REVIEW

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2025.2024-82
Cyprus J Med Sci 2025;10(2):87-93

Challenges of Cerebral Hemodynamic Disorders and Hypoxic-Ischemic Encephalopathy: Evaluating Current and Emerging Approaches from Neurological Emergencies to Intensive Care

Özlem Önder

Department of Neurology, Near East University Faculty of Medicine, Nicosia, North Cyprus

Abstract

Cerebral hemodynamic disorders and hypoxic-ischemic encephalopathy (HIE) pose significant challenges across various stages of medical care, from neurological emergencies to intensive care. These conditions, marked by impaired cerebral perfusion and oxygenation, lead to severe neurological deficits and present a complex interplay of pathophysiological mechanisms. This review provides a comprehensive evaluation of both current and emerging approaches to managing these disorders. It examines the pathophysiology of cerebral hemodynamic disturbances and HIE, focusing on the critical role of cerebral blood flow and oxygen delivery in brain function. The paper reviews existing diagnostic tools, including neuroimaging and biomarkers, and their limitations in detecting and assessing the severity of these conditions. It also highlights advances in therapeutic strategies, such as neuroprotective agents, advanced monitoring techniques, and novel interventions, aimed at improving patient outcomes. Special emphasis is placed on the transition from acute management in neurological emergencies to ongoing care in intensive settings, addressing the need for a multidisciplinary approach and continuous innovation. By integrating recent research findings and clinical experiences, this review underscores the importance of addressing these challenges to enhance patient care and optimize treatment outcomes for cerebral hemodynamic disorders and HIE.

Keywords: Cerebral blood flow, cerebral hemodynamics, hypoxic-ischemic encephalopathy, imaging methods, treatments

INTRODUCTION

Cerebral hypoperfusion is a critical condition characterized by inadequate blood flow to the brain, which can lead to significant neurological impairments and, if persistent, irreversible brain damage.[1] Due to the brain's high metabolic demands and limited energy reserves, it is especially vulnerable to reductions in blood supply.[2] Understanding the mechanisms, clinical implications, and management strategies of cerebral hypoperfusion is crucial for improving patient outcomes across various acute and chronic conditions.[3] Research and clinical practices are continually evolving to address these complexities and advance therapeutic approaches that mitigate neurovascular compromise and promote neurological recovery.

The recent review explores the multifaceted interplay between blood gas alterations and cerebral hypoperfusion, highlighting their profound impact on neurological function and clinical outcomes.

Mechanisms of Hypoxic-Ischemic Encephalopathy

Hypoxic-ischemic encephalopathy (HIE) is a severe brain injury resulting from a critical reduction in cerebral blood flow (CBF) and oxygen supply, leading to a cascade of pathological events that compromise

To cite this article: Önder Ö. Challenges of cerebral hemodynamic disorders and hypoxic-ischemic encephalopathy: evaluating current and emerging approaches from neurological emergencies to intensive care. Cyprus J Med Sci. 2025;10(2):87-93

ORCID ID of the author: Ö.Ö. 0000-0002-7133-9808.

Corresponding author: Özlem Önder
E-mail: ozlem.onder@neu.edu.tr
ORCID ID: orcid.org/0000-0002-7133-9808

Received: 30.08.2024
Accepted: 10.02.2025
Epub: 15.04.2025
Publication Date: 18.04.2025

neuronal function and viability.[4] The initial insult is characterized by hypoxia and ischemia, which disrupt cellular metabolism and deplete adenosine triphosphate (ATP) reserves, impairing the function of ATP-dependent ion pumps. This failure leads to neuronal depolarization and the accumulation of intracellular calcium and sodium, triggering excitotoxicity mediated by excessive glutamate release. Subsequently, the influx of calcium activates various enzymes, such as proteases, phospholipases, and endonucleases, which damage cellular structures, including membranes, cytoskeleton, and DNA.[5] Additionally, the overproduction of reactive oxygen species (ROS) and nitric oxide during the reoxygenation phase exacerbates oxidative stress, further harming neuronal and glial cells. The ensuing inflammatory response, characterized by the activation of microglia and the infiltration of leukocytes, releases cytokines and chemokines that perpetuate tissue damage.[6] The combination of excitotoxicity, oxidative stress, and inflammation ultimately leads to apoptosis and necrosis of neural cells, resulting in the characteristic neurological impairments associated with HIE.[7] Understanding these mechanisms is crucial for developing targeted therapeutic interventions aimed at mitigating neuronal damage and improving clinical outcomes in affected individuals.

Causes of Hypoxic-Ischemic Encephalopathy

Systemic causes of cerebral hypoperfusion: Cerebral hypoperfusion can arise from various systemic factors that compromise cerebral perfusion pressure (CPP).[8] One of the primary systemic causes is systemic hypotension, where a significant drop in mean arterial pressure results in reduced CPP, leading to decreased CBF.[9] Conditions such as shock, severe dehydration, or hemorrhage can precipitate systemic hypotension, further complicating cerebral perfusion. Impaired cardiac output, due to cardiac conditions like myocardial infarction, heart failure, or arrhythmias, also plays a critical role in cerebral hypoperfusion.[10] These conditions reduce the heart's ability to pump sufficient blood to the brain, thereby impairing oxygen and nutrient delivery to neural tissues. Cardiac arrest, in particular, causes an abrupt cessation of CBF, leading to global cerebral ischemia and potential neurological damage.[11] Additionally, the inappropriate use or overuse of antihypertensive medications, sedatives, and anesthetics can induce systemic hypotension, contributing to decreased cerebral perfusion.[12]

Local vascular causes of cerebral hypoperfusion: Local vascular factors are significant contributors to cerebral hypoperfusion, often leading to focal reductions in blood flow to specific brain regions. Obstruction of major cerebral arteries, commonly due to embolism or thrombosis, is a primary cause of localized cerebral hypoperfusion.[13] Conditions such as ischemic stroke and transient ischemic attacks result from these obstructions, which reduce blood supply to affected brain regions and cause neurological deficits. Severe atherosclerosis, characterized by the buildup of plaques within the arterial walls, can also lead to reduced CBF by narrowing the arteries and restricting blood passage.[14] Vasculitis, an inflammatory condition affecting blood vessels, can further contribute to vessel narrowing and occlusion, exacerbating the risk of cerebral hypoperfusion.[15] Furthermore, small vessel disease, particularly prevalent in individuals with diabetes, leads to endothelial dysfunction and damage to the microvasculature within the brain, significantly impacting cerebral perfusion. The compromised integrity of small blood vessels results in chronic cerebral hypoperfusion and poses a risk for cognitive decline and neurodegenerative conditions.[16]

Age-related and neurological factors in cerebral hypoperfusion: Age-related changes in the cardiovascular and neurological systems also play a critical role in the development of cerebral hypoperfusion. As individuals age, structural and functional changes in the cardiovascular system, such as increased arterial stiffness and reduced cardiac output, can diminish CBF.[17] These changes lead to a decrease in the brain's ability to maintain adequate perfusion, contributing to the risk of cerebral hypoperfusion in the elderly. Orthostatic hypotension, a condition more prevalent in older adults, causes transient reductions in CBF upon standing, increasing the risk of dizziness, falls, and syncope.[18] Additionally, neurological conditions can impair the brain's autoregulatory mechanisms, increasing intracranial pressure (ICP) and reducing CPP.[9] The inability of cerebral vessels to adequately regulate blood flow in response to changes in systemic blood pressure can exacerbate the risk of hypoperfusion, leading to potential neurological damage.[19] Understanding these age-related and neurological factors is essential for developing targeted interventions to mitigate cerebral hypoperfusion and its associated risks.

Clinical Manifestations

Cerebral hypoperfusion can lead to a range of clinical manifestations depending on the severity, duration, and areas of the brain affected. These manifestations can be acute or chronic and may vary from transient mild symptoms to severe and lasting neurological deficits.[20]

Acutely, one of the primary manifestations is syncope, characterized by a sudden and temporary loss of consciousness. This condition often results from a significant, albeit brief, reduction in CBF, which can occur in orthostatic hypotension or episodes of severe systemic hypotension.[21] Another acute manifestation is cognitive impairment, presenting as acute confusion or delirium. This condition is marked by disorientation, an inability to concentrate, and fluctuating levels of awareness, attributable to transient cerebral hypoperfusion. Short-term memory loss is also common in such scenarios where patients fail to recall recent events due to compromised blood flow in the vertebrobasilar artery system.[22]

Furthermore, focal neurological deficits, sensory changes, dizziness, and vertigo, visual or speech disturbance, closely mimicking stroke symptoms, are frequently observed in acute cases of inadequate cerebral perfusion.[23]

In contrast, chronic manifestations of inadequate CBF are characterized by more persistent and progressive conditions. Cognitive decline is a major concern, with vascular dementia being a prominent outcome. This condition involves a gradual deterioration in cognitive function, marked by memory impairment, executive dysfunction, and difficulties with reasoning and planning, often due to chronic cerebral hypoperfusion leading to small vessel disease.[24] Subcortical ischemic vascular disease, associated with white matter lesions and lacunar infarcts, is another chronic cognitive impairment linked to sustained hypoperfusion.[25] Chronic cerebral hypoperfusion can also lead to psychiatric symptoms, including depression and anxiety, as it impacts brain regions involved in mood regulation, such as the amygdala.[26]

Motor dysfunction is another significant chronic manifestation. Patients may develop gait disturbances, characterized by impaired coordination and walking difficulties often described as a "shuffling gait." This is due to chronic hypoperfusion affecting the basal ganglia and white matter tracts. Parkinsonism, exhibiting symptoms such as bradykinesia, rigidity,

and tremors, can also develop over time with prolonged inadequate blood flow to extrapyramidal motor control regions.[27]

Overall, these acute and chronic manifestations highlight the extensive and varied impact that inadequate CBF can have on different bodily systems and functions, necessitating timely and effective medical interventions to mitigate these effects.

Diagnosis and Monitoring

Clinical examination: Early diagnosis of cerebral hypoperfusion is critical for timely intervention and management. Key diagnostic tools encompass a multidimensional approach aimed at promptly identifying underlying causes and assessing the extent of CBF compromise.

The clinical examination of patients with HIE is a critical component of the diagnostic process, offering essential insights into the severity of cerebral injury and guiding immediate and long-term management strategies. Upon initial assessment, the evaluation typically begins with the determination of the patient's level of consciousness using the Glasgow Coma Scale (GCS), which quantitatively measures eye, verbal, and motor responses.[28] A lower GCS score, particularly a score of 8 or less, is indicative of severe neurological impairment and necessitates prompt intervention.[29] In addition to GCS, the examination of brainstem reflexes, including pupillary light reflexes, corneal reflexes, and oculocephalic responses, provides important information about brainstem integrity. Absent or asymmetric pupillary reactions, for instance, may suggest extensive brainstem or midbrain damage due to hypoxia.[30]

Motor responses are closely evaluated for the presence of decerebrate or decorticate posturing, both of which are associated with significant brain injury. Decerebrate posturing, characterized by extension and internal rotation of the arms and legs, typically indicates damage to the brainstem, while decorticate posturing, with flexion of the upper limbs and extension of the lower limbs, suggests injury above the level of the red nucleus, such as in the thalamus or cerebral hemispheres.[31] In the acute phase, myoclonus, a form of involuntary muscle jerking, may also be observed and is often associated with poor prognosis.[32]

Cranial nerve examination indicates localized brain injury or diffuse hypoxic damage. For instance, the presence of a unilateral cranial nerve deficit, such as facial asymmetry or dysphagia, may point to focal ischemic events secondary to HIE.[33] Furthermore, the presence of spontaneous or reflexive eye movements, or the lack thereof, can provide additional prognostic information; for example, absent oculocephalic reflexes may signify extensive brainstem involvement.[34]

In addition to neurological findings, a thorough systemic examination is necessary to identify potential underlying causes of hypoxia, such as cardiac arrest, respiratory failure, or severe hypotension, and to assess for signs of systemic hypoperfusion or multiorgan dysfunction.[35] Serial clinical examinations are essential, as they allow for the monitoring of neurological status over time, helping to track the progression or resolution of HIE and to adjust therapeutic strategies accordingly. The integration of clinical examination findings with laboratory, neuroimaging, and electrophysiological studies forms the foundation of comprehensive management in HIE, facilitating timely and appropriate interventions aimed at optimizing neurological outcomes.[36]

Role of blood gas changes on cerebral perfusion: Blood gases, including $PaCO_2$, PaO_2, and pH, play pivotal roles in the regulation of CBF. Alterations in these parameters can lead to significant changes, impacting brain function and potentially leading to neurological damage.[37] Understanding these components and their significance in hypoperfusion helps in diagnosing, managing, and monitoring a wide range of clinical conditions, ensuring optimal care in patients with cerebral hypoperfusion.[38]

Arterial blood gas analysis (ABGa) provides direct measurements that offer insights into the overall metabolic and respiratory functions. Pulse oximetry allows continuous, non-invasive monitoring of oxygen saturation, which is useful for detecting and managing hypoxemia in real-time. While convenient, pulse oximetry may not always accurately reflect PaO_2, particularly in cases of poor peripheral perfusion or carbon monoxide poisoning.[39]

Hypoxemia stabilizes hypoxia-inducible factors (HIFs), which regulate the expression of genes involved in adaptive responses to low oxygen, such as angiogenesis, erythropoiesis, and metabolic shifts.[40] Kaelin et al.[41] the pioneer researchers in HIFs, have been awarded with the Nobel Prize with the research decribing the important key proteins and key enzymes that participate in oxygen sensing and compensating pathways. HIFs have been maintaining their importance as an attractive and feasible target of therapeutic interventions to prevent the irreversible effects of acute or chronic hypoxemia.[42]

Hypercapnia induces various physiological changes that significantly affect CBF. Carbon dioxide readily diffuses across the blood-brain barrier (BBB) and combines with water to form carbonic acid, which dissociates into hydrogen ions and bicarbonate. The increase in hydrogen ions, acidosis, directly dilates cerebral blood vessels. Hypercapnia-induced acidosis also affects cellular metabolism, shifting the energy production from oxidative phosphorylation to glycolysis, which is less efficient and produces lactic acid. Potassium channels in cerebral blood vessels are activated by hypercapnia, causing hyperpolarization of smooth muscle cells and resulting in vasodilation. Hypercapnia-induced vasodilation can initially enhance cerebral perfusion, potentially beneficial in conditions with compromised CBF.[19] However, excessive or prolonged vasodilation can lead to increased intracranial pressure. Sustained hypercapnia may cause cerebral edema and elevated ICP, which can risk herniation and brainstem compression.[3]

Lactate has long been recognized as a marker of tissue hypoperfusion and hypoxia.[43] During hypoperfusion, oxygen delivery to tissues is insufficient to meet metabolic demands. Cells switch from aerobic to anaerobic metabolism, resulting in increased lactate production. The degree of lactate elevation correlates with the severity of hypoperfusion and can guide therapeutic interventions. Elevated lactate levels in CSF and blood may also reflect underlying mitochondrial dysfunction, not solely hypoxia, providing insights into neuronal health.[44] Ischemic stroke leads to localized cerebral hypoperfusion, causing rapid lactate accumulation in the affected brain region. Monitoring lactate levels during thrombolytic or endovascular therapy can provide insights into reperfusion success and tissue viability.[45] During cardiac arrest, the cessation of blood flow leads to global hypoxia and a rapid rise in lactate levels. Elevated lactate levels persist after return of spontaneous circulation (ROSC) due to ongoing tissue hypoxia and reperfusion injury, generally. Lactate levels can be used as a guide to evaluate the effectiveness of resuscitation efforts and the adequacy of oxygen delivery post-ROSC.[46]

Blood gas components interact with each other, and changes in one parameter affect others. For example, respiratory acidosis often prompts renal adjustments in bicarbonate levels, which is crucial for the blood's buffering system, maintaining pH within a narrow range.[47] Regular ABGa analysis is essential, particularly in intensive care settings for patients on mechanical ventilation or those with respiratory or metabolic disorders. Persistent or severe blood gas disturbances are associated with poor neurological outcomes. Early recognition and correction of these disturbances are crucial for improving patient prognosis and preventing long-term brain damage.

Current and emerging techniques in neuroimaging and diagnostic tools: Neuroimaging plays a role not only in the diagnosis, but also in prognostication and management of HIE in adults by providing critical insights into the extent and distribution of brain injury following a hypoxic event. Among the neuroimaging modalities, magnetic resonance imaging (MRI) is considered the gold standard for evaluating HIE due to its superior sensitivity in detecting both acute and chronic ischemic changes.[48] Diffusion-weighted imaging (DWI) is particularly valuable in the early detection of cytotoxic edema, which manifests as hyperintense regions on DWI and corresponds to areas of acute neuronal injury. These changes are often observed within hours of the hypoxic insult, with the basal ganglia, thalamus, hippocampus, and watershed areas being particularly vulnerable due to their high metabolic demand.[49] Fluid-attenuated inversion recovery sequences complement DWI by highlighting subacute and chronic ischemic changes, including gliosis and encephalomalacia, which may develop days to weeks after the initial event.[50]

As an emerging neuroimaging technique, functional MRI assesses brain activity by measuring changes in blood oxygenation, providing insight into the impact of HIE. It is being explored, along with diffusion tensor imaging techniques, for its potential to assess microstructural changes and functional connectivity disruptions in HIE.[51]

In addition to conventional MRI sequences, advanced techniques such as magnetic resonance spectroscopy (MRS) and perfusion MRI (pMRI) provide further insights into the metabolic and hemodynamic status of the brain. MRS allows for the non-invasive assessment of brain metabolites, including lactate, N-acetylaspartate (NAA), and choline, which can be altered in the context of ischemia. Elevated lactate levels detected by MRS indicate anaerobic metabolism, a hallmark of hypoxic injury, while reduced NAA levels suggest neuronal loss or dysfunction.[52] pMRI, on the other hand, enables the quantification of CBF and volume, providing crucial information about the adequacy of cerebral perfusion and identifying areas at risk of further infarction. Regions with significantly reduced perfusion are at higher risk of irreversible damage, guiding decisions regarding potential therapeutic interventions.[53]

Newer approaches, like arterial spin labeling MRI, a non-contrast method that magnetically labels inflowing blood to measure CBF, are being explored as a safer alternative for detecting early perfusion deficits in HIE patients, especially those with contraindications to contrast agents.[54]

Computed tomography (CT), although less sensitive than MRI, remains an essential tool in the acute setting due to its widespread availability and rapid acquisition. Non-contrast scans can identify early signs of hypoxic brain injury, such as the loss of gray-white matter differentiation, diffuse cerebral edema, and the presence of "reversal sign" or "white cerebellum sign," which are associated with poor prognosis.[55] CT perfusion imaging, similar to MRI, provides insights into CBF and can help differentiate between salvageable penumbra and infarcted core in the ischemic brain.[53]

Electroencephalography (EEG) provides real-time assessment of cerebral function and aids in both diagnosis and prognostication. In the acute phase of HIE, EEG is particularly valuable for detecting subclinical seizures, which are common in the context of diffuse brain injury but may not manifest with overt clinical signs. The presence of seizures on EEG is associated with further neuronal damage and can significantly worsen outcomes if not promptly managed.[56] In addition to identifying seizures, EEG patterns can reflect the severity of the encephalopathy. For instance, the presence of periodic discharges, burst suppression patterns, or generalized slowing on EEG often correlates with more severe brain injury and poorer neurological outcomes. Burst suppression is characterized by alternating periods of high-amplitude activity and flat line or low-amplitude activity and, in particular, is typically indicative of severe and often irreversible brain damage.[57]

Continuous EEG monitoring is frequently employed in the intensive care setting to provide ongoing evaluation of brain activity in patients with HIE, particularly those undergoing therapeutic interventions such as hypothermia.[58] This continuous monitoring allows for the timely detection and treatment of seizures and provides valuable information on the evolution of the encephalopathy over time. The reactivity of the EEG, defined as the ability of brain activity to change in response to external stimuli, is another important prognostic indicator. An EEG that lacks reactivity, especially in the absence of sedative medications, is generally associated with a poor prognosis.[59] Beyond seizure detection, quantitative EEG analysis, which involves the mathematical processing of EEG signals to extract additional information, is increasingly being explored for its potential to provide more nuanced prognostic data.[60]

Evoked potentials (EPs) are valuable electrophysiological tools in the assessment of HIE, offering objective measures of sensory pathway integrity and brainstem function. Among the various types of EPs, somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials (BAEPs) are most commonly employed in the context of HIE.[61] The prognostic value of EPs has been well-established, with studies consistently showing that absent cortical responses on SSEPs, particularly the N20 wave, are strongly predictive of poor outcomes in comatose patients following cardiac arrest, a common cause of HIE in adults. Similarly, the presence of prolonged latencies or the absence of key waveforms in BAEPs suggests extensive brainstem injury and is correlated with a higher likelihood of adverse outcomes, including persistent vegetative state or death.[62]

Biomarkers are emerging as valuable tools in the diagnosis, prognostication, and management of HIE in adults, offering the potential to detect brain injury at the molecular level and predict outcomes with greater accuracy. Among the most studied biomarkers in HIE are neuron-specific enolase (NSE), S100B protein, and glial fibrillary acidic protein (GFAP).[63] NSE is often elevated in correlation with the extent of brain damage and poor neurological outcomes in HIE patients. Measuring NSE levels in serum within the first 24 to 48 hours post-injury offers valuable prognostic information, aiding in the identification of patients who may benefit from aggressive neuroprotective therapies.[64]

S100B protein, primarily expressed by astrocytes, serves as a biomarker for glial cell damage and BBB disruption. Elevated serum S100B levels are associated with the severity of brain injury in HIE, with higher concentrations predicting a higher risk of death or severe neurological impairment; and its combination with other biomarkers or clinical parameters improves long-term prognostic accuracy.[65]

GFAP, an intermediate filament protein specific to astrocytes, is released into the bloodstream following astroglial injury and has emerged as a promising early biomarker for brain injury in HIE. Its elevated levels are useful in distinguishing between traumatic and non-traumatic brain injuries and in assessing the severity of diffuse axonal injury. Studies show that high GFAP levels within hours of the hypoxic event strongly predict poor neurological outcomes, highlighting its clinical utility.[66]

In addition to these established biomarkers, ongoing research is exploring the role of other molecules, such as microRNAs, interleukins, and oxidative stress markers, in the pathophysiology of HIE.[67] These novel biomarkers may provide further insights into the mechanisms of brain injury and recovery, potentially leading to the development of targeted therapeutic strategies. The integration of biomarker analysis with other diagnostic modalities, such as neuroimaging and electrophysiological studies, offers a more comprehensive approach to the management of HIE, enabling personalized treatment plans that are tailored to the specific needs of each patient.

Cerebral oximetry, a non-invasive technique using near-infrared spectroscopy to measure regional cerebral oxygen saturation, is becoming increasingly important in managing HIE in adults. It offers a real-time assessment of cerebral oxygenation, directly monitoring brain tissue oxygenation, unlike traditional systemic measures.[68] During therapeutic hypothermia, cerebral oximetry helps maintain safe oxygenation levels, reducing the risk of hypoxic episodes or reperfusion injury.[69] However, it mainly measures cortical oxygenation and can be influenced by factors like scalp edema and sensor placement, requiring careful interpretation. As technology advances, cerebral oximetry is expected to play an even greater role in neurocritical care, despite its current limitations.[70] Additionally, cerebral oximetry can be integrated with other monitoring modalities, such as EEG and ICP monitoring, to provide a comprehensive assessment of cerebral function and guide tailored interventions.[71] Despite these challenges, as technology advances and more research is conducted, the role of cerebral oximetry in HIE is likely to expand, further solidifying its place in neurocritical care.

Current and Emerging Treatments

In adults, the management of HIE focuses on limiting brain injury and promoting recovery through various pharmacological and neuroprotective strategies. One of the primary treatments under investigation is therapeutic hypothermia, which has shown success in neonates and is being explored for adult patients.[72] This approach involves cooling the body to reduce metabolic demand and inflammation, thereby mitigating brain damage.[58] Additionally, antioxidants such as N-acetylcysteine and edaravone are studied for their potential to reduce oxidative stress, a critical factor in neuronal injury following ischemic events.[73]

Anti-inflammatory drugs also play a significant role in HIE management. Minocycline, for instance, has demonstrated promise in reducing microglial activation and inflammation, which are key contributors to secondary brain injury.[4] Another critical area of focus is the prevention of glutamate excitotoxicity, a process in which excessive glutamate causes neuronal death. N-methyl-D-aspartate receptor antagonists like memantine are being investigated for their ability to counteract this mechanism. Similarly, calcium channel blockers such as nimodipine, traditionally used to manage subarachnoid hemorrhage, are considered for their potential to reduce calcium-mediated neuronal injury in HIE.[74]

In terms of neuroprotective strategies, erythropoietin has emerged as a potential therapeutic agent due to its anti-apoptotic and anti-inflammatory properties, which extend beyond its role in stimulating red blood cell production.[4] Stem cell therapy is another promising approach, with mesenchymal stem cells and neural stem cells showing potential in repairing and regenerating damaged brain tissue, although this field remains largely experimental. Growth factors, including insulin-like growth factor 1 and brain-derived neurotrophic factor, are also being explored for their roles in enhancing neuronal survival and promoting regeneration.[75]

Emerging therapies such as exosome-based treatments and preconditioning strategies are gaining attention in the scientific community. Exosomes, which are small vesicles that carry proteins, lipids, and RNAs, are being researched for their ability to deliver neuroprotective agents to the brain. Ischemic preconditioning, where brief episodes of sub-lethal ischemia are induced to build resistance to more severe ischemic insults, represents another innovative approach under investigation.[67] Furthermore, gene therapy offers a cutting-edge strategy by potentially enhancing the expression of protective genes or suppressing harmful ones in the context of HIE.[76]

The integration of combination therapies is a growing area of interest, as combining different pharmacological agents with neuroprotective strategies may yield better outcomes for patients. Although many of these strategies are still in experimental stages, they represent the future of HIE management, aiming to improve neurological recovery and reduce long-term disabilities associated with this condition.

CONCLUSION

Cerebral hypoperfusion is a critical condition with far-reaching implications for brain health. Effective management of cerebral hypoperfusion requires a comprehensive, multidisciplinary approach that addresses both acute and long-term needs. Early diagnosis and prompt intervention are critical to minimizing neuronal damage and improving outcomes. Advances in imaging techniques, neuroprotective therapies, and personalized medicine hold promise for enhancing the management of cerebral hypoperfusion in the future. Ongoing research is needed to better understand the pathophysiology of cerebral hypoperfusion, identify novel biomarkers, and develop targeted therapies. Integrating emerging technologies such as artificial intelligence and machine learning into clinical practice may improve the accuracy of diagnosis and the precision of treatment strategies.

MAIN POINTS

- Due to the brain's high metabolic demands, cerebral hypoperfusion rapidly leads to irreversible neurological damage, and chronic hypoperfusion contributes to vascular dementia and motor dysfunction, resulting in long-term complications.

- Disruptions in cerebral perfusion set the stage for progressive neurological deterioration, bridging acute deficits with chronic neurodegeneration.
- Multimodal neurodiagnostics, including advanced imaging techniques and electrophysiological assessments, alongside emerging biomarkers, provide a comprehensive framework for detecting hypoxic brain injury, prognosticating outcomes, and guiding therapeutic interventions.
- Neuroprotective interventions, ranging from therapeutic hypothermia and anti-inflammatory strategies to emerging stem cell and genetic therapies, hold transformative potential in mitigating neuronal injury and enhancing long-term recovery in hypoxic-ischemic encephalopathy.

Footnotes

Financial Disclosure: The author declared that this study had received no financial support.

REFERENCES

1. Schaller B, Graf R. Cerebral ischemia and reperfusion: the pathophysiologic concept as a basis for clinical therapy. J Cereb Blood Flow Metab. 2004; 24(4): 351-71.
2. Magistretti P, Allaman I. Brain energy and metabolism. In book: Neuroscience in the 21st Century. Cham: Springer International Publishing; 2022; pp. 2197-227.
3. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. Physiol Rev. 2021; 101(4): 1487-559.
4. Morganti-Kossmann MC, Semple BD, Hellewell SC, Bye N, Ziebell JM. The complexity of neuroinflammation consequent to traumatic brain injury: from research evidence to potential treatments. Acta Neuropathol. 2019; 137(5): 731-55.
5. Zhivotovsky B, Orrenius S. Calcium and cell death mechanisms: a perspective from the cell death community. Cell Calcium. 2011; 50(3): 211-21.
6. Alam A, Thelin EP, Tajsic T, Khan DZ, Khellaf A, Patani R, et al. Cellular infiltration in traumatic brain injury. J Neuroinflammation. 2020; 17(1): 328.
7. Zhao M, Zhu P, Fujino M, Zhuang J, Guo H, Sheikh I, et al. Oxidative stress in hypoxic-ischemic encephalopathy: molecular mechanisms and therapeutic strategies. Int J Mol Sci. 2016; 17(12): 2078.
8. Collins N, Abd-Elsayed A. Cerebral perfusion pressure. In Manual of Neuroanesthesia. 2017; 31-8.
9. Georgiadis D, Schwarz S, Baumgartner RW, Veltkamp R, Schwab S. Influence of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in patients with acute stroke. Stroke. 2001; 32(9): 2088-92.
10. van der Velpen IF, Yancy CW, Sorond FA, Sabayan B. Impaired cardiac function and cognitive brain aging. Can J Cardiol. 2017; 33(12): 1587-96.
11. Perkins GD, Callaway CW, Haywood K, Neumar RW, Lilja G, Rowland MJ, et al. Brain injury after cardiac arrest. Lancet. 2021; 398(10307): 1269-78.
12. Jain KK, Jain KK. Drug-Induced disturbances of consciousness. Drug-induced Neurological Disorders. 2021; 233-64.
13. Yu YP, Tan L. The vulnerability of vessels involved in the role of embolism and hypoperfusion in the mechanisms of ischemic cerebrovascular diseases. Biomed Res Int. 2016; 2016: 8531958.
14. Naiya T, Meganathan I, Ness N, Oudit GY, Murray A, Kassiri Z. Contribution of the arterial cells to atherosclerosis and plaque formation. Am J Physiol Heart Circ Physiol. 2024; 327(4): H804-23.
15. Li Y, Shang K, Cheng X, Zhang Z, Li Y, Shang K, et al. Cerebral vasculitis. In: Li H, Wang J, Zhang X, (eds). Radiology of Infectious and Inflammatory Diseases-Volume 1: Brain and Spinal Cord. Singapore: Springer Nature Singapore; 2023; pp. 237-54.
16. Yang Q, Wei X, Deng B, Chang Z, Jin D, Huang Y, et al. Cerebral small vessel disease alters neurovascular unit regulation of microcirculation integrity involved in vascular cognitive impairment. Neurobiol Dis. 2022; 170: 105750.
17. Tarumi T, Zhang R. Cerebral blood flow in normal aging adults: cardiovascular determinants, clinical implications, and aerobic fitness. J Neurochem. 2018; 144(5): 595-608.
18. Juraschek SP, Longstreth WT Jr, Lopez OL, Gottdiener JS, Lipsitz LA, Kuller LH, et al. Orthostatic hypotension, dizziness, neurology outcomes, and death in older adults. Neurology. 2020; 95(14): e1941-50.
19. Rudziński W, Swiat M, Tomaszewski M, Krejza J. Cerebral hemodynamics and investigations of cerebral blood flow regulation. Nucl Med Rev Cent East Eur. 2007; 10(1): 29-42.
20. Howard RS, Holmes PA, Koutroumanidis MA. Hypoxic-ischaemic brain injury. Pract Neurol. 2011; 11(1): 4-18.
21. Carlson MD. Syncope. In: Roos KL, (eds). Emergency neurology. Springer, Cham; 2021; pp. 89-98.
22. Zhang W, Fu W, Zhang Y. Association of cerebral hypoperfusion and poor collaterals with cognitive impairment in patients with severe vertebrobasilar artery stenosis. J Alzheimers Dis Rep. 2024; 8(1): 999-1007.
23. Testai FD. What caused this transient or persisting ischemic event?. In: Hankey GJ, Macleod M, Gorelick PB, Chen C, Caprio FZ, Mattle H, (eds). Warlow's stroke: practical management, 4th ed, 2019.
24. de la Torre JC. Are major dementias triggered by poor blood flow to the brain? Theoretical considerations. J Alzheimers Dis. 2017; 57(2): 353-71.
25. Rosenberg GA, Bjerke M, Wallin A. Multimodal markers of inflammation in the subcortical ischemic vascular disease type of vascular cognitive impairment. Stroke. 2014; 45(5): 1531-8.
26. Antypa D, Simos NJ, Kavroulakis E, Bertsias G, Fanouriakis A, Sidiropoulos P, et al. Anxiety and depression severity in neuropsychiatric SLE are associated with perfusion and functional connectivity changes of the frontolimbic neural circuit: a resting-state f(unctional) MRI study. Lupus Sci Med. 2021; 8(1): e000473.
27. Lassinger BK, Kwak C, Walford RL, Jankovic J. Atypical parkinsonism and motor neuron syndrome in a Biosphere 2 participant: a possible complication of chronic hypoxia and carbon monoxide toxicity? Mov Disord. 2004; 19(4): 465-9.
28. Edwards SL. Using the Glasgow Coma Scale: analysis and limitations. Br J Nurs. 2001; 10(2): 92-101.
29. Pisano F, Bilotta F. The predictive value of the Verbal Glasgow Coma Scale in traumatic brain injury: a systematic review. J Head Trauma Rehabil. 2024; 39(4): 273-83.
30. Howard RS. Coma and brainstem death. Medicine. 2012; 40(9): 500-6.
31. Tarulli A, Tarulli A. Coma. Neurology: A Clinician's Approach. 2016: 25-42.
32. Riva A, D'Onofrio G, Ferlazzo E, Pascarella A, Pasini E, Franceschetti S, et al. Myoclonus: differential diagnosis and current management. Epilepsia Open. 2024; 9(2): 486-500.
33. Rush B, Beard L, Furr M. Differential diagnosis and management of cranial nerve abnormalities. In: Furr M, Reed S, (eds). Equine Neurology: Blackwell Publishing, Ames; 2008; pp. 101-18.
34. Oli KK, Shrestha A. Coma and vegetative state. Case-based approach to common neurological disorders. Singapore: Springer Nature Singapore; 2024; pp. 287-96.

35. Douglas-Escobar M, Weiss MD. Hypoxic-ischemic encephalopathy: a review for the clinician. JAMA Pediatr. 2015; 169(4): 397-403.

36. Maciel CB, Barden MM, Greer DM. Neurologic recovery after cardiac arrest: a multifaceted puzzle requiring comprehensive coordinated care. Curr Treat Options Cardiovasc Med. 2017; 19(7): 52.

37. Payne SJ, Mohammad J, Tisdall MM, Tachtsidis I. Effects of arterial blood gas levels on cerebral blood flow and oxygen transport. Biomed Opt Express. 2011; 2(4): 966-79.

38. Byrne AL, Bennett M, Chatterji R, Symons R, Pace NL, Thomas PS. Peripheral venous and arterial blood gas analysis in adults: are they comparable? A systematic review and meta-analysis. Respirology. 2014; 19(2): 168-75.

39. Hieronymi U, Kramme R, Kronberg H. Respiratory monitoring and pulse oximetry. Springer Handbook of Medical Technology. Berlin, Heidelberg: Springer Berlin Heidelberg; 2012; pp. 971-85.

40. Speer R, Ratan RR. Hypoxic adaptation in the nervous system: promise for novel therapeutics for acute and chronic neurodegeneration. Adv Exp Med Biol. 2016; 903: 221-43.

41. Kaelin Jr WG, Ratcliffe PJ, Semenza GL. Out of breath: molecular description of cellular responses to hypoxia-2019 Nobel Prize for Physiology or Medicine. Curr Sci. 2019; 117(9): 1418.

42. Correia SC, Moreira PI. Hypoxia-inducible factor 1: a new hope to counteract neurodegeneration? J Neurochem. 2010; 112(1): 1-12.

43. Verhaeghe M, Hachimi-Idrissi S. Blood lactate and lactate kinetics as treatment and prognosis markers for tissue hypoperfusion. Acta Clin Belg. 2020; 75(1): 1-8.

44. Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. Nat Rev Neurosci. 2018; 19(4): 235-49.

45. Franke C, Brinker G, Pillekamp F, Hoehn M. Probability of metabolic tissue recovery after thrombolytic treatment of experimental stroke: a magnetic resonance spectroscopic imaging study in rat brain. J Cereb Blood Flow Metab. 2000; 20(3): 583-91.

46. Ward KR, Bisera J. Cardiac arrest resuscitation monitoring. have cardiac arrest in their personal libraries for ready ref-erence. Resuscitation; 2007; pp. 698.

47. Adrogué HJ, Madias NE. Respiratory acidosis, respiratory alkalosis, and mixed disorders. Comprehensive Clinical Nephrology E-book; 2023; p. 182.

48. Parmentier CEJ, de Vries LS, Groenendaal F. Magnetic resonance imaging in (near-)term infants with hypoxic-ischemic encephalopathy. Diagnostics (Basel). 2022; 12(3): 645.

49. Huisman TA. Diffusion-weighted imaging: basic concepts and application in cerebral stroke and head trauma. Eur Radiol. 2003; 13(10): 2283-97.

50. Himes NC, Young G. Background on imaging structural imaging. In Image-Guided Neurosurgery. 2015; 25-61.

51. Pinto CR, Duarte JV, Marques C, Vicente IN, Paiva C, Éloi J, et al. The role of early functional neuroimaging in predicting neurodevelopmental outcomes in neonatal encephalopathy. Eur J Pediatr. 2023; 182(3): 1191-200.

52. Shih MT, Singh AK, Wang AM, Patel S. Brain lesions with elevated lactic acid peaks on magnetic resonance spectroscopy. Curr Probl Diagn Radiol. 2004; 33(2): 85-95.

53. Demeestere J, Wouters A, Christensen S, Lemmens R, Lansberg MG. Review of perfusion imaging in acute ischemic stroke: from time to tissue. Stroke. 2020; 51(3): 1017-24.

54. Jaafar N, Alsop DC. Arterial spin labeling: key concepts and progress towards use as a clinical tool. Magn Reson Med Sci. 2024; 23(3): 352-66.

55. Rizvi T, Batchala P, Mukherjee S. Brain death: diagnosis and imaging techniques. Semin Ultrasound CT MR. 2018; 39(5): 515-29.

56. Walker MC. Diagnosis and treatment of nonconvulsive status epilepticus. CNS Drugs. 2001; 15(12): 931-9.

57. Rubinos C, Bruzzone MJ, Viswanathan V, Figueredo L, Maciel CB, LaRoche S. electroencephalography as a biomarker of prognosis in acute brain injury. Semin Neurol. 2023; 43(5): 675-88.

58. Variane GFT, Dahlen A, Pietrobom RFR, Rodrigues DP, Magalhães M, Mimica MJ, et al. Remote monitoring for seizures during therapeutic hypothermia in neonates with hypoxic-ischemic encephalopathy. JAMA Netw Open. 2023; 6(11): e2343429.

59. Admiraal MM, van Rootselaar AF, Hofmeijer J, Hoedemaekers CWE, van Kaam CR, Keijzer HM, et al. Electroencephalographic reactivity as predictor of neurological outcome in postanoxic coma: A multicenter prospective cohort study. Ann Neurol. 2019; 86(1): 17-27.

60. Fingelkurts AA, Fingelkurts AA. Quantitative electroencephalogram (qEEG) as a natural and non-invasive window into living brain and mind in the functional continuum of healthy and pathological conditions. Applied Sciences. 2022; 12(19): 9560.

61. Markand ON. Clinical evoked potentials: an illustrated manual. Springer Nature; 2020.

62. Lachance B, Wang Z, Badjatia N, Jia X. Somatosensory evoked potentials and neuroprognostication after cardiac arrest. Neurocrit Care. 2020; 32(3): 847-57.

63. Caramelo I, Coelho M, Rosado M, Cardoso CMP, Dinis A, Duarte CB, et al. Biomarkers of hypoxic-ischemic encephalopathy: a systematic review. World J Pediatr. 2023; 19(6): 505-48.

64. Agoston DV, Shutes-David A, Peskind ER. Biofluid biomarkers of traumatic brain injury. Brain Inj. 2017; 31(9): 1195-203.

65. Massaro AN, Wu YW, Bammler TK, Comstock B, Mathur A, McKinstry RC, et al. Plasma biomarkers of brain injury in neonatal hypoxic-ischemic encephalopathy. J Pediatr. 2018; 194: 67-75.

66. Chirica VI. Useful markers to assess traumatic and hypoxic brain injury. Rom J Leg Med. 2017; 25: 146-51.

67. Rasineni GK., Panigrahy N, Rath SN, Chinnaboina M, Konanki R, Chirla DK, et al. Diagnostic and therapeutic roles of the "omics" in hypoxic-ischemic encephalopathy in neonates. Bioengineering. 2022; 9(10): 498.

68. Steppan J, Hogue CW Jr. Cerebral and tissue oximetry. Best Pract Res Clin Anaesthesiol. 2014; 28(4): 429-39.

69. Skhirtladze-Dworschak K, Dworschak M. Cerebral oximetry and cardiac arrest. Semin Cardiothorac Vasc Anesth. 2013; 17(4): 269-75.

70. Sandroni C, Parnia S, Nolan JP. Cerebral oximetry in cardiac arrest: a potential role but with limitations. Intensive Care Med. 2019; 45(6): 904-6.

71. Schraag S. Combined monitoring-brain function monitoring and cerebral oximetry. J Cardiothorac Vasc Anesth. 2019; 33 (Suppl 1): S53-7.

72. Pedroza-García KA, Calderón-Vallejo D, Quintanar JL. Neonatal hypoxic-ischemic encephalopathy: perspectives of neuroprotective and neuroregenerative treatments. Neuropediatrics. 2022; 53(6): 402-17.

73. Jurcau A, Ardelean AI. Oxidative stress in ischemia/reperfusion injuries following acute ischemic stroke. Biomedicines. 2022; 10(3): 574.

74. Krieglstein J, el Nasr MS, Lippert K. Neuroprotection by memantine as increased by hypothermia and nimodipine. Eur J Pharm Sci. 1997; 5(2): 71-7.

75. Pimentel-Coelho PM, Mendez-Otero R. Cell therapy for neonatal hypoxic-ischemic encephalopathy. Stem Cells Dev. 2010; 19(3): 299-310.

76. Bao L, Chen M, Dai B, Lei Y, Qin D, Cheng M, et al. Nanoengineered therapeutic strategies targeting SNHG1 for mitigating microglial ischemia-reperfusion injury implications for hypoxic-ischemic encephalopathy. SLAS Technol. 2024; 29(4): 100167.