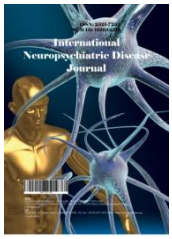

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Cerebral Autoregulation and Cardiovascular Physiology Dysfunction in Traumatic Brain Injury Cases: A Brief Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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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 dysfunction 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 79 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

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neurological, cognitive, and behavioral issues. Stress-induced catecholamine surges and inflammatory mediator production in response to trauma may also endanger cardiac disturbances. ECG changes in patients with severe traumatic brain injury are associated with cardiac dysfunction. Cardiac enzymes can be used as a diagnostic tool and indicate the patient's prognosis.

Conclusion: Cerebral autoregulation and cardiac physiological responses have a synergistic relationship in maintaining tissue homeostasis in patients with traumatic brain injury. Patients with TBI may experience cardiac dysfunction as a result of the body's exaggerated systemic response to brain injury.

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. Primary brain injury occurs as a result of energy being transmitted to brain tissue during impact [4]. Secondary brain injury is caused by a variety of factors, including edema, ischemia, excitotoxicity, and inflammation. In response to tissue injury, a disturbance of cerebral metabolism occurs, leading to the accumulation of lactic acid due to anaerobic glycolysis, increased membrane permeability and edema formation. Excitotoxicity occurs when neurons are overstimulated with excessive amounts of neurotransmitters, especially glutamate [5,6]. Contact-type injury and intracranial haemorrhage induced by acceleration/deceleration type injury can cause localized brain damage which manifest an edema of the brain. Following the first hit, a molecular, chemical, and inflammatory cascade causes further cerebral damage [7]. There are differences between adults and children in the severity physiological alterations of many organs caused by TBI.

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 [8]. TBI also causes a systemic inflammatory response syndrome, which leads to organ system dysfunction and failure [9]. 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.

GFAP, UCH-L1, S100B, and NSE are molecular biomarkers of TBI, which released by changes in physiological function of Blood-Brain Barrier (BBB). Despite several experimental research, to improve prediction power and lessen the bad outcome of TBI, clinical support of these biomarkers are still required. Interestingly, a few of these TBI biomarkers have been oxidatively changed to carbonyl groups, implying that oxidative stress markers may have predictive relevance for therapeutic strategy selection. Some medicines, such as corticosteroids and progesterone, have already been studied for TBI neuroprotection, although clinical usefulness has yet to be demonstrated in the advanced stages of the trials. In preclinical investigations, dietary antioxidants like curcumin, resveratrol, and sulforaphane have been demonstrated to reduce TBI-induced damage. As neuroprotection strategies, NRF2 are activated as antioxidant defenses caused by dietary of antioxidants which also known as carbonyl scavangers [10]

Despite the fact that the autonomic nervous system (ANS) is a part of the central nervous system (CNS), its function after a TBI has been largely disregarded. The sympathetic and parasympathetic nerve systems make up the autonomic nervous system, and the balance between their activities determines the autonomic nervous system's impact on various organs, particularly the heart. The influence of both systems has an effect on heart rate, which is one of the end results. The time domain and frequency domain are the two basic methods for determining heart rate variability (HRV) [11].

PSH (paroxysmal sympathetic hyperactivity) can occur in TBI patients. PSH, is marked by paroxysmal tachycardia and decerebrate body posture which are stiff limbs, straight legs, and head and neck tilted back. The syndrome is linked to a worse prognosis and more extended hospital stays [12–14]. 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 [14].

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. [9,15] 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. [16].

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 [17]. 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 79 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 [6,18]. In the United States, In 2019, 60,611 people died from traumatic brain injury, compared to 60,565 in 2018 [19]. Dewan et al. estimated that 69 million TBIs occur annually worldwide, most of which are mild [20]. 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 [21].

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 [22,23]. 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) [17,24].

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 [17,25].

Volumetric (compression/tension) and shear-type mechanical damage to brain tissue are the two types of damage. Tissue damage is predicted in

terms of its location, extent, intensity, and reversibility/irreversibility. Future directions of this research are considered, including the relationship between mechanical injury and physiological brain dysfunction, as well as applicability to important medical and engineering challenges [26]. 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 [27].

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 [28,29]. Unusual neuroimaging findings can be seen in individuals and athletes with repetitive head injuries from sport-related injuries as well as adults with a history of recurrent head trauma. A retired athlete, particularly with a history of sports-related head trauma and a history of repeated concussions, reported suffering from memory, psychomotor, and cognitive problems [30–32].

It's critical to study how physical pressures are transferred and transduced across all spatial scales of the brain in order to understand damage causes. Although the mechanical response of the brain is mostly determined by its material properties and biological structure, there are additional cellular mechanotransduction pathways. Exogenous mechanical stresses transmitted through sub-cellular components, such as extracellular matrix and cell adhesion molecules, to mechanosensitive intracellular structures that modulate mechanochemical signaling pathways can alter physiological processes [33].

3.2 Pathophysiology and Cerebral Autoregulation of TBI

TBI causes primary and secondary brain damage [34]. 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 [35,36]. The purpose of therapy and management is to prevent subsequent brain injury. TBI alters cerebral blood flow and impairs cerebral autoregulation [6,17,37–39]. Most severe TBI patients have brain autoregulation issues [40,41]. With 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 p CO_2 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 [42,43].

Normal cerebral blood flow is between 50 and 150 mmHg Cardiac perfusion pressure (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 [43–47]. Cerebral perfusion pressure is a stimulus that triggers an autoregulation response of the cerebrovascular system [39].

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 [7,37]. CO_2-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 [23,35,37,48]. The goal of continued care is to provide the brain with the best chance of recovery possible. It's critical to keep oxygenation, normocapnia, and haemodynamic balance. Adequate sedation and analgesia alleviate pain, anxiety, and agitation while also allowing mechanical ventilation to take place. The use of multimodality brain monitoring to adapt individual patient care is beneficial. Cerebral oxygenation, CBF measurement, microdialysis, and electrophysiological monitoring are all possible options for advanced monitoring. Early nutritional supplementation is linked to improved outcomes, and enteral feeding is preferred. Hyperglycemia has been linked to subsequent ischemic damage; hence proper metabolic monitoring is critical. Continued care aims to provide the brain the best chance of recovery possible. It is critical to keep oxygenation, normocapnia, and haemodynamic balance. Adequate sedation and analgesia help minimize pain, anxiety, and agitation while also allowing mechanical ventilation to occur [49].

Although there are changes in systemic blood pressure under normal condition, the cerebrovascular autoregulation mechanisms will maintain a steady cerebral blood flow (CBF). In the first phase, the reduced of systemic blood pressure and autoregulatory vasodilation, the CPP are initially decreased, which aims to keep CBF constant, leading to increase ICP. In the later phase, as ICP continues to rise, CPP falls below the ischemic threshold, and to reach a 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 systemic blood pressure of an injured brain, these autoregulatory mechanisms are significantly increased and often corrupted which are referred directly to the cerebral capillaries, resulting in a breakdown of the BBB, worsening cerebral edema, and increased ICP [50]. Hypocapnia and hyperventilation have been demonstrated to lower ICP and prevent hypotension in TBI patients [41,51–53].

TBI causes massive excitatory neurotransmitter release, especially glutamate. Glutamate release in combination with a loss of ionic equilibrium can cause mitochondrial malfunction as well as other cellular problems. An acute phase of neuroexcitation, for example, has been observed in the brain shortly after impact. This occurrence has been connected to the indiscriminate release of excitatory neurotransmitters such as glutamate. Furthermore, the loss of synaptic terminals may occur as a result of the gradual degeneration connected to the energy shortage, impairing the regulation of neuronal activity patterns that are critical to brain function. As evaluated by magnetoencephalography, patients with TBI were shown to have impaired connections between brain regions, interpreting that extensive injury may play an important role in the morbidity associated with TBI [33].

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. [7,42,54,55]. Furthermore, extracellular K+ increases with Na+/K+-ATPase pump failure, adding to cerebral edema [55]. 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 [55,56].

Accidents like a brain stroke or traumatic brain injury interrupted the Ca^{2+} homeostasis and rapidly caused neuronal death. This causes significant disturbance of Ca+ homeostasis in neurons, which leads to cell damage and death. It was shown that traumatic axonal deformation causes aberrant sodium inflow via mechanically sensitive Na channels, which leads to an increase in intra-axonal Ca^{2+} via the opening of VOCCs and reversal of the Na^{1+}/Ca^{2+} exchange. Ca^{2+} enters the cell primarily through the plasma membrane through two types of Ca^{2+} channels: ionotropic receptor-operated (ligand-gated) channels (ROCs) and voltage-operated Ca^{2+} channels (VOCCs). Direct binding of particular agonists activates Ca^{2+} influx through the ionotropic ROCs. N-methyl-D-aspartate receptors (NMDARs) and some a-amino-3-hydroxy-5-methylisoxazole-4-propionate acid receptors are Ca^{2+} permeable ROCs (AMPARs). The physiological agonist glutamate, the central nervous system's major excitatory neurotransmitter, activates these (CNS).

NMDARs provide effective Ca^{2+} entrance into neurons, so that in the CNS, NMDARs are particularly important [57]. Astrocytes are the most common cells in the brain, and they serve as a vital link between the circulatory system and neuronal upkeep. Although astrocytes are less sensitive to injury than neurons, they can both transmit and receive mechanical stresses from neurons during TBI. Astrocytes can provide damage signals to neurons via Ca^{2+} waves, send neurotransmitter signals, and change ion concentrations in the extracellular environment. The outcome of a microfluidic chamber that used a fast pressure serve to examine intracellular Ca2+ levels in cultured adult astrocytes show that the mechanically induced Ca2+ influx seen in neuron models for TBI is also present in astrocytes, and there is a viscoelastic/ plastic coupling of shear stress to the Ca2+ influx. The Ca2+ influx's source is yet unclear [58].

Because of their links to epilepsy and the role they potentially play in the construction of an integrated computational model of ion function for future research, high voltage-gated calcium ion channels are briefly reviewed here. CaV1 is the L-type calcium channel, CaV2 is the P/Q-type [CaV2.1], CaV2.2 is the R-type [CaV2.2], and CaV2.3 is the N-type [CaV2.3], and CaV3 is the T-type calcium channel. The genomic structure, mutation, pathophysiology, and pharmacology of these types have all been investigated. So far, the findings have been positive. The CaV2.1 P/Q type, along with the CaV3.2 T-type, has the highest association with epilepsy among the five types. They are both connected to IGE. In comparison to LVA channels, the HVA channel requires more depolarization. Despite this, both are connected to IGE, are pharmacologically sensitive, and have been shown to enhance epilepsy outcomes in patients when inhibited. The first sight of the possibility of hyperpolarized channels are provided by T-type channels and other low voltage-gated channels and negative charge transporters being connected to IGE. Congenital mutations associated to IGE have been linked to structural alterations and disease of these channels, indicating the prospect of sensitivity to more epigenetic, neuroinflammatory changes linked to more focal epilepsy such as TLE, post-traumatic epilepsy (PTE), and post-stroke epilepsy (PSE). Many polymorphisms in voltage-gated channels contribute to mutations that lead to structural and functional changes, but they do not resolve all of the issues about electrophysiologic dysfunction [59].

Protein Kinase C (PKC) activity has been associated with neuronal death in the aftermath of TBI, and it is intimately linked to glutamate receptor signaling. PKCα, PKCδ, and PKCε, three essential PKC isozymes, were found largely in endothelial cells but not in astrocytes. PKCα and PKCδ activity can trigger NMDA receptor uncoupling from spectrin via sigma-1 receptor activation, resulting in calcium oscillations. Calcium oscillations play a role in cell death and mitochondrial malfunction. Following damage, PKCα and PKCδ can hyperphosphorylate structural proteins like tau and TBI61 in the hippocampus. PKC activity, interestingly, reduces cerebral edema after a TBI [60].

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 [61,62]. 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 [62].

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 [14,50,62–64]. Hypothalamic and insular cortex injuries increase the risk of cardiac issues such as blood pressure changes, arrhythmias, and myocyte death [61,62].

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. (9,61) Following a TBI, neurogenic variables such as increased catecholamine release and inflammation may cause systemic issues [65]. As a whole, brain damage can cause systemic abnormalities such as increased sympathetic activity and immune system depression causing hypertension, tachycardia, arrhythmia, 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 [61,66]. Patient with TBI with previous systolic dysfunction is problematic because it may lead to secondary brain injuries, as adequate cardiac output is critical in maintaining CBF after injury. Poor outcomes are also seen in patient with early hypotension and hypertension after TBI. A research by Krishnamoorthy et al. find that in 7 people (22%) of 32 patients developed systolic dysfunction after TBI. Compared to patients who did not develop systolic dysfunction ($P<0.01$ for all comparison) that 7 patient who developed systolic dysfunction experienced early elevation of mean arterial pressure (MAP), systolic blood pressure (SBP), and heart rate [67].

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 15 – 33 % percent of moderate to severe TBI patients [68]. After TBI, PSH has been described as being associated with hyperthermia, tachycardia, hypertension, diaphoresis, tachypnea, dystonia (hypertonia or spasticity), and even motor features such as extensor/flexion posturing [69]. The dominant theory suggests that the damage of central autonomic network such as insular cortex, amygdala, hypothalamus, medulla, periaqueductal gray matter, parabrachial complex, and nucleus of the hypothalamus can lead to PSH. In fact, the pathophysiology of PSH is still unknown [68].

There is no widely effective treatment algorithm for PSH. Treatment aims to reduce associated adverse effect such as cardiac hypertrophy, muscle wasting, dehydration, 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 [70]. 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 CBF, lowering cerebral consumption of oxygen and glucose as metabolism slows [69].

3.5 Electrocardiographic (ECG) Abnormalities

Electrocardiographic (ECG) changes, including morphological changes and rhythm disturbances, are common in TBI. Several studies have shown that ECG changes in patients with severe traumatic brain injury are associated with cardiac dysfunction and increased hospital mortality [50,64,71]. The most common ECG changes in patients with SAH and intracerebral hemorrhage (ICH) are repolarization abnormalities such as QT interval prolongation and morphology changes in ST-segment and T wave. 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 [9,72]. Prolonged QT repolarization abnormalities and morphological late repolarization abnormalities (MERA), but not ischemic-like ECG changes, are associated with cardiac dysfunction after isolated TBI [50]. 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 [71]. A 12-lead ECG may be a helpful screening tool for isolated TBI patients with heart abnormalities prior to additional diagnostic investigations or therapies. The severity of brain injury, malignant cerebral edema, and extracranial disease, especially cardiac electrical dysfunction, are all associated with TBI-related mortality. Through central autonomic dysfunction with higher catecholamine levels, shifts in the potassium to sodium ion ratio, and the

inflammatory response associated with brain injury, cardiovascular damage resulting from a brain injury can lead to sudden cardiac death. Consequently, cardiovascular injury associated with brain injury, manifesting as aberrant electrocardiogram (ECG) readings, can have a significant impact on the outcome of TBI patients [73].

3.6 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 [74]. 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 [75]. A study exploring changes in CSF CK and CK-MB levels in TBI mortality revealed an increase in CSF CK and CK-MB after TBI. CSF CK-BB is also useful for clinically estimating the degree of brain damage and can be used to assess neurologic prognosis [76]. 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 to a high death rate in patients with TBI [77]. 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 is associated with LV dysfunction [9,78].

According to another study by Turner et al. (2013), biomarkers could one day be used to identify chronic traumatic encephalopathy (CTE). Additionally, using a biomarker, it may be feasible to follow illness severity and progression (s). A prospective CTE biomarker should be non-invasive, diagnostic, and linked to disease severity, allowing healthcare practitioners to follow the illness's progression. It should be sensitive enough to identify the condition and allow for a diagnosis when used in conjunction with clinical evidence of CTE symptoms and a history of recurrent head trauma. As previously stated, there is currently no approved way of detecting CTE prior to post-mortem pathological investigation. An easily available biomarker with the aforementioned qualities would provide clinicians with a valuable tool for diagnosing and tracking CTE patients. There is currently little research targeted at identifying a biomarker(s) specific for CTE. Numerous study have been conducted in order to determine biomarkers for TBI and other varieties of neurotrauma. One of the most challenging aspects of looking for a CTE biomarker is that the symptoms of CTE might be confused with those of a range of other neurologic illnesses. Conducting human clinical investigations in the search for acceptable biomarkers may become more complicated as a result of this. On the other hand, the neuropathology of CTE is not dissimilar to that of other neurodegenerative illnesses, as hyperphosphorylated tau and TDP-43 deposition are detected in a range of neurodegenerative diseases [79].

4. CONCLUSION

Cerebral autoregulation and cardiac physiological responses have a synergistic relationship in maintaining tissue homeostasis in patients with traumatic brain injury. Patients with TBI may experience cardiac dysfunction as a result of the body's exaggerated systemic response to brain injury. The use of ECG and cardiac biomarkers can help establish the diagnosis and indicate the prognosis of patients with suspected cardiac dysfunction. However, more research is needed to look at changes in cardiac enzyme levels and their correlation with the overall outcome of TBI.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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