Higher Mean Arterial Pressure Values Correlate with Neurologic Improvement in Patients with Initially Complete Spinal Cord Injuries

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BACKGROUND: Traumatic spinal cord injury (SCI) guidelines recommend to maintain mean arterial pressures (MAPs) above 85 mm Hg for 7 days following SCI to minimize spinal cord ischemia. Some physicians doubt that patients with initially complete injuries benefit.

OBJECTIVE: To assess the relationship between MAP augmentation and neurologic improvement in SCI patients stratified by initial American Spinal Injury Association Impairment Scale (AIS) score.

METHODS: High-frequency MAP values of acute SCI patients admitted over a 6-year period were recorded, and values were correlated with degree of neurologic recovery in an analysis stratified by postresuscitation AIS score.

RESULTS: Sixty-two patients with SCI were analyzed. Thirty-three patients were determined to have complete injuries, and of those 11 improved at least 1 AIS grade by discharge. The average MAP of initially AIS A patients who improved versus those who did not was significantly higher (96.6 ± 0.07 mm Hg vs. 94.4 ± 0.06 mm Hg, respectively; P < 0.001), and the proportion of MAP values <85 mm Hg was significantly lower (13.5% vs. 25.6%, respectively; P < 0.001). A positive correlation between MAP values and outcome was also observed in AIS B and C patients but not AIS D patients. These data raise the possibility that patients with an initially complete SCI may derive greater benefit from MAP augmentation than patients with initial AIS D injuries.

CONCLUSION: A positive correlation was observed between MAP values and neurologic recovery in AIS A, B, and C patients but not AIS D patients. These data suggest that patients with an initially complete SCI may derive greater benefit from MAP augmentation than patients with initial AIS D injuries.

INTRODUCTION

Traumatic spinal cord injury (SCI) affects 12,000 to 20,000 new individuals per year in the United States1,2 and often leaves patients with profound neurologic deficits. In addition to the personal cost of SCI, the cost to society is great; the direct and indirect costs of SCI in the United States are estimated to be $21.5 billion annually.1 In one study only 11.8% of spinal cord–injured patients were employed 1 year after the injury and only 35.2% were employed 20 years post injury versus 57.1% before SCI.1

In recent decades we have learned much about secondary injury processes and secondary insults that exacerbate SCI damage following the initial insult. Secondary injury involves a complex and highly interrelated series of molecular processes such as ionic dysregulation, free radical production, cytoskeletal degradation, and neuroinflammation.3 Despite what we have learned about secondary injury, we are as yet without a safe and effective therapeutic that attenuates these processes.3–13 Physicians have been more successful treating secondary insults that occur at the level of the organism and include hypoxia and hypotension.3–13 Indeed, supportive care aimed at preventing or reducing these insults is the mainstay of modern medical care and is credited...
with the improved mortality and morbidity seen following SCI in recent decades. Since their inception, guidelines for the management of acute SCI have recommended not only preventing hypotension but also augmenting blood pressure with vasoactive agents in the first week after injury. Specifically, the current guidelines advise that systolic blood pressure should not be less than 90 mm Hg at any time and that an average mean arterial pressure (MAP) above 85–90 mm Hg be maintained for 7 days following injury. Our group recently validated this recommendation with a large dataset of high-frequency MAP measurements obtained from 100 SCI patients. We found that maintenance of MAP values above 85 mm Hg correlated with improved neurologic recovery and that the benefit associated with MAP augmentation decreased over time. Importantly, we also found that the proportion of values <85 mm Hg correlated more strongly with outcome than mean values, suggesting that efforts to prevent even brief drops below threshold are important. Our analysis did not, however, inform the relevance of these findings to patients with initially complete SCI.

Recent publications suggest a substantially higher rate of neurologic improvement in initially American Spinal Injury Association Impairment Scale (AIS) A patients with contemporary management than has been seen in the past. Nonetheless, patients who present with initially complete SCI (AIS A) have the poorest prognosis for neurologic recovery and are vulnerable to the nihilism of treating physicians who may view aggressive care as being of little benefit in this population. To determine if the resource expenditure inherent to MAP augmentation is justified in initially AIS A patients, we performed an analysis to determine how the relationship between MAP and neurologic improvement is influenced by the baseline neurologic examination.

METHODS

As previously described, between the years 2005 and 2011 a computerized data acquisition system prospectively collected and stored data every minute from all patients treated in the Neurotrauma Intensive Care Unit (ICU) at San Francisco General Hospital, a high-volume level 1 trauma center. This system was Health Insurance Portability and Accountability Act compliant and approved by the local research ethics board. Recording with this system, developed in conjunction with Aristein Bioinformatics LLC, initiated automatically and immediately following admission to the Neurotrauma ICU. We retrospectively identified patients admitted with SCI and collected their demographic and neurologic data. Analyzed MAP values were measured via an arterial line. AIS scores were also collected via chart review and were obtained on initial presentation, following resuscitation, and before discharge. A high rate of loss to follow-up precluded an analysis of neurologic recovery after discharge.

MAP values for each patient were stored in a separate Micro
do Excel file on an encrypted computer. A Matlab program was used to extract data from each of these files and to calculate average MAP values, as well as the number of measurements below specified thresholds. The Matlab program allowed us to perform these analyses over specific epochs as specified by the analyst. We chose to analyze 80 different MAP thresholds (120–40 mm Hg with 1–mm Hg increments) as our group did previously. Results were stratified by postresuscitation AIS score and by presence or absence of subsequent neurologic improvement on the final predischARGE AIS score. Fidelity of the Matlab program was ensured by comparing to values obtained with Microsoft Excel. Microsoft Excel was used to create graphs and tables.

Statistical analysis was performed via SPSS version 23 software. For continuous data analysis of variance was performed as the first statistical test for a difference between means. When significant, Tukey’s and Bonferroni’s post-hoc tests were used to compare means among 3 or more groups. Binomial logistic regression was employed for dichotomous data, and Poisson regression was performed for count data. All error values and error bars presented herein reflect standard error.

RESULTS

Sixty-two patients with high-frequency arterial line blood pressure measurements were identified as having a traumatic SCI and postresuscitation neurologic examinations graded AIS A, B, C, or D. Thirty-three patients were AIS A, 17 were AIS B or C, and 12 were AIS D. We excluded 3 patients who had neurologic worsening subsequent to the postresuscitation examination due to small sample size. The AIS B and C groups were combined for analysis due to sample size limitations as only 2 patients were AIS B postresuscitation. Although some patients achieved more than 1 AIS grade of improvement, sample size limitations similarly required us to truncate outcomes with those who improved 1 or more AIS grades versus those who did not. Only the physiologic measurements from the first 3 days of admission were analyzed as our group previously demonstrated a strong correlation between MAP and outcome over this period in these patients.

The severity of the SCI, reflected by the postresuscitation AIS score, correlated with the Injury Severity Score (ISS) in the 3 groups (Table 1). The AIS A patients had an average ISS of 31.6 (±2.0) while the AIS B/C patients’ average ISS was 26.2 (±3.8) and the AIS D patients’ average ISS was 19.2 (±2.1) (P = 0.018). There was a significant difference in the percentage of patients who improved 1 or more AIS grade from admission to discharge among the groups (P = 0.0018). A total of 11 patients (33%) in the AIS A group had improvement of AIS grade from admission to discharge, with 8 of these patients improving greater than 1 AIS score. In the AIS B/C group, a total of 13 patients (76%) showed improvement from admission to discharge with the majority of patients only improving 1 AIS grade. In the AIS D group, 7 patients (58%) improved to AIS E by the time of discharge. The total hospital days were significantly greater for the AIS A patients with an average of 40 days (±7) versus the AIS B/C patients’ average of 17.6 days (±2.9) and the AIS D patients’ average of 9.9 days (±1.9) (P = 0.006). A significantly greater proportion of patients with thoracic injuries were initially complete than incomplete (P = 0.036). There was no significant difference found in age, percentage of patients requiring surgery, time to surgery, requirement of 2 vasopressors, or frequency of penetrating injury or proportion of injuries above
T6, which may be associated with neurogenic shock from disruption of descending sympathetics.

Patients who were AIS D on postresuscitation examination had a higher proportion of MAP measures >85 mm Hg than the other groups (Figure 1A). In an analysis stratified by postresuscitation AIS score (Figure 1B–D; Figure 2A–D) patients improving neurologically had higher MAP values than those who did not improve in both the AIS A and AIS B/C groups. The opposite relationship was seen in AIS D patients. This was true when both the proportion of MAP values below 80 different physiologic thresholds (40–120 mm Hg) were analyzed (see Figure 1) and the frequency of MAP values in 1 mm Hg bins from 40–120 mm Hg were examined (see Figure 2).

Figure 3 (top row) displays the average MAP for AIS A, B/C, and D groups over the first 3 days of admission to the Neurotrauma ICU. The average MAP for initially AIS A patients who improved at least 1 AIS grade was significantly higher than those who did not demonstrate improvement (96.6 ± 0.07 mm Hg vs. 94.4 ± 0.06 mm Hg; P < 0.001). The AIS B/C group showed a similar significant difference of average MAP in the improvement versus no improvement group (97.2 ± 0.08 mm Hg vs. 88.4 ± 0.1 mm Hg; P < 0.001). In the AIS D group, patients who did not improve neurologically had a higher MAP of 96.2 ± 0.11 mm Hg compared with patients who improved 1 AIS grade (average MAP of 89.5 ± 0.09 mm Hg, P < 0.001). Figure 3 (bottom row) displays the proportion of MAP values below the 85 mm Hg threshold for AIS A, B/C, and D groups over the first 3 days of admission to the Neurotrauma ICU. In the AIS A group there was a significantly greater proportion of MAP values recorded below the 85 mm Hg threshold in the no-improvement versus improvement groups (25.6% ± 1.0 vs. 13.5% ± 0.6; P < 0.001). Similarly, a greater proportion of MAP values below 85 mm Hg was revealed in the AIS B/C group in the no-improvement versus improvement groups (35.7% ± 0.3 vs. 18.0% ± 0.6; P < 0.001). However, in the AIS D group those who improved had a greater proportion of MAP values below the 85 mm Hg threshold than the no-improvement group (30.1% ± 0.2 vs. 19.6 ± 1.7; P < 0.001).

DISCUSSION

Given that blood pressure management is one of the few beneficial interventions that physicians currently have to offer patients with acute SCI, it is imperative that we increase our understanding of how MAP relates to neurologic improvement. Moreover, given the substantial costs associated with the administration and monitoring of vasoactive medications in the ICU, as well as their risk for complications, it is important to identify patients who may benefit less or not at all from this treatment strategy. We hypothesized that patients with an initial AIS score of A, as assessed on the postresuscitation neurologic examination, would show a weaker correlation between MAP values and outcome than those with incomplete injuries. Our results failed to support this hypothesis. Indeed, our results suggest the opposite—that those with marked neurologic deficits may benefit from MAP augmentation more than those with less severe deficits.

Table 1. Characteristics of Studied Patients Grouped by Postresuscitation American Spinal Injury Association Impairment Scale (AIS) Score

<table>
<thead>
<tr>
<th>AIS A (n = 33)</th>
<th>AIS B/C (n = 17)</th>
<th>AIS D (n = 12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.6 ± 3.1</td>
<td>53.1 ± 5.6</td>
<td>50 ± 6.6</td>
</tr>
<tr>
<td>ISS</td>
<td>31.6 ± 2</td>
<td>26.2 ± 3.8</td>
<td>19.2 ± 2.1</td>
</tr>
<tr>
<td>Improvement AIS</td>
<td>11 (33.3%)</td>
<td>13 (76.5%)</td>
<td>7 (58.3%)</td>
</tr>
<tr>
<td>1</td>
<td>3 (27.3%)</td>
<td>12 (92.3%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>8 (72.7%)</td>
<td>1 (7.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>33 (100%)</td>
<td>15 (88.2%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Timing of surgery</td>
<td>40.3 ± 5.9h</td>
<td>51.9 ± 4.8h</td>
<td>13.2 ± 1.3h</td>
</tr>
<tr>
<td>Total hospital days</td>
<td>40 ± 7</td>
<td>17.6 ± 2.9</td>
<td>9.9 ± 1.9</td>
</tr>
<tr>
<td>Total measurements</td>
<td>3153.6 ± 156.4</td>
<td>3039.8 ± 229.4</td>
<td>2894.7 ± 362.3</td>
</tr>
<tr>
<td>Penetrating</td>
<td>7 (21.2%)</td>
<td>2 (11.8%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Cervical</td>
<td>18 (54.5%)</td>
<td>14 (82.3%)</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>Thoracic</td>
<td>14 (42.4%)</td>
<td>1 (5.9%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1 (3%)</td>
<td>2 (11.8%)</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Injuries above T6</td>
<td>22 (66.7%)</td>
<td>14 (82.4%)</td>
<td>9 (78.3%)</td>
</tr>
<tr>
<td>Required 2 vasopressors</td>
<td>7 (21.2%)</td>
<td>6 (35.3%)</td>
<td>5 (41.7%)</td>
</tr>
</tbody>
</table>

The characteristics of analyzed patients grouped by postresuscitation AIS score are shown. For the continuous data the averages ± standard errors are reported. For categorical data we report the number of patients with the percentage of the total in parentheses. For continuous data, analysis of variance was performed for statistical analysis. For categorical data, binomial logistic regression was used. For total measurements, a Poisson regression was performed. Statistically significant values are denoted with bold face.
IMPORTANCE OF PREVENTING HYPOTENSION AND AUGMENTING MAP VALUES

Secondary insults play an important role in exacerbating neurologic injury following SCI. Indeed, hypotension is frequently seen following SCI, affecting an estimated 68% of AIS A and B patients. Common causes of hypotension in this population include neurogenic and hemorrhagic shock. Neurogenic shock results from disruption of descending sympathetic pathways in the spinal cord (at or above the T6 neurologic level) resulting in vasodilation, hypotension, and bradycardia. Hemorrhagic shock is often seen with concomitant injuries, which can be difficult to identify in patients with sensory deficits. It is also important to consider that neurogenic and hypovolemic shock can coexist. The consequence of these phenomena can be hypotension and ultimately spinal cord hypoxia and ischemia.

Despite the general acceptance of the blood pressure parameters recommended in the acute SCI guidelines, the data that support these recommendations have substantial limitations. In all cases the relationship between blood pressure and outcome was confounded by an overall aggressive care strategy, and in no case was comparison made to contemporaneous controls. Although the data inherent to this work and our previous work are correlative and do not inform causation, it substantially informs the relationship between MAP and outcome. Our previous publication reports evidence supporting efforts to maintain MAP values >85 mm Hg in spinal cord injured patients as these blood pressure values correlated with greater degree of neurologic improvement.

PATIENTS WITH AIS A, B, AND C BUT NOT D INJURIES DEMONSTRATED A POSITIVE CORRELATION BETWEEN MAP AND OUTCOME

Although published guidelines currently recommend the same blood pressure management irrespective of initial injury severity, it is recognized that severely injured patients may be subject to...
nihilism and less aggressive care. In our experience, many physicians provide less aggressive care to spinal cord injured patients with complete neurologic deficits because of doubts that it is of benefit. Importantly, our study demonstrated that higher blood pressures correlated with improved outcome in patients with initially motor and sensory complete injuries (see Figures 1A and 2). While our study does not provide evidence of a causal relationship, the presence of this relationship raises this possibility. Moreover, it suggests that patients with initially complete SCIs may benefit from MAP augmentation similar to those with AIS B/C injuries. This result suggests that nihilism is best avoided in these patients.

Surprisingly, patients with postresuscitation AIS scores of D did not show a positive correlation between MAP values and outcome. One possibility is that because these patients already had a higher proportion of MAP values >85 mm Hg than AIS A, B, and C patients (see Figure 1A), MAP augmentation in this group was not of additional benefit. The fact that AIS D patients can only improve by a single AIS score may also play a role. Another potential confound is that the AIS D patients had significantly fewer days in the hospital than the other groups, potentially allowing fewer of these patients to improve neurologically by the time of their outcome assessment. Duration of hospital stay did not differ between patients who improved neurologically versus those who did not, however (P = 0.498, binomial logistic regression; R² = 0.0001). Because of these issues, we do not feel that these data should discourage efforts to intensively monitor and treat blood pressure in AIS D patients.

We chose to examine MAP values only within the first 3 days after SCI, as our previous work demonstrated the strongest association between MAP and outcome early after SCI. The temporal relationship between MAP and neurologic improvement following SCI was subject to detailed analysis in our previous publication and benefit was seen for 5 to 7 days with diminishing benefit over time. An analysis of only the first 3 days post ICU admission shown here was thus for the sake of simplicity and should not be used as evidence to conclude that a short period of MAP augmentation is appropriate.
VASOPRESSOR COMPLICATIONS AND RISK INHERENT TO USE WITH COMPLETE SPINAL CORD INJURY

MAP augmentation with vasoactive agents is associated with a wide array of possible complications in critically injured patients including hypoperfusion of extremities and internal organs, dysrhythmias, hyperglycemia, myocardial infarction, and local effects, such as skin necrosis. In addition, the prolonged ICU stay and immobility inherent in administration of vasopressors can lead to numerous complications such as thromboembolism, pressure sores, and pneumonia. Complications associated with the administration of vasoactive agents following acute SCI were recently examined in detail in a series of SCI patients treated at our institution, which overlap with those included in the present study. In this work Inoue et al found that complications of vasopressor therapy were seen in 74% of patients (most commonly tachycardia). These complications were independently associated with the overall usages of dopamine (odds ratio [OR] 8.97; P < 0.001) and phenylephrine (OR, 5.92; P = 0.004), age > 60 years old (OR, 5.16; P = 0.043), and—of great relevance to the current study—complete SCI patients are likely at greater risk of complications because many have severe injury to autonomic innervation. This elevated risk of complications should be considered in the decision to administer vasopressor medication to AIS A patients in accordance with published guidelines and could prompt early cessation in the context of diminishing benefit with time, especially in the elderly (Hawryluk et al 2015).

INITIALLY COMPLETE SPINAL CORD INJURY AND NIHILISM

While it is true that patients with initially complete SCIs have the poorest prognosis, contemporary medical care is seeing substantial improvement in many of these patients. Our study found that 33% of patients who are AIS A at the postresuscitation neurologic examination will improve by at least 1 grade, and 24% improve by greater than one grade by the time of hospital discharge. This is similar to the conversions rates seen in the recent STASCIS and Cethrin studies. While aggressive care such as early surgical decompression and MAP augmentation is unlikely to benefit all initially complete SCI patients, such as the rare patient with a true
spinal cord transection, our data demonstrate that many may benefit.

**POTENTIAL CONFOUNDING EFFECTS**

Despite the “big data” inherent to our study, the limited number of patients studied prevents us from performing meaningful multivariate analyses, which could inform potential confounds relevant to our data. We have instead performed a series of univariate analyses of variables that could confound the results of our analysis (see Table 1). A number of confounds that could have detracted from the benefit of MAP augmentation in AIS D patients are described earlier. In addition, it is important to note that all AIS A patients required surgery and that the average time to surgery was 40.3 hours in this group. This time to surgery in the AIS D group was only 13.2 hours, although this difference was not statistically significant (see Table 1, P = 0.156). This likely reflects more severe, complex spinal injuries in AIS A patients, as well as the presence of other severe injuries, which is supported by the higher ISS values noted in this group. A greater effort to perform early surgery on those felt to have greater capacity for recovery may also be at least somewhat contributory. Largely on the basis of findings of the STASCIS study, current recommendations are to decompress and/or stabilize traumatic SCI patients within 24 hours of injury as this practice is associated with improved neurologic outcome in acute cervical SCI patients.37,39

Analysis of the proportion of patients receiving 2 vasopressors reveals that medical management of AIS A patients was not as aggressive as patients with less severe SCI in this study. Only 21.2% of patients in the AIS A group received 2 vasopressors, while 35.3% of patients and 41.7% of patients in the AIS B/C and AIS D groups, respectively, received 2 vasopressors. This is remarkable considering the lower MAP values seen in AIS A, B, and C patients compared with those AIS D on postresuscitation neurologic examination. This raises the possibility of nihilism in our institution, although alternate explanations are possible, such as the presence of other injuries precluding aggressive MAP augmentation such as an aortic dissection.

**REFERENCES**


**LIMITATIONS**

We have previously discussed many of the limitations inherent to our study.6 Our stratification of patients based on baseline postresuscitation AIS score led to a small number of patients in some groups. This mandated collapsing some of the groups in order to achieve meaningful results. Specifically, we had to collapse those with postresuscitation AIS scores of B or C into a single group. As well, we dichotomized outcomes into patients who improved or did not improve—sample size limitations prevented a discrimination of patients with different degrees of neurologic improvement. In addition, though our physiologic data were collected prospectively, the other data were collected retrospectively. Twenty-six patients were excluded because data from the neurologic examination were not available. Blood pressure values obtained in the prehospital setting and those from the emergency department were not available for analysis; the first recorded blood pressure values were obtained in the ICU in all cases.

**CONCLUSION**

To the authors’ knowledge this is the first study to date to analyze the association between MAP and neurologic improvement in patients stratified by their postresuscitation AIS score. Our data indicate that there is a positive correlation between higher MAP values and neurologic improvement in patients who are AIS A and B/C on the postresuscitation examination, but not those who are AIS D. Contrary to our hypothesis, these data thus suggest the possibility that AIS A patients may derive greater benefit from MAP augmentation than AIS D patients and that it is important to avoid nihilism when considering MAP augmentation in patients with initially complete SCIs. The higher rate of complications related to vasopressor administration in AIS A patients should be considered when deciding on the duration of therapy, however. Lack of apparent benefit from MAP augmentation in AIS D patients may be related to a number of possible confounds such as the higher baseline blood pressures observed in this group and should not discourage intensive MAP monitoring and treatment in these patients.

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