Speckle Tracking Analysis of Left Ventricular Systolic Function following Traumatic Brain Injury: A Pilot Prospective Observational Cohort Study

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Abstract

Background—Systolic dysfunction and reduction in left ventricular ejection fraction (LVEF) has been documented after traumatic brain injury (TBI). Speckle tracking is an emerging technology for myocardial strain assessment which has been utilized to identify subclinical myocardial dysfunction, and is most commonly reported as global longitudinal strain (GLS). We examined myocardial strain and regional strain patterns following moderate-severe TBI.

Methods—We conducted a prospective cohort study of moderate-severe TBI patients [Glasgow Coma Scale (GCS) ≥ 12] and age/gender-matched controls. Transthoracic echocardiography (TTE) was performed within the first day and 1 week following TBI. Myocardial function was assessed using both GLS and LVEF, and impaired systolic function was defined as GLS $> -16\%$ or LVEF $< 50\%$. Regional strain patterns and individual strain trajectories were examined.

Results—Thirty subjects were included, 15 patients with TBI and 15 age/gender-matched controls. Among patients with adequate echocardiographic windows, systolic dysfunction was observed in 2 (17%) patients using LVEF and 5 (38%) patients using GLS within the first day after TBI. Mean GLS was impaired in patients with TBI compared to controls ($-16.4 \pm 3.8\%$ vs. $-20.7 \pm 1.8\%$, $p = 0.001$). Regional myocardial examination revealed impaired strain primarily in the

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basal and mid-ventricular segments. There was no improvement in GLS from day 1 to day 7 ($p = 0.81$).

Conclusions—Myocardial strain abnormalities are common and persist for at least one week following moderate-severe TBI. Speckle tracking may be useful for the early diagnosis and monitoring of systolic dysfunction following TBI.

Keywords

traumatic brain injury; stress cardiomyopathy; echocardiography; trauma

Introduction

Traumatic brain injury (TBI) is major global health problem, and is a leading cause of death and disability following trauma¹. Hypotension is common following moderate-severe TBI and is associated with cerebral hypoperfusion and poor outcomes^{2,3}. Early myocardial injury and systolic dysfunction is being increasingly recognized following moderate-severe TBI^{4–6}, and is postulated to be due to systemic inflammation and catecholamine-excess after injury⁷. Furthermore, systolic dysfunction is associated with early hemodynamic instability following TBI⁸, and may contribute to cerebral hypoperfusion after injury from reduced cardiac output⁹. While international guidelines suggest hemodynamic targets early after severe TBI¹⁰, no studies have considered the function of the heart to inform these targets. An improved understanding of the burden of cardiac dysfunction following TBI may help to optimize resuscitation, thereby improving systemic and cerebral hemodynamics after injury.

While reduced left ventricular ejection fraction (LVEF) has been the traditional measure of clinical systolic dysfunction, recent advances in cardiac imaging using speckle-tracking have led to earlier detection of subclinical systolic dysfunction in a variety of critical illness paradigms, including sepsis¹¹ and aneurysmal subarachnoid hemorrhage (SAH)¹². Speckle-tracking is a novel technology that allows myocardial strain assessment, which quantifies myocardial deformation in the circumferential, radial, and longitudinal components of myocardial motion^{13,14}. Among these components, global longitudinal strain (GLS) is more sensitive than the classical measure of LVEF in detecting impaired systolic function¹³. Knowledge of early systolic dysfunction may lead to more personalized interventions tailored to optimize cardiac function and improve hemodynamics following TBI. However, despite the growing use of GLS to detect subclinical systolic dysfunction during critical illness, limited data is available in patients with TBI. We conducted a pilot prospective cohort study to examine early myocardial strain characteristics, compare GLS to LVEF in the detection of early systolic dysfunction, and examine regional strain patterns and longitudinal changes in GLS over the first week of hospitalization following moderate-severe TBI.

Materials and Methods

We conducted a pilot prospective observational cohort study among moderate-severe TBI patients, and used age and gender-matched healthy controls as a comparison group. The study was conducted at Harborview Medical Center, the only level 1 trauma center in the

northwest 4-state region of the United States (Washington, Alaska, Montana, and Idaho). The study was approved by the University of Washington's Institutional Review Board. The study was approved by the University of Washington's Institutional Review Board. Written consent was obtained from all participants. If subjects were unable to provide consent due to their neurologic injury, consent was obtained from their next of kin or designated power of attorney.

Inclusion / Exclusion Criteria

Patients were screened for a diagnosis of moderate-severe TBI within 24 hours of injury. After confirmation of mechanism of injury and computed tomography evidence of intracranial bleeding, TBI severity was assessed, based on the Glasgow Coma Scale score after resuscitation^{15,16}. Moderate-severe TBI was defined as a GCS score ≤ 12 after resuscitation. Because we wanted to focus on the effect of TBI on the heart, we restricted our population to isolated TBI, defined as non-head Abbreviated Injury Scale score < 3 in other body regions. Furthermore, we excluded patients older than 65 years, history of cardiac arrest, known ischemic or structural cardiac disease, and severe medical comorbidities (liver cirrhosis, chronic kidney disease, human immunodeficiency virus, history of chemotherapy, chronic obstructive pulmonary disease, pulmonary hypertension, and history of cerebrovascular disease). Our control group consisted of healthy age and gender-matched faculty and staff at Harborview Medical Center

Echocardiography and Strain Analysis

A focused transthoracic echocardiogram (TTE) was performed by an anesthesiologist-intensivist (VK) with certification in echocardiography within the first day after injury, using a Philips iE-33 ultrasound system (Bothell, WA), according to the American Society of Echocardiography guidelines¹⁷. The TTE examination was repeated at 7 days after injury. For the matched control subjects, one TTE exam was performed.

The TTE exam consisted of a two-dimensional, Doppler, and speckle tracking evaluation of left ventricular systolic and diastolic function, and assessed in the parasternal long-axis, parasternal short-axis, apical four-chamber, apical two-chamber, and apical three-chamber views. TTE exams in both healthy controls and in TBI patients were performed in the supine position when possible; if subjects had labile intracranial pressures, the exam was performed with 30 degrees of head elevation. Furthermore, measurements from echocardiographic windows with inadequate views (as determined by the study cardiologists), were excluded from the analysis. Systolic function using two-dimensional echocardiography was assessed with ejection fraction using the Simpson's method $[(LVEF) = (\text{left ventricular volume in diastole} - \text{left ventricular volume in systole}) / (\text{left ventricular volume in diastole})]$ and fractional shortening $[(FS), (\text{left ventricular internal diameter in diastole} - \text{left ventricular internal diameter in systole}) / (\text{left ventricular internal diameter in diastole})]$ ¹⁸, and systolic dysfunction was defined as an LVEF $< 50\%$.

A complete longitudinal strain analysis was performed to determine both GLS and regional strain (Figure 1). GLS was measured in the apical four-chamber, two-chamber, and three-chamber views. GLS was analyzed as a function of myocardial fiber shortening

(computational analysis of end-systolic length and end-diastolic length), and was calculated as an average of 16 segments of the myocardium. Because the LV shortens during systole, GLS is expressed as negative percentage values, with values closer to zero reflecting diminished systolic function. Using the speckle tracking approach, systolic dysfunction was defined as a GLS $> -16\%$, as previously described following subarachnoid hemorrhage¹². Regional strain maps were developed to quantify GLS at the base, mid, and apical regions of the left ventricle. All strain analyses were performed using QLAB ultrasound analytic software (Philips, Bothell, WA). The study cardiologists (EG, JL), blinded to the patient status or clinical details of patient management, reviewed echocardiogram examinations offline for data quality; in addition, all offline measurements of two-dimensional and speckle tracking data were performed in a blinded fashion by the study cardiologist (JL).

Statistical Analysis

As there is little prior data on cardiac strain following TBI, we conducted a pilot study and did not perform a formal *a priori* sample size calculation. We aimed to recruit a total of 30 subjects (15 patients with moderate-severe TBI and 15 healthy age and gender-matched control subjects) for our analyses. Descriptive statistics were used to examine demographic, clinical, radiographic, and echocardiographic characteristics of the patient cohort. For comparison of echocardiographic parameters, we used Student's t-tests and Chi-squared tests for the comparison of continuous and categorical variables, respectively. Dependent t-tests were used to examine longitudinal changes in GLS among patients with moderate-severe TBI. Strain maps were developed by taking the mean value of GLS across the subjects for each myocardial region, along with computation of standard deviations. All analyses were performed using Stata statistical software (StataCorp, College Station, Texas, USA).

Results

Study Population

After applying all inclusion criteria for the patients and age/gender-matched controls, we recruited a total of 30 subjects, 15 with moderate-severe TBI (Supplementary Figure 1, Supplemental Digital Content 1, <http://links.lww.com/JNA/A98>) and 15 healthy controls. Clinical and demographic characteristics of the patient cohort are shown in Table 1. Patients were relatively young (mean age 43 years) and primarily male (73%). No patients were on chronic cardiac medications, and one (7%) patient had a history of hypertension. Falls (40%) and motor vehicle collisions (40%) accounted for the majority of primary injury mechanisms, with all patients having evidence of intracranial bleeding on admission head computed tomography (CT) scan, including subdural hemorrhage (80%) and traumatic subarachnoid hemorrhage (80%). The cohort consisted of primarily severe TBI (mean admission GCS 5 ± 2.8), and required critical care interventions including vasopressors (33%), intracranial pressure monitoring (40%), and mechanical ventilation (87%).

Two-dimensional and Doppler Echocardiography

Echocardiographic characteristics in the patients and matched controls are shown in Table 2. Regarding two-dimensional echocardiographic characteristics, the left-ventricular internal

diameters in diastole ($p=0.08$) and systole ($p=0.71$) were similar in the moderate-severe TBI group and control group. The left-ventricular volume in diastole was similar in both groups ($p=0.06$) and the left-ventricular volume in systole was smaller in the group with moderate-severe TBI, as compared to the control group (41.9 ± 13.7 mL vs. 59.6 ± 22.6 mL, respectively; $p=0.03$), but the mean EF did not differ between the moderate-severe TBI and control groups (0.60 ± 0.11 vs. 0.58 ± 0.41 , respectively; $p=0.57$). Two (17%) patients with moderate-severe TBI had clinical systolic dysfunction ($EF < 50\%$), compared to 0 (0%) subjects in the control group ($p=0.19$). For diastolic parameters, pulsed-wave Doppler derived E-wave velocity did not differ in patients with moderate-severe TBI or the control group ($p=0.24$), but the A-wave velocity was higher in the group with moderate-severe TBI versus the control group (67.7 ± 22.7 cm/s vs. 40.6 ± 14.7 cm/s, respectively; $p=0.001$); despite this, the E-wave/A-wave ratios were similar between the groups ($p=0.13$). While the majority of tissue Doppler parameters did not differ between the groups, the lateral mitral annular a-prime velocity was higher in the moderate-severe TBI group, compared to the control group (13.0 ± 5.4 cm/s vs. 7.8 ± 2.7 cm/s, respectively; $p=0.003$).

Speckle-Tracking Echocardiography

Speckle-tracking parameters are shown in Table 2. GLS was significantly worse in the group with moderate-severe TBI, compared to the control group (-16.4 ± 3.8 vs. -20.7 ± 1.8 , respectively; $p=0.001$); using GLS, there was a higher proportion of patients with systolic dysfunction ($GLS > -16\%$) in the group with moderate-severe TBI, compared to controls (38% vs. 0%, respectively; $p=0.04$). Regional strain maps for patients with moderate-severe TBI and healthy controls are shown in Figure 2. All left-ventricular regions with abnormal strain were located in the base and mid-ventricular segments, with the apical segments of the left ventricle demonstrating preserved function.

Longitudinal Changes in Strain

Figure 3 describes the trajectory of GLS over the first week of hospitalization in patients with moderate-severe TBI. There was no improvement in GLS from day 1 (to day 7 ($-16.7 \pm 1.1\%$ vs. $-17.1 \pm 1.2\%$, respectively; $p=0.81$)) in the cohort of moderate-severe TBI patients. No improvement in GLS from day 1 to day 7 was found in either the group with initially impaired GLS ($-12.5 \pm 2.9\%$ vs. $-16.6 \pm 5.4\%$, $p=0.38$) or the group with normal GLS ($-18.8 \pm 1.7\%$ vs. $-17.4 \pm 3.9\%$, $p=0.30$). Among the 4 patients with impaired systolic function at baseline ($GLS > -16\%$) who were hospitalized for greater than one week, 2 (50%) improved to normal systolic function by 7 days after injury. In addition, as shown in Figure 2, the regional strain patterns found within 1 day of hospital admission persisted at one week after injury.

Discussion

The main findings of this pilot study are: 1) Myocardial strain abnormalities are common following moderate-severe TBI, suggesting a high burden of subclinical systolic dysfunction; 2.) GLS is more sensitive than LVEF in detecting early systolic dysfunction after TBI; 3) GLS abnormalities persist even at one week following TBI; and 4) The regional strain pattern following TBI represents primarily basal and mid-ventricular

dysfunction. Taken together, our findings suggest that systolic dysfunction is common following moderate-severe TBI and may have improved detection with speckle-tracking echocardiography, as compared to traditional methods of ascertaining systolic function.

While initially used for chronic cardiac disease, the use of speckle-tracking for myocardial strain assessment is growing in other critical illness paradigms, although data in TBI is limited. In the evaluation of sepsis-induced cardiac dysfunction, the use of strain measurements derived from speckle tracking has allowed the detection of impaired systolic function, even in the presence of normal LVEF¹⁹. In a pilot study of speckle tracking in 46 patients following severe aneurysmal SAH, impaired GLS and systolic dysfunction (GLS > -16%) was noted in 17 (37%) patients, while LVEF was largely preserved; furthermore, similar to our findings, regional strain abnormalities in this study were mainly noted in basal and mid-ventricular segments¹². In TBI, Cuisinier et al explored echocardiographic speckle tracking findings in 20 patients within 24 hours following severe TBI and reported that while median [range] EF of 61% [56%–76%] was generally normal, patients in their study had abnormal GLS values with a median [range] of -18% [-10.3% - -23.6%]; but the authors were not able to show a statistically significant difference from a control group of subjects undergoing surgery under general anesthesia²⁰. In the present study, we observed that 38% of patients with moderate-severe TBI had evidence of impaired strain (GLS > -16%) within one day of moderate-severe TBI, compared to only 17% of patients demonstrating impaired LVEF (EF<50%). Thus, subclinical systolic dysfunction was common in our patient population and likely would not have been diagnosed with more traditional measures of systolic function, such as ejection fraction or fractional shortening.

Strain abnormalities persisted after the initial phase of injury in several patients in the present study, with a lack of improvement in strain over the first week of hospitalization. The underlying pathophysiologic mechanisms of stress cardiomyopathies following neurologic injury have not been fully elucidated, but likely involve catecholamine-excess and systemic inflammation⁷; often these processes result in damage to the myocardium, with a pathologic finding of contraction band necrosis²¹. Injury to the cardiac substrate likely takes time to resolve, and may be reflected in the persistence of strain abnormalities in our study. Furthermore, it is possible that subclinical cardiac dysfunction following TBI may make the heart more sensitive to further dysfunction after other insults during the course of critical illness (such as sepsis, venous thromboembolism, or gastric bleeding), although this should be examined in future studies. In addition, future studies should evaluate long-term cardiac function following TBI and evaluate risk factors for persistence of cardiac dysfunction.

The majority of strain abnormalities in our cohort were localized to the basal and middle segments of the left ventricle. This pattern has been described in other neurogenic stress cardiomyopathies, and suggests a catecholamine-excess state as a potential underlying pathophysiologic mechanism. Similar to our findings in TBI, when evaluating strain abnormalities in patients with aneurysmal SAH, Cinotti et al found a significant gradient between the base and apical segments of the left ventricle (median GLS -13.5% versus -20%, respectively; p=0.001)¹². Catecholamine-excess has been well documented following severe TBI, and has been associated with poor outcomes²². Prior studies have found denser

sympathetic innervation of the base compared to the apex of the heart²³; thus, the present study findings add to the data supporting a possible direct catecholamine-mediated pathophysiologic mechanism for systolic dysfunction following TBI.

The findings of this study are clinically relevant. Our findings of a high burden of subclinical systolic dysfunction (normal LVEF, but abnormal GLS) suggest that cardiac dysfunction following TBI may be more common than observed in prior studies that used less sensitive echocardiographic methods; thus, cardiac dysfunction could be considered in the differential diagnosis of TBI patients who develop hypotension early after injury. Knowledge of cardiac dysfunction may add to the data required to better guide hemodynamic management and optimize cerebral blood flow following injury⁹. Lastly, given recent epidemiologic findings that patients with stress cardiomyopathies may experience a high burden of long-term cardiovascular morbidity²⁴, patients with TBI-induced systolic dysfunction may represent a population that requires close long-term follow-up for cardiovascular complications.

Our study had some limitations. First, several patient care interventions (sedation, vasopressors, fluids, and mechanical ventilation) may alter loading conditions in the heart; because of our small sample size, we were not able to fully control for these variables, and thus our analysis may be prone to residual confounding. Second, it is not possible to completely exclude prior underlying cardiac dysfunction in all subjects in our study, but this would be unlikely as we restricted our population to young patients who were free from a history of cardiovascular disease. Third, while strain has been evaluated following chronic cardiac disease, it has not fully been evaluated in detail in the critical care setting; thus, optimal values for strain abnormalities in the critical care setting are not clearly defined. Despite this, the present study showed higher (more impaired) GLS in the moderate-severe TBI population, compared to healthy age and gender-matched controls. Fourth, given that we measured cardiac function at day 7 after injury, sufficient time may not have been given to observe full recovery of cardiac function after injury. Lastly, little prior data has been described on strain abnormalities following neurologic injury; thus, while our pilot study adds to this growing literature base, our sample size was small and the findings should be considered exploratory and will require confirmation in larger studies.

In conclusion, this pilot study shows that strain abnormalities are common and persist for at least one week following moderate-severe TBI. GLS abnormalities are more sensitive than LVEF in detecting impaired systolic function following TBI and have a basal and mid-ventricular regional distribution. Speckle-tracking may be useful for the diagnosis and monitoring of systolic dysfunction following TBI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Differences in two-dimensional versus speckle tracking evaluation of left ventricular systolic function

Day 1**Day 5-7** **Patients with moderate-severe TBI** **Age/gender matched controls****Key:** **Figure 2:**

Regional strain "bull's eye" maps at day 1 and day 7 following moderate-severe TBI

Figure 3:
Longitudinal change in global longitudinal strain following moderate-severe TBI

Table 1

Demographic and clinical characteristics of patients with moderate-severe traumatic brain injury

	Patients with TBI (n = 15)
Age (years)	43 ± 13.5
Male Gender	11 (73%)
BMI	24.7 ± 2.9
Medical History	
Diabetes	0 (0%)
Hypertension	1 (7%)
Smoking	6 (40%)
Chronic medications	
Beta blockers	0 (0%)
Diuretics	0 (0%)
ACE inhibitors	0 (0%)
Injury Mechanism	
Fall	6 (40%)
Motor vehicle crash	6 (40%)
Other	3 (20%)
Initial Head CT Findings	
Epidural hemorrhage	1 (7%)
Subdural hemorrhage	12 (80%)
Subarachnoid hemorrhage	12 (80%)
Intraparenchymal hemorrhage	6 (40%)
Glasgow Coma Scale	
Admission GCS	5.0 ± 2.8
Highest GCS (within 24 hours)	8.7 ± 3.1
Lowest GCS (within 24 hours)	4.5 ± 2.5
Admission Hematocrit (%)	38.8 ± 5.9
Systolic Blood Pressure (mmHg)	
Admission SBP	136.5 ± 24.4
Lowest SBP within 24 hours	93.7 ± 13.1
Highest SBP within 24 hours	156.1 ± 18.6
Heart Rate (bpm)	
Admission Heart Rate	86.9 ± 24.0
Critical Care	
On vasopressors to maintain MAP>65 mmHg within 24 hours	5 (33%)
Need for mechanical ventilation	13 (87%)
ICP monitor placement	6 (40%)

Table 2.

Clinical parameters and echocardiographic data in 15 patients with moderate-severe traumatic brain injury and 15 age and gender matched healthy volunteers *

	Controls (n = 15)	Patients (n = 15)	p
Clinical Parameters			
Heart rate	66 ± 13	83 ± 26	0.03
Systolic blood pressure	125 ± 11	127 ± 16	0.74
Mean arterial pressure	92 ± 11	97 ± 13	0.22
2-Dimensional Echocardiography			
LVIDD ¹	4.7 ± 0.7	4.3 ± 0.6	0.08
LVIDS ²	3.4 ± 0.6	3.3 ± 0.7	0.71
Fractional Shortening ²	0.29 ± 0.07	0.24 ± 0.12	0.29
LVVD ³	144.1 ± 59.9	105.8 ± 31.2	0.06
LVVS ³	59.6 ± 22.6	41.9 ± 13.7	0.03
Ejection Fraction ³	0.58 ± 0.41	0.60 ± 0.11	0.57
Ejection Fraction < 50% ³	0 (0%)	2 (17%)	0.19
Doppler Echocardiography			
Mitral in-flow E-wave ⁴	73.5 ± 16.5	82.6 ± 23.3	0.24
Mitral in-flow A-wave ⁴	40.6 ± 14.7	67.7 ± 22.7	0.001
Mitral in-flow E/A ratio ⁵	2.5 ± 2.58	1.2 ± 0.43	0.13
Mitral Annular Tissue Doppler (septal)			
e-prime ⁶	10.1 ± 2.2	12.1 ± 4.9	0.15
a-prime ³	8.3 ± 2.92	9.3 ± 2.62	0.34
Mitral Annular Tissue Doppler (lateral)			
e-prime ⁶	13.3 ± 2.4	15.3 ± 4.3	0.14
a-prime ³	7.8 ± 2.7	13.0 ± 5.4	0.003
Speckle Tracking⁷ Echocardiography			
Global Longitudinal Strain *	-20.7 ± 1.8	-16.4 ± 3.8	0.001
Global Longitudinal Strain > -16% *	0 (0%)	5 (38%)	0.04

* Measurements from echocardiographic windows with inadequate views were excluded from the analysis. Measurements available for analysis are below:

¹Control n = 13, Patients n = 15

²Control n = 13, Patients n = 14

³Control n = 15, Patients n = 12

⁴, Control n = 15, Patients n = 13

⁵, Control n = 15, Patients n = 11

⁶, Control n = 15, Patients n = 14

⁷, Control n = 13, Patients n = 13

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