neurocritical care society Neurocrit Care (2017) 26:379–387
DOI 10.1007/s12028-016-0335-x

ORIGINAL RESEARCH

Association of Early Hemodynamic Profile and the Development of Systolic Dysfunction Following Traumatic Brain Injury

Vijay Krishnamoorthy[1,2,7] · Ali Rowhani-Rahbar[2,7] · Nophanan Chaikittisilpa[7] · Edward F. Gibbons[3,7] · Frederick P. Rivara[2,4,7] · Nancy R. Temkin[5,6,7] · Alex Quistberg[7] · Monica S. Vavilala[1,7]

Published online: 20 December 2016

Abstract

Background While systolic dysfunction has been observed following traumatic brain injury (TBI), the relationship between early hemodynamics and the development of systolic dysfunction has not been investigated. Our study aimed to determine the early hemodynamic profile that is associated with the development of systolic dysfunction after TBI.

Methods We conducted a prospective cohort study among patients under 65 years old without cardiac comorbidities who sustained moderate–severe TBI. Transthoracic echocardiography was performed within the first day after TBI to assess for systolic dysfunction. Hourly systolic blood pressure (SBP), mean arterial pressure (MAP), heart rate, and confounding clinical variables (sedatives, fluid balance, vasopressors, and osmotherapy) were collected during the first 24 h following admission. Multivariable linear mixed models assessed the early hemodynamic profile in patients who developed systolic dysfunction, compared to patients who did not develop systolic dysfunction.

Results Thirty-two patients were included, and 7 (22 %) developed systolic dysfunction after TBI. Patients who developed systolic dysfunction experienced early elevation of SBP, MAP, and heart rate, compared to patients who did not develop systolic dysfunction ($p < 0.01$ for all comparisons). Patients who developed systolic dysfunction experienced a greater rate of decrease in SBP [−10.2 mmHg (95 % CI −16.1, −4.2)] and MAP [−9.1 mmHg (95 % CI −13.9, −4.3)] over the first day of hospitalization, compared to patients who did not develop systolic dysfunction ($p < 0.01$ for both comparisons). All sensitivity analyses revealed no substantial changes from the primary model.

Conclusions Patients who develop systolic dysfunction following TBI have a distinctive hemodynamic profile, with early hypertension and tachycardia, followed by a decrease in blood pressure over the first day after TBI. This profile suggests an early maladaptive catecholamine-excess state as a potential underlying mechanism of TBI-induced systolic dysfunction.

Keywords Traumatic brain injury · Stress cardiomyopathy · Echocardiography · Trauma · Hemodynamics

✉ Vijay Krishnamoorthy
vkrish@u.washington.edu

1 Department of Anesthesiology and Pain Medicine, University of Washington, 1959 NE Pacific Street, BB-1469, Seattle, WA 98195, USA

2 Department of Epidemiology, University of Washington, Seattle, WA, USA

3 Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA, USA

4 Department of Pediatrics, University of Washington, Seattle, WA, USA

5 Department of Neurosurgery, University of Washington, Seattle, WA, USA

6 Department of Biostatistics, University of Washington, Seattle, WA, USA

7 Harborview Injury Prevention and Research Center, University of Washington, Seattle, WA, USA

Introduction

Traumatic brain injury (TBI) is a major public health problem and a significant contributor to major disability and mortality [1]. Recent data suggest 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 h 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 USA (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 ≤ 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 <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 from 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 2 days that followed the injury. Data were collected from the electronic medical record for demographic, clinical, and hemodynamic parameters. In particular, hourly noninvasive blood pressure and heart rate recordings over the first 24 h 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 h 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-h 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, three 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 vs. 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 vs. 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 h (SBP $\leq$ 90 mmHg, 43 and 32 %, respectively) and hypertension within the first 24 h (SBP $\geq$ 140 mmHg, 86 and 76 %, respectively). The mean admission heart rate was higher in the group with systolic dysfunction (105.6 vs. 81.4 bpm), and a higher proportion of patients in the group with systolic dysfunction required vasopressors within 24 h of admission (29 vs. 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 vs. 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 vs. 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 vs. 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 h after admission are shown in Figs. 1, 2, and 3. The unadjusted and adjusted rates of

Table 1 Demographic and clinical characteristics in TBI patients with and without systolic dysfunction

	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 comorbidities		
Pulmonary	0 (0 %)	0 (0 %)
Hypertension	1 (4 %)	0 (0 %)
Diabetes	2 (8 %)	0 (0 %)
Renal disease	0 (0 %)	0 (0 %)
Injury mechanism[a]		
Fall	8 (32 %)	2 (29 %)
Motor vehicle crash	6 (24 %)	4 (57 %)
Vehicle versus 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[b]		
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 h)	9.3 (2.1)	7.7 (5.1)
Lowest GCS (within 24 h)	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 h	98.4 (12.6)	96.1 (19.5)
Hypotension (SBP $\leq$ 90) in first 24 h	8 (32 %)	3 (43 %)
Hypertension (SBP $\geq$ 140) in first 24 h	19 (76 %)	6 (86 %)
Heart rate (bpm)[c]		
Admission heart rate	81.4 (18.1)	105.6 (33.3)
Critical care		
On vasopressors to maintain MAP $>$ 65 mmHg in first 24 h	4 (16 %)	2 (29 %)
ICP monitor placement	12 (48 %)	4 (57 %)
Need for intracranial surgery	9 (36 %)	3 (43 %)

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

CT computed tomography, *GCS* Glasgow Coma Scale, *bpm* beats per minute, *MAP* mean arterial pressure

[a] Some patients had more than one mechanism

[b] Some patients had multiple head CT findings

[c] All patients were in a normal sinus rhythm

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 h after admission, the group that developed systolic dysfunction had an adjusted mean SBP that was 12.6 mmHg

Table 2 Early transthoracic echocardiogram findings in moderate–severe TBI

	No systolic dysfunction ($n = 25$)	Systolic dysfunction ($n = 7$)	p value
Systolic function			
Left ventricle area end-diastole (cm^2)[a]	18.82 (4.47)	18.03 (6.22)	0.72
Left ventricle area end-systole (cm^2)[a]	8.73 (3.35)	937 (3.70)	0.68
Fractional area change (cm^2)[a]	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)][b]	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 (ms)	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

Bold values indicate $p < 0.05$

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

(95 % CI 8.1–17.2, $p < 0.001$) higher than the group that did not develop systolic dysfunction; during 13–24 h 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 h 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 h 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 h 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 h 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 h 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 h 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

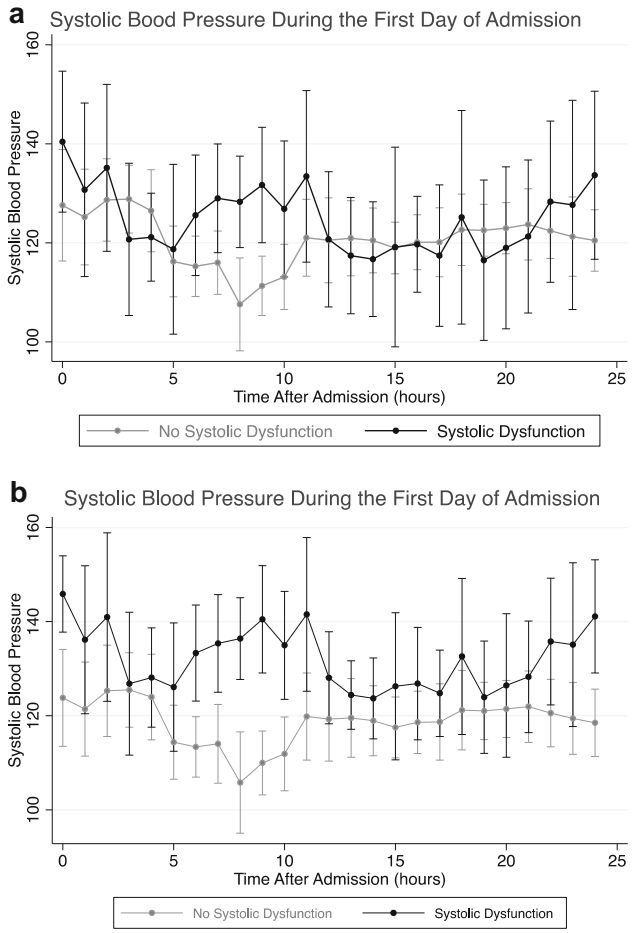

Fig. 1 **a** Unadjusted and **b** adjusted systolic blood pressure trajectory over 24 h following admission for moderate–severe traumatic brain injury. In above figure, *circles* represent mean values of adjusted systolic blood pressure and whiskers represent the 95 % confidence interval. Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

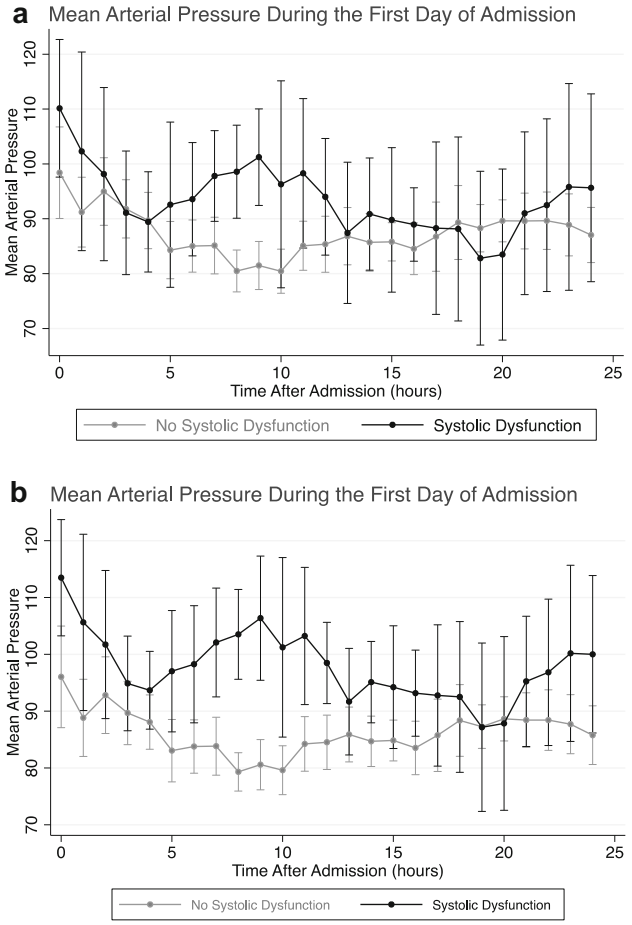

Fig. 2 **a** Unadjusted **b** adjusted mean arterial pressure trajectory over 24 h following admission for moderate–severe traumatic brain injury. In above figure, *circles* represent mean values of adjusted mean arterial pressure and whiskers represent the 95 % confidence interval. Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

pressure (ICP), and activation of the lower brain and hypothalamic neuroendocrine pathways [7]. Elevated catecholamine levels within 48 h 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

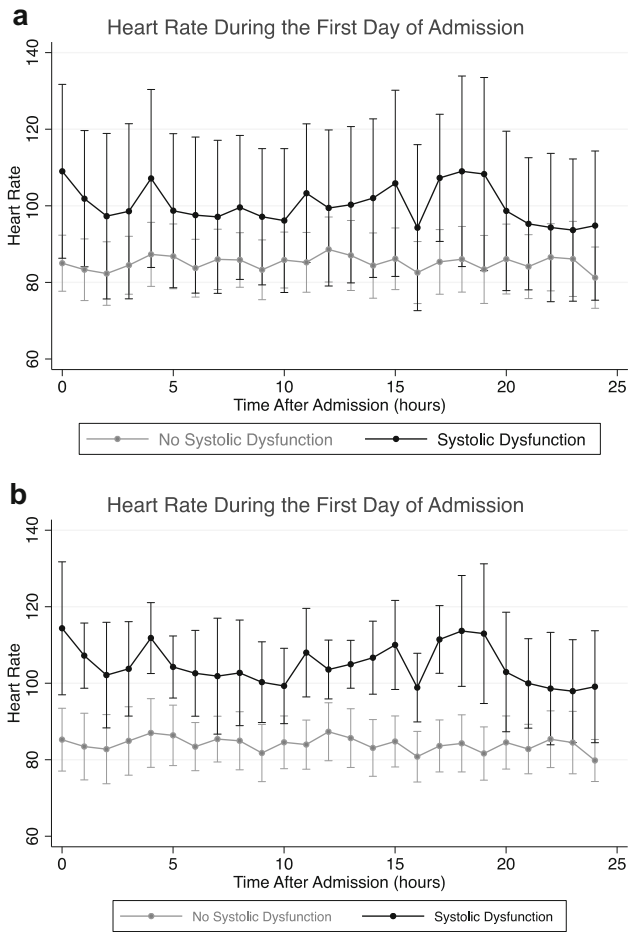

Fig. 3 **a** Unadjusted **b** adjusted heart rate trajectory over 24 h following admission for moderate–severe TBI. In above figure, *circles* represent mean values of adjusted heart rate and whiskers represent the 95 % confidence interval. Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

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

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[a] Mean (95 % CI)	*p*
Systolic blood pressure[b]	−8.6 (−14.4, −2.9)	0.003	−10.2 (−16.1, −4.2)	0.001
Mean arterial pressure[b]	−7.8 (−12.4, −3.2)	0.001	−9.1 (−13.9, −4.3)	<0.0001
Heart rate[b]	0.1 (−4.5, 4.7)	0.97	1.0 (−2.5, 1.2)	0.67

[a] Adjusted for age, gender, GCS, fluid balance, sedation, vasopressor use, osmotherapy, need for surgery

[b] 13–24 h after admission, compared 0–12 h after admission

relationship of hypertension preceding the development of systolic dysfunction in our cohort. In addition, longer-term changes in hemodynamic parameters (beyond 24 h) 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.

Funding NIH—National Research Service Award (T32 GM086270).

Compliance with Ethical Standards

Conflicts of interest None.

References

1. Rutland-Brown W, Langlois JA, Thomas KE, Xi YL. Incidence of traumatic brain injury in the United States, 2003. J Head Trauma Rehabil. 2006;21:544–8.
2. Prathep S, Sharma D, Hallman M, et al. Preliminary report on cardiac dysfunction after isolated traumatic brain injury. Crit Care Med. 2014;42:142–7.
3. Bybee KA, Prasad A. Stress-related cardiomyopathy syndromes. Circulation. 2008;118:397–409.
4. Meng L, Hou W, Chui J, Han R, Gelb AW. Cardiac output and cerebral blood flow: the integrated regulation of brain perfusion in adult humans. Anesthesiology. 2015;123:1198–208.
5. Zafar SN, Millham FH, Chang Y, et al. Presenting blood pressure in traumatic brain injury: a bimodal distribution of death. J Trauma. 2011;71:1179–84.
6. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24:294–302.
7. Krishnamoorthy V, Mackensen GB, Gibbons EF, Vavilala MS. Cardiac dysfunction after neurologic injury: What do we know and where are we going? Chest. 2016;149:1325–31.
8. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2:81–4.
9. Rimel RW, Jane JA, Edlich RF. An injury severity scale for comprehensive management of central nervous system trauma. JACEP. 1979;8:64–7.
10. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. J Neurotrauma. 2007;24(Suppl 1):S7–13.
11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18:1440–63.
12. Samuels MA. The brain–heart connection. Circulation. 2007;116:77–84.
13. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med. 2005;352:539–48.
14. Woolf PD, Hamill RW, Lee LA, Cox C, McDonald JV. The predictive value of catecholamines in assessing outcome in traumatic brain injury. J Neurosurg. 1987;66:875–82.
15. Hamill RW, Woolf PD, McDonald JV, Lee LA, Kelly M. Catecholamines predict outcome in traumatic brain injury. Ann Neurol. 1987;21:438–43.
16. Woolf PD, McDonald JV, Feliciano DV, Kelly MM, Nichols D, Cox C. The catecholamine response to multisystem trauma. Arch Surg. 1992;127:899–903.
17. Zaroff JG, Pawlikowska L, Miss JC, et al. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. Stroke. 2006;37:1680–5.
18. Naredi S, Eden E, Zall S, Stephensen H, Rydenhag B. A standardized neurosurgical neurointensive therapy directed toward vasogenic edema after severe traumatic brain injury: clinical results. Intensive Care Med. 1998;24:446–51.
19. Asgeirsson B, Grande PO, Nordstrom CH, Berntman L, Messeter K, Ryding E. Effects of hypotensive treatment with alpha 2-agonist and beta 1-antagonist on cerebral haemodynamics in severely head injured patients. Acta Anaesthesiol Scand. 1995;39:347–51.
20. Masuda T, Sato K, Yamamoto S, et al. Sympathetic nervous activity and myocardial damage immediately after subarachnoid hemorrhage in a unique animal model. Stroke. 2002;33:1671–6.
21. Moussouttas M, Mearns E, Walters A, DeCaro M. Plasma catecholamine profile of subarachnoid hemorrhage patients with neurogenic cardiomyopathy. Cerebrovasc Dis Extra. 2015;5:57–67.
22. Hunt D, Gore I. Myocardial lesions following experimental intracranial hemorrhage: prevention with propranolol. Am Heart J. 1972;83:232–6.
23. Krishnamoorthy V, Hiller DB, Ripper R, et al. Epinephrine induces rapid deterioration in pulmonary oxygen exchange in intact, anesthetized rats: a flow and pulmonary capillary pressure-dependent phenomenon. Anesthesiology. 2012;117:745–54.
24. Knackstedt C, Bekkers SC, Schummers G, et al. Fully automated versus standard tracking of left ventricular ejection fraction and longitudinal strain: the FAST-EFs Multicenter Study. J Am Coll Cardiol. 2015;66:1456–66.

25. Zieleskiewicz L, Contargyris C, Brun C, et al. Lung ultrasound predicts interstitial syndrome and hemodynamic profile in parturients with severe preeclampsia. Anesthesiology. 2014;120:906–14.
26. Alali AS, McCredie VA, Golan E, Shah PS, Nathens AB. Beta blockers for acute traumatic brain injury: a systematic review and meta-analysis. Neurocrit Care. 2014;20:514–23.
27. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233–70.