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Traumatic Brain Injury and Blood Pressure -- A Paradigm Shift

Sue Hughes | December 28, 2016

For patients with acute traumatic brain injury (TBI), the higher the prehospital systolic blood pressure the better — a finding that challenges the conventional wisdom that there is a clinically meaningful threshold, new research suggests.

The study — the largest to date to look at this issue — found a linear association between lowest prehospital systolic blood pressure and severity-adjusted probability of mortality across the whole range of pressures between 40 and 120 mmHg.

The researchers note these findings, which were published online December 7 in *JAMA Surgery*, show that for the injured brain, physiologically detrimental hypotension may occur at significantly higher blood pressure levels than current guidelines advise.

The researchers note the current study "is unique in both its size and its access to detailed prehospital data" and that their findings "highlight the need for specific trials comparing various blood pressure treatment thresholds well above the classic 90 mmHg."

"This data really changes how we think about blood pressure in patients with a serious brain injury in an acute setting. This is a major paradigm shift," study coauthor, Joshua Gaither, MD, associate professor of emergency medicine, College of Medicine, University of Arizona, Tucson, told *Medscape Medical News*.

"Historically we have been taught that when considering blood pressure in the setting of acute traumatic brain injury there is a magic number of 90 and as soon as the pressure is below 90 mmHg then damage will occur.

"We show in this study that this is not the case and for patients with systolic pressures anywhere between 40 and 120 mmHg, mortality rises as blood pressure falls. There is no magic cutoff. This suggests we need to treat blood pressure aggressively across a larger spectrum than previously thought," he added.

"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," the authors write.

Dr Gaither explained that TBI causes two types of damage: (1) the primary injury — the damage to the brain when the head is hit — which is thought to be irreversible, and (2) secondary damage caused by the injured brain being extra susceptible to secondary insults, such as low blood pressure.

He noted that current guidelines, which recommend maintaining blood pressure above 90 mmHg in these patients, are based on several small studies that were not big enough to look at the whole spectrum of blood pressure and so instead focused on comparing two groups above and below the 90-mmHg threshold.

"Our study, however, was much larger — we had prehospital blood pressure readings for many thousands of patients so we could look at it as a continuous variable, and we saw a continuous relationship between blood pressure and mortality — the lower the blood pressure the higher the mortality right up to a systolic of 120mmHg.

"It doesn't matter whether we are comparing systolic pressures of 120 and 110 or 110 and 100 or 100 and 90 — each of these 10-mmHg reductions was associated with an 18% increase in mortality," he added.

He cautioned, however, about making definitive recommendations on treatment targets based on this observational study.

"Because this is observational data we cannot say for sure that raising blood pressure will reduce mortality in these

patients. But it does show that the lower the blood pressure, the more likely a patient is to die. We really need a randomized trial to investigate whether more aggressive treatment with fluids does make a difference in terms of mortality in patients at all levels of blood pressure."

In the meantime, Dr Gaither suggests that keeping pressures up as high as possible up to 120 mmHg is a reasonable goal. "At present a paramedic may see a patient with a traumatic brain injury and a blood pressure of 110 mmHg and think that is okay, but our study suggests it will still be beneficial to treat such a patient with IV [intravenous] fluids to keep their pressure up."

"After this data, we have been advising our paramedics to give IV fluids to any patient whose blood pressure is trending down. If a patient has a systolic pressure of 120 mmHg then a few minutes later it has reduced to 110 mmHg, then we would say that patient is a candidate for aggressive IV fluids."

For the study, the researchers analyzed information from a large prehospital database established as a part of the Excellence in Prehospital Injury Care (EPIC) Traumatic Brain Injury Study to determine the association between systolic pressure and probability of death, adjusting for significant/important confounders. The study included 3844 patients age 10 years and older with moderate or severe TBI and a prehospital systolic pressure between 40 and 119 mmHg.

Results revealed a linear decreasing association between systolic pressure and adjusted probability of death across the entire blood pressure range. Each 10-point increase of systolic pressure was associated with a decrease in the adjusted odds of death of 18.8%.

The researchers point out that a key reason for evaluating the effect of blood pressure measured before hospital arrival is that the injured brain is so highly sensitive to changes in perfusion and the timeframe during which neuronal damage begins is so short.

"It is well established that secondary brain injury is initiated by even brief periods of compromised blood flow. Thus, decreased perfusion occurring during the prehospital time interval may have a profound effect on outcome," they write.

JAMA Surg. Published online December 7, 2016. Abstract

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Cite this article: Traumatic Brain Injury and Blood Pressure -- A Paradigm Shift. *Medscape*. Dec 28, 2016.

JAMA Surgery | Original Investigation

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

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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.

JAMA Surg. doi:10.1001/jamasurg.2016.4686
Published online December 7, 2016.

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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.

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.

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 patients 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 $\alpha = .05$.

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. (%)		*P* Value[b]
	Alive (n = 3316)	Dead (n = 528)	
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)	>.99
Yes	785 (23.7)	120 (22.7)	
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)	<.001
16-24	1038 (31.3)	19 (3.6)	
≥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)	<.001
Yes	282 (8.5)	162 (30.7)	
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.

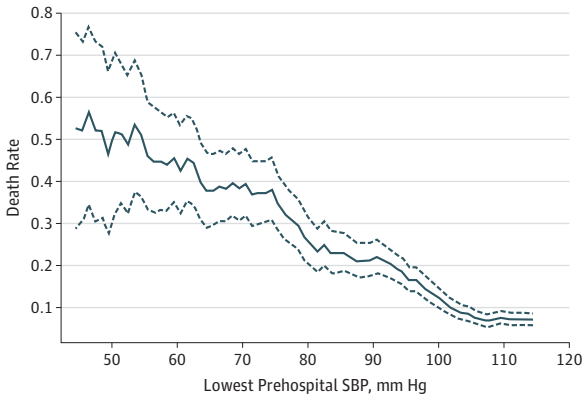
[a] Trauma center was also highly significant (not shown; *P* < .001).

[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.

under the curve is 0.705, and there is no cut point that gives satisfactory levels of both sensitivity and specificity to indicate 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 evaluated general trauma populations (ie, were not specific to patients 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 hospital arrival is because the injured brain is so highly sensitive to changes in perfusion, and the timeframe during which neuronal damage begins is so short. It is well established that secondary brain injury is initiated by even brief periods of compromised blood flow.[4,5,11-13,17,20,27] Thus, decreased perfusion occurring during the prehospital time interval may have a profound effect on outcome. Indeed, our results reveal a strong, independent association between mortality and blood pressure 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 interventions may be highly dependent on patients who are neurologically 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 evaluating the association between blood pressure and TBI mortality is the underlying assumption that there is a clinically relevant threshold. Some might argue that this is merely an operational reality inherent to the studies, that some level of hypotension 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 concept 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 implications of hypotension in the early care of patients with TBI. Visually evaluating the plot of adjusted mortality risk vs SBP

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

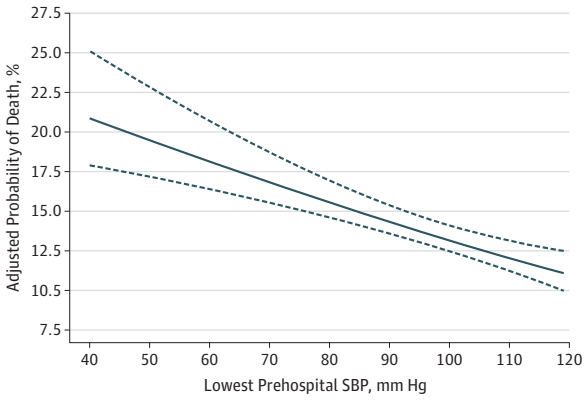
Covariate[a]	Odds Ratio (95% CI)[b]	*P* Value
Male		
No	1 [Reference]	.54
Yes	0.91 (0.67-1.23)	
Race		
African American	1 [Reference]	
Asian	1.09 (0.22-5.37)	
American Indian/Alaska Native	1.02 (0.36-2.88)	.75
White	1.29 (0.53-3.11)	
Other	1.19 (0.42-3.36)	
Unknown	2.89 (0.66-12.75)	
Hispanic ethnicity		
No	1 [Reference]	.06
Yes	0.61 (0.40-0.92)	
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]	<.001
16-24	2.63 (0.91-7.60)	
≥25	15.96 (6.00-42.50)	
Prehospital hypoxia		
No	1 [Reference]	<.001
Yes	1.89 (1.35-2.65)	
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.

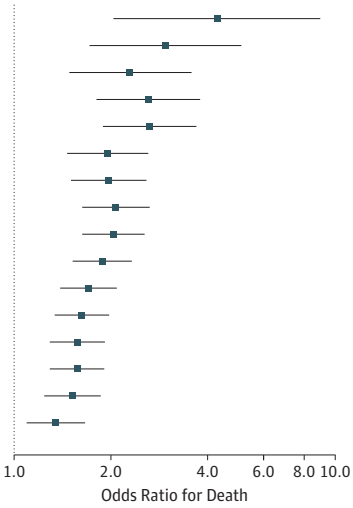
Figure 2. Adjusted Probability of Death by Lowest Systolic Blood Pressure (SBP)



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)



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 clarity 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.

ARTICLE INFORMATION

Accepted for Publication: September 20, 2016.

Published Online: December 7, 2016. doi:10.1001/jamasurg.2016.4686

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Statistical analysis: Hu, Chikani, Sherrill.
Obtained funding: Spaite, Bobrow, Denninghoff, Viscusi, Mullins.
Administrative, technical, or material support: Spaite, Bobrow, Barnhart, Gaither, Mullins.

Conflict of Interest Disclosures: Drs Spaite, Bobrow, Sherrill, Gaither, Denninghoff, Viscusi, and Adelson, Ms Chikani, and Mr Barnhart have received support from the National Institutes of Health via their university/academic appointments. No other disclosures were reported.

Funding/Support: Research reported in this article was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award R01NS071049.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Previous Presentations: Presented in part to the National Association of EMS Physicians; January 16, 2014; Tucson, Arizona; and to the International Brain Injury Association; March 19, 2014; San Francisco, California.

Disclaimer: Research reported in this publication was supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under Award Number R01NS071049. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Information: This is an observational, noninterventional analysis of a subset of the data in the Excellence in Prehospital Injury Care Traumatic Brain Injury Study. The parent study, while not a randomized clinical trial, is registered at ClinicalTrials.gov (NCT01339702).

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