Traditional systolic blood pressure targets underestimate hypotension-induced secondary brain injury

Megan Brenner, MD, MS, Deborah M. Stein, MD, MPH, Peter F. Hu, MS, Bizhan Aarabi, MD, Kevin Sheth, MD, *and* **Thomas M. Scalea, MD,** *Baltimore, Maryland*

AAST Continuing Medical Education Article

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the American College of Surgeons and the American Association for the Surgery of Trauma. The American College Surgeons is accredited by the ACCME to provide continuing medical education for physicians.

AMA PRA Category 1 Credits™

The American College of Surgeons designates this Journal-based CME article for a maximum of 1 *AMA PRA Category 1 Credit*™ for each article. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Credits can only be claimed online at this point.

AMERICAN COLLEGE OF SURGEONS
Inspiring Quality:
Highest Standards, Better Outcomes

Objectives

After reading the featured articles published in the *Journal of Trauma and Acute Care Surgery,* participants should be able to demonstrate increased understanding of the material specific to the article. Objectives for each article are featured at the beginning of each article and online. Test questions are at the end of the article, with a critique and specific location in the article referencing the question topic.

Claiming Credit

To claim credit, please visit the AAST website at http://www.aast.org/ and click on the "Education" tab. You must read the article, successfully complete the post-test and evaluation. Your CME certificate will be available immediately upon receiving a passing score of 75% or higher on the post-test. Post-tests receiving a score of below 75% will require a retake of the test to receive credit.

Disclosure Information

In accordance with the ACCME Accreditation Criteria, the American College of Surgeons, as the accredited provider of this journal activity, must ensure that anyone in a position to control the content of *J Trauma* articles selected for CME credit has disclosed all relevant financial relationships with any commercial interest. Disclosure forms are completed by the editorial staff, associate editors, reviewers, and all authors. The ACCME defines a 'commercial interest' as "any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients." "Relevant" financial relationships are those (in any amount) that may create a conflict of interest and occur within the 12 months preceding and during the time that the individual is engaged in writing the article. All reported conflicts are thoroughly managed in order to ensure any potential bias within the content is eliminated. However, if you perceive a bias within the article, please report the circumstances on the evaluation form.

Please note we have advised the authors that it is their responsibility to disclose within the article if they are describing the use of a device, product, or drug that is not FDA approved or the off-label use of an approved device, product, or drug or unapproved usage.

Disclosures of Significant Relationships with Relevant Commercial Companies/Organizations by the Editorial Staff:

Ernest E. Moore, MD, Editor, received research support from Haemonetics. David B. Hoyt, MD, Associate Editor/CME Editor, Ronald Maier, MD, Associate Editor, and Steven Shackford, MD, Associate Editor have nothing to disclose. Jennifer Crebs, Managing Editor, received consulting fees from Golden Helix, Expression Analysis, Illumina, and Lineagan. Jo Fields, Editorial Assistant, and Angela Sauaia, MD, Biostatistician, have nothing to disclose.

Author Disclosures: All authors have nothing to disclose.

Cost

For AAST members and *Journal of Trauma and Acute Care Surgery* subscribers there is no charge to participate in this activity. For those who are not a member or subscriber, the cost for each credit is $50.

System Requirements

The system requirements are as follows: Adobe® Reader 7.0 or above installed; Internet Explorer® 7 and above; Firefox® 3.0 and above, Chrome® 8.0 and above, or Safari™ 4.0 and above.

Questions

If you have any questions, please contact AAST at 800-789-4006. Paper test and evaluations will not be accepted.

Submitted: May 17, 2011, Revised: November 22, 2011, Accepted: January 12, 2012.
From the R Adams Cowley Shock Trauma Center (M.B., D.M.S., B.A., K.S., T.M.S.) and The Shock, Trauma and Anesthesiology Research Organized Research Center (D.M.S., P.F.H., T.M.S.), University of Maryland School of Medicine, Baltimore, Maryland.
Address for reprints: Megan Brenner, MD, Division of Critical Care/Program in Trauma, R Adams Cowley Shock Trauma Center, University of Maryland Medical Center, 22 South Greene Street, Baltimore, MD 21201; email: mbrenner@umm.edu.

DOI: 10.1097/TA.0b013e31824af90b

BACKGROUND: Vital signs, particularly blood pressure, are often manipulated to maximize perfusion and optimize recovery from severe traumatic brain injury (sTBI). We investigated the utility of automated continuously recorded vital signs to predict outcomes after sTBI.

METHODS: Sixty patients with head Abbreviated Injury Scale score ≥3, age >14 years, "isolated" TBI, and need for intracranial pressure monitoring were prospectively enrolled at a single, large urban tertiary care facility. Outcome was measured by mortality and extended Glasgow Outcome Scale (GOSE) at 12 months. Continuous, automated, digital data were collected every 6 seconds for 72 hours after admission, and 5-minute means of systolic blood pressure (SBP) were recorded. We calculated SBP as pressure × time dose (PTD) to describe the cumulative amplitude and duration of episodes above and below clinical thresholds. The extent and duration of the insults were calculated as percent time (%time), PTD, and PTD per day (PTD/D) of defined thresholds (SBP: <90 mm Hg, <100 mm Hg, <110 mm Hg, and <120 mm Hg; mean arterial pressure: <60 mm Hg and <70 mm Hg; heart rate: >100 bpm and >120 bpm; and SpO_2: <88% and <92%) for the first 12 hours, 24 hours, and 48 hours of intensive care unit admission. We analyzed their ability to predict mortality and GOSE by receiver operator characteristics.

RESULTS: Mean age was 33.9 (range, 16–83) years, mean admission Glasgow Coma Scale score 6.4 ± 3, and mean head Abbreviated Injury Scale score 4.2 ± 0.72. The 30-day mortality rate was 13.3%. Of the 45 patients in whom GOSE at 12 months was available, 28 (62%) had good neurologic outcomes (GOSE score >4). Traditional markers of poor outcome (admission SBP, admission Glasgow Coma Scale, and Marshall score) were not different between groups with good or poor outcome. PTD, PTD/D, and %time SBP <110 mm Hg and SBP <120 mm Hg predicted mortality at 12 hours, 24 hours, and 48 hours ($p < 0.04$). Percent time SBP <110 mm Hg in the first 24 hours was predictive of 12-month GOSE ($p = 0.02$). PTD/D SBP <120 mm Hg in the first 24 hours and PTD and PTD/D in the first 48 hours were also predictive of 12-month GOSE ($p < 0.05$).

CONCLUSIONS: Within the first 48 hours of intensive care unit admission, hypotension was found to be predictive of mortality and functional outcomes at higher thresholds than traditionally defined. Systemic blood pressure targets closer to 120 mm Hg may be more efficacious in minimizing secondary insults and particularly useful in settings without invasive intracranial monitoring capabilities. (*J Trauma.* 2012; 72: 1135–1139. Copyright © 2012 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: III, prognostic study.

KEY WORDS: Continuous vital signs; outcomes; secondary brain injury; hypotension.

Primary traumatic brain injury (TBI) may be worsened by variable physiologic conditions which may occur in the severely injured patient. The prevention of secondary brain injury by monitoring and manipulation of vital signs leads to improved outcomes in severe TBI (sTBI) patients.[1–4] Optimizing recovery from sTBI requires diligent correction of hypoxia, hypothermia, hypotension, and hypercoagulable states. The current recommendations for blood pressure control from the Brain Trauma Foundation include maintaining a systolic blood pressure (SBP) of >90 mm Hg to avoid the high morbidity and mortality associated with even single episodes of hypotension.[5] Some studies have found poor outcomes with SBP <95 mm Hg, but the optimal range has yet to be defined.

Continuous vital sign monitoring by automated systems has been shown to correlate more closely with outcomes than traditional manual end-hour recordings.[6] When the depth and duration of hypotensive insults are recorded using an automated system and displayed as pressure × time dose (PTD, mm Hg), a more complete description of the abnormal parameter becomes available. Although targets for intracranial pressure (ICP) and cerebral perfusion pressure may more closely correlate with intracerebral hemorrhage and the prevention of secondary brain injury, methods required for monitoring such as arterial lines and ICP catheters may not be easily accessible. Our goal was to use the two-dimensional continuous data to determine more sensitive targets for SBP which could improve functional outcomes in sTBI patients, even in settings without invasive monitoring capabilities.

METHODS

Patients at a large urban Level I trauma center were prospectively enrolled over a 2-year period. Inclusion criteria were age >14 years, admission within the first 6 hours after injury, Glasgow Coma Scale (GCS) score <9 on admission, and placement of a clinically indicated ICP monitor. sTBI was confirmed on admission computed tomography scan. Informed consent was obtained from the patients Legally Authorized Representative. Exclusion criteria were any body region other than brain with an Abbreviated Injury Scale (AIS) score >3 to exclude multisystem trauma, a nonsurvivable brain injury, or ICP monitoring initiated >24 hours postinjury or technical problems with the ICP monitoring device. The study was approved by the HRP Office of the University of Maryland School of Medicine.

Demographics, mechanisms of injury, head AIS, predicted survival, and injury severity score were recorded. Marshall Classification scores were assigned to all admission head computed tomography scans by a blinded reviewer. Outcome measures included in-hospital mortality and the extended Glasgow Outcome Scale (GOSE). The GOSE was used to evaluate long-term functional outcomes at 12 months after injury. GOSE was defined as GOSE at 12-month follow-up. For the seven patients who did not have a 12-month score, the last recorded value was used. In all seven cases, the patients had a GOSE score recorded between 6 months and 12 months. The GOSE of survivors was obtained by telephone interviews by an experienced trauma clinical research coordinator. GOSE 1–4 was defined as "poor functional

outcome" whereas GOSE 5–8 was defined as "good functional outcome."

The continuous vital signs are collected from a network of patient monitors throughout the trauma center. The recorder captured waveforms every 6 seconds for 72 hours after admission, and potential artifacts were removed from the central server. From these data, we calculated the 5-minute means of SBP as PTD, or pressure × time dose, to describe the cumulative amplitude and duration of episodes below the following clinical thresholds: SBP <90 mm Hg, <100 mm Hg, <110 mm Hg, and <120 mm Hg. There was no overlap of patients in each group. Means, maximum, and minimum were also recorded. The extent and duration of the insults were calculated for the first 12 hours, 24 hours, and 48 hours of ICU admission. Percent time (%time) was also recorded for each parameter in addition to PTD per day (PTD/D) to account for differences in hospital length of stay.

Arterial line measurements used to collect SBP were collected from the networked patient monitors (GE-Marquette-Solar-7000/8000) throughout the trauma center through the vital signs data recorder (VSDR). The VSDR captures waveforms every 6 seconds, and the collected data are compressed and transferred to a centralized VSDR server. Potential artifacts are cleaned by removing the VS data of first and last minute of patient stay, removing extreme outliers, and calculation of a moving median with a window size of five data points (30 seconds). The cleaning procedure discards <1% of data points leaving 5,206,860 points of VS data available for analysis. All traces of the 5-minute means were visually reviewed and confirmed by one of the clinician investigators.

The Students *t*-test was used to compare means for continuous data, whereas the Wilcoxon rank-sum statistic was used for nonnormally distributed data. The data were analyzed by receiver operator characteristics (ROC) to determine whether mortality and GOSE could be predicted by SBP at previously defined thresholds. $p < 0.05$ was considered statistically significant.

RESULTS

Sixty patients met inclusion criteria and were enrolled in the study, giving 3,999 hours of data (66.5 hours or 2.8 days per patient). The mean age was 33.9 (range, 16–83) years, mean admission GCS score 6.4 ± 3.1, and mean head AIS score 4.2 ± 0.72. The majority of patients were male (85%), and the in-hospital 30-day mortality rate was 13.3%.

Of the 45 patients in whom GOSE at 12 months was available, 28 (62%) had good functional outcome as defined by GOSE score >4. Traditional markers of poor outcome (admission GCS score, admission SBP, and Marshall score) were not different between groups with good or poor outcome (Table 1).

SBP was found to correlate with mortality at SBP <110 mm Hg and <120 mm Hg. PTD, PTD/D, and %time SBP <110 mm Hg and <120 mm Hg predicted mortality at 12 hours, 24 hours, and 48 hours (Tables 2 and 3), all with ROC values >0.72. SBP <110 mm Hg and <120 mm Hg in the first 24 hours as measured by %time and PTD/D, respectively, PTD, and PTD/D SBP <120 mm Hg in the first 48 hours predicted mortality and functional outcome at 12 months (ROC >0.68; Figs. 1 and 2). Neither SBP <90 mm Hg nor SBP <100 mm Hg correlated with mortality or functional outcomes within the first 48 hours of admission.

There was no correlation between hypotension and outcomes at 72 hours, perhaps due to the small number of patients who experienced episodes of hypotension so far into their hospitalization. Our aggressive TBI protocol results in fewer patients with SBP within the above described parameters.

TABLE 1. Characteristics of Study Subjects

	All Subjects (N = 60)							Survivors (N = 52)		
	All (N = 60)	Good Outcome* (n = 37)	Poor Outcome† (n = 23)	*p*	Survived (n = 52)	Died (n = 8)	*p*	Good Outcome* (n = 37)	Poor Outcome† (n = 23)	*p*
Age (yr), mean ± SD	33.9 ± 14.1	31.0 ± 11.4	38.6 ± 17.5	<0.05	33.7 ± 14.8	35.1 ± 11.8	0.8	31.0 ± 11.4	40.4 ± 20.1	0.04
Males, n (%)	51 (85.0)	34 (91.9)	17 (73.9)	0.06	45 (86.5)	6 (75.0)	0.4	34 (91.9)	11 (73.3)	0.08
Blunt mechanism of injury, n (%)	58 (96.7)	35 (94.6)	22 (100)	0.3	50 (96.1)	8 (100)	0.6	35 (94.6)	15 (100)	0.4
Head AIS, mean ± SD	4.2 ± 0.7	4.2 ± 0.7	4.3 ± 0.8	0.5	4.1 ± 0.7	4.6 ± 0.5	0.08	4.2 ± 0.7	4.1 ± 0.8	0.9
ISS, mean ± SD	28.5 ± 10.1	27.0 ± 9.8	30.6 ± 10.4	0.2	27.5 ± 9.7	33.9 ± 11.7	0.1	27.0 ± 9.8	28.9 ± 9.7	0.5
In-hospital mortality, n (%)	8 (13.3)	0 (0.0)	8 (36.4)	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Admission SBP, mean ± SD	141.3 ± 28.6	145.4 ± 22.6	134.7 ± 35.9	0.2	143.7 ± 26.8	125.5 ± 36.7	0.09	145.4 ± 22.6	139.6 ± 35.7	0.2
Admission GCS, mean ± SD	6.4 ± 3.1	6.8 ± 3.4	5.9 ± 2.5	0.3	6.8 ± 3.4	4.1 ± 1.5	0.02	6.8 ± 3.4	6.8 ± 2.4	1.0
Marshall score, mean ± SD	2.5 ± 0.9	2.3 ± 0.9	2.7 ± 1.0	0.1	2.4 ± 0.9	3.1 ± 0.9	0.03	2.3 ± 0.9	2.5 ± 0.9	0.5

SD, standard deviation.
* 12-month GOSE 5–8.
† 12-month GOSE 1–4.

TABLE 2. SBP <110 mm Hg at 12 h, 24 h, and 48 h Predicts Mortality by Automated Data Describing Extent and Duration of Insult

ROC	12 h	24 h	48 h
PTD	0.76*	0.72†	0.75†
PTD/D	0.76*	0.72†	0.75†
%time	0.76*	0.76*	0.79*

* $p = 0.01$.
† $p < 0.05$.
‡ $p < 0.001$.

TABLE 3. SBP <120 mm Hg at 12 h, 24 h, and 48 h Predicts Mortality by Automated Data Describing Extent and Duration of Insult

ROC	12 h	24 h	48 h
PTD	0.74*	0.77†	0.80‡
PTD/D	0.74*	0.77	0.80‡
%time	0.73*	0.76†	0.81‡

* $p < 0.05$.
† $p = 0.01$.
‡ $p < 0.001$.

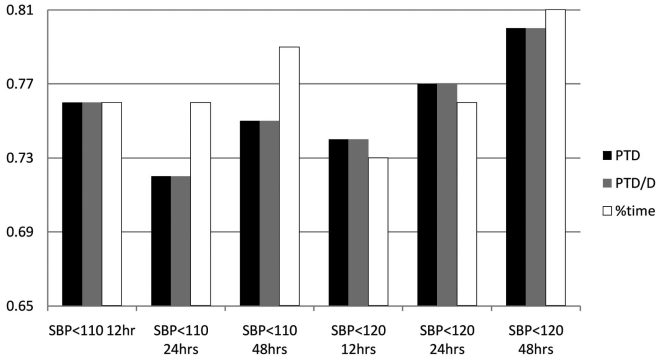

Figure 1. Mortality predicted by ROC for SBP <110 mm Hg and <120 mm Hg at 12 hours, 24 hours, and 48 hours.

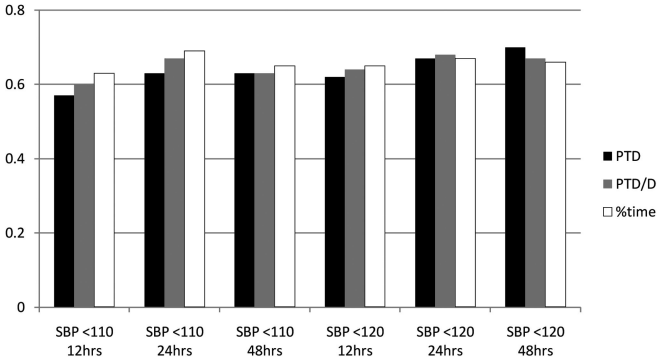

Figure 2. Twelve-month GOSE predicted by ROC for SBP <110 mm Hg and <120 mm Hg for 12 hours, 24 hours, and 48 hours of admission.

DISCUSSION

The incidence of sTBI, and its emotional, physical, and financial consequences are overwhelming. Approximately 1.5 million people are affected by TBI each year, resulting in 50,000 deaths, and many more with severe disability. Mortality rates can exceed >50% for sTBI, and >$100 billion annually is spent on recovery and rehabilitation.[7]

The use of continuous data collection allows linear, episodic data to be converted to two-dimensional analysis. The ability to define secondary brain insults as an area under the curve, or PTD, has been shown to be superior to manual recordings by defining the exact extent and duration of the insult. Our goal was to apply this sophisticated data collection tool to provide simple treatment recommendations for situations where invasive monitoring is not available or accessible, such as in the prehospital field or in combat. Depending on the resources available at some institutions, the use of invasive monitoring may be initiated beyond 12 hours to 24 hours of admission, during which time the opportunity to provide specific targeted therapy using SBP would be neglected.

Manley and others[3,4,8] have documented the negative impact of hypotension on TBI patients. In a prospective study, even brief episodes of hypotension were shown to increase mortality eightfold.[2] Additional prospective data from the Trauma Coma Data Bank cite a single episode of hypotension to be one of the most significant predictors of outcome in sTBI patients.[1,9] Based on these studies and others with similar findings, the Brain Trauma Foundation in its 3rd edition published in 2007 recommends maintaining SBP above 90 mm Hg to avoid the deleterious effects on patient outcome. The numeric value of 90 was chosen as a statistical threshold defined by blood pressure distributions for normal adults rather than a clinically defined threshold parameter. Although the Foundation recommends avoiding a single episode of SBP <90 mm Hg, it states "90 mm Hg should be a threshold to avoid; the actual values to target remain unclear."[5]

Recent data have suggested that thresholds >90 mm Hg should be avoided in sTBI patients to maximize outcomes. Guidelines from a European trauma center recommend a SBP target of 100 mm Hg to 110 mm Hg in blunt trauma patients with head injury,[10] whereas the European Brain Injury Consortium recommends maintaining a SBP ≥120 mm Hg.[11] A recent unpublished review of more than 15,000 patients with moderate to sTBI shows higher mortality at SBP thresholds of <110 mm Hg.[12] Our data failed to show a difference in outcome with SBP <90 mm Hg or <100 mm Hg, likely due to a combination of low power (small n =) and the aggressive TBI management protocol at our institution. For example, <20% of patients had SBP <90 mm Hg or <100 mm Hg within the first 48 hours.

Our data are derived from a sensitive and complex data collection tool which has led us to the conclusion that current recommendations for SBP in sTBI patients may require revision. Because of the ethical obligations to patients enrolled in research studies, it is unlikely that a prospective randomized trial could or should be performed. Until such time as the guidelines are reviewed, further evidence from multiple sources must corroborate our findings.

CONCLUSION

Within the first 48 hours of ICU admission, hypotension was not predictive of outcomes at traditionally defined thresholds of SBP <90 mm Hg or <100 mm Hg. Systemic blood pressure targets >120 mm Hg may be more efficacious in minimizing secondary insults and particularly useful in settings without invasive intracranial monitoring capabilities.

AUTHORSHIP

M.B. conducted the literature search. D.S., K.S., and B.A. designed this study. P.H., K.S., and B.A. collected data, which P.H. and M.B. analyzed. M.B., D.S., and T.S. interpreted the data. M.B. and T.S. wrote the manuscript; M.B. and D.S. prepared the figures.

DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J Neurosurg*. 1991;75:S59–S66.
2. Manley G, Knudson M, Morabito D, et al. Hypotension, hypoxia, and head injury: Frequency, duration, and consequences. *Arch Surg*. 2001; 136:1118–1123.
3. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma.* 2007;24(Suppl 1):S37–S44.
4. Andrews PJ, Sleeman DH, Statham PF, et al. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: A comparison between decision tree analysis and logistic regression. *J Neurosurg.* 2002;97:326–336.
5. Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe head injury. *J Neurotrauma.* 2007;24:S1–S106.
6. Kahraman S, Dutton RP, Hu P, et al. Automated measurement of 'Pressure*time dose' of intracranial hypertension best predicts outcome. *J Trauma.* 2010;69:110–118.
7. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. *J Head Trauma Rehabil.* 2006;21:544–548.
8. Schirmer-Mikalsen K, Vik A, Gisvold SE, et al. Severe head injury: Control of physiologic variables, organ failure and complications in the intensive care unit. *Acta Anaesthesiol Scand.* 2007;51:1194–1201.
9. Chestnut RM. Avoidance of hypotension: condition sine qua non of successful severe head-injury management. *J Trauma.* 1987;27:1007–1013.
10. Chiara O, Bucci L, Sara A, et al. Quality and quantity of volume replacement in trauma patients. *Minerva Anestesiol.* 2008;74:303–306.
11. Moppett IK. Traumatic brain injury: Assessment, resuscitation and early management. *Brit J Anes.* 2007;99:18–31.
12. Berry C, Ley EJ, Bukur M, Malinoski D, Margulies DR, Mirocha J, Salim A. Redefining hypotension in traumatic brain injury. *Injury.* 2011 Sept 20. [Epub ahead of print].

