Mortality and Prehospital Blood Pressure in Patients With Major Traumatic Brain Injury
Implications for the Hypotension Threshold

Daniel W. Spaite, MD; Chengcheng Hu, PhD; Bentley J. Bobrow, MD; Vatsal Chikani, MPH; Duane Sherrill, PhD; Bruce Barnhart, RN, CEP; Joshua B. Gaither, MD; Kurt R. Denninghoff, MD; Chad Viscusi, MD; Terry Mullins, MBA; P. David Adelson, MD

IMPORTANCE Current prehospital traumatic brain injury guidelines use a systolic blood pressure threshold of less than 90 mm Hg for treating hypotension for individuals 10 years and older based on studies showing higher mortality when blood pressure drops below this level. However, the guidelines also acknowledge the weakness of the supporting evidence.

OBJECTIVE To evaluate whether any statistically supportable threshold between systolic pressure and mortality emerges from the data a priori, without assuming that a cut point exists.

DESIGN, SETTING, AND PARTICIPANTS Observational evaluation of a large prehospital database established as a part of the Excellence in Prehospital Injury Care Traumatic Brain Injury Study. Patients from the preimplementation cohort (January 2007 to March 2014) 10 years and older with moderate or severe traumatic brain injury (Barell Matrix Type 1 classification, *International Classification of Diseases, Ninth Revision* head region severity score of 3 or greater, and/or Abbreviated Injury Scale head-region severity score of 3 or greater) and a prehospital systolic pressure between 40 and 119 mm Hg were included. The generalized additive model and logistic regression were used to determine the association between systolic pressure and probability of death, adjusting for significant/important confounders.

MAIN OUTCOMES AND MEASURES The main outcome measure was in-hospital mortality.

RESULTS Among the 3844 included patients, 2565 (66.7%) were male, and the median (range) age was 35 (10-99) years. The model revealed a monotonically decreasing association between systolic pressure and adjusted probability of death across the entire range (ie, from 40 to 119 mm Hg). Each 10-point increase of systolic pressure was associated with a decrease in the adjusted odds of death of 18.8% (adjusted odds ratio, 0.812; 95% CI, 0.748-0.883). Thus, the adjusted odds of mortality increased as much for a drop from 110 to 100 mm Hg as for a drop from 90 to 80 mm Hg, and so on throughout the range.

CONCLUSIONS AND RELEVANCE We found a linear association between lowest prehospital systolic blood pressure and severity-adjusted probability of mortality across an exceptionally wide range. There is no identifiable threshold or inflection point between 40 and 119 mm Hg. Thus, in patients with traumatic brain injury, the concept that 90 mm Hg represents a unique or important physiological cut point may be wrong. Furthermore, clinically meaningful hypotension may not be as low as current guidelines suggest. Randomized trials evaluating treatment levels significantly above 90 mm Hg are needed.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Daniel W. Spaite, MD, Department of Emergency Medicine, University of Arizona College of Medicine, 1501 N Campbell Ave, Tucson, AZ 85724 (Dan@aemrc.arizona.edu).

The societal burden of traumatic brain injury (TBI) is enormous; each year, TBI leads to 2.2 million emergency department visits, 280 000 hospitalizations, 52 000 deaths, and more than $60 billion in economic costs in the United States.[1,2] In addition, more than 5 million Americans have major long-term disabilities as a result of TBI.[1] Fortunately, there is growing evidence that proper and aggressive management of TBI in the minutes immediately following injury may improve patient outcomes by preventing or lessening secondary brain injury. This has led to the promulgation of evidence-based prehospital and in-hospital TBI treatment guidelines for both children and adults.[3-6]

One major focus of these guidelines is the prevention and treatment of hypotension.[4,5] This is because it has been firmly established that even a single episode of hypotension during the prehospital or early hospital phases of TBI management is associated with dramatic increases in mortality.[3,7-26] Many studies have shown that low blood pressure (variously defined) increases the risk of death. However, the nearly universal assumption that a specific, clinically relevant threshold actually exists is entirely without support. In other words, the design of essentially every relevant study presumes a priori that there is a cut point below which outcome significantly worsens. However, simply dichotomizing small populations and then showing that it is worse to have lower blood pressure than higher blood pressure is not the same as identifying a true threshold. A clinically meaningful cut point would be one that correlates with a marked change in physiological response and patient outcome if blood pressure drops below that particular level. This requires study populations that are large enough to allow evaluation of blood pressure as a continuous variable rather than merely as a categorical variable, eg, low vs not low.

Given the absence of prehospital studies evaluating this specific issue, we analyzed the association between the lowest systolic blood pressure (SBP; obtained prior to hospital arrival) and mortality among children 10 years and older and adults in the Excellence in Prehospital Injury Care (EPIC) TBI Study.[27] Specifically, we tested the null hypothesis that no supportable inflection point in the relationship between SBP and mortality (ie, a threshold) would emerge from the data when evaluated without reference to any given definition for hypotension.

Methods

Study Design, Setting, and Oversight
The parent study, EPIC, is evaluating the effect of implementing the prehospital TBI guidelines[3-6] for patients with major (ie, moderate or severe) TBI throughout Arizona. This is being done by using a before-after, multisystem, observational design. The study is expected to be completed in 2017 and has been described in detail elsewhere.[27] Rather than reiterating the details of the parent study here, we limit the description to the design attributes relevant to this specific secondary analysis. The patients in this evaluation are in the preimplementation cohort of the EPIC TBI Study. Postinterventional pa-

Key Points

Question Is there a prehospital hypotension threshold for mortality in patients with major traumatic brain injury?

Findings In this secondary analysis of the Excellence in Prehospital Injury Care Traumatic Brain Injury Study, the association between systolic blood pressure and adjusted probability of death was monotonic across a broad range (40-119 mm Hg), with each 10-point increase in systolic pressure associated with a decrease of 18.8% in the adjusted odds of death.

Meaning In patients with traumatic brain injury, the concept that 90 mm Hg represents a unique or important physiological cut point may be wrong, and clinically meaningful hypotension may not be as low as current guidelines suggest.

tients were excluded, since one of the emphases of guideline implementation is the prevention and aggressive treatment of hypotension. Thus, including these patients might introduce significant bias into this evaluation, as there was no intentional guideline implementation prior to the EPIC TBI Study.

The necessary regulatory approvals for the EPIC TBI Study have been obtained from the Arizona Department of Health Services and the State Attorney General. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board have approved the project and have determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitute human subjects research and have waived informed consent and approved the publication of deidentified data.

Data Collection
The Arizona State Trauma Registry contains extensive trauma center data on all patients taken to the 8 designated level I trauma centers in the state. From the Arizona State Trauma Registry, all patients meeting study criteria were entered into the EPIC database. Each participating emergency medical services (EMS) agency then received a list of the patients in the EPIC TBI Study that were cared for in their system. The patients were matched by incident date, name, and other patient identifiers. Either scanned copies (paper-based patient care records [PCRs]) or electronic data files (electronic PCRs) were then sent to the study data center for entry into the EPIC database. This provided an extensive linked data set for study patients, which includes both prehospital and trauma center data. The entire process of identifying patients, linking EMS and trauma center data, accessing EMS PCRs, entering data, and structuring the EPIC database have been reported.[27] More than 20 000 patients have been enrolled in the EPIC TBI Study and more than 31 000 EMS PCRs have been entered into the database (patients cared for by multiple agencies have more than 1 PCR). The successful linkage rate is exceptionally high (eg, throughout the study, patients with missing data for SBP has been consistently less than 5%).

Participants
Inclusion criteria for the EPIC Study were physical trauma, a trauma center diagnosis(es) consistent with TBI (ie, either

isolated or multisystem trauma that includes TBI), and at least one of the following definitions for moderate or severe TBI: Barell Matrix Type 1 classification, *International Classification of Diseases, Ninth Revision* head region severity score of 3 or greater, and/or Abbreviated Injury Scale head-region severity score of 3 or greater.[27]

Exclusion criteria for this subgroup analysis included age younger than 10 years, an SBP less than 40 mm Hg or 120 mm Hg or greater, interhospital transfers, and death before arrival to the emergency department. In addition, patients that were missing data for age, SBP, or trauma type (ie, penetrating vs blunt) were excluded. The 120 mm Hg upper limit was chosen because this represents the highest reported threshold in the previous literature[7-9,11,14,15,17-22,26,28-36] and because including a large number of patients with near-normal or normal perfusion in the mortality model would dilute the effects of the patients who are actually at risk for hypoperfusion.

Interventions
This is a secondary analysis of the preimplementation cohort and entails no interventions.

Main Outcome
The outcome is in-hospital mortality.[27]

Statistical Analysis
Continuous variables were summarized by median and range and were compared between the 2 cohorts (survived vs died) using the Wilcoxon rank sum test. Categorical variables were summarized by frequency and proportion (with 95% CIs) when appropriate and were compared between the 2 groups by Fisher exact test.

The overall trend in crude (unadjusted) mortality rates over the range of lowest prehospital SBP was explored using moving average plots. To plot the moving average, the crude death rate and corresponding 95% CI were calculated for patients with lowest SBP in each interval spanning 10 consecutive values (ie, 40-49 mm Hg, 41-50 mm Hg, 42-51 mm Hg, and so on, through 110-119 mm Hg). The estimated death rate and corresponding 95% CI were plotted against the midpoint of the interval (ie, the range of plotting is 44.5 mm Hg for 40-49 mm Hg, and so on, through 114.5 for the 110-119 mm Hg interval). The moving window of 10 mm Hg was selected to prevent any false cut points being created by data anomalies in the frequency of the last digit of lowest recorded SBP (eg, in the data set, even numbers were preferred to odd numbers, and the digit 0 was the most popular, followed by 8 and 6). Thus, using a window length of 10 prevents abnormalities arising from the uneven recording distribution of the last SBP digit.

The risk-adjusted associations between mortality and SBP were examined by logistic regression, which modeled the log odds of death, adjusting for important risk factors and potential confounders (ie, age, sex, race/ethnicity, payment source, trauma type, prehospital hypoxia, prehospital intubation, and treating trauma center). The linkage of EMS data to the Arizona State Trauma Registry allowed the use of actual diagnostic/anatomic injury scoring to adjust for overall injury severity (Injury Severity Score)[37] and TBI severity (*International*

Classification of Diseases, Ninth Revision head injury diagnoses matched to Abbreviated Injury Scale head-region score)[38-44] rather than having to rely on far less reliable prehospital physiological injury indicators (eg, Glasgow Coma Scale score). The effects of continuous variables (ie, SBP and age) in the logistic regression were fitted nonparametrically using penalized thin plate regression splines through the generalized additive model.[45] The model was penalized to avoid overfitting (excessive "wiggliness" in the transformation function due to random noise), and the smoothing parameters were chosen to optimize the Akaike Information Criterion, a measure of the predictive power of the model.[45] Thus, the functional forms of these variables were determined by the data.

The software environment R was used for the analysis,[46] and the R package mgcv[45,47] was used for the generalized additive model. P values were calculated from a Wald-type test using the Bayesian covariance matrix.[48] All tests were 2-sided with α = .05.

Results

Enrollment
There were 17 105 patients in the preintervention group from January 2007 to March 2014. Excluded were 1162 children (6.8%) younger than 10 years, 4823 (28.2%) interfacility transfers, and 6352 (37.1%) with a lowest prehospital SBP less than 40 mm Hg or 120 mm Hg or greater as well as 924 (5.4%) with missing data (SBP, 300; transfer status, 623; and trauma type, 1). This left 3844 patients (22.5%) in our study cohort.

Outcome and Analysis
Among these 3844 patients, 528 (13.7%) died. **Table 1** summarizes the demographic information and patient characteristics by survival status. **Figure 1** shows the crude (unadjusted) moving average of death rate by lowest EMS SBP. This plot reveals a relatively steady slope from 40 mm Hg to nearly 110 mm Hg. A logistic regression model was fitted that examined the effect of lowest prehospital SBP on mortality risk, controlling for risk adjusters and potential confounders. For continuous variables (ie, SBP and age), the functional form of the covariate effect was obtained nonparametrically with the value of the smoothing parameter calculated to optimize the Akaike Information Criterion. All other confounders were categorical (Table 1). **Table 2** shows the effects and P values of all covariates in the model (except for the continuous variables and treating trauma center, which were all significant at $P < .001$). As has been found by many previous studies,[7,8,11,17,18,49,50] hypoxia was a highly significant risk factor and was included as a confounder in the model. The data by trauma center, while parametric, are not shown in **Figure 2**. Because absolute anonymity is required by state regulations and the institutional review board (for patients, EMS agencies, and hospitals), we are not able to report specific trauma center–related data, even generically; because trauma center volumes are a matter of public record, presentation of these data could conceivably lead to hospital-specific information being inferred or identified (eg, because of comparisons of the sizes of the 95% CIs). However,

Table 1. Patient Characteristics by Survival Status

Characteristic[a]	No. (%) Alive (n = 3316)	Dead (n = 528)	P Value[b]
Age, median (range), y	34 (10-99)	42 (10-95)	<.001
Male			
No	1125 (33.9)	154 (29.2)	.04
Yes	2191 (66.1)	374 (70.8)	
Race			
African American	101 (3)	15 (2.8)	
Asian	38 (1.1)	5 (0.9)	
American Indian/Alaska Native	239 (7.2)	27 (5.1)	.53
White	2548 (76.8)	405 (76.7)	
Other	360 (10.9)	61 (11.6)	
Unknown	30 (0.9)	15 (2.8)	
Hispanic ethnicity			
No	2443 (73.7)	376 (71.2)	
Yes	785 (23.7)	120 (22.7)	>.99
Unknown	88 (2.7)	32 (6.1)	
Payer			
Private insurance	1291 (38.9)	139 (26.3)	
AHCCCS/Medicaid	987 (29.8)	136 (25.8)	
Medicare	356 (10.7)	85 (16.1)	<.001
Self-pay	497 (15)	115 (21.8)	
Other	151 (4.6)	25 (4.7)	
Unknown	34 (1)	28 (5.3)	
Trauma type			
Blunt	3196 (96.4)	392 (74.2)	<.001
Penetrating	120 (3.6)	136 (25.8)	
ICD-9 head region severity score			
1-3	2060 (62.1)	40 (7.6)	
4	883 (26.6)	53 (10)	<.001
5-6	331 (10)	425 (80.5)	
Unknown	42 (1.3)	10 (1.9)	
ICD-9 injury severity score			
1-14	1317 (39.7)	5 (0.9)	
16-24	1038 (31.3)	19 (3.6)	<.001
≥25	961 (29)	504 (95.5)	
Prehospital minimum SBP, median (range), mm Hg	107 (40-119)	92 (40-119)	<.001
Prehospital hypoxia			
No	2886 (87)	274 (51.9)	
Yes	282 (8.5)	162 (30.7)	<.001
Unknown	148 (4.5)	92 (17.4)	
Prehospital intubation			
No	2863 (86.3)	202 (38.3)	<.001
Yes	453 (13.7)	326 (61.7)	

Abbreviations: AHCCS, Arizona Health Care Cost Containment System; ICD-9, International Classification of Diseases, Ninth Revision; SBP, systolic blood pressure.

[a] Trauma center was also highly significant (not shown; P < .001).

[b] Fisher exact test used for categorical variables and Wilcoxon rank sum test used for continuous variables.

because treating trauma center was a significant confounder, we adjusted for it in the model.

In the optimal model (based on Akaike Information Criterion), the adjusted effect of lowest SBP on log odds of death was nearly perfectly linear, with an adjusted odds ratio of 0.812 (95% CI, 0.748-0.883; $P < .001$) associated with a 10-mm Hg increase in SBP at any level between 40 and 120 mm Hg (eg, a patient with an SBP of 110 mm Hg has an 18.8% lower adjusted odds of death than one with an SBP of 100 mm Hg, and

so on throughout the entire range). Figure 2 shows the adjusted probability of death over the range of 40 to 120 mm Hg. As can be seen, the rate of change in estimated probability of death is essentially constant. In other words, there is a striking absence of any identifiable threshold of SBP in relationship to mortality, and major reductions in both crude and adjusted mortality continue far to the right of the classic 90 mm Hg hypotension level. Additional evidence comes from the receiver operating characteristic curve plot of the data. The area

Figure 1. Unadjusted Moving Average of Death Rate by Lowest
Systolic Blood Pressure (SBP)
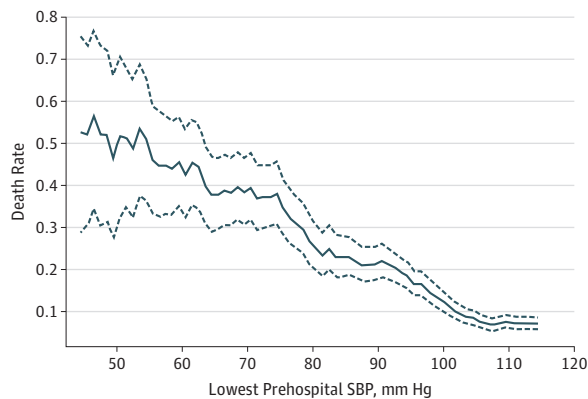
The solid line represents the moving average of the estimated death rate for
each interval spanning 10 consecutive values, and the dotted lines represent
the pointwise 95% CIs.

Table 2. Parametric Terms in the Multivariate Logistic Regression Model
for Death

Covariate[a]	Odds Ratio (95% CI)[b]	P Value
Male		
No	1 [Reference]	.54
Yes	0.91 (0.67-1.23)	
Race		
African American	1 [Reference]	
Asian	1.09 (0.22-5.37)	
American Indian/Alaska Native	1.02 (0.36-2.88)	.75
White	1.29 (0.53-3.11)	
Other	1.19 (0.42-3.36)	
Unknown	2.89 (0.66-12.75)	
Hispanic ethnicity		
No	1 [Reference]	
Yes	0.61 (0.40-0.92)	.06
Unknown	1.03 (0.46-2.34)	
Payer		
Private	1 [Reference]	
AHCCCS/Medicaid	1.24 (0.86-1.78)	
Medicare	1.72 (1.00-2.97)	<.001
Self-pay	3.65 (2.36-5.65)	
Other	1.76 (0.89-3.48)	
Unknown	9.56 (3.78-24.16)	
Trauma type		
Blunt	1 [Reference]	<.001
Penetrating	3.89 (2.53-5.98)	
***ICD-9* head region severity score**		
1-3	1 [Reference]	
4	1.34 (0.82-2.20)	<.001
5-6	13.2 (8.41-20.72)	
Unknown	6.31 (2.36-16.86)	
***ICD-9* injury severity score**		
1-14	1 [Reference]	
16-24	2.63 (0.91-7.60)	<.001
≥25	15.96 (6.00-42.50)	
Prehospital hypoxia		
No	1 [Reference]	
Yes	1.89 (1.35-2.65)	<.001
Unknown	4.3 (2.71-6.83)	
Prehospital intubation		
No	1 [Reference]	<.001
Yes	2.81 (2.08-3.78)	

Abbreviations: AHCCS, Arizona Health Care Cost Containment System;
ICD-9, International Classification of Diseases, Ninth Revision; SBP, systolic blood
pressure.

[a] Also adjusted for trauma centers (not shown; *P* < .001).

[b] Odds ratio for death compared with the referent category.

under the curve is 0.705, and there is no cut point that gives
satisfactory levels of both sensitivity and specificity to indi-
cate a threshold.

Discussion

The previous literature related to this investigation consists of
studies that were small,[7,8,11,14-21,23,24,26,29,30,34,50] had limited
or no prehospital data,[7,11,14-17,20,21,24,26,28,29,34,36,50] or evalu-
ated general trauma populations (ie, were not specific to pa-
tients with TBI).[35,51-55] The current study is unique in both its
size and its access to detailed prehospital data. A key reason
for evaluating the effect of blood pressure measured before hos-
pital arrival is because the injured brain is so highly sensitive
to changes in perfusion, and the timeframe during which neu-
ronal damage begins is so short. It is well established that sec-
ondary brain injury is initiated by even brief periods of com-
promised blood flow.[4,5,11-13,17,20,27] Thus, decreased perfusion
occurring during the prehospital time interval may have a pro-
found effect on outcome. Indeed, our results reveal a strong,
independent association between mortality and blood pres-
sure measured in the field. This is remarkable, given the large
number of factors that potentially affect survival in patients
with TBI. It appears that the effectiveness of subsequent in-
terventions may be highly dependent on patients who are neu-
rologically viable being delivered to the trauma center so they
have the potential to benefit from subsequent specialized care.

One of the most striking aspects of the literature evaluat-
ing the association between blood pressure and TBI mortality
is the underlying assumption that there is a clinically rel-
evant threshold. Some might argue that this is merely an op-
erational reality inherent to the studies, that some level of hy-
potension must be chosen as a treatment threshold. However,
even if the threshold concept isn't always explicitly affirmed,
its use is so ubiquitous that, functionally, it is treated as a given
in the literature. In other words, there is a nearly universal con-
cept of the existence of a level of SBP that represents a cut point,
below which it is highly deleterious to drop.

However, the results of the current investigation seem to
provide a significant contrast to current thinking about the im-
plications of hypotension in the early care of patients with TBI.
Visually evaluating the plot of adjusted mortality risk vs SBP

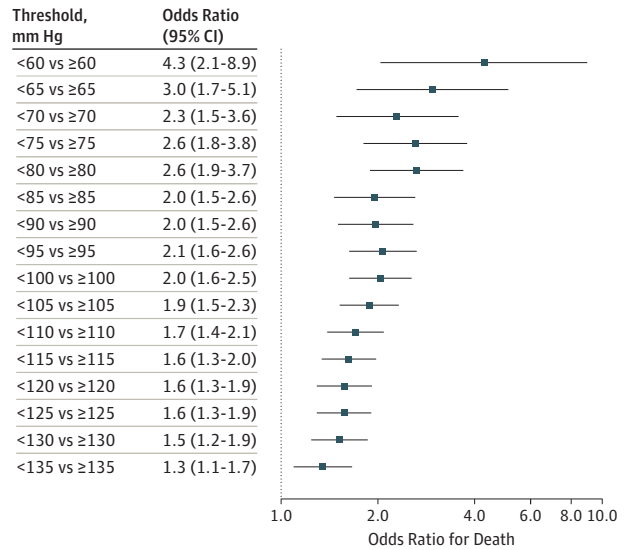Figure 2. Adjusted Probability of Death by Lowest Systolic Blood Pressure (SBP)
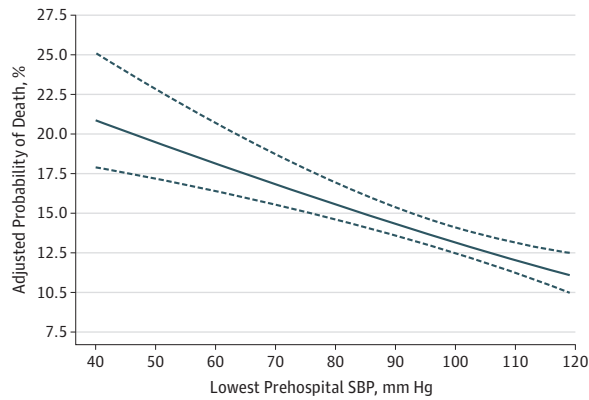
Adjusted probability of death shown over the range of 40 to 120 mm Hg. The rate shown is the marginal rate, in the sense that at any fixed value of SBP, the rate is the average of the predicted death rates for all patients in the data set with the SBP value changed to the fixed value and with values of all other covariates unchanged from the actual observed values. The dotted lines represent the pointwise 95% CIs.

Figure 3. Wide-Ranged Systolic Blood Pressure (SBP) Thresholds and Adjusted Odds Ratios of Death

Threshold, mm Hg	Odds Ratio (95% CI)
<60 vs ≥60	4.3 (2.1-8.9)
<65 vs ≥65	3.0 (1.7-5.1)
<70 vs ≥70	2.3 (1.5-3.6)
<75 vs ≥75	2.6 (1.8-3.8)
<80 vs ≥80	2.6 (1.9-3.7)
<85 vs ≥85	2.0 (1.5-2.6)
<90 vs ≥90	2.0 (1.5-2.6)
<95 vs ≥95	2.1 (1.6-2.6)
<100 vs ≥100	2.0 (1.6-2.5)
<105 vs ≥105	1.9 (1.5-2.3)
<110 vs ≥110	1.7 (1.4-2.1)
<115 vs ≥115	1.6 (1.3-2.0)
<120 vs ≥120	1.6 (1.3-1.9)
<125 vs ≥125	1.6 (1.3-1.9)
<130 vs ≥130	1.5 (1.2-1.9)
<135 vs ≥135	1.3 (1.1-1.7)

Odds Ratio for Death

The cohort of patients from the Excellence in Prehospital Injury Care study whose lowest prehospital SBP was between 40 and 200 mm Hg was dichotomized into "low" vs "not low" groups using various cut points in increments of 5 mm Hg. Logistic regression was used to estimate the odds ratio of death between the 2 groups, adjusting for factors shown in Table 2. Squares indicate estimated adjusted odds ratios, and error bars indicate 95% CIs.

(Figure 2) reveals a surprising finding—the absence of even a hint of a cut point at any level between 40 and 120 mm Hg. In addition, the mathematical expression of the data verifies this visual impression in that the association between SBP and the adjusted log odds of death is linear, with an adjusted odds ratio of 0.812 for mortality associated with a 10-mm Hg increase, regardless of the level being assessed. Thus, any 2 patients with an SBP difference of 10 mm Hg differ in their adjusted odds of death by 18.8%, which holds true across the entire SBP range. These results raise the possibility that, perhaps, no threshold exists in the sense that the concept is typically used. It appears that the threshold concept may have been artificially generated by investigations that, because of their small size, basically had no alternative but to deal with prehospital blood pressure dichotomously (ie, comparing low with not low). However, as this literature grew, the concept gained momentum and was incorporated into guidelines.

Another notable finding revealed by Figure 2 is the lack of a change in the slope even as the plot moves far to the right of the commonly applied definition for hypotension. This raises the possibility that clinically meaningful hypotension may not be as low as is currently thought for the injured brain. Indeed, despite the specifically recommended threshold, guidelines from the Brain Trauma Foundation also state that it is unclear what the threshold ought to be. Hence the explicit statement in the section on resuscitation end points: "The value of 90 mm Hg as a threshold for hypotension has been defined by blood pressure distributions for *normal* adults [emphasis added]. Thus, this is more a statistical than physiological finding."[5] Furthermore, the document goes on to forthrightly admit ambivalence about the recommended threshold: "Given the influence of cerebral perfusion pressure on outcome, it is possible that SBP higher than 90 mm Hg would be desirable during the prehospital and resuscitation phase, but no studies have been performed to corroborate this."[5] The lack of clar-

ity surrounding this issue led the guideline authors to give it high priority in the section on "Key Issues for Future Investigation." In the listing of recommended future research, the first topic is the identification of "the level of hypotension that correlates with poor outcome."[5]

A careful reading of the extant studies reflects the complexity of defining hypotension in the setting of TBI. In fact, the literature varies widely and contains reports that have used cut points as low as 79 mm Hg and as high as 120 mm Hg in adults.[7-9,11,14,15,17-22,26,28-36] Furthermore, the size and design of these studies preclude them from identifying "the" threshold, even if one actually exists. If previous prehospital studies had been larger, they would have been able to identify significant differences in outcomes using a wide range of potential thresholds, thereby revealing the arbitrary nature of choosing any one particular level.

To highlight this limitation in the current literature, we analyzed a broader cohort of patients in the EPIC database (SBP, 40-200 mm Hg) and dichotomized the cohort as "low" vs "not low" using various cut points in increments of 5 mm Hg. This yields the remarkable result that there is a statistically significant difference in the adjusted probability of death for thresholds as low as 60 mm Hg and as high as 135 mm Hg (**Figure 3**). In other words, one can pick any cut point throughout this range and obtain significant findings. Despite decades of assuming otherwise, it appears that the interaction between prehospital blood pressure and outcome may be physiologically continuous rather than dichotomous across a remarkably wide range. While it is hard to conceive of an approach to managing TBI that doesn't include some level of blood pressure that

requires treatment, it appears that the science that forms the basis for the current guidelines may require an entirely new way of thinking.

Limitations

This study has limitations. First, the design is observational. Thus, we cannot establish cause and effect relationships associated with the treatment of hypotension. For instance, these data do not prove that the therapeutic target for blood pressure should be higher than the current recommendations. However, they do highlight the great importance of perfusing the injured brain and that blood pressure is powerfully linked to outcome.[16,25,28] Furthermore, these results do appear to support the statements in the TBI guidelines cautioning that the current recommendations may allow blood pressure to drop too low before intervening. A related concern is that we have not accounted for treatment of hypotension in the model. The parent study is designed specifically to identify the influence of treatment on outcomes using a controlled before-after system design, and the Analysis Plan[27] includes only an interim analysis (completed) and a final analysis (scheduled) and does not allow for multiple looks at the interventional data. Thus, to prevent any encroachment on the main study hypotheses, we are deferring all evaluations of treatment effects until the final analysis. Second, this evaluation does not inform questions associated with blood pressure management after the early resuscitative phase of care. This is true for several reasons; ongoing pressure monitoring in neurocritical care uses mean arterial pressure and cerebral perfusion pressure rather than SBP, and the prehospital management of blood pressure

focuses solely on treating hypotension.[4] Thus, the implications of our study cannot be used to inform issues associated with ongoing intensive care unit management or controversies, such as enhancing/optimizing perfusion.[56,57] Third, there were some missing data. However, for a prehospital study, the rate of missing data is extremely low (eg, 1.8% missing data for SBP; no missing data for mortality). Fourth, the database contains only those SBPs that were documented by EMS. Thus, we cannot know for sure that the reported measurements reflected the actual lowest SBP. Finally, there is no way to independently verify the accuracy of blood pressure measurements. However, this is true of essentially all EMS investigations.[58] One great advantage of the EPIC TBI Study is that the data team abstracts the PCRs directly and comprehensively. This level of scrutiny and consistency of data access is rare in prehospital research.[58]

Conclusions

In a statewide, multisystem analysis of patients with major TBI, we found a linear association between the lowest prehospital SBP and the severity-adjusted probability of death across an exceptionally wide range. This suggests that there may not be a clinically meaningful threshold. Furthermore, for the injured brain, physiologically detrimental hypotension may occur at significantly higher levels than current guidelines suggest. These findings highlight the need for specific trials comparing various blood pressure treatment thresholds well above the classic 90 mm Hg.

REFERENCES

1. Bell JM, Brelding M, Jenkins EL, Haarbauer-Krupa J. *Report to Congress: Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation*. Atlanta, GA: US Centers for Disease Control and Prevention; 2014.

2. Finkelstein E, Corso PS, Miller TR. The incidence and economic burden of injuries in the United States. *J Epidemiol Community Health*. 2007;61(10): 926.

3. Adelson PD, Bratton SL, Carney NA, et al; American Association for Surgery of Trauma; Child Neurology Society; International Society for Pediatric Neurosurgery; International Trauma Anesthesia and Critical Care Society; Society of Critical Care Medicine; World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents: chapter 1: introduction. *Pediatr Crit Care Med*. 2003;4(3 suppl):S2-S4.

4. Badjatia N, Carney N, Crocco TJ, et al. Guidelines for prehospital management of traumatic brain injury 2nd edition. *Prehosp Emerg Care*. 2008;12 (suppl 1):S1-S52.

5. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2007;24(suppl 1):S1-S106.

6. Kochanek PM, Carney N, Adelson PD, et al; American Academy of Pediatrics-Section on Neurological Surgery; American Association of Neurological Surgeons/Congress of Neurological Surgeons; Child Neurology Society; European Society of Pediatric and Neonatal Intensive Care; Neurocritical Care Society; Pediatric Neurocritical Care Research Group; Society of Critical Care Medicine; Paediatric Intensive Care Society UK; Society for Neuroscience in Anesthesiology and Critical Care; World Federation of Pediatric Intensive and Critical Care Societies. Guidelines for the acute medical management of severe traumatic brain injury in infants, children, and adolescents: second edition. *Pediatr Crit Care Med*. 2012;13(suppl 1):S1-S82.

7. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. 1993; 34(2):216-222.

8. Fearnside MR, Cook RJ, McDougall P, McNeil RJ. The Westmead Head Injury Project outcome in severe head injury: a comparative analysis of pre-hospital, clinical and CT variables. *Br J Neurosurg*. 1993;7(3):267-279.

9. Shutter LA, Narayan RK. Blood pressure management in traumatic brain injury. *Ann Emerg Med*. 2008;51(3 suppl):S37-S38.

10. Jankowitz BT, Adelson PD. Pediatric traumatic brain injury: past, present and future. *Dev Neurosci*. 2006;28(4-5):264-275.

11. Gentleman D. Causes and effects of systemic complications among severely head injured patients transferred to a neurosurgical unit. *Int Surg*. 1992;77(4):297-302.

12. Pigula FA, Wald SL, Shackford SR, Vane DW. The effect of hypotension and hypoxia on children with severe head injuries. *J Pediatr Surg*. 1993;28(3): 310-314.

13. Kokoska ER, Smith GS, Pittman T, Weber TR. Early hypotension worsens neurological outcome in pediatric patients with moderately severe head trauma. *J Pediatr Surg*. 1998;33(2):333-338.

14. Miller JD, Becker DP. Secondary insults to the injured brain. *J R Coll Surg Edinb*. 1982;27(5):292-298.

15. Barton CW, Hemphill JC, Morabito D, Manley G. A novel method of evaluating the impact of secondary brain insults on functional outcomes in traumatic brain-injured patients. *Acad Emerg Med*. 2005;12(1):1-6.

16. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg*. 2001;136(10):1118-1123.

17. Price DJ, Murray A. The influence of hypoxia and hypotension on recovery from head injury. *Injury*. 1972;3(4):218-224.

18. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma*. 1996;40(5):764-767.

19. Carrel M, Moeschler O, Ravussin P, Favre JB, Boulard G. Prehospital air ambulance and systemic secondary cerebral damage in severe craniocerebral injuries [in French]. *Ann Fr Anesth Reanim*. 1994;13(3):326-335.

20. Kohi YM, Mendelow AD, Teasdale GM, Allardice GM. Extracranial insults and outcome in patients with acute head injury: relationship to the Glasgow Coma Scale. *Injury*. 1984;16(1):25-29.

21. Rose J, Valtonen S, Jennett B. Avoidable factors contributing to death after head injury. *Br Med J*. 1977;2(6087):615-618.

22. Chesnut RM, Ghajar J, Maas AIR, et al. Part 2: early indicators of prognosis in severe traumatic brain injury. *J Neurotrauma*. 2009;17(6-7):555. doi: 10.1089/neu.2000.17.555

23. Hill DA, Abraham KJ, West RH. Factors affecting outcome in the resuscitation of severely injured patients. *Aust N Z J Surg*. 1993;63(8):604-609.

24. Chesnut RM, Marshall SB, Piek J, Blunt BA, Klauber MR, Marshall LF. Early and late systemic hypotension as a frequent and fundamental source of cerebral ischemia following severe brain injury in the Traumatic Coma Data Bank. *Acta Neurochir Suppl (Wien)*. 1993;59:121-125.

25. McHugh GS, Engel DC, Butcher I, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24(2):287-293.

26. Miller JD, Sweet RC, Narayan R, Becker DP. Early insults to the injured brain. *JAMA*. 1978;240 (5):439-442.

27. Spaite DW, Bobrow BJ, Stolz U, et al. Evaluation of the impact of implementing the emergency medical services traumatic brain injury guidelines in Arizona: the Excellence in Prehospital Injury Care (EPIC) study methodology. *Acad Emerg Med*. 2014; 21(7):818-830.

28. Berry C, Ley EJ, Bukur M, et al. Redefining hypotension in traumatic brain injury. *Injury*. 2012; 43(11):1833-1837.

29. 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(1 suppl):S59-S66. http://thejns .org/doi/abs/10.3171/sup.1991.75.1s.0s59. Accessed February 15, 2016.

30. Chi JH, Knudson MM, Vassar MJ, et al. Prehospital hypoxia affects outcome in patients with traumatic brain injury: a prospective multicenter study. *J Trauma*. 2006;61(5):1134-1141.

31. Bernard SA, Nguyen V, Cameron P, et al. Prehospital rapid sequence intubation improves functional outcome for patients with severe traumatic brain injury: a randomized controlled trial. *Ann Surg*. 2010;252(6):959-965.

32. Walia S, Sutcliffe AJ. The relationship between blood glucose, mean arterial pressure and outcome after severe head injury: an observational study. *Injury*. 2002;33(4):339-344.

33. Cooke RS, McNicholl BP, Byrnes DP. Use of the Injury Severity Score in head injury. *Injury*. 1995; 26(6):399-400.

34. Graham DI, Adams JH. Ischaemic brain damage in fatal head injuries. *Lancet*. 1971;1(7693):265-266.

35. Edwards M, Ley E, Mirocha J, Hadjibashi AA, Margulies DR, Salim A. Defining hypotension in moderate to severely injured trauma patients:

raising the bar for the elderly. *Am Surg*. 2010;76 (10):1035-1038.

36. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. 2007;24(2):294-302.

37. Baker SP, O'Neill B, Haddon W Jr, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14(3):187-196.

38. Rutledge R, Osler T, Emery S, Kromhout-Schiro S. The end of the Injury Severity Score (ISS) and the Trauma and Injury Severity Score (TRISS): ICISS, an International Classification of Diseases, Ninth Revision-based prediction tool, outperforms both ISS and TRISS as predictors of trauma patient survival, hospital charges, and hospital length of stay. *J Trauma*. 1998;44(1):41-49.

39. Osler TM, Cohen M, Rogers FB, Camp L, Rutledge R, Shackford SR. Trauma registry injury coding is superfluous: a comparison of outcome prediction based on trauma registry International Classification of Diseases-Ninth Revision (ICD-9) and hospital information system ICD-9 codes. *J Trauma*. 1997;43(2):253-256.

40. Hannan EL, Farrell LS, Gorthy SF, et al. Predictors of mortality in adult patients with blunt injuries in New York State: a comparison of the Trauma and Injury Severity Score (TRISS) and the International Classification of Disease, Ninth Revision-based Injury Severity Score (ICISS). *J Trauma*. 1999;47(1):8-14.

41. Rutledge R, Hoyt DB, Eastman AB, et al. Comparison of the Injury Severity Score and ICD-9 diagnosis codes as predictors of outcome in injury: analysis of 44,032 patients. *J Trauma*. 1997;42(3):477-487, 487-489.

42. MacKenzie EJ, Steinwachs DM, Shankar B. Classifying trauma severity based on hospital discharge diagnoses. Validation of an ICD-9CM to AIS-85 conversion table. *Med Care*. 1989;27(4): 412-422.

43. MacKenzie EJ, Garthe EA. Compatibility of the ICD-9-CM and AIS-80: an update. *Am Assoc Auto Med Q J*. 1983;5:25-27.

44. Glance LG, Osler TM, Mukamel DB, Meredith W, Wagner J, Dick AW. TMPM-ICD9: a trauma mortality prediction model based on ICD-9-CM codes. *Ann Surg*. 2009;249(6):1032-1039.

45. Wood SN. *Generalized Additive Models: An Introduction With R*. Boca Raton, FL: Chapman & Hall/CRC; 2006.

46. The R Foundation. A language and environment for statistical computing. http://www .R-project.org/. Accessed October 5, 2015.

47. Wood SN. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. *J R Stat Soc B*. 2011;73:3-36. doi:10.1111/j.1467-9868.2010 .00749.x

48. Wood SN. On p-values for smooth components of an extended generalized additive model. *Biometrika*. 2013;100(1):221-228. doi:10.1093/biomet /ass048

49. Silverston P. Pulse oximetry at the roadside: a study of pulse oximetry in immediate care. *BMJ*. 1989;298(6675):711-713.

50. Cooke RS, McNicholl BP, Byrnes DP. Early management of severe head injury in Northern Ireland. *Injury*. 1995;26(6):395-397.

51. Bruns B, Gentilello L, Elliott A, Shafi S. Prehospital hypotension redefined. *J Trauma*. 2008;65(6):1217-1221.

52. Hasler RM, Nuesch E, Jüni P, Bouamra O, Exadaktylos AK, Lecky F. Systolic blood pressure below 110 mm Hg is associated with increased mortality in blunt major trauma patients: multicentre cohort study. *Resuscitation*. 2011;82(9): 1202-1207.

53. Hasler RM, Nüesch E, Jüni P, Bouamra O, Exadaktylos AK, Lecky F. Systolic blood pressure below 110 mmHg is associated with increased mortality in penetrating major trauma patients: multicentre cohort study. *Resuscitation*. 2012;83 (4):476-481.

54. Eastridge BJ, Salinas J, McManus JG, et al. Hypotension begins at 110 mm Hg: redefining "hypotension" with data. *J Trauma*. 2007;63(2): 291-297.

55. Edelman DA, White MT, Tyburski JG, Wilson RF. Post-traumatic hypotension: should systolic blood pressure of 90-109 mmHg be included? *Shock*. 2007;27(2):134-138.

56. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med*. 1999;27(10): 2086-2095.

57. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *J Neurosurg*. 2005;102(2):311-317.

58. Spaite DW, Valenzuela TD, Meislin HW. Barriers to EMS system evaluation: problems associated with field data collection. *Prehosp Disaster Med*. 1993;8(suppl 1):S35-S40.