

ASSOCIATION OF EARLY MYOCARDIAL WORKLOAD AND MORTALITY FOLLOWING MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT

Background: Cardiovascular dysfunction is increasingly recognized following traumatic brain injury (TBI), yet the association between early myocardial workload and mortality remains inadequately defined. Rate pressure product (RPP), a surrogate of myocardial oxygen demand, may serve as a simple bedside marker of cardiac stress after TBI.

Objective: To determine the association between admission myocardial workload and in-hospital mortality in patients with isolated moderate to severe TBI.

Methods: In this prospective observational study, 200 patients aged 18–65 years with isolated TBI (GCS <12) were enrolled. Admission RPP was calculated and categorized into five groups: <5000, 5000–9999, 10000–14999, 15000–19999, and >20000. Cardiac biomarkers, and transthoracic echocardiography were performed within 24–48 hours. LVEF <40% and regional wall motion abnormalities (RWMA) were recorded. The primary endpoint was in-hospital mortality. Logistic regression and ROC analyses were performed.

Results: Overall mortality was 35%. Mortality was highest in the lowest RPP group (53.8%; OR 3.68, $p=0.039$) compared with the reference group (10000–14999). Elevated RPP was also associated with increased mortality. Reduced LVEF (OR 11.6), RWMA (OR 8.6), elevated troponin (OR 3.91), and elevated CPK-MB (OR 1.05) were independent predictors of mortality. ROC analysis demonstrated modest predictive performance of troponin (AUC 0.615) and CPK-MB (AUC 0.643).

Conclusion: Both reduced and elevated myocardial workload at admission are associated with increased in-hospital mortality following moderate to severe TBI. Early cardiac dysfunction and biomarker elevation independently predict adverse outcomes.

KEYWORDS: Traumatic brain injury; Myocardial workload; Rate pressure product; Cardiac dysfunction; Mortality.

INTRODUCTION

Traumatic Brain Injury (TBI) is a significant worldwide public health issue and it is considered to be one of the primary causes of trauma morbidity and mortality across the world. It contributes approximately 30 percent of all deaths as a result of trauma and is overrepresented in the young adult age group in its prime working years.^[1] In addition to death, survivors in most cases have severe long-term neurological, cognitive, emotional and behavioral impairments that place them with high socioeconomic burden to families and health care systems.^[2] TBI is caused by acceleration-deceleration acceleration or head-on impact that causes primary neuronal damage, which is then followed by cascade events of secondary pathophysiological processes such as excitotoxicity, inflammation and systemic complications.^[3]

Although the main characteristic of TBI is neurological damages, dysfunction of extracranial organs especially cardiovascular is of critical interest as a determinant of outcome. There is extensive information on cardiovascular abnormalities after acute brain injury that involve hypertension, hypotension, arrhythmias, electrocardiographic changes, increase in cardiac biomarkers and left ventricular (LV) dysfunction.^[4,5] The proposed mechanisms include hyperactivation of sympathetic nervous system and catecholamine surge leading to systemic vasoconstriction, increased afterload and increased myocardial oxygen demand.^[6] Companionate coronary vasoconstriction could inhibit oxygen supply-demand fit and pre-empt subendocardial ischemia and reversible/irreversible myocardial dysfunction.

Early hemodynamic instability is prevalent in moderate to severe TBI and has been established independently as an indicator of poor neurological outcomes. Hypotension and hypertension on admission both have a negative influence on cerebral perfusion and exacerbate the secondary brain injury.^[7,8] Nonetheless, blood pressure might not be sufficient to indicate myocardial stress or heart-oxygen use. The interplay of the systolic blood pressure and the heart rate is more integrated to give a more accurate estimate of the workload of myocardium.

A simple bedside index of myocardial oxygen consumption and workload is the rate-pressure product (RPP) which is calculated as systolic blood pressure x heart rate. In cardiovascular medicine, increased RPP has been linked to ischemic events and poor outcome especially in hypertensives and patients with coronary artery disease.^[9] Both experimental and clinical evidence have shown that there is a high correlation between RPP and myocardial oxygen demand particularly in stress situations. RPP is a widely used technique in the fields of cardiology and exercise physiology, but it has not been studied in the environment of neurocritical care.

The maximum heart activity is necessary in TBI as the cardiac output in the system has a direct effect on cerebral blood circulation and delivery of oxygen to the brain. Cerebral perfusion may be impaired due to impaired myocardial performance and worsen secondary brain injury.^[10] On the other hand, the high myocardial workloads caused by the excess of catecholamines can lead to heart dysfunction, pulmonary edema, and hypotension in the system. Thus, low and high increased workload of the myocardium can be harmful when it comes to severe TBI.

Though there are earlier research reports where myocardial dysfunction and shifted hemodynamic indices were reported after TBI, there is still a gap in understanding the relationship between early myocardial workload, which is measured by RPP, and in-hospital mortality. The association, to be understood, might offer clinicians a non-invasive, readily available tool that could be used in early risk stratification and hemodynamic optimization.

Therefore, the current research was aimed at assessing the relationship between admission myocardial workload and in-hospital mortality in patients with isolated moderate to severe traumatic brain injury. We also sought to describe early myocardial workload phenotypes after TBI and whether RPP data gives prognostic information that is not available through traditional measurements of blood pressure.

MATERIALS AND METHODS

Study Design and Setting

The study was a prospective observational study carried out in the Departments of Anaesthesiology, Critical Care Medicine and Surgical Emergency at the Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Srinagar during the period of October 2019 to November 2021. The research was ethically sound and approved by the institutional head ethics committee.

Study Population

Two hundred patients with isolated moderate to severe traumatic brain injury (TBI) aged 18-65 years old were enrolled consecutively. The Glasgow Coma Scale (GCS) score was <12 at admission, which was defined as moderate to severe TBI. Both patients (male and female) were involved. Patients were not included when they were GCS score >12, had either significant extracranial injuries or a history of cardiopulmonary resuscitation before admission or when the systolic blood pressure or heart rate measurements were unavailable at presentation. It also excluded patients having known prior severe cardiac disease in order to reduce the confounding effect caused by baseline myocardial dysfunction.

Clinical Assessment and Hemodynamic Monitoring

In the surgical emergency department and trauma unit, upon admission, we introduced standard monitoring, comprising of continuous electrocardiography (ECG), non-invasive blood pressure monitoring, pulse oximetry, and temperature monitoring. The admission measurements of systolic blood pressure (SBP) and heart rate (HR) were noted prior to starting definitive therapeutic interventions.

The rate-pressure product (RPP) was calculated as:

$$\text{RPP} = \text{Systolic Blood Pressure} \times \text{Heart Rate}$$

Patients were categorized into five predefined RPP groups based on established human thresholds:

- <5,000
- 5,000–9,999
- 10,000–14,999 (reference group)
- 15,000–19,999
- 20,000

Laboratory and Biochemical Investigations

Blood samples were taken within a period of one hour after admission in the hospital after initial stabilization. Laboratory tests involved were complete blood count, serum electrolytes (sodium, potassium, calcium), arterial or venous blood gas, serum troponin, and creatine phosphokinase-MB (CPK-MB) levels. Cardiac biomarkers were identified at higher ranges in the institutional laboratories.

Cardiac Evaluation

Baseline 12-lead ECG was taken at the time of admission as part of treatment protocol. Two-dimensional transthoracic echocardiography was conducted 24-48 hours of admission or after any surgical intervention if needed. The standard procedures were used to measure left ventricular ejection fraction (LVEF) and LVEF less than 40% was deemed to indicate systolic dysfunction. The existence of abnormalities in the wall motion of the region (RWMA) was reported by a trained cardiologist who was unaware of the clinical outcome.

Clinical Management

Patients were treated using the institution protocols that were aligned to the current traumatic brain injury management principles. Normal care encompassed the use of intravenous fluids, antibiotics where necessary, gastric ulcer prophylaxis, analgesics, as well as sedatives. Propofol and rocuronium were used as endotracheal intubation when necessary to aid in the control of airways and mechanical ventilation.

Outcome Measures

The primary endpoint was in-hospital mortality. Secondary endpoints included functional outcome at discharge, assessed using the Glasgow Outcome Score (GOS). Patients were followed throughout their hospital stay until discharge or death.

Statistical Analysis

All statistical tests were done with GraphPad Prism (Version 9). Continuous variables were represented in the form of mean + standard deviation (SD) and compared with the help of Student t-test or with the one-way analysis of variance (ANOVA), depending on the type of the variables. Categorical variables were used as frequencies and percentages and were compared by using the fisher exact test.

Several logistic regression analysis was conducted to evaluate independent predictors of in-hospital mortality. Odds Ratios (ORs) with 95% confidence intervals (CI) were made. Spearman rank correlation coefficient or Kendall tau-b correlation was the correlation method used to assess clinical and biochemical parameters against mortality, based on the type of variables. The receiver operating characteristic (ROC) curve was used to calculate the area under the curve (AUC) and optimum cut-off values, sensitivity and specificity of cardiac biomarkers in predicting in-hospital mortality. A p-value < 0.05 was taken as statistically significant.

RESULTS

Study Population

Two hundred patients with isolated moderate to severe traumatic brain injury were analyzed. The cohort was predominantly young and male. Overall in-hospital mortality was 35%. Mortality was markedly higher among patients with admission GCS ≤ 8 compared to those with GCS 9–12 (Table 1).

Table 1. Baseline Clinical Characteristics of Study Population (n = 200)

Variable	Value
Age (years), mean $\pm$ SD	39.79 $\pm$ 24.11
Age 18–35 years	92 (46%)
Male sex	172 (86%)
Female sex	28 (14%)
Normal BMI	85 (42.5%)
Overweight	60 (30%)
Obese	55 (27.5%)
Overall in-hospital mortality	70 (35%)
Mortality in GCS ≤ 8	60%
Mortality in GCS 9–12	10%

Hemodynamic Profile According to Admission RPP

Patients were categorized into five groups based on admission rate pressure product (RPP). The distribution of systolic blood pressure and heart rate across RPP categories is shown in Table 2. Lower RPP values were primarily associated with hypotension and bradycardia, whereas higher RPP categories were predominantly characterized by hypertension and tachycardia.

Table 2. Hemodynamic Characteristics Stratified by Rate Pressure Product (RPP)

Parameter	<5000 (n=13)	5000–9999 (n=26)	10000–14999 (n=66)	15000–19999 (n=81)	>20000 (n=14)
Systolic Blood Pressure (mmHg)					
<90	9 (69.2%)	3 (11.5%)	1 (1.5%)	0	0
90–140	4 (30.7%)	16 (61.5%)	25 (37.8%)	10 (12.3%)	1 (7.2%)
>140	0	7 (26.9%)	40 (60.6%)	71 (87.6%)	13 (92.8%)
Heart Rate (beats/min)					
<60	10 (76.9%)	8 (30.7%)	2 (3.0%)	1 (1.2%)	0
60–100	3 (23.1%)	17 (65.3%)	51 (77.3%)	30 (37.0%)	2 (14.3%)
>100	0	1 (3.8%)	13 (19.7%)	50 (61.7%)	12 (85.7%)

Admission RPP and In-Hospital Mortality

The association between admission RPP and in-hospital mortality is presented in Table 3. Mortality varied across RPP categories, with the lowest mortality observed in the reference group (RPP 10000–14999). The highest mortality occurred in patients with markedly reduced RPP. Elevated RPP was also associated with increased mortality compared to the reference group.

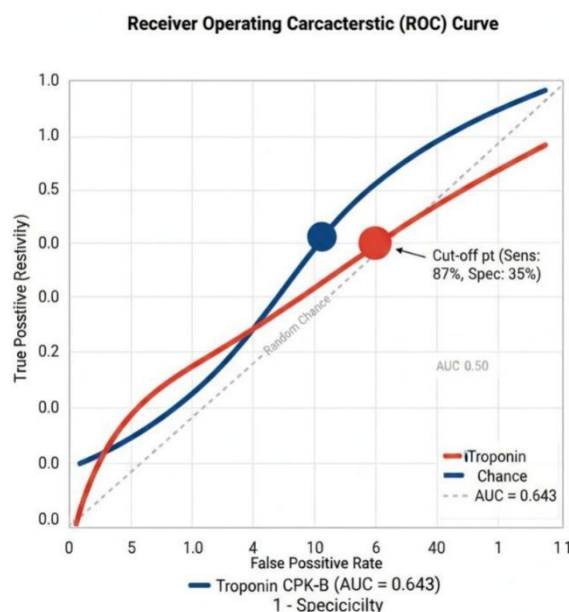
RPP Category	Total (n)	Deaths (n)	Mortality (%)	Odds Ratio	95% CI	p-value
<5000	13	7	53.8	3.68	1.07–12.64	0.039*
5000–9999	26	9	34.6	1.43	0.55–3.71	0.453
10000–14999†	66	20	30.7	Reference	—	—
15000–19999	81	27	33.7	1.15	0.57–2.31	0.695
>20000	14	7	43.7	1.72	0.52–5.62	0.366

*Statistically significant ($p < 0.05$)

Multivariable logistic regression analysis identified reduced left ventricular ejection fraction (LVEF <40%), presence of regional wall motion abnormalities (RWMA), elevated troponin, and elevated CPK-MB as independent predictors of in-hospital mortality (Table 4).

Variable	Odds Ratio	95% CI	p-value
LVEF <40%	11.60	3.89–34.57	0.0001*
RWMA	8.60	3.49–21.16	0.0001*
Elevated Troponin	3.91	1.54–9.87	0.004*
Elevated CPK-MB	1.05	1.01–1.08	0.002*

Receiver operating characteristic analysis demonstrated modest discriminatory performance of troponin and CPK-MB for predicting in-hospital mortality (Figure 1).



A large multicenter cohort study by Krishnamoorthy et al. (2018), which involved more than 26,000 patients with severe TBI, was the most relevant finding that included both depressed and elevated RPP at the time of admission as independent factors affecting in-hospital mortality. The lowest RPP (<5000) and the highest (>20,000) were found to have 50 and 25 percent more risk of mortality respectively, creating a U shape pattern which is comparable to the

current results.^[11] We find similarity in our data with this association, where the early myocardial workload is a sensitive physiological predictor of autonomic and cardiac dysfunction following brain trauma. The hypotension and bradycardia were mainly linked to low RPP values in our study which was also in-line with neurogenic shock or parasympathetic preeminence following severe TBI. This pathophysiological course has been associated with low cerebral perfusion and secondary ischemic damage.^[12] In contrast, high RPP values are probably indicative of over-stimulation of the sympathetic system and augmented myocardial oxygen requirement, which can instigate cardiac damage, arrhythmia, and additional deterioration of cerebral blood circulation.

Cardiac Dysfunction and Biomarkers

Consistent with previous work, in our multivariate model, lower LVEF, existence of regional wall motion abnormalities (RWMA), higher troponin, and higher CPK-MB were independently associated with reduced in-hospital mortality. The cardiac dysfunction observed is consistent with a systematic review and meta-analysis conducted by Ding et al. (2024), which indicated that one-third of TBI patients had myocardial injury and that the mortality rate in patients with high levels of troponins was increased five times.^[13] These results highlight the importance of neurocardiac interactions, in which catecholamine releases and autonomic dysregulation rise to cause myocardial strain and damage, despite lacking direct cardiac injury. In our ROC analysis, the predictive power of troponin and CPK-MB was only modest, which is in line with the earlier literature which indicates that although these biomarkers are indicative of myocardial stress, they alone are not a defining prognostic tool in TBI.^[14] The integration of cardiac biomarkers with echocardiographic results, which was done in this case, can improve prognostic values.

Hemodynamic Parameters and Mortality

A number of studies justify the role of optimum blood pressure and cardiac workload in the early period of TBI. Zafar et al. (2011) showed that both hypotension (<120 mmHg) and hypertension (>140 mmHg) at admission were significantly related to the higher mortality in isolated TBI, which showed a bimodal pattern of mortality just like the RPP results.^[15] Huang et al. (2022) also found U-shaped relationships between systolic blood pressure and mortality, indicating that both ends of the perfusion pressure can impair cerebral autoregulation and worsen the outcomes.^[16]

Mechanistic Considerations

Early dysautonomous functions are now becoming known as a predictor of TBI outcomes. Recent guidelines by Dong et al. (2024) suggested the use of a more in-depth analysis of the waveform to describe early autonomic perturbations after severe TBI, which showed the contribution of baroreflex dysfunction and sympathetic overdrive to cardiac workload regulation.^[17] These observations indicate that RPP may be used as a substitute of autonomic imbalance and cardiovascular stress.

Clinical Implications

Our findings, consistent with prior large-scale analyses, suggest that monitoring and optimizing myocardial workload early after TBI may improve patient outcomes. Identifying patients with both low and excessively high RPP could facilitate targeted hemodynamic interventions—such as fluid resuscitation, vasopressor titration, or cautious use of beta-blockers—to stabilize myocardial performance without compromising cerebral perfusion. Beta-blockade strategies, such as early esmolol use, have shown feasibility and potential survival benefits in recent phase 2a studies.^[18]

CONCLUSION

This research indicates that early myocardial workload, measured as admission rate pressure product (RPP), is linked to in-hospital mortality in patients with moderate to severe traumatic brain injury. Both significantly lowering and significantly increasing RPP were associated with adverse outcomes, indicating a nonlinear correlation between the outcomes of myocardial stress and survival. Moreover, objective indicators of heart dysfunction, such as the decrease in ejection fraction of the left ventricle, regional wall motion abnormalities, and increased cardiac biomarker levels were independently related to mortality. These results support the need to use early cardiovascular evaluation among TBI patients. The use of myocardial workload and cardiac function parameter in daily assessment can enhance the effectiveness of risk stratification and the adoption of hemodynamic optimization interventions in neurocritical care units.

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