# Association of Out-of-Hospital Hypotension Depth and Duration With Traumatic Brain Injury Mortality

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**Study objective:** Out-of-hospital hypotension has been associated with increased mortality in traumatic brain injury. The association of traumatic brain injury mortality with the depth or duration of out-of-hospital hypotension is unknown. We evaluated the relationship between the depth and duration of out-of-hospital hypotension and mortality in major traumatic brain injury.

**Methods:** We evaluated adults and older children with moderate or severe traumatic brain injury in the preimplementation cohort of Arizona's statewide Excellence in Prehospital Injury Care study. We used logistic regression to determine the association between the depth-duration dose of hypotension (depth of systolic blood pressure <90 mm Hg integrated over duration [minutes] of hypotension) and odds of inhospital death, controlling for significant confounders.

**Results:** There were 7,521 traumatic brain injury cases included (70.6% male patients; median age 40 years [interquartile range 24 to 58]). Mortality was 7.8% (95% confidence interval [CI] 7.2% to 8.5%) among the 6,982 patients without hypotension (systolic blood pressure ≥90 mm Hg) and 33.4% (95% CI 29.4% to 37.6%) among the 539 hypotensive patients (systolic blood pressure <90 mm Hg). Mortality was higher with increased hypotension dose: 0.01 to 14.99 mm Hg-minutes 16.3%; 15 to 49.99 mm Hg-minutes 28.1%; 50 to 141.99 mm Hg-minutes 38.8%; and greater than or equal to 142 mm Hg-minutes 50.4%. $Log_2$ (the logarithm in base 2) of hypotension dose was associated with traumatic brain injury mortality (adjusted odds ratio 1.19 [95% CI 1.14 to 1.25] per 2-fold increase of dose).

**Conclusion:** In this study, the depth and duration of out-of-hospital hypotension were associated with increased traumatic brain injury mortality. Assessments linking out-of-hospital blood pressure with traumatic brain injury outcomes should consider both depth and duration of hypotension. [Ann Emerg Med. 2017;70:522-530.]

Please see page 523 for the Editor's Capsule Summary of this article.



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SEE EDITORIAL, 531.

## INTRODUCTION

### Background

During the out-of-hospital and early inhospital resuscitative care of traumatic brain injury, hypotension is associated with increased mortality.[1-31] The literature supporting this concept is based on small series with only limited emergency medical services (EMS) data that characterized hypotension dichotomously (<90 or ≥90 mm Hg).[3,16,21,28-31] Thus, very little is known about the effect of the depth of hypotension. Another limitation of these studies is the absence of repeated blood pressure measurements. Because of this, there are no descriptions of the depth and duration of out-of-hospital hypotension in traumatic brain injury patients, to our knowledge.

### Importance

Hypotension is believed to reduce cerebral perfusion pressure to the injured brain.[4,6,11,26,32] Although not yet characterized, the extent of brain injury is likely linked to both the depth and duration of hypotensive episodes. Quantification of hypotension dose could offer an additional therapeutic target for refining out-of-hospital traumatic brain injury care.

### Goals of This Investigation

The objective of this study was to determine the association of out-of-hospital hypotension depth and duration with traumatic brain injury mortality.

**Editor's Capsule Summary**

*What is already known on this topic*

Out-of-hospital hypotension (systolic blood pressure <90 mm Hg) is associated with poor traumatic brain injury outcomes.

*What question this study addressed*

Are out-of-hospital hypotension duration and depth associated with traumatic brain injury outcomes?

*What this study adds to our knowledge*

In this study of 7,521 traumatic brain injuries in Arizona, each 2-fold increase in out-of-hospital hypotension dose (hypotension depth integrated across exposure time) was associated with a 20% increase in mortality.

*How this is relevant to clinical practice*

Traumatic brain injury research and clinical strategies should consider both hypotension depth and duration.

## MATERIALS AND METHODS

### Setting

Details of the Excellence in Prehospital Injury Care (EPIC) study have been described previously.[33-35] The study is evaluating the effect of implementing the EMS traumatic brain injury guidelines[36-39] in patients with major traumatic brain injury throughout Arizona, using a before-after, controlled, multisystem, observational design.[33] We obtained the necessary regulatory approvals for the study 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 constitutes human subjects research and have approved the publication of deidentified data.

### Selection of Participants

The patients in this evaluation were in the preimplementation cohort of the EPIC study (treated by an EMS agency between January 1, 2007, and March 31, 2014, without receiving study interventions). In this secondary analysis, we included patients aged 10 years or older with physical trauma who had trauma center diagnoses consistent with traumatic brain injury (isolated or multisystem trauma) and met at least one of the following definitions for moderate or severe ("major") traumatic brain injury: Centers for Disease Control and Prevention Barell Matrix-type 1, *International Classification of Diseases, Ninth Revision (ICD-9)* head region severity score greater than or equal to 3, and Abbreviated Injury Score greater than or equal to 3 for the head region.[33,34] We excluded cases with age younger than 10 years; interfacility transfer (or unknown); any systolic blood pressure greater than 200 mm Hg; systolic blood pressure 0, indicating traumatic arrest; missing important confounders or risk adjusters; and zero or only one recorded out-of-hospital systolic blood pressure with documented time between 6 hours before emergency department (ED) arrival and 10 minutes after ED arrival (excludes extreme or obviously inaccurate time data). The patients with only one timed, recorded systolic blood pressure measurement were excluded because at least 2 are needed to establish depth-duration dose.

### Methods of Measurement

The EPIC database contains the subset of patients from the Arizona State Trauma Registry meeting EPIC study criteria for major traumatic brain injury (defined above).[33-35] The registry has detailed inhospital data on all trauma patients taken to the state-designated Level I trauma centers in Arizona. All cases from the registry that meet the EPIC study criteria are entered into the database. Each participating EMS agency receives the list of study patients cared for in their system. The cases are matched by incident date, name, and other identifiers. Either scanned copies (paper-based patient care records) or electronic data files are sent to the EPIC data center. Database personnel then comprehensively abstract and enter the data, yielding an extensive, linked data set that includes both EMS and trauma center data. The processes of case identification, linkage, data entry, and data quality management have been reported in detail.[33] We have enrolled more than 20,000 cases into the EPIC study, and the Arizona State Trauma Registry and EMS data linkage rate is well over 90%.

We included all systolic blood pressure measurements with a recorded value and time. When multiple agencies cared for a given patient, we combined all available measurements. Patients who had at least 2 timed systolic blood pressure measurements were included in this analysis. We excluded cases with only one recorded systolic blood pressure measurement because the duration of hypotension could not be accurately estimated.

Our strategy for determining hypotension dosage was modeled after pharmacokinetic techniques.[40] We defined hypotension depth duration as the total amount of systolic hypotension (systolic blood pressure <90 mm Hg)

accumulated during a given time. Hypotensive depth referred to the difference between 90 mm Hg and the measured value. Duration referred to the total time during which systolic blood pressure was less than 90 mm Hg. To calculate the depth-duration dose, we linked consecutive systolic blood pressure measurements over time, calculating hypotension dose as the integrated "area under the curve" for values less than 90 mm Hg (Figure 1). In situations with multiple separate hypotensive episodes, we added the integrated values from all hypotensive segments (Figure 2).

### Outcome Measures

The primary outcome was survival to hospital discharge.[33] Deaths that occurred after hospital discharge were not included in the analysis.

### Primary Data Analysis

We determined traumatic brain injury mortality for the cohort and the quartile of hypotension dose. We then examined the association between mortality and dose by logistic regression, adjusting for potential confounders. Age, sex, race, ethnicity, Injury Severity Score, and head region injury score (*ICD-9* matched to Abbreviated Injury Score)[41-43] were included a priori in the model (because they have been used nearly universally in trauma risk adjustment). Trauma type (blunt versus penetrating), payment source, and treating trauma center were included because they have often been confounders in trauma outcome studies[44,45] and were found to be significant covariates in previous EPIC reports.[34,35]

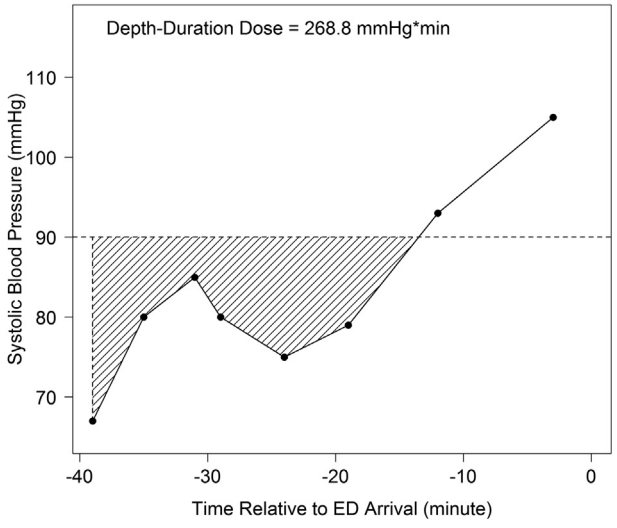


**Figure 1.** Depth-duration dose plot from a study patient. Depth-duration dose=total area of the shaded region under 90 mm Hg. When the dose is calculated, if either the first (as in this case) or last recorded SBP is a hypotensive value, the shaded region is closed by a vertical line passing through this point.

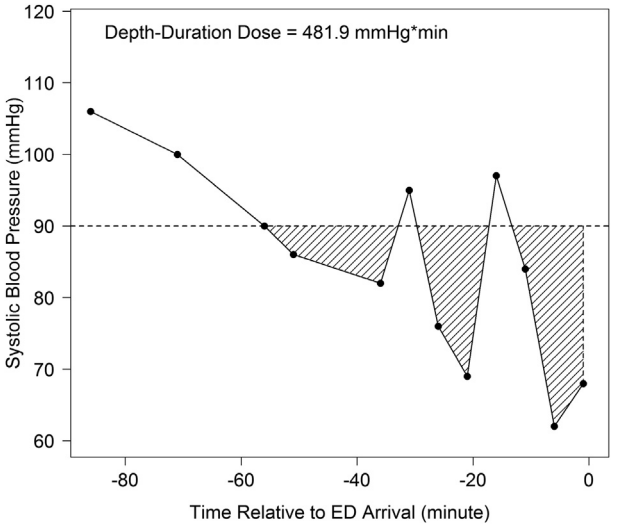


**Figure 2.** Depth-duration dose plot from a study patient with multiple hypotensive episodes. Depth-duration dose=total area of the shaded region under 90 mm Hg. When the dose is calculated, if either the first or last (as in this case) recorded SBP is a hypotensive value, the shaded region is closed by a vertical line passing through this point. This case shows a patient with 3 separate hypotensive episodes in which the total dose is the sum of the AUC from all of the shaded regions.

Because of the skewed distribution of hypotension dose, we log-transformed hypotension dose ($\log_2$[dose+1]). This approach yielded a value of 0 for patients without hypotension and positive values for hypotensive cases. The effects of the $\log_2$ hypotension dose and age in the regression were fitted nonparametrically with penalized thin-plate regression splines through the generalized additive model,[46] with the smoothing parameter chosen to optimize the Akaike information criterion. Nested models were compared with an analysis of deviance table. We assessed the fitted model by deviance residual plots and the area under the receiver operating characteristic curve (AUC) with 95% confidence interval (CI) obtained by the DeLong method.[47] We checked for collinearity with variance inflation factors for the parametric terms and concurvity for the nonparametric term. Mixed-effect models were used to assess the effect of the correlation of subjects treated by the same trauma center.

We evaluated the predictive power of the hypotension dose by first fitting a logistic regression model for survival with demographic variables as predictors (model 1), then adding the binary hypotensive indicator (<90 or ≥90 mm Hg) as another predictor (model 2), and then adding dose ($\log_2$[hypotension dose+1]) (model 3). The AUC was estimated for each model. We further evaluated predictive power by comparing different models, using the

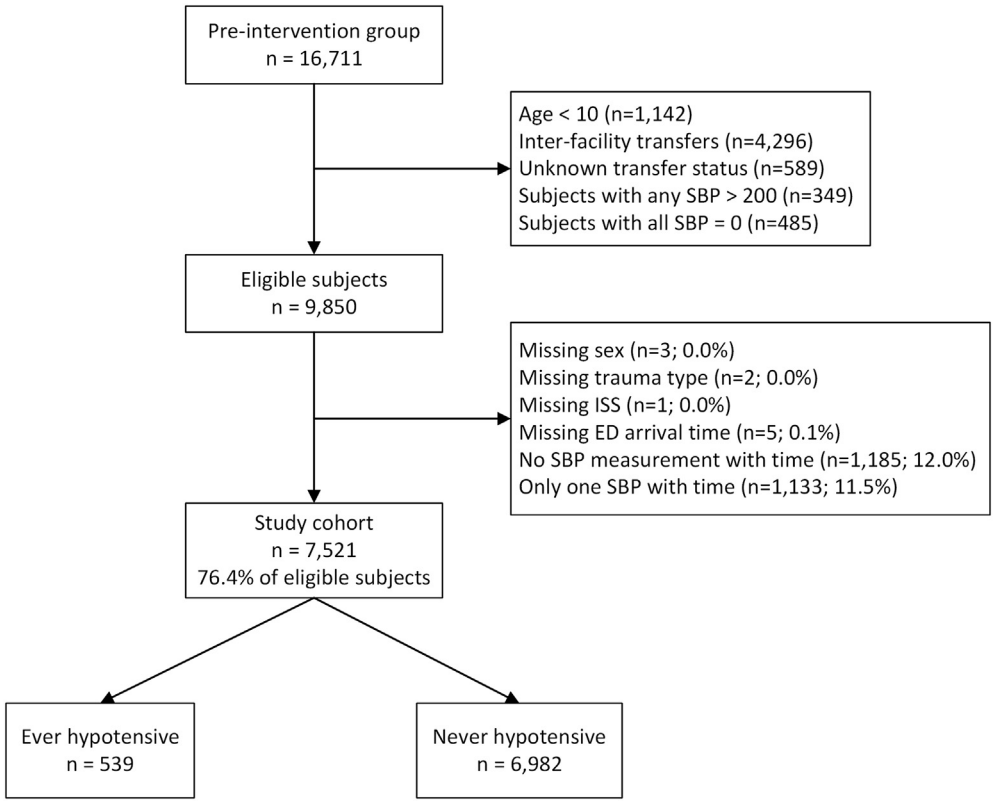


**Figure 3.** Case inclusion/exclusion flow chart. *SBP*, Systolic blood pressure; *ISS*, Injury Severity Score.

continuous net reclassification improvement,[48] with 95% CI estimated by the bootstrap method.

We used the software environment R for the analysis[49] and the R package mgcv[46,50] for the generalized additive model.

## RESULTS

Among 16,711 traumatic brain injury subjects, we included 7,521 in the analysis (Figure 3). Median age was 40 years (interquartile range 24 to 57), 70.6% were men, and overall mortality was 9.6% (95% CI 9.0% to 10.3%). In the study group, 539 patients (7.2%) had hypotension. Among patients with no hypotension, 7.8% died (95% CI 7.2% to 8.5%) compared with 33.4% (95% CI 29.4% to 37.6%) in the group with at least one hypotensive episode. Demographics and patient characteristics are shown in Table 1 (by hypotension status) and Appendix E1, available online at http://www.annemergmed.com (by survival status). Figure 4 shows the distribution of depth, duration, and dose among the 539 hypotensive patients. All factors associated with hypotension status were also associated with risk of death (trauma type, head region injury score, Injury Severity Score, and out-of-hospital hypoxia), whereas age and payment source were associated with death but not hypotension status. As with previous reports, risk-adjusted outcomes varied among trauma centers.[44,45] Thus, we adjusted for it in the model.

The unadjusted probability of death increased with higher hypotension dose (Figure 5). We used logistic regression to examine the association between $\log_2$ dose and the risk of death, controlling for potential confounders, with the effects of the continuous variables ($\log_2$ dose and age) modeled as nonparametric functions. We observed a monotonically increasing linear relationship between $\log_2$ dose and log odds of death (adjusted odds ratio [OR]=1.19; 95% CI 1.14 to 1.25) per 2-fold hypotension dose increase) (Table 2, Figure 6).

Deviance residual plots did not indicate any deviation from the model assumptions. The effect of dose (after transformation), when fitted as a nonparametric function, was not statistically different from a simple linear function. The AUC was estimated to be 0.952 (95% CI 0.945 to 0.958), indicating a high discriminative ability of the model. No multicollinearity was detected in the covariates.

As a sensitivity analysis, random trauma center effects were included in the model (instead of fixed effects) to explore the potential correlation among subjects treated by the same trauma center. The differences were minimal,

**Table 1.** Patient characteristics by hypotension status.

| Group | Never Hypotensive*† | Ever Hypotensive*† |
|---|---|---|
| No. of subjects | 6,982 | 539 |
| Age, y | 40 (24–58) | 37 (23–55) |
| **Male patient** | | |
| No | 2,047 (29.3) | 161 (29.9) |
| Yes | 4,935 (70.7) | 378 (70.1) |
| **Race** | | |
| Black | 234 (3.4) | 10 (1.9) |
| Asian | 68 (1) | 8 (1.5) |
| American Indian/Alaska Native | 388 (5.6) | 39 (7.2) |
| White | 5,373 (77) | 412 (76.4) |
| Other | 843 (12.1) | 59 (10.9) |
| Unknown | 76 (1.1) | 11 (2) |
| **Hispanic** | | |
| No | 5,256 (75.3) | 400 (74.2) |
| Yes | 1,512 (21.7) | 114 (21.2) |
| Unknown | 214 (3.1) | 25 (4.6) |
| **Payer** | | |
| Private | 2,593 (37.1) | 196 (36.4) |
| AHCCCS/Medicaid | 1,805 (25.9) | 154 (28.6) |
| Medicare | 1,062 (15.2) | 64 (11.9) |
| Self-pay | 1,084 (15.5) | 84 (15.6) |
| Other | 299 (4.3) | 26 (4.8) |
| Unknown | 139 (2) | 15 (2.8) |
| **Trauma type** | | |
| Blunt | 6,685 (95.7) | 463 (85.9) |
| Penetrating | 297 (4.3) | 76 (14.1) |
| **Head Region Severity Score *(ICD-9)*** | | |
| 1–3 | 4,043 (57.9) | 207 (38.4) |
| 4 | 1,835 (26.3) | 110 (20.4) |
| 5–6 | 1,027 (14.7) | 209 (38.8) |
| Unknown | 77 (1.1) | 13 (2.4) |
| **ISS *(ICD-9)*** | | |
| 1–14 | 2,954 (42.3) | 81 (15) |
| 16–24 | 2,147 (30.8) | 100 (18.6) |
| ≥25 | 1,881 (26.9) | 358 (66.4) |
| Hypotension dose (mm Hg-min) | 0 (0–0) | 49 (15–142.5) |
| **Out-of-hospital hypoxia** | | |
| No | 6,205 (88.9) | 348 (64.6) |
| Yes | 480 (6.9) | 147 (27.3) |
| Unknown | 297 (4.3) | 44 (8.2) |

*AHCCCS*, Arizona Health Care Cost Containment System.
*Median (interquartile range) for continuous variables and count (percentage) for categorical variables.
†Hypotension defined as systolic blood pressure less than 90 mm Hg.

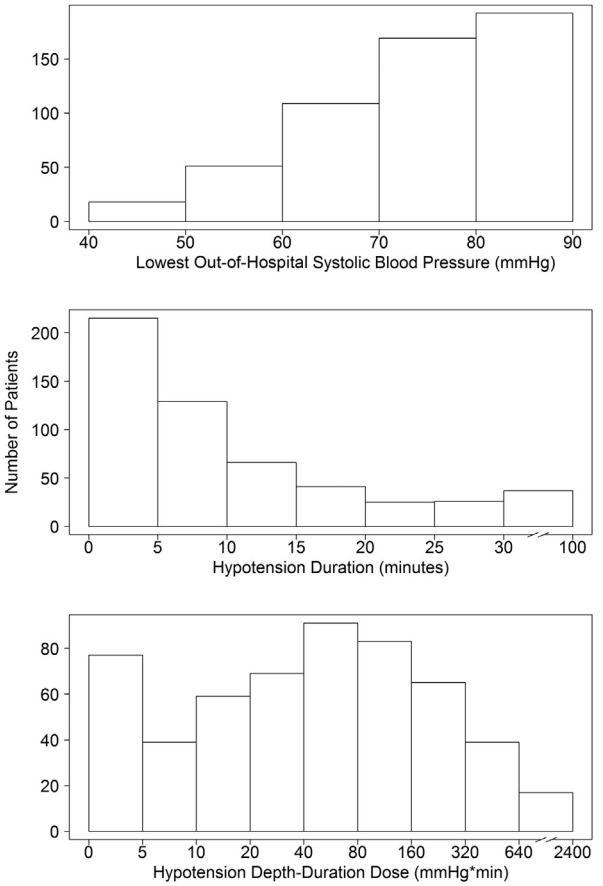


**Figure 4.** Distribution of hypotension depth, duration, and dose across the hypotensive cohort. Histograms show the proportions of hypotensive patients by depth, duration, and dose of hypotension.

with a change in the estimated OR for $\log_2$ dose of only 0.1% and in the standard error estimate for the corresponding regression coefficient of only 0.5%. Among the 8 trauma centers, there was an average of 940 subjects per site and the intraclass correlation coefficient for the trauma center effect was 0.066. In a separate sensitivity analysis, instead of $\log_2$ hypotension dose we included the standardized hypotension dose (dose minus the sample mean and then divided by the SD) in the logistic regression. The resulting inferences were similar (adjusted OR 1.27 per SD increase in hypotension dose; 95% CI 1.17 to 1.37) (Appendix E2, available online at http://www.annemergmed.com).

In a model with only basic demographic variables as predictors, the AUC was 0.585 (95% CI 0.563 to 0.607). Adding binary hypotension (systolic blood pressure <90 versus ≥90 mm Hg) improved AUC to 0.6635 (95% CI 0.6409 to 0.6860) and the net reclassification improvement was 39.1% (95% CI 32.5% to 45.5%). When hypotension dose ($\log_2$[dose+1]) was added to the binary model, the AUC improved slightly to 0.6638 (95% CI 0.6411 to 0.6865); the net reclassification improvement was 8.1% (95% CI –5.6% to 21.8%) for the dose-based model over the binary model. When the analysis was limited to the 539 subjects with hypotension, the basic model had an AUC of 0.616 (95% CI 0.566 to 0.666). Addition of hypotension dose improved AUC to 0.707 (95% CI 0.659 to 0.754), and the net reclassification improvement was 47.5% (95% CI 27.5% to 69.8%).

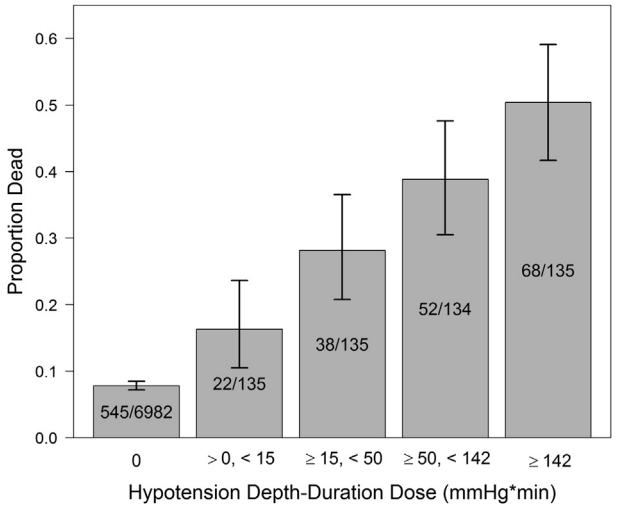


**Figure 5.** Unadjusted death proportion by hypotension dose categories. Error bars represent 95% CIs. Hypotension was defined as systolic blood pressure less than 90 mm Hg.

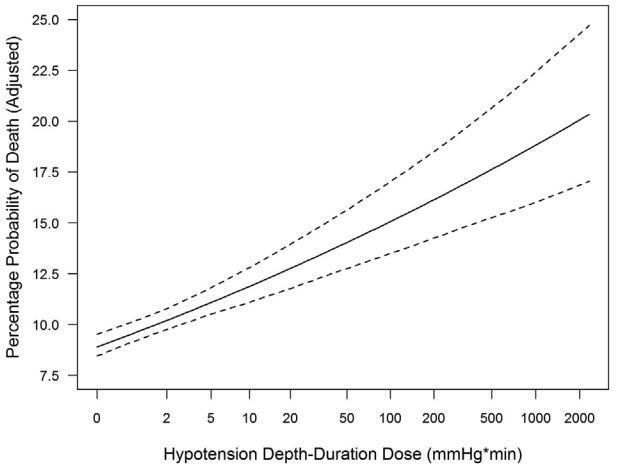


**Figure 6.** Relationship of hypotension depth-duration dose to adjusted probability of death. Dotted lines represent pointwise 95% confidence band. Hypotension was defined as systolic blood pressure less than 90 mm Hg. *x* axis is $\log_2$ scale.

**Table 2.** Logistic regression model for survival status.

| Variable* | Category | OR† | 95% CI |
|---|---|---|---|
| log2(SBP dose+1) | NA | 1.19 | (1.14–1.25) |
| Male patient | No | [Reference] | [Reference] |
| | Yes | 0.95 | (0.74–1.21) |
| Race | Black | [Reference] | [Reference] |
| | Asian | 1.77 | (0.51–6.15) |
| | American Indian/ Alaska Native | 2.07 | (0.92–4.65) |
| | White | 2.33 | (1.19–4.57) |
| | Other | 2.38 | (1.08–5.24) |
| | Unknown | 3.41 | (1.14–10.23) |
| Hispanic | No | [Reference] | [Reference] |
| | Yes | 0.55 | (0.39–0.79) |
| | Unknown | 1.43 | (0.78–2.60) |
| Payer | Private | [Reference] | [Reference] |
| | AHCCCS/Medicaid | 0.95 | (0.71–1.29) |
| | Medicare | 1.16 | (0.78–1.74) |
| | Self-pay | 3.27 | (2.31–4.61) |
| | Other | 1.56 | (0.95–2.57) |
| | Unknown | 2.86 | (1.44–5.65) |
| Trauma type | Blunt | [Reference] | [Reference] |
| | Penetrating | 4.96 | (3.54–6.95) |
| Head region severity score *(ICD-9)* | 1–3 | [Reference] | [Reference] |
| | 4 | 1.17 | (0.77–1.78) |
| | 5–6 | 14.21 | (9.64–20.96) |
| | Unknown | 6.29 | (2.70–14.64) |
| ISS *(ICD-9)* | 1–14 | [Reference] | [Reference] |
| | 16–24 | 4.92 | (2.18–11.09) |
| | ≥25 | 23.58 | (10.88–51.11) |
| Out-of-hospital hypoxia | No | [Reference] | [Reference] |
| | Yes | 2.47 | (1.88–3.24) |
| | Unknown | 2.91 | (1.96–4.31) |
| Age | Fitted nonparametrically | | |

*Also adjusted for treating trauma centers (details not shown).
†OR for death associated with 1-unit increase in continuous variable or compared with the referent category for categorical variables.

## LIMITATIONS

This study has limitations. The design is observational, and thus we could not determine whether the treatment of hypotension effectively reduced mortality (this hypothesis is part of the main study). However, this analysis did allow us, for the first time, to identify significant associations between the dose of hypotension and outcome.

There are missing data. Although the missing rate for EMS systolic blood pressure measurements is very low (<5%),[51] the addition of the requirement for 2 timed systolic blood pressure measurements for this analysis led to a rate of 23.6% (Figure 3). The database contains only measurements that were documented by EMS personnel, and we cannot independently verify their accuracy. However, the data are abstracted directly, consistently, and comprehensively from the patient care records. This level of data collection scrutiny is rare in EMS research.[51]

The hypotension dose estimate is affected by how frequently blood pressure was measured. Indeed, we found that a low measurement was more likely to be repeated quickly, which would lead to a more accurate estimation of the dose. However, the fact that nonhypotensive values tended to lead to fewer repeated measurements is not likely to have significantly affected our findings because the dose in nonhypotensive patients is zero regardless of how many times blood pressure was measured. Finally, we did not evaluate the effects of treatment. Future studies will assess the influence of traumatic brain injury care on outcomes.

## DISCUSSION

It is well established that out-of-hospital hypotension is associated with increased traumatic brain injury

mortality.[3,16,21,28-31,34,38,52] However, the literature that has shaped this understanding has evaluated hypotension as a simple dichotomy (<90 or ≥90 mm Hg).[3,16,21,28-31,38] To our knowledge, currently there are no published reports with data evaluating the effect of either the depth or the duration of out-of-hospital hypotension. The paucity of knowledge related to these parameters in the field is reflected in the most recent EMS traumatic brain injury treatment guidelines, which state that a major area needing investigation is identifying "the critical values for duration and magnitude of hypotensive…episodes."[38,53] Our study offers one of the first assessments of the association between hypotension dose and traumatic brain injury outcomes. These findings add to the increasing evidence that close and frequent blood pressure monitoring and management may contribute to improved traumatic brain injury outcomes.[4,7,8,15,23,30,32,33,36,38]

The EPIC database contains all vital signs measurements and their associated times that are recorded on the EMS patient care records. The data entry system allows an unlimited number of data entries for vital signs.[33,34] In fact, in this substudy, there are patients with as many as 25 EMS blood pressure measurements recorded in the database, and the median number is 4 per patient. This feature allows the plotting of out-of-hospital blood pressure over time and, hence, an estimation of the depth and duration of hypotensive events (Figures 1 and 2). These strengths allowed us to evaluate the hypotension dose as a novel measure.

Our study affirmed the presence of a dose-response association between hypotension dosage and mortality. The simple, unadjusted mortality rate increased significantly and consistently across the 4 quartiles (by dose) of hypotensive patients (Figure 5). Furthermore, a doubling of dose was associated with an adjusted OR for death of 1.19, and this association held over a wide range of hypotension doses (Figure 6). Thus, with other factors being equal, in hypotensive traumatic brain injury patients, a doubling of dose yielded a 19% increase in adjusted odds of death. For example, a patient in whom systolic blood pressure decreases to 80 mm Hg for 10 minutes (dose=100 mm Hg-minutes) has 19% higher odds of dying than one with a dose of only 50 mm Hg-minute (eg, 85 mm Hg for 10 minutes or 80 mm Hg for 5 minutes). Our findings not only provide evidence for the face validity of the dose-duration construct but also may support the notion of minimizing both hypotension depth and duration during clinical care.

Our findings did not show a marked improvement in model discrimination or net reclassification improvement for the hypotensive dosage model compared with the binary hypotension model in the overall study group. However, we believe this was predictable because 92.8% of the subjects were nonhypotensive. Hence, this comparison is dominated by the nonhypotensive patients, and only small improvement is expected when the entire study group is evaluated no matter how well the dose model discriminates between hypotensive patients. On the other hand, in the assessment of the hypotensive cohort, the binary model becomes moot because all patients in this subgroup have the same value (positive for hypotension) and, unlike depth-duration dose, it has no discriminative value among hypotensive patients. The implementation phase of the larger EPIC study is applying the evidence-based guidelines for out-of-hospital traumatic brain injury care. We plan to use the postimplementation cases not only to validate the current findings but also to identify alternate functional forms with clearer improvement of the dosage-based model over binary hypotension. For instance, because our previous work revealed a complete absence of an identifiable physiologic threshold anywhere between a systolic blood pressure of 40 and 120 mm Hg,[35] the discriminatory power of the model may improve when hypotension is defined as less than 100, less than 110, or less than 120 mm Hg.[53] Furthermore, when higher thresholds are evaluated, comparing the binary model versus the dose-based model in the overall study cohort will be pertinent because such a comparison will be much less likely to be dominated by the nonhypotensive subgroup. We will also be able to explore questions such as whether it is better to be less hypotensive longer or more hypotensive for a shorter time. The current study underscores the importance of hypotension dosage in traumatic brain injury care and sets the stage for these future analyses.

Another important consideration is how to implement these findings into EMS practice. We hesitate to recommend specific measures until additional validation has identified the most accurate model. However, our results do identify the technical challenges at hand. Calculation of hypotension dosage requires real-time computer decision support. Current portable cardiac monitors are able to give real-time feedback such as cardiopulmonary resuscitation chest compression rate, depth, and fraction.[54] Future efforts must consider the technologic support required to implement the new measure in traumatic brain injury patients.

In summary, this statewide, multisystem study of major traumatic brain injury found that the depth and duration of out-of-hospital hypotension were strongly associated with increased mortality. Assessments linking out-of-hospital blood pressure with traumatic brain injury outcomes should account for both the depth and duration of hypotension.

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*Author contributions:* DWS, BJB, JBG, KRD, PDA, CV, and DS were responsible for study concept and design. DWS, CH, BJB, VC, and BB were responsible for acquisition of the data. DWS, CH, BJB, VC, and DS were responsible for analysis and interpretation of the data. DWS, CH, and BJB were responsible for drafting the article. All authors were responsible for critical revision of the article for important intellectual content. CH, DS, and VC were responsible for statistical expertise. DWS, BJB, JBG, KRD, CV, and DS obtained funding. VC, BB, and TM were responsible for administrative, technical, and material support. DWS takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Appendix E1.** Patient characteristics by survival status.

| Group | Lived* | Died* |
|---|---|---|
| No. of subjects | 6,796 | 725 |
| Age, y | 40 (24–57) | 44 (26–65) |
| **Male patient** | | |
| No | 2,016 (29.7) | 192 (26.5) |
| Yes | 4,780 (70.3) | 533 (73.5) |
| **Race** | | |
| Black | 226 (3.3) | 18 (2.5) |
| Asian | 70 (1) | 6 (0.8) |
| American Indian/Alaska Native | 391 (5.8) | 36 (5) |
| White | 5,228 (76.9) | 557 (76.8) |
| Other | 811 (11.9) | 91 (12.6) |
| Unknown | 70 (1) | 17 (2.3) |
| **Hispanic** | | |
| No | 5,116 (75.3) | 540 (74.5) |
| Yes | 1,482 (21.8) | 144 (19.9) |
| Unknown | 198 (2.9) | 41 (5.7) |
| **Payer** | | |
| Private | 2,591 (38.1) | 198 (27.3) |
| AHCCCS/Medicaid | 1,804 (26.5) | 155 (21.4) |
| Medicare | 980 (14.4) | 146 (20.1) |
| Self-pay | 1,011 (14.9) | 157 (21.7) |
| Other | 286 (4.2) | 39 (5.4) |
| Unknown | 124 (1.8) | 30 (4.1) |
| **Trauma type** | | |
| Blunt | 6,602 (97.1) | 546 (75.3) |
| Penetrating | 194 (2.9) | 179 (24.7) |
| **Head Region Severity Score ISS *(ICD-9)*** | | |
| 1–3 | 4,202 (61.8) | 48 (6.6) |
| 4 | 1,875 (27.6) | 70 (9.7) |
| 5–6 | 640 (9.4) | 596 (82.2) |
| Unknown | 79 (1.2) | 11 (1.5) |
| **ISS *(ICD-9)*** | | |
| 1–14 | 3,026 (44.5) | 9 (1.2) |
| 16–24 | 2,209 (32.5) | 38 (5.2) |
| ≥25 | 1,561 (23) | 678 (93.5) |
| **Any exposure to low SBP†** | | |
| No | 6,437 (94.7) | 545 (75.2) |
| Yes | 359 (5.3) | 180 (24.8) |
| **Out-of-hospital hypoxia** | | |
| No | 6,125 (90.1) | 428 (59) |
| Yes | 416 (6.1) | 211 (29.1) |
| Unknown | 255 (3.8) | 86 (11.9) |

*Lived=survived to hospital discharge. Died=died in the hospital. Median (interquartile range) for continuous variables and count (percentage) for categorical variables.
†Hypotension defined as SBP less than 90 mm Hg.

**Appendix E2.** Logistic regression model for survival status with standardized hypotension dose.

| Variable* | Category | OR† | 95% CI |
|---|---|---|---|
| Standardized hypotension dose | NA | 1.27 | (1.17–1.37) |
| Male patient | No | [Reference] | [Reference] |
| | Yes | 0.93 | (0.73–1.18) |
| Race | Black | [Reference] | [Reference] |
| | Asian | 2.19 | (0.65–7.39) |
| | American Indian/Alaska Native | 2.25 | (1.01–5.03) |
| | White | 2.45 | (1.26–4.79) |
| | Other | 2.47 | (1.13–5.42) |
| | Unknown | 3.49 | (1.17–10.39) |
| Hispanic | No | [Reference] | [Reference] |
| | Yes | 0.56 | (0.40–0.80) |
| | Unknown | 1.52 | (0.85–2.75) |
| Payer | Private | [Reference] | [Reference] |
| | AHCCCS/Medicaid | 0.96 | (0.71–1.29) |
| | Medicare | 1.17 | (0.79–1.75) |
| | Self-pay | 3.28 | (2.32–4.62) |
| | Other | 1.56 | (0.95–2.56) |
| | Unknown | 2.91 | (1.48–5.71) |
| Trauma type | Blunt | [Reference] | [Reference] |
| | Penetrating | 5.15 | (3.68–7.20) |
| Head region severity score *(ICD-9)* | 1–3 | [Reference] | [Reference] |
| | 4 | 1.21 | (0.79–1.85) |
| | 5–6 | 15 | (10.09–22.30) |
| | Unknown | 7.08 | (3.04–16.50) |
| ISS *(ICD-9)* | 1–14 | [Reference] | [Reference] |
| | 16–24 | 4.95 | (2.20–11.16) |
| | ≥25 | 23.41 | (10.80–50.75) |
| Out-of-hospital hypoxia | No | [Reference] | [Reference] |
| | Yes | 2.6 | (1.98–3.41) |
| | Unknown | 2.88 | (1.94–4.27) |
| Age | Fitted nonparametrically | | |

*Also adjusted for treating trauma centers (details not shown).
†OR for death associated with 1-unit increase in continuous variable or compared with the referent category for categorical variables.