INTRODUCTION

Cardiac arrest in individuals with traumatic brain injury (TBI) presents a multidimensional and potentially fatal medical emergency, posing a unique challenge for healthcare personnel and physicians\(^1\). TBI is characterized by abrupt and substantial brain damage resulting from external forces, triggering a cascade of physiological events, including disturbances in cardiovascular function that can culminate in cardiac arrest\(^1\). The intricate interplay between neurological and cardiovascular pathologies identified in these cases underscores the necessity for a multidisciplinary approach to accurately diagnose, manage, and treat these conditions\(^1\). The occurrence of cardiac arrest in TBI patients significantly impacts both survival rates and neurological outcomes, creating a considerable obstacle to effective resuscitation and rehabilitation\(^1\). The presence of concurrent injuries or complications fur-
ther complicates this critical condition, making prompt recognition and treatment of cardiac arrest more challenging\(^2\). The pathophysiology of cardiac arrest in TBI involves a myriad of interacting factors. Elevated intracranial pressure, alterations in cerebral autoregulation, heightened sympathetic activity, and the incidence of secondary brain injuries are among the identified risk factors\(^2\)\(^-\)\(^5\). The objective of this study was to explore the intricate relationship between cardiac arrest and TBI, elucidating the underlying mechanisms, risk factors, and potential therapeutic options that may contribute to overall outcomes (Fig. 1)\(^2\)\(^-\)\(^5\).

**METHODS**

Cardiac arrest in TBI patients was the focus of this literature review, which aimed to synthesize and evaluate previous research on the subject. To gather up-to-date literature on this subject, electronic databases such as PubMed, Science Direct, and Web of Science were meticulously examined. Cardiopulmonary arrest, severe

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**Fig. 1.** This figure delineates the pathophysiological and cellulo-molecular alterations occurring during cardiac arrest in traumatic brain injury. PARP: Poly-ADP ribose polymerase; NK-kb: Nuclear factor kappa B; DAMP: Danger-associated molecular patterns.
brain damage, and neurological-circulatory abnormalities were some of the MeSH keywords utilized. To expand the data set, we also looked through the reference lists of selected papers. Because it did not include any direct human participants, this study did not need permission from the institutional board’s review for human research ethics.

Research with patients participating in either qualitative or quantitative investigations met the inclusion criteria. We only looked at items that were published in English. To guarantee a thorough examination of the results, only publications from peer-reviewed journals were considered. The abstracts and complete texts were evaluated by two authors who complied with the criteria for exclusion and inclusion, and a third author resolved any disagreements that arose to reduce the possibility of bias.

OVERVIEW

Yang et al. conducted a systematic review and meta-analysis comparing target temperature management (TTM) against normal temperature management (NTM) for cardiac arrest following TBI. In contrast to neurotherapeutic medicine, their meta-analysis revealed that TTM did not reduce mortality rates. However, it is noteworthy that for individuals with moderate or severe symptoms in the early stages, TTM might still hold potential in reducing death rates and improving prognosis. Specifically, TTM has demonstrated greater effectiveness in the early phases of moderate and severe conditions compared to NTM, leading to enhanced prognostic outcomes. Kochanek et al. emphasized in their review that managing clinical outcomes for infants and children who have experienced severe TBI or asphyxia-induced cardiac arrest involves a series of therapies spanning various medical settings from the field to emergency rooms, intensive care units, rehabilitation centers, and potentially beyond. Despite the distinctions between these widely recognized pediatric traumas, prompt implementation of interventions aimed at preventing neuronal death in either scenario is likely crucial, possibly beginning at the injury site. According to Kochanek et al., managing cerebral edema, a pathophysiological condition often treated in pediatric intensive care units (PICUs), is more favorable as prevention rather than cure. Finally, this research delves into alternative therapies for individuals with severe brain injuries, exploring the potential for altering damaged neural networks and enhancing regenerative processes.

PATHOPHYSIOLOGY

Individuals who have suffered TBI face an increased risk of cardiac arrest due to a complex interplay of factors stemming from direct damage to the brain and the body’s physiological responses to trauma. One primary etiology is the rise in intracranial pressure (ICP) resulting from a traumatic event. Elevated ICP can impact cerebral blood flow, escalating the risk of cardiovascular complications. TBI is associated with abnormalities in autoregulation that impair the brain’s ability to adequately control blood flow and perfusion, heightening the risk of cardiac arrest. The body’s physiological response to trauma includes increased sympathetic activity, potentially leading to substantial increases in heart rate and blood pressure, thereby elevating the risk of cardiac arrest. Furthermore, the development of anoxia and reperfusion injury following trauma, signifying damage due to the restoration of blood flow, can adversely affect vital organs such as the heart. Additionally, the systemic inflammatory response commonly observed after TBI can trigger a chain of physiological events significantly impacting cardiovascular function and increasing the risk of cardiac arrest. Individuals with TBI may experience issues with hypoxia and hypotension, further heightening the likelihood of cardiac arrest. TBIs can induce electrolyte imbalances, disrupting the heart’s normal electrical activity, potentially resulting in arrhythmias and cardiac arrest. Brainstem involvement, brain herniation, contusions, or hemorrhages within the brainstem can profoundly affect the body’s regulation of critical physiological functions, including heart activity.

EXPLORING THE ROLE OF BIOMARKERS

Biomarkers have emerged as critical diagnostic, prognostic, and therapeutic tools in the complex domains of TBI and cardiac arrest. Various biomarkers, extensively researched in the context of brain injuries, provide insights into severity and prognosis (Table 1). Proteins such as S100B, neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP) are among these indicators. Inflammatory biomarkers like interleukin-8 (IL-8) and molecular elements such as microRNAs have shown promise in diagnosis and prognosis. Jarvis and Fink note that these biomarkers can be detected in blood samples, cerebrospinal fluid, and through modern neuroimaging techniques, rendering them useful in clinical assessments. Identified biomarkers hold potential in tailoring treatment regimens for both TBI and cardiac arrest situations. However, to enhance diagnostic precision, discovering composite panels, developing consistent testing methodologies, and comprehensive evaluation of these biomarkers prior to clinical use are crucial. Nonetheless, transitioning biomarkers from research investigations to clinical practice necessitates a rigorous validation...
The utilization of biomarkers has the potential to improve the processes of diagnosis, treatment, and prognosis. Their work underscores the importance of supplementary prognostication, treatment, and prognosis. The compound NSC74429 has demonstrated neuroprotective effects against several modes of injury. There is a positive correlation between elevated levels of S-100B and IL-8 and unfavorable outcomes. TTM has the ability to enhance the prognosis of individuals with moderate and severe conditions. The importance of individualized treatments based on biomarkers is emphasized. The survival rate is associated with the GCS score and pupil reactivity.

Table 1. Synopsis of studies on cardiac arrest and traumatic brain injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors/year</th>
<th>Study Type</th>
<th>Population</th>
<th>Outcome Measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kochanek et al. 2001(^\text{10})</td>
<td>Review</td>
<td>Pediatric TBI and Cardiac Arrest</td>
<td>Diagnosis, Prognostication</td>
<td>The importance of individualized treatments based on biomarkers is emphasized.</td>
</tr>
<tr>
<td>2</td>
<td>Jackson et al. 2022(^\text{11})</td>
<td>Experimental</td>
<td>Neuroprotection</td>
<td>Experimental PHLPP inhibitors</td>
<td>The compound NSC74429 has demonstrated neuroprotective effects against several modes of injury.</td>
</tr>
<tr>
<td>3</td>
<td>Mussack et al. 2002(^\text{12})</td>
<td>Prospective Cohort</td>
<td>Cardiac Arrest and TBI</td>
<td>S-100B and IL-8 serum levels</td>
<td>There is a positive correlation between elevated levels of S-100B and IL-8 and unfavorable outcomes.</td>
</tr>
<tr>
<td>4</td>
<td>Yang et al. 2022(^\text{13})</td>
<td>Meta-Analysis</td>
<td>Cardiac Arrest and TBI</td>
<td>Mortality, Prognosis</td>
<td>TTM has the ability to enhance the prognosis of individuals with moderate and severe conditions.</td>
</tr>
<tr>
<td>5</td>
<td>Prout et al. 2017(^\text{14})</td>
<td>Review</td>
<td>Pediatric TBI and Cardiac Arrest</td>
<td>Biomarker Investigation</td>
<td>The utilization of biomarkers has the potential to improve the processes of diagnosis, treatment, and prognosis.</td>
</tr>
<tr>
<td>6</td>
<td>Zhao et al. 2021(^\text{15})</td>
<td>Retrospective Review</td>
<td>Cardiac Arrest and TBI</td>
<td>Survival, Neurological Function</td>
<td>The survival rate is associated with the GCS score and pupil reactivity.</td>
</tr>
</tbody>
</table>

TBI: Traumatic brain injury; GCS: Glasgow Coma Scale; TTM: Target temperature management.

**DIAGNOSTIC APPROACHES**

Diagnostic approaches for identifying cardiac arrest episodes in individuals with TBI encompass various clinical tests and monitoring techniques. The clinical assessment, encompassing vital signs, neurological function, and overall clinical well-being, remains crucial. Electrocardiogram (ECG) monitoring is vital to detect arrhythmias and irregularities signaling cardiac arrest\(^\text{17}\). Testing cardiac enzymes and troponin can also confirm heart involvement. Continuous electroencephalogram (EEG) monitoring aids in seizure detection and identifying changes in brain electrical activity suggesting cardiac issues. Sandroni et al. recognized somatosensory evoked potentials (SSEPs) and auditory evoked potentials (AEPs) as valuable in assessing sensory pathway integrity. These potentials can be used to evaluate the potential role of the brainstem in cardiac arrest occurrences. Monitoring ICP is crucial in managing TBI patients experiencing cardiac arrest as elevated ICP can restrict cerebral blood flow and worsen cardiac complications. Assessing brain structural integrity is pivotal to evaluating potential brainstem involvement and its impact on cardiac function. Reis et al.\(^\text{18}\) note that brain imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) provide valuable information. Laboratory tests, including blood analysis, can determine the body’s physiological response to TBI and unveil metabolic anomalies affecting cardiovascular health. Echocardiography enables real-time monitoring of cardiac dynamics and identification of anomalies in heart anatomy and function. Combining these diagnostic techniques establishes a comprehensive framework for detecting cardiac arrest in TBI patients, facilitating prompt interventions and tailored treatment strategies based on individual patient conditions\(^\text{17-20}\).
THERAPEUTIC INTERVENTIONS

Given the intricate interplay between neurological and circulatory factors, an integrated therapeutic approach is essential in managing cardiac arrest in individuals with TBI. Therapeutic options encompass a spectrum of interventions targeting resuscitation, hemodynamic stabilization, intracranial pressure control, and neurological outcomes improvement\(^{16-23}\). Restoring circulation relies on the prompt initiation of cardiopulmonary resuscitation (CPR) and adherence to advanced cardiac life support (ACLS) guidelines. Ensuring proper airway management to guarantee adequate oxygenation and breathing is crucial to reduce the risk of further neurological damage in TBI patients experiencing cardiac arrest. Maintaining hemodynamic stability is essential to supply adequate blood flow to the brain. Cronberg et al.\(^{1}\) highlight achieving optimal blood flow in the injured brain via techniques like fluid resuscitation and judicious use of vasoactive drugs. Therapeutic hypothermia emerges as a treatment option aimed at reducing secondary brain injury and improving neurological outcomes post-cardiac arrest. Precisely regulating body temperature is pivotal in this approach. Yang et al.\(^{9}\) suggest that customized temperature management plays a significant role in neuroprotection by reducing oxidative stress and inflammation through precise temperature regulation. Additionally, interventions aimed at enhancing oxygen delivery and maintaining cerebral perfusion pressure should be considered to foster tissue recovery and maintain metabolic equilibrium within circulatory and cerebral systems. Managing ICP assumes importance in TBI patients experiencing cardiac arrest. Strategies like head-of-bed elevation, osmotic agent administration, and adjustments to respiratory parameters aim to prevent ICP elevation. Neuroprotective strategies, such as vigilant avoidance of hypotension and hyperthermia, safeguard the vulnerable brain from further injury. Continuous monitoring is indispensable in treating cardiac arrest in TBI patients. Continuous monitoring of neurological status, hemodynamic parameters, and vital signs informs treatment decisions and evaluates intervention efficacy. Leveraging modern monitoring technologies, including cerebral oxygenation measures and intracranial pressure monitoring, has the potential to significantly enhance therapeutic precision and efficacy for patients.

ANIMAL MODEL EVIDENCE

Jackson et al.\(^{5}\) evaluated compounds NSC13378, NSC25247, and NSC74429 in animal models, highlighting promising chemical characteristics for potential CNS targeting. Before this study, no research on neuroprotection using PHLPP inhibitors had been conducted. Neuronal culture tests indicated that NSC74429 displayed the highest level of neuroprotection at micromolar concentrations. NSC74429 demonstrated neuroprotective effects against staurosporine-induced apoptosis, glutamate-induced excitotoxicity, and hydrogen peroxide-induced necrosis/oxidative stress. Subsequent testing revealed that administering NSC74429 at a dose of 1 mg/kg for three days enhanced hippocampal survival in both rat models of suffocating cardiac arrest and mouse models of severe traumatic brain injury.

CONCLUSION

Understanding the pathophysiological intricacies and reasons behind cardiac arrest in individuals with TBI holds paramount importance for medical practitioners. This comprehension is pivotal in enhancing the standard of patient care, elevating survival rates, and ultimately improving long-term neurological outcomes. The pursuit of novel therapies and advancements in multidisciplinary healthcare represents an ongoing endeavor aimed at mitigating the severe implications of cardiac arrest in TBI patients. Through this analysis of the intricate clinical scenario under consideration, our aim is to provide a comprehensive examination of current knowledge, underscore key areas necessitating further investigation, and foster continuous efforts to refine the treatment and enhance outcomes for individuals experiencing cardiac arrest in the context of TBI.

NOTES

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Ethics statement

This study was a literature review of previously published studies and was therefore exempt from institutional review board approval.

Author contributions

Conceptualization: OA, BC. Data curation: OA, VC. Formal analysis: OA, MMR, VC, AA. Methodology: OA, MMR, BC. Visualization: MMR, BC, VC. Project administration: OA. Writing - original draft: OA, Writing - review & editing: MMR, BC, AA.

Conflict of interest

There is no conflict of interest to disclose.
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