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Dustin Hatefi Date

The effects of mean arterial pressure during a critical window following acute traumatic brain injury – a survival analysis in the ProTECT cohort

By

Dustin Hatefi
Master of Public Health

Department of Epidemiology

Michael Goodman, MD
Committee Chair

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Dustin Hatefi

M.D., Georgetown University, 2011
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Thesis Committee Chair: Michael Goodman, MD

An abstract of
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Abstract

The effects of mean arterial pressure during a critical window following acute traumatic brain injury – a survival analysis in the ProTECT cohort

By Dustin Hatefi

Secondary insults following traumatic brain injury (TBI) are recognized as important determinants of prognosis. The association between early systolic hypotension and poor outcome has been established, but the role of low mean arterial pressure (MAP) has not been well defined.

This retrospective cohort study is aimed at characterizing the effects of low MAP expressed as proportion of total blood pressure recordings (pMAP) during a critical window of peak edema post-TBI (days 2 and 3). Data were collected from the ProTECT cohort, a clinical trial analyzing the safety of intravenous progesterone in the acute post-TBI period. The pMAP data on 98 subjects were dichotomized three ways: 1) by comparing subjects experiencing hypotension <80 mm Hg to those who did not 2) by dividing the study population using the median as the cutoff, and 3) by evaluating the persons in the upper tertile relative to the remainder of the sample. Data were collected on vital status after follow up, duration of follow up, age, sex, race, Glasgow coma scale score, injury severity score, early moderate to severe MAP hypotension (<65 mm Hg), and progesterone allocation. Descriptive information was compiled on all variables to evaluate for significant differences across pMAP exposure groups. Univariate analysis was performed using Kaplan-Meier survival curves for categorical data and unadjusted proportional hazards models for continuous data. Three multivariate proportional hazards models for each pMAP dichotomization scheme were created, adjusting for study covariates to obtain hazard ratios (HRs) and 95% confidence intervals (CIs). The main outcome of interest was survival time (days).

The only significant differences were observed for early hypotension, as high pMAP groups tended to have lower early MAPs. After adjustment, Cox regression analysis did not reveal any significant association between pMAP and survival with HR ranging from 1.11 to 1.45, depending on the dichotomization scheme. In contrast, progesterone significantly decreased mortality by 81-82% in all three models.

In conclusion, the data failed to show any significant effect of cumulative mean arterial hypotension during the two- to four-day interval post-TBI on survival in the ProTECT cohort. Progesterone, however, did significantly improve survival.

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INTRODUCTION

In the United States, traumatic brain injuries (TBI) result in 275,000 hospitalizations and 52,000 deaths annually.[1] Males are more likely to sustain TBI across all age groups and the highest rates of mortality are from motor vehicle accidents during the third decade of life.[1] Many studies have identified traumatic brain injury as a complex pathophysiologic entity with multiple pathways of lesion expansion that may occur after the primary, mechanical insult, thereby increasing morbidity and mortality.[2-6] With such a high annual incidence of TBI, much attention has been turned towards blunting the effects of these secondary insults that complicate treatment post-injury.

In the 1970's Graham and colleagues performed multiple autopsies on TBI victims and found the frequency of ischemic brain injury to be greater than 85%.[5,6] Following these reports, researchers began to focus on the effects of hypotension and hypoxia on preservation of brain function acutely following TBI. As will be discussed, numerous studies have been performed evaluating the association between hypotension and TBI outcome, however for ethical reasons current guidelines fail to recognize any high-quality, randomized, controlled trials (Level I evidence) to support management of blood pressure and oxygenation in the period immediately following TBI.[7] Instead, current guidelines make the recommendation to maintain systolic blood pressure (SBP) above 90 mm Hg based on well-designed, high-quality, observational studies (Level II evidence) and P_aO_2 greater than 60 mm Hg based on moderate to poor quality observational studies (Level III evidence).[7]

It is widely maintained that the cerebral perfusion pressure (CPP), defined as the difference between the mean arterial pressure (MAP) and the intracranial pressure (ICP), is critical in providing oxygen to the brain parenchyma.[8] Although the importance of MAP as the determinant of CPP has been recognized for years, most previous studies of TBI outcomes focused on the effects of SBP instead. Marmarou *et al*. retrospectively studied the effects of both ICP and SBP on Glasgow Outcome Scale (GOS) scores at 6 months post-injury.[9] In this study, ICP greater than 20 mm Hg and SBP less than 80 mm Hg were predictive of poor functional outcome. Two years later, Chestnut *et al*. prospectively analyzed the effects of admission SBP less than 90 mm Hg and hypoxia less than P_aO_2 of 60 mm Hg in severely brain-injured patients and found that a single episode of hypotension doubled post-TBI mortality.[3] These results stimulated the Brain Trauma Foundation to issue its recommendation to maintain SBP above 90 mm Hg post-TBI.[7] More recently, Manley *et al*. analyzed the effects of SBP below 90 mm Hg in a prospective study of moderately and severely brain-injured patients and also found that increased frequency and duration of hypotensive episodes elevated the risk of mortality.[10] Taken together, the above studies indicate that low SBP at presentation is one of the strongest predictors of poor outcome following TBI.

Though systolic hypotension has been identified with poor outcomes following TBI, it is the MAP, not the SBP, that is a direct determinant of CPP.[8] Under the assumption that CPP is the most important factor in preventing cerebral ischemia acutely after TBI, then it seems logical that the MAP is also directly related to poor outcome following TBI. Only a few studies have analyzed the effects of early mean arterial

hypotension on TBI outcome, and through sensitivity analyses established a MAP threshold of 80 mm Hg as a lower bound.[11,12] Furthermore, the Brain Trauma Foundation guidelines make a recommendation of maintaining CPP between 50 and 70 mm Hg while maintaining ICP below 20 mm Hg; from these numbers we may also rationalize a MAP threshold of 70 – 90 mm Hg.[7] Additionally, there is evidence that brain edema following TBI peaks at 2-3 days post-injury.[13] It is during this critical period that ICP is expected to rise thus necessitating a normal-to-high MAP to maintain CPP and brain tissue oxygenation. The present study seeks to examine the prognostic value of MAP and also analyze MAP deviations during this critical window of time in post-TBI care. We hypothesize that cumulative mean arterial blood pressure deviations below 80 mm Hg will negatively impact survival during the critical window of two to four days following blunt TBI.

METHODS

Study Design and Patient Sample

This is a retrospective cohort study evaluating the association between decreased MAP during the 25- to 72-hour interval following admission and survival among 100 subjects enrolled in a phase II clinical trial examining the safety of intravenous (IV) progesterone in the acute setting following TBI.[14] The current study analysis was granted a full exemption by both the Emory University and Grady Memorial Hospital Institutional Review Boards. The parent study that provided data for the current analysis has been described elsewhere.[14] Briefly, the ProTECT trial randomized 100 adult

subjects with a post-resuscitation Glasgow Coma Scale score of 4 to 12 in a 4:1 scheme to receive IV progesterone or placebo. Enrollment took place at an urban, Level I trauma center within 11 hours after blunt TBI following a proxy informed consent. Subjects were excluded from the study based on at least one the following criteria: 1) elevated blood alcohol level (greater than 250 mg/dL), 2) age less than 18 years, 3) evidence of penetrating brain injury, 4) unknown time of injury, 5) an admission SBP of less than 90 mm Hg, 6) hypoxia less than P_aO_2 60 mm Hg, 7) cardiac arrest, 8) non-survivable injury, 9) GCS <4 or >12, 10) spinal cord injury, 11) status epilepticus on arrival, 12) active breast or reproductive cancer, 13) pregnancy, 14) prisoner, and 15) known progesterone allergy. The primary outcomes of interest included 30-day mortality, and physiologic parameters such as systolic and diastolic blood pressure, MAP, CPP, ICP, temperature, and fluid balance. Treatment benefit was assessed based on the scores of the 30-day extended Glasgow Outcome Scale.

Main Outcome

The main outcome of interest in these analyses was survival time (in days) with the total follow up of 30 days (based on the ProTECT study protocol). Subjects that died before 30 days were considered to have the event, and those who were followed for less than 30 days, but did not die, were censored.

Main Exposure

The main exposure of interest in the present study was the proportion of hours with recorded MAP below 80 mm Hg (pMAP), a threshold based on previously published sensitivity analyses.[11,12] This exposure variable was obtained using hourly

MAP measurements for each subject recorded during the window from the start of day 2 (hour 25) and ending at the end of day 3 (hour 72). All hourly measurements were recorded at the initiation of the experimental IV infusion until death or discharge from the intensive care unit. Subjects dying before the exposure period in the first 24 hours were excluded from the analyses. We used the proportion, rather than the sum, of hours below a MAP threshold of 80 mm Hg to account for variable duration of observation and a variable number of recorded blood pressure values. The pMAP was dichotomized at three different cutpoints – at the pMAP of 0, at the median and at the upper tertile. The three alternative cutpoints were used because a clinically significant pMAP threshold has not been identified.

Covariates

The available demographic patient characteristics included age, sex, and race. Data on injury severity were collected including GCS score and injury severity score (ISS, an indicator of global injury severity). Glasgow Coma Scale scores were dichotomized as reflecting "severe" (GCS 4-8) or "moderate" (GCS 9-12) abnormality.[15] The abbreviated injury scale (AIS) was used to calculate ISS where $ISS = AIS_1^2 + AIS_2^2 + AIS_3^2$ ($AIS_{1\text{-}3}$ in these calculations were the three most severe AIS scores) for a maximum ISS of 75. Data on moderate to severe MAP hypotension before the exposure period (first 24 hours) were also collected in order to control for the effects of early hypotension. A threshold MAP of 65 mm Hg was used to distinguish subjects who experienced moderate to severe hypotension in the first 24 hours from those who did not. The threshold of MAP below 65 mm Hg in the first 24 hours was intended to adjust for

only the most significant MAP deviations in the first 24 hours. Additional information included mechanism of trauma, categorized as motor vehicle, struck pedestrian, bicycle accident, fall, or other head injury. Finally, data on progesterone treatment (the main intervention in the ProTECT study) versus placebo were also examined.

Statistical Analysis

Data analyses began with descriptive statistics that involved calculating frequencies and measures of central tendency and dispersion for the entire study group and for various categories of patients. Distributions of demographic and clinical characteristics were compared across different exposure groups using Student's *t*-tests for normal continuous data, Wilcoxon rank sum tests for non-parametric data, and c^2-tests or Fisher exact tests for categorical data. Unadjusted survival analyses of categorical data were carried out by constructing Kaplan-Meier survival curves for each exposure category of interest accompanied by the corresponding log-rank tests for statistical significance, while unadjusted survival analyses of continuous data were performed using univariate proportional hazards models. Statistical significance was set at the two-sided alpha error of ≤ 0.05 in all analyses.

Three models were produced: one comparing persons with no episodes of MAP <80 mm Hg (pMAP=0) to all other subjects, one with the pMAP dichotomized at the median, and one for the same outcome variable, but comparing the upper tertile to the rest of the sample. All models controlled for the following covariates based on their clinical relevance: age, sex, race, GCS score, ISS score, hypotension in the first 24 hours, and progesterone treatment. These covariates were selected based on *a priori*

considerations. Proportional hazard assumption testing began with visual inspection of the log(-log) curves. Only the variable indicating GCS category produced intersecting curves in violation of the proportional hazards assumption. To account for this violation, all multivariate Cox regression analyses were then stratified by GCS level to adjust for this time-dependent covariate. To confirm that the proportionality assumption was met in the rest of the study covariates, interaction terms were created between each variable and log(follow-up time) to test for significant interactions with time. There was no significant interaction found with time in any of the three models, thus it was determined that the proportionality assumption had not been violated with the remaining covariates. Finally, for each of the three models, evaluation of covariate interaction was performed for all two-way possibilities, however no interaction terms significantly contributed to any of the models. Results of the multivariate analyses were expressed as adjusted hazard ratios (HRs) along with the corresponding 95% confidence intervals (CIs). All statistical analyses were performed using SAS 9.2 (Cary, NC).

RESULTS

Descriptive statistics on the study sample

There were 100 subjects in the study sample however two were excluded because they died in the first 24 hours. Table I shows descriptive data for all variables in the study. Among all subjects that provided the data for the current analysis 71% were males, 35% were black, and 72% had a post-resuscitation GCS score of 4 to 8. Progesterone was allocated to 75 subjects in this sample; 23 received placebo. Of the 48

exposure hours for the main variable of interest, subjects were monitored on average for 30 hours. Thirty subjects (31%) did not have recorded MAP values below the threshold during the exposure window and an additional 15 subjects had pMAP values less than 7.5%.

As shown in Table 1, most subject characteristics, including age, sex, race and receipt of progesterone intervention were distributed approximately evenly across different pMAP groups. On the other hand, frequency of hypotensive episodes (<65 mm Hg) in the first 24 hours was significantly greater among persons with higher pMAP, regardless of the dichotomization scheme (all p-values <0.0001). Other notable findings included higher minimum MAP in the group with pMAP of 0% compared to the rest of the study sample (P<0.001), and a greater proportion of patients with severe GCS in the upper pMAP tertile relative to the two lower tertiles (p=0.04).

Survival analysis

Figures 1, 2 and 3 present Kaplan-Meier survival curves for each of the three pMAP dichotomization schemes: 0 versus >0, above versus below the median, and the upper tertile versus the two remaining tertiles. Though there was overlap in the confidence bands, the curves for the higher pMAP groups in all three figures were below the corresponding curves for the comparison groups. In keeping with the Kaplan-Meier curves, the unadjusted HRs for all three pMAP categories ranged between 1.81 and 2.07, but with all CIs including unity.

In multivariate Cox regression analysis similar results were observed (Table III). No statistically significant results were observed in any of the three models, with adjusted

HRs ranging from 1.11 to 1.45. In contrast, early moderate to severe hypotension was significantly associated with poor survival in two models (any hypotension and the upper tertile analyses). The adjusted models also revealed that only progesterone treatment had a consistent, statistically significant association with better outcome (HRs 0.18 to 0.19).

DISCUSSION

Our analyses demonstrated little, if any, evidence that cumulative duration of low MAP during the critical two- to four-day window following TBI is associated with survival. An interesting finding in this cohort is that patients that received progesterone treatment had better outcome (at least in terms of lower mortality) compared to the placebo group. This corroborates previously published reports for the survival benefit of progesterone infusion.[14,16]

It is important to consider our study in the context of previous research. Although much of the literature has focused on the role of SBP after TBI, some groups have attempted to assess the prognostic value of MAP deviations. Struchen *et al*. studied functional outcomes in 184 severe TBI patients with continuous ICP, MAP, and CPP measurements.[12] This study measured the duration of ICP greater than 25 mm Hg and MAP less than 80 mm Hg and discovered that both indicators affected functional outcomes as measured by GOS and by Disability Rating Scale for all subjects, but not among patients that survived.

In another study of severe TBI victims, Walia *et al*. measured MAP and maximum blood glucose within 24 hours of admission. They found that both the

minimum MAP and hyperglycemia were associated with increased mortality, though the association was stronger for hyperglycemia.[17]

Butcher *et al*., analyzed data from eight randomized controlled trials and one observational study to examine the association of blood pressure with GOS score.[18,19] In doing so, they found a smooth, U-shaped curve for both MAP and SBP, suggesting that both hypotension and hypertension may contribute to a worse GOS score. Upon adjusting for severity of injury, however, only the association with hypotension remained significant. Based on this work, the authors advocated changing management approach avoiding falling below a give threshold to reaching a target blood pressure goal rather than while also suggesting that a clear-cut "critical value" may not exist.[18]

Limitations

Limitations of this study should be noted. First, without ICP monitoring, we must rely on the assumption that ICP was elevated above baseline. Without the ability to calculate CPP for all subjects, it is unknown if MAP hypotension directly affected CPP and outcome. Of note, however, is some research has identified hypotension as a very strong predictor of poor outcome while not finding an association between low CPP and prognosis,[9] suggesting that systemic hypotension does not necessarily imply a reduced CPP if autoregulatory mechanisms remain in tact. In this study we were only able to evaluate hypotension independent of CPP value.

Similarly, our study operated under the assumption of "peak edema" during the exposure period based on previously published data.[13] With increased cerebral edema, ICP would be expected to increase, however we were unable to verify this increase in the

study subjects. Subjects whose edema peaked before day two or after day three would likely tolerate MAP hypotension during the exposure period better than those whose edema was at a maximum during this time.

Third, previous sensitivity analyses identified a MAP threshold of 80 mm Hg,[11,12] however other studies reported a more linear increase in risk associated with hypotension.[18] It is possible that a threshold of 80 mm Hg was not sensitive enough to identify survival differences in MAP deviation among exposure groups.

Finally, though all HRs were in the hypothesized direction, all estimates had wide confidence intervals. Thus it appears that this study was underpowered to reveal a significant association between pMAP and survival. In order to achieve 80% power to show statistically significant (at the 0.05 level) a HR of 1.4 given our baseline hazard rate, the ProTECT study would need to have enrolled approximately 370 subjects with an exposed to non-exposed ratio of 1:1..

CONCLUSION

The results of this study and the evidence from previous research indicate that much work is needed to better define post-TBI clinical and prognostic factors, particularly with regard to blood pressure. Our data show a strong association between early MAP hypotension and poor outcome, however the association was less evident during the hypothesized period of peak edema. Whereas systolic hypotension early in the admission is an established predictor of poor prognosis, the role of MAP and its relationship with the cerebral perfusion pressure remain unclear. An improvement in

brain tissue preservation following TBI will likely require better understanding of the specific MAP parameters that affect clinical prognosis, and the refinement of measurement techniques during the acute post-trauma period.

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Table I. Characteristics of the study sample stratified by the proportion of recorded hours with mean arterial pressure (MAP) below 80 mm Hg between days 2 and 4 post-injury

		Any Hypotension (n = 98)			Median Cutpoint (n = 98)			Upper Tertile Cutpoint (n = 98)		
	Overall*	pMAP >0% recorded hours	pMAP = 0% recorded hours	$p^{\dagger}$	Hypotensive >12.25%	Hypotensive ≤12.25%	$p^{\dagger}$	Hypotensive >23.1%	Hypotensive ≤23.1%	$p^{\dagger}$
n (%)	98	68 (69.4)	30 (30.6)	-	49 (50)	49 (50)	-	32 (32.7)	66 (67.3)	-
Male, n (%)	71 (72)	47 (69.12)	24 (80)	0.27	33 (67.4)	38 (77.6)	0.26	22 (68.8)	49 (74.2)	0.57
Black, n (%)	35 (35)	44 (64.7)	19 (63.3)	0.90	17 (34.7)	18 (36.7)	0.83	10 (31.3)	25 (37.9)	0.52
Age, median (IQR)	33 (23-46)	34.5 (19-48)	32 (23-42)	0.28	29 (21-46)	36 (25-46)	0.36	29 (21.5-47.5)	33 (25-45)	0.95
Age >33 years, n (%)	46 (47)	34 (50)	12 (40)	0.36	20 (40.8)	26 (53)	0.23	14 (43.8)	32 (48.5)	0.66
Severe GCS‡, n (%)	71 (72)	49 (72.06)	22 (73.33)	0.90	33 (67.4)	38 (77.6)	0.26	19 (59.4)	52 (78.8)	0.04
ISS§, mean (SD)	23.5 (9.3)	23.3 (8.8)	23.7 (10.4)	0.85	24.0 (8.8)	22.8 (9.7)	0.51	23.4 (7.9)	23.5 (9.9)	0.95
Progesterone, n (%)	75 (76.5)	53 (77.9)	22 (73.33)	0.62	37 (75.5)	38 (77.6)	0.81	24 (75)	51 (77.3)	0.80
Mechanism of Injury, n (%)										
Motor Vehicle	74 (75.5)	51 (75)	23 (76.7)		39 (79.6)	35 (71.4)		26 (81.3)	48 (72.7)	
Struck Pedestrian	3 (3)	3 (4.4)	0 (0)		2 (4)	1 (2)		1 (3.1)	2 (3)	
Bicycle	3 (3)	1 (1.5)	2 (6.7)	0.64	1 (2)	2 (4)	0.69	1 (3.1)	2 (3)	0.90
Fall	7 (7.1)	5 (7.4)	2 (6.7)		2 (4)	5 (10.2)		2 (6.3)	5 (7.6)	
Other	11 (11.2)	8 (11.8)	3 (10)		5 (10.2)	6 (12.24)		2 (6.3)	9 (13.6)	
Duration of BP monitoring, hours, mean (SD)	30.0 (9.3)	30.8 (8.7)	28.3 (10.6)	0.2249	30.4 (8.1)	29.6 (10.5)	0.675	29.9 (7.5)	30.1 (10.2)	0.91
Hypotensive episode <65 mm Hg in first 24h, n (%)	22 (22.7)	22 (32.8)	0 (0)	<0.0001	21 (43.8)	1 (2)	<0.0001	15 (46.9)	7 (10.8)	<0.0001
Minimum MAP, days 2-4, median (IQR)	73 (67-81)	71 (62-73)	83.5 (81-89)	<0.0001	67 (60-72)	81 (76-84)	0.36	62.5 (58.5-68)	78 (72-82)	0.95
Follow-up days, mean (SD)	26.4 (8.3)	26.0 (8.6)	27.5 (7.63)	0.84	25.4 (9.2)	27.5 (7.4)	0.23	25.2 (9.6)	27.0 (7.7)	0.29
30-day Mortality, n (%)	15 (15.3)	12 (17.7)	3 (10)	0.54	10 (20.4)	5 (10.2)	0.16	7 (21.9)	8 (12.1)	0.24

†p-values obtained using a Student's t-test for comparing means and a $\chi 2$ test for proportions; Wilcoxon rank sum tests were used for non-parametric data

‡Glasgow Coma Scale score; "severe" defined as GCS <9

§Injury severity score; calculated from the sum of the squares of the three worst ratings in the Abbreviated Injury Scale (AIS)

¥Median follow-up time for all columns was 30 days

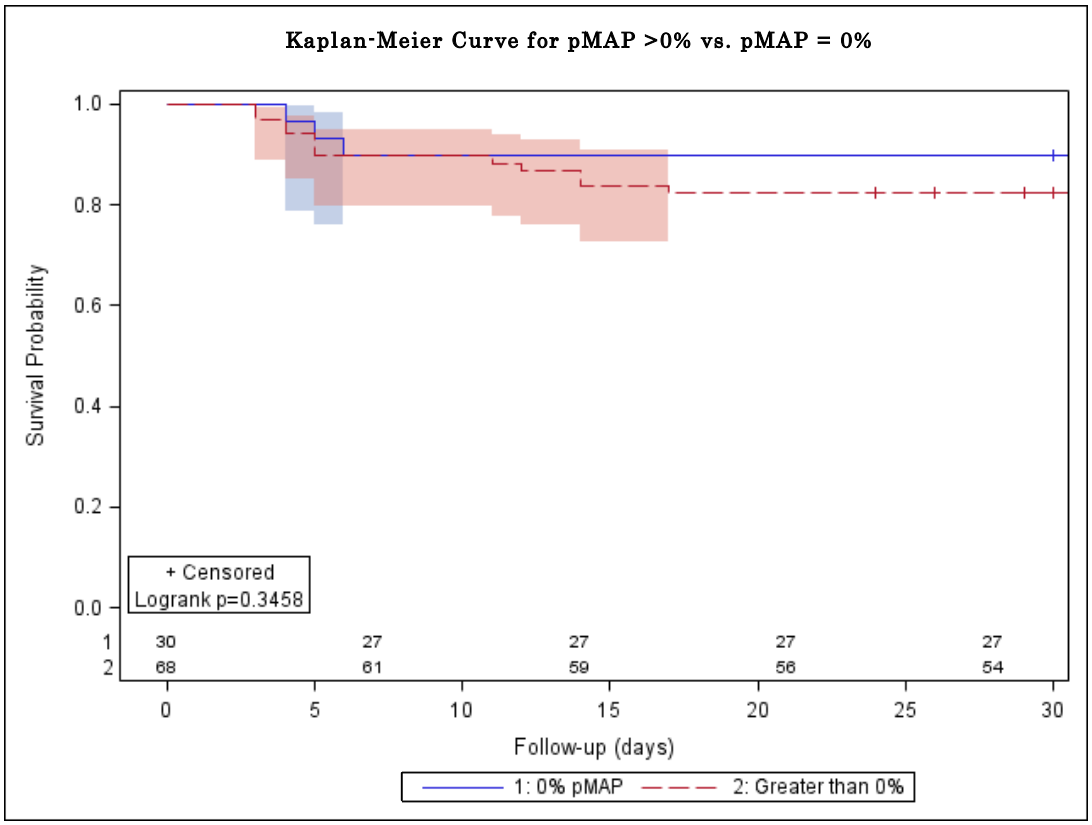

Figure 1. Kaplan-Meier survival analysis comparing sample subjects that experienced hypotension during the exposure window vs. those who did not.

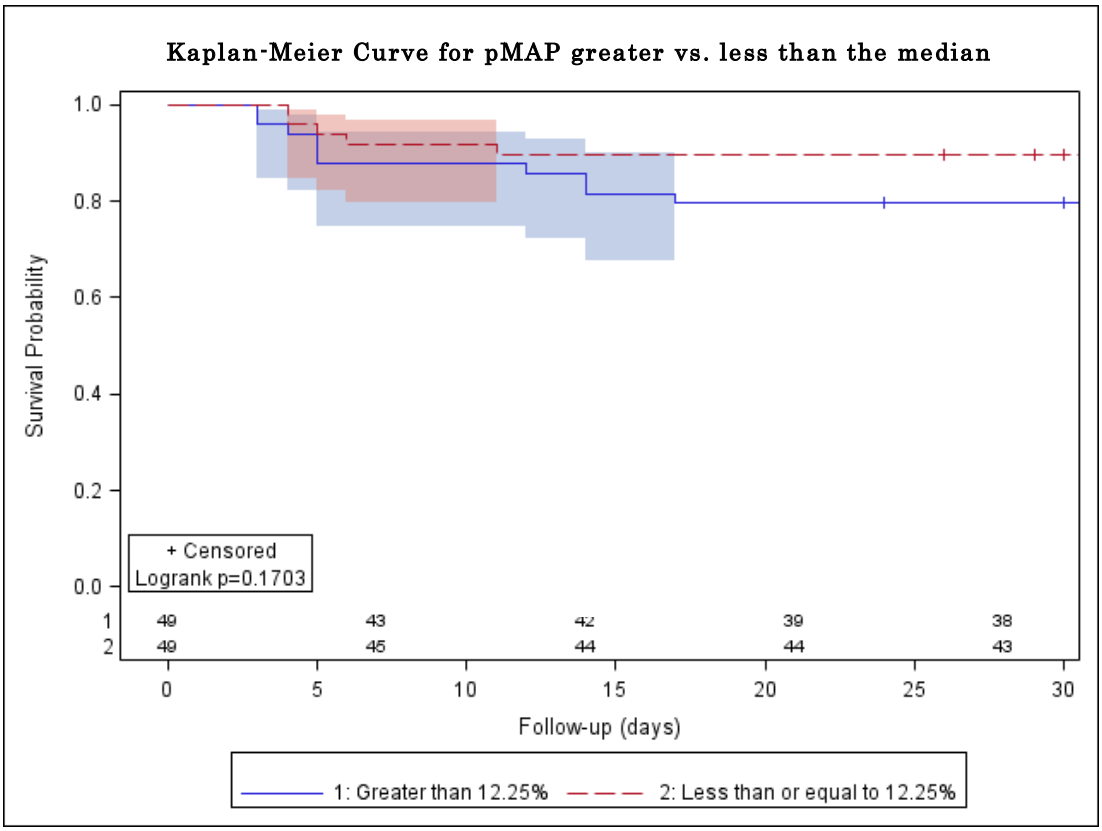

Figure 2. Kaplan-Meier survival analysis of pMAP stratified at the median value (12.25%).

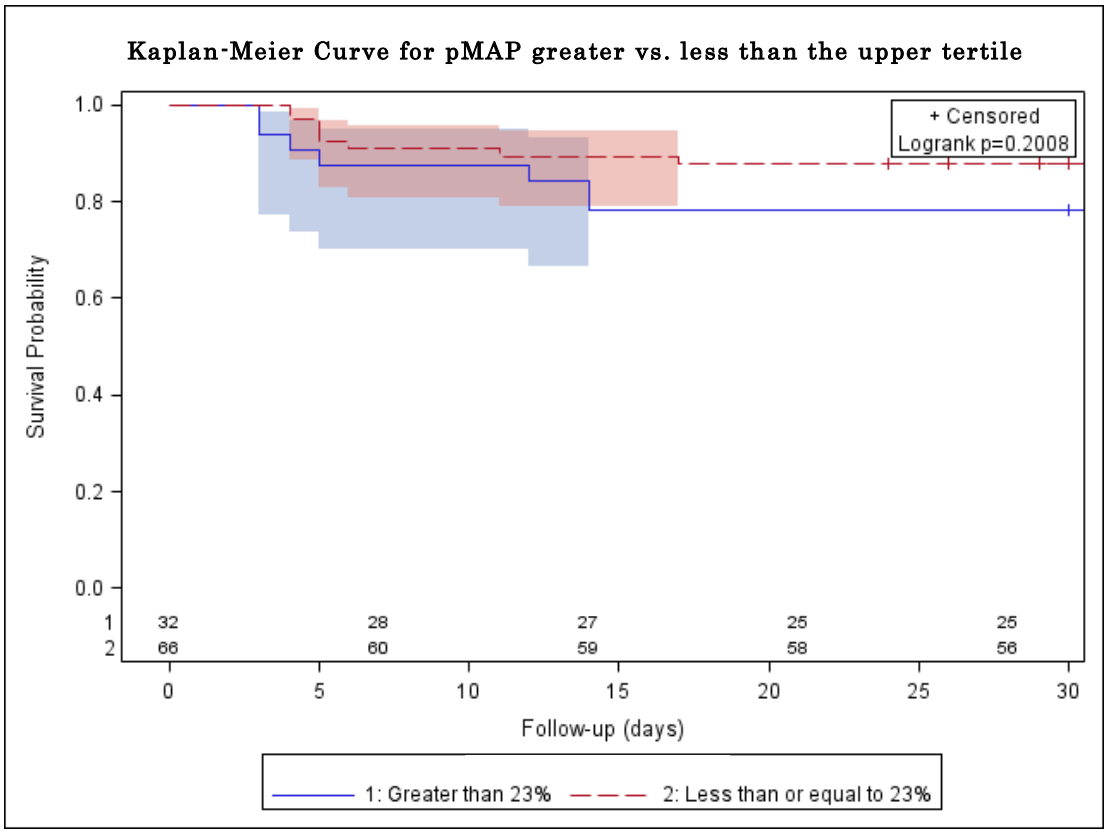

Figure 3. Kaplan-Meier survival analysis of pMAP stratified at the upper tertile cutpoint (23.1%).

Table II. Unadjusted hazard ratios for all study covariates

	HR	95% CI
Main Exposure		
Any Hypotension	1.81	(0.51 - 6.43)
Hypotensive >12.25% hours	2.07	(0.71 - 6.06)
Hypotensive >23.1% hours	1.91	(0.69 - 5.26)
Covariates		
Male	1.61	(0.46 - 5.72)
Black	0.63	(0.20 - 1.76)
Age >33 years	1.80	(0.64 - 5.06)
Severe GCS	1.50	(0.43 - 5.33)
ISS	1.00	(0.95 - 1.06)
Hypotensive episode <65 mm Hg in first 24h	2.45	(0.87 - 6.88)
Progesterone	0.32	(0.12 - 0.87)

*pMAP, stratified by those with hypotension vs. those without hypotension during the exposure period

Table III. Multivariate Cox regression stratified on GCS level* for models containing the main exposure 1) dichotomized at pMAP >0% vs. pMAP = 0%, 2) stratified at the median, and 3) stratified at the upper tertile

	Any Hypotension		Hypotension >12.25%		Hypotension >23.1%	
	n = 97‡		n = 97‡		n = 97‡	
	HR	95% CI	HR	95% CI	HR	95% CI
Main Exposure						
Hypotension	1.41	(0.35 - 5.72)	1.45	(0.39 - 5.41)	1.11	(0.32 - 3.80)
Covariates						
Male	2.34	(0.60 - 9.08)	2.25	(0.57 - 8.89)	2.31	(0.58 - 9.21)
Black	0.60	(0.18 - 1.97)	0.60	(0.18 - 1.98)	0.60	(0.18 - 2.01)
Age >33 years	1.62	(0.54 - 4.88)	1.68	(0.56 - 5.08)	1.64	(0.54 - 4.91)
ISS	1.00	(0.93 - 1.07)	1.00	(0.93 - 1.07)	1.00	(0.93 - 1.07)
Hypotensive episode in first 24h	4.25	(1.19 - 15.15)	3.83	(0.94 - 15.57)	4.55	(1.17 - 17.76)
Progesterone	0.18	(0.06 - 0.56)	0.19	(0.06 - 0.59)	0.19	(0.06 - 0.59)

*Stratification on GCS level performed because GCS showed evidence of violation of proportional hazards assumption

†Compared with subjects not having a MAP values under 80 mm Hg

‡n = 97 because one subject did not have any MAP values recorded in the first 24 hours