord were studied: ISP, SCPP, glucose, LPR, and $p_{\text{scf}}\text{O}_2$. We determined how often each parameter increases, is unchanged, or decreases during fever and compared with the corresponding frequencies for normothermia (Fig. 3). None of the three fever types affect ISP or SCPP (not shown), but all three are associated with low glucose, high LPR, and low $p_{\text{scf}}\text{O}_2$ (the changes in $p_{\text{scf}}\text{O}_2$ did not reach significance for inflammatory fever). We conclude that all three fever types are associated with metabolic stress at the injury site.





Our next hypothesis was that prolonged (>1 h) fever is associated with more metabolic stress at the injury site than brief (≤ 1 h) fever. Supplementary Figure S2 shows that the duration of each of the three fever types had no impact on ISP or SCPP. However, compared with brief fever, prolonged fever is associated with lower tissue glucose (neurogenic fever), higher LPR (inflammatory and infective fevers), and lower p_{sctO_2} (neurogenic, inflammatory, and infective fevers). We conclude that, for all three fever types, prolonged fever is associated with more metabolic stress at the injury site than brief fever.

We then investigated whether the spinal cord metabolic derangement precedes the fever by examining the 5 h before fever onset (Supplementary Fig. S3). Changes in ISP, SCPP, glucose, LPR, and p_{sctO_2} before neurogenic or inflammatory fever are no different than during normothermia. However, significant decrease in glucose, significant increase in LPR, and non-significant decrease in p_{sctO_2} occur before the onset of infective fever. We conclude that spinal cord metabolic derangement precedes the onset of infective, but not neurogenic or inflammatory, fever by at least 4 h.

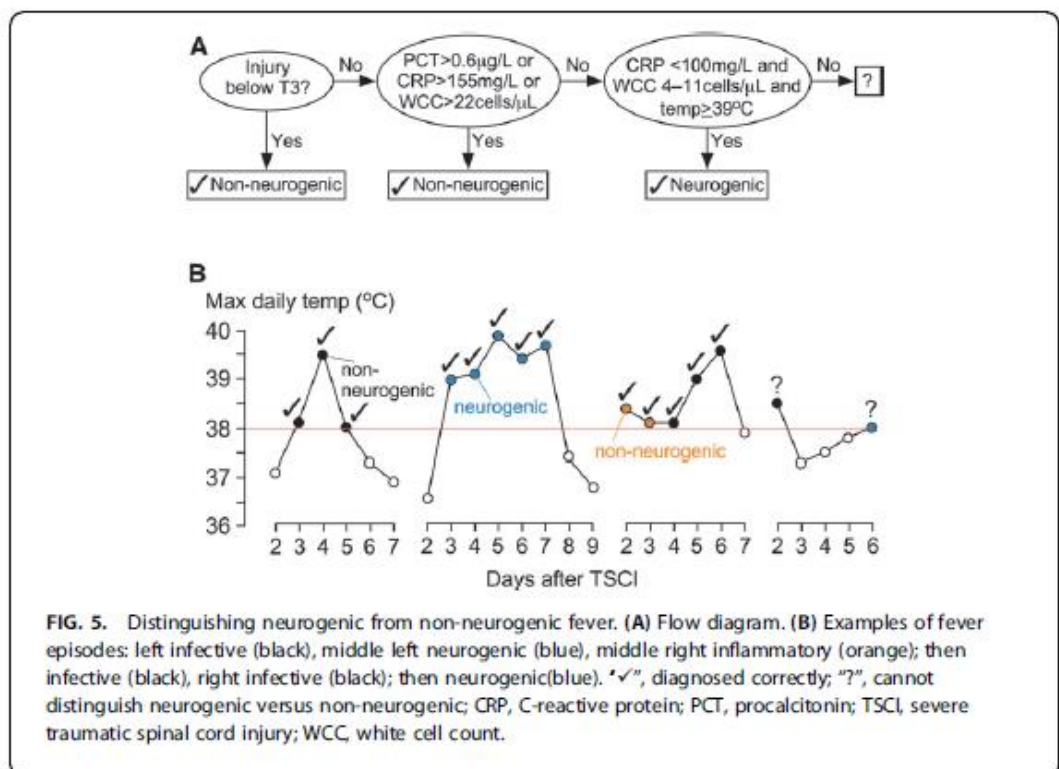
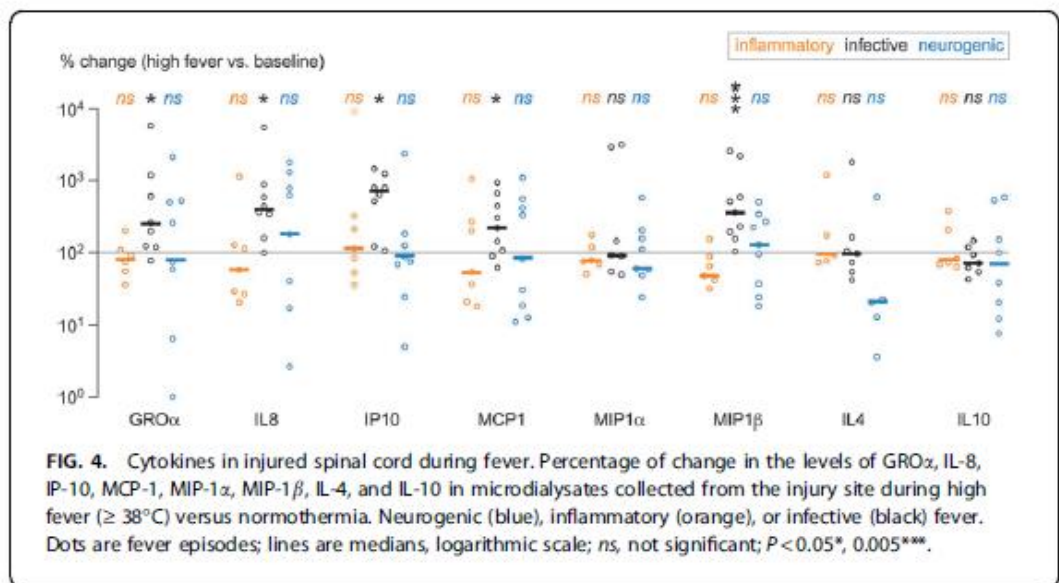
Injury site cytokines/chemokines

We asked whether fever is associated with increased cord inflammation, quantified as changes in the levels of cytokines/chemokines at the injury site during fever versus baseline. Figure 4 shows that neurogenic and inflammatory fevers are not associated with significant changes

in any assayed cytokines/chemokines, although wide variability between patients is observed. Infective fever is associated with significantly elevated levels of pro-inflammatory cytokines/chemokines (GRO α , IL-8, IP-10, MCP-1, MIP-1 β), but no significant change in the levels of anti-inflammatory cytokines/chemokines (IL-4, IL-10). These findings suggest that infective, but not neurogenic or inflammatory, fever is associated with increased injury site inflammation.

Neurogenic fever predictor

We hypothesised that it is possible to reliably distinguish neurogenic from non-neurogenic high fever by simple clinical tests. Patient characteristics (age, sex, level of injury, severity of injury) and daily fever characteristics (day from injury, maximum temperature, WCC, CRP, PCT) were entered into logistic regression, neural network, tree, stochastic gradient descent, and CN2 rule induction algorithms with accuracy assessed by leave-one-out cross-validation. All classifiers performed well in various evaluation metrics; in general, the classifiers employed five key discriminating features, including level of injury, WCC, CRP, PCT, and maximum daily temperature (Supplementary Fig. S4). Five simple clinical rules, based on these characteristics, allow 59.3% of high fever episodes to be classified with 100% accuracy, as neurogenic or non-neurogenic; the remaining 40.7% high fever episodes cannot be reliably classified (Supplementary Table S1). Figure 5 shows a simple flow chart to distinguish neurogenic from non-neurogenic fever with examples of fever episodes.



Discussion

We reported previously that, after acute TSCI, fever (axillary temperature $\geq 38^\circ\text{C}$) is associated with cord metabolic stress and impaired neurological recovery.¹⁷ Here, we refined our analysis to show that deranged injury site metabolism is a feature of all three major types of fever (neurogenic, inflammatory, infective) and, therefore, all three types of fever are probably harmful. Infective fever seems the most detrimental to the injured cord because it is also associated with elevated spinal cord levels of pro-inflammatory cytokines/chemokines. The three types of fever have different features that can be exploited to distinguish neurogenic from non-neurogenic fever with confidence.

The following mechanism may explain how fever causes metabolic stress at the injury site. Evidence from patients with TSCI,^{7,22–24} rodents,^{25,26} and pigs^{27–29} suggest that the injured cord is ischemic. By increasing the metabolic rate,³⁰ fever increases glucose and oxygen consumption, which accounts for the reduction in tissue glucose and $p_{\text{a-cO}_2}$ at the injury site that we detected during fever; these changes cannot be explained by reduced cord perfusion because fever does not affect SCPP or ISP. Tissue oxygen depletion during fever then exacerbates cord ischemia evidenced by rising LPR at the injury site. It follows that more prolonged fever is associated with more metabolic stress at the injury site. This mechanism may apply to all types of fever and all CNS ischemic pathologies, for example, fever worsens outcome in patients with TSCI,^{31–35} patients with TBI,^{36,37} and rodent TBI models^{38,39}; fever also increases infarct size and mortality, and worsens outcome in patients with stroke.^{40,41} Together, these findings suggest that prompt treatment of fever may improve outcome after TSCI.

Unlike other fevers, infective fever is linked to additional harmful effects. Infective fever is associated with elevated spinal cord levels of chemoattractants and activators of leukocytes including GRO α and IL-8 (neutrophils⁴²) as well as IP-10, MCP-1, and MIP-1 β (microglia,^{43,44} macrophages^{45–47}), without changes in IL-4 or IL-10, which are anti-inflammatory.⁴⁸ Neutrophils, microglia, and macrophages are abundant in acutely injured human²⁴ and rat^{49,50} spinal cord; their activation may cause further tissue damage.⁵¹ Our finding that cord metabolic stress precedes the onset of infective fever suggests detrimental factors other than temperature, likely to be leukocytes. The clinical implication is that treating fever without addressing the leukocytes is unlikely to eliminate the detrimental effect of infective fever.

The three types of fever have different characteristics:

1. Temperature: Infective and inflammatory fevers may be mediated by prostaglandins,^{52–54} but neuro-

genic fever is caused by interruption of thermoregulatory spinal cord pathways.⁵⁵ Neurogenic fever is thus poorly responsive to cyclooxygenase inhibition by paracetamol/non-steroidal anti-inflammatory drugs⁵⁶; this may explain why neurogenic fever is higher than non-neurogenic.

2. Time course: Neurogenic fever starts soon after TSCI and peaks at 1 week, likely related to evolving changes within the cord, for example, cord edema. Inflammatory fever is primarily from trauma to other organs/surgery and thus peaks early. Infection takes time to develop, which may explain why infective fever starts >48 h after TSCI.
3. Level of injury: Neurogenic fever is confined to injuries above vertebral level T4. This coincides with the level for temperature dysregulation in chronic TSCI⁵⁷ and autonomic dysreflexia.⁵⁸ The mechanism of neurogenic fever may be interruption of sympathetic supply to skin (trunk, legs) and internal organs thus disrupting vasoconstriction/dilation, which has a major impact on heat elimination. Alternatively, cervical interneurons (proprio-spinal neurons), which are major contributors to the plastic reorganization of spinal neuronal circuitry after cervical TSCI, for example, to sustain breathing, may play a role.⁵⁹ In contrast, inflammatory and infective fevers are not linked to the level of injury.
4. Peripheral sepsis: Unlike neurogenic fever, infective and inflammatory fevers are associated with more marked peripheral inflammation (higher WCC, CRP, PCT).

The three types of fever have different managements. Infective fever requires source identification and septic screening and is treated with antibiotics but may require additional measures, for example, change of peripheral line or urinary catheter, chest physiotherapy, or surgical lavage.^{34,60} Inflammatory fever is multi-factorial, driven by systemic inflammatory response to polytrauma, surgery, venous thromboembolism, or blood transfusion; management is supportive.^{61,62} Neurogenic fever, a unique and prominent feature in acute TSCI, is non-inflammatory but difficult to diagnose because of concomitant peripheral inflammation.^{63,64} Therefore, neurogenic fever is often managed as infective with unnecessary septic screens and overuse of antibiotics.

We showed that neurogenic fever has simple distinguishing features: TSCI above T4, higher temperature, and less peripheral inflammation (WCC, CRP, PCT). Using these, neurogenic fever can be confidently distinguished from non-neurogenic more than 50% of the time. Early and accurate diagnosis of neurogenic fever may reduce over-investigation and over-treatment with antibiotics that may, in turn, limit the emergence of

antibiotic resistance. There is no treatment for neurogenic fever after TSCI; bromocriptine merits investigation, based on reports of its effectiveness in eliminating neurogenic fever after TBI.^{65,66} Table 4 compares the pathological basis, diagnosis, and management of infective, inflammatory, and neurogenic fevers in patients with TSCI.

Our conclusions are supported by many hours of monitoring, but there are limitations. We show associations, not causality, and thus we cannot prove that treating fever will improve outcome; a randomized, controlled trial is needed. It is also unclear if the cytokines/chemokines are produced locally, for example, by microglia,⁶⁷ or enter the cord from the circulation; simultaneous assays using serum and injury site MD may help resolve this. Finally, the method of distinguishing neurogenic from non-neurogenic fever needs external validation. Our patient cohort is typical of the TSCI population with comparable demographics,^{68–70} fever,^{16,31,71} complications,^{69,72} and outcomes.^{69,72,73}

This study shows how monitoring from the injured spinal cord may help with clinical management in patients with acute, severe TSCI. Inserting probes intradurally is invasive and can only be done intra-operatively (posterior approach) under direct vision. To date, at St. George's Hospital, we have monitored using one (ISP),¹⁰ two

(ISP, MD),¹⁵ or three (ISP, MD, Licox)⁷ probes in more than 90 patients with TSCI. The monitoring technique does not increase the risk of neurological deterioration or wound infection, and the long-term neurological outcomes of our patients are comparable to those of other centers.⁷⁴

Conclusions

Our study provides evidence that fever may cause secondary damage after acute TSCI and illustrates how injury site monitoring may be used to determine how the spinal cord responds to injury to guide patient management. Further studies are required to determine if treating fever improves neurological outcome.

Transparency, Rigor, and Reproducibility Summary

The study was pre-registered at <https://clinicaltrials.gov/> (NCT02721615). The analysis plan was not formally pre-registered. A sample size of 100 subjects was planned based on the total availability of subjects recruited. Ninety-six participants were approached/screened, and measurements were collected from 95. After excluding cases of therapeutic hypothermia, expansion duroplasty, and loss to follow-up, 86 participants underwent final analysis and primary outcome assessment. Participants were blinded to the results of assessments throughout the study. Data collection and analyses were performed by investigators who were aware of relevant characteristics of the participants. Data were anonymized and labeled with codes, not linked to identifying information. Data from recruited subjects were acquired between September 2016 and December 2021. No repeat acquisition, analysis failure, or unexpected events occurred. The time required for data acquisition followed by pre-processing/analysis was up to 7 days and 2 days per patient, respectively. The data acquisition equipment, consumables, and software are available for purchase from the companies stated in the Methods section. Orange 3.34.0 is freeware.

Quantitative test-retest reproducibility was not required, because established and validated monitoring techniques in routine clinical use were employed: pressure probe (Codman), tissue oxygen catheter (Licox), MD (Solna, Sweden), and PCT. The test-retest reliability of the clinical outcome measures was not formally determined. Inclusion and exclusion criteria for ISCoPE are listed in the Methods section. The primary outcome measures (tissue glucose, tissue LPR, tissue cytokines, ISP, SCPP, and p_{scfO_2}) are not yet established standards in the field. AIS assessment is standard in the field. Future validation warrants a randomized control trial comparing groups of patients with TSCI with (1) continuous cord monitoring and perfusion targeted therapy versus (2) non-monitored patients. The other clinical outcome measure, PCT, as a differentiator of fever type is an emerging

Table 4. Comparison of the Pathological Basis, Diagnosis, and Management of Infective, Inflammatory, and Neurogenic Fevers in Patients With TSCI

	Neurogenic	Infective	Inflammatory
Likely pathological basis			
Causes	Damaged sympathetic	Infection	Trauma, surgery, DVT
Mediator	Sympathetic	Prostaglandins	Prostaglandins
Diagnosis (typical features)			
NLI	Above T4	Any	Any
Axillary temp. (°C)	≥ 39	< 39	< 39
Onset from TSCI (days)	> 1	> 2	0
Peak from TSCI (days)	7	No peak	2
End from TSCI (days)	10	No peak	10
WCC <22 cells/mL	✓		
CRP <155 mg/L	✓		
PCT <0.6 mg/L	✓		
Likely effect on TSCI			
Cord injury	↑	↑	↑
Cord metabolic demand	↑	↑	↑
Cord inflammation	→	↑	→
Likely effective management			
Paracetamol	×	✓	✓
NSAIDs	×	✓	✓
Bromocriptine	? ✓	×	×
Active cooling	✓	✓	✓
Antibiotic	×	✓	×

CRP, C-reactive protein; DVT, deep venous thrombosis; NLI, neurological level of injury; NSAID, non-steroidal anti-inflammatory drug; PCT, procalcitonin; TSCI, traumatic spinal cord injury; WCC, white cell count.

standard in the field. Normality, homogeneity of variances, and independence were assumed. When not met, non-parametric tests were considered. Adjusting for multiple comparisons was performed using logistic regression. Replication of the monitoring methods and evaluation of the study group was previously validated in an independent TSCI cohort.

De-identified data from this study are not public, however anonymized data, and the manuscript can be made available (subject to institutional ethical standards) by emailing the corresponding author. There is no analytic programming code associated with this study. The authors agree to provide the full content of the manuscript on request by contacting the corresponding author.

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Authors' Contributions

The authors contributed as follows. Ravindran Visagan: methodology, formal analysis, investigation, data curation, visualization. Siobhan Kearney: investigation. Christian Blex: investigation. Leonarda Serdani-Neuhaus: investigation. Marcel A. Kopp: investigation, resources, writing-review and editing. Jan M. Schwab: resources, writing-review and editing. Argyro Zoumprouli: methodology, investigation, resources, writing-review and editing, project administration. Marios C. Papadopoulos: conceptualization, methodology, investigation, resources, writing-review and editing, project administration, funding acquisition. Samira Saadoun: conceptualization, methodology, formal analysis, resources, writing-original draft, writing-review and editing, visualization, supervision, project administration, funding acquisition.

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Supplementary Material

Supplementary Figure S1
Supplementary Figure S2
Supplementary Figure S3
Supplementary Figure S4
Supplementary Table S1

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RESEARCH

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Spinal cord perfusion pressure correlates with breathing function in patients with acute, cervical traumatic spinal cord injuries: an observational study

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Abstract

Objective This study aims to determine the relationship between spinal cord perfusion pressure (SCPP) and breathing function in patients with acute cervical traumatic spinal cord injuries.

Methods We included 8 participants without cervical TSCI plus 13 patients with cervical traumatic spinal cord injuries, American Spinal Injury Association Impairment Scale grades A–C. In the TSCI patients, we monitored intraspinal pressure from the injury site for up to a week and computed the SCPP as mean arterial pressure minus intraspinal pressure. Breathing function was quantified by diaphragmatic electromyography using an EDI (electrical activity of the diaphragm) nasogastric tube as well as by ultrasound of the diaphragm and the intercostal muscles performed when sitting at 20°–30°.

Results We analysed 106 ultrasound examinations (total 1370 images/videos) and 198 EDI recordings in the patients with cervical traumatic spinal cord injuries. During quiet breathing, low SCPP (< 60 mmHg) was associated with reduced EDI-peak (measure of inspiratory effort) and EDI-min (measure of the tonic activity of the diaphragm), which increased and then plateaued at SCPP 60–100 mmHg. During quiet and deep breathing, the diaphragmatic thickening fraction (force of diaphragmatic contraction) plotted versus SCPP had an inverted-U relationship, with a peak at SCPP 80–90 mmHg. Diaphragmatic excursion (up and down movement of the diaphragm) during quiet breathing did not correlate with SCPP, but diaphragmatic excursion during deep breathing plotted versus SCPP had an inverse-U relationship with a peak at SCPP 80–90 mmHg. The thickening fraction of the intercostal muscles plotted versus SCPP also had inverted-U relationship, with normal intercostal function at SCPP 80–100 mmHg, but failure of the upper and middle intercostals to contract during inspiration (i.e. abdominal breathing) at SCPP < 80 or > 100 mmHg.

Conclusions After acute, cervical traumatic spinal cord injuries, breathing function depends on the SCPP. SCPP 80–90 mmHg correlates with optimum diaphragmatic and intercostal muscle function. Our findings raise the possibility that intervention to maintain SCPP in this range may accelerate ventilator liberation which may reduce stay in the neuro-intensive care unit.

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Keywords Diaphragm, Intensive care, Intercostal muscle, Monitoring, Perfusion pressure, Spinal cord injury

Background

Traumatic spinal cord injury (TSCI) is a devastating event, with annual global age-standardised incidence rate estimated at 13 patients per 100,000 people in 2016 [1]. There are no neuro-intensive care unit (NICU) treatments proved to improve neurological outcome. To facilitate the management of acute TSCI, we developed monitoring from the injured cord. We insert a pressure probe intradurally at the injury site to record intraspinal pressure (ISP) [2], used to compute spinal cord perfusion pressure (SCPP), analogous to intracranial and cerebral perfusion pressures in traumatic brain injury. SCPP, the net pressure that drives blood flow to the injured cord, is a key physiological parameter in TSCI. Increasing SCPP reduces cord ischaemia (tissue glucose rises [3], tissue oxygen ($p_{\text{scf}}\text{O}_2$) rises [4], tissue lactate/pyruvate ratio (LPR) falls) [3], enhances cord autoregulation [5], and improves motor [6], sensory [7], urinary bladder [8], and anal sphincter [9] functions.

Cervical TSCI is more disabling than thoracic TSCI, because cervical TSCI weakens the upper limbs and impairs breathing, blood pressure and body temperature control. Cervical TSCI causes diaphragmatic (nerve root supply C3–C5), intercostal (nerve root supply T1–T11), and abdominal wall (T7–L1) muscle dysfunction, leading to reduced vital capacity from muscle fatigue and secretion retention from impaired coughing [10]. The consequences are pneumonia, failed extubation, tracheostomy, and prolonged NICU stay [11]. Therefore, intervention to enhance breathing in acute cervical TSCI in NICU would be a major advance.

Our study aimed to determine whether SCPP affects the function of breathing muscles in patients with acute, cervical TSCI. We used ultrasound scanning (USS) to monitor non-invasively changes in diaphragmatic and intercostal muscle thickness and diaphragmatic excursion during breathing. We also recorded the electrical activity of the diaphragm (EDI) with NAVA (neurally adjusted ventilatory assist) nasogastric tubes [12, 13].

Methods

Institutional research board approvals

TSCI patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) clinical study at St. George's Hospital, London, UK. Approvals for ISCoPE, including consent form and patient information sheet 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 was 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 included in the study or their family members. ISCoPE is registered at www.clinicaltrials.gov and www.ichgcp.net as NCT02721615. Inclusion criteria were: (1) TSCI American Spinal Injury Association Impairment Scale (AIS) grade A, B, or C; (2) age 18–70 years; (3) timing between TSCI and surgery within 72 h. Exclusion criteria were: (1) patient unable to consent; (2) other significant co-morbidities; (3) penetrating TSCI.

Participants

Data were collected from 21 participants. We included all 13 cervical TSCI patients recruited to the ISCoPE study between September 2020 and January 2023 with viable ISP, SCPP, microdialysis (MD), and $p_{\text{scf}}\text{O}_2$ monitoring signals. Recordings of breathing function were made from patients when not attached to a ventilator or, if attached to a ventilator, patients initiated their own breaths with pressure support (PS) and positive end-expiratory pressure (PEEP) as chosen by the NICU team. We also included 8 controls (5 healthy participants, 3 thoracolumbar spinal injuries) who consented to ultrasound examination to establish technique feasibility, reproducibility, and normal parameters in non-TSCI participants. AIS classifications in the 3 thoracolumbar injuries were T8A, T9A and L1C. Lower intercostal function in the 2 thoracic injuries were excluded from final analysis.

Neurosurgical management

All patients were admitted to the neurosurgical unit at St. George's Hospital and underwent International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) assessments by a trained neurosurgical resident, which was repeated at 2–3 weeks post-TSCI and 6-month follow-up. Surgical decompression and spinal instrumentation were performed by a neurosurgeon. The type of surgery was based on clinical indication and surgeon preference and included posterior approach with lateral mass and/or pedicle screw plus rod fixation (Stryker Oasys for cervical; Stryker UK, Newbury, Berkshire, England). Anterior instrumentation, if performed, involved anterior cervical discectomy, placement of Tritanium-C Cage and Aviator plate (Stryker UK, Newbury, Berkshire, England). All patients received antibiotics at induction (cefuroxime 1.5g intravenously if no penicillin

allergy) and 48 h of vancomycin and gentamicin postoperatively according to body weight as standard hospital protocol. Pre-operative CT and MRI spine, then post-operative CT spine were performed, typically within 2 days, and post-operative MRI spine, typically within 1 week after probe removal.

SCPP monitoring

After posterior decompression of the spinal cord, under the operating microscope, a pressure probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) was placed intradurally between the dura and injured cord at the site of maximal cord swelling and secured to the skin with silk sutures. The pressure probe was connected to a Codman ICP box. Arterial blood pressure (ABP) was recorded from a radial artery catheter. Both ISP and ABP interface with the ICU Philips Intellivue MX800 monitor (Philips, Guildford, U.K.), which is connected to a laptop running ICM+ recording software (Cambridge, U.K.). ISP and ABP signals were sampled at 500 kHz and used to compute SCPP as mean arterial pressure (MAP) minus ISP. ISP is the same as intraparenchymal cord pressure at the injury site [14], which differs from cerebrospinal fluid (CSF) pressure measured above or below the injury because the swollen, injured cord is compressed against the dura, thus compartmentalising the intrathecal space as described in earlier publications [2, 15, 16]. Figure 1 shows the setup.

NICU management

Postoperatively, all patients were admitted to the NICU and reviewed daily by NICU and neurosurgery teams. Each patient's ventilation was supported as required, with corresponding sedation and timing of post-operative extubation dependent on the level and severity of TSCI. This included either timely extubation postoperatively or early tracheostomy. The surgical wound was reviewed daily, a post-operative drain was kept on gravity for 1 week, and the patient was frequently turned in bed to avoid pressure sores. To prevent venous thromboembolism, we used Flowtrons® and started prophylactic low-molecular-weight heparin at 24 h. Vasopressor support (norepinephrine) was administered as follows: in general, MAP was kept at >85 mmHg. If the MAP persistently fell <85 mmHg (or rose >100 mmHg), the norepinephrine dose was increased (or reduced) typically by 0.02 µg/kg/min, followed by assessment of the MAP response, prior to further titration to achieve the desired effect. Norepinephrine was not given to patients who self-maintained MAP >85 mmHg. NICU physicians did not act on ISP, SCPP, $p_{\text{scf}}\text{O}_2$ or MD values in line with the study's observational nature. The ISP, MD and $p_{\text{scf}}\text{O}_2$

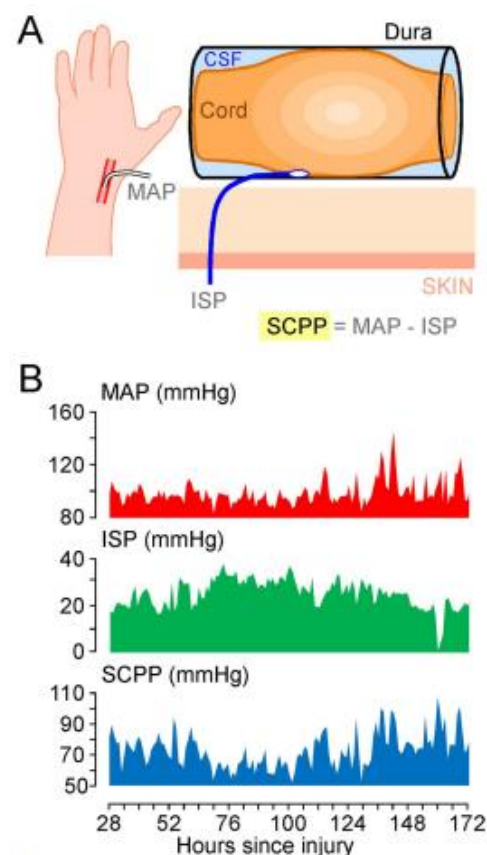


Fig. 1 Monitoring from the injured spinal cord. **A** Pressure probe at the injury site monitors ISP; arterial line monitors MAP; and SCPP is computed as MAP–ISP. **B** Example of MAP, ISP and SCPP signals from a C4 AIS B TSCI patient

probes were removed within a week, and the probe skin exit sites were sutured using nylon.

Electrical activity of the diaphragm

EDI was captured by the modified NAVA nasogastric tube (MAQUET, Solna, Sweden) inserted by NICU staff for feeding and to monitor EDI. Optimal catheter position was verified by X-Ray and ventilator onscreen signal guidance during placement. The EDI catheter was connected to the SERVO-U ventilator (Getinge, Göteborg, Sweden) via a specific EDI module (Maquet, Solna, Sweden). The Philips Intellivue MX800 monitor (Philips, Guildford, U.K.) was configured to the EDI signal through a laptop with ICM+ recording software

(Cambridge, U.K). Two parameters were used: EDI-peak (neural inspiratory effort responsible for the size and duration of the breath) and EDI-min (tonic activity of the diaphragm that prevents de-recruitment of alveoli in expiration). Figure 2A shows the setup.

Ultrasound scanning

Excursion of the left and right hemi-diaphragms was assessed with a 3.5–5.0 MHz GE C1–5 probe set on M-mode via the anterior subcostal window. During inspiration, the diaphragm contracts and moves caudally towards the transducer, recorded as upward motion on the M-mode trace. Excursion is the maximum vertical height of the M-mode signal from full expiration to inspiratory peak [17]. Diaphragmatic and intercostal muscle thickening was assessed bilaterally with a 10–15 MHz probe set on B-mode. Diaphragmatic

thickness was measured as described [18, 19] at the zone of apposition where the diaphragm is directly behind the inner aspect of the lower rib cage, with values obtained for quiet and deep breathing. For intercostal USS, the probe was oriented in the sagittal plane to record from the 2nd/3rd intercostals (upper intercostals), 5th/6th intercostals (middle intercostals), all measured in the mid-clavicular line, and from the 9th–11th intercostals (lower intercostals) measured in the anterior axillary line. Landmarks were marked on each participant's chest to enhance reproducibility of measurements. On each occasion, measurements were made for up to a minute, and the mean of each parameter (diaphragmatic excursion and thickness, intercostal thickness) was computed. Diaphragmatic or intercostal muscle thickening fraction during breathing was defined as: $(\text{thickness}_{\text{max}} - \text{thickness}_{\text{min}}) / \text{thickness}_{\text{min}} \times 100$. We

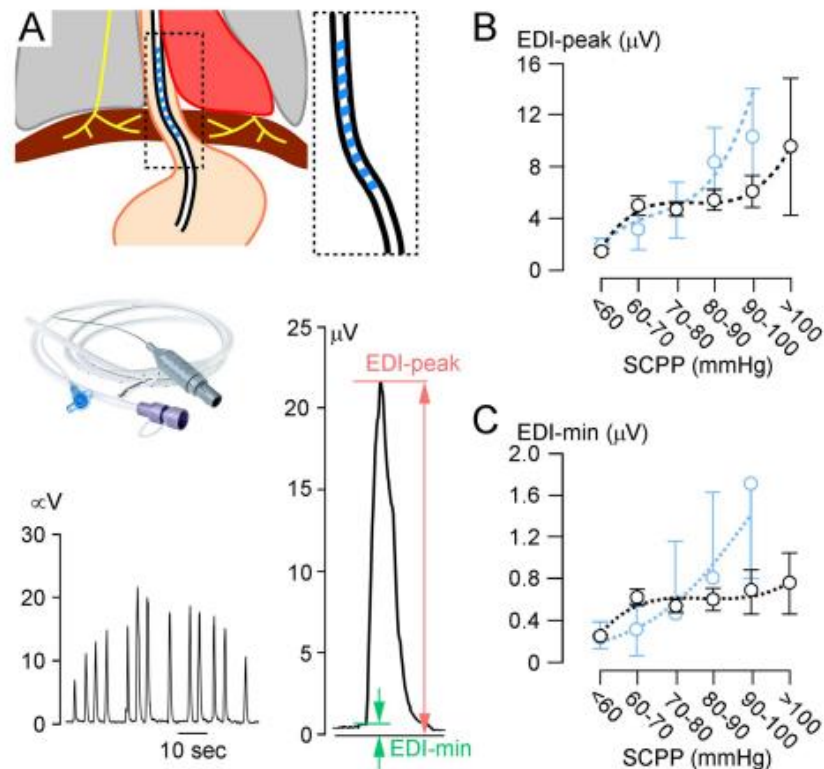


Fig. 2 Electrical activity of the diaphragm (EDI). **A** (top left) Schematic for EDI monitoring; (top right) Magnified view of EDI nasogastric tube with electrode contacts (blue); (middle) Photo of an EDI nasogastric tube; (bottom left) EDI recordings from a C8 A TSCI patient; (bottom right) Magnified view of EDI signal showing EDI-min and EDI-peak. Diaphragm EMG versus SCPP for **B** EDI-peak, and **C** EDI-min. Black, all recordings; blue, recordings when not attached to ventilator. Mean $\pm$ standard error. Best-fit polynomial curves (**B** black, cubic: $r^2 = 0.90$, **B** blue cubic: $r^2 = 0.98$, **C** black, cubic: $r^2 = 0.98$, **C** blue, quadratic: $r^2 = 0.95$). Sample sizes in Additional file 8

used the average of corresponding left and right measurements for each patient. Our diaphragm USS method aligns with recent expert consensus [20] and international guidelines [21].

Optimising assessments of breathing function

Following pilot studies in participants without cervical TSCI (not shown), we eliminated the effect of patient position on EDI and USS parameters by performing all measurements with the patients sitting at 20°–30° in bed. Patients did not have chest infection, confirmed on routine chest X-ray, during the measurements. USS and EDI recordings were done during spontaneous breathing to eliminate any confounding effects of mechanical ventilation. One investigator (RV) performed all USS recordings to eliminate inter-assessor variability. RV received training in respiratory USS from two consultant radiologists, who independently verified the method and measurement acquisition technique.

Statistical analysis

SCPP was acquired as a continuous signal using ICM+. Each USS assessment took typically 0.5–1 h. We averaged the SCPP for the duration of each USS and EDI assessment. We used best-fit linear, quadratic, and cubic polynomials for breathing function versus SCPP monitoring data and computed coefficients of determination (r^2) with data shown as mean $\pm$ standard error. The two norepinephrine groups (low vs high dose) were compared using two-tailed t -tests.

Results

Participant characteristics

We recruited 13 cervical TSCI patients. All participants and family members approached agreed for the patients to participate. Table 1 shows demographic information. Most (10/13) were males, and most (9/13) were younger than 60 years. On admission, 4/13 patients were AIS grade A, 7/13 grade B and 2/13 grade C. 10/13 patients had posterior surgery only, and 3/13 had combined anterior + posterior surgery. AIS grade at follow-up (on average 7.9 months) improved in 9, stayed the same in 3 and deteriorated in no one. 1/13 patient was not followed-up due to non-surgical mortality from chest sepsis after discharge. In 8 control participants (5 healthy + 3 thoracolumbar spinal injuries), we evaluated USS parameters in 38 exams. As in the TSCI group, most controls were male (7/8) and less than 60 years old (7/8), with mean age 41.1 years (range 27.0–63.9). No one had co-morbidities or chest injuries.

Patient complications

Table 2 lists complications in the cervical TSCI patient group. There was no post-operative CSF leak, wound infection, haematoma, or cord damage from the monitoring probes. 11/13 patients (84.6%) had non-compressive pseudomeningocele on the 2-week post-operative MRI, all conservatively managed. Non-surgical complications included chest infection in 7/13, urinary tract infection in 4/13 and delayed uncomplicated pressure ulcers successfully managed conservatively in 2/13.

Table 1 Demographic characteristics of cervical TSCI patients

No.	Age (years)	Sex	AIS admission	AIS follow-up	Follow-up (months)	Hours ISP monitoring
1	23.0	M	C5A	C7B	12.04	151
2	35.0	M	C5A	C3A	6.90	158
3	24.0	M	C5C	C5D	10.01	122
4	21.0	M	C4B	C4B	6.25	160
5	61.0	F	C5B	Lost		93
6	62.0	M	C6B	C5C	6.85	159
7	50.4	M	C4B	C1D	8.05	106
8	71.4	F	C5B	C7D	10.55	116
9	37.0	M	C5B	C5B	8.71	113
10	54.3	F	C1C	C3D	7.72	98
11	20.1	M	C5B	C5C	6.25	56
12	70.6	M	C5A	C5C	6.51	14
13	44.5	M	C5A	C6B	4.74	112
					Total	1458

AIS, American Spinal Injury Association Impairment Scale; F, female; ISP, intra spinal pressure; M, male

Table 2 Complications of cervical TSCI patients

Complication	No. of patients	%
<i>Probe related/surgical</i>		
CSF leak	0	0.0
Wound infection	0	0.0
Meningitis	0	0.0
Cord damage from probes	0	0.0
Post-operative hematoma	0	0.0
Further surgery/return to theatre	0	0.0
Pseudomeningocele	11*	84.6
Post-traumatic syrinx	0	0.0
<i>Non-surgical/delayed</i>		
Chest infection	7	53.8
Urine infection	4	30.8
Line/blood infection	1	7.7
Pulmonary embolus or DVT	0	0.0
Pressure ulcer	2	15.4
Delirium in NICU	1	7.7
Mortality	1**	7.7

*All non-compressive on post-operative MRI. 3/11 total resolution on 6 months MRI

**1/11 non-surgical mortality from pulmonary sepsis several months after surgery

Reproducibility and confounding factors

Based on 8 participants without cervical TSCI, the coefficients of variation for the USS measurements are: diaphragmatic excursion 7.5%, diaphragmatic thickening 5.3% (right 4.7%, left 5.8%), and intercostal thickening 3.0% (upper 3.7%, middle 2.0%, lower 3.3%). The TSCI patients received norepinephrine infusion during 81.6% of the USS and EDI measurements. To determine the effect of norepinephrine, we compared USS and EDI measurements made with TSCI patients on high ($>0.1 \mu\text{g/kg/min}$) versus low ($\leq 0.1 \mu\text{g/kg/min}$) norepinephrine dose. High norepinephrine dose was associated with higher MAP (96.2 vs 93.0 mmHg, $P < 0.005$), higher ISP (16.9 vs 8.9 mmHg, $P < 0.001$), lower SCPP (79.9 vs 85.1 mmHg, $P < 0.0005$) and lower % muscle thickening change during breathing for lower intercostals (-0.1 vs 4.6% , $P < 0.05$) with no effect on EDI-peak, EDI-min, diaphragmatic excursion (quiet + deep breathing), % diaphragmatic thickening change (quiet + deep breathing) or % muscle thickening change for upper and middle intercostals. EDI and USS recordings were not performed in patients with cardiorespiratory instability, significant pre-existing lung disease, pulmonary contusions, pneumonia, or pulmonary embolus that may have influenced diaphragmatic or intercostal muscle function. PS support and PEEP may influence the USS and EDI parameters; therefore, in addition to analysing all breathing function recordings,

we also analysed the subgroup related to non-ventilated patients.

SCPP correlates with injury site metabolism

We first determined whether SCPP correlates with injury site metabolism assessed using spinal cord tissue oxygen ($p_{\text{sc}t}\text{O}_2$) and microdialysis (MD) monitoring from the injury site. Details of the monitoring techniques are in Additional file 1. The relations between $p_{\text{sc}t}\text{O}_2$ versus SCPP and tissue glucose versus SCPP are inverted-U shaped, with the maximum at SCPP 70–90 mmHg, whereas increasing SCPP is associated with decreasing LPR (Additional file 2). These findings suggest that low SCPP indicates ischaemia and that both hypo- and hyper-perfusion may be detrimental to the injured spinal cord, with optimum SCPP at 70–90 mmHg.

SCPP correlates with diaphragmatic function

Figure 2B and C show the relationship between SCPP and EDI. SCPP < 60 mmHg is associated with low EDI-peak (diaphragmatic inspiratory effort) and EDI-min (diaphragmatic tonic activity). EDI-peak and EDI-min increase as SCPP increases > 60 mmHg, plateau at SCPP 60–90 mmHg, and increase further at SCPP > 90 mmHg. In non-ventilated patients, EDI varies with SCPP in a similar fashion. The diaphragmatic thickening fraction for quiet and deep breathing plotted versus SCPP has inverted-U relationship, with maxima at SCPP 80–90 mmHg (Fig. 3). Additional file 3 shows videos of normal and weak diaphragmatic contraction during quiet inspiration. During quiet breathing, there is no correlation between SCPP and diaphragmatic excursion, but during deep breathing, diaphragmatic excursion is low at SCPP < 60 mmHg, increases as SCPP increases > 60 mmHg, plateaus at SCPP 60–100 mmHg, and increases further at SCPP > 100 mmHg (Fig. 4). Diaphragmatic excursion when PEEP=0 and PS=0 also does not correlate with SCPP for quiet breathing but has inverse-U relationship with SCPP for deep breathing with peak at SCPP 80–90 mmHg. Additional file 4 shows videos of normal and reduced diaphragmatic excursion during deep inspiration. Figures 3 and 4 also show that the diaphragmatic thickening fractions and the diaphragmatic excursions for quiet and deep breathing in the control participants are generally low compared with the corresponding parameters in patients with cervical TSCI.

SCPP correlates with intercostal muscle function

Figure 5 shows the relationship between the thickening fractions of the upper, middle, and lower intercostal muscles plotted against SCPP. SCPP < 70 mmHg (upper and lower intercostals) and < 60 mmHg (middle intercostals) was associated with negative intercostal thickening

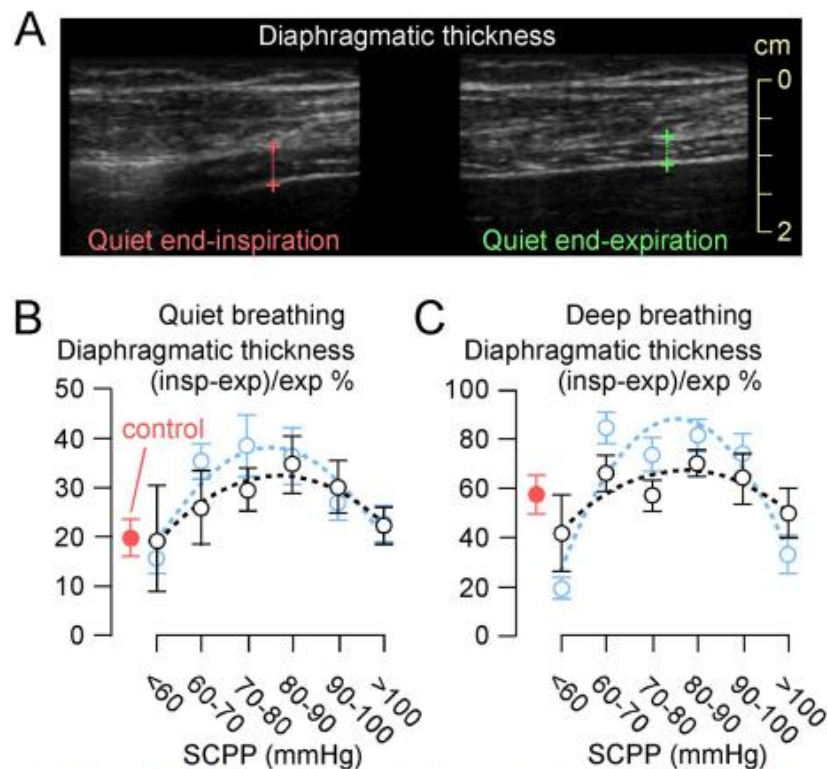


Fig. 3 Diaphragmatic thickening fraction. **A** Photos of ultrasound exam of right hemi-diaphragmatic muscle thickening during quiet breathing, at end-inspiration and at end-expiration. % change in diaphragm thickness = (inspiration – expiration)/expiration plotted versus SCPP **B** during quiet breathing, and **C** during deep breathing. Black, all recordings; blue, recordings when not attached to ventilator. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit quadratic (**B** black: $r^2 = 0.92$; **B** blue: $r^2 = 0.85$; **C** black: $r^2 = 0.72$; **C** blue: $r^2 = 0.84$). Sample sizes in Additional file 8

fraction, suggesting failure of the muscles to contract during inspiration (likely passive stretching, diaphragmatic breathing). For upper and middle intercostals, SCPP > 100 mmHg was also associated with failure of the muscles to contract during inspiration. Overall, SCPP 80–100 mmHg was optimal for allowing upper, middle, and lower intercostal muscles to contract during inspiration. Intercostal thickening fractions in non-ventilated patients correlate with SCPP in a similar fashion. Figure 5 also shows that, in the control participants, the upper, middle, and lower intercostals have positive thickening fractions, indicating intercostal muscle contraction during inspiration. Additional file 5 shows videos of normal and reduced intercostal muscle relaxation during quiet expiration.

Individual patient data

Figures 2, 3, 4 and 5 combine data from all patients. We asked whether the observed correlations between the different measures of breathing function and SCPP are maintained for individual patients. The table in Additional file 6 summarises the correlations for each breathing function measure versus SCPP for each patient. Plots of all individual patient relationships are summarised in Additional file 7. This analysis shows that the correlations between breathing function and SCPP seen with combined patient data generally also hold for individual patients. However, some patients have no such correlations and, in the patients that have correlations, the SCPP that optimises breathing function varies between patients.

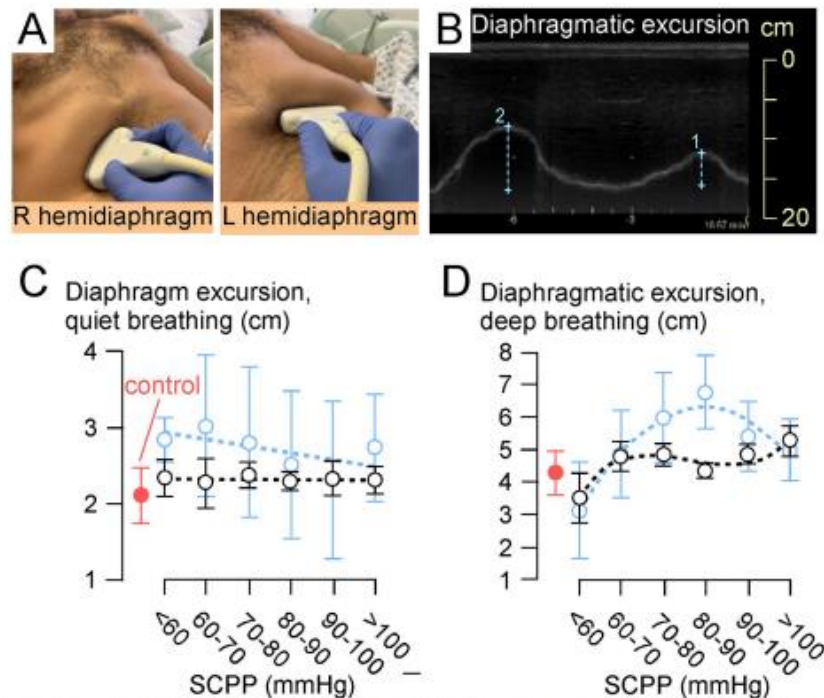


Fig. 4 Diaphragmatic excursion. **A** Placement of ultrasound probe to record diaphragmatic excursion from (left) right hemidiaphragm, and (right) left hemidiaphragm. **B** Diaphragmatic excursion measurements in M-mode. Diaphragm excursion plotted versus SCPP **C** during quiet breathing, and **D** during deep breathing. Black, all recordings; blue, recordings when not attached to ventilator. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit curve (**C** black, linear $r^2 = 0.00$; **C** blue, linear $r^2 = 0.38$; **D** black, cubic $r^2 = 0.79$; **D** blue, quadratic $r^2 = 0.93$). Sample sizes in Additional file 8

Discussion

We showed that monitoring breathing function in critically ill patients with acute TSCI in NICU using USS and EDI is feasible and reproducible. Our key finding is that SCPP correlates with breathing: the data suggest that too low SCPP (cord hypo-perfusion) and too high SCPP (cord hyper-perfusion) are associated with more impaired breathing, whereas SCPP 80–90 mmHg correlates with improved diaphragmatic and intercostal muscle contractility. These findings still hold even when only data from non-ventilated patients are considered to eliminate the effects of PEEP and PS on the function of breathing muscles.

USS is a non-invasive, non-ionising technique that provides high-resolution images in real-time with good reproducibility [22]. Disadvantages include the confounding effects of inotropic support, PEEP and PS on the measurements, whereas obesity, reduced compliance from critically ill patients, and technical factors (such

as patient position, probe location and angulation) also affect the recordings [23]. Subcostally scanning left hemidiaphragmatic excursion is challenging because of the small splenic window and lung masking; we had failure rate of 70.9%, compared with subcostally scanning right hemidiaphragmatic excursion. In the intensive care setting, diaphragmatic USS has been used to guide weaning from mechanical ventilation [17], evaluate diaphragmatic paralysis [24], and quantify the work of breathing [18]. We recommend devoting time to optimise the technique before using the data for clinical decision making.

The key diaphragmatic USS parameters are thickening fraction and excursion. Thickening fraction is a measure of the force of contraction of the diaphragm during inspiration [25]. Excursion is the diaphragm's up-and-down motion that contributes to the inspiratory lung volume [26]. Because of impaired intercostal muscle function, patients with cervical TSCI rely almost exclusively on diaphragmatic contraction to increase lung volume during

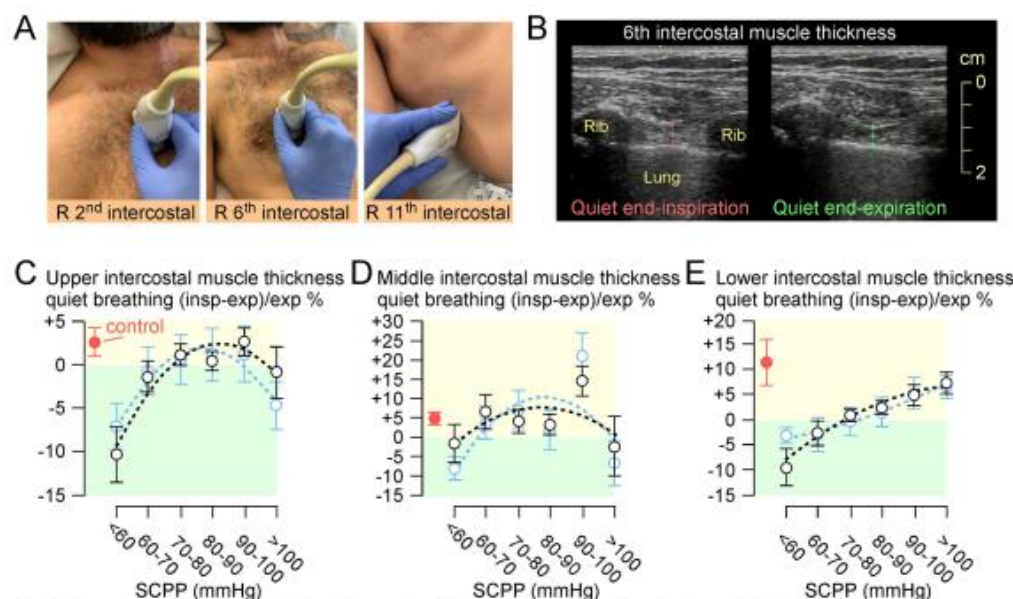


Fig. 5 Intercostal muscles thickening fraction. **A** Placement of ultrasound probe to record excursion from (left) right 2nd intercostal muscle, (middle) right 6th intercostal muscle and (right) right 11th intercostal muscle. Photos of ultrasound exam of right 6th intercostal muscle thickening during quiet breathing, at end-inspiration and at end-expiration. % change in intercostal muscle thickness during quiet breathing = (inspiration – expiration)/expiration. **B** in upper intercostal muscles, **C** in middle intercostal muscles, and **D** in lower intercostal muscles. Black, all recordings; blue, recordings when not attached to ventilator. Red is data from controls without cervical TSCI. Mean $\pm$ standard error. Best fit quadratic (**B** black: $r^2 = 0.91$; **B** blue: $r^2 = 0.94$; **C** black: $r^2 = 0.35$; **C** blue: $r^2 = 0.45$; **D** black: $r^2 = 0.98$; **D** blue: $r^2 = 0.97$). Sample sizes in Additional file 8

inspiration. By comparison, in normal participants, diaphragmatic contraction is responsible for 70% of the tidal volume and the intercostal muscles for 30% [27]. This may explain our observation that diaphragmatic thickening fraction and excursion are generally higher in patients with cervical TSCI than in control participants with intact intercostal muscle function. Our data show that, during quiet (tidal) breathing in patients with cervical TSCI, diaphragmatic excursion is independent of SCPP (i.e. the tidal volume is reached regardless of the SCPP). However, SCPP affects the force of diaphragmatic contraction, measured using the thickening fraction, with the strongest contraction at SCPP 80–90 mmHg. Deep breathing requires increased diaphragmatic effort to inflate and deflate the lungs to vital capacity; we found that, during deep breathing, SCPP has a major influence on diaphragmatic thickening fraction and excursion with optimum function at SCPP 80–90 mmHg.

Diaphragmatic function was further assessed using the EDI nasogastric tube, initially designed for NAVA ventilation [12, 13]. During quiet breathing, normal EDI-peak is 5–10 μ V, and normal EDI-min is up to 1 μ V. EDI-peak increases when the diaphragm has to contract more, e.g.

during respiratory distress, the EDI-peak may increase to 5–7 times above normal [28, 29]. Our data show that the EDI-peak is too low at SCPP < 60 mmHg, and that SCPP 60–100 mmHg is required for EDI-peak to normalise. We also found that low SCPP (< 60 mmHg) is associated with reduced EDI-min, a marker diaphragmatic tone marker. Reduced diaphragmatic tone is detrimental by allowing the abdominal contents to displace the diaphragm cranially, thus causing lung compression and atelectasis [30]. We found that SCPP 60–100 mmHg increases EDI-min, which may, in turn, facilitate tonic diaphragmatic contraction.

We also assessed the thickening of intercostal muscles, which are easily accessible by USS. Normally, the contribution of intercostal muscles to breathing increases with intense respiratory effort [31]. In our control group, the thickening fraction was low ($\leq 5\%$ for upper and middle intercostal muscles, 10% for low intercostals). In the cervical TSCI patients, we found an inverted-U relationship between intercostal thickening fraction and SCPP for upper and middle intercostals, with the maximum intercostal thickening fraction reaching normal level during quiet breathing at SCPP 80–90 mmHg. The thickening

fraction of low intercostal muscles increased with increasing SCPP. Negative thickening fraction, seen during spinal cord hypo- and hyper-perfusion, likely indicates passive stretching of the intercostal muscles during inspiration that may occur with diaphragmatic (abdominal) breathing.

Plots of individual patient breathing function versus SCPP, rather than using data from all patients combined, raises some interesting issues. First, the inverted U relationship between breathing function and SCPP, observed with the combined patient data, also seems to hold for individual patients in most cases. Second, the SCPP that optimises breathing function may vary between patients. Third, in some patients, breathing function is very sensitive to change in SCPP, but in others less so, ie. the gradient of the inverted-U relationship varies between patients. Finally, in some patients, no inverted-U correlation between breathing function and SCPP was detected; this could be because an optimum SCPP does not exist or because the optimum SCPP lies outside the range 60–100 mmHg. We urge caution when interpreting data from individual patients due to the small sample size.

A limitation of our study is the small number of patients. This precludes multivariate analysis to determine the effect of factors such as patient age, severity of injury, and level of injury on the relationship between breathing function and SCPP. However, the conclusions for the combined patient data are supported by 1458 h of SCPP monitoring and 106 serial USS examinations (total 1370 images/videos). The NICU setting with critically ill patients required to cooperate during the assessments was particularly challenging. Our findings raise the possibility that intervention to maintain SCPP 80–90 mmHg may improve breathing in patients with acute, cervical TSCI. A future refinement would be analysis of single patient data to allow individualised management, rather than applying the optimum SCPP obtained from combined patient data to all patients. This would require modification of the USS technique to provide more data-points per patient for real-time computation of the SCPP that optimises breathing function.

Conclusions

Acute cervical TSCI impairs breathing. Our study shows that SCPP 80–90 mmHg correlates with improved breathing function. Further studies are required to determine whether SCPP-driven protocol accelerates ventilator liberation and reduces NICU length of stay.

Abbreviations

ABP	Arterial blood pressure
AIS	American Spinal Injury Association Impairment Scale
EDI	Electrical activity of the diaphragm

ISP	Intraspinal pressure
LPR	Lactate/pyruvate ratio
MAP	Mean arterial pressure
MD	Microdialysis
NAVA	Neurally adjusted ventilatory assist
NICU	Neuro-intensive care unit
p_{scO_2}	Partial pressure of spinal cord tissue oxygen
SCPP	Spinal cord perfusion pressure
TSCI	Traumatic spinal cord injury
USS	Ultrasound scan

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-023-04643-y>.

Additional file 1: Supplementary methods

Additional file 2: Relations between SCPP and monitored parameters

Additional file 3: Diaphragmatic ultrasound videos, B-mode

Additional file 4: Diaphragmatic excursion videos, M-mode

Additional file 5: Intercostal muscle ultrasound videos

Additional file 6: Summary of correlations between individual patient's breathing function vs SCPP

Additional file 7: Plots of relations between individual patient's breathing function vs SCPP

Additional file 8: Sample sizes for each graph

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Author contributions

RV helped with patient recruitment and surgery, collected and analysed data, and helped write the manuscript. EB helped with patient recruitment, patient care in NICU, and data collection. AZ anaesthetised the patients, looked after the patients in NICU and helped with data interpretation and analysis. MCP operated on the patients, looked after them and helped with data interpretation and analysis. SS designed the project, directed data analysis, wrote the manuscript, and provided overall supervision for this project.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approvals for ISCoPE, including consent form and patient information sheet 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 was 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 included in the study or their family members.

Consent for publication

Not applicable.

Competing interests

SS and MCP are PIs on a research grant from Wings for Life spinal cord research foundation. MCP is Chairman of the Neurosciences Research foundation. AZ, EB and RV have no conflicts of interest.

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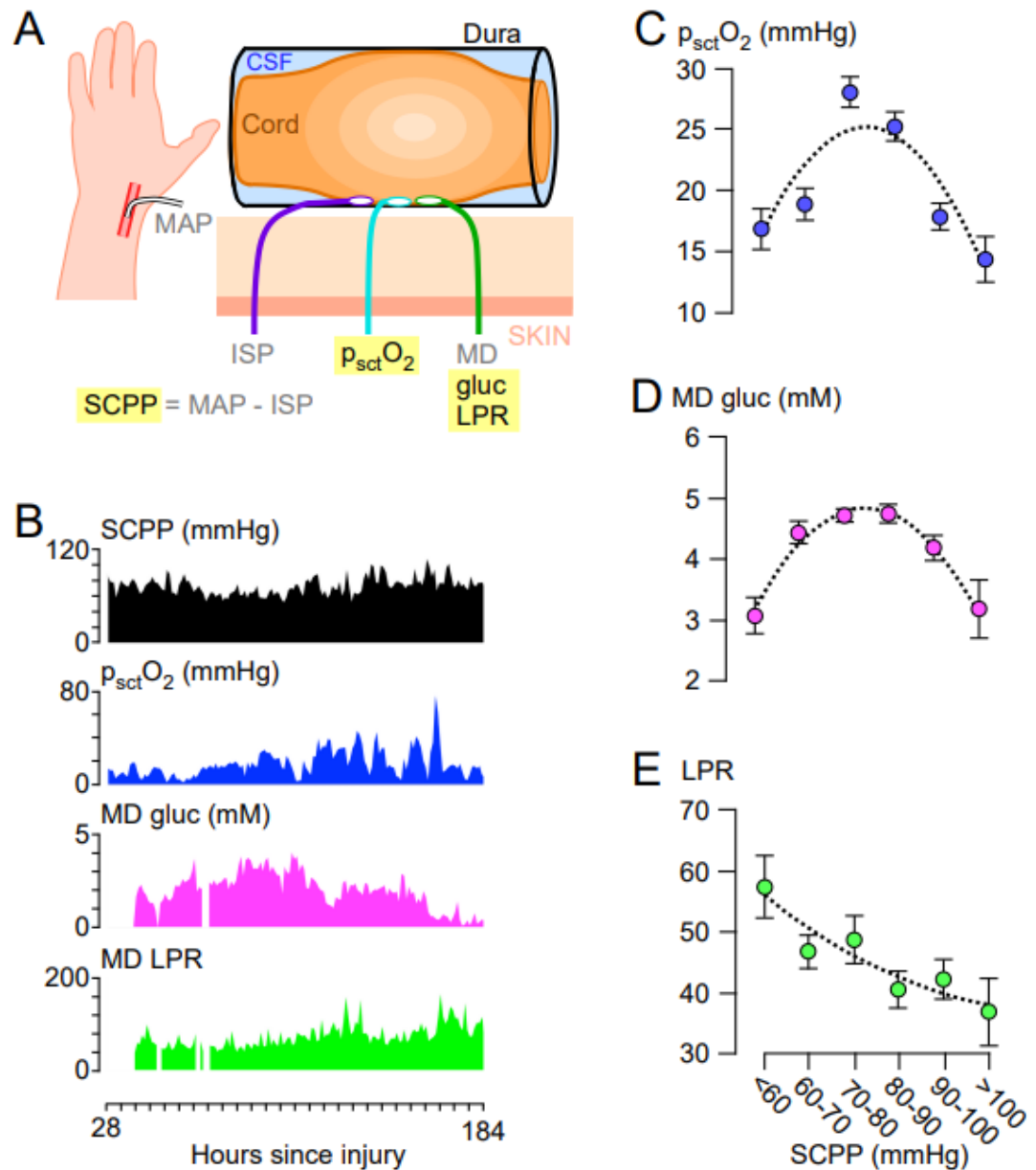
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ADDITIONAL FILE 1 – Supplementary methods

Tissue oxygen monitoring. An O₂ electrode (Licox - CC1P1, Integra, Sophia-Antipolis, France) was inserted intradurally at the site of maximal spinal cord swelling and was connected to a Licox P_iO₂ Monitor (Integra, Integra, Sophia-Antipolis, France), linked to a Philips Intellivue MX800 monitor (Philips, Guildford, UK), and connected to the laptop running ICM+ (Cambridge, U.K.). The Licox signal (Fig. 1) was sampled at 500 kHz.

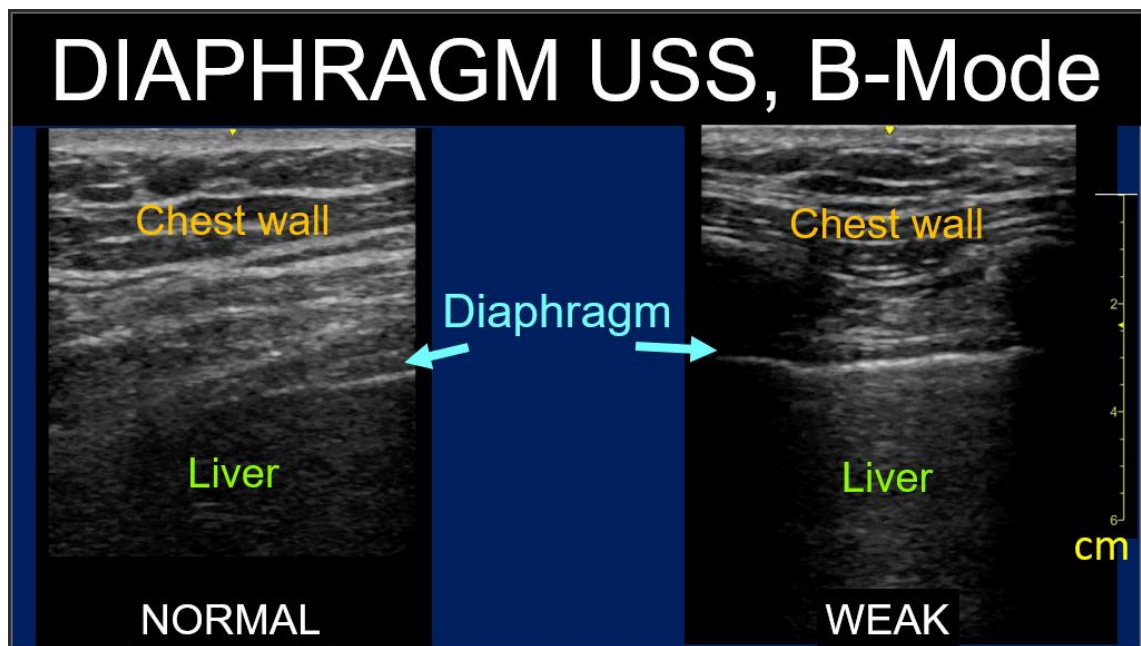
MD monitoring. A CMA61 MD catheter (CMA microdialysis AB, Solna, Sweden) was inserted intradurally at the site of maximal spinal cord swelling. MD was started postoperatively in the NICU as described^{19–21}. Central nervous system fluid (CMA microdialysis AB) was perfused at 0.3 µL/min using the CMA106 pump (CMA microdialysis AB). MD vials were changed hourly and analysed using ISCUS Flex (CMA microdialysis AB) for glucose, lactate, and pyruvate. LPR was calculated. The first two samples from each patient were discarded to allow priming of the MD catheter and stabilisation of the metabolite concentrations. 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from analysis. Our MD method measures cord surface metabolism at the injury site, which correlates with intraparenchymal injury site metabolism, but differs from metabolites measured from lumbar CSF^{19–21}.

Additional file 2. Relations between SCPP and monitored parameters

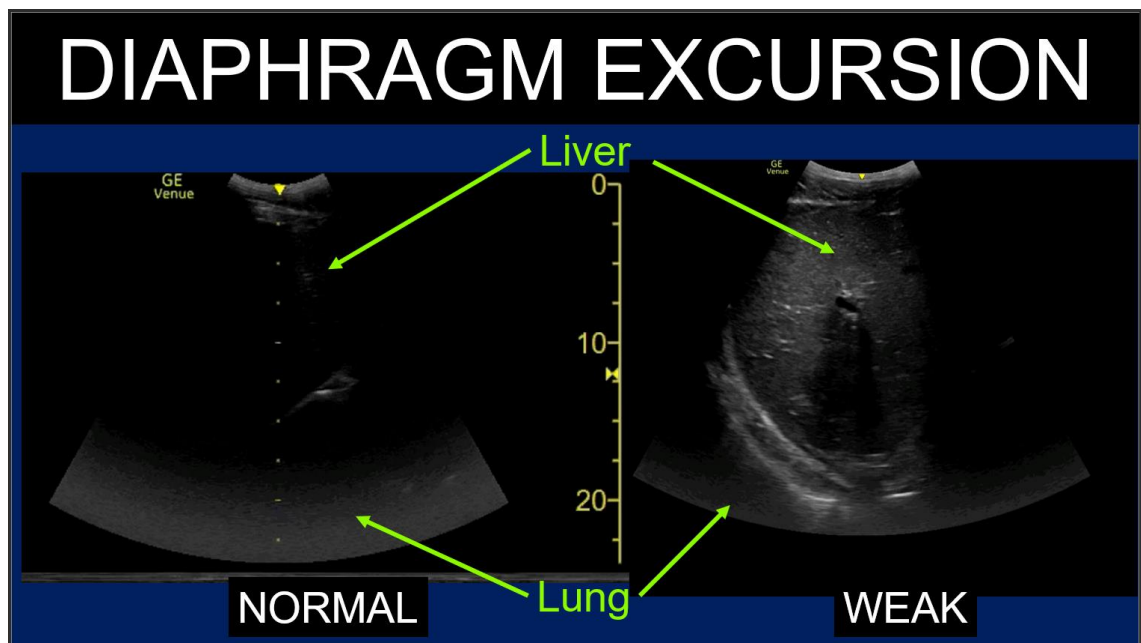


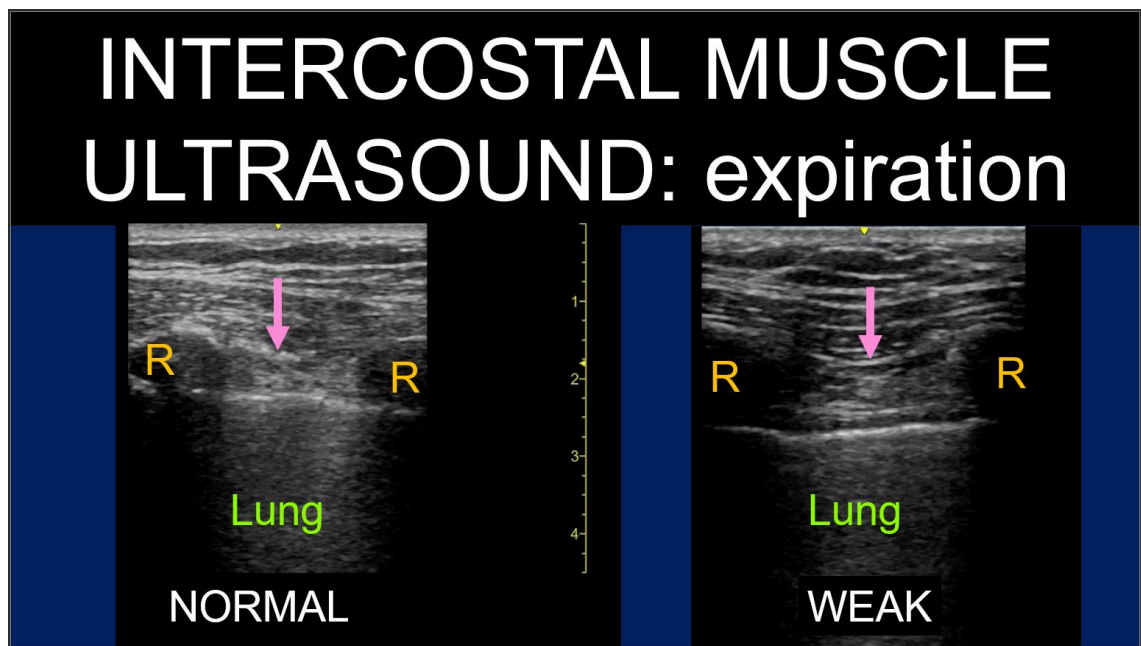
ADDITIONAL FILE 2. Monitoring setup. **A.** Monitoring from the injured spinal cord of Mean Arterial Pressure (MAP), Intra Spinal Pressure (ISP), Spinal Cord Perfusion Pressure (SCPP), Micro Dialysis (MD) to detect tissue glucose and tissue Lactate to Pyruvate Ratio (LPR), as well as tissue oxygen ($p_{sct}O_2$). **B.** Example of multimodality monitoring from a patient with cervical TSCI (21 years old, C4 ASIA B). Plots of **C.** $p_{sct}O_2$ vs. SCPP, **D.** tissue glucose vs. SCPP, and **E.** tissue LPR vs. SCPP. Mean $\pm$ standard error. Best-fit quadratics (D: $r^2 = 0.78$, E: $r^2 = 0.98$, F: $r^2 = 0.87$).

Additional file 3. Diaphragmatic ultrasound videos, B-mode



Additional file 4. Diaphragmatic excursion videos, M-mode



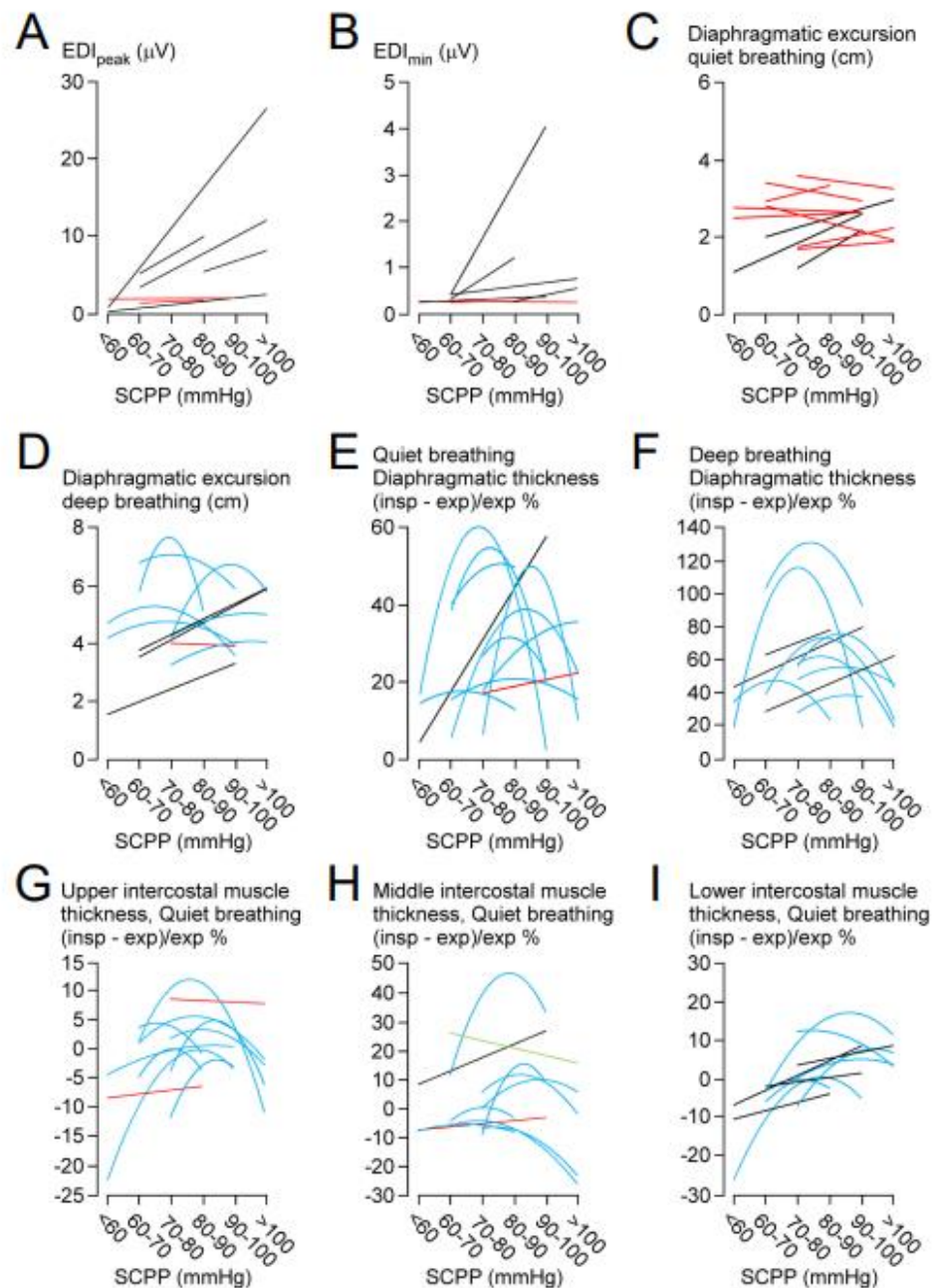


Additional file 6. Summary of correlations between individual patient's breathing function vs SCPP

ADDITIONAL FILE 6 – Individual patient correlations of breathing function vs. SCPP

MEASURE OF BREATHING FUNCTION	NO. OF PATIENTS	CORRELATION vs. SCPP				
		ALL PATIENTS COMBINED	INDIVIDUAL PATIENTS (% PATIENTS)			
			↑	↓	∩	→
EDI-peak	7	↑	71.4			28.6
EDI-min	7	↑	71.4			28.6
Diaphragm excursion (quiet)	11	→	27.3			72.7
Diaphragm excursion (deep)	11	∩	27.3		63.6	9.1
Diaphragm thickness (% change quiet)	11	∩	9.1		81.9	9.1
Diaphragm thickness (% change deep)	11	∩	27.3		72.7	
Upper intercostal thickness (% change)	11	∩			81.8	18.2
Middle intercostal thickness (% change)	11	∩	9.1	9.1	72.7	9.1
Lower intercostal thickness (% change)	10	↑	40.0		60.0	

Additional file 7. Plots of relations between individual patient's breathing function vs SCPP



ADDITIONAL FILE 7. Individual patient correlations of breathing function vs. SCPP. A. EDI_{peak} **B.** EDI_{min} . **C.** Diaphragmatic excursion (cm) during **C.** Quiet breathing, and **D.** Deep breathing. Change in diaphragmatic thickness (inspiration - expiration)/expiration % during **E.** Quiet breathing, and **F.** Deep breathing. Change in muscle thickness (inspiration - expiration)/expiration % during quiet breathing for **G.** Upper intercostal, **H.** Middle intercostal, and **I.** Lower intercostal. Best-fit linear with positive correlation (black), no correlation (red), and negative correlation (green). Best fit quadratic (blue).

Additional file 8. Sample sizes for each graph

ADDITIONAL FILE 8. Sample sizes

FIG. 2. Sample sizes.

	2B black	2C black	2B blue	2C blue
<60	8	6	5	5
60 – 70	31	30	8	8
70 – 80	54	52	26	25
80 – 90	55	53	22	23
90 – 100	37	34	3	3
>100	6	5		

FIG. 3. Sample sizes.

	3C black	3D black	3C blue	3D blue
<60	8	7	4	4
60 – 70	22	22	8	6
70 – 80	43	48	28	26
80 – 90	71	68	43	41
90 – 100	31	32	5	16
>100	11	12	9	8
Control	19	20		

FIG. 4. Sample sizes.

	4C black	4D black	4C blue	4D blue
<60	6	6	2	4
60 – 70	14	13	4	8
70 – 80	33	33	15	28
80 – 90	52	52	26	43
90 – 100	20	20	5	16
>100	9	8	9	8
Control	19	20		

FIG. 5. Sample sizes.

	5C black	5D black	5E black	5C blue	5D blue	5E blue
<60	8	8	8	4	4	4
60 – 70	24	24	24	6	8	8
70 – 80	50	50	48	26	28	28
80 – 90	80	80	74	41	44	44
90 – 100	36	36	28	16	18	18
>100	12	12	12	8	8	8
Control	20	19	8			

ADDITIONAL FILE 2. Sample sizes.

	p _{set} O ₂	Glucose	LPR
<60	28	19	24
60 – 70	119	148	169
70 – 80	283	429	424
80 – 90	276	437	413
90 – 100	125	156	175
>100	16	29	25