



ARTICLE

All over the MAP: describing pressure variability in acute spinal cord injury

Cameron M. Gee^{1,2}, Angela Tsang³, Lise M. Bélanger³, Leanna Ritchie³, Tamir Ailon⁴, Scott Paquette⁴, Raphaelle Charest-Morin², Nicolas Dea⁴, John Street², Charles G. Fisher², Marcel F. Dvorak^{1,2} and Brian K. Kwon^{1,2}

© The Author(s), under exclusive licence to International Spinal Cord Society 2022

STUDY DESIGN: Observational study.

OBJECTIVES: To examine the feasibility of meeting the current clinical guidelines for the hemodynamic management of acute spinal cord injury (SCI) which recommend maintaining mean arterial pressure (MAP) at 85–90 mmHg in the days following injury.

METHODS: This study examined data collected minute-by-minute to describe the pressure profile in the first 5 days following SCI in 16 patients admitted to the Intensive Care Unit at Vancouver General Hospital (40 ± 19 years, 13 M/3 F, C4-T11). MAP and intrathecal pressure (ITP) were monitored at 100 Hz by arterial and lumbar intrathecal catheters, respectively, and reported as the average of each minute. Spinal cord perfusion pressure was calculated as the difference between MAP and ITP. The minute-to-minute difference (MMdiff) of each pressure variable was calculated as the absolute difference between consecutive minutes.

RESULTS: Only 24 ± 7% of MAP recordings were between 85 and 90 mmHg. Average MAP MMDiff was ~3 mmHg. The percentage of MAP recordings within target range was negatively correlated with the degree of variability (i.e. MMDiff; $r = -0.64$, $p < 0.008$) whereas higher mean MAP was correlated with greater variability ($r = 0.57$, $p = 0.021$).

CONCLUSIONS: Our findings point to the ‘real life’ challenges in maintaining MAP in acute SCI patients. Given MAP fluctuated ~3 mmHg minute-to-minute, maintaining MAP within a 5 mmHg range with conventional volume replacement and vasopressors presents an almost impossible task for clinicians and warrants reconsideration of current management guidelines.

Spinal Cord (2022) 60:470–475; <https://doi.org/10.1038/s41393-022-00802-0>

INTRODUCTION

The devastating neurologic impairments that follow acute traumatic spinal cord injury (SCI) can be attributed to two injury phases, each associated with distinct pathophysiological mechanisms and recommendations for treatment [1]. The first phase, or primary injury, is a result of the initial trauma [1]. The subsequent secondary injury is characterised by oedema, alterations in energy metabolism, biochemical changes and, of importance to the present study, vascular changes [2].

One of the key pathophysiological mechanisms in mediating secondary damage is ischaemia [2], which has prompted much interest in the hemodynamic management of acute SCI in an effort to support adequate perfusion of the injured cord. Acute SCI can trigger significant cardiovascular abnormalities including altered vascular function following SCI that may, in part, be attributed to neurogenic shock causing loss of sympathetic tone below the level of the injury. This causes hypotension and venous pooling that subsequently leads to reduced blood flow to the injured cord [3], ischaemia, tissue necrosis [4], and impaired neurological recovery [5, 6].

In an effort to mitigate the potential ischaemic insult, clinical guidelines have been established to guide the acute hemodynamic management of SCI. First established in 2008 by the

Consortium for Spinal Cord Medicine [7], and reiterated by the Joint Guidelines Committee of the American Academy of Neurologic Surgeons and Congress of Neurological Surgeons (AANS/CNS) in 2013 [8, 9], these clinical practice guidelines state that ‘maintenance of mean arterial blood pressure between 85 and 90 mmHg for the first 7 days following an acute spinal cord injury is recommended.’ This mean arterial pressure (MAP) target is typically achieved through the use of intravenous volume replacement and vasopressors. While these guidelines are widely adopted, it is acknowledged that the justification for maintaining MAP between 85 and 90 mmHg is based largely upon retrospective studies or uncontrolled case reports and series, and the true effect of maintaining this target MAP on neurologic recovery remains uncertain [10].

One issue with previous studies on hemodynamic management and the targeting of a specific MAP is the frequency with which MAP is measured and reported. Given that the injured cord appears to be sensitive and vulnerable to changes in blood pressure, then it would be important to understand the length of time that the cord has been exposed to MAP within, above, and below the target range. For example, we previously reported on the frequency and distribution of hypotensive episodes in acute SCI patients either in a heavily monitored settings (e.g. operating

¹International Collaboration on Repair Discoveries, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. ²Department of Orthopaedics, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. ³Vancouver Spine Program, Vancouver General Hospital, Vancouver, BC, Canada. ⁴Division of Neurosurgery, Faculty of Medicine, University of British Columbia, Vancouver, BC, Canada. ✉email: brian.kwon@ubc.ca

Received: 1 January 2022 Revised: 30 March 2022 Accepted: 1 April 2022

Published online: 13 April 2022

Table 1. Patient demographics at admission.

	Age (years)	Sex	Mechanism of injury	Level of injury	AIS	Time monitored (hours)
1	19	M	Fall	C5	A	167
2	20	M	Sports	C4	A	88
3	29	F	Sports	C4	A	164
4	69	F	Fall	C6	A	70
5	21	M	Sports	T5	A	44
6	23	M	Sports	T4	A	109
7	32	M	Fall	C4	A	113
8	64	M	Fall	C4	A	96
9	30	M	Sports	C4	C	109
10	51	M	Fall	C5	A	92
11	71	M	Transport	T3	A	101
12	20	M	Transport	T3	A	94
13	36	F	Transport	T9	C	84
14	63	M	Fall	C5	C	112
15	29	M	Transport	T11	A	108
16	57	M	Sports	C4	C	102
Mean ± SD	40 ± 19	13M/3F			12A/4C	103 ± 30

Bold indicates $p < 0.05$.

AIS American Spinal Injury Association Impairment Scale (range: A–E).

room, ICU) [11] or during the injury resuscitation phases (e.g. triage hospital, emergency room) [12]. However, a major limitation of these studies was the lack of precise measurement of the duration and frequency of these hypotensive episodes. Even in our recent reports on intrathecal (ITP) and spinal cord perfusion pressure (SCPP), while monitoring was continuous, the analysis was conducted on data that was recorded each hour [13, 14]. Hence, while this work led to insights about the association of SCPP and neurologic outcome, it lacked granularity regarding how these pressure measures were changing on a minute-by-minute basis.

Such granularity was hinted at by Hawryluk et al. in their minute-by-minute MAP recordings of 100 acute SCI patients [15], in whom ~30% of the recordings were <85 mmHg during the first week post-injury. While the analyses demonstrated how the 'average' MAP was higher in those who improved their American Spinal Injury Association Impairment Scale (AIS) grade versus those who did not, the percentage of time spent within or above the recommended range or the variability in MAP on a minute-by-minute basis was not reported.

Therefore, the purpose of the present study was to analyse data from patients with acute SCI in whom high frequency data was collected by a multimodal neuro-intensive care monitoring system (ICM+; Cambridge Enterprise Ltd, Cambridge, UK). These analyses aimed to describe the pressure profile (i.e. MAP, ITP, SCPP) in the first week following SCI.

METHODS

Data presented herein represent patients enrolled at a single centre as part of a larger multi-centre clinical trial (The Canadian Multi-centre CSF Pressure Monitoring and Biomarker Study; CAMPER Study; ClinicalTrials.gov ID: NCT01279811). The study recruited adult patients with non-penetrating traumatic SCI admitted to Vancouver General Hospital <48 h from the time of injury. Exclusion criteria included concomitant trauma that prevented the ability of the patient to provide informed consent or the study team to collect outcome measures. Further, inclusion in the present subset required pressure data to be collected using high frequency data acquisition software, which was achieved by connecting the subjects' monitor to a laptop running ICM+.

Hemodynamic data was collected on the ICM+ at a higher frequency than previously reported and analyzed in a different manner to the larger

trial that has been published elsewhere [13]. All study procedures were approved by the University of British Columbia's Clinical Research Ethics Board (H10-01091), was registered at ClinicalTrials.gov (NCT01279811), and conformed to the Declaration of Helsinki.

Demographics

16 patients (40 ± 19 years, 13 M/3 F) were included in the present study (see Table 1). Pressure data was recorded for 103 ± 30 h (range: 44–167 h) totalling 1653 h or 99,195 minute-by-minute pressure recordings. The percentage of valid recordings, determined as data for which a measure of SCPP could be calculated for that minute, was 89 ± 10 % (range: 63–99 %).

Experimental protocol

All procedures have been detailed elsewhere [13]. Briefly, the protocol followed standard of care treatment following SCI including hemodynamic management wherein intensive care (ICU) staff targeted a MAP of 85–90 mmHg with volume augmentation and vasopressor support [9, 16]. MAP and ITP were measured by arterial and lumbar intrathecal catheter, respectively.

Pressure data analyses

The ICM+ system sampled data at 100 Hz and reported pressure indices as the average of each minute. Data was first filtered to remove recordings where MAP was <50 or >150 mmHg, ITP was >50 mmHg, or when either MAP or ITP was not recorded such that SCPP could not be calculated (i.e. 'valid' recording). The mean, standard deviation (SD), and coefficient of variation (COV) across the monitoring period were then calculated for each patient. The distributions of recordings are reported as <85, 85–90, and >90 mmHg based on current recommendations for hemodynamic management [9, 16]. Additionally, SCPP distribution is reported as the percentage of recordings where SCPP was <65 mmHg, which is associated with a higher relative risk of poor neurological recovery [17]. The distribution of ITP is reported as the percentage of recordings where ITP was >15 mmHg as it relates to the hypothesis of a follow-up multi-centre clinical trial wherein a target ITP will be maintained at <15 mmHg by cerebrospinal fluid drainage. Data from the present study will serve as a control (ClinicalTrials.gov ID: NCT03911492). The minute-to-minute difference (MMdiff) was calculated as the absolute difference between each minute's mean pressure and that of the previous minute. Finally, we examined each of the above indices for between-day differences as well as a comparison of daytime (0900–1700) and night-time hours (2300–0700) in recognition of the increased activity that patients likely undergo during the

day versus the night (e.g. imaging studies, chest physiotherapy, blood work, wound checks).

Vasopressor administration

Administration and dose of vasopressors, including norepinephrine, epinephrine, dopamine, and vasopressin was reported each hour in 15 patients. Statistical analyses were only performed for norepinephrine as it was the predominant vasopressor administered.

Neurological examination

The International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) [18] was used to determine the level and completeness of injury. An ISNCSCI exam was performed at admission except for in one patient who needed to be intubated at time of the exam—for this patient, the “baseline neurological function” is reported from the exam conducted the following day.

Statistics

Analyses were performed in GraphPad Prism (version 9.1.0 GraphPad Software, Inc., LaJolla, CA, USA). Before applying statistical analyses, a Shapiro–Wilk normality test was performed. A linear mixed effects model assessed between-day differences in MAP, ITP, and SCPP and, in the presence of a main effect, post-hoc tests were performed with Bonferroni’s multiple comparison test. Dependent samples *t* tests were used to assess differences in pressure indices between day and night. Correlations between vasopressor administration and MAP, MAP thresholds, and indices of MAP variability were assessed by Pearson’s correlation coefficient. All data are presented as mean \pm SD. Significance was set at $p < 0.05$.

RESULTS

Pressure variability

Descriptive and pressure variability data are presented in Table 2. The percentage of MAP recordings <85 , 85 – 90 , and >90 mmHg

Table 2. Descriptive pressure data.

	MAP	ITP	SCPP
Mean \pm SD (mmHg)	92 \pm 3	13 \pm 6	79 \pm 7
COV (%)	10 \pm 2	47 \pm 17	13 \pm 3
MMdiff (mmHg)	2.84 \pm 1.08	0.80 \pm 0.51	2.82 \pm 1.09

COV coefficient of variation, MAP mean arterial pressure, MMdiff minute-to-minute difference, ITP intrathecal pressure, SCPP spinal cord perfusion pressure.

were 20 ± 12 , 24 ± 7 , and $57 \pm 16\%$, respectively. ITP was >15 mmHg for $39 \pm 31\%$ and SCPP was <65 mmHg on $14 \pm 16\%$ of the time. Figure 1A provides a representative hour from one patient wherein mean MAP, ITP, SCPP as well as time within thresholds is equal to the group average.

Correlations between MAP indices and percentage of recordings within each threshold are presented in Table 3. There was a moderate positive correlation between MAP and MMdiff ($p = 0.021$). Time spent within the recommended MAP range of 85 – 90 mmHg held a moderate negative correlation with indices of variability (i.e. COV and MMdiff) (all $p < 0.017$). Collectively, these correlations suggest that a higher MAP is associated with greater blood pressure variability and that limiting such variability is associated with achieving the target MAP. Indices of variability each held moderate to strong positive correlations with one another (all $p < 0.002$).

Analyses of between-day differences revealed a main effect for MAP ($p = 0.042$) with a significant difference between MAP on days 1 and 4 (91 ± 3 vs. 94 ± 5 mmHg, $p = 0.02$; Fig. 1B). There was a main effect for SCPP ($p = 0.033$) but post-hoc comparisons did not reveal any significant differences between days (Fig. 1B). Differences between day and night pressure and variability indices are presented in Fig. 2.

Vasopressor administration

Mean norepinephrine dosage over the monitoring period was 11 ± 3 mcg/min, range: 6 – 17 mcg/min) and was not different between days and mean norepinephrine dosage over the entire monitoring period did not significantly correlate with any MAP indices (see Table 3).

While the most widely used vasopressor was norepinephrine, three patients additionally received dopamine while in intensive care (10 ± 3 mcg/min for 36 ± 28 h), one received epinephrine (1 mcg/min for 9 h), and three received vasopressin (0.03 ± 0.01 mcg/min for 8 ± 10 h).

DISCUSSION

The present study is the first to describe minute-by-minute MAP, ITP, and SCPP in acute traumatic SCI. The most striking finding is the considerable minute-by-minute variability in MAP, such that the average MAP changed ~ 3 mmHg every minute. The 2013 AANS/CNS guidelines state that ‘maintenance of MAP between 85 and 90 mmHg for the first 7 days following an acute SCI is recommended’ [16]. Our

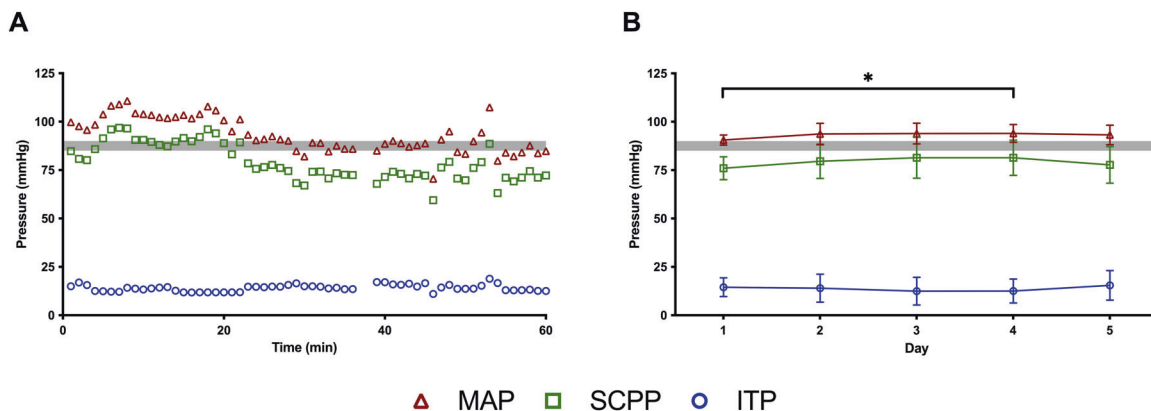


Fig. 1 Example hour of minute-by-minute pressure recordings. **A** Mean MAP (red triangles), ITP (blue circles), and SCPP (green squares) is representative of group mean averages reported in Table 2 and time spent within each MAP threshold is representative of that reported within the text. Shaded grey area represents the target mean arterial pressure of 85 – 90 mmHg. **B** Group mean daily averages for MAP (triangles), ITP (circles), and SCPP (squares). Main effect for mean arterial pressure $p = 0.042$, main effect for spinal cord perfusion pressure = 0.033 . Asterisk (*) symbol indicates $p = 0.02$ for mean arterial pressure day 1 vs. day 4. ITP intrathecal pressure, MAP mean arterial pressure, SCPP spinal cord perfusion pressure.

Table 3. Pearson correlation coefficients for indices of mean arterial pressure.

	<85 (%)	85–90 (%)	>90 (%)	COV (%)	MMdiff (mmHg)	NE (mcg/min)
MAP mean (mmHg)	−0.81	−0.75	0.93	0.43	0.57	0.00
<85 (%)		0.39	−0.91	0.10	−0.10	0.08
85–90 (%)			−0.74	−0.59	−0.64	0.23
>90 (%)				0.18	0.35	−0.16
COV (%)					0.82	0.45
MMdiff (mmHg)						0.32

Bold indicates $p < 0.05$.

COV coefficient of variation, MAP mean arterial pressure, MMdiff minute-to-minute difference, NE norepinephrine.

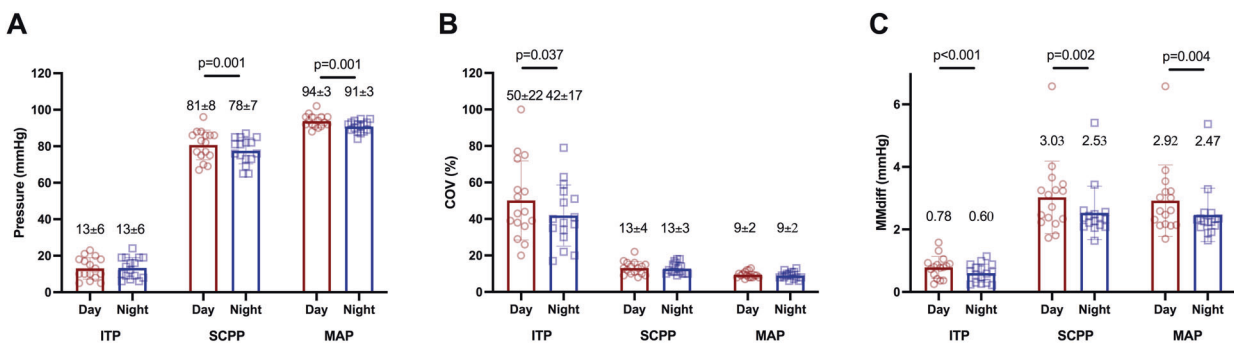


Fig. 2 Daytime vs. night pressure profile. Day (0900–1700 h, red circles) vs. night (2300–0700 h, blue squares) comparison of pressure (A) mean values, (B) COV, and (C) MMdiff. COV coefficient of variation, ITP intrathecal pressure, MAP mean arterial pressure, MMdiff minute-to-minute difference, SCPP spinal cord perfusion pressure.

findings point to the ‘real life’ challenge of adhering to these guidelines. These challenges are underscored by the observation that MAP was only within the guidelines of 85–90 mmHg ~24% of the time during which patients were managed in the ICU setting. In fact, the majority of the recordings ($57 \pm 16\%$) were above 90 mmHg, suggesting that in an effort to keep patients within the 85–90 mmHg range and avoid hypotension, the tendency is to ‘overshoot’ the target. The effect of being somewhat ‘hypertensive’ in this acute post-injury period is poorly understood, although the previous work of Hawryluk et al. would suggest that average MAPs that exceeded 90 mmHg, as well as less time with MAP <85 mmHg, were associated with greater neurologic recovery [15].

Pressure profile in the first 5 days following SCI

In monitoring the minute-by-minute changes in MAP over the first 5 days following traumatic SCI we observed similar findings to Hawryluk et al. who reported that only one in four measures of MAP are within the recommended MAP target as per the guidelines, with the majority of recordings >90 mmHg [15]. The present data demonstrates that higher mean MAP during the first 5 days following SCI is correlated with larger minute-by-minute differences in MAP. Conversely, less variability (measured by COV and MMdiff,) was associated with more recordings in the range of 85–90 mmHg.

In the context of the guidelines for hemodynamic management, these findings highlight the potential of interventions that may limit MAP variability and maintain optimal MAP—in other words, provide more precise control of MAP. In this respect, one potential treatment option that warrants further investigation is an implanted epidural electrical stimulator, which has shown promise in preventing hypotension in the pre-clinical setting and warrants further investigation in the clinical and/or acute setting [19]. Similarly, a

non-invasive transcutaneous stimulator has proven effective in preventing both episodes of hypotension in individuals with chronic SCI [20] and hypertension in rodents with sub-acute SCI [21].

Due to the majority of patients having an AIS-A we were unable to conduct analyses on how the severity of SCI relates to pressure variability and/or the ability for ICU staff to maintain MAP at target. As such, whether differing hemodynamic guidelines for patients presenting with SCI of varying severities should be adopted is one potential area of future research.

In the uninjured population, blood pressure variability is associated with increased risk of cardiovascular events and mortality [22]. Similarly, MAP variability is associated with poor neurological outcome 30 days post-stroke [23], but it is unknown if this is true in acute SCI. Further research is required to understand not only the associated risks but also the determinants of the observed hemodynamic variability. Among able-bodied individuals, blood pressure variability is associated with increased sympathetic activity [24]. However, we believe this an unlikely mechanism in the presence of neurogenic shock and, among those with high-level SCI, the interruption of communication between higher centres and sympathetic pre-ganglionic neurons within the cord [25]. We suggest that the observed variability may be due to an inability of the autonomic nervous system to appropriately respond to stimuli that influence blood pressure in the setting of acute SCI. Though it should be noted that debate remains as to whether cardiovascular variability is in fact a true measure of sympathovagal balance [26].

This is the first study to report on the variability in ITP and SCPP and we believe is of importance to future research and clinical practice guidelines regarding the acute management of patients with traumatic SCI. For example, *is it reasonable to recommend*

maintaining MAP within a 5 mmHg range when the MAP normally fluctuates through a range of around 3 mmHg every minute? We found ITP to be highly variable compared to both MAP and SCPP (i.e. higher COV). One potential mechanism for the observed ITP variability may be explained by its relationship with the patency of the intrathecal space (described below). Given that lowering ITP by CSF drainage has been demonstrated to enhance SCPP and spinal cord blood flow in a porcine model [27], knowledge of high ITP variability in humans with SCI and its mechanisms in the present study may be an important consideration in the clinical implementation of CSF drainage.

Daytime vs. night pressure profile

One explanation for the observed variability is that it may be exacerbated by activities that the patients are subjected to during the day. To determine whether the movement of the patient could explain the variability, we compared the pressure profile during day and night (i.e. when patients movements are presumably higher and lower, respectively).

Higher MAP and SCPP during the day were accompanied by greater minute-to-minute variability in all pressure indices. While patient movement or wakefulness may be responsible for the significant differences in daytime and night variability, it is important to note that there is considerable pressure variability even at night, and this may have some clinical significance. We take this to support our discussion questioning the practical application of meeting the guidelines for hemodynamic management by ICU staff as the variability appears to be largely unrelated to patient movement.

Whether the observed night-time variability is greater following SCI than in able-bodied individuals is unknown. While blood pressure variability has been assessed during bed rest in able-bodied individuals previously [28], our ability to make comparisons are limited as we are unaware of studies that have monitored minute-by-minute blood pressure in able-bodied individuals.

Lower night-time MAP (i.e. nocturnal dip) is a widely documented circadian pattern in uninjured individuals due to the withdrawal of sympathetic activity [29]. However, we do not expect that this mechanism explains the lower night-time MAP in the present study for a number of reasons. First, a normal nocturnal dip is considered to be a decrease in blood pressure of 10% or more [29], which was not present in a single patient in the present study. Second, in the presence of neurogenic shock wherein the medullary connections to sympathetic pre-ganglionic neurons are interrupted [25], sympathetic activity is already limited and can not therefore be further 'withdrawn'. Third, were nocturnal dip present we would expect to have observed a larger dip among patients with lower injuries in whom descending sympathetic pathways remain at least partially intact, as has been observed in individuals with intermediate and chronic SCI [30].

Limitations

First, we acknowledge that the sample size in the present investigation is too small to draw conclusions regarding the relationship between pressure indices and the neurologic characteristics of the injury (e.g. baseline AIS grade, or improvement in AIS grade/motor score). In essence, this study did not aim to analyze how hemodynamic management affected outcome, but rather to examine the clinical practicality of, and generate hypotheses around, the hemodynamic management of acute SCI. While preliminary in nature, we believe these data can help other groups who do not have the ability to collect hemodynamic measures at such a high frequency understand the challenges involved in meeting the current guidelines for hemodynamic management in acute SCI.

Second, we have assumed that MAP and/or SCPP dictate spinal cord blood flow and oxygenation. However, data from the porcine model has found an imbalance between blood flow and oxygenation that suggests this relationship may not be linear

[31]. Future research in the clinical setting with direct assessment of spinal cord oxygenation is needed to better understand this relationship. Until then, we and others will be largely dependent upon metrics of systemic MAP.

Finally, as we were unable to include an able-bodied control group or other patient groups, we cannot be certain that our findings are specific to acute SCI. Future studies should aim to determine mechanisms of pressure variability in both non-SCI populations and SCI populations of varying level and severity.

In examining the variability of the pressure profile in the first week following traumatic SCI, we have described some of the real-life challenges faced by ICU staff in meeting the guidelines for the hemodynamic management of acute SCI, which themselves are based on weak clinical evidence [10]. The clinical reality is that the hemodynamic management of an acute SCI patient is likely influenced by clinician preference, their 'belief' in the relationship between specific MAP targets and neurologic recovery, and the ability to keep the patient within an ICU setting for up to 7 days. This clinical reality in combination with our observations about the challenge of actually adhering to the current recommendations in the way that they are specifically written point to the need to revisit the guidelines for hemodynamic management of acute SCI.

DATA AVAILABILITY

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

REFERENCES

- Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. *Nat Rev Dis Prim*. 2017;3. <https://doi.org/10.1038/nrdp.2017.18>.
- Tator CH, Fehlings MG. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg*. 1991;75:15–26.
- Lehmann KG, Lane JG, Piepmeier JM, Batsford WP. Cardiovascular abnormalities accompanying acute spinal cord injury in humans: Incidence, time course and severity. *J Am Coll Cardiol*. 1987;10:46–52.
- Wallace MC, Tator CH, Frazee P. Relationship between posttraumatic ischemia and hemorrhage in the injured rat spinal cord as shown by colloidal carbon angiography. *Neurosurgery*. 1986;18:433–9.
- Dakson A, Brandman D, Thibault-Halman G, Christie SD. Optimization of the mean arterial pressure and timing of surgical decompression in traumatic spinal cord injury: a retrospective study. *Spinal Cord*. 2017;55:1033–8.
- Cohn JA, Wright J, McKenna SL, Bushnik T. Impact of mean arterial blood pressure during the first seven days post spinal cord injury. *Top Spinal Cord Inj Rehabil*. 2010;15:96–106.
- Early acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. *J Spinal Cord Med*. 2008;31:403–79.
- Ryken TC, Hurlbert RJ, Hadley MN, Aarabi B, Dhall SS, Gelb DE, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. *Neurosurgery*. 2013;72:84–92.
- Walters BC, Hadley MN, Hurlbert RJ, Aarabi B, Dhall SS, Gelb DE, et al. Guidelines for the management of acute cervical spine and spinal cord injuries: 2013 update. *Neurosurgery*. 2013;60:82–91.
- Evaniew N, Mazlouman SJ, Belley-Côté EP, Jacobs WB, Kwon BK. Interventions to optimize spinal cord perfusion in patients with acute traumatic spinal cord injuries: a systematic review. *J Neurotrauma*. 2020;37:1127–39.
- Kong CY, Hosseini AM, Belanger LM, Ronco JJ, Paquette SJ, Boyd MC, et al. A prospective evaluation of hemodynamic management in acute spinal cord injury patients. *Spinal Cord*. 2013;51:466–71.
- Tee JW, Altaf F, Belanger L, Ailon T, Street J, Paquette S, et al. Mean arterial blood pressure management of acute traumatic spinal cord injured patients during the pre-hospital and early admission period. *J Neurotrauma*. 2017;34:1271–7.
- Squair JW, Bélanger LM, Tsang A, Ritchie L, Mac-Thiong JM, Parent S, et al. Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury. *Neurology*. 2017;89:1660–7.
- Squair JW, Bélanger LM, Tsang A, Ritchie L, Mac-Thiong JM, Parent S, et al. Empirical targets for acute hemodynamic management of individuals with spinal cord injury. *Neurology*. 2019;93:e1205–11.
- Hawrylyuk G, Whetstone W, Saigal R, Ferguson A, Talbott J, Bresnahan J, et al. Mean arterial blood pressure correlates with neurological recovery after human spinal cord injury: analysis of high frequency physiologic data. *J Neurotrauma*. 2015;32:1958–67.

16. Ryken TC, Hurlbert RJ, Hadley MN, Aarabi B, Dhall SS, Gelb DE, et al. The acute cardiopulmonary management of patients with cervical spinal cord injuries. *Neurosurgery*. 2013;72:84–92.
17. Squair JW, Bélanger LM, Tsang A, Ritchie L, Mac-Thiong JM, Parent S, et al. Empirical targets for acute hemodynamic management of individuals with spinal cord injury. *Neurology*. 2019;93:E1205–11.
18. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, et al. International standards for neurological classification of spinal cord injury (revised 2011). *J Spinal Cord Med*. 2011;34:535–46.
19. Squair JW, Gautier M, Mahe L, Soriano JE, Rowald A, Bichat A, et al. Neuroprosthetic baroreflex controls haemodynamics after spinal cord injury. *Nature*. 2021;590:308–14.
20. Phillips AA, Squair JW, Sayenko DG, Edgerton VR, Gerasimenko Y, Krassioukov AV. An autonomic neuroprosthesis: noninvasive electrical spinal cord stimulation restores autonomic cardiovascular function in individuals with spinal cord injury. *J Neurotrauma*. 2018;35:446–51.
21. Sachdeva R, Nightingale TE, Pawar K, Kalimullina T, Mesa A, Marwaha A, et al. Noninvasive neuroprosthesis promotes cardiovascular recovery after spinal cord injury. *Neurotherapeutics*. 2021;1:3.
22. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol*. 2013;10:143–55.
23. Dawson SL, Manktelow BN, Robinson TG, Panerai RB, Potter JF. Which parameters of beat-to-beat blood pressure and variability best predict early outcome after acute ischemic stroke? *Stroke*. 2000;31:463–8.
24. Narkiewicz K, Winnicki M, Schroeder K, Phillips BG, Kato M, Cwalina E, et al. Relationship between muscle sympathetic nerve activity and diurnal blood pressure profile. *Hypertension*. 2002;39:168–72.
25. Weaver LC, Fleming JC, Mathias CJ, Krassioukov AV. Disordered cardiovascular control after spinal cord injury. *Handb Clin Neurol*. 2012;109:213–33.
26. Parati G, Mancia G, Di Rienzo M, Castiglioni P, Taylor JA, Studinger P. Point: counterpoint: cardiovascular variability is/is not an index of autonomic control of circulation. *J Appl Physiol*. 2006;101:676–82.
27. Martirosyan NL, Kalani MYS, Bichard WD, Baaj AA, Fernando Gonzalez L, Preul MC, et al. Cerebrospinal fluid drainage and induced hypertension improve spinal cord perfusion after acute spinal cord injury in pigs. *Neurosurgery*. 2015;76:461–8.
28. Shiraishi M, Kamo T, Nemoto S, Narita M, Kamegai M, Baevsky RM, et al. Blood pressure variability during 120-day head-down bed rest in humans. *Biomed Pharmacother*. 2003;57:35–8.
29. Seo WS, Oh HS. The circadian rhythms of blood pressure and heart rate in the hypertensive subjects: dippers and non-dippers. *Yonsei Med J*. 2002;43:320–8.
30. Hubli M, Gee CM, Krassioukov AV. Refined assessment of blood pressure instability after spinal cord injury. *Am J Hypertens*. 2015;28:173–81.
31. Streijger F, So K, Manouchehri N, Tigchelaar S, Lee JHT, Okon EB, et al. Changes in pressure, hemodynamics, and metabolism within the spinal cord during the first 7 days after injury using a Porcine model. *J Neurotrauma*. 2017;34:3336–50.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the support of our funders—Praxis Spinal Cord Institute, Vancouver Coastal Health Research Institute and Michael Smith Foundation for Health Research—for their support. We thank the patients and their families for providing consent to our data collection that formed the present paper.

AUTHOR CONTRIBUTIONS

CMG analysed data, interpreted results, and drafted the paper for important intellectual content. AT, LMB, LR, TA, SP, RCM, ND, JS, CGF, and MCF collected data and revised the manuscript for important intellectual content. BKK conceived of and designed the work that led to the submission, interpreted results, and revised the paper for important intellectual content. All authors approved the final version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

FUNDING

Funding for this clinical trial was primarily received from Praxis Spinal Cord Institute (formerly the Rick Hansen Institute). Additional funds were received from the Vancouver Coastal Health Research Institute and Michael Smith Foundation for Health Research. BKK is the Canada Research Chair in SCI.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research. Ethics approval was received from the University of British Columbia Clinical Research Ethics Board.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Brian K. Kwon.

Reprints and permission information is available at <http://www.nature.com/reprints>

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.