Cardiac dysfunction following brain death after severe pediatric traumatic brain injury: A preliminary study of 32 children

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ABSTRACT

Background: Cardiac dysfunction after brain death has been described in a variety of brain injury paradigms but is not well understood after severe pediatric traumatic brain injury (TBI). Cardiac dysfunction may have implications for organ donation in this patient population.

Materials and Methods: We conducted a retrospective cohort study of pediatric patients with severe TBI, both with and without a diagnosis of brain death, who underwent echocardiography during the first 2 weeks after TBI, between the period of 2003–2011. We examined cardiac dysfunction in patients with and without a diagnosis of brain death.

Results: In all, 32 (2.3%) of 1,413 severe pediatric TBI patients underwent echocardiogram evaluation. Most patients had head abbreviated injury score 5 (range 2–6) and subdural hematoma (34.4%). Ten patients with TBI had brain death compared with 22 severe TBI patients who did not have brain death. Four (40%) of 10 pediatric TBI patients with brain death had a low ejection fraction (EF) compared with 1 (4.5%) of 22 pediatric TBI patients without brain death who had low EF (OR = 14, P = 0.024).

Conclusions: The incidence of cardiac dysfunction is higher among pediatric severe TBI patients with a diagnosis of brain death, as compared to patients without brain death. This finding may have implications for cardiac organ donation from this population and deserves further study.

Key Words: Cardiac dysfunction, children, traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a major public health problem, accounting for a high morbidity and mortality rates in children and youth.[1] The National Center for Injury Prevention and Control estimates that over 510,000 traumatic brain injury (TBI) cases occur annually in children 0–14 years of age in the United States.[2] Traumatic brain injury adversely affects survival and long-term functional sequelae among survivors.[3,4] Ten percent of TBI is classified as severe and associated with a mortality rate of approximately 50%.[5] Severe TBI patients with brain death constitute a large proportion of heart transplant donors.[6,7]

While cardiac dysfunction after brain death has been described in a variety of brain injury paradigms,[8] it has not been well described after TBI in the pediatric population, although the pathophysiology may be similar. As most neurologic causes of brain death in the pediatric population tend to occur after trauma,[9] patients with severe TBI and brain death make a large proportion of pediatric patients presenting for possible organ donation.[10] To understand the association between TBI-induced brain death and cardiac function, we examined the incidence of cardiac dysfunction among severe pediatric TBI patients, both with and without a diagnosis of brain death.
MATERIALS AND METHODS

We conducted a retrospective cohort study among pediatric patients with severe TBI, both with and without a diagnosis of brain death, who underwent echocardiography during the first 2 weeks after TBI between 2003 and 2011. We compared cardiac dysfunction among patients who were diagnosed with brain death, as compared with patients who were not diagnosed with brain death.

Setting

The study was performed at Harborview Medical Center (HMC), a 413-bed county medical center in Seattle, WA, affiliated with the University of Washington and is the only Level 1 trauma center in the northwest region of the United States. The study was approved by the University of Washington Institutional Review Board.

Study population

Pediatric severe TBI [defined as admission Glasgow Coma Scale (GCS) ≤8 or head Abbreviated Injury Scale (AIS) ≥3] patients who underwent echocardiography during the first 2 weeks after TBI between 2003 and 2011 were examined. Eligibility criteria included: (1) Age < 18 years; (2) Discharge diagnosis of TBI (ICD 9 codes 800-801.9, 803-804.9 or 850-854.1), (3) Presence of transthoracic or transesophageal echocardiogram report in the medical record within 14 days of TBI admission, and (4) No documentation of cardiac arrest or cardiopulmonary resuscitation.

Data sources

Data sources were the HMC Trauma Registry, HMC billing data, and HMC electronic medical records. A list of eligible patients were identified from the HMC Trauma registry (N = 1,413) and linked to the HMC billing data source to yield a list of patients with severe TBI who underwent echocardiograms (N = 47). Fifteen patients were excluded because 1) echocardiogram coding was inaccurate (N = 4), and 2) echocardiograms were performed beyond 14 days of TBI admission (N = 11).

Clinical care of patients with severe TBI

During the study period, patients were resuscitated according to institutional practice. For severe TBI patients, the 2003 Infant, Children and Adolescents Brain Trauma Foundation Guidelines (14) were followed including: Intracranial pressure monitoring, maintaining intracranial pressure (intracranial pressure) <20 mmHg, maintaining a minimum cerebral perfusion pressure (CPP) 40–50 mm Hg, avoiding prophylactic severe hyperventilation to a PaCO₂ <30 mm Hg, keeping SaO₂ >90%, and using cooling/warming blankets or intravascular cooling devices when necessary for maintenance of normothermia. First-line vasopressor choice for severe hypotension was norepinephrine. Practices involving requests for echocardiogram were not standardized during the time of this study and echocardiograms were requested at the discretion of the primary attending intensivist.

Outcome Measures

The main outcome measured was the presence of cardiac dysfunction based on echocardiogram findings, defined as the presence or absence of abnormal echocardiogram findings (ejection fraction [EF] <50% or regional wall motion abnormality [RWMA] grades 1 = normal, 2 = mild hypokinesis, 3 = severe hypokinesis, 4 = akinesis and 5 = dyskinesis).

Statistical Analyses

Statistical analyses were performed by Statistical Package for the Social Sciences software (SPSS19.0, Chicago, Illinois) and STATA 12.0 (College Station, Texas) software. Descriptive statistics were used to describe clinical characteristics, echocardiogram findings, computed tomography scan defined TBI lesions, and mortality; data are presented as median and standard deviation for non-parametric variables. A Student’s t-test was used to examine differences between normally distributed continuous variables, a Mann-Whitney U test was used to test for differences in these non-parametric continuous data, and Chi-squared analysis was used to test for differences between categorical variables. Univariate logistic regression was performed to calculate odds ratios and 95% confidence intervals. Due to multiple testing, a significant P value of 0.025 was set, using a Bonferroni correction.

RESULTS

Patient characteristics and final sample

Thirty-two children with severe TBI underwent echocardiography within 14 days of admission; 10 (31.2%) of these patients were declared brain dead secondary to their primary neurologic event, and none of the patients suffered a cardiac arrest and subsequent cardiopulmonary resuscitation. Patients had a median of age of 16 years and were predominantly male (75%). Differences were not seen in clinical characteristics between severe TBI patients who were and were not declared brain dead [Table 1].

In the group of severe pediatric TBI without brain death, associated injuries included: Orthopedic (14; 63.6%), chest (12; 54.5%), abdominal (6; 27.3%), and isolated TBI (6; 27.3%). In the group of severe pediatric TBI with brain death, associated injuries included: Orthopedic (2; 20%), chest (3; 30%), abdominal (2; 20%), and isolated TBI (5; 50%). No significant difference was observed in the proportion of severe pediatric TBI patients with or without brain death who had chest injuries (P = 0.21).
Echocardiogram findings

In all, 32 (2.3%) of 1,413 pediatric TBI patients underwent echocardiogram evaluation. Median time to echocardiogram for the entire cohort of 32 patients was 3 days (1–13 days) after TBI. Of the 32 patients, 28 (87.5%) patients had a transthoracic echocardiogram (TTE) performed, 2 (6.3%) patients underwent only transesophageal echocardiography (TEE), and 2 (6.3%) patients underwent TEE in addition to TTE.

Table 2 shows the early echocardiogram findings from severe pediatric TBI patients with and without brain death. Four (40%) of 10 pediatric TBI patients who were brain dead had low EF (39 ± 10%) and RWMA (1 mild hypokinesis, 2 severe hypokinesis and 1 akinesis). One (4.5%) of 22 severe pediatric TBI patients without brain death had a low EF. Three (13.6%) of 22 severe TBI patients without brain death had RWMA (2 mild hypokinesis and 1 severe hypokinesis). Patients with severe TBI and brain death had a higher incidence of low EF than non-brain dead patients (OR 14, 95% CI 1.31–150.02, P = 0.024) but no higher incidence of RWMA (OR 4.2, 95% CI 0.73–24.44, P = 0.165).

DISCUSSION

The main finding of our study is that cardiac dysfunction was more common in pediatric patients with TBI-induced brain death as compared to TBI patients without brain death. This finding may have clinical significance for the pediatric cardiac donor population, especially because the incidence of cardiac dysfunction in this population is similar to the adult brain death population, where echocardiographic abnormalities are found in as many as 42% of patients with brain death,[7,8,11] causing the loss of potential heart donors for transplantation.[12] Previous studies have reported ventricular dysfunction after various neurologic injuries, but not TBI. Physiologic stress is hypothesized as a mechanism for cardiac dysfunction,[13‑19] including in brain dead patients.[20] Our findings show that low EF occurred frequently in this sample of severe pediatric TBI patients, and our incidence is consistent with the range of 9%–30%, which reported in adults with subarachnoid hemorrhage,[21,22] and 42% reported after brain death.[8] This similarity suggests that the observed cardiac dysfunction in this sample represents stress related cardiomyopathy, a phenomenon which has never been reported in pediatric TBI but is well recognized in adult

| Echocardiogram findings | All Severe TBI (N = 32) | Severe TBI without brain death (N = 22) | Severe TBI with brain death (N = 10) | P |
|-------------------------|-------------------------|----------------------------------------|-------------------------------------|---|
| Clinical characteristics |                         |                                        |                                     |   |
| Age (years)             | 16 (1-17)               | 16 (1-17)                              | 16 (13-17)                          | 0.98 |
| Male gender (%)         | 75                      | 72.7                                   | 80.0                                | 0.66 |
| Admission Glasgow coma scale | 3 (3-7)               | 3 (3-7)                                | 3                                   | 0.33 |
| Head abbreviated injury score | 5 (3-6)               | 5 (3-5)                                | 5 (3-6)                             | 0.23 |
| Injury severity score   | 42 (9-75)               | 50 (9-57)                              | 37 (16-75)                          | 1.00 |
| CT diagnosis            |                         |                                        |                                     |   |
| Subdural hematoma       | 11 (34.4)               | 4 (18.2)                               | 7 (70.0)                            |   |
| Subarachnoid hemorrhage | 5 (15.6)                | 5 (22.7)                               | 0                                   |   |
| No intracerbral hemorrhage | 4 (12.5)             | 4 (18.2)                               | 0                                   |   |
| Contusion               | 3 (9.4)                 | 3 (13.6)                               | 0                                   |   |
| Intraparenchymal hemorrhage | 2 (6.3)               | 1 (4.5)                                | 1 (10.0)                            |   |
| Epidural hematoma       | 2 (6.3)                 | 2 (9.1)                                | 0                                   |   |
| Infarction              | 2 (6.3)                 | 1 (4.5)                                | 1 (10.0)                            |   |
| Others                  | 3 (9.3)                 | 2 (9.0)                                | 1 (10.0)                            |   |
| All cause in-hospital mortality | 14 (43.8)         | 5 (22.7)                               | N/A                                 |   |

Table 2: Clinical characteristics and early echocardiogram findings of pediatric patients with severe traumatic brain injury (n = 22) and brain death patients (n = 10)

TBI = Traumatic brain injury, LVEF = Left ventricular ejection fraction, RWMA = Regional wall motion abnormalities. Data as n (%) or median (range)

Table 2: Early echocardiogram findings in final sample of severe pediatric traumatic brain injury without brain death (N = 22) and TBI with brain death (N = 10)

| LVEF                  | All Severe TBI (N = 32) | Severe TBI without brain death (N = 22) | Severe TBI with brain death (N = 10) | P |
|-----------------------|------------------------|----------------------------------------|-------------------------------------|---|
| Low (LVEF < 50%)      | 5 (15.6)               | 1 (4.5)                                | 4 (40)                              | 0.024 |
| Normal (LVEF ≥50%)    | 27 (84.4)              | 21 (95.5)                              | 6 (60)                              |   |
| RWMA grade            |                         |                                        |                                     |   |
| Normal                | 25 (78.1)              | 19 (86.4)                              | 6 (60)                              | 0.165 |
| Abnormal              | 7 (21.9)               | 3 (13.6)                               | 4 (40)                              |   |
| Mild hypokinesis      | 3 (9.4)                | 2 (9.1)                                | 1 (10)                              |   |
| Severe hypokinesis    | 3 (9.4)                | 1 (4.5)                                | 2 (20)                              |   |
| Akinetic              | 1 (3.1)                | 0                                      | 1 (10)                              |   |
| Dyskinetic            | 0                      | 0                                      | 0                                   |   |

TBI = Traumatic brain injury, LVEF = Left ventricular ejection fraction, RWMA = Regional wall motion abnormalities
neurological conditions. Myocardial dysfunction after brain death has not only been reported as common, but may also represent a common pathway of an end-stage cardiac injury, which may have multiple etiologies, including TBI.

Three main theories explaining the pathogenesis of brain injury induced cardiac dysfunction include multi-vessel coronary spasm causing ischemia, microvascular dysfunction, and the catecholamine hypothesis. Catecholamine-induced cardiac injury is one theory explaining the underlying cause of cardiac dysfunction in adult TBI patients; plasma catecholamine concentrations (noradrenaline, adrenaline and 3-methoxy-4-hydroxy-phenylethylene glycol) are elevated one day after TBI. Using SAH as the best-studied model of cardiac dysfunction after neurologic injury, we observe that adult patients with SAH have an increase in plasma norepinephrine within 48 hours after the hemorrhage, which persists during the first week and normalizes by six months.

Potential pediatric heart donors have been shown previously to have a high prevalence of left ventricular systolic and diastolic dysfunction. The ventricular dysfunction is likely to be worse in younger patients because of a greater density of β-adrenergic receptors within myocardium in the setting of a sudden increase in sympathetic activity. Interestingly, a longer interval between brain death and donor cardiectomy improved rejection-free survival in the recipient, presumably secondary to hemodynamic optimization of the donor prior to transplant.

There are several limitations to our study. First, this was a single-center retrospective study, and the sample size is small. However, this was a preliminary study to determine initial impressions of the incidence of cardiac dysfunction in pediatric TBI. Second, echocardiogram timing and utilization were driven by clinical care needs and not by study design, thus creating a possible selection bias toward patients with a greater degree of hemodynamic compromise; furthermore, because pre-injury echocardiograms were not collected, the possibility of reverse causality cannot be fully excluded. Third, the majority of patients in our study were adolescents, and the generalizability of our findings to a younger patient population may be limited. However, despite the study limitations, our study documents cardiac dysfunction, which has the potential to impact both hemodynamic management of the pediatric TBI patient with brain death and transplantation outcomes from donor pediatric TBI patients with brain death.

**CONCLUSION**

In summary, to our knowledge, our preliminary study is the first to document an effect of severe TBI on cardiac function by echocardiogram early after injury in children. Brain death, representing the most severe form of TBI, demonstrated the highest rate of cardiac dysfunction. Because of the small sample size and limitations on generalizability, hopefully our data can open the door for larger prospective studies evaluating cardiac dysfunction after pediatric TBI with and without brain death.

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