Incidence, Longitudinal Trajectory, and Hemodynamic Implications of Cardiac Dysfunction Following Traumatic Brain Injury

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Abstract

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Traumatic brain injury (TBI) is a major public heath problem and leading cause of death and disability worldwide. While hemodynamic instability is common following TBI and associated with increased mortality, few studies have evaluated the function of the heart following TBI. Understanding the role of cardiac dysfunction following TBI represents a major gap in the literature. To address this, the primary aims of the dissertation in isolated moderate-severe TBI patients were: 1) To determine the incidence, longitudinal course, and admission risk factors for systolic dysfunction, 2) To determine the early hemodynamic profile in patients who develop systolic dysfunction, and 3) To examine the association of early myocardial workload and in-hospital mortality. In aim #1, we conducted a prospective cohort study using transthoracic echocardiography (TTE) to

determine the incidence of systolic dysfunction within 24 hours following moderate-severe TBI, compared to mild TBI (control group); in addition, we examined the longitudinal course of systolic function over the first week of hospitalization following moderate-severe TBI. In aim #2, we conducted a secondary analysis of the prospective cohort study described in aim #1; we used multivariable linear mixed models to examine the early hemodynamic profile that is associated with the development of systolic dysfunction following moderate-severe TBI. In aim #3, we conducted a retrospective cohort study using the National Trauma Databank (NTDB) to examine the association of the admission rate-pressure product (RRP) with in-hospital mortality following severe TBI. Completion of these aims has helped to uncover a new link between the brain and heart following TBI, and will lead to future studies aiming to personalize hemodynamic management to improve outcomes following TBI.

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Manuscript #1 (Aim #1): Early Dysfunction Following Traumatic Brain Injury: A Cohort Study

Introduction

Traumatic brain injury (TBI) is sustained by more than 1.7 million individuals annually, and contributes to 30% of all injury-related deaths in the United States(1). Patients with moderate-severe TBI experience hypotension [defined commonly as systolic blood pressure (SBP) < 90 mmHg] early after hospitalization(2), which can lead to poor blood flow to an injured brain(3, 4) and worse mortality and functional outcomes following TBI(5, 6). Experimental studies and clinical observations in other non-TBI neurologic disease paradigms, such as subarachnoid hemorrhage (SAH), suggest that acute systolic cardiac dysfunction may be responsible for the early hypotension that is often associated with catastrophic neurologic processes(7, 8).

The approach to fluid management and selection of vasoactive agents should be directed by the status of cardiac function in TBI. For example, current data suggests that intravenous phenylephrine is the most commonly used vasopressor following severe TBI (9). However, without knowledge of the status of the heart, it is difficult to examine which vasoactive agent will best improve cerebral perfusion in an individual TBI patient. Currently, outside of a retrospective study (10) and case reports (11), there is little prospective data on what happens to cardiac function after TBI. To increase our understanding of brain-heart interactions and to provide information that would guide the management of systemic and cerebral hemodynamics following TBI, we aimed to

determine the incidence, longitudinal course, and admission risk factors for systolic dysfunction in patients hospitalized with isolated moderate-severe TBI. We hypothesized that systolic dysfunction would be relatively common after moderate-severe TBI and greater TBI severity would result in more systolic dysfunction.

Methods

We conducted a prospective cohort study among moderate-severe TBI patients, using mild TBI patients as a comparison group, at Harborview Medical Center, a 413-bed tertiary care center and the only Level 1 adult and pediatric trauma center for a 4-state region in the United States (Washington, Alaska, Montana, and Idaho). The study was approved by the University of Washington Institutional Review Board.

Study Population

Patients were screened for a diagnosis of mild TBI and moderate-severe TBI within 24 hours of injury. TBI was defined according to the Centers for Disease Control and Prevention(12), and TBI severity was based on the admission Glasgow Coma Scale score (GCS) after resuscitation(13, 14). Mild TBI was defined by a GCS score $\geq$ 13, and moderate-severe TBI was defined by a GCS score $\leq$ 12. We excluded patients older than 65 years and any patient with a documented history of ischemic heart disease, congenital heart disease, moderate or severe valvular heart disease, and systolic or diastolic heart failure. We excluded patients with severe systemic comorbidities (liver cirrhosis, greater than stage 2 chronic kidney disease, human immunodeficiency virus infection, a history of chemotherapy, greater than stage 2 chronic obstructive pulmonary disease, pulmonary hypertension, or a history of cerebrovascular disease). Furthermore, we excluded patients with a body region Abbreviated Injury Scale (AIS) score of greater than 2 in the chest or abdomen, patients with spinal cord injuries, patients who sustained a cardiac arrest prior to enrollment, and any patients requiring greater than 2 units of packed red blood cells as part of their initial resuscitation in the emergency department and (if required) operating room.

Study Procedures

Following recruitment, a transthoracic echocardiogram (TTE) was performed within the day following injury. For patients with mild TBI, a single TTE exam was performed; and for patients with moderate-severe TBI, the initial TTE was performed, along with a repeat TTE exam within 2-4 days and 7-9 days following injury. Among patients in whom clinical instability or medical procedures (i.e. surgery) precluded a research TTE within the specified time frame, the TTE was performed as early as possible after clinical stability was achieved. Data were collected from clinical records for demographic, clinical, radiographic, and hemodynamic data.

Transthoracic Echocardiography

All TTE examinations were performed by an anesthesiologist-intensivist (VK) with certification in echocardiography, using a Philips iE-33 ultrasound system (Bothell, WA) and utilizing two-dimensional and Doppler imaging technology according to the American Society of Echocardiography guidelines(15). The focused exam consisted of evaluation of left ventricular systolic and diastolic function, primarily assessed in the parasternal, apical, and subcostal windows. As many moderate-severe TBI patients had labile intracranial pressures, especially with changes in position, all research TTE exams were performed in the supine position; therefore, systolic function was primarily assessed in the parasternal long-axis window (basal fractional shortening) rather than in the apical windows (ejection fraction, which requires adequate imaging of the cardiac apex without foreshortening(16), and is best obtained in the left lateral decubitus position). The study cardiologist (EG), blinded to the patient status or clinical details of patient management, reviewed all echocardiogram examinations offline for data quality, and any exams with inadequate imaging windows for assessment of systolic function were excluded from analysis. The study certified cardiac sonographer (CP), also blinded

to patient exposure status or clinical details, performed all cardiac measurements offline, including left ventricular diameters, areas, and Doppler measurements of mitral inflow and septal tissue velocity. A randomly selected group of images, representing approximately 15% of the patient population, was selected for repeated ventricular diameter measurement by CP (6 weeks after the initial measurements) and EG for determination of intraobserver and interobserver variability, respectively.

Echocardiographic Outcomes

Systolic function was assessed using endocardial fractional shortening [(left ventricular internal diameter in diastole – left ventricular internal diameter in systole) / (left ventricular internal diameter in diastole)], a highly reproducible and validated method for linear assessment of left ventricular function that has been used in multiple clinical studies(15). In comparing the mild versus moderate-severe TBI groups, our primary outcome was systolic dysfunction, defined as a fractional shortening less than 25%(15), recorded on the first echocardiogram after injury. Secondary outcomes included diastolic dysfunction, defined as a mitral annular septal tissue velocity [e'(s)] < 8 cm/s(17), and change in systolic and diastolic function over the first week of hospitalization in patients with moderate-severe TBI.

Statistical Analysis

Sample size calculations were based on the expected incidence of systolic dysfunction in moderate-severe TBI versus mild TBI derived from retrospective studies from our research group(10, 18) and previous literature from other neurologic injury paradigms (approximately 20% versus <1%, respectively). We calculated that 62 patients (31 patients in each group) would be required to reject the null hypothesis of no difference in systolic function between groups with mild and moderate-severe TBI, with an alpha level

of 0.05 and power of 0.8. Assuming that approximately 10% of patients would not have adequate echocardiographic windows to assess fractional shortening, we aimed to recruit 35 patients per group. Descriptive statistics examined the demographic, clinical, radiographic, and echocardiographic characteristics of the cohort. The incidence of systolic dysfunction within the day after injury was calculated. For comparison of echocardiographic parameters between groups with mild and moderate-severe TBI, a Student's t-test or a Fisher's exact test was used. A Fisher's exact test was used to examine the differences in the proportions of patients with systolic and diastolic dysfunction in the moderate-severe (exposed) and mild (comparison) TBI groups. Univariate and multivariable Poisson regression models (with adjustment for age, gender, intracranial lesion, Glasgow Coma Scale score, systolic blood pressure, fluid balance, sedative use, vasopressor use, osmotherapy use, and need for intracranial surgery) with robust standard errors were used to calculate the relative risk of factors present on admission for the development of systolic dysfunction among patients with moderate-severe TBI. Interobserver and intraobserver variability was evaluated using Bland-Altman analysis(19), and expressed as a mean difference (bias) and limits of agreement. All analyses were performed using Stata version 13.0 statistical software (StataCorp, Texas, USA).

Results

During June to August 2015, 99 TBI patients were met criteria for screening and 29 patients were excluded, primarily due to refusal to participate in the study, the presence of polytrauma, and the presence of underlying cardiac disease. A total of 70 patients were recruited, with 64 patients (32 with moderate-severe TBI and 32 with mild TBI) having adequate echocardiographic windows for final analysis. In eight patients, a research TTE within the first day following injury was unable to be performed due to clinical circumstances (prolonged transport time, resuscitation, clinical procedures, or surgery) and the initial TTE was performed within 2 days after injury.

Baseline demographic and clinical characteristics in the patients with mild and moderate-severe TBI are shown in Table 1. Both groups were relatively young (mean age 36.2 and 36.5 years, respectively), primarily male (69% and 84%, respectively), and mainly free from medical comorbidities. A greater proportion of the moderate-severe TBI group had intracranial hemorrhage on initial head CT than in the mild TBI group, with the majority of moderate-severe TBI patients (66%) having multiple types of hemorrhage on initial head CT. Mean admission systolic blood pressure (SBP) was greater in the moderate-severe TBI than the mild TBI group (132.3 mmHg vs. 125.5 mmHg), although a greater proportion of moderate-severe TBI than mild TBI patients (34% vs. 13%, respectively) experienced hypotension (SBP $\leq$ 90 mmHg) within 24 hours of admission, with 19% requiring vasopressors.

Initial echocardiogram findings are shown in Table 2. The incidence of early systolic dysfunction in patients with mild TBI was 0%, compared to 22% in patients with moderate-severe TBI ($p<0.01$). Patients with moderate-severe TBI had a greater left

ventricle area in diastole and systole, as well as greater left ventricle internal diameter at end-systole. Mean fractional shortening was significantly lower in moderate-severe TBI patients, compared to mild TBI patients (p=0.01). The mild and moderate-severe TBI groups both had similar values of most diastolic parameters, although moderate-severe TBI patients had a significantly lower mean deceleration time compared to mild TBI patients (122.5 versus 162.6 msec).

Among available echocardiograms within the day after injury all patients with moderate-severe TBI, the median (IQR) fractional shortening was 29% (25% - 34%), with improvement to 33% (30% - 36%) by 7-9 days after injury. Figure 1 describes the change in fractional shortening over the first week of hospitalization in moderate-severe TBI patients with early systolic dysfunction. Among available echocardiograms with the day after injury, the median (IQR) fractional shortening was 20% (16% - 21%), with improvement to 32% (29% - 34%) by 7-9 days after injury.

Clinical care during the first 24 hours after injury in patients with moderate-severe TBI is shown in Table 3. Vasopressors were used in 29% of patients with systolic dysfunction, compared to 16% of patients without systolic dysfunction. The use of mannitol (57% versus 40%, respectively) and hypertonic saline (43% versus 16%, respectively) was more common in patients with systolic dysfunction than patients without systolic dysfunction. In-hospital mortality occurred in 3 (43%) patients with systolic dysfunction and 1 (4%) patient without systolic dysfunction. Table 4 shows admission risk factors that are associated with the development of systolic dysfunction in the moderate-severe TBI cohort. On multivariable analysis, age (RR 0.87, 95% CI 0.79 – 0.94, p=0.001) and GCS score on admission (RR 0.34, 95% CI 0.20 – 0.58, p < 0.0001) were independently associated with the development of systolic dysfunction following moderate-severe TBI.

Interobserver reliability determined the mean difference (bias) in left ventricular internal diameter in diastole measurements between observers to be 0.15 cm, with all observations falling within the 95% limits of agreement (-0.80 – 0.50). Intraobserver reliability determined the mean difference (bias) in left ventricular internal diameter in diastole measurements within the same observer (6 weeks apart) to be 0.12 cm, with all observations falling within the 95% limits of agreement (-0.43 – 0.18).

Discussion

In this study, we aimed to provide information on the incidence, trajectory and risk factors associated with cardiac dysfunction after TBI. The primary findings of our study are that: 1) Early systolic dysfunction can occur in previously healthy patients following moderate-severe TBI, 2) Systolic function recovers within the week following injury, and 3) Younger age and greater TBI severity (as measured by admission GCS score) are independently associated with the development of systolic dysfunction early after TBI. To our knowledge, this is the first study to prospectively document and examine the trajectory of systolic function after moderate-severe TBI.

Very little and methodologically limited data exists on cardiac function following TBI. A retrospective study documented the occurrence of systolic dysfunction among TBI patients who underwent echocardiography(10), but TTE was performed at the discretion of the clinical team and the study findings may have been limited by selection bias. In contrast, our current study evaluated cardiac function in all moderate-severe TBI patients meeting stringent criteria (which excluded patients with a high probability of pre-existing cardiac disease or non-TBI induced cardiac dysfunction) – this approach limited selection bias and improved the ability to the isolate the effect of TBI on the heart. Another prospective study(20) demonstrated troponin elevation in 31% of patients following moderate-severe TBI; while echocardiographic dysfunction was not demonstrated in that study, the majority of echocardiograms were performed several days after injury, a period by which most patients in our study had recovered normal systolic function. Acute systolic dysfunction has also been observed after several severe acute non-TBI neurologic diseases including acute emotional distress(21) (classic Takotsubo's cardiomyopathy), SAH(22), ischemic stroke(23, 24), epilepsy(25, 26), and brain death(27).

In this study, we observed that patients with systolic dysfunction showed marked improvement in cardiac function over their first week of hospitalization. This pattern of improvement is faster than observed following SAH(22), and potentially mirrors the improvement in cerebral edema over the first 2-3 days of injury, rather than the more protracted course of SAH, which includes both the initial hemorrhage and delayed cerebral ischemia from vasospasm(28). It is also possible that the most intense early treatments for cerebral perfusion (i.e. sedation to control ICP, vasopressors, and aggressive resuscitation) are generally de-escalated by 3-7 days after injury, accounting for improved cardiac loading conditions and improved systolic function. Future studies should use more load-independent measures of systolic function, such as the utilization of cardiac MRI or myocardial deformation imaging(29), to better measure intrinsic myocardial dysfunction versus changes in loading conditions.

We found younger age and lower GCS score as the only independent admission risk factors for the development of systolic dysfunction among moderate-severe TBI patients. Our findings also suggested that lower admission systolic blood pressure may be associated with systolic dysfunction, and future studies should examine the hemodynamic implications of systolic dysfunction in more detail. Furthermore, mechanistic studies should better elucidate whether hypotension is a cause or effect of systolic dysfunction following TBI. While systolic dysfunction following neurologic injury is postulated to occur secondary to both dysregulated systemic inflammation and a catecholamine-excess state(30), myocardial catecholamine responsiveness decreases with age(31, 32) and may represent one possible explanation for our finding of a greater risk of systolic dysfunction with younger age. The relationship between initial severity of neurologic injury and systolic dysfunction has been described in other neurologic

diseases. For example, in subarachnoid hemorrhage, greater myocardial injury is associated with worse admission clinical symptoms and greater blood load on the initial CT scan(33). Our study findings further contribute to the understanding of the relationship between severity of neurologic injury and the development of systolic dysfunction in neurocritically ill patients.

Apart from a lower deceleration time (a suggestion of restrictive filling independent of elevated E/e' ratio), we did not observe worse diastolic function in moderate-severe TBI patients, compared to mild TBI patients. One possible reason for this is that the traditional definitions of diastolic dysfunction have been derived in patients with chronic cardiac disease, and these definitions may be inadequate to identify patients with acute diastolic dysfunction secondary to brain-heart interactions or acute changes in loading conditions due to fluid resuscitation. While most studies in the neurocardiac literature have focused mainly on systolic dysfunction, diastolic dysfunction may be a clinically important finding, and future studies should evaluate diastolic function following TBI in more detail.

The findings of our study have clinical relevance. Currently, the approach to early hemodynamic management after TBI does not involve evaluation of the heart, and abnormalities are assumed to be a result of the physiologic stress of brain injury(34), fluid shifts, and/or effects of sedatives(35, 36). Knowledge of early systolic function may allow a more rational use of fluids and vasopressors to optimize cerebral blood flow following TBI. For example, international guidelines(37) suggest maintenance of a cerebral perfusion pressure (CPP) of 50-70 mmHg, given a high risk of the acute respiratory distress syndrome (ARDS) at CPP > 70 mmHg(38). Unfortunately, data informing this recommendation are devoid of the consideration of cardiac function, as

presumed ARDS may have been the result of cardiogenic edema in patients with undiagnosed systolic dysfunction who required high doses of vasopressors and fluid infusions in an attempt to reach CPP targets. Thus, knowledge of cardiac function may add to the multimodal data that could help inform rational vasopressor choices and individualize CPP targets in this patient population. Furthermore, as adequate cardiac output is critical for maintenance of cerebral blood flow(39), prevention of the development systolic dysfunction (for example, through the use of low-dose beta-blockade) may also represent a therapeutic target; interestingly, through mechanisms which have not been delineated, early exposure to beta-blockers have been shown to be associated with a survival benefit following TBI(40).

There are some limitations to our study. First, patient care interventions such as sedation, vasopressors, or fluid resuscitation make it impossible to tease out the natural effect of brain injury from subsequent clinical management in causing systolic dysfunction; while we did control for these variables to the best extent possible, there remains the possibility of residual confounding. Thus, the mechanistic underpinnings of our findings require further studies. Second, we chose fractional shortening as our main measure of systolic function rather than the more traditional measure of ejection fraction – the reason for this choice centers around the difficulty in placing many patients in a left lateral decubitus position (due to labile intracranial pressures with patient movement), thus limiting imaging of the true cardiac apex. Fractional shortening may overestimate systolic function in patients with regional wall motion abnormalities beyond the cardiac base, and may lead to an underestimation of the burden of systolic dysfunction in the TBI population. However, calculation of fractional shortening has a strong record of reproducibility and has been used successfully in many clinical studies(41). Third, it is impossible to fully establish that none of our patients had systolic dysfunction prior to

their TBI, but this would be unlikely as we sampled a population that was young and had no history of cardiovascular disease prior to their injury. Furthermore, patients with systolic dysfunction recovered to normal function over the first week, suggesting a stress (rather than pre-existing) cardiomyopathy. Lastly, due to the small sample size of our study, our findings should be confirmed in larger and heterogeneous TBI populations.

Conclusions

We found that systolic dysfunction occurred in 22% of previously healthy patients following moderate-severe TBI; furthermore, younger age and lower admission GCS score were independently associated with the development of systolic dysfunction after injury. Our findings provide new information, and suggest that TBI severity adversely impacts cardiac function. Future research should correlate cardiac function with cardiac biomarker changes, examine underlying mechanisms, examine factors associated with improvement in cardiac function, and test therapies to optimize cardiac function following TBI.

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Table 1: Demographic and Clinical Characteristics in Mild and Moderate-Severe Traumatic Brain Injury Patients[a]

Variable	Mild TBI (n=32)	Moderate-Severe TBI (n=32)
Age (years)	36.2 (11.0)	36.5 (13.3)
Race		
White	18 (56%)	21 (66%)
Black	6 (19%)	3 (9%)
Hispanic	5 (16%)	3 (9%)
Asian / Pacific Islander	3 (9%)	2 (6%)
Native American	0 (0%)	3 (9%)
Male Gender	22 (69%)	27 (84%)
Medical Co-morbidities		
Pulmonary	0 (0%)	0 (0%)
Hypertension	1 (3%)	1 (3%)
Diabetes	0 (0%)	2 (6%)
Renal Disease	0 (0%)	0 (0%)
Injury Mechanism		
Fall	6 (19%)	10 (31%)
Motor vehicle crash	11 (34%)	10 (31%)
Vehicle vs. pedestrian	3 (9%)	5 (16%)

Bicycle crash	3 (9%)	1 (3%)
Gunshot to head	0 (0%)	1 (3%)
Assault	6 (19%)	3 (9%)
Other	3 (9%)	2 (6%)
Initial Head CT Findings[b]		
Epidural hemorrhage	4 (13%)	5 (16%)
Subdural hemorrhage	7 (22%)	24 (75%)
Subarachnoid hemorrhage	2 (6%)	23 (72%)
Intraparenchymal hemorrhage	4 (13%)	15 (47%)
Glasgow Coma Scale		
Admission GCS	14.8 (0.4)	5.2 (2.5)
Highest GCS (within 24 hours)	15.0 (0.2)	9.0 (3.0)
Lowest GCS (within 24 hours)	14.5 (0.8)	4.8 (2.4)
Admission Hematocrit (%)	40.6 (4.5)	38.0 (5.3)

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables.
[b]Some patients had multiple head CT findings.
CT=Computed Tomography; GCS=Glasgow Coma Scale; bpm=beats per minute; MAP=mean arterial pressure

Table 2: Early Echocardiographic Findings in Mild and Moderate-Severe Traumatic Brain Injury[a]

Cardiac Functional Parameters	Mild TBI (n=32)	Moderate-Severe TBI (n=32)	p
Systolic Function[b,c]			
Left Ventricle Area End-Diastole (cm^2)	16.15 (3.68)	18.60 (4.88)	**0.04**
Left Ventricle Area End-Systole (cm^2)	6.99 (1.93)	8.90 (3.39)	**0.01**
Fractional Area Change (cm^2)	0.57 (0.06)	0.53 (0.11)	0.10
Left Ventricle Internal Diameter End-Diastole (cm)	4.55 (0.45)	4.64 (0.61)	0.47
Left Ventricle Internal Diameter End-Systole (cm)	3.02 (0.43)	3.28 (0.60)	**0.05**
Fractional Shortening	0.34 (0.06)	0.30 (0.07)	**0.01**
Mitral Annular Septal Tissue Velocity [S'(s) (cm/s)]	8.21 (1.92)	9.49 (2.36)	**0.05**
Mitral Annular Septal Tissue Velocity [S'(s)] < 6 cm/s	3 (9%)	2 (6%)	0.42
Systolic Dysfunction (Fractional Shortening < 0.25)	**0 (0%)**	**7 (22%)**	**<0.01**
Diastolic Function[d,e]			
Mitral Inflow Peak Early Filling [E wave (cm/s)]	69.65 (12.53)	67.44 (19.64)	0.62
Mitral Inflow Peak Late Filling [A wave (cm/s)]	52.01 (14.08)	46.52 (12.83)	0.17
E-wave to A-wave Ratio	1.43 (0.42)	1.55 (0.57)	0.41
E-wave to A-wave Ratio < 1	4 (13%)	5 (16%)	0.47
E-wave to A-wave Ratio > 2	3 (9%)	5 (16%)	0.33
Mitral Inflow E-wave Deceleration Time (msec)	162.59 (39.18)	122.5 (43.51)	**<0.01**
Mitral Annular Septal Tissue Velocity [e'(s) (cm/s)]	10.28 (2.46)	9.46 (2.74)	0.28
E-wave to e'(s) Ratio	7.05 (1.85)	7.33 (2.01)	0.62
E-wave to e'(s) Ratio > 8	6 (19%)	11 (34%)	0.22
Mitral Annular Septal Tissue Velocity [e'(s)] < 8 cm/s	5 (16%)	9 (28%)	0.31

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables
[b]Systolic area, diastolic area, and fractional area change from data available in 28 subjects mild TBI and 26 with moderate-severe TBI
[c]Mitral annular tissue Doppler velocities from data available in 21 subjects with mild TBI and 26 with moderate-severe TBI

Table 3: Clinical Care in Moderate-Severe TBI Patients[a]

Variable	No systolic dysfunction (n=25)	Systolic dysfunction (n=7)	p
Age (years)	39.1 (13.7)	27.1 (5.6)	**0.03**
Male Gender	21 (84%)	6 (86%)	0.91
Glasgow Coma Scale			
Admission GCS	5.7 (2.5)	3.4 (1.1)	**0.03**
Highest GCS (within 24 hours)	9.3 (2.1)	7.7 (5.1)	0.22
Lowest GCS (within 24 hours)	4.8 (2.0)	4.9 (3.8)	0.99
Admission Hematocrit (%)	38.0 (5.2)	37.9 (6.2)	0.96
Systolic Blood Pressure (mmHg)			
Admission SBP	131.9 (25.2)	133.9 (19.4)	0.85
Lowest SBP in first 24 hours	98.4 (12.6)	96.1 (19.5)	0.71
Hypotension (SBP≤90) in first 24 hours	8 (32%)	3 (43%)	0.59
Hypertension (SBP≥140) in first 24 hours	19 (76%)	6 (86%)	0.58
Admission Oxygen Saturation (%)	96.4 (3.2)	92.9 (8.1)	0.09
Vasopressor[b]	4 (16%)	2 (29%)	0.45
Phenylephrine	3 (12%)	1 (14%)	0.87
Maximum Dose (mcg/kg/min)	1.5 (0)	15 (0)	n/a
Norepinephrine	1 (4%)	1 (14%)	0.32
Maximum Dose (mcg/kg/min)	0.2 (0)	0.2 (0)	n/a
Anti-Hypertensive Use[b]	0 (0%)	0 (0%)	n/a
Intracranial Procedures[b]			

ICP monitor placement	12 (48%)	4 (57%)	0.67
Need for intracranial surgery	9 (36%)	3 (43%)	0.74
Mechanical Ventilation[b]	25 (100%)	7 (100%)	n/a
Propofol Sedation[b]			
Any Use	25 (100%)	7 (100%)	n/a
Maximum Dose (mcg/kg/min)	43.6 (24.9)	53.6 (21.0)	0.34
Osmotherapy[b]			
Mannitol	10 (40%)	4 (57%)	0.42
Hypertonic Saline	4 (16%)	3 (43%)	0.13
Fluid Balance (mL)[b]			
Intake	5395 (2558.0)	6776 (4692.4)	0.31
Output	3098 (1440.8)	3688 (1269.1)	0.33
Fluid Balance	2297 (2404.6)	3088 (4202.6)	0.52

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables.
[b]In first 24 hours after admission
GCS=Glasgow Coma Scale; SBP = systolic blood pressure; mmHg = millimeters of mercury; mL = milliliters

Table 4: Admission Risk Factors for Systolic Dysfunction Following Moderate-Severe TBI

	Univariate[a]			Multivariable[b,c]		
Variable	**Relative Risk**	**95% CI**	**p**	**Relative Risk**	**95 % CI**	**p**
Age	**0.93**	**0.88 - 0.97**	**0.001**	**0.87**	**0.79 - 0.94**	**0.001**
Male Gender	1.11	0.16 - 7.58	0.91	1.19	0.17 - 8.58	0.86
Initial Head CT Findings						
Epidural Hemorrhage	0.9	0.13 - 6.14	0.91	2.42	0.37 - 15.68	0.13
Subarachnoid Hemorrhage	0.52	0.14 - 1.92	0.33	2.29	0.58 - 9.06	0.24
Intraparenchymal Hemorrhage	0.85	0.22 - 3.27	0.81	0.04	0.001 - 1.77	0.09
Subdural Hemorrhage	0.83	0.19 - 3.57	0.81	1.02	0.25 – 4.18	0.97
Admission Glasgow Coma Scale	**0.6**	**0.37 - 0.99**	**0.05**	**0.34**	**0.20 - 0.58**	**<0.0001**
Admission Systolic Blood Pressure	1.00	0.98 - 1.03	0.82	0.95	0.91 - 1.00	0.05

[a,b] Poisson regression models with robust standard errors
[c] Adjusted for all admission risk factors in the univariate analysis, in addition to 24-hour fluid balance, propofol sedation, vasopressor use, osmotherapy use, mechanical ventilation, and need for intracranial surgery

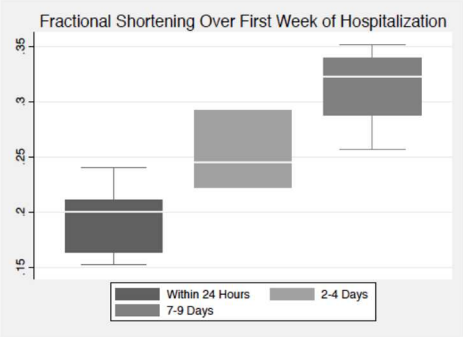

Figure 1: Change in Fractional Shortening Over the First Week of Hospitalization in Patients with Moderate-Severe Traumatic Brain Injury and Initial Systolic Dysfunction[a,b]

[a]In above boxplots, solid line represents median value, box represents interquartile range, and whiskers represent adjacent values

[b]Echocardiograms at approximately 3 days and 1 week after injury were performed in the majority to patients, although some exams are missing secondary to clinical procedures, patient death, or patient discharge from the hospital

Manuscript #2 (Aim #2): Association of Early Hemodynamic Profile and the Development of Systolic Dysfunction Following Traumatic Brain Injury

Introduction

Traumatic brain injury (TBI) is a major public health problem, and a significant contributor to major disability and mortality[1]. Recent data suggests that systolic dysfunction may occur following TBI[2], and likely represents a form of stress cardiomyopathy observed in other neurologic injury paradigms[3]. Systolic dysfunction after TBI is problematic because it may contribute to secondary brain injuries, as adequate cardiac output is an important factor in maintaining cerebral blood flow after injury[4]. Early hypotension and hypertension after TBI are also detrimental because they are both associated with poor outcomes following TBI[5,6]; furthermore, early hemodynamic parameters may vary in TBI patients who do and do not develop systolic dysfunction. Yet, no study has examined the association of early hemodynamics with the development of systolic dysfunction after TBI.

Experimental and clinical studies implicate a maladaptive catecholamine excess state as a primary cause of both early hypertension and systolic dysfunction after other severe neurologic diseases, such as subarachnoid hemorrhage[7]. Knowledge of the early hemodynamic profile in TBI patients who develop systolic dysfunction can improve understanding of the underlying mechanisms of systolic dysfunction and may provide a therapeutic target to prevent the development of systolic dysfunction after injury and improve outcomes. To address this gap in knowledge, we conducted a prospective

cohort study to determine the early hemodynamic profile (over the first 24 hours after admission) in patients who develop systolic dysfunction following moderate-severe TBI compared to TBI patients who do not develop systolic dysfunction after injury.

Methods

We conducted a prospective cohort study among patients with moderate-severe TBI. The study was conducted at Harborview Medical Center, the only Level 1 adult and pediatric trauma center for a 4-state region in the United States (Washington, Alaska, Montana, and Idaho). The study was approved by the University of Washington Institutional Review Board.

Study Population

Study procedures took place in the Neuroscience and Trauma Intensive Care Units at Harborview Medical Center (Seattle, WA). Traumatic brain injury severity was based on the admission Glasgow Coma Scale, as previously described[8,9], with moderate-severe TBI having an admission (or first examination off sedation and neuromuscular blockade) GCS score $\leq$ 12. We excluded patients older than 65 years, patients with documented history of cardiac disease, and any patient who sustained a cardiac arrest prior to evaluation. Furthermore, we excluded patients with significant systemic diseases that are associated with systolic dysfunction (liver cirrhosis, greater than stage 2 chronic kidney disease, HIV, history of chemotherapy, greater than stage 2 chronic obstructive pulmonary disease, pulmonary hypertension, or a history of cerebrovascular disease). Lastly, we excluded patients with polytrauma, defined as a body region Abbreviated Injury Scale (AIS) score of greater than 2 in the chest or abdomen, patients with spinal cord injuries, and any patients requiring greater than 2 units of packed red blood cells as part of their initial resuscitation.

Clinical TBI Care

Patients were resuscitated according to local protocols consistent with the Brain Trauma Foundation guidelines[10], including placement of an intracranial pressure (ICP) monitor in

severe TBI, with maintenance of an ICP of less than 20 mmHg, arterial partial pressure of carbon dioxide of 35-40 mmHg, blood glucose < 180 mg/dL, and avoidance of fever through the use of antipyretic medications or surface cooling devices. For hemodynamic management, a minimum cerebral perfusion pressure of 50 mmHg was targeted in the presence of an ICP monitor; a systolic blood pressure > 90 mmHg was targeted in the absence of an ICP monitor. Hourly clinical monitoring for neurologic deterioration was always performed.

Study Procedures, Data Collection, and Echocardiography

Informed consent was obtained either from the patient or the patient's surrogate decision-maker. Following this, a transthoracic echocardiogram (TTE) was performed during the first day after injury when possible. Among patients with clinical instability or medical procedures that precluded a TTE within the first day after injury, the TTE was performed within the two days that followed the injury. Data were collected from the electronic medical record for demographic, clinical, and hemodynamic parameters. In particular, hourly non-invasive blood pressure and heart rate recordings over the first 24 hours after admission were collected, with hourly assessment of fluid balance, vasopressor use, osmotherapy use (most commonly mannitol or hypertonic saline), sedative infusions, and need for surgical treatment.

All TTE examinations were performed according to the American Society of Echocardiography guidelines[11] by an anesthesiologist-intensivist (VK) with certification in echocardiography. The TTE exam was focused on the evaluation of left ventricular systolic and diastolic function, assessed in the parasternal, apical, and subcostal windows. All research TTE exams were performed in the supine position due to concerns for high intracranial pressure in many patients. Therefore, systolic function was

primarily assessed in a linear fashion in the parasternal long-axis window using endocardial fractional shortening [(left ventricular internal diameter in diastole – left ventricular internal diameter in systole) / (left ventricular internal diameter in diastole)], a validated method for assessment of left ventricular function[11]. Systolic dysfunction was defined as a fractional shortening less than 25%[11]. The study cardiologist (EG) was blinded to all clinical details, and reviewed all echocardiogram examinations offline for data quality; a certified cardiac sonographer (also blinded to clinical details) performed all cardiac measurements offline.

Statistical Analysis

Descriptive statistics were used to examine the demographic, clinical, and TTE characteristics of the cohort. Comparison of TTE parameters between groups with and without early systolic dysfunction was achieved using a Student's t-test or a Fisher's exact test. Unadjusted and adjusted linear mixed models (with adjustment for age, gender, admission GCS, fluid balance, vasopressor use, need for surgery, use of osmotherapy, and sedative infusions) were used to estimate the mean difference (and 95% confidence interval) in systolic blood pressure, mean arterial pressure, and heart rate between baseline and hourly time points, with an interaction term for the presence/absence of systolic dysfunction – marginal mean values from these models were plotted to demonstrate blood pressure and heart rate trajectory over the first 24 hours of admission, stratified by patients who did and did not develop systolic dysfunction. Furthermore, unadjusted and adjusted linear mixed models (adjusted for the above covariates, and an interaction term for the presence/absence of systolic dysfunction) were used to analyze systolic blood pressure, mean arterial pressure, and heart rate change during 12-hour epochs after admission. Sensitivity analyses were conducted to verify the robustness of the results, using different functional forms to

model time and excluding primary model covariates, including vasopressor use, fluid balance, osmotherapy, and sedative infusions. All analyses were performed using Stata statistical software (StataCorp, College Station, Texas, USA).

Results

A total of 35 patients with moderate-severe TBI were recruited and underwent a baseline TTE exam. After review of all echocardiograms, 3 patients were excluded due to unsuitable echocardiographic windows for assessment of systolic function, leaving 32 patients for analysis. In eight patients, a research TTE within the first day after injury was not able to be performed due to clinical circumstances (i.e. ongoing resuscitation, clinical procedures, or surgery) – in these patients, the baseline TTE was performed within 2 days after admission.

Demographic and clinical characteristics of the cohort, stratified by the presence or absence of systolic dysfunction on baseline TTE, are shown in Table 1. The group that developed systolic dysfunction was younger compared to the group that did not develop systolic dysfunction (mean age 27.1 versus 39.1 years, respectively). Both groups were primarily male, and free of major systemic disease, including respiratory and renal diseases. A higher proportion of patients who developed systolic dysfunction, compared to those who did not develop systolic dysfunction experienced a motor vehicle collision as the primary injury mechanism (57% versus 24%, respectively). Both groups had high proportions of intracranial hemorrhage on the initial head computed tomography (CT), but the group that developed systolic dysfunction had a lower mean admission Glasgow Coma Scale (GCS) score (3.4 versus 5.7). Admission SBP was similar in patients who developed and did not develop systolic dysfunction, and both groups experienced hypotension within the first 24 hours (SBP $\leq$ 90mmHg, 43% and 32%, respectively) and hypertension within the first 24 hours (SBP $\geq$ 140mmHg, 86% and 76%, respectively). The mean admission heart rate was higher in the group with systolic dysfunction (105.6 versus 81.4 bpm), and a higher proportion of patients in the group with systolic dysfunction required vasopressors within 24 hours of admission (29% versus 16%).

Echocardiographic findings are described in Table 2. Systolic dysfunction was present in 7 (22%) patients. Mean fractional shortening was 20% in the group with systolic dysfunction, compared to 32% in the group without systolic dysfunction ($p < 0.001$), primarily driven by a larger mean left-ventricular internal diameter in systole (3.91 versus 3.10 cm, $p < 0.001$). Mitral annular septal tissue velocity, a measure of longitudinal left ventricular contractility, did not differ between the groups (9.49 versus 9.60 cm/s, $p=0.65$). Diastolic parameters were similar between both groups, including E to A ratio, mitral annular septal tissue velocity [e'(s)], and E to e'(s) ratio. The group with systolic dysfunction had a higher early mitral inflow, demonstrated by a higher E-wave velocity (83.7 versus 63.0 cm/s, $p=0.02$).

The unadjusted and adjusted (after adjustment for age, gender, admission GCS, fluid balance, vasopressor use, sedation, surgical therapy, and osmotherapy) SBP, MAP, and heart rate (stratified by the presence/absence of systolic dysfunction) over the first 24 hours after admission are shown in Figures 1, 2, and 3. The unadjusted and adjusted rates of change of SBP, MAP, and heart rate (in patients who developed systolic dysfunction, compared to patients who did not develop systolic dysfunction) over the first day of hospitalization are shown in Table 3. During the first 12 hours after admission, the group that developed systolic dysfunction had an adjusted mean SBP that was 12.6 mmHg (95% CI: 8.1 – 17.2, $p<0.001$) higher than the group that did not develop systolic dysfunction; during 13-24 hours after admission, the mean SBP decreased at a greater rate (10.2 mmHg, 95% CI: 4.2 – 16.1) in the group with systolic dysfunction, compared to the group without systolic dysfunction ($p<0.01$). During the first 12 hours after admission, the group that developed systolic dysfunction had an adjusted mean MAP that was 15.9 mmHg (95% CI: 12.2 – 19.5, $p<0.001$) higher than the group that did not

develop systolic dysfunction; during 13-24 hours after admission, the mean arterial pressure decreased at a greater rate (9.1 mmHg, 95% CI: 4.3 – 13.9) in the group with systolic dysfunction, compared to the group without systolic dysfunction ($p<0.0001$). During the first 12 hours after admission, the group that developed systolic dysfunction had an adjusted mean heart rate that was 23.7 bpm (95% CI: 20.1 – 27.2, $p<0.001$) higher than the group that did not develop systolic dysfunction; during 13-24 hours after admission, the mean heart rate did not have a statistically significant decrease in the group with systolic dysfunction, compared to the group without systolic dysfunction ($p=0.67$). All sensitivity analyses revealed no substantial changes in the magnitude or direction of regression estimates from the primary model.

Discussion

Our primary finding is that patients who develop systolic dysfunction following TBI have a distinct hemodynamic profile over the first 24 hours after admission, compared to TBI patients who do not develop systolic dysfunction. To our knowledge, our findings provide the first evaluation of the hemodynamic profile that is associated with the development of systolic dysfunction following neurologic injury.

We found that the hemodynamic profile associated with the development of systolic dysfunction after TBI is that of early hypertension and tachycardia, followed by a decrease in blood pressure after 12 hours following admission. This finding suggests an early maladaptive activation of the sympathetic nervous system and excessive catecholamine release as one potential underlying mechanism for systolic dysfunction following TBI. The maladaptive release of catecholamines has been proposed as the primary underlying mechanism of both neurogenic stunned myocardium following subarachnoid hemorrhage[12], as well as non-neurologic stress cardiomyopathies[13]. Both preclinical and clinical studies have established that catecholamine release is triggered after severe injury to the brain by regional injury to the brain, elevation in intracranial pressure (ICP), and activation of the lower brain and hypothalamic neuroendocrine pathways[7]. Elevated catecholamine levels within 48 hours of TBI have been shown to be prognostic of a poor outcome[14,15], including worse GCS at 1 week, a higher number of ventilator days and length of stay, as well as worsened survival[16]. Future studies in TBI populations should more clearly elucidate the time course of catecholamine elevations following TBI and their relationship with systolic dysfunction and other organ injury; in addition, other mechanistic factors, such as neuroinflammation[7] and adrenergic receptor genetic polymorphisms[17], should be explored.

The result of excess systemic catecholamine release is often an early increase in arterial blood pressure and heart rate, and while this hemodynamic response may be adaptive to a point, ongoing catecholamine-induced hypertension may also cause secondary brain damage by aggravation of vasogenic edema[18,19], as well as myocardial injury[12,20,21]. Several preclinical models have shown that the initial elevation of blood pressure following catecholamine excess is generally followed by both myocardial dysfunction and eventual hemodynamic collapse; interestingly, pretreatment with either adrenalectomy, alpha-blockers, or beta-blockers may mitigate this effect[22,23]. Thus, while a catecholamine-excess state (and consequent hypertension) may initially be protective following injury, dysregulated catecholamine excess appears to be associated with cardiac dysfunction and poor physiological outcomes. As cardiac output is a critical component of cerebral blood flow[4], it is plausible that impaired cardiac function as a result of catecholamine-excess may contribute to impaired cerebral blood flow and poor outcomes after TBI, although this hypothesis would require future investigation.

While patients with moderate-severe TBI and systolic dysfunction had reduced radial left ventricular function (as measured by fractional shortening) in our study, it was preserved longitudinally (as measured by the peak mitral annular septal tissue velocity in systole), suggesting potential early compensation for impaired radial function. This is a hypothesis-generating observation, and future studies incorporating a comprehensive evaluation of regional wall motion and left-ventricular strain evaluation[24] may be able to shed more light on the complex radial, circumferential, and longitudinal changes in ventricular function following TBI. Aside from an increased E-wave velocity, we did not observe worse diastolic function in moderate-severe TBI patients with systolic dysfunction; this may be because diastolic dysfunction is primarily described in chronic heart disease, and these definitions may lack the sensitivity needed to identify acute

diastolic dysfunction as a result of brain-heart interactions. Diastolic dysfunction may be a clinically meaningful finding, as it may alter fluid and vasopressor therapy, as well as better stratify patients at high risk for developing pulmonary edema[25]. As our study was not designed or powered for the complex evaluation of diastolic function in the TBI population, our findings should be considered exploratory, and future studies should evaluate diastolic function following TBI in further depth.

Our findings have mechanistic and therapeutic implications in the management of patients with moderate-severe TBI. Our findings of the unique hemodynamic profile that is associated with the development of systolic dysfunction after injury helps to shed light on the role of sympathetic excess in the pathogenesis of systolic dysfunction following TBI. In addition, our findings may contribute to possible therapeutic implications for blood pressure management early after TBI. There is a growing body of literature suggesting that early catecholamine reduction through beta-blockade may be beneficial in TBI[26], potentially due to their modulating effect of the maladaptive catecholamine-excess state following severe TBI. Further research is required to evaluate whether attenuation of the catecholamine excess state may reduce sympathetically-mediated myocardial damage following TBI.

There are several limitations to our study. First, our sample size was small, which can decrease the precision of regression estimates; but we were able to harness a large number of hemodynamic measurements in each patient, and our statistical inferences were robust in multiple sensitivity analyses. Second, as it is not feasible to continuously measure cardiac function from the time of injury to determine exactly when systolic dysfunction developed, it is impossible to fully establish a cause-effect relationship of

hypertension preceding the development of systolic dysfunction in our cohort. In addition, longer-term changes in hemodynamic parameters (beyond 24 hours) become more challenging to study without concurrent cardiac data. Despite this, the observation of hypertension preceding cardiovascular dysfunction and collapse is in line with many preclinical studies on catecholamine-excess states. Third, we chose fractional shortening as our primary measure of systolic dysfunction (rather than the more traditional measure of ejection fraction), as it was unsafe to place many patients in a left lateral decubitus position due to labile intracranial pressures making it difficult to image the true cardiac apex. Despite this, calculation of fractional shortening has a strong record of reproducibility and has been used in many clinical studies[27]. Fourth, it is impossible to rule out the potential for unmeasured or residual confounding in our regression models, although we were able to control for the large majority of likely confounding variables in our models. Lastly, it not possible to establish that none of our patients had systolic dysfunction prior to their TBI, but this would be unlikely as we included a population that was young and had no history of cardiovascular disease prior to inclusion in our study.

In conclusion, patients who develop systolic dysfunction following TBI have a distinctive hemodynamic profile, compared to patients who do not develop systolic dysfunction. Our findings have both mechanistic and therapeutic implications in brain-heart interactions. Future research should more clearly elucidate the biochemical mechanistic pathways leading to systolic dysfunction following TBI.

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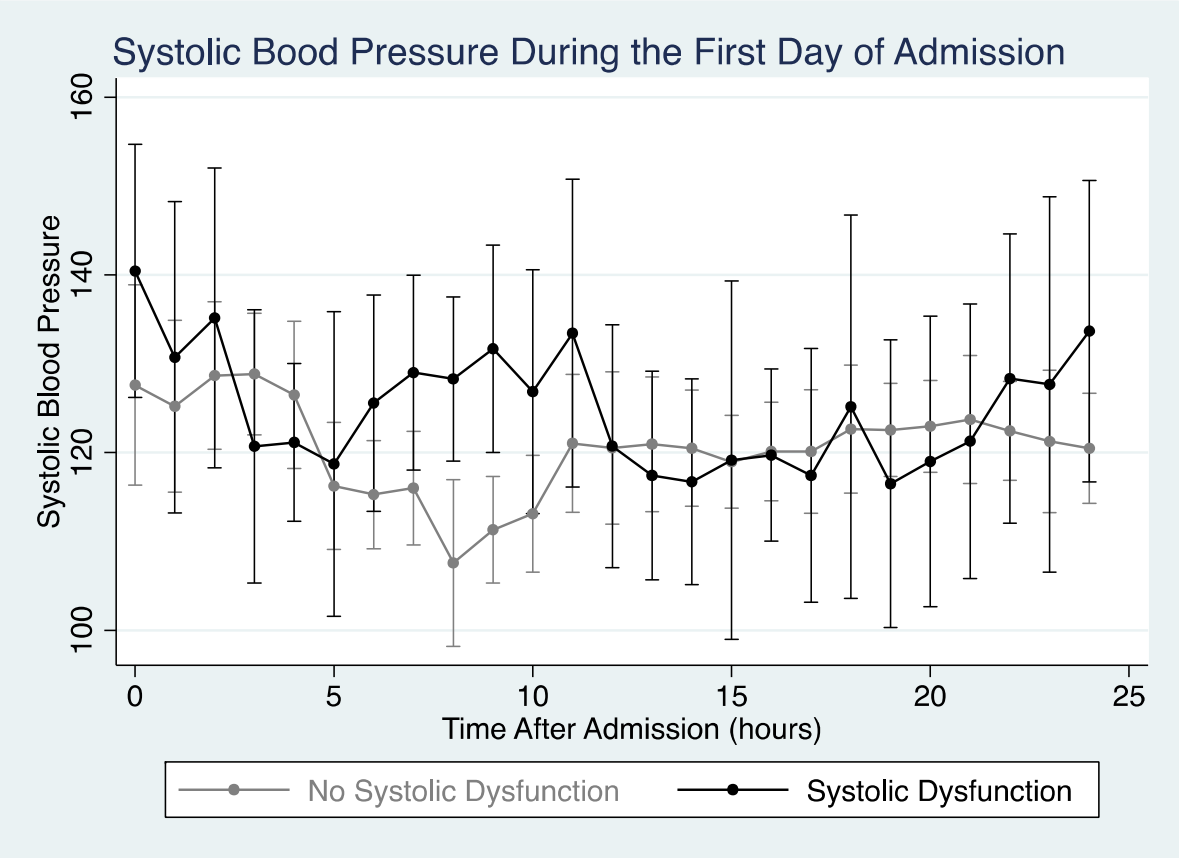
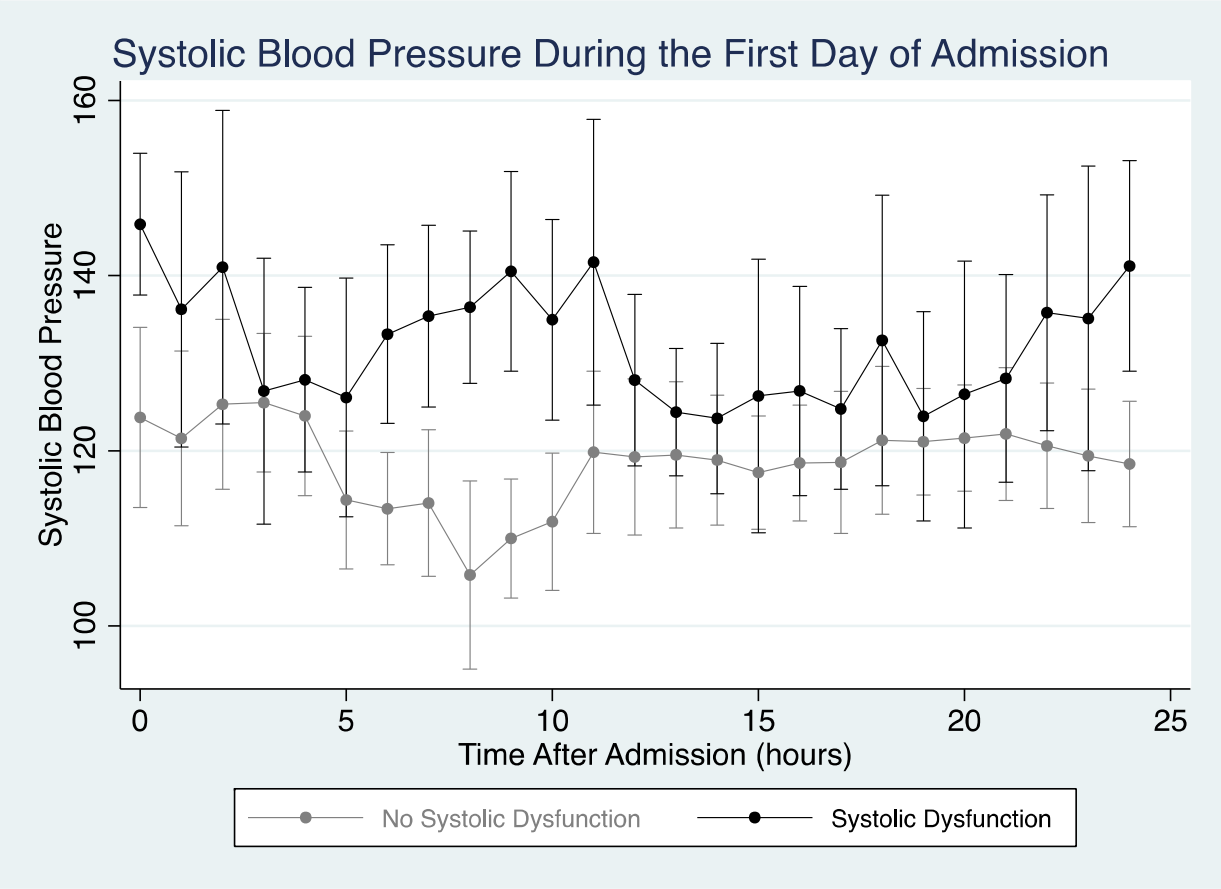
Figure 1a: Unadjusted Systolic Blood Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a]



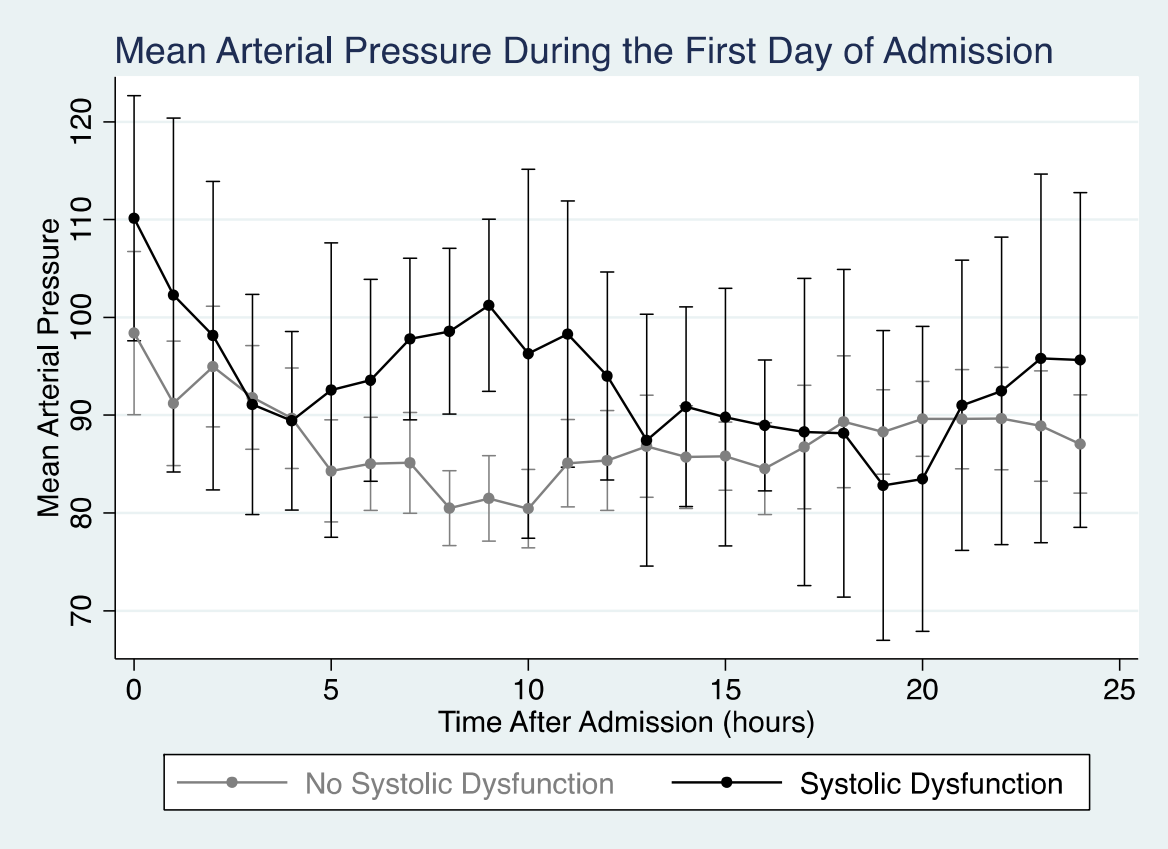
[a]In above figure, circles represent mean values of adjusted systolic blood pressure and whiskers represent the 95% confidence interval

Figure 1b: Adjusted Systolic Blood Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a,b]



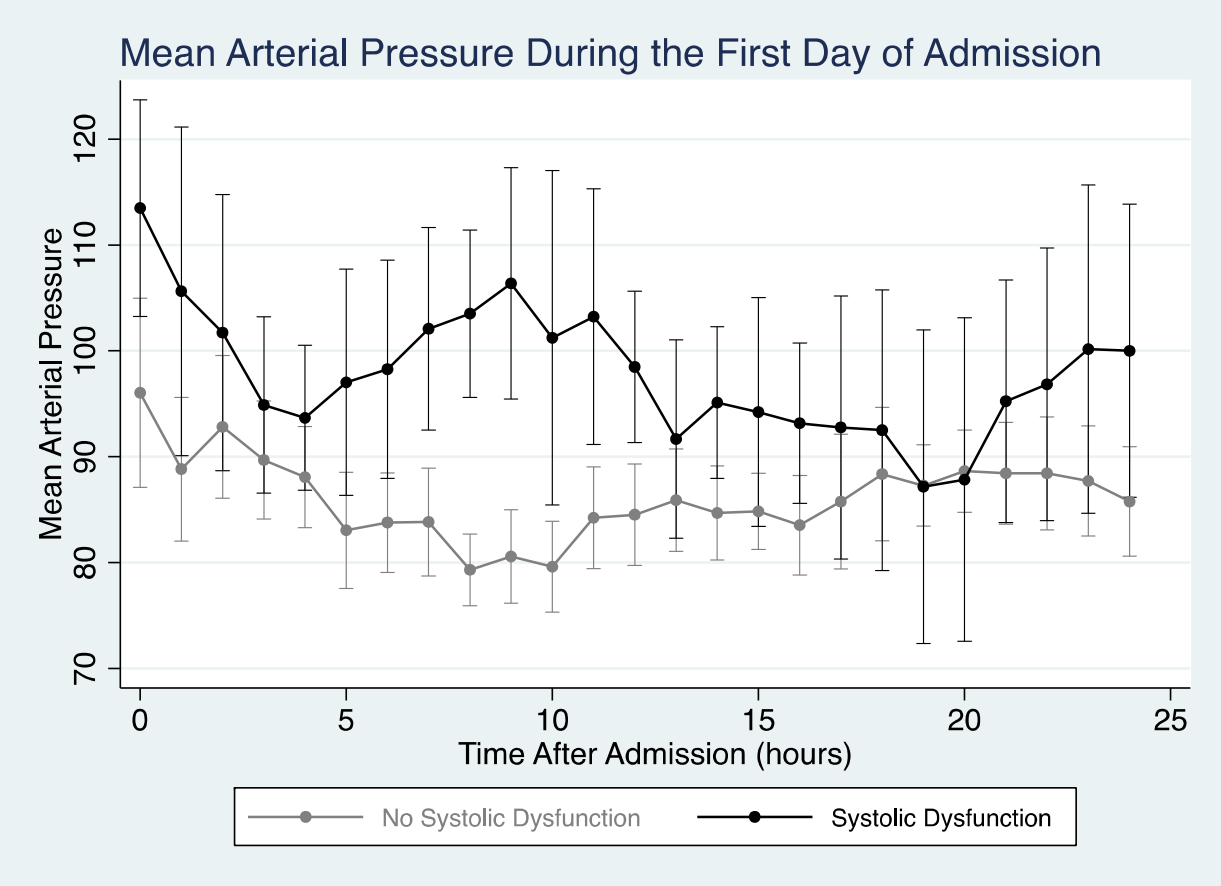
[a]In above figure, circles represent mean values of adjusted systolic blood pressure and whiskers represent the 95% confidence interval
[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

Figure 2a: Unadjusted Mean Arterial Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a]



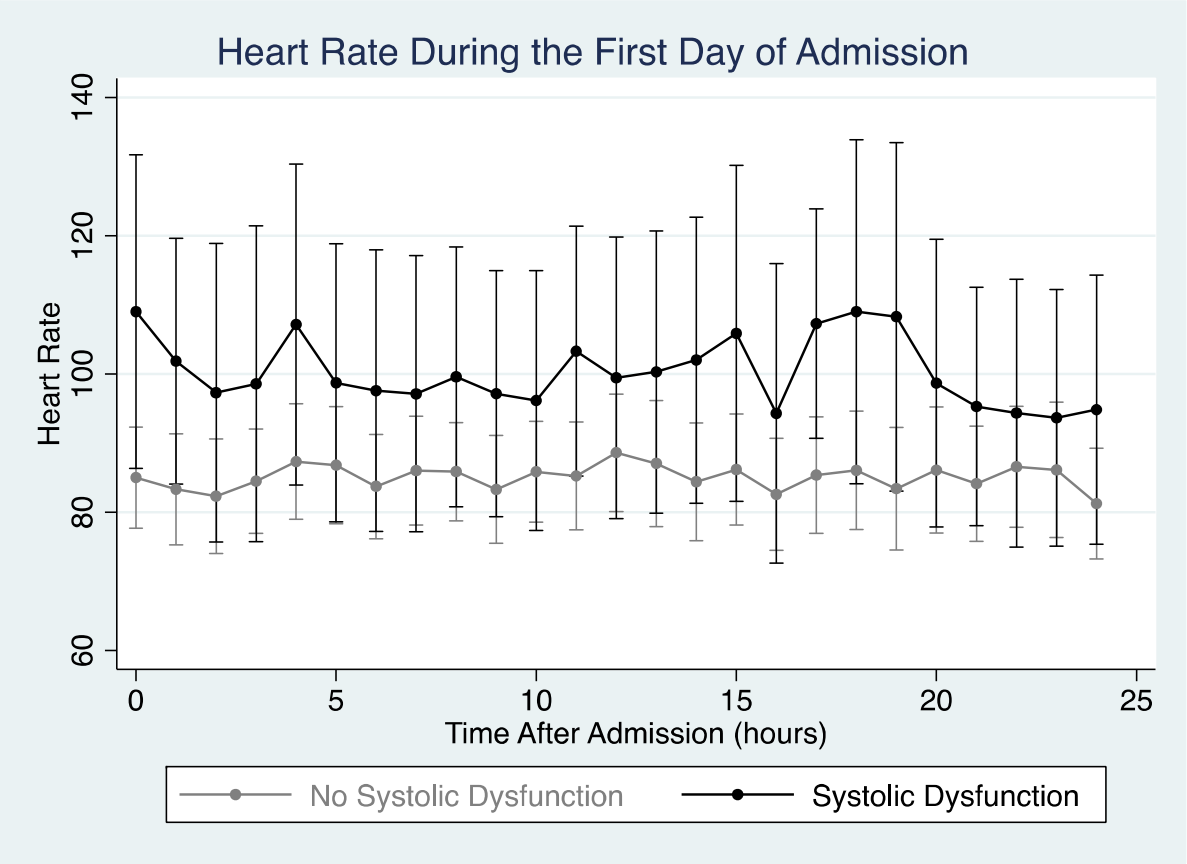
[a]In above figure, circles represent mean values of adjusted mean arterial pressure and whiskers represent the 95% confidence interval

Figure 2b: Adjusted Mean Arterial Pressure Trajectory Over 24 Hours Following Admission for Moderate-Severe Traumatic Brain Injury[a,b]



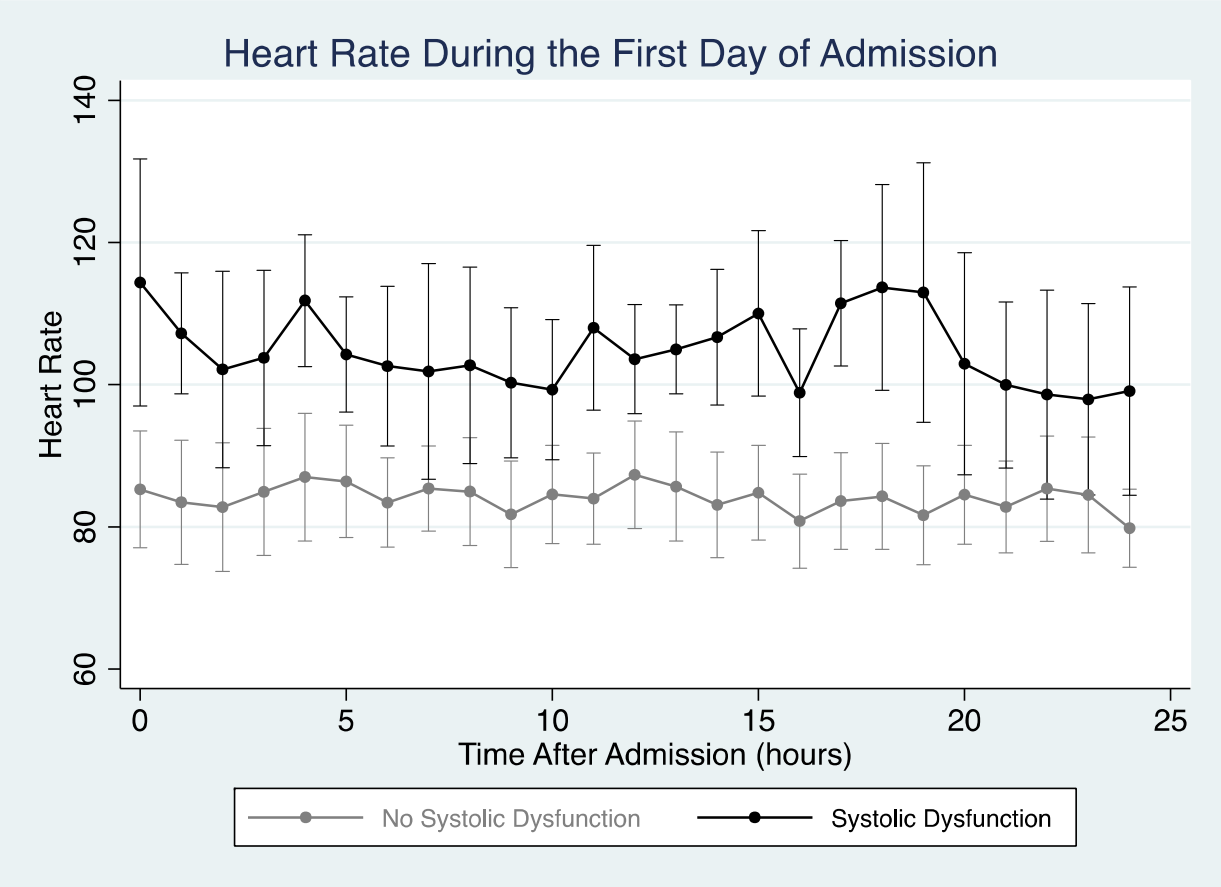
[a]In above figure, circles represent mean values of adjusted mean arterial pressure and whiskers represent the 95% confidence interval
[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

Figure 3a: Unadjusted Heart Rate Trajectory Over 24 Hours Following Admission for Moderate-Severe TBI[a]



[a]In above figure, circles represent mean values of adjusted heart rate and whiskers represent the 95% confidence interval

Figure 3b: Adjusted Heart Rate Trajectory Over 24 Hours Following Admission for Moderate-Severe TBI[a,b]



[a]In above figure, circles represent mean values of adjusted heart rate and whiskers represent the 95% confidence interval
[b]Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

Table 1: Demographic and Clinical Characteristics in TBI Patients with and without Systolic Dysfunction[a]

	No systolic dysfunction (n=25)	Systolic dysfunction (n=7)
Age (years)	39.1 (13.7)	27.1 (5.6)
Race		
White	17 (68%)	4 (57%)
Black	2 (8%)	1 (14%)
Other	6 (24%)	2 (29%)
Male Gender	21 (84%)	6 (86%)
Medical Co-morbidities		
Pulmonary	0 (0%)	0 (0%)
Hypertension	1 (4%)	0 (0%)
Diabetes	2 (8%)	0 (0%)
Renal Disease	0 (0%)	0 (0%)
Injury Mechanism[b]		
Fall	8 (32%)	2 (29%)
Motor vehicle crash	6 (24%)	4 (57%)
Vehicle vs. pedestrian	4 (16%)	1 (14%)
Gunshot to head	0 (0%)	1 (14%)
Assault	3 (12%)	0 (0%)
Other	4 (16%)	0 (0%)
Initial Head CT Findings[c]		
Epidural hemorrhage	4 (16%)	1 (14%)
Subdural hemorrhage	19 (76%)	5 (71%)

Subarachnoid hemorrhage	19 (76%)	4 (57%)
Intraparenchymal hemorrhage	12 (48%)	3 (43%)
Glasgow Coma Scale		
Admission GCS	5.7 (2.5)	3.4 (1.1)
Highest GCS (within 24 hours)	9.3 (2.1)	7.7 (5.1)
Lowest GCS (within 24 hours)	4.8 (2.0)	4.9 (3.8)
Admission Hematocrit (%)	38.0 (5.2)	37.9 (6.2)
Systolic Blood Pressure (mmHg)		
Admission SBP	131.9 (25.2)	133.9 (19.4)
Lowest SBP in first 24 hours	98.4 (12.6)	96.1 (19.5)
Hypotension (SBP≤90) in first 24 hours	8 (32%)	3 (43%)
Hypertension (SBP≥140) in first 24 hours	19 (76%)	6 (86%)
Heart Rate (bpm)[d]		
Admission Heart Rate	81.4 (18.1)	105.6 (33.3)
Critical Care		
On vasopressors to maintain MAP>65 mmHg in first 24 hours	4 (16%)	2 (29%)
ICP monitor placement	12 (48%)	4 (57%)
Need for intracranial surgery	9 (36%)	3 (43%)

[a]Values are mean(SD) for continuous variables and n(%) for categorical variables.
[b]Some patients had more that one mechanism
[c]Some patients had multiple head CT findings
[d]All patients were in a normal sinus rhythm
CT=Computed Tomography; GCS=Glasgow Coma Scale; bpm=beats per minute; MAP=mean arterial pressure

Table 2: Early Transthoracic Echocardiogram Findings in Moderate-Severe TBI

	No Systolic Dysfunction (n=25)	Systolic Dysfunction (n=7)	p-value
Systolic Function[a,b]			
Left Ventricle Area End-Diastole (cm^2)	18.82 (4.47)	18.03 (6.22)	0.72
Left Ventricle Area End-Systole (cm^2)	8.73 (3.35)	937 (3.70)	0.68
Fractional Area Change (cm^2)	0.55 (0.09)	0.48 (0.14)	0.15
Left Ventricle Internal Diameter End-Diastole (cm)	4.58 (0.55)	4.87 (0.80)	0.27
Left Ventricle Internal Diameter End-Systole (cm)	3.10 (0.43)	3.91 (0.73)	**<0.001**
Fractional Shortening	0.32 (0.05)	0.20 (0.03)	**<0.001**
Mitral Annular Septal Tissue Velocity [S'(s) (cm/s)]	9.6 (2.30)	9.49 (2.36)	0.65
Diastolic Function[c]			
Mitral Inflow Peak Early Filling [E wave (cm/s)]	63.0 (17.76)	83.73 (18.78)	**0.02**
Mitral Inflow Peak Late Filling [A wave (cm/s)]	45.06 (12.42)	52.64 (14.16)	0.24
E-wave to A-wave Ratio	1.52 (0.59)	1.65 (0.51)	0.66
E-wave to A-wave Ratio < 1	4 (19%)	1 (20%)	0.69
E-wave to A-wave Ratio > 2	3 (14%)	2 (40%)	0.24
Mitral Inflow E-wave Deceleration Time (msec)	127.27 (45.69)	105 (31.46)	0.27
Mitral Annular Septal Tissue Velocity [e'(s) (cm/s)]	8.91 (2.44)	11.37 (3.12)	0.28
E-wave to e'(s) Ratio	7.19 (1.99)	7.79 (2.22)	0.54
Mitral Annular Septal Tissue Velocity [e'(s)] < 8 cm/s	8 (38%)	1 (17%)	0.32

Values are mean(SD) for continuous variables and n(%) for categorical variables.

[a] Data available in 26 subjects

[b] Data available in 26 subjects

[c] Doppler velocities from data available in 28 subjects. Tissues Doppler velocities from data available in 27 subjects.

Table 3: Rate of Change of Hemodynamic Variables in Patients with Systolic Dysfunction Compared to Patients without Systolic Dysfunction over the First Day after Admission

	Crude Mean (95% CI)	p	Adjusted* Mean (95% CI)	p
Systolic Blood Pressure**	-8.6 (-14.4, -2.9)	0.003	-10.2 (-16.1, -4.2)	0.001
Mean Arterial Pressure**	-7.8 (-12.4, -3.2)	0.001	-9.1 (-13.9, -4.3)	<0.0001
Heart Rate**	0.1 (-4.5, 4.7)	0.97	1.0 (-2.5, 1.2)	0.67

* Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery
**13-24 hours after admission, compared 0-12 hours after admission

Manuscript #3 (Aim #3): Association of Early Myocardial Workload and Mortality Following Severe Traumatic Brain Injury: An Analysis of the National Trauma Databank

Introduction

Adult traumatic brain injury (TBI) is a worldwide public health problem and contributes to 30% of all injury-related deaths(1). Severe TBI often results in early blood pressure instability (both hypertension and hypotension). Recent investigations have suggested this hemodynamic profile is associated with myocardial dysfunction following TBI(2). Furthermore, early blood pressure instability is associated with poor TBI outcomes(3, 4). While early intervention for hypotension following TBI has been recommended by international TBI guidelines(5, 6), no studies have evaluated the status of the heart when making rational choices of agents to control hemodynamics following TBI. A more thorough evaluation of cardiac status following TBI has the potential to improve hemodynamic management and improve outcomes.

The rate-pressure product (RPP, the product of systolic blood pressure and heart rate) is a bedside index of myocardial workload and is a reliable indicator of myocardial oxygen demand and consumption(7-9). While elevated myocardial workload has been strongly correlated with ischemic cardiac events in patients with heart disease(10) and during exercise(11), data on myocardial workload in the clinical neuroscience literature is limited. Optimal cardiac performance is crucial to maintaining cardiac output and in turn cerebral blood flow following neurologic injury, and increased myocardial workload may eventually lead to impaired cardiac function, reduced cerebral blood flow, and poor

functional outcomes(12). The RPP may represent an easily measured bedside variable to clinically assess myocardial workload and optimize hemodynamic management following severe TBI. To further understand the impact of early myocardial workload on TBI outcomes, our study's primary aims were to: 1.) Describe the early myocardial workload profile following severe TBI, 2.) Examine the association between the admission myocardial workload profile and mortality, and 3.) Examine the association between the early myocardial workload profile in addition to blood pressure alone and mortality following severe TBI.

Methods

National Trauma Data Bank

Our study used data from the National Trauma Data Bank (NTDB), a national trauma registry created and operated by the American College of Surgeons. The NTDB has the mission to provide the trauma community with accessible and "consistent, quality data"(13). The NTDB is the largest assembled trauma registry, with the goal being "to inform the medical community, the public, and decision makers about a wide variety of issues that characterize the current state of care for injured persons."(14) Within the NTDB, each subject is de-identified and is assigned a unique identification number, which can be used to link data across multiple files. Because the NTDB is fully de-identified and does not meet the regulatory definition of human subjects research, our study was exempt from institutional review board approval.

Study Design and Population

We conducted a retrospective cohort study using the NTDB data for the years 2007-2014. We linked all data files per year (using the de-identified patient number), including files for demographic data, facility data, emergency department data, injury characteristics, discharge diagnoses, procedures, and disposition. In order to narrow our population to adult patients admitted to the hospital with an isolated severe TBI, we made the following exclusions: patients less than 18 years of age, patients without an International Classification of Diseases (ICD) code for TBI, patients with an emergency department Glasgow Coma Scale (GCS) score of greater than 8, and patients not admitted to the hospital. In addition to the clinical GCS variable, we also used the head Abbreviated Injury Score to assess TBI severity, as it outperforms the GCS score as a predictor of outcome after TBI(15); and we excluded patients with a head AIS score of less than 4, which represents the threshold for severe TBI(16). In order to focus on the

effect of the isolated brain injury on myocardial workload (and remove the confounding effects of significant blood loss and non-head injuries), we excluded patients with penetrating head injuries and patients with an AIS score of greater than 2 in non-head body regions. As our primary exposure involved the assessment of myocardial workload using emergency department vital signs, we excluded patients with missing or invalid blood pressure and heart rate data. We also excluded patients who died within 24 hours of admission based on the rationale that early mortality may not have been related to myocardial workload, but rather the severity of the initial neurologic injury. Lastly, we excluded patients who experienced a hospital transfer, as we wanted to capture the admission hemodynamic variables as close to the time of injury as possible, as well as final hospital discharge disposition.

Exposures, Outcomes, and Confounders

Our primary exposure of interest was the admission RPP, calculated as the emergency department systolic blood pressure multiplied by the emergency department heart rate. RPP thresholds for the primary analysis were chosen based on clinical studies demonstrating the mean resting and submaximal RPP thresholds in a patient population that was negative for stress-induced cardiac ischemia and free of cardiovascular medications(17), and rounded to the nearest ten-thousand for an easily interpretable bedside clinical threshold; thus, the reference RPP values selected were between 10,000 to 20,000. These RPP thresholds were further subdivided in the primary analysis in order to examine a dose-response effect of RPP on mortality into the following groups: less than 5,000; 5,000 to 9,999; 10,000 to 14,999; 15,000 to 19,999; and greater than 20,000. As different myocardial workloads (using RPP) and outcomes have not been rigorously evaluated in the neuroscience literature, we tested the robustness of the direction of the risk of mortality at low and high RPPs using sensitivity analyses with

differing RPP thresholds, using 7,500 and 22,500 for lower and upper limits, respectively.

In addition to detailed admission hemodynamic data, relevant demographic, clinical, and injury severity variables of interest included age, gender, Injury Severity Score (ISS), admission total GCS score, the need for mechanical ventilation during the hospitalization, and injury mechanism. Each facility in the NTDB was assigned a unique facility identification number, allowing facility-level factors to be collected [facility size, teaching status, and trauma level designation]; all of our analyses were adjusted for clustering by facility. Our primary outcome of interest was in-hospital mortality**.**
In order to select appropriate variables for adjustment in our statistical models, we created directed acyclic graphs (DAG) to construct causal diagrams of the relationship between early myocardial workload and mortality using available NTDB variables. Our final DAG (based on prior knowledge and biologic plausibility) included variables for adjustment that closely resembled the data driven approach for confounder adjustment in the NTDB, which strongly suggests a "minimum set" of confounding variables that are necessary for adjustment in NTDB mortality analyses(18). All variables in our final model were included in the "minimal set," including age, gender, blood pressure and heart rate (captured in the RPP), GCS score, ISS, and mechanical ventilation.

Statistical Analysis

We described the demographic and clinical characteristics of the patient cohort, stratified by RPP categories. We further described RPP categories by hemodynamic characteristics, both as continuous and categorical variables. Continuous variables are reported as means and standard deviation; and categorical variables are reported as

counts and percentages. We calculated the cumulative incidence of in-hospital mortality, stratified by RPP categories.

For our analyses, we calculated univariate and multivariable estimates of the association between RPP levels and in-hospital mortality using Poisson regression models with clustered robust standard error estimates relaxing the assumption that observations from the same hospital are independent. We adjusted our analysis for age, gender, ISS score, total GCS score, and need for mechanical ventilation. As we hypothesized a "U"-shaped dose-response relationship between RPP level and outcome, RPP was grouped *a priori* into 5 categories, with the middle category (10,000 to 14,999) serving as the reference group. To assess the influence of age on the shape of the relationship between RPP levels and mortality, we conducted an additional analysis stratified by age categories. In addition, we divided our cohort into blood pressure groups [hypotensive (SBP<90 mmHg), normotensive (SBP 90-140 mmHg), and hypertensive(SBP>140 mmHg)] to analyze the association between blood pressure alone versus blood pressure with a high/low RPP and in-hospital mortality. Sensitivity analyses were conducted to test the robustness of our results at differing low and high RPP cut-points. We report effect measures as relative risk with 95% confidence intervals. All analyses were conducted using Stata 13.0 (College Station, Texas).

Results

All patients from the NTDB from 2007 to 2014 (N=5,843,837) were initially included in the patient sample. Among these patients, 71,999 patients with severe isolated TBI patients were identified. After all exclusions we arrived at our final cohort of 26,412 patients (Figure 1).

Demographic, Clinical, and Myocardial Workload Characteristics

Table 1 describes the demographic and clinical characteristics of the cohort, stratified by RPP categories [<10,000 (low RPP), 10,000 to 15,000 (middle RPP), >15,000 (high RPP)]. In all groups, the majority of patients were young (44% aged 18-44) and primarily male (73%). The majority of patients in our cohort were white (66%), and the primary injury mechanism was fall-related (43%), followed by motor-vehicle related injuries (34%). The admission GCS [mean(SD) 4.4(1.9)] score was low in the cohort, suggesting severe injury in all RPP groups. Overall, 8,316 (31%) of the patients in our cohort experienced in-hospital mortality.

Hemodynamic characteristics of the cohort, stratified by myocardial workload, are summarized in Table 2. In the lowest RPP group (<5,000), RPP was primarily driven by bradycardia (72%), while 43% of patients were normotensive. The next RPP group (5,000 – 9,999) included patients who were primarily normotensive (68%) and with a normal heart rate (67%). In the reference RPP group (10,000 – 14,999), the majority of patients had a normal heart rate (77%), and were both normotensive (48%) and hypertensive (51%). Both high RPP groups (RRP $\geq$ 15,000) were primarily driven by hypertension [RPP 15,000 – 19,999 (81%), RPP $\geq$ 20,000 (97%)] and tachycardia [RPP 15,000 – 19,999 (61%), RPP $\geq$ 20,000 (91%).

Association Between Myocardial Workload and In-Hospital Mortality

The association between admission myocardial workload and in-hospital mortality is examined in Table 3. The cumulative mortality was lowest in the reference RPP group (28.1%, 95% CI: 27.3% - 29.0%), and was higher in a stepwise fashion in both the low and high RPP groups. Compared to the reference RPP group, in-hospital mortality was an absolute 22 percentage points higher in the lowest RPP group (cumulative mortality 50.2%, 95% CI: 43.6% - 56.9%) and an absolute 11 percentage points higher in the highest RPP group (cumulative mortality 39.2%, 95% CI: 37.4% - 40.9%). On multivariable regression analysis, the lowest RPP group was associated with a 50% increased risk of mortality, compared to the reference RPP group (relative risk 1.50, 95% CI: 1.31-1.76, $p<0.0001$); and the highest RPP group was associated with a 25% increased risk of mortality, compared to the reference RPP group (relative risk 1.25, 95% CI: 1.18 – 1.92, $p<0.0001$). Sensitivity analyses using differing RPP cut-points consistently demonstrated this “U-shaped” relationship.

Figure 2 examines the association of admission myocardial workload and in-hospital mortality, stratified by the age categories of 18-44, 45-64, and $\geq$65 years. Overall, the association between admission RPP and in-hospital mortality is blunted by older age. In the lowest RPP category, younger patients had a higher risk of in-hospital mortality (relative risk 2.00, 95% CI: 1.53 – 2.61, $p<0.0001$) than middle-age (relative risk 1.63, 95% CI: 1.34 – 1.99, $p<0.0001$) and elderly (relative risk 1.14, 95% CI: 0.93 – 1.41, $p=0.21$) patients. In the highest RPP category, younger patients also had a higher risk of in-hospital mortality (relative risk 1.54, 95% CI: 1.35 – 1.76, $p<0.0001$) than middle-age (relative risk 1.22, 95% CI: 1.11 – 1.34, $p<0.0001$) and elderly (relative risk 1.16, 95% CI: 1.09 – 1.24, $p<0.0001$) patients. The risk of in-hospital mortality was statistically significant ($p<0.05$) for all age-groups only in the highest RPP category.

Myocardial Workload in Addition to Blood Pressure Alone

The association between myocardial workload in addition to blood pressure alone and in-hospital mortality following severe TBI is examined in panels shown in Figure 3. Among patients with admission hypertension following severe TBI, patients with an elevated myocardial workload had a higher risk of in-hospital mortality (relative risk 1.28, 95% CI: 1.21 – 1.35, $p<0.0001$) than patients without an elevated myocardial workload (relative risk 1.14, 95% CI: 1.09 – 1.19, $p<0.0001$), compared to normotensive patients. Compared to patients with admission normotension without elevated or depressed myocardial workload, patients with an elevated myocardial workload (relative risk 1.70, 95% CI: 1.37 – 2.13, $p<0.0001$) and depressed myocardial workload (relative risk 1.62, 95% CI: 1.35 – 1.95, $p<0.0001$) had an increased risk of in-hospital mortality. Among patients with admission hypotension, patients with (relative risk 1.54, 95% CI: 1.27 – 1.85, $p<0.0001$) and without (relative risk 1.55, 95% CI: 1.41 – 1.70, $p<0.0001$) depressed myocardial workloads had a similar risk of in-hospital mortality, compared to patients with admission normotension.

Discussion

The main findings of our study are the following: 1.) Depressed and elevated myocardial workload profiles are common following isolated severe TBI, 2.) The admission myocardial workload profile is strongly associated with in-hospital mortality in a "U-shaped" fashion, and 3.) The admission myocardial workload profile provides additional prognostic information beyond blood pressure alone in predicting in-hospital mortality following severe TBI. Optimization of the myocardial workload profile may potentially represent a novel hemodynamic target to improve myocardial performance and clinical outcomes following severe TBI.

Measuring myocardial workload in response to stress using RPP has been studied in the cardiology and exercise physiology literature. Prior studies have demonstrated that the RPP highly correlates with invasive measures of myocardial oxygen consumption(7, 8), and thus represents a simple and non-invasive bedside measurement of myocardial workload. Both inadequate myocardial workload response to stress, as well as chest pain at increased myocardial workloads have been demonstrated in patients with ischemic heart disease(17). While the mechanisms driving myocardial workload remain to be fully elucidated in TBI, elevations in myocardial workload following severe TBI may be a clinical manifestation of the catecholamine-excess state that is often triggered following severe neurologic injuries(19-21).

We found that an elevated admission myocardial workload was associated with increased in-hospital mortality following severe TBI, especially at RPP levels that exceed human submaximal RPP thresholds. While an elevated RPP may initially be protective by helping to maintain cerebral blood flow in the setting of impaired cerebral autoregulation following injury(22), this myocardial workload profile may eventually

become maladaptive, contribute to myocardial dysfunction(2), and may ultimately lead to reduced cardiac output after injury. As cardiac output is a critical determinant of cerebral perfusion(12), this could leave the injured brain susceptible to secondary brain injuries. In addition, recent observational studies(23, 24) and a meta-analysis(25) have suggested that beta-blockers have been associated with improved outcomes following TBI, but the mechanisms remain unclear. It is possible that the catecholamine reduction and improvements in myocardial workload conditions(26) induced by beta-blockers may ultimately improve cardiac output and cerebral perfusion. Furthermore, rather than administering beta-blockers to all patients following severe TBI, beta-blockers may be ideally suited for the subgroup of severe TBI patients with elevated myocardial workload, although this should be rigorously examined in future studies.

In our study, we also found that a reduced myocardial workload was associated with excess in-hospital mortality following severe TBI. While admission hypotension was relatively uncommon in our cohort (2.7%), reduced myocardial workload on admission was a much more common scenario (21.8%). Thus, recognizing and treating hypotension may not be enough to prevent reductions in cerebral blood flow, as suboptimal myocardial workload (in the face of a normal blood pressure) may also contribute. While the traditional approach to vasopressor choice following TBI has frequently involved the use of alpha-agonists without inotropic effects (i.e. phenylephrine)(27), this may paradoxically worsen myocardial workload and cardiac output, despite normalization of blood pressure(28). By moving myocardial workload into a more optimal range, vasopressors with alpha-adrenergic and inotropic effects (i.e. norepinephrine) may be better suited to correct blood pressure and improve cardiac output following TBI, but this should be evaluated in future studies.

We found that the effect of myocardial workload on mortality was blunted by older age, and there may be several reasons for this. First, older patients have a less robust hemodynamic response to exercise as compared to younger patients(29), and may not be able to generate a increased myocardial workload profile for a prolonged period in response to stress. Second, as the myocardial response to catecholamines decreases with age(30, 31), the cardiac response to catecholamine-excess may be more pronounced in the younger population. Lastly, the ideal RPP for optimal cardiac performance likely varies by age, and future studies should more closely examine RPP cut-points by age.

We found that the addition of myocardial workload data to patients with admission normotension and hypertension provided added risk-stratification for in-hospital mortality. While international guidelines emphasize that normotension is the hemodynamic goal following severe TBI(5), we found that patients with normotension and both low and high myocardial workloads did worse than patients with normotension alone. Furthermore, among hypertensive patients in our cohort, patients with hypertension and an elevated myocardial workload did worse than patients with hypertension alone. Thus, our data suggests that hemodynamic goals following TBI should move beyond blood pressure alone, and may need to consider the cardiovascular system in its entirety, including the heart, systemic circulation, and end-organ (particularly brain) perfusion. The evolution of multimodal monitoring following TBI(32) may allow a more personalized approach to hemodynamic management following TBI, although appropriate goal parameters must be evaluated in future studies.

There are some limitations to our study. First, due to the nature of a large administrative dataset, granular details on patient management in the hospital were not available; thus,

it is impossible to fully eliminate the possibility of residual confounding in our analysis. To minimize residual confounding, we sharply restricted our cohort to define a study population of patients with isolated severe TBI, in order to remove the confounding effects of less severe TBI and other injuries (i.e. polytrauma). Second, because only admission hemodynamic variables were available in our dataset, we were unable to assess the effect of treatment of depressed/elevated RPP on mortality; thus, future studies should more closely examine treatment effects of RPP following severe TBI. Third, due to limitations of disposition data in the NTDB, we were only able to capture in-hospital mortality following severe TBI; and future studies, should examine long-term mortality, as well as neurocognitive outcomes beyond mortality alone. Lastly, due the observational nature of our study, it is impossible to fully establish a causal link from our study alone.

In conclusion, the admission myocardial workload profile is associated with in-hospital mortality following severe TBI in a “U-shaped” fashion. Our findings are novel, and suggest that cardiac performance is important following severe TBI. Future studies should more closely evaluate cardiac function, establish ideal myocardial workload targets, and examine the impact of personalized hemodynamic management to optimize cerebral perfusion and clinical outcomes following severe TBI.

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Table 1. Demographic and Clinical Characteristics of Patients with Isolated Severe TBI* **

Rate-Pressure Product	Total	< 10,000	10,000 – 14,999	> 15,000
N	26,412 (100%)	5,753 (21.8%)	11,343 (42.9%)	9,316 (35.3%)
Age (years)		46.1 ± 20.2	47.7 ± 20.5	51.2 ± 20.6
18-44	11,591 (43.9%)	2,855 (49.6%)	5,228 (46.1%)	3,508 (37.7%)
45-64	7,818 (29.8%)	1,619 (28.1%)	3,318 (29.3%)	2,941 (31.6%)
≥ 65	6,355 (24.1%)	1,173 (20.4%)	2,580 (22.8%)	2,602 (27.9%)
Male	19,289 (73.0%)	4,173 (72.5%)	8,317 (73.3%)	6,799 (73.0%)
Race				
White	17,392 (65.9%)	3,815 (66.3%)	7,533 (66.4%)	6,044 (64.9%)
Hispanic	3,298 (12.5%)	730 (12.7%)	1,390 (12.3%)	1,178 (12.6%)
African American	2,993 (11.3%)	614 (10.7%)	1,208 (10.7%)	1,171 (12.6%)
Asian/PI	718 (2.7%)	138 (2.4%)	328 (2.8%)	259 (2.8%)
Other	1,135 (4.3%)	246 (4.3%)	494 (4.4%)	388 (4.2%)
Missing	876 (3.3%)	210 (3.7%)	390 (3.4%)	276 (3.0%)
Injury Mechanism				
Motor –vehicle related	8,876 (33.6%)	2,035 (35.4%)	3,990 (35.2%)	2,851 (30.6%)
Fall	11,278 (42.7%)	2,235 (38.9%)	4,625 (40.8%)	4,418 (47.4%)
Transport, other	1,964 (7.4%)	496 (8.6%)	879 (7.8%)	589 (6.3%)
Struck by/against	2,158 (8.2%)	497 (8.6%)	982 (8.7%)	679 (7.3%)
Other	2,136 (8.1%)	490 (8.5%)	867 (7.6%)	779 (8.4%)
Admission GCS Score	4.4 ± 1.9	4.2 ± 1.8	4.5 ± 1.9	4.5 ± 1.8
Head AIS Score	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4	4.2 ± 0.4
Injury Severity Score	18.0 ± 9.1	18.5 ± 9.3	17.8 ± 9.2	18.1 ± 8.9

*Data are presented as mean ± SD and counts(percentage)
**Column percentage do not add up to 100% in some categories due to missing data
GCS=Glasgow Coma Scale; AIS=Abbreviated Injury Scale

Table 2. Hemodynamic Characteristics Stratified by Rate-Pressure Product*

Rate-Pressure Product	< 5,000	5,000-9,999	10000–14,999	15,000-19,999	≥ 20,000
N	299 (0.9%)	5,524 (21.0%)	11,343(42.9%)	6,288 (23.8%)	3,028 (11.5%)
Systolic Blood Pressure (mmHg)	89 ± 31	123 ± 26	144 ± 26	165 ± 28	191 ± 30
< 90	117 (51.1%)	477 (8.6%)	105 (0.9%)	1 (0.0%)	0 (0.0%)
90-140	98 (42.8%)	3,749 (67.9%)	5,444 (48.0%)	1,211 (19.3%)	103 (3.4%)
> 140	14 (6.1%)	1,298 (23.5%)	5,794 (51.1%)	5,076 (80.7%)	2,925 (96.6%)
Heart Rate (bpm)	51 ± 19	69 ± 16	89 ± 17	107 ± 18	127 ± 22
< 60	165 (72.1%)	1,558 (28.2%)	243 (2.1%)	0 (0.0%)	0 (0.0%)
60-100	62 (27.1%)	3,723 (67.4%)	8,727 (76.9%)	2,436 (38.7%)	262 (8.7%)
> 100	2 (0.9%)	243 (4.4%)	2,373 (20.9%)	3,852 (61.3%)	2,766 (91.4%)

*Data are presented as mean ± SD and counts(percentage)
mmHg=millimeters of mercury; bpm=beats per minute

Table 3. Association of Admission Rate-Pressure Product with In-Hospital Mortality

	Total	Mortality	Cumulative mortality	95 % CI	Univariate		Multivariable*	
Rate-Pressure Product					**Relative Risk**	**95 % CI**	**Relative Risk**	**95% CI**
< 5,000	229	115	50.2%	43.6% - 56.9%	1.79	1.54-2.07	1.50	1.31-1.76
5,000-9,999	5,524	1,816	32.9%	31.6% - 34.1%	1.17	1.11-1.23	1.16	1.11-1.22
10,000-14,999 (ref)	11,343	3,190	28.1%	27.3% – 29.0%	1.0 (ref)	N/A	1.0 (ref)	N/A
15,000-19,999	6,288	2,009	32.0%	30.8% - 31.1%	1.14	1.08-1.19	1.07	1.02-1.12
> 20,000	3,028	1,186	39.2%	37.4% - 40.9%	1.39	1.32-1.47	1.25	1.18-1.92

*Adjusted for age, gender, injury severity score, admission Glasgow coma scale, need for mechanical ventilation

Figure 1

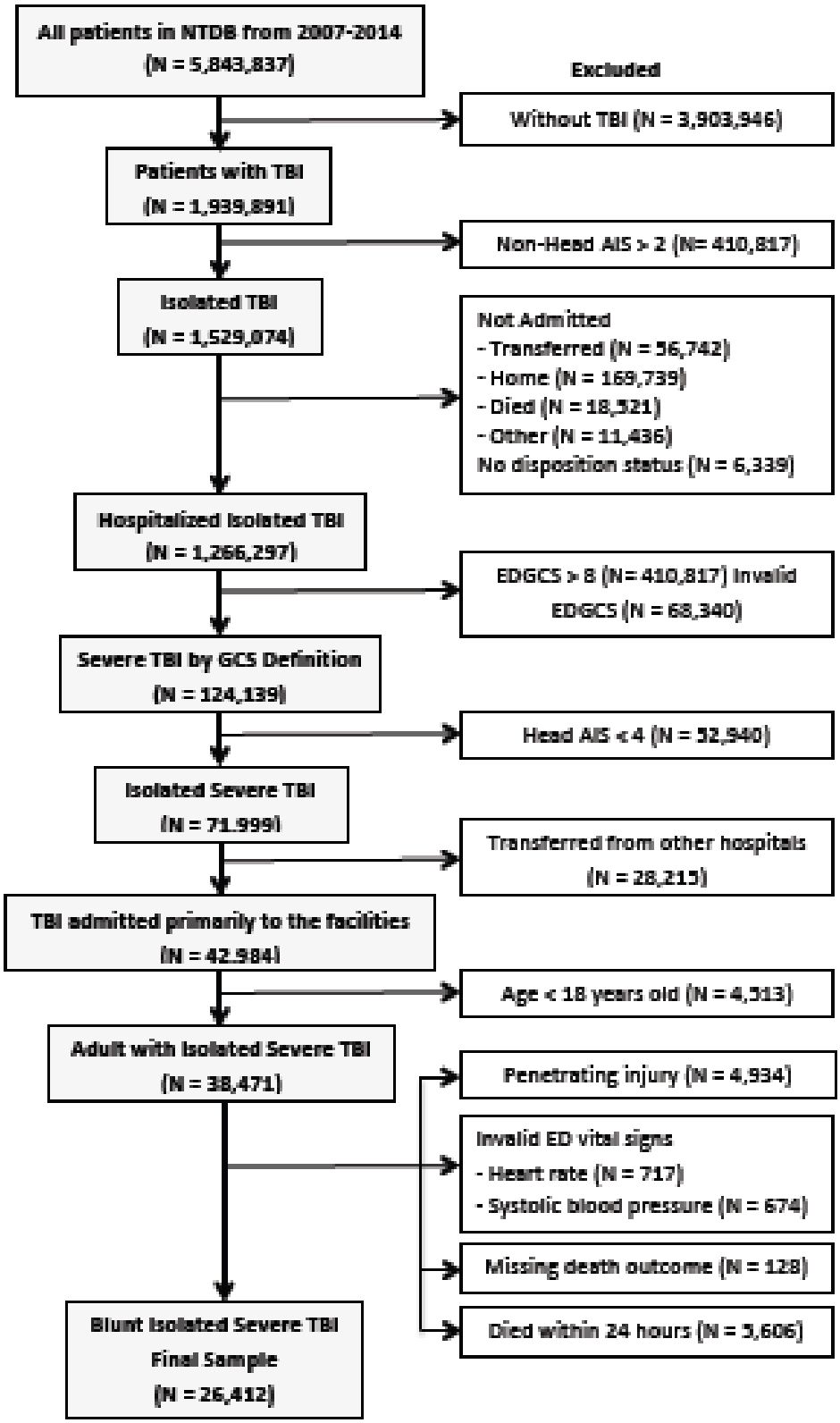
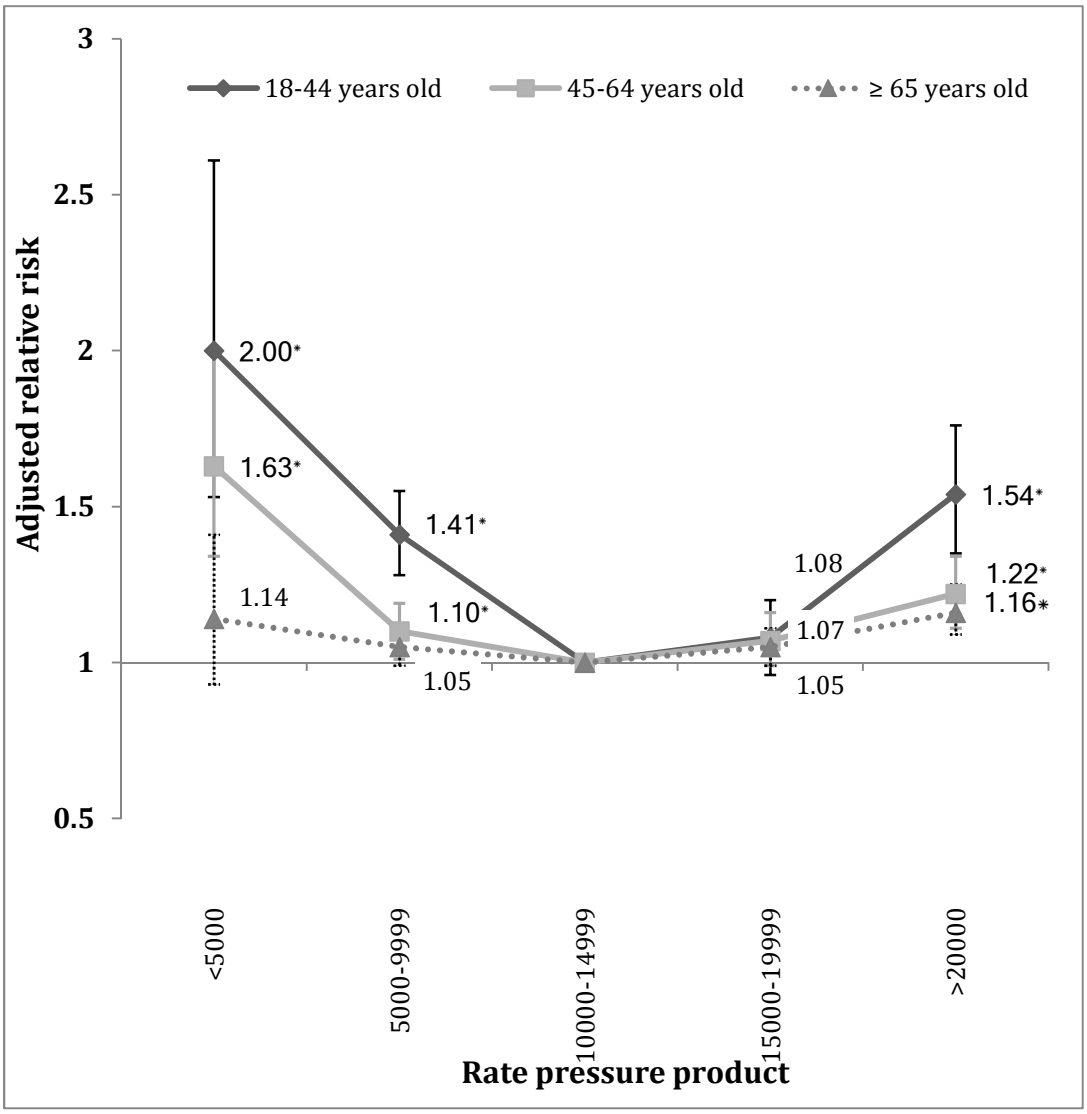
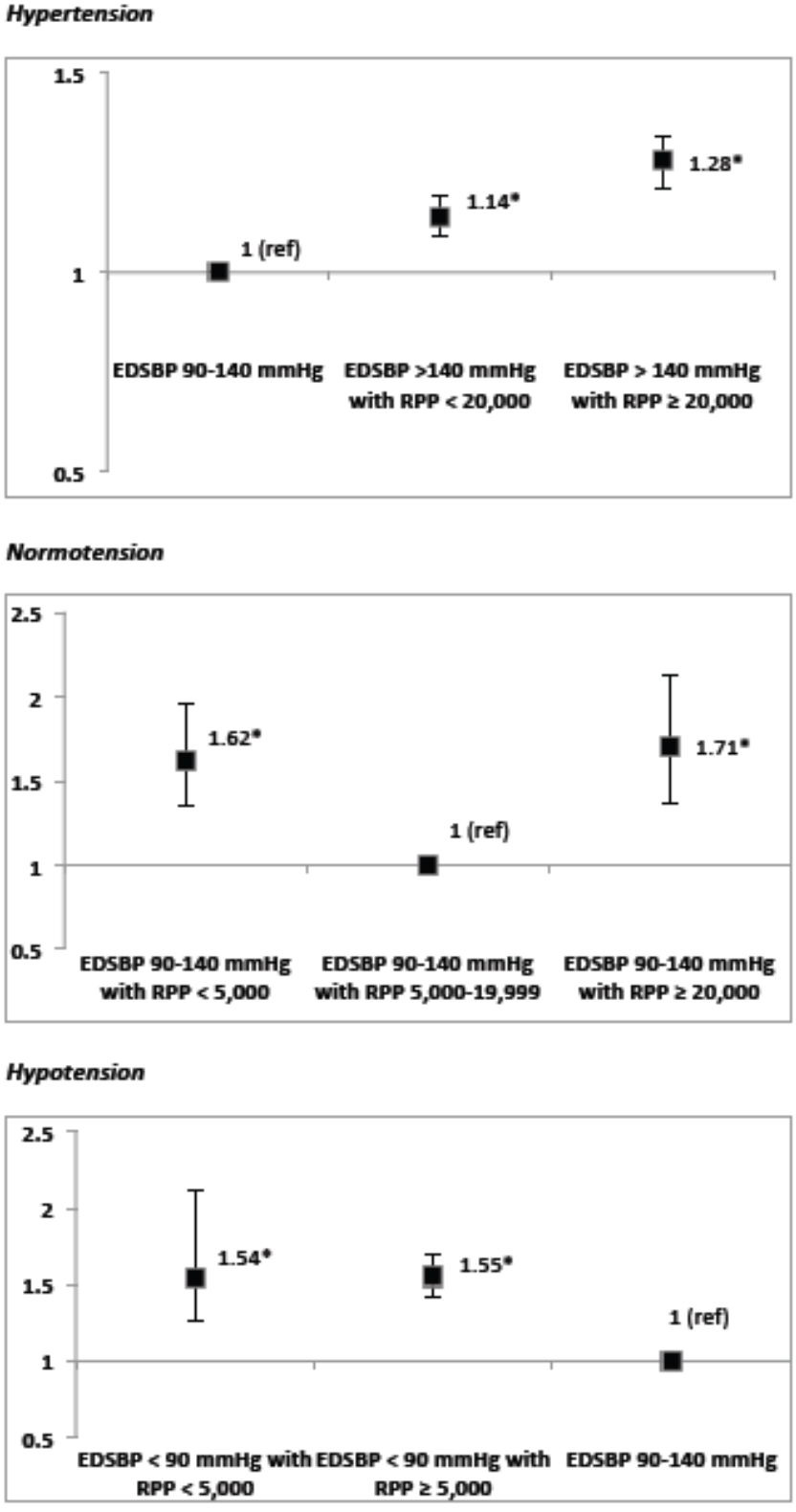

All patients in NTDB from 2007-2014
(N = 5,843,837)
Excluded
Without TBI (N = 3,903,946)
Patients with TBI
(N = 1,939,891)
Non-Head AIS > 2 (N= 410,817)
Isolated TBI
(N = 1,529,074)
Not Admitted
- Transferred (N = 56,742)
- Home (N = 169,739)
- Died (N = 18,521)
- Other (N = 11,436)
No disposition status (N = 6,339)
Hospitalized Isolated TBI
(N = 1,266,297)
EDGCS > 8 (N= 410,817) Invalid
EDGCS (N = 68,340)
Severe TBI by GCS Definition
(N = 124,139)
Head AIS < 4 (N = 52,940)
Isolated Severe TBI
(N = 71,999)
Transferred from other hospitals
(N = 28,215)
TBI admitted primarily to the facilities
(N = 42,984)
Age < 18 years old (N = 4,513)
Adult with Isolated Severe TBI
(N = 38,471)
Penetrating injury (N = 4,934)
Invalid ED vital signs
- Heart rate (N = 717)
- Systolic blood pressure (N = 674)
Missing death outcome (N = 128)
Died within 24 hours (N = 5,606)
Blunt Isolated Severe TBI
Final Sample
(N = 26,412)

Figure 2



*p<0.05

Figure 3



Y-axis is adjusted relative risk of in-hospital mortality in all panels
***p<0.05**