

The impact of blood pressure management after spinal cord injury: a systematic review of the literature

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OBJECTIVE Spinal cord injury (SCI) results in significant morbidity and mortality. Improving neurological recovery by reducing secondary injury is a major principle in the management of SCI. To minimize secondary injury, blood pressure (BP) augmentation has been advocated. The objective of this study was to review the evidence behind BP management after SCI.

METHODS This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Using the PubMed database, the authors identified studies that investigated BP management after acute SCI. Information on BP goals, duration of BP management, vasopressor selection, and neurological outcomes were analyzed.

RESULTS Eleven studies that met inclusion criteria were identified. Nine studies were retrospective, and 2 were single-cohort prospective investigations. Of the 9 retrospective studies, 7 reported a goal mean arterial pressure (MAP) of higher than 85 mm Hg. For the 2 prospective studies, the MAP goals were higher than 85 mm Hg and higher than 90 mm Hg. The duration of BP management varied from more than 24 hours to 7 days in 6 of the retrospective studies that reported the duration of treatment. In both prospective studies, the duration of treatment was 7 days. In the 2 prospective studies, neurological outcomes were stable to improved with BP management. The retrospective studies, however, were contradictory with regard to the correlation of BP management and outcomes. Dopamine, norepinephrine, and phenylephrine were the agents that were frequently used to augment BP. However, more complications have been associated with dopamine use than with the other vasopressors.

CONCLUSIONS There are no high-quality data regarding optimal BP goals and duration in the management of acute SCI. Based on the highest level of evidence available from the 2 prospective studies, MAP goals of 85–90 mm Hg for a duration of 5–7 days should be considered. Norepinephrine for cervical and upper thoracic injuries and phenylephrine or norepinephrine for mid- to lower thoracic injuries should be considered.

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KEY WORDS spinal cord injury; blood pressure; MAP goals; MAP duration; vasopressors; mean arterial blood pressure

SPINAL cord injury (SCI) is estimated to occur at an incidence approximating 17,000 cases per year, and there are currently approximately 300,000 people living with the sequelae of a SCI. Spinal cord injury results in significant personal costs and considerably decreases independence as well as quality of life. Lifetime expenses

resulting from a SCI range from \$1.1 million to \$2.6 million, depending on extent of injury.²³ Despite significant research investment, there has been modest advancement in the perioperative and postoperative management of patients with SCI.

The principles of management for SCI generally include

ABBREVIATIONS AANS = American Association of Neurological Surgeons; AIS = ASIA Impairment Scale; ASIA = American Spinal Injury Association; BP = blood pressure; CNS = Congress of Neurological Surgeons; MAP = mean arterial pressure; SCI = spinal cord injury.

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early decompression and stabilization,⁵ with prevention of secondary injury following the initial insult. A number of strategies have been investigated for minimizing secondary injury, including blood pressure (BP) augmentation with volume support and vasopressors; therapeutic hypothermia;¹⁵ medications to decrease inflammation, such as riluzole,³ glibenclamide,²⁸ and Rho-antagonists;² and steroids, as well as agents promoting plasticity and axonal regeneration, such as Nogo-A.¹ However, many of these interventions remain at the trial stage and have not advanced to routine clinical use.

BP control in the management of SCI remains an area of frequent discussion, although there are limited high-quality data and the strength of management recommendations is limited. Current recommendations according to the guidelines of the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) Joint Section on Spine and Peripheral Nerves advise correcting hypotension and maintaining a mean arterial pressure (MAP) goal of 85–90 mm Hg for 7 days postinjury.³² The Consortium for Spinal Cord Medicine formally recommends avoiding hypotension.¹⁰

There is general agreement as well as evidence that hypotension with neurological injury results in poorer outcomes;^{8,25} however, evidence that increasing BP promotes improved outcomes is significantly more limited. In addition, it is not clear if the costs of promoting higher BP for a longer duration of time, which include invasive monitoring, risks of vasopressor use, and longer intensive care unit stays, outweigh the benefits.

The goal of this systematic review was to compile and analyze the data on BP management in patients who have sustained SCI and to examine the current recommendations and the basis on which they are made. Specifically, this paper focuses not only on BP goals and duration of BP management but also examines the choice of vasopressors.

Methods

Literature Search and Inclusion Criteria

We conducted a systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²² Using the PubMed database, we first identified relevant articles using the search terms “spinal cord injury” AND “blood pressure” published until July 25, 2017. Based on review of the article titles, we selected relevant titles related to our review. We excluded articles that were not written in the English language. These titles underwent an abstract review, after which unrelated titles were excluded. Additional relevant publications were identified and added after review of reference lists. The remaining articles underwent a full-text review. Articles without full text were excluded. Animal studies were also excluded.

Data Extraction and Outcome Measures

We extracted the following data from each relevant article: first author, year of publication, study type, presence of comparison group, length of follow-up, MAP goal, MAP goal duration, and outcome measures.

Results

Study Selection

We identified a total of 1743 articles through our database search. After title review and removal of duplicates, 1689 articles were excluded, and 56 articles underwent abstract and full-text review. After reference review, 4 additional studies were included. Forty-five articles were excluded on full-text review. The reasons for exclusion of studies were incorrect study type, foreign language, animal studies, inability to obtain the full text, and lack of collection of data on neurological outcome. Eleven studies met the criteria for review. Two of these studies were prospective and 9 were retrospective. The search flow diagram is displayed in Fig. 1.

Relationship of MAP Goals to Outcomes

A total of 11 studies were identified in which BP and neurological outcome data for SCI patients during the acute postinjury period were collected (Table 1). Two studies were prospective. These studies evaluated the outcomes of patients who suffered SCIs and were managed after injury and stabilization following protocols that included targeted MAP goals.^{20,31} Nine studies were retrospective reviews that collected information on MAP after SCI as well as neurological outcome measures throughout the postinjury period.^{6,9,16,17,19,21,27,33}

Levi et al.²⁰ performed a prospective study in which the authors described the outcomes of a group of 50 patients who underwent spinal immobilization or fixation as indicated, with their postinjury care at a trauma center between 1990 and 1991. An MAP goal higher than 90 mm Hg was maintained with fluids and dopamine for the 1st week after injury, although some patients required the addition of dobutamine for additional support. Given that 82% of patients showed stable or improved neurological function at the 6-week follow-up as measured by their Frankel grade, the authors concluded that pursuing aggressive MAP goals was feasible and of relatively low risk. There was no control group.

Vale et al.³¹ performed a prospective study describing the results of 77 patients with SCI who were treated at their institution between 1992 and 1997. These patients underwent spinal immobilization or fixation. Their postoperative care included an MAP goal higher than 85 mm Hg for 7 days. Sixty-four patients underwent follow-up for at least 12 months postinjury, and all patients showed stable examination or neurological improvement at the 12-month follow-up as measured by the American Spinal Injury Association (ASIA) motor index score and the ASIA Impairment Scale (AIS) grade. There was no comparison group. The authors concluded that BP augmentation improves neurological outcomes but stated the need for randomized trials to identify the ideal MAP goal.

Wolf et al.³³ retrospectively reviewed data for 52 patients who sustained a SCI between 1987 and 1990 due to bilateral facet dislocation. The patients were managed after decompression with an MAP goal greater than 85 mm Hg for 5 days. Neurological function was recorded using the modified Frankel grade of Benzel and Larson⁴ as well as the Yale Scale score.⁷ Twenty-two patients underwent

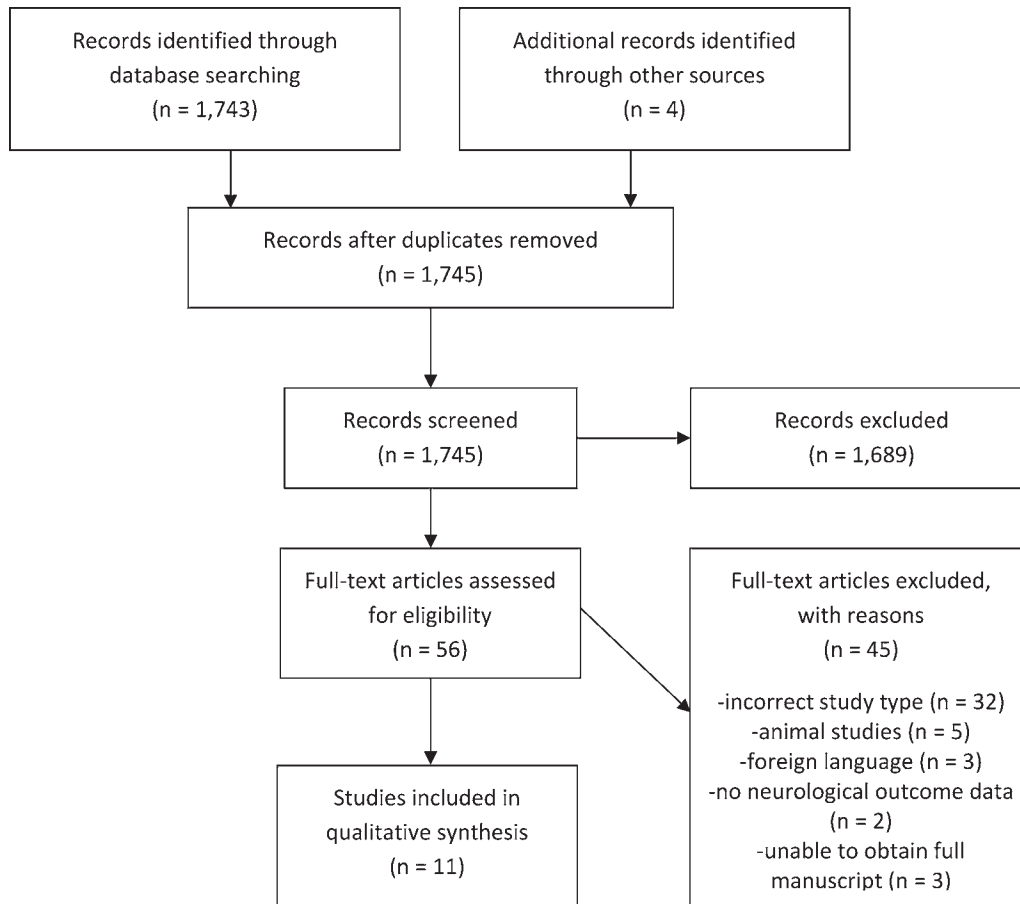


FIG. 1. Flow diagram showing the selection process for this systematic review of BP management after SCI.

follow-up for at least 12 months postinjury. All of these patients had stability or improvement in their functional grade. There were no comparison or control groups.

Cohn et al.⁷ retrospectively reviewed 17 patients presenting with quadriplegia between 2000 and 2006 in whom MAP recording was performed at least 3 times daily for 7 days postinjury. The authors estimated the amount of time patients spent with MAP above thresholds of 85, 75, and 65 mm Hg. The authors estimated that patients had MAP greater than 85 mm Hg 33% of the time, greater than 75 mm Hg 65% of the time, and greater than 65 mm Hg 91% of the time. Neurological outcome as measured by AIS grade and ASIA motor score was not found to be related to duration of time at a goal of MAP greater than 75 or 85 mm Hg. Patients underwent follow-up until the time of discharge.

Hawryluk et al.¹⁶ retrospectively reviewed MAP data for 74 SCI patients who underwent postinjury treatment between 2005 and 2011 and were managed with an MAP goal greater than 85 mm Hg for 5 days postinjury. This patient population is a subset of the group that was initially studied in Inoue et al.,¹⁷ the results of which are described below. Although this was a retrospective review, the MAP data were collected prospectively. The authors collected 1-minute-interval MAP measurements and interestingly found that about 25% of all MAPs for the first 5 days postinjury were lower than the goal. The patients

who exhibited the greatest neurological improvement as measured by AIS grade had fewer MAP measurements lower than the goal compared with patients without neurological improvement. The authors reported that their data suggested that an MAP of 70–75 mm Hg appeared to be the threshold at which neurological benefit is correlated with MAP goals. In addition, the authors noted that the first 2–3 days after injury with elevated MAP correlated most strongly with recovery. Patients underwent follow-up until the time of discharge.

Readdy et al.²⁷ retrospectively analyzed 34 patients who presented with traumatic central cord syndrome between 2005 and 2011 and had MAP goals of higher than 85 mm Hg for greater than 24 hours. AIS grades were obtained as a measure of neurological outcome, and patients underwent follow-up throughout their hospitalization until discharge. Fifty-six percent of patients improved at least 1 neurological grade by the time of discharge. The remaining patients had an unchanged AIS grade at discharge.

Inoue et al.¹⁷ retrospectively reviewed 131 patients who were admitted with SCI between 2005 and 2011 and received vasopressors to maintain MAP goals of higher than 85 mm Hg. Although this was a retrospective review, the MAP data were collected prospectively. This patient population was also analyzed in the studies by Hawryluk et al.¹⁶ and Catapano et al.,⁶ which are also reviewed in this paper. MAP goals were maintained for 5 days before

TABLE 1. Pertinent characteristics of the 11 articles included in this systematic review of BP management after spinal cord injury

Authors & Year	Data Collection	Study Type	Comparison Group	Neurological Outcome Measure	No. of Pts	MAP Goal (mm Hg)	MAP Goal Duration	Length of Follow-Up
Catapano et al., 2016	Retrospective	Case series	No	AIS grade	62	NS	NS	Until discharge
Cohn et al., 2010	Retrospective	Case series	No	AIS grade, ASIA motor score	17	NS	NS	Until discharge
Dakson et al., 2017	Retrospective	Comparative	Yes	AIS grade, ASIA motor score	94*	>85	5 days	After neurorehabilitation
Hawryluk et al., 2015	Retrospective	Case series	No	AIS grade	74	>85	5 days	Until discharge
Inoue et al., 2014	Retrospective	Case series	No	AIS grade	131	>85	7 days	Until discharge
Kepler et al., 2015	Retrospective	Case series	No	ASIA motor score	92	>85	≥5 days	Until hospital Day 5
Levi et al., 1993	Prospective	Case series	No	Frankel grade	50	>90	7 days	6 wks
Martin et al., 2015	Retrospective	Case series	No	ASIA motor score	105	NS	NS	Until discharge
Readdy et al., 2015	Retrospective	Case series	No	AIS grade	34	>85	>24 hrs	Until discharge
Vale et al., 1997	Prospective	Case series	No	AIS grade, ASIA motor score	77	>85	7 days	12 mos
Wolf et al., 1991	Retrospective	Case series	No	Modified Frankel score, Yale Scale score	52	>85	5 days	12 mos

NS = not specified; Pts = patients.

* Serial MAP data collected for 50 of these patients.

being relaxed to lower levels. AIS grades were collected as outcome measures up until the time of discharge from the hospital; no association was found between neurological outcome and the use of vasopressors to maintain MAP goals. There was no comparison or control group.

Kepler et al.¹⁹ retrospectively reviewed 92 patients who were admitted between 2006 and 2009 for an acute SCI, with an MAP goal of higher than 85 mm Hg for at least 5 days. Outcomes compared the ASIA motor scores on admission and on hospital Day 5, which showed an overall decrease in neurological function over that period of an average of 2.2 points on the ASIA motor impairment scale. There was no comparison or control group.

Martin et al.²¹ retrospectively reviewed acute cervical and thoracic SCIs in 105 patients between 2007 and 2009 and evaluated the average MAP and lowest MAP hourly for the first 3 days after hospitalization. MAP levels were collected for the first 72 hours of the patient's hospitalization period. ASIA motor scores were collected as outcome measures during the hospitalization period. There was no correlation between neurological outcomes and the use of vasopressors or number of failures to meet MAP goals.

Catapano et al.⁶ retrospectively reviewed 62 patients who presented between 2005 and 2011 with traumatic SCI. This patient population was also previously studied by Inoue et al.¹⁷ as well as by Hawryluk et al.,¹⁶ both of which are summarized above. The authors compared the average MAPs as well as the proportion of MAPs lower than 85 mm Hg with their outcomes, as measured by comparing AIS grades at presentation and discharge. MAPs were analyzed only for the first 3 days after injury. There was a correlation between improvement and a greater proportion of MAPs higher than 85 mm Hg in patients presenting with AIS Grade A, B, or C.

Dakson et al.¹¹ retrospectively reviewed 94 patients who presented with SCI between 2006 and 2010. Serial hourly

MAPs were collected for 50 of these patients. MAP lower than 85 mm Hg for more than 2 consecutive hours in the 5 days postinjury was defined as suboptimal BP management. AIS grade and ASIA motor scores were collected as neurological outcome data. Forty-one patients (82%) did not meet the MAP goal in this study. The 9 patients (18%) who did meet the MAP goal demonstrated an improved AIS grade compared with patients who did not meet the MAP goal, as well as a statistically significantly greater improvement in ASIA motor score at discharge from acute care. The improvement in AIS grade for the group that achieved MAP goals persisted at later points of follow-up, although the ASIA motor score improvement did not persist.

MAP Goal Duration

Current recommendations for the duration of elevated MAP goals are 7 days of elevated MAP to 85–90 mm Hg per the guidelines of the AANS/CNS Joint Committee on Spine and Peripheral Nerves.³² This duration is derived from the protocol of the studies by Levi, Vale, and their colleagues, which were performed in the 1990s. In the Vale³¹ study, 7 days was chosen as the duration based on experimental data on maximum swelling measured at 5 days postinjury in experimentally induced SCI in monkeys.³⁴ A number of other studies on MAP goals in SCI have had protocols with an MAP goal duration of less than 7 days. It does not appear that there are any studies that compare outcomes related to different durations of MAP goals.

Hawryluk et al.¹⁶ collected 1-minute-interval MAP measurements for patients who were admitted with SCI and found that average MAP values correlated most strongly with neurological outcome for the first 2–3 days after injury. The authors did find that the proportion of MAP measurements below the BP goal correlated with outcome for

the first 7 days after injury. Hawryluk,¹⁶ Kepler,¹⁹ Inoue,¹⁷ Wolf,³³ and Dakson¹¹ and their colleagues described methods in which elevated MAP goals were pursued for 5 days postinjury, rather than 7 days, and they did not report the occurrence of an associated neurological decline with the shorter duration of elevated BP goals.

Vasopressor Selection

Among the studies referenced, there were a variety of different vasopressors used to maintain the respective MAP goals. The most recent AANS/CNS Joint Committee guidelines do not make a specific recommendation regarding the type of vasopressor to use for their recommendation of elevated MAP goals of 85–90 mm Hg.³² The Consortium for Spinal Cord Medicine¹⁰ recommends dopamine or norepinephrine for cervical or high thoracic regions, as hypotension may result from loss of sympathetic tone and require an agent with alpha and beta adrenergic effect. For low thoracic regions, phenylephrine is suggested, as vasodilation is suspected to be the cause of hypotension.

Inoue et al.¹⁷ described in detail their experiences with the use of dopamine and phenylephrine. Dopamine was found to cause major complications at a rate of 10% compared with phenylephrine, which caused major complications at a rate of 3%. These major complications included ST segment elevation on electrocardiography, troponin elevations, atrial fibrillation, and ventricular tachycardia. Readdy et al.²⁷ used dopamine as the first-line vasopressor in 79% of patients and phenylephrine as the first-line agent in 21% of patients. Thirty percent of patients receiving dopamine experienced atrial fibrillation, ventricular tachycardia, or elevated troponins. Only 4.5% of patients receiving phenylephrine experienced these complications.

Dopamine and phenylephrine have historically been the primary vasopressors used in the study of SCI. Epinephrine and dobutamine have generally been avoided due to their cardiac side effects.¹⁷ Norepinephrine was used in multiple studies and historically has been a second- or third-line agent. In the study by Vale et al.,³¹ norepinephrine was used as a second-line vasopressor to supplement dopamine. Hawryluk et al.¹⁶ only used norepinephrine in 1% of their patients as a first-line vasopressor. Inoue et al.¹⁷ administered norepinephrine to 5% of their patients, and Dakson et al.¹¹ used norepinephrine exclusively in their study. There has been increasing interest and use of norepinephrine as the vasopressor of choice for SCI due to the demonstrated higher complication rate associated with dopamine use in SCI patients. There is also increasing evidence in the intensive care unit literature showing dopamine is associated with a greater mortality rate as well as being more arrhythmogenic compared with other vasopressors.^{12,13}

There are limited data available for adequate comparison of phenylephrine versus norepinephrine as first-line agents in mid- to low thoracic SCI, and the recommendations have largely been based on the pharmacological properties of these agents.^{10,14,18,26,29} The pure alpha agonist activity of phenylephrine results in a decreased risk of arrhythmogenic side effects, although reflex bradycardia and peripheral vasoconstriction can occur. Norepinephrine's mixed alpha and beta effect decreases the risk of

bradycardia and vasoconstriction; however, its positive inotropic and chronotropic effects can result in arrhythmias and other cardiac complications.

Discussion

Although there has been significant interest in the topic of promoting hypertension in SCI patients in the acute postinjury phase for the past several decades, there is limited and low-quality evidence regarding the risks and benefits of this practice. The basis of MAP goals and duration are most commonly attributed to 2 articles from the 1990s, which were both prospective studies reporting the goal of elevation of MAP for a specified duration of time postinjury.^{20,31} Based on a sound theoretical basis, other retrospective reviews and case series, and anecdotal reports, the practice of promoting elevated MAP goals is widely practiced and is formally recommended by the AANS/CNS Joint Committee guidelines.³²

There are risks, however, associated with establishing elevated MAP in the period after SCI, which include complications due to vasopressor use, invasive monitoring, decreased patient mobilization, and prolonged hospitalization. Some of these risks, in particular vasopressor use, have been quantified and demonstrated to cause potentially major complications. Presently, the risk-benefit profile for vasopressor use is unclear, given the lack of definitive high-level evidence of BP augmentation in improving neurological recovery after SCI.

With regard to the optimal MAP, there have been no comparison studies to date, randomized or nonrandomized, comparing differences in outcome with different MAP goals. The formal recommendation of MAP of 85–90 mm Hg appears to be derived from studies of Levi and Vale and their colleagues,^{20,31} in which MAP goals of 90 and 85 mm Hg were chosen, respectively, without a clear explanation. There is the possibility that lower MAP goals may achieve similar results with less risk. Given that BP augmentation is currently the standard of care after SCI based on current recommendations, future studies in this patient population involving control groups will have to carefully consider the potential ethical questions of providing nonstandard-of-care treatment to a control group. This question is currently under investigation via the MAPS trial: Mean Arterial Pressure in Spinal Cord Injury (MAPS): Determination of Noninferiority of a Mean Arterial Pressure Goal of 65 mm Hg Compared with a Mean Arterial Pressure Goal of 85 mm Hg in Acute Human Traumatic Spinal Cord Injury (clinicaltrials.gov no. NCT02232165).³⁰

The duration of maintaining elevated MAP is currently recommended at 7 days, although no studies have compared different durations. A number of retrospective review papers have reported pursuing elevated MAP goals for a total of 5 days and did not indicate adverse outcomes related to this duration.

Recommended vasopressors for BP augmentation in SCI patients have historically generally been phenylephrine for mid- to low thoracic injuries and dopamine for high thoracic and cervical injuries, given its alpha and beta adrenergic effect.¹⁰ Norepinephrine has been used as well, but to a much lesser degree. Over the past several

years, there has been increasing evidence that norepinephrine is superior to dopamine in the treatment of shock; the authors of a randomized controlled trial reported a higher mortality and complications with dopamine use.²⁴ Although this trial was not conducted in SCI patients, the results are certainly worth consideration.

Limitations

This review is significantly limited by a number of important factors. At the individual study level, there were often low numbers of patients, follow-up was limited, and almost all of the studies lacked comparison groups. Across each study, there were different MAP goals and outcome measures, and protocols differed significantly. At the review level, there is the potential that our search did not uncover all relevant research, the possibility of reporting bias and publication bias, and the potential for not reporting all significant published information.

Conclusions

BP management in the acute period after SCI is a treatment of significant importance given the severe morbidity associated with SCI. Unfortunately, there is limited high-quality evidence to guide BP management, and further research is essential. Based on the prospective studies, which provide the highest level of evidence available, MAP goals of 85–90 mm Hg for 5–7 days postinjury should be considered. With regard to the optimal vasopressor, dopamine should be avoided. Norepinephrine should be considered as a first-line agent for cervical and upper thoracic SCIs, given evidence that it has a lower risk profile than dopamine. For SCIs in the mid- to lower thoracic spine, norepinephrine or phenylephrine should be considered as first-line agents.

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