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Acute, severe traumatic spinal cord injury: improving urinary bladder function by optimising spinal cord perfusion

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Table of contents title: Improving urinary bladder function after spinal cord injury

Manuscript keywords: Blood pressure, Cystometry, Detrusor, Microdialysis, Spinal cord injury, Urodynamics

Funding: Supported by Wings for Life Spinal Cord Research Foundation and the Neurosciences Research Foundation (Fletcher Fund).

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} =cabdominal (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

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ABSTRACT

We investigated the effect of acute, severe traumatic spinal cord injury (TSCI) on the urinary bladder and hypothesised that increasing the spinal cord perfusion pressure (SCPP) improves bladder function. In 13 adults with TSCI (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 SCPP and performed filling cystometry. Patents were followed up for 8 months on average. The 13 patients had 63 fill cycles; 38 cycles had unfavourable urodynamics, i.e dangerously low compliance (<20mL/cmH_2O), detrusor overactivity or dangerously high end-fill pressure (>40cmH_2O). Unfavourable urodynamics correlated with periods of injury site hypoperfusion (SCPP<60mmHg), hyperperfusion (SCPP>100mmHg), tissue glucose <3mM and tissue lactate-to-pyruvate ratio >30. Increasing SCPP from 67.0 ± 2.3mmHg (average ± standard error) to 92.1 ± 3.0mmHg, significantly reduced, from 534 to 365mL, 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 (>100mL/cmH_2O) maintained high compliance at follow-up. We conclude that unfavourable urodynamics develop within days of TSCI, thus challenging the prevailing notion that the detrusor is initially acontractile. Urodynamics performed acutely, identify patients with dangerously low compliance likely to benefit from early intervention. At this early stage, bladder function was found to be dynamic, influenced by fluctuations in the physiology and metabolism at the injury site; therefore, optimising 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 rationalise ICU management, we developed injury site monitoring.[3] The techniques are safe[4] and aim to individualise 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 optimising 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 compartmentalising 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 noradrenaline 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 haematuria, 5/13 (38.5 %) had pneumonia and 1/13 (7.7 %) had pulmonary embolism. *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 haematoma 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 50, 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 summarises the variabilities in bladder compliance, DO and detrusor pressure at end-fill for each patient. We hypothesised 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 ischaemia (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 minimises 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 ischaemia (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 or inotropes 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 or noradrenaline (Supplement 3).

Long-term outcome. Average follow-up was 8 months (range 2 – 19). 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 4).

DISCUSSION

We showed that >90 % patients develop periods of unfavourable urodynamics within days of TSCI, including dangerously low bladder compliance, dangerously high detrusor pressure at end-fill and DO. Unfavourable urodynamics fluctuate; they become more pronounced when the injured cord is hypo- or hyperperfused, glucopenic or ischaemic (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. 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 optimise 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.

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 noradrenaline, raising the possibility of a direct, inhibitory effect of noradrenaline on bladder contraction potentially masking DO and reducing compliance. Our analysis suggests that propofol, fentanyl and noradrenaline did not significantly influence the urodynamics. 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 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 urodynamic testing.

CONCLUSIONS

Filling cystometry, performed within days of TSCI, identifies early patients with unfavourable urodynamics. Our findings suggest that individualised therapy in acute TSCI, by monitoring and optimising cord physiology and metabolism, will likely improve not only limb motor function and sensation, but also urinary function.

ACKNOWLEDGMENTS

We thank the neurosurgeons at St. George's Hospital, King's College Hospital and Hurstwood Park Neurological Centre as well as the spinal orthopaedic surgeons at St. George's Hospital who helped recruit patients. The neuroanaesthetic, Neuro-ICU and operating theatre staff at St. George's Hospital helped with data collection.

DISCLOSURES

SS and MCP are PI's on a research grant from Wings for Life Spinal Cord Research Foundation and MCP is PI on a research grant from the Neurosciences Research Foundation (Fletcher Fund). FRAH, MG, ES, AZ and SK have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

FRAH: Data acquisition, data interpretation, data analysis; SK: Data acquisition; ES: Design, data interpretation; MJG: Data acquisition; AZ: Data acquisition, data interpretation; MCP: Conception, data interpretation; SS: Conception, design, data analysis, data interpretation.

FUNDING

Supported by grants to SS and MCP from Wings for Life Spinal Cord Research Foundation and to MCP from the Neurosciences Research Foundation (Fletcher Fund). FRAH is a Royal College of Surgeons of England research fellow. SK is supported by NIHR CRN.

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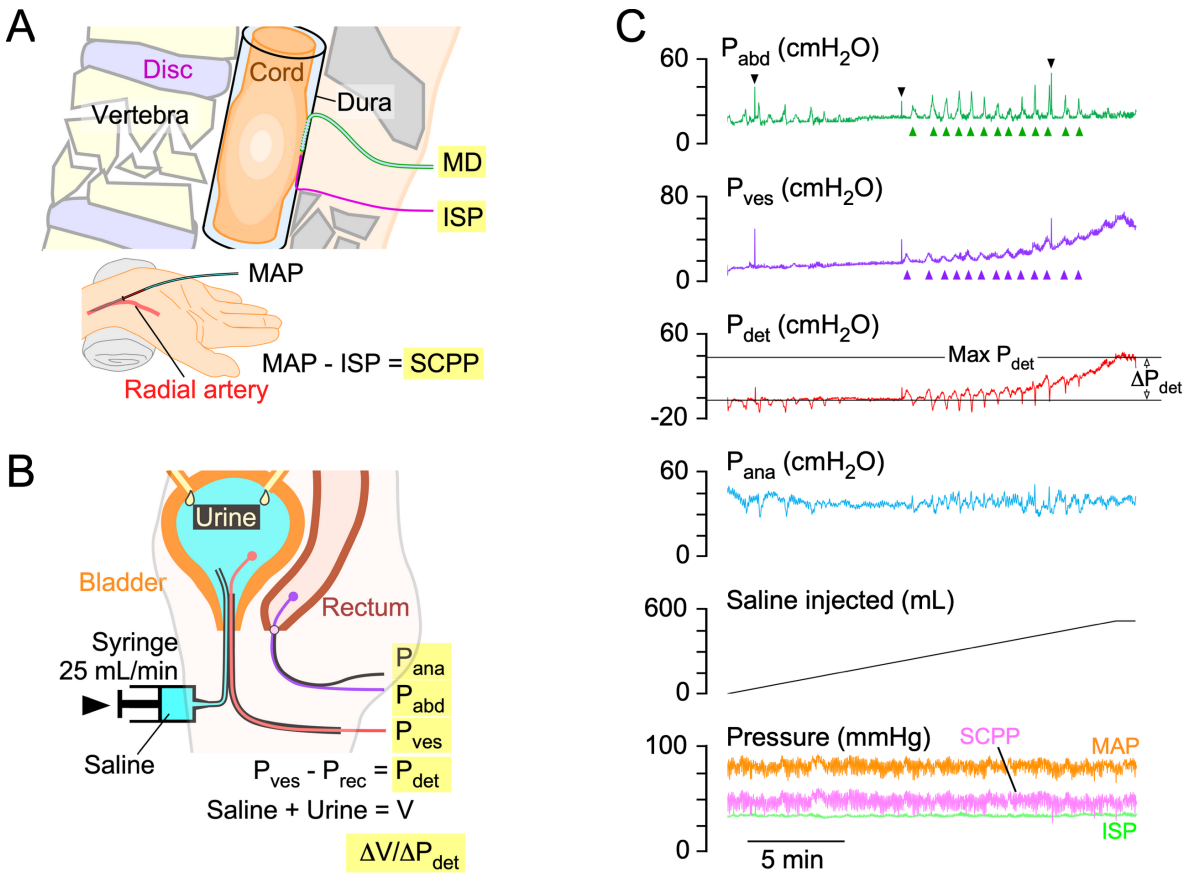


FIGURE 1

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).

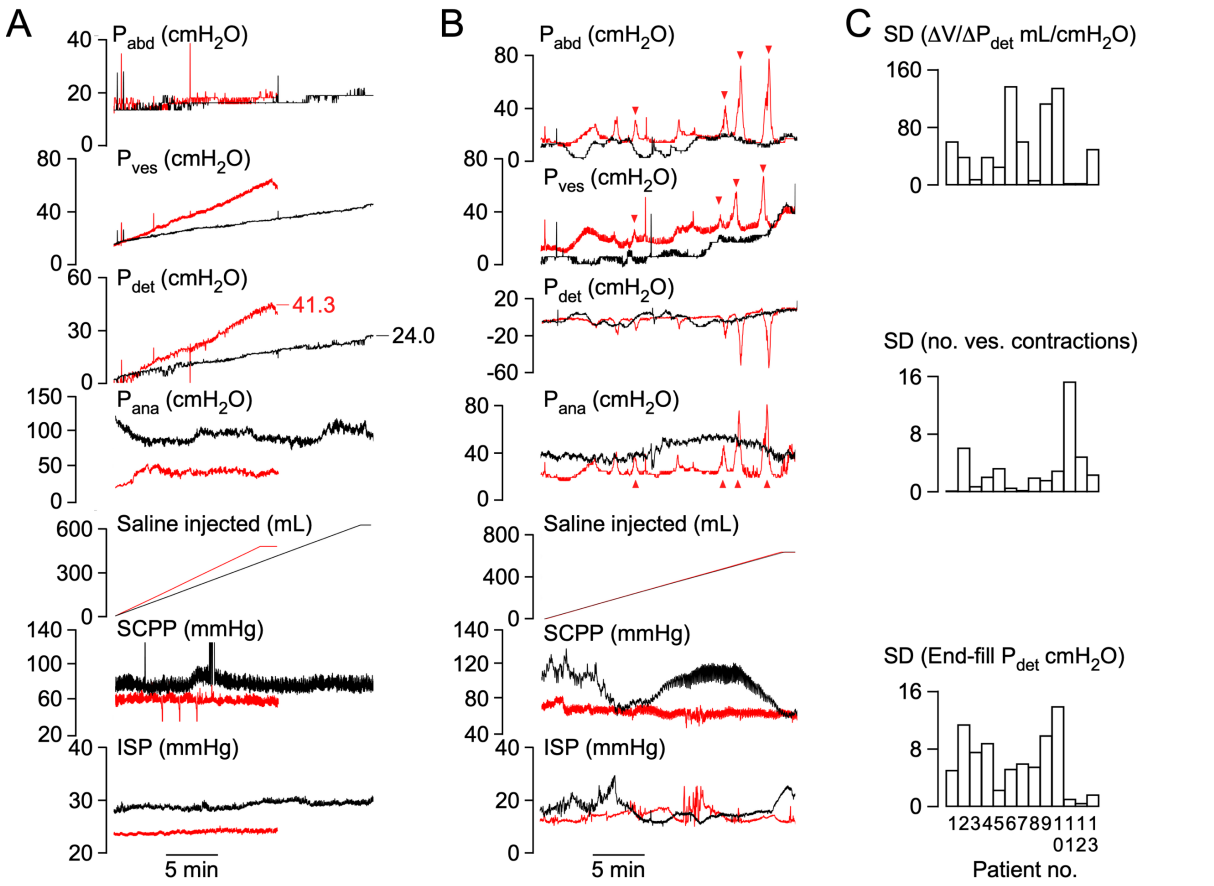


FIGURE 2

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.

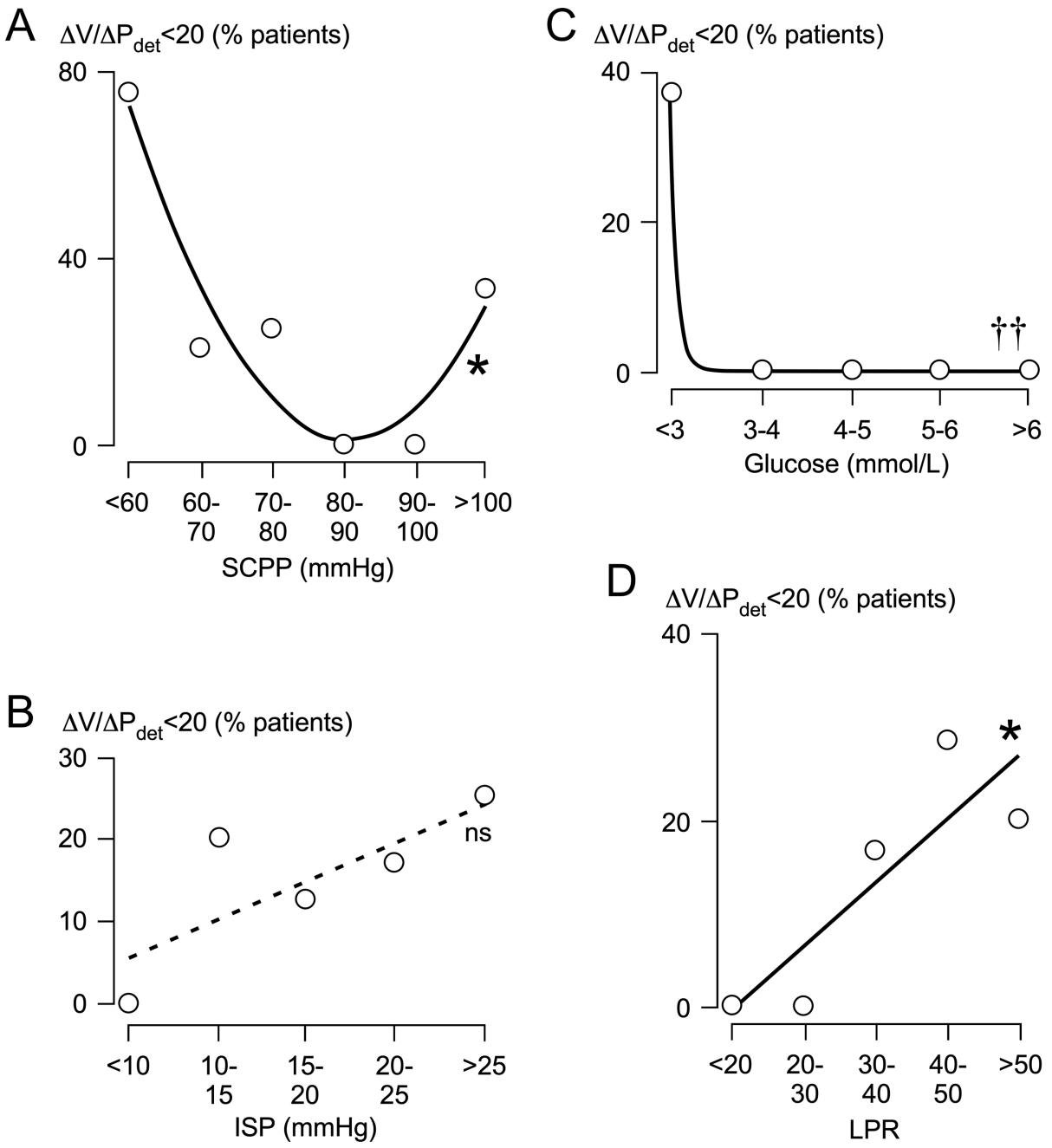


FIGURE 3

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.

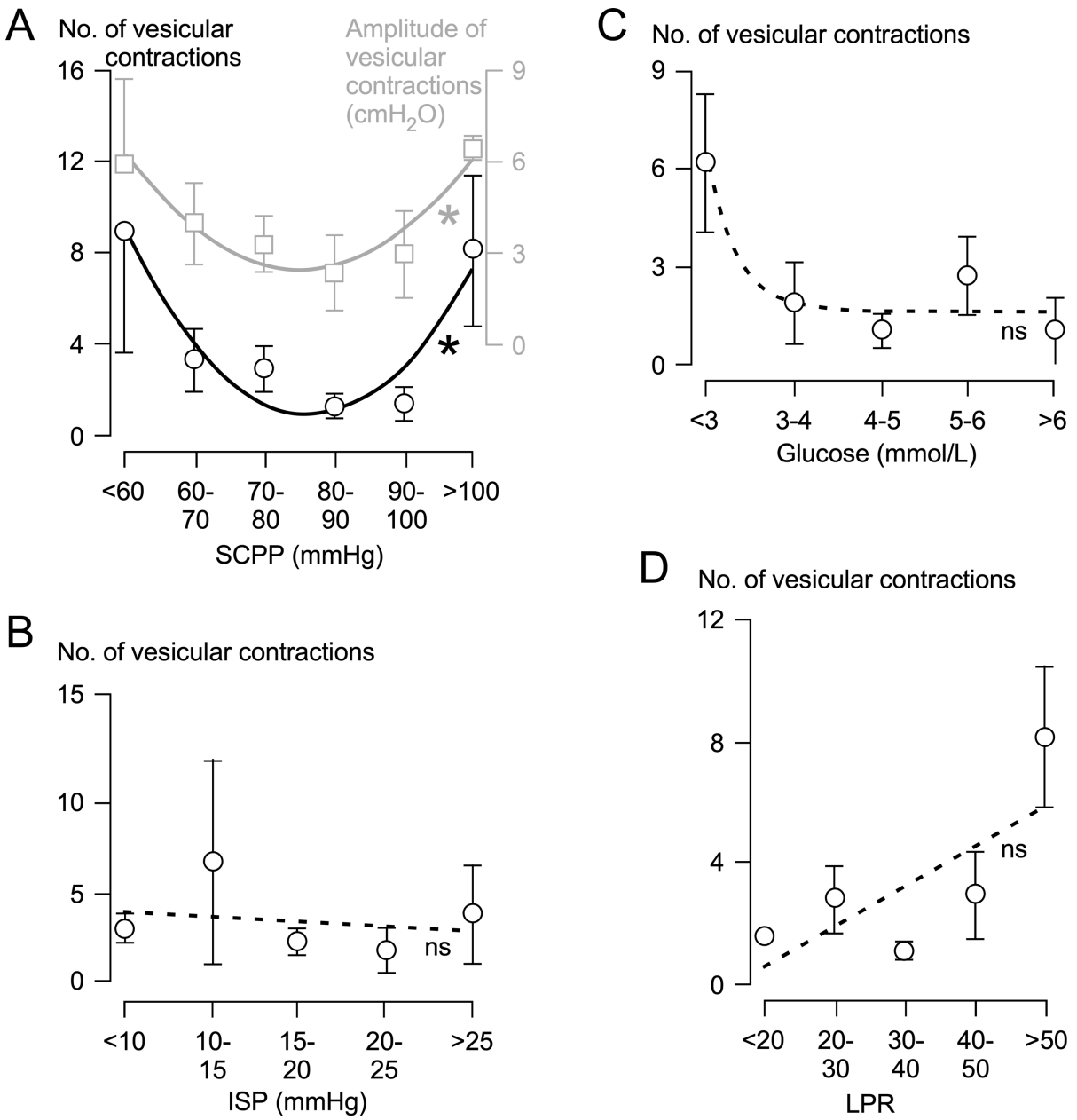


FIGURE 4

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.

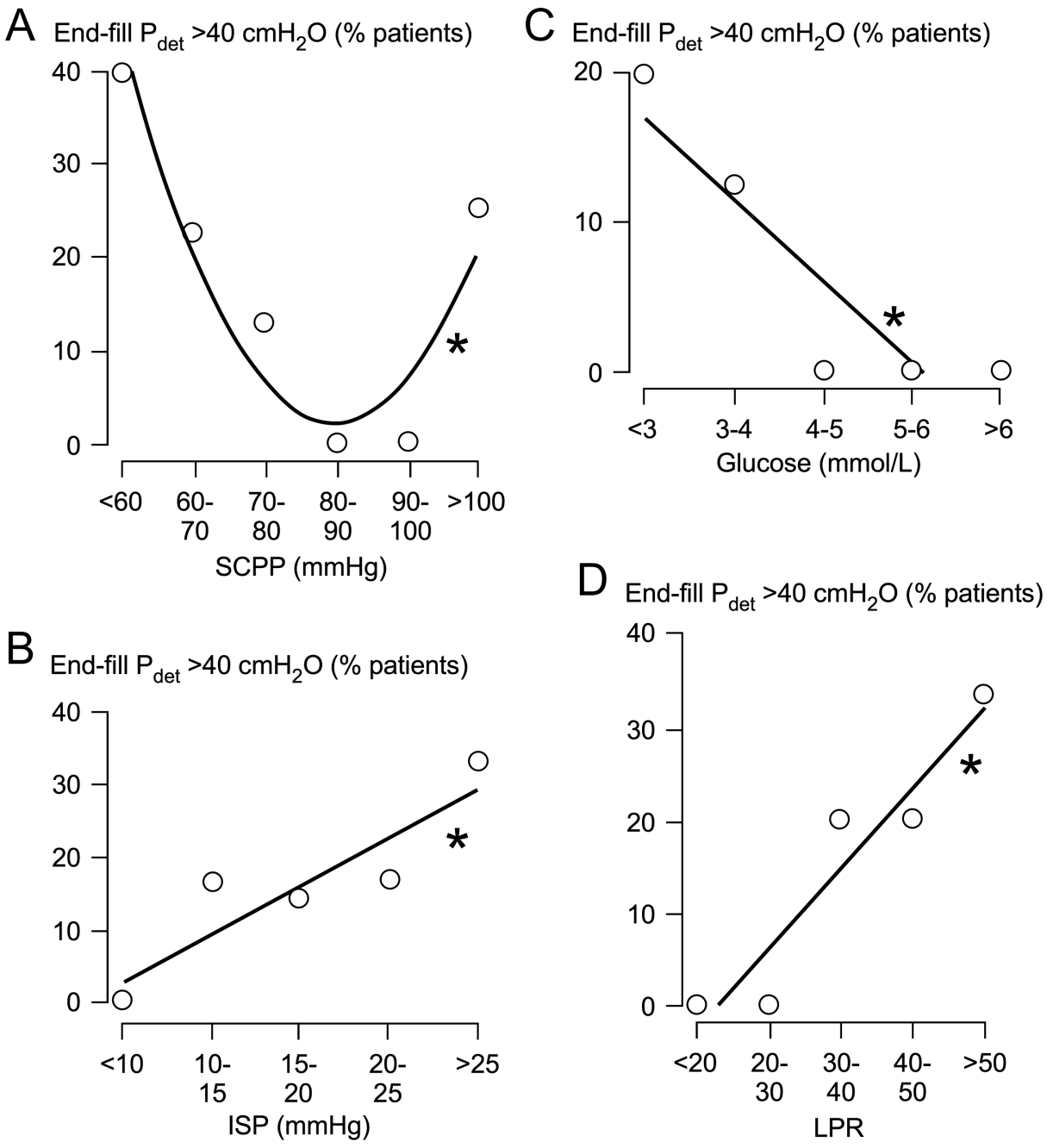


FIGURE 5

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, $\hat{R}^2 = 0.87$). $P < 0.05^*$.

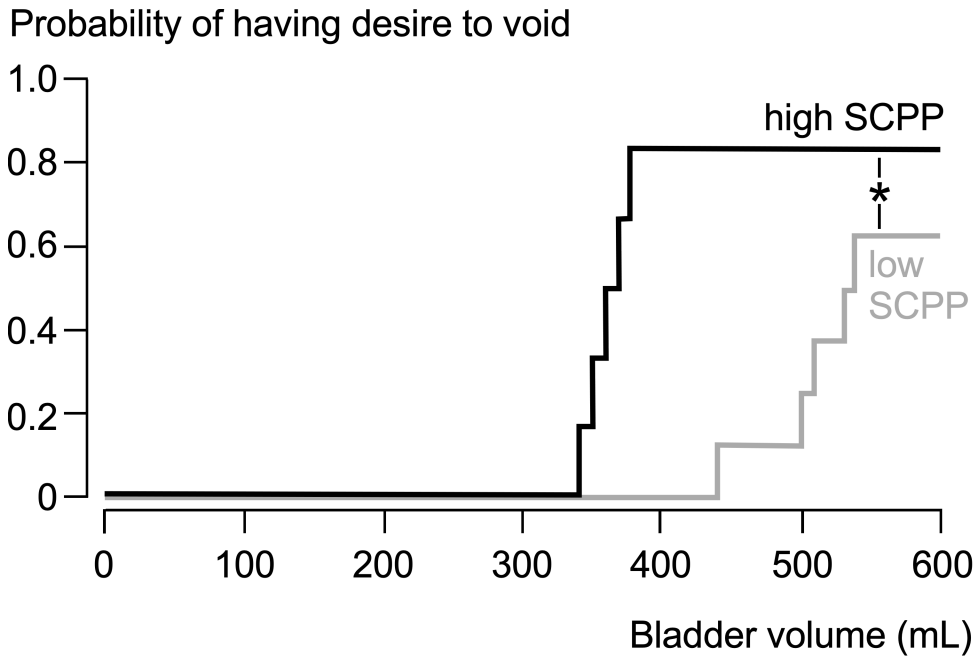
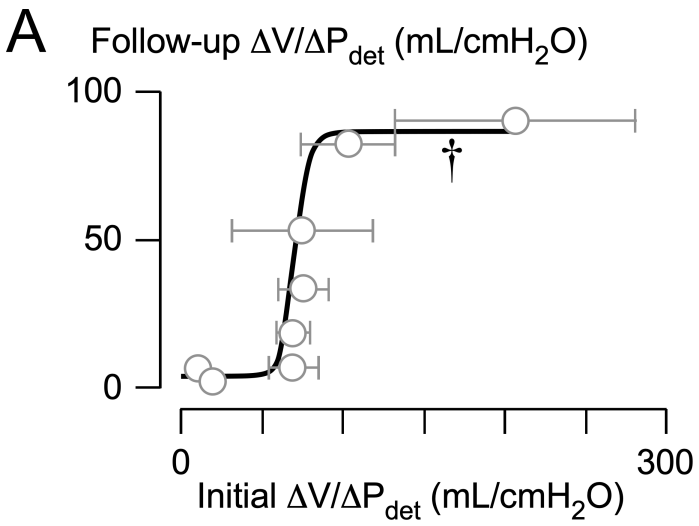


FIGURE 6

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.



B

Sensation to void*

FOLLOWUP \ PRESENTATION	Yes	No
Yes	3	0
No	0	4

FIGURE 7

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. $P < 0.05^*$, $0.001^\dagger$.

SUPPLEMENT 1. Patient details.

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; y, years

Supplement 2. Summary of urodynamic findings.

Patients: no.	13
Fill cycles: no.	63
Fill cycles/patient: average (range)	4.8 (2.0 – 6.0)
Timing of fill cycle from surgery: average days (range)	4.2 (2.0 – 7.0)
Unfavourable urodynamics: no. of fill cycles	38
Compliance <20 mL/cmH_2O	12
Detrusor overactivity	35
End-fill detrusor pressure >40 cmH_2O	10
Maximal bladder fill: average (range)	
Infused saline in mL	571 (340 – 600)
V_{max}, Infused saline + urine produced in mL	652 (400 – 1,300)
Drugs: no. of fill cycles	
Propofol	36
Fentanyl	40
Noradrenaline	60
Bladder medications: no. of fill cycles	
None	63
Anti-muscarinic	0
α-blocker	0
Injury site parameters during fill cycle: average (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)
Norepinephrine in μg/kg/min: average (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.

Supplement 3. Lack of effect of propofol, fentanyl, norepinephrine.

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			

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			

NOREPINEPHRINE

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			

BLADDER SENSATION VS. NO BLADDER SENSATION (no. of fill cycles)

PROPOFOL

Dose	Sensation	No sensation
0	5	4
100	5	0
	FISHER EXACT	
	P	0.22077922

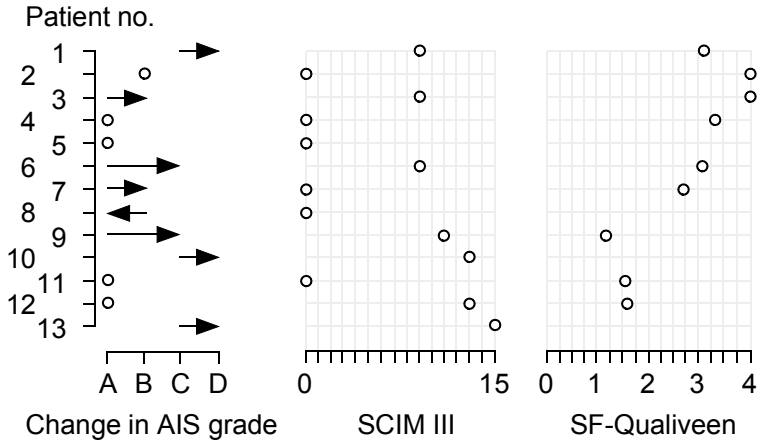
FENTANYL

Dose	Sensation	No sensation
0	5	4
100	5	0
	FISHER EXACT	
	P	0.22077922

NOREPINEPHRINE

Dose	Sensation	No sensation
0-0.2	4	4
0.21-0.4	6	0
	FISHER EXACT	
	P	0.08491508

Supplement 4. Long-term outcomes 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.