Review Article

CEREBRAL AUTOREGULATION AND CARDIOVASCULAR PHYSIOLOGY DYSFUNCTION IN TRAUMATIC BRAIN INJURY CASES: A BRIEF REVIEW

ABSTRACT

Introduction: Traumatic brain injury (TBI) is one of the leading causes of death and disability in the early years of life. Post-TBI physiological alterations vary across adult and pediatric patients and severity. This disease affects the quality of life of most people. Acute hemiparesis can cause cognitive impairments. It may also impact mood, memory, and decision-making. Furthermore, parasympathetic dysfunction and sympathetic activation appear to contribute to cardiac injury via modulation of the myocardial inflammatory response via acetylcholine receptors.
Purpose: This review aims to explain the neuronal response and cardiac biomarkers after traumatic brain injury cases.
Methods: The review used Pubmed and Google Scholar to search for articles on traumatic brain injury, neuronal response, and cardiac biomarkers. The articles were chosen for their language, publishing, content, exposure, and outcome. The main reference is obtained from up to 60 articles that meet the inclusion requirements.
Results: TBI can cause localized brain injury or diffuse brain injury from physical trauma such as diffuse axonal injury or brain edema. Repeated concussions raise the likelihood of chronic neurological, cognitive, and behavioral issues. Stress-induced catecholamine surges and inflammatory mediator production in response to trauma may also endanger cardiac disturbances.
Conclusion: The brain and heart work together to preserve tissue homeostasis after TBI. The expression of biomarkers that detect brain and nerve tissue damage proves this illness.

Keywords: Traumatic brain injury, Cerebral autoregulation, Cardiac biomarkers, cardiac dysfunction,

1. INTRODUCTION

Traumatic brain injury (TBI) is caused by an external force on the brain, causing cognitive, physical, and psychosocial functioning problems. TBI is one of the leading causes of death and disability in the adolescent years. (1,2) TBI occurs in approximately 102 people per 100,000 in the United States each year, with 80,000 developing long-term disability. (3)

TBI is caused by motor vehicle accidents, falls, gunshot wounds, work injuries, and sports injuries. Substance addiction and alcoholism are risk factors.(3) TBI has two main mechanisms: primary and secondary injury. Brain edema is caused by localized brain damage caused by contact-type injury and intracranial haemorrhage induced by acceleration/deceleration type injury. Following the first hit, a molecular, chemical, and inflammatory cascade causes

further cerebral damage. (4) The severity of post-TBI physiological alterations in many organs varies between adults and children.

The diffuse injury occurs more frequently in young patients than focal injury in adults. Insensible fluid and heat loss and hypothermia will have a greater impact on youngsters than adults. In fact, post-TBI pediatric patients' CBF and volume alterations differed across young children, older children, and adults. (5) TBI also causes a systemic inflammatory response syndrome, which leads to organ system dysfunction and failure. (6) Post-TBI individuals experience physiological or anatomical changes that impact their quality of life. There are cognitive, behavioural, and hemiparetic consequences. It may also impact mood, memory, and decision-making.

PSH (paroxysmal sympathetic hyperactivity) can occur in TBI patients. Surprisingly, this syndrome is marked by decerebrate body posture and paroxysmal tachycardia. The syndrome is linked to a worse prognosis and more extended hospital stays. (7–9) Furthermore, parasympathetic dysfunction and sympathetic activation appear to contribute to cardiac injury via modulation of the myocardial inflammatory response via acetylcholine receptors. Uncontrolled myocardial inflammation causes myocardial dysfunction and cell death. (9)

Post-TBI cardiovascular problems increase morbidity and mortality. Hypertension, hypotension, ECG alterations, cardiac arrhythmias, indicators of cardiac damage, and left ventricular failure are all possible. Because the anomalies are usually reversible, the focus should be on general supportive care and treating the underlying brain injury. cTnI elevation has been found in 20–68% of individuals. (6,10) cTnI is 100 percent sensitive and 86 percent specific for detecting LV dysfunction, compared to 29 and 100 percent for CK-MB. A high cTnI response is an independent predictor of acute regional wall motion abnormalities (WMAs) and is associated with an elevated risk of death and poor functional outcome in survivors. Decreased sensitivity of the heart to catecholamines following brain injury. Elevated BNP levels are also linked to LV dysfunction. SAH increases the risk of cardiovascular comorbidities, hospital stays, and poor outcomes or mortality linked with cardiac arrhythmias. Increased circulating cTnI is a marker of poor cardiac performance in SAH patients, including ST-segment elevation in MI, progressive myocardial hypertrophy, fibrosis, and cardiovascular mortality. (11)

The variability of TBI makes it difficult to quantify damage and predict patient fate. The variability of TBI makes it challenging to measure trauma and predict patient outcomes appropriately. Studies suggest that negative TBI outcomes (including disability, low life satisfaction, and memory loss) increase in prevalence with TBI severity. (12) This review seeks to explain cerebral autoregulation and cardiovascular dysfunction following TBI.

2. METHODS

The literature search in this review was carried out using Pubmed and Google Scholar databases with three main keywords: traumatic brain injury, neuronal response after TBI, and cardiac biomarkers in TBI cases. The articles were selected based on language, type of publication, suitability of methods, characteristics of the subject, exposure, and outcome. All references that match the inclusion criteria are processed using the Mendeley® citation manager, whereas 66 articles are obtained as the main reference.

3. RESULTS AND DISCUSSION

Traumatic brain injury (TBI) is the primary cause of disability and mortality in the United States. (13,14) Dewan et al. estimated that 69 million TBIs occur annually, most of which are mild. (15) In 2019, 60,611 people died from traumatic brain injury, compared to 60,565 in 2018, with the greatest mortality rate per 100,000 population being 76.7 percent in 2019. TBIs were most commonly caused by car accidents and falls, with gunshot wounds being the most lethal. Although TBI morbidity and death are high in low- and middle-income nations, new public health breakthroughs and policies appear to reduce TBI mortality effectively. (16)

TBI is classified as mild, moderate, or severe based on clinical variables such as consciousness length and severity. The Glasgow Coma Scale (GCS) can be used to stratify TBI severity after resuscitation. A GCS score of 13-15 is mild, 9-12 is moderate, and 3-8 is severe. (17,18) Symptoms range from physical to cognitive and behavioural issues. Mild TBI demands speedy recovery, whereas severe TBI necessitates an extended stay in the ICU (ICU). (12,19)

3.1 Biomechanisms of TBI

TBI can cause localized brain injury (contusion, laceration, and intracranial haemorrhage) or diffuse brain injury (accelerated/decelerated) from physical trauma (diffuse axonal injury or brain edema). TBI can be caused by impact, inertia, penetration, or blast overpressure. The force of rotation, translation, or deceleration induced by blunt trauma

damages brain tissue. These forces enhanced intracranial tension by lowering the brain's latency behind the skull during rapid movement. These stress gradients cause axonal damage by stretching and shearing axons. (12,20)

Using six post-mortem head and neck cadavers, Alshareef et al. discovered that brain movement is dependent on axial rotation, resulting in massive brain displacement. The test displaced the mid-cerebrum the most, while the cerebellum and brainstem shifted less. Greater mobility in the brain was observed with higher angular velocity and shorter pulse length. (21)

Repeated concussions increase the likelihood of chronic neurological, cognitive, and behavioural problems. Several studies examining the effects of repeated concussions in animal models using imaging or molecular methods have demonstrated significant behavioural disturbances and microglial activation after brain damage. Mild TBI in a mouse model causes short-term brain structural and histologic changes, learning and memory deficits, and impaired motor skills, which appear identical to mild TBI in humans. (22,23) Unusual neuroimaging findings in individuals and athletes who had repeated head injuries as opposed to older age groups. A retired athlete with a history of concussions suffers memory, psychomotor, and cognitive issues. (24–26)

3.2 Pathophysiology and Cerebral Autoregulation of TBI

TBI causes primary and secondary brain damage. (27) Secondary brain injury occurs when numerous mechanical stresses cause brain tissue destruction, decreased cerebral blood flow, and metabolic changes. Secondary brain injury is a pathological response to an initial brain injury that includes changes in cerebral blood flow, vasospasm, BBB disruption, and edema. (28,29) The purpose of therapy and management is to prevent subsequent brain injury. TBI alters cerebral blood flow and impairs cerebral autoregulation (12,14,30–32). Most severe TBI patients have brain autoregulation issues. (33,34) Any changes that occur in blood pressure or metabolism, the brain will use cerebral autoregulation mechanisms to maintain oxygen and cerebral blood flow to meet the brain's needs. Autoregulation is thought to have four mechanisms. The myogenic mechanism by which changes in transmural pressure can cause vascular smooth muscle to contract. Nerve supply to cerebral blood vessels is a neurogenic mechanism. For example, activation of alpha adrenoceptors enhances inhibition of autoregulation, causing cerebral vasoconstriction. Metabolic systems can contribute to microvascular autoregulation when changes in the microenvironment, such as pCO2 and H+, cause vasodilation. The endothelium also secretes vasodilators such as nitric oxide and vasoconstrictors such as endothelin-1 and thromboxane A2, which modulate cerebrovascular tone. (35,36)

Normal cerebral blood flow is between 50 and 150 mmHg CPP or 60 and 160 mmHg MAP (MAP). Hypoperfusion (CBF 15 ml/100g/min) causes cerebral ischemia. Early hyperperfusion or hyperemia in TBI patients (CBF > 55 ml/100 g/min) can worsen patient outcomes by increasing the likelihood of increased cerebral blood volume (CBV) and intracranial pressure (ICP). CBF and CPP can predict patient outcomes. Early-stage severe TBI patients with Xenon-Computed Tomography had reduced CBF. (36–40) Cerebral perfusion pressure is stimulation that triggers an autoregulation response of the cerebrovascular system. (32)

Reduced cerebral perfusion pressure induces cerebral vein dilatation and hence increased cerebral blood volume. In general, lower cerebral perfusion pressure means lower baseline vascular pressure. Hyperperfusion above the autoregulation limit may cause hyperemia. In fact, a decline in SAP below the normal level can cause brain ischemia. (4,30) CO2-reactivity and hyper- or hypocapnia-induced dilatation and constriction of cerebral blood vessels are needed for sufficient CBF. Vasoconstriction induces hypocarbia, decreasing CBV and CBF. Hypoventilation causes blood vessel dilation, raising CBV and ICP. (18,28,30,41)

In normal brain conditions, cerebrovascular autoregulation mechanisms will maintain a constant cerebral blood flow, despite changes in systemic blood pressure. In the first phase, CPP initially decreases due to reduced systemic blood pressure and autoregulatory vasodilation, which aims to maintain cerebral blood flow, leading to increased ICP; Therefore. In the later phase, as ICP continues to rise, CPP falls below the ischemic threshold, and to re-establish normal CPP, systemic blood pressure then rises. In the last phase, autoregulatory vasoconstriction occurs to stabilize the balance between systemic blood pressure and CPP. In the injured brain, these autoregulatory mechanisms are often impaired, and significant increases in systemic blood pressure are referred directly to the cerebral capillaries, resulting in a breakdown of the blood-brain barrier, worsening cerebral edema, and increased ICP.(42) Hypocapnia and hyperventilation have been demonstrated to lower ICP and prevent hypotension in TBI patients. (34,43–45) TBI causes massive excitatory neurotransmitter release, especially glutamate. Extracellular glutamate causes overstimulation of ionotropic and metabotropic glutamate receptors with Ca+, Na+, and K+ movements. To compensate for the ionic pump Na+/K+-ATPase movement, cells, particularly astrocytes, engage in catabolic cycles, resulting in an unending metabolic stream that isolates cells. (4,35,46,47) Furthermore, extracellular K+ increases with Na+/K+-ATPase pump failure, adding to cerebral edema. (47) Edema is an increase in brain tissue fluid, including individual cells and interstitial space.

Vasogenic and cytotoxic edema. Vasogenic edema occurs when liquid accumulates in the perivascular region, causing alterations in CBF and increased intracranial pressure (ICP). Particle channels activated by cytotoxic edema cause a flood of water into the intracellular space of several cell types, further disrupting the BBB.(47,48)

3.3 Autonomic Nervous System and Cardiovascular Dysfunction

This system includes the insular and medial prefrontal cortex, cerebral amygdala, terminal stria, hypothalamus and periaqueductal grey tissue. (49,50) The amygdala is thought to modulate autonomic, endocrine, and cardiovascular responses. The autonomic nervous system is divided into two parts: sympathetic and parasympathetic (PNS). The parasympathetic nervous system (PNS) has less influence on peripheral blood vessels and is active under calmer conditions. The ANS innervates cardiac muscle, smooth muscle, and different endocrine and exocrine glands, regulating the actions of most tissues and organ systems. The ANS regulates blood pressure, digestion, bladder contraction, eye focus, and body temperature. (50)

The hypothalamic–pituitary–adrenal axis regulates stress, exercise, and metabolism. The suprachiasmatic nucleus releases C-reactive protein, which stimulates the adrenal gland to release cortisol. Stress causes an increase in a sympathetic tone which causes heart enlargement and myocardial ischemia. However, studies have indicated that cardiac abnormalities, particularly autonomic dysfunction, are related to higher mortality and morbidity in TBI. (9,50–53) Hypothalamic and insular cortex injuries increase the risk of cardiac issues such as blood pressure changes, arrhythmias, and myocyte death. (49,50)

In response to trauma, stress-induced catecholamine surges and inflammatory mediator production may also endanger cardiac myocytes. TBI and SAH create a systemic catecholamine "storm" that activates the adrenal glands and increases sympathetic outflow. (6,49) Following a TBI, neurogenic variables such as increased catecholamine release and inflammation may cause systemic issues. (54) As a whole, brain damage can cause systemic abnormalities such as increased sympathetic activity and immune system depression causing hypertension, tachycardia, arrythmia, and an increase in oxygen demand, which can lead to subendocardial ischemia and ventricular dysfunction. This is due to unopposed peripheral vasodilation and heart failure. Regular vasopressor/inotropic medication usually lowers arterial pressure. Norepinephrine is routinely used after a TBI to regulate arterial pressure and CPP reliably. (49,55) Systolic dysfunction following a TBI is problematic because it may contribute to secondary brain injuries, as adequate cardiac output is critical in maintaining cerebral blood flow after injury. Early hypotension and hypertension after TBI are also harmful because they are both linked to poor outcomes after TBI. Krishnamoorthy et al. found that thirty-two patients were included, and 7 (22 %) developed systolic dysfunction after TBI. Patients who developed systolic dysfunction experienced early elevation of systolic blood pressure (SBP), mean arterial pressure (MAP), and heart rate, compared to patients who did not develop systolic dysfunction ($P<0.01$ for all comparisons). (56)

3.4 Paroxysmal sympathetic hyperactivity

TBI, stroke, anoxic brain injury, tumors, infections, spinal injuries, and serotonin syndrome are all examples of PSH. The prevalence of PSH ranges from 8–to 33 percent, with TBI accounting for 79.4 percent of cases. PSH affects 80 percent of patients with moderate to severe TBI and 15–33 percent of patients with severe TBI. After traumatic brain injury (TBI), paroxysmal sympathetic hyperactivity (PSH) has been described as being associated with hyperthermia, hypertension, tachycardia, tachypnea, diaphoresis, dystonia (hypertonia or spasticity), and even motor features such as extensor/flexion posturing.(57) The pathophysiology of PSH is unknown, but the dominant theory suggests that the central autonomic network (insular cortex, amygdala, hypothalamus, medulla, periaqueductal gray matter, parabrachial complex, and nucleus of the hypothalamus) fails.(58)

There is no widely accepted treatment algorithm for PSH. Treatment aims to reduce associated adverse events such as cardiac hypertrophy, dehydration, muscle wasting, contractures, and delayed recovery, contributing to increased morbidity. Multiple medications are frequently required to control the various symptoms. Bromocriptine, a dopaminergic agent, has been shown to reduce body temperature and sweating. Clonidine and other alpha agonists reduce heart rate and blood pressure.(59) Beta-blockers protect the heart by lowering heart rate, perfusion volume, and mean arterial pressure. This effect reduces myocardial oxygen consumption, preventing a heart attack. Beta-blockers also have a neuroprotective effect by lowering cerebral blood flow, lowering cerebral consumption of oxygen and glucose as metabolism slows.(58)

3.5 Electrocardiographic (ECG) Abnormalities

Electrocardiographic (ECG) changes, including morphological changes and rhythm disturbances, are common in TBI. Several studies have shown ECG changes in patients with severe traumatic brain injury and are associated with cardiac dysfunction and increased hospital mortality.(52,53,60) Repolarization abnormalities such as QT interval prolongation and changes in ST-segment and T wave morphology are the most common ECG changes in patients with SAH and intracerebral hemorrhage (ICH). ST segment changes, flat or inverted T waves, prominent U waves, and QTc interval prolongation (QTc is the QT interval corrected for heart rate) are the most common findings. (61,62) Prolonged QT repolarization abnormalities and morphological late repolarization abnormalities (MERA), but not ischemic-like ECG changes, are associated with cardiac dysfunction after isolated TBI. (53) A study of 198 adult patients admitted to the ICU with TBI showed ECG abnormalities consisting of impaired ventricular repolarization, conduction disturbances, QTc prolongation and arrhythmias. Arrhythmias are found more frequently in patients with diffuse brain injury. Even so, abnormalities on the ECG cannot pinpoint the location of the lesion in the brain. (60) A 12-lead ECG may be a helpful screening tool for isolated TBI patients with heart abnormalities prior to additional diagnostic investigations or therapies.

3.5 Cardiac Biomarkers in TBI

TBI has a progressive pathology: alterations occur over time and follow the initial trauma. An objective indicator of normal biological processes, pathogenic processes, or response to exposure or intervention (including therapeutic intervention) is a biomarker. (63) To diagnose myocardial damage and LV dysfunction, cardiac troponin I (cTnI) is preferred over CK-MB. CK-MB can elevate due to skeletal muscle injury, renal failure, intramuscular injection, intense activity, and exposure to toxins and drugs. (64) High troponin levels have been identified in traumatic and nontraumatic brain injuries. Acute myocardial injury produces serum cardiac troponins, which are solely produced by wounded myocardial cells. According to a pooled research, Higher cTn is strongly related with a high death rate in patients with TBI. (65) Myocytes produce BNP (B-type natriuretic peptide) and are elevated in conditions of heart disease, sepsis, stroke, TBI, and blood-brain barrier disorders. Elevated serum BNP are associated with LV dysfunction. (6,66)

4. CONCLUSION

Cerebral autoregulation and heart have a synergistic relationship in maintaining tissue homeostasis after TBI. This condition is proved by the production of biomarkers that can be detected specifically for damage to brain and nerve tissue. Specific follow-up studies looking at more general biomarkers will greatly assist in the diagnosis of TBI brain damage.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

REFERENCES

1. Agustia N, Utami GT, Nauli FA. Gambaran Kualitas Hidup Pasien Pasca Mengalami Cedera Kepala: Literature Review. Jkep. 2021;6(2):146–58.
2. Irdesel J, Aydiner SB, Akgoz S. Rehabilitation outcome after traumatic brain injury. Neurocirugia. 2007;18(1):5–15.
3. Bushnik T, Hanks RA, Kreutzer J, Rosenthal M. Etiology of traumatic brain injury: Characterization of differential outcomes up to 1 year postinjury. Archives of Physical Medicine and Rehabilitation. 2003 Feb 1;84(2):255–62.
4. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. Vol. 99, British Journal of Anaesthesia. Oxford University Press; 2007. p. 4–9.
5. Figaji AA. Anatomical and Physiological Differences between Children and Adults Relevant to Traumatic Brain Injury and the Implications for Clinical Assessment and Care. Frontiers in Neurology [Internet]. 2017 Dec 14 [cited 2022 May 9];8(DEC). Available from: /pmc/articles/PMC5735372/
6. Gregory T, Smith M. Cardiovascular complications of brain injury. Continuing Education in Anaesthesia, Critical Care and Pain. 2012;12(2):67–71.
7. Siponkoski ST, Wilson L, Steinbüchel N von, Sarajuuri J, Koskinen S. Quality of life after traumatic brain injury: Finnish experience of the QOLIBRI in residential rehabilitation. J Rehabil Med [Internet]. 2013 [cited 2022 May 9];45(8):835–42. Available from: https://pubmed.ncbi.nlm.nih.gov/24002322/

8. Khalid F, Yang GL, McGuire JL, Robson MJ, Foreman B, Ngwenya LB, et al. Autonomic dysfunction following traumatic brain injury: Translational insights. Neurosurgical Focus. 2019;47(5).
9. Hilz MJ, Liu M, Roy S, Wang R. Autonomic dysfunction in the neurological intensive care unit. Clin Auton Res [Internet]. 2019 Jun 1 [cited 2022 May 9];29(3):301–11. Available from: https://pubmed.ncbi.nlm.nih.gov/30022321/
10. Caro DHJ. The Yin and Yang of Integrated Care: Systemic Imperatives for Traumatic Brain Injuries. The Open Public Health Journal. 2014;7:6–11.
11. Chen Z, Venkat P, Seyfried D, Chopp M, Yan T, Chen J. Brain-Heart Interaction: Cardiac Complications after Stroke. Vol. 121, Circulation Research. Lippincott Williams and Wilkins; 2017. p. 451–68.
12. Blennow K, Brody DL, Kochanek PM, Levin H, McKee A, Ribbers GM, et al. Traumatic brain injuries. Nature Reviews Disease Primers. 2016 Nov 17;2.
13. Galgano M, Toshkezi G, Qiu X, Russell T, Chin L, Zhao LR. Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors. Cell Transplantation [Internet]. 2017;26(7):1118–30. Available from: https://us.sagepub.com/en-us/nam/open-access-at-sage
14. Ng SY, Lee AYW. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Vol. 13, Frontiers in Cellular Neuroscience. Frontiers Media S.A.; 2019.
15. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg [Internet]. 2019;130:1080–97. Available from: https://thejns.org/doi/abs/10.3171/2017.10.JNS17352
16. Khellaf A, Danyal ·, Khan Z, Helmy A. Recent advances in traumatic brain injury. Journal of Neurology [Internet]. 2019;266:2878–89. Available from: https://doi.org/10.1007/s00415-019-09541-4
17. Vella MA, Crandall M, Patel MB. Acute Management of Traumatic Brain Injury HHS Public Access. Surg Clin North Am. 2017;97(5):1015–30.
18. Chung P, Khan F. Traumatic Brain Injury (TBI): Overview of Diagnosis and Treatment. Journal of Neurology & Neurophysiology. 2013;05(01).
19. Kowalski RG, Flora ;, Hammond M, Weintraub AH, Nakase-Richardson R, Zafonte RD, et al. Recovery of Consciousness and Functional Outcome in Moderate and Severe Traumatic Brain Injury Supplemental content. JAMA Neurol [Internet]. 2021;78(5):548–57. Available from: https://jamanetwork.com/
20. Stemper BD, Pintar FA. Biomechanics of concussion. Vol. 28, Progress in Neurological Surgery. S. Karger AG; 2014. p. 14–27.
21. Alshareef A, Giudice JS, Forman J, Shedd DF, Reynier KA, Wu T, et al. Biomechanics of the Human Brain during Dynamic Rotation of the Head. J Neurotrauma. 2020;37:1546–55.
22. Yang Z, Wang P, Morgan D, Bruijnzeel AW, Lin D, Pan J, et al. Temporal MRI characterization, neurobiochemical and neurobehavioral changes in a mouse repetitive concussive head injury model OPEN. Nature Publishing Group [Internet]. 2015; Available from: www.nature.com/scientificreports/
23. Robinson S, Berglass JB, Denson JL, Berkner J, Anstine C v, Winer JL, et al. Microstructural and Microglial Changes After Repetitive Mild Traumatic Brain Injury in Mice HHS Public Access. J Neurosci Res. 2017;95(4):1025–35.
24. Cunningham J, Broglio SP, O'grady M, Wilson F. History of Sport-Related Concussion and Long-Term Clinical Cognitive Health Outcomes in Retired Athletes: A Systematic Review. Journal of Athletic Training [Internet]. 2020;55(2):132–58. Available from: http://dx.doi.org/10.4085/1062-6050-297-18.S1
25. Diaz-Arrastia R, Gugger J, Lippa S, Wojtowicz M, Victoria Echlin H, Rahimi A. Systematic Review of the Long-Term Neuroimaging Correlates of Mild Traumatic Brain Injury and Repetitive Head Injuries. Frontiers in Neurology | www.frontiersin.org [Internet]. 2021;1:726425. Available from: www.frontiersin.org
26. Mckee AC, Cantu RC, Nowinski CJ, Tessa Hedley-Whyte E, Gavett BE, Budson AE, et al. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. J Neuropathol Exp Neurol [Internet]. 2009;68(7):709–35. Available from: https://academic.oup.com/jnen/article/68/7/709/2917002
27. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management. Vol. 104, Medical Clinics of North America. W.B. Saunders; 2020. p. 213–38.
28. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiological Reviews [Internet]. 2021 Oct 1 [cited 2022 Apr 27];101(4):1487. Available from: /pmc/articles/PMC8576366/
29. Riera JJ, Parthasarathy AB, Zheng Y, Duffin J, Sobczyk O, McKetton L, et al. Cerebrovascular Resistance: The Basis of Cerebrovascular Reactivity. Front Neurosci [Internet]. 2018;12:409. Available from: www.frontiersin.org
30. Kinoshita K. Traumatic brain injury: Pathophysiology for neurocritical care. Vol. 4, Journal of Intensive Care. BioMed Central Ltd.; 2016.
31. Algattas H, Huang JH. Traumatic Brain Injury pathophysiology and treatments: Early, intermediate, and late phases post-injury. Vol. 15, International Journal of Molecular Sciences. MDPI; 2014. p. 309–41.
32. Sheriff FG, Hinson HE. Pathophysiology and Clinical Management of Moderate and Severe Traumatic Brain Injury in the ICU HHS Public Access. Semin Neurol. 2015;35(1):42–9.

33. Gunge Riberholt C, Damkjaer Olesen N, Thing M, Bogh Juhl C, Mehlsen J, Hvass Petersen T. Impaired Cerebral Autoregulation during Head Up Tilt in Patients with Severe Brain Injury. PLoS One [Internet]. 2016;11(5). Available from: www.glostruphospital.dk
34. Zeiler FA, Mathieu F, Monteiro M, Glocker B, Ercole A, Beqiri E, et al. Diffuse Intracranial Injury Patterns Are Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study. Journal of Neurotrauma [Internet]. 2020 [cited 2022 Apr 26];37(14):1597. Available from: /pmc/articles/PMC7336886/
35. Rivera-Lara L, Zorilla-Vaca A, Geocadin RG, Healy RJ, Ziai W, Mirski MA. Cerebral Autoregulation-oriented Therapy at the Bedside. Anesthesiology [Internet]. 2017;126(6):1187–99. Available from: http://pubs.asahq.org/anesthesiology/article-pdf/126/6/1187/519196/20170600_0-00032.pdf
36. Armstead WM. Cerebral Blood Flow Autoregulation and Dysautoregulation. Anesthesiol Clin. 2016;34(3):465–77.
37. Honda M, Ichibayashi R, Yokomuro H, Yoshihara K, Masuda H, Haga D, et al. Early Cerebral Circulation Disturbance in Patients Suffering from Severe Traumatic Brain Injury (TBI): A Xenon CT and Perfusion CT Study. Neurol Med Chir. 2016;56:501–9.
38. Inoue Y, Shiozaki T, Tasaki O, Hayakata T, Ikegawa H, Yoshiya K, et al. Changes in Cerebral Blood Flow from the Acute to the Chronic Phase of Severe Head Injury. JOURNAL OF NEUROTRAUMA. 2005;22(12):1411–8.
39. Lassen NA, Christensen MS. Physiology of Cerebral Blood Flow. BrJ Anaesth. 1976;48:719.
40. ter Laan M, van Dijk JMC, Elting JWJ, Staal MJ, Absalom AR. Sympathetic regulation of cerebral blood flow in humans: A review. Vol. 111, British Journal of Anaesthesia. Oxford University Press; 2013. p. 361–7.
41. Salehi A, Zhang JH, Obenaus A. Response of the cerebral vasculature following traumatic brain injury. Journal of Cerebral Blood Flow & Metabolism. 2017;37(7):2320–39.
42. Krishnamoorthy V, Prathep S, Sharma D, Gibbons E, Vavilala MS. Association between electrocardiographic fi ndings and cardiac dysfunction in adult isolated traumatic brain injury. Indian Journal of Critical Care Medicine September [Internet]. 2014;18(9):570–4. Available from: www.ijccm.org
43. Rangel-Castilla L, Lara LR, Gopinath S, Swank PR, Valadka A, Robertson C. Cerebral Hemodynamic Effects of Acute Hyperoxia and Hyperventilation after Severe Traumatic Brain Injury. Journal of Neurotrauma. 2010;27:1853–63.
44. Puppo C, Kasprowicz M, Steiner LA, Yelicich B, Afrodite Lalou D, Smielewski P, et al. Hypocapnia after traumatic brain injury: how does it affect the time constant of the cerebral circulation? Journal of Clinical Monitoring and Computing [Internet]. 2020;34:461–8. Available from: https://doi.org/10.1007/s10877-019-00331-x
45. Beqiri E, Czosnyka M, Lalou AD, Zeiler FA, Fedriga M, Steiner LA, et al. Influence of mild-moderate hypocapnia on intracranial pressure slow waves activity in TBI. Acta Neurochirurgia [Internet]. 2020;162:345–56. Available from: https://doi.org/10.1007/s00701-019-04118-6
46. Jamjoom AAB, Rhodes J, Andrews PJD, Grant SGN. The synapse in traumatic brain injury. Brain. 2021;144(1):18–31.
47. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Vol. 145, Neuropharmacology. Elsevier Ltd; 2019. p. 230–46.
48. Cash A, Theus MH. Mechanisms of Blood-Brain Barrier Dysfunction in Traumatic Brain Injury. IntJMolSci [Internet]. 2020;21(9):3344. Available from: www.mdpi.com/journal/ijms
49. Padilla-Zambrano HS, García-Ballestas E. “Broken Heart Syndrome” Cardiovascular Manifestations of Traumatic Brain Injury. Heart Mind [Internet]. 2018;2(1):12–5. Available from: http://www.heartmindjournal.org
50. Esterov D, Greenwald BD. Autonomic dysfunction after mild traumatic brain injury. Brain Sciences. 2017 Apr;7(8).
51. Chaikittisilpa N, Krishnamoorthy V, Lele A v, Qiu Q, Vavilala MS. Characterizing the Relationship between Systemic Inflammatory Response Syndrome and Early Cardiac Dysfunction in Traumatic Brain Injury HHS Public Access. J Neurosci Res. 2018;96(4):661–70.
52. Prathep S, Sharma D, Hallman M, Joffe A, Krishnamoorthy V, MacKensen GB, et al. Preliminary Report on Cardiac Dysfunction after Isolated Traumatic Brain Injury. Crit Care Med [Internet]. 2014 Jan [cited 2022 May 21];42(1):142–7. Available from: /pmc/articles/PMC3841242/
53. Krishnamoorthy V, Prathep S, Sharma D, Gibbons E, Vavilala MS. Association between electrocardiographic findings and cardiac dysfunction in adult isolated traumatic brain injury. Indian jpurnal of Critical Care Medicine [Internet]. 2014;18(9):570–4. Available from: www.ijccm.org
54. Andersson EE, Bedics BK, Falkmer T. Mild Traumatic Brain Injuries: A 10-Year Follow-Up. J Rehabil Med. 2011;43:323–9.
55. Gutierrez-Orozco F, Chitchumroonchokchai C, Lesinski GB, Suksamrarn S, Failla ML. α-Mangostin: Anti-Inflammatory Activity and Metabolism by Human Cells. J Agric Food Chem [Internet]. 2013 Apr 24 [cited 2022 May 9];61(16):3891. Available from: /pmc/articles/PMC3793015/
56. Krishnamoorthy V, Rowhani-Rahbar A, Chaikittisilpa N, Gibbons • Edward F, Frederick •, Rivara P, et al. Association of Early Hemodynamic Profile and the Development of Systolic Dysfunction Following Traumatic Brain Injury. Neurocrit Care. 2017;26:379–87.

57. Wang F, Kodali M, Upadhya D, Zhang GM, Zheng RZ, Lei ZQ, et al. Identification and Management of Paroxysmal Sympathetic Hyperactivity After Traumatic Brain Injury. Frontiers in Neurology | www.frontiersin.org [Internet]. 2020;11:81. Available from: www.frontiersin.org
58. Nguembu S, Meloni M, Eve Endalle G, Dokponou H, Dada OE, Senyuy WP, et al. Paroxysmal Sympathetic Hyperactivity in Moderate-to-Severe Traumatic Brain Injury and the Role of Beta-Blockers: A Scoping Review. Emergency Medicine International [Internet]. 2021;2021. Available from: https://doi.org/10.1155/2021/5589239
59. Stecker M, Meyer KS. Understanding paroxysmal sympathetic hyperactivity after traumatic brain injury. Surg Neurol Int [Internet]. 2014;5:S490–2. Available from: http://www.surgicalneurologyint.com
60. Lenstra JJ, Kuznecova-Keppel Hesselink L, la Bastide-van Gemert S, Jacobs B, Nijsten MWN, van der Horst ICC, et al. The Association of Early Electrocardiographic Abnormalities With Brain Injury Severity and Outcome in Severe Traumatic Brain Injury. Frontiers in Neurology [Internet]. 2021 Jan 8 [cited 2022 May 21];11:597737. Available from: /pmc/articles/PMC7819976/
61. Masoud Hashemian A, Ahmadi K, Taherinia A, Davood Sharifi M, Ramezani J, Behzad Jazayeri S, et al. ECG changes of cardiac origin in elderly patients with traumatic brain injury. Med J Islam Repub Iran [Internet]. 2015;29:306. Available from: http://mjiri.iums.ac.ir
62. Gregory T, Smith M. Cardiovascular complications of brain injury. Continuing Education in Anaesthesia, Critical Care and Pain. 2012;12(2):67–71.
63. Davanzo JR, Sieg EP, Timmons SD. Management of Traumatic Brain Injury. Vol. 97, Surgical Clinics of North America. W.B. Saunders; 2017. p. 1237–53.
64. Babuin L, Jaffe AS. Troponin: the biomarker of choice for the detection of cardiac injury. CMAJ [Internet]. 2005 Nov 8 [cited 2022 May 21];173(10):1191–202. Available from: https://pubmed.ncbi.nlm.nih.gov/16275971/
65. El-Menyar A, Sathian B, Wahlen BM, Al-Thani H. Serum cardiac troponins as prognostic markers in patients with traumatic and non-traumatic brain injuries: A meta-analysis. Am J Emerg Med [Internet]. 2019 Jan 1 [cited 2022 May 21];37(1):133–42. Available from: https://pubmed.ncbi.nlm.nih.gov/30318278/
66. El-Menyar A, Goyal A, Latifi R, Al-Thani H, Frishman W. Brain-Heart Interactions in Traumatic Brain Injury. Cardiology in Review. 2017;25(6):279–88.