Pilot study: Advanced hemodynamic monitoring after acute spinal cord injury. Keep the pressure up?

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Abstract

Background: Although the use of vasopressors to maintain hemodynamic goals after acute spinal cord injury (SCI) is still recommended, evidence regarding the target values and possible risks of this practice is limited and data on hemodynamic parameters unaffected by catecholamines are rare. In this pilot study we show the hemodynamic profile of patients with acute SCI mainly unbiased by vasopressor use and other factors that influence the cardiovascular system.

Methods: From March 2018 until March 2020, we conducted a prospective, single-center pilot study including 30 patients with acute SCI. Factors that could affect the cardiocirculatory system other than the SCI (sepsis, pre-existing heart disease or multiple trauma) led to the exclusion. A total of 386 measurements were performed using the PiCCO™ system.

Results: Mean systemic vascular resistance index (SVRI, *1447.23±324.71 dyn*s*cm^{-5}*m^2*), mean central venous pressure (CVP, *10.69±3.16*) and mean global end-diastolic volume index (GEDVI, 801.79±158.95 ml/m^2) deviated from the reference range while mean cardiac index (CI), mean stroke volume index (SI), mean arterial pressure (MAP), and mean heart rate (HR) were within the reference range as indicated in the literature. A mixed model analysis showed a significant negative relationship between norepinephrine treatment and MAP (83.97 vs 73,69 mmHg, p<0.001), SVRI (1463.40 vs 1332,14 dyn*s*cm^{-5}*m^2, p=0.001) and GEDVI (808.89 vs 759,39 ml/m^2, p=0,001).

Conclusion: These findings could lead to an adaptation of the target range for SVRI and MAP in patients with acute SCI and therefore reduce the use of vasopressors.

Background

Acute spinal cord injury (SCI) can lead to hemodynamically relevant vasoplegia of the peripheral vessels and bradycardia due to the abrupt loss of sympathetic control and over-stimulation of the parasympathetic nervous system. The extent of these symptoms depends on the level of the SCI with lesions above T6 in particular being associated with hemodynamic instability [1]. However, the loss of motor function in lesions below Th6 may also contribute to a loss off peripheral resistance due to blood stasis and edema of the lower limps. Resulting autonomic dysreflexia in both groups can lead to severe orthostatic hypotension which conflicts with the need for early mobilization [2, 3]. In severe cases it can lead to a neurogenic shock in which organ perfusion is critically reduced [4–9] Therefore, patients with acute SCI are considered hemodynamically unstable and many initially need intensive care surveillance and treatment including close hemodynamic monitoring and vasopressor therapy [10–12]. The PiCCO™ system is an established method for hemodynamic monitoring and is used routinely in hemodynamically unstable intensive care patients, including those with acute SCI [13–16].

There is limited data on cardiocirculatory response in patients with acute SCI. While a few previous studies assessed hemodynamics using Swan-Ganz catheter, the results obtained were always biased by

vasopressor use and were limited to the first week after the SCI [11, 17]. Our aim was to show the hemodynamic profile of patients suffering from acute SCI over a longer period of time and unbiased by vasopressor use as well as other factors that might influence the cardio circular system i.e., heart failure and sepsis.

Methods

Study design and oversight

The study was conducted prospectively in a single center. Informed consent was obtained either from the patients or their legal representatives prior to inclusion. The study was approved by the Ethics Committee of the Ruhr University Bochum (No. 17-6002-BR).

Patient population

All patients treated in the intensive care unit (ICU) of the university hospital Bergmannsheil Bochum between March 2018 and March 2020 suffering from traumatic SCI with an acute onset of neurological symptoms (< 24h) and who required regular arterial blood gas analyses or invasive blood pressure monitoring as part of their treatment were eligible for inclusion. The patients underwent neurological examination according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) by the American Spinal Injury Association (ASIA) and the International Spinal Cord Society.[18] Patients under 18 years of age as well as patients who did not require regular blood gas analysis or invasive blood pressure monitoring were not included. Furthermore, patients with a known heart failure were not included. In those cases where information on heart failure was not available, we excluded all patients that had a history of heart attack, cardiovascular intervention such as coronary-stenting or bypass-surgery as well as cardiac arrhythmia. In addition, patients with elevated inflammatory parameters (CRP > 10mg/dl and/or leucocytes > 13/nl) and/or a body temperature > 39°C and patients receiving antibiotics were not included. If patients already enclosed developed signs of inflammation or sepsis, these measurements were not used for the analysis. Furthermore, patients with multiple injuries (injury severity score > 16) were excluded.

Measurements

The “PICCO2” system from Pulsion (PiCCO™, PULSION Medical Systems, Munich, Germany) with a module for the M1046A monitor system from Philips was used to measure the cardiac index (CI), the stroke volume index (SI), the systemic vascular resistance index (SVRI) and the global end-diastolic volume index (GEDVI). The measurements were carried out according to the manufacturer's manual (Instructions for Use Picco2, Version 3.0). As part of the standard intensive care monitoring an arterial catheter as well as a central venous catheter were placed. In all patients the thermodilution solution was administered via a central venous catheter placed either in the internal jugular or subclavian vein. The choice of catheter was left to the attending physician. A chest-x-ray was employed to check for the correct catheter tip placement. The arterial catheter (PiCCO catheter 5F 20cm) was always placed in the femoral

artery. In patients with SCI placing a femoral arterial catheter is standard practice in our ICU as it allows for a hindrance free training of the upper body. Furthermore, early mobilisation can be realized as the placement in a large arterial vessel ensures a continuous measurement even with a flexed hip. Whereas catheters placed in the radial, brachial or axillary artery are smaller and more likely to malfunction due to voluntary or involuntary movement of the arms. For the individual measurements, the application of 4x 20ml cold (8–10°C) NaCl 0.9% solution was used. Saline solution was administered as it is recommended in the Instructions for Use of the PiCCO system, since Glucose solutions have been associated with malfunction of the injection valve at the CVC. Furthermore, as thermodilution boluses accounted for at least 250ml/day, this volume of 5% glucose solution might affect the blood sugar levels in diabetic as well as non-diabetic patients. During the stay in the ICU, the hemodynamic parameters were measured by means of thermodilution at least 3 times a day (once per shift in a three-shift system). Additionally, the heart rate (HR), the MAP, the central venous pressure (CVP) as well as the use of vasopressors were noted. CVP measurement was performed according to the usual practices of our ICU. The pressure measurement device was connected to the distal lumen of the CVC. It was then positioned at the mid thoracic level. The zero reference was carefully calibrated. The mean CVP value displayed on the monitor was noted. In ventilated patients the mean CVP was documented after three respiratory cycles without mechanical ventilation interruption. The only vasopressor administered was norepinephrine. The indication to start pharmacological vasoconstriction was left to the attending physician. In general, it was initiated when either the MAP dropped below 70mmHg or when the patient presented signs of reduced organ perfusion i.e., elevated serum lactate, oliguria, dizziness. As a standard practice in the ICU of the university hospital Bergmannsheil Bochum all catheters are removed at the earliest possible time regardless of the underlying disease. The measurements were stopped once regular arterial blood gas analyses or invasive blood pressure monitoring were no longer indicated. In acute SCI this was the case when the patients were hemodynamically stable in bed and under mobilisation as well as when mechanical ventilation was no longer required or when patients requiring prolonged ventilation showed a stable blood gas analysis for more than 48 hours.

Statistical analysis

The data were stored in a strictly pseudonymous form in Excel (Microsoft® Excel® for Microsoft 365 MSO). The statistical evaluation was carried out with SPSS statistical software (Version 25, IBM Corp., Armonk, NY, USA) and R Core Team (Version 2017, R: A language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria). The data were first aggregated by subject and then a descriptive statistical analysis (mean, standard deviation, standard error) was conducted. A mixed model analysis was carried out to check whether there are any differences in the values of the respective criterion variables during the administration of norepinephrine.

Results

Thirty patients (age 55 ± 19 years, 27 men and 3 women) were included. On average, the first measurement was taken 12 ± 18 days after SCI. Data were collected over a period of 8 ± 5 days. Three of

the patients died during their stay in the hospital after being released from the ICU (Table 1).

Table 1
Patient population and length of stay

	N	Minimum	Maximum	Mean ± SD
Age (years)	30	18	82	55 ± 19
Weight (kg)	30	60	88	77 ± 7
Height (cm)	30	160	190	179 ± 8
Body Surface Area (m^2)	30	1.6	2.3	2.0 ± 0.1
Time to first Measurement (days)	30	1	89	12 ± 18
Mean duration of Measurement (days)	30	1	20	8 ± 5
Length of ICU stay (days)	30	6	49	22 ± 12
Length of hospital stay (days)	30	22	370	136 ± 95
ICU intensive care unit, SD standard deviation				

25 subjects suffered from an injury to the cervical or high-thoracic spinal cord (C2-Th6). 5 patients had a lesion of the lower thoracic or lumbar spine. The majority of patients suffered from a severe cervical or high-thoracic SCI according to the ASIA Impairment Scale (AIS). (Table 2)

Table 2
Level and Severity of SCI according to the ISNCSCI

Level	ASIA impairment score	n (%)
C2-Th6	AIS A	14 (56)
	AIS B	4 (16)
	AIS C	6 (24)
	AIS D	1 (4)
	Total	25 (100)
below Th6	AIS A	3 (60)
	AIS B	1 (20)
	AIS E	1 (20)
	Total	5 (100)

ASIA american spinal injury association, AIS asia impairment scale, ISNCSCI international standards for neurological classification of spinal cord injury, SCI spinal cord injury

When comparing measurements regardless of vasopressor use SVRI (1447.23 ± 324.71 dyn*s*cm^{-5}*m^2, 95%-confidence interval (95%-CI) [1323.72, 1570.75]), CVP (10.69 ± 3.16, 95%-CI [9.48, 11.90]) and GEDVI (801.79 ± 158.95, 95%-CI [741.24, 862.16] deviated from the reference ranges (SVRI 1700–2400 dyn*s*cm^{-5}*m^2, CVP 1–7 mmHg, GEDVI 680-800ml/m^2) as specified in the literature (Table 3), while CI, SI, HR and MAP were within the reference range.

Table 3
Comparison of mean values to the reference range

	N	Minimum	Maximum	Mean ± SD	95%-CI	Reference Range
CI (l/min/m^2)	30	2.43	5.78	4.14 ± 0,84	[3.83, 4.46]	3.0–5.0
SI (ml/m^2)	30	37.17	82.04	58.69 ± 10.93	[54.57, 62.89]	40–60
SVRI (dyn*s*cm^{-5}*m^2)	30	973.22	2538.25	**1447.23 ± 324.71**	[1323.72, 1570.75]	1700–2400
HR (bpm)	30	54.88	100.00	72.62 ± 12.62	[67.82, 77.42]	60–80
MAP (mmHg)	30	65.88	112.43	81.55 ± 10.45	[77.57, 85.53]	70–90
CVP (mmHg)	30	3.33	15.41	**10.69 ± 3.16**	[9.48, 11.90]	1–7
GEDVI (ml/m^2)	30	503.45	1132.00	**801.79 ± 158.95**	[741.24, 862.16]	680–800

Relevant deviation highlighted in bold. CI cardiac index, CVP central venous pressure, GEDVI global end-diastolic volume index HR heart rate, MAP mean arterial pressure, SD standard deviation, SI stroke volume index, SVRI systemic vascular resistance index, 95%-CI 95%-confidence interval

There were 19 patients requiring vasopressor therapy on at least one measurement. A mixed model analysis was carried out to check whether there were any differences in the values of the respective criterion variables CI, SI, SVRI, GEDVI, MAP and CVP during the administration of norepinephrine. There was variation for all criterion variables at population level. The addition of the binary predictor variable "norepinephrine" showed a significant negative relationship for the SVRI, GEDVI and MAP (Table 4).

Table 4
Model parameters detecting differences in CI, SI, SVRI, GEDVI, MAP and CVP with norepinephrine use

Parameter	Intercept only	Fixed slopes	*p*
Regression coefficants (fixed effects)			
Intercept (CI)	4.18	4.21	
Norepinephrin	-	-0.17	0.06
Intercept (SI)	58.41	58.90	
Norepinephrin	-	-2.06	0.066
Intercept (SVRI)	1432.98	1463.40	
Norepinephrin	-	-131.26	**0.001****
Intercept (GEDVI)	797.39	808.89	
Norepinephrin	-	-49.50	**0.001****
Intercept (MAP)	81.59	83.97	
Norepinephrin	-	-10.28	**< .001*****
Intercept (CVP)	10.84	10.90	
Norepinephrin	-	-0.25	0.707
Variance components (random effects)			
Residuals/Intercept (CI)	0.48/0.61	0.48/0.63	
Residuals/Intercept (SI)	71.03/105.74	70.39/106.17	
Residuals/Intercept (SVRI)	96536/83336	94204/81045	
Residuals/Intercept (GEDVI)	10367/22248	9968/23418	
Residuals/Intercept (MAP)	143.8/91.1	128.7/85.6	
Residuals/Intercept (CVP)	27.30/6.05	27.27/6.14	
Intraclass Correlation Coefficants			
CI	0.56		
SI	0.59		
SVRI	0.46		
GEDVI	0.68		
MAP	0.38		
CVP	0.18		

Parameter	Intercept only	Fixed slopes	*p*

*Relevant deviation highlighted in bold. CI cardiac index, CVP central venous pressure, GEDVI global end-diastolic volume index HR heart rate, MAP mean arterial pressure, SD standard deviation, SI stroke volume index, SVRI systemic vascular resistance index, ** p < .01, *** p < .001*

Discussion

In this study we performed invasive hemodynamic monitoring in patients suffering from acute SCI using the thermodilution-based PiCCO™ system. To our knowledge, this is the first study that provides advanced hemodynamic monitoring of patients with SCI that are not treated with vasopressors and in which data is not biased by septic or cardiogenic shock.

Few studies have examined advanced hemodynamic parameters in patients with acute SCI. In 1993 Levi et al used hemodynamic monitoring via Swan-Ganz catheter in 50 patients with SCI to maintain a hemodynamic profile with adequate cardiac output [17]. Similarly, Vale et al. maintained mean arterial blood pressure above 85 mmHg in 77 patients with acute SCI also using a Swan-Ganz catheter to monitor the hemodynamic status [11]. Both prospective studies aimed to show that maintaining a certain hemodynamic profile improved neurological outcome of patients with acute SCI and ultimately lead to the recommendation to keep the MAP > 85mmHg for the first 7 days after acute SCI. However, data was collected only within the first week after injury and most measurements were obtained under the influence of vasopressors. Furthermore, the MAP goal as well as the period of time for that goal were selected arbitrarily. Another study used impedance cardiography to assess the hemodynamic profiles in 9 patients with neurogenic shock after acute SCI, but only one measurement was obtained from each patient on admission and use of vasopressors was not reported [19]. In 2019 Squair et al monitored MAP and central spinal fluid pressure during the first week after injury and suggested that spinal cord perfusion pressure rather than MAP was an indicator of neurologic outcome [20]. As in previous studies the measurements were taken within the first week postinjury and vasopressors were used to maintain the MAP goals.

By contrast, our data consists of hemodynamic measurements performed largely without the use of vasopressors. Factors that could affect the cardiocirculatory system other than the SCI such as infections, sepsis or pre-existing heart disease led to exclusion of patients. Hence, our study provides a mostly unbiased hemodynamic profiling of patients with acute SCI.

SVRI was reduced significantly compared to the resistance considered normal in non-SCI patients whether patients required vasopressor therapy or not. Since the SVRI is calculated from MAP, CVP and CI, the reduced vascular resistance can be attributed to a change in one of these values. A consistently high CVP, a high-normal CI and a standard MAP were shown both with catecholamine therapy and without pharmacological vasoconstriction. Our data therefore suggests that in acute SCI cardiac output is increased to compensate for the loss of the afterload (SVRI). The increase in cardiac output could be explained by an increase in preload. CVP is used as a marker for preload in the formula for SVRI

mentioned above. Since the venous pressure can be influenced by many factors and is not recommended on its own for neither volume status nor fluid responsiveness [21], we included the GEDVI as a preload marker. In accordance with the CVP, GEDVI lies at the upper margin of the reference range. This supports the theory, that the cardiac output is increased by an augmented preload. In addition to a reduced SVRI independent of vasopressor use, the mixed model analysis shows a negative correlation between MAP, SVRI as well as GEDVI and norepinephrine treatment. CI, SI and CVP were not affected by vasopressor use. As a standard practice in the ICU of the university hospital Bergmannsheil Bochum an MAP of 70mmHg is tolerated in patients with SCI if there are no signs of reduced organ perfusion i.e., serum lactate, oliguria, dizziness. Therefore, whenever the MAP dropped below 70mmHg norepinephrine was used to achieve an MAP of 70mmHg. Hence, the mean MAP under vasopressor therapy (73,69mmHg) was lower than without norepinephrine treatment (83,97mmHg) (Table 4). Since the calculation of the SVRI relies on the MAP a negative correlation for the peripheral resistance due to the MAP goal was to be expected. Whenever vasopressor support was indicated, the loss of peripheral resistance could not be compensated for by an increase in preload and consecutively by an increase of the cardiac index. As a result, the GEDVI was also lower under norepinephrine treatment. Due to this compensation mechanism, a sufficient perfusion seems to be maintained even with reduced peripheral resistance. From a cardiocirculatory point of view, it can be assumed that a lower resistance can be tolerated and thus an adjustment of the reference value is to be considered as long as the patient does not show signs of reduced organ perfusion.

In clinical practice, the aforementioned evidence has led to relatively high MAP goals in patients with SCI. However, the resulting use of vasopressors and consecutive need for invasive monitoring leads to delays in patient mobilization and longer hospitalization [22].

Our data suggests that adjustment of the target values for MAP and SVRI could be justified and lead to a more focused application as well as reduced dosage of vasopressors. We acknowledge that this study did not assess the neurological outcome of patients and therefore cannot say whether a more restrictive use of vasopressors for blood pressure management might lead to a worse neurological outcome. However, to our knowledge, there is no evidence that “high normal” blood pressure (MAP 85mmHg) leads to a better neurological outcome than normotension. Rather, based on the experience in severe cerebral trauma, the spinal perfusion pressure seems to be responsible for a difference in outcome.[20] Therefore, a general recommendation of a “high normal” MAP goal in light of the aforementioned negative effects of vasopressor use should be critically questioned.

Furthermore, use of thermodilution-based PiCCO™ system could serve as a safe and easy-to-use means of hemodynamic monitoring in acute SCI. However, the use of the thermodilution based measurements is limited to the ICU and only reserved for those patients who need invasive blood pressure monitoring or regular blood gas analysis as part of the intensive care treatment. The indication to maintain or remove a central catheter in the ICU setting especially in the case of invasive blood pressure monitoring using vasopressors must be questioned daily. In the author’s view, a continuous surveillance of the blood pressure in patients with SCI is a key aspect in early mobilization as it allows for a quick an accurate

adaptation of the vasopressor dosage if the blood pressure suddenly drops. In the author's experience the arterial catheter itself does not delay early mobilization, rather the vasopressor therapy often hinders the physician to begin mobilization. Especially in Patients with acute SCI the blood pressure may vary greatly depending on the patients' position. Therefore, in our view, invasive monitoring is mandatory in early mobilization.

As maintaining central catheters only for research purposes might escalate cures without any clinical need, we did not include a set period of time for measurements in our study protocol. Therefore, the duration of measurements varies greatly between patients (Table 1). Additionally, the start of measurements was delayed depending on the duration of the initial external treatment (Table 1). Since the university hospital Bergmannsheil Bochum is listed as a specialised centre for SCI, patients are admitted directly after trauma as well as transferred from various regions of Germany. Both adaptations to the study protocol renders our study less comparable to the studies mentioned earlier. However, in light of the main focus of our study i.e., hemodynamic profiles over a longer period of time, this adaptation was justified.

Some of the hemodynamic measurements were performed while patients were ventilated and/or sedated, which may have biased measurement. Furthermore, we did not differentiate between the neurological level/location of the SCI.

In addition, the number of patients enrolled in the study is very small. With the begin of the corona crisis the number of traumatic SCI cases dropped significantly and less patients than initially anticipated were included. This could reduce the statistical power of our findings.

Further studies that examine the hemodynamic profile after acute SCI with a greater patient collective are needed for a better understanding of the cardiocirculatory changes caused by SCI. Long-term follow-up and regular assessment of the neurological status of these patients could show whether a certain hemodynamic profile might yield a higher or lower chance of neurological improvement and complications.

Conclusions

In a cohort of patients with acute SCI, systemic vascular resistance index was lower than the reference range. This was observed independent of use of vasopressors. Cardiocirculatory monitoring using the PiCCO™ system is easy-to use, and could help define new cardiocirculatory goals in acute SCI.

Abbreviations

95%-CI 95% confidence interval

AIS ASIA Impairment Scale

ASIA American Spinal Injury Association

CI cardiac index

CVP central venous pressure

DGUV German Statutory Accident Insurance

GEDVI Global End-Diastolic Volume Index

HR heart rate

ICU intensive care unit

ISNCSCI International Standards for Neurological Classification of Spinal Cord Injury

MAP mean arterial pressure

SCI spinal cord injury

SD standard deviation

SI stroke volume index

SVRI systemic vascular resistance index

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Ruhr University Bochum (No. 17-6002-BR). Informed consent was obtained either from the patients or their legal representatives prior to inclusion.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The article was conceptualized by UH and ND. Patient selection was done by ND with the help of MA. Measurements and data collection were performed by OJ and ND and have been supervised by UH and CWa. The statistical analysis was carried out by CWe. The original draft was prepared by ND followed by a review and editing process of all authors. The project administration and supervision were done by UH and TS.

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