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Monitoring the injury site in patients with acute severe traumatic spinal cord injuries in the intensive care unit.

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Thesis submitted for the award of Doctor of Philosophy
August 2020

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Responsibility Statement

I confirm that this work is my own and that I have acknowledged others when they have contributed to the work. There is no intentional misrepresentation of results and I confirm that I carry responsibility for the scientific integrity of this work.

My PhD supervisors, Dr Saadoun and Prof Papadopoulos, conceived the ideas for this work and designed the studies. Prof Edwards, my third supervisor, offered pastoral support and advice during my PhD. Prof Papadopoulos performed the surgery on these patients and inserted the monitoring probes. Alongside Mathew Gallagher (former PhD student), I recruited the patients to the study and collected all of the data. Research nurse Siobhan Kearney helped me perform the urodynamic investigations. Eskinder Solomon (clinical scientist with interest in urodynamic studies) helped to conceive the methods for the urodynamic studies and analyse that data. The patients were clinically managed by Prof Papadopoulos and Dr Zoumprouli (neuro intensive care consultant) alongside ICU nurses and doctors on the neuro intensive care unit at St Georges Hospital. Dr Saadoun and I analysed the data and we prepared the text, figures and tables for the manuscripts which I have listed below. My thesis is based on the papers our group has written during my tenure as a PhD student.

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Publications

Publications associated with PhD Thesis.

1. Hogg FRA, Gallagher MJ, Chen S, Zoumprouli A, Papadopoulos MC, Saadoun S. **Predictors of Intraspinal Pressure and Optimal Cord Perfusion Pressure After Traumatic Spinal Cord Injury.** Neurocrit Care. 2019 Apr; 30(2): 421-428.
2. Hogg FRA, Gallagher MJ, Kearney S, Zoumprouli A, Papadoupoulos MC, Saadoun S. **Acute Spinal Cord Injury: Monitoring Lumbar Cerebrospinal Fluid Provides Limited Information about the Injury Site.** J Neurotrauma. 2020 May 1; 37(9): 1156-1164.
3. Gallagher MJ, Hogg FRA, Kearney S, Kopp MA, Blex C, Serdani L, Sherwood O, Schwab JM, Zoumprouli A, Papadopoulos MC, Saadoun S. **Effects of local hypothermia-rewarming on physiology, metabolism and inflammation of the acutely injured human spinal cord.** Sci Rep. 2020 May 15; 10(1): 8125.
4. Hogg FRA, Kearney S, Zoumprouli A, Papadopoulos MC, Saadoun S. **Acute spinal cord injury: correlations and causal relations between spinal pressure, spinal cord perfusion pressure, lactate-to-pyruvate ratio and limb power.** Neurocrit Care. 2021 Feb; 34(1):121-129
5. Hogg FRA, Kearney S, Soloman E, Gallagher MJ Zoumprouli A, Papadopoulos MC, Saadoun S. **Spinal cord perfusion pressure influences urinary bladder function in patients with acute spinal cord injuries.** In print with Journal of Neurosurgery Spine.
6. Hogg FRA, Kearney S, Gallagher MJ Zoumprouli A, Papadopoulos MC, Saadoun S. **Spinal cord perfusion pressure correlates with anal sphincter function in a cohort of patients with acute, severe traumatic spinal cord injuries.** Neurocrit Care 2021 June 07 (EPub ahead of print)

Relevant publications for PhD thesis.

1. Gallagher MJ, Hogg FRA, Zoumprouli A, Papadopoulos MC, Saadoun S. **Spinal cord blood flow in patients with acute spinal cord injuries.** J Neurotrauma. 2019 Mar 19; 36(6): 919-929.
2. Gallagher MJ, Lopez DM, Sheen HV, Hogg FRA, Zoumprouli A, Papadopoulos MC, Saadoun S. **Heterogeneous effect of increasing spinal cord perfusion pressure on spinal evoked potentials recorded from the acutely injured human spinal cord.** J Crit Care 2020 Apr; 56: 145-151.

3. Chen S, Gallagher MJ, Hogg F, Papadopoulos MC, Saadoun S. **Visibility Graph Analysis of Intraspinal Pressure Signal Predicts Functional Outcome in Spinal Cord Injured Patients. J Neurotrauma.** 2018 Dec 15; 35(24): 2947-2956.

Prizes

1. European Association of Neurosurgeons Aesculap research prize: shortlisted as finalist for paper ‘Spinal cord perfusion pressure influences urinary bladder function in patients with acute spinal cord injuries’ June 2021.
2. Society of British Neurosurgeons: Campbell Connolly Award for Neurotrauma for paper ‘Spinal cord perfusion pressure influences urinary bladder function in patients with acute spinal cord injuries’ May 2021.
3. Society of British Neurosurgeons prize for best poster ‘Predictors of intraspinal pressure and optimal cord perfusion pressure after traumatic spinal cord injury’. September 2018.
4. Royal College of Surgeons Research Fellowship, May 2018.

Abbreviations

AANS – American association of neurological surgeons

ABP –Arterial blood pressure

AIS – ASIA impairment scale

AP – Anal pressure

ASIA – American spinal injuries association

BASIC- Brain and spinal injury centre score

CSF – Cerebrospinal fluid

CSFP – Spinal pressure calculated from the lumbar CSF space

CT – Computed tomography

DO – Detrusor Overactivity

DSD – Detrusor Sphincter Dysnergia

ICP – Intracranial pressure

ICU – Intensive care unit

ISCOPE – Injured spinal cord pressure evaluation study

ISP – Intraspinal pressure

LPR – Lactate-to-pyruvate ratio

MAP – Mean arterial pressure

MCC – Maximal Canal Compression

MD – Microdialysis

MRI – Magnetic resonance imaging

MSCC – Maximal spinal cord compression

NICU – Neuro-intensive care unit

NLI – Neurological level of injury

P_{abd} – Abdominal pressure

P_{ana} – Anal sphincter pressure

P_{det}– Detrusor Pressure

P_{ves}– Bladder Pressure

PRx – Cerebral pressure reactivity

RAIR – Recto-anal inhibitory reflex

SAH – Subarachnoid haemorrhage

SCBF – Spinal cord blood flow

SCPP – Spinal cord perfusion pressure calculated from MAP-ISP

$SCPP_{(csf)}$ - Spinal cord perfusion pressure calculated from MAP-CSFP

$SCPP_{opt}$ - SCPP that optimizes pressure reactivity

$SCPP_{opt(csf)}$ - SCPP that optimizes pressure reactivity calculated from CSFP

sPRx- Spinal pressure reactivity

$sPRx_{(csf)}$ - Spinal pressure reactivity calculated from CSFP

TBI – Traumatic brain injury

TSCI – Traumatic spinal cord injury

UD – Urodynamics

UDI – Urodynamic Investigations

V_{max}– Total volume in bladder at end fill

Figures

1. Schematic showing position of monitoring probes 31
2. Example showing patient with TSCI who underwent injury site monitoring. 32
3. ISP monitoring technique. 41
4. ICM+ signals. 44
5. Example of the U-shaped curve showing $SCPP_{opt...}$ 45
6. Spinal cord injury MRI grading systems: maximal spinal cord compression, maximal canal compression and spinal cord occupation ratio 51
7. Spinal cord injury MRI grading systems: CSF effacement around spinal cord, sagittal length of T2 signal change, normal cord in injured cord, percentage cord signal change 52
8. Spinal cord injury MRI grading systems: BASIC grade axial T2 imaging 53
9. Spinal cord injury MRI grading systems: sagittal grade 54
10. ISP *versus* level of spinal cord injury 58
11. ISP *versus* age 59
12. ISP *versus* extent of decompression.. 60
13. ISP *versus* intra-operative blood loss 61
14. ISP *versus* excess alcohol consumption 62
15. ISP correlation with $SCPP_{opt}$ 65
16. Level of spinal cord injury (cervical, thoracic, conus) correlation with $SCPP_{opt}$ 66
17. Schematic showing set up for injury site monitoring and CSFP monitoring 72
18. Comparing ISP and CSFP waveforms 79
19. Comparing ISP and CSFP Signals 1 80
20. Comparing ISP and CSFP Signals 2 81
21. Frequency domain analysis of ISP and CSFP 82
22. Comparing the slope of the pulse wave for ISP and CSFP 1 83
23. Comparing the slope of the pulse wave for ISP and CSFP 2 84
24. Comparing the latency of onset of ISP and CSFP waveforms 85
25. ISP *versus* CSFP 87
26. Correlation of ISP and CSFP 1.. 88
27. Correlation of ISP and CSFP 2.. 89
28. Correlation of ISP and CSFP 3.. 90
29. Physiological parameters computed from ISP *versus* CSFP: SCPP and $SCPP_{csf}$ 92
30. Physiological parameters computed from ISP *versus* CSFP: sPRxand $sPRx_{(csf}$ 93
31. Physiological parameters computed from ISP *versus* CSFP: $SCPP_{opt}$ and $SCPP_{opt(csf)}$ 94

32. Biochemical parameters at injury site *versus* CSF: Lactate..... 95
33. Biochemical parameters at injury site *versus* CSF: Pyruvate 96
34. Biochemical parameters at injury site *versus* CSF: LPR. 97
35. Biochemical parameters at injury site *versus* CSF: Glucose. 98
36. Biochemical parameters at injury site *versus* CSF: Glutamate..... 99
37. Biochemical parameters at injury site *versus* CSF: Glycerol 100
38. The effect of draining lumbar CSF on ISP 1 102
39. The effect of draining lumbar CSF on ISP 2 103
40. The relation between cord oedema and concordance between ISP and CSFP signals... 105
41. Monitoring setup for assessing the correlation between limb power and injury site parameters in motor incomplete TSCI..... 111
42. Correlation of the standardised motor score with ISP 115
43. Correlation of the standardised motor score and SCPP 116
44. Correlation of the standardised motor score and MAP..... 117
45. Correlation of the standardised motor score and injury site metabolism..... 119
46. Correlation of ISP and injury site metabolism..... 121
47. Correlation of SCPP and injury site metabolism 122
48. Granger causality relations for ISP, SCPP, LPR and motor score..... 124
49. Schematic of setup for injury site monitoring and cooling..... 129
50. Clinical setup for injury site monitoring and cooling 130
51. Pre-operative MRI imaging for the patients who underwent injury site cooling 134
52. Extradural cool/re-warm regime 137
53. Actual extradural temperature at target extradural temperatures 33 and 37 ^{o}C..... 138
54. Core temperature at target extradural temperatures 33 and 37 ^{o}C 139
55. Effect of cooling-rewarming on ISP 141
56. Effect of cooling-rewarming on MAP 142
57. Effect of cooling-rewarming on SCPP 143
58. Effect of cooling-rewarming on injury site Glucose..... 145
59. Effect of cooling-rewarming on injury site Lactate 146
60. Effect of cooling-rewarming on injury site Pyruvate 147
61. Effect of cooling-rewarming on injury site LPR 148
62. Effect of cooling-rewarming on injury site Glutamate 149
63. Effect of cooling-rewarming on injury site Glycerol..... 150
64. Effect of cooling-rewarming on injury site IL1α 152

65. Effect of cooling-rewarming on injury site IL1β 153
66. Effect of cooling-rewarming on injury site IL8 154
67. Effect of cooling-rewarming on injury site IL4 155
68. Effect of cooling-rewarming on injury site IL10 156
69. Effect of cooling-rewarming on injury site IP10 157
70. Effect of cooling-rewarming on injury site MCP1 158
71. Effect of cooling-rewarming on injury site MIP1α 159
72. Effect of cooling-rewarming on injury site MIP1β 160
73. Effect of cooling-rewarming on injury site GROα 161
74. Schematic of injury site monitoring used during UDI 171
75. Schematic showing cystometry setup 173
76. Example cystometry trace 178
77. Variability of unfavourable urodynamic parameters: poor compliance 180
78. Variability of unfavourable urodynamic parameters: DSD 181
79. Variability of urodynamic parameters in each patient 182
80. Bladder compliance correlation with SCPP 184
81. Bladder compliance correlation with ISP 185
82. Bladder compliance correlation with injury site glucose 186
83. Bladder compliance correlation with injury site LPR 187
84. Effect of propofol dose on unfavourable urodynamic parameters. 188
85. Effect of fentanyl dose on unfavourable urodynamic parameters. 189
86. Effect of noradrenaline dose on unfavourable urodynamic parameters. 190
87. Detrusor overactivity correlation with SCPP 192
88. Detrusor overactivity versus ISP 193
89. Detrusor overactivity versus injury site glucose 194
90. Detrusor overactivity versus injury site LPR 195
91. Detrusor sphincter dyssynergia versus SCPP 197
92. Detrusor sphincter dyssynergia versus ISP 198
93. Detrusor sphincter dyssynergia versus injury site glucose 199
94. Detrusor sphincter dyssynergia versus injury site LPR 200
95. Maximal detrusor pressure versus SCPP 202
96. Maximal detrusor pressure versus ISP 203
97. Maximal detrusor pressure versus injury site glucose 204
98. Maximal detrusor pressure versus injury site LPR 205
99. Bladder volume at first desire to void versus spinal cord perfusion 207

100. Bladder sensation is not affected by propofol, fentanyl or noradrenaline 208
101. Long term urological outcomes – bladder compliance 210
102. Long term urological outcomes – bladder sensation 211
103. Long term neurological and urological outcomes 212
104. Schematic showing setup for monitoring and anal manometry 218
105. Schematic showing the recto-anal inhibitory reflex 219
106. Examples of signals monitored simultaneously during anorectal manometry 221
107. Correlation between SCPP and anal pressure 225
108. Plot of maximum anal pressure versus SCPP for individual patients 226
109. Plot of mean anal pressure versus ISP for individual patients 227
110. Plot of maximum anal pressure versus ISP for individual patients 228
111. Effect of surgical decompression on mean resting AP 229
112. Typical RAIR signals 231
113. Mean high and low SCPPs corresponding to RAIR measurements for each patient 232
114. Effect of SCPP on the RAIR mean baseline anal pressure 233
115. Effect of SCPP on the RAIR recovery time 234
116. Effect of SCPP on the RAIR % amplitude reduction 235
117. Effect of cough on anal pressure 237
118. Effect of SCPP on anal pressure during cough 238
119. Effect of SCPP on anal pressure during cough: mean maximum anal pressure 239
120. Effect of SCPP on anal pressure during cough: mean change in anal pressure 240
121. Effect of SCPP on prolonged squeeze anal pressure 242
122. Effect of SCPP on prolonged squeeze anal pressure: endurance time 243
123. Effect of SCPP on prolonged squeeze anal pressure: change in anal pressure 244

Tables

1. ASIA Grading 25
2. Inclusion and exclusion criteria for the ISCoPE trial 30
3. Parameters monitored in the ISCoPE study with comparisons to TBI monitoring 33
4. Definitions of patient related factors assessed for each TSCI patient 47
5. Definitions of injury related factors assessed for each TSCI patient 48
6. Definitions of management related factors assessed for each TSCI patient 49
7. Definitions of pre-operative MRI related factors assessed for each TSCI patient 50
8. Demographics of patients for project assessing predictors of ISP and $SCPP_{opt}$ after TSCI 56
9. Confusion matrix of multi-variate logistic regression model for predicting mean ISP for the first 24 h after surgery 63
10. Confusion matrix of multi-variate ordinal logistic regression model for predicting $SCPP_{opt}$ for the first 24 h after surgery 67
11. Demographics of patients for project assessing injury site monitoring *versus* lumbar CSF monitoring 76
12. Complications of patients in project looking at injury site monitoring *versus* lumbar CSF monitoring 77
13. Demographic of the AIS grade C patients 113
14. Inflammatory cytokines and chemokines in TSCI 132
15. Demographics of patients who underwent injury site cooling 135
16. Wound complications of localised hypothermia 163
17. Demographics of patients who underwent UDI 175
18. Summary of UDI findings 177
19. Demographics of patients who underwent anorectal manometry 222
20. Definitions of SCIM bowel scores 223

Appendices

1. ISCoPE protocol 264
2. ISCoPE patient information sheets 292
3. ISCoPE consent form 304
4. Ethical amendments and approvals for ISCoPE study 305
5. ASIA form 309
6. Publications associated with thesis 311
7. Publications written during PhD but not included in thesis 389

Contents

Responsibility statement **2**

Acknowledgments **3**

Publications **4**

Prizes **6**

Abbreviations **7**

List of figures **9**

List of tables **13**

Appendices **14**

Thesis abstract **20**

1. Introduction **22**

1.1 Background 22

1.2 Acute management 20

1.2.1. Clinical Assessment *23*
1.2.2. Surgical versus active physiological conservative management *26*
1.2.3 Blood pressure *27*
1.2.4 ICU admission *27*
1.2.5 Therapeutic hypothermia *27*
1.2.6 Urinary bladder *28*
1.2.7 Monitoring from the injury site *28*

1.3 Key results from ISCoPE to date 34

1.3,1. Intraspinal pressure (ISP) *34*
1.3.2 Spinal cord perfusion pressure (SCPP), spinal pressure reactivity (sPRx) and optimal spinal cord perfusion pressure ($SCPP_{opt}$) *34*
1.3.3 Spinal cord metabolism *35*

1.4 Aims of the thesis 37

2. Chapter 1: Predictors of intraspinal pressure (ISP) and optimal spinal cord perfusion pressure ($SCPP_{opt}$) after TSCI **38**

2.1 Introduction 38

2.2 Aim 38

2.3 Methods 38

2.3.1 Institutional approvals *38*
2.3.2 Patient recruitment *38*
2.3.3 Surgery and probe insertion *39*
2.3.4 ICU bedside ISP monitoring *42*
2.3.5 ICU clinical management *42*
2.3.6 Imaging *42*

2.3.7 Clinical assessments *43*
2.3.8 Signal analysis *43*
2.3.9 Biomarkers for predicting ISP and SPP_{opt} *46*
2.3.10 Statistical analysis *55*
2.4 Results 55
2.4.1 Patient characteristics *55*
2.4.2 Predictors of mean ISP *57*
2.4.3 Predictors of mean 24 hr $SCPP_{opt}$ *64*
2.5 Discussion 68
2.6 Conclusions 69

3. Chapter 2: Acute spinal cord injury: monitoring the lumbar cerebrospinal fluid provides limited information about the injury site 70
3.1 Introduction 70
3.2 Aim 70
3.3 Methods 70
3.3.1 Institutional approvals *70*
3.3.2 Patient recruitment *70*
3.3.3 Clinical examination and imaging *71*
3.3.4 Probe insertion *71*
3.3.5 Monitoring and lumbar CSF drainage *73*
3.3.6 Microdialysis setup and analysis *73*
3.3.7 Signal analysis *74*
3.3.8.Statistical analysis *74*
3.4 Results 75
3.4.1 Patient characteristics *75*
3.4.2 Complications *75*
3.4.3 ISP versus CSFP waveform shapes *78*
3.4.4 ISP versus CSFP signals *86*
3.4.5 SCPP, sPRx, $SCPP_{opt}$ and metabolites *91*
3.4.6 Effect on ISP of CSFP drainage *101*
3.4.7 Cord swelling and CSFP versus ISP correlation *104*
3.5 Discussion 106
3.6 Conclusions 107

4. Chapter 3: Acute spinal cord injury: correlations and causal relations between intraspinal pressure, spinal cord perfusion pressure, lactate-to-pyruvate ratio and limb power 108
4.1 Introduction 108
4.2 Aim 109
4.3 Methods 109

4.3.1 Institutional approvals ... *109*
4.3.2 Patient recruitment ... *109*
4.3.3 Clinical examination and imaging ... *109*
4.3.4 Probe insertion ... *109*
4.3.5 Intraspinal pressure monitoring ... *109*
4.3.6 Microdialysis setup and analysis ... *109*
4.3.7 Standardisation of limb motor score ... *109*
4.3.8 Statistical analysis ... *109*

4.4 Results ... 112

4.4.1 Patient characteristics ... *112*
4.4.2 Complications ... *112*
4.4.3 Motor score strongly correlates with injury site physiology ... *114*
4.4.4 Motor score strongly correlates with injury site metabolism ... *118*
4.4.5 Injury site physiology and metabolism are closely correlated ... *120*
4.4.6 Causality analysis ... *123*

4.5 Discussion ... 125

4.6 Conclusions ... 126

5. Chapter 4: Effects of local hypothermia-rewarming on physiology, metabolism and inflammation of the acutely injured human spinal cord ... 127

5.1 Introduction ... 127

5.2 Aim ... 127

5.3 Methods ... 127

5.3.1 Institutional approvals ... *128*
5.3.2 Inclusion/Exclusion criteria ... *128*
5.3.3 Clinical examination and investigation ... *128*
5.3.4 Surgery and probe insertion ... *128*
5.3.5 Cooling catheter ... *128*
5.3.6 ISP and microdialysis monitoring ... *131*
5.3.7 ICU patient management ... *131*
5.3.8 Multiplex ELISA for cytokines/chemokines ... *131*
5.3.9 Cooling-rewarming ... *133*
5.3.10 Data and statistical analysis ... *133*

5.4 Results ... 133

5.4.1 Patient characteristics ... *133*
5.4.2 Cooling-rewarming ... *136*
5.4.3 Injury site physiology ... *140*
5.4.4 Injury site metabolism ... *144*
5.4.5 Injury site inflammation ... *151*
5.4.6 Complications ... *162*
5.4.7 Outcomes ... *162*

5.5 Discussion ... 164

5.6 Limitations ... 166

5.7 Conclusions ... 166

6. Chapter 5: Improving bladder function in patients with acute spinal cord injuries by optimising injury site perfusion 168

6.1 Introduction 168

6.2 Aim 168

6.3 Methods 168

6.3.1 Institutional approvals 168
6.3.2 Inclusion/Exclusion criteria 169
6.3.3 Clinical examination and investigation 169
6.3.4 Surgery and probe insertion 169
6.3.5 ISP, ABP and microdialysis monitoring 169
6.3.6 Urodynamic investigations 172
6.3.7 Statistical analysis 174

6.4 Results 174

6.4.1 Patient characteristics 174
6.4.2 Urodynamics 176
6.4.3 Complications 179
6.4.4 Variability of urodynamic parameters 179
6.4.5 Bladder compliance correlates with injury site physiology and metabolism 183
6.4.6 Detrusor overactivity correlates with injury site physiology 191
6.4.7 Detrusor sphincter dyssnergia correlates with injury site physiology and metabolism 196
6.4.8 Maximal detrusor pressure correlates with injury site physiology and metabolism 201
6.4.9 Bladder sensation at first desire to void correlates with spinal cord perfusion 206
6.4.10 Long-term outcome 209

6.5 Discussion 213

6.6 Conclusions 214

7. Chapter 6: Effect of spinal cord perfusion pressure on anal function in patients with acute severe traumatic spinal cord injuries 215

7.1 Introduction 215

7.2 Aim 215

7.3 Methods 215

7.3.1 Institutional approvals 215
7.3.2 Inclusion/Exclusion criteria 215
7.3.3 Clinical examination and investigation 215
7.3.4 Surgery and probe insertion 216
7.3.5 ISP and ABP monitoring 216
7.3.6 Signal analysis 216
7.3.7 Anal manometry assessments 216
7.3.8 Statistical analysis 217

7.4 Results 220
7.4.1 Patient characteristics 220
7.4.2 Complications 220
7.4.3 Resting anal pressure 224
7.4.4 Recto-anal inhibitory reflex 230
7.4.5 Anal pressure during cough 236
7.4.6 Anal pressure during squeeze 241
7.4.7 Rectal sensation 245
7.5 Discussion 245
7.6 Conclusions 246

8. Discussion 247
9. Limitations 250
10. Overall conclusions 251

References 252
Appendices 264

Thesis Abstract

Background

Acute, severe traumatic spinal cord injury (TSCI) is devastating, resulting in paralysis and bladder/bowel incontinence. No treatment improves outcomes.

Aims

We recruited patients with TSCI to determine whether:

1) Pre-operative biomarkers can predict intraspinal pressure (ISP) and optimal spinal cord perfusion pressure ($SCPP_{opt}$).
2) Monitoring the lumbar cerebrospinal fluid (CSF) space is analogous to monitoring the injury site.
3) Fluctuations in injury site physiological and metabolic parameters are causatively linked to changes in limb power.
4) Local hypothermia-rewarming alters injury site physiology, metabolism and inflammation.
5) Urinary bladder and anal sphincter function are influenced by fluctuations in injury site physiology and metabolism.

Methods

Patients with acute severe TSCI underwent surgical fixation and insertion of subdural ISP and microdialysis probes (+/- lumbar drain, +/- local cooling device). Injury site monitoring was performed on neuro-intensive care for up to a week. Clinical assessments were performed +/- urodynamic investigations, +/- anorectal manometry. A small cohort had local hypothermia-rewarming.

Results

Our key findings are:

1) Injury site physiology and metabolism cannot be predicted pre-operatively from clinical and radiological biomarkers.
2) ISP and lumbar CSF pressures are different.
3) Injury site physiology and metabolism are causally linked to fluctuations in limb power.

4) Most TSCI patients develop unfavourable urodynamics which are influenced by injury site physiology and metabolism.
5) Anal sphincter function is influenced by changes in SCPP.
6) Local hypothermia-rewarming cause deranged injury site physiology, metabolism and inflammation and is associated with wound infections.

Conclusions

TSCI is a multi-system disease. Injury site multi-modal monitoring can calculate key parameters such as ISP and SCPP. Injury site physiology and metabolism varies and correlates with motor, bladder and sphincter outcomes. Cooling does not optimise the injury site. Our findings support individualised patient monitoring and management through optimising SCPP and ISP in patients with acute severe TSCI.

1. Introduction

1.1 Background

Traumatic spinal cord injury (TSCI) is a devastating life event often resulting in severe life-long disability including motor paralysis, bladder/bowel incontinence, sexual dysfunction, autonomic dysfunction and, in the case of cervical trauma, impaired breathing. TSCI affects ~180,000 people globally each year and has a prevalence of between 236 and 4,187 per million[1]. There is global variation in the incidence and causes of TSCI, reflecting the local sociodemographic. Worldwide, TSCI primarily affects young men, but an aging population produced a second peak from geriatric, fall-related cervical TSCI[2]. Road traffic accidents and falls are the leading causes of TSCI; other causes include crush-injuries, diving and violence[1].

The neurological effects of TSCI are usually permanent and there is no cure. 5 % of patients have neurological deterioration after the injury[3]. In the USA, incomplete tetraplegia is the most common outcome (47.6 % of cases) followed by incomplete paraplegia (19.9 %), complete paraplegia (19.6 %) and complete tetraplegia (12.3 %). Fewer than 1 % of patients are discharged neurologically normal[4]. Life expectancy after TSCI has improved since World War II due to improved medical management, but is still below national average. Renal failure used to be the leading cause of death; this has diminished with better bladder management and urological surveillance. The current leading causes of mortality in those surviving beyond year 1 are respiratory, circulatory, neoplastic and urological[5].

Due to substantial disability and life-long care needs, the economic burden of severe TSCI is huge. The estimated annual spend per year in the UK is £1.43 billion (£1.2 million per case). Age at injury and injury severity greatly impact on costs[6]. Life quality after TSCI is severely impacted with 70 % of patients having chronic pain, which affects mood and functioning[7] and many patients experiencing high levels of depression[8] and suicide [9].

My thesis focuses on acute TSCI management and the impact of monitoring from the injury site.

1.2 Acute Management

In 2016, a NICE guidance was published for best management of TSCI in the UK[10]. Recommendations include:

- Pre-hospital management in a timely systematic assessment and systemic support where needed, identification of neurological deficits (including motor weakness, loss of

sensation and priapism), spinal immobilisation and appropriate mechanisms of extrication. Patients should be transferred to major trauma centres experienced in TSCI.

- In-hospital, initial management follows Advanced Trauma Life Support (ATLS) principles where systems are examined and stabilised in order of life-threatening severity.
- Neurological deficits are identified in the primary survey and whole-body CT is strongly recommended when there is suspicion of TSCI with subsequent MRI.
- American Spinal Injuries Association (ASIA) Impairment Scale (AIS) grade and injury level should be established in the secondary survey by completing the ASIA International Standards Examination[11]. Vital capacity and ability to cough should also be documented.
- Patients with TSCI should be referred to the neurosurgical team and local spinal injuries unit within 4 hours. Management of the spinal injuries to be decided by those teams.
- Not using methylprednisolone, nimodipine or naloxone for neuroprotection.
- Not using neuropathic pain medications for prevention of neuropathic pain.
- Direct and informative communication to patients and relatives.
- A lifetime of personalised care guided by a spinal cord injury centre.

The guidance does not address the more controversial aspects of management described below. Our research concentrates on some of these controversies and shows how information obtained from injury site monitoring may be used to guide clinical decisions.

1.2.1 Clinical Assessment

The current internationally commonly used classification for spinal cord injuries is the American Spinal Injury Association Impairment Scale (ASIA)/International Spinal Cord Society (ISCoS) neurological standard scale (AIS) best known as the ASIA impairment scale. This scoring system was developed in 1982 and was updated and revised in 1987, 1990, 1992, 1996, 2011, 2015, 2019[12]. Prior this the Frankel scale was widely used, a 5 point severity scale with patients classified as complete (grade A), sensory only (grade B), motor useless (grade C), motor useful (grade D) and complete recovery/no deficit (grade E). The AIS grades are a modification of the Frankel scale,[13] See Table 1.

All scoring systems have limitations. The Frankel scale did not incorporate the level of injury into the classification and is criticised for its subjectivity in classifying motor function a‘ 'useful and useless’[13]. It was also found to have limited responsiveness to subtle improvements in neurological recovery. The ASIA scale may ‘over’ classify injuries e.g: a

patient with a motor complete injury with sensation below the level of the injury but no sacral sensation (ASIA Grade A, Frankel Grade B) may have a better prognosis than a patient with no motor or sensory function below the level of injury (ASIA Grade A, Frankel Grade A). Some groups are concerned that clinical care may be affected by this difference and under estimate the outcomes of some ASIA A patients. In a prospective multicentre cohort study the AIS grading system was found to be a poor prognostic measure for predicting ambulatory outcomes for patients with TSCI and the use of alternative functional ambulation outcome measures was recommended.[14]

Table 1. ASIA Impairment Scale Edition 2000

ASIA Impairment Scale		**Lesion**
A	No motor or sensory function is preserved in the sacral segments S4-5	Complete
B	Sensory but no motor function is preserved below the neurological level and includes the sacral segments S4-5	Incomplete
C	Motor function is preserved below the neurological level and more than half the key muscles have a muscle grade less than 3	Incomplete
D	Motor function is preserved below the neurological level and more than half the key muscles have a muscle grade of 3 or more	Incomplete
E	Motor and sensory functions are normal	Normal

1.2.2 Surgical versus active physiological conservative management

No randomised controlled trials have ever compared surgical fixation against conservative management in TSCI and a Cochrane review in 2008 recommended 'good quality controlled trials' to address this issue[3]. The benefits of spinal stabilisation surgery as agreed by the UK spinal societies include: stabilising the spine, preventing re-injury to the cord, pain reduction, reducing late deformity, optimising nursing care, reducing complications (respiratory, decubitus ulcers, venous thromboembolism) and early rehabilitation/mobilisation[3]. Some surgeons argue against early surgery citing the risks of secondary damage to the physiologically unstable spinal cord by multiple transfers, manipulation to the cord during surgery and changes in physiological parameters during surgical anaesthetic extending the TSCI[15]. Active conservative physiological management (APCM) involves between 4-6 weeks of recumbency with the aim to rest the injured tissue, allow restoration of the blood brain barrier, prevent hypotension or changes in vital capacity which exacerbate secondary injury by poor cord perfusion or oxygenation and allow the autonomic nervous system reflexes to return prior to the physical rehabilitation[16]. The aim of APCM is to achieve the maximum possible neuro-functional recovery as predicted from the extent of partial sparing and impairment of long sensory and sensory-motor tracts as assessed on admission with Frankel grading. The density of the lesion is described by: the length of the 'zone of partial preservation (ZPP)' which is limited to the three distal segments below the last neurologically normal segment in Complete Frankel A patients; sensory sparing without motor sparing distal to the ZPP in incomplete Frankel B; sensory sparing and minimal cortico-spinal sparing that cannot generate meaningful leg movement in Frankel C; sensory sparing and motor sparing that can generate movement of the lower limbs to enable patients to walk with or without orthosis but with impaired autonomic functions in Frankel D and normal sensory, motor and sphincter functions in Frankel E patients. This was described in Frankel's original manuscript in 1969 that also describes the neuro-functional definition of the grades. There is variability in UK practice but most support early surgical stabilisation, decompression and active physiotherapy[17].

The timing of surgical decompression is debated. The 2012 STASICS trial found that cervical cord decompression <24 hours after TSCI (mean 14.2 hours (+/- 5.4 hours)) was safe and associated with better neurological outcomes than 'late' surgery (mean 48.3 hours (+/- 29.3)). These findings are also supported by two further cohort studies performed by the same group [18,19]. However, STASCIS was not randomised and the two arms were not well matched. In 2017, the AO spine recommended early surgery and decompression[20] but NICE[10]

and the AANS[21] make no recommendation. All of the patients investigated here were operated on within 72 hours of injury, that was arbitrarily chosen due to the NHS setup.

1.2.3 Blood Pressure

Hypotension after TSCI is common due to neurogenic shock from sympathetic disconnection with unopposed parasympathetic. There is indirect evidence that pursuing aggressive blood pressure targets after TSCI improves mortality and neurological outcome[22]. Based on level III evidence, the AANS recommends maintaining mean arterial (MAP) of 85 – 90 mmHg for the first 7 days following TSCI[21], but there is no level I evidence to support this and UK practice is variable[17]. In the thesis, we will promote the concept of spinal cord perfusion pressure (SCPP), rather than MAP, as the parameter to target based on the notion that two patients may have the same MAP but different spinal cord pressures i.e. different SCPPs.

1.2.4 Intensive Care Unit admission

A review of observational studies suggests reduced morbidity and mortality in patients routinely admitted to an Intensive Care Unit (ICU) following TSCI and recommends management in the ICU for the first 7 – 14 days after TSCI with continuous cardiopulmonary monitoring, particularly for cervical injuries[23]. The studies that are were reviewed for this paper were however all level III evidence, with variable control groups for comparison (some comparing patients admitted early vs late to ICU, some comparing patients managed on ICU vs the ward, some without comparison groups). The AANS support ICU management in the acute stages[23], though there is no NICE recommendation for this[10]. All of the patients included in my thesis were initially managed in the neuro-ICU (NICU) at St. George's.

1.2.5 Therapeutic Hypothermia

Fever is common after TSCI, its origin may be infective or neurogenic. Fever is associated with more deranged spinal cord metabolism than normothermia. An infective aetiology for fever appears more detrimental than neurogenic. Patients with high fever burden had worse overall neurological recovery.[24]

Data from animal models suggest that cooling after TSCI improves histological and functional outcomes[25,26]. A small phase I study[27] assessing the outcomes of intravascular cooling to 33^{o}C on Cervical AIS A patients showed improvement to incomplete injuries in 42.8% (compared to 26% in case matched controls from the European Multi-centre Study in Human Spinal Cord Injury database[14]) with no increase in complications. In Eurotherm

(large, randomised controlled trial assessing therapeutic hypothermia in traumatic brain injury, (TBI)), cooling did not improve outcomes[28]. Currently, there is no level I evidence to support cooling after TSCI. Our injury site monitoring techniques provide a unique opportunity to characterise the effects of local hypothermia and re-warming on the physiology and metabolism at the injury site.

1.2.6 Urinary bladder

Classical teaching is that, early after TSCI, the bladder enters a period of "spinal shock" typically lasting 1 – 12 months during which the detrusor is atonic and hypercompliant[29]; at the end of this phase, a reflex neurogenic bladder is established. A comprehensive document recommends the following managing for the chronic neurogenic bladder[30]:

- Surveillance (clinical review, video urodynamics, renal ultrasound scans, investigations for urinary tract infections, monitoring for bladder stones/bladder cancer)
- Treatments to improve bladder storage (behavioural management, anti-muscarinic, bladder wall Botulinum injections, augmentation cystoplasty, ileal conduit diversion)

There is no NICE guidance on bladder management in the acute phase of TSCI. In the thesis, we performed filling cystometry within the first 10 days after TSCI to determine whether the detrusor is indeed atonic, as generally believed, and whether interventions to increase the SCPP improve urological outcome.

1.2.7 Monitoring from the injury site

Monitoring from the injured brain is common practice in severe TBI aiming to optimise brain physiology and metabolism to prevent secondary injury and improve outcome[31]. Intracranial pressure (ICP) monitoring is typically performed with a tip transducer inserted into the brain parenchyma/subdural space or via an external ventricular drain (EVD) connected to a fluid coupled transducer – all 3 techniques have equivalent accuracy[32,33]. ICP is used to calculate cerebral perfusion pressure (CPP = MAP – ICP) and pressure reactivity index (PRx), which is the running correlation co-efficient of ICP and MAP, a marker of cerebral autoregulation. PRx can be plotted against CPP to find the optimum CPP (CPP_{opt}), the CPP which optimises PRx. Multi-modal monitoring involves monitoring parameters other than just pressure including brain tissue oxygen (with Licox probe), metabolites (with microdialysis catheter) and electrical activity (with electrocorticography).

Although there is no level I evidence to support ICP-guided therapy in TBI, current guidelines recommend ICP monitoring and CPP optimisation to prevent secondary brain ischaemia and infarction[34,35]. Elevated ICP (>22mmHg) and CPP (<60mmHg) can be treated with: nomocapnea (PCO_2 4.5 – 5.0 kPa), osmotic diuretics, anti-epileptic medications, sedation, paralysis, ionotropic support, cranial elevation and surgical decompression (decompressive crainectomy plus dural opening)[34-37]. Observational evidence supports individualised targeted CPP therapy based on optimum PRx for more favourable neurological outcomes [38,39]. ICP and brain tissue oxygen-guided therapies have been shown to reduce brain tissue hypoxia with trends towards better neurological outcomes[40]. Observational data indicates that tissue metabolite levels correspond with physiological stress and neurological outcomes[41-43]

Despite many parallels between TSCI and TBI injury site monitoring for TSCI remains experimental. Some groups have monitored pressure via a lumbar drain placed distal to the injury site following TSCI, termed cerebrospinal fluid pressure (CSFP)[44-46]. CSFP has poor signal pulsatility and drop out in patients with cord swelling and dural compression thus raising concerns about the reliability of this approach. As part of our studies here, we investigated whether ISP and CSFP monitoring are equivalent.

In 2010, the Injured Spinal Cord Pressure Evaluation (ISCoPE) study was set up at St Georges Hospital London to develop multi-modal monitoring from the injury site after TSCI. ISCoPE recruits patients with severe (AIS A – C) acute (within 72 hours of injury) TSCI who require surgical fixation. Inclusion and exclusion criteria are listed in Table 2. After posterior decompression, a small durotomy is made and monitoring probes (pressure, microdialysis) are inserted into the subdural space. Patients are monitored for up to 7 days following the TSCI. Figures. 1 – 2 show details of the monitoring setup. Table 3 compares TSCI monitoring to TBI monitoring. The ISCoPE results will be further discussed in the next section and the methods explained in detail in the chapters of this thesis.

Table 2. Inclusion and Exclusion Criteria for ISCoPE Trial

Inclusion Criteria	**Exclusion Criteria**
Severe TSCI (ASIA AIS A-C) Age 18-70 Surgery within 72 hours of injury	Life-limiting major co-morbidities Penetrating Injury Unable to consent

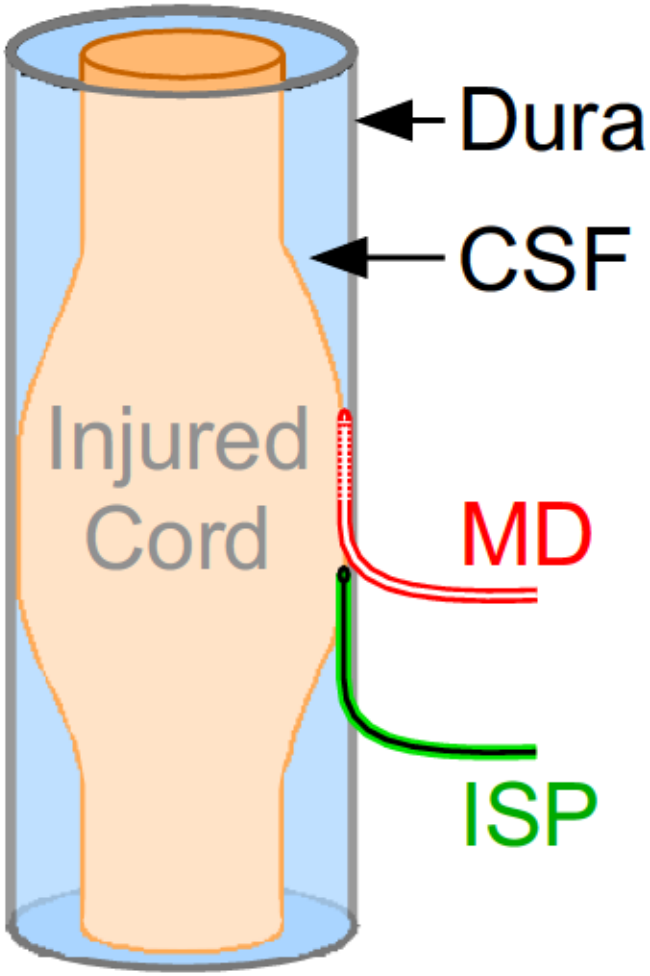


Fig. 1. Schematic showing position of monitoring probes. An intraspinal pressure probe (ISP) and Microdialysis (MD) catheter are inserted intradurally at the level of the spinal cord injury where they monitor the injured cord.

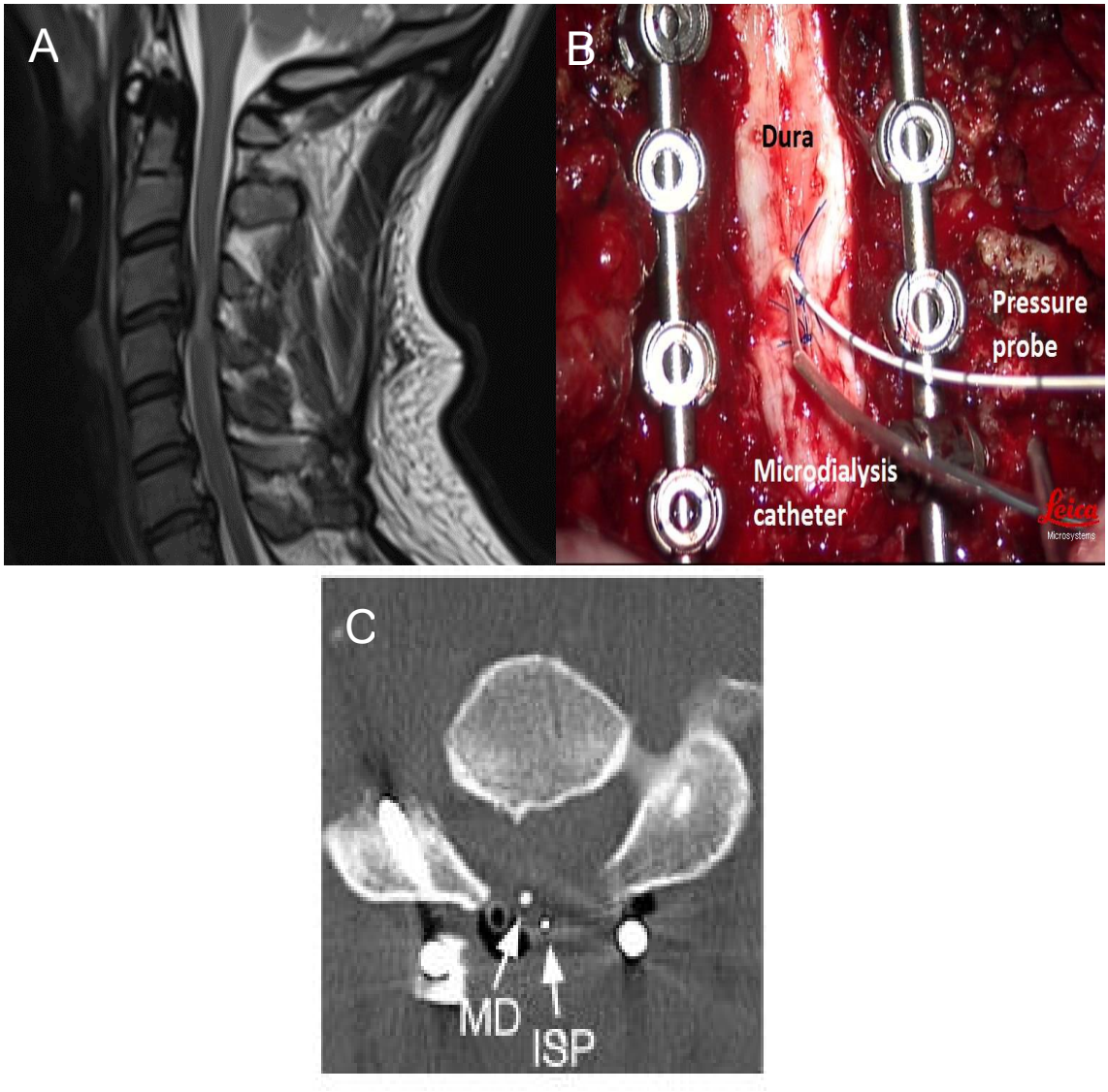


Fig. 2. Monitoring probes. A. Pre-operative sagittal T2 MRI of a patient with a spinal cord injury at C3/4. B. Intra-operative photo showing posterior spinal cord with durotomy at the injury site through which ISP and microdialysis probes are inserted. C. Post-operative axial CT with ISP probe and microdialysis (MD) catheter in situ.

Table 3. Parameters monitored in the ISCoPE study with comparisons to TBI monitoring.

Parameter monitored	**TSCI**	**TBI**
Injury site pressure	ISP = Intra-spinal pressure *Measured with pressure probe placed sub-durally at the injury site*	ICP = Intra-cranial pressure *Measured with pressure probe placed into the brain parenchyma/ sub-dural space/intraventricular system (if monitored with an external ventricular drain)*
Blood pressure	MAP = Mean arterial pressure *Measured from a radial arterial line*	
Perfusion pressure	SCPP = Spinal cord perfusion pressure *SCPP = MAP – ISP*	CPP = cerebral perfusion pressure *CPP = MAP - ICP*
Pressure reactivity index	sPRx – spinal pressure reactivity *Running correlation co-efficient of ISP and MAP. Values >0 indicate poor autoregulation, values <0 good autoregulation*	PRx = pressure reactivity. *Running correlation coefficient of ICP and MAP. Values >0 indicate poor autoregulation, values <0 good autoregulation*
Optimal perfusion pressure	$SCPP_{opt}$ = optimal spinal cord perfusion pressure *The SCPP that optimises sPRx*	CPP_{opt} = optimal cerebral perfusion pressure *The CPP that optimises PRx*
Metabolic profile [Glucose, Lactate, Pyruvate, Glycerol, Glutamate, Lactate Pyruvate Ratio (LPR)]	Surface microdialysis probe	Intraparenchymal microdialysis probe

1.3 Key results from ISCoPE to date

1.3.1 Intraspinal pressure

The subdural Codman pressure probe monitors ISP. The ISP waveform has 3 peaks (P1 percussion, P2 tidal, P3 dicrotic) and prominent cardiac and respiratory peaks on Fast Fourier Transformation thus making it comparable to ICP[47,48]. Compartmentalisation at the injury site is observed (higher ISP where the spinal cord has swollen against the dura in comparison to pressure measurements from cranial and caudal to the injury site)[49]. High ISP correlates with worse neurological outcomes[50] (intra-thecal pressure (CSFP) measured with a lumbar drain does not[45]). Patients with more severe TSCI show loss of ISP signal complexity i.e. the spinal cord becomes less resilient to external stress[51] and network theory analysis of the ISP signal in TSCI shows that the topological structure of the ISP signal (network diameter, modularity, eccentricity and small world-ness) is sensitive to adverse events at the injury site and can be used to predict neurological outcomes[52].

Unlike their effect on ICP, hypocapnea, mannitol and lowering the dose of sevoflurane have no effect on ISP[47]. High ISP is still seen after bony decompression, likely from cord compression against the dura, which is not routinely opened in spinal decompression; high ISP can be reduced by performing an expansion duroplasty, which may be associated with improved neurological outcomes[53-55]. Manoeuvres shown to increase SCPP are vasopressors (by increasing MAP)[47] and expansion duroplasty (by reducing ISP)[53].

A review of the first 14 patients who underwent monitoring from the injury site revealed that our techniques are safe[56]. The complications encountered with injury site monitoring include: CSF leak (8%), dislodged probe (3%) and asymptomatic pseudomeningocele which resolves on follow up MRI at 6 months (20%). For recent reviews please see [57,58]. In the studies here, ISP is a key parameter that was monitored in all patients.

1.3.2 Spinal cord perfusion pressure (SCPP), spinal pressure reactivity (sPRx) and optimal spinal cord perfusion pressure ($SCPP_{opt}$)

Spinal cord perfusion pressure (SCPP) is calculated by subtracting ISP from MAP. sPRx is the running correlation coefficient of ISP *versus* MAP. sPRx ≤0 indicates inverse correlation between ISP and the slow fluctuations of ABP i.e. reactive vascular bed and intact autoregulation. sPRx >0 means positive correlation between the slow components of the ABP and ISP indicating deficient vascular reactivity and impaired autoregulation. sPRx

plotted against SCPP produces a U-shaped curve indicating that hypo and hyper-perfusion are both detrimental to the cord. $SCPP_{opt}$ is the SCPP which minimises sPRx[59].

Higher SCPP is associated with better neurological outcomes (AIS grade conversion at 6-12 months)[45,60]. Increasing SCPP can acutely correlate with improved clinical neurological examination[47], improved neurophysiological assessments (increased amplitude of motor and somatosensory evoked potentials) [47 61], better autoregulation [47,62], better drug delivery to the spinal cord[63] and a better cord metabolic profile[63,64].

Plotting sPRx against SCPP produces wide variabilities in $SCPP_{opt}$ (up to 60mmHg), $SCPP_{opt}$ values can vary with time in each patient and most patients have a range of SCPP that optimises sPRx[62]. We have thus recently modified the concept of $SCPP_{opt}$ to continuous $SCPP_{opt}$ ($cSCPP_{opt}$) computed as the SCPP that minimises the sPRx in a moving 4 hour window[62]. Data from TBI shows that patients managed with CPP close to CPP_{opt} have better outcomes than those who are hypo-perfused (CPP is below CPP_{opt}) or hyper-perfused (CPP exceeds CPP_{opt})[65]. We do not yet know whether the same applies for TSCI as more data are needed. For recent reviews see [57,58].

Variable states of spinal cord blood flow (SCBF) have been revealed by using intra-operative laser speckle contrast imaging to visualise spinal cord blood flow. Hyperperfusion of the spinal cord resulted in an asymmetrical pattern of SCBF, increasing it in some areas and reducing it in others. This phenomenon was named ‘ blood-pressure induced local steal’ which may explain why hyper-perfusion appears detrimental in TSCI[66].

1.3.3 Spinal cord metabolism

Microdialysis monitors substrate delivery and metabolism at the cellular level and should be interpreted in conjunction with other physiological parameters (ISP, SCPP, sPRx, fever). Metabolites most commonly monitored include glucose, lactate, pyruvate, glycerol and glutamate, the lactate pyruvate ratio (LPR) is calculated by Lactate x 1,000 / pyruvate. In TBI there is no absolute consensus on normal or abnormal values of microdialysate but threshold levels have been suggested to indicate when the brain is at risk[43]. Glucose is the main substrate for CNS metabolism, in brain injury periods of low glucose (defined as both <0.2mM and <0.8mM)[41,67-69] and high glucose[70] are associated with unfavourable outcomes. LPR is a marker of cellular redox status, it can be increased from failure of oxygen delivery (low pyruvate, ischaemic hypoxia) or from non-ischaemic causes (normal or high pyruvate - mitochondrial dysfunction)[43]. In TBI high LPR (>25) is associated with poor outcomes[69,70]. Glutamate is an excitatory neurotransmitter, excess release is seen in cerebral ischaemia and

in TBI higher levels are associated with poorer clinical outcomes[71]. Glycerol is a maker of cell membrane breakdown and oxidative stress, in TBI it has limited specificity as systemic levels affect cerebral levels. There is no evidence to link higher brain glycerol with worse outcomes in TBI. The measurement of glucose, lactate and LPR is considered more useful than glutamate and glycerol[43]. Microdialysis is a focal technique which limits its utility in TBI where there are often large areas of heterogenous injury that may be missed by a distant catheter[70].

In TSCI monitoring injury site metabolites with surface microdialysis has shown comparable injury states with TBI: ischaemic, infarcted, hyperperfused and near normal in human[63] and porcine models[72]. Injury site metabolism is monitored with a microdialysis catheter placed sub-durally at the injury site. The microdialysis catheter is perfused with isotonic CNS perfusion fluid at a constant rate of 0.3 μL / minute. The transit time between the semi-permeable catheter membrane and the collecting vial is 24 minutes. Microdialysis vials are changed hourly, stored at 4 ^{o}C, batch analysed at 24 hours for concentrations of glucose, lactate, pyruvate, glycerol and glutamate. Vials are stored long term at -80^{o}C and can be analysed for other molecules that can cross the microdialysis membrane (i.e. <20kDa) such as inflammatory cytokines. Surface metabolite values correlate with intraparenchymal values (correlation coefficient of 0.56 - 0.91) but not with metabolites in the CSF below the injury (correlation coefficient of 0.02-0.5)[73] which is consistent with animal studies comparing surface with intraparenchymal microdialysis in the heart[74], liver[75] and small bowel[76]. Normal metabolites in the spinal cord are not known but our group has found injury site responses are largely patient specific and enhanced neurological outcomes correlated with more normal metabolic states[64].

1.4 Aims of Thesis

1. To determine whether clinical and radiological biomarkers can be used to predict ISP and $SCPP_{opt}$ as a robust alternative to spinal cord pressure monitoring in TSCI.

2. To determine whether monitoring caudal to the injury site in the lumbar CSF space provides comparable information to monitoring at the injury site in TSCI.

3. To determine whether fluctuations in physiological and metabolic parameters in patients with incomplete TSCI monitored from the injury site are causatively linked to changes in limb power.

4. To assess the effects of local hypothermia on injury site physiology, metabolism and inflammation in TSCI.

5. To determine whether, after severe acute TSCI bladder function is influenced by fluctuations in physiological and metabolic parameters monitored from the injury site.

6. To determine whether, after severe acute TSCI anal sphincter function is influenced by fluctuations in physiological and metabolic parameters monitored from the injury site

2. CHAPTER 1: Predictors of intraspinal pressure and optimal cord perfusion pressure after traumatic spinal cord injury

2.1 Introduction

ISP and $SCPP_{opt}$ vary significantly between patients[47,59,62], so adopting the AANS MAP target of 85 – 95 mmHg could lead to periods where the spinal cord is sub-optimally perfused. Therefore, to meaningfully manage TSCI, the ISP and SCPP parameters are essential. Though the methods of monitoring ISP and SCPP from the injury site after TSCI are safe[56] and allow individualised management of TSCI patients, but they are invasive and not widely used. We, therefore, asked whether there are MRI or clinical biomarkers that could be used to predict ISP or $SCPP_{opt}$. Such biomarkers would be a major advance in the management of TSCI by allowing clinicians to estimate non-invasively ISP and $SCPP_{opt}$. This is analogous to estimating ICP in TBI patients by looking at clinical and CT biomarkers e.g. dilated pupil, collapsed third ventricle, uncal herniation, effaced basal cisterns.

2.2 Aim

To determine whether clinical and radiological biomarkers can be used to predict ISP and $SCPP_{opt}$ as a robust alternative to spinal cord pressure monitoring in TSCI.

2.3 Methods

2.3.1 Institutional approvals

Patients were recruited as part of the ISCoPE) study which is registered with ClinicalTrials.gov as NCT02721615. Approvals for ISCoPE 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).

2.3.2 Patient recruitment

We included all TSCI patients recruited to ISCoPE between October 2010 and December 2017 i.e. severe (ASIA AIS A – C) acute (within 72 hours of injury) TSCI patients who require surgical fixation from three major trauma centres in the South East of the UK (St Georges Hospital, Kings College Hospital and the Royal Sussex County Hospital). See Table 2 for inclusion/exclusion criteria. Patients are transferred to the NICU at St Georges Hospital where a senior neurosurgical registrar examines the patient and completes an AIS assessment.

Patients that meet inclusion criteria (or their next of kin) are approached about the trial and a Patient Information Sheet (PIS) is provided and all questions answered. If the patient wishes to proceed a consent form is signed. See Appendix 1 for copies of ISCoPE trial patient information sheets and consent forms.

Recruitment to the ISCoPE trial faces the challenge of recruiting critically ill patients to time critical clinical research in the acute phase of clinical illness. Patients who are admitted to an intensive care environment may lack decisional capacity due to the nature of their illness (pain, trauma, shock) or due to the need for sedation[77]. Patients with spinal cord injuries wish for cure and experimental treatments or 'research' can be falsely appealing in this setting. The ISCoPE trial acknowledges these difficulties and is subject to rigourous ethical scrutiny by the St George's, University of London Joint Research Office and the National Research Ethics Service London–St Giles Committee (No. 10/H0807/23). Respect for patient autonomy and ethical principles are maintained. The team involved with the ISCoPE trial include numerous clinicians who are all involved in ensuring that patients recruited to the study are fully informed and have capacity to consent to clinical research. Patients are reviewed by the study team on multiple occasions during the period of monitoring and at follow up and capacity checks/ongoing verbal consent to research are performed at regular intervals.

2.3.3 Surgery and probe insertion

Surgical decompression and spinal instrumentation were performed based on patient requirements and surgical preference. All patients underwent a posterior approach to the spine +/- spinal instrumentation +/- bony posterior decompression/laminectomy. Some patients with cervical injuries also require anterior stabilisation +/- decompression.

To insert the pressure probe into the sub-dural space an operative microscope was used. A dural incision was made in the midline with a '15' blade scalpel and sharp hook one level caudal to the injury, the arachnoid opened and CSF seen. The ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) was calibrated and then inserted into the subdural space and advanced cranially so its tip sits level with the injury site and place of maximal cord swelling. The Codman probe was chosen for its reliability and length (75cm) which allows it to extend to the monitoring station at patients bedside. The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). Some patients also had a duroplasty which involved a midline longitudinal dural incision performed under the microscope with subsequent placement of elliptical dural patch (Durepair®; Medtronic;

Hertfordshire UK) secured in place with sutures to expand the intradural space[53]. A wound drain was placed over the dura and tunnelled into the paraspinal muscles and left on gravity settings. The surgical wound is closed with vicryl sutures in layers and nylon sutures close the skin. The pressure probe and drain are held in place with silk sutures with a purse string suture around the exit points to minimise the risks of CSF leak. The wound is dressed with a self-adhesive dressing (Mepore® Molnlycke Healthcare) and an anti-microbial incise drape (Ioban® 3M Healthcare) is applied over the wound and probes. Figure 2, 3 illustrate.

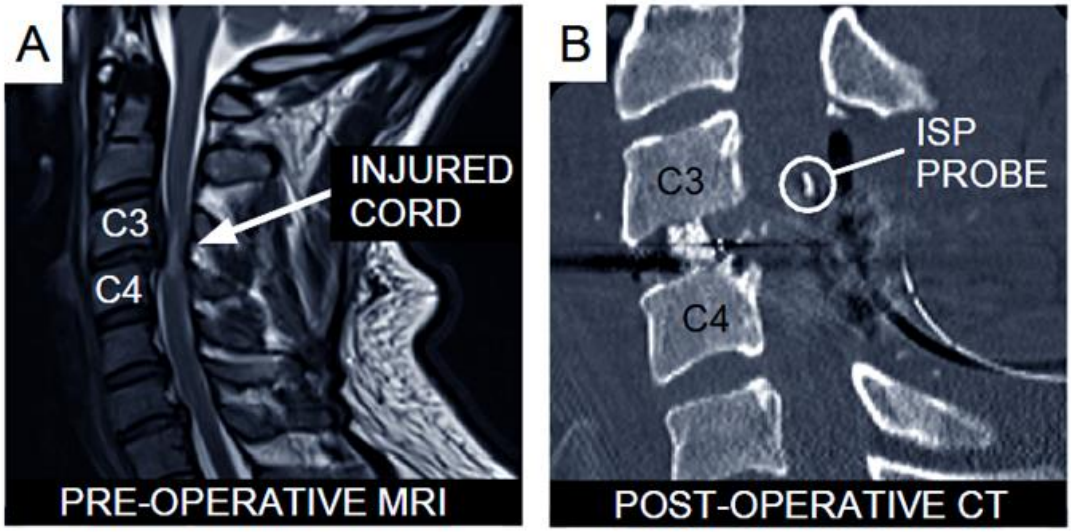


Fig. 3. ISP monitoring technique. A. Preoperative MRI of a 37-year-old male patient with TSCI AIS grade C at C3/4. **B.** Postoperative CT of same patient showing C3/4 anterior cervical cage, posterior C3/4 laminectomies and ISP probe (circled).

2.3.4 ICU bedside ISP monitoring

The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.7.3.5 (AD Instruments, Oxford, UK). Arterial blood pressure was recorded from a radial artery catheter, kept at the level of the phlebostatic axis, connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz for up to 7 days following surgery.

2.3.5 ICU Clinical management

Patients are transferred back to the NICU following surgery and remain there for the duration of spinal monitoring and clinical need. Patients are nursed in bed on a pressure reliving mattress on their side (where possible) to take pressure off the laminectomy site. Antibiotic prophylaxis is given for 48 hours after surgery with vancomycin and gentamicin, this is the standard regimen given to patients following instrumented spinal fusion. Chemical (sub-cutaneous low molecular weight heparin given 24 hours post-surgery and held for 12 hours pre and post probe removal) and mechanical (compression stockings and mechanical intermittent calf compression) venous thromboprophylaxis were administered.

Ventilatory support is managed by the NICU team. Blood pressure targets are set on a daily basis to cover a range of spinal cord perfusion pressures. Ionotropic/vasopressor support was given mostly with intravenous nor-adrenaline (mixed as 4 mg / 50 ml, 5 % dextrose) through a central venous line, or whilst central access was being established intravenous metaraminol (mixed as10 mg / 20 ml, 0.9 % saline) via a peripheral venous line. The ICU nurses titrate and record the hourly doses on the ICU chart.

All patients are reviewed and examined daily by the research team, any complications or concerns are recorded and actioned immediately. Daily blood tests are performed including full blood count, renal and liver profile, cardiac enzymes, c-reactive protein and clotting function.

2.3.6 Imaging

All patients have a CT scan and MRI scan on admission prior to surgery. Post-operatively patients have a CT scan to check the position of the spinal instrumentation and probes. An MRI scan is performed at 2-6 weeks and 6-12 months post injury.

2.3.7 Clinical Assessments

Neurological assessment with the International Standards for Neurological Classification for Spinal Cord Injury (ISNCSCI) was performed by a neurosurgeon trained in the assessment on admission, prior to discharge to the spinal rehabilitation unit and at outpatient appointments which occur between 3-18 months following surgery (see Appendix 1 for example form.)

2.3.8 Signal analysis.

Data was cleaned using Labchart v.8 (AD Instruments, Oxford, UK). This involves removing signal artefact e.g. large fluctuations in ISP which might occur during a patients repositioning or unphysiological blood pressure traces which might occur when the arterial line is flushed. Data was analysed using Intensive Care Monitoring Plus (ICM+) (www.neurosurg.cam.ac.uk/icmplus), a program created for multi-modal neuro-intensive care monitoring and ICP waveform analysis[78](see Figure 4). We processed signals to compute SCPP (as ISP minus MAP) and sPRx (as the running correlation coefficient over 5 minute windows between ISP and MAP).

Microsoft Excel was used to produce sPRx *vs.* SCPP plots and estimate the $SCPP_{opt}$ as the minimum of the curve for the first 24 hours of patient monitoring (see Figure 5). We computed average ISP and SCPP over the first 24 hours. The ISP monitoring setup is illustrated in Fig. 3. We defined ISP as high if >20mmHg and normal if <20mmHg based on our previous ISP analysis in patients with TSCI versus controls[47]. We chose the first 24 hours of ISP monitoring, because this was the closest to the timing of the pre-operative MRI that was used to determine the imaging features. Also, because ISP was monitored for varying durations (1 – 7 d), we only included the first 24 h after surgical decompression to standardise the duration of monitoring.

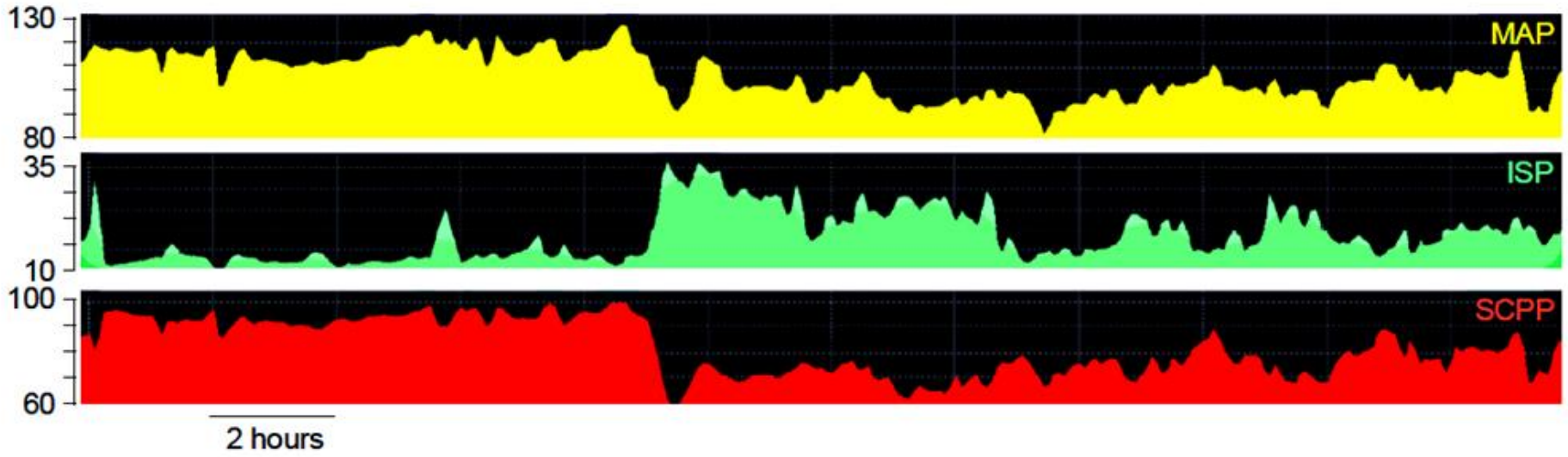


Fig. 4. ICM + Signals. Example ICM+ trace from 37-year-old male patient with TSCI AIS grade C at C3/4 showing mean arterial pressure (MAP), intraspinal pressure (ISP) and spinal cord perfusion pressure (SCPP) signals.

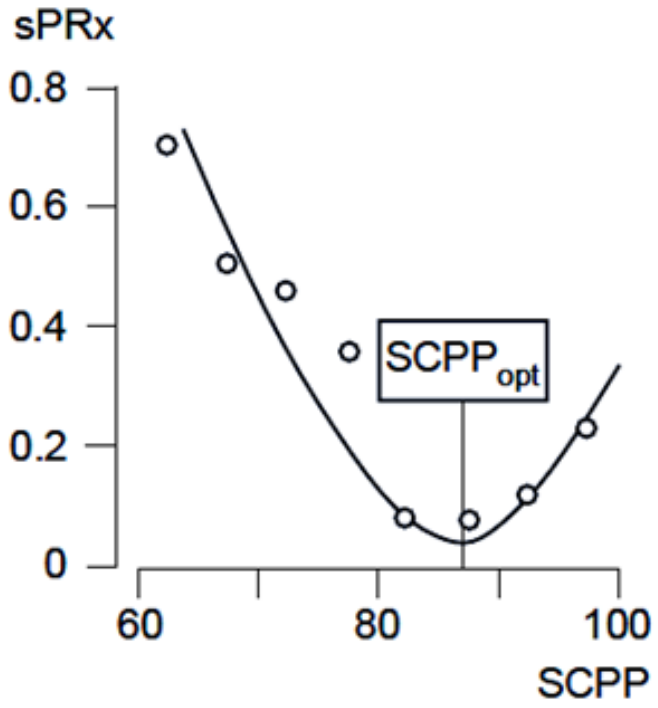


Fig. 5. Optimal Spinal Cord Perfusion Pressure. sPRx *vs.* SCPP plot to determine $SCPP_{opt}$. from the first 24 hours of monitoring from a 37-year-old male patient with TSCI AIS grade C at C3/4.

2.3.9 Biomarkers for predicting ISP and $SCPP_{opt}$

Biomarkers were divided into patient, injury, management and pre-operative MRI related factors. Information about the variables was collected from patient notes, operative records and pre-operative MRI scans without knowledge of the ISP, SCPP and $SCPP_{opt}$ data.

28 factors were collected for each patient. Patient-related factors (Table 4) (age, sex, smoking, hypertension, diabetes, history of excess alcohol consumption, body mass index), injury-related factors (Table 5) (level of injury i.e. cervical / thoracic / conus, AIS grade on admission, primary survey MAP), management-related factors from surgical and anaesthetic charts (Table 6) (hours from injury to surgery, duration of surgery, intraoperative blood loss, extent of decompression i.e. spinal alignment / spinal alignment + laminectomy / spinal alignment + laminectomy + duroplasty, surgical approach i.e. posterior / anterior + posterior, mean MAP during surgery) and pre-operative MRI-related factors (Table 7) (epidural hematoma, intraparenchymal hematoma, cord transection, number of sagittal intervertebral levels with complete loss of cerebrospinal fluid signal, injured level average spinal cord occupation rate (mid sagittal T2 cord/dural sac diameter, calculated at each vertebral and intravertebral level throughout injury site and averaged[79]), maximum spinal cord compression MSCC (calculated from T2 mid sagittal cord diameter at compression site/average cord diameter at closest non compressed region above and below the level of injury[80,81]) (Fig. 6), maximum canal compromise MCC (calculated from T2 mid sagittal canal diameter at compression site/average canal diameter at closest non compressed region above and below the level of injury[80]) (Fig. 6), longitudinal extent of T2 signal abnormality[82] (Fig. 7), average normal cord in injured cord (mid sagittal T2 cord diameter – signal change diameter, calculated at the injury level and averaged, based on 'space available for cord'[83]) (Fig. 7), average % cord signal change at injured level (mid-sagittal T2 diameter of cord signal change / cord diameter x100 based on 'spinal cord occupation ratio'[79]) (Fig. 7), Brain And Spinal injury Center score BASIC[84] (Fig. 8) and sagittal grade (based on mid-sagittal T2 signal change pattern, grade 1-4[85]) (Fig. 9)).

Table 4. Definitions of Patient Related Factors assessed for each TSCI patient.

Patient related factors.	
Age	
Sex	
Smoking	Any history of smoking, either past or present
Hypertension	Pre-existing diagnosis of hypertension, identified in medical / GP records
Diabetes Mellitus	Any diagnosis of type ½ diabetes mellitus identified in medical / GP records
Excess alcohol consumption	As recorded in medical / GP records
Body Mass Index	Patients weight on admission to hospital (kg)/height (metres)^2

Table 5. Definitions of Injury Related Factors assessed for each TSCI patient.

Injury Related Factors.	
Level of Injury	Classified as: cervical (C1-7), thoracic (T1-T11) and conus (T12-L1)
AIS grade on admission	American spinal injury association Impairment Scale[86] assessed by neurosurgical team
Primary Survey Mean Arterial Blood Pressure (MAP)	The lowest mean arterial pressure (calculated by 1/3 systolic blood pressure + 2/3 diastolic blood pressure) recorded in trauma admission notes.

Table 6. Definitions of Management Related Factors assessed for each TSCI patient

Management Related Factors.	
Hours from injury to surgery	
Duration of surgery	As documented in operative notes
Intraoperative Haemorrhage	Blood loss recorded from operative notes. Estimated circulating volume based on estimation of 75mls/kg. Blood loss as a percentage of circulating volume computed. Grade of intra operative haemorrhage assigned (Grade 1 <15%, Grade 2 15- 30%, Grade 3 30-40%, Grade 4 >40%)[87]
Extent of decompression	Spinal alignment / Spinal alignment and laminectomy / Spinal alignment and laminectomy and duroplasty
Surgical Approach	Posterior / Posterior and anterior
Mean MAP during surgery	Average of the mean arterial pressures (calculated by 1/3 systolic blood pressure + 2/3 diastolic blood pressure) recorded in anaesthetic operative notes.

Table 7. Definitions of Pre-operative MRI Related Factors assessed for each TSCI patient.

Pre-operative MRI related factors	
Epidural haematoma	Assessed on T1 and T2 weighted sagittal and axial images
Intra-parenchymal haematoma	Assessed on T1 and T2 weighted sagittal and axial images
Cord transection	Assess on T2 weighted sagittal imaging and deemed present if cord completely obliterated with complete translocation of anterior and posterior cord margins cranial and caudal to injury.
Number of sagittal intervertebral levels with complete loss of cerebrospinal fluid (CSF) signal	Graded qualitatively on T2 weighted mid.sagittal imaging. Pattern defined as normal (CSF visible around the spinal cord), partial (partial effacement of CSF around the spinal cord) and complete (total loss of CSF signal around the spinal cord) (Figure 7)
Injured Level Average Spinal Cord Occupation Rate (SCOR)	Mid Sagittal Cord Diameter / Mid sagittal dural sac diameter *100 Calculated at each vertebral and intravertebral level throughout the region of spinal injury. (Figure 6)
BASIC Grade	Grade 0 – no cord signal abnormality, Grade 1 – T2 hyperintensity confined to grey matter, Grade 2 – intrameduallary T2 hyperintensity extends beyond grey matter margins involving some but not all of the white matter, Grade 3 – T2 hyperintensity involving grey matter and all of the white matter, Grade 4 – T2 signal hyperintensity with area of hypointensity representing haemorrhage in the cord (Figure 8)
Sagittal Grade	Grade 1 – no signal change, Grade 2 single level T2 hyperintensity, Grade 3 >1 vertebral level T2 signal hyperintensity, Grade 4 T2 signal hyperintensity with areas of hypointensity representing haemorrhage (Figure 9)
Longitudinal extent of T2 weighted cord signal abnormality	Measured in mm on mid sagittal T2 weighted imaging (Figure 7)
Maximum Spinal Cord Compression (MSCC)	Diameter of spinal cord at maximal compromise / average diameter of spinal cord above & below x100% (Figure 6)
Maximal Canal Compromise (MCC)	Diameter of canal at maximal compromise / average diameter of canal above & below injury x100% (Figure 6)
Average normal Cord in injured cord	Mid Sagittal T2 Cord diameter – Mid Signal change diameter Based on ‘space available for cord’ calculation and developed for this analysis (Figure 7)
Percentage Injured Cord Signal Change	(mid sagittal diameter of cord signal change / mid sagittal cord diameter) x100 Based on ‘spinal cord occupation ratio’ and developed for this analysis. (Figure 7)

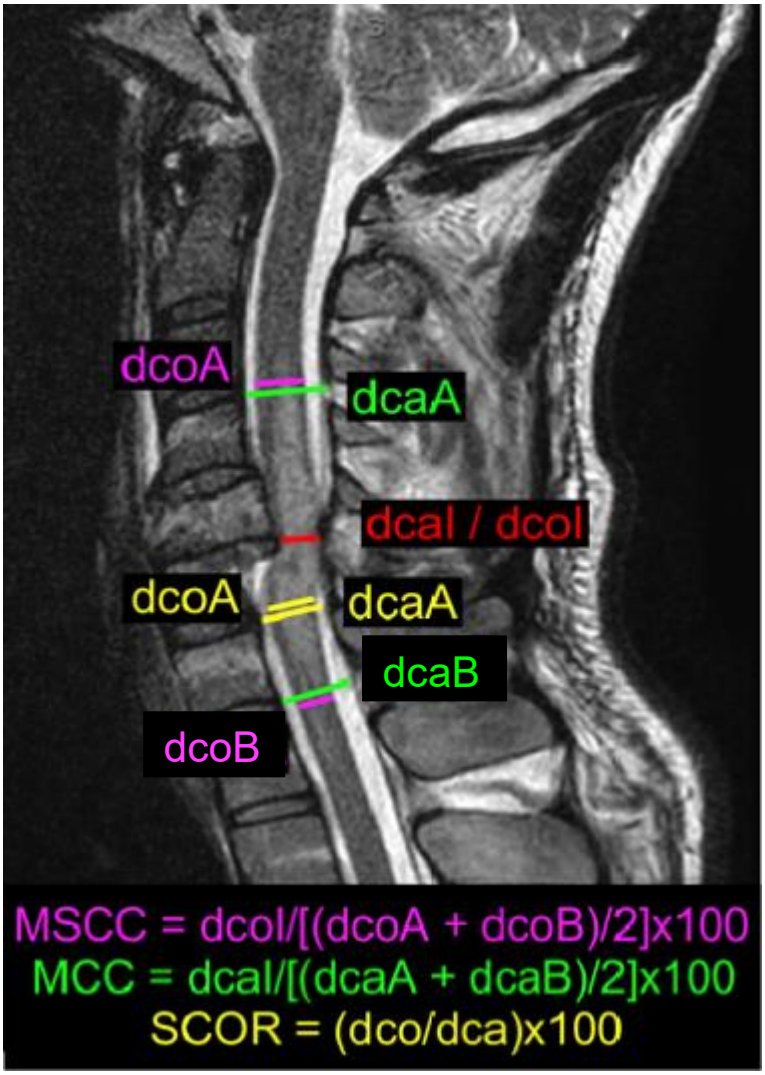


Fig. 6. Spinal cord injury MRI grading systems: Maximal Spinal Cord Compression (MSCC), Maximal Canal Compression (MCC) and Spinal Cord Occupation Ratio (SCOR). dca = canal diameter, dcaA = canal diameter above the injury, dcaB = canal diameter below the injury, dcaI = canal diameter at injury level, dco = spinal cord diameter, dcoA = spinal cord diameter above the injury, dcoB = spinal cord diameter below the injury, dcoI = spinal cord diameter at injury level

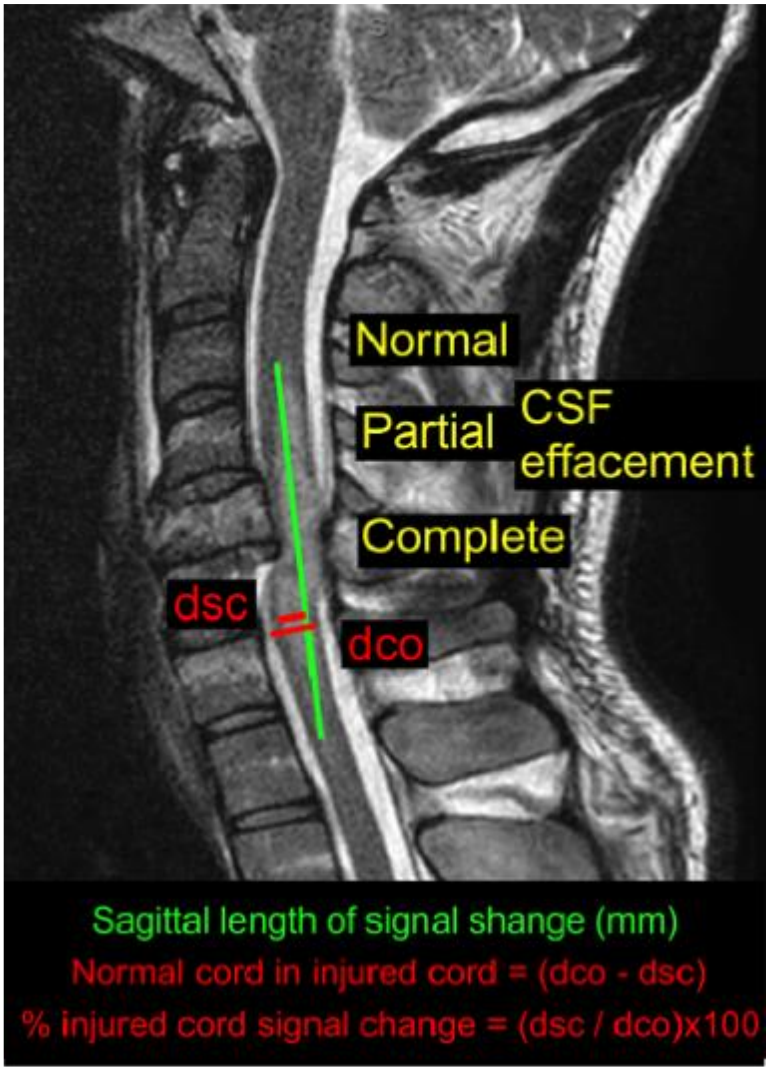


Fig. 7. Spinal cord injury MRI grading systems: CSF effacement around spinal cord, Sagittal length of T2 signal change, Normal cord in injured cord, Percentage of cord signal change. dco = spinal cord diameter, dsc= diameter of cord signal change

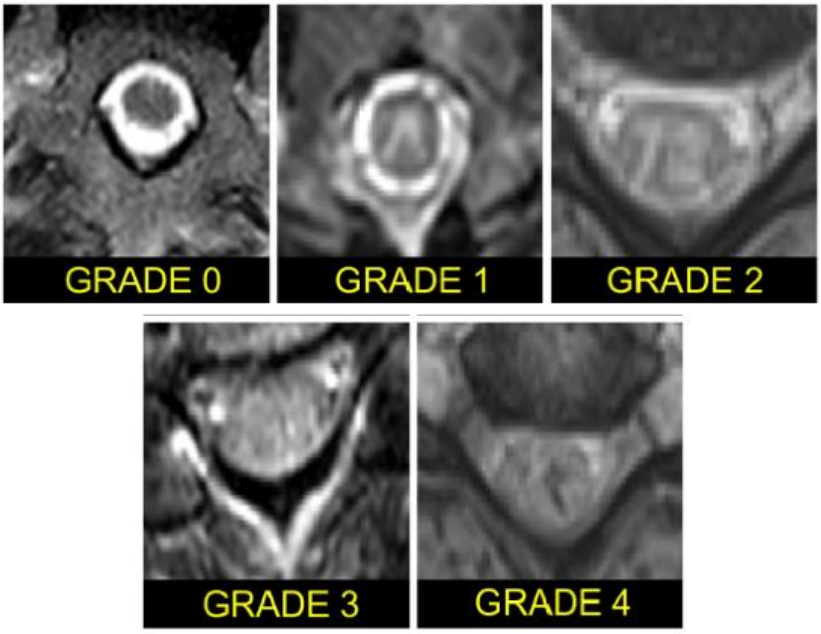


Fig. 8. Spinal cord injury MRI grading systems: BASIC Grade Axial T2 Weighted Imaging. Grade 0: No signal change, Grade 1: Hyperintensity confined to grey matter, Grade 2: Hyperintensity spreads beyond grey matter to involve some but not all white matter, Grade 3: Hyperintensity involves whole axial cord, Grade 4: Area of hypointensity indicative of haemorrhage

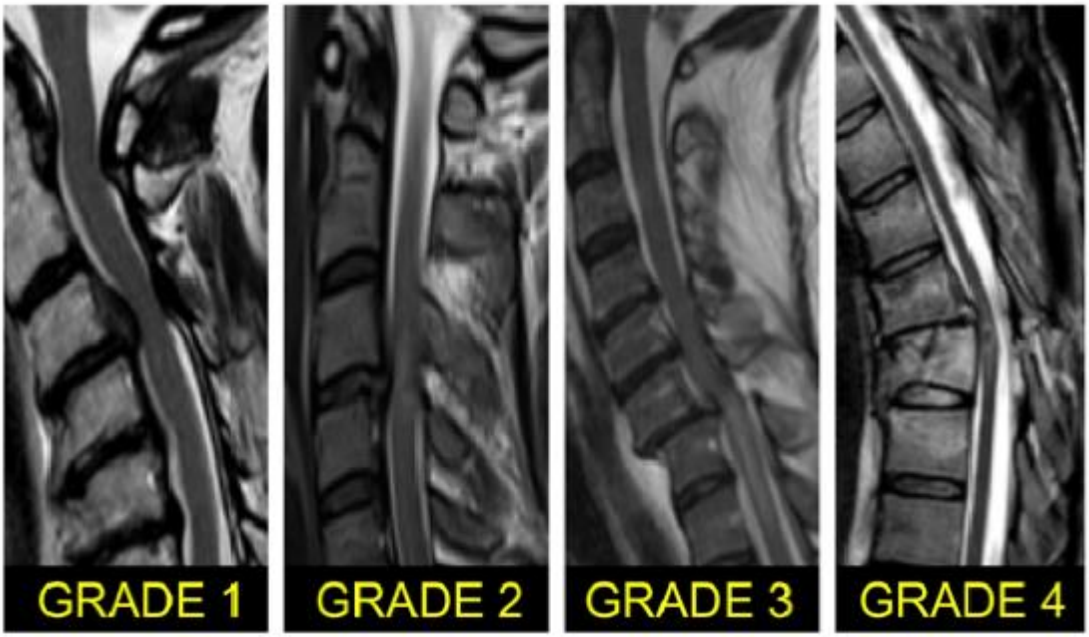


Fig. 9. Spinal cord injury MRI grading systems: Sagittal Grade. Grade 1: No cord signal change, Grade 2: T2 hyperintensity confined to only 1vertebral body, Grade 3: T2 hyperintensity spanning >1 vertebral body, Grade 4: Area of hypointensity indicative of haematoma

2.3.10 Statistical analysis

Analyses were done with XLStat Biomed (v.18.07, Addinsoft, New York, USA) with the help of Dr Saadoun. For univariate analyses, we used Mann-Whitney-U or Wilcoxon rank sum with post-hoc Dunn to investigate differences in ISP or $SCPP_{opt}$ between the factors. In the multi-variate logistic regression analysis for ISP, we chose the best model based on likelihood by including factors with $P<0.1$ and removing factors already in the model if $P>0.2$ when a new factor is added. In the multi-variate ordinal logistic regression analysis for $SCPP_{opt}$, we chose a stepwise forward model based on the Wald criterion; the model enters factors with $P<0.1$ and removes factors already in the model if $P>0.2$ when a new factor is added. Correlations between two factors were quantified with the Spearman rank correlation coefficient "ρ".

2.4 Results

2.4.1 Patient characteristics

Table 8 summarizes details of the 64 patients. Most are young, with 80 % less than 60 years old. Males outnumber females by 3.2:1. Cervical TSCIs are more common than thoracic or conus at 52 *vs.* 34 *vs.* 14 %. Most patients had neurologically complete TSCI on admission i.e. 67 % were ASIA grade A. 51 % (34/64) had U-shaped sPRx *vs.* SCPP curves for the first 24 hours after surgery thus allowing $SCPP_{opt}$ to be computed. Mean $SCPP_{opt}$ for all patients was 74 mmHg (range 48–103). 13 % (8/64), all AIS grade A or B, had no U-shaped sPRx *vs.* SCPP curve for the first 24 hours after surgery. The remaining 36 % (22/64) patients appeared to have U-shaped sPRx *vs.* SCPP curves, but the range of SCPPs did not reach the minimum and thus exact $SCPP_{opt}$ could not be calculated.

Table 8. Patient Demographics.

CHARACTERISTIC	VALUE
PATIENTS (total no.)	64
AGE IN YEARS (mean, range)	42 (19-70)
SEX (m:f)	49:15
ADMISSION AIS GRADE (no. of patients A:B:C)	43:8:13
LEVEL OF INJURY (no. of patients ce:th:co)	33:22:9
INJURY TO SURGERY (hours mean, range)	39.27 (9-72)
SURGICAL APPROACH (no. of patients post:ant+post)	54:10
DECOMPRESSION (no. of patients sp-al:sp-al+lami:sp-al+lami+duro)	9:46:9

AIS = American spinal injuries association impairment scale; ant = anterior; ce = cervical; co = conus; duro = duroplasty; f = female; lami = laminectomy; m = male; post = posterior; sp-al = spinal alignment; th = thoracic.

2.4.2 Predictors of mean ISP

In the univariate analysis, only 5/28 characteristics that were examined correlated with ISP. The 5 characteristics that were associated with higher mean ISP were: lower level of injury (Fig. 10), younger age (Fig. 11), not having a duroplasty (Fig. 12), more intraoperative haemorrhage (Fig. 13) and no history of excess alcohol consumption (Fig. 14). None of the MRI characteristics that we investigated correlated with mean ISP.

A multi-variate logistic regression model based on these 5 characteristics could classify ISP as normal (<20 mmHg) *vs.* high (≥20 mmHg) with 73 % accuracy (Table 9). In this multi-variate model, which takes into account interactions between the characteristics, no excess alcohol consumption (odds ratio 9.6), lower injury level (odds ratio cervical to thoracic to conus 3.3), no expansion duroplasty (odds ratio 3.2) and younger age (odds ratio per decade 1.5) remained significant predictors of high ISP. Intraoperative haemorrhage was no longer significant because of collinearity with the level of injury (ρ=0.59), i.e. more haemorrhage when operating in the thoracolumbar spine.

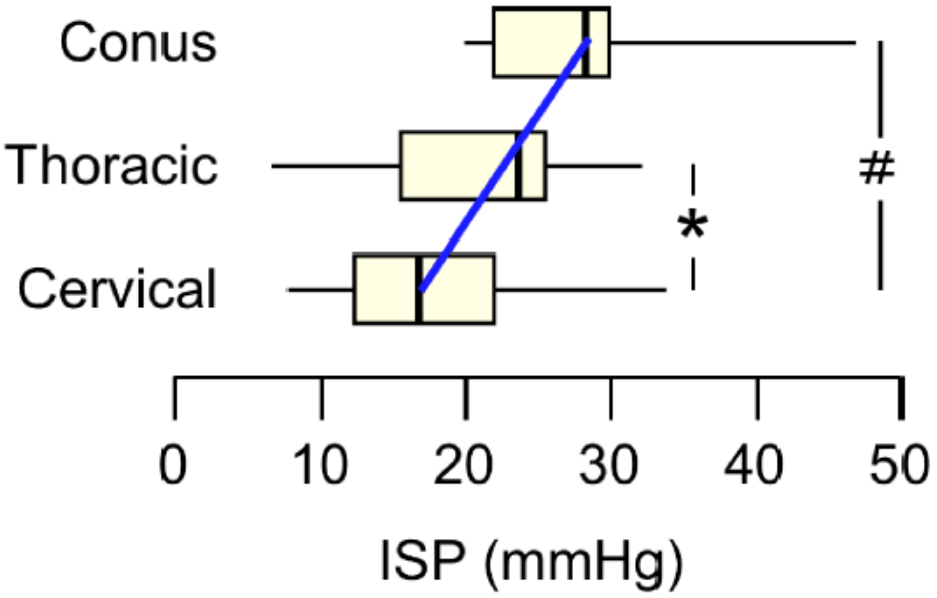


Fig. 10. ISP *versus* Level of spinal cord injury. Grouped as cervical, thoracic, conus. Box plots show median, upper and lower quartiles, minimum and maximum. Gray trend-line. $P<$ 0.05*, 0.005$^{\#}$.

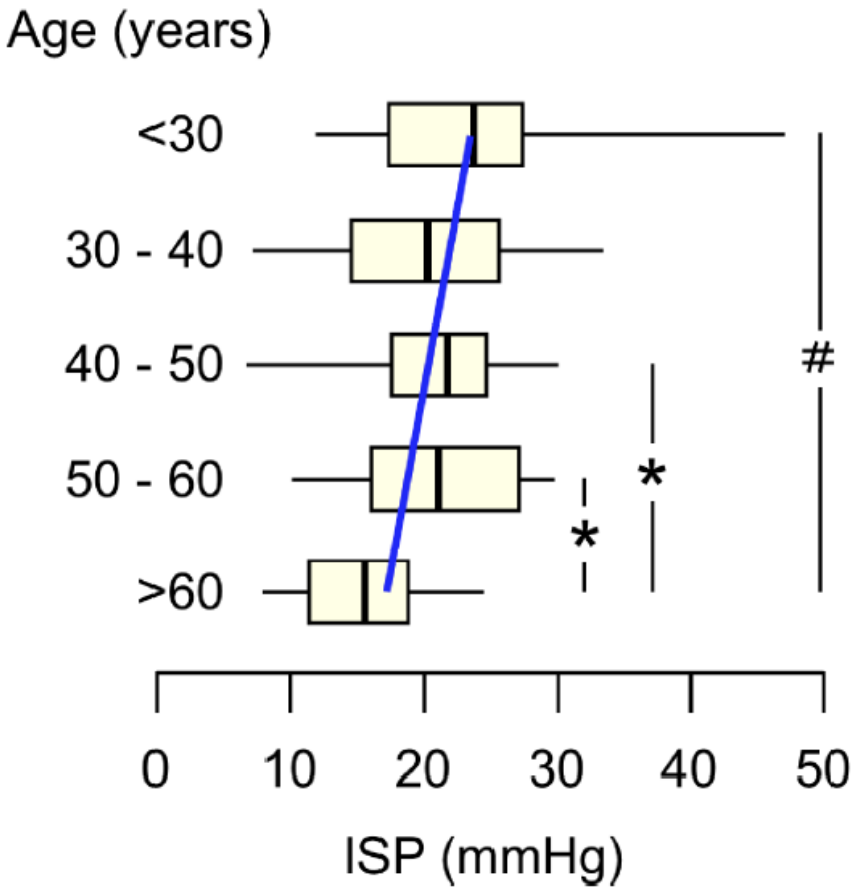


Fig. 11. ISP *versus* Age. Grouped in years (<30, 30 – 40, 40 – 50, 50 – 60, >60). Box plots show median, upper and lower quartiles, minimum and maximum. Gray trend-line. $P< 0.05$*, $0.005^{\#}$.

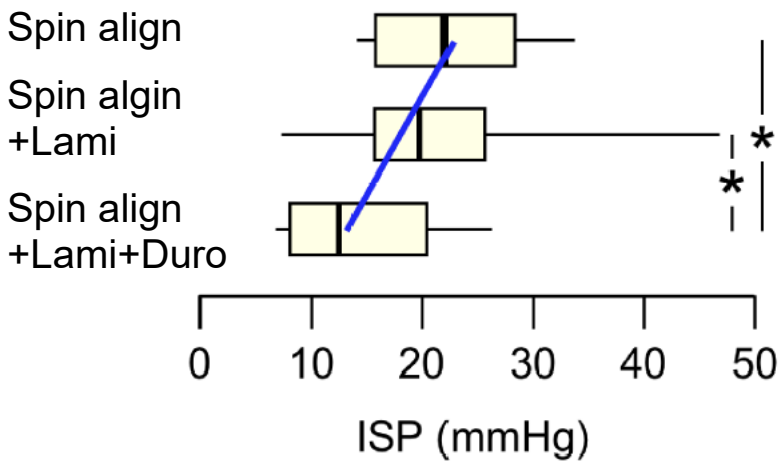


Fig. 12. ISP *versus* Extent of decompression. Grouped as Spinal Alignment, Spinal Alignment + Laminectomy, Spinal Alignment + Laminectomy + Duroplasty. Box plots show median, upper and lower quartiles, minimum and maximum. Grey trend-line. $P < 0.05$*

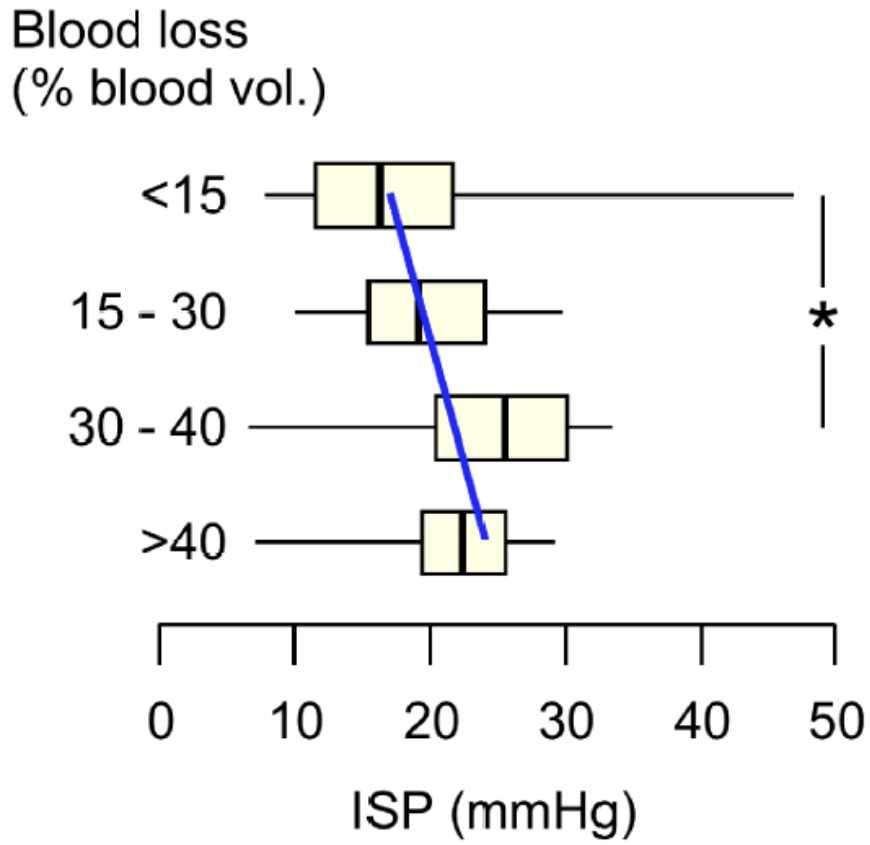


Fig. 13. ISP *versus* Intraoperative blood loss. Grouped as % of total blood volume (<15 %, 15 – 30 %, 30 – 40 %, >40 %). Box plots show median, upper and lower quartiles, minimum and maximum. Gray trend-line. $P < 0.05$*

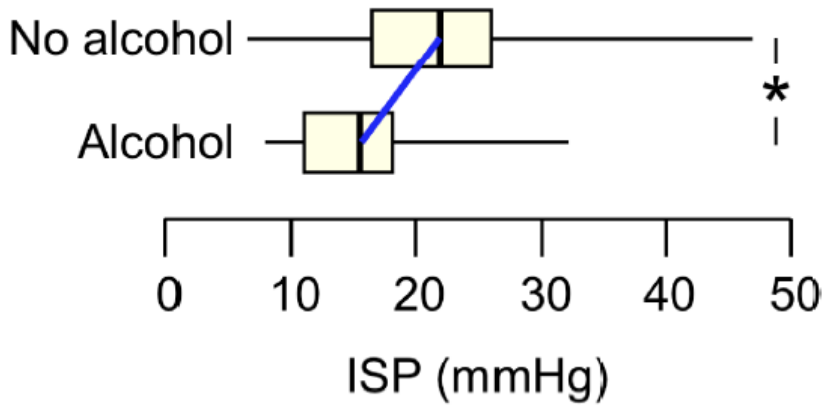


Fig. 14. ISP *versus* Excess alcohol consumption. Box plots show median, upper and lower quartiles, minimum and maximum. Gray trend-line. $P < 0.05$*

Table 9. Confusion matrix of multi-variate logistic regression model for predicting mean ISP for the first 24 h after surgery.

	NORMAL ISP (PREDICTED)	HIGH ISP (PREDICTED)	TOTAL	% CORRECT
NORMAL ISP (ACTUAL)	25	8	33	77.8
HIGH ISP (ACTUAL)	9	21	30	70.0
TOTAL	34	29	63*	73.0

Classifier based on five factors: Age group (<30, 30-40, 40-50, 50-60, >60), alcohol consumption (yes/no), spinal level of injury (cervical/thoracic/conus), extent of decompression (spinal alignement, spinal alignement + laminectomy, spinal alignment + laminectomy + duroplasty), intraoperative haemorrhage (as % of circulating volume: <15, 15-30, 30-40, >40). Area under receiver operated characteristic curve = 0.84. To identify normal ISP: Positive predictive value =73%, Negative predictive value = 76%,. To identify high ISP: Positive predictive value = 72%, Negative predictive value = 74%.

**1/64 patients omitted because of missing intraoperative data*

2.4.3 Predictors of mean 24 h $SCPP_{opt}$

Each patient was assigned to a $SCPP_{opt}$ group as low (<60 mmHg), low-medium (60–70 mmHg), high-medium (70–80 mmHg) or high (>80 mmHg). This allowed us to analyse 51 patients in total, by including not only the 34 patients who had exact $SCPP_{opt}$, but also 8 patients with $SCPP_{opt}$>80 mmHg and 9 patients with $SCPP_{opt}$<60 mmHg. In univariate analysis, only 2/29 factors that were examined correlated with lower mean $SCPP_{opt}$: higher mean 24 h ISP (Fig. 15) and lower spinal level of injury (Fig. 16). These two factors (level of spinal cord injury, mean 24 h ISP) were correlated (ρ=0.49). Like ISP, no MRI factors correlated with mean $SCPP_{opt}$. An ordinal logistic regression model based on these two factors could classify $SCPP_{opt}$ as low, low-medium, high-medium or high with only 42 % accuracy (Table 10).

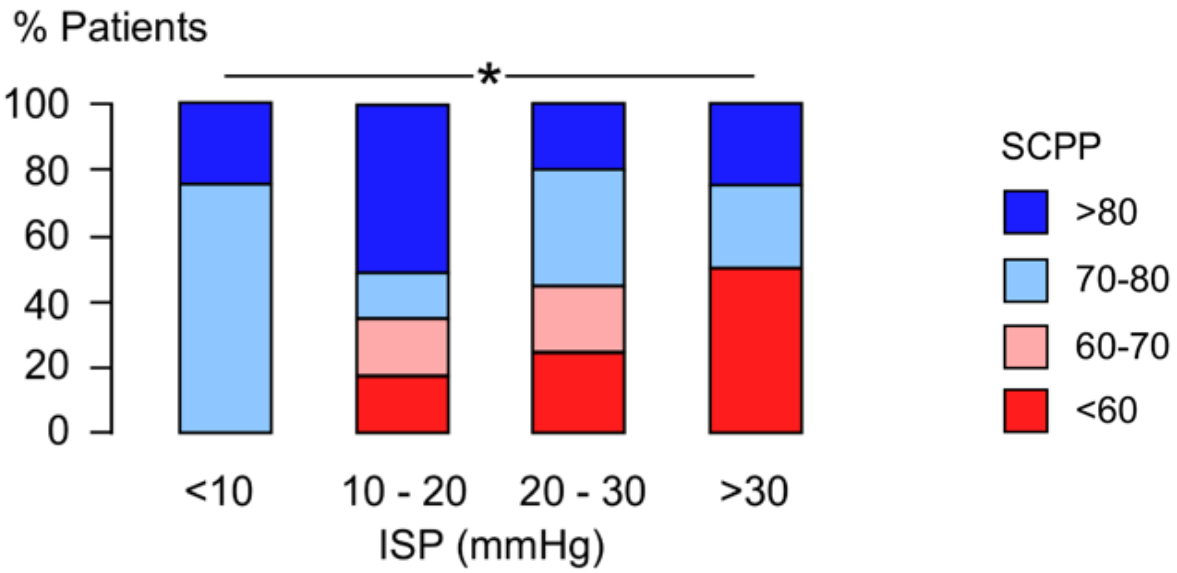


Fig. 15. ISP correlation with $SCPP_{opt}$. Mean ISP group (<10, 10–20, 20–30, >30 mmHg). $SCPP_{opt}$ grouped as <60, 60–70, 70–80, >80 mmHg. $P< 0.05$*.

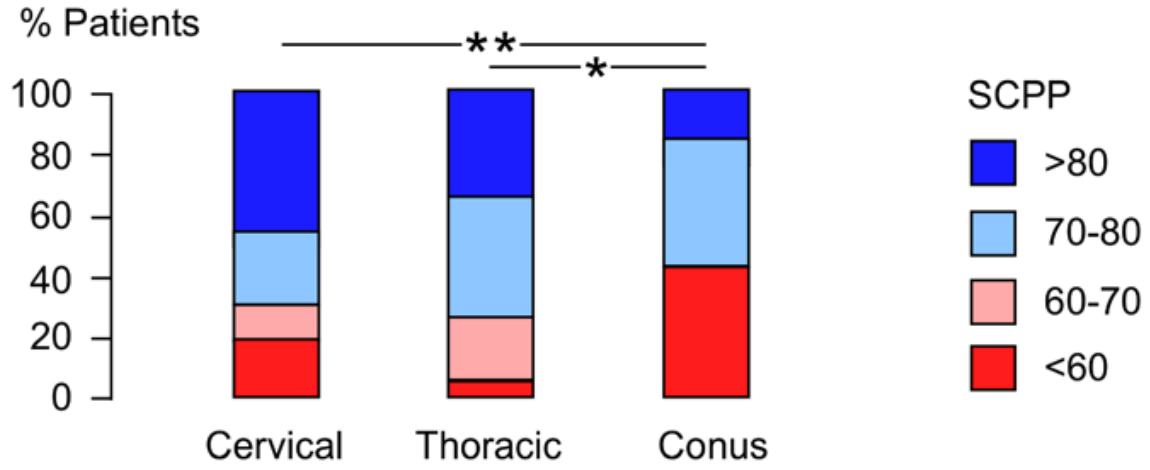


Fig. 16. Level of spinal cord injury (cervical, thoracic, conus) correlation with $SCPP_{opt}$. $SCPP_{opt}$ grouped as <60, 60–70, 70–80, >80 mmHg. *P*< 0.05*, 0.01**.

Table 10. Confusion matrix of multi-variate ordinal logistic regression model for predicting $SCPP_{opt}$ for the first 24 h after surgery.

$SCPP_{opt}$ mmHg		**PREDICTED**					
		<60	**60–70**	**70–80**	**>80**	**TOTAL**	**% CORRECT**
ACTUAL	**<60**	4	0	1	5	10	40.0
	60–70	3	0	3	3	9	0.0
	70–80	1	0	6	7	14	42.9
	>80	1	0	2	15	18	83.3
TOTAL		8	0	6	37	51*	41.6

*Classifier based on two factors: Mean24 h and spinal level of injury (cervical/thoracic/conus).*13/64 patients omitted because $SCPP_{opt}$ could not be binned into one of these groups (<60, 60-70, 70-80, >80). To identify SCPPopt <60: Positive predictive value = 44%, Negative predictive value = 85%. To identify SCPPopt 60-70: Positive predictive value = NAN, Negative predictive value = 82%. To identify SCPPopt 70-80: Positive predictive value = 50%, Negative predictive value = 80%. To identify SCPPopt > 80: Positive predictive value = 50%, Negative predictive value = 86%*

2.5 Discussion

We showed that, after a TSCI, clinical features may be used to predict whether ISP is elevated, but clinical features cannot accurately predict $SCPP_{opt}$. Risk factors for high ISP include younger age, conus injury, no chronic history of excessive alcohol intake, no duroplasty and large intraoperative blood loss. We also showed that patients with conus injuries and those with high ISP have low $SCPP_{opt}$ and that some patients with severe TSCI have no computable $SCPP_{opt}$. Interestingly, no pre-operative MRI characteristics correlate with ISP or $SCPP_{opt}$.

Clinical features that correlate with ISP may shed light on the pathophysiology of TSCI. The factor that protects the most from elevated ISP is history of excess alcohol consumption documented in the patient notes. The underlying mechanism may be cord atrophy, i.e. more CSF space to accommodate the swollen cord, analogous to TBI where alcohol-related brain atrophy might protect from elevated ICP.[88-90] Expansion duroplasty and the level of injury have comparable protective effect on ISP. We already showed that duroplasty significantly reduces ISP after TSCI by enlarging the CSF space around the injured cord.[53] The higher ISP with conus medullaris injuries is likely related to the reduced CSF space around the conus medullaris compared with the larger CSF space higher up the spine.[91] The next factor that correlates with lower ISP is older age, perhaps because of cord atrophy in older patients, analogous to age-related brain atrophy[92,93] or because spinal cord injuries in older patients are less likely to be from high energy trauma therefore the spinal cord is less likely to swell. Higher ISP in patients with more intraoperative bleeding may be due to the level of TSCI rather than the bleeding *per se*, based on the positive correlation between surgical blood loss and level of TSCI. Alternatively, intraoperative fluid resuscitation may play a role, with larger fluid volumes administered exacerbating the edema at the injury site. The unifying theme here is that ISP after TSCI is determined by the relative dimensions of the cord at the injury site compared with the surrounding CSF space. Larger CSF space (cord atrophy, cervicothoracic injuries, duroplasty) is associated with lower ISP.

We showed that $SCPP_{opt}$ is lower in patients with higher ISP or conus TSCI. Though high SCPP is beneficial by reducing ischemia, these observations suggest that, as the spinal cord becomes more compressed, high SCPP may become detrimental. The mechanism might be blood-pressure induced local steal, a phenomenon whereby increasing the MAP when the cord is swollen causes a "paradoxical" decrease in blood flow at the injury site.[94] Knowledge of $SCPP_{opt}$ is clinically important to reduce secondary cord damage by hypo- or hyper-perfusion. Since clinical features do not accurately predict $SCPP_{opt}$, invasive ISP monitoring

remains the only way of determining $SCPP_{opt}$. A recent study showed that SCPP can be calculated by monitoring CSF pressure using a lumbar catheter and that SCPP measured in this way better correlates with outcome than MAP.[45] Monitoring CSF pressure is less invasive than monitoring ISP. However, the relation between SCPP measured by ISP monitoring *vs.* by lumbar drain is unclear. It is also unclear whether CSF pressure can be used to compute sPRx and $SCPP_{opt}$.

An unanticipated finding is that no MRI features correlated with ISP or $SCPP_{opt}$. This may be because we used pre-operative MRIs, done when the spinal anatomy was abnormal. Surgery restores the normal spinal alignment thus causing major anatomical changes at the injury site. MRI done immediately after surgery may thus be more informative for estimating ISP and $SCPP_{opt}$ than pre-operative MRIs. Earlier studies support the notion pre-operative MRI features only weakly correlate with outcome and, in general, post-operative MRIs are more informative.[95-97] The take home message is that pre-operative MRIs cannot be relied upon to estimate the degree of cord compression or the optimal MAP to target after surgery.

2.6 Conclusions

To conclude, our study supports the notion that ISP is determined by the size of the CSF space surrounding the injured cord. In other words, after TSCI, the cord swells and is compressed by the dura,[98] thus factors that increase the surrounding CSF space may be beneficial.[53] Based on our data, we urge caution when increasing the MAP without knowing the $SCPP_{opt}$ in patients whose injured cord is very compressed, because high SCPP may be detrimental. To date, $SCPP_{opt}$ can only be accurately determined by ISP monitoring.

3. CHAPTER 2: Acute spinal cord injury: monitoring the lumbar cerebrospinal fluid provides limited information about the injury site

3.1 Introduction

Some doctors monitor lumbar cerebrospinal fluid pressure (CSFP) rather than ISP and compute $SCPP_{(csf)}$ as MAP – CSFP rather than $SCPP_{(ISP)}$ as MAP – ISP[44-46]. $SCPP_{(csf)}$ but not CSFP has been shown to correlate with neurological outcomes[45]. Monitoring from the lumbar CSF is achieved by placing a lumbar drain/catheter, which can easily be done in ICU. The lumbar catheter can also be used therapeutically to drain CSF to increase cord perfusion in after TSCI and in patients undergoing aortic aneurysm repair[99-102]. In contrast, monitoring from the injury site requires surgery to expose the dura at the injury site and insert probes intradurally under a microscope. Monitoring from the lumbar CSF compartment is therefore less invasive and easier to accomplish than injury site monitoring.

Results from the ISCoPE study have shown that injury site pressure is distinct from subdural caudal to the injury, due to swelling of the spinal cord against the dura [49] if this is so it would pose problems for lumbar catheter pressure monitoring due to a spinal block causing separate pressure compartments at the injury site and below. I therefore chose to monitor simultaneously from the injury site and from the lumbar CSF space in patients with acute, severe TSCI to define the relationship between CSFP *versus* ISP, $SCPP_{(csf)}$ *versus* $SCPP_{(ISP)}$ and metabolite levels in the lumbar CSF *versus* injury site. I also wanted to determine the effect of draining lumbar CSF on ISP.

3.2 Aim

To determine whether monitoring caudal to the injury site in the lumbar CSF space provides comparable information to monitoring at the injury site in TSCI.

3.3 Methods

3.3.1 Institutional Approvals

Patients were recruited as part of the ISCoPE study. Please see Section 2.3.1 for details of ethical approvals.

3.3.2 Patient recruitment

We recruited TSCI patients who were enrolled into the ISCoPE trial in the period October

2017 – February 2019. See Table 2 for inclusion/exclusion criteria to ISCoPE. See section 2.3.2 for details of recruitment processes.

3.3.3 Clinical examination and imaging

As outlined in section 2.3.6 and 2.3.7 all patients were admitted to the neurosurgical unit at St. George's Hospital and underwent ISNCSCI AIS assessment by a neurosurgical registrar trained in AIS. All patients had CT and MRI imaging of the spine before surgery and within 2 to 6 weeks after surgery. Although I did not find any biomarkers that were able to predict ISP and SCPP[103] I measured the longitudinal extent of T2 cord signal change on the pre-operative MRI to quantitatively represent the amount of spinal cord oedema [82,104].

3.3.4 Probe insertion

As outlined in section 2.3.3 surgical decompression and spinal instrumentation were performed based on patient requirements and surgeon preference. During surgery an ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) and an microdialysis catheter (CMA61: CMA microdialysis AB, Solna, Sweden) were placed intradurally on the surface of the injured cord at the site of maximal cord swelling. The CMA microdialysis 61 catheter (most commonly used for hepatic microdialysis) was originally chosen for the trial for its catheter length (to allow tunnelling out of the wound). The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). At the end of surgery, a lumbar drain was inserted at the L4/5 or L3/4 disc space and advanced 15 – 20 cm from the skin edge. Figure 17 shows the set up.

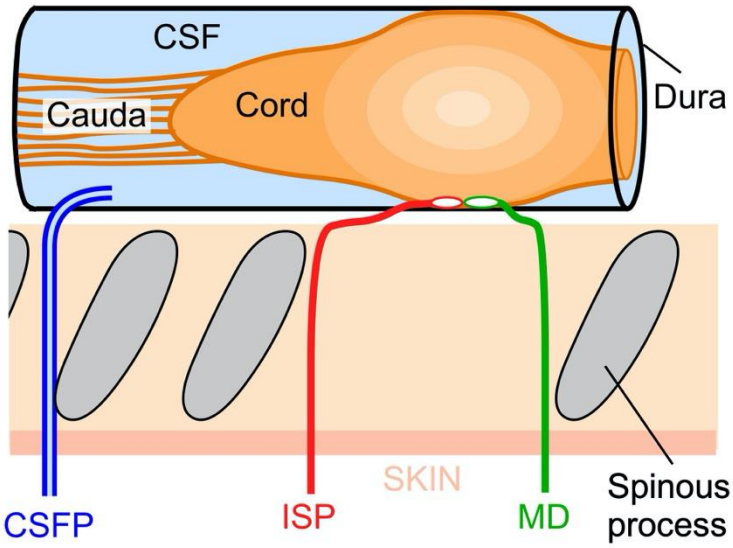


Fig. 17. Monitoring setup. Schematic to illustrate ISP, CSFP and microdialysis monitoring. With the patient lying flat, ISP is monitored by a pressure probe placed subdurally at the injury site and CSFP from a catheter placed in the lumbar CSF space. A microdialysis catheter is also placed next to the pressure probe.

3.3.5 Monitoring and lumbar CSF drainage

The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.7.3.5 (AD Instruments, Oxford, UK). The lumbar catheter was connected to an external drainage system (Integra™ AccuDrain® External CSF Drainage System) which was attached to a pressure transducer and closed to the drain. It was then connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) and in turn connected to the PowerLab system. Nurses were instructed to keep the transducer at the level of the lumbar spine. We chose to level the transducer at the level of the lumbar spine as this is the routine place for zeroing the lumbar drain in our intensive care unit and we wanted to ensure consistency between patients. Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) and in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz and patients were monitored for up to 7 days. With the patient lying flat, up to 10 ml CSF was drained each time from the lumbar catheter to assess the effect on ISP. No more than 30 ml of CSF was drained in a 24-hour period.

3.3.6 Microdialysis setup and analysis

Microdialysis was started postoperatively in the ICU as described [24,63,64]. The microdialysis catheter is connected to a CNS CMA106 pump (CMA microdialysis AB) filled with CNS perfusion fluid (CMA microdialysis AB) which contains NaCl 147 mmol / L, KCl 2.7 mmol / L, $CaCl_2$ 1.2 mmol / L and $MgCl_2$ 0.85 mmol / L. This fluid perfuses the catheter at rate of 0.3 μL/min, there is a delay in transit from the microdialysis semi-permeable membrane to the microdialysis vial of 24 minutes. Microdialysis vials were changed hourly and analyzed using ISCUS Flex (CMA microdialysis AB) for the following metabolites: glucose, lactate, pyruvate, glycerol, glutamate and lactate-to-pyruvate ratio (LPR) (Lactate x 1,000 / pyruvate). The first two samples from each patient were discarded to allow priming of the microdialysis catheter and stabilization of the metabolite concentrations. 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from analysis. Samples of CSF were collected at each CSF drainage and were used to measure the same metabolites. CSF metabolite levels were then compared against corresponding metabolite levels at the injury site obtained from the corresponding time of sampling.

3.3.7 Signal analysis

Data was analysed using Labchart v.8 (AD Instruments, Oxford, UK) and ICM+ (www.neurosurg.cam.ac.uk/icmplus) to compare ISP *versus* CSFP signals including morphology of individual waveforms, entire period mean values and duration of pulseless CSFP. The running correlation between CSFP and ISP defined as the Pearson correlation coefficient of the preceding 60 one-second averages of CSFP *vs.* ISP, updated each minute was computed for each patient. I hypothesised that the timing of the ISP and CSFP waveforms would be greatly influenced by compliance, i.e. a more compliant compartment will transmit pulses more slowly than a less compliant one. I therefore computed two elements of pulse wave timing: the latency (λ) between the onset of an ISP waveform and the onset of the corresponding CSFP waveform as well as the slope of each pulse wave ($\delta P/\delta T$). Frequency-domain analysis of the ISP and CSFP waveforms was performed using a Fast Fourier Transformation to determine cardiac and respiratory contributions to these signals. Three two-hour traces of waveform signals were analysed for each patient corresponding to periods that the CSFP was very, minimally and non-pulsatile. ISP and CSFP were also used to compute the following: SCPP = MAP – ISP, $SCPP_{(csf)}$ = MAP – CSFP, $sPRx_{ISP}$ = running correlation coefficient between MAP and ISP, $sPRx_{(csf)}$ = running correlation coefficient between MAP and CSFP, $SCPP_{opt(ISP)}$ = SCPP at minimum $sPRx_{(ISP)}$, and $SCPP_{opt(csf)}$ = $SCPP_{(csf)}$ at minimum $sPRx_{(csf)}$.

3.3.8 Statistical analysis

Statistical analysis was performed in conjunction with Dr Saadoun. The Pearson coefficient was used to examine the correlations between CSFP *versus* ISP, $SCPP_{(csf)}$ *versus* $SCPP_{(ISP)}$, $SCPP_{opt(csf)}$ *versus* $SCPP_{opt(ISP)}$, $sPRx_{(csf)}$ *versus* $xPRx_{(ISP)}$, metabolite concentrations in lumbar CSF *versus* microdialysate as well as extent of cord oedema (length of T2 signal abnormality on pre-operative MRI) *versus* mean Pearson correlation coefficient between CSFP and ISP. The change in ISP ((ΔISP) as a result of draining lumbar CSF was defined as 15-minute mean ISP prior to drainage minus 15-minute mean ISP ten minutes after drainage and was compared using Student's t-test for all the repeats in each patient. $\delta P/\delta T$ values for CSP *versus* ISP were compared using Student's t-test. The different groups λ were compared by multiple Student's t-tests with Bonferroni correction.

3.4 Results

3.4.1 Patient Demographics

Data were collected from 13 consecutive patients aged 26 – 67 years (mean 47). Most (62 %) patients had complete (AIS A) injuries and most (70 %) had cervical injuries. All patients underwent posterior surgical bony decompression including laminectomy and fusion with 31 % also requiring concurrent anterior stabilisation. Mean duration of follow-up was about half a year. At follow-up, most patients (54 %) had improved by one of more AIS grade, some (38 %) remained the same and one patient (8 %) deteriorated by one AIS grade. Mean duration of monitoring was 4 – 5 days and mean number of microdialysis - CSF matched sample pairs per patient was eight. Details are in Table 11.

3.4.2 Complications

In three patients (23 %), the lumbar drain stopped working and was re-sited or removed. One patient (8 %) with poorly-controlled diabetes mellitus developed a post-operative E. Coli septicaemia from urosepsis followed by E. Coli wound infection 17 days after surgery; the infection was eliminated with wound washout plus six weeks of intravenous antibiotics. Of note, this was the only ISCoPE patient who developed a wound infection out of the 76 who underwent multi-modality injury site monitoring to date (2010 – 9) giving an overall infection risk of 1.3 %. CSF leak from the probe skin exit site was observed in 4/13 patients (31 %) and was successfully stopped by placing additional skin sutures. Six of the thirteen patients (46 %) had asymptomatic, non-compressive pseudo-meningoceles noted on post-operative MRI, done within 2 – 3 months of TSCI, which resolved on the 1-year post-operative MRI. Details are in Table 12.

Table 11. Patient demographic characteristics

PATIENT NO.	AGE YEARS	SEX	SITE	TYPE OF SURGERY POST / ANT+POST	ADMISSION AIS GRADE	FOLLOW UP AIS	DURATION OF FOLLOW UP (months)	DURATION OF MONITORING (hours)	NUMBER OF SIMULTANEOUS MICRODIALYSIS and CSF SAMPLES
1	67	M	C3	Post	A	A	1	104.25	0
2	67	M	C4	Post	C	C	12	127.93	8
3	32	M	C4	Ant+Post	C	D	10	150.93	3
4	39	M	T7	Post	A	B	15	113.12	11
5	35	M	C4	Ant+Post	C	A	12	84.5	7
6	27	M	L1	Post	C	D	6	111.78	9
7	50	M	C5	Post	B	B	2	139	14
8	47	M	T8	Post	A	C	12	105.63	9
9*	57	M	C4	Post	A	A	3	147.15	12
10	66	M	C4	Post	A	A	4	128.5	12
11	46	M	T12	Post	A	C	4	51.78	3
12	52	M	C5	Ant+Post	A	B	2	127.56	12
13	26	M	C6	Ant+Post	A	B	1	70.5	8

*Ant, anterior; M, male; Post, posterior. *Permanent pacemaker so did not have MRI*

Table 12. Complications

COMPLICATION	NO. OF PATIENTS	COMMENTS
Wound infection	1	Brittle diabetes and E. Coli bacteraemia from urosepsis. Wound swabs also grew E Coli. Infection eradicated by wound washout and 6 weeks ceftriaxone.
CSF Leak around probes	4	All managed with re-suturing of probe exit site with no further leaks.
Lumbar drain blocked	2	In one patient, lumbar drain stopped transducing a pressure wave and would not drain nor flush so lumbar drain was removed. In the second patient, lumbar drain was re-sited without complication.
Pseudo-meningocele on 6 week MRI	6	All clinically asymptomatic. In 3/6, pseudo-meningocele resolved on MRI at one year. 3/6 awaiting one year follow up MRI.

3.4.3 ISP *versus* CSFP waveform shapes

Morphologically, the ISP waveforms were comparable to the intracranial pressure waveforms with three major peaks: percussion, tidal and dicrotic[59]. In contrast, the CSFP waveforms appeared flatter than ISP and less pulsatile with non-pulsatile periods (Figs. 18-20). Frequency domain analysis for ISP revealed respiratory and heartbeat peaks (+ harmonics) with either peak the tallest. Flat CSFP waveform had no frequency peaks, the minimally pulsatile CSFP waveform had only the respiratory peak whereas more pulsatile CSFP had both respiratory and heartbeat peaks with the respiratory peak always the tallest (Fig. 21). Timing analysis was performed for each patient in 50 randomly chosen waveforms and revealed significantly steeper $\delta P/\delta T$ slope for ISP than CSFP waveforms (Figs. 22-23) and significant delay, by >100 ms in most cases, between the onset of the CSFP pulse compared with the corresponding ISP pulse (Fig. 24).

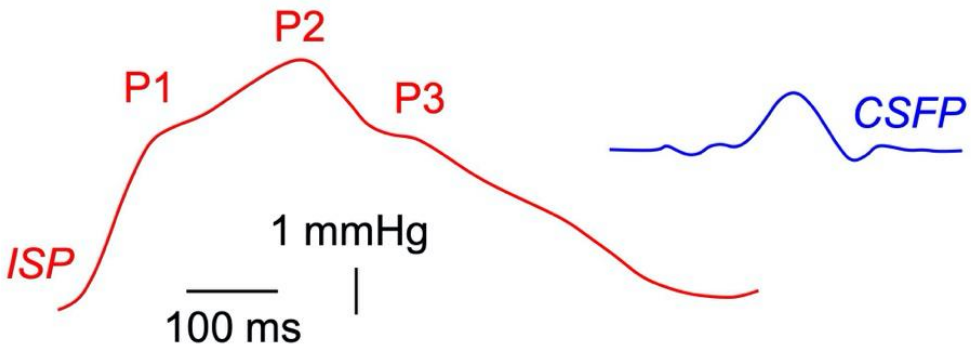


Fig. 18. Comparing ISP and CSFP Waveforms. Typical ISP and CSFP waveforms. P1 percussion peak, P2 tidal peak, P3 dicrotic peak.

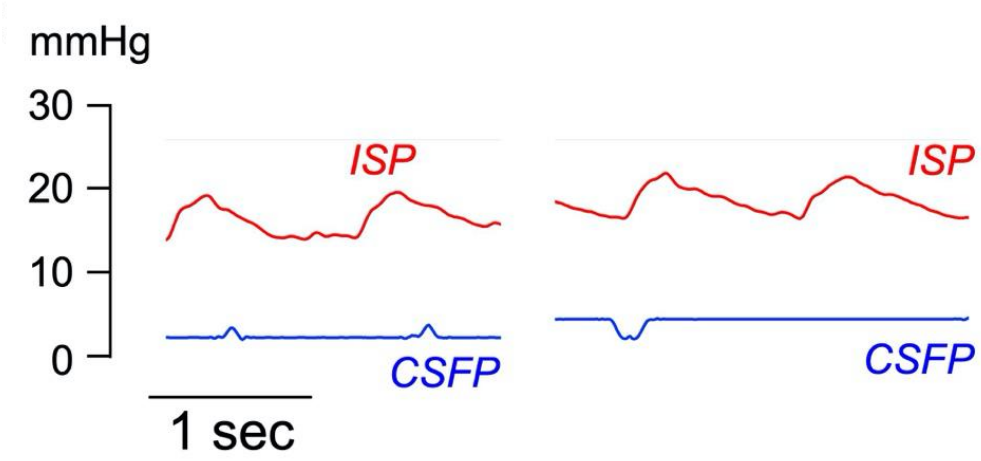


Fig. 19. Comparing ISP and CSFP signals. Examples of simultaneously measured ISP and CSFP signals over 2 – 3 second period. CSFP waveforms are flatter than ISP and less pulsatile with non-pulsatile periods

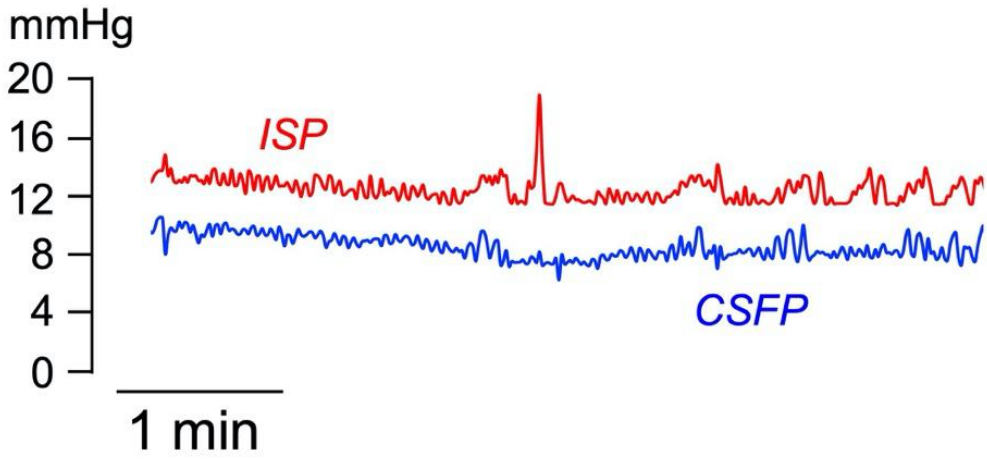


Fig. 20. Comparing ISP and CSFP signals. Example of simultaneously measured ISP and CSFP signal from one patient over a 5 minute period.

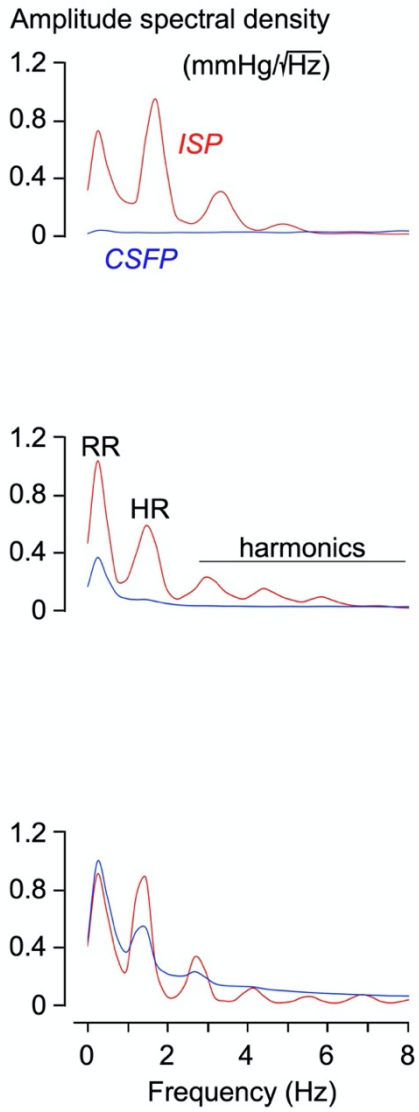


Fig. 21. Frequency Domain Analysis of ISP and CSFP. FFT of 2-hour long ISP and corresponding CSFP from the same patient at different points in monitoring. Signals show amplitude spectral density (mmHg/√Hz) *versus* frequency (Hz). (*top*) CSFP signal with no pulsation, (*middle*) CSFP signal with some pulsation, (*bottom*) CSFP signal with prominent pulsation. Peaks correspond to respiratory rate (RR), heart rate (HR) and harmonics.

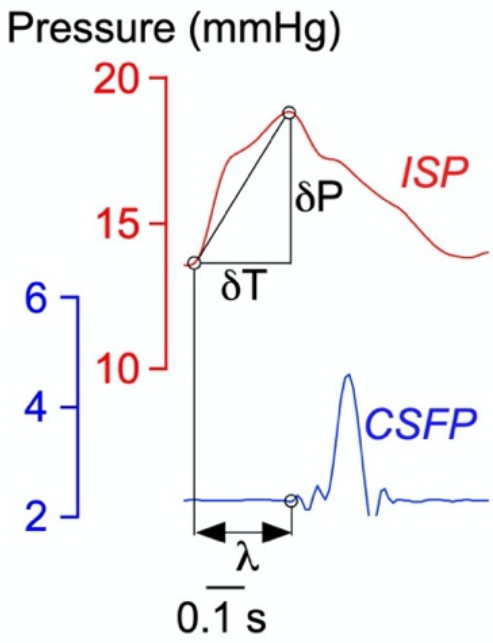


Fig. 22. Comparing the pulse wave of ISP and CSFP. Example trace showing how δP/δT (slope of pulse wave) and λ (ISP – CSFP latency) were calculated.

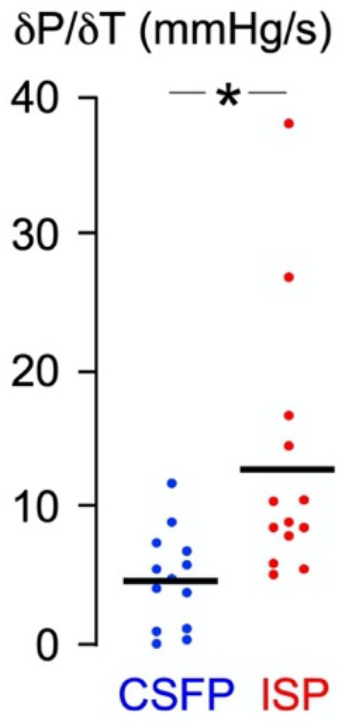


Fig. 23. Comparing the pulse waves of ISP and CSFP. Analysis of 50 waveforms for each patient. Plot of mean δP/δT of the CSFP and ISP waveforms for each patient (dot). Lines are means. $P < 0.05^{*}$,

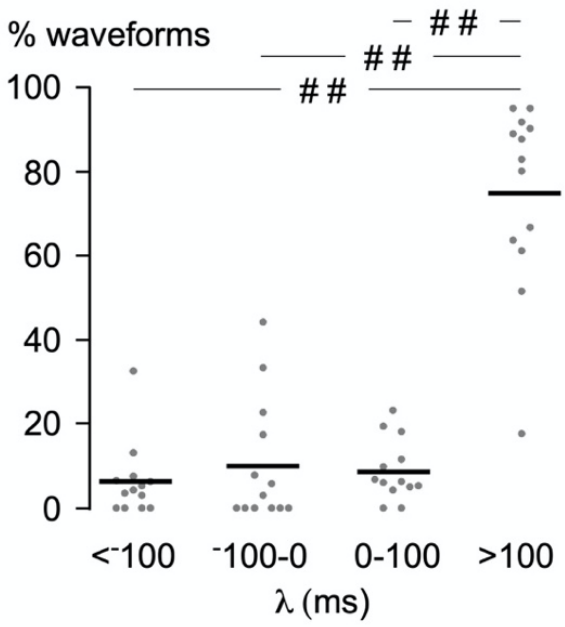


Fig. 24. Comparing the latency between onset of ISP and CSFP waveforms. Analysis of 50 waveforms from each patient. Plot of mean λ for each patient (dot). Lines are means. *P <0.001*[##]

3.4.4 ISP *versus* CSFP signals

When averaged over the entire monitoring period, ISP was higher than the CSFP by ~5 mmHg. A plot of average CSP *versus* average ISP for the 13 patients showed no overall correlation: in 6/13 patients, mean ISP – mean CSFP >5 mmHg, in 2/13 patients mean CSFP – mean ISP >5 mmHg and in 5/13 patients mean ISP and mean CSFP were within 5 mmHg (Fig. 25). Closer inspection of these signals revealed periods when the ISP and CSFP pulsations appeared uncorrelated and other periods when the CSFP and the ISP pulsations appeared almost identical (Fig. 26). To evaluate this time-variability in the correlation between the CSFP and the ISP signals their running correlation coefficient was computed. The running correlation coefficient was >0.7 for >75 % of the time in 3/13 patients (2 cervical +1 thoracic injuries), 25 – 75 % of the time in 3/13 patients (all cervical) and <25 % of the time in 7/13 patients (4 cervical + 2 thoracic + 1 conus) (Fig. 27). There were periods of positive CSFP *versus* ISP correlation, periods of no correlation and periods of anti-correlation (Fig. 28). There was no significant difference in the running coefficient between cervical *versus* thoracolumbar TSCIs.

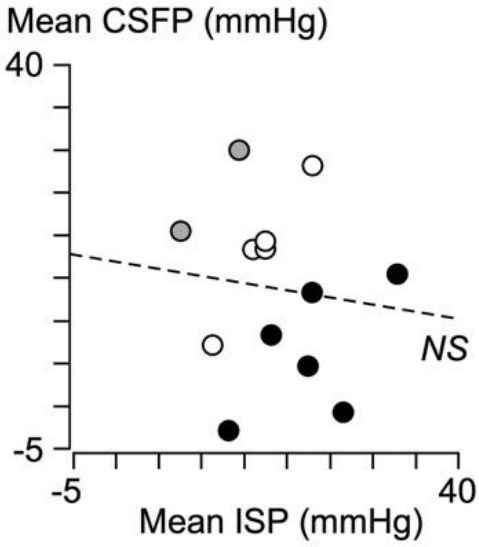


Fig. 25. ISP *versus* CSFP. Average ISP *versus* average CSFP for entire monitoring period. Best-fit straight line, R = -0.11. White circles (|ISP – CSFP| ≤ 5 mmHg), gray circles (CSFP – ISP > 5 mmHg), black circles (ISP – CSFP > 5 mmHg). *NS*, not significant.

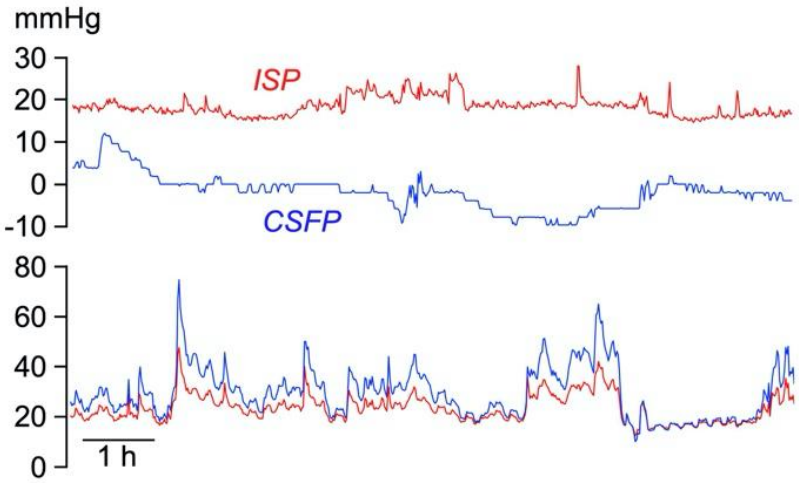


Fig. 26. Correlation of ISP and CSFP. Example of ISP signal and simultaneously-recorded CSFP signal, monitored over 10 hours, that correlate (*top*) poorly and (*bottom*) well.

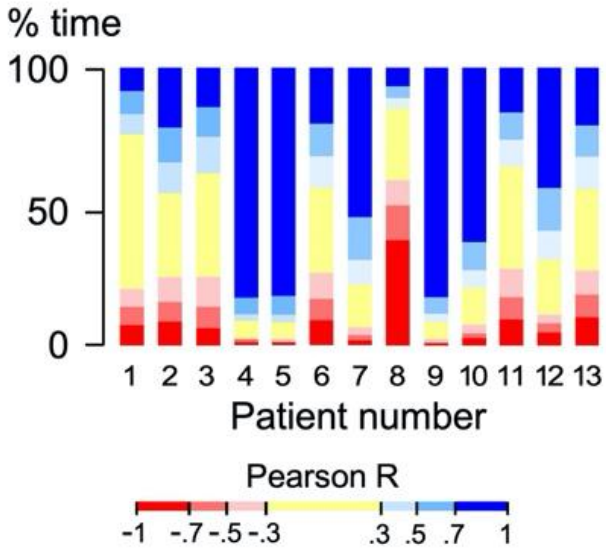


Fig. 27. Correlation of ISP and CSFP. Distribution of running Pearson Rank between ISP and CSFP for each patient for the whole period of monitoring.

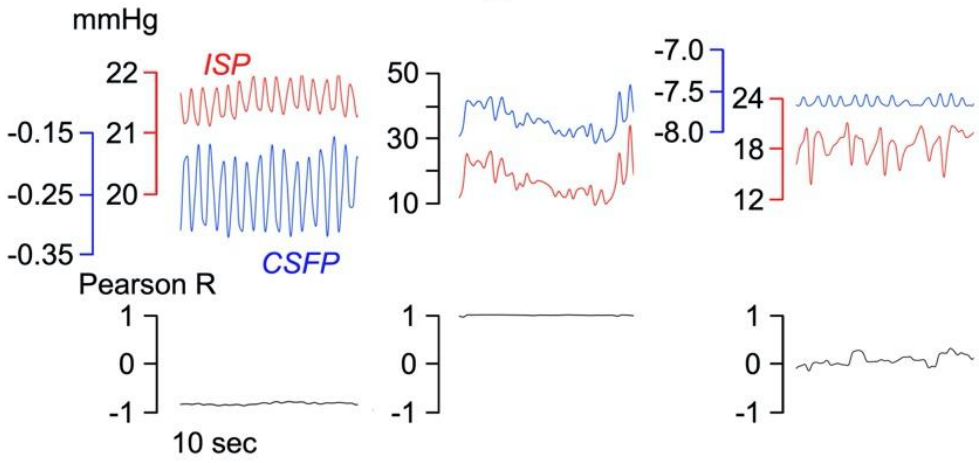


Fig. 28. Correlation of ISP and CSFP. Example of ISP signal and simultaneously-recorded CSFP signal, monitored over 10 seconds, with (*left*) negative, (*middle*) positive, and (*middle*) no correlation. Below are corresponding plots of Pearson R *versus* time.

3.4.5 SCPP, sPRx, $SCPP_{opt}$ and metabolites

Overall, there was no significant correlation between $SCPP_{(csf)}$ *versus* $SCPP_{(ISP)}$ (Fig. 29), $sPRx_{(csf)}$ *versus* $sPRx_{(ISP)}$ (Fig. 30) or $SCPP_{opt(csf)}$ *versus* $SCPP_{opt(ISP)}$ (Fig. 31). Also, the overall levels of metabolites measured from the injury site by microdialysis *versus* the corresponding levels in the lumbar CSF did not significantly correlate for lactate, pyruvate and LPR (Figs. 32-34 respectively) though there were significant, albeit weak, positive correlations for glucose, glutamate and glycerol (Figs. 35-37 respectively). When examining individual patients, significant positive correlations between injury site and lumbar CSF levels were found in 8/12 for glucose, 8/12 for glutamate, 6/12 for glycerol.

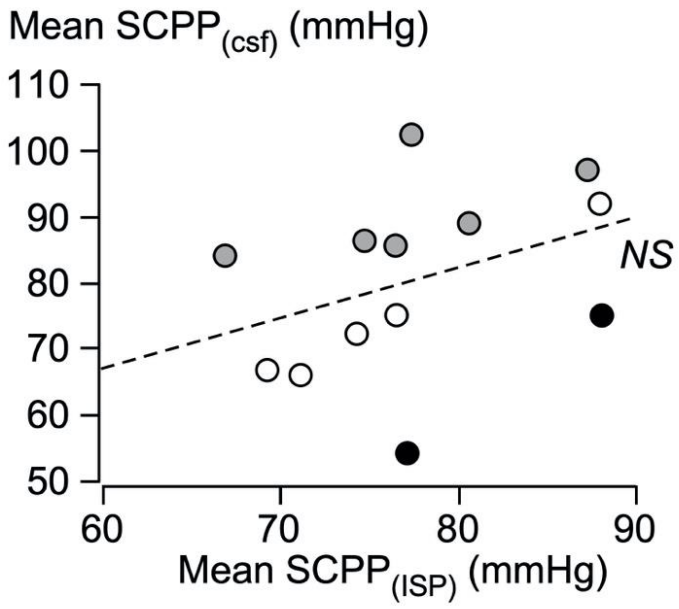


Fig. 29. Physiological parameters computed from ISP *versus* CSFP: SCPP and $SCPP_{CSF}$. Average SCPP computed from CSF ($SCPP_{CSF}$) *versus* average SCPP computed from CSFP ($SCPP_{ISP}$), R = 0.39. White circles ($|SCPP_{(csf)} - SCPP_{(ISP)}| \leq 5$ mmHg), gray circles ($SCPP_{(csf)} - SCPP_{(ISP)} > 5$ mmHg), black circles ($SCPP_{(csf)} - SCPP_{(ISP)} < 5$ mmHg). Best-fit straight lines. *NS*, not significant.

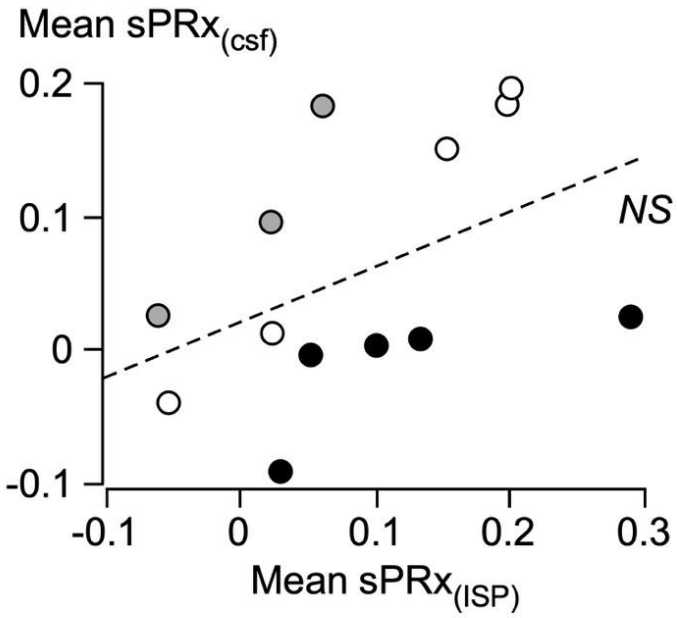


Fig. 30. Physiological parameters computed from ISP *versus* CSFP: sPRx and $sPRx_{(csf)}$. Average sPRx computed from CSF ($sPRx_{(csf)}$) *versus* average sPRx computed from ISP ($sPRx_{(ISP)}$), R = 0.45. White circles ($|sPRx_{(csf)} - sPRx_{(ISP)}| \leq 0.05$), gray circles ($sPRx_{(csf)} - sPRx_{(ISP)} > 0.05$), black circles ($sPRx_{(csf)} - sPRx_{(ISP)} < 0.05$). Best-fit straight lines. *NS*, not significant.

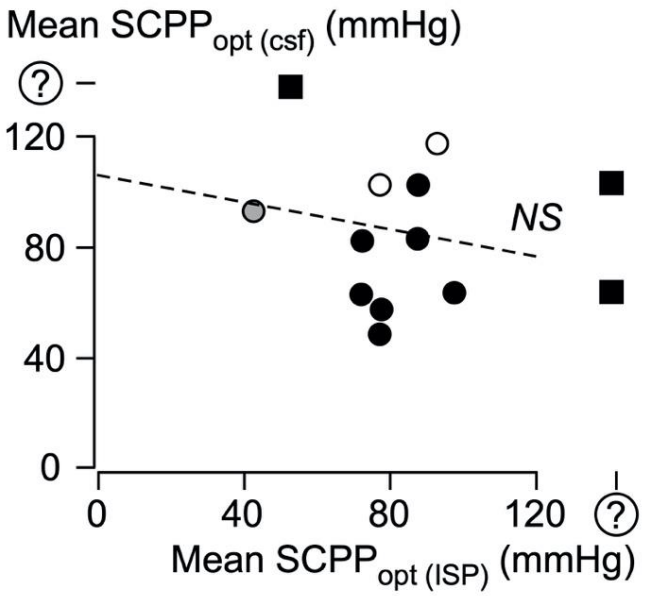


Fig. 31. Physiological parameters computed from ISP *versus* CSFP: $SCPP_{opt}$ and $SCPP_{opt(csf)}$. Overall $SCPP_{opt}$ computed from CSF ($SCPP_{opt(csf)}$) *versus* overall $SCPP_{opt}$ computed from ISP ($SCPP_{opt(ISP)}$), R = -0.22. White circles ($|SCPP_{opt(csf)} - SCPP_{opt(ISP)}| \leq 5$ mmHg), gray circles ($SCPP_{opt(csf)} - SCPP_{opt(ISP)} > 5$ mmHg), black circles ($SCPP_{opt(csf)} - SCPP_{opt(ISP)} < 5$ mmHg), black squares $SCPP_{opt}$ could not be calculated. Best-fit straight lines. *NS*, not significant.

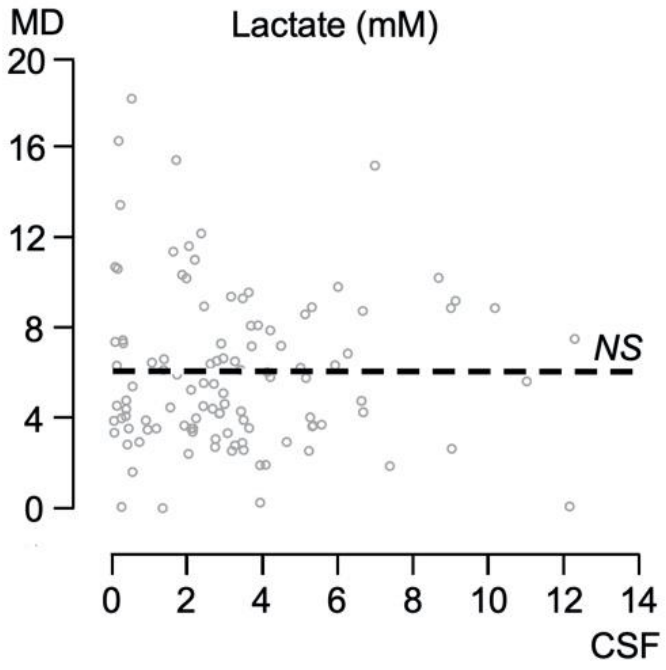


Fig. 32. Biochemical parameters from microdialysis at injury site *versus* in lumbar CSF: Lactate. Plot of microdialysis *versus* lumbar CSF values with best-fit straight line for [Lactate] in mM (R = 0.0007). Data from 12 patients. *NS*, not significant.

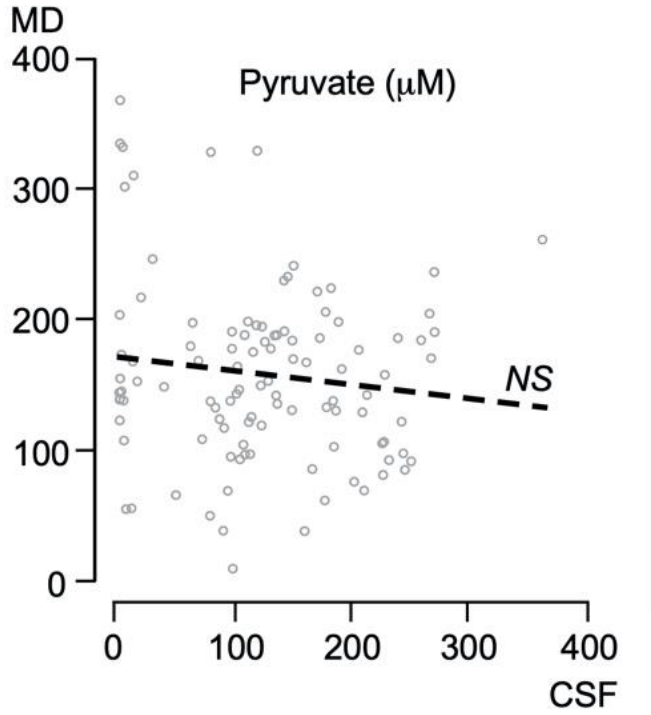


Fig. 33. Biochemical parameters from microdialysis at injury site *versus* in lumbar CSF: Pyruvate. Plot of microdialysis *versus* lumbar CSF values with best-fit straight line for [Pyruvate] in μM (R = -0.12). Data from 12 patients. *NS*, not significant.

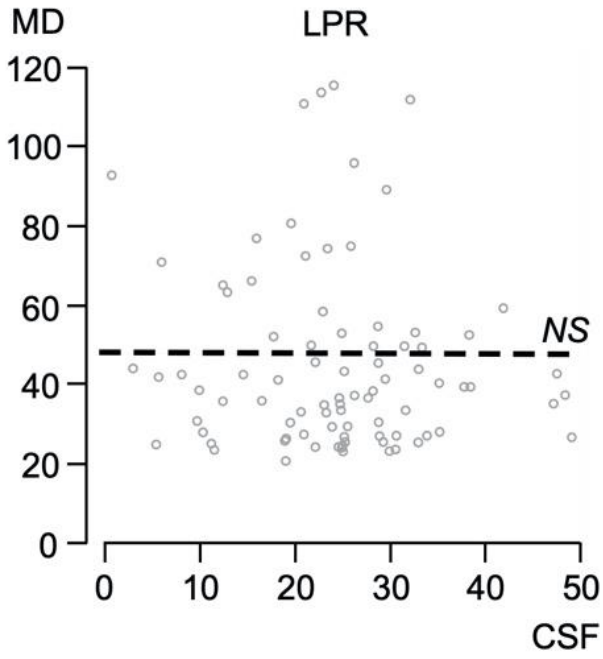


Fig. 34. Biochemical parameters from microdialysis at injury site *versus* in lumbar LPR. Plots of microdialysis *versus* lumbar CSF values with best-fit straight line for Lactate-to-pyruvate ratio – LPR (R = -0.05). Data from 12 patients. *NS*, not significant.

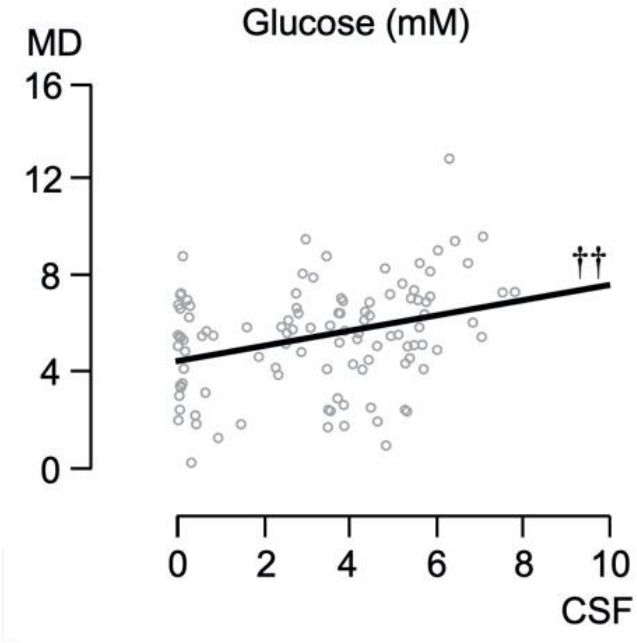


Fig. 35. Biochemical parameters from microdialysis at injury site *versus* in lumbar CSF: Glucose. Plot of microdialysis *versus* lumbar CSF values with best-fit straight line for [Glucose] in mM (R = 0.32). Data from 12 patients. *P < 0.0001*††

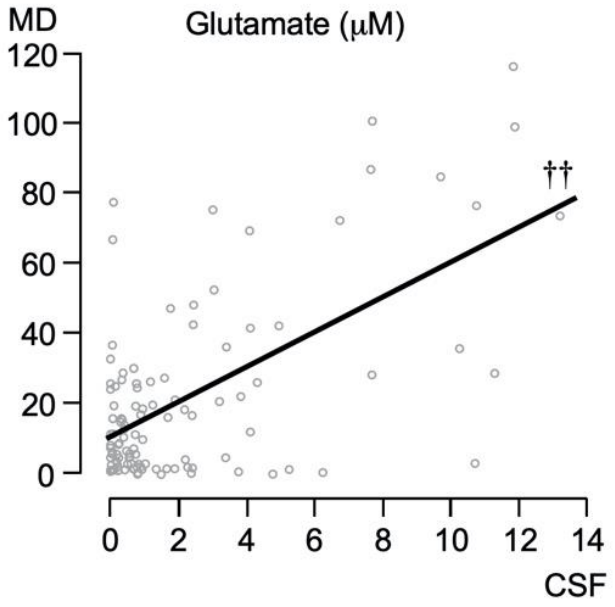


Fig. 36. Biochemical parameters from microdialysis at injury site *versus* in lumbar: Glutamate Plots of microdialysis *versus* lumbar CSF values with best-fit straight line for [Glutamate] in μM (R = 0.61). Data from 12 patients. *P < 0.0001*††

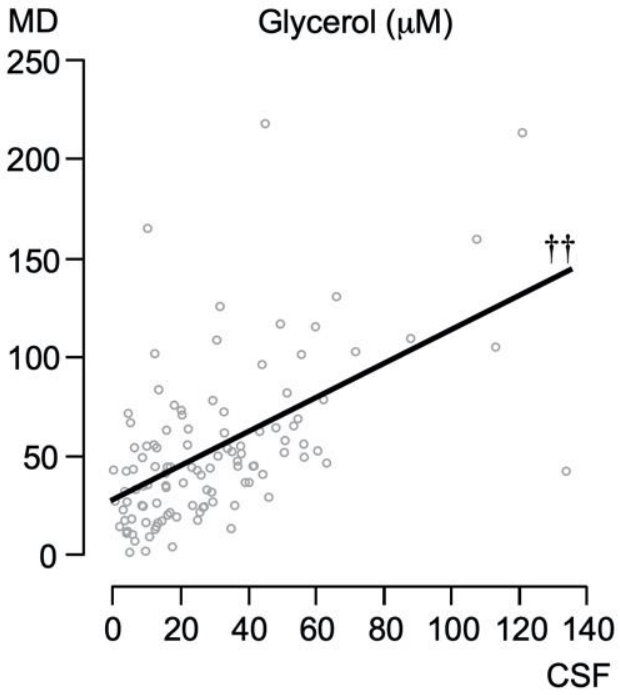


Fig. 37. Biochemical parameters from microdialysis at injury site *versus* in lumbar CSF: Glycerol. Plots of microdialysis *versus* lumbar CSF values with best-fit straight line for [Glycerol] in μM (R = 0.56). Data from 12 patients. $P < 0.0001^{††}$.

3.4.6 Effect on ISP of CSF drainage

In 12/13 patients, with the patient lying flat I drained ~10 mL CSF through the lumbar catheter on several occasions to assess the effects of CSF drainage on ISP and CSFP. CSF drainage had variable effect on ISP (Fig. 38). On average, in 7/12 patients there was no change in ISP, in 4/12 patients there was a significant small reduction in ISP by <5 mmHg and in 1/12 patients there was a large drop in ISP by 5 – 10 mmHg (Fig. 39). In 3/12 patients, on some occasions, I observed the phenomenon of 'dry tap', where CSF would not be drained even though the lumbar catheter was patent (i.e. able to flush and transduced a pressure wave). This resolved in 2/3 patients, but persisted in 1/3 (patient 10) after day 2 even though the lumbar drain appeared in the spinal canal on the post-operative CT. A dry tap was also observed in 1 patient when the lumbar drain was inserted in theatre.

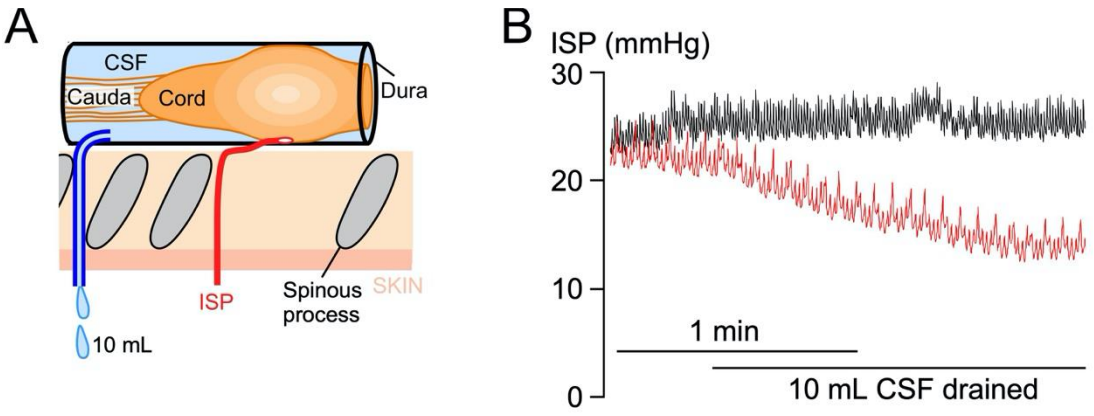


Fig. 38. Effect of draining lumbar CSF on ISP. A. Setup. With the patient lying flat, ISP is monitored by a pressure probe placed subdurally at the injury site whilst 10 mL lumbar CSF were drained. **B.** Examples from two patients (black, red) of ISP traces during draining 10 mL lumbar CSF.

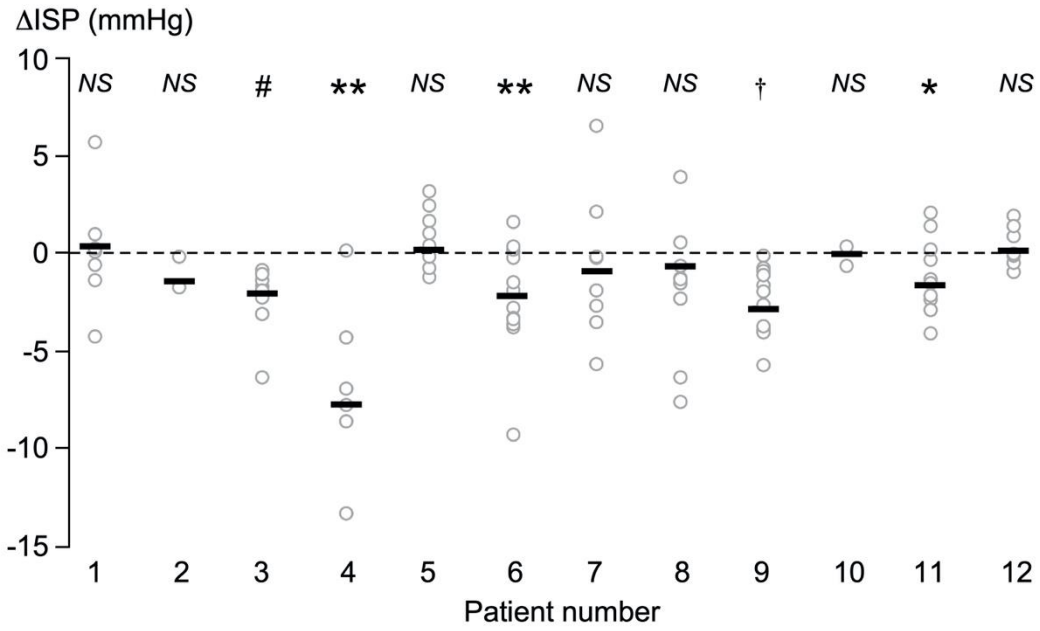


Fig. 39. Effect of draining lumbar CSF on ISP. Plot of ΔISP as a result of draining 10 mL lumbar CSF (circles are individual values, lines are means) from 12/13 patients. *$P < 0.05^{*}$, 0.01^{**}, $0.005^{\#}$, $0.001^{\#\#}$, $0.0005^{\dagger}$; NS*, not significant.

3.4.7 Cord swelling and CSFP *versus* ISP Correlation

I hypothesised that if the injured cord was not very swollen, that it would be surrounded by CSF and, therefore, the ISP and the CSFP signals would be similar, i.e. their correlation would be high. Conversely, if the cord is very swollen, it will become compressed against the dura. In this case, the ISP is the pressure of the swollen cord against the dura, whereas the CSFP is the pressure in the lumbar CSF and, therefore, there will be loss of correlation between CSFP *versus* ISP. The longitudinal extent of cord signal change on pre-operative T2 MRI, used as a measure of cord oedema, inversely correlated with the mean CSFP *versus* ISP correlation coefficient (Fig. 40). In other words, patients with less spinal cord swelling had stronger positive correlations between their CSFP and their ISP signals thus supporting my hypothesis.

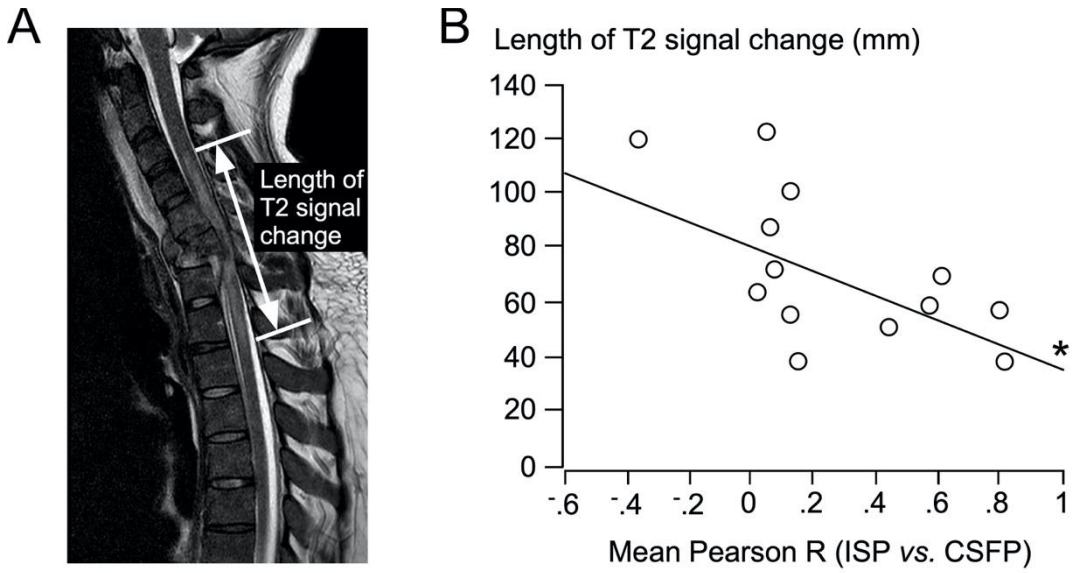


Fig. 40. Relation between cord oedema and concordance between ISP and CSFP signals. **A.** T2 mid-sagittal MRI showing length of cord signal change. **B.** Plot of length of cord signal change in mm *versus* mean Pearson R (ISP *versus* CSFP). R = 0.66, $P < 0.05^{*}$

3.5 Discussion

Our key finding is that, after acute severe TSCIs, the values of physiological (i.e. ISP, SCPP, sPRx, $SCPP_{opt}$) and biochemical (i.e. glucose, lactate, pyruvate, LPR, glutamate, glucose) parameters measured at the injury site markedly differ from equivalent measurements from the lumbar CSF. Lack of correlation between ISP and CSFP likely occurs when the injured cord is compressed against the dura, i.e. there is no CSF around the injury site. The presence of periods with high correlation between ISP and CSFP suggests that cord compression is a dynamic process. These ideas are supported by our earlier finding of a pressure profile along the injured cord[47,49] and our current observation that patients with more cord swelling on pre-operative MRI have poorer correlation between ISP and CSFP.

ISP and CSFP pulse timings suggest that the injury site and the lumbar CSF have different physical properties. CSFP pulses have lower $\delta P/\delta T$ and lag behind ISP pulses; this means that ISP pulses are in a 'tight' compartment (low compliance, cord compressed against dura), but CSFP pulses are in a 'loose' compartment (lumbar CSF)[105]. ISP has two prominent frequency peaks (cardiac, respiratory), as previously shown [47,59], but CSFP may be flat (no peaks), a little pulsatile (respiratory peak only) or more pulsatile (two peaks, respiratory taller than cardiac). Lack of lumbar CSF pulsatility in TSCI was also noted by Kwon et al. who found correlation with cord compression on MRI[46]. We propose that the swollen cord inhibits the caudal transmission of cord and CSF pulsations to the lumbar CSF thus causing CSFP pulsatility to diminish. In our ventilated patients, lung pressure fluctuations likely produce venous pressure fluctuations that are transmitted to the CSFP regardless of cord compression. This may explain why the respiratory frequency peak in CSFP often persists even when the cardiac frequency peak has disappeared.

Over the last few years, we showed how the ISP signal can be used to derive several physiological parameters (SCPP, sPRx and $SCPP_{opt}$)[47,48,59,98] that correlate with injury site metabolism[24], acute neurological status[47] and long-term neurological outcome[50] and may guide the management of TSCI patients in ICU. We observed major differences between these parameters computed using ISP *versus* CSFP. The differences arise because of the overall lack of correlation between ISP and CSFP. During periods that the spinal cord is not compressed, ISP ≈ CSFP and thus $SCPP_{(ISP)} \approx SCPP_{(csf)}$. Therefore, $SCPP_{(csf)}$ carries some information about $SCPP_{(ISP)}$; this may explain why $SCPP_{(csf)}$ has some predictive power in TSCI[45]. Neurological outcome correlates better with $SCPP_{(ISP)}$[50] than $SCPP_{(csf)}$[45], probably because $SCPP_{ISP}$ carries more information about the injury site than $SCPP_{CSF}$. Together, our

findings suggest that CSFP monitoring is less cumbersome than ISP monitoring, but cannot reliably estimate ISP, SCPP, sPRx or $SCPP_{opt}$.

Lumbar CSF drainage has been used to improve cord perfusion after TSCI in patients[46] and pig models[106]. In our study, CSF drainage did not reliably reduce ISP in most TSCI patients, probably because of the lack of CSF around the injury site. Our observation of 'dry taps' on several occasions, also noted by Kwon et al.[46], supports the idea of a block in the flow of CSF caused by the swollen cord compressed against the dura. In patients with CSF around the injured cord, lumbar CSF drainage is predicted to reduce ISP, (Patient 4, Fig. 5). Even in this patient, however, ISP decreased only on some occasions, which suggests that the cord is intermittently compressed. Ways to reliably increase SCPP include vasopressors to increase MAP[47] or expansion duroplasty to reduce ISP[53].

Tissue microdialysis is widely used when managing patients with brain injuries[107] (see section 1.3.3). Previous work has shown that microdialysis also provides clinically important information after TSCI[63,64]. Our data suggest that metabolite levels at the injury site differ from corresponding levels in the lumbar CSF. An explanation is that the microdialysis catheter samples metabolites from the extracellular space at the injury site, but metabolites are shed into the lumbar CSF not only from the injury site, but also from the cord below. Differences in metabolite levels at the injury site *versus* lumbar CSF were more pronounced for lactate, pyruvate and LPR probably because the cord below the injury has healthier metabolism than the injury site. Tissue [glucose] at the injury site correlated with lumbar CSF [glucose]; a possible explanation is that both concentrations are influenced by serum [glucose][8,108]. [Glutamate] and [glycerol] at the injury site also correlated with lumbar CSF levels; this may be because the normal cord does not release glutamate or glycerol, i.e. the glutamate and glycerol in the lumbar CSF originated entirely from the injury site. Despite reaching statistical significance, the correlations of injury site *versus* lumbar CSF for [glucose], [glutamate] and [glycerol] were weak with large inter-patient variability.

3.6 Conclusions

We conclude that, after TSCI, monitoring from the lumbar CSF offers limited information about the injury site and that drainage of lumbar CSF does not reliably improve cord perfusion. To monitor pathological events within the injured cord, we advocate directly accessing the injury site, which previous work has shown to be safe[56] and may be used to obtain multi-modality data[47,64].

4. CHAPTER 3: Acute spinal cord injury: correlations and causal relations between intraspinal pressure, spinal cord perfusion pressure, lactate-to-pyruvate ratio and limb power

4.1 Introduction

Having established that there are limited pre-operative biomarkers to predict physiological parameters of acute severe TSCI[103] and that the alternatives to invasive injury site pressure monitoring (monitoring CSFP) are less effective[109] our group sought to explore whether clinical monitoring (in patients with incomplete injuries) correlated with (and therefore had predictive capabilities) spinal cord physiology and metabolism.

Invasive monitoring of patients with severe acute TSCI was developed to improve the management of patients [110]. Monitoring ISP and SCPP [50,62,103] with a pressure probe, as well as injury site metabolism with a microdialysis catheter[63,64] is safe and analogous to multi-modality monitoring for brain injury[56]. ISP and SCPP correlate with injury site metabolism[24], neurological status[47] and long-term neurological outcomes[50]. Patients with neurologically complete traumatic spinal cord injuries have more deranged cord metabolism than those with neurologically incomplete injuries[63]. The relations between ISP, SCPP and injury site metabolism *versus* neurological outcome are correlations that do not imply causation.

The question whether changes in ISP, SCPP and injury site metabolism *cause* changes in limb power is paramount because it implies that interventions to normalize ISP, SCPP and injury site metabolism would improve limb power. To determine causation, we focused on grade C (American Spinal Injury Association Impairment Scale) injuries because they have some intact limb power below the injury. Limb motor score, intraspinal pressure, spinal cord perfusion pressure and injury site lactate-to-pyruvate ratio were monitored for up to a week after surgery. We used these time series to investigate the hypothesis that fluctuations in motor score are caused by fluctuations in the physiology and metabolism at the injury site. We employed the concept of causality proposed by econometrician Clive Granger[111] in 1969 and recently reviewed[112] for its application in neuroscience. Granger causality (G-causality) is based on the idea that causes precede (and therefore help predict) effect, therefore time-series data can identify causal interactions between variables and one time series can be used to forecast another. For example, a variable such as SCPP (which evolves in time) would be said to 'Granger-cause' another time-evolving variable, such as motor score, if predictions of motor score based on its own past and on the past of SCPP were better than predictions of

motor score based solely on its own past. Therefore, if changes in ISP, SCPP and injury site metabolism at the injury site cause changes in motor score this would suggest that interventions to normalize these monitored parameters would likely improve limb power.

4.2 Aim

To determine whether fluctuations in physiological and metabolic parameters in patients with incomplete TSCI monitored from the injury site are causatively linked to changes in limb power.

4.3 Methods

4.3.1 Institutional Approvals

Patients were recruited as part of the ISCoPE study. Please see Section 2.3.1 for details of ethical approvals.

4.3.2 Patient recruitment

We selected all grade C (American Spinal Injuries Association Impairment Scale) traumatic spinal cord injury patients who were enrolled into the ISCoPE study for the period October 2011 – January 2020. See Table 2 for inclusion/exclusion criteria to ISCoPE. See section 2.3.2 for details of recruitment processes.

4.3.3 Clinical examination and imaging

As outlined in section 2.3.6 and 2.3.7 all patients were admitted to the neurosurgical unit at St. George's Hospital and underwent International Standards for Neurological Classification of Spinal Cord Injury assessments by a trained neurosurgical resident, which was repeated at discharge and follow up clinic. Post-operatively, all patients were admitted to the Atkinson Morley Neuro Intensive Care Unit. As standard clinical care, all TSCI patients undergo regular motor limb assessments by intensive care nurses trained in Medical Research Council (MRC) grading of limb power. These assessments are performed with the patient off sedation or during a sedation hold and recorded in spinal assessment charts. As stated before, all patients had CT and MRI of the spine before surgery and within four weeks of surgery

4.3.4 Probe insertion

Surgical decompression, instrumentation and ISP and microdialysis probe insertion were performed as outlined in section 2.3.3 and 3.3.4 .

4.3.5 Intraspinal pressure monitoring

ISP and ABP monitoring set up was performed as outlined in section 2.3.4.

4.3.6 Microdialysis setup and analysis

Microdialysis was started postoperatively in the neuro-intensive care unit as described in section 3.3.6 and previous publictions[24,63,64]

4.3.7 Standardisation of limb motor score

The motor scores in the spinal assessment charts were standardised by subtracting the minimum post-operative motor score for each patient from all motor scores for that patient. Standardised motor scores were compared to intraspinal pressure, mean arterial pressure, spinal cord perfusion pressure and microdialysis values averaged over the hour corresponding to the neurological assessment (Fig. 41).

4.3.8 Statistical analysis

Motor score (y) *versus* ISP (x) was fitted with an exponential decay curve $y = A + Be^{-Cx}$, motor score *versus* SCPP and *versus* LPR were fitted with linear equations, whereas motor score (y) *versus* MAP (x) was fitted with a bounded exponential curve $y = A + B(1 - e^{-Cx})$ using the online free curve fitting service (https://mycurvefit.com/). Plots are mean ± standard error. For Granger causality analysis of the standardised motor score, ISP, SCPP and LPR time series, the Granger function in the Cloud Causal Analytics Toolkit (http://cox-associates.com/) was used that employs vector autoregression (VAR) models to test for causal relations. The model was tested with a lag of 1, 2 and 3 to see if the results were the same for different lag levels.

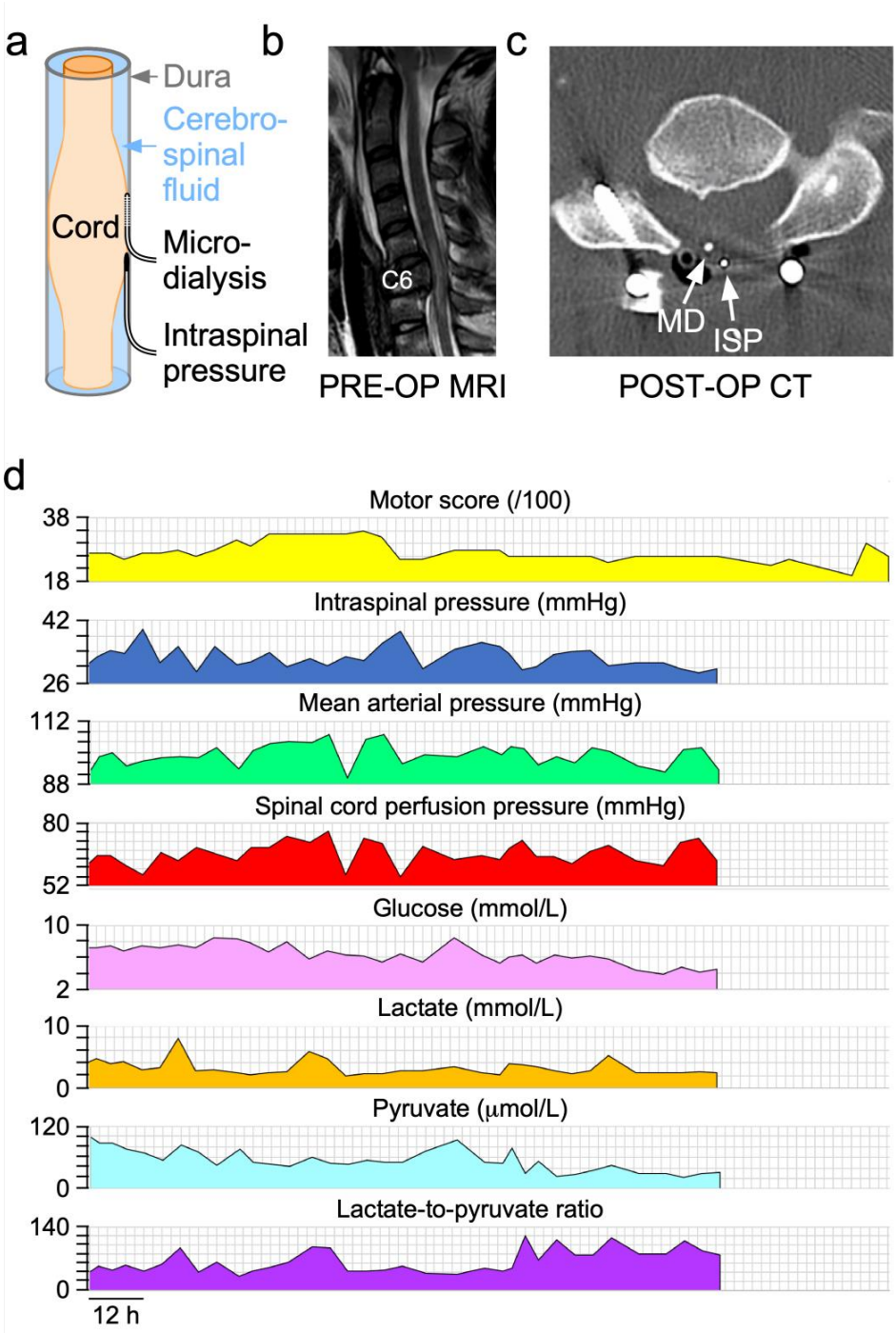


Fig. 41. Monitoring setup. A. Intraspinal pressure probe and microdialysis catheter inserted intradurally to monitor from injured cord. **B.** Pre-operative sagittal T2 MRI of patient no. 45 with spinal cord injury at C6. **C.** Post-operative axial CT with intraspinal pressure probe and microdialysis catheter *in situ*. **D.** Multi-modality monitoring of motor score (yellow), intraspinal pressure (blue), mean arterial pressure (green), spinal cord perfusion pressure (red) as well as injury site glucose (pink), lactate (orange), pyruvate (cyan) and lactate-to-pyruvate ratio (purple).

4.4 Results

4.4.1 Patient Characteristics

All patients recruited to the ISCoPE study between 2011 to 2019 who had grade C injuries based on the American Association of Spinal Cord Injury Impairment Scale were selected. There were 19 patients, with average age 47 years (range 19 – 70), of which 14 (74 %) were male and 5 (26 %) female. Fourteen (74 %) had cervical and 5 (26 %) had thoracolumbar injuries. Of the 19 patients, 12 (63 %) had posterior surgical approach plus laminectomy, 5 had anterior plus posterior approach and laminectomy (26 %) and 2 (11 %) had posterior approach without laminectomy. Mean time from injury to surgery was 38 hours. All 19 patients had intraspinal pressure monitoring and 13 (68 %) also had microdialysis monitoring. The mean duration of intraspinal pressure monitoring was 5.1 days (range 1.8 – 6.8) and of microdialysis monitoring 3.7 days (range 0 – 6.8). The mean number of motor examinations during the monitored period was 19 (range 5 – 37), this variability mainly related to the patients' clinical condition i.e. those with severe respiratory issues requiring deep sedation which precluded sedation holds had fewer examinations. Table 13 has details.

4.4.2 Complications

Two patients (11 %) had cerebrospinal fluid leak from around the probe skin exit site which stopped with additional sutures and 4 patients (21 %) had asymptomatic pseudomeningocele on the post-operative MRI. Four patients (21 %) had chest sepsis and 1 (5.3 %) patient developed Korsakoff psychosis from alcohol withdrawal.

Table 13. Demographic details of the AIS grade C patients.

Pt. No.	Study No.	Age (y)	Sex	Level	Surgical approach	Lami	Injury to surgery (h)	ISP monitoring (h)	Microdialysis monitoring (h)	No. of motor exams
1	8	64	F	C5	Post	No	47	94	0	6
2	9	49	F	C5	Post	Yes	16	43	0	6
3	10	54	M	T12	Post	Yes	48	117	0	13
4	13	65	M	C4	Post+Ant	Yes	11	68	0	10
5	20	59	M	C6	Post	Yes	32	71	0	14
6	40	70	F	C4	Post	Yes	20	156	156	23
7	44	26	M	T12	Post	Yes	46	160	35	23
8	45	37	M	C4	Post+Ant	Yes	29	136	138	25
9	50	63	M	C7	Post	Yes	47	105	0	12
10	52	19	M	C6	Post	Yes	41	145	145	28
11	54	63	M	C5	Post	Yes	58	138	137	25
12	61	56	F	L1	Post	Yes	31	114	161	27
13	66	67	M	C4	Post	No	38	160	157	25
14	67	32	M	C4	Post+Ant	Yes	22	159	163	35
15	68	37	F	L3	Post	Yes	23	139	125	22
16	70	35	M	C4	Post+Ant	Yes	39	112	109	5
17	71	27	M	L1	Post	Yes	41	144	145	37
18	81	54	M	C4	Post	Yes	69	161	150	25
19	84	22	M	C6	Post+Ant	Yes	70	84	82	5

Ant, anterior; C, cervical; F, female; h, hours; Lami, laminectomy; M, male; No., number; Post, posterior; Pt., patient; T, thoracic; y, years

4.4.3 Motor score correlates with injury site physiology

Using data from all 19 patients, strong relationships were observed between standardised motor score *versus* ISP, *versus* SCPP and *versus* MAP. The curve $y = 3.9 + 33.4e^{-1.1x}$ fitted well the relationship between average motor score (y) *versus* ISP class (x = 1,…,8 respectively defined as <5, …, 35 – 40 mmHg). Reduction in ISP from >20 to <5 mmHg was associated with an average gain of about 11 motor points, whereas fluctuations in ISP in the range 20 – 40 mmHg were not associated with changes in average motor score (Fig. 42). The line $y = 1.4x - 3.9$ fitted well the relationship between average standardised motor score (y) *versus* SCPP (x = 1,…,7 respectively defined as 40 – 50, …, 100 – 110 mmHg). Increasing SCPP from <50 mmHg, up to 110 mmHg, was associated with an average gain of about 8 motor points. Increasing SCPP beyond 110 mmHg was associated with a reduction in motor score (Fig. 43). The curve $y = -0.1 + 2.4(1 - e^{-0.4x})$ fitted well the relationship between average standardised motor score (y) *versus* MAP (x = 1,…,11 respectively defined as <75, …, >120 mmHg). Increase in MAP from <75 to 95 mmHg was associated with an average gain of about 4 motor points whereas fluctuations in MAP in the range 95 – 130 mmHg were not associated with changes in average standardised motor score (Fig. 44).

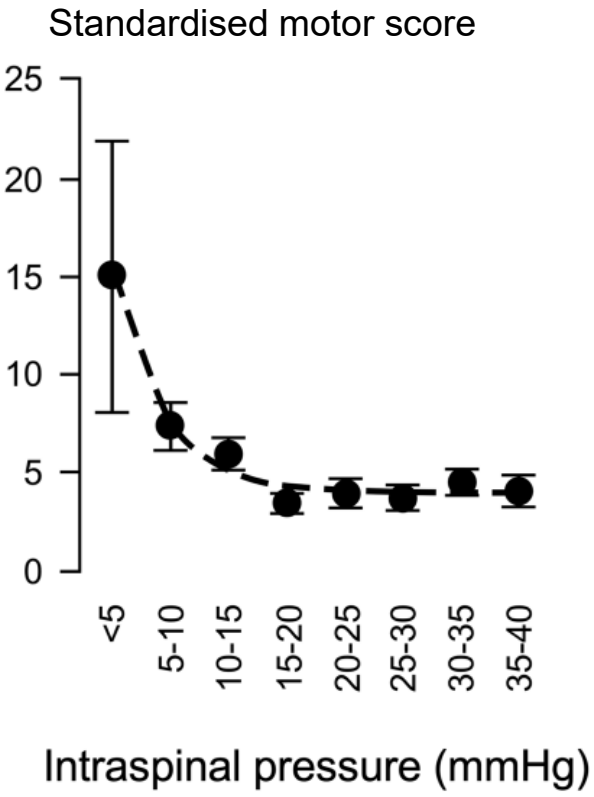


Fig. 42. Standardised motor score correlation with ISP. Standardised motor score *versus* intraspinal pressure. Mean ± standard error. Trends (dotted line) modelled as exponential decay *(R = 0.99, P < 0.0005)*

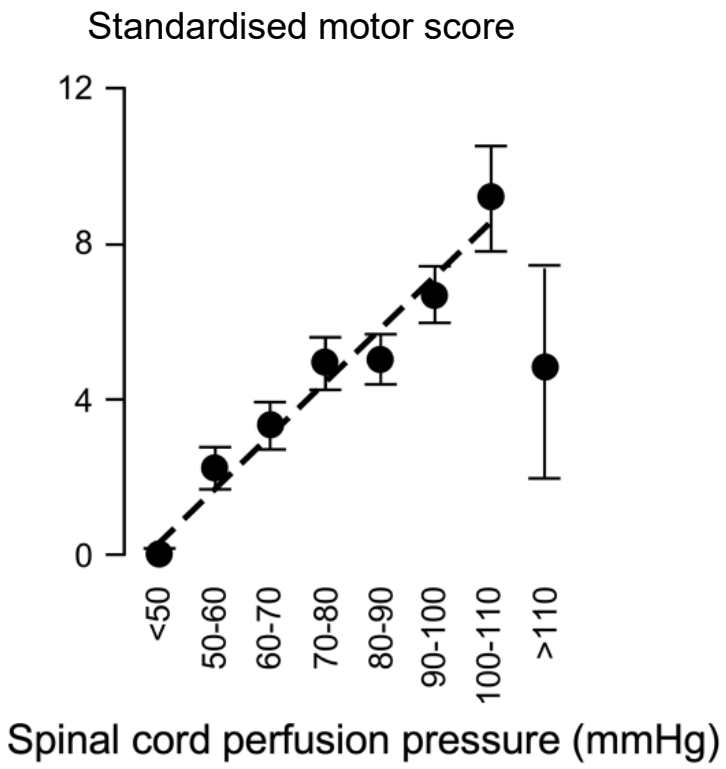


Fig. 43. Standardised motor score correlation with spinal cord perfusion pressure.
Standardised motor score *versus* spinal cord perfusion pressure. Mean ± standard error. Trends (dotted line) linear in the range <50 to 110 mmHg *(R = 0.98, P < 0.0005)*

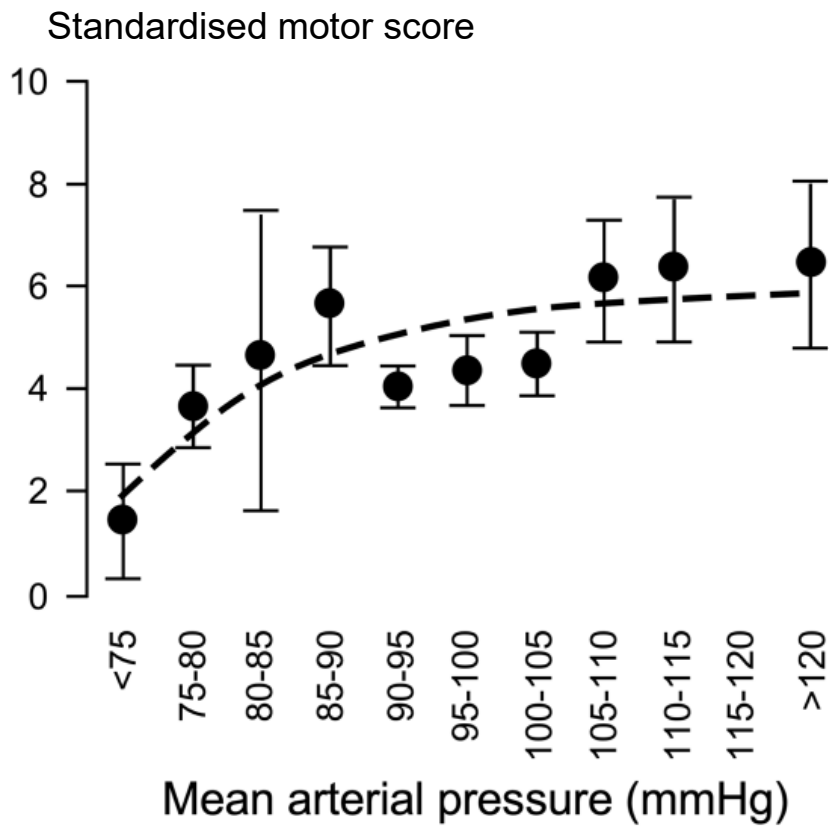


Fig. 44. Standardised motor score correlation with mean arterial pressure. Standardised motor score *versus* Mean arterial pressure. Mean ± standard error. Trends (dotted line) modelled as bounded exponential ($R = 0.85$, $P < 0.05$).

4.4.4 Motor score strongly correlates with injury site metabolism

Fig. 45 shows that the line $y = -0.8x + 8.3$ fits well the relation between average standardised motor score (y) *versus* LPR class (x = 2, …, 6 respectively defined as 20 – 30, …, >70), plotted using data from the 14 patients who had microdialysis monitoring. Reductions in the lactate-to-pyruvate ratio from >70 to 20 – 30, was associated with an average gain of about 4 motor points. Reductions in the LPR below 20, was associated with a reduction in average standardised motor score. Increases in the LPR from 20 – 30 to 30 – 40 was associated with no changes in pyruvate but an increase in lactate. As LPR increased beyond 40, both pyruvate and lactate dropped.

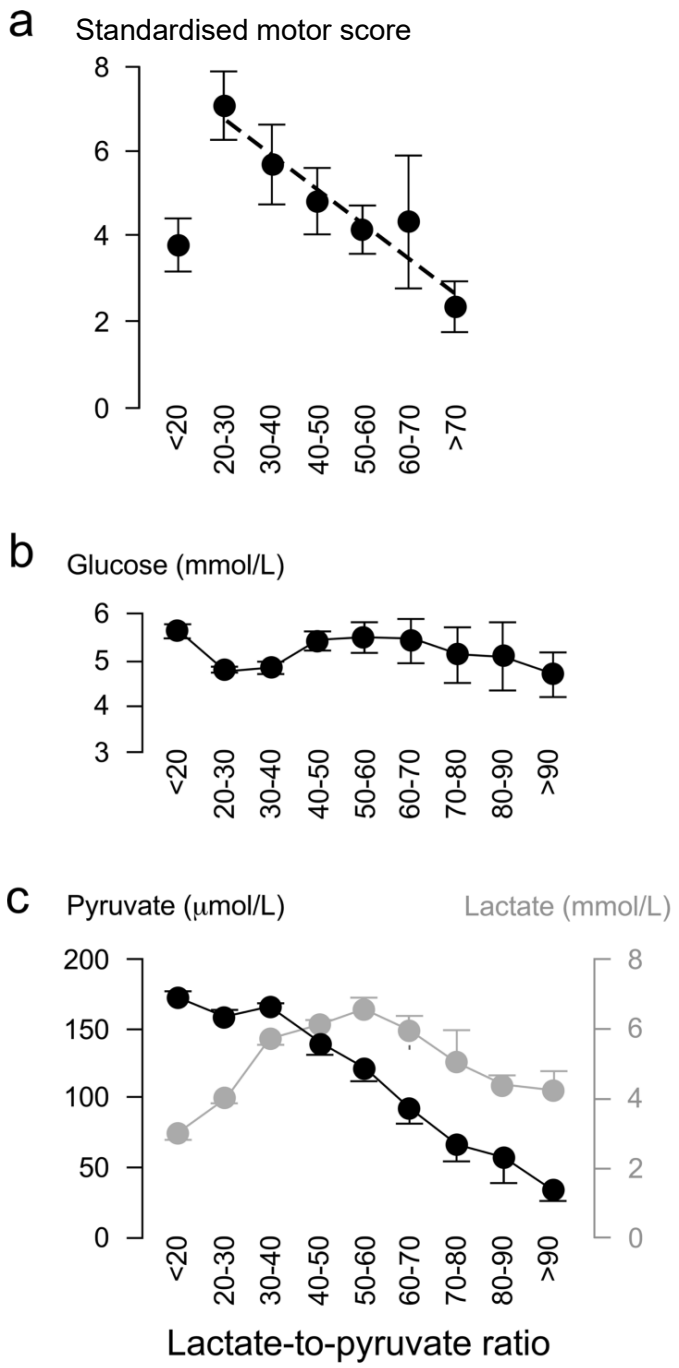


Fig. 45. Standardised motor score correlation with injury site metabolism. A. Relation between standardised motor score and LPR. **B.** Glucose and **C.** Lactate + Pyruvate *versus* LPR. Mean ± standard error. In A, the dotted line is the best fit straight line for LPR in the range 20 to >70 mmHg, $R = 0.96$, $P < 0.005$.

4.4.5 Injury site physiology and metabolism are closely related

Fig. 46 shows how ISP relates to injury site metabolism. LPR (y) and ISP class (x = 1, …, 9 respectively defined as <5, …, >40 mmHg) positively correlated according $y = 5.0x + 20.5$. As ISP increased, glucose increased, whereas lactate and pyruvate fell. Fig. 47 shows how SCPP is related to injury site metabolism. LPR (y) and SCPP class (x = 1, …, 8 respectively defined as <60, …, >120 mmHg) negatively correlated according $y = -4.3x + 54.3$. As SCPP increased up to 110 mmHg, glucose remained constant, whereas lactate and pyruvate slightly increased. As SCPP increased beyond 110 mmHg, glucose and pyruvate rose, whereas lactate fell.

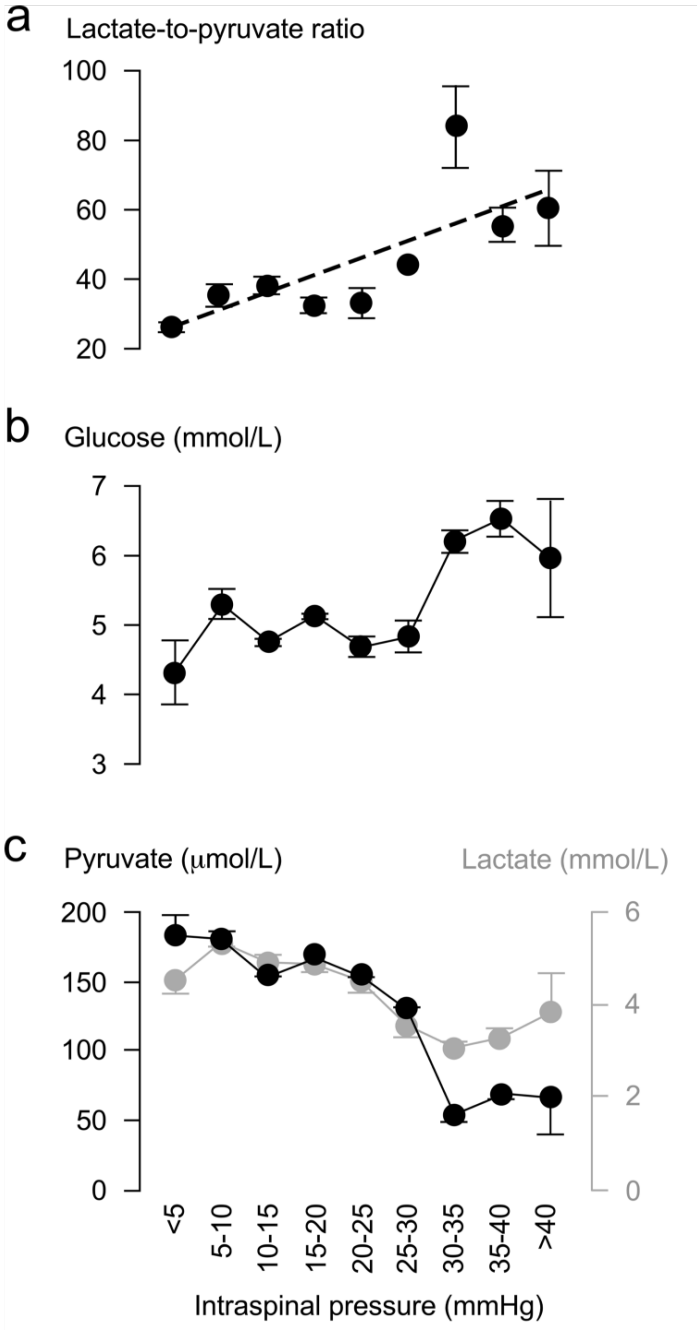


Fig. 46. Intraspinal pressure correlates with injury site metabolism. A. Injury site LPR, **B.** injury site glucose and **C.** injury site pyruvate (black) + lactate (gray), *versus* ISP. Mean ± standard error.

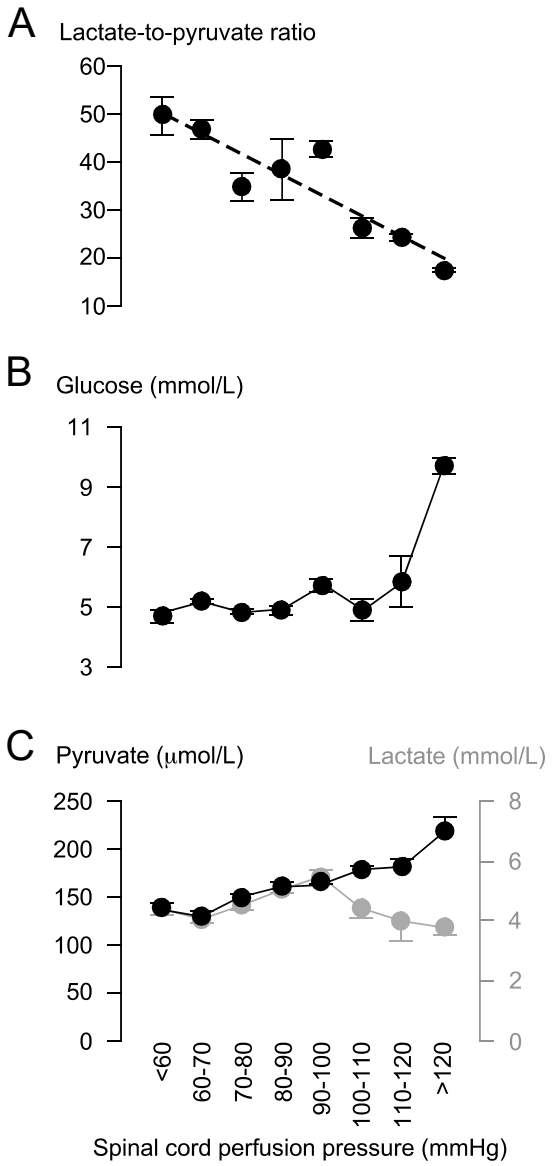


Fig. 47. Spinal cord perfusion pressure correlates with injury site metabolism. A. Injury site glucose **B.** injury site lactate-to-pyruvate ratio and **C.** injury site pyruvate (black) + lactate (gray), *versus* ISP. Mean ± standard error

4.4.6 Causality analysis

Granger causal relations between the motor score, ISP, SCPP and LPR time series are illustrated in Fig. 48. Increases in LPR Granger-causes increased ISP, decreased SCPP and decreased motor score. In other words, worse injury site metabolism increases cord swelling, reduces cord perfusion and increases limb weakness. Increasing SCPP Granger-causes decreased LPR and increased motor score. In other words, increases in spinal cord perfusion improves spinal cord metabolism and improves limb weakness. Increasing ISP Granger-causes increased LPR, decreased SCPP and decreased motor score. In other words, increased cord swelling reduces cord perfusion, worsens cord metabolism and increases limb weakness.

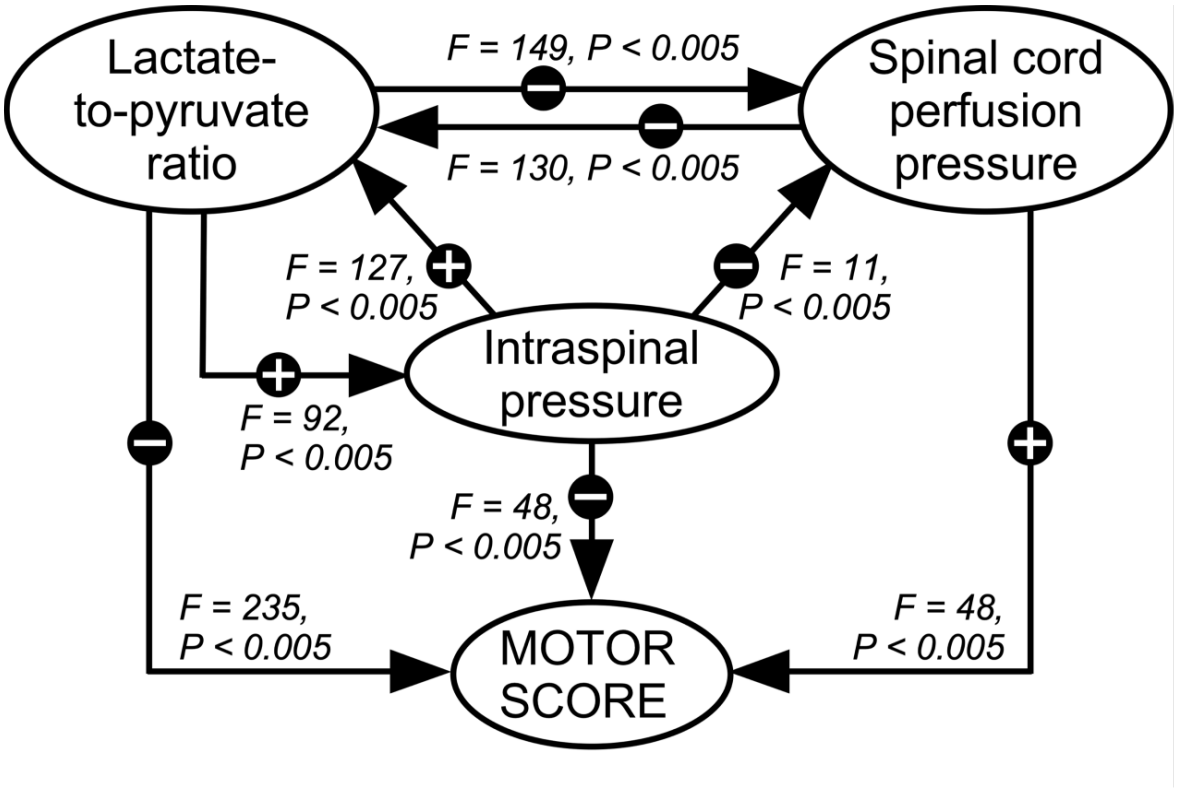


Fig. 48. Granger causality relations. Each arrow indicates the direction of information flow, i.e. causal influence, with corresponding *F* and *P* values. '+' or '–' indicate the correlation between the variables. Causality arrows are shown if $P < 0.05$. Analysis is shown for lag = 1, but also holds for lag = 2 or 3.

4.5 Discussion

This study indicates that after TSCI, fluctuations in injury site physiology (cord oedema, cord perfusion) and metabolism (LPR) influences fluctuations in limb power. To define the relations between events at the injury site and limb power, I monitored patients with acute, motor-incomplete spinal cord injuries and applied the statistical concept of Granger causality.

Multiple correlations between injury site physiology, metabolism and neurological status were defined. There were seven interesting findings to highlight: First, optimal ISP is less than 5 mmHg, i.e. no cord compression. Second, increase in ISP from 20 to 40 mmHg is associated with increase in LPR, but no reduction in limb power, probably because the standardised motor score is already very low. Third, as SCPP increases, LPR decreases (less ischemia) and limb power improves but, beyond 110 mmHg, limb power decreases suggesting that hyper-perfusing the injury site is detrimental. Metabolically, hyper-perfusion is characterised by very low (less than 20) LPR and high glucose; though this is aerobic metabolism, our data suggest that the high glucose is detrimental as previously reported[113-115] due to increased inflammation, increased free radicals and endoplasmic reticulum stress. Fourth, the relation between MAP and motor score plateaus with MAP beyond 85 – 90 mmHg, which interestingly corresponds to the recommended target[116]. A possible explanation is that low MAP indicates injury site ischemia regardless of ISP, but above 90 mmHg, the same MAP corresponds to injury site ischemia in some patients and hyper-perfusion in others. In practical terms our results suggest that increasing SCPP improves limb power more than increasing the MAP. Fifth, the correlations between ISP and SCPP *versus* limb power are reminiscent of similar relations *versus* neurological improvement at 9 – 12 months observed in previous studies from the ISCoPE group.[50] Sixth, though there is inverse correlation between LPR and limb power, LPR below 20 appears detrimental likely related to hyper-perfusion state described above. Seventh, as LPR increases up to 50 – 60, pyruvate decreases and lactate increases (indicating compensatory switch from aerobic to anaerobic metabolism at the injury site), but as LPR increases beyond 60, both pyruvate and lactate decrease (indicating overall suppression of aerobic and anaerobic metabolism). Though the findings described here provide a unique insight into how spinal cord physiological and metabolic events relate to limb power, they are associations that do not imply causations.

Establishing causation in medicine is based on the totality of evidence that includes strong association, biological mechanism, consistent finding, temporal sequence and dose-response[117]. In the absence of a randomized trial, which is considered the "gold standard" to establish causation[118,119], we investigated causal relations in our observational data using

Granger analysis[111,112]. Granger's definition of causality satisfies two intuitive notions: first, the cause always precedes the effect, second, the cause carries unique information about the future effect, i.e. there is information flow from the past of the cause to the future of the effect that cannot be accounted for by the past of the effect. Implicit in these notions is that intervention to alter the cause should result in a predictable change in the future of the effect. Advantages of Granger are that it is expressed in relatively straightforward mathematics that permit hypothesis testing and provide information about the strength of each causality[118,119]. Alternative analyses that can distinguish between causation and correlation may be performed, e.g. convergent cross mapping, which is based on complexity theory and, unlike Granger, does not assume linear relations or a stochastic system in which the influences of causal variables are independent[120].

The causal relations between LPR, SCPP, ISP and standardised motor score in Fig. 48 make biological sense. A metabolic insult (high LPR e.g. from hypoxia or infection) causes cord swelling (high ISP), causes reduction in cord perfusion and causes impaired neuronal function (reduced motor score). Increase in spinal cord perfusion causes increase in aerobic metabolism at the injury site (decreased LPR) and causes the motor score to improve. Cord swelling (increase in ISP) causes more anaerobic metabolism (LPR increases), causes drop in SCPP (equals MAP minus ISP) and causes reduction in limb power. Interestingly, Granger analysis did not produce absurdities e.g. change in limb power causes physiological or metabolic changes at the injury site. A key finding in Fig. 47 are several positive feedback loops (vicious cycles) e.g. increased LPR causes increased cord swelling, in turn causing increase in LPR. Multi-step vicious cycles are also evident, e.g. increased LPR causes increased cord swelling (ISP), which causes decreased SCPP, in turn causing increase in LPR. The presence of so many vicious cycles implies that insults to the injury site (e.g. hypoxia, acidosis etc.) are amplified, thus emphasising the importance of treating such insults to prevent secondary cord damage.

4.6 Conclusions

Patients with acute, motor-incomplete TSCI provide a unique opportunity to define the relations between LPR, SCPP, ISP and limb power. The nature of such correlations e.g. linear, exponential decay etc. shed light on the pathophysiological events at the injury site. But correlation does not imply cause. Granger analysis indicates causal relationships between LPR, SCPP, ISP and limb power indicating that interventions to normalize deranged spinal cord physiology and metabolism after TSCI will improve neurological outcomes.

5. CHAPTER 4: Effects of local hypothermia-rewarming on physiology, metabolism and inflammation of the acutely injured human spinal cord

5.1 Introduction

Hypothermia is being investigated as a potential therapy for TBI[28,121,122] and TSCI[27] based on pre-clinical data which suggests that hypothermia is neuroprotective. In animal models of TBI, hypothermia has been shown reduce: the metabolic rate, inflammation, oedema, oxidative stress, excitotoxicity, electrolyte imbalance and apoptotic and necrotic cell death in vulnerable tissue[123-128]. Transition from bench to clinic is less promising, randomised controlled human trials have failed to show functional benefit of hypothermia in patients with TBI [28,122]. In TSCI animal models are similarly promising: rodent models of TSCI show improved histological and functional outcomes after hypothermia [25,129]. Small, non-randomised studies in human TSCI patients have shown improved functional outcomes after local[130,131] and systemic hypothermia[27,132]. To date, there is no level one evidence to support hypothermia in TBI or TSCI.

Despite the interest in therapeutic hypothermia for neurologic injury, there is little mechanistic data from humans defining the effects of hypothermia on the human CNS. In TSCI patients, the effect of cooling and rewarming on cord swelling, metabolism and inflammation are unknown. We do not know if hypothermia and rewarming have beneficial or adverse effects on the injured human spinal cord. Our techniques of multi-modal monitoring from the injury site [24,47,49,56,60,63,64] offer a unique insight into the effect of local hypothermia and rewarming on injury site physiology, metabolism and inflammation in TSCI patients.

5.2 Aim

To assess the effects of local hypothermia on injury site physiology, metabolism and inflammation in TSCI.

5.3 Methods

Methods (and patient recruitment) outlined below were formulated prior to my tenure as a PhD Student by my colleague Mathew Gallagher, Dr Saadoun and Prof Papadopoulos. I contributed to the analysis of results for this study.

5.3.1 Institutional Approvals

Hypothermia–rewarming was approved as a sub-study of the ISCoPE (Injured Spinal Cord Pressure Evaluation) study for TSCI by St George's, University of London Joint Research Office and the National Research Ethics Service London–St Giles committee (no. 10/H0807/23). The ISCoPE study is registered at ClinicalTrials.gov as NCT02721615. The approvals, patient information sheet, consent form and substantial amendment for this sub-study can be viewed in Appendix 1.

5.3.2 Inclusion/Exclusion criteria

Inclusion/exclusion criteria were the same as previous (see Table 2) aside that cervical injuries were excluded because of the length of the cooling balloon.

5.3.3 Clinical examination and investigations

Examinations and imaging were performed as previously described in sections 2.3.6 and 2.3.7. On the NICU, core temperature was recorded continuously from a urinary catheter temperature probe.

5.3.4 Surgery and Probe Insertion

All patients had a posterior approach plus laminectomy and pedicle screw fixation two levels above and two levels below using the Xia 3 system (Stryker, Newbury, UK). ISP and microdialysis probes were inserted as outlined previously in sections 2.3.3 and 3.3.4. Fig. 49 shows set up.

5.3.5 Cooling catheter

A sterile cooling balloon, part of a closed catheter loop system (Cool line catheter, Zoll medical, Cheshire, UK), and sterile thermometer (Smiths Medical, Ashford, UK) were tunnelled into the wound cavity and placed extradurally. A wound drain was inserted for a week and was set 'under gravity'. The wound was closed in layers using vicryl sutures with nylon sutures for the skin. In NICU, the wound was covered with an electric warming blanket set at 37 ^{0}C (CosyTherm mattress, Inspiration healthcare, Rotherham, UK). Figs. 49 and 50 shows the set up.

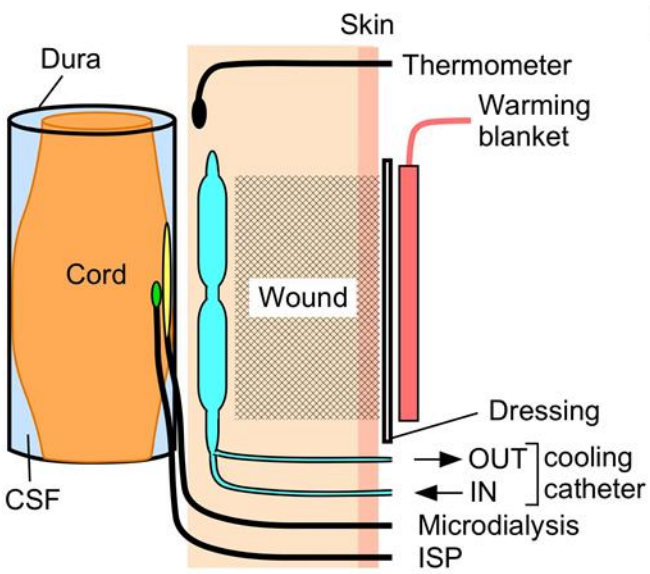


Fig. 49. Schematic of setup for monitoring and cooling. ISP probe and microdialysis catheter lie intradurally, on the surface of the injured cord. Cooling catheter and thermometer are extradural. A heating pad is placed on the skin.

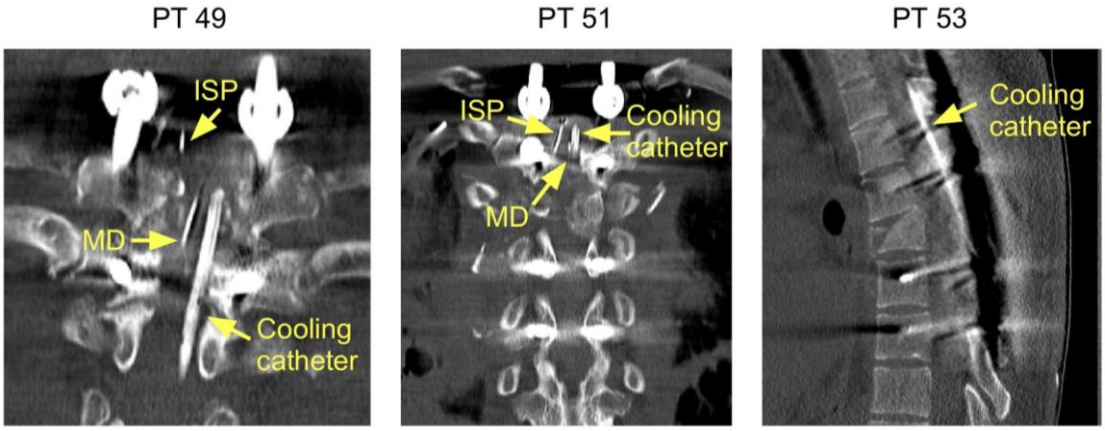


Fig. 50. Clinical setup. Post-operative spinal CT showing position of ISP probe, microdialysis and cooling cooling catheters.

5.3.6 ISP and Microdialysis monitoring

The monitoring setup for ISP and ABP was as outlined in section 2.3.4. Microdialysis set up and analysis is as described in section 3.3.6.

5.3.7 ICU patient management

Clinical management of patients is as outlined in section 2.3.5.

5.3.8 Multiplex ELISA for cytokines/chemokines

Microdialysis vials for the patients were grouped by sampling period 6 hours pre-cooling, 6 hours at 33 ^{0}C and 6 hours post-rewarming i.e. at 37 ^{0}C and then sent to the Charité Universitätsmedizin Berlin (stored at -80^{0}C) so that concentrations of cytokines/chemokines in the microdialysis fluid could be analysed. Analysis was performed using multiplex electrochemiluminescence assay panel (Meso Scale Discovery, Rockville, microdialysis, USA) using the following antibody sets from the U-PLEX Biomarker Group 1 Human Assays panel (K15067L): IL1α, IL1β, IL4, IL8, IL10, IP10, GROα, MCP1, MIP1α, MIP1β. These molecules were selected because they have been implicated in the pathophysiology of spinal cord injury[133-147](please see Table 14 for details of the roles of each inflammatory mediator in the inflammatory response in TSCI), they are <30 kDa (i.e. can cross the microdialysis membrane) and they are part of our multiplex electrochemiluminescence assay panel.

Table 14. Inflammatory cytokines and chemokines in TSCI

Cytokine	Pro or Anti-Inflammatory	Secreted By	Effects	Role in TSCI	CV (%)
IL1α	Pro	Macrophages Neutrophils Epithelial cells Endothelial cell	Production of inflammation. Fever. Sepsis.	IL1α deletion protects oligodendrocytes after SCI.[133] IL1α activates microglia/macrophages after SCI[135]	16.5
IL1β	Pro	Macrophages Neutrophils Epithelial cells Endothelial cell	Production of inflammation. Fever. Sepsis.	IL1β is upregulated in human SCI. [136] IL1β may cause chronic pain after SCI[137]	3.6
IL-4	Anti	T cells Basophils Mast cells	Regulates humoral + adaptive immunity. Decreases production of Th1 cells, macrophages, IFNγ and IL12. Promotes activation of macrophages into M2 cells and inhibits activation into M1 cells.	IL4 reduces cavity formation after SCI.[138] Systemic IL4 administration is neuroprotective after SCI[148]	7.3
IL-8	Pro	Macrophages Neutrophils Endothelial cell	Induces chemotaxis in neutrophils and other granulocytes, causing them to migrate toward the site of infection and stimulates phagocytosis once they have arrived.	IL8 is upregulated in human SCI[149]	2.2
IL-10	Anti	Macrophages Lymphocytes	Suppresses cytokine secretion, antigen presentation and CD4+ T cell activation and inhibits lipopolysaccharide and bacterial mediated induction of pro-inflammatory cytokines.	IL10 limits inflammation & improves outcome after SCI.[139] IL10 is beneficial after SCI[140]	15.1
IP10	Pro	Macrophages Endothelial cells Fibroblasts	Secreted in response to IFNγ. Promotes chemoattraction for macrophages, T cells, NK cells and dendritic cells and promotes T cell adhesion to endothelial cells.	Neutralisation of IP10 reduces apoptosis and increases axon sprouting after SCI[142] Neutralisation of IP10 enhances tissue sparing and angiogenesis following SCI[141]	2.7
GRO α	Pro	Macrophages Neutrophils Epithelial cells	Neutrophil chemoattraction.	Increased expression after SCI[143] Neutrophil chemoattraction after SCI and role of GROα[144]	5.5
MCP1	Pro	Macrophages Dendritic cells	Recruits macrophages, memory T cells and dendritic cells to the sites of inflammation produced by tissue injury or infection.	MCP1 is upregulated in human SCI[149] Monocyte recruitment + myelin removal delayed after SCI in mice with non-functional MCP1[145]	5.4
MIP1 α	Pro	Macrophages	Recruitment and activation of polymorphonuclear leukocytes.	Increased MIP1α expression after SCI[146]	14.3
MIP β	Pro	Macrophages	Chemoattractant for natural killer cells, monocytes and a variety of other immune cells.	Increased MIP1β after SCI[147] Increased MIP1β after SCI[134]	4.5

CV = Coefficient of Variation of Assay

5.3.9 Cooling-rewarming

A closed temperature system pumping sterile saline into the balloon catheter (Thermoguard XP temperature management system, Zoll Medical, Cheshire, UK) was connected at the bedside in NICU. Cooling was started 12 hours after surgery to allow baseline cord physiological and microdialysis measurements to be obtained. In the first patient, the temperature was reduced by 1 ^{0}C every 12 hours until the target of 33^{0}C. This slow reduction allowed real-time analysis of microdialysis samples and repeat neurological examinations to ensure no clinical deterioration. After 12 hours at 33 ^{0}C, the cord was rewarmed to 37 ^{0}C at 0.5 ^{0}C/hour. In subsequent patients, the cord was cooled to 33 ^{0}C in one step and, after 72 hours, rewarmed at 0.5 ^{0}C/hour to 37 ^{0}C.

5.3.10 Data and statistical analysis

For ISP, SCPP and metabolites, we compared the 12 hourly values at 37 ^{0}C immediately preceding hypothermia vs. the 12 hourly values at 33 ^{0}C vs. the first 12 hourly values at 37 ^{0}C i.e. post-rewarming. For cytokines/chemokines, we compared the 6 hourly values at 37 ^{0}C immediately preceding hypothermia vs. 6 hourly values at 33 ^{0}C vs. the first 6 hourly values at 37 ^{0}C i.e. post-rewarming. The three temperature groups (pre-hypothermia, hypothermia, post-rewarming) were compared pairwise by Kruskal-Wallis + post-hoc Dunn-Bonferroni for each patient. Analysis was done using XLStat Biomed v2018.1 for Mac (Addinsoft, Paris, France). Statistical significance was taken as $P < 0.05$.

5.4 Results

5.4.1 Patient characteristics

We recruited the five consecutive patients with severe thoracic TSCIs (Fig. 51). Most were young (aged 45.4 ± 7.1 years, mean ± standard error) and male (66.7 %). The delay between TSCI and surgery was 47.4 ± 9.6 hours and the injury to cooling time 70.4 ± 9.3 hours. At 18.2 ± 5.1 months follow up, total motor score increased by 8.8 ± 8.5, total pin prick score by 6.8 ± 6.5 and total light touch score by 2.6 ± 2.5 points. Overall, two patients (40 %) had improved by at least one AIS grade. For further details see Table 15.

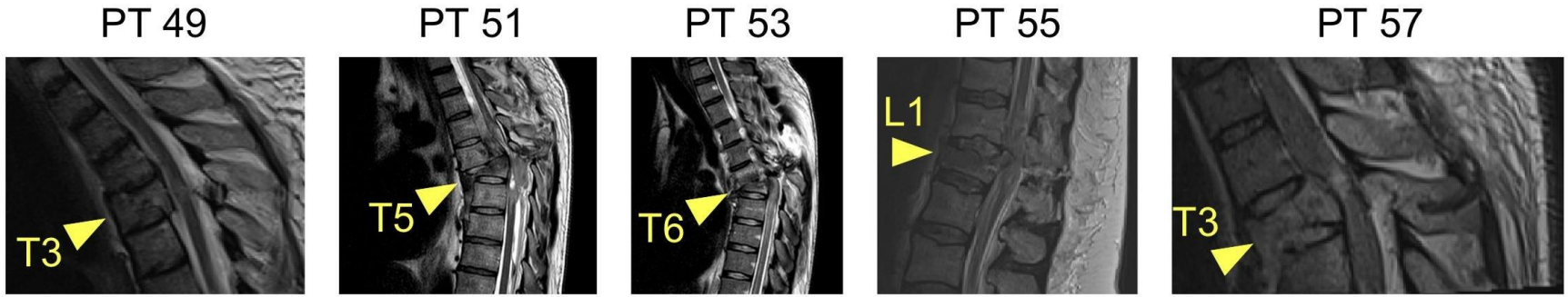


Fig. 51. Sagittal T2 pre-operative spinal MRI of the five patients

Table 15. Patient Demographics

PT	AGE	SEX	INJURY TO SURGERY (Hours)	INJURY TO COOLING (Hours)	INJURY LEVEL	ADMISSION				FOLLOWUP				FOLLOWUP (MONTHS)
						AIS	TMS	TPP	TLT	AIS	TMS	TPP	TLT	
49	66	F	65	88	T3	B	50	54	54	D	89	83	61	29
51	36	M	49	71	T5	A	50	52	52	A	50	48	48	25
53	30	M	21	45	T6	A	50	52	52	A	50	52	52	22
*55	52	F	36	60	T12	A	51	81	80	B	56	88	88	6
57	43	M	66	88	T3	A	50	40	40	A	50	42	42	9

*F, Female; M, Male; NLI, AIS, American spinal injuries association Impairment Scale; PT, patient; TLT, total light touch score; TMS, total motor score; TPP, total pin prick score; *No cooling, equipment failure*

5.4.2 Cooling–rewarming

The patients tolerated local hypothermia and rewarming well without pain, discomfort or shivering. Throughout the cooling and rewarming, all patients were alert, orientated and self-ventilating with no changes in their neurological examinations. Except for the first patient (PT 49), who was subjected to a slow cooling protocol for safety, all subsequent patients reached the target extradural temperature of 33 ^{0}C in 20 minutes (Fig. 52). In all patients, the cooling protocol reduced the extradural temperature to the target value (Fig. 53) without causing a significant change in the core temperature (Fig 54).

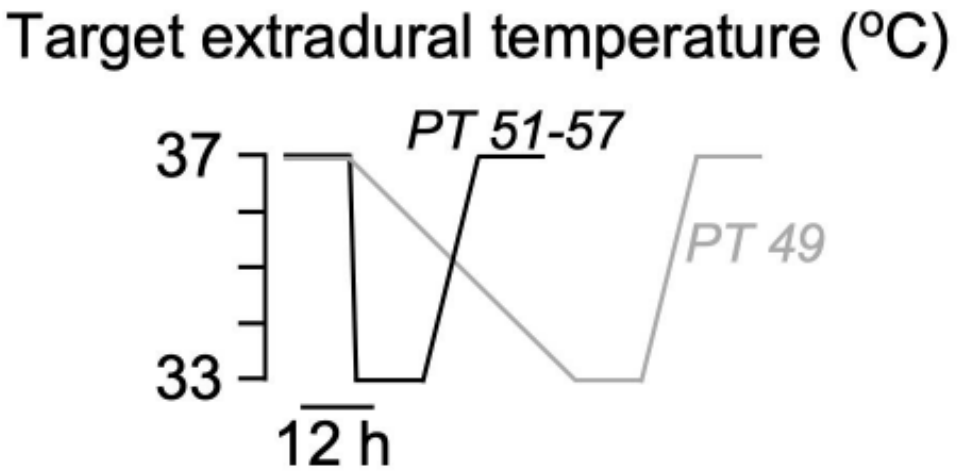


Fig. 52. Extradural cool/re-warm regime

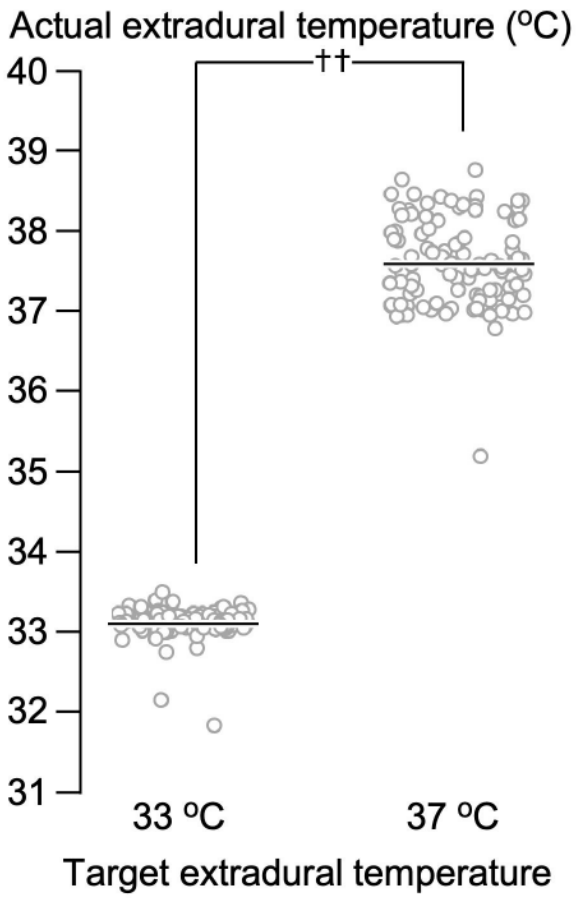


Fig. 53. Actual extradural temperature at target extradural temperatures 33 and 37 ºC.
$P < 0.0001^{††}$

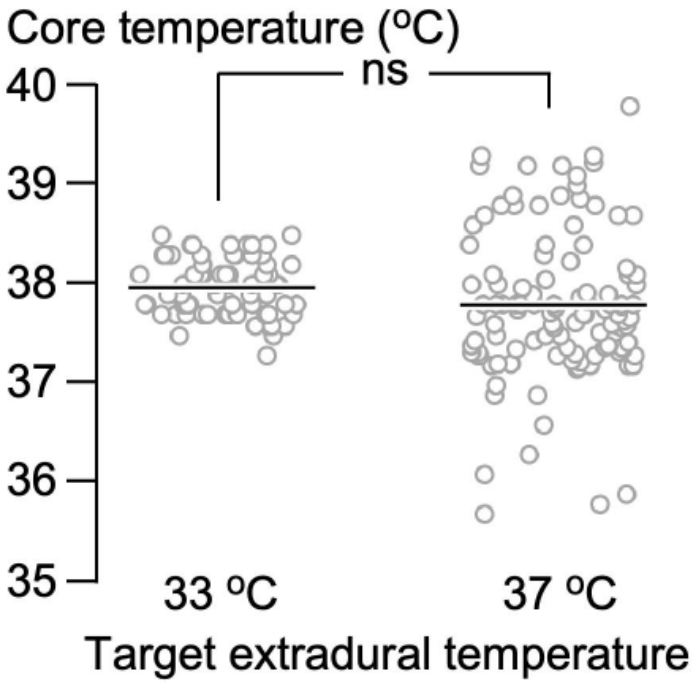


Fig. 54. Core temperature at target extradural temperatures 33 and 37 ºC. Not significant ns

5.4.3 Injury site physiology

In the 12 hours before the start of the cool–rewarm protocol, mean spinal cord ISP was 12.7 mmHg and SCPP at 83.3 mmHg with MAP at 93.1 mmHg. Cooling from 37 to 33 ^{0}C did not produce any significant changes in ISP, SCPP or MAP. Re-warming from 33 to 37 ^{0}C was associated with significant increase in mean ISP by 13.2 mmHg and significant decrease in mean SCPP by 14.6 mmHg compared with corresponding average pre-cooling baseline levels. MAP remained unaffected. For further details see Figs. 55-57.

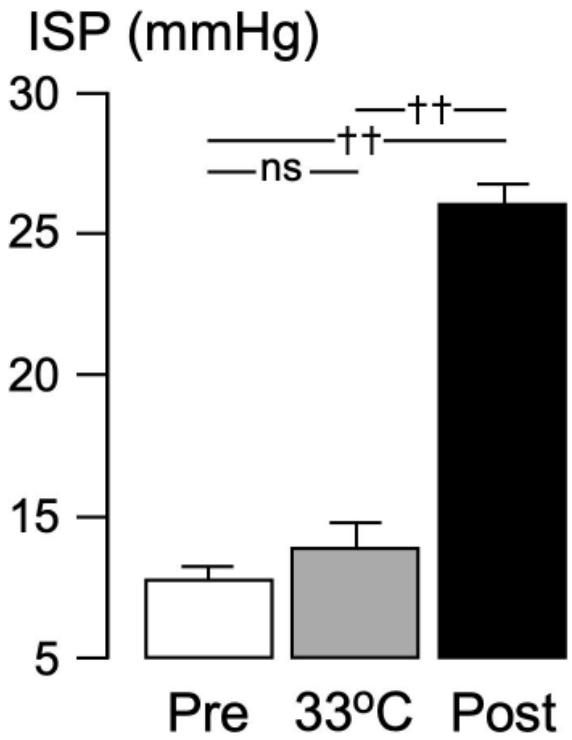


Fig. 55. Effect of cooling-rewarming on ISP. ISP for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant, ns; $P < 0.0001^{\dagger\dagger}$.

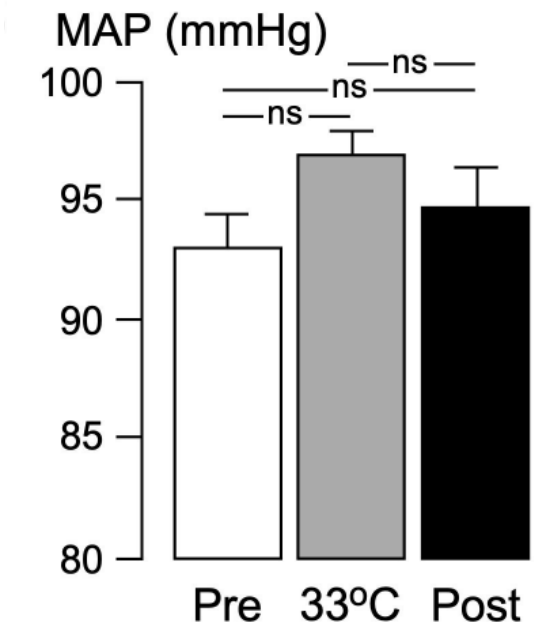


Fig. 56. Effect of cooling-rewarming on MAP. MAP for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant, ns.

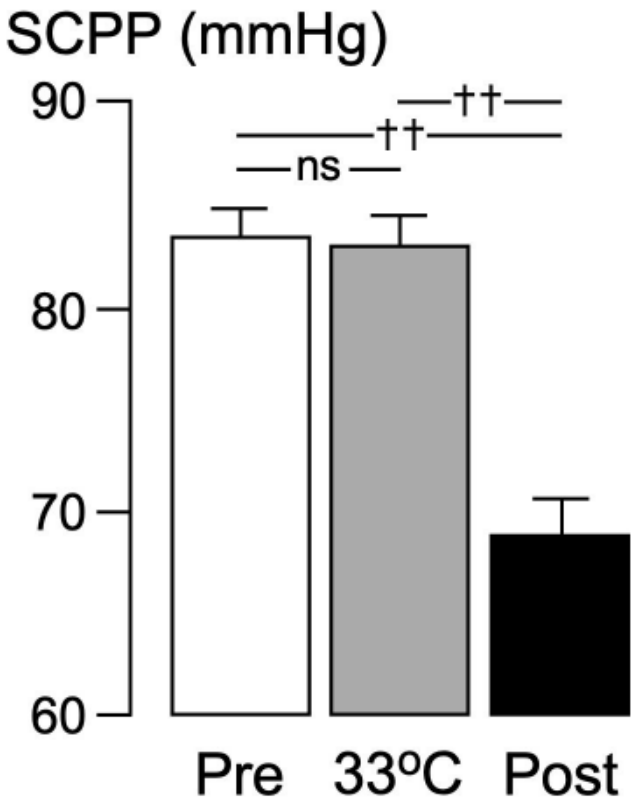


Fig. 57. Effect of cooling-rewarming on SCPP. SCPP for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant, ns; $P < 0.0001^{\dagger\dagger}$.

5.4.4 Injury site metabolism

In the 12 hours before the start of the cool-rewarm protocol, baseline spinal cord injury site glucose concentration was 2.3 mM, lactate 5.1 mM, pyruvate 148.5 μM, LPR 33.9, glutamate 10.9 μM and glycerol 54.5 μM. Cooling and rewarming had a major impact on injury site metabolism. Cooling was associated with significant increase in injury site glucose by 1.0 mM, significant increase in lactate by 1.9 mM, no change in pyruvate, significant increase in LPR by 113.0, significant increase in glutamate by 6.4 μM and significant decrease in glycerol by 13.4 μM. Compared with average pre-cooling baseline levels, rewarming was associated with significant decrease in injury site glucose by 0.9 mM, significant increase in lactate by 3.9 mM, no change in pyruvate, significant increase in LPR by 314.9, no change in glutamate by 6.4 μM and significant decrease in glycerol by 30.0 μM. Please see Figs. 58-63.

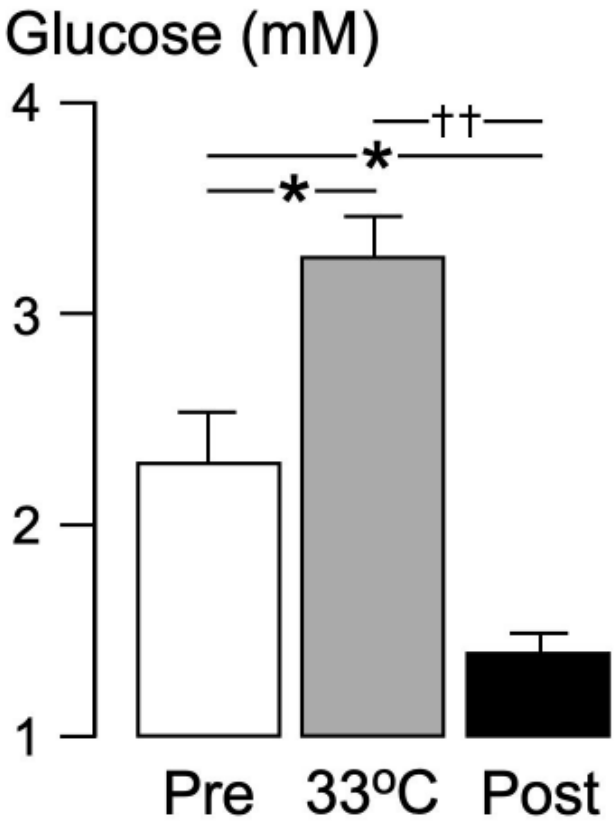


Fig. 58. Effect of cooling-rewarming on injury site glucose. Glucose levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. $P < 0.05^{*}$, $< 0.0001^{\dagger\dagger}$

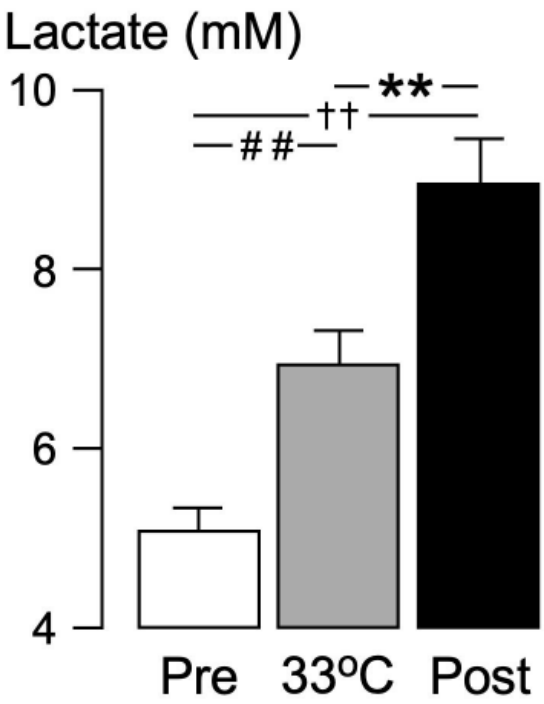


Fig. 59. Effect of cooling-rewarming on injury site lactate. Lactate levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. $P < 0.05^{*}$, p<0.01**, $<0.001^{\#\#}$, $< 0.0001^{\dagger\dagger}$

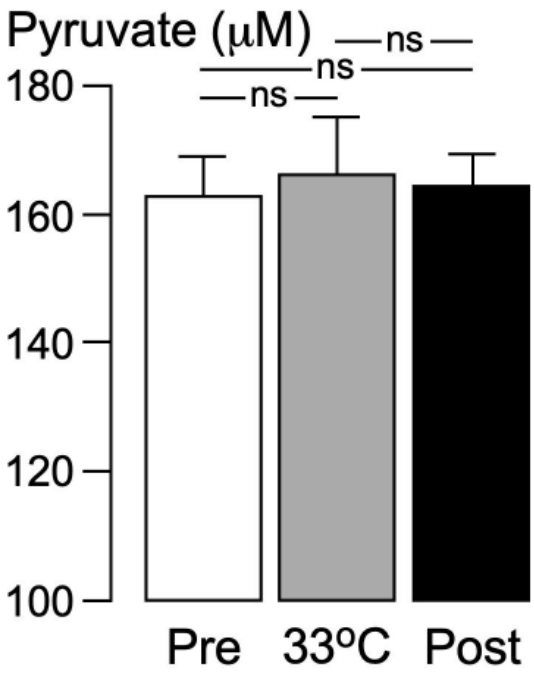


Fig. 60. Effect of cooling-rewarming on injury site pyruvate. Pyruvate levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. ns not significant

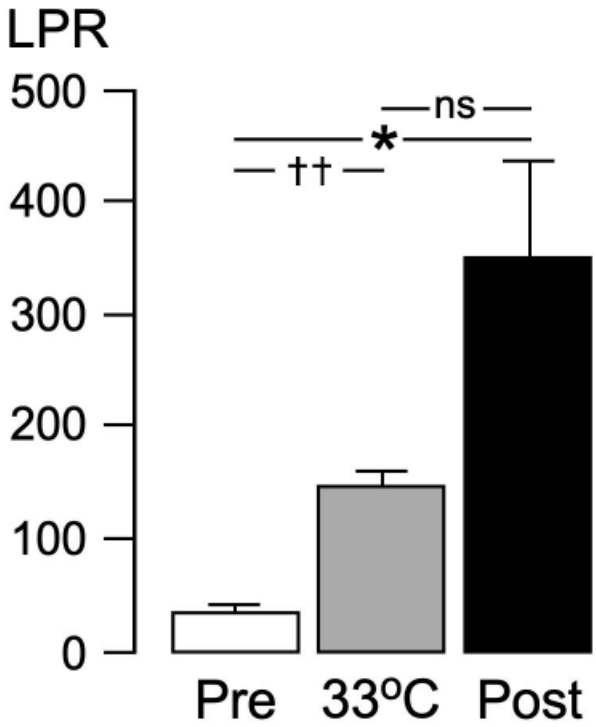


Fig. 61. Effect of cooling-rewarming on injury site LPR. LPR for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. ns not significant, $P < 0.05^{*}$, $< 0.0001^{\dagger\dagger}$

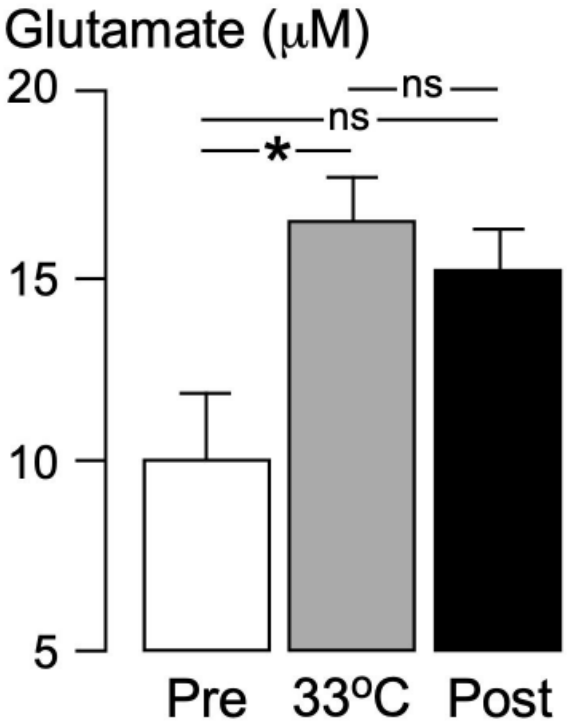


Fig. 62. Effect of cooling-rewarming on injury site glutamate. Glutamate levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. ns not significant, $P < 0.05^{*}$

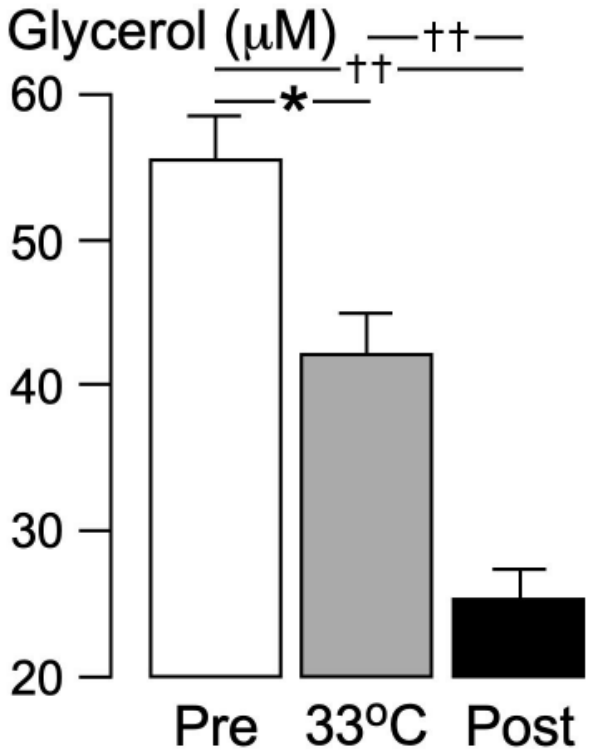


Fig. 63. Effect of cooling-rewarming on injury site glycerol. Glycerol levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. $P < 0.05^{*}$, $< 0.0001^{\dagger\dagger}$

5.4.5 Injury site inflammation

In the 12 hours before the start of the cool-rewarm protocol, baseline spinal cord IL1α concentration was 5.6 pg/mL, injury site IL1β was 13.5 pg/mL, injury site IL8 was 2,013.9 pg/mL, injury site IL4 was 0.3 pg/mL, injury site IL10 was 1.0 pg/mL, injury site IP10 was 66.4 pg/mL, injury site MCP1 was 1,821.5 pg/mL, injury site MIP1α was 67.0 pg/mL, injury site MIP1β was 111.2 pg/mL and injury site GROα was 268.8 pg/mL. The concentrations of injury site inflammatory cytokines significantly decreased with cooling by 62.8 % for IL1β, 87.1 % for IL8, 58.7 % for MCP1, 69.8 % for MIP1α and 37.0 % for MIP1β. Compared with hypothermia, there was rebound significant increase in the concentrations of inflammatory cytokines on rewarming by 465 .3 % for IL1β 606.1 % for IL8, 241.6 % for IL4, 848.1 % for IL10 and 222.4 for MIP1α. For details see Figs. 64-73.

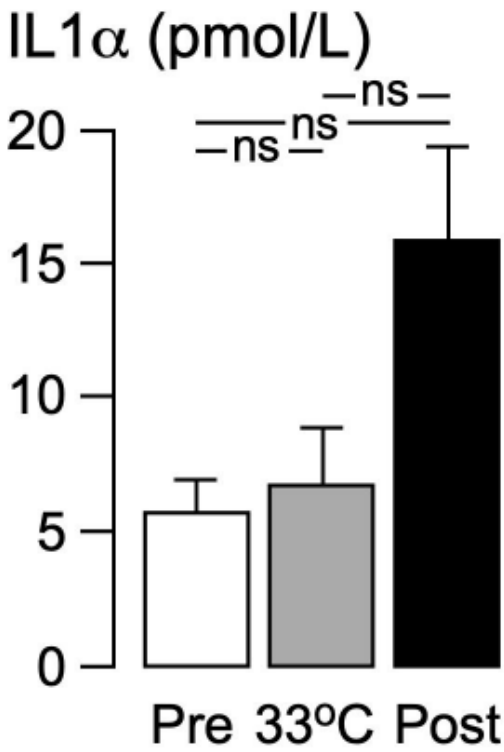


Fig. 64. Effect of cooling-rewarming on injury site IL1α. IL1α levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns

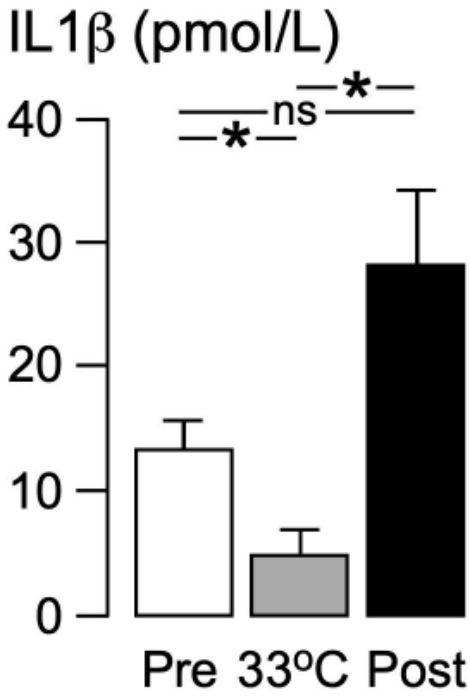


Fig. 65. Effect of cooling-rewarming on injury site IL1β. IL1β levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$

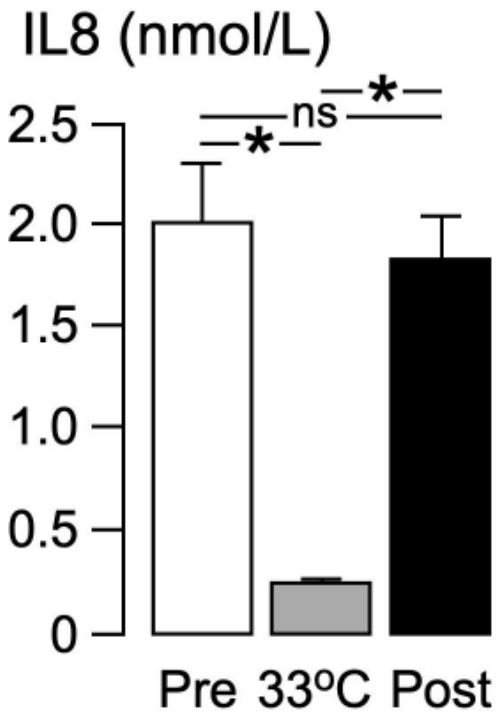


Fig. 66. Effect of cooling-rewarming on injury site IL8. IL8 levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$

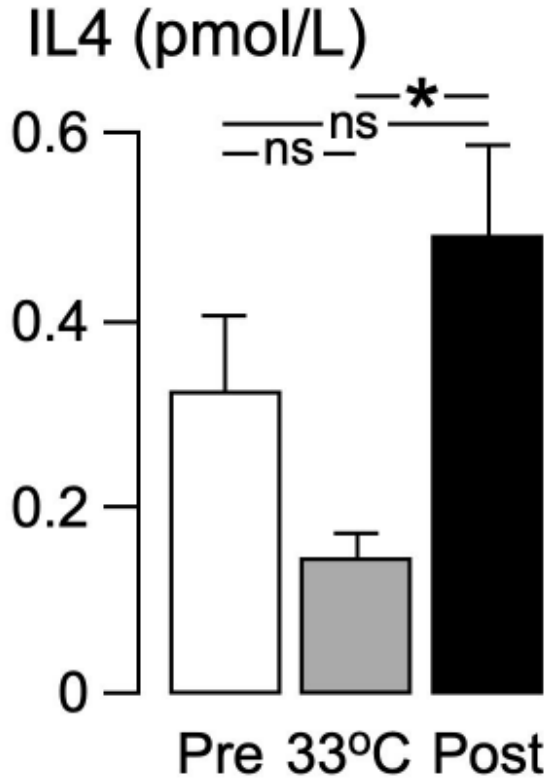


Fig. 67. Effect of cooling-rewarming on injury site IL4. IL4 levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$

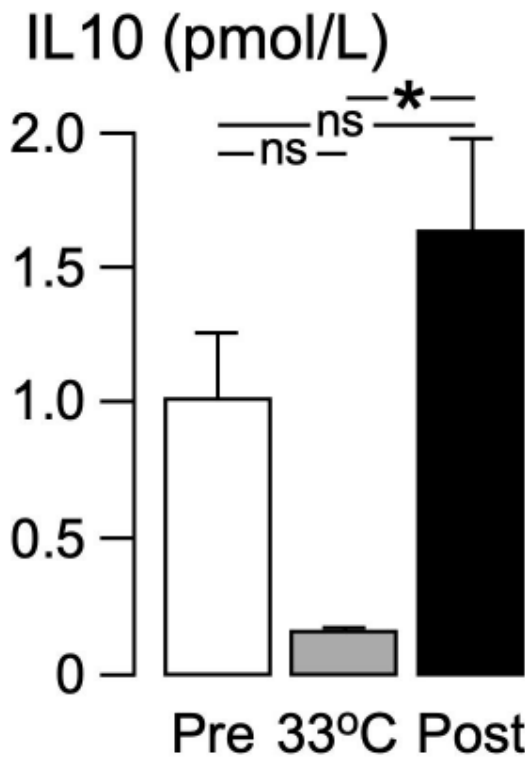


Fig. 68. Effect of cooling-rewarming on injury site IL10. IL10 levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$

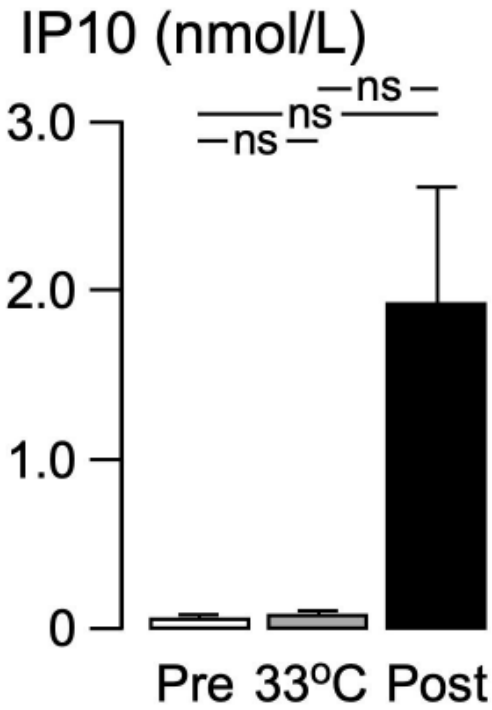


Fig. 69. Effect of cooling-rewarming on injury site IP10. IP10 levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns

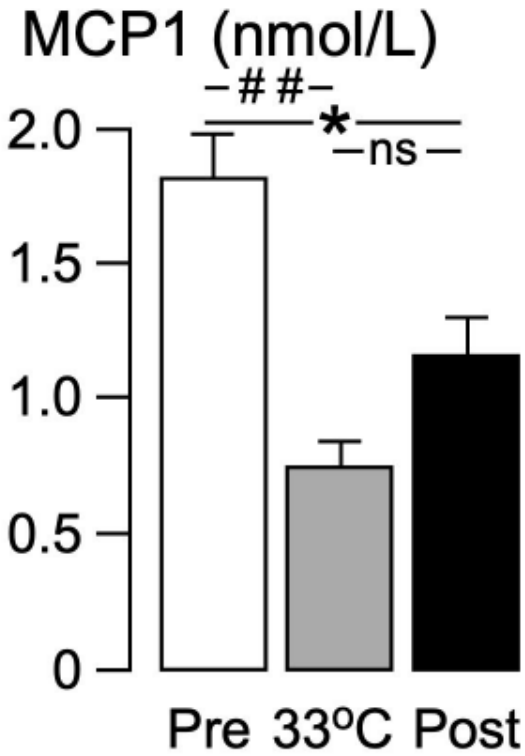


Fig. 70. Effect of cooling-rewarming on injury site MCP1. MCP1 levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$, $<0.001^{\#\#}$

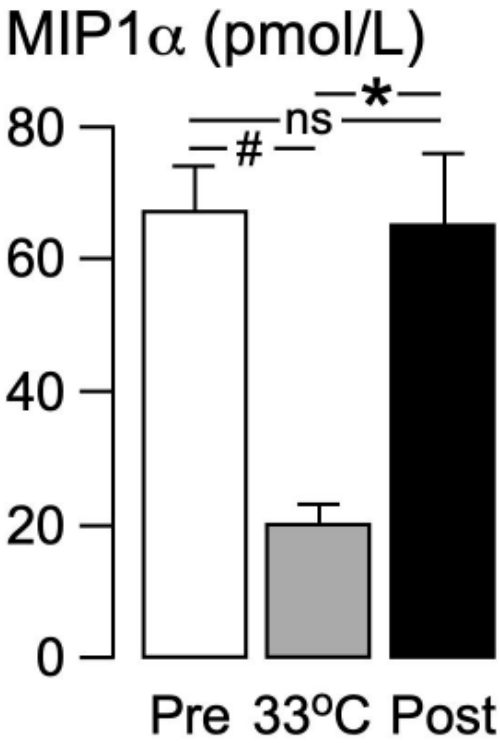


Fig. 71. Effect of cooling-rewarming on injury site MIP1α. MIP1α levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$, $<0.005^{\#}$

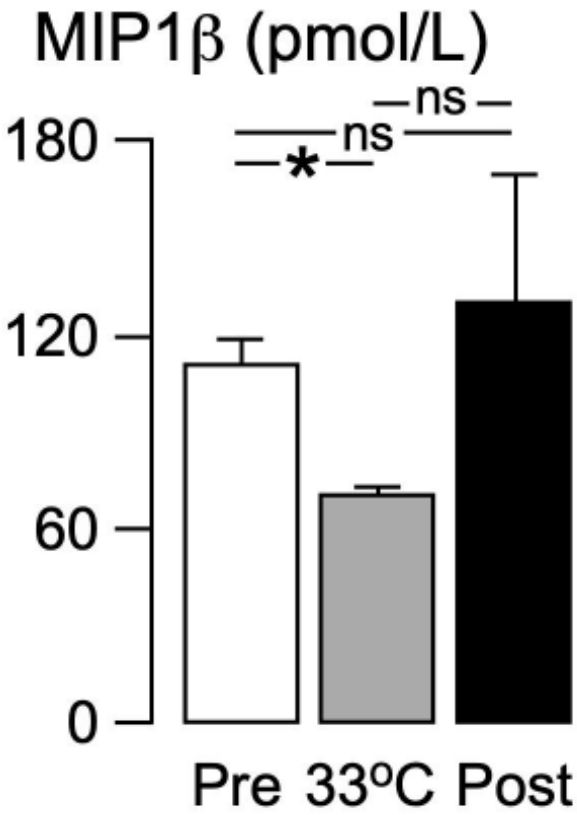


Fig. 72. Effect of cooling-rewarming on injury site MIP1β. MIP1β levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns, $P < 0.05^{*}$

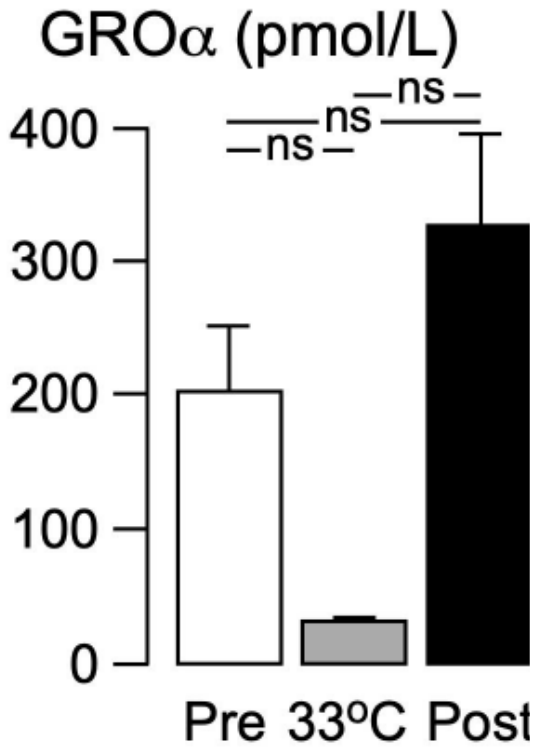


Fig. 73. Effect of cooling-rewarming on injury site GROα. GROα levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 ºC) and for 24 h after the end of re-warming (black, Post). Mean +/- standard error. Not significant ns

5.4.6 Complications

Spinal cord cooling and rewarming was associated with complications, summarized in Table 16. In 1/5 (20 %) patients, the equipment failed; there was a hole in the cooling catheter balloon that allowed the cooled sterile saline fluid to enter the wound cavity and leave through the wound drain. In this patient, cooling was stopped and the catheter was removed. Three of the five (60 %) patients had culture positive delayed wound infections of which two needed a wound washout under general anaesthetic. They received antibiotics with the metalwork *in situ* and recovered with no deterioration in ISNCSCI neurological scores. In contrast, we have had 1 wound infection in the 78 patients recruited to the ISCoPE trial (2010-20) who underwent multi-modality injury site without spinal cooling-rewarming. After discussion with the sponsors was well as our neurosurgical, intensive care unit and microbiology colleagues, the decision was taken to prematurely terminate the study.

5.4.7 Outcomes

At a mean follow-up of 36 weeks, 2/5 (40 %) patients had improved their AIS grade, one from A to B and the other from B to D. We observed increase in mean ISNCSCI total motor score by 8.8 points (0 – 39), pin prick sensation of 6.8 points (-4 – 29) and total light touch sensation of 2.6 points (-4 – 8). The wounds were well-healed at follow-up.

Table 16: Wound Complications of localised hypothermia

PATIENT	WOUND BREAKDOWN	WOUND BACTERIA	SURGICAL WOUND TREATMENT	ANTIBIOTICS	OUTCOME
49	Yes	*E. coli* *S. aureus*	Day 16 lumbar drain Day 43 debridement	52 days	Wound well-healed
51	No	No	No	No	Wound well-healed
53	No	*E. coli*	No	45 days	Wound well-healed
*55	No	No	No	No	Wound well-healed
57	Yes	*S. aureus*	Day 22 pus aspirated Day 24 debridement	56 days	Wound well-healed

**No cooling, equipment failure*

5.5 Discussion

Although hypothermia has shown promise in managing neurological injuries, systemic hypothermia is associated with coagulopathy, electrolyte disturbances, myocardiac ischemia, atrial fibrillation, sepsis, pneumonia and altered drug metabolism[150] - we therefore employed local hypothermia aiming to avoid these complications. During local hypothermia–rewarming in awake TSCI patients, there was no discomfort nor shivering and no change in ISNCSCI motor and sensory scores. However, hypothermia–rewarming adversely affected the physiology, metabolism and inflammatory response of the injury site with increased cord swelling (high ISP), worse cord perfusion (lower SCPP), worsened cord metabolism and increased tissue inflammation. The rewarming phase appears to be the most detrimental. Furthermore hypothermia–rewarming was associated with increased risk of delayed deep wound infections.

In a previous study of local hypothermia, cooling was performed during surgery. After spinal decompression, a cooling device was placed extradurally and the spinal cord was cooled at a rapid rate using an extradural device set at 6 ^{0}C with hypothermia lasting 3 – 4 hours followed by rapid rewarming. The mean time to cooling was within 7 hours of TSCI and the cooling device was removed from the cord prior to surgical closure[130]. In comparison we started hypothermia later on, cooled within 20 min (apart from the first patient) to 33 ^{0}C for 12 hours, left the cooling device in the surgical wound and rewarmed slowly at 0.5 ^{0}C/h. It has been suggested that slower rewarming (<0.5 ^{0}C/h) might be more beneficial to avoid a mismatch between local blood perfusion and metabolism[151]. Because of high wound infection rates our study was terminated early and we were unable to study the effects of more prolonged hypothermia or slower rewarming on ISP, SCPP, cord metabolism and cord inflammation.

Hypothermia had no significant impact on ISP, whereas rewarming was associated with a marked rebound rise in ISP by 13.2 mmHg. MAP remained constant throughout, meaning SCPP dropped by 14.6 mmHg during rewarming due to the increase in ISP. Our findings mirror observations in human TBI, where hypothermia caused non-significant decrease in intracranial pressure (ICP)[28,122] and rewarming caused a rebound rise in ICP[152]. The effects of hypothermia–rewarming on ICP may relate to blood flow changes, i.e. vasoconstriction during hypothermia and vasodilatation during rewarming[153]. In our patients, baseline ISP was not elevated, at 12.7 mmHg, which may explain why hypothermia did not reduce ISP. The ISP rise we observed after rewarming may have been caused by increased inflammation within the injured cord related to reperfusion. There is substantial evidence that

during reperfusion, leukocytes become activated to release multiple inflammatory factors[154], consistent with the marked rise in the injury site cytokines/chemokine levels observed here.

Hypothermia was associated with a rise in inury site glucose, lactate and LPR without change in pyruvate. Rewarming was associated with a marked fall in injury site glucose, further rise in lactate and LPR, again with constant pyruvate. Hypothermia is known to reduce cellular metabolism and in the brain, for every 1 ^{0}C drop in temperature, there is a 6 % drop in cerebral metabolic rate[153], which would reduce cellular glucose consumption at the injury site and explain the rise in injury site glucose concentration. After rewarming, the fall in glucose would be due to increased cellular metabolic rate and increased glucose consumption. In the brain lactate is both a by-product of anaerobic metabolism and a neuronal energy substrate[155]. Several mechanisms may therefore account for the rise in injury site lactate (with constant pyruvate) with cooling and further rise with rewarming: a depleted O_2 supply from reduced SCPP increases anaerobic metabolism increasing lactate release from cells; denaturing of pyruvate dehydrogenase by cooling diverting pyruvate to lactate rather than into the tricarboxylic acid cycle and increased uptake of lactate at the injury site from the circulation to meet increased metabolic requirements. The relative contributions of these mechanisms may differ in hypothermia *vs.* rewarming. As yet the underlying mechanisms for this phenomenon remain conjecture but the main finding is that hypothermia–rewarming is associated with a marked changes/impairment of spinal cord metabolism at the injury site.

Hypothermia–rewarming was also associated with rise in injury site glutamate and fall in injury site glycerol. Glutamate is an excitatory neurotransmitter that in excess causes excitotoxic damage to neurons, excess release is seen in ischaemia and excess levels are associated with worse outcomes in TBI and sub-arachnoid haemorrhage[43]. Glycerol is released into the extracellular fluid during plasma cell membrane lysis, it is a marker of cell membrane breakdown and oxidative stress however it has limited specificity in TBI as it can be influenced by systemic levels or administration of glycerol containing substances and there is no definitive data to link glycerol levels with outcome in TBI[43]. In human TBI, hypothermia–rewarming was generally associated with reduced ventricular CSF glutamate[156], we have shown that injury site glutamate has no strong correlation with lumbar CSF glutamate so this trend is not comparable to our results. Interestingly, during the 12 hours before the onset of hypothermia, injury site glutamate was rising at a rate of 1.3 μM/h, whereas glycerol was decreasing at a rate of 2.6 μM/h so it is possible that changes in injury

site glutamate and glycerol largely represent trends related to the injury rather than the effects of hypothermia or rewarming. It may also be that with increasing metabolic dysfunction with hypothermia-rewarming the spinal cord releases more glutamate exacerbating this already present trend. If there was cell death and cell lysis we would expect glycerol to rise – it may be that like in TBI this is a non-specific marker in TSCI or that cellular death had not yet occurred and they were just metabolically deranged.

The effects of hypothermia and rewarming on injury site cytokines/chemokines was very interesting. Hypothermia led to a marked reduction in the concentrations of injury site cytokines/chemokines whereas rewarming led to a significant rise to levels higher than pre-cooling. The effect of hypothermia in suppressing inflammation after TSCI mirrors findings in animal models[157] but animal models have not studied the effects of rewarming on inflammation. Suppression of inflammation induced by hypothermia may be beneficial to the damaged spinal cord, but it may also predispose to wound infection. An earlier study using local early cooling reported a wound infection rate of 10 %[130] and our study found 60 % wound infection rate, this difference may reflect the methods in which cooling was performed (the former only intraoperative, for shorter duration) but an infection of 10% is significantly above the number of wound infections we have seen in our non-cooled ISCoPE patients (one wound infection in 78 patients giving and infection rate of 1.2%). Potential ways to reduce wound infection risk in future trials include prolonged antibiotics and iodine impregnated occlusive dressings. The rebound increase in tissue inflammation is potentially detrimental to the injured cord e.g. by increasing vasogenic oedema from breakdown of the blood-spinal cord barrier[154].

5.6 Limitations

The results are limited by the small sample size and lack of controls. Without direct control data we are unable to definitively conclude that the changes observed during the cooling or rewarming period relate to the effects of hypothermia rather than the pathological processes underlying spinal cord injuries at that time point following injury. Additionally there may be other paradigms for spinal cooling which work better than the methods we adopted.

5.7 Conclusions

Local hypothermia–rewarming after TSCI is associated with increased spinal cord swelling, reduced cord perfusion, more deranged cord metabolism, increased cord inflammation and

increased risk of wound infection. Based on these findings, we suggest caution when attempting to use hypothermia–rewarming therapeutically in TSCI patients.

6. CHAPTER 5: Improving bladder function in patients with acute spinal cord injuries by optimising injury site perfusion

6.1 Introduction

Chronic TSCI often leads to unfavourable urodynamics i.e. low bladder compliance (<20 ml/cmH_2O), detrusor overactivity and detrusor sphincter dyssynergia. As a result, detrusor pressure rises (>40 cmH_2O) causing vesico-ureteral reflux, hydronephrosis and, ultimately, renal failure[158]. Before urological surveillance became established, 50 % TSCI patients died from renal failure[159]. Even now, renal failure remains the fourth leading cause of death after TSCI despite better urological management[5]. Improving bladder function is one of the top priorities according to TSCI patients, carers and health experts[160,161].

Unlike chronic TSCI, the effect of acute TSCI on urinary bladder function is poorly understood. Current thinking is that, early after TSCI, the detrusor becomes acontractile (spinal shock phase) and, within weeks, a reflex neurogenic bladder gradually develops[29]. Here, we performed filling cystometry in the first 10 days after TSCI whilst also monitoring from the injury site. We asked if, at this early stage, the detrusor is indeed acontractile and whether bladder function could be improved by interventions to increase SCPP.

6.2 Aim

To determine whether, after severe acute TSCI bladder function is influenced by fluctuations in physiological and metabolic parameters monitored from the injury site.

6.3 Methods

6.3.1 Institutional Approvals

Urodynamic investigations were approved as a sub-study (Amendment 10) of the ISCoPE (Injured Spinal Cord Pressure Evaluation) study for TSCI. Approvals for ISCoPE, including the consent form and patient information sheet, were obtained by the St Georges Joint Research Office and the National Research Ethic Service – Camberwell St Giles Committee (No 10/H0807/23). ISCoPE is registered at www.clinical trials.gov as NCT02721615. ISCOPE is being conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

6.3.2 Inclusion/Exclusion Criteria

We prospectively recruited a cohort of consecutive TSCI patients who were enrolled into the ISCoPE trial in the period June 2018 – August 2019. Inclusion/exclusion criteria were the same as previous (see Table 2). Patients with history urinary dysfunction or renal failure or other contraindications to undergo urodynamic investigations were not included in this substudy.

6.3.3 Clinical examination and imaging

Clinical examination / assessments and imaging were performed as previously described in sections 2.3.6 and 2.3.7. Patients were followed up periodically in the outpatient clinic that includes assessment of AIS grade and completion of validated patient recorded outcome measures using the 'Spinal Cord Independence measures" (SCIM III) and Short Form Qualiveen (SF-Qualiveen)[162,163]. SCIM III bladder scores range from 0 – 15 (0 = indwelling catheter, 3 = residual urine volume (RUV) >100cc; no regular catheterisation or assisted intermittent catheterisation, ,6 = residual urinary volume <100cc or intermittent self catheterisation; needs assistance for applying drainage instrument, 9 = intermittent self catheterisation; uses external drainage instrument; does not need assistance for applying, 11 = intermittent self catheterisation; continent between catheterisations; does not use external drainage instrument, 13= residual urinary volume <100cc; needs only external urinary drainage; no assistance is required for drainage; 15 = residual urinary volume < 100cc; continent; does not use external drainage). SF-Qualiveen scores range from 0-4, 0 = no impact of urinary symptoms on quality of life, 4= severe impact of urinary problems on quality of life). Details of follow up urodynamic investigations were collected where possible.

6.3.4 Surgery and Probe Insertion

Surgery and probe insertion were performed as outlined previously in sections 2.3.3 and 3.3.4.

6.3.5 ISP, ABP and Microdialysis Monitoring

The monitoring setup for ISP and ABP was as outlined in section 2.3.4. Microdialysis set up and analysis is as described in section 3.3.6. Fig. 74 shows set up. Microdialysis vials were changed hourly and analyzed using ISCUS Flex (CMA Microdialysis AB) for glucose, lactate and pyruvate and the lactate-to-pyruvate ratio (LPR) was computed. The first two

samples from each patient were discarded to allow priming of the microdialysis catheter and stabilization of the metabolite concentrations. 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from analysis.

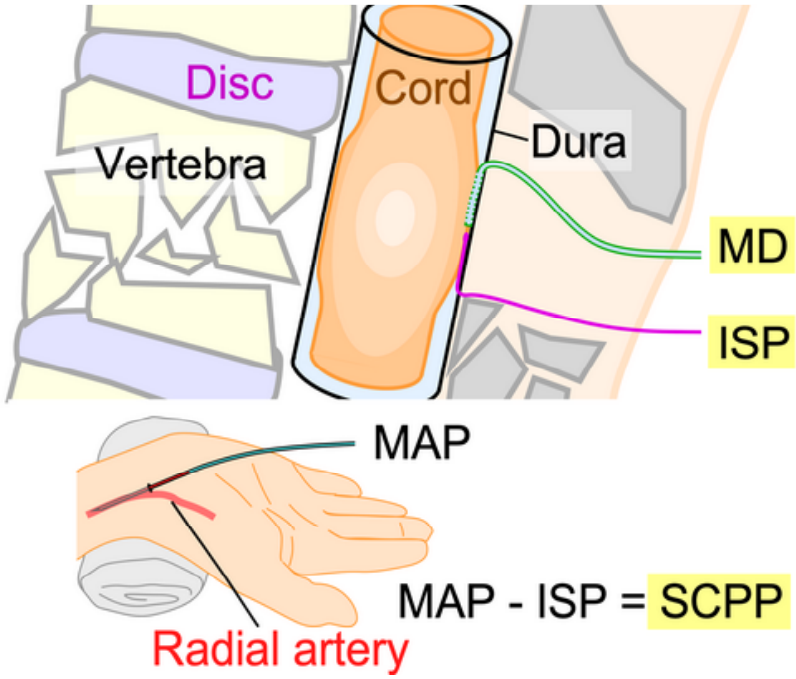


Fig 74. Injury site monitoring set up: *(top)* ISP probe and microdialysis catheter placed intradurally at injury site. *(bottom)* Catheter in radial artery to monitor MAP. SCPP = MAP – ISP.

6.3.6 Urodynamic investigations

Filling cystometry was performed in the week after surgery according to international guidelines[164] (Fig. 75) by a myself and ICU research nurse Siobhan Kearney. I was trained in urodynamic investigations by Eskinder Soloman (consultant clinical scientist with a special interest in diagnostic tests for functional urological problems) who also helped develop the protocol for this study. In addition to attending clinics at Guys Hospital to observe UDI studies, I also successfully completed a 3 day examined course "Certificate in Urodynamics" run by the Bristol Urological Institute. Patients were investigated, where possible, sitting at 45^0 without sedation. The bladder was filled through a transurethral double-lumen catheter (Bard Medical, Crawley, UK) with 0.9 % saline at 25 mL/min. Intra-vesicular pressure (P_{ves}) was monitored through the other lumen by a water-perfused pressure monitor zeroed at the pubic symphysis. Rectal (P_{rec}) and anal sphincter (P_{ana}) pressures were also monitored using a 4-channel water-perfused anorectal manometer (Ardmore Healthcare, Middleton on Sea, UK) respectively leveled at the pubic symphysis and anal verge. Pressure probes were connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK), in turn attached to the PowerLab system and sampled at 1kHz. The bladder was filled to 600 mL or until the detrusor pressure $P_{det} = P_{ves} – P_{rec}$ reached 40 cmH_20. Patients were asked to report first bladder sensation.

V_{max} is the volume drained from the bladder at end-fill (saline infused + urine produced). Bladder compliance ($\Delta V/\Delta P_{det}$) was computed by dividing bladder volume change by change in detrusor pressure. P_{ana} and P_{rec} were used as respective surrogate markers of urethral and abdominal pressures. Detrusor overactivity was quantified as the number of bladder contractions (transient pressure rises in P_{ves}) per fill cycle. Detrusor sphincter dysnergia was quantified as the number of bladder and rectal/anal contractions (synchronous transient rises in P_{ves} and P_{rec}/P_{ana}).

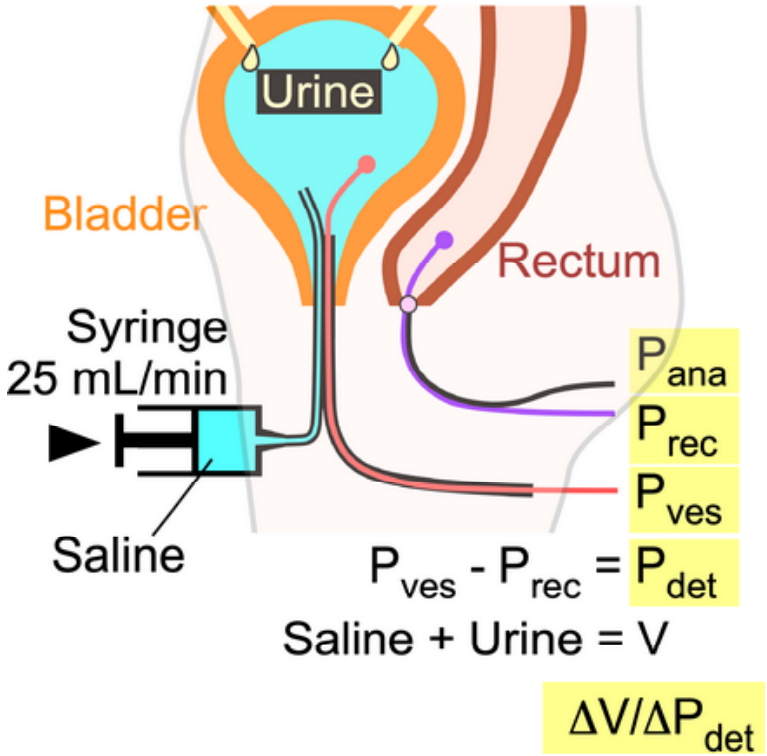


Fig. 75. Cystometry set up. Normal saline is infused at 25 mL/min into bladder up to 600 mL. Probes monitor intravesical (P_{ves}), rectal (P_{rec}) and anal (P_{ana}) pressures. Detrusor pressure $P_{det} = P_{ves} – P_{rec}$. Bladder volume V = infused saline + urine produced. Bladder compliance is $\Delta V/\Delta P_{det}$. Key parameters highlighted yellow.

6.3.7 Statistical analysis

Plots of urodynamic parameters (bladder compliance, DO, DSD, maximum detrusor pressure) *vs.* injury site characteristics (SCPP, ISP, injury site glucose, injury site LPR) were fitted with linear, quadratic or exponential regression curve, chosen to minimize the Akaike Information Criterion. Adjusted coefficients of determination ($\hat{R}^2$) were computed using https://mycurvefit.com with $\hat{R}^2$ >0.5 considered strong correlation. The relation between compliance at presentation vs. follow-up was fitted with a sigmoid curve. We tested whether the drugs patients were taking as part of routine ICU management post TSCI (propofol, fentanyl, norepinephrine) affected urodynamic parameters by ANOVA to compare three groups: no drug, low-dose, high dose. We tested whether a drug (propofol, fentanyl, norepinephrine) affects bladder sensation by Fisher exact test on a 2×3 contingency table to compare the number of fill cycles with / without sensation with no drug / low-dose / high dose using http://vassarstats.net. Bladder volumes at first sensation were analyzed by Kaplan-Meier plots and log-rank. Numbers of patients with and without sensation to void during bladder-fill at presentation *vs.* follow-up was compared by Fisher exact test on a 2×2 contingency table using http://vassarstats.net. Plots are average ± standard error with statistical significance taken at P <0.05.

6.4 Results

6.4.1 Patient characteristics

Data were collected from 13 patients aged 22.0 – 67.0 years (average 47.1), 12 (92.3 %) males and 1 (7.7 %) female. 8/13 (61.5 %) patients had cervical injuries, 4/13 (30.8 %) thoracic and 1/13 (7.7 %) conus. 8/13 (61.5 %) patients had AIS A injuries, 2/13 (15.4 %) AIS B and 3/13 (23.1 %) AIS C. All patients had posterior surgical bony decompression with laminectomy and fusion; 2/13 (15.4 %) also had concurrent anterior stabilization. Surgery was performed 14 – 70 hours after TSCI (average 41.9). Details are in Table 17.

Table 17. Patient demographics.

Pt. No.	Age (y)	Sex	Injury Level	AIS Grade	Surgical Approach	TSCI to surgery (h)
1	27	M	L1	C	Post+Lami	41
2	50	M	C5	B	Post+Lami	14
3	47	M	T8	A	Post+Lami	23
4	57	M	C4	A	Post+Lami	35
5	66	M	C4	A	Post+Lami	40
6	46	M	T12	A	Post+Lami	18
7	26	M	C6	A	Ant+Post+Lami	39
8	67	F	C2	B	Post+Lami	69
9	55	M	T7	A	Post+Lami	45
10	54	M	C4	C	Post+Lami	69
11	44	M	C7	A	Post+Lami	32
12	51	M	T7	A	Post+Lami	50
13	22	M	C6	C	Ant+Post+Lami	70

AIS, American spinal injuries association Impairment Scale; Ant, anterior; C, cervical; F, female; h, hours; Lami, laminectomy; M, male; No., number; Post, posterior; Pt., patient; T, thoracic;

6.4.2 Urodynamics

We performed 63 bladder fill cycles in the 13 patients at 2 – 7 days after surgery. For details, see Table 18. Underactive or normal bladder was found in 39.7 % cycles from 8 patients; 60.3 % cycles from 12 patients had unfavourable urodynamic parameters i.e. one or more of the following: bladder compliance <20 cmH_2O in 19.0 %, DO in 55.6 %, DSD in 46.0 % and maximal storage pressure >40 cmH_2O in 15.9 %. We infused 340.0 – 600.0 mL normal saline into the bladder, corresponding to V_{max} of 400.0 – 1,300.0 mL. Patients were on propofol during 57.1 % of fill cycles, fentanyl during 63.4 % and norepinephrine during 95.2 %. No one received bladder-modulating drugs and no one had history of lower urinary tract symptoms. The fill cycles were performed over a wide range of SCPP (42.1 – 109.9 mmHg), ISP (7.7 – 35.4 mmHg), injury site glucose (0.0 – 8.2 mM) and injury site LPR (16.9 – 98.0). Fig. 76 shows a set of urodynamic signals in a patient with DO and DSD.

Table 18. Summary of urodynamic findings.

Patients: no.	13
Fill cycles: no.	63
Fill cycles/patient: mean (range)	4.8 (2.0 – 6.0)
Timing of fill cycle from surgery: mean days (range)	4.2 (2.0 – 7.0)
Underactive or normal bladder: no. of fill cycles	25
Unfavourable urodynamics: no. of fill cycles	38
Compliance <20 cmH_2O/mL	12
Detrusor over-activity	35
Detrusor-sphincter dys-synergia	29
Maximal detrusor pressure >40 cmH_2O	10
Maximal bladder fill: mean (range)	
Infused saline in mL	571.5 (340.0 – 600.0)
V_{max}, Infused saline + urine produced in mL	652.1 (400.0 – 1,300.0)
Drugs: no. of fill cycles	
Propofol	36
Fentanyl	40
Norepinephrine	60
Bladder medications: no. of fill cycles	
None	63
Anti-muscarinic	0
α-blocker	0
Injury site parameters during fill cycle: mean (range)	
SCPP in mmHg	77.5 (42.1 – 109.9)
ISP in mmHg	19.2 (7.7 – 35.4)
Tissue glucose in mM	4.4 (0.0 – 8.2)
Tissue LPR	37.5 (16.9 – 98.0)
Nor-epinephrine in μg/kg/min: mean (range)	0.1 (0.0 – 0.3)

ISP, Intraspinal Pressure; LPR, lactate-to-pyruvate ratio; SCPP, Spinal Cord Perfusion Pressure; TSCI, Traumatic Spinal Cord Injury.

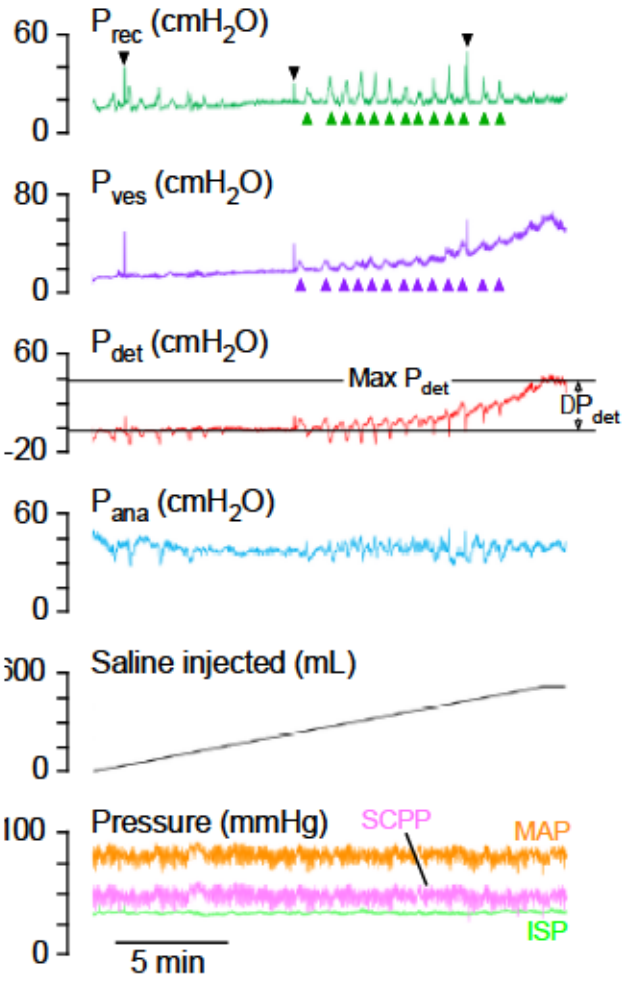


Fig. 76. Example of cystometry trace with concomitant injury site monitoring.

Cystometry patient no. 12 (T7 AIS A) at day 4 post-TSCI. $\Delta V/\Delta P_{det}$ = 12 mL/cmH_2O; at V_{max} (520 mL), P_{rec} = 19 cmH_2O, P_{ves} = 60 cmH_2O and P_{det} = 39 cmH_2O. Arrowheads: black (cough), purple (bladder contractions), green (rectal contractions).

6.4.3 Complications

Adverse Events: 1/13 (7.7 %) patient developed a sacral pressure ulcer, 1/13 (7.7 %) had persistent priapism and penile meatal pressure ulcer from the indwelling catheter, 1/13 (7.7 %) had microscopic haematuria, 5/13 (38.5 %) had chest infection and 1/13 (7.7 %) had pulmonary embolism. *Adverse Reactions:* 7/13 (53.8 %) patients had asymptomatic pseudomeningocele (on MRI). There were no *Serious Adverse Events*, no *Serious Adverse Reactions* and no *Suspected Unexpected Serious Adverse Reactions defined as per 'good clinical practice (GCP)' guidelines*[165]. No one had spinal cord damage or hematoma from the probes (based on MRI and neurological examination), no cerebrospinal fluid leak, no wound infection or meningitis, no urinary infection and no deterioration in renal function.

6.4.4 Variability of urodynamic parameters

Inspection of traces from repeat fill cycles revealed high variability in the unfavourable urodynamic parameters. For example, Fig. 77 shows that, in patient no. 3, increase in SCPP (from 59.7 to 80.7 mmHg) was associated with a large reduction in maximal detrusor pressure (from 41.3 to 24.0 cmH_2O) and a large increase in bladder compliance (from 12.0 to 28.6 mL/cmH_2O). Fig. 78 shows another example (patient no. 50) where increase in SCPP (from 65.5 to 94.5 mmHg) was associated with elimination of DSD, but had little or no effect on bladder compliance or maximal detrusor pressure. Fig. 79 summarizes the variabilities in bladder compliance, DO, DSD and detrusor pressure at end-fill for each patient. We hypothesised that these within-patient fluctuations in the urodynamic parameters are caused by fluctuations in the physiology and metabolism of the injured cord. If our hypothesis holds, there should be strong correlations between the urodynamic parameters and the parameters we monitor from the injury site.

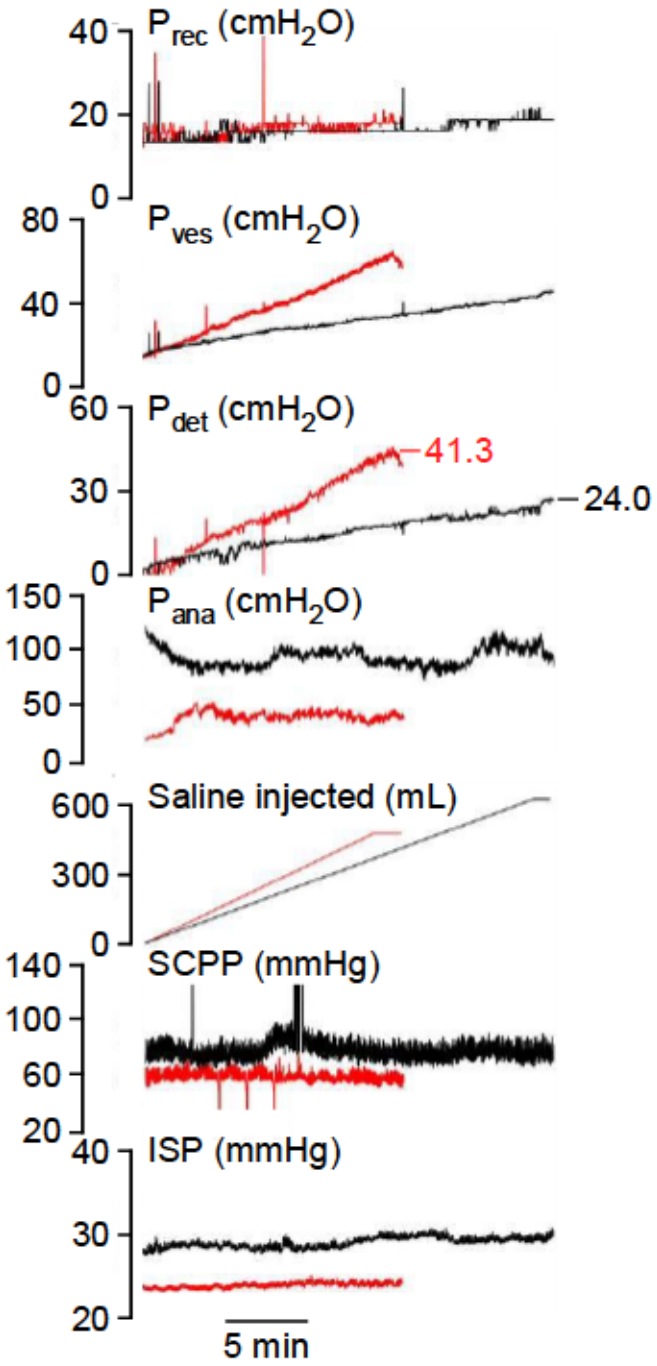


Fig. 77. Variability of unfavourable urodynamic parameters. Cystometry patient no. 3 (T8 AIS A). Day 4 post TSCI (black): SCPP 80.7 mmHg, $\Delta V/\Delta P_{det}$ = 28.6 mL/cmH_2O, max P_{det} = 24.0 cmH_2O. Day 2 post TSCI (red): SCPP 59.7 mmHg, $\Delta V/\Delta P_{det}$ = 12.0 mL/cmH_2O, max P_{det} = 41.3 cmH_2O.

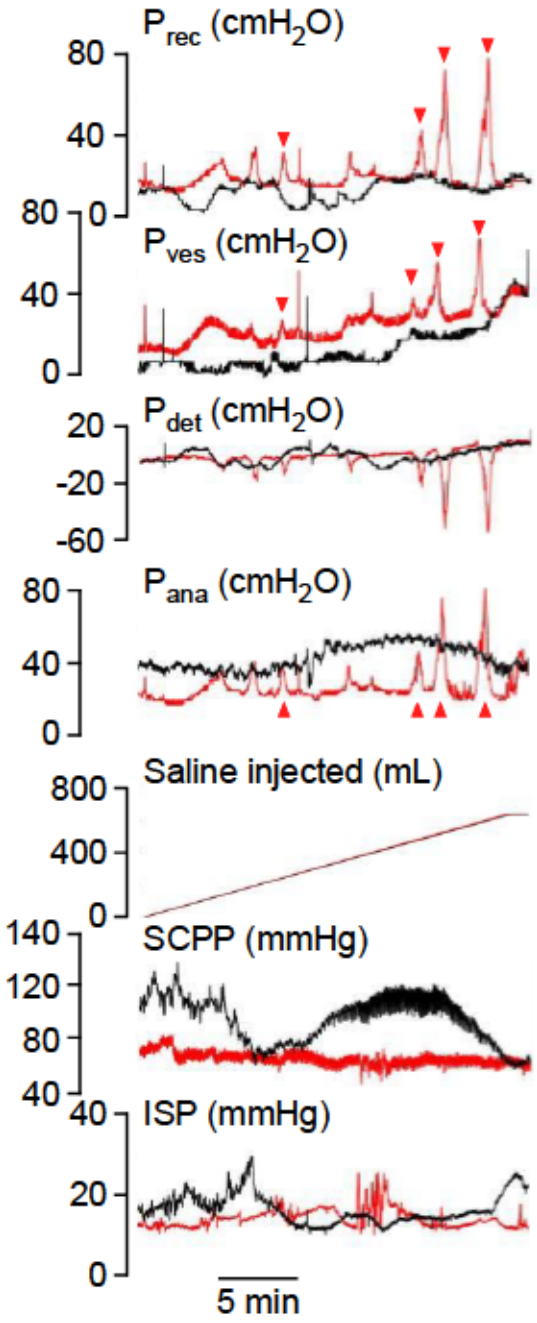


Fig. 78. Variability of unfavourable urodynamic parameters. Cystometry patient no. 5 (C4 AIS A). Day 4 post TSCI (black): SCPP 94.5 mmHg, $\Delta V/\Delta P_{det}$ = 48.0 mL/cmH_2O, max P_{det} = 8.8 cmH_2O. Day 3 post TSCI (red): SCPP 65.5 mmHg, $\Delta V/\Delta P_{det}$ = 42.0 mL/cmH_2O, max P_{det} = 9.1 cmH_2O, simultaneous vesicular-anal-rectal contractions at 245, 490, 524 and 599 mL (arrows)

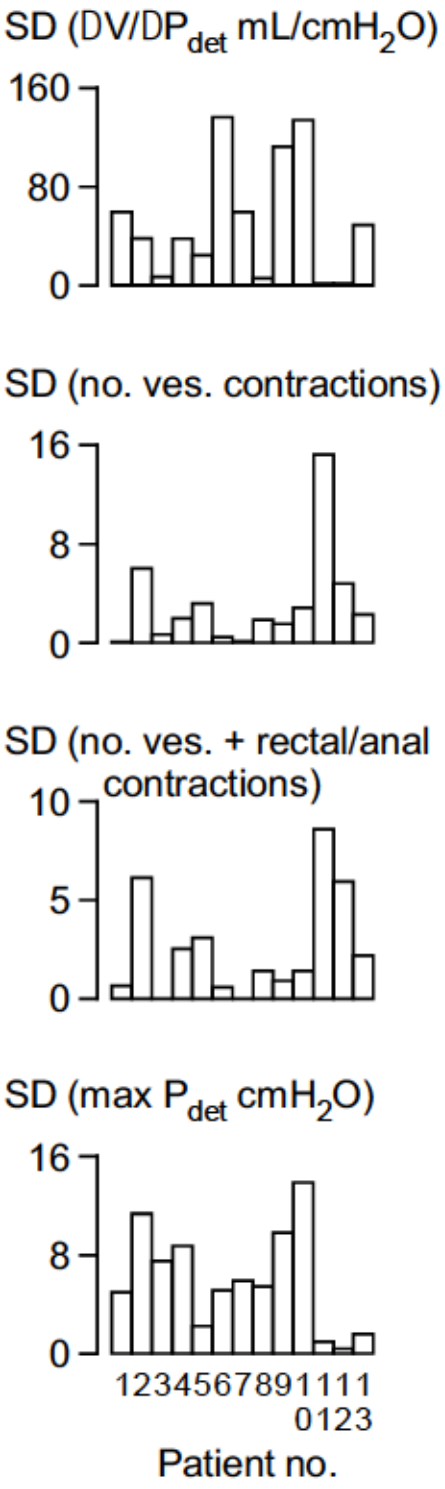


Fig. 79. Variability of urodynamic parameters in each patient. Standard deviation (SD) of bladder compliance ($\Delta V/\Delta P_{det}$), no. of vesicular contractions (DO), no. of simultaneous vesicular and rectal/anal contractions (DSD), and detrusor pressure at end-fill (max P_{det}) for patients 1 – 13.

6.4.5 Bladder compliance correlates with injury site physiology and metabolism

Figs. 80-83 shows plots of the percentage of patients with very low bladder compliance (<20 mL/cmH_2O) *vs.* average SCPP, ISP, injury site glucose and injury site LPR measured from the injured spinal cord during each fill cycle. The relation with SCPP is U-shaped with the optimum SCPP, that eliminates the probability of having dangerously low compliance, at ~80 – 90 mmHg. The percentage of patients with dangerously low bladder compliance was significantly higher during periods of low injury site glucose (<3 mM) and during periods of ischemia (LPR >30) at the injury site, but did not significantly correlate with ISP. Bladder compliance was not significantly affected by propofol, fentanyl or norepinephrine (Fig. 84-86). These findings indicate that periods of improved injury site perfusion and metabolism are associated with improved bladder compliance.

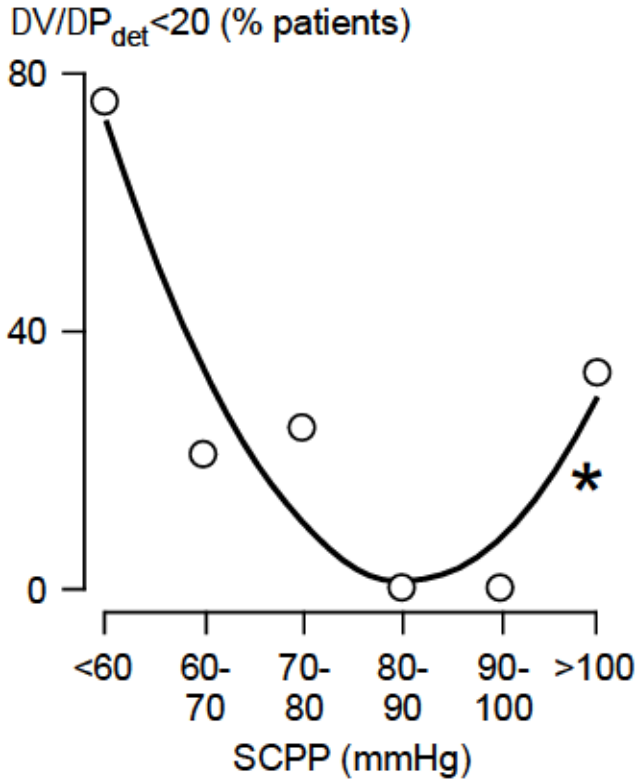


Fig. 80. Bladder compliance *versus* SCPP. % patients with $\Delta V/\Delta P_{det}$ <20 cmH_2O *vs.* SCPP (quadratic regression, $\hat{R}^2 = 0.78$). **P* <0.05. Mean +/- standard error.

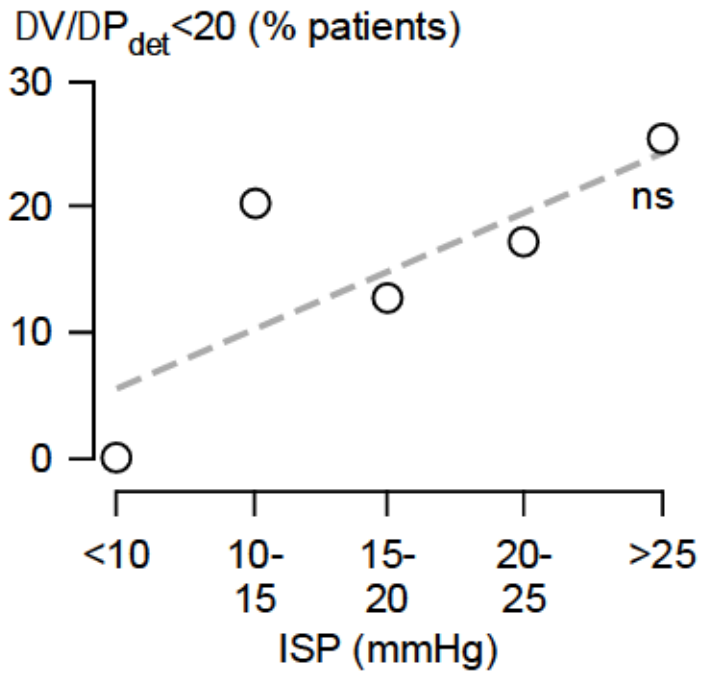


Fig. 81. Bladder compliance *versus* ISP. % patients with $\Delta V/\Delta P_{det}$ <20 cmH_2O *vs.* ISP (best-fit straight line, $\hat{R}^2 = 0.48$). ns = not significant. Mean +/- standard error.

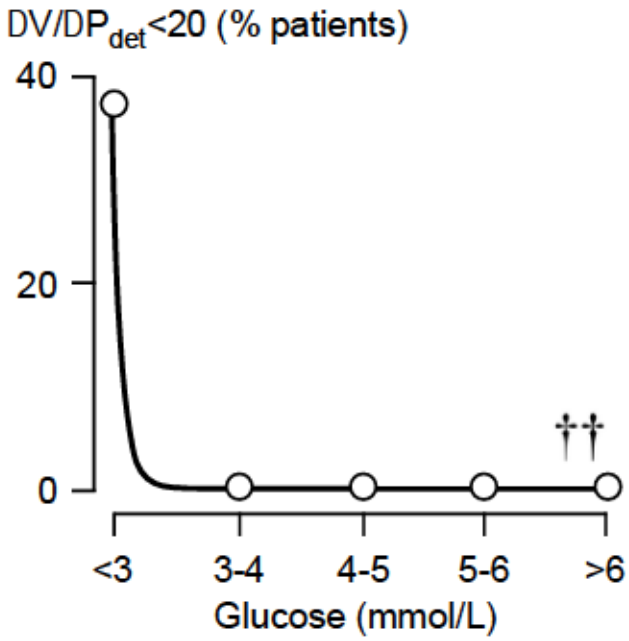


Fig. 82. Bladder compliance *versus* injury site glucose. % patients with $\Delta V/\Delta P_{det}$ <20 cmH_2O *vs.* injury site glucose (best-fit exponential, $\hat{R}^2 = 1.00$). $^{\dagger\dagger}P$ <0.00005. Mean +/- standard error.

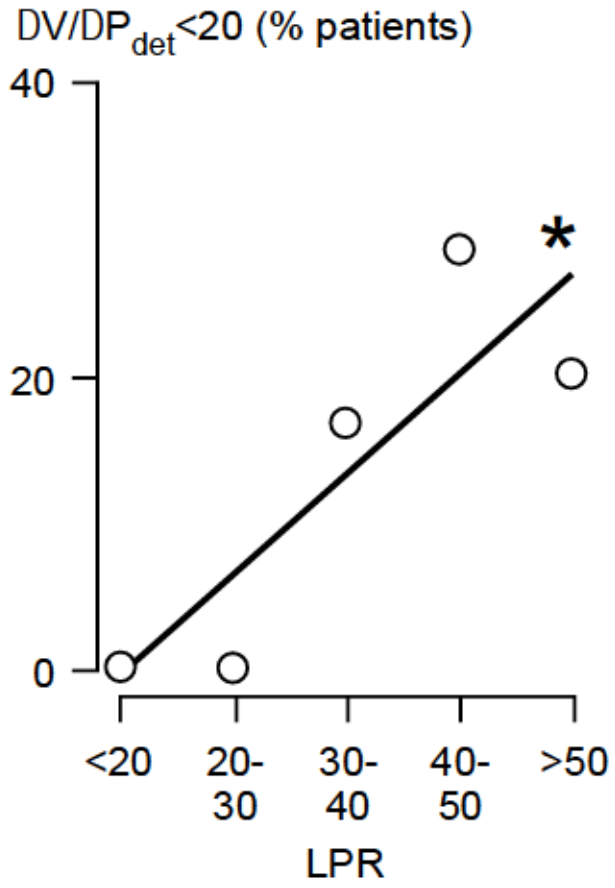


Fig. 83. Bladder compliance *versus* injury site LPR. % patients with $\Delta V/\Delta P_{det}$ <20 cmH_2O *vs.* injury site LPR (best-fit straight line, $R^2 = 0.86$). *P <0.05. Mean +/- standard error.

PROPOFOL

Dose	Max P_{det}	Compliance	DO	DSD
0	17.4	64.8	5.0	3.2
1-100	7.1	75.6	2.4	2.1
101-200	14.5	68.4	1.9	1.2

Max P_{det}

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	949.9994	2	474.9997	1.9329	0.1536
error	14,744.7393	60	245.7457		
total	15,694.7388	62			

Compliance

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	706.1481	2	353.0741	0.0599	0.9420
error	353,896.2674	60	5,898.2711		
total	354,602.4156	62			

DO

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	125.6500	2	62.8250	1.8104	0.1729
error	1,978.0000	57	34.7018		
total	2,103.6500	59			

DSD

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	40.8977	2	20.4489	1.3031	0.2798
error	878.7633	56	15.6922		
total	919.6610	58			

Fig. 84. Propofol dose has no effect on unfavourable urodynamic parameters.

FENTANYL

Dose	Max P_{det}	Compliance	DO	DSD
0	16.5	71.7	5.4	3.3
1-100	12.2	60.4	2.1	1.7
>100	12.7	74.7	2.1	1.4

Max P_{det}

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	245.7606	2	122.8803	0.4772	0.6228
error	15,448.9781	60	257.4830		
total	15,694.7388	62			

Compliance

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	2,420.0764	2	1,210.0382	0.2061	0.8143
error	352,182.3391	60	5,869.7057		
total	354,602.4156	62			

DO

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	155.4202	2	77.7101	2.2736	0.1122
error	1,948.2298	57	34.1795		
total	2,103.6500	59			

DSD

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	44.8657	2	22.4329	1.4360	0.2465
error	874.7953	56	15.6213		
total	919.6610	58			

Fig. 85. Fentanyl dose has no effect on unfavourable urodynamic parameters.

NORADRENALINE

Dose	Max P_{det}	Compliance	DO	DSD
0.00-0.10	17.7	47.5	3.6	2.7
0.11-0.20	12.5	95.6	3.3	1.8
0.21-0.30	8.0	60.7	2.8	2.1

Max P_{det}

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	789.4534	2	394.7267	1.5889	0.2126
error	14,905.2854	60	248.4214		
total	15,694.7388	62			

Compliance

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	30,631.5174	2	15,315.7587	2.8365	0.0665
error	323,970.8982	60	5,399.5150		
total	354,602.4156	62			

DO

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	5.3537	2	2.6769	0.0727	0.9300
error	2,098.2963	57	36.8122		
total	2,103.6500	59			

DSD

One-way ANOVA of your k=3 independent treatments:

source	sum of squares SS	degrees of freedom ν	mean square MS	F statistic	p-value
treatment	10.3638	2	5.1819	0.3191	0.7281
error	909.2972	56	16.2375		
total	919.6610	58			

Fig. 86. Noradrenaline dose has no effect on unfavourable urodynamic parameters.

6.4.6 Detrusor overactivity correlates with injury site physiology

Figs. 87-90 shows how the severity of detrusor overactivity (quantified as the number of transient bladder contractions) is related to the average SCPP, ISP, injury site glucose and injury site LPR measured from the injured spinal cord during each fill cycle. Detrusor overactivity was more frequent during periods of spinal cord hypo- and hyperperfusion with the optimum SCPP, that minimizes DO, at ~75 – 85 mmHg. Detrusor overactivity did not significantly correlate with ISP. Though Detrusor overactivity occurred more frequently during periods of low cord injury site glucose and high cord injury site LPR, these relations were not significant. Detrusor overactivity was not significantly affected by propofol, fentanyl or norepinephrine (Figs 84-86). Our findings indicate that periods of improved injury site perfusion are associated with less Detrursor overactivity.

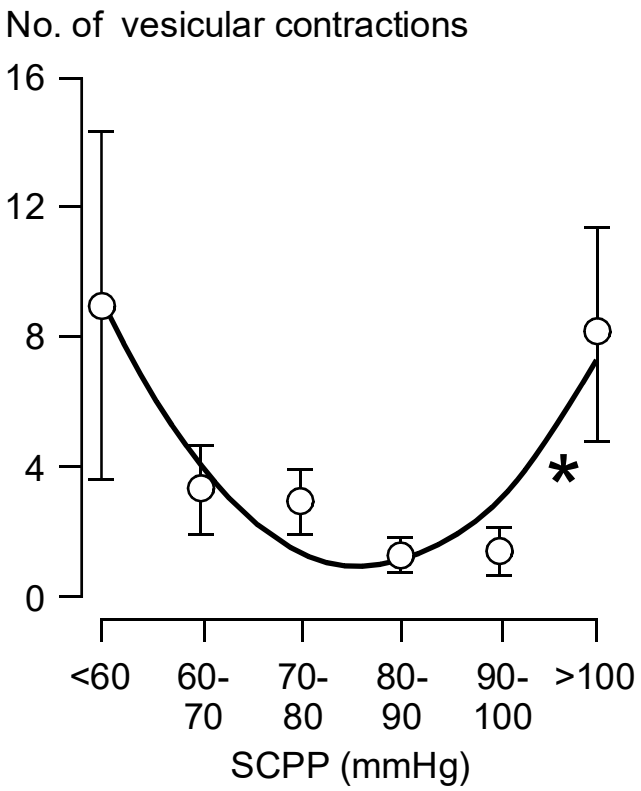


Fig. 87. Detrusor overactivity *versus* SCPP. Number of vesicular contractions *vs.* SCPP (best fit quadratic, $\hat{R}^2 = 0.79$), $^{*}P < 0.05$. Mean +/- standard error.

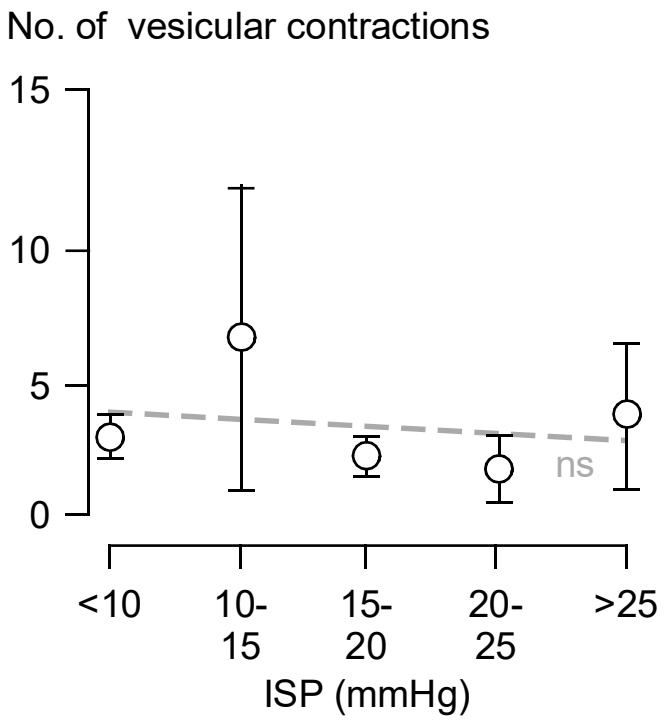


Fig. 88. Detrusor overactivity *versus* ISP. Number of vesicular contractions *vs.* ISP (best-fit straight line, $\hat{R}^2$ = -0.26), ns = not significant. Mean +/- standard error.

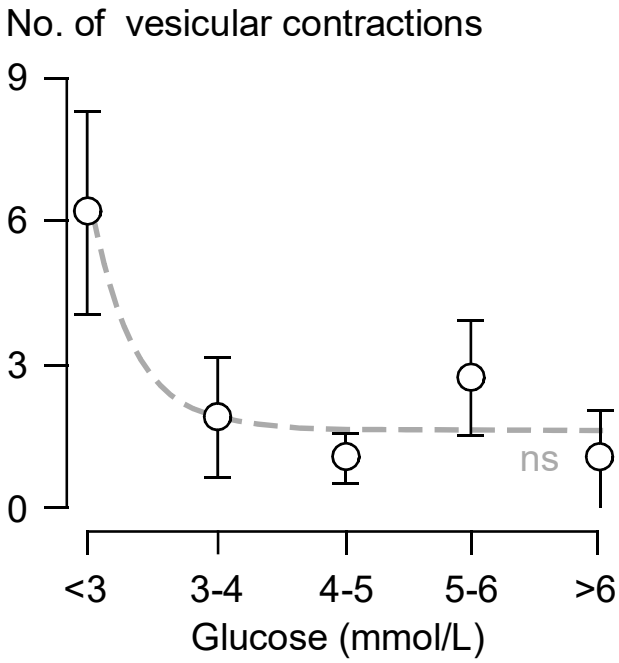


Fig. 89. Detrusor overactivity *versus* injury site glucose Number of vesicular contractions *vs.* injury site glucose (best-fit exponential decay, $\hat{R}^2 = 0.73$), ns = not significant. Mean +/- standard error.

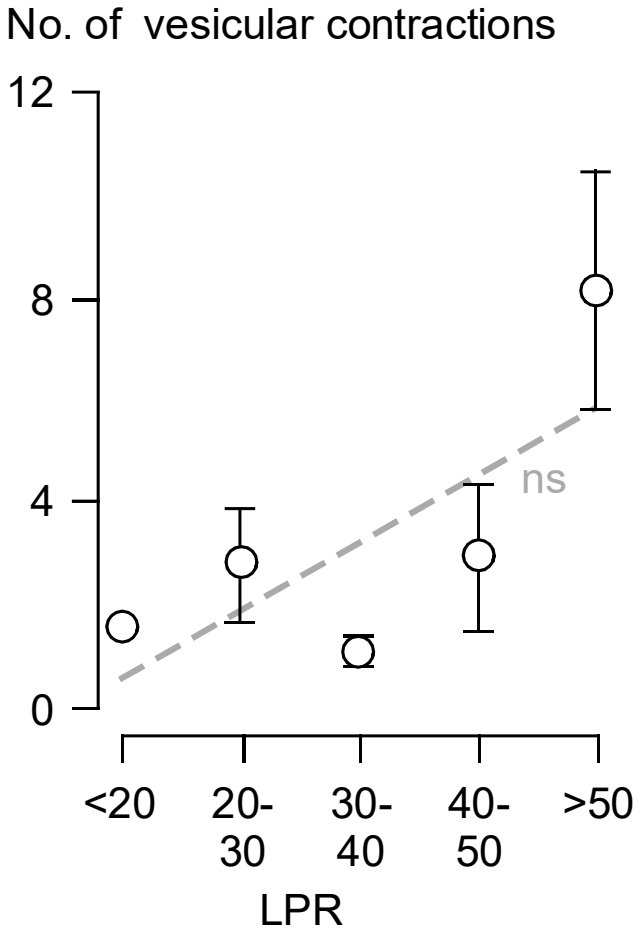


Fig. 90. Detrusor overactivity *versus* injury site LPR. Number of vesicular contractions *vs.* injury site LPR (best-fit straight line, $\hat{R}^2 = 0.42$) ns = not significant. Mean +/- standard error.

6.4.7 Detrusor sphincter dyssynergia correlates with injury site physiology and metabolism

Figs. 91-94 shows how the severity of detrusor sphincter dysnergia (quantified as the number of synchronous bladder and anal-rectal transient contractions without Valsalva) is related to the average SCPP, ISP, injury site glucose and injury site LPR measured from the injured spinal cord during each fill cycle. Detrusor sphincter dysnergia was more frequent during periods of spinal cord hypo- and hyperperfusion with the optimum SCPP, that minimizes detrusor sphincter dysnergia, at ~80 – 90 mmHg. Detrusor sphincter dysnergia did not significantly correlate with ISP. We found significant positive linear relation between the severity of detrusor sphincter dysnergia and LPR. Though detrusor sphincter dysnergia occurred more frequently during periods of cord glucopenia, this relation was not significant. Detrusor sphincter dysnergia was not significantly affected by propofol, fentanyl or norepinephrine (Figs. 84-86). These findings indicate that periods of improved injury site perfusion are associated with less detrusor sphincter dysnergia.

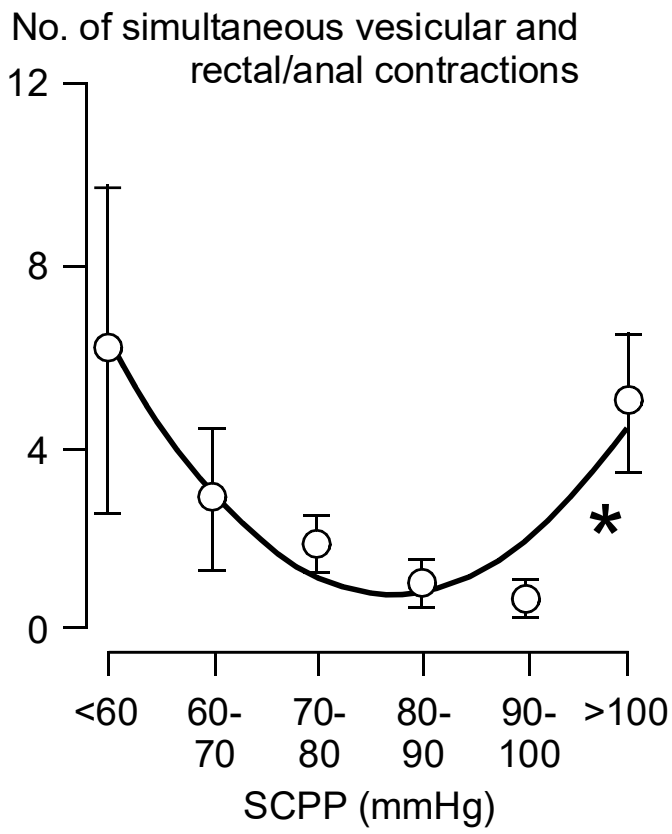


Fig. 91. Detrusor sphincter dyssynergia *versus* SCPP. Number of simultaneous vesicular and rectal contractions *vs.* **A.** SCPP (quadratic regression, $\hat{R}^2 = 0.84$). $^{*}P < 0.05$. Mean +/- standard error.

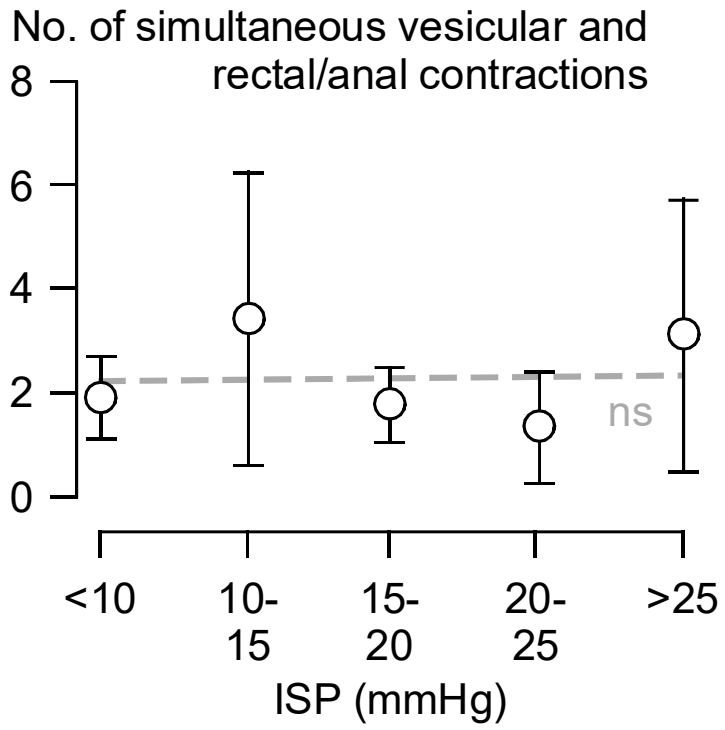


Fig. 92. Detrusor sphincter dyssynergia *versus* ISP. Number of simultaneous vesicular and rectal contractions *vs.* ISP (best-fit straight line, $\hat{R}^2$ = -0.33). ns = not significant. Mean +/- standard error.

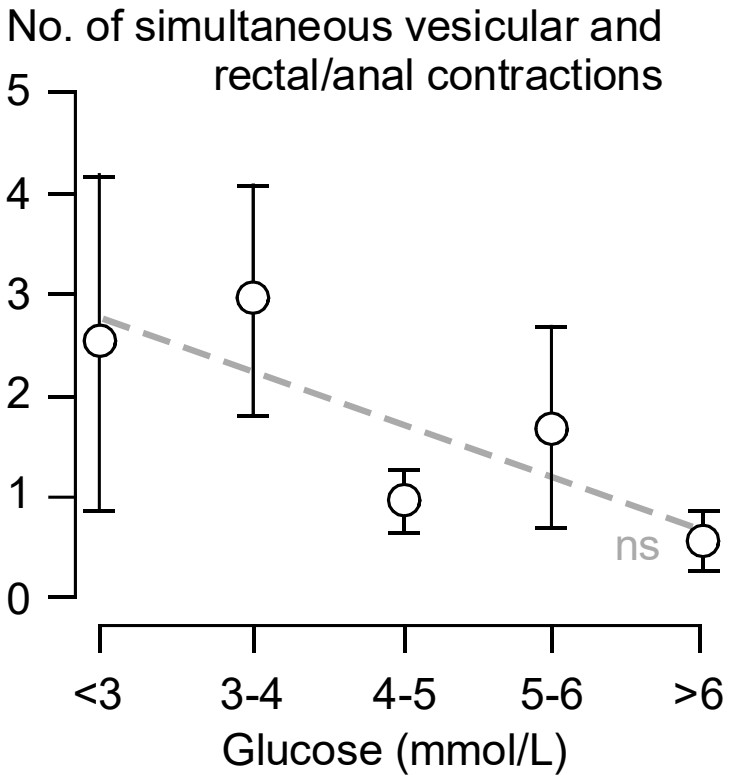


Fig. 93. Detrusor sphincter dyssynergia *versus* injury site glucose. Number of simultaneous vesicular and rectal contractions *vs.* injury site glucose (best-fit exponential decay, $\hat{R}^2 = 0.14$), and **D.** injury site LPR (best-fit straight line, $\hat{R}^2 = 0.97$). ns = not significant. Mean +/- standard error.

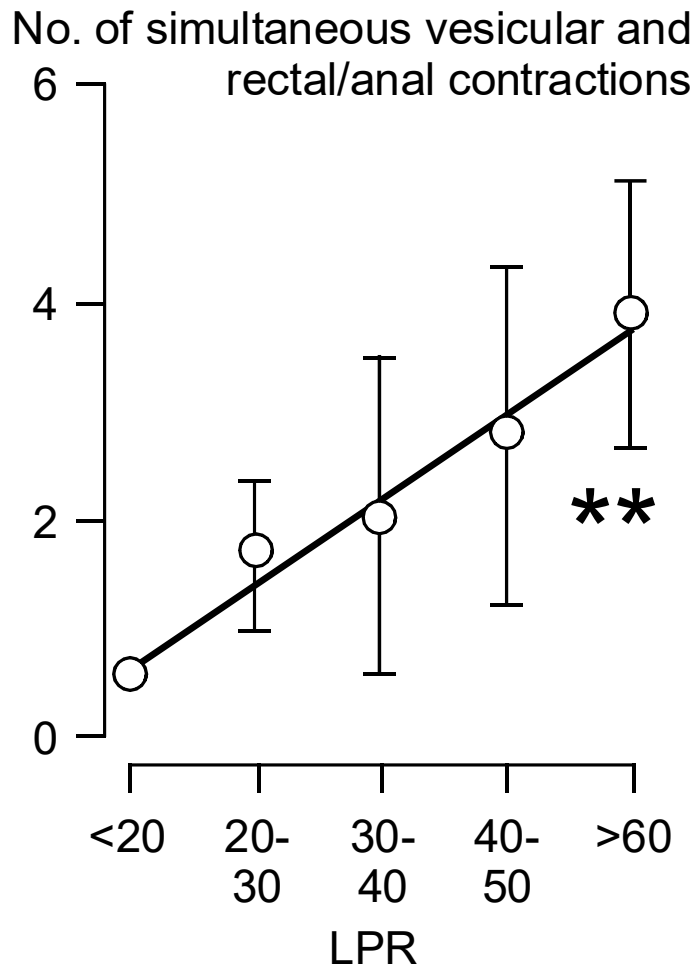


Fig. 94. Detrusor sphincter dyssynergia *versus* injury site LPR. Number of simultaneous vesicular and rectal contractions *vs.* injury site LPR (best-fit straight line, $\hat{R}^2 = 0.97$). $^{**}P < 0.005$. Mean +/- standard error.

6.4.8 Maximal detrusor pressure correlates with injury site physiology and metabolism

Figs. 95-98 shows plots of the percentage of patients with dangerously high end-fill detrusor pressure (max P_{det} >40 cmH_2O) *vs.* average SCPP, ISP, injury site glucose and injury site LPR measured from the injured spinal cord during each fill cycle. The relation with SCPP is U-shaped with the optimum SCPP, that eliminates dangerously high end-fill detrusor pressure, at ~80 – 90 mmHg. The percentage of patients with dangerously high end-fill detrusor pressure was significantly higher during periods of spinal cord swelling (ISP >10 mmHg), periods of low injury site glucose (<4 mM) and periods of ischemia (LPR >30) at the injury site. End-fill detrusor pressure was not significantly affected by propofol, fentanyl or norepinephrine (Figs. 84-86). Our findings indicate that periods of improved injury site physiological and metabolic parameters are associated with lower detrusor pressure during the storage phase.

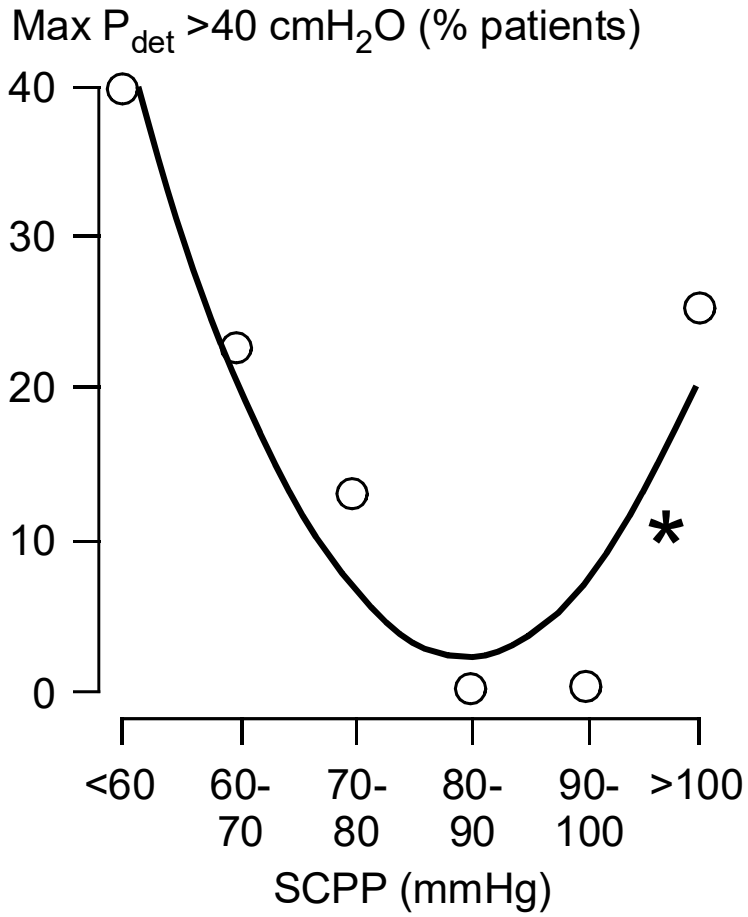


Fig. 95. Maximal detrusor pressure *versus* SCPP. % patients with maximal detrusor pressure >40 cmH_2O *vs.* SCPP (quadratic regression, $\hat{R}^2 = 0.83$), $^*P < 0.05$.

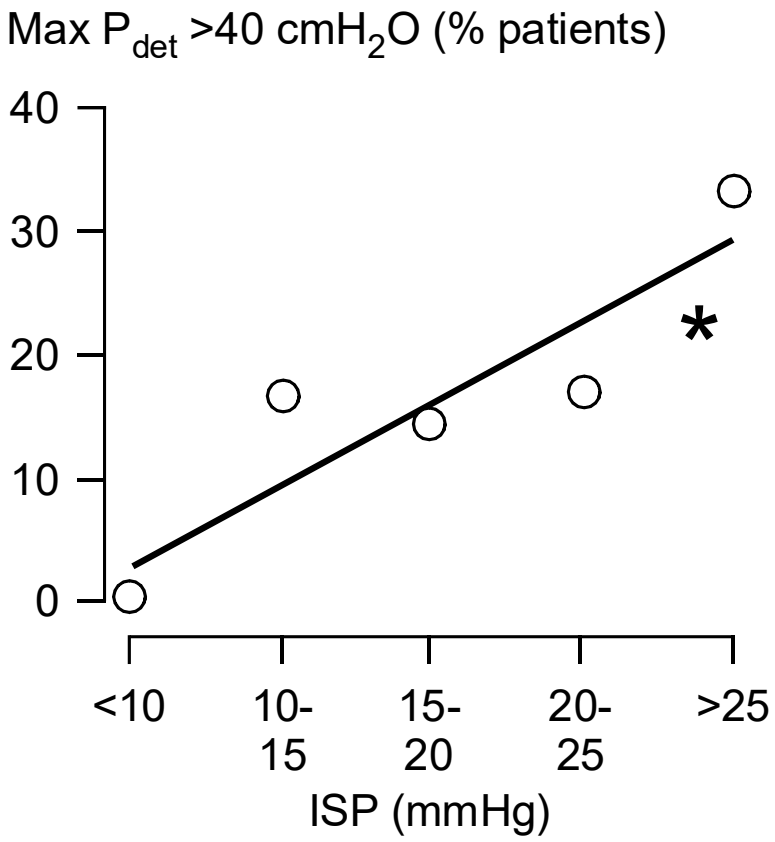


Fig. 96. Maximal detrusor pressure *versus* ISP. % patients with maximal detrusor pressure >40 cmH_2O *vs* ISP (best-fit straight line, $\hat{R}^2 = 0.72$), $^*P < 0.05$.

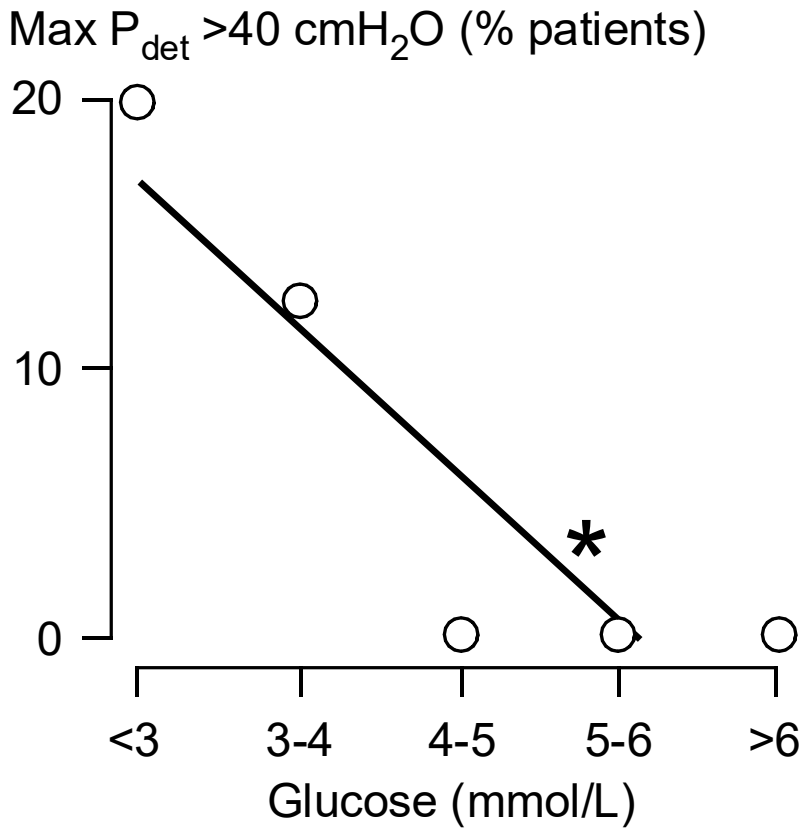


Fig. 97. Maximal detrusor pressure *versus* injury site glucose. % patients with maximal detrusor pressure >40 cmH_2O *vs.* injury site glucose (best-fit straight line, $\hat{R}^2 = 0.73$). $^*P < 0.05$.

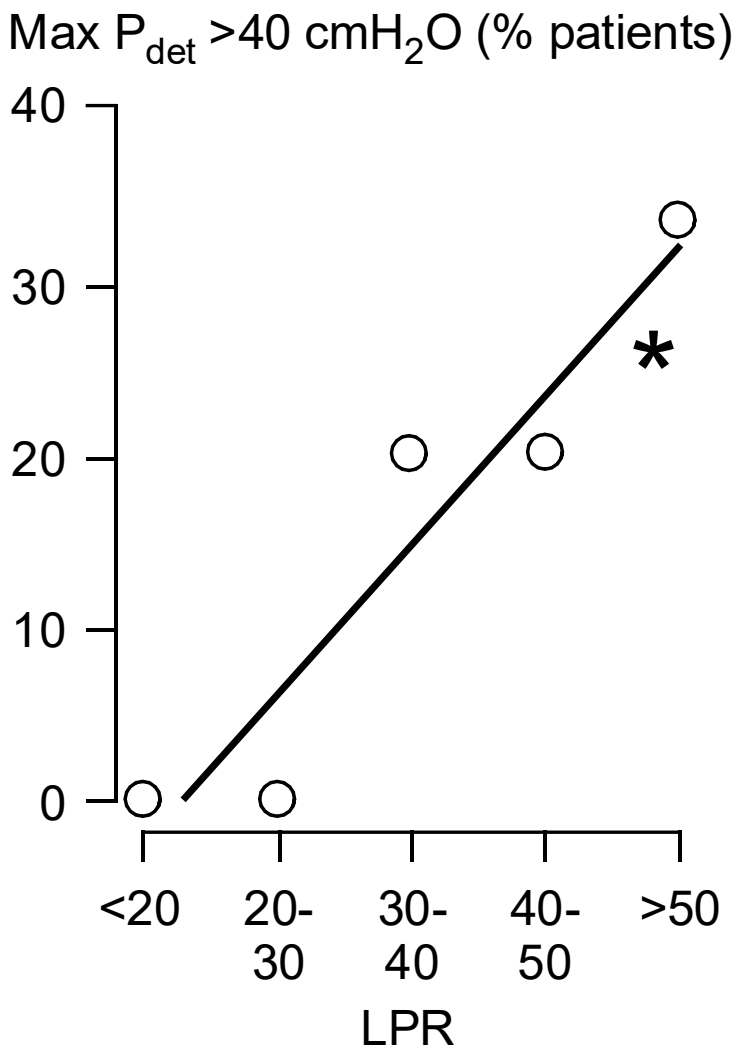


Fig. 98. Maximal detrusor pressure *versus* injury site LPR. % patients with maximal detrusor pressure >40 cmH_2O *vs.* injury site LPR (best-fit straight line, $\hat{R}^2 = 0.87$). $^*P < 0.05$.

6.4.9 Bladder volume at first desire to void correlates with spinal cord perfusion

Bladder sensation was assessable in 10 patients; the other 3 were sedated to aid ventilation. Of these 10, only 4 had bladder sensation, 3 AIS C on admission plus 1 AIS A on admission who improved to AIS C at follow-up. These 4 patients had 14 fill cycles; For each patient, fill cycles were classed as high or low SCPP, with at least 20 mmHg difference between them, resulting in 8 high (82.6 – 100.5 mmHg) and 6 low (56.2 – 74.1 mmHg) SCPP fill cycles. Fig. 99 shows that the median bladder volume at which sensation is first experienced is significantly smaller for fill cycles at high *vs.* low SCPP (365 *vs.* 534 mL). In these 4 patients, the probability of experiencing bladder sensation during a fill cycle was not significantly affected by propofol, fentanyl or norepinephrine (Fig. 100). Thus, periods of improved spinal cord perfusion are associated with improved bladder sensation.

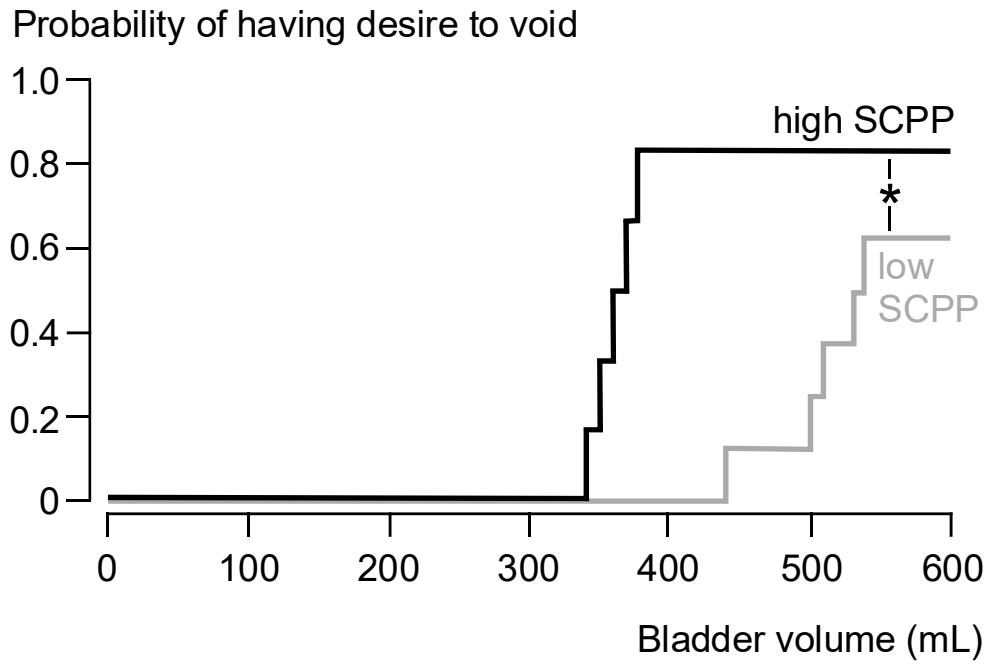


Fig. 99. Bladder volume at first desire to void *versus* spinal cord perfusion. Probability of experiencing desire to void *vs.* bladder volume at high (92.1 +/- 3.0 mmHg) vs. low (67.0 +/- 2.3 mmHg) SCPP. $^{*}P < 0.05$. Mean +/- standard error.

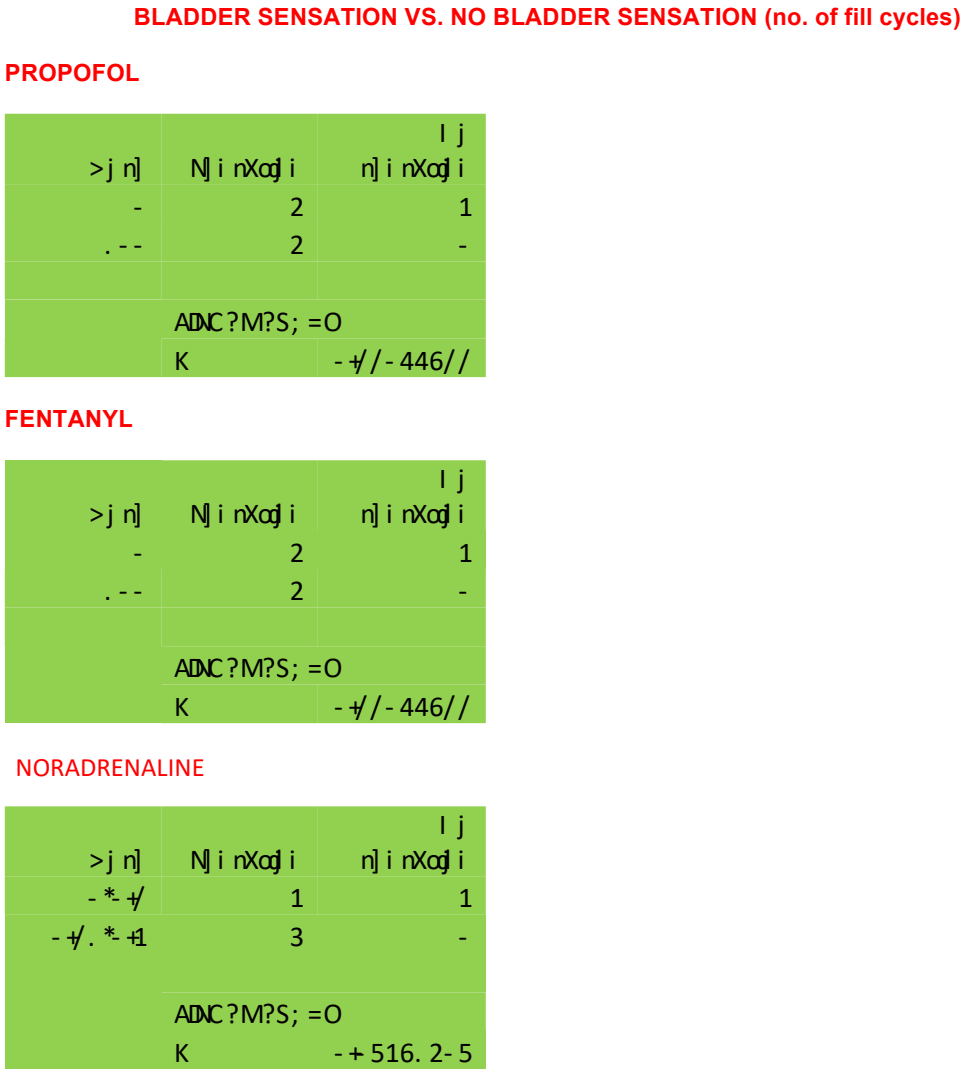


Fig. 100. Bladder sensation is not affected by propofol, fentanyl or noradrenaline.

6.4.10 Long-term outcome

Average follow-up was 8 months (range 2 – 19). Bladder compliance assessed acutely correlated with compliance at follow-up. All patients with desire to void during bladder fill at initial presentation maintained the desire at follow-up, but with decrease in bladder volume causing first sensation to void from 442 ± 55 mL to 260 ± 31 mL (average ± standard error). Noone with lack of desire to void at presentation recovered the desire at follow-up. DO at initial presentation did not correlate with DO at follow-up (not shown). Details are in Figs. 101-102. At follow-up, 7/13 patients (53.8 %) improved by one or more AIS grade, 5/13 (38.5 %) remained the same and 1/13 (7.7 %) deteriorated by one AIS grade, comparable to our earlier findings[56]. At follow-up, SCIM III bladder scores ranged 0 – 15 (and SF-Qualiveen scores 1.13 – 4.00. Fig. 103 shows details.

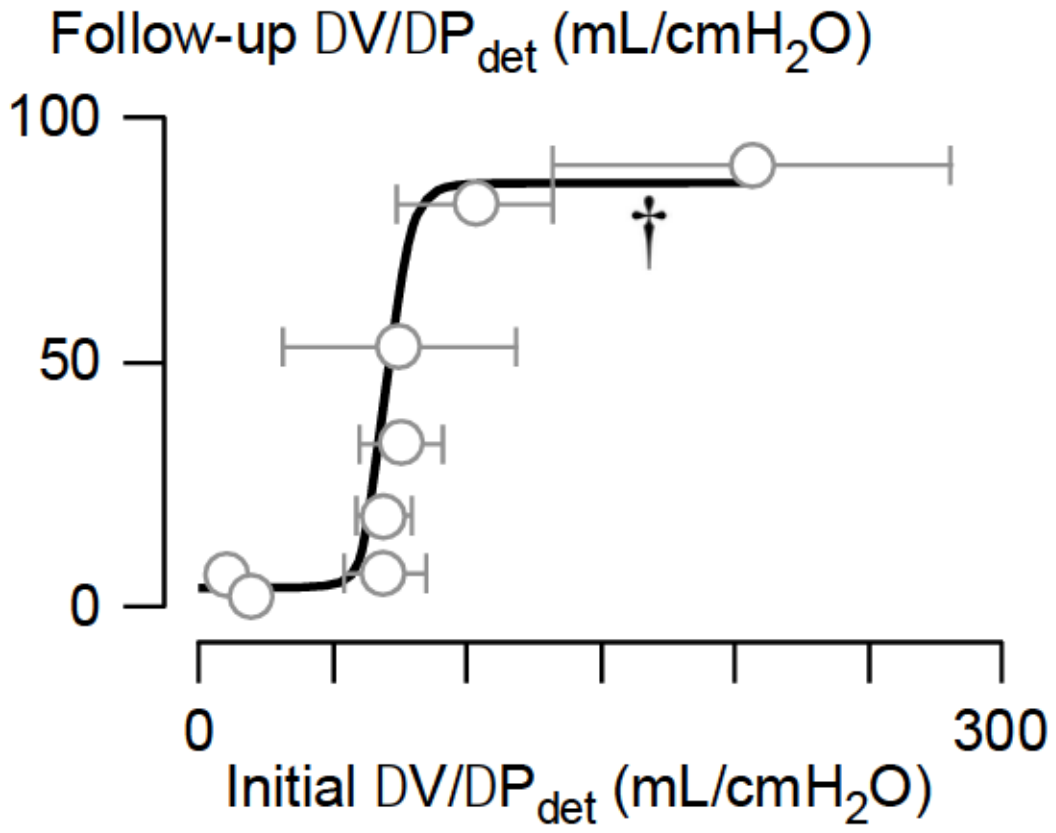


Fig. 101 Long-term outcome. Bladder compliance at initial presentation *vs.* follow-up with best-fit sigmoid curve, $\tilde{R}^2 = 0.90$. Average ± standard error. $P < 0.001$ †.

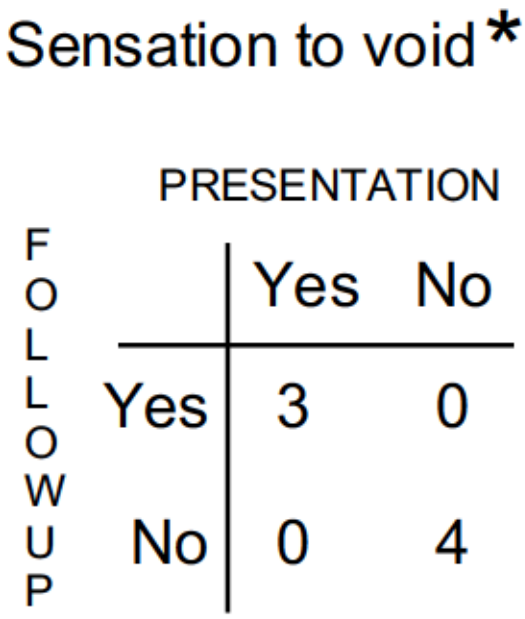


Fig. 102. Long-term outcome. No. of patients with and without sensation to void during bladder fill at presentation *vs.* follow-up. $P < 0.05^{*}$.

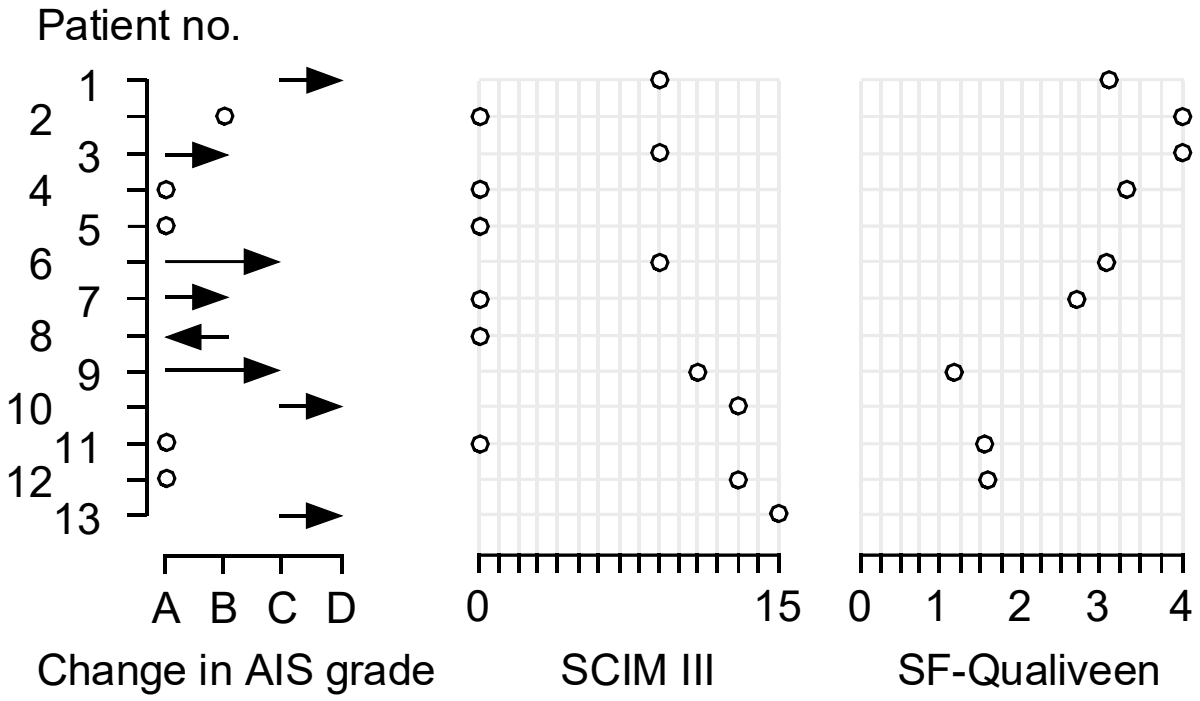


Fig. 103. Long-term outcome for patients 1-13. *(left)* Change in AIS at follow-up Vs. presentation. Circle, no change. *(middle)* SCIM III at follow up. *(right)* SF-Qualiveen at follow up.

6.5 Discussion

We showed that >90 % patients develop periods of unfavourable urodynamics within the first 10 days after TSCI, including bladder compliance <20 mL/cmH_2O, detrusor pressure at end fill >40 cmH_2O, DO and DSD. A key finding is that the unfavourable urodynamic parameters are dynamic, i.e. they become more pronounced when the injured cord is hypoperfused (<60 mmHg), hyperperfused (>100 mmHg), has low injury site glucose (<3 mM) or high injury site LPR (>30). For example, during periods of SCPP 80 – 90 mmHg, <40 % TSCI patients had unfavourable urodynamics. By intervening to eliminate hypoperfusion, we could improve bladder sensation with first desire to void occurring at smaller bladder volume.

Our results challenge the prevailing dogma, that the detrusor is acontractile early after TSCI (spinal shock phase) with late development of neurogenic bladder and agree with the few published studies that have also reported unfavourable urodynamics in most patients within 40 days of TSCI[166-168]; in our study, unfavourable urodynamic parameters were detected as soon as 48 hours. The initial effect of severe TSCI on limbs is hypotonia and hyporeflexia, later progressing to spasticity and hyperreflexia[29]. It is generally assumed that the detrusor muscle behaves similarly to the limb muscles, i.e. early acontractility then spasticity. In our study, unfavourable urodynamics were detected in AIS grade A, B and C patients. This finding is in agreement with an earlier report that ambulatory and non-ambulatory patients with acute TSCI have similar risk of unfavourable urodynamics. Together, these observations suggest discordance in the early responses to TSCI of limb muscles *vs.* the detrusor[167].

Some experts have recommended early urodynamic investigations after TSCI[166-168]. The serial, early testing done here revealed high within-patient variability in urodynamic parameters, likely determined by dynamic events at the injury site. For example, periods of spinal cord hypoperfusion, spinal cord compression, glucopenia and ischemia are associated with dangerously low bladder compliance, DO, DSD and high end-fill detrusor pressures. Conversely, periods of adequate cord perfusion without ischemia are associated with normal bladder compliance, no DO, no DSD and low end-fill detrusor pressures. The high variability of urodynamic testing, when performed acutely after a TSCI, limits its clinical value.

On the other hand, the dynamic nature of urodynamic parameters and its dependence on events at the injury site suggest that interventions to improve injury site physiology and metabolism will likely improve bladder function. For example, intervention to increase SCPP (=MAP – ISP) may be achieved by vasopressors to increase MAP[169] or expansion duroplasty to reduce ISP[53]. Increasing SCPP, would increase spinal cord glucose and reduce spinal cord

LPR[63] and, consequently, improve neuronal activity at the injury site thus leading to improved bladder function. In our study, intervention to transiently increase SCPP reduced the threshold volume for bladder sensation. Our earlier work, using limb power and sensory level as outcomes[50,110,169,170], and the current study investigating bladder function suggest that SCPP is the key parameter to monitor and optimize for improving outcome after acute TSCI.

Some aspects of bladder function assessed acutely correlated with corresponding measurements at follow-up. The relation between average bladder compliance at presentation *vs.* follow-up was sigmoidal, i.e. patients with low initial bladder compliance (<20 mL/cmH_2O) had low bladder compliance at follow-up, patients with intermediate (50 – 100 mL/cmH_2O) bladder compliance initially ultimately developed either low or normal bladder compliance at follow-up, whereas patients with high initial bladder compliance (>100 mL/cmH_2O) also had high bladder compliance at follow-up. These findings suggest that the intermediate bladder compliance patient group may be the most sensitive to SCPP management. Though SCPP may not influence the presence or absence of the sensation to void, SCPP may affect the bladder volume at which the first sensation occurs.

This study has limitations: First, though best urodynamic practice recommends awake and interactive patients, some of our patients were sedated because they required ventilation. Second, some patients received norepinephrine infusion, raising the possibility of a direct effect of norepinephrine on the bladder. Our analysis suggests that propofol, fentanyl and norepinephrine did not significantly influence the urodynamic parameters. Third, because of the acute ICU setting, we were unable to perform additional studies, e.g. flow or video-urodynamics. Fourth, the numbers of patients in our study is relatively small, due to the difficulty in performing multiple urodynamic assessments in acutely injured patients in ICU. Importantly, no patient experienced complications directly related to our urodynamic tests.

6.6 Conclusions

Our findings add further support to individualised therapy in patients with acute TSCI in ICU, achieved by monitoring and optimising spinal cord physiology (ISP and SCPP) and metabolism (injury site glucose and LPR). It is possible that such therapies might improve not only limb motor function and sensation, but also urinary function.

CHAPTER 6: Effect of spinal cord perfusion pressure on anal function in patients with acute, severe traumatic spinal cord injuries

6.3 Introduction

Bowel and anal sphincter dysfunction after TSCI results from a combination of impaired voluntary sphincter/pelvic floor control and interrupted autonomic activity. Bladder and bowel recovery are ranked on par with motor recovery by TSCI patients when prioritising recovery goals[171]. We examined the relationship between early anal sphincter function and physiological parameters in patients with severe acute TSCI (AIS A-C) by performing anal manometry during multi-modal spinal monitoring in the first 10 days after injury. From our research to date, we hypothesised that fluctuations in anal resting pressure, squeeze/cough increment, recto-inhibitory reflex (RAIR) and rectal balloon sensation would be influenced by injury site physiology/severity raising the possibility that intervening to normalise these parameters may improve/influence long term bowel continence outcomes.

6.4 Aim

To determine whether, after severe acute TSCI anal sphincter function is influenced by fluctuations in physiological and metabolic parameters monitored from the injury site.

7.3 Methods

7.3.1 Institutional Approvals

Patients were recruited as part of the ISCoPE study. Please see Section 2.3.1 for details of ethical approvals.

7.3.2 Inclusion/Exclusion Criteria

We prospectively recruited a cohort of consecutive TSCI patients who were enrolled into the ISCoPE trial in the period June 2018 – August 2019. Inclusion/exclusion criteria were the same as previous (see Table 2).

7.3.3 Clinical examination and imaging

Clinical assessments and imaging were performed as previously described in sections 2.3.6 and 2.3.7. Patients were followed up periodically in the outpatient clinic that includes assessment of AIS grade, Spinal Cord Independence Measures III (SCIM III)[172] and

Neurogenic Bowel Dysfunction Score (NBD)[173]. The SCIM III bowel score is 0, Irregular timing or very low frequency (less than once in 3 days) of bowel movements; 5, Regular timing, but requires assistance (e.g. for applying suppositories) – rare accidents (less than twice a month); 8, Regular bowel movements, without assistance – rare accidents (less than twice a month); 10, Regular bowel movements, without assistance – no accidents. In the NBD score, bowel dysfunction is classed as 0 – 6, very minor; 7 – 9; minor; 10 – 13, moderate; 14+, severe.

7.3.4 Surgery and Probe insertion

Surgery and probe insertion were performed as outlined previously in sections 2.3.3 and 3.3.4.

7.3.5 ISP and ABP Monitoring

The monitoring setup for ISP and ABP was as outlined in section 2.3.4. ISP and arterial blood pressure signals were sampled at 1 kHz and patients were monitored for up to 7 days.

7.3.6 Signal analysis

Data was analysed using Labchart v.8 (AD Instruments, Oxford, UK) and ICM+ (www.neurosurg.cam.ac.uk/icmplus). ISP and ABP was used to compute: SCPP = MAP – ISP.

7.3.7 Anal Manometry Assessment

All patients underwent anorectal manometry in the ICU at a range of SCPP over the week following surgery at the same time as injury site monitoring. Anal sphincter pressure (AP) was monitored with a 4 channel water perfused anorectal manometer (Ardmore) levelled at the anal verge. The pressure monitor was connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) and in turn connected to the PowerLab system where they were sampled at 1kHz. Fig 104 shows set up. Anorectal manometry was performed according to international guidance[174]. I attended anorectal manometry clinics at St Peters Hospital in Chertsey and was trained in the techniques. Resting AP, cough pressure, squeeze pressure, recto-inhibitory reflex and balloon threshold tests were performed. Resting AP was calculated as mean resting pressure (average of 4 channels – excluding channels thought to be a rectal pressure trace) and also maximal AP. Cough

pressure was defined as maximum AP during cough and increment from resting pressure (ΔAP). Prolonged anal squeeze (10 seconds) was assessed for endurance time (duration of time the patient could voluntarily sustain an increase in AP >50% of maximal incremental squeeze pressure during the long squeeze) and difference in pressure from resting pressure (ΔAP). The recto-inhibitory reflex was performed by rapid inflation and deflation of the rectal balloon (to 50mls) and was assessed for: baseline AP, latency, maximal amplitude, amplitude reduction, recovery time and duration (Fig. 105). Rectal sensation threshold tests were performed by filling the rectal balloon with 50mls increments (to 500mls) and asking the patient to comment on: first sensation, first desire to defaecate and urgency to defaecate. A group of patients also underwent sphincter pressure monitoring in theatre to assess the effects of surgical decompression on resting AP. Repeat assessments were performed in each patient over a range of SCPP.

7.3.8 Statistical analysis

Plots of anal manometry parameters (resting AP, prolonged squeeze endurance time, prolonged squeeze change in AP (ΔAP)) *vs.* SCPP were fitted with best fit quadratic or linear regression curve, chosen to minimize the Akaike Information Criterion. Adjusted coefficients of determination ($\hat{R}^2$) were computed using https://mycurvefit.com with $\hat{R}^2$ >0.5 considered strong correlation. The relation between mean values of components of RAIR (baseline AP, recovery time, % amplitude reduction) and cough (maximum AP, mean change in AP) at high and low SCPP were compared using Student's t-test. Analysis was done using XLStat Biomed v2018.1 for Mac (Addinsoft, Paris, France). Statistical significance was taken as $P < 0.05$.

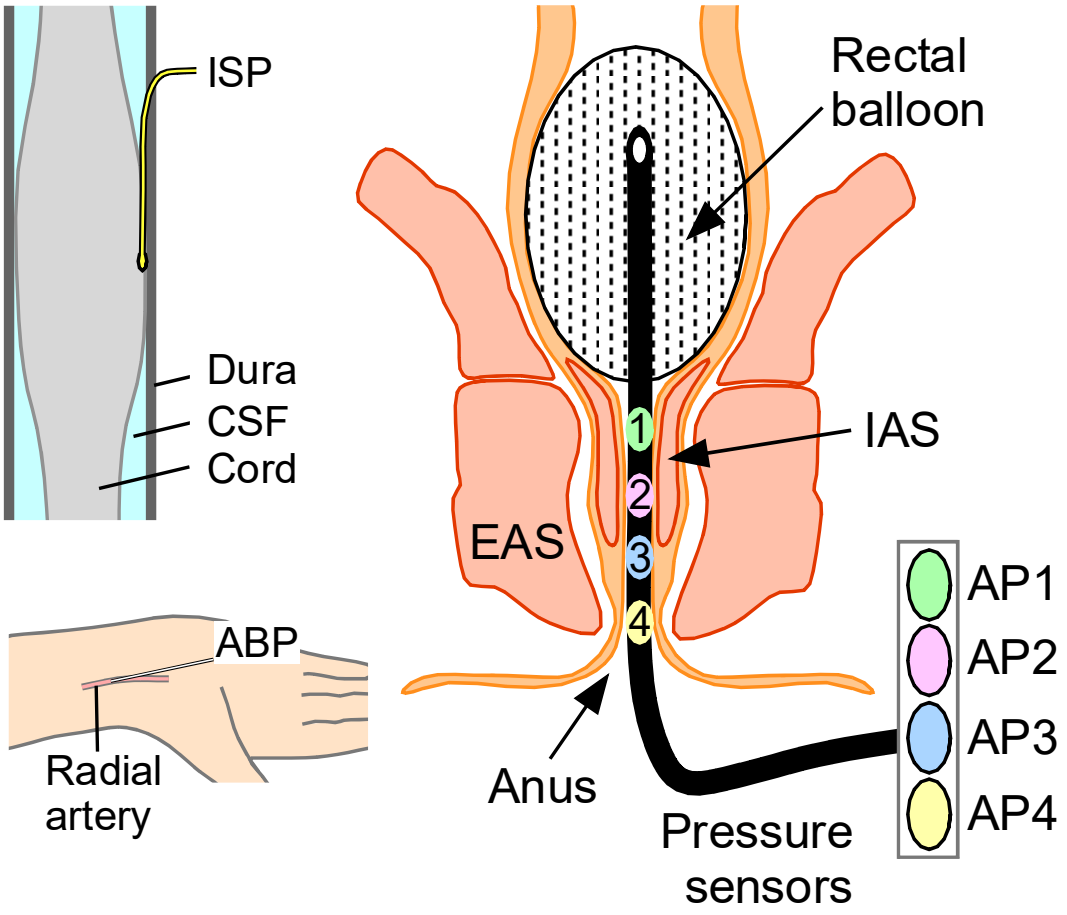


Fig. 104. Setup for monitoring. (*top left*) Intradural pressure probe monitors ISP. (*bottom left*) Radial artery catheter monitors ABP, used to compute SCPP as MAP minus ISP. (*right*) Anal probe monitors from 4 pressure sensors to compute average AP and maximum AP. Rectal balloon used to assess sensation.

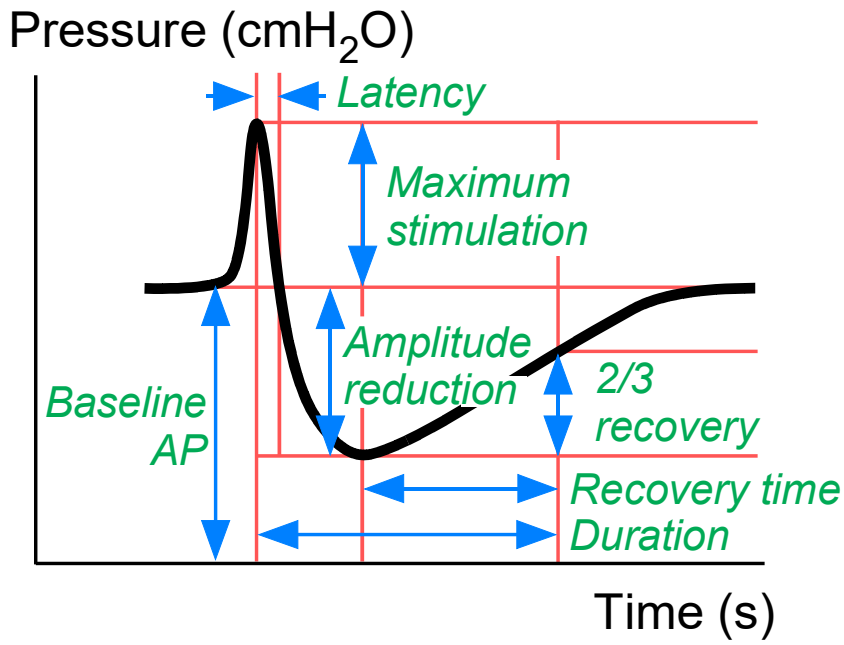


Fig. 105. Recto-anal inhibitory reflex (RAIR). Schematic showing characteristics of the RAIR signal.

7.4 Results

7.4.1 Patient Characteristics

Data was collected from 14 patients aged 22 – 67 years (mean 47), 13 male and 1 female, recruited to the ISCOPE trial between June 2018 and 2019. Most (65%) patients had complete (AIS A) injuries and most (65%) had cervical injuries. All patients underwent posterior surgical bony decompression including laminectomy and fusion with 21% also requiring concurrent anterior stabilisation. Mean follow up was 8 months (range 2-19). At follow-up, most patients (57%) had improved by one of more AIS grades, 35 % remained the same and one patient (7%) deteriorated by one AIS grade. Mean duration of monitoring was 4 – 5 days, most patients had 4 repeat assessments of anal manometry parameters during this period (range 2-8) at a range of SCPP. Some of the patients were sedated to facilitate respiratory support so squeeze tests and threshold tests could not be performed in this group. See Fig. 106 for example traces.

At follow up the NBD score classified 3 patients as having minor-, 4 moderate and 7 severe problems. On SCIM III bowel scores 1 patient scored 0, 7 patients scored 5, 4 patients scored 8 and 2 patients scored 10. Details are in Table 19. Definitions of SCIM bowel scores are in Table 20.

7.4.2 Complications

There were no complications associated with ano-rectal manometry. 7 patients had asymptomatic pseudomeningoceles on post-operative MRI scan, 5 patients were treated for chest sepsis, 1 patient had a pulmonary embolism and 1 developed a sacral pressure sore.

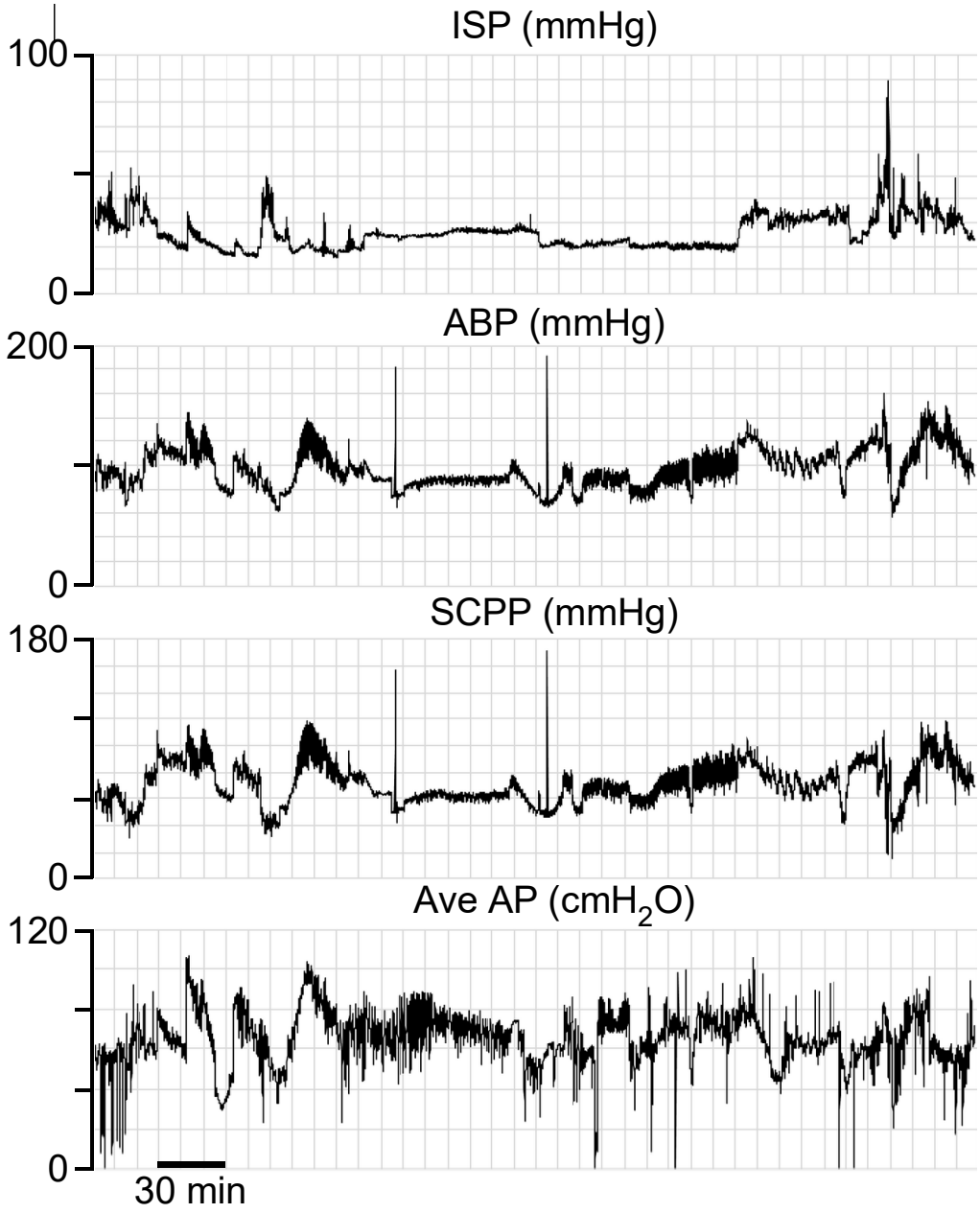


Fig. 106. Examples of signals monitored simultaneously including ISP, ABP, SCPP and average AP.

Table 19. Patient demographics.

Pt. No.	Age (y)	Sex	Injury Level	AIS Grade	Surgical Approach	Lami	Injury to surgery (h)	AIS at Follow up	Duration of Follow up (months)	SCIM III Bowel Score at Follow Up	NBD Score At Follow Up
71	27	M	L1	C	Post	Y	41	D	6	8	15
72	50	M	C5	B	Post	Y	14	B	19	5	18
73	47	M	T8	A	Post	Y	23	B	12	0	21
74	57	M	C4	A	Post	Y	35	A	8	5	11
75	66	M	C4	A	Post	Y	40	A	7	5	19
76	46	M	T12	A	Post	Y	18	C	9	8	28
77	52	M	C5	A	Ant+Post	Y	40	B	8	5	15
78	26	M	C6	A	Ant+Post	Y	39	B	12	10	2
79	67	F	C2	B	Post	Y	69	A	2	5	19
80	55	M	T7	A	Post	Y	45	C	14	8	10
81	54	M	C4	C	Post	Y	69	D	6	8	2
82	44	M	C7	A	Post	Y	32	A	4	5	10
83	51	M	T7	A	Post	Y	50	A	5	5	13
84	22	M	C6	C	Ant+Post	Y	70	D	2	10	0

AIS, American spinal injuries association Impairment Scale; Ant, anterior; C, cervical; F, female; FU (follow up); h, hours; Lami, laminectomy; M, male; No., number; Post, posterior; Pt., patient; T, thoracic; y, years;

Table 20. Definitions of SCIM Bowel Scores.

0	Irregular timing or very low frequency (less than once in 3 days) of bowel movements
5	Regular timing, but requires assistance (e.g. for applying suppositories); rare accidents (less than twice a month)
8	Regular bowel movements, without assistance; rare accidents (less than twice a month)
10	Regular bowel movements, without assistance; no accidents

7.4.3 Resting Anal Pressure

Collectively 14 hours of resting anal pressure data was collected (mean per patient 61.75 mins, SEM 15.14). Average mean resting AP was 41.07 cmH_20 (which is appreciably lower than the average for healthy male patients 99 cmH_20[175]). For most patients, at higher SCPP there was higher resting AP (Fig. 107). When the data was grouped, mean AP showed an inverted U-shaped curve with lower resting AP at extremes of cord perfusion (mean +/- standard error with best-fit quadratic, $R^2 = 0.82$) which is consistent with our previous results which show less optimal clinical and metabolic parameters at very high and very low SCPP. Maximal AP vs SCPP showed a similar correlation (higher pressure with better cord perfusion) (Fig. 108). There was no clear relationship between mean nor maximum resting AP and ISP (Figs. 109-10) and there was no significant change in resting AP intra-operatively pre and post spinal cord decompression in the seven patients who had intra-operative sphincter monitoring (Fig. 111).

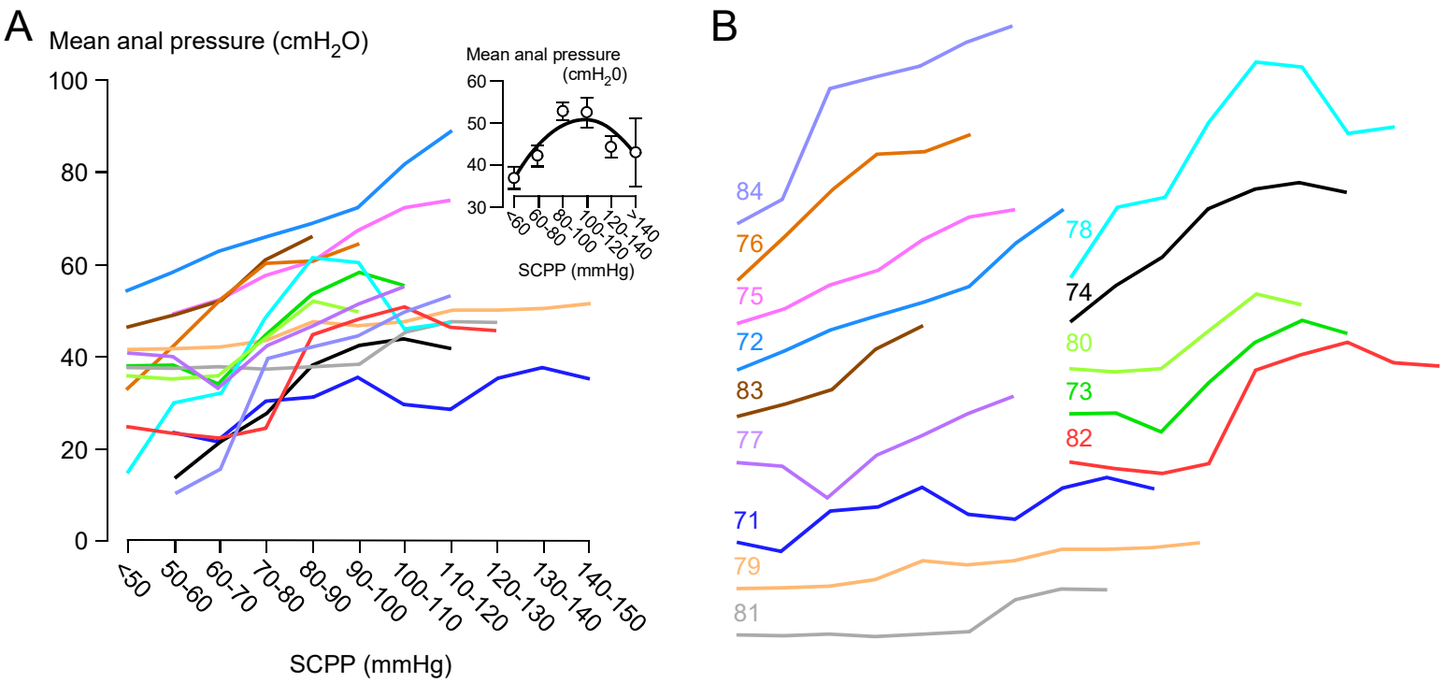


Fig. 107. Correlation between SCPP and Anal pressure. A. Anal Pressure *vs.* SCPP for each of the 14 patients. (*inset)* AP averaged for all patients *vs.* SCPP. Mean +/- standard error with best-fit quadratic, R^2 = 0.82. **B.** Individual curves from A. spread out. Colours correspond to patients as shown.

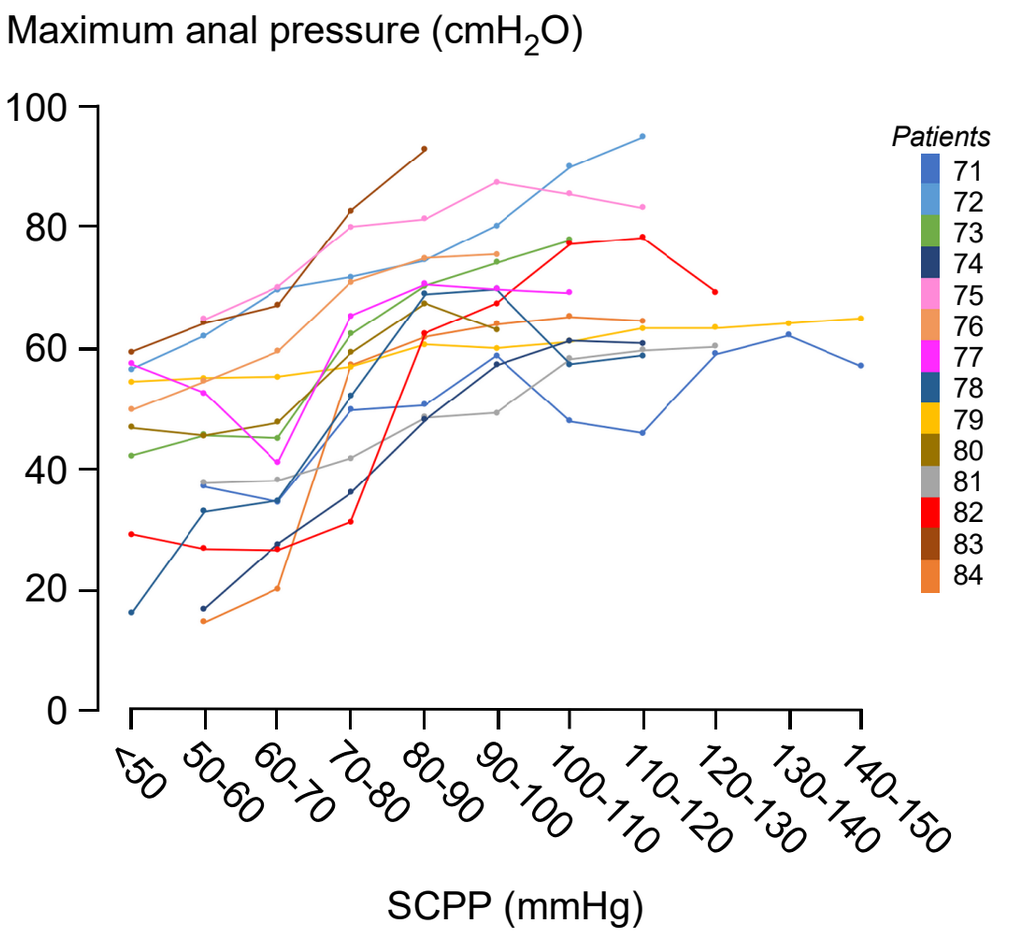


Fig. 108. Plot of maximum anal pressure versus SCPP for individual patients. Each patient is a different colour.

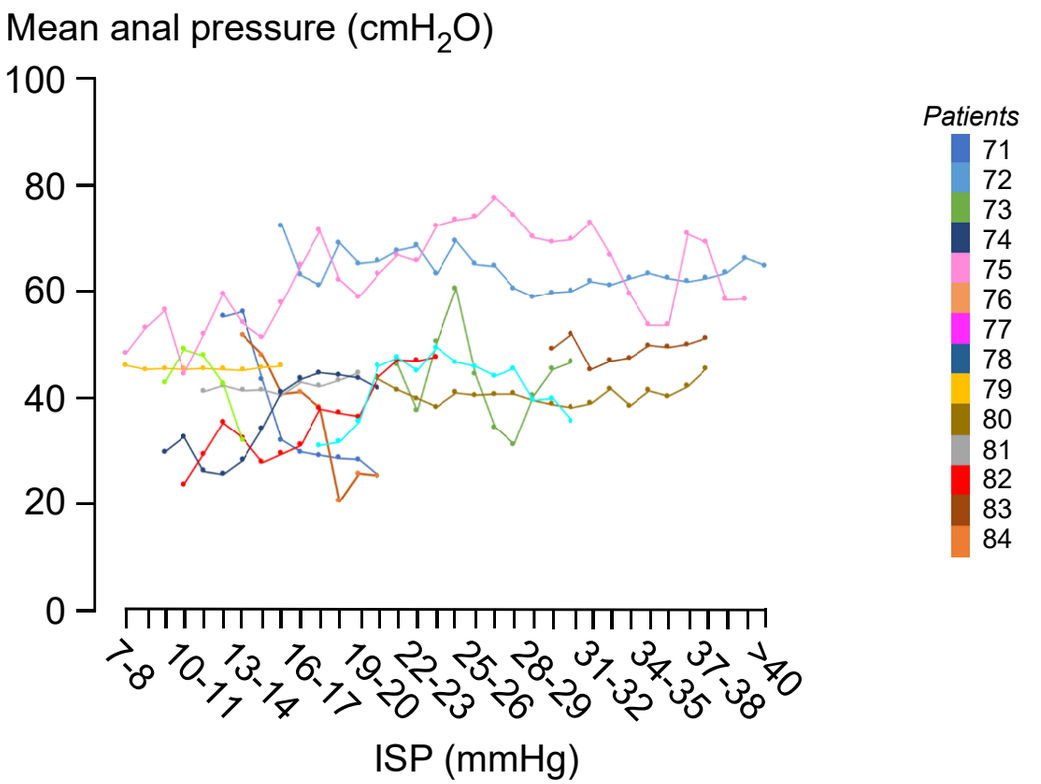


Fig. 109. Plot of mean anal pressure versus ISP for individual patients. Each patient is a different colour.

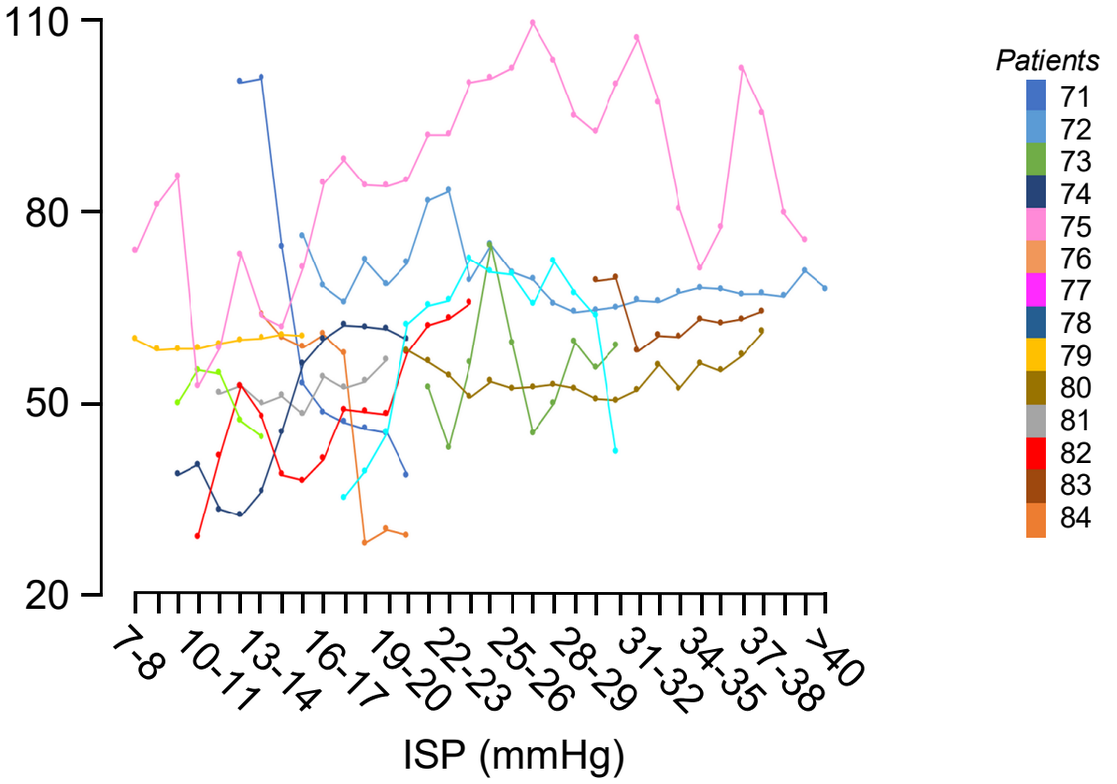


Fig. 110. Plot of maximum anal pressure versus ISP for individual patients. Each patient is a different colour.

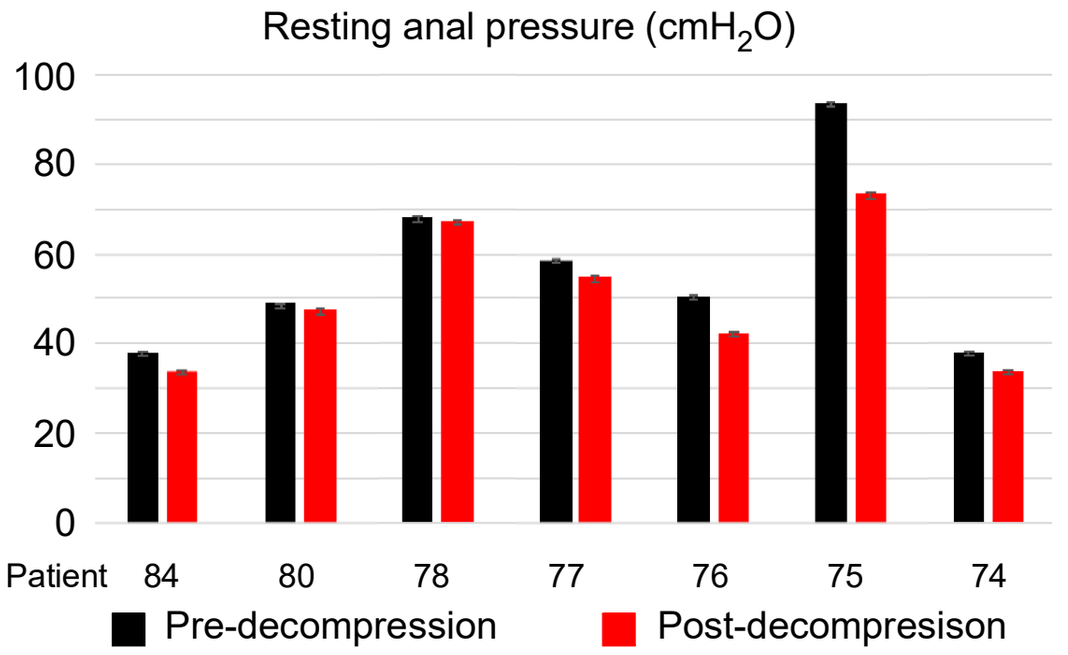
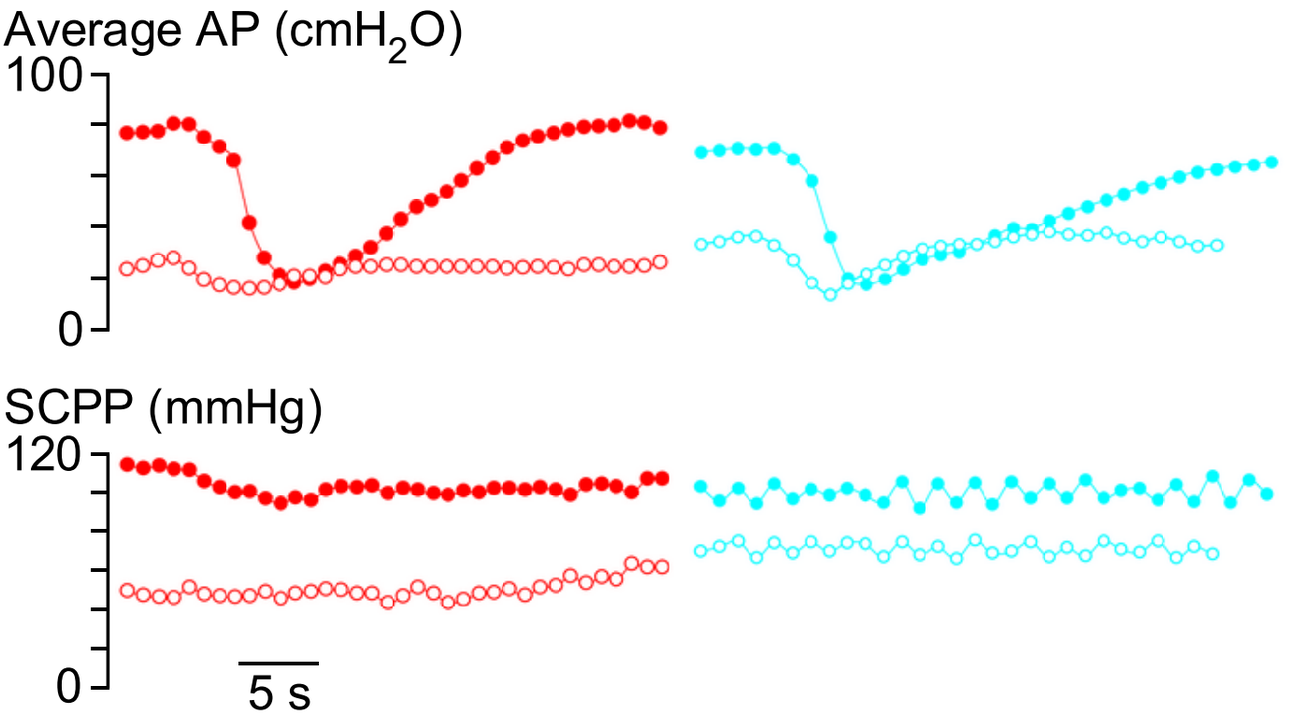


Fig. 111. Effect of surgical decompression on mean resting anal pressure in seven patients.

7.4.4 Recto-anal inhibitory reflex (RAIR)

The RAIR was observed in all patients, see Fig. 111 for example traces. RAIRs were performed at high and low SCPP (Fig. 113). Similar to our results showing better resting anal pressure at higher SCPP, the baseline AP prior to the RAIR was significantly higher at higher SCPP (Fig. 114). The RAIR recovery time was longer at higher SCPP by approximately 2 seconds (Fig. 115) which possibly reflects the greater amplitude reduction which was also seen at high SCPP (Fig. 116) and longer trajectory of recovery. Previous studies have shown that SCI patients have a more pronounced RAIR than controls, at higher SCPP the RAIR was also more pronounced.



Fig, 112. Typical RAIR signals. From patients 82 (red) and 78 (blue) at low (open circles) and high (solid circles) SCPPs.

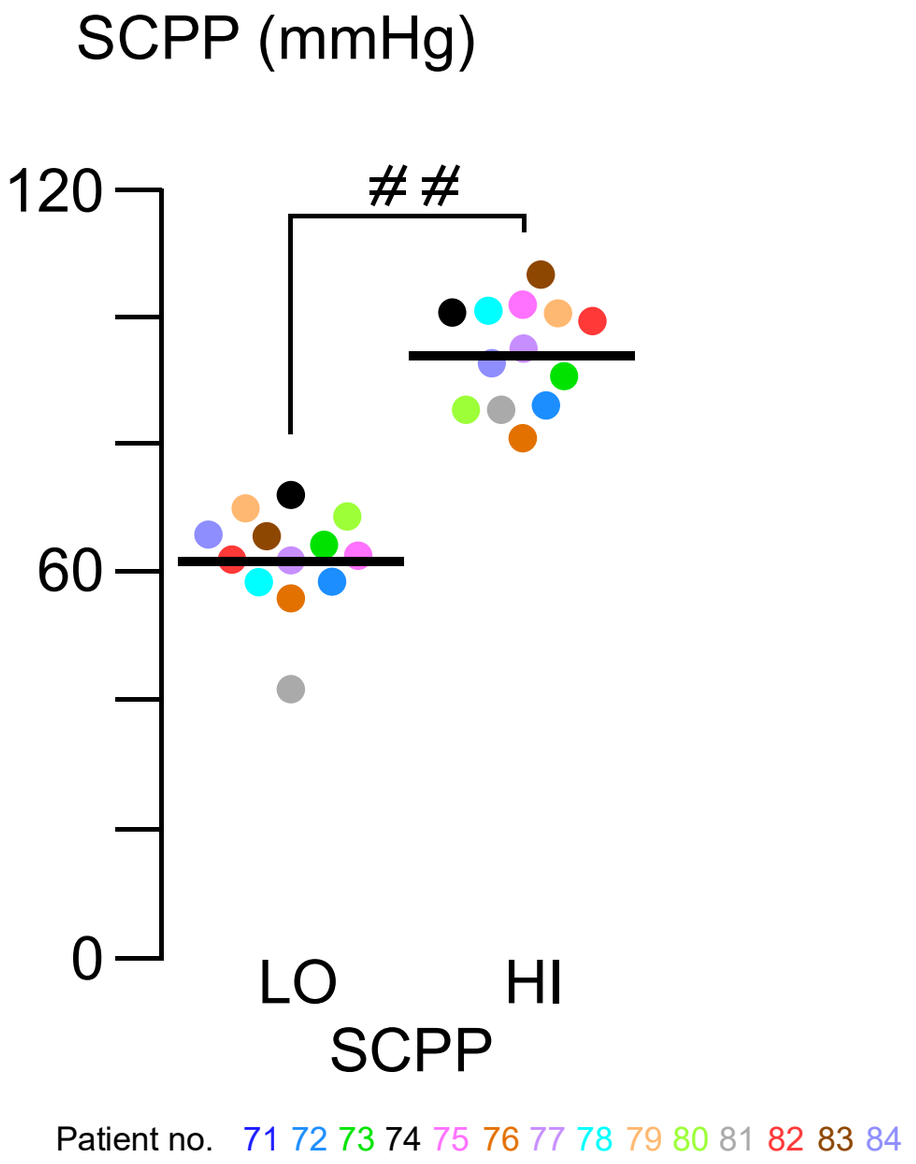


Fig. 113. Mean high (HI) and mean low (LO) SCPPs corresponding to the RAIR measurements for each patient. Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP. Colour-codes for patients 71 – 84. P <0.0001$^{\#\#}$

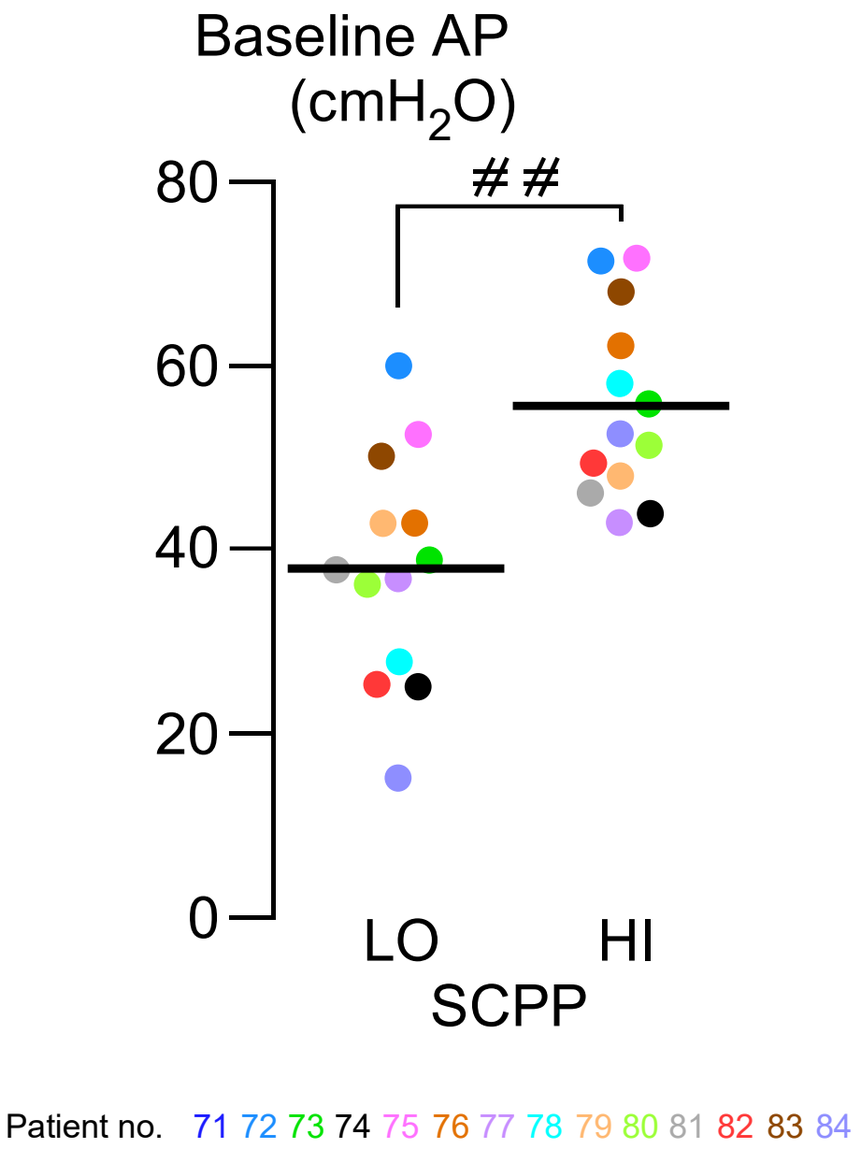


Fig. 114. Effect of SCPP on the RAIR Mean baseline anal pressure (AP). Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP of mean baseline anal pressure. Colour-codes for patients 71 – 84. P <0.0001$^{\#\#}$

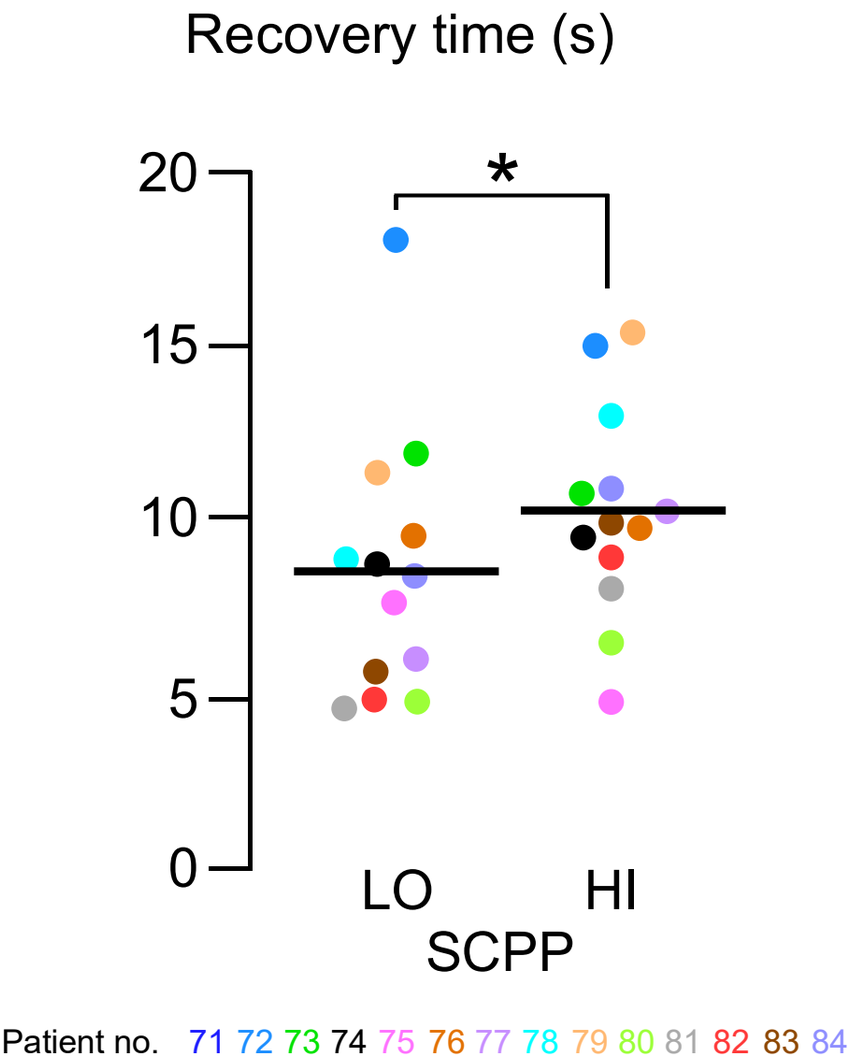


Fig. 115. Effect of SCPP on the RAIR recovery time. Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP of recovery time. Colour-codes for patients 71 – 84. $P < 0.05^{*}$

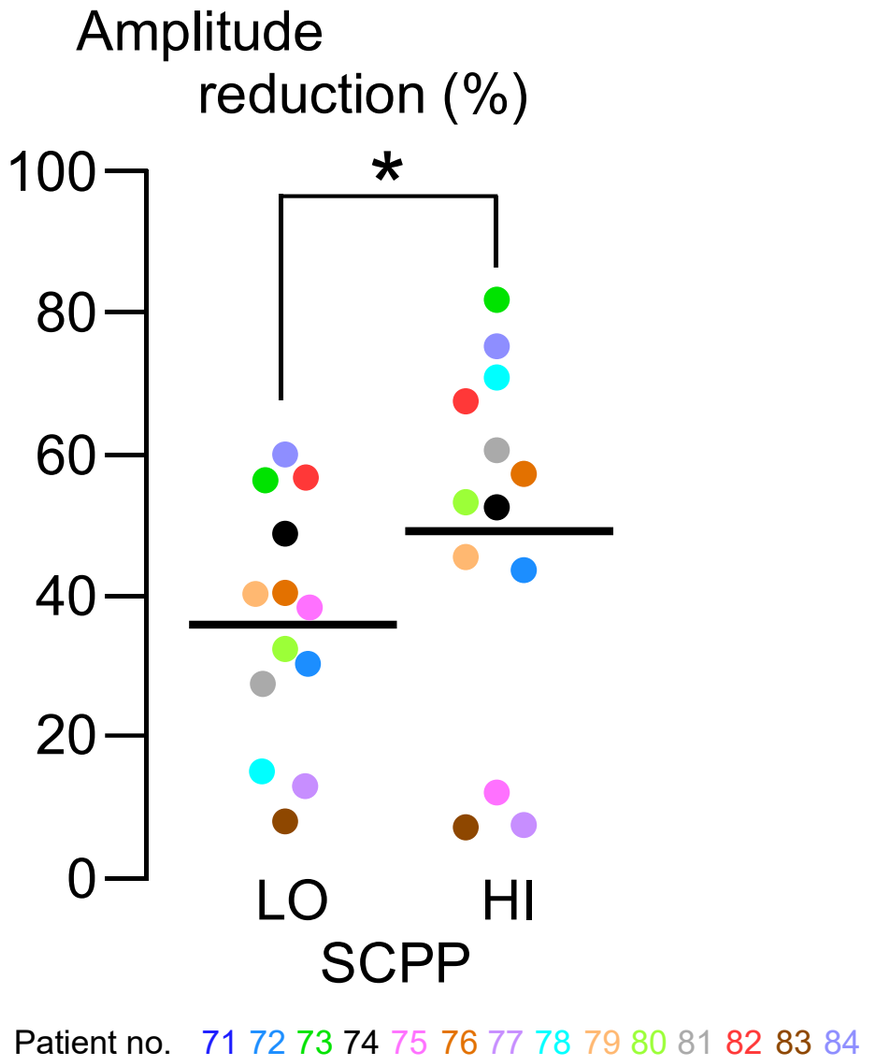


Fig. 116. Effect of SCPP on the RAIR % amplitude reduction. Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP of % amplitude reduction. Colour-codes for patients 71 – 84. $P < 0.05^{*}$

7.4.5 Anal Pressure During Cough

Cough tests were performed in all patients at high and low SCPP (Fig. 117-118). At higher SCPP, the mean of the maximum AP of each cough was significantly higher, by over 20cmH_20 ($P < 0.0001$) (Fig. 119). The difference in AP from resting pressure prior to the cough was also higher, by over 10cmH_20 ($P < 0.0001$) (Fig. 120). As episodes of incontinence are more likely during Valsalva, this indicates that continence is better at higher SCPP.

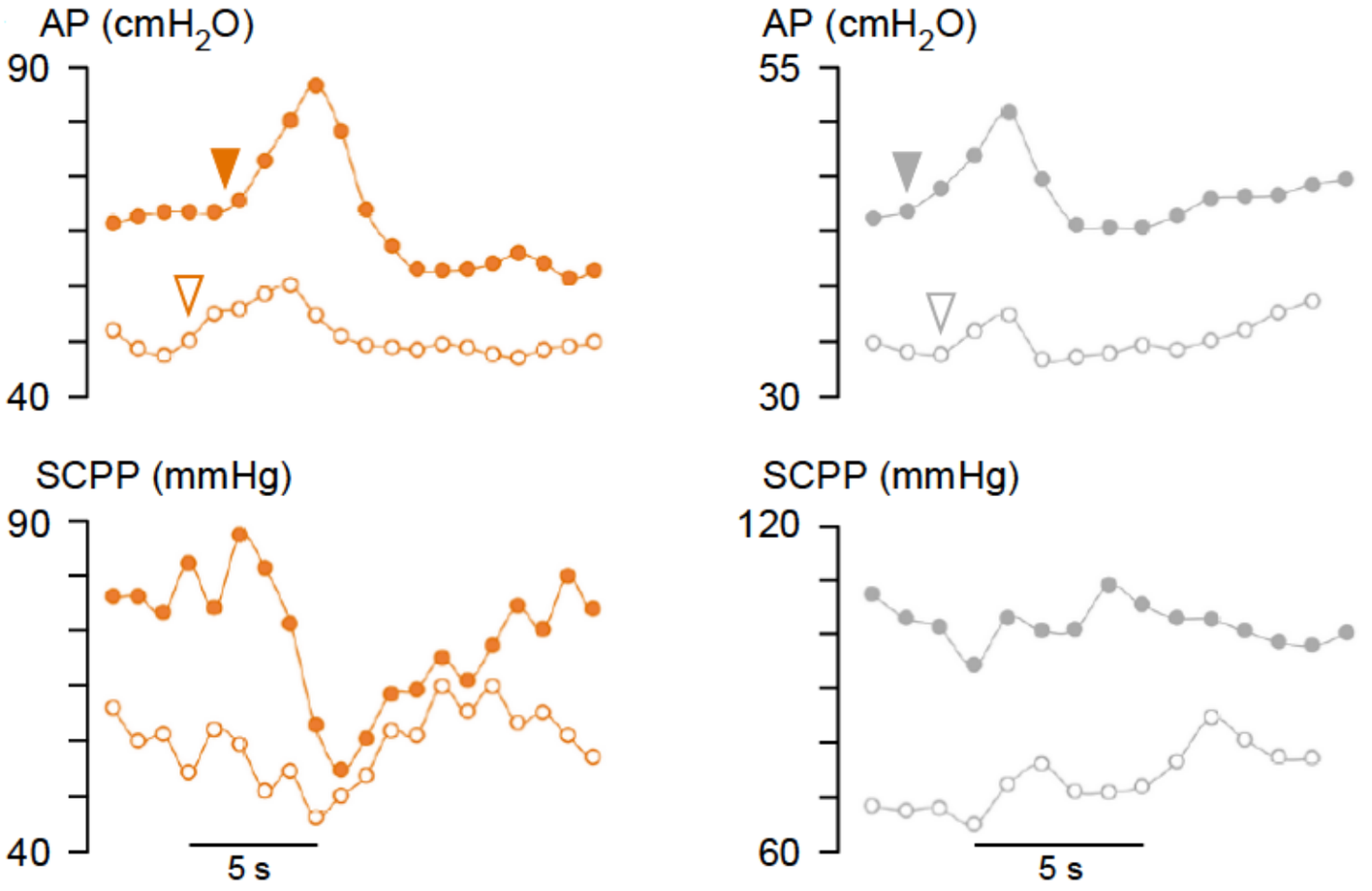


Fig. 117. Effect of cough on anal pressure. Anal pressure changes during cough for patients 76 (*left*) and 81 (*right*) at low (open circles) and high (solid circles) SCPPs.

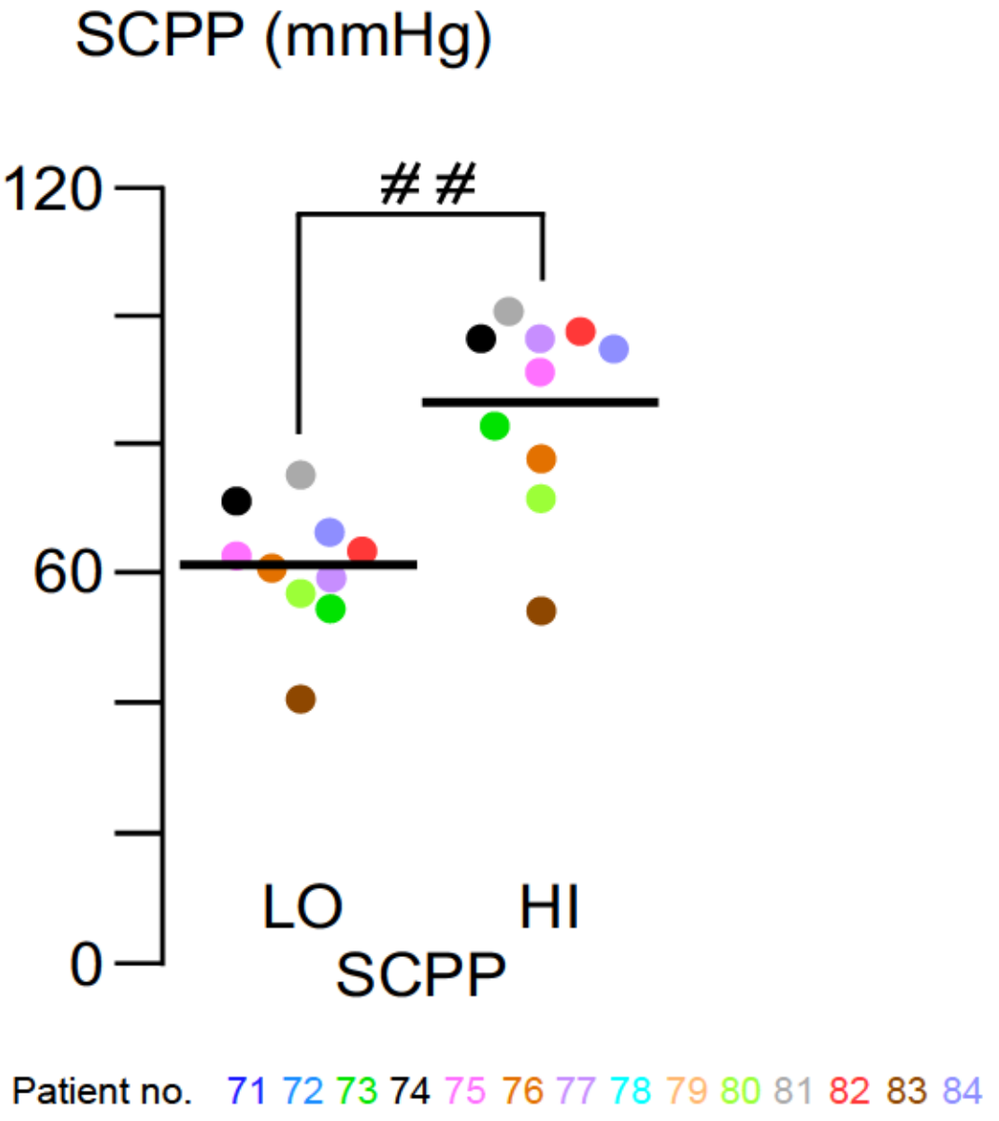


Fig. 118. Effects of SCPP on anal pressure during cough. Mean high (HI) and mean low (LO) SCPPs corresponding to the cough measurements for each patient. Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP. Colour-codes for patients 71 – 84. $P < 0.0001^{\#\#}$

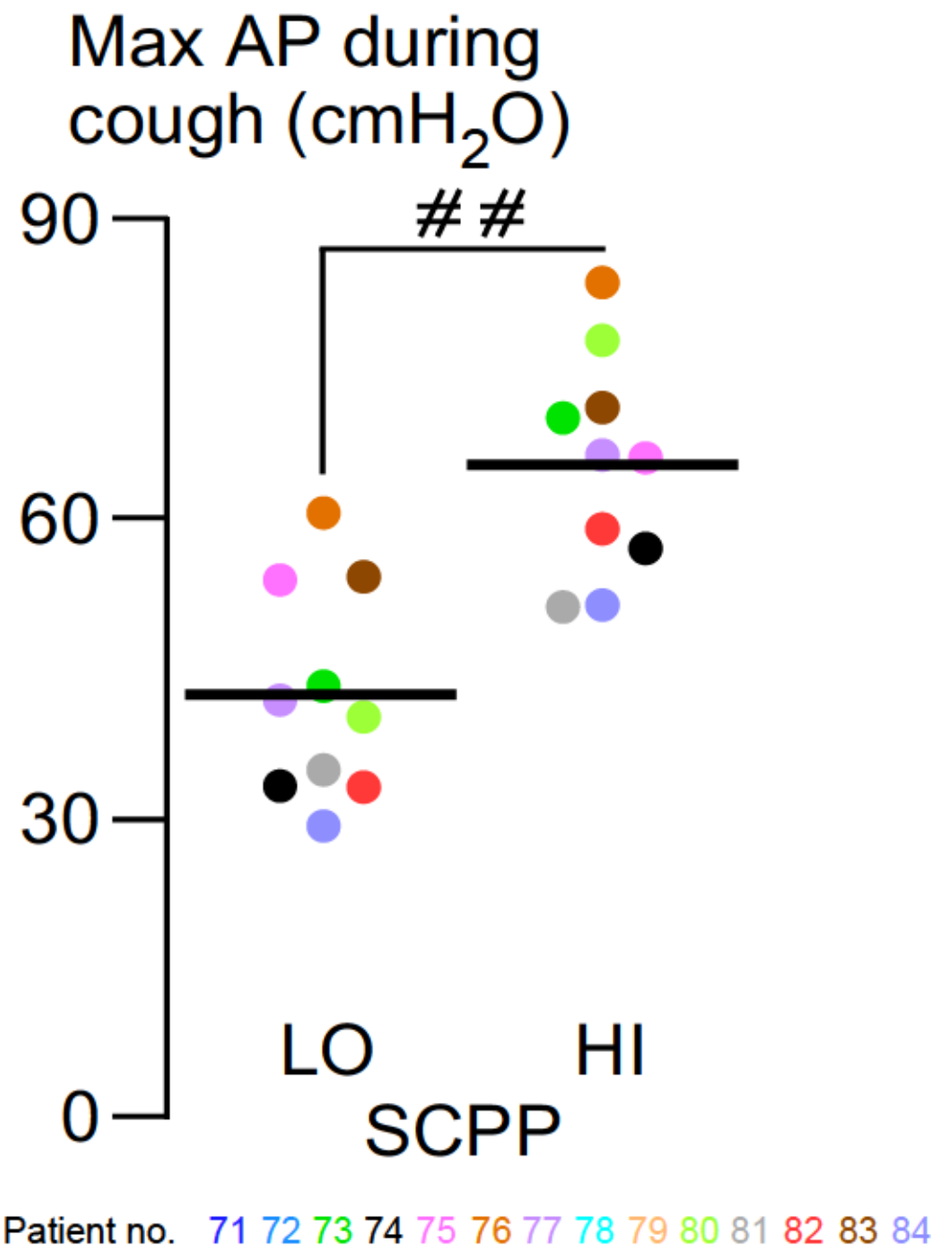


Fig. 119. Effects of SCPP on anal pressure during cough: mean maximum anal pressure. Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP. Colour-codes for patients 71 – 84. P $<0.0001^{\#\#}$

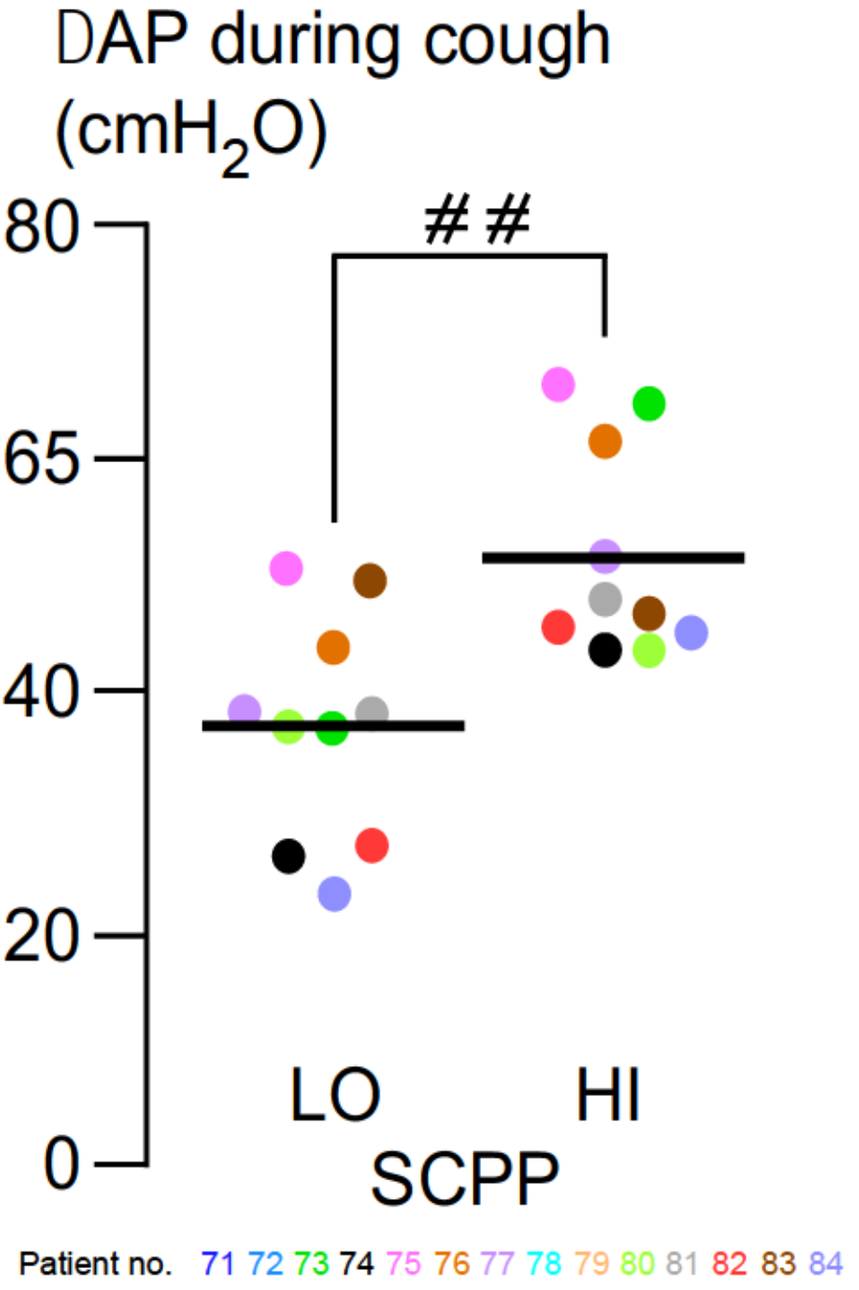


Fig. 120. Effects of SCPP on anal pressure during cough: mean change in anal pressure (ΔAP). Plots showing individual patient values (points) and means (lines) at HI vs. LO SCPP. Colour-codes for patients 71 – 84. $P < 0.0001^{\#\#}$

7.4.6 Anal Pressure During Squeeze

The ability of the anal sphincter to increase in pressure during squeeze was significantly reduced when compared to normal male controls as described in the literature (mean endurance time 16 seconds, mean change in anal pressure (ΔAP) 195cmH_20)[175]. Higher SCPP favoured a stronger sphincter response, see Fig. 121 for examples. Best fit straight line fits well the relationship between prolonged anal squeeze endurance time and SCPP with higher SCPP favouring longer squeeze (R^2 = 0.93) (Fig. 122). An inverted U-shaped curve fits the relationship between ΔAP and SCPP, with the sphincter showing a stronger response at SCPP between 60-100mmHg and weaker response at hypo- and hyper-perfusion (R^2 = 0.87) (Fig. 123).

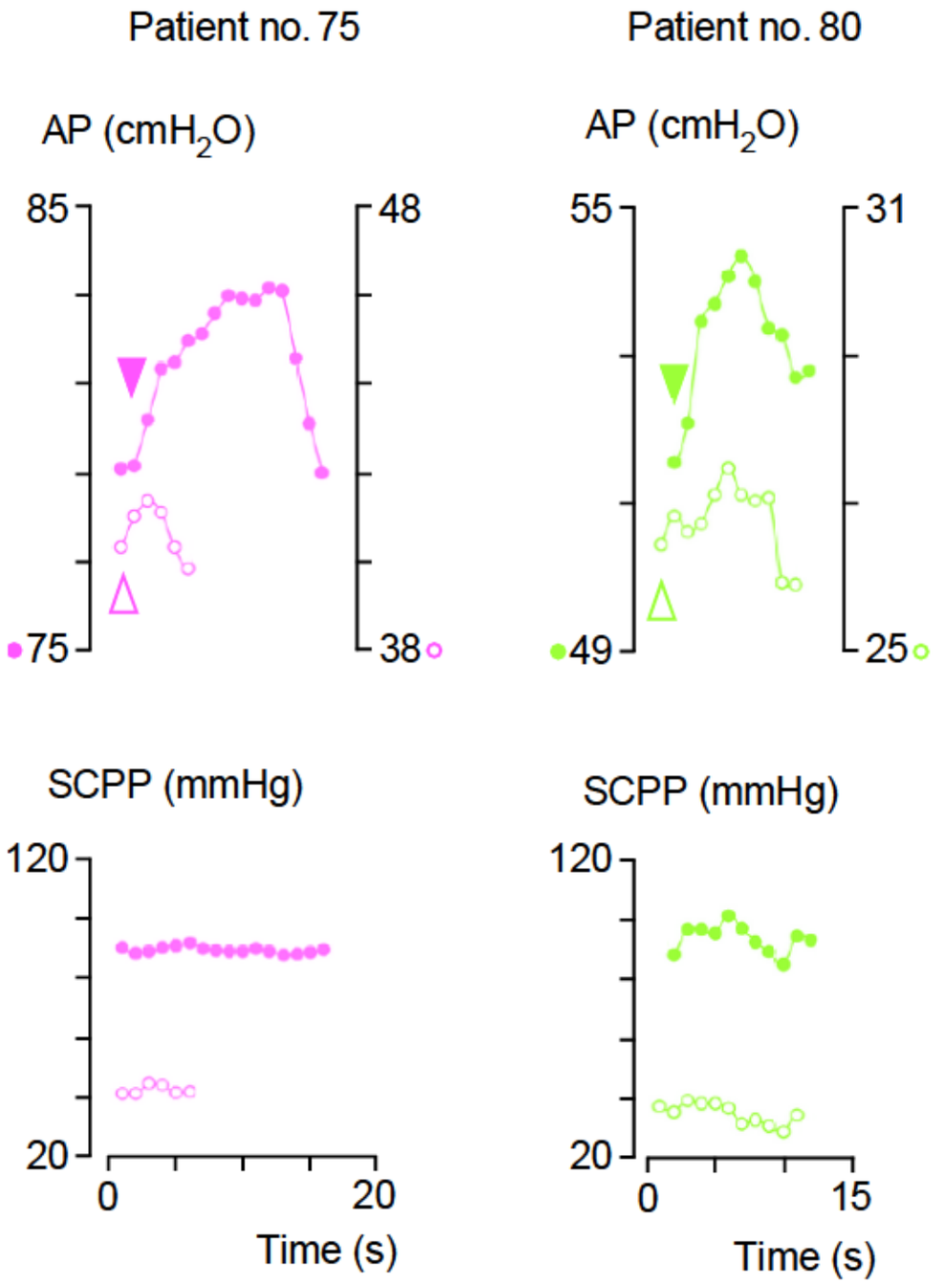


Fig. 121. Effect of SCPP on prolonged squeeze anal pressure. AP changes during squeeze for patients 75 (*left*) and 80 (*right*) at low (open circles) *vs.* high (solid circles) SCPPs.

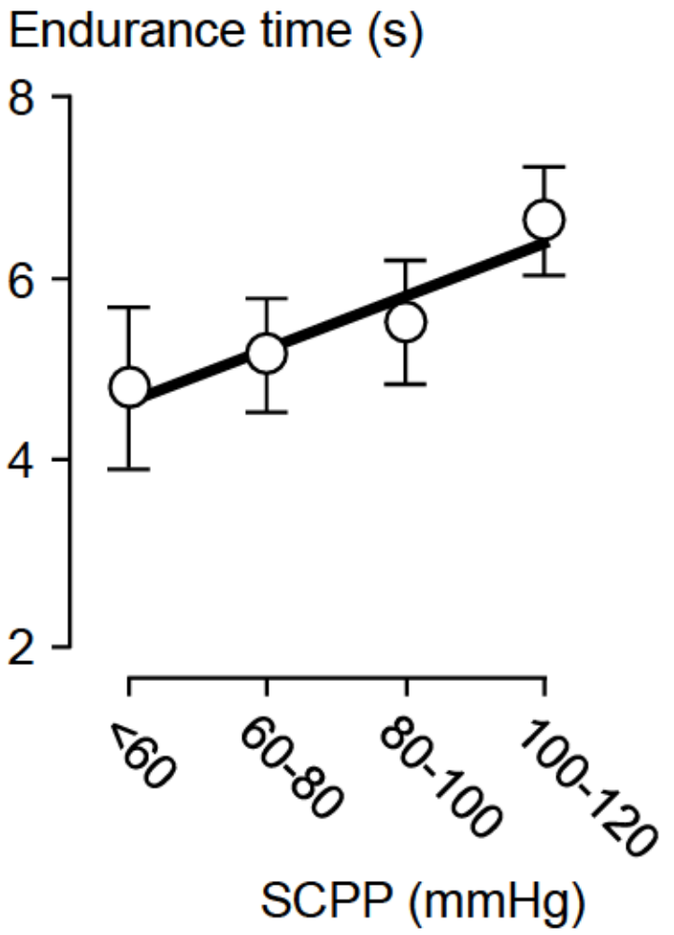


Fig. 122. Effect of SCPP on prolonged squeeze anal pressure: endurance time. Endurance time, N = 10, mean +/- standard error. Best-fit straight line ($R^2 = 0.93$).

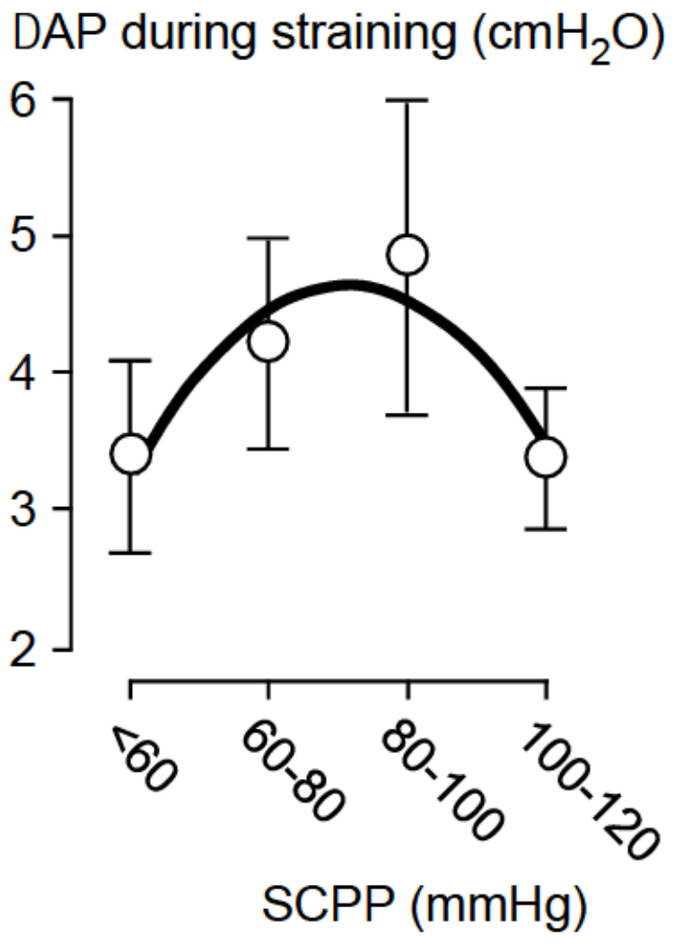


Fig. 123. Effect of SCPP on prolonged squeeze anal pressure- Change in anal pressure (ΔAP). N = 10, mean +/- standard error. Quadratic ($R^2 = 0.87$).

7.4.7 Rectal sensation

Threshold tests for rectal sensation were performed in 10/14 patients at high and low SCPP. The untested 4 patients were sedated for ventilatory reasons. 6/10 patients reported some form of rectal sensation during the tests 4 were AIS A and 2 were AIS C. At follow up all with rectal sensation during threshold tests had remained or converted to an incomplete injury. The 4 patients who did not have rectal sensation were all complete injuries and all remained so. We created survival curves to show the different responses in rectal sensation at high and low SCPP. The probability of not experiencing constant rectal sensation versus volume of the balloon was the same at high and low SCPP. The probability of not experiencing the first urge to defaecate versus volume of the balloon was higher at lower SCPP. The probability of not reaching the maximum tolerance versus volume of the balloon was higher at lower SCPP. None of these comparisons were statistically significant which may reflect the small sample size.

7.5 Discussion

Bowel dysfunction affects 80% of patients with SCI and is often ranked as more problematic than urinary incontinence or sexual dysfunction[176]. Constipation, diarrhoea, and nausea are common, most patients take drugs and many need help to defaecate. Bowel regimens take up considerable time. Faecal incontinence is common and can be unpredictable. Some patients can achieve normal bowel frequency with drugs and manual stimulation[177]. Anorectal manometry offers us insight into the function of the anal sphincter which is relevant to long term bowel outcomes. Additionally anal sphincter function/anorectal sensation is a very important component of the AIS score and the ability to predict ongoing outcomes for patients with TSCI[14]. Being able to improve anal sphincter function early on or improving rectal sensations by optimising injury site physiology is a compelling prospect.

We have shown that some of the key components of continence (resting AP, AP during cough and AP during squeeze) significantly improves at higher SCPP. Interestingly, we found the RAIR was more pronounced at better SCPP with greater amplitude reduction and recovery time (indicating a bigger chance of incontinence with a load in the rectum from anal relaxation). The RAIR is an involuntary enteric reflex known to be preserved and more pronounced in TSCI[178]. It is possible that the stronger RAIR at better SCPP reflects the higher resting AP to start with.

We did not detect an effect of increasing SCPP on the rectal volumes required to elicit sensations (first sensation, first urge to defaecate, maximum tolerance). The data show a trend, i.e. increasing SCPP reduces the rectal volume required to first produce desire to defaecate or to first produce maximum tolerance, though these findings did not reach significance. The small number of patients in our study may be the limiting factor here and it is possible that increasing the number of patients may yield significance.

This study has limitations: first, some of our patients were sedated because they required ventilation which prohibited them from participating in squeeze or threshold tests. Second, some patients received

noradrenaline infusions, raising the possibility of a direct effect of norepinephrine on the anal sphincter. Third, because of the acute ICU setting, we were unable to perform additional studies, e.g. high resolution ano-rectal manometry, anal ultrasound. Finally the analysis of results for anorectal manometry was limited by the time constraints of my PhD.

7.6 Conclusions

Similar to our previous studies which show that changing physiological parameters such as SCPP can improve limb motor function, sensation and bladder function these results indicate a similar response from the anal sphincter and further support the concept of individualised therapy in patients with acute TSCI in ICU.

7. Discussion

Our key findings were that after TSCI injury site physiology and metabolism cannot be predicted pre-operatively based purely on clinical and radiological biomarkers and is distinct from monitoring spinal pressure from the lumbar CSF space. In real time, injury site physiology and metabolism correlates (and can be used to predict) fluctuations in limb power in incomplete TSCI. We found that most TSCI patients develop unfavourable urodynamics acutely which is dynamic and greatly influenced by the physiology and metabolism at the injury site. Anal sphincter function is also appreciably different with changes in SCPP. Novel therapies such as injury site cooling cause more deranged injury site physiology, metabolism and inflammation and are associated with post-operative wound infections.

The ISCoPE study developed techniques to monitor ISP and SCPP from the injury site to compute $SCPP_{opt}$ in patients with acute TSCI. We hypothesised that ISP and $SCPP_{opt}$ can be predicted using clinical factors instead of ISP monitoring. In 64 TSCI patients we studied how well 28 factors correlate with mean ISP or $SCPP_{opt}$ including 7 patient-related, 3 injury-related, 6 management-related and 12 pre-operative MRI-related factors. We found most patients had U-shaped sPRx *vs.* SCPP curves allowing $SCPP_{opt}$ to be computed. 5/28 factors were associated with lower ISP: older age, excess alcohol consumption, non-conus medullaris injury, expansion duroplasty and less intra-operative bleeding. In a multi-variate logistic regression model, these 5 factors predicted ISP as normal or high with 73% accuracy. Only 2/28 factors correlated with lower $SCPP_{opt}$: higher mean ISP, conus medullaris injury. In an ordinal multi-variate logistic regression model, these 2 factors predicted $SCPP_{opt}$ as low, medium low, medium high or high with only 42% accuracy. No MRI factors correlated with ISP or $SCPP_{opt}$. We concluded that elevated ISP can be predicted by certain clinical factors. Modifiable factors that may lower ISP are: reducing surgical bleeding and performing expansion duroplasty. No factors accurately predict $SCPP_{opt}$; thus, invasive monitoring remains the only way to estimate $SCPP_{opt}$.

Other groups monitor spinal pressure following TSCI with a lumbar drain placed distal to the injury[44-46], we wanted to determine whether, after TSCI monitoring from the lumbar CSF space provided comparable information as monitoring from the injury site. In 13 TSCI patients we simultaneously monitored, for up to a week, CSFP and ISP from the injury site and computed the SCPP, sPRx. and $SCPP_{opt}$. from both. We also assessed the effect of draining 10 mL lumbar CSF on ISP. Metabolites from the injury site, sampled by microdialysis, were compared with metabolites in the lumbar CSF. ISP and CSFP signals appeared different: ISP was pulsatile, but CSFP had low pulse pressure and was non-pulsatile 21 % of the time. Overall, there was weak or no correlation between physiological parameters measured at injury site and in the lumbar CSF space. CSF drainage caused no significant change in ISP in 7/12 patients, a drop by <5 mmHg in 4/12 patients and a drop (by ~8 mmHg) in 1/12 patient. Periods of low ISP were associated with more pulsatile CSFP and stronger correlation between CSFP *versus* ISP. Patients with less cord oedema on MRI had stronger correlation between

CSFP *versus* ISP. Metabolite levels in the lumbar CSF *versus* injury site did not correlate for lactate, pyruvate or lactate-to-pyruvate ratio and had significant, but weak, correlation for glucose, glutamate and glycerol. We concluded that after severe TSCI, the cord swells against the dura thus obstructing CSF flow. As a result, monitoring from the lumbar CSF provides limited information about physiological and biochemical events at the injury site and lumbar CSF drainage does not effectively reduce ISP.

We hypothesised that, after TSCI fluctuations in physiological and metabolic parameters, monitored from the injury site were causatively linked to changes in limb power. In 19 patients correlations with motor incomplete TSCI we examined correlations between limb power, ISP, SCPP and cord metabolism and performed Granger causality analysis. Motor score versus ISP had exponential decay relation, motor score versus SCPP had linear relation and motor score versus LPR also had linear relation. Increased ISP Granger-caused increase in LPR, decrease in SCPP and decrease in motor score. Increased SCPP Granger-caused decrease in LPR and increase in motor score. Increased LPR Granger-caused increase in ISP, decrease in SCPP and decrease in motor score. Causality analysis also revealed multiple vicious cycles, which suggests that insults to the cord become amplified and should be promptly treated to reduce secondary damage. Our analysis indicates causative relations between ISP, SCPP, LPR and limb motor score. Thus, monitoring these variables and intervening to normalize them is likely to improve limb power.

We wanted to determine the effect of local hypothermia and rewarming on the injured human spinal cord. In five patients with TSCI we induced local cord hypothermia (33^0C) then gradual rewarming (37^0C) whilst monitoring pressure and metabolism and inflammatory mediators at the injury site. The cooling protocol did not cause discomfort or neurological deterioration. Cooling did not affect cord physiology (no change in ISP or SCPP), but markedly altered cord metabolism (increased glucose, lactate, LPR, glutamate and decreased glycerol) and markedly reduced cord inflammation (reduced IL1β, IL8, MCP, MIP1α, MIP1β). Rewarming significantly worsened cord physiology (increased ICP, decreased SCPP), cord metabolism (increased lactate and LPR, decreased glucose and glycerol) and cord inflammation (increased IL1β, IL8, IL4, IL10, MCP, MIP1α). The study was terminated because three patients developed delayed wound infections likely related to the hypothermia. At 18-month follow-up, two patients improved (AIS A to B, B to D) and three stayed the same (AIS A). We showed that local hypothermia–rewarming after TSCI is associated with increased spinal cord swelling, reduced cord perfusion, deranged cord metabolism, increased cord inflammation and increased risk of wound infection. Based on these findings, we urge caution when attempting to use hypothermia–rewarming therapeutically in TSCI patients.

Chronic TSCI often leads to unfavourable urodynamics i.e. low bladder compliance (<20 ml/cmH_2O), detrusor overactivity (DO) and detrusor sphincter dyssynergia (DSD). As a result, detrusor pressure rises (>40 cmH_2O) causing vesico-ureteral reflux, hydronephrosis and, ultimately, renal failure[158]. Before urological surveillance became established, 50 % TSCI patients died from renal failure[159]. We wanted to characterise the

effect of acute TSCI injury site physiology and metabolism on urinary bladder function. We performed filling cystometry in 13 patients with TSCI (a total of 63 fill cycles). 38 cycles had unfavourable urodynamics defined as one or more of bladder compliance <20 cmH_2O in 12, detrusor overactivity in 35, detrusor sphincter dyssynergia in 29 and maximal storage pressure >40 cmH_2O in 10. Unfavourable urodynamics were more prominent during periods of cord hypoperfusion (spinal cord perfusion pressure <60 mmHg), hyperperfusion (spinal cord perfusion pressure >100 mmHg), low (<3 mM) injury site glucose and high (>30) injury site lactate-to-pyruvate ratio at the injury site. Increasing spinal cord perfusion pressure from 67.0 ± 2.3 mmHg (average ± standard error) to 92.1 ± 3.0 mmHg, significantly reduced, from 534 to 365 mL, the median bladder volume at which the desire to void was first experienced. We found that most TSCI patients develop unfavourable urodynamics within 10 days of injury challenging the prevailing notion of acontractile detrusor occurring acutely. Bladder function was found to be dynamic and greatly influenced by the physiology and metabolism at the injury site. Therefore, optimising spinal cord perfusion and metabolism in the acute phase may improve urological outcome.

8. Limitations

Our study has limitations. TSCI is rare and the numbers of patients in our studies are relatively small, we had to terminate the hypothermia study due to increased wound complication rates which again limited numbers. Some of our patients were sedated because they required ventilation which limits some of the interactive clinical assessments for limb power, UDI and anorectal manometry. SCPP was altered in patients by using vasopresssors (not by lowering ISP as we have previously shown is possible with expansion duraplasty[53]), raising the possibility of a direct effect of noradrenaline on end organ function, although our analysis did not suggest this. The acute ICU setting limited our ability to perform additional studies, e.g. flow or video-urodynamics and high resolution anorectal manometry.

9. Overall Conclusions

TSCI is a multi-system disease. In the early stages of injury, we showed that fluctuations in injury site physiology and metabolism correlate with motor function, bladder and anal function and that optimising SCPP improves these clinical outcomes in the acute stage. This is consistent with previous findings where we showed that lower ISP and higher SCPP correlate with better injury site metabolism which is associated with: improved somatosensory evoked potential conduction[61], lower fever burden[179] and long term AIS grade improvement [50]. Measuring ISP and SCPP requires invasive injury site monitoring and offers valuable insights into cord physiology when exploring novel techniques to improve neurological outcomes, such as cord cooling.

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Appendix 1: ISCoPE Protocol



Injured Spinal Cord Pressure Evaluation (ISCoPE)

Sponsor's Project Number: 09.0151 **Clinical trials.gov:** NCT01975493
REC Reference Number: 10/H0807/23
IRAS ID: 38379

Protocol Version and Date: 13 20/12/2017

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Funding Source: Api [ ] [Yt oc] R dl bn aj mgab] nkd XgZj n[n]n] Xmzc aj pi [Xodj i aj ggj r dl b k]] m n]hqd] r Xi [oc] l] pmjn nZd] i Z] n M] n] Xmzc Aj pi [Xodj i

Information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorisation from St George's Joint Research & Enterprise Office (JREO) or its affiliates.

Statement

The Chief Investigator (CI) and the Sponsor representative have discussed this protocol version. The investigators agree to perform the investigations and to abide by this protocol except where departures from it are mutually agreed in writing.

The Investigator agrees to conduct the trial in compliance with the protocol, GCP (R2), the Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the UK Policy Framework for Health and Social Care Research, the Sponsor's SOPs, and other regulatory requirements as appropriate.

This protocol has been written in accordance to the Sponsor's procedure identified as: JREOSOP0039 "Protocol Design" and is intended for use at UK sites only

Chief Investigator Marios Papadopoulos St George's, University of London	Signature	Date

Acknowledgements and Protocol contributories

Marios Papadopoulos (MCP) and Samira Saadoun (SS) conceived the study, Melissa Werndle (MW) Isaac Phang (IP) Mathew Gallagher (MJG), Florence Hogg (FRAH) initiated study design and implemented. All authors contributed to refinement of study protocol and approved final manuscript.

Funders of the study have no influence on design, collection, management, analysis or interpretation of data.

Contents

1 List of abbreviations 2
2 Roles and Responsibilities. 3
3 Study synopsis 4
4 Background 5
4.1 Study Rationale 6
5 Study objectives ..... -
Mdhf, <] i] adbn ..... /
6 Trial design 1
6.1 Schematic of Study design 1
7 Participation selection criteria 2
7.1 Inclusion criteria 2
7.2 Exclusion criteria 2
8 Participant Recruitment process 2
9 Study procedures 3
9.1 Informed consent 3
9.2 Discontinuation/withdrawal of participants and stopping rules 4
9.5 Participant transfers 4
9.6 Lost to Follow up 5
9.7 Definition of the End of Trial 5
10 Study Procedures 5
10.1 Screening assessments 5
10.2 Baseline assessments 5
10.3 Interventions 5
11 Safety Events 6
11.1 Definitions 6
11.2 Recording Adverse Events (AEs) ..... /-
11.3 Investigator Responsibilities relating to Safety Reporting ..... /-
11.4 Notification of deaths ..... /-
12 Data management and quality assurance ..... /-
12.1 Confidentiality ..... /-
12.2 Data collection tool ..... /.
12.3 Data handling and analysis ..... /.
13 Archiving arrangements ..... /.
14 Statistical design ..... /.
14.1 Statistical input in trial design ..... /.
14.2 Endpoints ..... /.
14.2.1 Primary endpoints ..... /.
14.2.2 Secondary endpoints ..... //
15 Committees in involved in the trial ..... //
16 Direct access to source data ..... //
17 Ethics and Research Governance requirements ..... //
17.1 Annual Progress Reports (APRs) ..... /0
17.2 Notification of Serious Breaches of GCP and/or the protocol ..... /0

18 Finance 10
19 Insurance and indemnity 10
20 IP and development policy 10
21 Publication policy 11
21.1 Before the official completion of the Trial, ... 11
21.2 Up to 180 days after the official completion of the Trial 11
21.3 Beyond 180 days after the official completion of the Trial 12
22 Statement of Compliance 12
23 List of Protocol appendices 12
11 Mamizn 12

1 List of abbreviations

ASIA	American Spinal Injury Association
CE	Conformité Européene
CI	Chief Investigator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
EEG	Electroencephalogram
GCP	Good Clinical Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ICG	Indocyanine green angiography
ISF	Investigator Site File
JREO	Joint Research and Enterprise Office
MRI	Magnetic Resonance Imaging
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
REC	Research Ethics Committee
SDV	Source Document Verification
SOP	Standard Operating Procedure
TMG	Trial Management Group

2 Roles and Responsibilities.

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Trial Management Group:

Membership: Prof Marios Papadopoulos, Dr Samira Saadoun, Dr Argy Zoumprouli, Neurosurgical research fellow. Membership will also consist of personnel involved in daily operational issues in the management of the trial and will act upon advice/recommendations received by the sponsor

3 Study synopsis

Brief title:	ISCoPE (Injured spinal cord pressure evaluation)
Official title:	?qXgpXcqji jacc] kjcjicdKgX[q]mn]]aa]Zoj akmjnnpmjXaojmmkdlXgZjmjh dlepmb
Sponsor reference number:	09.0151
Public database identifier	NCT01975493
Study type & Phase	Pilot, interventional
Study design	Prospective
Study Population/disease condition	Severe spinal cord injury ASIA A-C
Eligibility criteria:	***Inclusion criteria:*** Adults (18 – 70 years old) with severe cord injury (ASIA A-C: See Appendix 2), Surgery within 72hrs of injury, speaks English ***Exclusion criteria:*** Patients with major co-morbidity, or concurrent injury. Penetrating injury
Target number of participants	*100*
Criteria for evaluation	**Primary outcome measure(s)** Iph Y]mjacdbc Zjmjhkmjnnpmj]kdhj[]n %92hdl)9.2hh Cb&k]m[Xt)>pmXcqji jacdbc kmjnnpmj9.2hh Cb&k]m[Xt **Secondary outcome measure(s)** Kmjnji Z]jaGpi[Y]mb;)<)=rXq]n[pmdlbhjiobjmdlbk]ng[7lpXicdbXcdq]h]Xnpmjhjiojak]mapmqji rdbc D=B Xibqjbm%kct7ZcXib]ncj H?Kn,NN?Knrdbc ZcXib]ndl kmjnnpmj+=cXib]dlnkdlXgZjmjhh]oXYjgdb]nrdbc kmjnnpmj+=cXib]dl nkdlXgZjmjhkmjnnpmjXi[h]oXYjgdb]nrdbc ctkjcc]mhdK+Kmjn]iZ]Xi[ ]aa]Zoj ankmjX[dlb[]kjgXmdhXcqjindlnkdlXgZjmjh+Oc]Pmjn[tiXhdZnja XZpo]nkdlXgZjmjhdlepmb
Sources of funding	***Wings for life Spinal cord Research Foundation***
Sponsor	***St Georges University Hospitals NHS Foundation Trust***
Key Contact names	Sponsor representative : Debbie Rolfe Email [redacted] Tel: [redacted] Fax [redacted] Chief Investigator: Professor Marios Papadopoulos Tel: [redacted]

4 Background

; Yj po X cc j pn Xi [k] j kg] X t] Xmd cc] P i ob][F d b[j h npmqob] X nk d XgZj nh d epmo Ypo Xmh g ao kXmXgn][j mr c]] gZc Xdm Yj pi [+ Cc] Xi i pXgZj no j a ZXmh aj mnk d XgZj nh d epmo qoZodh n oh h j nh cc Xi cXga X Yqggi kj pi [n V. OWR] k nj kj n] cc Xo Xao] mnk d XgZj nh d epmo) Zj nh k nj nnpnh Xo cc] d epmo nob] noh] n) [Xh Xbd b cc] nk d XgZj nh apmoc] mYt ohZc X] h dK+ Cc] qXgp] j a h] Xnpmd b Xi [nh[pZd b Zj nh k nj nnpnh Xao] mnk d XgZj nh d epmo oh pi f i j r i +

Cc] nh oh [dh Zo] qd[ ] i Z] anjh nj [ ] i o ncp[d] n cc Xo Zj nh nr] ggd b Xao] mnk d XgZj nh d epmo oh cXmh apg Yt d Zmh Xnd b Zj nh k nj nnpnh Xo cc] d epmo nob] V. - VWD X h j pn] nk d XgZj nh d epmo h j [ ] g cc] nr j ggi Zj nh r Xn Zj h k nj nn] [XbXd no npnnjn pi [d b [pnX] q] i Xao] mYj i t [ ] Zj h k nj nnq i) r obc Zj nh k nj nnpnh Y] cr]] i O- Xi [O2 h h C b Xo cr j [Xt n Xao] md epmo %N]] Adbpnh . &+H dZ] gXZf d b cc] Zj nh r Xo] mZc Xi i] gk nj o] d XI pXk j nd *1 cX[g] nn Zj nh nr] ggd b) g i r] mZj nh k nj nnpnh Xo cc] nk d XgZj nh d epmo nob] Xi [Y] co] mi] pnjn g i bdZXgj poZj h] +

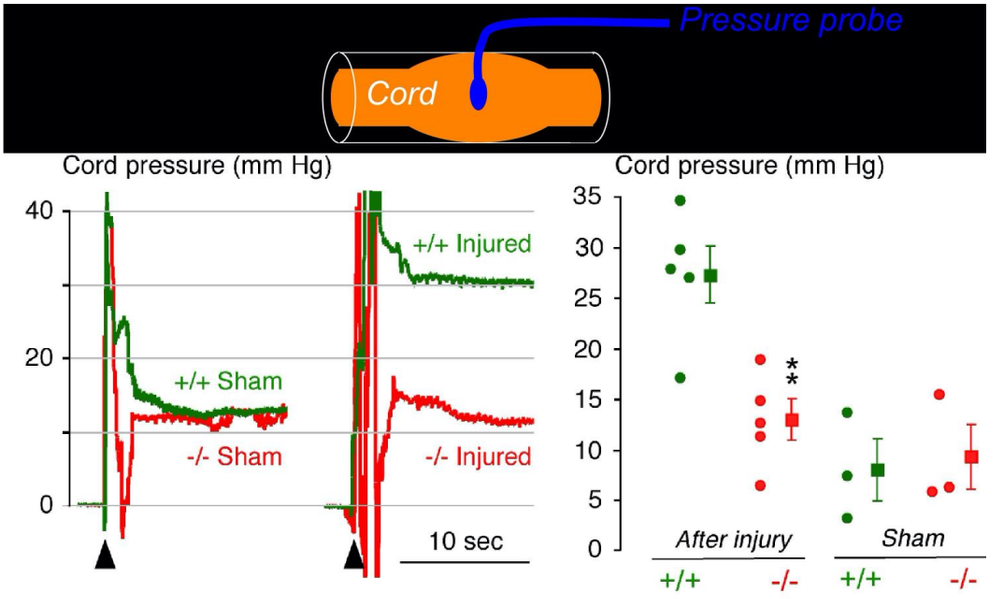


FIG. 1: Mouse spinal cord injury model. A. ?g loXo][Zj nh k nj nnpnh Xo cc] d epmo nob] / [Xt n Xao] m N=D Xi [Yj i t [ ] Zj h k nj nnq i + %j k &. > d Kbm Xh j a k nj nnpnh k nj Y] d n] no] [d o j cc] Zj nh a j m k nj nnpnh nj Zj nh d bn+ %j o j h g ao& M] k nj n] i o Xoob] nk d XgZj nh k nj nnpnh nj Zj nh d bn %Xmj nr nc j r n d n] noq i j a k nj Y] d o j cc] Zj nh+%j o j h nobco&Nph h Xmo j a C3 Zj nh k nj nnpnh n d NcXh h dZ] Xi [h dZ] Xao] mZj h k nj nnq i N=D+I j o j i j mh XgZj nh k nj nnpnh n d nc Xh r q[o t k] %, (&h dZ])] g loXo][Zj nh k nj nnpnh n d d epmo[(, (h dZ]) Xi [nh[pZ] [Zj nh nr] ggd b d ; L K1*i pgg%, *&h dZ] +H] Xi (, *N?H)'' *P* 8 - + - 2 + %Anjh NXX[j pi] o Xg+ *Brain* / - - 5). 0. 6/ 54*65&

Cc] nh oh Xgnj d [dh Zo] qd[ ] i Z] anjh c ph Xi nop[d] n) r cdZc npbb] non cc Xo nk d XgZj nh nr] ggd b oh cXmh apg+Cc]] so] i o j a Zj nh nr] ggd b Xao] mnk d XgZj nh d epmo d q] mn] g t Zj nh h gXo] n r obc j poZj h] V0)2)6WD h Xi t kXoq] i on r obc nk d XgZj nh d epmo cc] nr j ggi Zj nh Xk k] Xmn] s k Xi [ ] [XbXd no cc] [pnX] q] i Xao] mYj i t nh Xgb i h] i o %N] XcoXZc] [Adbpnh / &+

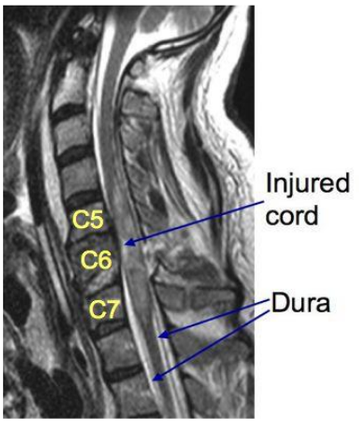


FIG. 2: Human spinal cord injury. NXbobXgO/ H MDncjr olb cc] olepmh[Zjmh+Cc] Zjmh Xkk]Xmn nr jggli Xi[Zjh kmjmm][XbXolnocc] npmmjpi[olb[pmX Xo=2–=4]q]i ocjpbc cc] nkolXgZXi Xg[dXh]o]mohX[]lpXo]+

Apmoc]mnpkkjmoajmocc] X[q]mm]]aa]Zojai]pmXgoohnp] nr]ggolbjij poZjh] Zjh]nanjh YmXol olepmo nop[o]n+;ao]mYmXol olepmo) Yjit[]Zjh kmjmnoli Xgi] %6]mh][ZmXio]Zojht&[j]nijo mh[pZ] olomXZmXiodXgkmjhnnpmh Y]ZXpn] jak]mnohojio[pmXgZjh kmjmnoli+>pnolb[]Zjh kmjhnnoq] ZmXio]Zojht)cc]mhajmh)cc] [pmX oh Xgr Xtnr o[]gt jk]i][\3WWD nkolXgZjmh[]Zjh kmjmnoli) cjr]q]mhcc] nkolXg[pmX oh ijojk]i][Xao]mYjit mhXgbih]io+J k]iolb cc] [pmX%pnjncjht Xi[[pmXkgXnot&ol mXoh j[]gnXao]mZ]mqdZXgZjmh olepmo mhnpgonol Y]coo]mapiZoojiXgmhZjq]mo Xi[glnnnkolXgZjmh nZXmoohnp]+V.3W

4.1 Study Rationale

Oc] olepmh[nkolXg Zjmh oh Zjh kmjmm][Yt Yjit h XgXgbih]io Xi[Zjmh nr]ggolb+=pmmhio h Xi Xb]h]io olqjgq]nmhXgbiolb Xi[aslolb cc] Yjit amXbh]ion pnolb h]oXgnZmhrn)mh[n Xi[kgXo]nV.)1WVR] ctkjcc]moh] ccXoYjit mhXgbih]io Xgi] [j]nijoX[]lpXo]gt[]Zjh kmjhnn cc] nr jggli Zjmh)rcdZc mhh Xoln Zjh kmjmm][XbXolnocc] npmmjpi[olb[pmX%M] Aobpmh O&+R]r qgg []q]gik X ijq]gh]ocj[cj h]Xnpmh Zjmh kmjhnnpmh Xocc] olepmo mob] Xao]mnkolXgZjmh olepmo Xi[[]o]mh ol]r c]cc]moc] Zjmh kmjhnnpmh moh]n)cjr gi ib cc] Zjmh kmjhnnpmh oh cobc Xi[ol r cXo kmjkjmogi jakXoo]ion cc] Zjmh kmjhnnpmh moh]n+

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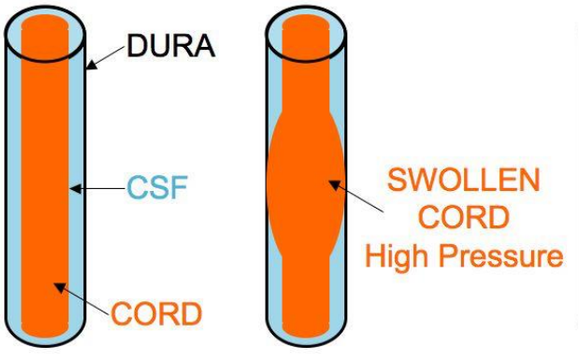


FIG. 3: Concept of dural cord compression+A. I j mh XgZj mh npmnpi [ ] [Yt Z] mhYmnkdXgapd[%NA&Xi [[pmX+**B.** Nr j gdi Zj mh Zj h kmhmn] [XbXdnocc] i j i *[dnoj indYg [pmXZXpn] ncdbc dcmXkXmhi Zct h XgZj mh kmhmnpmh+

5 Study objectives

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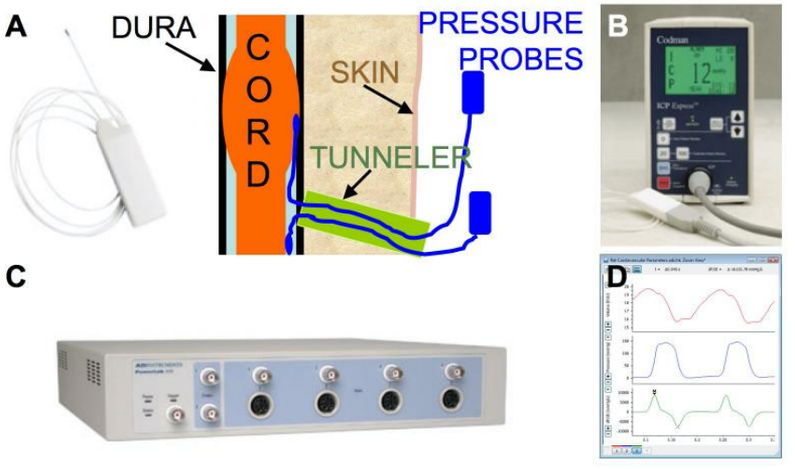


FIG. 4. Human cord pressure monitoring. A. %Gac&=j[hXihdZmjkmjY]+%Mdbco&Kmjkjn][dln]modjiojZcidlp]6Orj hdZmjkmjY]nXmjhXnn][ocmjpbcnfdlXi[pi[]ngtdlbnjaoohnp]robcXopii]glmXi[dln]mo][ocmjpbc[pnX[dhoXgojdlepntn obj pi[]m[dhjZoqdhgji+PndlbdlonXjk]mXodu]apjpjmnZjkt Xi[Zjiodlpjpnkmjmnpmjhjiobjndlbcc]ZXcc]ojmnXmjhXnn][Y]or]]i[pnXXi[Zjmj+Jii]ZXcc]ojmnhkgXZ][Xocc]glq]gjadlepntn%c]kjdlojahXsdhphkmjmnpmj&Xi[cc]jcc]mY]gir cc]glq]gjadlepntn+Oc]kmjmnpmjkmjnY]ohcc]inJZpnj[jicjcc]nfdlrobcnpopmj+Oc]kmjmnpmjkmjnY]ohXooXZc][cjXB. =j[hXihjiobjmhgdf][cjXC.Kjr]ngKYdlojnaXZ])XooXZc][cjD.XK=mpiidlbGXY=cXmo*4njaorXmjhcj[]ojZoXi[XiXgtn] cc]mjZmj][nobiXg+Kjr]nGXY。GXY=cXmo4Xmjhamjhcj

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Risk/Benefits

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6 Trial design

6.1 Schematic of Study design

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2. Final sponsorship and host site permissions,

All subjects who wish to enter the study will be fully screened and consented by the Chief Investigator, or an appropriate delegate. As detailed below

Participants will be recruited via St Georges NHS Hospital

9 Study procedures

9.1 Informed consent

Please note, it is essential that all trial personnel/staff undertaking the informed consent process has signed the Sponsor's Delegation of Responsibilities Log JREOLOG0004 to ensure that the person has been delegated the responsibility by the study CI/PI. All personnel taking informed consent must be GCP trained. Refer to Sponsor SOP JREOSOP0027

Informed consent from the participant, or personal consultee opinion must be obtained following explanation of the aims, methods, benefits and potential hazards of the trial and before any trial specific procedures are performed. The only procedures that may be performed in advance of written informed consent being taken are those that would have been performed on all participants in the same situation as routine clinical practice.

Following the patient's spinal injury they would be transferred by the emergency services to the most appropriate local hospital for assessment and treatment. NOK or relatives will be identified and informed via the emergency services routine policy and procedures.

The trauma team at that hospital will screen such patients for the ISCOPE trial and if they think appropriate candidates will refer to the ISCOPE research team. If the ISCOPE team finds them appropriate for the study the local team would inform the patient / patients NOK about it and see if they wanted to be transferred to SGH for discussion with the research team.

Some patients require intubation and sedation for transfer which means on arrival to SGH they temporarily lack capacity to consent to inclusion in the trial. If this is the case the personal consultee (Relative or friend) will be consulted about the study and be asked to provide a positive opinion on whether their relative would want to be included.

A consultee information sheet and consent form will be provided and a personal consultee signature indicating positive opinion for study inclusion will be requested. The original copy will be placed in the study folder and a copy will be placed in the participant medical notes. A copy of the study information sheet and the signed form will be provided to the personal consultee.

For potential participants who lack decisional capacity and a personal consultee proxy was obtained the participants informed agreement will be obtained once they regain decisional capacity. This request will be documented in the participant medical notes together with their decision to provide consent for continued study participation or not.

The Investigator or designee will explain that the patients are under no obligation to enter or be entered into the trial and that they can withdraw at any time during the trial, without having to give a reason.

For participants that consent but are unable to sign the consent form due to arm/hand weakness will have 2 witnesses sign on their behalf. At least 1 witness will not be directly involved with the study.

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant/personal consultee. A signed & dated consent form will be retained in the medical notes and an original copy will be placed in the ISF.

If new information results in significant changes to the risk–benefit assessment, the consent form will be reviewed and updated if necessary. All participants, including those already being treated, will be informed of the new information, given a copy of the revised consent form and asked to re-consent if they choose to continue in the study.

9.2 Discontinuation/withdrawal of participants and stopping rules

In consenting to the trial, participants are consenting to trial interventions, trial follow up and data collection. However, an individual participant may stop the intervention early or be stopped early for any one of the following reasons:

Intercurrent illness that prevents further protocol intervention

Any change in participant's condition that is in the investigator's opinion justifies the discontinuation of protocol intervention

Withdrawal of consent from the participant or the participant NOK

As participation in the trial is entirely voluntary, the participant may choose to discontinue participation at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their participation a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights. Participants who discontinue study participation, for any of the above reasons, should remain in the study for the purpose of follow up and data analysis.

If a participant chooses to discontinue they should be continued to be followed up as closely as possible to the follow-up schedule defined in the protocol, providing they are willing. However if the participant confirms they do not wish to participate in the scheduled follow up data collection visits then data that has already been collected should be kept and analysed according to the ITT principle for all participants who stop follow up early.

Participants who stop the trial follow up early will not be replaced

The study will be discontinued if major complications arise in any patient directly related to the study interventions.

9.5 Participant transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed up at another sponsor approved trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRF should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

9.6 Lost to Follow up

For studies conducted in the UK you may wish to utilise using the NHS number to trace participants whom may have changed their GP- specific consent will be required to utilise this

9.7 Definition of the End of Trial

This is defined as the Last Patient last data entry point. The REC requires notification of the end of trial within 90 days of its planned completion or within 15 days if the study is terminated early. Refer to JREOSOP0015 and inform the JREO to facilitate assistance and compliance with requirements

10 Study Procedures

10.1 Screening assessments

Patient demographics, past medical history, medication history, concurrent injuries, ASIA score

10.2 Baseline assessments

ASIA score and pre-operative MRI whole spine

10.3 Interventions

Intra-operatively following spinal decompression and required instrumentation. The following procedures may be performed:

1. ICG angiography
2. Expansion duroplasty – using commercially available synthetic dura replacement
3. Insertion of up to three sub dural monitoring probes (pressure/microdialysis/tissue oxygen/EEG). Durotomy one vertebral level below the injury site, probes advanced under microscope to level of injury site. Durotomy closed with fibrin glue +/- suture. Probes will be tunnelled to the skin and secured with sutures.
4. Insertion of intra parenchymal microdialysis catheter – tunnelled and secured in the same manner as sub dural probes.
5. Monitoring of spinal cord blood flow – using commercially available probes used to measure intra-cranial blood flow
6. Placement of extra dural cooling catheter – using commercially available intravascular cooling catheter which we will lie in an extra dural position and tunnel out to the skin where it will be secured with sutures.

Once the patient has returned to the intensive care unit:

1. Recording from the monitoring probes will continue for up to 7 days
2. Localised cord hypothermia may be induced

3. Patients may undergo somatosensory evoked potentials +/- motor evoked potentials

4. Patients may be given intravenous dexamethasone

5. Removal of the monitoring probes +/- cooling catheter will take place using local anaesthetic on the intensive care unit. The exit sites of the probe swill be sutured.

6. Urodynamic testing through existing urinary catheter with additional rectal pressure probe may be performed.

Following removal of monitoring probes

1. Patients will undergo a repeat MRI of the spine

2. Patients will have a repeat ASIA grade prior to discharge

Out patients 6 – 12 months after injury

1. Repeat ASIA grade

2. Wound review

3. If urinary catheterisation still present and a recent urodynamic test has not been recently performed at the spinal rehabilitation unit- a repeat urodynamic test may be requested.

11 Safety Events

11.1 Definitions

Adverse Event (AE)—any untoward medical occurrence in a participant whether it is considered to be related to the intervention or not, that includes a clinical sign, symptom, or condition and /or an observation of a near incident. (This does not include pre-existing conditions recorded as such at baseline)

Serious Adverse Event (SAE)—any Adverse Event or untoward medical occurrence in a trial participant that can be wholly or partly to the intervention which resulted in any of the following:

- Results in death; or
- Is life-threatening (places the participant, in the view of the Investigator, at immediate risk of death)
- Requires hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of participants regardless of time of diagnosis).
- Or is another important medical condition

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

11.2 Recording Adverse Events (AEs)

All Adverse Events will be recorded in the hospital notes in the first instance.

A record of all AEs, whether related or unrelated to the treatment will also be kept in the CRF and the Sponsor's AE Log JREOLOG0007. *Please note, that all **SAEs** must be recorded in the CRF.*

If the Investigator suspects that the disease or condition has progressed faster due to the intervention, then he will report this as an unexpected adverse event to the sponsor.

11.3 Investigator Responsibilities relating to Safety Reporting

Collection, recording and reporting of AEs (including serious and non-serious events and reactions) to the Sponsor will be done according to the Sponsor's Safety reporting for non-CTIMP studies SOP JREOSOP0033.

All SAEs will be recorded in the hospital notes and the CRF, and the Sponsor's AE Recording Log JREOLOG0007. The AE Log will be sent to the Sponsor on request and every 2 months.

All SAEs will be reported both to the Sponsor via the JREO & REC *using the SAE report form for research other than CTIMPs (non-CTIMPs) published on the HRA website* The Chief or Principal Investigator at any participating site will complete the SAE form which will be faxed both to the JREO on 020 8725 0794 or E-mailed to adverseevents@sgul.ac.uk, within 48hrs of the Investigator becoming aware of the event, and via email to the relevant REC.

The Chief or Principal Investigator will respond to any SAE queries raised by the Sponsor as soon as possible. Follow up reports must continually be completed within acceptable time-frames and sent as detailed above until the reportable event is considered resolved

Events will be followed up until resolution; any appropriate follow-up information will be clearly marked as such and reported to the sponsor via the JREO as above in a timely manner.

Full reports should be completed and submitted to REC within 15 days of the event

11.4 Notification of deaths

Only deaths that are assessed to be caused by the trial intervention will be reported to the Sponsor. This report will be immediate.

12 Data management and quality assurance

12.1 Confidentiality

All data will be handled in accordance with the Data Protection Act 1998.

The Case Report Forms (CRFs) will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only, will be used for identification. The

sponsor Subject ID log JREOLOG0002 can be used to cross reference participant's identifiable information.

12.2 Data collection tool

Case Report Forms will be designed by the CI. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log JREOLOG0004 will identify all trial personnel responsible for data collection, entry, handling and managing the database

Data that may be recorded directly into the CRFs will be cord pressure, arterial blood pressure, central venous pressure, blood gases and posture.

12.3 Data handling and analysis

Raw data from monitoring probes will be recorded using AD Instruments Labchart. This will be stored in raw form and exported into Microsoft Excel. Microdialysis data will be exported from the lab analyser using Microsoft Excel. Data from the patients notes will be transcribed into Microsoft Excel. MRI data will be kept on the hospital servers.

All data will be stored on the University servers and backed up on study laptops.

Quality Control should be applied at each stage of data handling to ensure that all data are reliable and have been processed correctly.

13 Archiving arrangements

The trial essential documents along with the trial database will be archived in accordance with the sponsor SOP JREOSOP0016. The agreed archiving period for this trial will be 10 years

14 Statistical design

14.1 Statistical input in trial design

This is a pilot study – no statistical input has been sought.

14.2 Endpoints

14.2.1 Primary endpoints

Each patient will be monitored for up to 1 week. Primary endpoints: Number of high cord pressure episodes (> 5min, > 15 mmHg) per day, Duration of high pressure >15 mmHg) per day.

14.2.2 Secondary endpoints

Presence of Lundberg A, B, C waves during monitoring period; quantitative measurement of perfusion with ICG angiography; changes to MEPs/SSEPs with changes in pressure. Changes in spinal cord metabolites with changes in pressure. Change in spinal cord pressure and metabolites with hypothermia. Presence and effect of spreading depolarisations in spinal cord. The urodynamics of acute spinal cord injury.

15 Committees in involved in the trial

Trial Management Group (TMG) The TMG meet 3-4 times annually and more frequently as and when required due to participant events or protocol requirements. The Sponsor is consulted as/when deemed necessary.

16 Direct access to source data

The Investigator(s)/institution(s) will permit trial-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

17 Ethics and Research Governance requirements

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D). If conducting the study at St Georges contact the governance team within the JREO for any assistance.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, which was given favourable opinion by the Research Ethics Committee (REC) and HRA.

The Chief Investigator will be provided (via the Sponsor) with file indexes E.G. JREODOC0003 TMF index and JREODOC0004 ISF index for use with SOP JREOSOP0019 'Preparation and Maintenance of the TMF' The CI will be responsible for the maintenance of the TMF and may delegate the responsibility of ISF file maintenance to the PI at each participating site.

It is the responsibility of the Principal Investigator at each site to ensure that all subsequent amendments gain the necessary approval. Refer to JREOSOP0011 'Management of Amendments'.

Within 90 days after the end of the trial, the CI and Sponsor will ensure that the REC is notified that the trial has finished. If the trial is terminated prematurely, those reports will be made within 15 days after the end of the trial. Refer to JREOSOP0015 'End of study declaration'

The CI will supply an End of Study report of the clinical trial to the REC within one year after the end of the trial. The sponsor can provide JREODOC0059 End of study Report template

17.1 Annual Progress Reports (APRs)

The Chief Investigator will prepare the APR in accordance with JREOSOP0043. Following review by the sponsor the report will be sent to the REC. The APR is due for submission annually within 30 days of the anniversary date on which the favourable opinion was given by the Ethics committee, until the trial is declared ended.

17.2 Notification of Serious Breaches of GCP and/or the protocol

Any Protocol Deviations, Violations will be documented using JREODOC0061, and entered onto the Sponsor's log JREOLOG0005. Potential Serious Breaches and Urgent Safety Measures will be recorded both on the Sponsor's Log JREOLOG0005 and processed according to JREOSOP0012 and where necessary JREOSOP0032

A "serious breach" is a breach which is likely to effect to a significant degree:

(a) The safety or physical or mental integrity of the participants of the trial; or
(b) The scientific value of the trial.

The CI will notify the Sponsor immediately of any case where there exists a possible occurrence of a serious breach

18 Finance

The study will be funded from various sources. Currently these are the Neurosciences Research Foundation and Wings for Life – spinal cord research foundation.

19 Insurance and indemnity

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

20 IP and development policy

Unless otherwise specified in agreements, the following guidelines shall apply: All Intellectual Property Rights and Know How (IP) related to the Protocol and the Trial are and shall remain the property of the Sponsor excluding

1) Pre-existing IP related to clinical procedures of any Hospital.

2) Pre-existing IP related to analytical procedures of any external laboratory.

All contributors

shall assign their its rights in relation to all Intellectual Property Rights and in all Know How, not excluded above to the Sponsor and at the request and expense of the Sponsor, shall execute all such documents and do all such other acts as the Sponsor may reasonably require in order to vest fully and effectively all such Intellectual Property Rights and Know How in the Sponsor or its nominee.

shall promptly disclose to the Sponsor any Know How generated pursuant to this Protocol and not excluded above and undertake treat such Know How as confidential information jointly owned between it and the Sponsor

Nothing in this section shall be construed so as to prevent or hinder and medical professional from using Know How gained during the performance of the Trial in the furtherance of its normal business activities, to the extent such use does not result in the disclosure or misuse of Confidential Information or the infringement of any Intellectual Property Right of the Sponsor.

21 Publication policy

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

21.1 Before the official completion of the Trial,

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the Steering Committee/the Funder shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

21.2 Up to 180 days after the official completion of the Trial

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.

- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.

- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

21.3 Beyond 180 days after the official completion of the Trial

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

22 Statement of Compliance

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws and statutes of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 1998, the Human Medicines Regulations 2012, ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK policy framework for Health and Social care research v3.2 October 2017.

This study will be conducted in compliance with the protocol approved by the REC and according to GCP standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and REC except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and REC as soon as possible.

23 List of Protocol appendices

Appendix 1 *Asia Score*

24 References

1] AANS abstract in www.medscape.com/viewarticle/573672?src=rss, accessed 1.7.09

[2] Blight AR (1983). Cellular morphology of chronic spinal cord injury in the cat: analysis of myelinated axons by line sampling. Neuroscience 1983; 10:52143.

[3] Boldin C et al. (2006). Predicting neurologic recovery in cervical spinal cord injury with postoperative MR imaging. Spine 31:5549.

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Appendix 1. **ASIA score**

ASIA SCORE	TYPE OF INJURY	DESCRIPTION
A	*Complete SCI*	*No motor or sensory function below the level of injury*
B	*Incomplete SCI*	*There is sensory but no motor function below the level of injury*
C	*Incomplete SCI*	*There is sensory and motor function below the level of injury. >50 % of the key muscles have a motor grade <3*
D	*Incomplete SCI*	*There is sensory and motor function below the level of injury. >50 % of the key muscles have a motor grade ≥3*
E	*No SCI*	*Motor and sensory scores normal below the level of injury*

Classification of the severity of spinal cord injury (SCI) by the American Spinal Injury Association (ASIA). Nj i njm apiZogj ohoj mo][Xnoj pZc Xi [kdl kmdZf nj inXogj indl]XZc [ ]mh Xoj h]+Oc] h joj mapiZogj ja.- f]t h pnZgj nj i]XZc nd[ ] jacc] Yj [t Xmh oj mo][Xi [bmX[ ][XZZjmhdl boj oc] H M=nZXgj %) i j kjr]m7.) agZf] mj ah jq]h]io7/) njh] h jq]h]io Ypo i j oXbXdl no bmXqdbt 70) h jq] n XbXdl no bmXqdbt Ypoi j oXbXdl no mhmdhoXi Z] 71) h jq] n XbXdl no bmXqdbt Xi [mhmdhoXi Z] Ypor]Xf 72) i j mh Xgkjr]m&+

Appendix 2: ISCoPE Patient Information Sheets

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 effects of temperature change including cooling*
- *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 your injury on your bladder function*

Why have I been invited?

Because you have suffered a spinal cord injury. Initially, we aim to study about one hundred 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,* ***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 "durotomy." 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.

2. Spinal Cooling where a cooling tube will be placed near the spinal cord for up to a week.

After your surgery we would like to do some early tests to assess your bladder function which will involve monitoring its pressure through your urinary catheter and also

involves inserting a small rectal probe during the tests. This will help us to assess the function of your bladder during the stages of recovery from your 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. 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?
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 find out whether temperature changes affects your spinal cord

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).

The risks of cooling are unknown, cooling is widely used to limit brain damage in patients with brain injury. It is likely that cooling increases the risk of wound infection. Treatment of a wound infection may require intravenous antibiotics and a further operation to washout the wound.

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.
Your spinal cord temperature may be lowered by taking part. We do not know if lowering the spinal cord temperature 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

If something goes wrong and you are harmed during the research and this is due to someone's negligence, you may have grounds for legal action for compensation against the Sponsor (e.g. St Georges University Hospitals NHS Foundation Trust), but you may have to pay your legal costs. The normal NHS complaints mechanism is available to you.

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.

What will happen to any samples I give?
No samples will be collected.

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. 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: *Marios C. Papadopoulos*
Consultant Neurosurgeon
Atkinson Morley Wing
St. George's Hospital
Blackshaw Road
London SW17 0QT.

Tel. [redacted]
Fax. [redacted]
E-Mail. [redacted]

Participant Information Sheet for next of kin consent

Study Title: Injured Spinal Cord Pressure Evaluation (ISCoPE)

CI: Prof Marios Papadopoulos IRAS ID: 38379

We invite your next of kin 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 your next of kin. 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 your next of kin 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 effects of temperature change including cooling*
- *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 bladder function*

Why has your next of kin been invited?

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

Do they have to take part?

No. It is up to you to decide on their behalf. If you decide to, you will be given this information sheet to keep and will be asked to sign a consent form. You are free to withdraw them at any time without giving a reason. We will ask for consent from your next of kin once they are able to give consent. A decision to withdraw them from the study or for them to not take part will not affect the standard of care that they will receive.

What will happen to them if they take part?

*We will insert **probes** next to their spinal cord and attach them to a computer to measure **cord pressure**, **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 their spinal cord is found to be swollen during the operation to fix their spine, we may perform one or more additional procedures:

1. *a "durotomy." 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.*
2. *Spinal Cooling where a cooling tube will be placed near the spinal cord for up to a week*

After their surgery we would like to do some early tests to assess the effects of their spinal injury on their bladder function. This will involve monitoring bladder pressure through the urinary catheter and also involves inserting a small rectal probe during the tests. This will help us to assess bladder 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. We may also perform further urodynamic tests to assess their bladder function or request details of any recently performed urodynamic test results from the spinal rehabilitation unit.*

What do I have to do?
If you would like them 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 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 find out whether temperature changes affects the spinal cord

What are the risks of taking part?
The chance of your relative 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).

The risks of cooling are unknown, cooling is widely used to limit brain damage in patients with brain injury. It is likely that cooling increases the risk of wound infection. Treatment of a wound infection may require intravenous antibiotics and a further operation to washout the wound.

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.
Their spinal cord temperature may be lowered by taking part. We do not know if lowering the spinal cord temperature 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 your next of kin 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 your next of kin 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 will happen if I don't want my next of kin to carry on with this study?
You can withdraw your next of kin 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 your next of kin 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

If something goes wrong and your next of kin is harmed during the research and this is due to someone's negligence, you may have grounds for legal action for compensation against the Sponsor (e.g. St Georges University Hospitals NHS Foundation Trust), but you may have to pay your legal costs. The normal NHS complaints mechanism is available to you.

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 your next of kin'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 your Next of Kins identity to be revealed.
Once participation in this study is agreed we will notify your next of Kin'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, your next of kin will be given a code so that their details are not revealed (anonymised). Any data collected from them will be stored under this code.

What will happen to any samples my next of kin gives?
No samples will be collected.

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. Your next of kin 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. 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: *Marios C. Papadopoulos*
Consultant Neurosurgeon
Atkinson Morley Wing
St. George's Hospital
Blackshaw Road
London SW17 0QT.

Tel. [redacted]
Fax. [redacted]
E-Mail. [redacted]

Participant Information Sheet following next of kin consent

Study Title: Injured Spinal Cord Pressure Evaluation (ISCoPE)
CI: Prof Marios Papadopoulos IRAS ID: 38379

We requested permission from your next of kin to include you in a research study.

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 effects of temperature change including cooling*
- *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 your injury on your bladder function*

Why you were/ have been invited?

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

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

No. It is up to you to decide.
At the time of your hospital admission and prior to the operation on your spine you were unable to decide about whether to be included in this study we explained the purpose of this study to your relative/Next of Kin and requested permission from them on your behalf.
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**, **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 the spinal cord is/was found to be swollen during the operation to fix the spine, one or more additional procedures may have been performed:

1. a "durotomy." 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.
2. Spinal Cooling where a cooling tube will be placed near the spinal cord for up to a week

After your surgery we would like to do some early tests to assess your bladder function which will involve monitoring its pressure through your urinary catheter and also involves inserting a small rectal probe during the tests. This will help us to assess the function of your bladder during the stages of recovery from your 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?
If you would like to continue to take part in our study you need 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 find out whether temperature changes affects your spinal cord

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).
The risks of cooling are unknown, cooling is widely used to limit brain damage in patients with brain injury. It is likely that cooling increases the risk of wound infection. Treatment of a wound infection may require intravenous antibiotics and a further operation to washout the wound.

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.
The spinal cord temperature may be lowered by taking part. We do not know if lowering the spinal cord temperature 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
If something goes wrong and you are harmed during the research and this is due to someone's negligence, you may have grounds for legal action for compensation against the Sponsor (e.g. St Georges University Hospitals NHS Foundation Trust), but you may have to pay your legal costs. The normal NHS complaints mechanism is available to you.

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.

What will happen to any samples I give?
No samples will be collected.

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. 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: *Marios C. Papadopoulos*
Consultant Neurosurgeon
Atkinson Morley Wing
St. George's Hospital
Blackshaw Road
London SW17 0QT.

Tel. [redacted]
Fax. [redacted]
E-Mail. [redacted]

Appendix 3: Consent Form

St George's Healthcare NHS
NHS Trust

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

CONSENT FORM

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

Name of Principal investigator: _____

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 ask questions. ☐
2. I understand that my/my next of kins participation is voluntary and that I/they am/are 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/their medical notes may be looked at by responsible individuals from participating NHS Trusts where it is relevant to my taking part in research. Responsible individuals are doctors involved in the study.* I give permission for these doctors to access my records. ☐
4. I agree/I agree for my next of kin to take part in the above study. ☐

**Responsible Individuals: Mr. M. Papadopoulos (consultant neurosurgeon), Dr. A. Zoumprouli (consultant in neuro-intensive care), Dr. M. Georgala (consultant neurophysiologist), Dr. Philip Rich (consultant neuroradiologist), Mr. David Choi (consultant neurosurgeon), Mr. Kia Rezajooi (consultant neurosurgeon), Mr. Nick Thomas (consultant Neurosurgeon) and a research doctor in neurosurgery.*

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature
Next of kin providing consent	Date	Signature
Name of Witness (If participant cannot sign) (but verbally consents)	Date	Signature

1 form for Patient; 1 to be kept as part of the study documentation; 1 to be kept with medical notes (original)

Version 4, 31/10/2017

Appendix 4: Ethical Amendments and Approvals

NHS
Health Research Authority

London - Camberwell St Giles Research Ethics Committee

Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 01173421391

02 March 2016

Mr. Marios Papadopoulos
Reader and Honorary Consultant in Neurosurgery
University of London
Department of Neurosurgery (AMW)
St. George's Hospital
Blackshaw Road
Tootin
SW17 0QT

Dear Mr. Papadopoulos

Study title:	**Evaluation of the potential adverse effect of pressure after spinal cord injury**
REC reference:	**10/H0807/23**
Amendment number:	**Substantial Amendment 7**
Amendment date:	**07 February 2016**
IRAS project ID:	**38379**

The above amendment was reviewed by the Sub-Committee 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.

The Sub-Committee approved the following:

1. An extra dural cooling catheter to evaluate the effect of hypothermia on the spinal cord.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*

Notice of Substantial Amendment (non-CTIMP) [Use of extra dural cooling catheter]	Amendment 7	07 February 2016
Participant information sheet (PIS)	10 (tracked)	09 February 2016
Research protocol or project proposal	11 (tracked)	07 February 2016

Membership of the Committee

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

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0807/23:	**Please quote this number on all correspondence**

Yours sincerely

pp [redacted]

Mr John Richardson
Chair

E-mail: nrescommittee.london-camberwellstgiles@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to:

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

NHS
Health Research Authority

London - Camberwell St Giles Research Ethics Committee
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Tel: 02071048044

01 February 2018

Debbie Rolfe
St George's, University of London and St George's Healthcare NHS Trust
Cranmer Terrace SW17 ORE
London
SW17 ORE

Dear Ms Rolfe

Study title:	**Evaluation of the potential adverse effect of pressure after spinal cord injury**
REC reference:	**10/H0807/23**
Amendment number:	**Amendment 10 04/01/2018**
Amendment date:	**04 January 2018**
IRAS project ID:	**38379**

Thank you for submitting the above amendment, which was received on 30 January 2018. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_ReadyForSubmission]	Amendment 10 04/01/2018	04 January 2018
Participant information sheet (PIS) [Participant Information Sheet for NOK v2]	2	05 January 2018
Participant information sheet (PIS) [Participant Information Sheet for NOK v2TC]	2	05 January 2018
Participant information sheet (PIS) [Participant Information Sheet_v13 TC]	13	20 December 2017
Participant information sheet (PIS) [Participant Information Sheet_v13]	13	20 December 2017
Participant information sheet (PIS) [PIS after NOK consent v2]	2	05 January 2018
Participant information sheet (PIS) [PIS after NOK consent v2TC]	2	05 January 2018
Research protocol or project proposal [ISCOPE protocol v13 TC]	13	20 December 2017
Research protocol or project proposal [ISCOPE protocol v13]	13	20 December 2017

Notification of the Committee's decision

The Committee will issue an ethical opinion on the amendment within a maximum of 35 days from the date of receipt.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval for the research.

We are pleased to welcome researchers and R & D staff at our Research Ethics Service Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

10/H0807/23:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Tina Cavaliere
REC Manager

Email: nrescommittee.london-camberwellstgiles@nhs.net

Copy to:

Mr. Marios Papadopoulos (please CC [redacted]) , St. George's, University of London

Appendix 5: ASIA form

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position

5 = (normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal range of motion)

Sensory Grading

0 = Absent

1 = Altered, either decreased/impaired sensation or hypersensitivity

2 = Normal

NT = Not testable

Non Key Muscle Functions (optional)

May be used to assign a motor level to differentiate AIS B vs. C

Movement	Root level
Shoulder: Flexion, extension, abduction, adduction, internal and external rotation **Elbow:** Supination	**C5**
Elbow: Pronation **Wrist:** Flexion	**C6**
Finger: Flexion at proximal joint, extension. **Thumb:** Flexion, extension and abduction in plane of thumb	**C7**
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	**C8**
Finger: Abduction of the index finger	**T1**
Hip: Adduction	**L2**
Hip: External rotation	**L3**
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	**L4**
Hallux and Toe: DIP and PIP flexion and abduction	**L5**
Hallux: Adduction	**S1**

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved below the neurological level**, and more than half of key muscle functions below the neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

D = Motor Incomplete. Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

** For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The International Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***neurological level of injury*** is used.



INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY



Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI)
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete.***
*Otherwise, injury is **Incomplete.***

5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? **If YES, AIS=A** and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury Motor Complete? **If YES, AIS=B**

NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?

NO ↓ **AIS=C** **YES** ↓ **AIS=D**

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

Appendix 6: Publications Associated with Thesis

Neurocrit Care
https://doi.org/10.1007/s12028-018-0616-7

NEUROCRITICAL CARE SOCIETY

ORIGINAL ARTICLE



Predictors of Intraspinal Pressure and Optimal Cord Perfusion Pressure After Traumatic Spinal Cord Injury

Florence R. A. Hogg[1], Mathew J. Gallagher[1], Suliang Chen[1], Argyro Zoumprouli[2], Marios C. Papadopoulos[1] and Samira Saadoun[1*]

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Abstract

Background/Objectives: We recently developed techniques to monitor intraspinal pressure (ISP) and spinal cord perfusion pressure (SCPP) from the injury site to compute the optimum SCPP ($SCPP_{opt}$) in patients with acute traumatic spinal cord injury (TSCI). We hypothesized that ISP and $SCPP_{opt}$ can be predicted using clinical factors instead of ISP monitoring.

Methods: Sixty-four TSCI patients, grades A–C (American spinal injuries association Impairment Scale, AIS), were analyzed. For 24 h after surgery, we monitored ISP and SCPP and computed $SCPP_{opt}$ (SCPP that optimizes pressure reactivity). We studied how well 28 factors correlate with mean ISP or $SCPP_{opt}$ including 7 patient-related, 3 injury-related, 6 management-related, and 12 preoperative MRI-related factors.

Results: All patients underwent surgery to restore normal spinal alignment within 72 h of injury. Fifty-one percentage had U-shaped sPRx versus SCPP curves, thus allowing $SCPP_{opt}$ to be computed. Thirteen percentage, all AIS grade A or B, had no U-shaped sPRx versus SCPP curves. Thirty-six percentage (22/64) had U-shaped sPRx versus SCPP curves, but the SCPP did not reach the minimum of the curve, and thus, an exact $SCPP_{opt}$ could not be calculated. In total 5/28 factors were associated with lower ISP: older age, excess alcohol consumption, nonconus medullaris injury, expansion duroplasty, and less intraoperative bleeding. In a multivariate logistic regression model, these 5 factors predicted ISP as normal or high with 73% accuracy. Only 2/28 factors correlated with lower $SCPP_{opt}$: higher mean ISP and conus medullaris injury. In an ordinal multivariate logistic regression model, these 2 factors predicted $SCPP_{opt}$ as low, medium–low, medium–high, or high with only 42% accuracy. No MRI factors correlated with ISP or $SCPP_{opt}$.

Conclusions: Elevated ISP can be predicted by clinical factors. Modifiable factors that may lower ISP are: reducing surgical bleeding and performing expansion duroplasty. No factors accurately predict $SCPP_{opt}$; thus, invasive monitoring remains the only way to estimate $SCPP_{opt}$.

Keywords: Blood pressure, Perfusion pressure, Spinal cord injury, Trauma

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[1] Academic Neurosurgery Unit, Molecular and Clinical Sciences Institute, St. George's, University of London, London SW17 0RE, UK
Full list of author information is available at the end of the article
Co-senior authors: Marios C. Papadopoulos and Samira Saadoun.

This work was performed at the Neurosurgery and Neuro-intensive care units, Atkinson Morley Wing, St. George's Hospital in London, UK.

Springer

Introduction

Traumatic spinal cord injury (TSCI) is a catastrophic condition: Over a third of patients do not recover sensation or voluntary movement below the injury [1]. No treatment has been proved to improve outcome [2], and therefore, patient management remains variable [3]. To guide the management of patients with acute, severe

TSCI in the intensive care unit, we introduced intraspinal pressure (ISP) monitoring from the injury site [4, 5]. The technique is safe [6] and allows us to compute the spinal cord perfusion pressure (SCPP) as mean arterial pressure (MAP) minus ISP and the spinal pressure reactivity index (sPRx) as the running correlation coefficient between ISP and MAP. sPRx measures the pressure reactivity of the vascular bed, i.e., autoregulation. sPRx ≤ 0 indicates intact vascular pressure reactivity, whereas sPRx > 0 indicates deficient vascular pressure reactivity. At low SCPP (hypo-perfusion) and high SCPP (hyperperfusion), autoregulation is impaired (i.e., high sPRx) [7–9]. Thus, the sPRx versus SCPP plot is U-shaped and the optimum SCPP ($SCPP_{opt}$) is the minimum of the curve. The U-shaped curve is not always present and may vary throughout the period of monitoring; when computed in patients with head injury or spinal cord injury, a U-shaped sPRx versus SCPP relation is present approximately 50% of the time. ISP, SCPP, $SCPP_{opt}$, and sPRx for TSCI are, respectively, analogous to intracranial pressure (ICP), cerebral perfusion pressure (CPP), optimum CPP (CPP_{opt}), and cerebrovascular pressure reactivity (PRx) for traumatic brain injury (TBI) [10].

TSCI patients with mean SCPP $\approx$ $SCPP_{opt}$ more often improve their AIS (American spinal injuries association Impairment Scale) grade than patients with SCPP very different from $SCPP_{opt}$ [8]. Thus, targeting the $SCPP_{opt}$ could form the basis for individualizing the treatment of TSCI in a physiologically meaningful manner. When compared with the current guideline of maintaining MAP at 85–95 mmHg in all TSCI patients [11], the concept of individualized management, based on $SCPP_{opt}$, represents a paradigm shift. A universal MAP target is inadequate because TSCI patients have different ISPs and because the $SCPP_{opt}$ varies widely between patients [4, 5, 8]. The aim here is to identify clinical and magnetic resonance imaging (MRI) features for predicting ISP and $SCPP_{opt}$ in each TSCI patient. The ability to estimate ISP and $SCPP_{opt}$ noninvasively would be a major advance by allowing doctors to calculate a target MAP for each TSCI patient without ISP monitoring.

Materials and Methods

Institutional Approvals

Patients were recruited as part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) study (ClinicalTrials.gov as NCT02721615). Approvals for ISCoPE 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).

Patient Recruitment

We include all (consecutive) TSCI patients recruited between October 2010 and December 2017. Inclusion criteria are: (1) severe TSCI defined as AIS grade A, B, or C; (2) age 18–70 years; (3) timing between TSCI and surgery within 72 h. Exclusion criteria are: (1) patient unable to consent; (2) other major comorbidities; (3) penetrating TSCI.

Surgery and ISP Monitoring

Surgical decompression and spinal instrumentation were performed based on patient requirements and surgeon preference. Some patients also had duroplasty as described [12]. During surgery, an ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) was placed intradurally on the surface of the injured cord at the site of maximal cord swelling. The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.7.3.5 (AD Instruments, Oxford, UK). Arterial blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK), and in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz for 24 h after surgery. When the spinal cord is swollen and compressed against the dura, the subdural pressure (i.e., ISP) and intraparenchymal pressure at the injury site are the same. In this case, ISP is higher than cerebrospinal fluid (CSF) pressure above or below the injury site—details are given elsewhere [5, 6, 13–15].

ISP, SCPP, and $SCPP_{opt}$

We processed signals using ICM + to compute SCPP (as ISP minus MAP) and sPRx (as the running correlation coefficient between ISP and MAP). Microsoft Excel was used to produce sPRx versus SCPP plots and estimate the $SCPP_{opt}$ as the minimum of the curve. We used the ISP and MAP signals recorded over the 24 h after surgery to compute the average ISP, the average SCPP, as well as the overall $SCPP_{opt}$. The ISP monitoring setup is illustrated in Fig. 1. We chose the first 24 h of ISP monitoring, because these are the closest to the timing of the preoperative MRI that was used to determine the imaging features. Also, because ISP was monitored for different periods in different patients, we only included the first 24 h to standardize the duration of monitoring. We arbitrarily defined ISP as high if > 20 mmHg and normal if ≤ 20 mmHg based on our previous ISP analysis in patients with TSCI versus controls [5]. The study protocol intentionally did not set ISP or SCPP targets, and the ethical approval was to monitor ISP and SCPP, but not

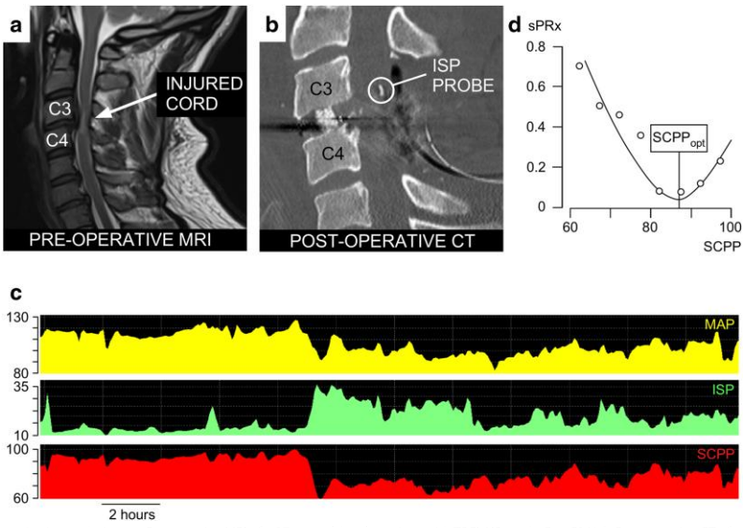


Fig. 1 ISP monitoring technique. **a** Preoperative MRI of a 37-year-old male patient with TSCI AIS grade C at C3/4. **b** Postoperative CT of same patient showing C3/4 anterior cervical cage, posterior C3/4 laminectomies, and ISP probe (circled). **c** MAP, ISP SCPP signals. **d** sPRx versus SCPP plot. Minimum is SCPP$_{opt}$

use these values to alter management. This arrangement allowed us to study the injured cord over a wide range of ISPs and SCPPs. MAP was managed at the discretion of the consultant intensive care physician. In general, MAP 80–100 mmHg was maintained for a week after TSCI.

Clinical Features

A total of 28 factors were collected for each patient as follows:

1. Age,
2. Sex,
3. Smoking,
4. Hypertension,
5. Diabetes,
6. History of excess alcohol consumption,
7. Body mass index,
8. Level of injury, i.e., cervical/thoracic/conus,
9. AIS grade on admission,
10. Primary survey MAP,
11. Hours from injury to surgery,
12. Duration of surgery,
13. Intraoperative blood loss,
14. Extent of decompression i.e., spinal alignment/spinal alignment + laminectomy/spinal alignment + laminectomy + duroplasty,
15. Surgical approach, i.e., posterior/anterior + posterior,
16. Mean MAP during surgery,
17. Epidural hematoma,
18. Intraparenchymal hematoma,
19. Cord transection,
20. Number of sagittal inter-vertebral levels with no CSF signal [16],
21. Injury level average spinal cord occupation rate: SCOR [16],
21. Brain and spinal injury center score BASIC [17],
23. Sagittal grade 1–4 [18],
24. Longitudinal extent of T2 signal abnormality [19],
25. Maximum spinal cord compression MSCC [20, 21],
26. Maximum canal compromise MCC [20],
27. Average normal cord in injured cord [22],
28. Average % cord signal change at injured level [16].

Detailed definitions of the 28 factors are given in the Supplement. Data regarding the 28 factors were collected without knowledge of the ISP, SCPP, and SCPP$_{opt}$ data.

Statistical Analysis

Analyses were carried out with XLStat Biomed (v.18.07, Addinsoft, New York, USA). For univariate analyses, we used Mann–Whitney U or Wilcoxon rank sum with post hoc Dunn to investigate differences in ISP or $SCPP_{opt}$ between the factors. In the multivariate logistic regression analysis for ISP, we chose the best model based on likelihood by including factors with $P < 0.1$ and removing factors already in the model if $P > 0.2$ when a new factor is added. In the multivariate ordinal logistic regression analysis for $SCPP_{opt}$, we chose a stepwise forward model based on the Wald criterion; the model enters factors with $P < 0.1$ and removes factors already in the model if $P > 0.2$ when a new factor is added. Correlations between two factors were quantified with the Spearman's rank correlation coefficient "ρ".

Results

Patient Characteristics

Table 1 provides information on the demographic characteristics of the 64 patients. Most are young, with 80% < 60 years old. Males outnumber females by 3.2:1. Cervical TSCIs are more common than thoracic or conus at 52 versus 34 versus 14%. Most patients had neurologically complete TSCI on admission, i.e., 67% were ASIA grade A. Fifty-one percentage (34/64) had U-shaped sPRx versus SCPP curves for the first 24 h after surgery, thus allowing $SCPP_{opt}$ to be computed. Mean $SCPP_{opt}$ for all patients was 74 mmHg (range 48–103). Thirteen percentage (8/64), all AIS grade A or B, had no U-shaped sPRx versus SCPP curve for the first 24 h after surgery. The remaining 36% (22/64) patients appeared to have U-shaped sPRx versus SCPP curves, but the range of SCPPs did not reach the minimum, and thus, exact $SCPP_{opt}$ could not be calculated.

Table 1 Patient demographic characteristics

Characteristic	Value
Patients (total no.)	64
Age in years (mean, range)	42 (19–70)
Sex (m:f)	49:15
Body mass index[a] (no of patients: < 18.5:18.5–24.9:25–29.9: > 30)	2:30:15:16
Admission AIS grade (no. of patients A:B:C)	43:8:13
Level of injury (no. of patients ce:th:co)	33:22:9
Injury to surgery (hours mean, range)	39.27 (9–72)
Surgical approach (no. of patients post:ant + post)	54:10
Decompression (no. of patients sp-al:sp-al + lami:sp-al + lami + duro)	9:46:9

AIS American spinal injuries association Impairment Scale; *ant* anterior; *ce* cervical; *co* conus; *duro* duroplasty; *f* female; *lami* laminectomy; *m* male; *post* posterior; *sp-al* spinal alignment; *th* thoracic

[a] Data missing in one patient

Predictors of Mean ISP

In univariate analysis, only 5/28 characteristics that were examined correlated with ISP. The 5 characteristics that were associated with higher mean ISP are no excess alcohol consumption, lower cord injury, not having a duroplasty, younger age, and more intraoperative blood loss (Fig. 2). Interestingly, none of the 12 MRI characteristics that we investigated correlated with mean ISP. A multivariate logistic regression model based on these 5 characteristics could classify ISP as normal (< 20 mmHg) versus high (≥ 20 mmHg) with 73% accuracy (Table 2). In this multivariate model, which takes into account interactions between the characteristics, no excess alcohol consumption (odds ratio 9.6, 95% CI 1.2–74.9), lower injury level (odds ratio cervical to thoracic to conus 3.3, 95% CI 1.1–10.3), no expansion duroplasty (odds ratio 3.2, 95% CI 1.1–12.3), and younger age (odds ratio per decade 1.5, 95% CI 1.1–2.4) remained significant (each at $P < 0.05$) predictors of high ISP. Intraoperative blood loss was no longer significant because of collinearity with the level of injury ($\rho = 0.59$), i.e., more blood loss when operating lower down the spine.

Predictors of Mean 24-h $SCPP_{opt}$

Each patient was assigned to a $SCPP_{opt}$ group as low (< 60 mmHg), low–medium (60–70 mmHg), high–medium (70–80 mmHg), or high (> 80 mmHg). This allowed us to analyze 51 patients in total, by including not only the 34 patients who had exact $SCPP_{opt}$, but also 8 patients with $SCPP_{opt} > 80$ mmHg and 9 patients with $SCPP_{opt} < 60$ mmHg. In univariate analysis, only 2/29 factors that were examined correlated with lower mean $SCPP_{opt}$: higher mean 24-h ISP and lower spinal level of injury (Fig. 3a, b). These two factors (level of spinal cord injury and mean 24-h ISP) were correlated ($\rho = 0.49$). Interestingly, again none of the 12 MRI factors correlated with mean $SCPP_{opt}$. An ordinal logistic regression model based on these two factors could classify $SCPP_{opt}$ as low, low–medium, high–medium, or high with only 42% accuracy (Table 3).

Discussion

In this study we have shown that after a TSCI clinical features may be used to predict whether ISP is elevated, but

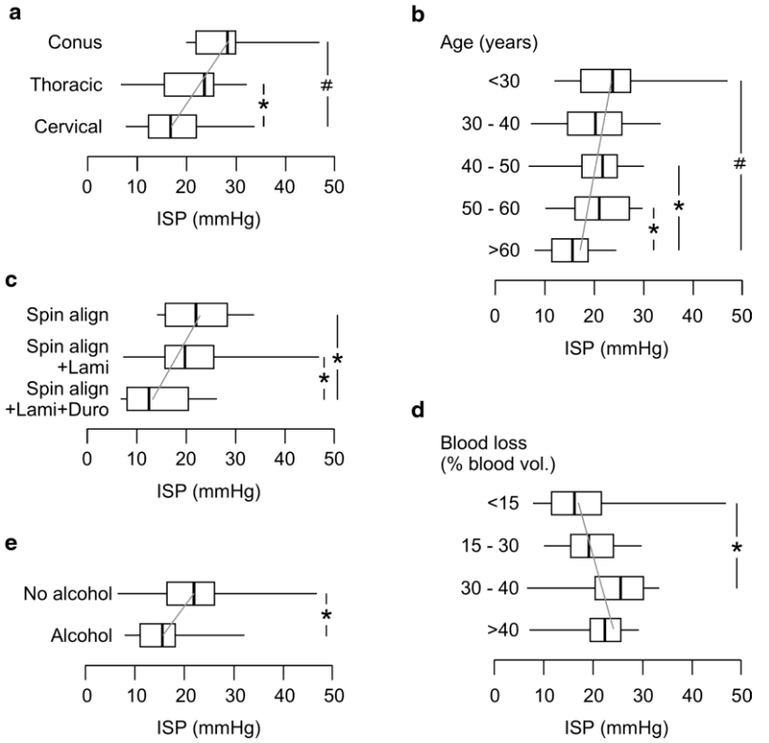


Fig. 2 Factors that correlate with mean ISP. **a** Level of spinal cord injury (cervical, thoracic, conus). **b** Age group in years (< 30, 30 – 40, 40 – 50, 50 – 60, > 60). **c** Extent of decompression (Spinal Alignment, Spinal Alignment + Laminectomy, Spinal Alignment + Laminectomy + Duroplasty). **d** Intraoperative blood loss as % of total blood volume (< 15%, 15 – 30%, 30 – 40%, > 40%). **e** Excess alcohol consumption. Box plots show median, upper and lower quartiles, minimum and maximum. Gray trend line. $P < 0.05^{*}$, $0.005^{\#}$

Table 2 Confusion matrix of multivariate logistic regression model for predicting mean ISP for the first 24 h after surgery

	Normal ISP (predicted)	High ISP (predicted)	Total	% Correct
Normal ISP (actual)	25	8	33	77.8
High ISP (actual)	9	21	30	70.0
Total	34	29	63[a]	73.0

Classifier based on five factors: age group (< 30, 30–40, 40–50, 50–60, > 60), alcohol consumption (yes/no), spinal level of injury (cervical/thoracic/conus), extent of decompression (spinal alignment, spinal alignment + laminectomy, spinal alignment + laminectomy + duroplasty), and intraoperative hemorrhage (as % of circulating volume: < 15, 15–30, 30–40, > 40). Area under receiver operating characteristic curve = 0.84

ISP intraspinalpressure

[a] 1/64 patients omitted because of missing intraoperative data

clinical features cannot accurately predict $SCPP_{opt}$. Risk factors for high ISP include younger age, conus injury, no excessive alcohol intake, no duroplasty, and large intraoperative blood loss. We also showed that patients with

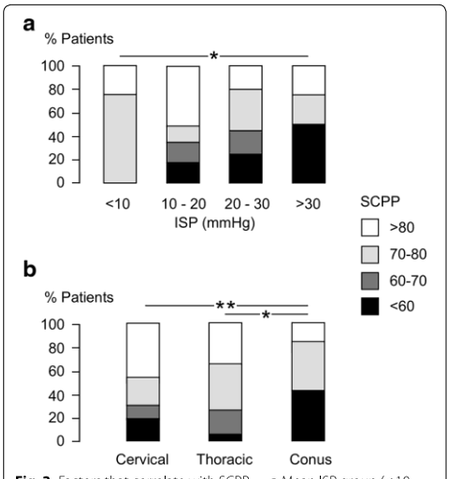


Fig. 3 Factors that correlate with $SCPP_{opt}$. **a** Mean ISP group (< 10, 10–20, 20–30, > 30 mmHg). **b** Level of spinal cord injury (cervical, thoracic, conus). $SCPP_{opt}$ grouped as < 60, 60–70, 70–80, > 80 mmHg. $P < 0.05$*, 0.01**

conus injuries and those with high ISP have low $SCPP_{opt}$ and that some patients with severe TSCI have no computable $SCPP_{opt}$. There were no MRI features associated with ISP or $SCPP_{opt}$.

Clinical features that correlate with ISP may shed light on the pathophysiology of TSCI. The factor that protects the most from elevated ISP is history of excess alcohol consumption documented in the patient notes. The underlying mechanism may be cord atrophy, i.e., more CSF space to accommodate the swollen cord, analogous to TBI where alcohol-related brain atrophy might protect from elevated ICP [23–25]. Expansion duroplasty and the level of injury have comparable protective effect on ISP. We already showed that duroplasty significantly reduces ISP after TSCI by enlarging the CSF space around the injured cord [12]. The higher ISP with conus medullaris injuries is likely related to the reduced CSF space around the conus medullaris compared with the larger CSF space higher up the spine [26]. The next factor that correlates with lower ISP is older age, perhaps because of cord atrophy in older patients, analogous to age-related brain atrophy [27, 28]. Higher ISP in patients with more intraoperative bleeding may be due to the level of TSCI rather than the bleeding per se, based on the positive correlation between surgical blood loss and level of TSCI. Alternatively, intraoperative fluid resuscitation may play a role, with larger fluid volumes administered exacerbating the edema at the injury site. The unifying theme here is that ISP after TSCI is determined by the relative dimensions of the cord at the injury site compared with the surrounding CSF space. Larger CSF space (cord atrophy, cervicothoracic injuries, duroplasty) is associated with lower ISP.

We showed that $SCPP_{opt}$ is lower in patients with higher ISP or conus TSCI. Though high SCPP is beneficial by reducing ischemia, these observations suggest that as the spinal cord becomes more compressed, high SCPP may become detrimental. The mechanism might be blood pressure induced local steal, a phenomenon whereby increasing the MAP when the cord is swollen causes a "paradoxical" decrease in blood flow at the injury site [29]. Knowledge of $SCPP_{opt}$ is clinically important to reduce secondary cord damage by hypo- or hyper-perfusion. Since clinical features do not accurately predict $SCPP_{opt}$, invasive ISP monitoring remains the only way of determining $SCPP_{opt}$. A recent study showed that SCPP can be calculated by monitoring CSF pressure using a lumbar catheter and that SCPP measured in

Table 3 Confusion matrix of multivariate ordinal logistic regression model for predicting $SCPP_{opt}$ for the first 24 h after surgery

$SCPP_{opt}$ mmHg	Predicted					
	<60	60–70	70–80	>80	Total	% Correct
Actual						
<60	4	0	1	5	10	40.0
60–70	3	0	3	3	9	0.0
70–80	1	0	6	7	14	42.9
>80	1	0	2	15	18	83.3
Total						
	8	0	6	37	51[a]	41.6

Classifier based on two factors: mean 24 h and spinal level of injury (cervical/thoracic/conus)

SCPP spinalcord perfusion pressure

[a] 13/64 patients omitted because $SCPP_{opt}$ could not be binned into one of these groups (< 60, 60–70, 70–80, > 80)

this way better correlates with outcome than MAP [30]. Monitoring CSF pressure is less invasive than monitoring ISP. However, the relation between SCPP measured by ISP monitoring and by lumbar drain is unclear. It is also unclear whether CSF pressure can be used to compute sPRx and $SCPP_{opt}$.

An unanticipated finding is that no MRI features correlated with ISP or $SCPP_{opt}$. This may be because we used preoperative MRIs, performed when the spinal anatomy was abnormal. Surgery restores the normal spinal alignment, thus causing major anatomical changes at the injury site. MRI performed immediately after surgery may thus be more informative for estimating ISP and $SCPP_{opt}$ than preoperative MRIs. Earlier studies support the notion preoperative MRI features only weakly correlate with outcome, and in general, postoperative MRIs are more informative [31–33]. The take-home message is that preoperative MRIs cannot be relied upon to estimate the degree of cord compression or the optimal MAP to target after surgery.

Our study has limitations. ISP monitoring is an invasive technique, and currently, ours is the only unit that performs such monitoring in acute TSCI. Corroboration of our results in other centers is essential. Thus, the concepts of ISP, SCPP, $SCPP_{opt,}$ and sPRx remain theoretical and a randomized study to assess outcomes of patients managed according to their individual injury site physiology rather than applying universal MAP targets is necessary before ISP monitoring becomes definitively recommended. Finally, our cohort of 64 patients is relatively small, and thus, weaker associations between the 28 clinical features investigated here ISP and $SCPP_{opt}$ might be missed.

Conclusions

To conclude, our study supports the notion that ISP is determined by the size of the CSF space surrounding the injured cord. In other words, after TSCI, the cord swells and is compressed by the dura [34], thus, factors that increase the surrounding CSF space such as expansion duraplasty may be beneficial [12]. Based on our data, we urge caution when increasing the MAP, without knowing the $SCPP_{opt}$, in patients whose injured cord is very compressed, i.e., high ISP. The individualized U-shaped curves suggest that $SCPP > SCPP_{opt}$ may be detrimental. Hyper-perfusing injured cord is associated with more deranged injury site metabolism [35]. In TBI patients, hyper-perfusion of the brain is associated with worse neurological outcome [36], although this finding has not yet been replicated in TSCI (due to insufficient number of TSCI patients exceeding the $SCPP_{opt}$), the same trend may apply [8]. To date, the only way to avoid hyper-perfusing the injured cord is by determining the $SCPP_{opt}$ by ISP monitoring.

At present there is no consensus about the correct paradigm for managing acute TSCI [2, 3, 37, 38] although there is growing evidence and support for a randomized trial to assess whether novel treatments such as invasive ISP monitoring, SCPP optimization, and expansion duroplasty improve outcomes [39].

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-018-0616-7) contains supplementary material, which is available to authorized users.

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Authors' contributions
FRAH collected and analyzed data and helped write the manuscript and produce the figures. MJG collected and analyzed data, and SC helped with data analysis. AZ anaesthetized the patients and helped with data collection and contributed key ideas to the manuscript. MCP operated on all the patients, helped with data analysis, and co-wrote the manuscript. SS designed the study, did data analysis, produced the figures, co-wrote the manuscript, and provided overall supervision for the project.

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Compliance with Ethical Standards

Conflict of interest
The authors declare that they have no conflict of interest.

Ethical Approval
All procedures performed here were in accordance with the ethical standards of the institutional and national research committees and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Acute Spinal Cord Injury: Monitoring Lumbar Cerebrospinal Fluid Provides Limited Information about the Injury Site

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Abstract

In some centers, monitoring lumbar cerebrospinal fluid (CSF) is used to guide management of patients with acute traumatic spinal cord injuries (TSCI) and draining lumbar CSF to improve spinal cord perfusion. Here, we investigate whether the lumbar CSF provides accurate information about the injury site and the effect of draining lumbar CSF on injury site perfusion. In 13 TSCI patients, we simultaneously monitored lumbar CSF pressure (CSFP) and intraspinal pressure (ISP) from the injury site. Using CSFP or ISP, we computed spinal cord perfusion pressure (SCPP), vascular pressure reactivity index (sPRx) and optimum SCPP ($SCPP_{opt}$). We also assessed the effect on ISP of draining 10 mL CSF. Metabolites at the injury site were compared with metabolites in the lumbar CSF. We found that ISP was pulsatile, but CSFP had low pulse pressure and was non-pulsatile 21% of the time. There was weak or no correlation between CSFP versus ISP (R = -0.11), $SCPP_{(csf)}$ versus $SCPP_{(ISP)}$ (R = 0.39), and $sPRx_{(csf)}$ versus $sPRx_{(ISP)}$ (R = 0.45). CSF drainage caused no significant change in ISP in 7/12 patients and a significant drop of <5 mm Hg in 4/12 patients and of *8 mm Hg in 1/12 patients. Metabolite concentrations in the CSF versus the injury site did not correlate for lactate (R = 0.00), pyruvate (R = -0.12) or lactate-to-pyruvate ratio (R = -0.05) with weak correlations noted for glucose (R = 0.31), glutamate (R = 0.61), and glycerol (R = 0.56). We conclude that, after a severe TSCI, monitoring from the lumbar CSF provides only limited information about the injury site and that lumbar CSF drainage does not effectively reduce ISP in most patients.

Keywords: Clinical management of central nervous system injury; CSF; microdialysis; TSCI

Introduction

Traumatic spinal cord injury (TSCI) is a devastating event that affects *180,000 people globally each year.[1] Prognosis is poor: more than one third of patients have complete paraplegia or quadriplegia, <1 % are discharged neurologically normal, and their life expectancy is below the national average.[2] There is no treatment proven to improve outcome after TSCI.[3]

To optimize the early management of TSCI, we developed multi-modality monitoring from the injury site in patients in the intensive care unit (ICU);[4] we monitor intraspinal pressure (ISP) and compute spinal cord perfusion pressure (SCPP) as mean arterial pressure (MAP) minus ISP.[5–7] We also monitor injury site metabolism by microdialysis (MD).[8,9] These techniques are safe, and are analogous to multi-modality monitoring in traumatic brain injury.[10] Our data show that ISP and SCPP are clinically important parameters that correlate with injury site metabolism,[11] neurological status,[12] and long-term neurological outcome.[6]

Monitoring from the injury site allows intervention to reduce secondary damage; for example, increasing SCPP to reduce cord ischemia. We showed that low SCPP and high SCPP may both be detrimental, and proposed the concept of optimum SCPP ($SCPP_{opt}$) as the SCPP that maximizes vascular reactivity.[12] ISP monitoring allows individualized management by targeting each patient's $SCPP_{opt}$ rather than applying the same MAP to all.[5] MD monitoring revealed that some periods of high ISP are associated with hypometabolim (low tissue glucose, high lactate-to-pyruvate ratio [LPR], high glutamate, high glycerol) and may benefit from increasing SCPP, whereas other periods of high ISP are associated with hypermetabolism (low tissue glucose, LPR, low glutamate, low glycerol) and, therefore, increasing SCPP may be detrimental.[8,9] MD monitoring has also revealed that fever is associated with metabolic derangement at the injury site. Therefore, monitoring from the injury site may help clinical management.[13]

Some physicians monitor lumbar cerebrospinal fluid pressure (CSFP) rather than ISP and compute $SCPP_{(csf)}$ as MAP – CSFP

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rather than $SCPP_{(ISP)}$ as MAP – ISP.[14–16] Monitoring from the lumbar CSF is achieved by placing a lumbar catheter, which can easily be done in the ICU. The lumbar catheter is also used therapeutically to drain CSF to increase cord perfusion in after TSCI and in patients undergoing aortic aneurysm repair.[17–20] In contrast, monitoring from the injury site requires surgery to expose the dura at the injury site and insert probes intradurally under a microscope. Thus, monitoring from the lumbar CSF compartment is less invasive and easier to accomplish than injury site monitoring.

In this study, we monitored simultaneously from the injury site and from the lumbar CSF space in patients with acute, severe TSCI to define the relationship between CSFP versus ISP, $SCPP_{(csf)}$ versus $SCPP_{(ISP)}$, and metabolite levels in the lumbar CSF versus injury site. We also determined the effect of draining lumbar CSF on ISP.

Methods

Institutional research board approvals

Approvals for the Injured Spinal Cord Pressure Evaluation (ISCoPE) study including the consent form and patient information sheet were obtained by the St Georges Joint Research Office and the National Research Ethic Service – Camberwell St Giles Committee (No 10/H0807/23). ISCoPE is registered at www.clinical trials.gov as NCT02721615.

Inclusion/exclusion criteria

We recruited TSCI patients who were enrolled into the ISCoPE trial in the period October 2017–February 2019. Inclusion criteria for ISCoPE are: severe TSCI defined as American Spinal Injury Association Impairment Scale (AIS) grades A–C, age 18–70 years, and surgery performed within 72h of TSCI. Exclusion criteria are: major comorbidities, inability to obtain consent, and penetrating SCI.

Clinical examination and imaging

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) AIS assessment by a neurosurgical resident trained in AIS. All patients had computed tomography (CT) and magnetic resonance imaging (MRI) of the spine imaging before surgery and within 2 weeks after surgery. We measured the longitudinal extent of T2 cord signal change on the pre-operative MRI as a biomarker of cord edema.

Probe insertion

Surgical decompression and spinal instrumentation were performed based on patient requirements and surgeon preference. During surgery, an ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) and a MD catheter (CMA61: CMA microdialysis AB, Solna, Sweden) were placed intradurally on the surface of the injured cord at the site of maximal cord swelling. The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). At the end of surgery, a lumbar catheter was inserted at the L4/5 or L3/4 disc levels and advanced 15–20 cm from the skin edge. Figure 1Ashows the setup.

Monitoring and lumbar CSF drainage

The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.7.3.5 (AD Instruments, Oxford, UK). The lumbar catheter was connected to an external drainage system (Integra™ AccuDrain® External CSF Drainage System) which was attached to a pressure transducer and

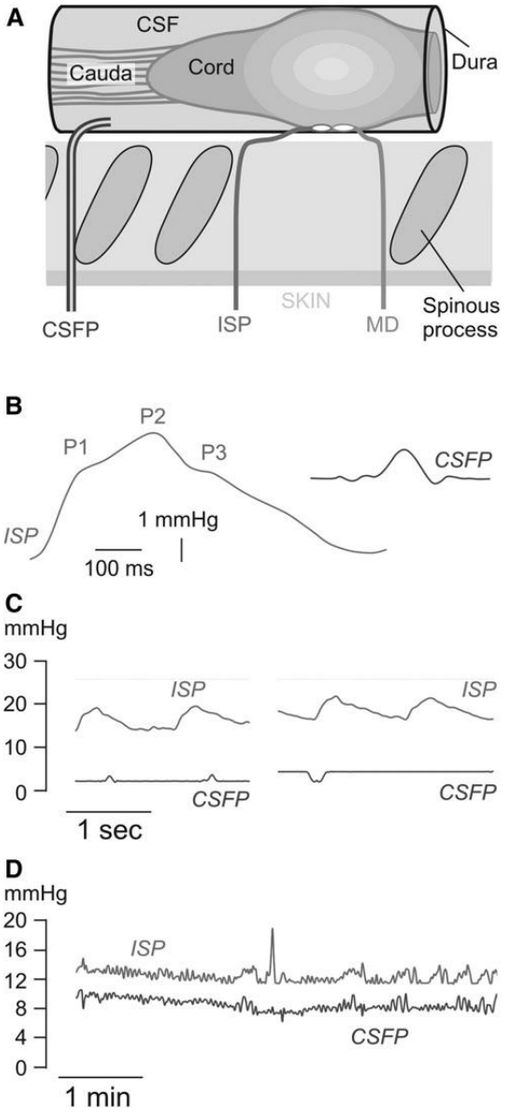


FIG. 1. Monitoring setup. (A) Schematic to illustrate intraspinal pressure (ISP), cerebrospinal fluid pressure (CSFP), and microdialysis (MD) monitoring. With the patient lying flat, ISP is monitored by a pressure probe placed subdurally at the injury site and CSFP is monitored from a catheter placed in the lumbar CSF space. Am MD catheter is also placed next to the pressure probe. (B) Typical ISP and CSFP waveforms. P1 percussion peak, P2 tidal peak, P3 dicrotic peak. Examples of ISP and simultaneously measured CSFP signals over (C) 2–3 sec and (D) 5 min.

closed to the drain. It was then connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) and in turn connected to the PowerLab system. Nurses were instructed to keep the transducer at the level of the lumbar spine. Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) and in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz and patients were monitored for up to 7 days. With the patient lying flat, up to 10 mL CSF was drained each time from the lumbar catheter to assess the effect on ISP. No more than 30 mL of CSF was drained in a 24 h period.

MD setup and analysis

MD was started postoperatively in the ICU as described.[8,9,11] Central nervous system (CNS) perfusion fluid (CMA microdialysis AB) was perfused at 0.3 lL/min using the CMA106 pump (CMA microdialysis AB). MD vials were changed hourly and analyzed using ISCUS Flex (CMA microdialysis AB) for the following metabolites: glucose, lactate, pyruvate, glycerol, glutamate, and LPR. Samples of CSF were collected at each CSF drainage and were used to measure the same metabolites. CSF metabolite levels were then compared against corresponding metabolite levels at the injury site obtained from the same hour of sampling.

Signal analysis

Data were analysed using Labchart v.8 (AD Instruments, Oxford, UK) and ICM+ (www.neurosurg.cam.ac.uk/icmplus) to compare ISP versus CSFP signals including morphology of individual waveforms, entire period mean values, and duration of pulseless CSFP. We also computed the running correlation between CSFP and ISP defined as the Pearson correlation coefficient of the preceding 60 1-sec averages of CSFP versus ISP, updated each minute. We argued that the timing of the ISP and CSFP waveforms will be greatly influenced by compliance; that is, a more compliant compartment will transmit pulses more slowly than a less compliant one. We thus also computed two elements of pulse wave timing: the latency (k) between the onset of an ISP waveform and the onset of the corresponding CSFP waveform as well as the slope of each pulse wave (dP/dT). Frequency-domain analysis of the ISP and CSFP waveforms was performed using a Fast Fourier Transformation to determine cardiac and respiratory contributions to these signals. Three 2-h traces of waveform signals were analyzed for each patient corresponding to periods that the CSFP was very, minimally, and non-pulsatile. ISP and CSFP were also used to compute the following: SCPP = MAP – ISP, $SCPP_{(csf)}$ = MAP – CSFP, $sPRx_{ISP}$ = running correlation coefficient between MAP and ISP, $sPRx_{(csf)}$ = running correlation coefficient between MAP and CSFP, $SCPP_{opt(ISP)}$ = SCPP at minimum $sPRx_{(ISP)}$, and $SCPP_{opt(csf)}$ = $SCPP_{(csf)}$ at minimum $sPRx_{(csf)}$.

Statistical analysis

b AU5

The Pearson coefficient was used to examine the correlations between CSFP versus ISP, $SCPP_{(csf)}$ versus $SCPP_{(ISP)}$, $SCPP_{opt(csf)}$ versus $SCPP_{opt(ISP)}$, $sPRx_{(csf)}$ versus $xPRx_{(ISP)}$, metabolite concentrations in lumbar CSF versus microdialysate as well as extent of cord edema (length of T2 signal abnormality on pre-operative MRI) versus mean Pearson correlation coefficient between CSFP and ISP. The change in ISP (DISP) as a result of draining lumbar CSF was defined as 15 min mean ISP prior to drainage minus 15 min mean ISP 10 min after drainage, and was compared using Student's *t* test for all the repeats in each patient. dP/dT values for CSP versus ISP were compared using Student's *t* test. The different k groups were compared by multiple Student's *t* tests with Bonferroni correction.

Results

Patient demographics

Data were collected from 13 consecutive patients 26–67 years of age (mean 47). Most (62%) patients had complete (AIS A) injuries and most (70%) had cervical injuries. All patients underwent posterior surgical bony decompression including laminectomy and fusion, with 31% also requiring concurrent anterior stabilization. Mean duration of follow-up was *6 months. At follow-up, most patients (54%) had improved by one or more AIS grade, some (38%) remained the same, and one patient (8%) deteriorated by one AIS grade. Mean duration of monitoring was 4–5 days and mean number of MD-CSF matched sample pairs per patient was eight. Details are in Table 1.

b T1

Complications

In three patients (23 %), the lumbar drain stopped working and was re-sited or removed. One patient (8%) with poorly controlled diabetes mellitus developed a post-operative *Escherichia coli*

Table 1. Patient Demographic Characteristics

Patient no.	*Age years*	*Sex*	*Site*	*Type of surgery post / ant+post*	*Admission AIS grade*	*Follow-up AIS*	*Duration of follow-up (months)*	*Duration of monitoring (h)*	*Number of simultaneous MD and CSF samples*
1	67	M	C3	Post	A	A	1	104.25	0
2	67	M	C4	Post	C	C	12	127.93	8
3	32	M	C4	Ant+Post	C	D	10	150.93	3
4	39	M	T7	Post	A	B	15	115.12	11
5	35	M	C4	Ant+Post	C	A	12	84.5	7
6	27	M	L1	Post	C	D	6	111.78	9
7	50	M	C5	Post	B	B	2	139	14
8	47	M	T8	Post	A	C	12	105.63	9
9[a]	57	M	C4	Post	A	A	3	147.15	12
10	66	M	C4	Post	A	A	4	128.5	12
11	46	M	T12	Post	A	C	4	51.78	3
12	52	M	C5	Ant+Post	A	B	2	127.56	12
13	26	M	C6	Ant+Post	A	B	1	70.5	8

[a]Patient had a permanent pacemaker so did not have magnetic resonance imagining (MRI).
AIS, American Spinal Injury Association Impairment Scale; MD, microdialysis; CSF, cerebrospinal fluid.

Table 2. Complications

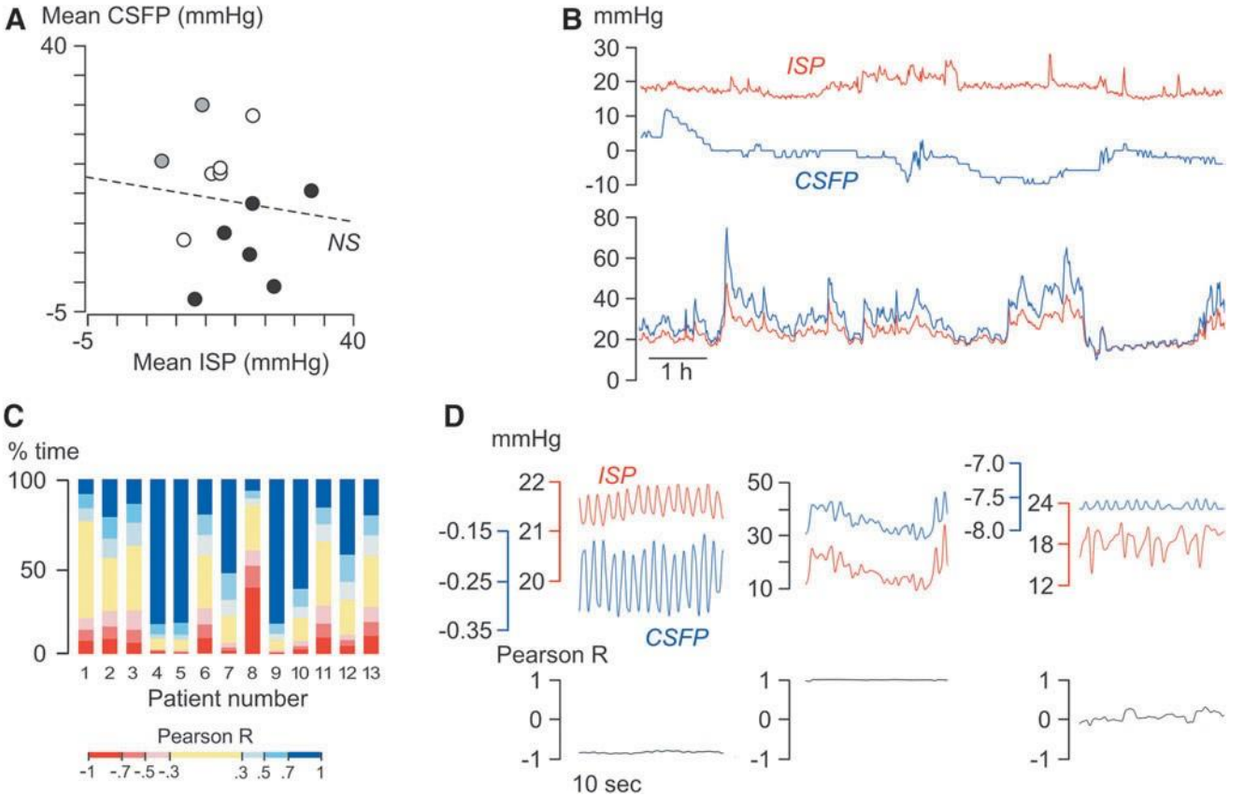
Complication	*No. of patients*	*Comments*
Wound infection	1	Brittle diabetes and *E. coli* bacteraemia from urosepsis. Wound swabs also grew *E. coli.* Infection eradicated by wound washout and 6 weeks ceftriaxone.
CSF Leak around probes	4	All managed with re-suturing of probe exit site with no further leaks.
Lumbar drain blocked	2	In one patient, lumbar drain stopped transducing a pressure wave and would not drain or flush, so lumbar drain was removed. In the second patient, lumbar drain was re-sited without complication.
Pseudomeningocele on 6 week MRI	6	All clinically asymptomatic. In 3/6, pseudomeningocele resolved on MRI at 1 year. 3/6 awaiting 1 year follow-up MRI.

CSF, cerebrospinal fluid; MRI, magnetic resonance imaging.

septicemia from urosepsis followed by *E. coli* wound infection 17 days after surgery; the infection was eliminated with wound washout plus 6 weeks of intravenous antibiotics. It is of note that this was the only ISCoPE patient who developed a wound infection out of the 76 who underwent multi-modality injury site monitoring to date (2010–19), giving an overall infection risk of 1.3%. CSF leak from the probe skin exit site was observed in 4/13 patients (31%) and was successfully stopped by placing additional skin sutures. Six of the thirteen patients (46%) had asymptomatic, non-compressive pseudo-meningoceles noted on post-operative MRI, performed within 2–3 months of TSCI, which resolved on the 1-year post-operative MRI. Details are in Table 2. b T2

ISP versus CSFP waveform shapes

Morphologically, the ISP waveforms were comparable to the intracranial pressure waveforms with three major peaks: percussion, tidal, and dicrotic.[21] In contrast, the CSFP waveforms appeared flatter than the ISP waveforms and were less pulsatile with non-pulsatile periods (Fig. 1B–D). Additional comparisons



4C c

FIG. 2. Intraspinal pressure (ISP) versus cerebrospinal fluid pressure (CSFP). (A) Average ISP versus average CSFP for entire monitoring period. Best-fit straight line, R = -0.11. White circles (ISP – CSFP £5 mm Hg), gray circles (CSFP–ISP >5 mm Hg), black circles (ISP–CSFP >5 mm Hg). (B) Example of ISP signal and simultaneously recorded CSFP signal, monitored over 10 h, that correlate (*top*) poorly and (*bottom*) well. (C) Distribution of running Pearson R between ISP and CSFP for each patient. (D) Example of ISP signal and simultaneously recorded CSFP signal, monitored over 10 sec, with (*left*) negative, (*middle*) positive, and (*right*) no corre- lation. Below are corresponding plots of Pearson R versus time. NS, not significant.

SF1 c between ISP and CSFP waveforms are in the Figure S1. Frequency domain analysis for ISP revealed respiratory and heartbeat peaks (+ harmonics) with either peak the tallest. Flat CSFP had no frequency peaks and minimally pulsatile CSFP had only the respiratory peak, whereas more pulsatile CSFP had both respiratory and heartbeat peaks, with the respiratory peak always the tallest. Timing analysis revealed significantly steeper dP/dT slope for ISP than for CSFP waveforms and significant delay, by >100 ms in most cases, between the onset of the CSFP pulse compared with the corresponding ISP pulse.

ISP versus CSFP signals

When averaged over the entire monitoring period, ISP was higher than the CSFP by *5 mm Hg. A plot of average CSP *versus* average ISP for the 13 patients showed no overall correlation: in 6/13 patients, mean ISP – mean CSFP >5 mm Hg, in 2/13 patients mean CSFP – mean ISP >5 mm Hg, and in 5/13 patients, mean ISP
F2 c and mean CSFP were within 5 mm Hg (Fig. 2A). Closer inspection of these signals revealed periods when the ISP and CSFP pulsations appeared uncorrelated, and other periods when the CSFP and the ISP pulsations appeared almost identical (Fig. 2B). To evaluate this time variability in the correlation between the CSFP and the ISP signals, we computed their running correlation coefficient (Fig. 2C, D). The running correlation coefficient was >0.7 for >75 % of the time in 3/13 patients (2 cervical +1 thoracic injuries), 25–75 % of the time in 3/13 patients (all cervical) and <25 % of the time in 7/13 patients (4 cervical +2 thoracic +1 conus). We noted periods of positive CSFP versus ISP correlation, periods of no correlation and periods of anti-correlation. There was no significant difference in the running coefficient between cervical and thoracolumbar TSCIs.

SCPP, sPRx, $SCPP_{opt}$ and metabolites

Overall, there was no significant correlation between $SCPP_{(csf)}$ versus $SCPP_{(ISP)}$, $sPRx_{(csf)}$ versus $sPRx_{(ISP)}$, or $SCPP_{opt(csf)}$ versus
F3 c $SCPP_{opt(ISP)}$ (Fig. 3). Also, the overall levels of metabolites measured from the injury site by microdialysis versus the corresponding levels in the lumbar CSF did not significantly correlate for lactate, pyruvate, and LPR, although there were significant, albeit weak, positive correlations for glucose, glutamate, and glycerol
F4 c (Fig. 4). When we examined individual patients, significant positive correlations between injury site and lumbar CSF levels were found in 8/12 for glucose, 8/12 for glutamate, and 6/12 for glycerol.

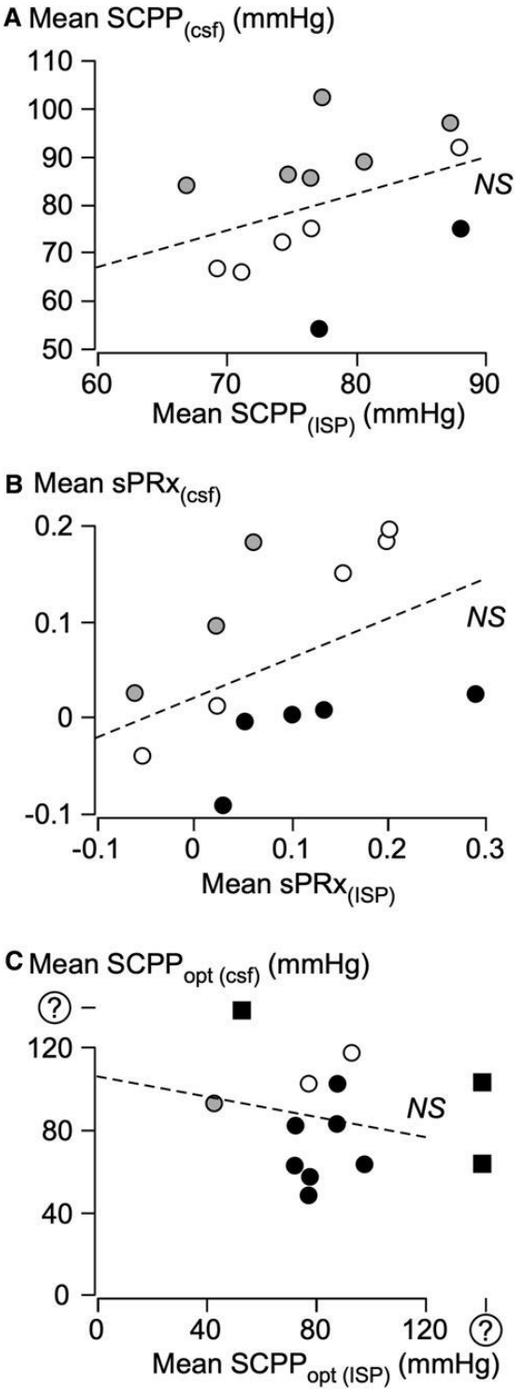


FIG. 3. Physiological parameters computed from intraspinal pressure (ISP) versus cerebrospinal fluid pressure (CSFP). (A) Average spinal cord perfusion pressure (SCPP) computed from CSF ($SCPP_{CSF}$) versus average SCPP computed from CSFP ($SCPP_{ISP}$), R = 0.39. White circles ($SCPP_{(csf)}$ – $SCPP_{(ISP)}$ £ 5 mm Hg), gray circles ($SCPP_{(csf)}$ – $SCPP_{(ISP)}$ > 5 mm Hg), black circles ($SCPP_{(csf)}$ – $SCPP_{(ISP)}$ < 5 mm Hg). (B) Average vascular pressure reactivity index (sPRx) computed from CSF ($sPRx_{(csf)}$) versus average sPRx computed from ISP ($sPRx_{(ISP)}$), R = 0.45. White circles ($sPRx_{(csf)}$ – $sPRx_{(ISP)}$ £ 0.05), gray circles ($sPRx_{(csf)}$ – $sPRx_{(ISP)}$ > 0.05), black circles ($sPRx_{(csf)}$ – $sPRx_{(ISP)}$ < 0.05). (C) Overall $SCPP_{opt}$ computed from CSF ($SCPP_{opt(csf)}$) versus overall $SCPP_{opt}$ computed from ISP ($SCPP_{opt(ISP)}$), R = -0.22. White circles ($SCPP_{opt(csf)}$ – $SCPP_{opt(ISP)}$ £ 5 mm Hg), gray circles ($SCPP_{opt(csf)}$ – $SCPP_{opt(ISP)}$ > 5 mm Hg), black circles ($SCPP_{opt(csf)}$ – $SCPP_{opt(ISP)}$ < 5 mm Hg). Best-fit straight lines.
AU3 c NS, not significant.

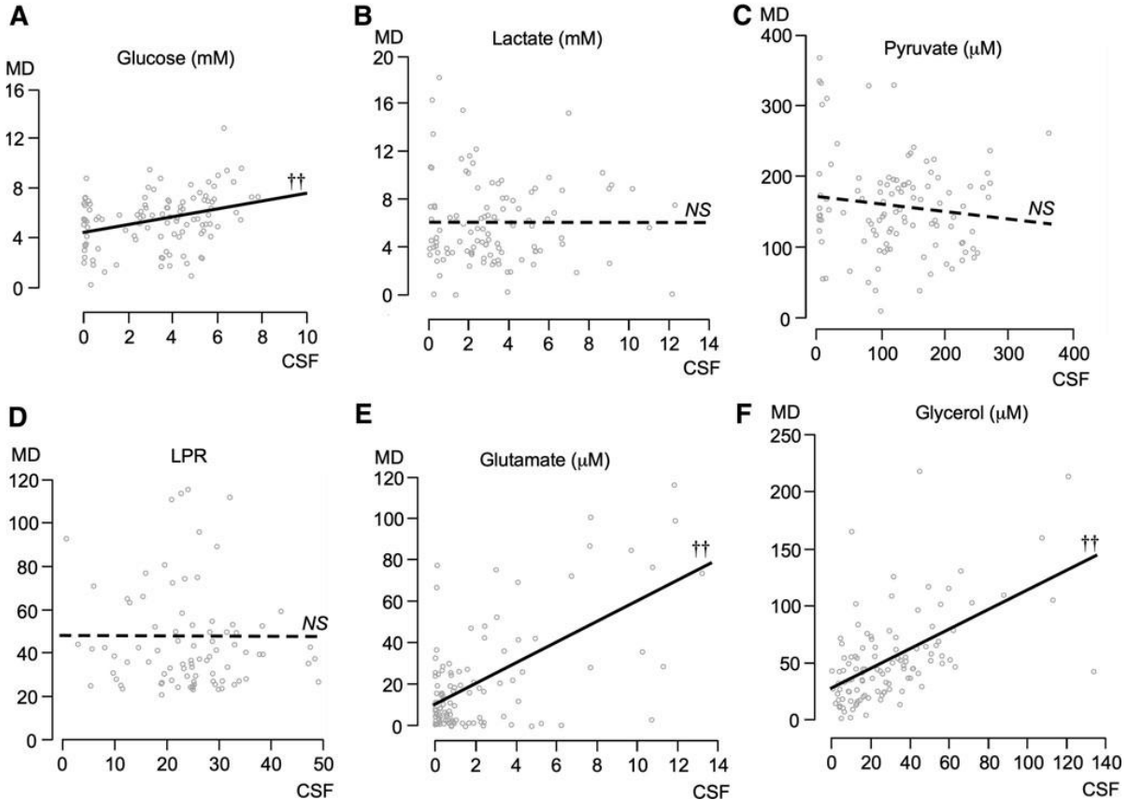


FIG. 4. Biochemical parameters at injury site versus cerebrospinal fluid (CSF). Plots of microdialysis (MD) versus lumbar CSF values with best-fit straight line for (A) Glucose in mM ($R=0.32$), (B) Lactate in mM ($R=0.0007$), (C) Pyruvate in lM ($R=-0.12$), (C) Lactate-to-pyruvate ratio (LPR) ($R=-0.05$), (E) Glutamate in lM ($R=0.61$), and (E) Glycerol in lM ($R=0.56$). Data from 12 patients. $^{\dagger\dagger}p < 0.0001$; NS, not significant.

Effect on ISP of CSF drainage

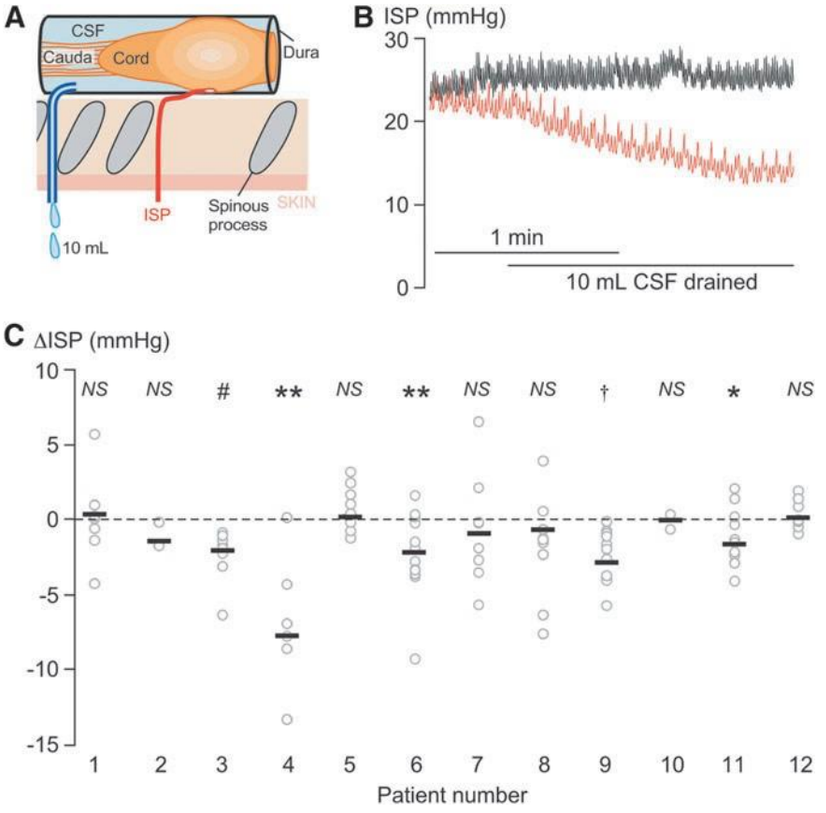
In 12/13 patients, we drained *10 mL CSF through the lumbar catheter on several occasions. CSF drainage had variable effect on ISP: on average, in 7/12 patients there was no change in ISP, in 4/12 patients there was a significant small reduction in ISP by <5 mm Hg, and in 1/12 patients there was a large drop in ISP by 5–10 mm Hg (Fig. 5). In 3/12 patients, on some occasions, we observed the phenomenon of ''dry tap,'' in which CSF would not be drained even though the lumbar catheter was patent (i.e., able to flush and transduced a pressure wave). This resolved in 2/3 patients, but persisted in 1/3 (patient 10) after day 2, even though the lumbar drain appeared in the spinal canal on the post-operative CT.

Cord swelling and CSFP versus ISP correlation

We hypothesized that if the injured cord is not very swollen, it will be surrounded by CSF and, therefore, the ISP and the CSFP signals will be similar; that is, their correlation will be high. Conversely, if the cord is very swollen, it will become compressed against the dura. In this case, the ISP is the pressure of the swollen cord against the dura, whereas the CSFP is the pressure in the lumbar CSF and, therefore, there will be loss of correlation between CSFP and ISP. The longitudinal extent of cord signal change on pre-operative T2 MRI, used as a measure of cord edema, inversely correlated with the mean CSFP *versus* ISP correlation coefficient (Fig. 6). In other words, patients with less swollen spinal cords had stronger positive correlations between their CSFP and their ISP signals, thus supporting our hypothesis.

Discussion

Our key finding is that, after acute severe TSCIs, the values of physiological (i.e., ISP, SCPP, sPRx, $SCPP_{opt}$) and biochemical (i.e. glucose, lactate, pyruvate, LPR, glutamate, glucose) parameters measured at the injury site markedly differ from equivalent measurements from the lumbar CSF. Lack of correlation between ISP and CSFP likely occurs when the injured cord is compressed against the dura; that is, when there is no CSF around the injury site. The presence of periods with high correlation between ISP and CSFP suggests that cord compression is a dynamic process. These ideas are supported by our earlier finding of a pressure profile along the injured cord[12,22] and our current observation that patients with more cord swelling on pre-operative MRI have poorer correlation between ISP and CSFP.



4C c

FIG. 5. Effect of draining lumbar cerebrospinal fluid (CSF) on intraspinal pressure (ISP). (A) Setup. With the patient lying flat, ISP is monitored by a pressure probe placed subdurally at the injury site while 10 mL lumbar CSF was drained. (B) Examples from two patients (black, red) of ISP traces during draining 10 mL lumbar CSF. (C) Plot of DISP as a result of draining 10 mL lumbar CSF (circles are individual values, lines are means) from 12/13 patients. $*p < 0.05$; $**p = 0.01$; $^{\#}p = 0.005$; $^{\#\#}p = 0.001$; $^{\dagger}p = 0.0005$; NS, not significant.

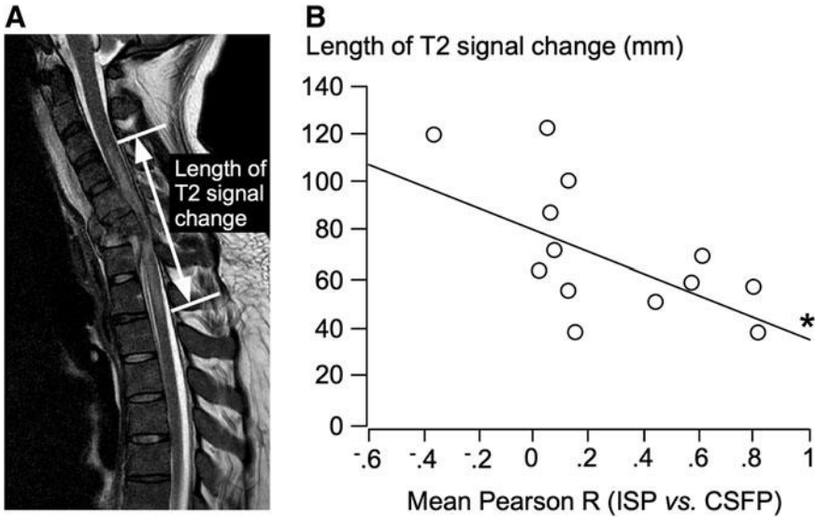


FIG. 6. Relation between cord edema and concordance between intraspinal pressure (ISP) and cerebrospinal fluid pressure (CSFP) signals. (A) T2 mid-sagittal magnetic resonance imaging (MRI) showing length of cord signal change. (B) Plot of length of cord signal change in mm versus mean Pearson R (ISP versus CSFP). $R = 0.66$, $p < 0.05$.

ISP and CSFP pulse timings suggest that the injury site and the lumbar CSF have different physical properties. CSFP pulses have lower dP/dT and lag behind ISP pulses; this means that ISP pulses are in a ''tight'' compartment (low compliance, cord compressed against dura), but CSFP pulses are in a ''loose'' compartment (lumbar CSF).[23] ISP has two prominent frequency peaks (cardiac, respiratory), as previously shown,[12,21] but CSFP may be flat (no peaks), a little pulsatile (respiratory peak only), or more pul- satile (two peaks, respiratory taller than cardiac). Lack of lumbar CSF pulsatility in TSCI was also noted by Kwon and coworkers who found correlation with cord compression on MRI.[16] We pro- pose that the swollen cord inhibits the caudal transmission of cord and CSF pulsations to the lumbar CSF, thus causing CSFP pulsa- tility to diminish. In our ventilated patients, lung pressure fluctua- tions likely produce venous pressure fluctuations that are transmitted to the CSFP regardless of cord compression. This may explain why the respiratory frequency peak in CSFP often persists even when the cardiac frequency peak has disappeared.

Over the last few years, we showed how the ISP signal can be used to derive several physiological parameters (SCPP, sPRx, and $SCPP_{opt}$)[12,21,24,25] that correlate with injury site metabolism,[11] acute neurological status,[12] and long-term neurological outcome,[6] and may guide the management of TSCI patients in ICU. We ob- served major differences between these parameters computed using ISP versus CSFP. The differences arise because of the overall lack of correlation between ISP and CSFP. During periods that the spinal cord is not compressed, ISP & CSFP and therefore $SCPP_{(ISP)}$ & $SCPP_{(csf)}$. Therefore, $SCPP_{(csf)}$ carries some information about $SCPP_{(ISP)}$; this may explain why $SCPP_{(csf)}$ has some predictive power in TSCI.[15] Neurological outcome correlates better with $SCPP_{(ISP)}$[6] than with $SCPP_{(csf)}$,[15] probably because $SCPP_{ISP}$ carries more information about the injury site than $SCPP_{CSF}$. Together, our findings suggest that CSFP monitoring is less cumbersome than ISP monitoring, but cannot reliably estimate ISP, SCPP, sPRx, or $SCPP_{opt}$.

Lumbar CSF drainage has been used to improve cord perfusion after TSCI in patients[16] and pig models.[26] In our study, CSF drainage did not reliably reduce ISP in most TSCI patients, prob- ably because of the lack of CSF around the injury site. Our ob- servation of ''dry taps'' on several occasions, also noted by Kwon and coworkers,[16] supports the idea of a block in the flow of CSF caused by the swollen cord compressed against the dura. In patients with CSF around the injured cord, lumbar CSF drainage is pre- dicted to reduce ISP (Patient 4, Fig. 5). Even in this patient, how- ever, ISP decreased only on some occasions, which suggests that the cord is intermittently compressed. Ways to reliably increase SCPP include vasopressors to increase MAP[12] or expansion dur- oplasty to reduce ISP.[27]

Tissue MD is widely used when managing patients with brain injuries.[28] We showed that MD also provides clinically important information after TSCI.[8,9] Our data suggest that metabolite levels at the injury site differ from corresponding levels in the lumbar CSF. An explanation is that the MD catheter samples metabolites from the extracellular space at the injury site, but metabolites are shed into the lumbar CSF not only from the injury site, but also from the cord below. Differences in metabolite levels at the injury site versus lumbar CSF were more pronounced for lactate, pyruvate, and LPR, probably because the cord below the injury has a healthier me- tabolism than the injury site. Tissue (glucose) at the injury site correlated with lumbar CSF (glucose); a possible explanation is that both concentrations are influenced by serum (glucose).[8,29] Gluta- mate and glycerol at the injury site also correlated with lumbar CSF levels; this may be because the normal cord does not release glu- tamate or glycerol; that is, the glutamate and glycerol in the lumbar CSF originated entirely from the injury site. Despite reaching sta- tistical significance, the correlations of injury site versus lumbar CSF for glucose, glutamate, and glycerol were weak with large interpatient variability.

By analogy with intracranial pressure monitoring for brain in- jury, ISP monitoring for TSCI may be helpful to guide management in the most severely injured patients.[13] To date, we have only monitored ISP and MD in patients with severe TSCI; that is, AIS A, B, or C at baseline. Potential risks of injury site monitoring include mechanical spinal cord damage; subdural haematoma, dural CSF leak causing pseudomeningocele, or leak though the skin; menin- gitis; and probe retention requiring surgery to remove. In a study of 42 patients who had ISP monitoring, complications were probe displacement in 2.4%, CSF leak requiring wound resuturing in 7.1%, and asymptomatic pseudomeningocele in 19.0%, which re- solved within 6 months.[10] There were no serious probe-related complications such as meningitis, wound infection, subdural he- matoma, wound breakdown, or neurological deterioration.

Based on our findings, we urge caution when interpreting data obtained from the lumbar CSF in TSCI patients. To monitor pathological events within the injured cord, we advocate directly accessing the injury site, which is safe,[10] and may be used to obtain multi-modality data including ISP, SCPP, sPRx, $SCPP_{opt}$, and MD.[9,12]

Conclusions

In 13 patients with TSCI, monitoring from the injury site was compared with monitoring from the lumbar CSF. The effect of draining lumbar CSF on injury site perfusion was also assessed. We conclude that monitoring from the lumbar CSF offers limited in- formation about the injury site, and that drainage of lumbar CSF does not improve cord perfusion in most patients.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Figure S1

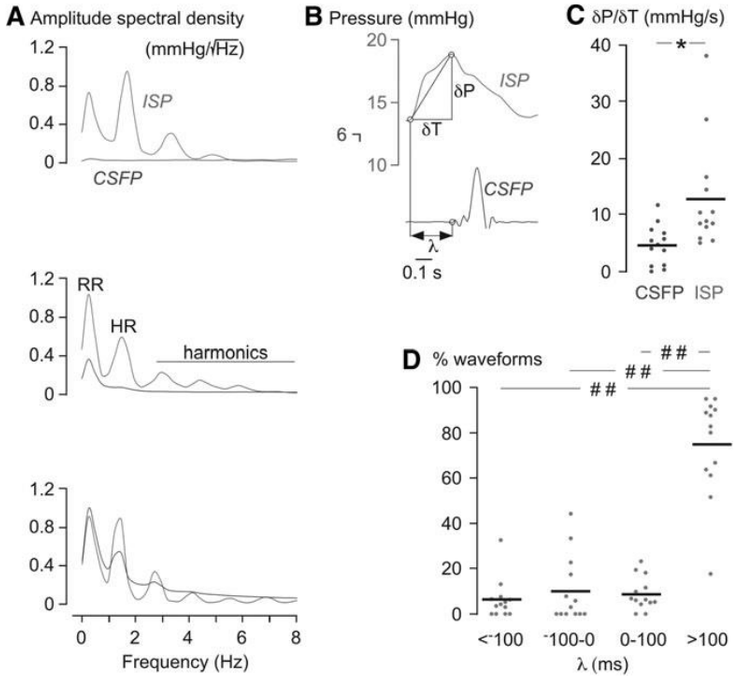
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Supplementary Data



AU4c SUPPLEMENTARY FIG. S1. Further analysis of intraspinal pressure (ISP) versus cerebrospinal fluid pressure (CSFP) signals. (A) FFT of 2 h long ISP and corresponding CSFP signals showing amplitude spectral density (mm Hg/Hz) versus frequency (Hz), *(top)* CSFP signal with no pulsation, *(middle)* CSFP signal with some pulsation, *(bottom)* CSFP signal with prominent pulsation. Peaks correspond to respiratory rate (RR), heart rate (HR), and harmonics. (B) ISP and CSFP signal characteristics: d P/dT (slope of pulse wave) and k (ISP – CSFP latency). (C) Plot of mean d P/dT of the ISP and CSFP waveforms for each patient (dot). Lines are means. (D) Plot of mean k for each patient (dot). Lines are means. *$p < 0.05$; ##$p < 0.001$.

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NEUROCRITICAL CARE SOCIETY

ORIGINAL WORK

Acute Spinal Cord Injury: Correlations and Causal Relations Between Intraspinal Pressure, Spinal Cord Perfusion Pressure, Lactate-to-Pyruvate Ratio, and Limb Power

Florence R. A. Hogg[1], Siobhan Kearney[1], Argyro Zoumprouli[2], Marios C. Papadopoulos[1] and Samira Saadoun[1*]

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Abstract

Background/Objective: We have recently developed monitoring from the injury site in patients with acute, severe traumatic spinal cord injuries to facilitate their management in the intensive care unit. This is analogous to monitoring from the brain in patients with traumatic brain injuries. This study aims to determine whether, after traumatic spinal cord injury, fluctuations in the monitored physiological, and metabolic parameters at the injury site are causally linked to changes in limb power.

Methods: This is an observational study of a cohort of adult patients with motor-incomplete spinal cord injuries, i.e., grade C American spinal injuries association Impairment Scale. A pressure probe and a microdialysis catheter were placed intradurally at the injury site. For up to a week after surgery, we monitored limb power, intraspinal pressure, spinal cord perfusion pressure, and tissue lactate-to-pyruvate ratio. We established correlations between these variables and performed Granger causality analysis.

Results: Nineteen patients, aged 22–70 years, were recruited. Motor score versus intraspinal pressure had exponential decay relation (intraspinal pressure rise to 20 mmHg was associated with drop of 11 motor points, but little drop in motor points as intraspinal pressure rose further, $R^2 = 0.98$). Motor score versus spinal cord perfusion pressure (up to 110 mmHg) had linear relation (1.4 motor point rise/10 mmHg rise in spinal cord perfusion pressure, $R^2 = 0.96$). Motor score versus lactate-to-pyruvate ratio (greater than 20) also had linear relation (0.8 motor score drop/10-point rise in lactate-to-pyruvate ratio, $R^2 = 0.92$). Increased intraspinal pressure Granger-caused increase in lactate-to-pyruvate ratio, decrease in spinal cord perfusion, and decrease in motor score. Increased spinal cord perfusion Granger-caused decrease in lactate-to-pyruvate ratio and increase in motor score. Increased lactate-to-pyruvate ratio Granger-caused increase in intraspinal pressure, decrease in spinal cord perfusion, and decrease in motor score. Causality analysis also revealed multiple vicious cycles that amplify insults to the cord thus exacerbating cord damage.

Conclusion: Monitoring intraspinal pressure, spinal cord perfusion pressure, lactate-to-pyruvate ratio, and intervening to normalize these parameters are likely to improve limb power.

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Keywords: Blood pressure, Intraspinal pressure, LPR, Management, Microdialysis, Monitoring, Spinal cord injury

Introduction

Traumatic spinal cord injury (TSCI) affects about 180,000 people globally each year [1]. Prognosis is generally poor. For example, more than a third of patients have paraplegia or quadriplegia, fewer than 1% are discharged neurologically normal and life expectancy is below national averages [2]. No treatment for acute TSCI has been proven to improve outcome: the effects of early surgery [3–7], intravenous methylprednisolone [8–12] or maintaining mean arterial pressure (MAP) 85–90 mmHg for a week after TSCI [13–16] remain controversial [17].

To improve the management of patients with TSCI in the intensive care unit (ICU), multi-modality monitoring from the injury site has been suggested [18]. Intraspinal pressure (ISP) and spinal cord perfusion pressure (SCPP) [19–21] are monitored with a pressure probe, as well as injury site metabolism with a microdialysis (MD) catheter [22, 23]. These techniques are safe and analogous to multi-modality monitoring for brain injury [24]. ISP and SCPP correlate with injury site metabolism [25], neurological status [26], and long-term neurological outcome [20], and patients with neurologically complete TSCIs have more deranged cord metabolism than those with neurologically incomplete injuries [22]. These relations between ISP, SCPP, and injury site metabolism versus neurological outcome are associations that do not imply causation.

The objective of our study is to address the question whether changes in ISP, SCPP, and injury site metabolism *cause* changes in limb power. This is paramount because it implies that interventions to normalize ISP, SCPP, and injury site metabolism would improve limb power. To determine causation, we focused on grade C (American Spinal Injury Association Impairment Scale, AIS) injuries because they have some intact limb power below the injury. Limb motor score, ISP, SCPP, and injury site lactate-to-pyruvate ratio (LPR) were monitored for up to a week after surgery. We used these time series to investigate the hypothesis that fluctuations in motor score are caused by fluctuations in the physiology and metabolism at the injury site. We employed the concept of causality proposed by Clive Granger [27] and recently reviewed [28], i.e., a variable, such as SCPP, which evolves in time, Granger-causes another time-evolving variable, such as motor score, if predictions of motor score based on its own past and on the past of SCPP are better than predictions of motor score based solely on its own past.

Methods

Institutional Research Board Approvals

Injured Spinal Cord Pressure Evaluation (ISCoPE) is a clinical study at St. George's Hospital in London, U.K., registered at www.clinical trials.gov as NCT02721615. Approvals for the ISCoPE study including the consent form and patient information sheet were obtained by the St. Georges Joint Research Office and the U.K. National Research Ethic Service—Camberwell St Giles Committee (No 10/H0807/23). The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Study Design

We investigated the correlations and causal relations between ISP, SCPP, tissue LPR, glutamate, and standardized motor score in AIS C TSCI patients.

Inclusion/Exclusion Criteria

We selected all AIS grade C TSCI patients who were enrolled into ISCoPE for the period October 2011–January 2020. Inclusion criteria for ISCoPE are: severe TSCI grades A–C, age 18–70 years and surgery performed within 72 h of injury. Exclusion criteria are: major comorbidity, inability to obtain consent, and penetrating TSCI. The ISCoPE study initially aimed to develop ISP monitoring from the injury site. In 2014, we also started monitoring MD. The current study includes AIS grade C patients who only had ISP monitoring (recruited 2011–4) as well as those who also had MD monitoring (recruited 2014–2020).

Clinical Examination and Imaging

All patients were admitted to the neurosurgical unit at St. George's Hospital and underwent International Standards for Neurological Classification of Spinal Cord Injury assessments by a trained neurosurgical resident, which was repeated at discharge and in follow-up clinic. Postoperatively, all patients were admitted to the Neuro-ICU. As standard clinical care in our unit, all TSCI patients undergo regular motor limb assessments by nurses trained in Medical Research Council grading of limb power. These assessments were performed with the patient off sedation or during a sedation hold and recorded in spinal assessment charts. Patients had CT and MRI of the spine before surgery and within four weeks of surgery.

Probe Insertion

Surgical decompression and spinal instrumentation were performed by a neurosurgeon based on patient requirements and surgeon preference. Surgical decompression was laminectomy with or without corpectomy with spinal instrumentation based on surgeon preference. Posterior fixation was with lateral mass screws for the cervical spine and pedicle screws for the thoracic spine. Anterior cervical fixation was with vertebral body plate and screws. During the posterior approach, a pressure probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) and a MD catheter (CMA61: CMA microdialysis AB, Solna, Sweden) were placed intradurally on the surface of the injured cord at the site of maximal cord swelling based on the preoperative MRI (Fig. 1). The dural opening was sutured and supplemented with fibrin glue (Tisseel®, Baxter, UK). Postoperative CT with the probes in situ confirmed positioning.

Intraspinal Pressure and Blood Pressure Monitoring

The pressure probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.8 (AD Instruments, Oxford, UK). Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK), in turn connected to the PowerLab system. ISP and blood pressure signals were sampled at 1 kHz, and patients were monitored for up to a week. Data were analyzed using Labchart version 8 (AD Instruments, Oxford, UK) and ICM+ (www.neurosurg.cam.ac.uk/icmplus). We computed SCPP as MAP–ISP. ISP is different from intrathecal pressure measured above or below the injury because the swollen, injured cord is compressed against the dura thus compartmentalizing the intrathecal space as illustrated in Fig. 1a and described in earlier publications [29–31].

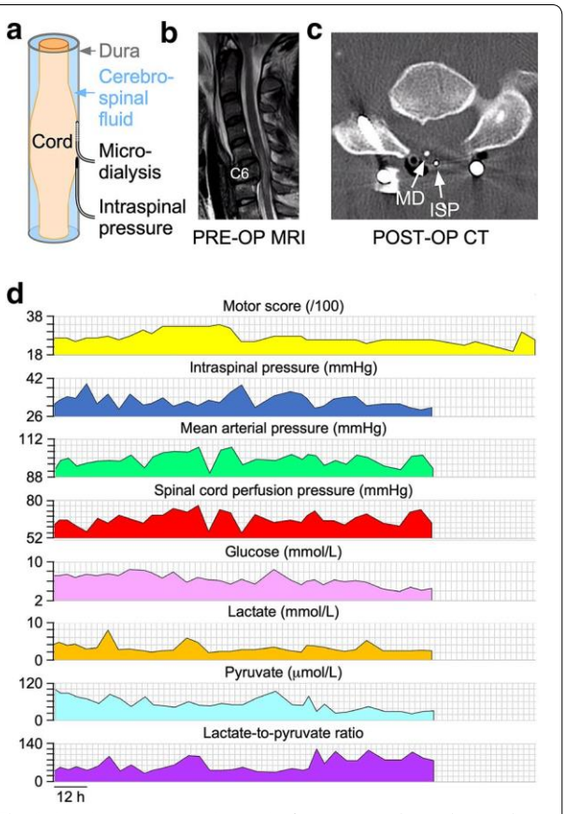


Fig. 1 Monitoring setup. **a** Intraspinal pressure probe and microdialysis catheter inserted intradurally to monitor from injured cord. **b** Preoperative sagittal T2 MRI of patient no. 52 with spinal cord injury at C6. **c**. Postoperative axial CT with intraspinal pressure probe and microdialysis catheter in situ. **d** Multi-modality monitoring of motor score (yellow), intraspinal pressure (blue), mean arterial pressure (green), spinal cord perfusion pressure (red) as well as tissue glucose (pink), lactate (orange), pyruvate (cyan), and lactate-to-pyruvate ratio (purple) (Color figure online)

Microdialysis Setup and Analysis

MD was started postoperatively in the Neuro-ICU as described [22, 23, 25]. 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 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. 100-fold changes in metabolite concentration, compared with the preceding hour, were excluded from analysis. Metabolite levels were compared to corresponding hourly averages of ISP, MAP, and SCPP. 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 cerebrospinal fluid [22, 23, 32].

Standardization of Limb Motor Score

The motor scores in the spinal assessment charts were standardized by subtracting the minimum postoperative motor score for each patient from all motor scores for that patient. Standardized motor scores were compared to ISP, MAP, SCPP, and MD values averaged over the hour corresponding to the neurological assessment.

Summary of Variables/Outcomes

We obtained matched values of ISP, SCPP, tissue glucose, LPR, and standardized motor score. To avoid bias, data

were analyzed blindly, i.e., each variable/outcome was obtained and listed for analysis without knowledge of the other associated variables.

Statistical Analysis

Motor score (y) versus ISP (x) was fitted with an exponential decay curve $y = A + Be^{-Cx}$, motor score versus SCPP and versus LPR were fitted with linear equations, whereas motor score (y) versus MAP (x) was fitted with a bounded exponential curve $y = A + B(1 - e^{-Cx})$ using the online free curve fitting service (https://mycurvefit.com/). Plots are mean ± standard error. For Granger causality analysis of the standardized motor score, ISP, SCPP, and LPR time series, we used the Granger function in the Cloud Causal Analytics Toolkit (https://cox-associates.com/) that employs vector autoregression models to test for causal relations. For details, see Supplement.

Results

Participants

There were 19 patients, with average age 47 years (range 19–70), of which 14 (74%) were male and 5 (26%) female. Fourteen (74%) had cervical and 5 (26%) thoracolumbar injuries. Of the 19 patients, 12 (63%) had posterior surgical approach plus laminectomy, 5 had anterior plus posterior approach and laminectomy (26%) and 2 (11%) had posterior approach without laminectomy. Mean time from injury to surgery was 38 h. All 19 patients had ISP monitoring and 13 (68%) also had MD monitoring. The mean duration of ISP monitoring was 5.1 days (range 1.8–6.8) and of MD monitoring 3.7 days (range 0–6.8). The mean number of motor exams in the monitored period was 19 (range 5–37). Table 1 has details.

Complications

Two patients (11%) had cerebrospinal fluid leak from around the probe skin exit site which stopped with additional sutures, and 4 patients (21%) had asymptomatic pseudomeningocele on the postoperative MRI. Four patients (21%) had chest sepsis, and 1 (5.3%) patient developed Korsakoff psychosis from alcohol withdrawal.

Motor Score Strongly Correlates with Injury Site Physiology

Figure 2 shows the relations between standardized motor score versus ISP, versus SCPP, and versus MAP using data from all 19 patients. The curve $y = 3.9 + 33.4e^{-1.1x}$ fits well with the relation between average motor score (y) versus ISP class ($x = 1, \ldots, 8$, respectively, defined as < 5, …, 35 – 40 mmHg). Reduction in ISP from > 20 to < 5 mmHg is associated with an average gain of about 11 motor points, whereas fluctuations in ISP in the range 20–40 mmHg are not associated with changes in average motor score. The line $y = 1.4x - 3.9$ fits well with the relation between average standardized motor

Table 1 Demographic details of the AIS grade C patients

Pt. No	Study no	Age (y)	Sex	Level	Surgical approach	Lami	Injury to surgery (h)	ISP monitoring (h)	MD monitoring (h)	No. of motor exams
1	8	64	F	C5	Post	No	47	94	0	6
2	9	49	F	C5	Post	Yes	16	43	0	6
3	10	54	M	T12	Post	Yes	48	117	0	13
4	13	65	M	C4	Post + Ant	Yes	11	68	0	10
5	20	59	M	C6	Post	Yes	32	71	0	14
6	40	70	F	C4	Post	Yes	20	156	156	23
7	44	26	M	T12	Post	Yes	46	160	35	23
8	45	37	M	C4	Post + Ant	Yes	29	136	138	25
9	50	63	M	C7	Post	Yes	47	105	0	12
10	52	19	M	C6	Post	Yes	41	145	145	28
11	54	63	M	C5	Post	Yes	58	138	137	25
12	61	56	F	L1	Post	Yes	31	114	161	27
13	66	67	M	C4	Post	No	38	160	157	25
14	67	32	M	C4	Post + Ant	Yes	22	159	163	35
15	68	37	F	L3	Post	Yes	23	139	125	22
16	70	35	M	C4	Post + Ant	Yes	39	112	109	5
17	71	27	M	L1	Post	Yes	41	144	145	37
18	81	54	M	C4	Post	Yes	69	161	150	25
19	84	22	M	C6	Post + Ant	Yes	70	84	82	5

Ant anterior, *C* cervical, *F* female, *h* hours, *Lami* laminectomy, *L* lumbar, *M* male, *No.* number, *Post* posterior, *Pt.* patient, *T* thoracic, *y* years

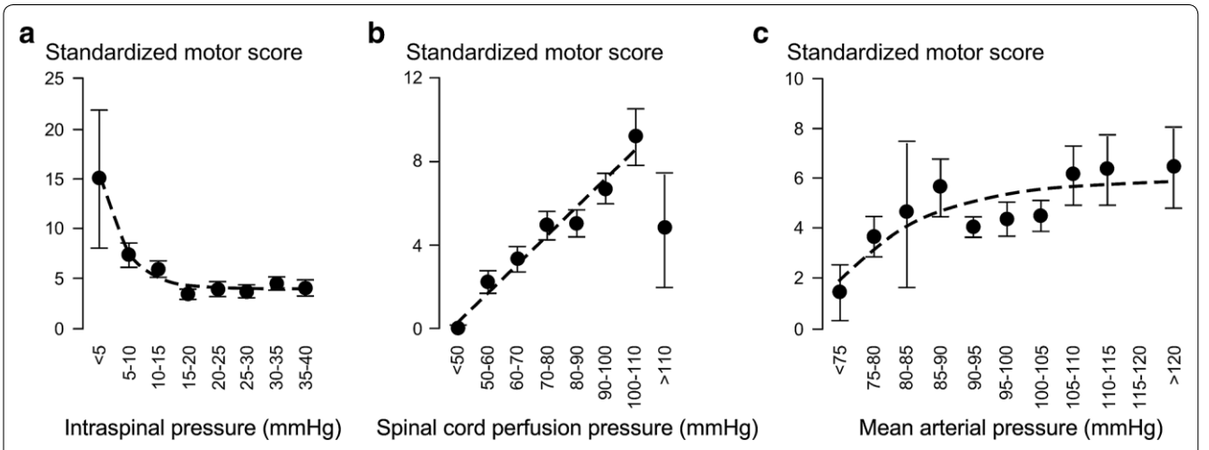


Fig. 2 Standardized motor score correlates with injury site physiology. Standardized motor score versus **a** intraspinal pressure, **b** spinal cord perfusion pressure and **c** mean arterial pressure. Mean ± standard error. Trends (dotted gray line) modeled as exponential decay (intraspinal pressure, $R^2 = 0.98$, $P < 0.0005$), linear (spinal cord perfusion pressure in the range < 50 to 110 mmHg, $R^2 = 0.96$, $P < 0.0005$), and bounded exponential (Mean arterial pressure, $R^2 = 0.73$, $P < 0.05$)

score (y) versus SCPP class ($x = 1$, …, 7, respectively, defined as 40–50, …, 100–110 mmHg). Increasing SCPP from < 50 mmHg, up to 110 mmHg, is associated with an average gain of about 8–9 motor points. Increasing SCPP beyond 110 mmHg is associated with a reduction in motor score. The curve $y = -0.1 + 6.0(1 - e^{-0.4x})$ fits well with the relation between average standardized motor score (y) versus MAP class ($x = 1$, …, 11, respectively, defined as < 75, …, > 120 mmHg). Increase in MAP from < 75 to 95 mmHg is associated with an average gain of about 4 motor points, whereas fluctuations in MAP in the range 95–130 mmHg are not associated with changes in average standardized motor score.

Motor Score Strongly Correlates with Injury Site Metabolism

Figure 3 shows that the line $y = -0.8x + 8.3$ fits well with the relation between average standardized motor score (y) versus LPR class ($x = 2$, …, 6, respectively, defined as 20–30, …, > 70), plotted using data from the 13 patients who had MD monitoring. Reducing the LPR from > 70 to 20–30 is associated with an average gain of about 4 motor points. Reducing the LPR below 20 is associated with a reduction in average standardized motor score. Increasing the LPR from 20–30 to 30–40 was associated with no change in pyruvate but increase in lactate. As LPR increases beyond 50, both pyruvate and lactate drop.

Injury Site Physiology and Metabolism Are Closely Related

Figure 4 shows how ISP is related to injury site metabolism. LPR (y) and ISP class ($x = 1$, …, 9, respectively, defined as < 5, …, > 40 mmHg) positively correlate according to $y = 5.0x + 20.5$. As ISP increases, glucose increases, whereas lactate and pyruvate fall. Figure 5 shows how SCPP is related to injury site metabolism. LPR (y) and SCPP class ($x = 1$, …, 8, respectively, defined as < 60, …, > 120 mmHg) negatively correlate according to $y = -4.3x + 54.3$. As SCPP increases up to 110 mmHg, glucose remains constant, whereas lactate and pyruvate slightly increase. As SCPP increases beyond 110 mmHg, glucose and pyruvate rise, whereas lactate falls.

Causality Analysis

Granger-causal relations between the motor score, ISP, SCPP, and LPR time series are illustrated in Fig. 6. Increasing LPR Granger-causes increased ISP, decreased SCPP, and decreased motor score. In other words, worse injury site metabolism increases cord swelling, reduces cord perfusion, and increases limb weakness. Increasing SCPP Granger-causes decreased LPR and increased motor score. In other words, improving spinal cord perfusion improves spinal cord metabolism and improves limb weakness. Increasing ISP Granger-causes increased LPR, decreased SCPP, and decreased motor score. In other words, increased cord swelling reduces cord perfusion, worsens cord metabolism, and increases limb weakness.

Discussion

Key Results

We showed that, after spinal cord injury, fluctuations in injury site physiology (cord edema, cord perfusion) and metabolism (LPR) Granger-cause fluctuations in limb power. These causal relations between events at the

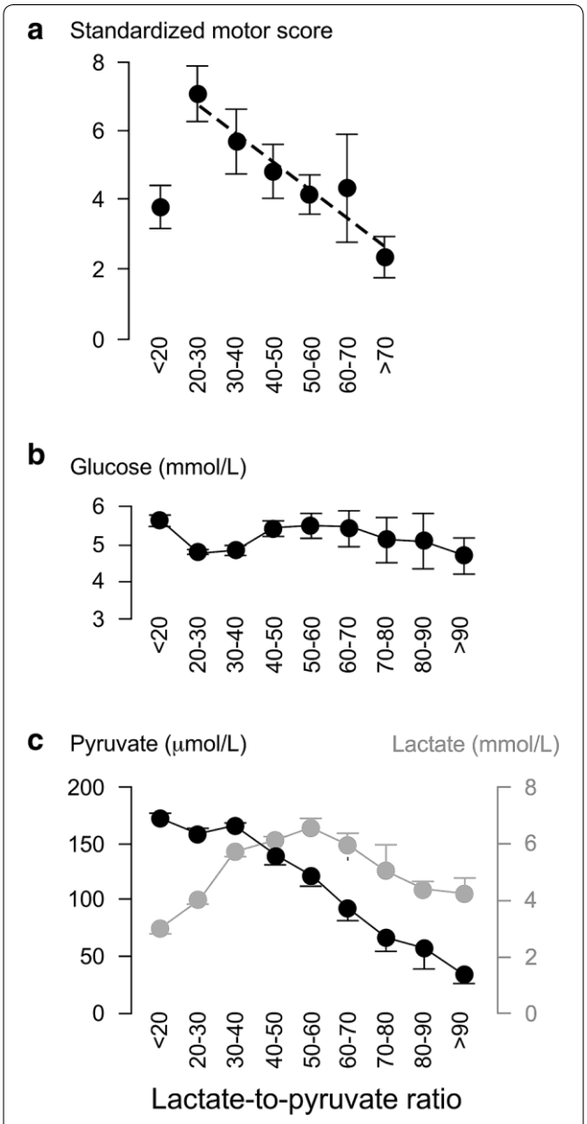


Fig. 3 Standardized motor score correlates with injury site metabolism. **a** Relation between standardized motor score and lactate-to-pyruvate ratio. **b** Glucose and **c** Lactate + Pyruvate versus lactate-to-pyruvate ratio. Mean ± standard error. In a, the dotted line is the best fit straight line for lactate-to-pyruvate ratio in the range 20 to > 70 mmHg, $R^2 = 0.92$, $P < 0.005$

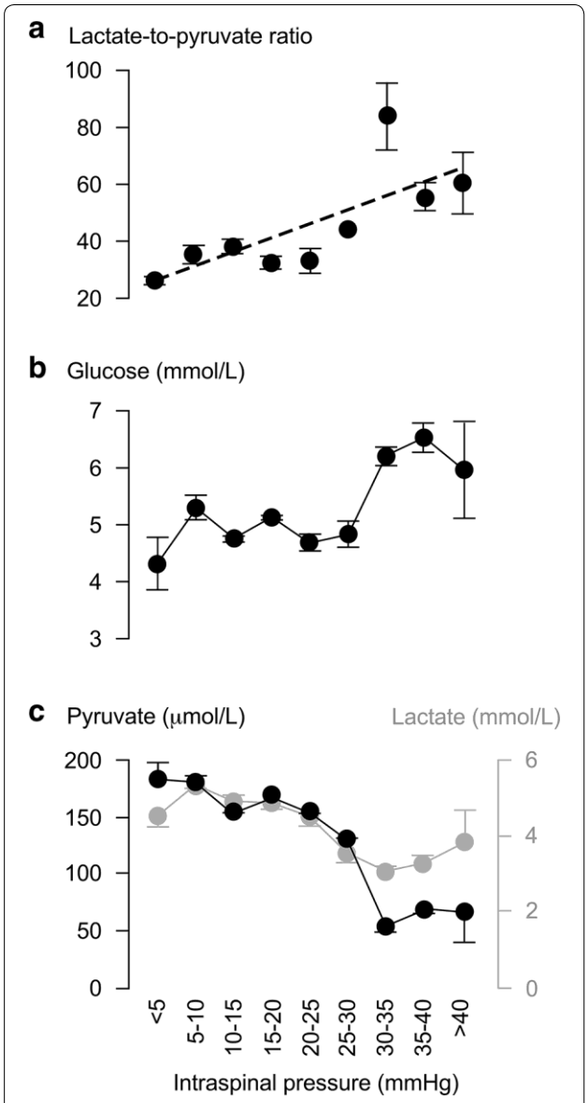


Fig. 4 Intraspinal pressure correlates with injury site metabolism. **a** Tissue glucose, **b** tissue lactate-to-pyruvate ratio and **c** tissue pyruvate (black) + lactate (gray), versus Intraspinal pressure. Mean ± standard error. In a, best fit straight line $R^2 = 0.57$, $P < 0.05$

injury site and limb power were established by monitoring patients with acute, motor-incomplete spinal cord injuries.

Limitations

Though the study has a relatively small number of patients (19), our conclusions are supported by a large amount of monitoring data including 2,306 h of ISP and SCPP monitoring, 1,703 h of MD monitoring and 366 motor examinations. Another issue is that causality is a deeply philosophical concept with many possible answers that do not satisfy everyone, compared with our definition of causality, which is purely mathematical.

Granger Causality

Establishing causation in medicine is based on the totality of evidence that includes strong association, biological mechanism, consistent finding, temporal sequence,

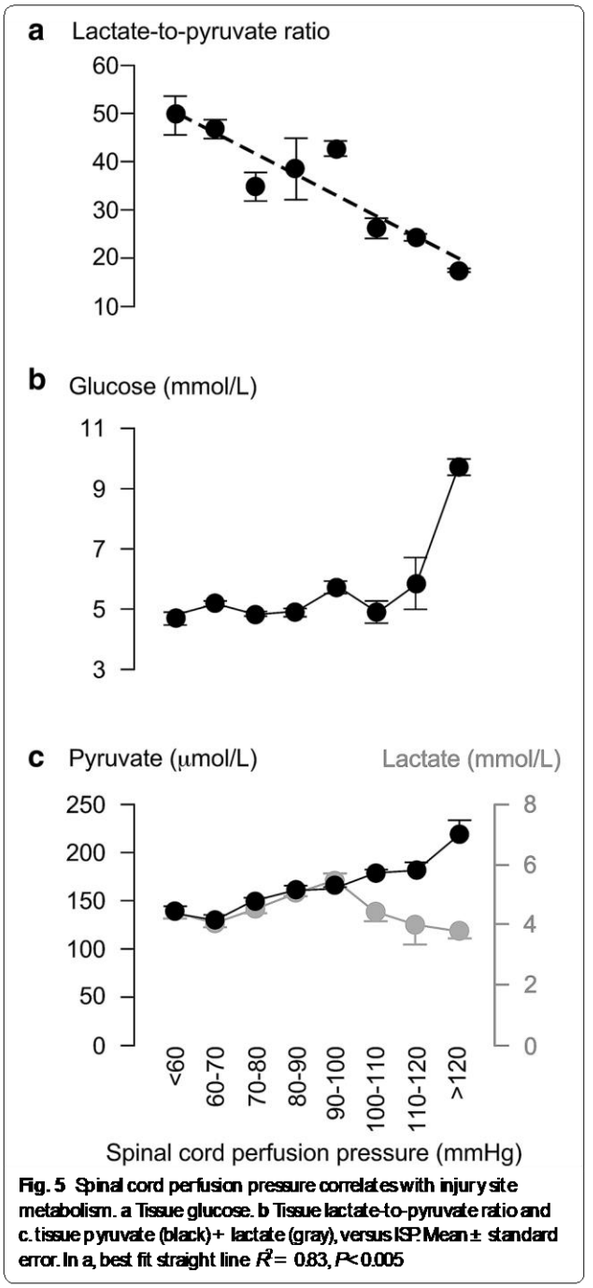


Fig. 5 Spinal cord perfusion pressure correlates with injury site metabolism. a Tissue glucose. b Tissue lactate-to-pyruvate ratio and c. tissue pyruvate (black)+ lactate (gray), versus ISP. Mean ± standard error. In a, best fit straight line $R^2 = 0.83$, $P < 0.005$

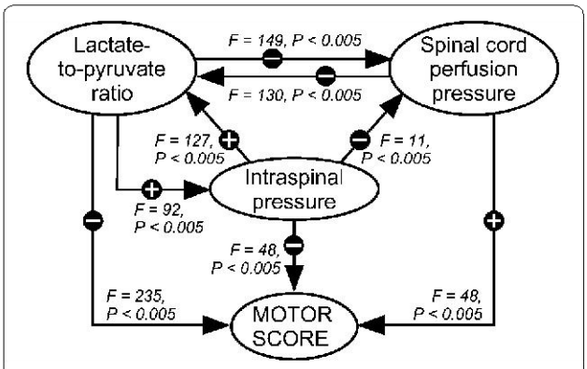


Fig. 6 Granger causality relations. Each arrow indicates the direction of information flow, i.e., causal influence, with corresponding *F* and *P* values. '+ ' or '–' indicate the correlation between the variables. Causality arrows are shown if $P < 0.05$. Analysis is shown for lag = 1, but also holds for lag = 2 or 3. For details, see supplement

and dose–response [33]. In the absence of a randomized trial, which is considered the "gold standard" to establish causation [34, 35], we investigated causal relations in our observational data using Granger analysis [27, 28]. Granger's definition of causality, initially developed for financial forecasting, satisfies two intuitive notions: First, the cause always precedes the effect. Second, the cause carries unique information about the future effect, i.e., there is information flow from the past of the cause to the future of the effect that cannot be accounted for by the past of the effect. Implicit in these notions is that intervention to alter the cause should result in a predictable change in the future of the effect. Advantages of Granger are that it is expressed in relatively straightforward mathematics that permit hypothesis testing and provide information about the strength of each causality [34, 35]. Alternative analyses that can distinguish between causation and correlation may be performed, e.g., convergent cross mapping, which is based on complexity theory and, unlike Granger, does not assume linear relations [36].

Interpretation of Correlations

Multiple correlations between injury site physiology, metabolism, and neurological status were defined. Here, we highlight some interesting findings: First, optimal ISP is less than 5 mmHg, i.e., no cord compression. Second, increase in ISP from 20 to 40 mmHg is associated with increase in LPR, but no reduction in limb power, probably because the standardized motor score is already very low. ird, as SCPP increases, LPR decreases (less ischemia) and limb power improves but, beyond 110 mmHg, limb power decreases, suggesting that hyperperfusing the injury site is detrimental. Metabolically, hyper-perfusion is characterized by very low (less than 20) LPR and high glucose; though this is aerobic metabolism, our data suggest that the high glucose is detrimental as previously reported [37–39] due to increased endoplasmic reticulum stress, inflammation and free radicals. Fourth, increasing the MAP beyond 85–90 mmHg, which remarkably corresponds to the recommended target [40], does not improve limb power. A possible explanation is that low MAP indicates injury site ischemia

regardless of ISP, but above 90 mmHg, the same MAP corresponds to injury site ischemia in some patients and hyper-perfusion in others. In practical terms, increasing the SCPP improves limb power more than increasing the MAP. Fifth, the correlations between ISP and SCPP versus limb power are reminiscent of similar relations versus neurological improvement at 9–12 months [20]. Sixth, though there is inverse correlation between LPR and limb power, LPR below 20 appears detrimental likely related to hyper-perfusion state described above. Seventh, as LPR increases up to 50–60, pyruvate decreases and lactate increases (indicating compensatory switch from aerobic to anaerobic metabolism at the injury site), but as LPR increases beyond 60, both pyruvate and lactate decrease (indicating overall suppression of aerobic and anaerobic metabolism). Though the findings described here provide a unique insight into how spinal cord physiological and metabolic events relate to limb power, they are associations that do not imply causations.

Interpretation of Causal Effects

The causal relations between LPR, SCPP, ISP, and standardized motor score in Fig. 6 make biological sense. A metabolic insult (high LPR, e.g., from hypoxia or infection) Granger-causes cord swelling (high ISP), Granger-causes reduction in cord perfusion, and Granger-causes impaired neuronal function (reduced motor score). Increase in spinal cord perfusion Granger-causes increase in aerobic metabolism at the injury site (decreased LPR) and Granger-causes the motor score to improve. Cord swelling (increase in ISP) Granger-causes more anaerobic metabolism (LPR increases), Granger-causes drop in SCPP (=MAP – ISP) and Granger-causes reduction in limb power. Interestingly, Granger analysis did not produce absurdities, e.g., change in limb power Granger-causes physiological or metabolic changes at the injury site. A key finding in Fig. 6 is several positive feedback loops (vicious cycles), e.g., increased LPR Granger-causes increased cord swelling, in turn Granger-causing increase in LPR. Multi-step vicious cycles are also evident, e.g., increased LPR Granger-causes increased cord swelling, which Granger-causes decreased SCPP, in turn Granger-causing increase in LPR. The presence of so many vicious cycles implies that insults to the injury site (e.g., hypoxia, acidosis, etc.) are amplified, thus emphasising the importance of treating such insults to prevent secondary cord damage.

Implications for Treatment

ISP is increased by cord compression from bone fragments, hematoma, and dura. Decompression of the injured cord including duroplasty would reduce ISP [41]. MAP may be increased using vasopressors [30]. Reducing ISP and increasing MAP will, in turn, increase SCPP. Interventions to reduce LPR (other than reducing ISP and increasing SCPP) include management of hypoxia, fever, and acidosis (e.g., limiting blood loss during surgery) [21, 32].

Generalizability

To study the relations between physiological/metabolic events at the injury site and limb power, we focused here only on AIS C TSCI patients. Our key conclusion that reducing ISP, increasing SCPP, and reducing LPR improve neurological status is likely to apply to all injury severities. Future studies may explore this further, e.g., by determining the effect of increasing SCPP on sensory level in AIS A and B TSCI patients.

Conclusions

The causal relationships described here suggest that interventions to normalize LPR, SCPP, and ISP are likely to improve limb power in AIS C TSCI patients.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s12028-020-00988-2) contains supplementary material, which is available to authorized users.

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Author Contribution
FRAH collected and analyzed data. SK collected data. AZ anesthetized the patients and looked after them in the ICU. MCP operated on the patients and had overall responsibility for their clinical care. SS analyzed data, plotted graphs, wrote the manuscript and had overall supervision of the project. All authors read and approved the final manuscript.

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Conflict of interest
All authors have no conflicts of interest.

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Effects of local hypothermia–rewarming on physiology, metabolism and inflammation of acutely injured human spinal cord

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In five patients with acute, severe thoracic traumatic spinal cord injuries (TSCIs), American spinal injuries association Impairment Scale (AIS) grades A–C, we induced cord hypothermia (33 °C) then rewarming (37 °C). A pressure probe and a microdialysis catheter were placed intradurally at the injury site to monitor intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP), tissue metabolism and inflammation. Cord hypothermia–rewarming, applied to awake patients, did not cause discomfort or neurological deterioration. Cooling did not affect cord physiology (ISP, SCPP), but markedly altered cord metabolism (increased glucose, lactate, lactate/pyruvate ratio (LPR), glutamate; decreased glycerol) and markedly reduced cord inflammation (reduced IL1β, IL8, MCP, MIP1α, MIP1β). Compared with pre-cooling baseline, rewarming was associated with significantly worse cord physiology (increased ICP, decreased SCPP), cord metabolism (increased lactate, LPR; decreased glucose, glycerol) and cord inflammation (increased IL1β, IL8, IL4, IL10, MCP, MIP1α). The study was terminated because three patients developed delayed wound infections. At 18-months, two patients improved and three stayed the same. We conclude that, after TSCI, hypothermia is potentially beneficial by reducing cord inflammation, though after rewarming these benefits are lost due to increases in cord swelling, ischemia and inflammation. We thus urge caution when using hypothermia–rewarming therapeutically in TSCI.

Hypothermia is being investigated as a potential therapy for traumatic brain injury (TBI)[1] and traumatic spinal cord injury (TSCI)[2] based on compelling evidence from several laboratories and animal species that hypothermia is neuroprotective. In animal models of TBI, hypothermia has been shown to target many pathological processes including reducing the metabolic rate, inflammation, edema, oxidative stress, excitotoxicity, electrolyte imbalance as well as apoptotic and necrotic cell death in vulnerable tissue[3–8]. Despite the encouraging findings of animal studies, randomized controlled human trials have failed to show functional benefit of hypothermia in TBI patients[1,9,10]. Therapeutic hypothermia is also beneficial in animal models of TSCI: rodent models of TSCI show improved histological and functional outcomes after hypothermia[11,12]. Small, non-randomized studies of TSCI patients also suggest improved functional outcomes after local[13,14] or systemic hypothermia[2,15]. To date, there are no published randomized controlled trials of hypothermia for TSCI.

Despite the wide interest in therapeutic hypothermia for CNS injuries, there is paucity of mechanistic data from humans regarding the effect of hypothermia on the injury site. In TSCI patients, the effect of cooling and rewarming on cord swelling, metabolism and inflammation are unknown. It is thus unclear if hypothermia and

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rewarming have beneficial or adverse effects on the injured human spinal cord. The lack of mechanistic information from TSCI patients is due to the lack of advanced monitoring from the injury site. Our group has developed techniques to monitor intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP) and tissue metabolism from the injury site[16–23]. Here, we applied our monitoring techniques to define the effect of local hypothermia and rewarming on injury site physiology, metabolism and inflammation in TSCI patients.

Methods

Institutional research board approvals. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (World Medical Association Declaration of Helsinki 2000). Hypothermia–rewarming was approved as a sub-study (Amendment 7) of the ISCoPE (Injured Spinal Cord Pressure Evaluation) study for TSCI. Written consent was obtained from all patients. The hypothermia study, including the patient information sheet and the consent form, was approved by the St George's, University of London Joint Research Office and the National Research Ethics Service London–St Giles committee (no. 10/H0807/23). ISCoPE is registered as NCT02721615 at UK Clinical trials gateway since 01/09/2010 and at ClinicalTrials.gov since 29/03/2016. The study protocol, patient consent form, patient information sheet and Amendment 7 are enclosed.

Inclusion/exclusion criteria. This prospective patient cohort was recruited between September 2016 and February 2017. Inclusion criteria were: (1) Severe TSCI defined as American spinal injuries association Impairment Scale (AIS) grade A, B, or C; (2) Age 18–70 years; (3) Surgery within 72 hours of TSCI; (4) Thoracic injury (we excluded cervical injuries because of the length of the cooling balloon). Exclusion criteria were: (1) Other major co-morbidities or concurrent injuries; (2) Penetrating TSCI; (3) No consent.

Clinical assessments and investigations. Examinations were performed according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) on admission, before discharge to the spinal rehabilitation facility (4–8 weeks) and during outpatient follow-ups (6–29 months). The patients were assessed by a neurosurgical TSCI research fellow trained in the ISNCSCI examination. CT and MRI scans of the whole spine were obtained on admission, a post-operative CT was done at 24–48 hours after surgery and a post-operative MRI after probe removal. On the Neuro-Intensive Care Unit (NICU), core temperature was recorded continuously from a urinary catheter temperature probe.

Spinal fixation. Surgery was done posteriorly and aimed to restore the normal spinal alignment with laminectomies for bony decompression. Pedicle screws were inserted two levels above and two levels below the fracture and were linked with rods secured with blockers, using the Xia 3 system (Stryker, Newbury, UK).

ISP probe and microdialysis catheter. An ISP probe (Codman Microsensor Transducer, Depuy Synthes, Leeds, UK) and a MD catheter (CMA 61, CMA microdialysis AB, Sweden) were tunnelled through the skin into the wound cavity. Under the operating microscope, the dura and arachnoid were opened one level below the injury. The ISP probe and MD catheter were inserted through the durotomy and advanced on the cord surface until the tips were at the site of maximal cord swelling. The dural opening was sutured and supplemented with Tisseel (Baxter, UK). The ISP probe and MD catheter were sutured to the skin. These techniques are described in detail in our earlier publications[16–23].

Cooling catheter. A sterile cooling balloon, part of a closed catheter loop system (Cool line catheter, Zoll medical, Cheshire, UK), and sterile thermometer (Smiths Medical, Ashford, UK) were tunnelled into the wound cavity and placed extradurally. A wound drain was inserted for a week and was set 'under gravity'. The wound was closed in layers using vicryl sutures with nylon sutures for the skin. We gave 5,000 units dalteparin daily, starting at 24 hours after surgery. Dalteparin was omitted at 24 hours before and at 6 hours after removing the probes and wound drain. Prophylactic intravenous vancomycin/gentamicin were administered for 48 hours as per hospital protocol. In NICU, the wound was covered with an electric warming blanket set at 37 °C (CosyTherm mattress, Inspiration healthcare, Rotherham, UK).

Monitoring setup. The ISP probe was connected to a Codman ICP box linked by a ML221 amplifier to a PowerLab running LabChart software (version 7.3.5; ADInstruments). Arterial blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz for 7 days. LabChart was used to analyze the signals and compute SCPP, defined as MAP minus ISP. We previously showed that ISP measured this way is different from intrathecal pressure measured above or below the injury site because the swollen, injured cord is compressed against the surrounding dura thus compartmentalising the intrathecal space[18,22,23]. MD monitoring was started postoperatively in the NICU. CNS perfusion fluid (CMA Microdialysis AB, Sweden) was perfused at 0.3 µL/min using the CMA106 infusion pump (CMA Microdialysis AB, Sweden). MD vials were changed hourly and stored at 4 °C. The first two samples from each patient were discarded to allow priming of the MD catheter and stabilization of metabolite concentrations. Samples were batch-analyzed up to 24 hours later using ISCUS Flex (CMA Microdialysis AB, Sweden) for glucose, lactate, pyruvate, glycerol, glutamate and lactate-to-pyruvate ratio (LPR). 100-fold changes in metabolite concentration, and 10-fold changes in LPR, compared with the preceding hour, were excluded. We previously showed that our MD method measures injury site surface metabolism, which correlates well with intraparenchymal metabolism ($r = 0.56–0.91$), but differs from metabolites measured from the lumbar cerebrospinal fluid (CSF) ($r = 0.23–0.50$)[16–18].

Cytokines/chemokines. 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 spinal cord injury (see supplement), they are <30 kDa (i.e. can cross the MD membrane) and they are part of our multiplex electrochemiluminescence assay panel. For each patient, MD vials were grouped by sampling period: 6 hours pre-cooling, 6 hours at 33 °C and 6 hours post-rewarming i.e. at 37 °C. MD vials, each containing about 10 μL, were stored at −80 °C and analyzed 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 (K15067L): IL1α, IL1β, IL4, IL8, IL10, IP10, GROα, MCP1, MIP1α, MIP1β. 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. 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.

Cooling-rewarming. A closed temperature system pumping sterile saline into the balloon catheter (Thermoguard XP temperature management system, Zoll Medical, Cheshire, UK) was connected at the bedside in NICU. Cooling was started at 12 hours after surgery, thus allowing baseline cord physiological and MD measurements to be obtained. In the first patient, the target temperature was reduced by 1 °C every 12 hours (37 to 33 °C). This slow reduction allowed real-time analysis of microdialysis samples and repeat neurological examinations to ensure no deterioration. After 12 hours at 33 °C, the cord was rewarmed to 37 °C at 0.5 °C/hour. In subsequent patients, the cord was cooled to 33 °C in one step and, after 72 hours, rewarmed at 0.5 °C/hour to 37 °C.

Data analysis and statistics. For ISP, SCPP and metabolites, we compared the 12 values at 37 °C immediately preceding hypothermia (taken hourly) *vs*. the 12 values at 33 °C (taken hourly) *vs*. the first 12 values at 37 °C i.e. post-rewarming (taken hourly). For cytokines/chemokines, we compared the 6 values at 37 °C immediately preceding hypothermia (taken hourly) *vs*. 6 values at 33 °C (taken hourly) *vs*. the first 6 values at 37 °C i.e. post-rewarming (taken hourly). In each case, the three temperature groups (pre-hypothermia, hypothermia, post-rewarming) were compared pairwise by Kruskal-Wallis + post-hoc Dunn-Bonferroni. Analysis was done using XLStat Biomed version 2018.1 for Mac (Addinsoft, Paris, France). Statistical significance was taken as $P < 0.05$.

Results

Patient details. We recruited five consecutive patients with severe thoracic TSCIs (Fig. 1). Most were young (aged 45.4 ± 7.1 years, mean ± standard error) and male (66.7%). The delay between TSCI and surgery was 47.4 ± 9.6 hours and the injury to cooling time 70.4 ± 9.3 hours. At 18.2 ± 5.1 months follow up, total motor score increased by 8.8 ± 8.5, total pin prick score by 6.8 ± 6.5 and total light touch score by 2.6 ± 2.5 points. Overall, two patients (40%) had improved by at least one AIS grade. For further details see Table 1 and Fig. 1a. Subsequent analysis includes all patients.

Cooling–rewarming. Local hypothermia and rewarming were well tolerated without causing pain, discomfort or shivering. Throughout the cooling and rewarming phases, all patients remained alert, orientated and self-ventilating with no changes in their neurological examinations. Details of our setup for cooling–rewarming and monitoring are shown in Fig. 1b,c. Except for the first patient (PT 49), who was subjected to a slow cooling protocol for safety, all subsequent patients reached the target extradural temperature of 33 °C in 20 minutes. In all patients, the cooling protocol reduced the extradural temperature to the target value without causing a significant change in the core temperature (Fig. 2).

Injury site physiology. In the 12 hours before the start of the cool–rewarm protocol, baseline spinal cord ISP was 12.7 mmHg and SCPP at 83.3 mmHg with MAP at 93.1 mmHg. Cooling from 37 to 33 °C did not produce any significant changes in ISP, SCPP or MAP. Rewarming from 33 to 37 °C was associated with significant increase in ISP by 13.2 mmHg and significant decrease in SCPP by 14.6 mmHg compared with corresponding average pre-cooling baseline levels, whereas MAP remained unaffected. For further details see Fig. 3.

Injury site metabolism. In the 12 hours before the start of the cool-rewarm protocol, baseline spinal cord tissue glucose concentration was 2.3 mM, tissue lactate 5.1 mM, tissue pyruvate 148.5 μM, tissue LPR 33.9, tissue glutamate 10.9 μM and tissue glycerol 54.5 μM. Cooling and rewarming had a major impact on injury site metabolism. Cooling was associated with significant increase in tissue glucose by 1.0 mM, significant increase in lactate by 1.9 mM, no change in pyruvate, significant increase in LPR by 113.0, significant increase in glutamate by 6.4 μM and significant decrease in glycerol by 13.4 μM. Compared with average pre-cooling baseline levels, rewarming was associated with significant decrease in tissue glucose by 0.9 mM, significant increase in lactate by 3.9 mM, no change in pyruvate, significant increase in LPR by 314.9, no change in glutamate by 6.4 μM and significant decrease in glycerol by 30.0 μM. For details see Fig. 4.

Injury site inflammation. In the 12 hours before the start of the cool-rewarm protocol, baseline spinal cord IL1α concentration was 5.6 pg/mL, tissue IL1β was 13.5 pg/mL, tissue IL8 was 2,013.9 pg/mL, tissue IL4 was 0.3 pg/mL, tissue IL10 was 1.0 pg/mL, tissue IP10 was 66.4 pg/mL, tissue MCP1 was 1,821.5 pg/mL, tissue MIP1α was 67.0 pg/mL, tissue MIP1β was 111.2 pg/mL and tissue GROα was 268.8 pg/mL. The concentrations of injury site inflammatory cytokines significantly decreased with cooling by 62.8% for IL1β, 87.1% for IL8, 58.7% for MCP1, 69.8% for MIP1α and 37.0% for MIP1β. Compared with hypothermia, there was rebound significant increase in the concentrations of inflammatory cytokines on rewarming by 465 .3% for IL1β, 606.1% for IL8,

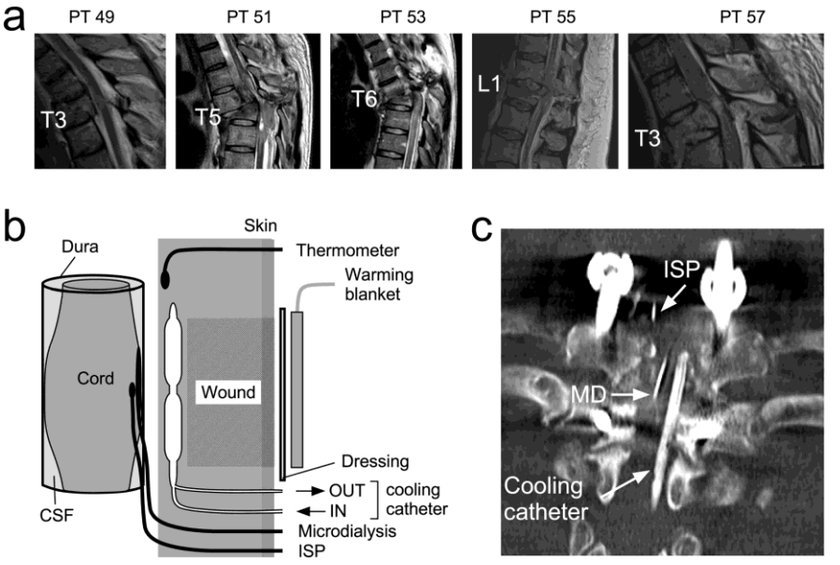


Figure 1. Setup. (**a**) Sagittal T2 pre-operative spinal MRI of the five patients (ISCoPE No. 49, 51, 53, 55, 57). Label shows fractured vertebra. (**b**) Schematic of setup for monitoring and cooling produced using Canvas Draw 3 for MacOS, https://www.canvasgfx.com/en/products/canvas-draw/. ISP probe and microdialysis catheter lie intradurally, on the surface of the injured cord. Cooling catheter and thermometer are extradural. A heating pad is placed on the skin. (**c**) Post-operative spinal CT showing ISP probe, microdialysis (MD) and cooling catheters.

PT	Age	Sex	Injury to surgery (hours)	Injury to cooling (hours)	Injury level	Admission				Followup				Followup (months)
						AIS	TMS	TPP	TLT	AIS	TMS	TPP	TLT	
49	66	F	65	88	T3	B	50	54	54	D	89	83	61	29
51	36	M	49	71	T5	A	50	52	52	A	50	48	48	25
53	30	M	21	45	T6	A	50	52	52	A	50	52	52	22
*55	52	F	36	60	L1	A	51	81	80	B	56	88	88	6
57	43	M	66	88	T3	A	50	40	40	A	50	42	42	9

Table 1. Demographics of the five patients in the study. F, Female; M, Male; AIS, American spinal injuries association Impairment Scale; PT, patient; TLT, total light touch score; TMS, total motor score; TPP, total pin prick score; *No cooling, equipment failure.

241.6% for IL4, 848.1% for IL10 and 222.4 for MIP1α. A markedly, though statistically non-significant rise in cytokine/chemokine concentration after rewarming was also observed for IL1α, IP10, and GROα. Compared with baseline, after rewarming the levels of IL1α, IL1β, IL4, IL10, IP10, MIP1β and GROα were higher whereas the levels of IL8, MCP1 and MIP1α were lower; these changes were not significant except for MCP1. For details see Fig. 5.

Complications. Spinal cord cooling and rewarming was associated with complications, summarized in Table 2. In 1/5 (20%) patients, the equipment failed; there was a hole in the cooling catheter balloon that allowed the cooled sterile saline fluid to enter the wound cavity and leave through the wound drain. In this patient, cooling was stopped and the catheter was removed. Three of the five (60%) patients had culture positive delayed wound infections; in two of the three patients, we performed wound washout under general anesthetic. These three patients received antibiotics with the metalwork *in situ* and recovered with no deterioration in ISNCSCI neurological scores. In contrast, we have reported no wound infections in 42 consecutive patients that had spinal cord monitoring without hypothermia[21]. After discussion with the sponsors was well as our neurosurgical, intensive care unit and microbiology colleagues, the decision was taken to prematurely terminate the study.

Outcomes. At a mean follow-up of 36 weeks, 2/5 (40%) patients improved AIS grade, one from A to B and the other from B to D. We observed increase in mean ISNCSCI total motor score by 8.8 points (0–39), pin prick

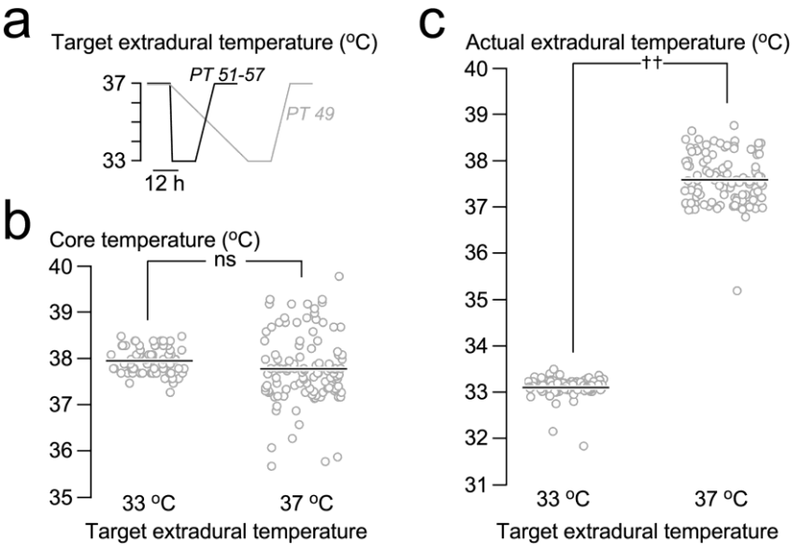


Figure 2. Relations between various temperatures. (**a**) Extradural cool/rewarm regime. (**b**) Core temperature at target extradural temperatures 33 and 37 °C. (**c**) Actual extradural temperature at target extradural temperatures 33 and 37 °C. (**b,c**) Show raw data and mean. Not significant ns, $P < 0.0001^{††}$.

sensation of 6.8 points (−4–29) and total light touch sensation of 2.6 points (−4–8). The wounds appeared well-healed at follow-up.

Discussion

We employed local hypothermia aiming to avoid the side effects of systemic hypothermia i.e. coagulopathy, electrolyte disturbances, myocardiac ischemia, atrial fibrillation, sepsis, pneumonia and altered drug metabolism[24]. Our key findings are that, during hypothermia–rewarming in awake TSCI patients, there is no discomfort or shivering and no change in ISNCSCI motor and sensory scores. The hypothermia phase was potentially beneficial, by reducing injury site inflammation, though during the rewarming phase these benefits were lost due to rebound increases in injury site swelling, ischemia and inflammation. The study was terminated early because of delayed wound infections in 60% of patients. The major weaknesses of our study are the small sample size and the lack of a control group.

In a previous study of local hypothermia, cooling was induced within 7 hours of TSCI at a rapid rate using an extradural device set at 6 °C; hypothermia lasted 3–4 hours with rapid rewarming[13]. In comparison, we started hypothermia later on, cooled within 20 min (apart from the first patient) to 33 °C for 12 hours and rewarmed slowly at 0.5 °C/h. It has been suggested that slower rewarming (<0.5 °C/h) might be more beneficial[25]. We do not know whether earlier onset hypothermia or more prolonged hypothermia or slower rewarming might have shown beneficial effects on ISP, SCPP, cord metabolism and cord inflammation. Because our study was terminated early; we were unable to study the effects of these changes on the injured spinal cord.

Hypothermia had no significant impact on baseline ISP, whereas rewarming was associated with a marked rebound rise in ISP by 13.2 mmHg. Since the MAP remained constant throughout, the ISP rise caused a marked drop in SCPP by 14.6 mmHg. These findings mirror observations in human TBI, where hypothermia caused non-significant decrease in intracranial pressure (ICP)[9,10] and rewarming caused rebound rise in ICP[26]. The effects of hypothermia–rewarming on ICP may be related to blood flow changes, i.e. vasoconstriction during hypothermia and vasodilatation during rewarming[27]. In our patients, baseline ISP was not elevated, at 12.7 mmHg, which may explain why hypothermia did not reduce ISP. The ISP rise we observed after rewarming may have been caused by increased inflammation within the injured cord related to reperfusion. There is substantial evidence that during reperfusion, leukocytes become activated to release multiple inflammatory factors[28], consistent with the marked rise in the tissue cytokines/chemokine levels observed here.

Hypothermia was associated with a rise in tissue glucose, lactate and LPR without change in pyruvate. Rewarming was associated with a marked fall in tissue glucose, rise in lactate and LPR, again with constant pyruvate. Hypothermia is known to reduce cellular metabolism and, in brain, for every 1 °C drop in temperature, there is a 6% drop in cerebral metabolic rate, which is expected to reduce glucose consumption at the injury site[27], thus explaining the rise in tissue glucose concentration. After rewarming, the cord tissue glucose level fell probably due to increased cellular utilisation. In the brain, lactate is not only a by-product of anaerobic metabolism, but may

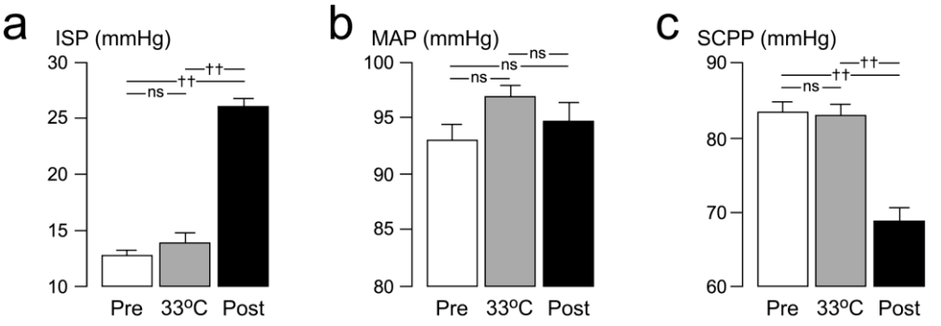


Figure 3. Effect of cooling-rewarming on ISP, MAP and SCPP. (**a**) ISP, (**b**) MAP and (**c**) SCPP for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 °C) and for 24 h after the end of rewarming (black, Post). Mean + /− standard error. Not significant, ns; $P < 0.0001^{††}$.

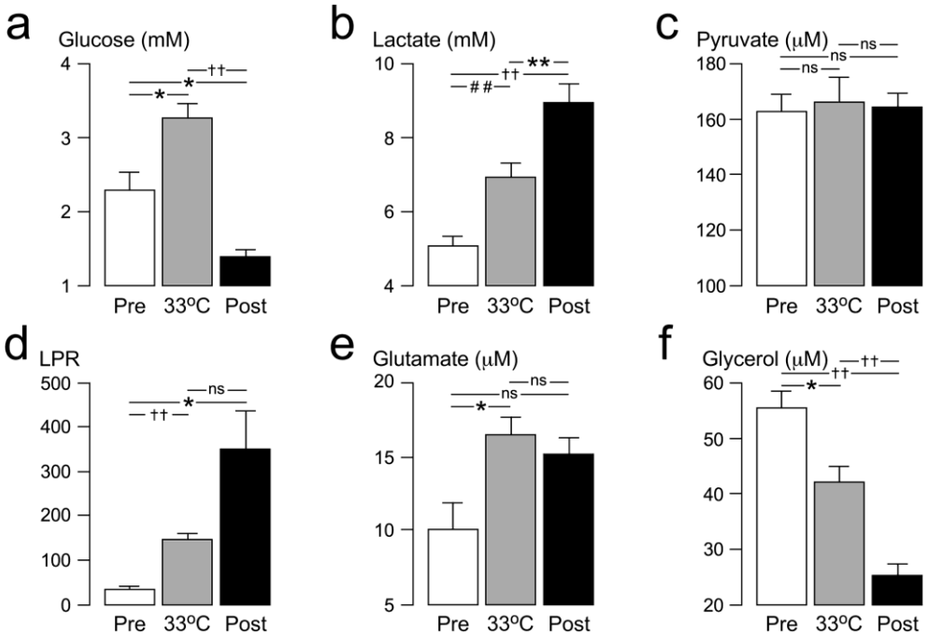


Figure 4. Effect of cooling-rewarming on injury site metabolites. (**a**) Glucose, (**b**) Lactate, (**c**) Pyruvate, (**d**) Lactate-to-pyruvate ratio (LPR), (**e**) Glutamate and (**f**). Glycerol. Metabolite levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 °C) and for 24 h after the end of rewarming (black, Post). Mean + /− standard error. ns not significant, $P < 0.05^{*}$, $<0.001^{\#\#}$, $<0.0001^{††}$.

also be a neuronal energy substrate[29]. Several mechanisms may thus account for the rise in tissue lactate, without change in tissue pyruvate, during hypothermia and rewarming e.g. depleted O_2 supply thus increased anaerobic metabolism, failure of pyruvate dehydrogenase thus diverting pyruvate to lactate rather than into the tricarboxylic acid cycle and increased uptake of lactate at the injury site from the circulation. The relative contributions of these mechanisms may differ in hypothermia *vs.* rewarming. Whatever the underlying mechanisms, the main finding here is that hypothermia–rewarming is associated with a marked impairment of metabolism at the injury site.

Hypothermia–rewarming was also associated with rise in tissue glutamate and fall in tissue glycerol. Glutamate is an excitatory amino acid that causes excitotoxic damage to neurons, whereas glycerol is released

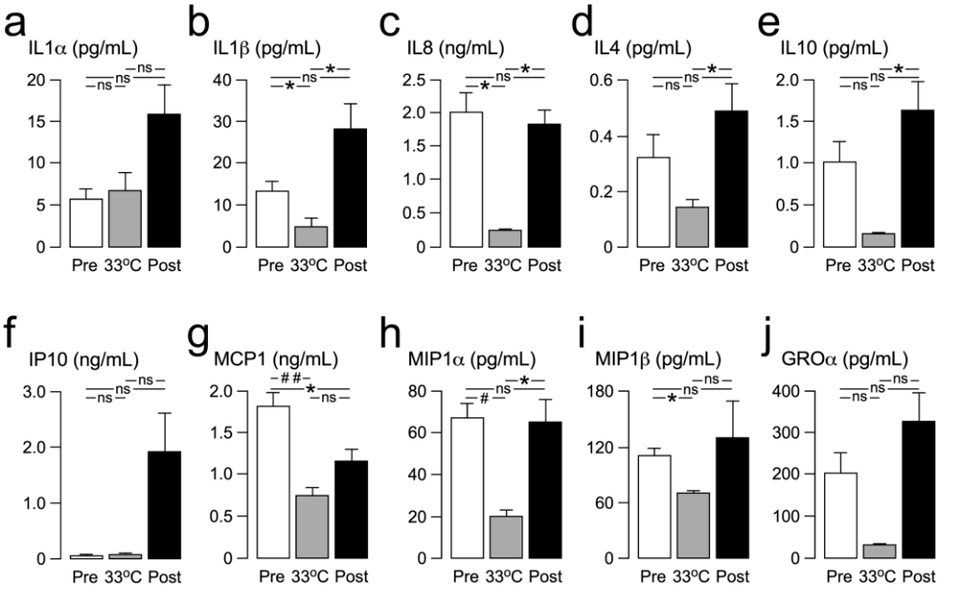


Figure 5. Effect of cooling-rewarming on injury site inflammatory mediators. (**a**) IL1α, (**b**) IL1β, (**c**) IL8, (**d**) IL4, (**e**) IL10, (**f**) IP10, (**g**) MCP1, (**h**) MIP1α, (**i**) MIP1β and (**j**). GROα. Mediator levels for 12 h before start of cooling (white, Pre), for 12 h at minimum temperature (gray, 33 °C) and for 24 h after the end of rewarming (black, Post). Mean + /- standard error. Not significant ns, $P < 0.05^{*}$, $<0.005^{\#}$, $<0.001^{\#\#}$.

Patient	Wound breakdown	Wound bacteria	Surgical wound treatment	Antibiotics	Outcome
49	Yes	*E. coli S. aureus*	Day 16 lumbar drain Day 43 debridement	52 days	Wound well-healed
51	No	No	No	No	Wound well-healed
53	No	*E. coli*	No	45 days	Wound well-healed
*55	No	No	No	No	Wound well-healed
57	Yes	*S. aureus*	Day 22 pus aspirated Day 24 debridement	56 days	Wound well-healed

Table 2. Wound complications of localized hypothermia. *No cooling, equipment failure.

into the extracellular fluid during plasma cell membrane lysis[30]. Interestingly, during the 12 hours before the onset of hypothermia, tissue glutamate was rising at a rate of 1.3 μM/h, whereas glycerol was decreasing at a rate of 2.6 μM/h. One possibility, therefore, is that changes in tissue glutamate and glycerol largely represent trends related to the timing from the injury rather than the effects of hypothermia or rewarming. In human TBI, hypothermia–rewarming is generally associated with reduced ventricular CSF glutamate[31]. Other possibilities to explain our observation of increased MD glutamate during hypothermia in TSCI are lack of strong correlation between CSF *vs*. MD glutamate, as we have recently shown[32], or even differences in the cell-level responses to traumatic injury of the spinal cord compared with the brain[33].

A striking finding in our study is the marked reduction in the concentrations of tissue cytokines/chemokines during hypothermia followed by rebound enhancement of tissue inflammation associated with rewarming, generally to above pre-hypothermia baselines. Several cell types likely secrete cytokines at the injury site including neutrophils, macrophages, microglia, lymphocytes, astrocytes and endothelial cells. The differential responses of these cytokines to hypothermia-rewarming may be due to differential responses of these cell types to hypothermia-rewarming. The effect of hypothermia in suppressing inflammation after TSCI mirrors findings in animal models[34] though the effect of rewarming on inflammation has not been investigated. On the one hand, the suppression of inflammation induced by hypothermia may be beneficial to the damaged spinal cord, but on the other hand it may predispose to wound infection. An earlier study reported a wound infection rate of 10%[13] and our study found 60% wound infection rate. Potential ways to reduce wound infection risk in future trials

include prolonged antibiotics and iodine impregnated occlusive dressings. The rebound increase in tissue inflammation is potentially detrimental to the injured cord e.g. by increasing vasogenic edema from breakdown of the blood-spinal cord barrier[28].

Based on our findings here, we urge caution when performing trials of hypothermia for TSCI without simultaneously monitoring from the injury site to determine in real time the impact on the injured spinal cord.

Data availability

All data generated or analyzed during this study are included in this published article.

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Author contributions
M.J.G. collected and analyzed data and wrote part of the manuscript. F.R.A.H. and S.K. collected data. M.K., C.B. and L.S. analyzed microdialysis samples and obtained the cytokine/chemokine data under the supervision of J.M.S. O.S. analyzed data. A.Z. anaesthetized the patients for surgery and looked after them in ICU. M.C.P. did the surgery, inserted the probes and supervised clinical management. SS provided overall supervision for the project, analyzed data and wrote the manuscript. All authors read and approved the final version.

Competing interests
The authors declare no competing interests.

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ORIGINAL WORK

Spinal Cord Perfusion Pressure Correlates with Anal Sphincter Function in a Cohort of Patients with Acute, Severe Traumatic Spinal Cord Injuries

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Abstract

Background: Acute, severe traumatic spinal cord injury often causes fecal incontinence. Currently, there are no treatments to improve anal function after traumatic spinal cord injury. Our study aims to determine whether, after traumatic spinal cord injury, anal function can be improved by interventions in the neuro-intensive care unit to alter the spinal cord perfusion pressure at the injury site.

Methods: We recruited a cohort of patients with acute, severe traumatic spinal cord injuries (American Spinal Injury Association Impairment Scale grades A–C). They underwent surgical fixation within 72 h of the injury and insertion of an intrathecal pressure probe at the injury site to monitor intraspinal pressure and compute spinal cord perfusion pressure as mean arterial pressure minus intraspinal pressure. Injury-site monitoring was performed at the neuro-intensive care unit for up to a week after injury. During monitoring, anorectal manometry was also conducted over a range of spinal cord perfusion pressures.

Results: Data were collected from 14 patients with consecutive traumatic spinal cord injury aged 22–67 years. The mean resting anal pressure was 44 cmH_2O, which is considerably lower than the average for healthy patients, previously reported at 99 cmH_2O. Mean resting anal pressure versus spinal cord perfusion pressure had an inverted U-shaped relation ($\hat{R}^2 = 0.82$), with the highest resting anal pressures being at a spinal cord perfusion pressure of approximately 100 mmHg. The recto-anal inhibitory reflex (transient relaxation of the internal anal sphincter during rectal distension), which is important for maintaining fecal continence, was present in 90% of attempts at high (90 mmHg) spinal cord perfusion pressure versus 70% of attempts at low (60 mmHg) spinal cord perfusion pressure ($P < 0.05$). During cough, the rise in anal pressure from baseline was 51 cmH_2O at high (86 mmHg) spinal cord perfusion pressure versus 37 cmH_2O at low (62 mmHg) spinal cord perfusion pressure ($P < 0.0001$). During anal squeeze, higher spinal cord perfusion pressure was associated with longer endurance time and spinal cord perfusion pressure of 70–90 mmHg was associated with stronger squeeze. There were no complications associated with anorectal manometry.

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Conclusions: Our data indicate that spinal cord injury causes severe disruption of anal sphincter function. Several key components of anal continence (resting anal pressure, recto-anal inhibitory reflex, and anal pressure during cough and squeeze) markedly improve at higher spinal cord perfusion pressure. Maintaining too high of spinal cord perfusion pressure may worsen anal continence.

Keywords: Anal sphincter, Anal manometry, Blood pressure, Spinal cord injury, Spinal cord perfusion pressure

Introduction

Traumatic spinal cord injury (TSCI) is a devastating event resulting in life-long disability, including limb weakness, bladder and bowel incontinence, sexual dysfunction, autonomic dysfunction, and, in cervical trauma, impaired breathing. TSCI affects approximately 180,000 people globally each year [1]. A major problem after TSCI is anal sphincter dysfunction from impaired control of the voluntary sphincter, impaired control of pelvic floor muscles, and impaired autonomic activity. Bowel function is ranked on par with limb weakness by patients with TSCI when prioritizing recovery goals [2]. Bowel dysfunction affects approximately 80% of patients with TSCI and is often ranked as more problematic than urinary incontinence or sexual dysfunction [3]. Fecal incontinence is common and often unpredictable. Constipation, diarrhea, and nausea are also commonly encountered, and most patients take drugs and require manual stimulation to defecate [4]. Such bowel regimens may consume a considerable amount of time.

Anal function may be assessed with anorectal manometry (ARM), which measures anal pressure (AP), rectal sensation, and the neural reflexes needed for normal defecation [5]. ARM allows the study of the sphincter when straining, resting, and squeezing to identify incontinence issues linked to the inability of the muscles to contract correctly and difficulties in defecating due to the incomplete opening and releasing of the sphincter muscles.

To improve the management of patients with TSCI in the neuro-intensive care unit (neuro-ICU), our group has developed monitoring from the injury site [6–9]. We monitor intraspinal pressure (ISP) and calculate spinal cord perfusion pressure (SCPP) as the mean arterial pressure (MAP) minus ISP. Monitoring is safe [10] and analogous to intracranial pressure and cerebral perfusion pressure monitoring for brain injury [11]. ISP and SCPP are clinically important parameters that correlate with injury-site metabolism [7, 12], neurological status [6, 13], urinary function [14], and long-term outcome [15].

Our objective was to test the effect of TSCI on anal function in the acute care setting. We performed ARM while also monitoring ISP and SCPP in the first 10 days after TSCI. We hypothesized that AP, change in AP (ΔAP) during squeeze or cough, recto-anal inhibitory reflex (RAIR), and rectal sensation are all influenced by ISP and SCPP. We also hypothesized that interventions to normalize these parameters could improve anal sphincter function.

Methods

Institutional Research Board Approvals

Approvals for the Injured Spinal Cord Pressure Evaluation (ISCoPE) study, including the consent form and patient information sheet, were obtained by the St. George's Joint Research Office and the National Research Ethics Service–Camberwell St. Giles Ethics Committee (No. 10/H0807/23). ISCoPE is registered at www.ClinicalTrials.gov under identifier NCT02721615.

Inclusion and Exclusion Criteria

We recruited patients with consecutive TSCI who were enrolled in the ISCoPE trial in the period of June 2018–August 2019. Inclusion criteria for ISCoPE were severe TSCI (defined as American Spinal Injury Association Impairment Scale [AIS] grades A–C), age 18–70 years, and surgery performed within 72 h of TSCI. Exclusion criteria were major comorbidities, the inability to obtain consent, and penetrating TSCI.

Clinical Examination and Imaging

All patients were admitted to the neurosurgical unit at St. George's Hospital and underwent an International Standards for Neurological Classification of Spinal Cord Injury AIS assessment by a neurosurgical resident trained in AIS, which was repeated at discharge and at the follow-up outpatient clinic. All patients had computed tomography and magnetic resonance imaging of the spine before surgery and within 4 weeks of surgery.

Bowel Function at Follow-Up

In clinic, functional and quality of life measures were completed using two standard scales, the Spinal Cord Independence Measure III (SCIM III) bowel score [16] and the Neurogenic Bowel Dysfunction (NBD) score [17]. The SCIM III bowel scores are the following: 0, irregular timing or very low frequency (less than once in 3 days) of bowel movements; 5, regular timing, but requires assistance (e.g., for applying suppositories), and rare accidents (less than twice a month); 8, regular bowel movements, without assistance, and rare accidents (less than twice a

month); and 10, regular bowel movements, without assistance, and no accidents. In the NBD score, bowel dysfunction is classified as the following: 0–6, very minor; 7–9, minor; 10–13, moderate; and 14 or higher, severe.

Spinal Surgery

Surgical decompression, including laminectomies and spinal instrumentation, was performed based on patient requirements and surgeon preference. Lateral mass screws (cervical spine) or pedicle screws (thoracolumbar spine) were inserted above and below the fracture and were linked to rods secured with blockers using Oasys or Xia 3 (Stryker, Newbury, UK). Postoperatively, all patients were managed in the neuro-ICU.

Probe Insertion

During posterior surgery, a pressure probe (Codman Microsensor Transducer; DePuy Synthes, Leeds, UK) was inserted through the skin into the wound cavity. Using a microscope, the dura and arachnoid were opened one level below the injury. The pressure probe was inserted intradurally, with the tip placed at the site of maximal cord swelling. The dural opening was sutured. This technique is described in detail elsewhere [6, 9, 10, 12, 13, 15, 18, 19]. ISP measured this way differs from intrathecal pressure measured above or below the injury site because the injured cord is compressed against the dura, thus compartmentalizing the intrathecal space [15, 20–22].

ISP and Arterial Blood Pressure Monitoring

The ISP probe was connected to a Codman intracranial pressure box linked via an ML221 amplifier connected to a PowerLab running LabChart 8 (ADInstruments, Oxford, UK). Blood pressure was recorded from a radial artery catheter connected to the Philips IntelliVue MX800 bedside monitoring system (Philips, Guildford, UK) and, in turn, connected to the PowerLab system. ISP and arterial blood pressure (ABP) signals were sampled at 1 kHz, and patients were monitored for up to 7 days. Figure 1 shows the setup. Data were analyzed using LabChart 8 (ADInstruments) and ICM + (University of Cambridge, Cambridge, UK; available at: www.neurosurg.cam.ac.uk/icmplus). ISP and ABP were used to compute SCPP = MAP − ISP.

Neuro-ICU Clinical Management

Patients were transferred to the neuro-ICU following surgery and remained there for the duration of spinal cord monitoring and clinical need. Patients were nursed on pressure-relieving mattresses on their side, when possible, to take pressure off the laminectomy site. Antibiotic prophylaxis was given for 48 h after surgery with vancomycin and gentamicin, which is the standard regimen in our hospital for instrumented spinal fusion. Subcutaneous prophylactic low-molecular-weight heparin was started at 24 h post surgery (held for 12 h pre and post probe removal). Mechanical (compression stockings, intermittent calf compression) thromboprophylaxis was

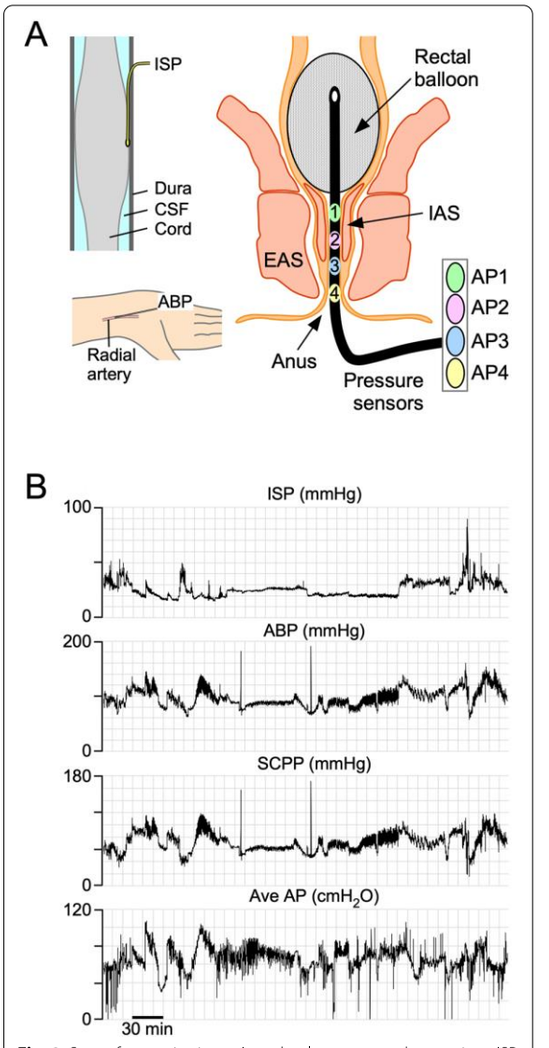


Fig. 1 Setup for monitoring. **a** Intradural pressure probe monitors ISP (top left). Radial artery catheter monitors ABP, used to compute SCPP as MAP minus ISP (bottom left). Anal probe monitors from four pressure sensors to compute average AP and maximum AP (right). Rectal balloon used to assess sensation. **b** Examples of signals monitored simultaneously, including ISP, ABP, SCPP, and average AP. ABP arterial blood pressure, AP anal pressure, CSF cerebro spinal fluid, EAS external anal sphincter, IAS internal anal sphincter, ISP intraspinal pressure, MAP mean arterial pressure, SCPP spinal cord perfusion pressure

used throughout. Ventilatory support was managed by the neuro-ICU team. MAP targets were at the discretion of the neuro-ICU (unrelated to ISP or SCPP), except for when the SCPP was altered to produce low and high SCPP for ARM measurements. Ionotropic support was provided with intravenous noradrenaline through a central venous line or, while central access was being established, with intravenous metaraminol via a peripheral venous line. All patients were reviewed and examined daily by the research team, and any complications or concerns were recorded and actioned immediately. Per neuro-ICU protocols, daily blood tests were performed, including full blood cell count, renal and liver profile, cardiac enzymes, C-reactive protein, and clotting function.

ARM

All patients underwent ARM in the neuro-ICU over a wide range of SCPPs in the week following surgery. The duration of ARM was determined by how long the patient was able to tolerate the intervention and whether the clinical condition of the patient was appropriate for this testing. AP was sampled at 1 kHz with a 4-channel water perfused manometer (Ardmore, Middleton-on-Sea, UK) leveled at the anal verge (Fig. 1). The pressure monitor was connected to the Philips IntelliVue MX800 bedside monitoring system (Philips), which, in turn, was connected to the PowerLab system. AP was monitored at rest, during cough, during squeeze, and during the RAIR and balloon threshold testing. Resting and maximal AP was taken as the mean of the four channels, excluding rectal recordings. During cough, we noted the maximum AP and the increment from resting AP (ΔAP). During prolonged (10 s) anal squeeze, we noted the endurance time (duration AP as greater than 50% of maximum) and the increase in AP from resting pressure (ΔAP). The RAIR was performed by rapid inflation to 50 ml and deflation of the rectal balloon and was assessed for baseline AP, latency, maximal amplitude, amplitude reduction, recovery time, and duration. Rectal sensation threshold tests were estimated by filling the rectal balloon at 50-ml increments (to a maximum of 500 ml) and by asking the patient to comment on first sensation, first desire to defecate, and urgency to defecate. For cough, squeeze, and RAIR, repeated assessments were performed in each patient at low and high SCPP.

Variables Assessed and Bias

We investigated the relation between baseline AP and SCPP, the characteristics of the RAIR at low versus high SCPP, the effect of cough on AP at low versus high SCPP, and the effect of voluntary anal squeeze on AP at low versus high SCPP. For baseline AP, we used data from the entire monitoring period at 1 Hz. The average hours of monitoring for each patient were 1.9 (range 0.4–12). To assess RAIR, cough, and rectal sensation (elicited by inflating a rectal balloon), SCPP was manipulated using noradrenaline. Each patient had a period when the dose of noradrenaline was reduced and a period when the noradrenaline was increased. Each figure highlights the average SCPP for each patient at their low and high SCPP periods of monitoring. We also asked the patients to strain at different SCPPs. To minimize bias, the ARM data were obtained without knowledge of the SCPP.

Statistics

Plots of ARM parameters (resting AP, prolonged squeeze endurance time, prolonged squeeze ΔAP vs. SCPP) were fitted with the best-fit quadratic or linear regression curve, chosen to minimize the Akaike information criterion. Adjusted coefficients of determination ($\hat{R}^2$) were computed using MyCurveFit (https://mycurvefit.com), with $\hat{R}^2$ values greater than 0.5 being considered a strong correlation. The relation between mean values of components of RAIR (baseline AP, recovery time, percentage of amplitude reduction) and cough (maximum AP, mean ΔAP) at high and low SCPP were compared using Student's *t* test. The correlation between AIS grade or SCPP and anal sphincter outcome was assessed using Kendall's tau-b correlation coefficient. Analysis was done using XLSTAT Biomed v2018.1 for Mac (Addinsoft, Paris, France). Statistical significance was taken as *P* values of less than 0.05.

Results

Patient Demographics

Data were obtained from 14 patients aged 22–67 years (mean 47.4): 13 men and 1 woman. Most (64.3%) patients had complete (AIS grade A) injuries, and most (64.3%) had cervical injuries. All patients had posterior surgical bony decompression, including laminectomy and fusion, with 21.4% also requiring anterior stabilization. The mean follow-up time was 8.1 months (range 2–19). At follow-up, most (71.4%) patients had improved by one of more AIS grades, 21.4% remained the same, and 7.2% deteriorated by one AIS grade. These demographics are summarized in Table 1.

ARM

We monitored resting AP for an average of 1.9 h per patient (range 0.4–12) over an average of 2.1 days per patient (range 1–4). Per patient, the average number of coughs was 11.8 (range 1–36), the average number of voluntary squeezes was 4.9 (range 0–13), and the average number of RAIRs was 10.9 (range 0–19). In some patients, the cough and squeeze tests could not be performed because of sedation used for respiratory support.

Table 1 Patient details

Pt. No.	Age (y)	Sex	Injury level	AIS	Injury to surgery (h)	Surgery	Follow-up (m)	Follow-up AIS
71	27	M	L1	C	41	Post + Lami	6	D
72	50	M	C5	B	14	Post + Lami	19	B
73	47	M	T8	A	23	Post + Lami	12	B
74	57	M	C4	A	35	Post + Lami	8	A
75	66	M	C4	A	40	Post + Lami	7	A
76	46	M	T12	A	18	Post + Lami	9	C
77	52	M	C5	A	40	Ant + Post + Lami	8	B
78	26	M	C6	A	39	Ant + Post + Lami	12	B
79	67	F	C2	B	69	Post + Lami	2	A
80	55	M	T7	A	45	Post + Lami	14	C
81	54	M	C4	C	69	Post + Lami	6	D
82	44	M	C7	A	32	Post + Lami	4	A
83	51	M	T7	A	50	Post + Lami	5	A
84	22	M	C6	C	70	Ant + Post + Lami	2	D
	Mean (SEM)	**M:F (*n*)**	**C:T:L (*n*)**	**A:B:C:D (*n*)**	**Mean (SEM)**	**Ant, Post, Lami/14 (*n*)**	**Mean (SEM)**	**A:B:C:D (*n*)**
All	47.4 (3.7)	13:1	9:4:1	9:2:3:0	41.8 (4.8)	3, 14, 14/14	8.1 (1.3)	5:4:2:3

AIS, American Spinal Injuryies Association Impairment Scale; Ant, anterior; C, cervical; F, female; h, hours; L, lumbar; Lami, laminectomy; m, months; M, male; No., number, Post, posterior, Pt., patient; Post, posterior; SEM, standard error of the mean; Pt., patient; T, thoracic; y, years

At follow-up, the NBD score classified 21.4% of patients as having minor, 28.6% moderate, and 50.0% severe bowel problems. For the SCIM III bowel scores, 7.1% of patients scored 0, 50.0% scored 5, 28.6% scored 8, and 14.3% scored 10. Details are in Table 2.

Complications

There were no complications associated with ARM. Seven patients had asymptomatic pseudo-meningoceles on the postoperative magnetic resonance imaging scan, five were treated for chest sepsis, one had a pulmonary embolism, and one developed a sacral pressure sore.

Resting AP

Altogether, we collected 26.3 h of resting AP data, i.e., 1.9 ± 0.8 h per patient. Average resting AP was 44.3 cmH_2O, which is considerably lower than the average for healthy male patients, previously reported at 99 cmH_2O [23]. For most patients, higher SCPP was associated with higher resting AP, but when the data were grouped, mean AP versus SCPP showed an inverted U-shaped relation ($\tilde{R}^2 = 0.82$; Fig. 2). Maximal AP showed a similar correlation with SCPP as mean AP (Supplementary Fig. 1). In the seven patients who had intraoperative monitoring, there was no significant change in resting AP pre versus post bony spinal cord decompression (Supplementary Fig. 2). There was no correlation between the average or maximum resting AP and ISP (Supplementary Figs. 3 and 4). Also, there was no correlation between the dose of noradrenaline and the average AP, thus making it unlikely that the relation between SCPP and AP is due to a direct effect of noradrenaline on the anal sphincter (Supplementary Fig. 5). Because low resting AP is associated with incontinence, our findings suggest improved fecal continence at higher SCPP.

RAIR

The RAIR was observed in all 13 patients in whom it was tested but not in all traces from each patient (Fig. 3). The SCPP had a major impact on the RAIR: compared with low SCPP (60.3 mmHg), high SCPP (90.0 mmHg) was associated with a higher baseline AP (55.6 vs. 35.2 cmH_2O, respectively), and the RAIR was more likely to be present at the higher SCPP (89.7 vs. 69.5% of attempts). When considering only the AP traces with the RAIR present, there was no difference in the RAIR characteristics (excitation latency, duration of reflex, percentage of amplitude reduction, recovery time) at low versus high SCPP. The RAIR is an essential reflex for the voluntary control of defecation because it enables the rectum to discriminate between gas, liquid, and solid contents [24, 25]. Therefore, the more frequent presence of the RAIR at higher SCPP suggests an increased continence at higher SCPP.

AP During Cough

Cough tests were performed in all patients. In 11 patients, cough was assessed at high (81.6 mmHg) and

Table 2 Summary of anorectal manometry investigations

Pt. No.	Monitoring duration (h)	Monitoring span (d)	Mean resting AP (cmH_2O)	No. of coughs (*n*)	No. of strains (*n*)	No. of RAIRs (*n*)	SCIM III bowel score[a]	NBD score[b]
71	12.0	1	30.2	8	0	0	8	15
72	4.0	3	64.8	1	0	3	5	18
73	1.4	4	42.7	36	0	8	0	21
74	1.7	3	32.0	12	0	16	5	11
75	0.8	3	59.5	23	13	15	5	19
76	0.5	2	54.3	16	10	11	8	28
77	0.9	2	42.2	13	12	9	5	15
78	0.8	2	47.1	1	1	15	10	2
79	0.4	1	45.4	1	1	19	5	19
80	0.7	2	40.3	8	7	9	8	10
81	0.8	2	41.3	10	7	13	8	2
82	0.9	2	34.1	12	7	12	5	10
83	0.4	1	48.3	7	8	11	5	13
84	1.1	2	37.8	17	2	12	10	0
	Mean SEM	Mean SEM	Mean SEM	Mean SEM	Mean SEM	Mean SEM	Mean SEM	Mean SEM
Mean (SEM)	1.9 (0.8)	2.1 (0.2)	44.3 (2.7)	11.8 (2.5)	4.9 (1.3)	10.9 (1.3)	6.2 (0.7)	13.1 (2.1)

AP, anal pressure; d, days; h, hours; NBD, neurogenic bowel dysfunction; No., number; Pt., patient; RAIR, recto-anal inhibitory reflex; SCIM III, Spinal Cord Independence Measure III; SEM, standard error of the mean; SCIM III, Spinal Cord Independence Measure

[a] SCIM III: 0, irregular timing or very low frequency (less than once in 3 days) of bowel movements; 5, regular timing, but requires assistance (e.g., for applying suppositories)—rare accidents (less than twice a month); 8, regular bowel movements, without assistance—rare accidents (less than twice a month); 10, regular bowel movements, without assistance—no accidents

[b] Bowel dysfunction: 0–6, very minor; 7–9, minor; 10–13, moderate; 14+, severe

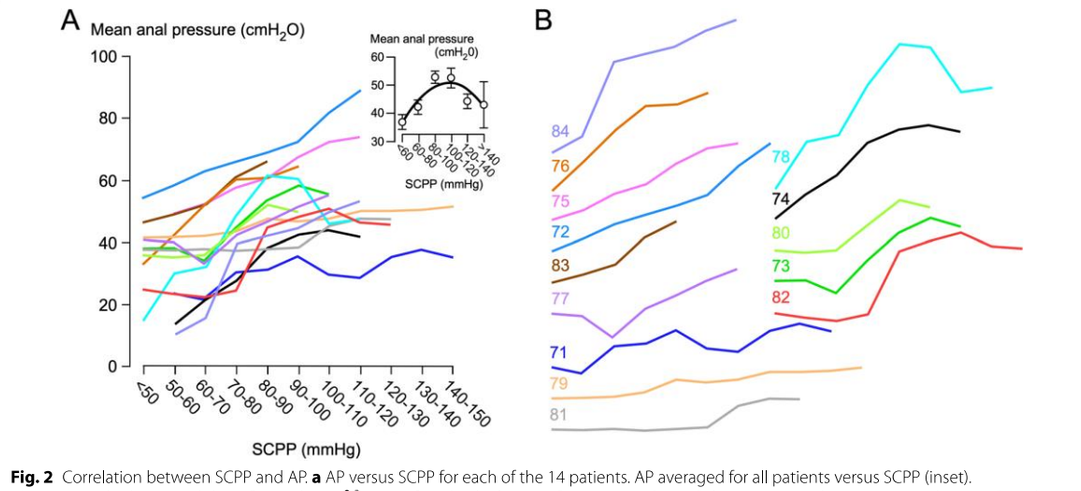


Fig. 2 Correlation between SCPP and AP. **a** AP versus SCPP for each of the 14 patients. AP averaged for all patients versus SCPP (inset). Mean ± standard error with best-fit quadratic, $\bar{R}^2 = 0.82$. **b** Individual curves from **a** spread out. Colors correspond to patients as shown. AP anal pressure, SCPP spinal cord perfusion pressure

low (61.4 mmHg) SCPP (Fig. 4). At high SCPP, the maximum AP during cough was significantly higher than at low SCPP by over 20.0 cmH_2O ($P < 0.0001$) on average. The increase in AP compared with resting pressure prior to the cough was also higher at high versus low SCPP by approximately 14.7 cmH_2O ($P < 0.0001$) on average.

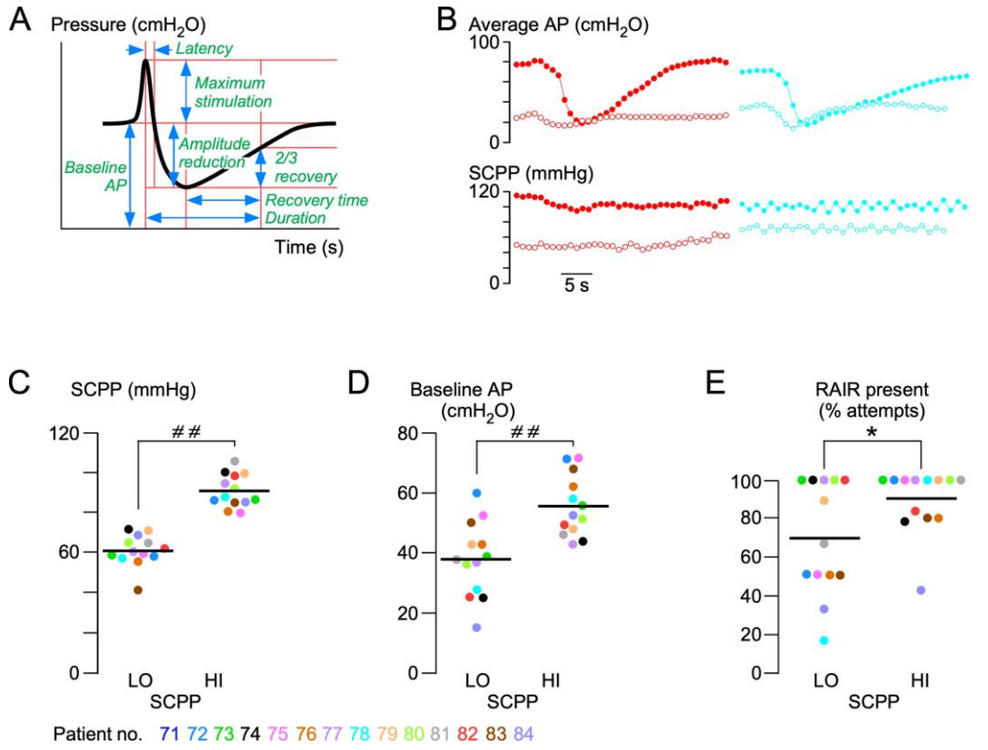


Fig. 3 Effect of SCPP on the RAIR. **a** Schematic showing characteristics of the RAIR signal. **b** Typical RAIR signals from patients 82 (left) and 78 (right) at low (open circles) and high (solid circles) SCPPs. **c** Mean high (HI) and mean low (LO) SCPPs corresponding to the RAIR measurements for each patient. Plots showing individual patient values (points) and means (lines) at HI versus LO SCPP of mean baseline AP (**d**), recovery time (**e**), and percentage amplitude reduction of the RAIRs (**f**). Color codes for patients 71–84. $^{*}P < 0.05$, $^{\#\#}P < 0.0001$. *AP* anal pressure, *RAIR* recto-anal inhibitory reflex, *SCPP* spinal cord perfusion pressure

Because episodes of incontinence are more likely during cough, our data indicate that anal sphincter continence is improved at higher SCPP.

AP During Voluntary Squeeze

Increase in AP during squeeze was significantly reduced in our patients compared with reported normal male controls (mean endurance time 5.3 vs. 16 s, mean ΔAP 3.7 vs. 195 cmH_2O) [23]. Figure 5 shows that the sphincter response has a longer endurance at a higher SCPP. An inverted U-shaped curve fit the relationship between ΔAP and SCPP, with the sphincter showing a stronger response at a SCPP of approximately 80 mmHg and a weaker response at hypoperfusion and hyperperfusion ($\hat{R}^2 = 0.87$).

Rectal Sensation

Threshold tests for rectal sensation were performed in 10 of 14 patients at high and low SCPP. The other four patients were sedated for ventilatory reasons. Six of ten patients reported rectal sensation during the tests (4 AIS grade A, 2 AIS grade C). At follow-up, all six patients who had rectal sensation at presentation had the same or improved AIS grade. The four patients lacking rectal sensation at presentation all had AIS grade A and remained so. The probability of experiencing rectal sensation, first urge to defaecate, or maximum tolerance versus volume of the balloon was the same at high and low SCPP (Supplementary Fig. 6).

Role of MAP

We tested whether MAP could be used as a surrogate for SCPP (Supplementary Fig. 7). In all patients, there was a strong positive correlation between MAP and SCPP but with wide interpatient variability. As MAP increases, mean AP increases and then plateaus, but as SCPP increases, mean AP rises and then falls (Fig. 2). For prolonged squeeze (Fig. 5), there was a strong linear

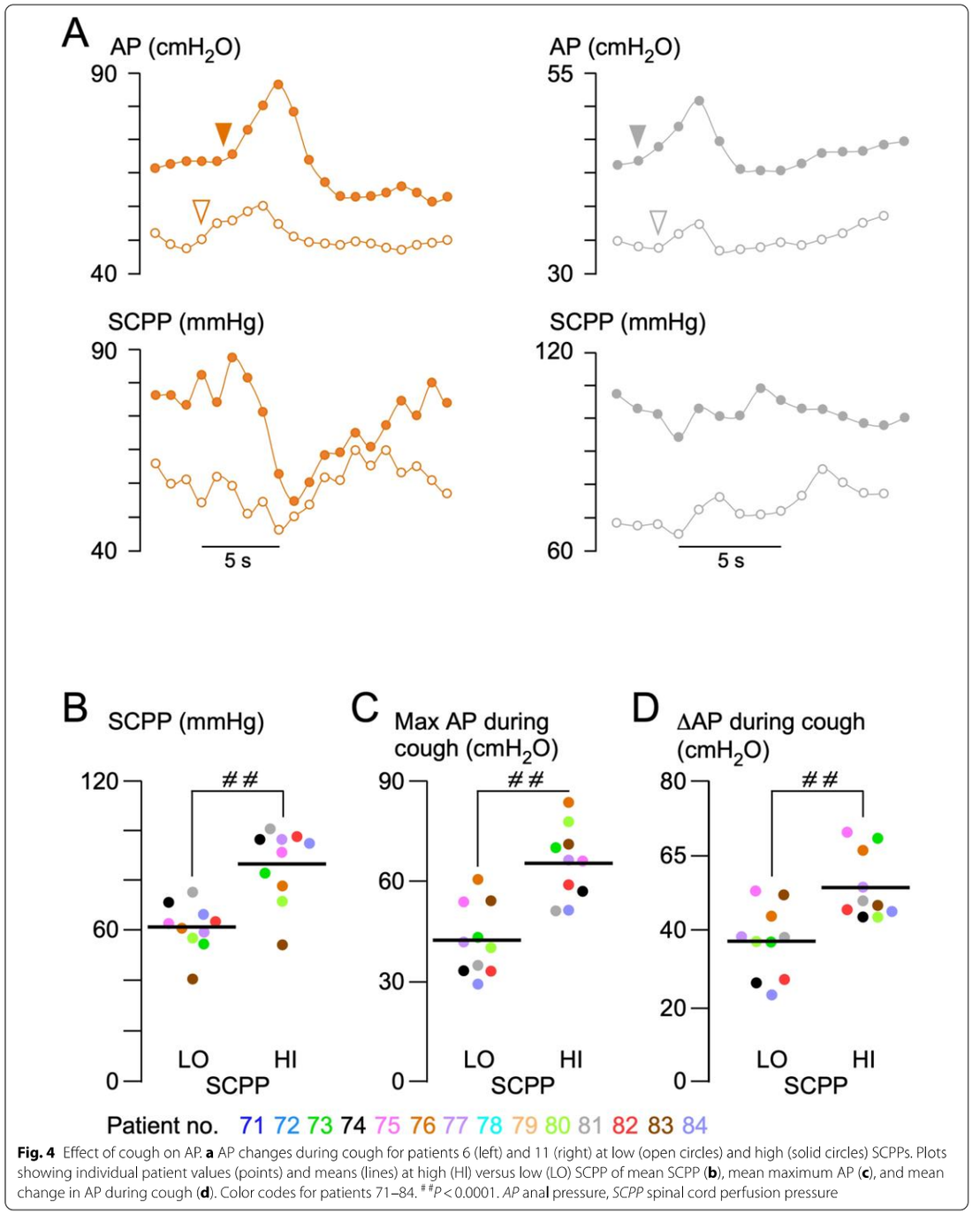


Fig. 4 Effect of cough on AP. **a** AP changes during cough for patients 6 (left) and 11 (right) at low (open circles) and high (solid circles) SCPPs. Plots showing individual patient values (points) and means (lines) at high (HI) versus low (LO) SCPP of mean SCPP (**b**), mean maximum AP (**c**), and mean change in AP during cough (**d**). Color codes for patients 71–84. $^{\#\#}P < 0.0001$. *AP* anal pressure, *SCPP* spinal cord perfusion pressure

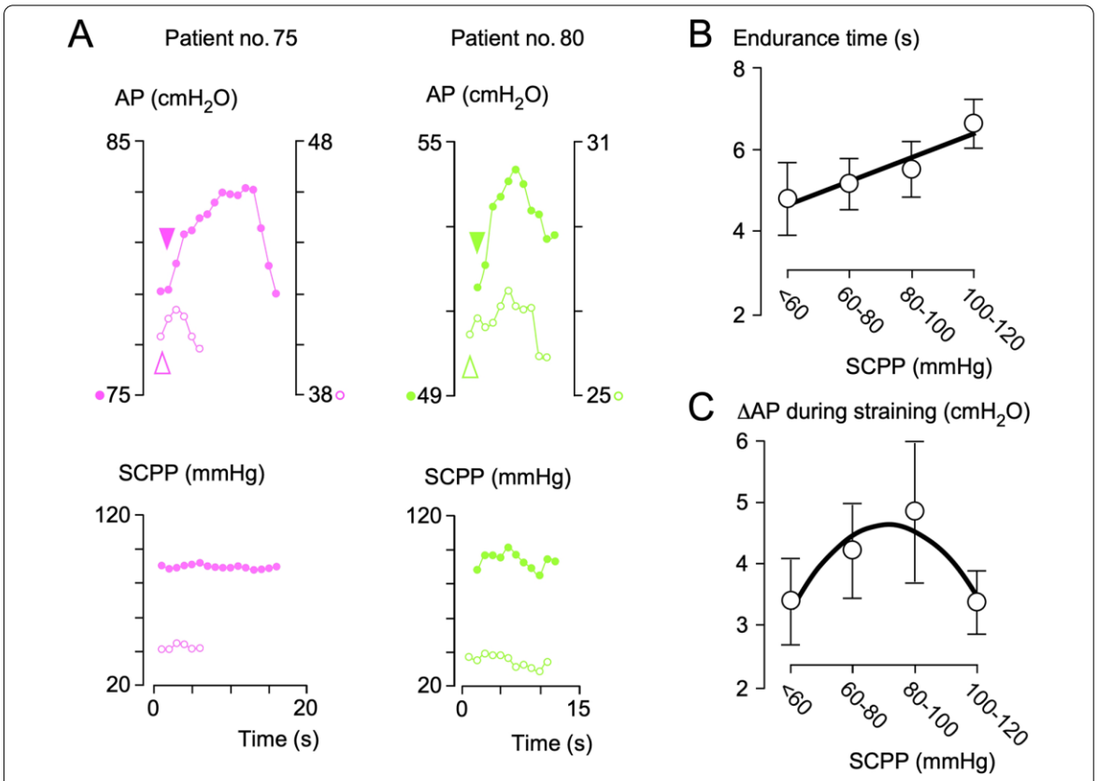


Fig. 5 Effect of prolonged squeeze on AP. **a** AP changes during squeeze for patients 5 (left) and 10 (right) at low (open circles) versus high (solid circles) SCPPs. Plots of endurance time (**b**) and change in AP (**c**) during straining. $N = 10$, mean ± standard error. Best-fit straight line (**a**, $\tilde{R}^2 = 0.93$) and quadratic (**b**, $\tilde{R}^2 = 0.87$). *AP* anal pressure, *SCPP* spinal cord perfusion pressure

correlation between endurance time and SCPP and a strong correlation between ΔAP and SCPP but no correlation between endurance time and MAP ($\tilde{R}^2 = 0.07$) and only a weak correlation between ΔAP and MAP ($\tilde{R}^2 = 0.47$). We conclude that MAP is not a good surrogate for SCPP.

Long-Term Outcomes

There was no correlation between AIS grade on admission and anal sphincter function at follow-up (NBD and SCIM III bowel scores). There was a significant correlation between the average SCPP on admission and anal sphincter function at follow-up assessed with the NBD score ($P < 0.05$) but not with the SCIM III bowel score (see Fig. 6).

Discussion

We showed that TSCI causes severe disruption of anal sphincter function. Our key finding is that intervention to increase the SCPP improves several components of anal continence, including resting AP, RAIR, AP during cough, and AP during squeeze. We also showed evidence that too high of SCPP may worsen anal sphincter continence. Being able to improve anal sphincter function early by optimizing the SCPP is a compelling prospect.

The reported variability in ARM findings and its dependence on physiological changes at the injury site (e.g., change in SCPP) suggest that interventions to optimize injury-site physiology may improve anal function. This is further supported by the finding that the average SCPP on admission correlated with the NBD score at follow-up. Ultimately, a randomized controlled trial is required to definitively determine whether intervening to optimize the SCPP improves outcome. Intervention to increase SCPP (SCPP = MAP − ISP) may be achieved by increasing the MAP using inotropes [6] or by reducing the ISP using expansion duroplasty [26]. The finding that overincreasing the SCPP may worsen anal sphincter function suggests that not only hypoperfusion but also hyperperfusion at the injury site is detrimental. The

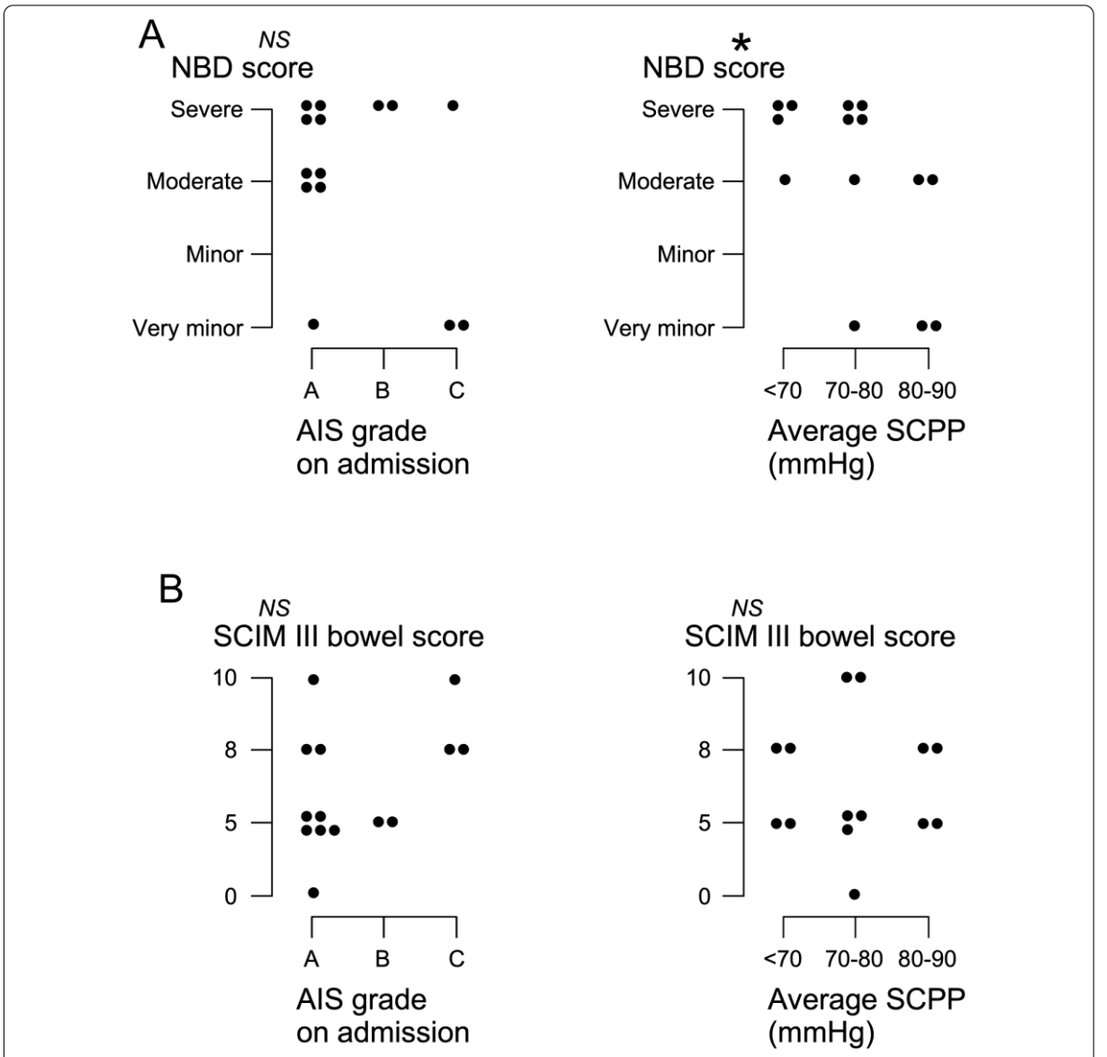


Fig. 6 Bowel function at follow-up. **a** NBD scores versus (left) AIS grade and (right) versus average SCPP on admission. **b** SCIM III bowel scores versus (left) AIS grade and (right) versus average SCPP on admission. *$P < 0.05$. *AIS* American Spinal Injury Association Impairment Scale, *NBD* Neurogenic Bowel Dysfunction, *NS* not significant, *SCIM III* Spinal Cord Independence Measure III, *SCPP* spinal cord perfusion pressure

notion that injury-site hyperperfusion is detrimental after TSCI is also supported by our earlier studies that used injury-site autoregulation [6], injury-site blood flow [27], limb power [13], and urinary bladder function [14] as outcomes.

ARM offers mechanistic insight into the impact of TSCI on anal sphincter function. We found that in the acute phase, TSCI causes relaxation of the anal sphincter. The anal sphincter no longer contracts effectively in response to cough or voluntary squeeze, and the RAIR is not always present. As a result of these disruptions, fecal continence can no longer be maintained.

We did not detect an effect of increasing SCPP on the rectal volumes required to elicit sensations (first sensation, first urge to defecate, maximum tolerance). The data show a trend, i.e., increasing SCPP reduces the rectal volume required to first produce desire to defecate or to first produce maximum tolerance, although these findings did

not reach significance. The small number of patients in our study may be the limiting factor here, and it is possible that increasing the number of patients may yield significance.

Our study has limitations. First, some patients were sedated because they required ventilation, which prohibited them from participating in the squeeze and sensory threshold tests. Second, some patients received noradrenaline infusions, raising the possibility of a direct effect of noradrenaline on the anal sphincter. Our finding that the dose of noradrenaline does not correlate with resting AP suggests that a direct effect of noradrenaline on the anal sphincter is unlikely. Third, because of the acute intensive care unit setting, we were unable to perform additional studies, e.g., high resolution ARM or anal ultrasound. Fourth, the number of patients in our study is relatively small because of the difficulty in performing multiple ARM assessments in patients with acute injuries in the neuro-ICU. Importantly, no patient experienced complications directly related to ARM testing. The outcomes of patients with TSCI who undergo monitoring from the injury site are comparable with the outcomes of patients who were not monitored, as previously reported [10].

The finding that optimizing SCPP is associated with improved anal sphincter function is in line with our earlier findings that optimizing SCPP is associated with improved limb motor score [6, 13], sensory level [28], and urinary bladder function [14]. Our analysis suggests that using MAP as a surrogate for SCPP is inadequate because patients who have the same MAP and different ISP will have different SCPP. A randomized controlled trial, Duroplasty for Injured Spinal Cord with Uncontrolled Swelling, funded by the UK National Institute for Health Research (NIHR130048), has been set up to determine if expansion duroplasty improves neurological outcomes, including anal sphincter function, compared with standard treatment for patients with acute, severe cervical TSCI. The trial includes optional monitoring from the injury site.

Conclusions

Our ARM findings suggest that individualized therapy in acute TSCI, through monitoring and optimizing spinal cord physiology and metabolism, may improve not only limb motor function, sensation, and urinary function but also anal sphincter function.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s12028-021-01232-1.

Abbreviations
ABP: Arterial blood pressure; AP: Anal pressure; ARM: Anorectal manometry; ISCoPE: Injured spinal cord pressure evaluation; ISP: Intra cranial pressure; MAP: Mean arterial pressure; NBD: Neurogenic bowel dysfunction; NICU: Neuro-intensive care unit; RAIR: Recto-anal inhibitory reflex; SCIM: Spinal cord independence measure; SCPP: Spinal cord perfusion pressure.

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Author contributions
FRAH, SK, MJG, and AZ contributed for data collection. FRAH contributed for data analysis. FRAH, MCP, and SS contributed for writing manuscript. AZ looked after patients. MCP operated on patients. AZ, MC, and SS contributed for data interpretation. SS contributed for constructed figures and overall suervision. Authorship requirements have been met, and the final manuscript was approved by all authors.

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Conflicts of interest
The authors declare no conflicts of interest.

Ethical approval/informed consent
The authors have adhered to ethical guidelines and indicate ethical approvals from the institutional review board and the use of informed consent, as appropriate.

Clinical trial registration
www.ClinicalTrials.gov: NCT02721615.

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Acute, severe traumatic spinal cord injury: improving urinary bladder function by optimizing spinal cord perfusion

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ABBREVIATIONS

AIS = American spinal injuries association impairment scale

DO = detrusor overactivity

$\Delta V/\Delta P_{det}$ = bladder compliance

ICU = intensive care unit

ISCoPE = injured spinal cord pressure evaluation study

ISP = intraspinal pressure

LPR = lactate-to-pyruvate ratio

MAP = mean arterial pressure

MD = microdialysis

P_{abd} = abdominal (rectal) pressure

P_{ana} = anal sphincter pressure

P_{det} = detrusor pressure ($P_{ves} – P_{abd}$)

P_{ves} = intravesical pressure

SCIM III = spinal cord independence measure version 3

SCPP = spinal cord perfusion pressure

TSCI = traumatic spinal cord injury

V_{max} = volume drained from the bladder at end-fill

ABSTRACT

OBJECTIVE. To investigate the effect of acute, severe traumatic spinal cord injury on the urinary bladder. To investigate the hypothesis that increasing the spinal cord perfusion pressure improves bladder function.

METHODS. In 13 adults with traumatic spinal cord injury (American spinal injuries association Impairment Scale, grades A – C), we placed intradurally at the injury site a pressure probe and a microdialysis catheter. We varied the spinal cord perfusion pressure and performed filling cystometry. Patents were followed up for 12 months on average.

RESULTS. The 13 patients had 63 fill cycles; 38 cycles had unfavorable urodynamics, i.e dangerously low compliance (<20 mL/cmH_2O), detrusor overactivity or dangerously high end-fill pressure (>40 cmH_2O). Unfavorable urodynamics correlated with periods of injury site hypoperfusion (spinal cord perfusion pressure < 60 mmHg), hyperperfusion (spinal cord perfusion pressure > 100 mmHg), tissue glucose <3mM and tissue lactate-to-pyruvate ratio >30. Increasing spinal cord perfusion pressure from 67.0 ± 2.3 mmHg (average ± standard error) to 92.1 ± 3.0 mmHg, significantly reduced, from 534 to 365 mL, the median bladder volume at which desire to void was first experienced. All patients with dangerously low average initial compliance maintained low compliance at follow-up, whereas all patients with high average initial compliance (>100 mL/cmH_2O) maintained high compliance at follow-up.

CONCLUSIONS. We conclude that unfavorable urodynamics develop within days of traumatic spinal cord injury, thus challenging the prevailing notion that the detrusor is initially acontractile.

Urodynamic studies performed acutely, identify patients with dangerously low compliance likely to benefit from early intervention. At this early stage, bladder function is dynamic, influenced by fluctuations in the physiology and metabolism at the injury site; therefore, optimizing spinal cord perfusion is likely to improve urological outcome.

INTRODUCTION

The management of acute severe traumatic spinal cord injury (TSCI) in the intensive care unit (ICU) varies widely, e.g. American guidelines recommend mean arterial pressure (MAP) of 85 – 90 mmHg for a week after injury, whereas UK centres have no MAP targets.[1,2] To rationalize ICU management, we developed injury site monitoring.[3] The techniques are safe[4] and aim to individualize management.[5,6] We monitor Intraspinal Pressure (ISP), Spinal Cord Perfusion Pressure (SCPP)[5-8] and cord metabolism.[9-11] ISP and SCPP are clinically important parameters that correlate with injury site metabolism,[9-11] neurological status[6,12,13] and long-term outcome[14] and are causally linked to limb power.[12]

Chronic TSCI often leads to unfavourable urodynamics defined as dangerously low bladder compliance (<20 mL/cmH_2O), detrusor overactivity (DO) and detrusor sphincter dyssynergia. As a result, detrusor pressure rises (>40 cmH_2O) causing vesicoureteral reflux, hydronephrosis and, ultimately, renal failure.[15] Before urological surveillance became established, about 50 % TSCI patients died from renal failure.[16] Even now, renal failure remains the fourth leading cause of death after TSCI.[17] Improving bladder function is one of the top priorities according to TSCI patients, carers and health experts.[18,19]

Unlike chronic TSCI, the effect of acute TSCI on bladder function is poorly understood. Current thinking is that, early after TSCI, the detrusor becomes acontractile (spinal shock) and, within weeks, a reflex neurogenic bladder gradually develops.[20] Here, we performed filling cystometry in the first few days after TSCI whilst also monitoring from the injury site in ICU. We asked whether, during this acute phase, the detrusor is indeed acontractile or whether unfavourable urodynamics develop earlier than expected. We also asked whether bladder function could be improved by optimizing spinal cord perfusion.

MATERIALS AND METHODS

Approvals. Urodynamic investigations were approved as a substudy of the ISCoPE (Injured Spinal Cord Pressure Evaluation) study. Approvals were obtained from the St Georges Joint Research Office and the National Research Ethics Service – Camberwell St Giles Committee (No 10/H0807/23). ISCoPE is registered at www.clinical trials.gov as NCT02721615. Informed consent was obtained from all participants.

Inclusion/Exclusion. We prospectively recruited consecutive TSCI patients enrolled into ISCoPE in the period June 2018 – August 2019. Inclusion criteria are: 1) Severe TSCI (American spinal injuries association Impairment Scale (AIS) grades A – C); 2) Age 18 – 70 years, and 3) Surgery performed within 72 hours of TSCI. Exclusion criteria are: 1) Major comorbidities; 2) Inability to obtain consent, and 3) Penetrating TSCI.

Clinical assessments / imaging. Patients were admitted to the neurosurgical unit at St. George's Hospital and underwent AIS assessment by a trained neurosurgeon, repeated at discharge and at follow-up. Whole spine CT and MRI were obtained before surgery, a CT was done within 48 hours after surgery and an MRI after probe removal. Patients were followed up in outpatient clinic with assessment of AIS grade, SCIM III and SF-Qualiveen.

Spinal surgery. Surgical decompression including laminectomies and spinal instrumentation were performed based on patient requirements and surgeon preference. Lateral mass screws (cervical spine) or pedicle screws (thoracolumbar spine) were inserted above and below the

fracture and were linked with rods secured with blockers, using Oasys or Xia 3 (Stryker, Newbury, UK).

Probe insertion. During posterior surgery, an ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) and a microdialysis (MD) catheter (CMA61: CMA microdialysis AB, Solna, Sweden) were inserted through the skin into the wound cavity. Using a microscope, the dura + arachnoid were opened one level below the injury. The ISP probe and MD catheter were inserted intradurally with the tips placed at the site of maximal cord swelling (Fig. 1A). The dural opening was sutured. These techniques are described elsewhere.[4,6,8,10-12,14,21] ISP and MD measured this way differ from intrathecal pressure and MD measured above or below the injury site because the injured cord is compressed against the dura thus compartmentalizing the intrathecal space.[14,22-24]

ISP setup. Postoperatively, patients were managed in Neuro-ICU. The ISP probe was connected to a Codman ICP box linked via a ML221 amplifier to a PowerLab running LabChart v.8 (AD Instruments, Oxford, UK). Blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK), in turn connected to PowerLab. ISP and arterial blood pressure signals were sampled at 1 kHz and patients were monitored for up to a week. Data were analysed using Labchart v.8 (AD Instruments, Oxford, UK) and ICM+ (www.neurosurg.cam.ac.uk/icmplus). SCPP was computed as MAP – ISP (Fig. 1A).

MD setup. MD was started postoperatively in the neuro-ICU as described.[9-11,25] CNS perfusion fluid was perfused at 0.3 μL/min using the CMA106 pump (CMA microdialysis AB, Linton, UK). MD vials were changed hourly and analysed using ISCUS Flex (CMA microdialysis AB, Linton, UK) for glucose, lactate and pyruvate and lactate-to-pyruvate ratio (LPR) was computed. The first two samples from each patient were discarded to allow priming of the catheter and stabilisation of metabolite concentrations. 100x changes in metabolite concentration, compared with the preceding hour, were excluded from analysis.

Urodynamics. Filling cystometry was performed in the first week postoperatively according to international guidelines[26] (Fig. 1B). Patients were investigated, where possible, sitting at 45^0 without sedation. The bladder was filled through a transurethral double-lumen catheter (Bard Medical, Crawley, UK) with 0.9 % saline at 25 mL/min. Intravesical pressure (P_{ves}) was monitored through the other lumen by a water-perfused pressure monitor zeroed at the pubic symphysis. Abdominal (P_{abd}) and anal sphincter (P_{ana}) pressures were monitored using a 4-channel water-perfused anorectal manometer (Ardmore Healthcare, Middleton-on-Sea, UK), respectively levelled at the pubic symphysis and anal verge. Pressure probes were connected to the Philips Intellivue MX800 monitor (Philips, Guildford, UK), in turn attached to PowerLab and sampled at 1 kHz. The bladder was filled to 600 mL or until detrusor pressure $P_{det} = P_{ves} - P_{abd}$ reached 40 cmH_2O. Patients were asked to report first bladder sensation.

V_{max} is the volume drained from the bladder at end-fill (saline infused + urine produced). Bladder compliance ($\Delta V/\Delta P_{det}$) is bladder volume change divided by change in detrusor pressure. P_{ana} and P_{abd} (rectal pressure) were respective surrogate markers of urethral and abdominal

pressures. DO is the transient increase in P_{det} during filling, quantified as the number, amplitude and fill volume at onset of phasic bladder contractions for each fill cycle.

Statistics. Urodynamic parameters *vs*. injury site characteristics were fitted with linear, quadratic or exponential regressions; compliance at presentation *vs*. follow-up was fitted with a sigmoid curve. Adjusted coefficients of determination ($\hat{R}^2$) were computed (https://mycurvefit.com). We tested if drugs affect urodynamics (ANOVA) or bladder sensation using Fisher exact test on 2×3 contingency tables (http://vassarstats.net). Bladder volumes at first sensation were analysed by Kaplan-Meier plots and logrank. Numbers of patients with/without sensation during bladder fill at presentation *vs*. follow-up were compared by Fisher exact test on a 2×2 contingency table (http://vassarstats.net). Plots show average ± standard error. Significance was P <0.05.

RESULTS

Patients. We recruited 13 patients aged 22.0 – 67.0 years (average 47.1), 12 (92.3 %) males and 1 (7.7 %) female (Supplement 1). 8/13 (61.5 %) patients had cervical injuries, 4/13 (30.8 %) thoracic and 1/13 (7.7 %) conus. 8/13 (61.5 %) patients had AIS A injuries, 2/13 (15.4 %) AIS B and 3/13 (23.1 %) AIS C. All patients had posterior bony decompression with laminectomy and fusion; 2/13 (15.4 %) also had anterior stabilisation. Surgery was performed 14 – 70 hours after TSCI (average 41.9).

Urodynamics. We performed 63 bladder fill cycles in the 13 patients at 2 – 7 days after surgery (Supplement 2). 60.3 % cycles from 12 patients had unfavourable urodynamics i.e. bladder compliance <20 mL/cmH_2O (19.0 %), DO (55.6 %) and end-fill storage pressure >40 cmH_2O

(15.9 %). We infused 340 – 600 mL saline into the bladder, corresponding to V_{max} of 400 – 1,300 mL. Patients received propofol during 57.1 % of fill cycles, fentanyl during 63.4 % and norepinephrine during 95.2 %. Fill cycles were performed over a wide range of SCPP (42.1 – 109.9 mmHg), ISP (7.7 – 35.4 mmHg), injury site tissue glucose (0.0 – 8.2 mM) and LPR (16.9 – 98.0). Fig. 1C shows a typical set of urodynamics with DO and guarding reflex.

Complications. *Adverse Events:* 1/13 (7.7 %) patient developed a sacral pressure ulcer, 1/13 (7.7 %) had penile meatal pressure ulcer from the indwelling catheter, 1/13 (7.7 %) had microscopic hematuria, 5/13 (38.5 %) had pneumonia and 1/13 (7.7 %) had pulmonary embolism. 1/13 (7.7 %) patient had developed a syrinx shown on MRI scan at 15 month follow up. *Adverse Reactions:* 7/13 (53.8 %) patients had asymptomatic pseudomeningocele. There were no *Serious Adverse Events*, no *Serious Adverse Reactions* and no *Suspected Unexpected Serious Adverse Reactions*. No one had cord damage or hematoma from the probes (MRI, neurological examination), no cerebrospinal fluid leak, no wound infection or meningitis, no urinary infection and no deterioration in renal function.

Variability of urodynamic measurements. Repeat fill cycles revealed variability in the unfavourable urodynamics. For example, in patient 3, increase in SCPP (59.7 to 80.7 mmHg) reduced end-fill detrusor pressure (41.3 to 24.0 cmH_2O) and increased bladder compliance (12.0 to 28.6 mL/cmH_2O) (Fig. 2A). In patient 5, increase in SCPP (65.5 to 94.5 mmHg) eliminated DO but had little effect on bladder compliance or end-fill detrusor pressure (Fig. 2B). Fig. 2C summarizes the variabilities in bladder compliance, DO and detrusor pressure at end-fill for each patient. We hypothesized that these fluctuations in urodynamics are caused by fluctuations in the

physiology and metabolism of the injured cord. If our hypothesis holds, there should be strong correlations between urodynamic and injury site parameters.

Bladder compliance correlates with injury site physiology and metabolism. Fig. 3 shows plots of the number of patients with dangerously low bladder compliance (<20 mL/cmH_2O) *vs*. average SCPP, ISP, tissue glucose or tissue LPR (measured from the injured cord during cyctometry). The relation with SCPP is U-shaped with the optimum SCPP, that eliminates dangerously low compliance, at ~80 – 90 mmHg. The percentage of patients with dangerously low bladder compliance was significantly higher during periods of low tissue glucose (<3 mM) or ischemia (LPR >30) at the injury site but did not significantly correlate with ISP. Thus, improved injury site perfusion and metabolism are associated with improved bladder compliance.

Detrusor overactivity correlates with injury site physiology. Fig. 4 shows how the severity of DO is related to the average SCPP, ISP, tissue glucose and tissue LPR measured from the injured cord during each fill cycle. Phasic bladder contractions were more frequent, and their amplitudes were larger, during periods of spinal cord hypo- and hyperperfusion with the optimum SCPP, that minimizes DO, at ~75 – 85 mmHg. Though the onset of DO occurred at lower fill volumes during hypo- and hyperperfusion, compared with normal perfusion, the relations were not significant (not shown). The number of phasic bladder contractions did not significantly correlate with ISP. DO occurred more frequently during periods of low cord tissue glucose and high LPR, but the relations were not significant. There were also no significant correlations between the amplitudes of phasic bladder contractions or the fill volume at onset *vs*. ISP, *vs*. tissue glucose or

vs. tissue LPR (not shown). These findings indicate that improved injury site perfusion is associated with less DO.

End-fill detrusor pressure correlates with injury site physiology and metabolism. Fig. 5 shows plots of the percentage of patients with dangerously high end-fill detrusor pressure (>40 cmH_2O) *vs*. average SCPP, ISP, tissue glucose and LPR measured from the injured cord during each fill cycle. The relation with SCPP is U-shaped with the optimum SCPP, that eliminates dangerously high end-fill detrusor pressure, at ~80 – 90 mmHg. The percentage of patients with dangerously high end-fill detrusor pressure was significantly higher during periods of spinal cord swelling (ISP >10 mmHg), periods of low tissue glucose (<4 mM) and periods of ischemia (LPR >30) at the injury site. Thus, improved injury site physiological and metabolic parameters are associated with lower detrusor pressure at end-fill.

Bladder volume at first desire to void correlates with spinal cord perfusion. Bladder sensation was assessable in 10 patients; the other 3 were sedated to aid ventilation. Of these 10, only 4 had bladder sensation, 3 AIS C on admission plus 1 AIS A on admission who was AIS C at follow-up. These 4 patients had 14 fill cycles; For each patient, fill cycles were classed as high or low SCPP, with at least 20 mmHg difference between them, resulting in 8 high (82.6 – 100.5 mmHg) and 6 low (56.2 – 74.1 mmHg) SCPP fill cycles. The median bladder volume at which sensation was first experienced was significantly smaller for fill cycles at high *vs*. low SCPP (365 *vs*. 534 mL) (Fig. 6). Thus, improved spinal cord perfusion is associated with improved bladder sensation.

No significant effect of sedation, inotropes day after injury or spinal cord level on urodynamics. Bladder compliance, number of phasic bladder contractions per fill, end-fill detrusor pressure and the probability of experiencing bladder sensation during a fill cycle were not significantly influenced by propofol, fentanyl, norepinephrine (Supplement 3), day after TSCI (Supplement 4) or cervical *vs*. thoracic injury level (Supplement 5).

Long-term outcome. Average follow-up was 12 months, range 2 – 25 (Supplement 1). Bladder compliance assessed acutely correlated with compliance at follow-up (Fig. 7). All patients with bladder sensation at presentation were sensate at follow-up, but with decrease in bladder volume causing first sensation to void from 442 ± 55 mL to 260 ± 31 mL (average ± standard error). No one with absent sensation at presentation recovered the sensation at follow-up. DO at presentation did not correlate with DO at follow-up (not shown). At follow-up, 7/13 patients (53.8 %) improved by one or more AIS grade, 5/13 (38.5 %) remained the same and 1/13 (7.7 %) deteriorated by one AIS grade, comparable to earlier findings.[4] At follow-up, SCIM III ranged 0 – 15 and SF-Qualiveen 1.13 – 4.00 (Supplement 6).

DISCUSSION

We showed that >90 % patients develop periods of unfavorable urodynamics within days of TSCI, including dangerously low bladder compliance, dangerously high detrusor pressure at end-fill and DO. Unfavorable urodynamics fluctuate; they become more pronounced when the injured cord is hypo- or hyperperfused, glucopenic or ischemic (high tissue LPR). By intervening to eliminate hypoperfusion, we could improve bladder sensation with first desire to void occurring at smaller volume.

Our results challenge the prevailing dogma, that the detrusor is acontractile early after TSCI with late development of overreactive bladder and agree with the few studies reporting unfavourable urodynamics in most patients within 40 days of TSCI;[27-29] in our study, unfavourable urodynamics were detectable as soon as 48 hours of TSCI. Initially, after severe TSCI, limbs are hypotonic/hyporeflexic, later progressing to spasticity/hyperreflexia.[20] It is assumed that the detrusor behaves similarly (initially acontractile, then overactive). Our data indicate discordance in the early responses to TSCI of limb muscles *vs*. the detrusor.

Variability in the urodynamic parameters and their dependence on events at the injury site suggest that interventions to improve injury site physiology and metabolism will likely improve bladder function. For example, intervention to increase SCPP (=MAP – ISP) may be achieved using inotropes to increase MAP[6] or expansion duroplasty to reduce ISP.[30] Increasing SCPP may increases cord tissue glucose and reduce cord LPR,[12] which may improve neuronal activity at the injury site thus leading to improved bladder function. In our study, transiently increasing the SCPP reduced the threshold volume for bladder sensation. The finding that SCPP ≥100 mmHg worsens bladder function supports the idea that not only hypoperfusion, but also hyperperfusion, is detrimental for the injured cord; we urge caution, however, because this statement relies on only a single point on each graph (Figs. 3A, 4A, 5A). Our earlier work, using limb power and sensory level as outcomes,[6,12-14] and the current study of bladder function suggest that SCPP is the key parameter to monitor and optimize after acute TSCI.

Some aspects of bladder function, assessed acutely, correlated with corresponding measurements at follow-up. The relation between average bladder compliance at presentation *vs*. follow-up was sigmoidal, i.e. patients with low initial compliance (<20 mL/cmH_2O) had low compliance at follow-up, patients with intermediate (50 – 100 mL/cmH_2O) compliance initially

had low or normal compliance at follow-up, whereas patients with high initial compliance (>100 mL/cmH_2O) also had high compliance at follow-up. These findings suggest that patients with intermediate bladder compliance may be the most sensitive to SCPP management. Improving cord perfusion did not influence the presence or absence of the sensation to void but reduced the bladder volume at which the first sensation occurred. Compliance is the most important urodynamic parameter affecting renal function. Thus, identifying the TSCI patients with dangerously low bladder compliance early, would allow for more aggressive intervention before renal function has deteriorated. Based on our findings, we recommend that any early urodynamic testing is done once the SCPP has been optimised.

This study has limitations: First, though best urodynamic practice recommends awake/interactive patients, some patients were sedated because they required ventilation. Second, some patients received norepinephrine, raising the possibility of a direct, inhibitory effect of norepinephrine on bladder contraction potentially masking DO and reducing compliance. Our analysis suggests that propofol, fentanyl and norepinephrine did not significantly influence the urodynamics; however, there may be unknown confounding factors that we did not explore. Third, because of the acute ICU setting, we were unable to perform flow or video-urodynamics. Fourth, the number of patients in our study is small, due to the difficulty in performing multiple urodynamic assessments in acutely injured patients in ICU and due to the relative infrequency of TSCI. Fifth, injuries varied in spinal level (cervical *vs*. thoracic) and severity; our study was too small to assess difference between these groups. Sixth, whilst all urodynamic tests were performed within 8 days of injury, there was variability in the timing of the studies, which related to each patient's clinical progress and suitability for testing. Our analysis suggests that day from TSCI did not significantly influence the urodynamic parameters.

Seventh, it is impossible to conclude that intervening to improve spinal cord perfusion improves long-term outcome; this would require a randomized, controlled trial. Importantly, no patient experienced complications directly related to urodynamic testing.

CONCLUSIONS

Filling cystometry, performed within days of TSCI, identifies early patients with unfavourable urodynamics. Our findings suggest that individualized therapy in acute TSCI, by monitoring and optimizing cord physiology and metabolism, will likely improve not only limb motor function and sensation, but also urinary function.

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DISCLOSURES

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FIGURE LEGENDS

Fig. 1. Setup for injury site monitoring and cystometry. A. Injury site: *(top)* ISP probe and MD catheter placed intradurally at injury site. *(bottom)* Catheter in radial artery to monitor MAP. SCPP = MAP – ISP. **B.** Filling cystometry: Normal saline is infused at 25 mL/min into bladder up to 600 mL. Probes monitor intravesical (P_{ves}), abdominal (P_{abd}) and anal (P_{ana}) pressures. Detrusor pressure $P_{det} = P_{ves} - P_{abd}$. Bladder volume V = infused saline + urine produced. Bladder compliance is $\Delta V/\Delta P_{det}$. Key parameters highlighted yellow. **C.** Cystometry patient no. 12 (T7 AIS A) at day 4 post-TSCI. $\Delta V/\Delta P_{det}$ = 12 mL/cmH_2O; at V_{max} (520 mL), P_{abd} = 19 cmH_2O, P_{ves} = 60 cmH_2O and P_{det} = 39 cmH_2O. Arrowheads: black (cough), purple (bladder contractions), green (rectal contractions).

Fig. 2. Variability of urodynamic parameters in each patient. A. Cystometry patient 3 (T8 AIS A). Day 4 post TSCI (black): SCPP 80.7 mmHg, $\Delta V/\Delta P_{det}$ 28.6 mL/cmH_2O, end-fill P_{det} 24.0 cmH_2O. Day 2 post TSCI (red): SCPP 59.7 mmHg, $\Delta V/\Delta P_{det}$ 12.0 mL/cmH_2O, end-fill P_{det} 41.3 cmH_2O. **B.** Cystometry patient 5 (C4 AIS A). Day 4 post TSCI (black): SCPP 94.5 mmHg, $\Delta V/\Delta P_{det}$ 48.0 mL/cmH_2O, end-fill P_{det} 8.8 cmH_2O. Day 3 post TSCI (red): SCPP 65.5 mmHg, $\Delta V/\Delta P_{det}$ 42.0 mL/cmH_2O, end-fill P_{det} 9.1 cmH_2O, vesicular contractions associated with anal-rectal contractions (guarding reflex, arrows) at 245, 490, 524, 599 mL. **C.** Standard deviation (SD) of bladder compliance ($\Delta V/\Delta P_{det}$), no. of vesicular contractions (DO) and detrusor pressure at end-fill (end-fill P_{det}) for patients 1 – 13.

Fig. 3. Bladder compliance correlates with injury site physiology and metabolism. % patients with $\Delta V/\Delta P_{det}$ <20 cmH_2O *vs*. **A.** SCPP (best-fit quadratic, $\hat{R}^2$ = 0.78), **B.** ISP (best-fit

line, $\hat{R}^2$ = 0.48), **C.** tissue glucose (best-fit exponential, $\hat{R}^2$ = 1.00), and **D.** tissue LPR (best-fit line, $\hat{R}^2$ = 0.86). P <0.05*, 0.00005††. ns = not significant. Average ± standard error.

Fig. 4. Detrusor overactivity correlates with injury site physiology. A. Number and amplitude of vesicular contractions *vs*. SCPP (best fit quadratics, $\hat{R}^2$ = 0.79 for number, $\hat{R}^2$ = 0.84 for amplitude). Number of vesicular contractions *vs*. **B.** ISP (best-fit straight line, $\hat{R}^2$ = -0.26), **C.** tissue glucose (best-fit exponential decay, $\hat{R}^2$ = 0.73), and **D.** tissue LPR (best-fit straight line, $\hat{R}^2$ = 0.42) P < 0.05*. ns = not significant. Average ± standard error.

Fig. 5. End-fill detrusor pressure correlates with injury site physiology and metabolism. % patients with end-fill detrusor pressure >40 cmH_2O *vs*. **A.** SCPP (quadratic regression, $\hat{R}^2$ = 0.83), **B.** ISP (best-fit straight line, $\hat{R}^2$ = 0.72), **C.** tissue glucose (best-fit straight line, $\hat{R}^2$ = 0.73), and **D.** tissue LPR (best-fit straight line, $\hat{R}^2$ = 0.87). P < 0.05*.

Fig. 6. Bladder volume at first desire to void correlates with spinal cord perfusion. Probability of experiencing desire to void *vs*. bladder volume at high (92.1 ± 3.0 mmHg) vs. low (67.0 ± 2.3 mmHg) SCPP. P < 0.05*. Average ± standard error.

Fig. 7. Long-term outcome. A. Bladder compliance at initial presentation *vs*. follow-up with best-fit sigmoid curve, $\hat{R}^2$ = 0.90. Average ± standard error. **C.** No. of patients with and without sensation to void during bladder fill at presentation *vs*. follow-up. P < 0.05*, 0.001†.

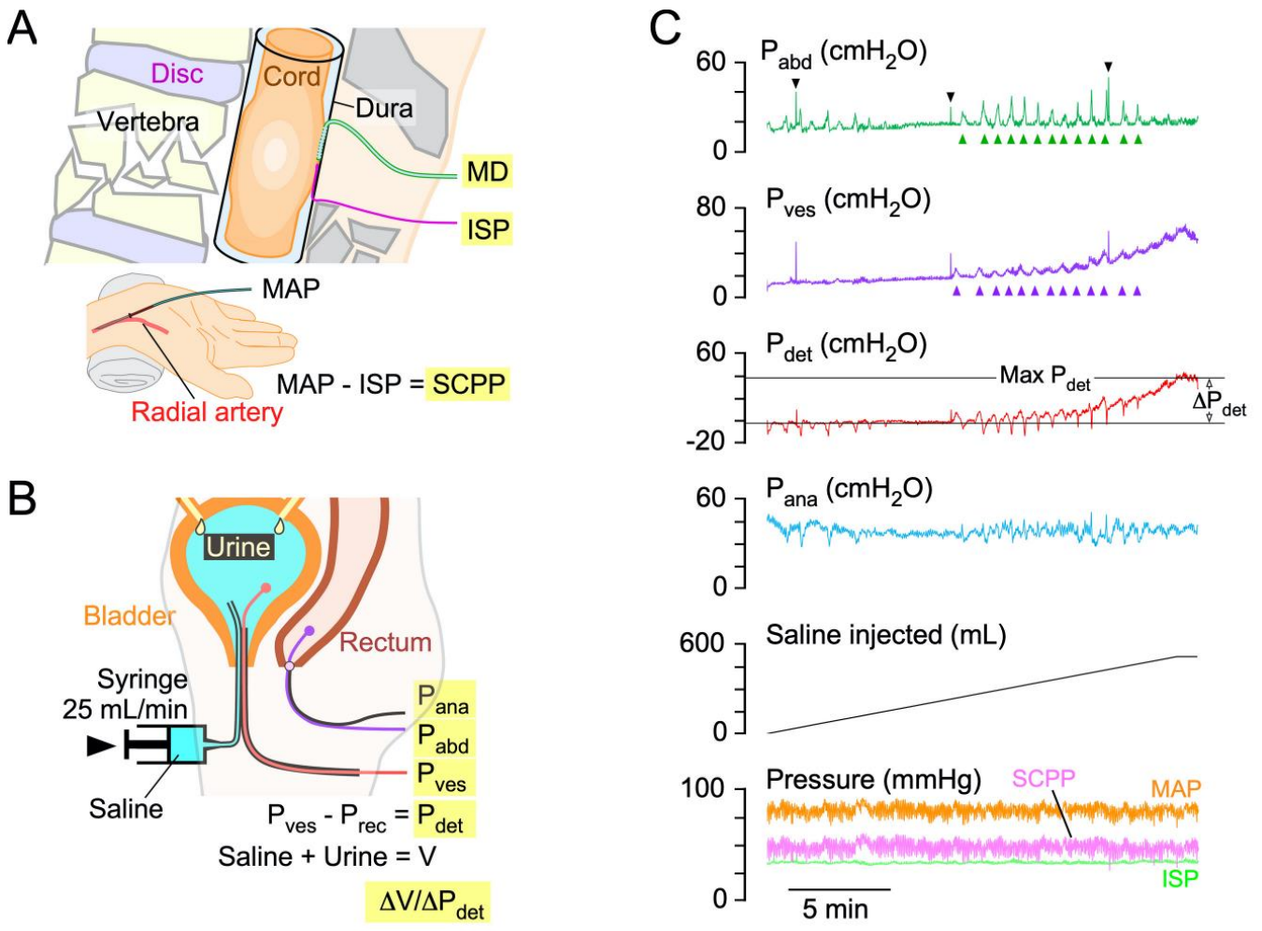

A
Disc
Cord
Dura
Vertebra
MD
ISP
MAP
MAP - ISP = SCPP
Radial artery
B
Urine
Bladder
Rectum
Syringe
25 mL/min
Saline
P_{ana}
P_{abd}
P_{ves}
$P_{ves} - P_{rec} = P_{det}$
Saline + Urine = V
$\Delta V/\Delta P_{det}$
C
P_{abd} (cmH_2O)
60
0
P_{ves} (cmH_2O)
80
0
P_{det} (cmH_2O)
60
-20
Max P_{det}
ΔP_{det}
P_{ana} (cmH_2O)
60
0
Saline injected (mL)
600
0
Pressure (mmHg)
SCPP
MAP
ISP
100
0
5 min

FIGURE 1

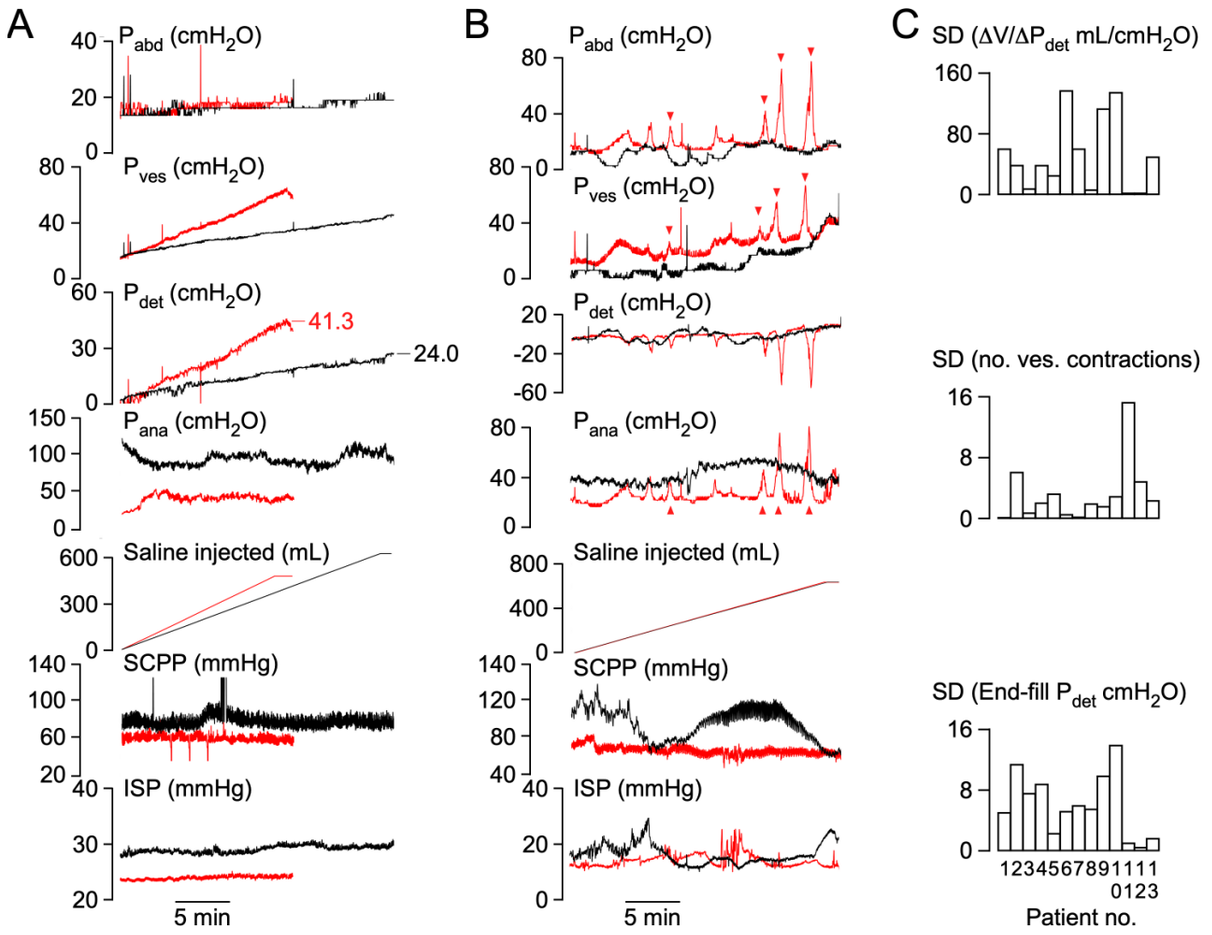

A
B
C
P_{abd} (cmH_2O)
P_{ves} (cmH_2O)
P_{det} (cmH_2O)
41.3
24.0
P_{ana} (cmH_2O)
Saline injected (mL)
SCPP (mmHg)
ISP (mmHg)
5 min
SD ($\Delta V/\Delta P_{det}$ mL/cmH_2O)
SD (no. ves. contractions)
SD (End-fill P_{det} cmH_2O)
1234567891111
0123
Patient no.

FIGURE 2

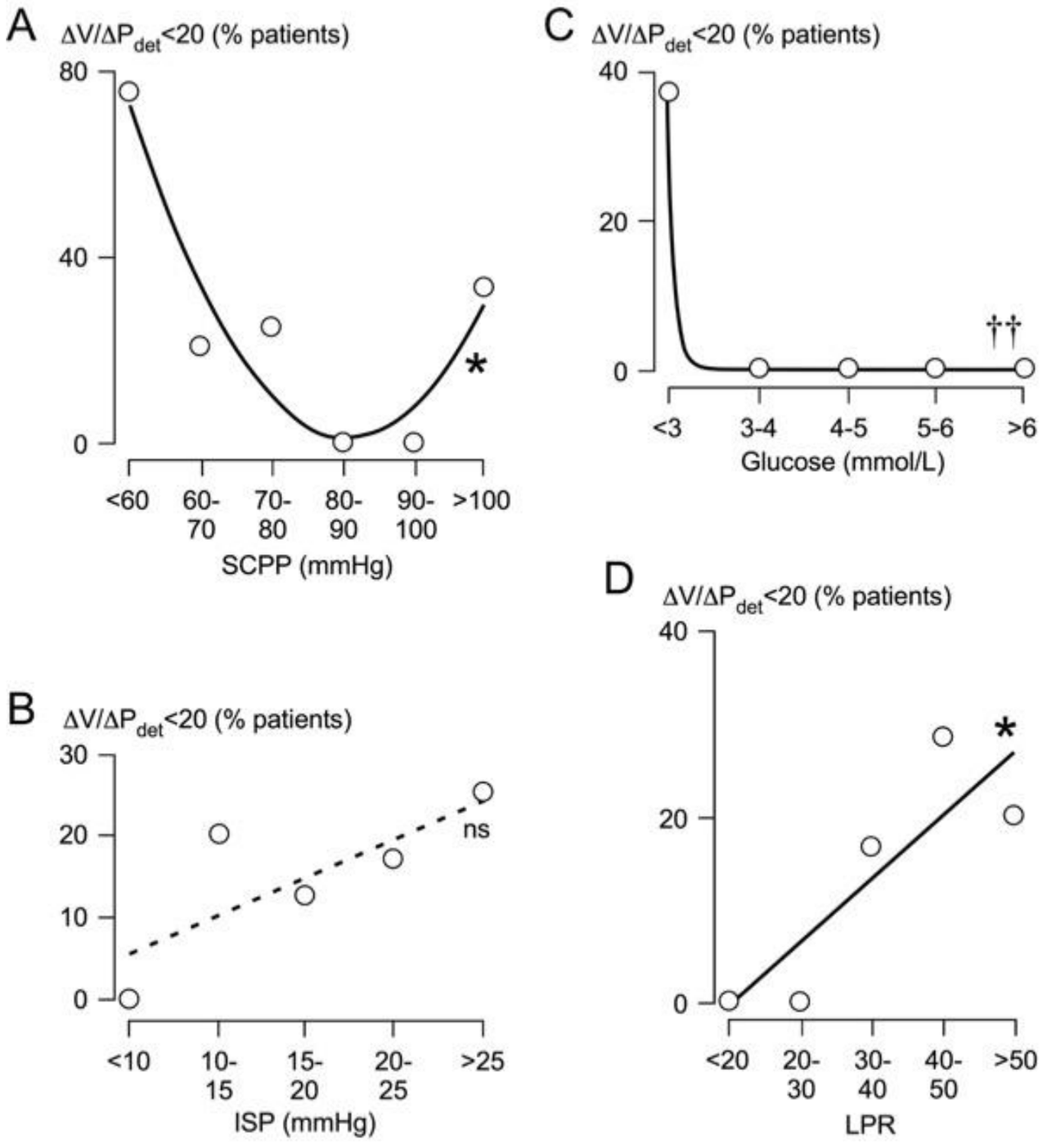

A
ΔV/ΔP_det<20 (% patients)
80
40
0
*
<60
60-70
70-80
80-90
90-100
>100
SCPP (mmHg)
B
ΔV/ΔP_det<20 (% patients)
30
20
10
0
ns
<10
10-15
15-20
20-25
>25
ISP (mmHg)
C
ΔV/ΔP_det<20 (% patients)
40
20
0
††
<3
3-4
4-5
5-6
>6
Glucose (mmol/L)
D
ΔV/ΔP_det<20 (% patients)
40
20
0
*
<20
20-30
30-40
40-50
>50
LPR

FIGURE 3

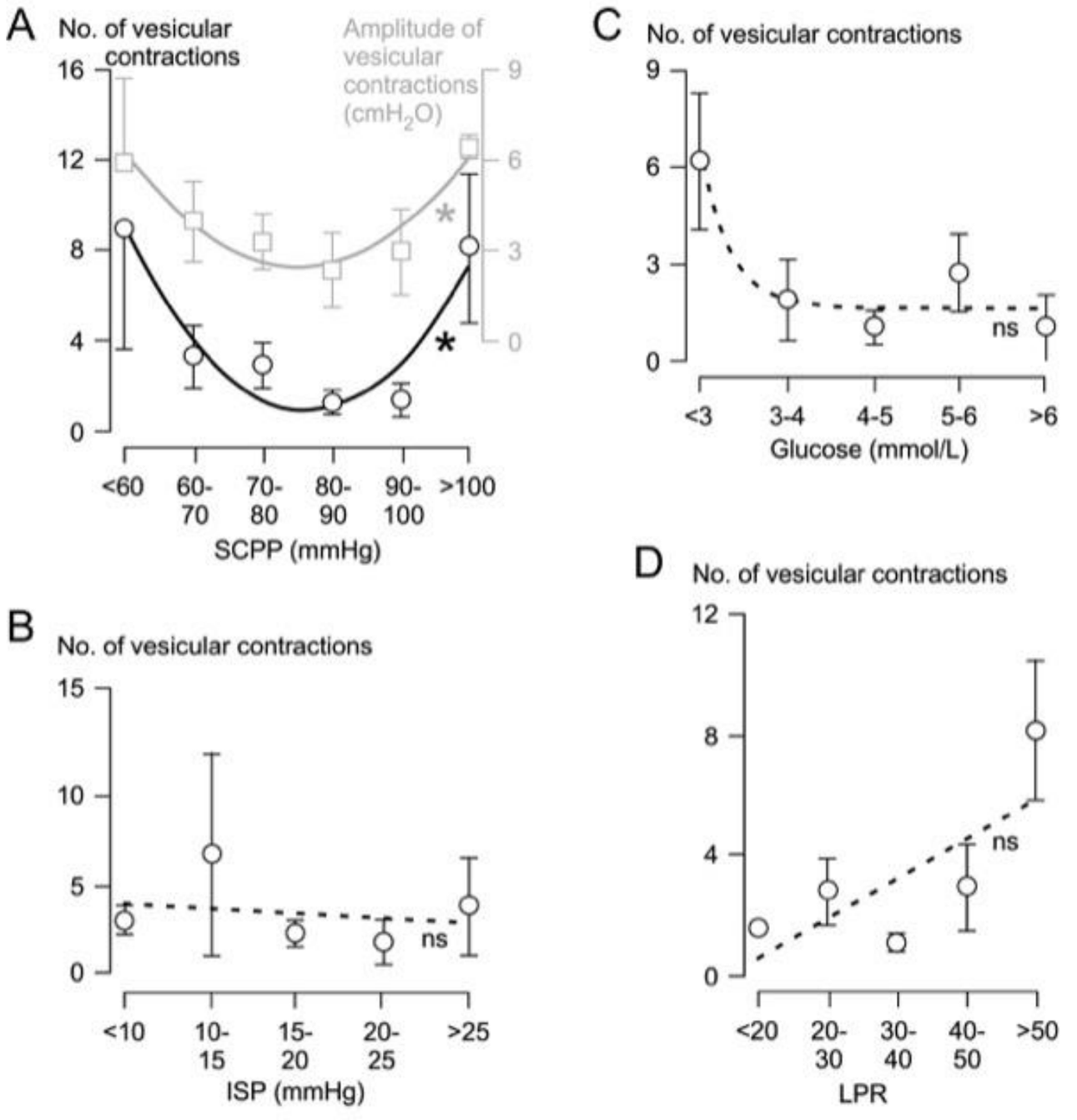

A
No. of vesicular contractions
Amplitude of vesicular contractions (cmH2O)
16
12
8
4
0
9
6
3
0
*
*
<60
60-70
70-80
80-90
90-100
>100
SCPP (mmHg)
B
No. of vesicular contractions
15
10
5
0
ns
<10
10-15
15-20
20-25
>25
ISP (mmHg)
C
No. of vesicular contractions
9
6
3
0
ns
<3
3-4
4-5
5-6
>6
Glucose (mmol/L)
D
No. of vesicular contractions
12
8
4
0
ns
<20
20-30
30-40
40-50
>50
LPR

FIGURE 4

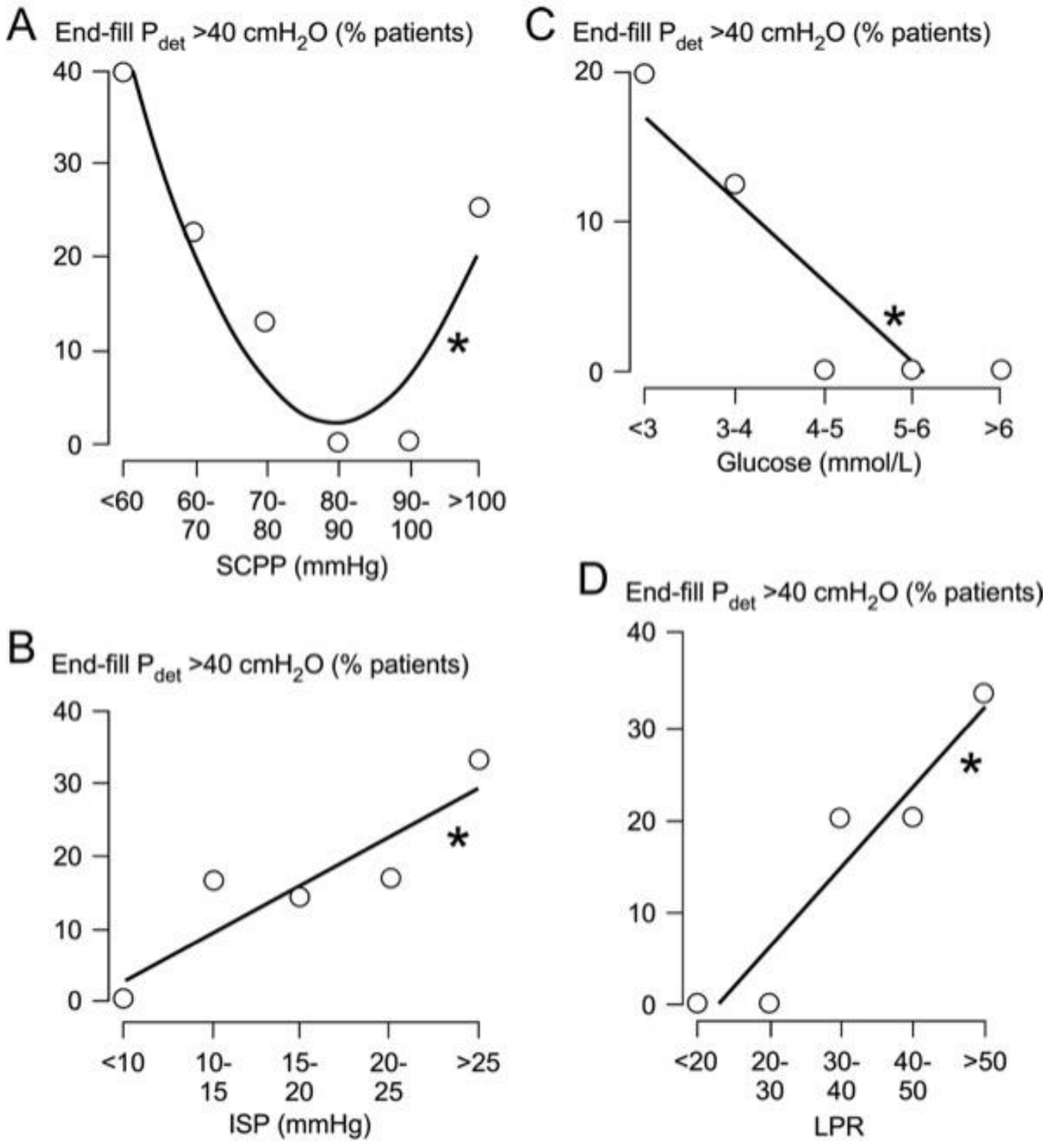

A
End-fill P_{det} >40 cmH_2O (% patients)
40
30
20
10
0
*
<60
60-70
70-80
80-90
90-100
>100
SCPP (mmHg)
B
End-fill P_{det} >40 cmH_2O (% patients)
40
30
20
10
0
*
<10
10-15
15-20
20-25
>25
ISP (mmHg)
C
End-fill P_{det} >40 cmH_2O (% patients)
20
10
0
*
<3
3-4
4-5
5-6
>6
Glucose (mmol/L)
D
End-fill P_{det} >40 cmH_2O (% patients)
40
30
20
10
0
*
<20
20-30
30-40
40-50
>50
LPR

FIGURE 5

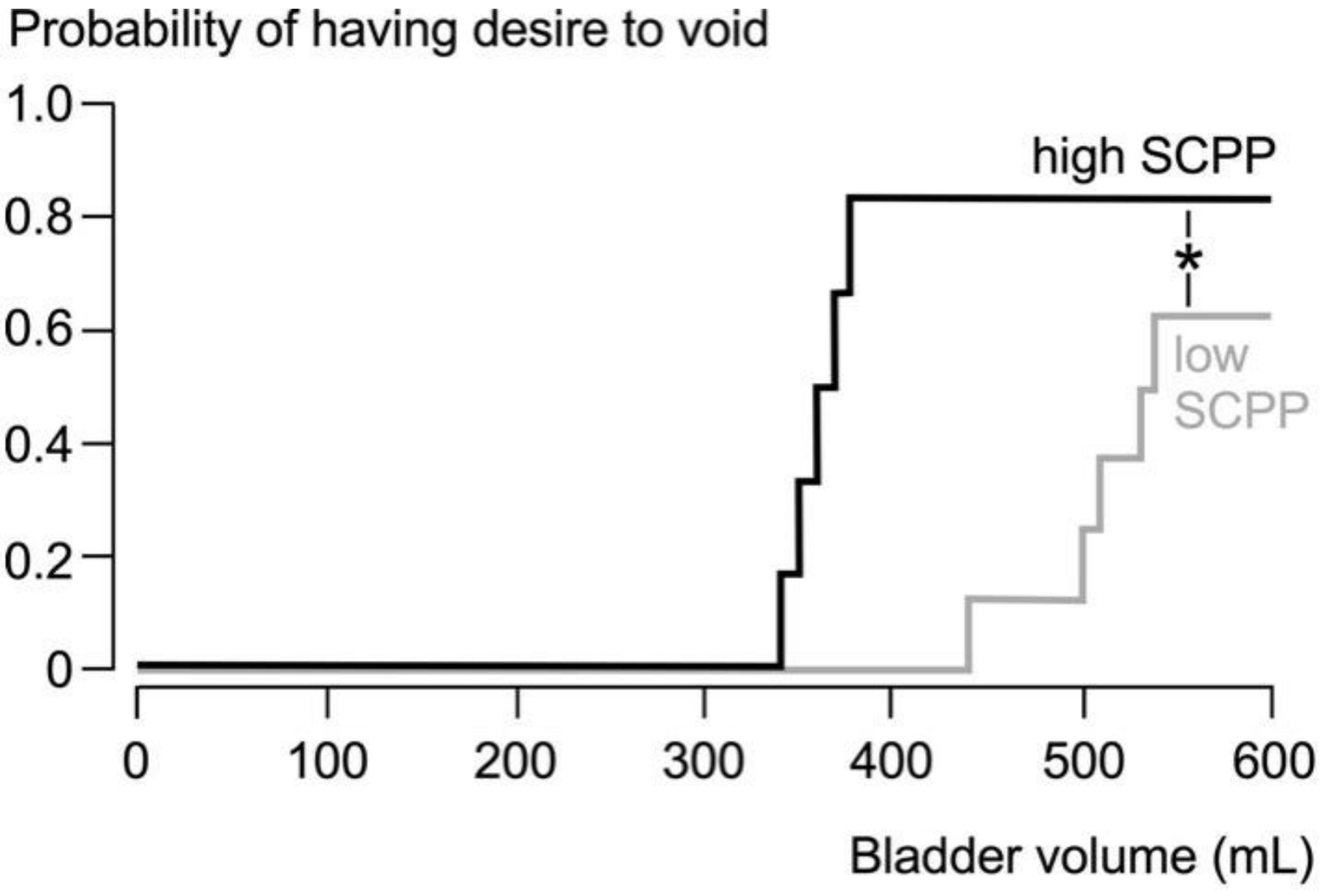
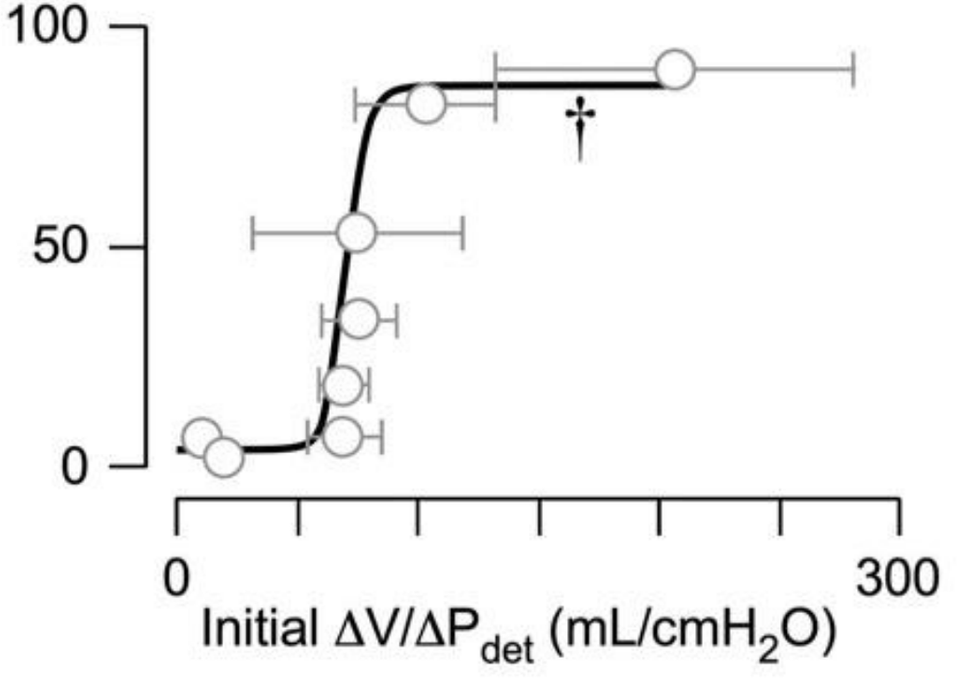

Probability of having desire to void
1.0
0.8
0.6
0.4
0.2
0
high SCPP
*
low
SCPP
0
100
200
300
400
500
600
Bladder volume (mL)

FIGURE 6

A



B

Sensation to void*

FOLLOWUP	PRESENTATION: Yes	PRESENTATION: No
Yes	3	0
No	0	4

FIGURE 7

Appendix 7: Publications written during PhD, but not part of thesis

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Original Article

Spinal Cord Blood Flow in Patients

NEU-2018-5961-ver9-Gallagher_1P.3d 11/08/18 7:38pm Page 2

image SCBF at the injury site and define the relation between blood pressure and SCBF.

Methods

Institutional approvals

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

Patient recruitment

The TSCI patient cohort was recruited prospectively between June 2016 and December 2017. Inclusion criteria are: 1) severe TSCI defined as American Spinal Injuries 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 are: 1) patient unable to consent; 2) other major comorbidities; and 3) penetrating TSCI. Non-TSCI patients were recruited and consented as part of their elective neurosurgical procedures.

Clinical assessments

A neurological AIS examination was performed on admission and before discharge to the spinal rehabilitation facility, at 4–8 weeks after injury. Further AIS examinations were performed at the 6- to 12-month outpatient follow-up appointment. Computed tomography and magnetic resonance (MR) scans of the whole spine were performed on admission.

Anesthesia and surgery

Patients were anesthetized with inhalational or intravenous agents. Intraoperative patient monitoring included pulse oximetry, end-tidal pCO_2, electrocardiogram, core temperature, and arterial blood pressure by an arterial catheter. Arterial blood gases were recorded every hour intraoperatively. Unless otherwise stated, MAP was 80–90 mm Hg, arterial pO_2 >13 kPa, and pCO_2 4.5–6.0 kPa. Surgical decompression (laminectomy ± corpectomy) and spinal instrumentation were performed based on individual patient requirements and surgeon preference.

Laser speckle contrast imaging

A portable LSCI device with a near-infrared laser diode at 785 nm (MoorFLPI; Moor Instruments Ltd., Axminster, UK) was mounted on a trolley by a rigid, extendable arm. During LSCI recording, the dural surface was kept clear of blood and background illumination was removed (i.e., operating theater lights were off). The imager was positioned perpendicular at 25 cm from the dura using fixed-length aiming lasers. Tissue perfusion was recorded with purpose-designed data acquisition software (MoorFLPI measurement software, Version V4.0; Moor Instruments) installed on a laptop. Frames were acquired at 150 × 116 pixels resolution, exposure of 20 ms, and spatial processing time constant of 100 ms at a sampling rate of 25 Hz. These settings allowed rapid changes of SCBF to be detected even within a cardiac cycle. Imaging field size was adjusted according to the patient habitus to include the entire exposed dura. SCBF is displayed as flux in arbitrary units (a.u.). LSCI uses calibration on a phantom to fix a point on a scale. All measurements are made relative to this in a.u. of perfusion that cannot be converted to absolute values of flow in mL/100 g of tissue/min, nor are they linear relative to absolute flow.

Effect of mean arterial pressure and arterial pCO_2 after traumatic spinal cord injury

A target MAP increase of 20 mm Hg was achieved by intravenous norepinephrine. We used norepinephrine because our hospital guidelines recommend norepinephrine as a first-line agent for MAP maintenance. Arterial pCO_2 was changed by altering minute ventilation and checked with arterial blood gas sampling. MAP, arterial pCO_2, and arterial pO_2 were kept constant for at least 5 min before LSCI. Arterial pO_2 and pCO_2 were kept constant when studying the effect of MAP change on SCBF. The arterial blood pressure signal was recorded from the anesthetic monitors simultaneously with flux measurement using a laptop running Labchart software (v7.3.5; ADInstruments Ltd, Oxford, UK).

Factors affecting spinal cord blood flow

Effect of cerebrospinal fluid (CSF) depth on LSCI recording was tested using an LSCI calibration block (MoorFLPI; Moor Instruments) set at varying depths of motionless normal saline solution in a water bath. Thirty-second recordings were repeated four times at each depth after resetting the calibration block, resulting in 3000 frames analyzed per depth. The effect of the dura and effect of change in MAP or pCO_2 on SCBF with dura open were tested in patients undergoing spinal intradural meningioma excision or foramen magnum decompression. The effect of the dura was recorded from 2 control patients with the dura intact, with a metal (McDonald) retractor covering the dura or with a McDonald retractor placed subdurally through a small transverse durotomy, and with the dura fully open. Each position was recorded with a mean of 5000 frames. Effect of MAP or pCO_2 change was examined in 3 control patients with the dura open. A mean of 5000 frames were analyzed for each physiological state.

Analysis of spinal cord blood flow images

Post-hoc analysis of SCBF images was performed. Recorded frames were reviewed for artefact (e.g., suctioning/blood). "Clean" frames were selected and averaged using the Moor software (Moor Instruments) into sequences of 100 consecutive frames spanning 4 sec. In all control tests, the averaged frames were analyzed after selecting a region of interest (ROI) with the MoorFLPI custom software to give a mean ± standard deviation flux value. In TSCI patients, averaged frames were exported as 256 grayscale images into ImageJ software (Freeware; National Institutes of Health, Bethesda, MD), where a chronological stack was created. We placed a rectangular selection window that avoided large-surface vasculature in corresponding positions on the dura of each frame in the stack. Using a custom-written macro plug-in, grayness pixel averages were computed for each frame in the stack to produce an average image. The following parameters were calculated from the average image. *Minimum flux* = minimum flux reading, *Maximum flux* = maximum flux reading, *% Flux gradient* = 100 × (maximum flux − minimum flux)/maximum flux, *% Cord infarct* = % of pixels with flux ≤25% of maximum, *% Cord penumbra* = % of pixels with flux 25–75% of maximum flux in the image, *Mean total flux* = Mean flux value for all pixels, *Delta max flux* = Maximum flux value at high MAP minus maximum flux at low MAP.

Intraspinal pressure probe and microdialysis catheter

After LSCI recording, an ISP probe (Codman Microsensor Transducer®; Depuy Synthes, Leeds, UK) and microdialysis catheter (CMA61; CMA Microdialysis AB, Solna, Sweden) were tunnelled through the skin into the laminectomy wound cavity. As previously described,[5–7,27] under the operating microscope, the dura and arachnoid were opened one level below the injury. The ISP probe and microdialysis catheter were inserted through

NEU-2018-5961-ver9-Gallagher_1P.3d 11/08/18 7:38pm Page 3

the durotomy and advanced under the arachnoid and placed on the surface of the dorsal columns until the tips were at the site of maximal cord swelling. The dural opening was sutured and supplemented with fibrin glue (Tisseel®; Baxter Healthcare Ltd., Baxter, UK). The ISP probe and microdialysis catheter were secured to the skin with silk sutures. A wound drain under gravity was placed for a week. We gave 5000 u of dalteparin daily starting at 24 h after surgery. Dalteparin was omitted 24 h before and 6 h after removing the probes and wound drain.

Intraspinal pressure and spinal cord perfusion pressure monitoring

The ISP probe was connected to a Codman ICP box linked by a ML221 amplifier to a PowerLab running LabChart software (v.7.3.5; ADInstruments). Arterial blood pressure was recorded from a radial artery catheter connected to the Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK) in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz for 24 h. LabChart was used to analyze the signals and compute SCPP, defined as MAP minus ISP. We computed the mean ± standard deviation ISP and SCPP. We have previously shown that ISP measured this way is different to intrathecal pressure measured above or below the injury site because the swollen, injured cord is compressed against the surrounding dura, thus compartmentalizing the intrathecal space. Details are given elsewhere.[5,7,27,28]

Microdialysis monitoring

Microdialysis monitoring was started postoperatively in the neurointensive care unit for 24 h. Central nervous system perfusion fluid (CMA Microdialysis AB) was perfused at a rate of 0.3 μL/min using the CMA106 infusion pump (CMA Microdialysis AB). Microdialysis vials were changed hourly, stored at 4^{0}C, and batch analyzed up to 24 h later using ISCUS Flex (CMA Microdialysis AB). The first two samples from each patient were discarded to allow priming of the microdialysis catheter and stabilization of the metabolite concentrations. All samples were analyzed for glucose, lactate, pyruvate, glycerol, and glutamate and the lactate to pyruvate ratio (LPR) was calculated. Changes (100-fold) in metabolite concentration compared with the preceding hour were excluded from analysis. Twenty-four-hour mean ± standard deviation values were computed. We previously showed that this microdialysis method measures the injury-site surface metabolism (glucose, lactate, pyruvate, glutamate, and glycerol), which correlates with intraparenchymal metabolism (correlation coefficients, 0.56–0.91), but is different from metabolites measured from CSF above or below (correlation coefficients, 0.23–0.50). Details are given elsewhere.[6,9,29]

Statistical analysis

Analyses were done with XLStat Biomed (v.18.07; Addinsoft, New York, NY). For the effect of CSF depth, we used one-way analysis of variance and pot-hoc two-tailed Dunn. Cord LSCI signals with dura open versus dura closed, LSCI signals from dura versus dura covered and LSCI signals at high versus low arterial pCO_2 were compared by two-tailed *t*-tests. Correlations between SCBF and MAP, SCBF and SCPP, SCBF indices and tissue metabolism, or SCBF indices and sensory outcome were examined with Spearman ρ. Metabolic signatures of the three SCBF patterns were compared by principal component analysis on the five metabolites (glucose, lactate, pyruvate, glutamate, and glycerol), and levels of each metabolite were pairwise compared by two-tailed Kruskal–Wallis. Significance was at $p < 0.05$.

Results

Patient characteristics

We recruited and imaged 22 patients with severe TSCI. Patients received sevoflurane (20 of 22; 91%) or propofol (2 of 22; 9%). Most patients were young (72.7%; <60 years old) and male (72.7%). Overall, 54.5% had cervical injuries, 31.8% thoracic, and 13.7% conus medullaris injuries. On admission, 54.5% had AIS A injuries, 13.7% AIS B, and 31.8% AIS C. LSCI recording was within 24 h of TSCI in 4.5% of patients, at 24–48 h days in 35.5%, and 48–72 h in 50.0%. Follow-up was 7.1 months, on average, during which 41% of patients improved at least one AIS grade. We analyzed 5359.1 ± 2896.9 (mean ± standard deviation) frames per patient with approximately equal numbers at low versus high MAP. MAP change was 24.0 ± 14.3 mm Hg (mean ± standard deviation). All TSCI patients had complete loss of CSF around the injured cord on pre-operative MR imaging (MRI). Patient characteristics are summarized in Table 1 and are shown in detail in Supplementary Table 1 (see online supplementary material at http://www.liebertpub.com). We also imaged the spinal cord after opening the dura in 2 patients undergoing foramen magnum decompression for Chiari I malformation and 2 patients undergoing excision of intradural spinal meningioma.

Effects of cerebrospinal fluid, cardiorespiratory pulsations, and dura on laser speckle contrast imaging signal

We first examined the effect of CSF depth (i.e., the length that the infrared beam has to travel through CSF before hitting the target) on the LSCI signal with a calibration block immersed in artificial CSF (Supplementary Fig. 1A) (see online supplementary material at http://www.liebertpub.com). Increasing CSF depth from zero to 0.3 cm reduced flux by ~24%, with no further appreciable decrease in flux between CSF depths 0.6 and 0.9 cm. Effects of cardiac and respiratory pulsations on the spinal cord LSCI signal were then tested in non-TSCI patients who had durotomy (that eliminates the effects of CSF and dura). Supplementary Figure 1B (see online supplementary material at http://www.liebertpub.com) and Supplementary Video 1 (see online supplementary material at http://www.liebertpub.com) show that SCBF is higher in systole compared with diastole (by up to ~30%) and varies with respiration by (5–10%). Finally, we tested the effect of the dura on the spinal cord LSCI signal (Supplementary Fig. 1C) (see online supplementary material at http://www.liebertpub.com).

Table 1. Patient Characteristics

Characteristic	*Value*
Age (mean ± s.d.)	42.1 ± 17.2
Sex (M : F)	16 : 6
Injury site (C3-7 : T1-11 : T12-L1)	12 : 7 : 3
Admission AIS grade (A : B : C)	12 : 3 : 7
Follow-up AIS grade (A : B : C : D)	8 : 4 : 6 : 4
Months of follow-up (mean ± s.d.)	7.1 ± 4.1
Hours from injury to LSCI (mean ± s.d.)	46.3 ± 15.5
Haemoglobin g/L (mean ± s.d.)	120.1 ± 16.9
Low MAP (mean ± s.d.)	83.5 ± 10.1
High MAP (mean ± s.d.)	107.1 ± 15.7

AIS, American spinal injuries association Impairment Scale, C, cervical; F, female; L, lumbar; M, male; s.d., standard deviation; T, thoracic

NEU-2018-5961-ver9-Gallagher_1P.3d 11/08/18 7:38pm Page 4

There were significant differences in the LSCI for the different dural states: With the dura open and no CSF, flux was significantly higher (by ~24%) compared to flux with dura intact and CSF present. The dura recorded low flux readings, comparable to background, which suggests that CSF rather than dura that attenuates the LSCI signal.

Effect of mean arterial pressure and arterial pCO_2 on laser speckle contrast imaging signal

Figure 1A shows examples of intact and impaired spinal cord autoregulation in a patient who had durotomy and no CSF overlying the cord. At a low MAP (70–80 mm Hg), autoregulation was impaired (i.e., SCBF correlated with MAP). At a higher MAP (90–95 mm Hg), autoregulation was intact (i.e., SCBF was constant despite changes in MAP). SCBF was sensitive to changes in arterial pCO_2 (Fig. 1B; Supplementary Video 2) (see online supplementary material at http://www.liebertpub.com): Hypercapnia (mean arterial pCO_2 = 7.46 kPa) was associated with significantly higher SCBF compared with normocapnia (mean arterial pCO_2 = 5.34 kPa). ◀ SV2

Three distinct patterns of spinal cord blood flow after traumatic spinal cord injury

We observed three distinct patterns of SCBF after TSCI, which we term the necrosis-penumbra pattern found in 6 of 22 (27.2%) patients, the hyperperfusion pattern found in 7 of 22 (31.8%) patients, and the patchy-perfusion pattern found in 9 of 22 (40.9%) patients. These patterns are illustrated in Figure 2A–C and Supplementary Videos 3–5 (see online supplementary material

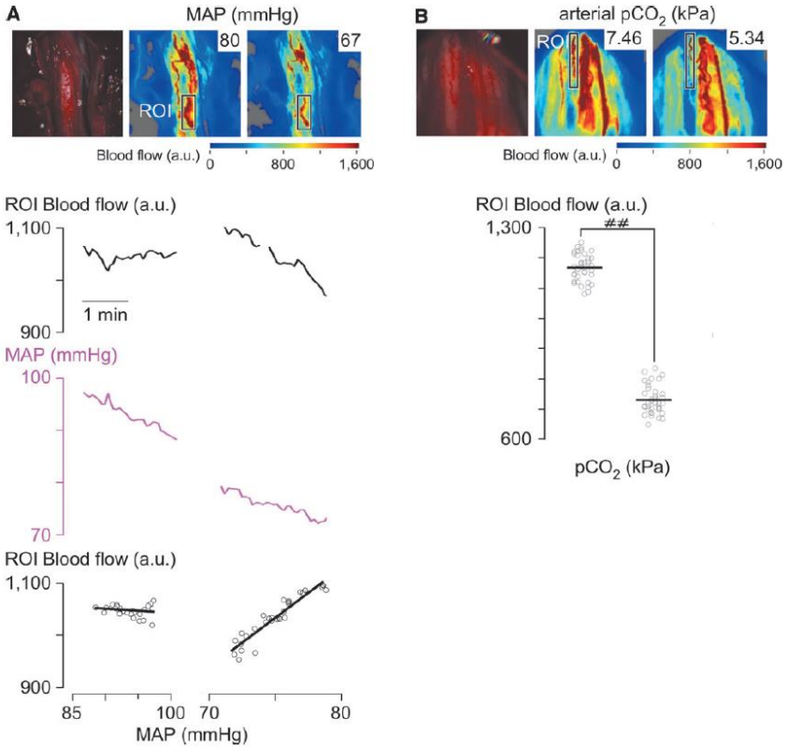


FIG. 1. Effect of changes in MAP and arterial pCO_2 on LSCI signal. (**A**; top) Bright-field photo and LSCI photos at high (80 mm Hg) and low (67 mm Hg) MAP. (Bottom) ROI blood flow (black) and MAP (pink) versus time with autoregulation intact (left) or impaired (right). (**B**; top) Bright-field photo and LSCI photos at high (7.46 kPa) and low (5.34 kPa) arterial pCO_2. (Bottom) ROI blood flow versus arterial pCO_2. In (A), ROI blood flow versus MAP Spearman $\rho = -0.12$ (left), 0.96 (right). In (B), circles = measurements, bars = means. $^{\#\#}p < 0.0001$. a.u., arbitrary units; LSCI, laser speckle contrast imaging; MAP, mean arterial pressure; ROI, region of interest;

MRI Photo LSCI MAP 1 LSCI MAP 2

at http://www.liebertpub.com). The necrosis-penumbra SCBF pattern is characterized by a central region of very low SCBF (necrosis), intermediate SCBF above and below (penumbra, as defined above flux values 25–75% of maximum), and normal SCBF more distally. Necrosis-penumbra was only observed in thoracolumbar TSCI. The hyperperfusion SCBF pattern is characterized by very high SCBF throughout the injury site and was only observed in cervical TSCI. The patchy-perfusion SCBF pattern is characterized by irregular regions of ischemic and hyperemic SCBF and was observed in five cervical and four thoracic TSCIs. These SCBF patterns were independent of the MAP. The TSCI to LSCI time intervals for the three SCBF patterns are not significantly different. We then visualized the metabolic profiles at the injury site by representing each TSCI patient as a point in a three-dimensional scatterplot with the first three principal components of the five microdialysis metabolites as the (x, y, z) coordinates. Patients clustered according to the SCBF pattern at their injury sites (Fig. 2D), thus indicating that three patterns of SCBF have markedly different metabolic profiles. Details of the metabolism of each SCBF pattern are summarized in Supplementary Table 2 (see online supplementary material at http://www.liebertpub.com).

Impaired spinal cord autoregulation after traumatic spinal cord injury

We investigated further the effect of change in MAP in the 6 of 22 (27.3%) patients with the necrosis-penumbra pattern of blood flow (Fig. 3; Supplementary Video 6) (see online supplementary material at http://www.liebertpub.com). These patients had very low SCBF at the injury site, likely indicating necrosis, intermediate SCBF on either side of the injury site, indicating penumbra, and normal SCBF distal to the penumbra. A drop in MAP did not affect the low SCBF within the necrotic site, produced a sustained fall in SCBF in the penumbra (i.e., impaired autoregulation), but only a transient drop in SCBF in normal spinal cord which recovered (i.e., intact autoregulation).

Effect of increasing mean arterial pressure on spinal cord blood flow after traumatic spinal cord injury

Intervening to increase MAP had a variety of effects on SCBF at the injury site, quantified as mean total flux: In 14 of 22 (63.6%) patients, mean total flux increased; in 3 of 22 (13.6%) patients, mean total flux decreased, and in the 5 of 22 (22.8%) there was no change. We then observed an unanticipated phenomenon, which we term blood pressure–induced local steal, in 5 of 14 (35.7%) of the patients who had increased mean total flux with higher MAP: Increasing MAP caused an increase in the LSCI signal from some parts of the injured cord, but a decrease in the LSCI signal from other parts of the cord (Fig. 4A; Supplementary Video 7) (see online supplementary material at http://www.liebertpub.com). We arbitrarily classified pixels in each LSCI image into three groups, that is, normal (flux 75–100% of maximum), penumbral (flux 25–75% of maximum), and necrotic (flux <25% of maximum). Interestingly, the local steal phenomenon only occurred in penumbral pixels. In some patients, we observed another phenomenon, which we term diastolic ischemia, in which parts of the injured cord were well perfused in systole, but inadequately perfused in diastole (Fig. 4B; Supplementary Video 8) (see online supplementary material at http://www.liebertpub.com). Diastolic ischemia was observed in 7 of 19 patients who had MAP 85–90 mm Hg.

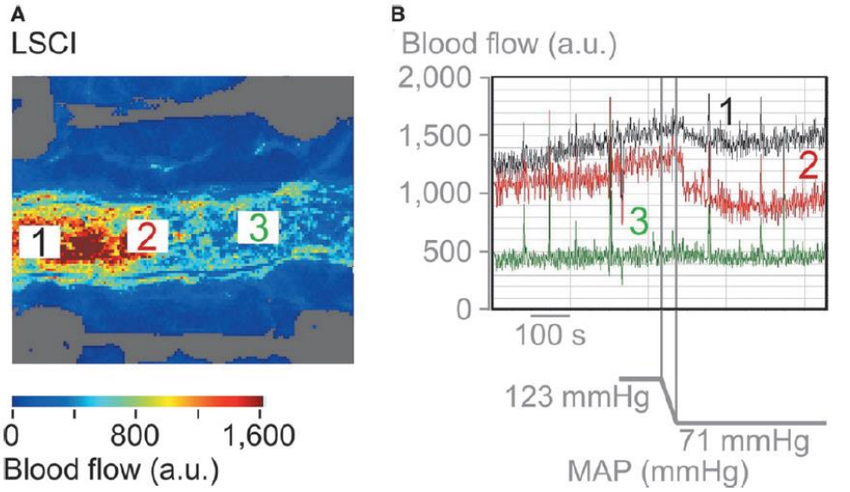


FIG. 3. Autoregulation at the injury site. (**A**) LSCI of injury site of a T3 AIS B patient showing three regions of interest (1 = normal cord, 2 = penumbra, 3 = ischemic cord). (**B**) Plots of blood flow versus time for the three regions of interest. Vertical gray lines indicate drop in MAP from 123 to 71 mm Hg. AIS, American Spinal Injuries Association Impairment Scale; a.u., arbitrary units; LSCI, laser speckle contrast imaging; MAP, mean arterial pressure.

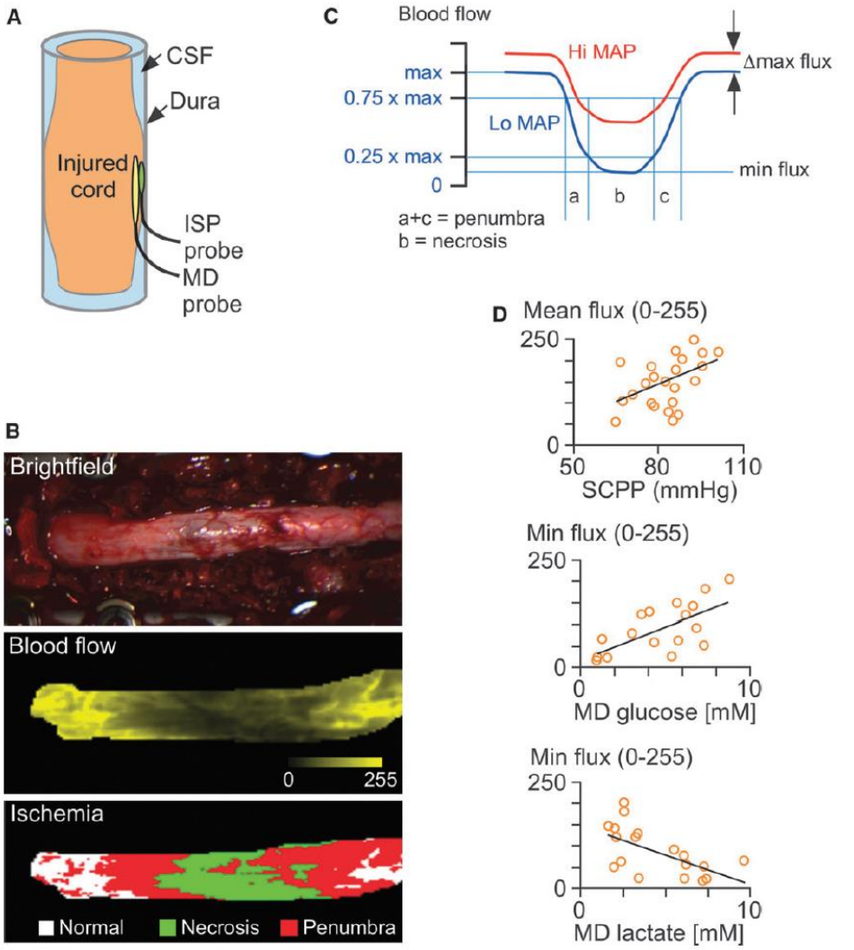


FIG. 5. Correlations between LSCI and injury-site physiology/biochemistry. (**A**) Schematic showing ISP and MD probes placed intradurally on the spinal cord surface at the injury site. (**B**) T6 AIS A. (Top) Intraoperative bright-field photo of injury site after laminectomy and fusion, (Middle upper) corresponding LSCI MAP 70 mm Hg with pixel intensity graded 0–255, (Middle lower) LSCI image recolored to show normal flow, penumbra, and necrosis/infarct. (C) Definitions of LSCI parameters, including min flux, max flux, Δmax flux, penumbra (blood flow at 25–75% of max), and necrosis/infarct (blood flow <25% of max). (**D**) Mean flux (graded 0–255) versus mean SCPP (24 h postoperatively) and best-fit trendline (Spearman $\rho = 0.53$; $p = 0.01$), Min flux (graded 0–255) versus mean MD glucose (24 h postoperatively) and best-fit trendline (Spearman $\rho = 0.63$; $p < 0.01$), Min flux (graded 0–255) versus mean MD lactate (24 h post-operatively), and best-fit trendline (Spearman $\rho = -0.58$; $p < 0.01$). AIS, American Spinal Injuries Association Impairment Scale; CSF, cerebrospinal fluid; ISP, intraspinal pressure; LSCI, laser speckle contrast imaging; MAP, mean arterial pressure; MD, microdialysis; SCPP, spinal cord perfusion pressure.

NEU-2018-5961-ver9-Gallagher_1P.3d 11/08/18 7:44pm Page 9



differences in spinal cord blood supply between humans, rodents,[35]

NEU-2018-5961-ver9-Gallagher_1P.3d 11/08/18 7:44pm Page 10

intervening to increase MAP may not always be beneficial. This hypothesis could be tested in future studies that utilize a functional measure, such as motor or somatosensory evoked responses, in addition to SCBF monitoring to determine whether blood pressure–induced local steal causes a reduction in spinal cord electrical activity.

SCBF measured by LSCI may have several applications in spinal cord surgery. SCBF may be used as an endpoint in TSCI trials, for example, to test early versus late bony decompression, bony decompression plus duroplasty versus bony decompression alone, or therapeutic drug versus placebo. Changes in SCBF may aid the neurosurgeon, for example, increase in SCBF may indicate adequate spinal cord decompression, whereas reduction in SCBF may indicate complete resection of a spinal cord vascular malformation. Imaging dorsal column SCBF in response to limb stimulation might provide functional information that complements neurophysiological monitoring to increase the safety of intradural tumor resection.

Conclusions

LSCI was used to measure SCBF after TSCI noninvasively during surgery. We observed several novel phenomena, not previously described in animal models, including three distinct pathological patterns of SCBF after TSCI, blood pressure–induced local steal as well as diastolic ischemia. SCBF correlates with injury-site physiology and metabolism as well as clinical outcome.

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Author Disclosure Statement

No competing financial interests exist.

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

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ABSTRACT

Purpose: To investigate the effect of increasing spinal cord perfusion pressure (SCPP) on sensory evoked potentials (SEPs) and injury site metabolism in patients with severe traumatic spinal cord injury TSCI.
Materials and methods: In 12 TSCI patients we placed a pressure probe, a microdialysis catheter and a strip electrode with 8 contacts on the surface of the injured cord. We monitored SCPP, lactate-to-pyruvate ratio (LPR) and SEPs (after median or posterior tibial nerve stimulation).
Results: Increase in SCPP by ~20 mmHg produced a heterogeneous response in SEPs and injury site metabolism. In some patients, SEP amplitudes increased and the LPR decreased indicating improved tissue metab
olism. In others, SEP amplitudes decreased and the LPR increased indicating more impaired metabolism. Compared with patients who did not improve at follow-up, those who improved had significantly more electrode contacts with SEP amplitude increase in response to increasing SCPP.
Conclusions: Increasing SCPP after acute, severe TSCI may be beneficial (if associated with increase in SEP amplitude) or detrimental (if associated with decrease in SEP amplitude). Our findings support individualized management of patients with acute, severe TSCI guided by monitoring from the injury site rather than applying universal blood pressure targets as is current clinical practice.

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1. Introduction

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

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

SEPs are typically elicited by stimulating a peripheral nerve and recording from skin electrodes placed cranially to assess the functional integrity of the dorsal columns. Depending on the severity of TSCI,

Abbreviations: AIS, American spinal injuries association Impairment Scale; BASIC score, Brain and Spinal Injury Center score; CSF, cerebrospinal fluid; ISCoPE, Injured Spinal Cord Pressure Evaluation study; ISP, intraspinal pressure; LPR, lactate-to-pyruvate ratio; MAP, mean arterial pressure; MD, microdialysis; NICU, neuro-intensive care unit; SCBF, spinal cord blood flow; SCPP, spinal cord perfusion pressure; $SCPP_{opt}$, optimum spinal cord perfusion pressure; SEP, spinal somatosensory evoked potential; sPRx, spinal pressure reactivity index; TSCI, traumatic spinal cord injury.

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

2. Materials and methods

2.1. Institutional approvals

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

2.2. Patient recruitment

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

2.3. Clinical assessments

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

2.4. Surgery

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

2.5. Intraspinal pressure probe, microdialysis and subdural electrodes

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

2.6. ISP and SCPP monitoring

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

2.7. Microdialysis

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

2.8. Spinal cord SEPs

SEPs were recorded by a highly specialized clinical neurophysiologist, supervised by a consultant neurophysiologist using a XLTEK Protektor 32 system with a bipolar stimulating bar electrode (Natus Neuro, Middleton, WI, USA). Sampling rate was 30 kHz, downsampled to 7538 Hz for analysis, with bandpass filter 30–1.5 kHz. For the upper limbs, we stimulated the median nerve (wrist) and for the lower limbs the posterior tibial nerve (ankle). In each patient, optimal stimulation was determined by observing repetitive muscle contraction of the abductor pollicis brevis or flexor hallucis brevis; subsequent runs were performed at the same intensity at 1.9 Hz. As control, we obtained surface recordings using Ag/AgCl cup electrodes (Unimed, Surrey, UK) filled with Ten20 conductive paste (Weaver & Co, Colorado, USA) with Nuprep skin preparation gel (Weaver & Co, Colorado, USA). Impedances were <5 kΩ. We also obtained control responses from peripheral nerves using electrodes placed at Erb's point and popliteal fossa with the ground electrode at Fz. SEPs were recorded from the subdural electrode strip with a reference electrode placed on the neck. Each run was the averaged of 300 accepted sweeps with at least two runs obtained for each limb. Responses were recorded after lower limb stimulation for thoracic injuries and after upper then lower limb stimulation for cervical injuries at MAP 65–70 mmHg; then, MAP was increased using intravenous norepinephrine by ~20 mmHg and kept constant for 10 min before the SEPs were repeated.

2.9. SEP signal analysis

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

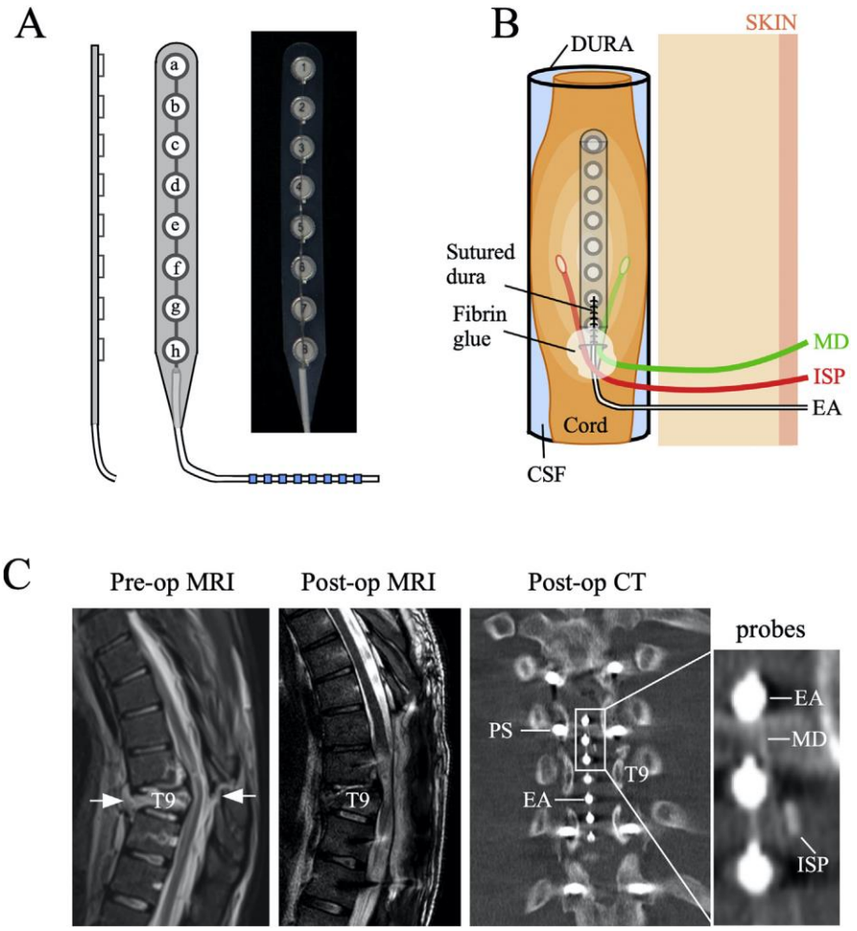


Fig. 1. Setup for recording SEP, ISP and MD from injury site. A. ADTech Medical 8-contact electrode strip. B. Schematic showing subdural position of electrode array (EA), ISP probe and MD catheter on cord surface, sutured dural opening and fibrin glue. C. Pre-operative MRI, post-operative CT and post-operative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

2.10. MRI/CT analysis

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

2.11. Statistical analysis

Analyses were done with XLStat Biomed (v.18.07; Addinsoft, NY, USA). SEP assessor agreement was tested with Cohen's κ. LPR *versus* SCPP and *versus* [glucose] for the two groups (BETTER SEP, WORSE SEP) was tested with two-way ANOVA and *post hoc* Fisher's least significant difference test. AIS grade improvement *versus* active contacts and *versus* amplitude increase was tested by two tailed *t*-test. Significance was at $P < .05$.

Table 1
Patient details.

Characteristic	Description	Value
Patients	Number	12
Sex	Male: Female	8: 4
Age	Mean ± SD	40 ± 18
	Median (range)	35 (19–63)
Site of injury	No. of patients: C1–4, C5–8, T1-L1, ventilator dependent	1, 6, 5, 0
Admission: Injury severity	No. of patients: AIS A, B, C	4, 1, 7
Follow-up: Injury severity	No. of patients: AIS A, B, C	4, 1, 3, 4
Follow-up (months)	Mean ± SD	8 ± 4
	Median (range)	8 (3–15)
AIS grade change	No. of patients: −1: 0: 1	1: 7: 4
Surgical approach	Anterior: Posterior: Both	0: 10: 2
Injury to surgery: hours	Mean ± SD	44 ± 15
	Median (range)	41 (22–72)
Injury to SEP: hours	Mean ± SD	158 ± 27
	Median (range)	152 (120–205)

AIS, American spinal injuries association Impairment Scale; SE, standard error; SEP, somatosensory evoked potentials.

Table 2
Complications. Table shows probe-related and unrelated complications.

	Complication	No. of Patients
Probe-related	CSF leak from wound	0 / 12
	CSF leak from probe skin site	3 / 12
	Meningitis	0 / 12
	Wound breakdown	0 / 12
	Wound infection	0 / 12
Unrelated	Paralytic ileus	1 / 12
	Pneumonia	3 / 12
	Venous line infection	2 / 12
	Urinary tract infection	2 / 12

3. Results

3.1. Patient characteristics

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

3.2. Injury site monitoring is safe

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

3.3. Overall SEP analysis

Of the 96 electrode contacts (12 patients × 8), four did not contact the cord according to the CT thus having no SEP. Overall, two independent and blinded assessors agreed 86% of the time regarding the presence / absence of SEPs ($\kappa = 0.72$, $P < .0005$). SEP signals had a wide range of amplitudes and latencies from 1.0–112.7 μV, 8.2–16.6 ms (upper limb stimulation) and 0.3–29.5 μV, 17.9–30.6 ms (lower limb stimulation). Electrode contacts cranial to the site of maximal MRI injury (BASIC score 3 or 4) were ~50% less likely to have detectable SEP signals than contacts with the same BASIC score, but caudal to the injury site (Fig. 2). Also, AIS grade inversely correlated with the probability of SEP detection cranial to the injury: 13% AIS A patients had SEPs cranial to the injury, compared with 45% AIS C patients. Thus, monitoring SEPs from the injured cord may be used to assess the severity of injury.

3.4. Increasing SCPP produces heterogeneous SEP amplitude changes

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

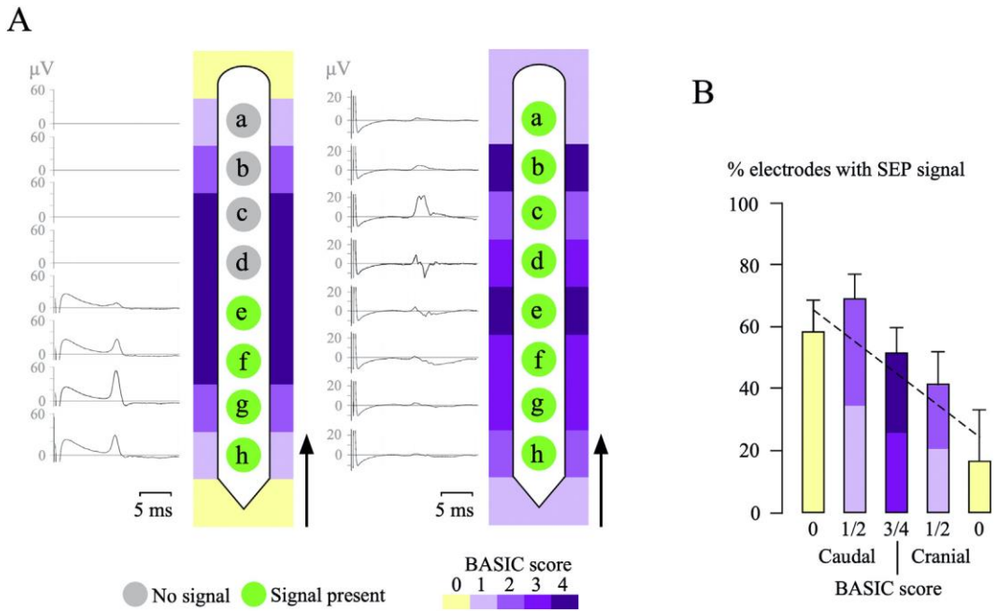


Fig. 2. SEP signal depends on injury severity. A. SEPs from two patients: (left) 28-year-old C5 AIS A, and (right) 32-year-old C4 AIS C. Green electrodes (signal recordable), black electrodes (no detectable signal), 'off' (electrode not in contact with cord). BASIC score corresponding to each electrode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

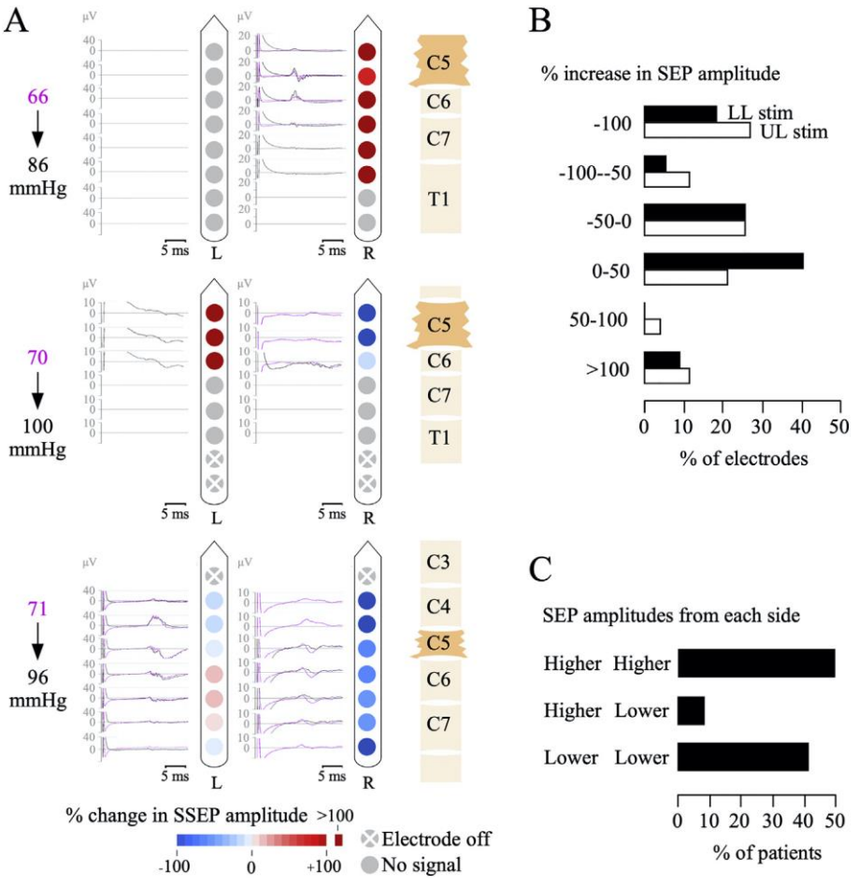


Fig. 3. Effect of increasing SCPP on SEP amplitude. A. SEPs in three patients at low (pink) and high (black) SCPP: (top) 19-year-old C5 AIS A (middle), 53-year-old C5 AIS A (bottom), 63-year-old C5 AIS C. (left) SEPs at low and high SCPP, (middle). % change in SEP amplitude in response to SCPP increase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

was −5–5%) and with lower limb stimulation by −5.4–3.8% (in 34/36 electrodes latency change was −5–5%).

3.5. Injury site LPR correlates with SEP amplitude change in response to SCPP increase

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

3.6. SEPs correlate with neurological outcome

SEPs significantly correlated with neurological outcome. In response to increased SCPP, the patients who improved an AIS grade had a greater increase in total active contacts (all limbs combined) than those that did not improve (22.7% increase *versus* 0.4% increase, $P < .0001$). Furthermore, with all limbs combined, the number of active contacts with amplitude increase when SCPP increased was higher in patients who improved an AIS grade compared to those that did not (75.1% *versus* 47.1%, $P < .0001$).

4. Discussion

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

4.1. SEPs correlate with severity of injury

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

4.2. Heterogeneous SEP response to SCPP increase

We found heterogeneous SEP amplitude responses when SCPP increased: In 50% patients, SEP amplitudes increased overall with left

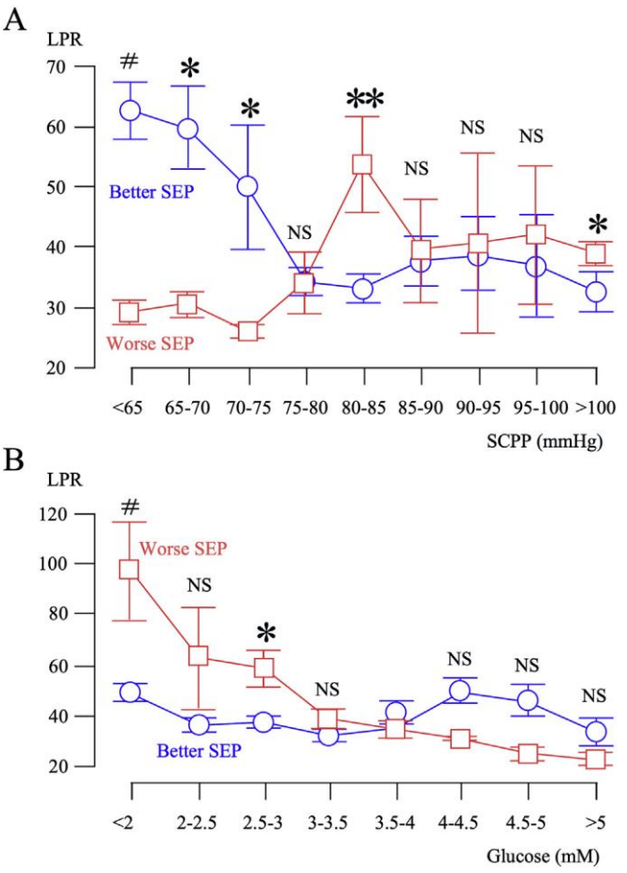


Fig. 4. Effect of increasing SCPP on injury site metabolism. A. Plot of injury site LPR vs. SCPP recorded for eight hours before SEPs. B. Plot of injury site LPR vs. injury site glucose recorded for eight hours before SEPs. Patients whose SEP amplitude increases (blue circles, Better SEP) or decreases (red squares, Worse SEP) with increase in SCPP. Mean +/− standard error. P < .05*, 0.01**, 0.005# for corresponding points, NS = not significant. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and right limb stimulations, suggesting that the SCPP increase was beneficial. In 42% patients SEP amplitudes decreased overall with left and right limb stimulations, *i.e.* increasing SCPP appeared detrimental. These findings support our concept that too high and too low SCPPs are detrimental, *i.e.* there is an intermediate $SCPP_{opt}$. $SCPP_{opt}$ which is individualistic [25] and varies temporally [9]. Our data suggest that universal MAP targets [9] or intervention to increase the MAP without monitoring SCPP and without computing a target $SCPP_{opt}$ may damage the injured cord.

4.3. SEP response to SCPP increase correlates with injury site metabolism

We found profound differences in the metabolism of the injured cord between patients who had BETTER SEPs compared with WORSE SEPs in response to increasing the SCPP. In patients with BETTER SEPs, increasing the SCPP reduced the LPR *i.e.* improved tissue metabolism, with no change in the LPR when injury site [glucose] increased. We hypothesize that O_2, but not glucose, supply to the injury site is the limiting factor here. In these patients, increasing the SCPP may increase SCBF at the injury site thus reducing injury site hypoxia, in turn increasing SEP amplitudes. In contrast, in patients with WORSE SEP amplitudes, increasing the SCPP increased the LPR, *i.e.* worsened metabolism, and there was decrease in the LPR when injury site [glucose] increased. Increasing the SCPP in these patients may produce local steal at the injury site [12] thus increasing the LPR, and worsening the SEP. Glucose supply may be a limiting factor here thus explaining why increase in tissue [glucose] improves injury site metabolism (decreases LPR).

4.4. Potential role of injury site penumbra

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

4.5. Limitations of the study

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

4.6. Clinical significance

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

5. Conclusions

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

Funding

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Financial disclosure

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Declaration of Competing Interest

There are no conflicts of interest.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.12.019.

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Visibility Graph Analysis of Intraspinal Pressure Signal Predicts Functional Outcome in Spinal Cord Injured Patients

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Abstract

To guide management of patients with acute spinal cord injuries, we developed intraspinal pressure monitoring from the injury site. Here, we examine the complex fluctuations in the intraspinal pressure signal using network theory. We analyzed 7097 h of intraspinal pressure data from 58 patients with severe cord injuries. Intraspinal pressure signals were split into hourly windows. Each window was mapped into a visibility graph as follows. Vertical bars were drawn at 0.1 Hz representing signal amplitudes. Each bar produced a node, thus totalling 360 nodes per graph. Two nodes were linked with an edge if the straight line through the nodes did not intersect a bar. We computed several topological metrics for each graph including diameter, modularity, eccentricity, and small-worldness. Patients were followed up for 20 months on average. Our data show that the topological structure of intraspinal pressure visibility graphs is highly sensitive to pathological events at the injury site, including cord compression (high intraspinal pressure), ischemia (low spinal cord perfusion pressure), and deranged autoregulation (high spinal pressure reactivity index). These pathological changes correlate with long graph diameter, high modularity, high eccentricity and reduced small-worldness. In a multivariate logistical regression model, age, neurological status on admission, and average node eccentricity were independent predictors of neurological improvement. We conclude that analysis of intraspinal pressure fluctuations after spinal cord injury as graphs, rather than as time series, captures clinically important information. Our novel technique may be applied to other signals recorded from injured central nervous system (CNS); for example, intracranial pressure, tissue metabolite, and oxygen levels.

Keywords: intensive care unit; intraspinal pressure; monitoring; network theory; spinal cord injury

Introduction

Traumatic spinal cord injury (TSCI) is a devastating condition with generally poor outlook.[1,2] Most patients are young males with complete injuries who remain paralyzed without control of bladder, bowel, or sexual function. There is no treatment proven to improve outcome after acute, severe TSCI,[3] and, consequently, current medical and surgical management practices are variable.[4] Following the primary injury, further cord damage may occur, for example, from ongoing cord compression, low blood pressure,[5] peripheral infections,[6] and fever.[7]

To prevent such secondary cord damage, we introduced monitoring from the injury site in patients in the intensive care unit (ICU).[1,8,9] We monitor intraspinal pressure (ISP), spinal cord perfusion pressure (SCPP) and the vascular pressure reactivity (sPRx), which is used to compute the optimum SCPP.[10] These monitoring techniques are safe[11] and are analogous to monitoring intracranial pressure (ICP) and cerebral perfusion pressure (CPP) after traumatic brain injury (TBI). Several lines of evidence suggest that ISP and SCPP are clinically important physiological parameters: first, higher SCPP correlates with better injury site metabolism (higher glucose, lower lactate-to-pyruvate ratio, lower glutamate, lower glycerol) determined by microdialysis.[12] Second, intervention to increase SCPP in TSCI patients improves neurological status in some patients.[1] Third, lower mean ISP and higher mean SCPP correlate with improved long-term neurological outcome.[13] Fourth, intervening to increase SCPP increases the amplitude of motor evoked responses monitored from below the injury site in some patients.[1]

The ISP signal (and its brain equivalent, the ICP) is a complex time series; therefore, conventional analysis, for example computing mean ISP amplitude, loses biologically important information hidden within the various complex patterns of signal fluctuations. To access such hidden information, we analyzed the ISP signals from a different perspective. We first map each hourly ISP time series into a visibility graph.[14] We then determine the topological structure of these graphs using analytical tools developed in complex network theory; for example, diameter, modularity, eccentricity, and small-worldness.[15] Our data show that the topological characteristics of ISP graphs are highly sensitive to adverse events at the injury site such as cord compression (increased ISP), hypoperfusion (reduced SCPP), and impaired vascular pressure reactivity (increased sPRx). Remarkably, these topological metrics correlate with neurological outcome.

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NEU-2018-5775-ver9-Chen_1P.3d 09/06/18 4:31pm Page 2

Methods

Approvals

Patients were part of the Injured Spinal Cord Pressure Evaluation (ISCoPE) study (https://clinicaltrials.gov, NCT02721615). Approvals were obtained from the St. George's, University of London Joint Research Office and the National Research Ethics Service London–St. Giles Committee. Informed consent was obtained from all participants included in the study.

Patient recruitment

All patients were treated at the Department of Neurosurgery and the Neuro-ICU at St. George's Hospital in London. ISCoPE inclusion criteria are: (1) Severe TSCI defined as American Spinal Injuries Association Impairment Scale (AIS) grades A–C, (2) Age 18–70 years, and (3) Timing between TSCI and surgery ≤72 h. Exclusion criteria are: (1) Inability to consent, (2) Major comorbidities, or (3) Penetrating TSCI. This is a consecutive series of ISCoPE patients from 2010 to 2017.

Insertion of ISP probe

After bony realignment and posterior fixation, the ISP probe (Codman Microsensor Transducer®, Depuy Synthes, Leeds, UK) was placed intraoperatively under the dura on the spinal cord surface at the site of maximal cord swelling as determined from magnetic resonance imaging (MRI). The probe monitors pressure, which is generated by the swollen injured cord compressed against the dura. These ISP recordings differ from corresponding values obtained from proximal or distal cord or extradurally. Details are given elsewhere.[1,8,11–13,16,17]

ISP, SCPP

The ISP probe was connected to a Codman ICP box linked via an ML221 amplifier to a PowerLab running LabChart v.7.3.5 (AD Instruments, Oxford, UK). Arterial blood pressure was recorded from a radial artery catheter kept at heart level and connected to a Philips Intellivue MX800 bedside monitoring system (Philips, Guildford, UK), which was in turn connected to the PowerLab system. ISP and arterial blood pressure signals were sampled at 1 kHz for up to 7 days. LabChart was used to analyze the signals and compute SCPP as mean arterial pressure (MAP) minus ISP. Spinal pressure reactivity index (sPRx) was computed as the running correlation coefficient over 5 min between MAP and ISP. Details are given elsewhere.[1,8,11–13,16,17]

Patient assessments

Neurological examinations to record the AIS grade were performed by neurosurgical research fellows who are experienced neurosurgical residents trained according to the International Standards for Neurological Classification of Spinal Cord Injury. Patients were examined on admission, prior to discharge to the spinal rehabilitation center, and during outpatient appointments. A computed tomography (CT) scan and an MRI of the whole spine were performed on admission, another CT was performed within 48 h of surgery, another MRI was performed within 2 weeks of surgery, and another MRI was performed at 6–12 months after surgery.

Converting ISP signals into graphs

The ISP time series was re-sampled at 0.1 Hz and split into non-overlapping hourly windows. The natural visibility algorithm proposed by Lacasa and coworkers[14] was programed into MATLAB (https://uk.mathworks.com) and applied to each hourly ISP signal to identify nodes and links and to obtain the adjacency matrix, which shows if points (nodes) are visualized by other nodes. The algorithm maps each 0.1 Hz ISP value onto a node, which is connected to any node that has a visibility link. For details see supplementary text (see online supplementary material at http://www.liebertpub.com).

Graph metrics

We characterized the following topological metrics for each graph. *Graph diameter* is the shortest path between the two most distant nodes.[15] *Graph modularity* measures how a graph is structured and identifies communities/clusters.[18] *Graph eccentricity* captures how important nodes are in a graph.[15] We computed average E. *Clustering coefficient* indicates the extent to which neighbors of a node are neighbors of each other. *Average path length* shows, on average, the number of steps it takes to get from one node to another. *Small-worldness* is quantified by the coefficient σ. If $\sigma > 1$, then the graph is small-world; that is, it is characterized by a high clustering coefficient and short average path length.[19] Each measure gives a single value per hourly ISP graph that can be plotted against corresponding hourly ISP, SCPP. and sPRx values. For details see supplementary text (see online supplementary material at http://www.liebertpub.com). ◀ST

Graph visualization

The adjacency matrix was analyzed using the Girvan–Newman algorithm[18] to detect embedded groups/clusters of nodes within the graph. To display the graphs, node data (node ID, degrees) and edge data (source nodes, target nodes, weights) were imported into Gephi (v.0.9.2, https://gephi.org) within the MATLAB environment. The FORCEATLAS2 layout algorithm within GEPHI was used to disperse groups of nodes and give space around larger nodes. We checked "prevent overlap" and set "scaling" to 50 in the parameter settings. The function was kept running until the network was mostly stabilized. Nodes and edges were then colored to display clusters, centrality, and quality features of the graph.

Simulated signals

We investigated the effect of different types of signal fluctuations on graph topology by considering the effect of the following modifications on a sinusoidal signal: no modification, narrow trough, narrow peak, transiently elevated baseline, wide peak, and wide peak with smaller peaks on top. We chose these modifications based on our observations of many ISP signals, aiming to model clinically important events: For example, in our earlier work we showed that a regular ISP signal has low complexity and is pathological.[20] High ISP, as occurs after a severe TSCI, often has transient troughs. A normal ISP signal, as occurs with less severe TSCI, has transient narrow peaks, and its baseline fluctuates because of respiration and autoregulatory response to changes in MAP. After a severe TSCI, there are often prolonged elevations in ISP.

Statistical analysis

Data are shown as mean ± standard error of the mean (SEM). We computed Pearson correlation coefficients. Statistical significance was taken at $p < 0.05$. Logistical regression analysis was performed using XLStat Biomed v.2018.1 using the logit model. For multivariate logistical regression, we chose the best model with a minimum of 1 and a maximum of 8 variables, to maximize the likelihood ratio.

Results

Patient details

During the study period, 61 consecutive patients met the inclusion/exclusion criteria and were asked to enter the study: 59 patients accepted and 2 patients refused. We therefore recruited 59

TABLE 1. PATIENT DETAILS

Characteristic	*Number*
Number of patients[a]	58
Age (mean ± SEM)	41.4 ± 2.0
Sex (Male : female)	46 : 12
Level of injury (Ce : Th : Lu)	30 : 25 : 3
Surgery (posterior : anterior+posterior)	50 : 8
Admission AIS (A : B : C)	40 : 8 : 10
Follow-up AIS (A : B : C : D : E)[b]	32 : 6 : 7 : 11 :1
Hours of monitoring (mean ± SEM)	131.4 ± 4.8
Months of follow-up (mean ± SEM), range	20.0 ± 1.2, 11.4–36.0

[a]Fifty-nine consecutive patients were recruited, but the intraspinal pressure (ISP) probe failed in one patient; therefore, 58 patients are included.
[b]One patient was lost to follow-up; therefore follow-up data was from 57 patients.
AIS, American Spinal Injuries Association Impairment Scale; SEM, standard error of the mean; Ce, cervical; Lu, lumbar; Th, thoracic.

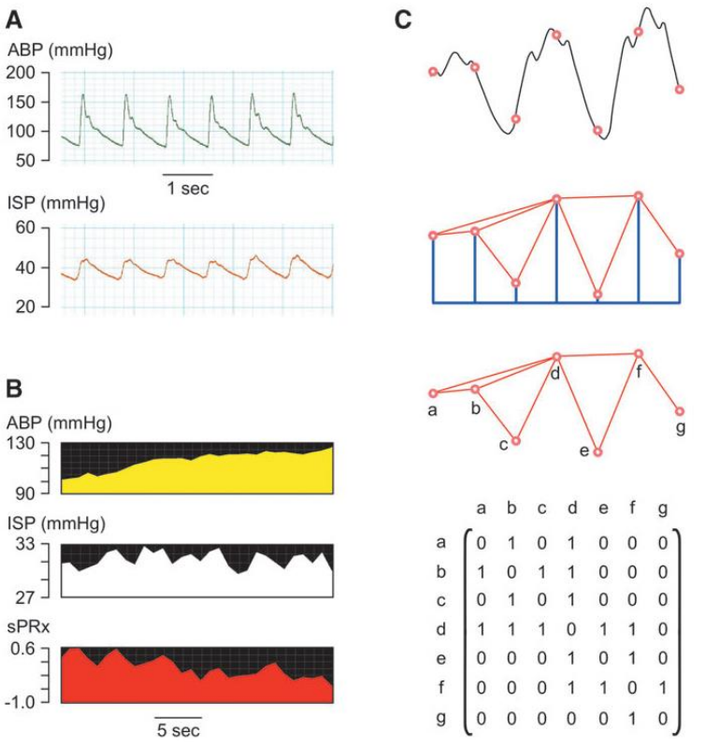
TSCI patients. In 1 patient, the ISP probe became dislodged and, therefore, data from 58 patients are analyzed. Patients were generally young (81.0% <60 years old) and mostly male (79.3%). Most patients (69.0%) had complete TSCI (i.e., AIS grade A) on admission. Approximately half of them had cervical injuries (51.7%) and half (48.3%) had thoracic/lumbar injuries. All patients underwent posterior surgical approaches, but 14.2% also had anterior surgery. On average, ISP monitoring continued for 5–6 days after surgery in the ICU. Mean follow-up was 20 months both in patients who improved AIS grade(s) and in those who did not. Patient details are summarized in Table 1. ◀T1

Complications

In this patient cohort, we recorded the following complications, likely related to ISP monitoring: pseudomeningocele (15/58, 25.9%), cerebrospinal fluid (CSF) leak (8/58, 13.8%), meningitis (0/58, 0.0%), wound infection (0/58, 0.0%), probe-associated hematoma or cord damage (0/58, 0.0%), and worse AIS grade (0/58, 0.0%). Pseudomeningocele was detected on the first post-operative MRI performed at 1–2 weeks after surgery and resolved on MRI performed at 6–12 months after surgery. CSF leak through probe skin exit sites or through the wound during monitoring was stopped by placement of extra skin sutures. There was no need to re-operate on any patient as a result of ISP monitoring.

Visibility graphs

Figure 1A shows examples of ISP and MAP signals obtained ◀F1 from the injury site of a patient. The signals were imported into



4C ▶

FIG. 1. Patient monitoring and visibility graph construction. **(A)** Examples of arterial blood pressure (ABP) and intraspinal pressure (ISP) signals. **(B)** ABP and ISP signal data imported in ICM+ to compute other signals; for example, vascular pressure reactivity (sPRx). **(C)** Stages in constructing a visibility graph (top to bottom): The ISP signal is marked at regular intervals (a – g). Visibility lines (red) are drawn to link nodes in the graph. Finally, the adjacency matrix is constructed with entries "1" if two nodes are connected and "0" if they are not.

ICM+ to compute SCPP and sPRx (Fig. 1B). ISP data were transformed into visibility graphs as summarized in Figure 1C. ISP time series were first divided into non-overlapping hourly windows. For each window, vertical bars were drawn at regular intervals representing ISP amplitude such that each bar corresponds to a node in the graph. Two nodes were linked with an edge if the straight line linking the nodes did not intersect a bar. The adjacency matrix A_{ij} was then constructed with entries "1" if two nodes were linked or "0" if the nodes were unlinked. Although we computed many topological metrics of ISP graphs, here we focus on D, Q, E, and σ.

Graph diameter

Diameter is the geodesic path between the two nodes that are farthest apart. Figure 2A and B show examples of two hourly ISP signals and their respective graphs, one with long and one with short diameter. We found a strong positive correlation between ISP and graph diameter as well as between sPRx and graph diameter, but found strong negative correlation between SCPP and graph diameter (Fig. 2C). Therefore, cord compression, ischemia, and loss of autoregulation are associated with increased graph diameter. Figure 2D shows the effect of various ISP fluctuations on graph diameter. A sinusoidal signal has long diameter. Introducing a narrow trough only slightly shortens the diameter, but a narrow peak or transiently elevated baseline greatly reduces the diameter by providing bridging nodes. A wide peak with or without smaller peaks on top has little influence on the diameter. Thus, irregular signals with transient peaks or transient baseline elevations have short diameter, whereas regular signals or signals with prolonged elevations have longer diameter.

Graph modularity

The nodes within a graph may form cliques, such that nodes within a clique are strongly linked, but cliques only weakly link with each other. Modularity measures how well cliques link between them and is high if the cliques poorly interlink. Figure 3A

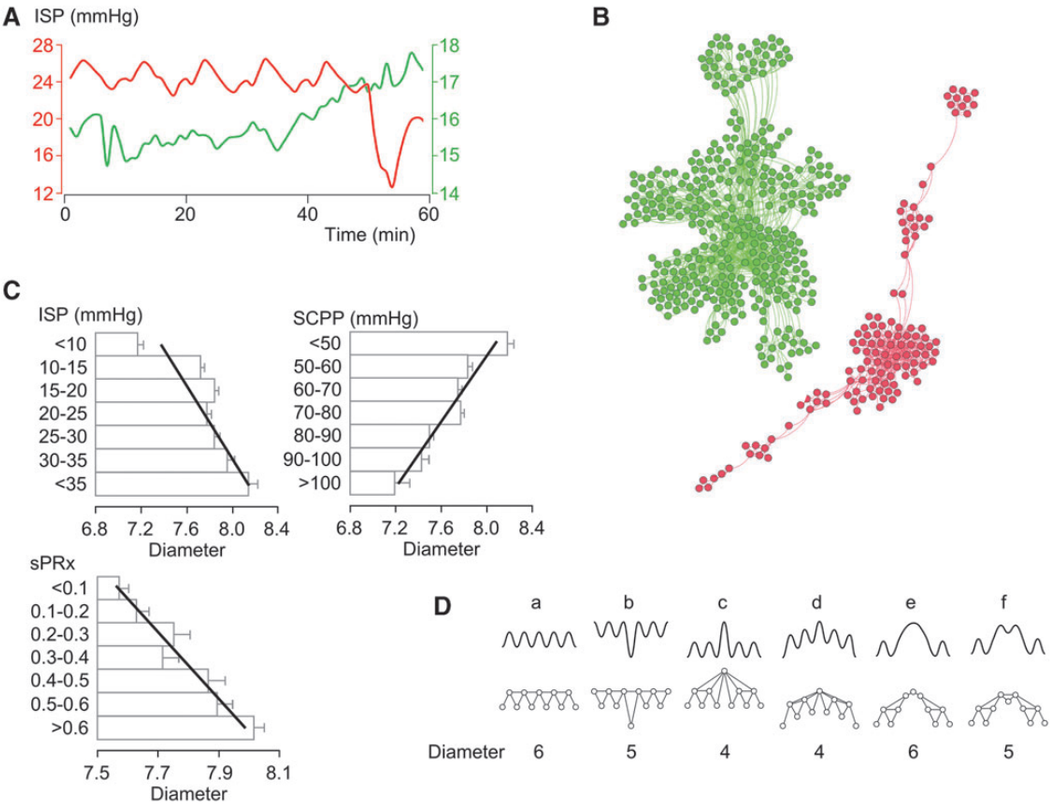
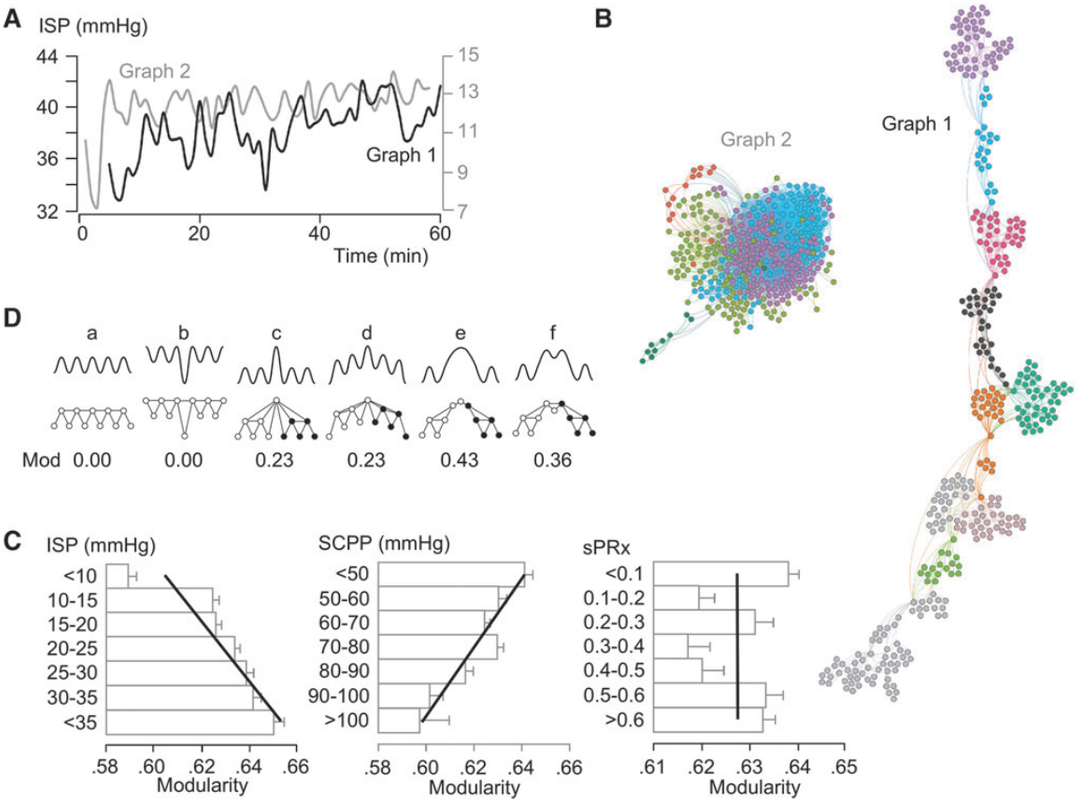


FIG. 2. Graph diameter. Diameter is the shortest path between the two most distant nodes. **(A)** Representative hourly intraspinal pressure (ISP) signals from two patients. **(B)** Graphs corresponding to the ISP signals in **A** with diameters 6 (green) and 14 (red). **(C)** Plots of ISP, spinal cord perfusion pressure (SCPP), and vascular pressure reactivity (sPRx) versus graph diameter for all hours in the 58 patients with best-fit trend lines $R=0.87$, $p<0.05$ (ISP); $R=-0.96$, $p<0.0005$ (SCPP); $R=0.97$, $p<0.0005$ (sPRx). Mean ± standard error. **(D)** Schematic showing effects of various signal fluctuations on graph diameter. **(a)** Sinusoidal. **(b)** Narrow trough. **(c)** Narrow peak. **(d)** Transient baseline increase. **(e)** Large wide peak. **(f)** Peaks on large wide peak.

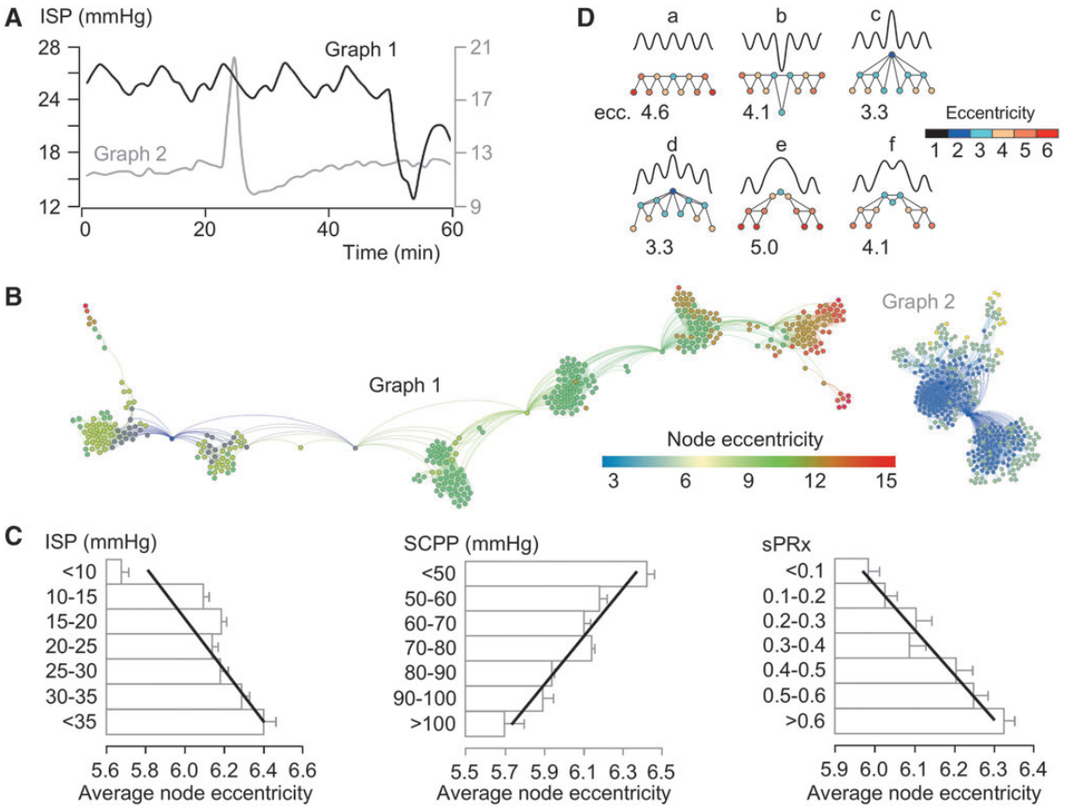


4C ▶ **FIG. 3.** Graph modularity. Modularity measures how a graph is structured and identifies communities/clusters. **(A)** Representative hourly intraspinal pressure (ISP) signals from two patients. **(B)** Graphs corresponding to the ISP signals in **A**. Graph 1, 5 clusters; Graph 2, 10 clusters. Clusters are assigned different colors. **(C)** Plots of ISP, spinal cord perfusion pressure (SCPP), and vascular pressure reactivity (sPRx) versus graph modularity for all hours in the 58 patients with best-fit trend lines $R=0.90$, $p<0.01$ (ISP); $R=-0.95$, $p<0.005$ (SCPP); $R=0.00$, not significant (sPRx). Mean ± standard error. **(D)** Schematic showing effects of various signal fluctuations on graph modularity. **(a)** Sinusoidal. **(b)** Narrow trough. **(c)** Narrow peak. **(d)** Transient baseline increase. **(e)** Large wide peak. **(f)** Peaks on large wide peak. Two node clusters colored (white, black).

and B show examples of two ISP hourly signals and their respective graphs, one with high and one with low modularity. There was strong positive correlation between ISP and graph modularity, strong negative correlation between SCPP and graph modularity, F4 ▶ but no correlation between sPRx and graph modularity (Fig. 4C). These data suggest that cord compression and ischemia, but not loss of autoregulation, are associated with increased graph Q. Figure 3D uses model signals to explain how different signal fluctuations influence modularity. A sinusoidal signal with or without a narrow trough or peak, with or without flat baseline, has zero modularity. A tall, wide peak increases modularity by splitting the graph into two poorly interlinked modules. Peaks on top of the wide peak slightly increase the number of links between the modules, thus slightly reducing modularity.

Graph eccentricity

To find eccentricity, we compute the geodesic path between node i and each other node and choose the longest of these paths. Therefore, if the eccentricity of a node is high, at least one other node lies far from it. Low eccentricity means that all other nodes are near. Averaging the eccentricity values of all the nodes yields the average eccentricity of the graph. Figure 4A and B show examples of two ISP hourly signals and their respective graphs, one with high and one with low average eccentricity. We found strong positive correlation between ISP and average eccentricity as well as between sPRx and average eccentricity, but strong negative correlation between SCPP and average node eccentricity (Fig. 2C). These data suggest that cord compression, ischemia, and loss of autoregulation are associated with increased graph average node eccentricity. Figure 4D shows how fluctuation patterns in the ISP signal influence the eccentricity. A sinusoidal signal has generally high eccentricities. A narrow trough only slightly reduces average eccentricity, but a narrow peak or transiently elevated baseline greatly reduces average node eccentricity by providing bridging nodes. A wide peak increases average eccentricity, but smaller peaks on top of the wide peak only modestly influence eccentricity. Thus, signals with transient peaks or transient baseline elevations have low eccentricities, but regular signals or prolonged elevations increase eccentricity.



4C ▶ **FIG. 4.** Graph eccentricity. Eccentricity measures how important nodes are in a graph. **(A)** Representative hourly intraspinal pressure (ISP) signals from two patients. **(B)** Graphs corresponding to the ISP signals in **A** with nodes colored according to eccentricity. Eccentricity color scale. **(C)** Plots of ISP, spinal cord perfusion pressure (SCPP), and vascular pressure reactivity (sPRx) versus graph mean node eccentricity for all hours in the 58 patients with best-fit trend lines $R=0.87$, $p<0.05$ (ISP); $R=-0.96$, $p<0.0005$ (SCPP); $R=0.98$, $p<0.0005$ (sPRx). Mean ± standard error. **(D)** Schematic showing effects of various signal fluctuations on eccentricity centrality. **(a)** Sinusoidal. **(b)** Narrow trough. **(c)** Narrow peak. **(d)** Transient baseline increase. **(e)** Large wide peak. **(f)** Peaks on large wide peak. Eccentricity color scale.

Graph small-worldness

A small-world graph is characterized by a high clustering coefficient and a short average path length. This means that most nodes are not directly linked, but any nodes directly linked to a node are likely to be linked to each other. Also, most nodes can be reached from any other node by a small number of steps. Because small-world graphs have special properties and are ubiquitous in nature,[19] we investi- F5 ▶ gated whether the ISP signals produce small-world graphs. Figure 5A and B show examples of two ISP hourly signals and their respective graphs, one with high and one with low σ. We found strong negative correlation between ISP and σ as well as between sPRx and σ, but strong positive correlation between SCPP and σ (Fig. 5C). These data suggest that cord compression, ischemia, and loss of autoregulation are associated with reduced σ of ISP graphs. Figure 5D shows how fluctuation patterns in the ISP signal may influence the ratio of clustering coefficient to average path length, a measure of small-worldness. A sinusoidal signal has low σ. A narrow trough only slightly increases clustering coefficient and reduces average path length, thus slightly increasing σ. A narrow peak or transiently elevated baseline slightly increases the clustering coefficient, but greatly reduce the average path length, thus greatly increasing σ. A wide peak reduces the clustering coefficient and increases the average path length, thus reducing σ. Small peaks on top of a wide peak do not affect the clustering coefficient and slightly reduce the average path length, thus only modestly influencing σ. Overall, signals with transient peaks or transient baseline elevations have high σ, but regular signals or signals with prolonged elevations have low σ.

Patient outcome

At follow-up, 65.5% (38/58) patients did not improve, 17.2% (10/58) improved by one AIS grade, 15.5% (9/58) improved by two or more grades, and 1.8% (1/58) were lost to follow-up. Figure 6 ◀F6 shows that shorter graph diameter, smaller average node eccentricity, lower modularity, and higher σ correlate with AIS grade improvement. In univariate analysis, the following variables significantly correlated with AIS grade improvement: higher AIS

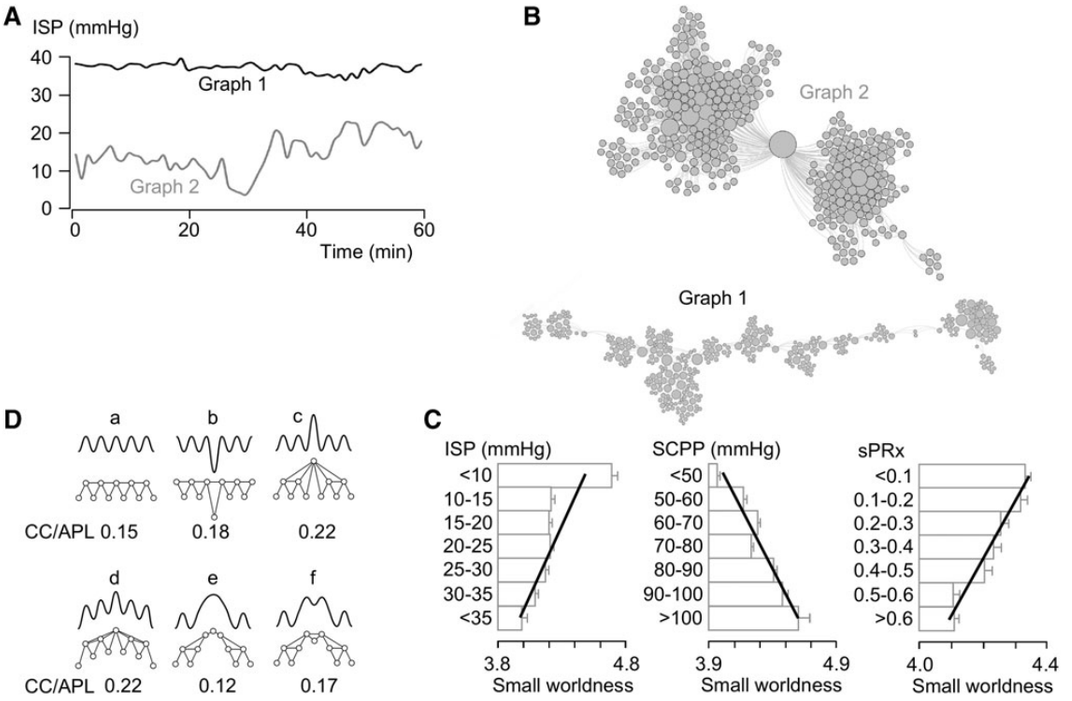


FIG. 5. Graph small-worldness. In small-world graphs, most nodes are not directly linked, but any nodes directly linked to a node are likely to be linked to each other. Small-world graphs have coefficient $\sigma > 1$. **(A)** Representative hourly ISP signals from two patients. **(B)** Graphs corresponding to the intraspinal pressure (ISP) signals in **A** showing node hubs; that is, node radius proportional to node degree. **(C)** Plots of ISP, spinal cord perfusion pressure (SCPP), and vascular pressure reactivity (sPRx) versus graph small-worldness for all hours in the 58 patients with best-fit trend lines $R = -0.83$, $p < 0.05$ (ISP); $R = 0.97$, $p < 0.0005$ (SCPP); $R = -0.98$, $p < 0.0005$ (sPRx). Mean ± standard error. **(D)** Schematic showing effects of various signal fluctuations on small-worldness (cluster coefficient [CC], average path length [APL], CC/APL). **(a)** Sinusoidal (CC = 0.70, APL = 4.73, CC/APL = 0.15). **(b)** Narrow trough (CC = 0.76, APL = 4.09, CC/APL = 0.18). **(c)** Narrow peak (CC = 0.73, APL = 3.36, CC/APL = 0.22). **(d)** Transient baseline increase (CC = 0.73, APL = 3.36, CC/APL = 0.22). **(e)** Large wide peak (CC = 0.61, APL = 5.09, CC/APL = 0.12). **(f)** Peaks on large wide peak (CC = 0.70, APL = 4.09, CC/APL = 0.17).

grade on admission, younger patient age, lower ISP (average of entire signal), higher SCPP (average of entire signal), shorter graph diameter, lower modularity, lower average node eccentricity, and higher σ. For each patient, we averaged graph diameter, modularity, and mean node eccentricity over all ISP graphs. In multivariate analysis, AIS grade on admission, SCPP, and graph average node eccentricity remained independent prognostic factors. The odds ratios indicate the following: a patient with one higher AIS grade on admission than another has a 4.2 times better chance of AIS grade conversion at follow-up. For every 1 mm Hg increase in average SCPP, there is a 10% higher chance of AIS grade conversion at follow-up. For every 1 unit increase average node eccentricity, there is 90% lower chance of AIS grade conversion at follow-up. The results of univariate and multivariate logistic regression analysis T2 ▶ are summarized in Table 2. The corresponding receiver operating characteristic (ROC) curve for the multivariate model had an area under the curve (AUC) value of 0.845, indicating a good classifier. A leave-one-out cross validation (LOO-CV) yielded a classification accuracy of 73.65%. Details are in the supplementary text (see online supplementary material at http://www.liebertpub.com).

Discussion

We showed that ISP signals can be converted into graphs using the visibility algorithm. The graphs can then be analyzed using the powerful tools of complex network theory to quantify their topological structures including size, presence of clusters, connections between clusters, accessibility of nodes from other nodes, APL, and ◀ AU3 small-world properties. Our key finding is that these graphs inherit in their topologies fundamental information from the original ISP time series. The topological structures of ISP graphs are, therefore, highly sensitive to the pathological changes that occur at the injury site; for example, cord compression (high ISP), ischemia (low SCPP), and impaired autoregulation (high sPRx). The visibility algorithm thus allows the complex dynamics of the ISP signal to be analyzed from a novel angle.

It is necessary to determine what are the advantages of analyzing ISP as graphs instead of time series. Time series are used to compare amplitudes (e.g., mean, trend, variability) that have clinical meaning.[1] For example, higher mean ISP means more severe cord compression. If ISP is decreasing, then cord compression is improving.

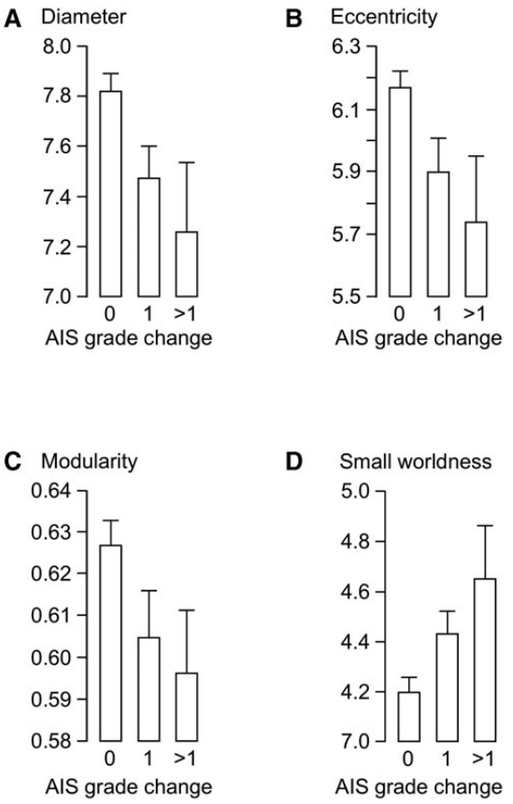


FIG. 6. Neurological outcome. For each patient, we computed average diameter, modularity, mean node eccentricity, and small-worldness of all the graphs in the monitoring period. Bar graphs showing **(A)** Average patient graph diameter. **(B)** Average patient mean node eccentricity. **(C)** Average patient modularity. **(D)** Average patient small-worldness versus American Spinal Injuries Association Impairment Scale (AIS) grade change; that is, AIS grade at follow-up minus AIS grade at presentation. Mean ± standard error for 57 patients (1 of the 58 patients was lost to follow-up).

TABLE 2. RESULTS OF UNIVARIATE AND MULTIVARIATE LOGISTICAL REGRESSION ANALYSIS

	Univariate		*Multivariate*	
Variable	*OR*	p *Value*	*OR*	p *Value*
Admission AIS grade	4.2	<0.001	4.2	<0.05
Patient age (years)	0.9	<0.005		NS
SCPP (mmHg)[a]	1.1	<0.05	1.1	<0.05
ISP (mmHg)[a]	0.9	<0.05		NS
Graph diameter[b]	0.1	<0.005		NS
Graph modularity[b]	0.0	<0.05		NS
Graph eccentricity[b]	0.1	<0.005	0.1	<0.05
Graph small-worldness[b]	14.4	<0.005		NS

[a]Average over entire monitoring period.
[b]Average of all ISP graphs for each patient.
Binary outcome was no AIS Grade increase (0) versus at least 1 AIS grade increase (1).
AIS, American Spinal Injuries Association Impairment Scale; ISP, intraspinal pressure; NS, not significant; OR, odds ratio; SCPP, spinal cord perfusion pressure.

High ISP variability may indicate mechanical spinal instability causing fluctuating cord compression. Time series are also used to identify correlations with biological meaning; for example, higher ISP correlates with worse neurological outcome.[13] When ISP increases then sPRx increases (impaired autoregulation)[1,8] and tissue lactate-to-pyruvate ratio also increases (increased tissue ischemia).[12] Unlike time series, ISP graph topology is not affected by ISP amplitude[14]; a sinusoidal signal produces identical visibility graphs regardless of whether it fluctuates between +5 and +10 or between +30 and +35. Graph topology is, however, sensitive to patterns of fluctuations that may have little effect on amplitude; a narrow peak or transient rise in ISP baseline provides bridging nodes that reduce graph D and average E and increase σ. In contrast, a periodic signal has long graph D, high E, and low σ. Q increases with wide peaks in the signal, but, compared with a sinusoidal signal, baseline signal fluctuations do not reduce Q. Such fluctuation patterns may have biological meaning. For example, a normal ISP or ICP signal has irregularities; for example, narrow peaks (straining, coughing) and a fluctuating baseline (from respiration or autoregulatory response to fluctuations in MAP),[1,8] which may reduce D and E and increase σ. With increased cord compression, ISP exhibits large, wide peaks that may increase D, E, and Q as well as reducing σ. Loss of autoregulation would increase D and E as well as reducing σ without much effect on Q. Therefore, the various graph metrics used here likely capture clinically important information that is difficult to appreciate from the original ISP signal. This may explain why these graph metrics correlate with patient outcome. The multivariate logistical regression model, based on AIS grade on admission, SCPP, and graph average node eccentricity, has good predictive value evident by the high AUC value of the ROC curve and the high classification accuracy of LOO-CV. The prognostic power of the graph metrics requires additional validation in future studies using different sets of TSCI patients.

Unlike ISP monitoring for TSCI, ICP monitoring for severe TBI has been the standard of care in developed countries for many years.[21,22] The early management of patients with TBI is focused on limiting secondary injury by reducing ICP below 25 mm Hg and increasing CPP above 60 mm Hg. Our group has developed analogous techniques for monitoring ISP and SCPP in patients with TSCI.[1,8,11] Recently, the value of ICP monitoring in TBI has been questioned because of absence of class I evidence that ICP-directed management improves outcome.[23] Large observational studies[24,25] and sophisticated analysis of ICP signals[26] indicate that ICP-directed treatments have the potential to improve outcome, provided that patient care is targeted to individualized optimal CPP values that vary widely among patients. The ISP monitoring field has much to learn from the pitfalls of ICP monitoring; for example, by avoiding universal treatment thresholds and individualizing management instead.[10] ISP monitoring is invasive, but the complications are not serious and include CSF leak through the probe skin exit site, pseudomeningocele, and probe dislodgement.[11] To date, we have used AIS grade conversion as the only outcome measure; in future studies, other outcome measures should also be used to make the findings more robust. In TBI patients, some neuro-ICUs monitor tissue oxygen and metabolism in addition to ICP and CPP.[27,28] This is also possible in TSCI patients by using microdialysis to monitor injury site metabolism.[12,16] Although monitoring many physiological and

biochemical parameters from the injury site makes sense, the clinical value of multi-modality monitoring has been challenged, because of the lack of clinically relevant analysis techniques. Visualizing data as networks, as described here, might make clinically relevant changes in the monitored parameters easier to appreciate.

Transformation of time series into graphs has only become possible recently.[14] There have been several attempts to apply this technique in medicine; for example, to predict the onset of ventricular fibrillation by electrocardiogram (ECG),[29] diagnose Alzheimer's disease,[30] or analyze seizure patterns by electroencephalogram (EEG),[31] as well as in fields outside of medicine; for example to predict the magnitude of growth of stock prices using price time series[32] or to predict tourist demand for holiday resorts.[33] These techniques could also be applied to ICP signals after TBI and other signals recorded from injured brain or spinal cord; for example, tissue oxygen or metabolite levels monitored by microdialysis. A sliding 1 h window updated every minute could be used to provide real-time information in ICU on ISP graph topology.

We showed that ISP graphs have small-word properties. There are many examples of small-world networks in nature including chemical reaction networks, healthy neuronal connections, social networks, and networks of world airports.[34] Small-worldness confers advantages to networks such as robustness to external insults and scale invariance, as well as efficient storage, transmission, and retrieval of information. Our data indicate that the small-worldness metric σ decreases with increasing cord compression, decreasing cord perfusion, and more deranged cord autoregulation. Therefore, as the secondary insults become more severe, ISP graphs become more disorganised with longer average path length and smaller clustering coefficient. These topological changes in the ISP graphs likely arise from disorganization in the various processes that give rise to the ISP signal; for example, cardiac and respiratory pulsations, intraspinal compliance, spinal cord blood flow, oxygenation, and metabolism. Therefore, σ provides information about the state of the injury site from a novel perspective.

Since the original article reporting the natural visibility algorithm, several variations have been published. Directed graphs could be used to incorporate temporal information in the network; for example, if node i corresponds to a future time compared with node j, and they are visible to each other, then there is connection from $i \rightarrow j$ but not from $i \leftarrow j$.[35] There is also a technique to map multivariate time series into multiplex graphs[36] that may enable analysis of multi-modality monitoring data from the injury site; for example, ISP, tissue oxygen, and microdialysis. Such studies are beyond the scope of this article. Our study has provided proof of principle that this novel research avenue is interesting to pursue when analyzing and interpreting complex signals from injured brain or spinal cord.

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EQ1 ▶ ## Author Contributions

AU4 ▶ S.C. wrote software and analyzed the data to produce all the networks and metric data. M.J. G. and F.H. collected and cleaned the raw data and patient demographics. M.C.P. performed the surgical procedures, looked after the patients, and inserted the probes. M.C.P. and S.S. analyzed the data, produced the figures, and wrote the manuscript. S.S. supervised the project.

Author Disclosure Statement

No competing financial interests exist.

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