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Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury

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Supplemental data at Neurology.org

ABSTRACT

Objective: To determine whether spinal cord perfusion pressure (SCPP) as measured with a lumbar intrathecal catheter is a more predictive measure of neurologic outcome than the conventionally measured mean arterial pressure (MAP).

Methods: A total of 92 individuals with acute spinal cord injury were enrolled in this multicenter prospective observational clinical trial. MAP and CSF pressure (CSFP) were monitored during the first week postinjury. Neurologic impairment was assessed at baseline and at 6 months postinjury. We used logistic regression, systematic iterations of relative risk, and Cox proportional hazard models to examine hemodynamic patterns commensurate with neurologic outcome.

Results: We found that SCPP (odds ratio 1.039, $p = 0.002$) is independently associated with positive neurologic recovery. The relative risk for not recovering neurologic function continually increased as individuals were exposed to SCPP below 50 mm Hg. Individuals who improved in neurologic grade dropped below SCPP of 50 mm Hg fewer times than those who did not improve ($p = 0.012$). This effect was not observed for MAP or CSFP. Those who were exposed to SCPP below 50 mm Hg were less likely to improve from their baseline neurologic impairment grade ($p = 0.0056$).

Conclusions: We demonstrate that maintaining SCPP above 50 mm Hg is a strong predictor of improved neurologic recovery following spinal cord injury. This suggests that SCPP (the difference between MAP and CSFP) can provide useful information to guide the hemodynamic management of patients with acute spinal cord injury. ***Neurology*® 2017;89:1–8**

GLOSSARY

AIS = American Spinal Injury Association Impairment Scale; **CI** = confidence interval; **CSFP** = CSF pressure; **ISNCSCI** = International Standards for Neurologic Classification of SCI; **MAP** = mean arterial pressure; **OR** = odds ratio; **RR** = relative risk; **SCPP** = spinal cord perfusion pressure.

The current clinical practice guidelines for hemodynamic management of acute spinal cord injury recommend that the mean arterial pressure (MAP) be maintained between 85 and 90 mm Hg for the first 7 days postinjury, with the use of vasopressors if necessary.[1–5] A potentially important limitation with the present approach is the exclusive focus on MAP and not spinal cord perfusion pressure (SCPP). In traumatic brain injury, hemodynamic management includes monitoring of intracranial pressure to calculate and act upon cerebral perfusion pressure.[6–8]

Recent groundbreaking work by Saadoun et al.[9] has shown that pressure catheters placed subdurally at the site of injury predict neurologic outcome at 9–12 months postinjury. We have also been monitoring SCPP but with standard lumbar intrathecal catheters. We have reported on the use of lumbar intrathecal catheters to drain CSF in patients with acute spinal cord injury,[10] but the utility of monitoring CSF pressure (CSFP) in the lumbar spine (distal to injury) as it relates to neurologic recovery has not yet been evaluated.

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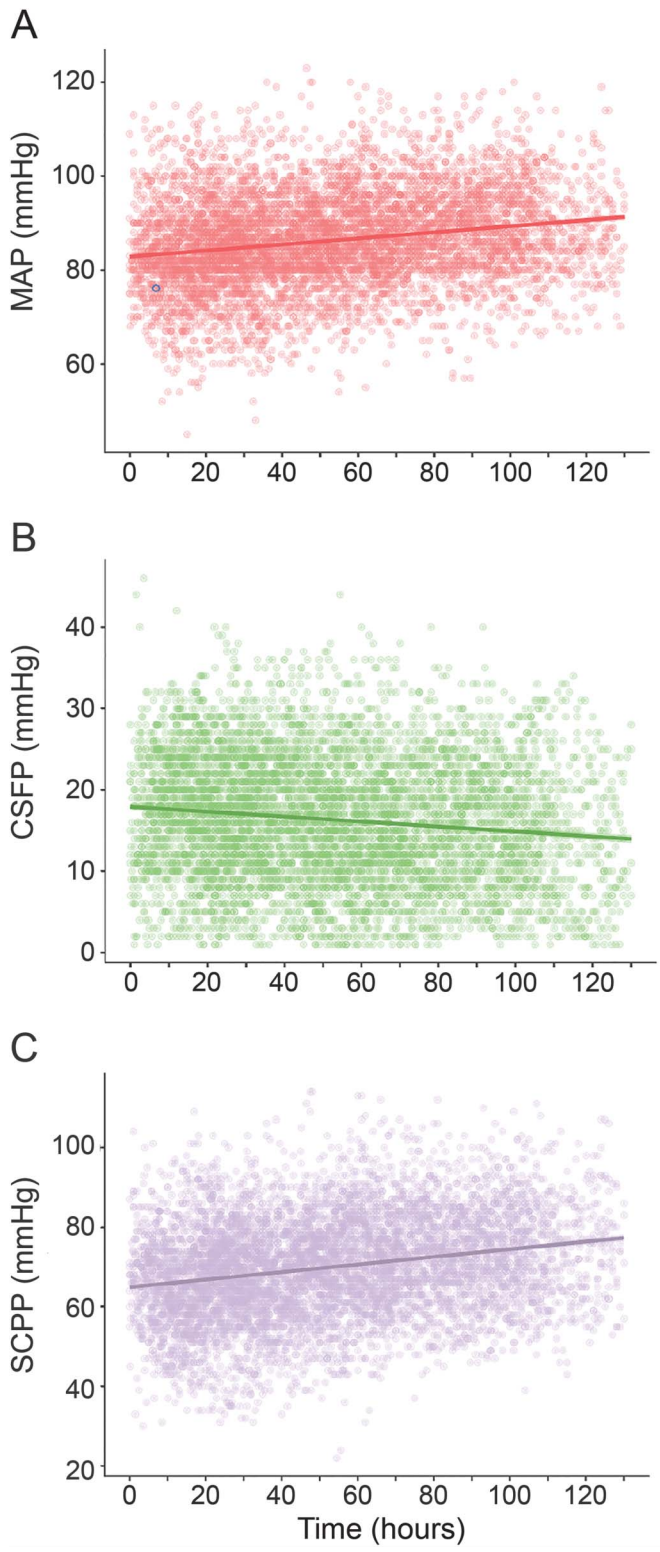
The aim of the present study was to determine the independent relationship of SCPP (measured with a lumbar intrathecal catheter) to neurologic outcome and to determine a clinically useful nadir below which patients are at risk for poor neurologic recovery. We hypothesized that those individuals exposed to low SCPP during the first 5 days postinjury would be more likely to have poor neurologic recovery.

Figure 1 Raw hemodynamic data



Data were collected on an hourly basis for each participant and plotted over time postinjury (dots). Fitted linear regression lines represent the association between measurement and time for all individuals. CSFP = CSF pressure; MAP = mean arterial pressure; SCPP = spinal cord perfusion pressure.

METHODS **Clinical trial enrollment.** Patient recruitment began at our single institution in March 2006 and was expanded into a multicenter prospective observational study in September 2012 with sites in Halifax, London, Ontario, and Montreal. Individuals sustaining an acute spinal cord injury were enrolled if they met the following inclusion criteria: (1) American Spinal Injury Association Impairment Scale (AIS) grade A, B (motor-complete), or C (motor-incomplete) spinal cord injury upon presentation; (2) spinal bony injury between C0 and L1 inclusive; (3) the ability to have a lumbar catheter inserted within 48 hours of injury; and (4) the ability to be assessed clinically for a valid, reliable neurologic examination. Exclusion criteria included concomitant head injuries; concomitant major trauma to the chest, pelvis, or extremities that required invasive intervention (e.g., internal or external fixation); or too sedated or intoxicated to provide a valid neurologic examination.

Standard protocol approvals, registrations, and patient consents. The clinical trial protocol for conducting this prospective observational study at this single institution was approved by our local institutional review board (#H10-01091); a subsequent multicenter extension of this study is registered with ClinicalTrials.gov (NCT01279811). Patient consent was obtained according to the declaration of Helsinki. All methodology and results are presented according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[11]

Hemodynamic monitoring. For CSFP monitoring, an intrathecal catheter {Perifix FX 19-G [25/CS], 100 cm, SPRINGWND, radiopaque open tip epidural catheter (Braun [Aschaffenburg, Germany] 333514), or an external drainage and monitoring system, barium impregnated, 80 cm, 1.5 mm OD/0.7 mm ID, closed tip lumbar catheter (Medtronic [Langhorne, PA] 46914)} was inserted in the lumbar spine at L2/3 or L3/4. The catheter was advanced 15–20 cm from the entry point on the skin surface, secured with a sterile dressing, and then brought out over the shoulder and secured with Mepore tape along its exposed length. The intrathecal catheter was then connected to a Duet external drainage and monitoring system (Medtronic 46914). MAP was monitored via a standard arterial catheter placed during initial management. Both the CSFP and MAP transducers were connected to a General Electric (Fairfield, CT) Carescape patient monitor (B850) for monitoring of CSFP and arterial waveforms and pressures (schematic of the monitoring setup is provided in figure e-1 at Neurology.org). These monitors are tested and calibrated annually to confirm accuracy to within ±2 mm Hg. Both the CSFP and arterial pressure transducers were zeroed to atmosphere and leveled at the phlebostatic axis. The CSF catheters were kept in place for up to 120 hours.[10] Digital data from patient monitors were sampled continuously and manually recorded hourly. SCPP was calculated as the difference between MAP and CSFP, and was therefore not provided to clinicians in real time. MAP was targeted at 80–85 mm Hg during the first 120 hours after enrollment. Initial support of the MAP was by volume augmentation (i.e., crystalloid, colloid, or whole blood as

required) followed by the initiation of vasopressor support with norepinephrine, phenylephrine, dopamine, or, in a few instances, a combination of 2 of these vasopressors. The decision of how to support the target MAP was at the discretion of the attending anesthesiologist or intensivist. CSFP was not manipulated.

Neurologic outcome assessment. Upon presentation, all patients underwent formal neurologic testing according to the International Standards for Neurologic Classification of SCI (ISNCSCI) and were assigned a baseline AIS grade.[12] All baseline neurologic examinations and subsequent neurologic monitoring were conducted by clinical staff specifically trained to conduct the ISNCSCI examination. The ISNCSCI examination was repeated at 6 months postinjury, at which point the majority of neurologic recovery has occurred.[13] AIS conversion was defined as a change in 1 AIS grade.

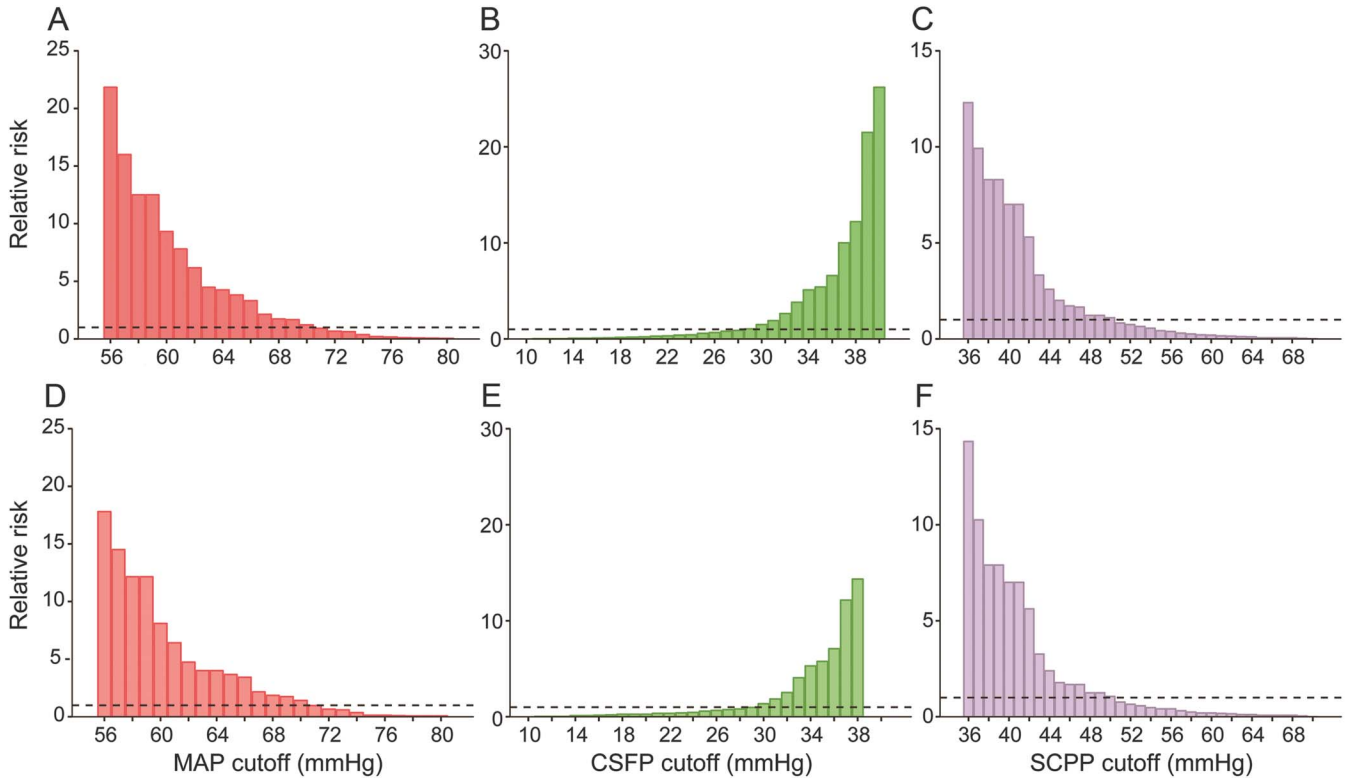
Statistical analyses. We used the statistical computing software R (R Core Team, 2012) to examine differences in hemodynamic patterns between individuals with AIS A/B vs AIS C using independent-samples *t* tests. Next, a case-control design was implemented, where participants were stratified according to their AIS conversion status. For logistic regression models, conversion status was used as the outcome variable, with MAP, CSFP, or SCPP inserted as independent fixed factors. Multiple observations for each participant were corrected through clustering. To provide clinically relevant management guidelines, we systematically examined the relative risk (RR) of conversion by determining exposure to different hemodynamic cutoffs. To visualize the combined contributions of MAP and CSFP to conversion risk, we used additive RR modeling (RR_1+RR_2-1). We performed univariate regression of the number of times an individual deviated outside the set cutoff. We examined differences in the number of times individuals deviated outside of each cutoff between those that AIS converted vs those that did not using independent samples *t* tests. Univariate Kaplan-Meier models and Cox proportional hazard models were used to assess risk for conversion, and also to assess risk for total motor score improvement ≥6.

RESULTS

Participants. A total of 102 individuals were monitored following acute spinal cord injury. Two individuals died in the hospital. Eight individuals were lost to follow-up. There were 72 male and 20 female participants. Cervical injuries were most common (n = 55), followed by thoracic (n = 28) and lumbar (n = 9). Average time to decompression was 20 ± 11 hours from the time of injury. Further demographic details are reported in table e-1. No infectious or other complications resulted from the lumbar catheter placement.

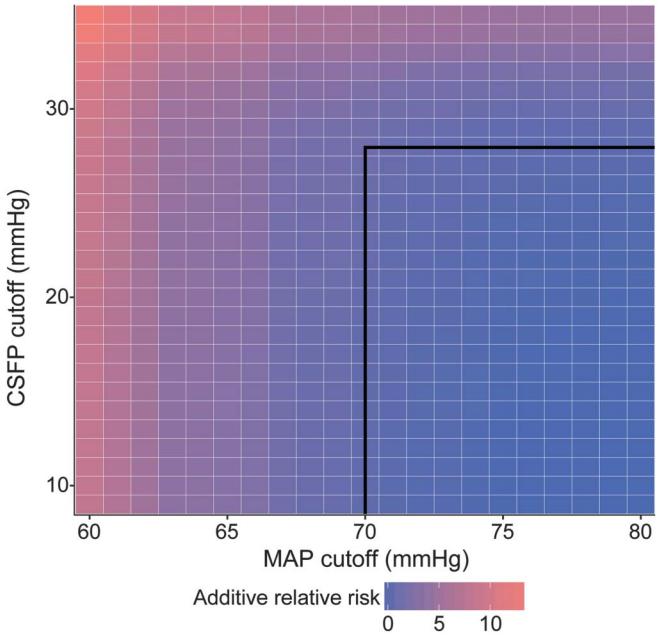
Hemodynamics during the first 5 days postinjury differs by initial injury severity. During the first 5 days postinjury, we found MAP (β = 0.038 mm Hg) and

Figure 2 Relative risk of not positively converting American Spinal Injury Association Impairment Scale (AIS) grade



Relative risk of not positively converting AIS grade from baseline to 6 months increases with poor hemodynamic management during the first 5 days postinjury. Using systematic iterative relative risk calculations, we demonstrate that an individual exposed to low mean arterial pressure (MAP) (A), high CSF pressure (CSFP) (B), or low spinal cord perfusion pressure (SCPP) (C) increases their risk of poor neurologic outcome, and that this risk increases with more dramatic changes in hemodynamics. Dotted line represents a relative risk of 1. Thresholds for crossing a relative risk of 1 for MAP, CSFP, and SCPP were 70, 29, and 50 mm Hg, respectively. This finding was consistent in a subanalysis where only individuals with a baseline AIS score of A were considered (n = 57; D–F).

Figure 3 Additive relative risk (RR) matrix reveals optimal hemodynamic management range



By combining our RR data from mean arterial pressure (MAP) and CSF pressure (CSFP), we determine that MAP should be maintained above 70 mm Hg and CSFP below 29 mm Hg (where blue is a low RR of poor conversion). The black line represents the ideal clinical management scenario.

SCPP ($\beta = 0.067$ mm Hg) increased and CSFP ($\beta = -0.029$ mm Hg) decreased with time (hours) postinjury ($p < 0.001$ for all; figure 1). Individuals with AIS C on initial designation had significantly higher MAP ($\beta = 4.0$ mm Hg, $p = 0.028$) and SCPP ($\beta = 6.4$ mm Hg, $p = 0.008$) vs individuals with AIS A and B, while CSFP was significantly lower in AIS C ($p = 0.031$).

Six-month follow-up neurologic recovery data. From baseline to follow-up, there was a significant improvement in upper extremity motor score (30.68 ± 18.17 vs 36.68 ± 15.25), lower extremity motor score (3.09 ± 7.51 vs 13.46 ± 18.54), and total motor score (33.79 ± 19.57 vs 49.61 ± 26.70) across all participants (all $p < 1.25e-09$). Conversion between AIS grades from baseline to follow-up is reported in table e-2. At the 6-month follow-up, 43 individuals converted AIS grade in a positive direction, and none converted AIS grade in a negative direction (table e-2). We found no significant association between time to decompression and AIS conversion at 6 months ($p = 0.16$).

SCPP is positively associated with increased odds of conversion. We found that both MAP (odds ratio [OR] 1.037, confidence interval [CI] 1.011–1.063, $p = 0.004$) and CSFP (OR = 0.958, CI = 0.923–0.995, $p = 0.027$) during the first 5 days postinjury were independently predictive of a positive conversion at 6 months. In an independent logistic regression, we found that SCPP was predictive of positive conversion at 6 months, whereby for every 5 mm Hg higher SCPP the odds of converting were increased by 19.5% (OR = 1.039, CI = 1.011–1.063, $p = 0.004$). Further, we found similar results when examining motor score improvement instead of conversion status (MAP: OR = 1.038, CI = 1.013–1.064, $p = 0.003$; CSFP: OR = 0.956, CI = 0.921–0.992, $p = 0.002$; SCPP: OR = 1.039, CI = 1.016–1.063, $p = 0.001$).

Systematic RR permutations reveal optimal hemodynamic management measures. By systematically altering hemodynamic cutoffs, we show that RR for not improving an AIS grade (i.e., having poor neurologic recovery) continually increases as individuals are exposed to lower MAP, higher CSFP, and lower SCPP (figure 2). Next, using additive RR calculations, we visualized the risk of exposure to both low MAP and high CSFP (figure 3). Using this, we suggest that SCPP should be maintained above 50 mm Hg through a combination of MAP and CSFP manipulations (figure 3). To validate our suggested monitoring strategy, we performed univariate linear regression and demonstrate that the number of times SCPP pressure drops below 50 mm Hg is a predictor of conversion status (OR 0.9, CI 0.81–0.98, $p = 0.031$; table 1), while a MAP or CSFP cutoff did not predict any clinical outcome (all $p > 0.32$). Moreover, the number of times individuals drop below SCPP 50 mm Hg was higher in those who did not convert ($p = 0.023$; figure 4), while this effect was not found for a MAP cutoff of 70 mm Hg (all $p > 0.34$).

Table 1 Univariate logistic regression results for hemodynamic cutoffs and clinical outcomes

	UEMS, Δ	LEMS, Δ	TMS, Δ	Conversion
MAP <70 mm Hg	0.017 (−0.2 to 0.23)	0.076 (−0.29 to 0.44)	0.16 (−0.36 to 0.69)	1 (0.98 to 1.1)
CSFP >29 mm Hg	0.03 (−0.13 to 0.19)	0.15 (−0.12 to 0.41)	0.21 (−0.17 to 0.6)	1 (0.98 to 1)
SCPP <50 mm Hg	0.018 (−0.24 to 0.28)	−0.31 (−0.75 to 0.14)	−0.24 (−0.88 to 0.4)	0.9 (0.81 to 0.98)[a]

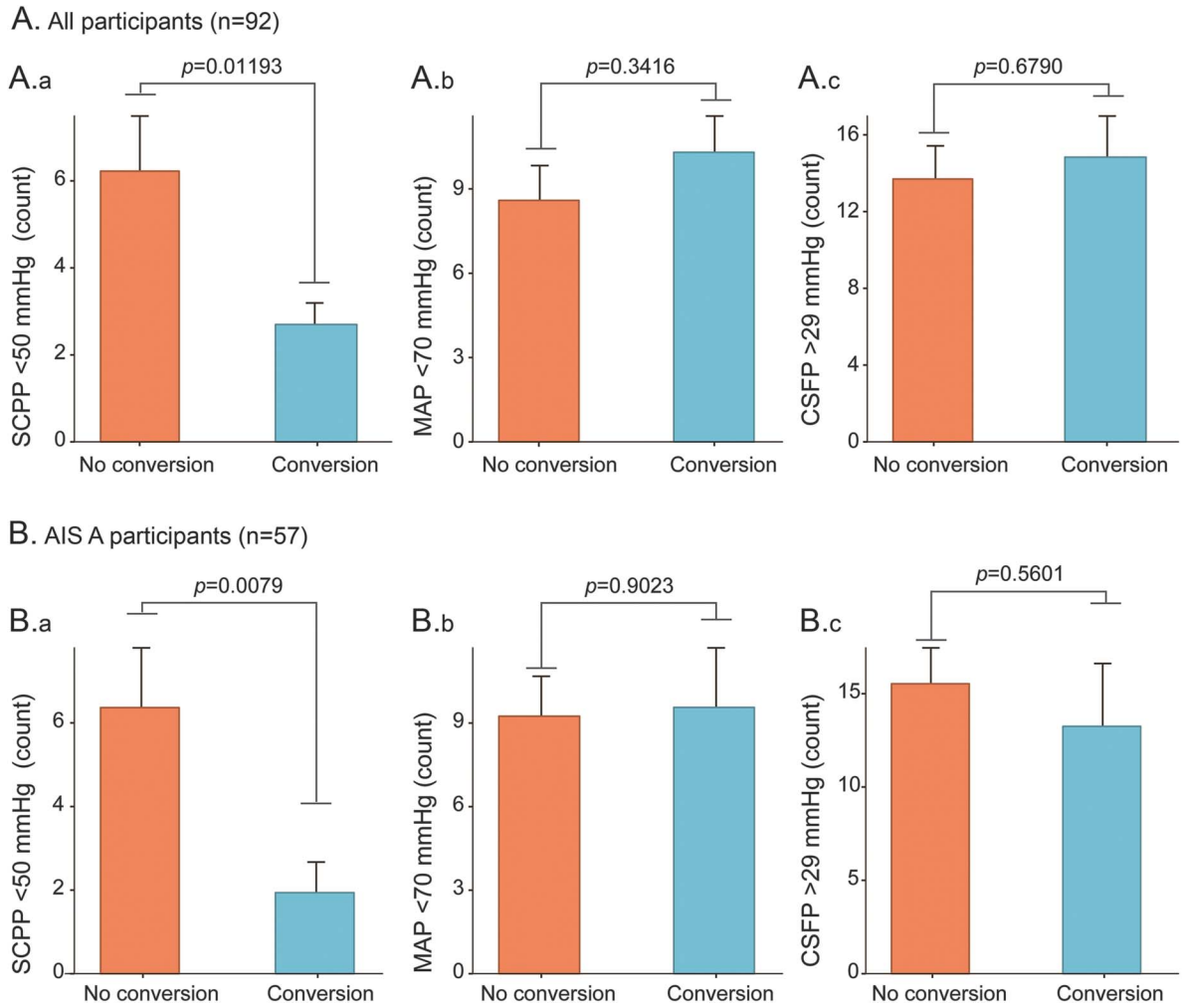
Abbreviations: CSFP = CSF pressure; LEMS = lower extremity motor score; MAP = mean arterial pressure; SCPP = spinal cord perfusion pressure; TMS = total motor score; UEMS = upper extremity motor score.
Δ = Change from baseline to 6 months. Values are adjusted odds ratios (95% confidence intervals).
[a] $p < 0.05$.

One factor to consider is whether this relationship is dependent upon baseline injury severity. We found that the relationships between SCPP and outcome were identical when considering only the AIS A patients (figure 4, B.a–B.c). Finally, by setting an exposure cutoff at 50 mm Hg for SCPP, we observed a significant likelihood ratio test for both conversion and improvement in total motor score under a Cox hazard ratio model in both our complete sample and our AIS A individuals (figure 5). Conversely, for an exposure cutoff of 70 mm Hg for MAP, the hazard ratio models were not significant for conversion status or motor score improvement, in our full sample or in a subanalysis of AIS A only individuals (all $p > 0.22$).

DISCUSSION We provide evidence from our multicenter trial that SCPP as measured by lumbar intrathecal catheterization is a predictor of neurologic outcome following traumatic spinal cord injury. Moreover, using systematic observations of RR, we show that exposure to low SCPP increases the risk of poor neurologic recovery. We substantiate this finding by demonstrating that the number of times individuals deviate outside specific SCPP cutoffs is related to poor neurologic recovery. We found this relationship held in a subanalysis of individuals with neurologically complete injuries (AIS A). Finally, we found that low SCPP was primarily occurring in the first few days after injury. Conversely, the number of times individuals deviated outside a MAP or CSFP cutoff was not predictive of neurologic outcome. Our findings therefore provide evidence that supports the assessment of SCPP in the acute phase after traumatic spinal cord injury.

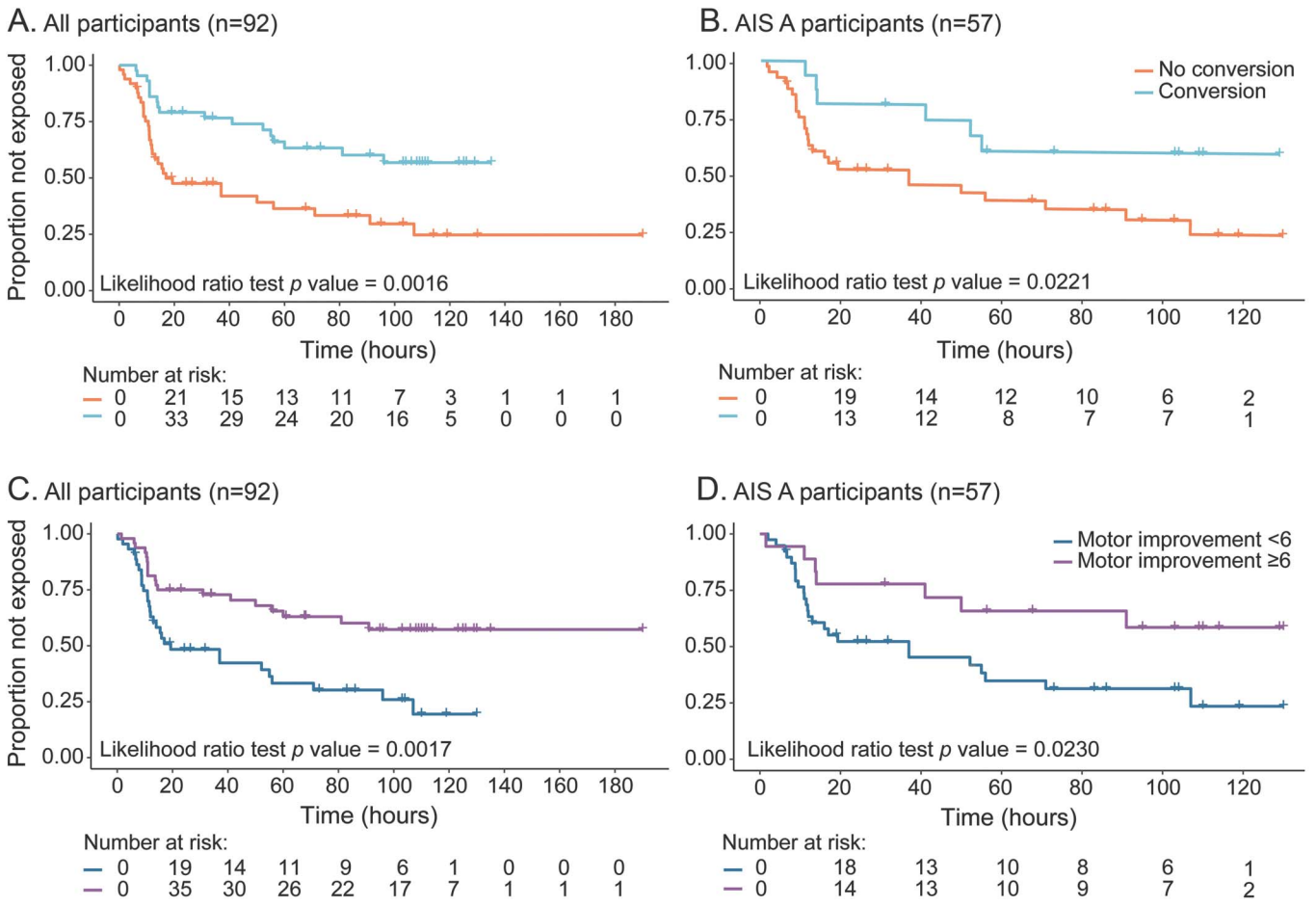
The influence of current hemodynamic management practices of augmenting MAP[2] on neurologic

Figure 4 **Frequency of deviations outside cutoffs between conversion status**



The number of times (count) individuals drop below set cutoffs is significantly different between those who do not convert (orange) and those who convert (blue). This effect was observed only for spinal cord perfusion pressure (SCPP) (A.a), but not for mean arterial pressure (MAP) (A.b) or CSF pressure (CSFP) (A.c) cutoffs. This finding was consistent in a subanalysis where only individuals with a baseline American Spinal Injury Association Impairment Scale score of A were considered (n = 57; B.a–B.c). Bar plots represent the mean and error bars the standard error. CSFP cutoffs represent the number of times an individual exceeds the pressure value. Cutoffs were established based on relative risk thresholds obtained from figure 3.

Figure 5 Low perfusion pressure exposures occur primarily within the first day postinjury



Kaplan-Meier plot of exposure status to spinal cord perfusion pressure below 50 mm Hg, split by conversion (A, B) or by total motor score improvement (C, D). Cox proportional hazard models revealed a statistically significant likelihood ratio test between those who neurologically improved (i.e., conversion [p = 0.0018]) and total motor score improvement (p = 0.0017) vs those that did not improve. This finding was consistent in a subanalysis where only individuals with a baseline American Spinal Injury Association Impairment Scale (AIS) score of A were considered (n = 57; B and D; p = 0.0221, p = 0.0230).

outcome in acute spinal cord injury is still unclear.[14,15] Arguably the most compelling supportive evidence is a recent study that reported improved neurologic outcomes when MAP was consistently above 70–75 mm Hg during the first week, which is 10–15 mm Hg below the current clinical guidelines.[14] Although our RR analysis indicates that risk for poor neurologic improvement occurs when MAP falls below 70 mm Hg, we show that using such a MAP cutoff is not a good indicator of whether neurologic improvement will occur. Conversely, using 3 different statistical approaches, we found that using a SCPP cutoff of 50 mm Hg is a robust marker of whether neurologic outcomes will improve.

Our findings are conceptually in agreement with Saadoun et al.,[9] who demonstrated that intraspinal pressure measured at the site of injury can predict neurologic outcome in SCI. A distinct difference, however, is that Saadoun et al. measured intraspinal pressure at the injury site, whereas we measured CSFP caudal to the injury site within the lumbar cistern. They revealed that the pressure was greatest at the site of occlusion, directly at the injury level, and that this was equivalent to the pressure recorded from inside the injured spinal cord.[16] We too have suggested that occlusion of the CSF space due to swelling might establish differential pressures across the injury site.[10,17] It is recognized, however, that spinal cord swelling postinjury is variable among patients, and the degree of swelling also changes with time. Measurement of CSFP in the lumbar cistern would therefore not necessarily be an invalid reflection of what is occurring at the injury site. However, an assessment of how such pressures could be used and—importantly—whether they reflected neurologic outcome was warranted. The advantage of measuring CSFP with lumbar catheterization is related to the ease of application, technical familiarity of the procedure, and lack of risk of mechanically damaging the already injured spinal cord with the pressure catheter.

It is notable that our proposed management strategy is strikingly similar to that currently applied in the

setting of traumatic brain injury, where intracranial cerebral perfusion pressure monitoring is the mainstay of acute management.[7,8,18,19] While the most recent neurosurgical guidelines provide Level IIB evidence to maintain cerebral perfusion pressure between 60 and 70 mm Hg,[19] the authors acknowledge that the lower limit of this monitoring is currently unknown. Here, we suggest a cutoff of at least 50 mm Hg in traumatic spinal cord injury. Such a SCPP could potentially be achieved by either raising MAP with vasopressors or lowering CSFP with drainage of CSF (or some combination of both). Lowering the CSFP by draining CSF may allow one to achieve the desired SCPP with a lower MAP, thereby reducing the need for extensive vasopressor support, which comes with its own complications.[1,15] Put together, these data warrant future validation, and provide a testable hypothesis against which standard management could be compared, obviating the ethical limitations of withholding hemodynamic optimization in the acute setting. Whether the difference in perfusion pressure recommendation arising from our findings compared to the traumatic brain injury population reflect a true physiologic difference or are the result of a lack of evidence in both fields supporting the notion of a true nadir remains to be determined. It is of note that our derived perfusion pressure cutoff of 50 mm Hg is supported by canine work, where spinal cord microvessel flow was preserved only when SCPP was maintained above 50 mm Hg.[20]

It is important to note the potential influence of decompression within our data. Early surgical decompression is beneficial for neurologic recovery, and the average time to decompression was less than 24 hours postinjury (considered to be early surgery). The exact effect of surgical decompression on SCPP is unclear without a method of directly measuring it at the injury site, but we have previously reported an increase in CSFP postdecompression.[10] Such increases coupled with a low MAP may result in periods of low SCPP in the postinjury period.

Together, our findings suggest that optimizing SCPP during the acute post–spinal cord injury period provides a novel target to improve neurologic outcome. By utilizing diverse statistical methodology, we provide multiple lines of evidence that maintaining SCPP above 50 mm Hg through both MAP and CSFP monitoring is associated with better neurologic outcome.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the work. L.M.B., A.T., L.R., J.-M.M.-T., S. Parent, S.C., C.B., S.D., J.S., T.A., S. Paquette, N.D., C.G.F., M.F.D., and B.K.K. collected the data. J.W.S. and C.R. W. conducted the analysis. J.W.S., C.R.W., and B.K.K. drafted the manuscript. All authors approved the final version and agree to be accountable for all aspects of the work.

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DISCLOSURE

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