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The Neonatal Cardio-Renal-Brain Axis in Hypoxic-Ischemic Encephalopathy: An Emerging Paradigm in Precision Neurocritical Care

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Abstract

Hypoxic-ischaemic encephalopathy (HIE) remains one of the leading causes of neonatal mortality and long-term neurodevelopmental disability worldwide despite major advances in neonatal intensive care and the widespread implementation of therapeutic hypothermia. Traditionally, HIE has been viewed predominantly as a cerebral disorder, with clinical management focused largely on neuroprotection and seizure control. However, growing evidence suggests that perinatal hypoxia-ischaemia induces a complex multisystem response involving profound interactions between cardiovascular dysfunction, acute kidney injury, cerebral autoregulatory failure, systemic inflammation, and metabolic disturbances. Myocardial injury may lead to reduced cardiac output and impaired cerebral perfusion, while renal dysfunction contributes to fluid imbalance, altered drug pharmacokinetics, and amplification of inflammatory pathways that further exacerbate secondary brain injury. Therapeutic hypothermia, although neuroprotective, introduces additional physiological alterations that influence myocardial performance, systemic vascular resistance, and renal blood flow. These interdependent mechanisms have led to increasing recognition of a neonatal cardio-renal-brain axis as a central determinant of neurological recovery following perinatal asphyxia. This review explores current understanding of organ crosstalk in HIE, examines emerging biomarkers and monitoring strategies, and discusses how multimodal haemodynamic assessment may facilitate a transition from protocol-driven treatment toward precision neurocritical care in the neonatal intensive care unit.

Keywords: Hypoxic-ischaemic encephalopathy; neonatal haemodynamics; therapeutic hypothermia; acute kidney injury; precision neurocritical care

1. Introduction

Few conditions in neonatal medicine present clinicians with challenges as complex and time-sensitive as hypoxic-ischaemic encephalopathy (HIE). Despite considerable advances in obstetric care, neonatal resuscitation, and intensive care medicine, perinatal asphyxia continues to affect approximately one to three infants per 1,000 live births in high-income countries, with substantially higher rates reported in low- and middle-income settings. Survivors frequently face lifelong neurodevelopmental consequences including cerebral palsy, epilepsy, cognitive impairment, behavioural disorders, and sensory deficits.

The introduction of therapeutic hypothermia transformed neonatal neurocritical care and remains the only intervention with proven neuroprotective efficacy for moderate and severe HIE. Nevertheless, nearly half of treated infants either die or develop significant neurological impairment despite receiving optimal cooling

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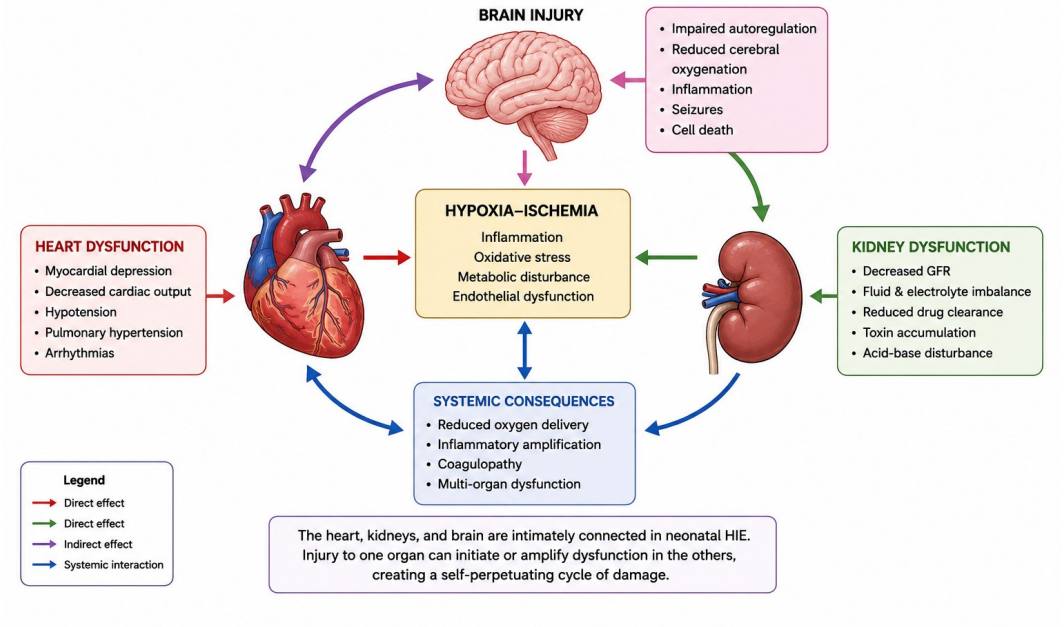
therapy. Such observations suggest that brain injury following perinatal asphyxia cannot be fully explained by cerebral mechanisms alone.

For decades, clinical attention in HIE has focused primarily on neuronal energy failure, excitotoxicity, oxidative stress, and neuroinflammation. Although these pathways undoubtedly play central roles, severe intrapartum hypoxia rarely affects the brain in isolation. The fetus responds to oxygen deprivation through redistribution of cardiac output toward vital organs, a compensatory mechanism commonly referred to as the "brain-sparing effect." When hypoxia becomes prolonged or severe, however, these adaptive responses become overwhelmed, resulting in widespread systemic injury involving the myocardium, kidneys, lungs, liver, and gastrointestinal tract.

Among these organs, the heart and kidneys appear to exert particularly important influences on neurological recovery. Myocardial dysfunction may compromise cerebral perfusion during the vulnerable reperfusion period, while acute kidney injury alters fluid homeostasis, drug clearance, inflammatory signaling, and metabolic stability. Conversely, evolving cerebral injury can influence autonomic regulation and cardiovascular function, creating a dynamic cycle of reciprocal organ interactions.

The concept of a cardio-renal syndrome is well established in adult medicine, particularly in patients with heart failure and critical illness. In neonatology, however, a broader and more integrated understanding of the relationship between cardiac function, renal physiology, and cerebral perfusion has only recently begun to emerge. Increasing use of targeted neonatal echocardiography, near-infrared spectroscopy, continuous electroencephalographic monitoring, and novel biomarkers has highlighted the existence of a complex cardio-renal-brain axis that may significantly influence outcomes following hypoxic-ischaemic injury.

Figure 1. The Neonatal Cardio-Renal-Brain Axis in Hypoxic-Ischemic Encephalopathy



Recognition of this interconnected physiology has important clinical implications. Management strategies based solely on blood pressure thresholds or neurological examination may fail to identify occult circulatory compromise, impaired cerebral autoregulation, or evolving renal dysfunction. Precision neurocritical care therefore requires a shift from organ-specific treatment toward integrated haemodynamic assessment and individualized therapeutic decision-making.

This review explores current evidence regarding cardiovascular dysfunction, acute kidney injury, and cerebral autoregulatory disturbances in neonatal HIE, examines the physiological interactions between these systems during therapeutic hypothermia, and discusses emerging approaches that may support the development of precision haemodynamic management in neonatal neurocritical care.

2. Evolution of the Brain-Centric Model of HIE and the Emergence of the Cardio-Renal-Brain Axis

2.1. From a Neurological Disease to a Multisystem Disorder

For many years, neonatal hypoxic-ischaemic encephalopathy was regarded primarily as a disease of cerebral injury. Research efforts understandably focused on neuronal apoptosis, excitotoxicity, oxidative stress, mitochondrial dysfunction, and inflammatory cascades occurring within the central nervous system. This brain-centred approach led to major advances in understanding the mechanisms of primary and secondary energy failure and ultimately paved the way for the introduction of therapeutic hypothermia.

However, clinical observations have increasingly challenged the concept of HIE as an isolated neurological disorder. Infants with severe perinatal asphyxia frequently demonstrate evidence of myocardial dysfunction, pulmonary hypertension, acute kidney injury, hepatic impairment, coagulopathy, adrenal insufficiency, and gastrointestinal injury within the first hours after birth. Indeed, the severity of extracerebral organ dysfunction often parallels the degree of neurological injury and may independently influence survival and neurodevelopmental outcome.

Recent studies suggest that approximately 60–80% of infants with moderate or severe HIE exhibit some degree of cardiovascular compromise, while acute kidney injury develops in up to 50% of cooled infants. These findings indicate that systemic hypoxia-ischaemia produces a complex pattern of organ crosstalk rather than isolated cerebral injury.

2.2. The Fetal Brain-Sparing Response

During acute hypoxia, the fetus activates several adaptive mechanisms aimed at preserving oxygen delivery to vital organs. Redistribution of cardiac output occurs through peripheral vasoconstriction and preferential perfusion of the brain, heart, and adrenal glands, a physiological response commonly referred to as the **brain-sparing effect**.

This adaptive circulation is mediated through:

- sympathetic nervous system activation,
- catecholamine release,
- peripheral vasoconstriction,
- increased coronary blood flow,
- cerebral vasodilatation.

Under mild or transient hypoxic conditions, these compensatory mechanisms may successfully preserve cerebral oxygenation and limit organ injury.

However, prolonged or severe asphyxia overwhelms these protective responses.

Progressive myocardial hypoxia leads to declining cardiac output, impaired ventricular contractility, and loss of compensatory redistribution. Once systemic perfusion falls below a critical threshold, oxygen delivery to both central and peripheral organs deteriorates rapidly, initiating widespread cellular injury.

Table 1. Common Causes of Hypoxic-Ischemic Encephalopathy (HIE)

Antepartum Causes		Intrapartum Causes	
Cause	**Examples / Details**	**Cause**	**Examples / Details**
Maternal Factors	• Hypertension, preeclampsia, eclampsia • Diabetes mellitus • Antepatrum hemorrhage • Smoking, alcohol or drug use • Maternal infections (chorioamnionitis, TORCH)	**Uterine Factors**	• Uterine tachysystole • Prolonged labor • Uterine rupture • Inadequate uterine contractions • Use of excessive oxytocin
Placental Factors	• Placental abruption • Placenta previa with hemorrhage • Uteroplacental insufficiency • Placental infarction or thrombosis • Chronic placental insufficiency	**Fetal Factors**	• Fetal distress (abnormal FHR patterns) • Cord prolapse or compression • Nuchal cord • Shoulder dystocia • Malpresentation
Fetal Factors	• Fetal growth restriction (IUGR) • Congenital anomalies (especially cardiac) • Multiple gestation complications • Fetal anemia (alloimmunization) • Hydrops fetalis	**Umbilical Cord Factors**	• Cord compression • Cord prolapse • True knot in cord • Short cord • Cord around neck or body
Amniotic Fluid Abnormalities	• Oligohydramnios • Polyhydramnios • Meconium-stained amniotic fluid (antepartum)	**Delivery Factors**	• Instrumental delivery complications • Difficult or prolonged second stage • Fetal head entrapment • Failed instrumental delivery
Other Factors	• Post-term pregnancy • Umbilical cord abnormalities (velamentous insertion) • Maternal autoimmune disease • Exposure to toxins or medications	**Other Factors**	• Maternal hypotension • Excessive blood loss • Maternal hypoxia or respiratory compromise • General anesthesia

Note: HIE is typically the result of a combination of factors rather than a single cause. The severity and duration of hypoxia-ischemia determine the extent of brain injury.

2.3. Reperfusion Injury: The Beginning of Organ Crosstalk

The restoration of circulation following successful resuscitation is essential for survival but paradoxically initiates additional injury pathways.

Reoxygenation triggers:

- generation of reactive oxygen species,
- mitochondrial dysfunction,
- endothelial activation,
- inflammatory cytokine release,
- leukocyte recruitment,
- microvascular dysfunction.

This phenomenon, commonly referred to as reperfusion injury, contributes substantially to secondary energy failure occurring during the first 6–48 hours after birth.

Importantly, these processes occur simultaneously within multiple organs.

Myocardial injury reduces systemic blood flow and oxygen delivery, renal dysfunction impairs metabolic homeostasis and inflammatory clearance, while cerebral autoregulatory disturbances increase susceptibility to fluctuations in perfusion pressure. Rather than acting independently, these injuries amplify one another through a network of haemodynamic and inflammatory interactions.

2.4. The Heart as a Driver of Neurological Recovery

The neonatal myocardium possesses limited contractile reserve compared with older children and adults. Reduced compliance, immature calcium handling, and limited ability to augment stroke volume make the newborn heart particularly vulnerable to hypoxic injury.

Following perinatal asphyxia, myocardial dysfunction may manifest as:

- impaired left ventricular contractility,
- right ventricular dysfunction,
- reduced cardiac output,
- tricuspid regurgitation,
- systemic hypotension,
- persistent pulmonary hypertension of the newborn (PPHN).

Importantly, normal blood pressure does not necessarily indicate adequate systemic blood flow.

Several studies using functional echocardiography have demonstrated that infants with HIE may exhibit significantly reduced cardiac output despite maintaining blood pressure values within conventional reference ranges. Such occult low-output states may contribute to impaired cerebral perfusion during the critical period of secondary brain injury.

These observations have shifted attention away from isolated blood pressure targets toward more comprehensive haemodynamic assessment.

2.5. The Kidney as an Active Participant Rather Than a Passive Victim

Historically, acute kidney injury in HIE was viewed primarily as a marker of severe asphyxia rather than an active contributor to disease progression.

Emerging evidence suggests otherwise.

Renal dysfunction may contribute to neurological injury through several mechanisms:

- impaired fluid regulation,
- electrolyte disturbances,
- altered clearance of anticonvulsants and vasoactive medications,
- amplification of systemic inflammation,
- accumulation of metabolic toxins,
- endothelial dysfunction.

Experimental studies have demonstrated bidirectional communication between injured kidneys and the central nervous system mediated through inflammatory cytokines, oxidative stress pathways, and neurohumoral activation.

The kidney therefore functions not merely as an innocent bystander but as an active component of the evolving neurocritical illness.

2.6. The Cardio-Renal-Brain Axis: A New Conceptual Framework

The traditional organ-based model of neonatal intensive care may no longer adequately reflect the complexity of modern neurocritical care.

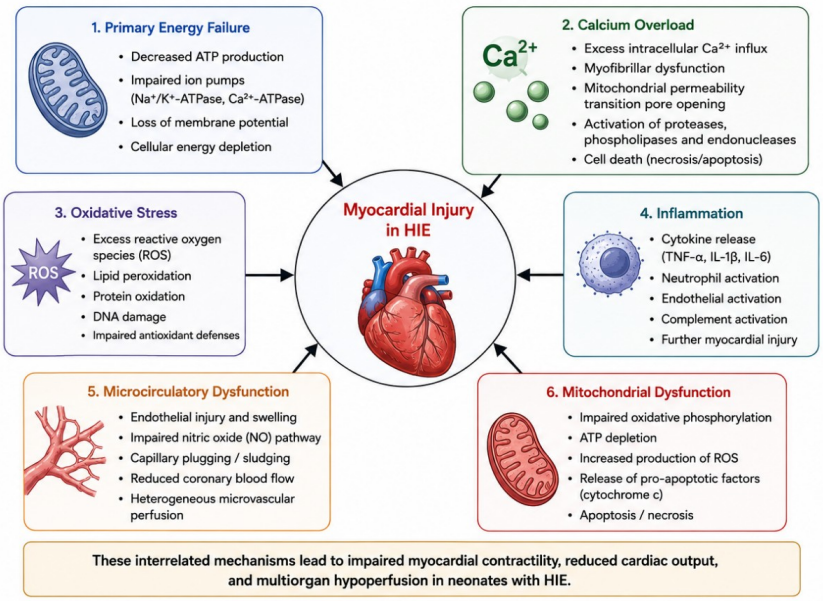
A more integrated model recognizes that:

- cardiac dysfunction influences cerebral perfusion,
- cerebral injury alters autonomic cardiovascular regulation,
- renal dysfunction modifies inflammatory and metabolic responses,
- therapeutic interventions targeting one organ may affect another.

The outcome following HIE therefore reflects not only the severity of cerebral injury but also the resilience of the entire physiological network supporting cerebral recovery.

This concept forms the basis of the **neonatal cardio-renal-brain axis**, an emerging framework that may help guide future strategies in individualized haemodynamic management.

Figure 3. Mechanisms of Myocardial Injury in Neonatal HIE



Abbreviations: *ATP, adenosine triphosphate; Ca^{2+}, calcium; HIE, hypoxic-ischemic encephalopathy; IL, interleukin; NO, nitric oxide; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-alpha.*

3. Cardiovascular Dysfunction in HIE: The Heart-Brain Connection

3.1. The Vulnerable Neonatal Myocardium

The neonatal myocardium enters extrauterine life with relatively little physiological reserve. Compared with older children and adults, the newborn heart has limited capacity to increase stroke volume, making cardiac output heavily dependent on heart rate and preload conditions. Reduced ventricular compliance, immature calcium handling, fewer organized contractile elements, and limited capacity to augment stroke volume render the newborn myocardium particularly susceptible to hypoxic injury.

During perinatal asphyxia, myocardial oxygen consumption remains high despite declining oxygen delivery. Although coronary perfusion initially increases as part of the fetal adaptive response, prolonged hypoxia eventually overwhelms compensatory mechanisms, leading to myocardial ischemia and cellular injury.

In clinical practice, myocardial dysfunction is often less obvious than neurological injury and may easily be overlooked during the initial stabilization period. Nevertheless, subtle reductions in cardiac output may have important consequences for cerebral oxygen delivery during the hours in which secondary brain injury evolves.

3.2. Pathophysiology of Myocardial Injury in HIE

Myocardial injury following perinatal asphyxia is multifactorial and evolves over several phases.

Primary hypoxic injury

Reduced oxygen delivery results in:

- ATP depletion,
- anaerobic metabolism,
- intracellular acidosis,
- impaired calcium transport,
- contractile dysfunction.

Reperfusion injury

Following restoration of circulation:

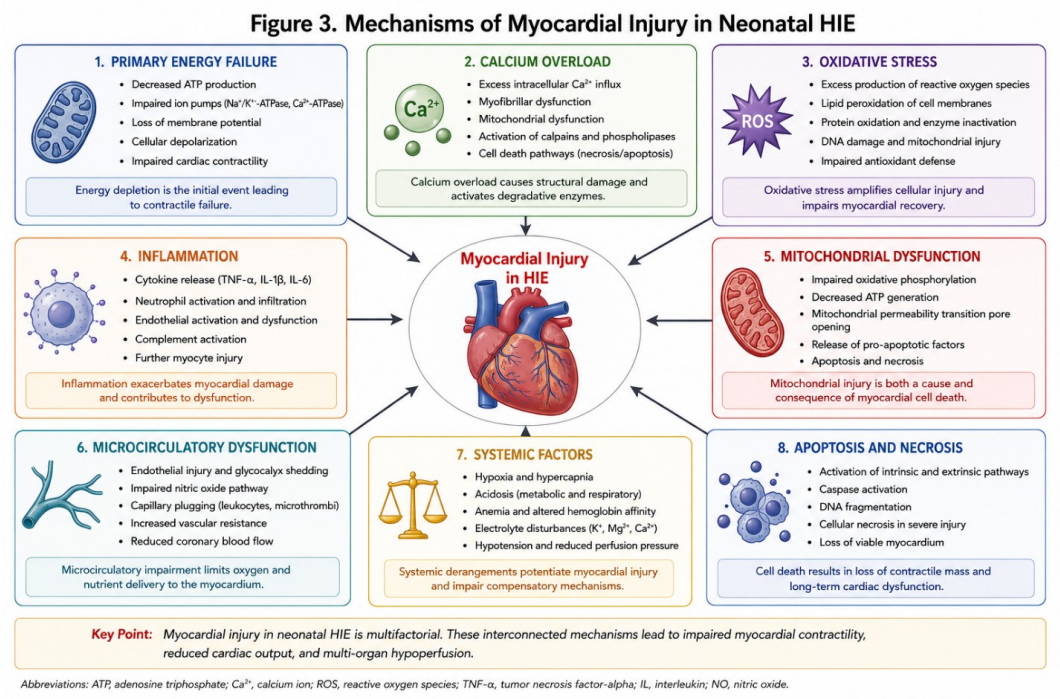
- reactive oxygen species accumulate,
- mitochondrial injury develops,
- inflammatory cytokines are released,
- endothelial dysfunction impairs microvascular flow.

Secondary inflammatory phase

Over subsequent hours:

- cytokine activation persists,
- oxidative stress continues,
- myocardial stunning may occur.

These mechanisms resemble those described in adult post-cardiac arrest syndrome and contribute to transient or prolonged ventricular dysfunction.



3.3. Clinical Manifestations of Cardiovascular Dysfunction

Cardiovascular abnormalities occur frequently in infants with moderate and severe HIE.

Clinical manifestations include:

- systemic hypotension,
- poor peripheral perfusion,
- prolonged capillary refill time,
- metabolic acidosis,
- elevated lactate concentrations,
- ventricular dysfunction,
- pulmonary hypertension,
- arrhythmias.

However, overt circulatory collapse represents only the most severe end of a broad haemodynamic spectrum.

Neonatologists are familiar with infants who maintain acceptable arterial pressures while simultaneously demonstrating persistent metabolic acidosis, prolonged capillary refill, and reduced urine output. Such observations illustrate the limitations of blood pressure as a surrogate for adequate systemic perfusion.

This phenomenon has important implications for neonatal neurocritical care because cerebral oxygen delivery depends primarily on cardiac output rather than arterial pressure alone

Table 2. Cardiovascular manifestations in neonatal HIE

Cardiovascular finding	Mechanism	Potential neurological consequence
Left ventricular dysfunction	Myocardial ischemia	Reduced cerebral blood flow
Right ventricular dysfunction	Increased pulmonary vascular resistance	Reduced systemic oxygen delivery
Pulmonary hypertension	Pulmonary vasoconstriction	Hypoxaemia
Tricuspid regurgitation	RV pressure overload	Reduced cardiac efficiency
Bradycardia during cooling	Hypothermia-induced physiological response	Usually benign
Low cardiac output syndrome	Myocardial stunning	Secondary brain injury

3.4. Left Ventricular Dysfunction

Left ventricular dysfunction is among the most frequently reported cardiovascular abnormalities in HIE.

Functional echocardiographic studies have demonstrated:

- reduced ejection fraction,
- impaired shortening fraction,
- decreased stroke volume,
- reduced cardiac output.

The resulting reduction in systemic blood flow may compromise cerebral perfusion during the latent phase of injury, a period during which secondary neuronal injury remains potentially modifiable.

This observation raises an important clinical question:

Should haemodynamic support in HIE target blood pressure, cardiac output, or cerebral oxygen delivery?

Increasingly, evidence suggests that focusing exclusively on blood pressure may overlook clinically important reductions in systemic perfusion.

3.5. Right Ventricular Dysfunction and Pulmonary Hypertension

Pulmonary vascular dysfunction is common after severe perinatal asphyxia.

Contributing mechanisms include:

- endothelial injury,
- impaired nitric oxide signaling,
- pulmonary vasoconstriction,
- meconium aspiration,
- ventricular interdependence.

Persistent pulmonary hypertension of the newborn (PPHN) occurs in a significant proportion of infants undergoing therapeutic hypothermia.

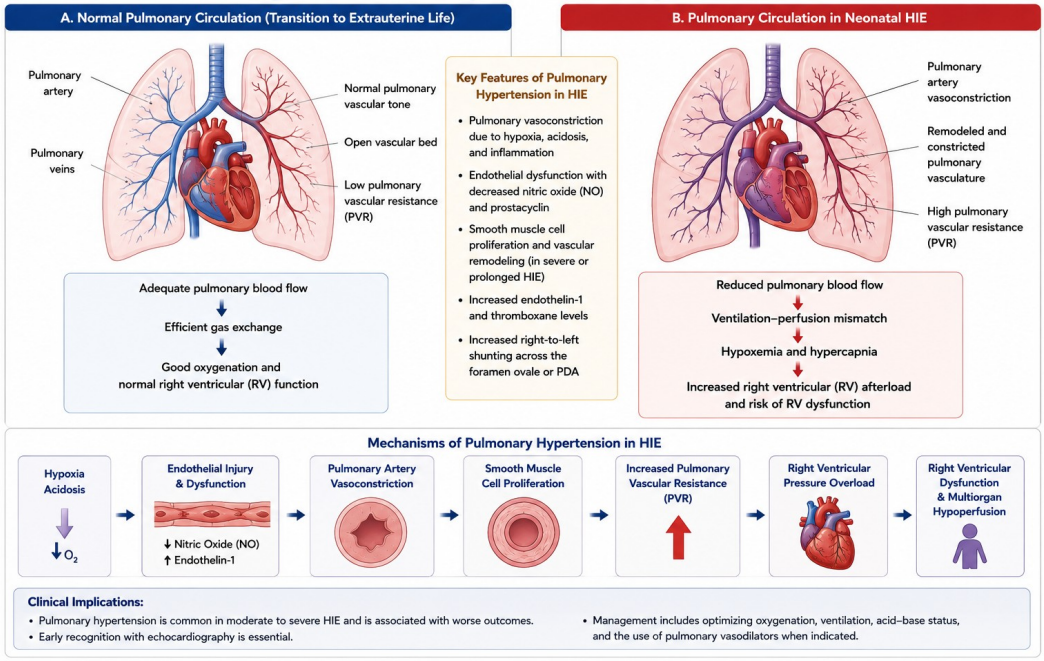
Elevated pulmonary vascular resistance increases right ventricular afterload, resulting in:

- tricuspid regurgitation,

- septal flattening,
- reduced left ventricular filling,
- worsening systemic perfusion.

The interaction between pulmonary and systemic circulations highlights the complexity of haemodynamic management in these infants.

Figure 4. Pulmonary Vascular Changes in Neonatal HIE



3.6. Biomarkers of Myocardial Injury

Biochemical markers have increasingly been used to assess myocardial involvement in HIE.

Cardiac Troponin I and Troponin T

Elevated troponin concentrations correlate with:

- severity of asphyxia,
- ventricular dysfunction,
- need for inotropic support,
- adverse neurological outcome.

B-type Natriuretic Peptide (BNP)

BNP and NT-proBNP reflect:

- ventricular wall stress,
- pulmonary hypertension,
- volume overload.

These biomarkers may provide valuable adjunctive information when interpreted alongside echocardiographic findings.

Table 3. Hemodynamic Targets in Neonatal HIE

Parameter	Target / Goal	Rationale / Comments
Mean Arterial Pressure (MAP)	≥ Gestational age in weeks (mmHg)	Maintain adequate organ perfusion. Adjust for clinical context and trends.
Lactate	< 2 mmol/L and decreasing trend	Indicator of global tissue perfusion and adequacy of oxygen delivery.
Superior Vena Cava Flow (TnECHO)	40–70 mL/kg/min	Reflects systemic blood flow and cardiac output.
Cardiac Index	> 3.3 L/min/m²	Adequate cardiac output for tissue perfusion.
Central Venous Oxygen Saturation ($ScvO_2$)	> 70%	Surrogate for balance between oxygen delivery and consumption.
Cerebral rSO_2 (NIRS)	55–85%	Maintain within autoregulatory range; avoid prolonged hypo- or hyper-oxygenation.
Urine Output	> 1 mL/kg/hour	Early marker of adequate renal perfusion and fluid status.
Temperature (during cooling)	33.0–34.0 °C	Therapeutic hypothermia for 72 hours.
Temperature (during rewarming)	Increase by 0.25–0.5 °C/hour to 36.5–37.0 °C	Slow, controlled rewarming to prevent hemodynamic instability.
Hemoglobin	> 12 g/dL	Ensure adequate oxygen carrying capacity; individualize based on clinical status.

Note: *Targets should be individualized based on gestational age, severity of encephalopathy, comorbid conditions, and dynamic clinical assessment. Trends are more important than single values.*

Abbreviations: MAP, mean arterial pressure; TnECHO, targeted neonatal echocardiography; rSO_2, regional cerebral oxygen saturation; $ScvO_2$, central venous oxygen saturation; NIRS, near-infrared spectroscopy.

3.7. The Limitations of Blood Pressure

Despite its limitations, blood pressure continues to dominate haemodynamic decision-making in many neonatal units, largely because it is continuously available and easy to interpret.

However, blood pressure alone provides limited information regarding:

- stroke volume,
- cardiac output,
- systemic blood flow,
- organ perfusion,
- cerebral oxygen delivery.

An infant may maintain normal arterial pressure through increased systemic vascular resistance while simultaneously experiencing severe reductions in cardiac output.

Consequently, reliance on blood pressure alone may result in under-recognition of haemodynamic compromise.

3.8. Targeted Neonatal Echocardiography: Looking Beyond Numbers

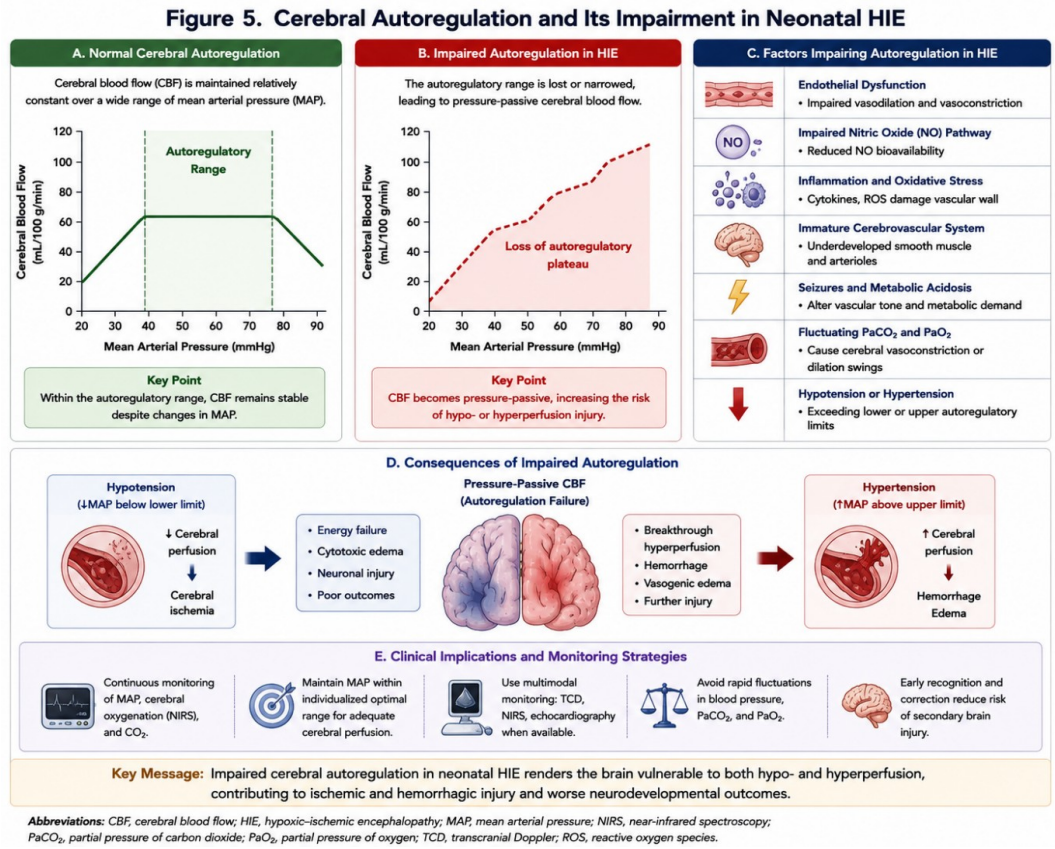
The growing use of targeted neonatal echocardiography (TnECHO) has transformed haemodynamic assessment in neonatal intensive care.

Functional echocardiography allows bedside evaluation of:

- ventricular performance,
- cardiac output,
- pulmonary pressures,
- ductal shunting,

- filling status,
- systemic blood flow.

In infants with HIE, TnECHO facilitates individualized haemodynamic management and may identify circulatory abnormalities before the onset of overt clinical deterioration.



3.9. Therapeutic Hypothermia and Cardiovascular Physiology

Therapeutic hypothermia significantly alters cardiovascular physiology.

Expected physiological effects include:

- sinus bradycardia,
- increased systemic vascular resistance,
- reduced metabolic demand,
- altered myocardial contractility.

Distinguishing physiological adaptation from pathological circulatory compromise may be challenging.

For example, a heart rate of 80–90 beats per minute during cooling may represent normal physiological slowing rather than cardiovascular instability.

This distinction is critical to avoid unnecessary interventions that may themselves adversely affect cerebral haemodynamics.

3.10. Clinical Implications

The recognition of cardiovascular dysfunction as a major determinant of neurological recovery represents an important shift in neonatal neurocritical care.

The objective is no longer simply maintaining blood pressure within an acceptable range.

Instead, modern haemodynamic management increasingly seeks to optimize:

- cardiac output,
- cerebral oxygen delivery,
- tissue perfusion,
- end-organ function.

Such an approach forms the foundation of precision haemodynamic management in HIE.

4. Renal Dysfunction in HIE: The Forgotten Organ in Neurocritical Care

4.1. Acute Kidney Injury in HIE: More Common Than Previously Appreciated

Although neurological injury understandably dominates clinical attention in neonatal HIE, the kidneys are among the organs most vulnerable to hypoxic-ischaemic insult. Owing to their high metabolic demands and dependence on continuous perfusion, the neonatal kidneys are particularly susceptible to reductions in oxygen delivery and systemic blood flow.

Contemporary studies suggest that acute kidney injury (AKI) develops in approximately one-third to one-half of infants with moderate to severe HIE, with reported incidences varying according to diagnostic criteria and patient populations. Importantly, therapeutic hypothermia does not eliminate the risk of renal injury, and AKI remains common even among cooled infants receiving modern neurocritical care.

For many years renal dysfunction was considered largely a consequence of severe perinatal asphyxia rather than a contributor to ongoing injury. This perception is gradually changing.Increasing evidence, however, suggests that AKI itself contributes to ongoing systemic inflammation, metabolic instability, and secondary organ injury.

The kidney should therefore be regarded not merely as a victim of hypoxia but as an active participant in the pathophysiology of HIE.

4.2. Why the Neonatal Kidney Is Particularly Vulnerable

Several characteristics of neonatal renal physiology increase susceptibility to hypoxic injury.

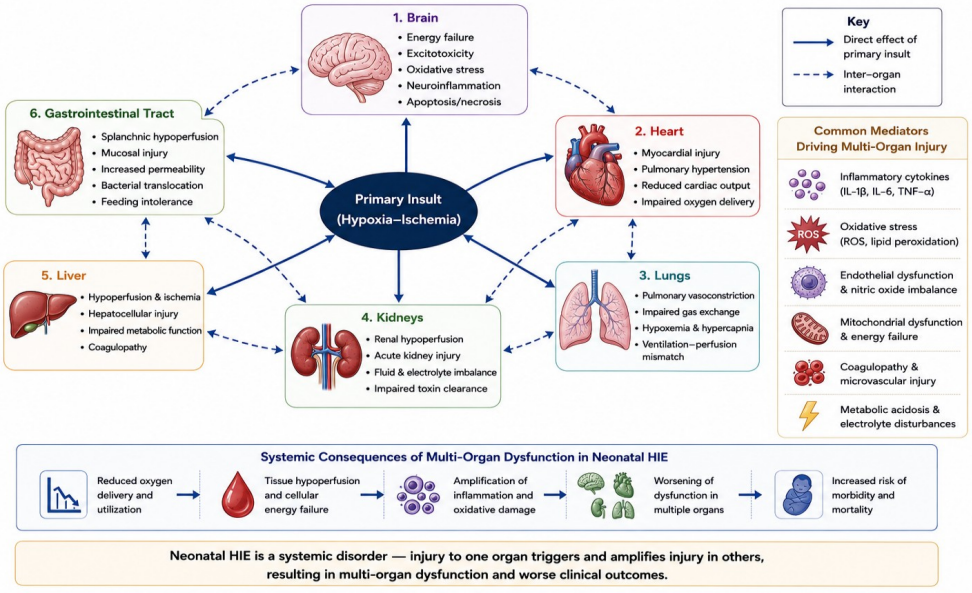
These include:

- relatively low baseline glomerular filtration rate,
- immature tubular function,
- limited autoregulatory reserve,
- high oxygen consumption within the renal medulla,
- dependence on adequate systemic perfusion.

During fetal adaptation to hypoxia, renal blood flow decreases significantly as circulation is preferentially redistributed toward the brain, heart, and adrenal glands. While this compensatory mechanism may preserve cerebral oxygenation during transient stress, prolonged reductions in renal perfusion rapidly lead to ischemic tubular injury.

The resulting damage predominantly affects the renal tubules, although glomerular and vascular injury may also occur in severe cases.

Figure 6. Multi-Organ Interactions and Systemic Consequences in Neonatal HIE



Abbreviations: HIE, hypoxic–ischemic encephalopathy; ROS, reactive oxygen species; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

4.3. Pathophysiological Mechanisms of AKI in HIE

Renal injury in HIE is multifactorial and rarely attributable to ischemia alone.

Major contributors include:

Ischaemic injury

- reduced renal perfusion pressure,
- prolonged vasoconstriction,
- decreased oxygen delivery.

Reperfusion injury

- reactive oxygen species generation,
- mitochondrial dysfunction,
- endothelial injury.

Inflammatory activation

- cytokine release,
- leukocyte infiltration,
- microvascular dysfunction.

Haemodynamic instability

- myocardial dysfunction,
- low cardiac output states,
- pulmonary hypertension.

The coexistence of cardiac dysfunction and renal injury reinforces the concept of a neonatal cardio-renal syndrome occurring within the broader framework of HIE.

4.4. Diagnostic Challenges

Diagnosing acute kidney injury in newborn infants remains frustratingly difficult, particularly during the first days of life when physiological adaptation and maternal creatinine transfer complicate interpretation of laboratory findings.

Traditional markers such as serum creatinine have several limitations:

- maternal creatinine contributes significantly during the first postnatal days,
- creatinine rises relatively late after injury,
- values may remain normal despite substantial nephron damage.

Urine output monitoring is also imperfect because some infants develop non-oliguric AKI.

Consequently, clinicians may underestimate the true burden of renal injury during the early phase of HIE.

Table 4. Limitations of conventional AKI markers in neonates

Marker	Limitation
Serum creatinine	Influenced by maternal creatinine
Urine output	Poor sensitivity for non-oliguric AKI
Blood urea nitrogen	Influenced by hydration and nutrition
Fractional sodium excretion	Variable in preterm and sick neonates

4.5. Emerging Biomarkers of Renal Injury

The search for earlier and more sensitive biomarkers has generated considerable interest in neonatal nephrology.

Promising biomarkers include:

Neutrophil gelatinase-associated lipocalin (NGAL)

One of the earliest markers of tubular injury and often rises before serum creatinine changes become apparent.

Cystatin C

Reflects glomerular filtration more accurately than creatinine and is less influenced by maternal physiology.

Kidney injury molecule-1 (KIM-1)

Associated with proximal tubular damage.

Interleukin-18

May provide additional information regarding inflammatory renal injury.

These biomarkers may eventually facilitate earlier diagnosis and allow more individualized management strategies.

Table 5. Emerging renal biomarkers in neonatal HIE

Biomarker	Primary role	Potential clinical utility
NGAL	Tubular injury	Early detection of AKI
Cystatin C	Glomerular filtration	Assessment of renal function
KIM-1	Tubular damage	Severity stratification
IL-18	Inflammation	Prediction of progression
Urinary albumin	Glomerular injury	Monitoring renal recovery

4.6. The Kidney-Brain Connection

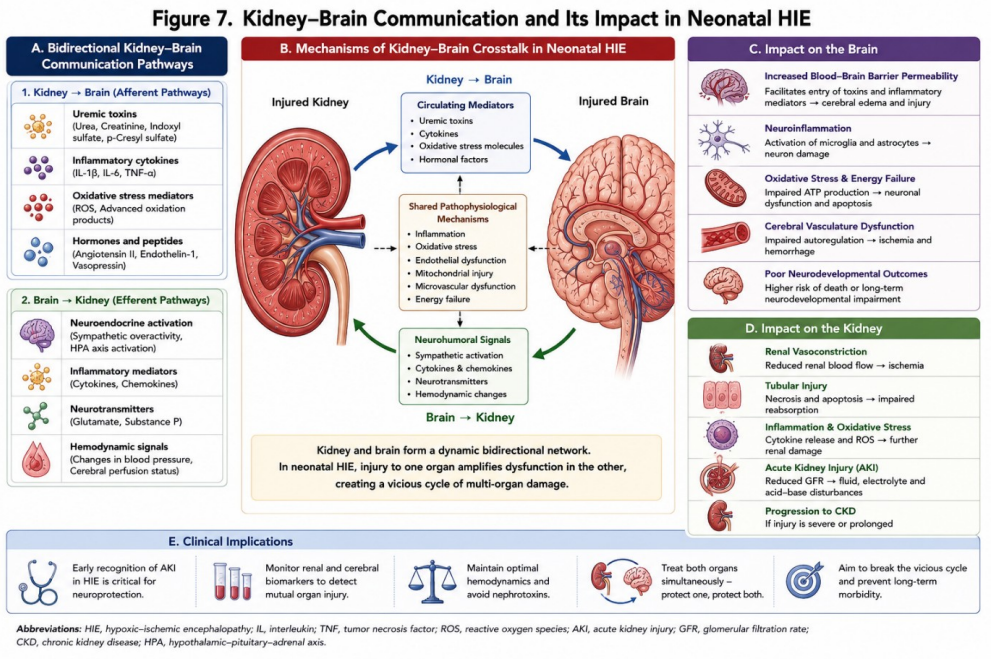
One of the more fascinating developments in neonatal physiology has been the recognition that the injured kidney and injured brain communicate in ways that extend far beyond simple haemodynamics.

Experimental models suggest that renal injury may influence neurological outcomes through several mechanisms:

- systemic cytokine release,
- oxidative stress,
- endothelial dysfunction,
- altered blood-brain barrier permeability,
- microvascular injury,
- activation of neuroinflammatory pathways.

Similarly, severe cerebral injury may alter renal perfusion through autonomic dysregulation and neurohumoral activation.

This reciprocal interaction forms a central component of the emerging cardio-renal-brain axis.



4.7. Therapeutic Hypothermia and Renal Physiology

Therapeutic hypothermia influences renal physiology in several important ways.

Potential effects include:

- reduction in renal metabolic demand,
- altered renal blood flow,
- changes in drug clearance,
- delayed creatinine kinetics.

Although cooling may exert some protective effects on renal tissue, current evidence remains inconclusive regarding its ability to prevent AKI.

From a practical standpoint, clinicians must remain aware that therapeutic hypothermia may substantially alter the pharmacokinetics of commonly used medications including:

- phenobarbital,
- morphine,
- gentamicin,
- amikacin,
- vancomycin.

Renal dysfunction further amplifies this variability, creating significant challenges for individualized dosing.

4.8. Implications for Precision Pharmacology

The interaction between HIE, hypothermia, and renal dysfunction introduces considerable complexity into neonatal pharmacotherapy.

Standard dosing regimens may not adequately account for:

- altered volume of distribution,
- reduced renal clearance,
- hepatic dysfunction,
- changing organ perfusion.

Future precision medicine approaches may integrate:

- therapeutic drug monitoring,
- biomarker profiling,
- functional haemodynamic assessment,
- pharmacokinetic modelling.

Such strategies align closely with the broader principles of precision neurocritical care.

4.9. Long-Term Consequences

Although neurological outcomes dominate follow-up programmes for survivors of HIE, increasing attention is being directed toward long-term renal health.

Potential consequences include:

- reduced nephron number,
- hypertension,
- chronic kidney disease,
- impaired renal reserve.

Whether early renal injury contributes directly to adverse neurodevelopmental outcomes remains an active area of investigation.

4.10. Clinical Implications

Recognition of AKI as an active contributor rather than a passive marker of disease severity has important implications for neonatal practice.

Management should include:

- careful fluid balance monitoring,
- avoidance of nephrotoxic medications where possible,
- early recognition of evolving renal dysfunction,
- individualized drug dosing,
- integration of renal assessment into haemodynamic decision-making.

Such an approach supports the transition from isolated organ management toward systems-based neurocritical care.

5. Cerebral Autoregulation and the Brain Within the Cardio-Renal-Brain Axis

5.1. The Brain at the Centre of a Systemic Disease

Although the concept of HIE has evolved beyond a purely neurological disorder, Although neonatal encephalopathy is increasingly recognized as a multisystem disorder, long-term outcome remains largely determined by the extent of cerebral recovery.

What has changed is our understanding of how cerebral injury develops and progresses.

The neonatal brain does not exist in physiological isolation. Cerebral oxygen delivery depends on an intricate balance between:

- cardiac output,
- arterial oxygen content,
- cerebrovascular autoregulation,
- systemic inflammatory status,
- metabolic homeostasis.

Disturbance of any component of this network may influence the trajectory of neurological recovery following hypoxic-ischaemic injury.

The challenge for modern neurocritical care is therefore not simply to protect neurons, but to preserve the physiological environment in which neuronal recovery can occur.

5.2. Primary and Secondary Energy Failure

The pathophysiology of HIE is traditionally described as a biphasic process consisting of primary and secondary energy failure.

Primary Energy Failure

During the initial hypoxic-ischaemic insult:

- cerebral oxygen delivery falls,
- oxidative phosphorylation ceases,
- ATP stores become depleted,
- anaerobic glycolysis predominates,
- intracellular acidosis develops.

Failure of ATP-dependent ion pumps results in:

- membrane depolarization,
- sodium influx,
- intracellular calcium accumulation,
- glutamate release,
- excitotoxic neuronal injury.

If the insult is sufficiently severe, immediate cell death occurs.

Latent Phase

Following successful resuscitation, a transient period of partial metabolic recovery may occur.

This latent phase typically lasts approximately 6 hours and represents the therapeutic window during which interventions such as therapeutic hypothermia exert their greatest benefit.

Importantly, haemodynamic instability during this period may significantly influence subsequent injury progression.

Secondary Energy Failure

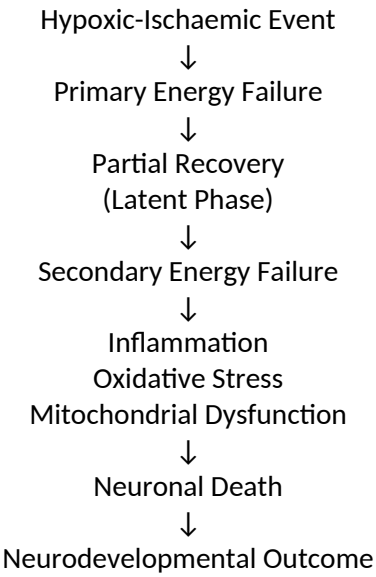
Secondary injury develops over the following 6 to 72 hours and is characterized by:

- mitochondrial dysfunction,
- oxidative stress,
- inflammation,
- apoptosis,
- microvascular dysfunction,
- cerebral edema.

Unlike primary injury, many components of secondary energy failure remain potentially modifiable.

This principle forms the biological basis of contemporary neuroprotective strategies.

Figure 8. Temporal evolution of cerebral injury following perinatal asphyxia



5.3. Cerebral Autoregulation: The Protective Mechanism

Under normal physiological conditions, cerebral autoregulation maintains relatively stable cerebral blood flow despite fluctuations in systemic blood pressure.

This mechanism depends upon:

- cerebrovascular smooth muscle function,
- endothelial integrity,

- metabolic regulation,
- autonomic nervous system input.

In healthy neonates, autoregulation allows the brain to maintain adequate perfusion across a range of systemic pressures.

This protective mechanism minimizes both ischemic injury and hyperperfusion-related damage.

5.4. Loss of Cerebral Autoregulation in HIE

Hypoxic-ischaemic injury disrupts cerebral autoregulatory mechanisms through multiple pathways:

- endothelial injury,
- impaired nitric oxide signaling,
- oxidative stress,
- inflammation,
- microvascular dysfunction.

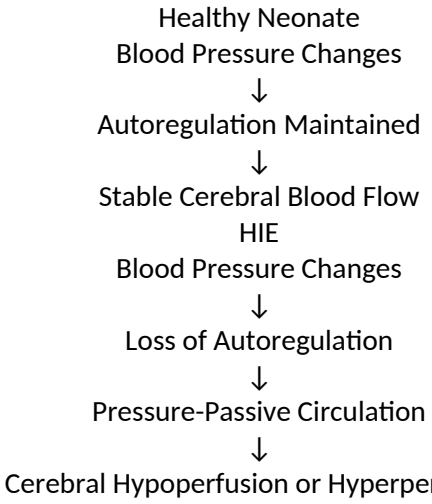
As autoregulation fails, cerebral blood flow becomes increasingly pressure-passive.

Under these conditions:

- hypotension may precipitate cerebral ischemia,
- hypertension may contribute to cerebral edema and hemorrhage,
- fluctuations in systemic blood flow become directly transmitted to the injured brain.

This loss of autoregulatory reserve may explain why infants with apparently stable systemic parameters occasionally experience unexpected neurological deterioration.

Figure 9. Cerebral autoregulation in health and HIE



5.5. Cardiac Output and Cerebral Oxygen Delivery

For decades, clinicians have relied heavily on arterial blood pressure as a marker of adequate cerebral perfusion. The relationship between the two, however, is considerably more complex.

However, cerebral oxygen delivery depends more fundamentally upon:

Cerebral Oxygen Delivery = Cardiac Output × Arterial Oxygen Content

Consequently:

- normal blood pressure does not guarantee adequate cerebral perfusion,
- reduced cardiac output may coexist with acceptable arterial pressures,
- myocardial dysfunction may impair neurological recovery despite stable haemodynamics.

These observations reinforce the importance of integrating cardiac assessment into neurocritical care.

Table 6. Determinants of cerebral oxygen delivery

Variable	Clinical relevance
Cardiac output	Primary determinant of cerebral perfusion
Hemoglobin concentration	Determines oxygen carrying capacity
Arterial oxygen saturation	Influences oxygen content
Cerebral autoregulation	Maintains stable blood flow
Pulmonary vascular resistance	Affects systemic oxygen delivery

5.6. Neuroinflammation and Organ Crosstalk

Secondary brain injury involves complex interactions between the central nervous system and peripheral organs.

Inflammatory mediators released following myocardial injury and acute kidney injury may contribute to:

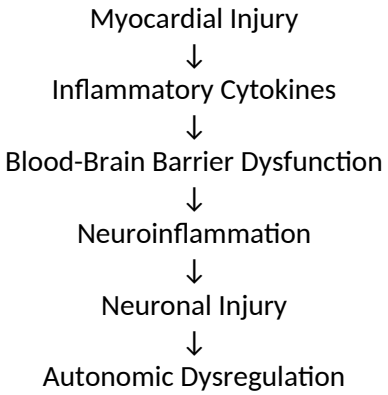
- endothelial dysfunction,
- blood-brain barrier disruption,
- microglial activation,
- neuronal apoptosis.

Similarly, severe cerebral injury may induce:

- autonomic instability,
- altered vascular tone,
- neuroendocrine dysregulation.

These interactions create a self-perpetuating cycle of systemic injury and neurological deterioration.

Figure 10. Inflammatory amplification within the cardio-renal-brain axis



↓

Further Cardiovascular Instability

5.7. Near-Infrared Spectroscopy and Cerebral Monitoring

Near infrared spectroscopy (NIRS) has emerged as an important tool for continuous assessment of cerebral oxygenation.

Potential advantages include:

- non-invasive monitoring,
- continuous trend analysis,
- early detection of cerebral hypoperfusion,
- assessment of autoregulatory status.

When combined with:

- targeted neonatal echocardiography,
- amplitude-integrated EEG,
- invasive blood pressure monitoring,

NIRS may contribute to individualized haemodynamic management strategies.

Table 7. Monitoring modalities in neonatal neurocritical care

Modality	Primary information provided
TnECHO	Cardiac function and output
NIRS	Cerebral oxygenation
aEEG	Electrical brain activity
Continuous EEG	Seizure detection
Lactate	Global perfusion
Troponin	Myocardial injury
NGAL	Renal injury

5.8. Biomarkers of Cerebral Injury

Several biomarkers have been investigated as indicators of neurological injury severity.

Promising candidates include:

- neuron-specific enolase (NSE),
- S100B protein,
- glial fibrillary acidic protein (GFAP),
- ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1).

Although these biomarkers remain largely investigational, future integration with cardiac and renal biomarkers may improve risk stratification.

Table 4. Biomarkers in Hypoxic-Ischemic Encephalopathy (HIE)

Biomarker Category	Biomarker	Clinical Significance / Utility
Cardiac Biomarkers	• **Troponin I (cTnI)**	Marker of myocardial injury; correlates with severity and outcome.
	• **NT-proBNP**	Indicator of ventricular strain and dysfunction; prognostic value.
	• **CK-MB**	Less specific; supportive marker of myocardial injury.
Renal Biomarkers	• **NGAL** (Neutrophil Gelatinase–Associated Lipocalin)	Early marker of AKI; rises within 2–6 h of insult.
	• **Cystatin C**	More sensitive than creatinine for early GFR decline.
	• **KIM-1** (Kidney Injury Molecule-1)	Reflects tubular injury; useful for risk stratification.
	• **IL-18** (Interleukin-18)	Associated with renal inflammation and injury severity.
Brain Injury Biomarkers	• **Neuron Specific Enolase** (NSE)	Neuronal injury marker; levels correlate with severity and prognosis.
	• **S100B**	Astrocyte activation/injury marker; predictor of outcome.
	• **GFAP** (Glial Fibrillary Acidic Protein)	Specific marker of astroglial injury; elevated in severe HIE.
	• **UCH-L1** (Ubiquitin Carboxy-Terminal Hydrolase L1)	Emerging marker of neuronal injury; may improve prognostication.
Inflammatory Biomarkers	• **IL-6** (Interleukin-6)	Reflects systemic inflammatory response; associated with severity.
	• **TNF-α** (Tumor Necrosis Factor-alpha)	Pro-inflammatory cytokine; contributes to secondary injury.
	• **CRP** (C-Reactive Protein)	Non-specific marker; may support risk assessment.

Note: Biomarkers should be interpreted in the clinical context and in combination with other parameters. Serial measurements and trends are more informative than single values.

Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; HIE, hypoxic-ischemic encephalopathy; IL, interleukin; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NSE, neuron specific enolase; TNF, tumor necrosis factor.

5.9. Toward Individualized Cerebral Perfusion Targets

The concept of a universal blood pressure threshold for all infants with HIE is increasingly being questioned.

Future haemodynamic management may instead involve individualized targets based upon:

- cerebral oxygenation,
- cardiac output,
- autoregulatory status,
- metabolic markers,
- biomarker profiles.

Such an approach represents a fundamental shift from protocol-driven care toward precision neurocritical medicine.

5.10. Clinical Implications

Preserving cerebral recovery requires more than preventing seizures and initiating therapeutic hypothermia.

Optimal neuroprotection may depend equally upon:

- maintaining adequate systemic blood flow,
- avoiding excessive haemodynamic variability,
- supporting myocardial function,
- preserving renal homeostasis,

- minimizing systemic inflammation.

The injured brain ultimately reflects the health of the entire physiological network supporting it.

6. Therapeutic Hypothermia and Organ Crosstalk: Balancing Neuroprotection and Systemic Physiology

6.1. Therapeutic Hypothermia: A Landmark Achievement in Neonatal Medicine

The introduction of therapeutic hypothermia (TH) fundamentally changed the landscape of neonatal neurocritical care. By reducing cerebral metabolism and interrupting pathways involved in secondary energy failure, TH remains the only intervention consistently shown to improve survival and neurodevelopmental outcomes in infants with moderate and severe HIE.

The standard protocol of cooling to 33–34°C for 72 hours followed by gradual rewarming has become routine practice across neonatal intensive care units worldwide.

However, therapeutic hypothermia was designed primarily as a neuroprotective intervention. Its physiological effects extend far beyond the brain, influencing virtually every organ system involved in the cardio-renal-brain axis.

Understanding these systemic effects is essential for individualized patient management.

6.2. Cooling Alters the Entire Cardiovascular Environment

Therapeutic hypothermia creates a physiological state that differs substantially from normal neonatal adaptation, and many of the resulting cardiovascular changes should be interpreted within this context rather than automatically regarded as evidence of disease

Expected findings include:

- sinus bradycardia,
- increased systemic vascular resistance,
- reduced myocardial oxygen consumption,
- decreased metabolic demand,
- reduced cardiac output.

The challenge for clinicians lies in distinguishing normal adaptation from clinically significant circulatory compromise.

For example, a heart rate of 85 beats per minute during cooling may represent an expected physiological response, whereas the same heart rate in a normothermic infant could suggest significant illness.

Clinical context therefore becomes critically important.

Table 9. Expected cardiovascular effects of therapeutic hypothermia

Physiological parameter	Expected response during cooling
Heart rate	Decreases
Systemic vascular resistance	Increases
Metabolic rate	Decreases
Oxygen consumption	Decreases
Cardiac output	Mild reduction

Lactate production	Usually decreases over time

6.3. Myocardial Performance During Cooling

The interaction between therapeutic hypothermia and myocardial function remains complex.

Potential beneficial effects include:

- reduced myocardial oxygen demand,
- attenuation of oxidative stress,
- reduction in inflammatory activation,
- stabilization of cellular metabolism.

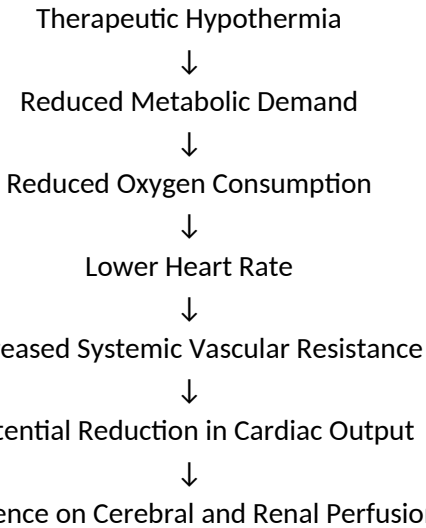
Conversely, cooling may also:

- reduce myocardial contractility,
- increase afterload,
- exacerbate pre-existing ventricular dysfunction.

Infants with significant myocardial injury may therefore exhibit haemodynamic deterioration during cooling despite apparent neurological stability.

These observations further support the role of serial functional echocardiography during therapeutic hypothermia.

Figure 11. Cardiovascular effects of therapeutic hypothermia



6.4. Renal Physiology During Cooling

Therapeutic hypothermia also influences renal function through several mechanisms.

Observed effects include:

- reduced glomerular filtration rate,
- decreased renal blood flow,
- altered tubular function,

- reduced urine output in some infants.

Although these changes may partially reflect physiological adaptation, they may also complicate the diagnosis of evolving acute kidney injury.

Interpretation of serum creatinine concentrations becomes particularly challenging during cooling because both hypothermia and renal injury influence creatinine kinetics.

6.5. Hypothermia and Drug Pharmacokinetics

Perhaps one of the most underappreciated consequences of therapeutic hypothermia is its effect on drug disposition.

Cooling alters:

- hepatic metabolism,
- renal clearance,
- protein binding,
- enzyme activity,
- tissue distribution. Consequently, infants undergoing TH frequently demonstrate reduced clearance of medications commonly used in neurocritical care.

Table 10. Medications affected by therapeutic hypothermia

Medication	Major pharmacokinetic effect
Morphine	Reduced clearance
Phenobarbital	Prolonged half-life
Midazolam	Reduced metabolism
Gentamicin	Reduced renal clearance
Amikacin	Reduced renal clearance
Vancomycin	Increased accumulation risk

These changes become even more pronounced in the presence of acute kidney injury or hepatic dysfunction.

A precision pharmacology approach may therefore become increasingly important in future neurocritical care practice.

6.6. The Rewarming Phase: An Under-Recognized Vulnerable Period

In many units, considerable attention is understandably devoted to the initiation of cooling therapy, yet experienced clinicians often regard the rewarming phase as equally deserving of vigilance.

Rewarming induces several physiological changes:

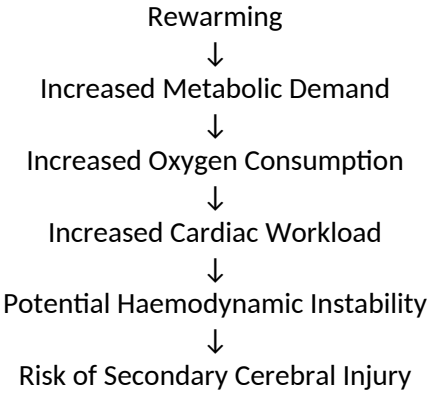
- increased metabolic demand,
- rising oxygen consumption,
- changes in vascular tone,
- alterations in cardiac output,
- shifts in fluid balance.

Rapid rewarming may theoretically contribute to:

- haemodynamic instability,
- cerebral reperfusion injury,
- seizure activity.

For these reasons, gradual and carefully monitored rewarming remains standard practice.

Figure 12. Physiological changes during rewarming



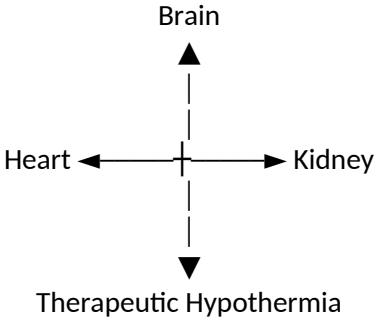
6.7. Organ Crosstalk During Cooling

Therapeutic hypothermia modifies interactions between all components of the cardio-renal-brain axis.

Examples include:
Heart → Brain : Reduced cardiac output may influence cerebral oxygen delivery.
Kidney → Brain: Reduced renal clearance alters anticonvulsant pharmacokinetics and fluid balance.
Brain → Heart: Autonomic dysregulation may contribute to cardiovascular instability.
Heart → Kidney: Reduced systemic blood flow may worsen renal perfusion.

The physiological state of each organ therefore influences the others.

Figure 13. Organ interactions during therapeutic hypothermia



6.8. The Case for Multimodal Monitoring

The complexity of these interactions challenges traditional approaches based solely on blood pressure and routine laboratory testing.

Increasingly, experts advocate multimodal monitoring involving:

- targeted neonatal echocardiography,
- cerebral NIRS,
- invasive arterial pressure monitoring,
- continuous EEG,

- renal biomarkers,
- serial lactate measurements.

Such an approach provides a more comprehensive understanding of the physiological state of the infant.

Table 11. Multimodal monitoring during therapeutic hypothermia

Monitoring modality	Organ system assessed	Potential clinical value
TnECHO	Heart	Cardiac output and ventricular function
NIRS	Brain	Cerebral oxygenation
EEG/aEEG	Brain	Seizures and cerebral function
Lactate	Global	Tissue perfusion
Troponin	Heart	Myocardial injury
NGAL	Kidney	Early AKI detection

6.9. Precision Neurocritical Care: Moving Beyond Protocols

Current cooling protocols largely apply identical management strategies to all infants meeting eligibility criteria.

Yet considerable heterogeneity exists in:

- myocardial function,
- renal reserve,
- inflammatory response,
- cerebral autoregulation,
- drug metabolism.

Future care may therefore shift toward individualized physiological targets rather than standardized treatment algorithms.

Potential components include:

- personalized blood pressure targets,
- individualized vasoactive therapy,
- biomarker-guided interventions,
- pharmacokinetic dosing models,
- AI-supported prediction tools.

6.10. Clinical Implications

Therapeutic hypothermia should no longer be viewed simply as a cooling intervention.

Rather, it represents a complex physiological state that modifies interactions among the cardiovascular, renal, and neurological systems.

Successful neuroprotection depends not only on reducing cerebral metabolism but also on maintaining systemic conditions that support recovery throughout the entire cardio-renal-brain axis.

7. Precision Neurocritical Care: The Future of HIE Management

7.1. Why Precision Medicine Matters in HIE

One of the most striking observations in neonatal neurocritical care is the considerable variability in outcomes among infants with apparently similar degrees of encephalopathy.

Two infants may:

- meet identical cooling criteria,
- have similar Apgar scores,
- demonstrate comparable MRI findings,

yet experience markedly different neurodevelopmental trajectories.

This variability reflects the biological heterogeneity of HIE itself.

Differences in:

- myocardial reserve,
- cerebral autoregulation,
- inflammatory response,
- genetic susceptibility,
- renal function,
- pharmacokinetic profiles,

may all influence recovery.

These observations have driven increasing interest in **precision neurocritical care**, an approach that seeks to tailor treatment according to the physiological characteristics of the individual infant rather than relying solely on standardized protocols.

7.2. Moving Beyond Blood Pressure Targets

Traditional haemodynamic management has often focused on maintaining arterial blood pressure above predefined thresholds.

However, blood pressure alone provides limited information regarding:

- cerebral oxygen delivery,
- systemic blood flow,
- myocardial performance,
- organ perfusion.

Future management strategies may instead aim to optimize:

- cardiac output,
- cerebral oxygen extraction,
- autoregulatory function,

- renal perfusion,
- tissue oxygenation.

The objective shifts from achieving normal numbers to maintaining optimal physiology.

Figure 14. Evolution of haemodynamic targets in neonatal HIE

Traditional Approach

Blood Pressure
↓
Treatment Decisions
Precision Approach

Cardiac Output
+ Cerebral Oxygenation
+ Autoregulation
+ Renal Function
+ Biomarkers
↓
Individualized Therapy

7.3. Targeted Neonatal Echocardiography as a Decision-Making Tool

Targeted neonatal echocardiography (TnECHO) has emerged as one of the most important advances in neonatal haemodynamic assessment.

Unlike conventional echocardiography, which primarily evaluates structural abnormalities, TnECHO focuses on functional cardiovascular physiology.

Parameters that may guide management include:

- ventricular function,
- superior vena cava flow,
- cardiac output,
- pulmonary artery pressure,
- ductal shunting,
- preload assessment.

Repeated assessments allow clinicians to identify evolving physiological changes and adjust treatment accordingly.

Table 12. Potential applications of TnECHO in HIE

Clinical question	Echocardiographic assessment
Is cardiac output adequate?	Ventricular output measurements
Is hypotension due to myocardial dysfunction?	Ventricular performance assessment
Is pulmonary hypertension present?	Pulmonary pressure estimation
Does the ductus contribute to instability?	Ductal flow pattern
Is fluid responsiveness likely?	Preload assessment

7.4. Near-Infrared Spectroscopy and Cerebral Oxygenation

Near-infrared spectroscopy offers continuous bedside monitoring of regional cerebral oxygen saturation.

Potential applications include:

- detection of occult cerebral hypoperfusion,
- assessment of oxygen extraction,
- identification of autoregulatory failure,
- evaluation of treatment response.

The combination of NIRS and echocardiography may provide valuable insight into the relationship between systemic circulation and cerebral oxygen delivery.

Figure 15. Multimodal physiological monitoring in precision neurocritical care

Targeted Echocardiography
+
Cerebral NIRS
+
Continuous EEG
+
Biomarkers
+
Laboratory Trends
+
Clinical Examination
↓
Integrated Physiological Profile
↓
Individualized Treatment Strategy

7.5. Biomarker Panels Rather Than Single Biomarkers

Current practice often relies on isolated biomarkers.

Future strategies may involve integrated biomarker panels representing multiple organ systems.

Table 13. Proposed biomarker panel for the cardio-renal-brain axis

Organ system	Biomarker	Clinical purpose
Brain	NSE	Neuronal injury
Brain	GFAP	Astrocytic injury
Heart	Troponin I	Myocardial injury
Heart	NT-proBNP	Ventricular strain
Kidney	NGAL	Early AKI detection
Kidney	Cystatin C	Renal filtration
Systemic	Lactate	Global perfusion
Inflammatory	IL-6	Systemic inflammation

7.6. Precision Pharmacology

Drug disposition in infants with HIE is highly dynamic.

Factors influencing pharmacokinetics include:

- therapeutic hypothermia,
- myocardial dysfunction,
- acute kidney injury,

- hepatic injury,
- altered protein binding.

As a result, standard dosing schedules may lead to either under-treatment or toxicity.

Future pharmacological strategies may incorporate:

- therapeutic drug monitoring,
- pharmacometric modelling,
- Bayesian dosing algorithms,
- real-time renal function assessment.

Such approaches are particularly relevant for anticonvulsants, sedatives, and antimicrobials.

7.7. Artificial Intelligence and Predictive Analytics

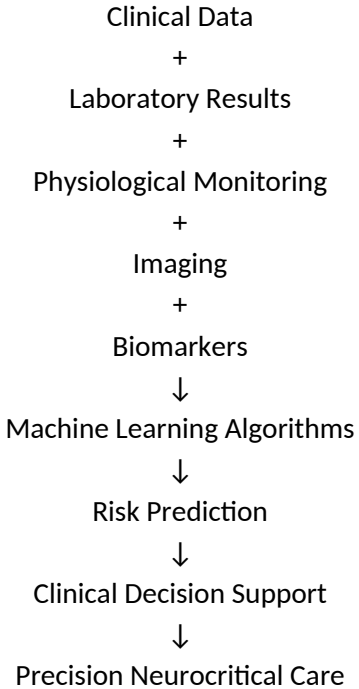
Artificial intelligence has generated considerable excitement within critical care medicine, although its eventual role within neonatal practice remains to be fully defined

Potential applications in HIE include:

- prediction of haemodynamic deterioration,
- seizure forecasting,
- individualized cooling strategies,
- risk stratification,
- outcome prediction.

One potential advantage of machine learning approaches lies in their ability to identify complex physiological patterns that are difficult for clinicians to recognize in real time.

Figure 16. Artificial intelligence within the cardio-renal-brain axis



7.8. The Emerging Concept of the Digital Twin

Although still largely confined to research environments, the concept of the digital twin offers an intriguing glimpse into the future of individualized intensive care.

A digital twin is a virtual physiological model of an individual patient that continuously updates using real-time clinical data.

In theory, such systems could simulate:

- haemodynamic responses,
- drug pharmacokinetics,
- cerebral oxygen delivery,
- responses to interventions.

Clinicians could therefore test therapeutic strategies within a virtual environment before applying them to the patient.

Although currently experimental, this technology may eventually redefine individualized neonatal care.

7.9. Challenges to Implementation

Several barriers remain before precision neurocritical care becomes routine practice.

These include:

- limited availability of TnECHO expertise,
- lack of standardized cerebral perfusion targets,
- cost of advanced monitoring,
- insufficient validation of biomarkers,
- data integration challenges.

Multicentre collaborative research will be essential to address these limitations.

Table 14. Barriers to implementation of precision neurocritical care

Challenge	Potential solution
Limited expertise	Training programmes
Cost of monitoring	Technology development
Data overload	AI-assisted interpretation
Lack of evidence	Prospective trials
Variable practice patterns	Consensus guidelines

7.10. A New Philosophy of Care

Perhaps the greatest contribution of precision neurocritical care lies not in technology itself but in the change in clinical philosophy that accompanies it.

The question is no longer:

"Is the blood pressure normal?"

but rather:

"Is this infant receiving the physiological support required for neurological recovery?"

This represents a subtle but profound shift in the way clinicians approach neonatal brain injury.

8. Future Directions and Research Priorities

8.1. The Need for a Paradigm Shift

The success of therapeutic hypothermia has undoubtedly transformed neonatal care, yet it has also exposed the limitations of our current understanding of HIE. Despite standardized cooling protocols and improvements in neonatal intensive care, a substantial proportion of affected infants continue to experience death or significant neurodevelopmental impairment.

These observations suggest that neuroprotection alone may not be sufficient.

Future progress will likely depend upon a broader physiological approach that recognizes the interconnected nature of cerebral, cardiovascular, and renal function following perinatal hypoxia-ischaemia.

The emerging cardio-renal-brain axis provides a framework for this transition.

8.2. Defining Optimal Haemodynamic Targets

One of the most important unanswered questions in neonatal neurocritical care concerns haemodynamic goals.

Current practice often relies on arbitrary blood pressure thresholds derived from gestational age or birth weight.

However, these values may not accurately reflect:

- cerebral blood flow,
- systemic oxygen delivery,
- autoregulatory status,
- myocardial performance.

Future studies should attempt to define:

- optimal cardiac output targets,
- individualized cerebral perfusion thresholds,
- organ-specific oxygen delivery requirements,
- haemodynamic parameters associated with improved neurodevelopmental outcomes.

Table 15. Key unanswered haemodynamic questions in HIE

Clinical Question	Current Status
What is the optimal blood pressure target?	Unknown
Should treatment target cardiac output rather than blood pressure?	Under investigation
Can cerebral oxygenation guide vasoactive therapy?	Promising but unproven
How should pulmonary hypertension influence haemodynamic targets?	Limited evidence
Can multimodal monitoring improve outcomes?	Requires prospective

	trials

8.3. Validation of Biomarkers Across the Cardio-Renal-Brain Axis

Although numerous biomarkers have shown promise individually, few have been validated as components of an integrated physiological model.

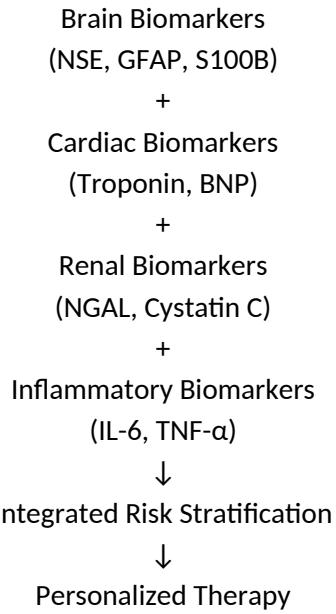
Future research priorities include:

- combining neurological and extracerebral biomarkers,
- developing risk stratification algorithms,
- identifying early predictors of deterioration,
- evaluating response to therapy.

The ideal biomarker panel would provide real-time information regarding:

- neuronal injury,
- myocardial function,
- renal injury,
- inflammation,
- systemic perfusion.

Figure 17. Proposed integrated biomarker model



8.4. The Search for Individualized Neuroprotection

Therapeutic hypothermia represents a uniform intervention applied to a biologically heterogeneous population.

Future approaches may involve tailoring therapy according to:

- severity of encephalopathy,
- haemodynamic profile,

- inflammatory phenotype,
- biomarker expression,
- genetic susceptibility.

Potential individualized interventions may include:

- optimized vasoactive support,
- precision anticonvulsant dosing,
- targeted anti-inflammatory therapies,
- adjunctive neuroprotective agents.

Such strategies move beyond protocol-based treatment toward true precision medicine.

8.5. Artificial Intelligence and Clinical Decision Support

Modern neonatal intensive care units generate enormous quantities of physiological data.

These include:

- heart rate trends,
- blood pressure waveforms,
- oxygen saturation patterns,
- EEG signals,
- laboratory results,
- echocardiographic measurements.

Human clinicians may struggle to integrate these data streams in real time.

Artificial intelligence offers the possibility of:

- detecting subtle physiological deterioration,
- predicting haemodynamic instability,
- identifying early seizure activity,
- estimating neurodevelopmental risk.

Importantly, AI should be viewed as a clinical support tool rather than a replacement for clinical judgment.

8.6. Development of a Neonatal Cardio-Renal-Brain Score

One potential future direction involves creation of a composite physiological score incorporating:

Cardiovascular variables

- cardiac output,
- ventricular function,
- troponin levels.

Renal variables

- urine output,
- NGAL,
- creatinine trends.

Neurological variables

- aEEG findings,
- cerebral NIRS,
- neurological examination.

Such a score may provide a more comprehensive assessment of disease severity than existing neurological staging systems alone.

Table 16. Proposed components of a neonatal cardio-renal-brain score

Domain	Example Variables
Cardiac	Cardiac output, troponin, ventricular function
Renal	Creatinine, NGAL, urine output
Cerebral	aEEG, NIRS, MRI findings
Systemic	Lactate, inflammatory markers

8.7. Multicentre Collaboration and Standardization

The rarity of severe HIE within individual centres presents important research challenges.

Progress will require:

- international collaboration,
- standardized definitions,
- harmonized monitoring protocols,
- shared databases.

Large multicentre studies will be essential for validating emerging technologies and determining their impact on long-term outcomes.

8.8. Beyond Survival: A Broader Definition of Success

Historically, studies in HIE have focused primarily on mortality and severe disability.

Future research should also consider:

- cognitive outcomes,
- executive function,
- behaviour,
- quality of life,
- cardiovascular health,
- renal function.

The concept of survivorship in neonatology continues to evolve.

Protecting the brain remains essential, but preserving lifelong health across multiple organ systems may become equally important.

Figure 18. The future vision of neonatal precision neurocritical care

Multimodal Monitoring
+
Biomarkers
+
Targeted Echocardiography
+
Artificial Intelligence
+
Precision Pharmacology
↓
Individualized Physiological Support
↓
Improved Long-Term Outcomes

9. Conclusion

Hypoxic-ischaemic encephalopathy has traditionally been regarded as a disease of the brain. Increasing evidence, however, suggests that this perspective is incomplete.

Perinatal hypoxia-ischaemia initiates a complex multisystem response involving the heart, kidneys, and brain, with each organ influencing the function and recovery of the others through haemodynamic, metabolic, inflammatory, and neurohumoral pathways.

Myocardial dysfunction may compromise cerebral perfusion during the vulnerable period of secondary energy failure, while acute kidney injury contributes to metabolic instability, altered pharmacokinetics, and systemic inflammation. Therapeutic hypothermia, although neuroprotective, further modifies these interactions by altering cardiovascular physiology and renal function.

Recognition of this interconnected physiology supports the emergence of the neonatal cardio-renal-brain axis as a new conceptual framework for understanding HIE.

The implications are profound. Management strategies based solely on blood pressure targets or neurological examination may fail to capture the complexity of the critically ill infant undergoing neuroprotective care. Future progress is likely to depend upon integrated physiological monitoring, multimodal biomarkers, precision pharmacology, and individualized haemodynamic support.

The future of neonatal neurocritical care may therefore lie not in treating the injured brain in isolation, but in preserving the integrity of the physiological network that sustains cerebral recovery.

9.1. Practical Bedside Implications for the Neonatologist

The recognition of a neonatal cardio-renal-brain axis carries implications that extend beyond physiology and into everyday clinical practice. Although many of the concepts discussed in this review remain under active investigation, several practical principles can already be incorporated into contemporary neonatal neurocritical care.

9.1.1. Look Beyond Blood Pressure

For decades, blood pressure has served as the principal haemodynamic target in infants with HIE. However, arterial pressure alone provides limited insight into systemic blood flow or cerebral oxygen delivery.

Particular caution should be exercised in infants who demonstrate:

- persistent metabolic acidosis,
- prolonged capillary refill,
- oliguria,
- elevated lactate concentrations,
- increasing inotropic requirements,

despite apparently acceptable blood pressure values.

In such situations, occult low cardiac output should be considered.

9.1.2. Consider Early Functional Echocardiography

Targeted neonatal echocardiography may identify important haemodynamic abnormalities that are not evident on routine clinical assessment.

Potential indications include:

- unexplained metabolic acidosis,
- hypotension resistant to volume expansion,
- suspected pulmonary hypertension,
- persistent oliguria,
- rising lactate concentrations,
- significant oxygen requirement during cooling.

Serial assessments may provide greater clinical value than isolated examinations because cardiovascular physiology evolves rapidly during the first 72 hours following injury.

9.1.3. Renal Function Requires Active Surveillance

Renal dysfunction frequently develops early in the course of neonatal encephalopathy and may remain clinically silent during the initial phase of illness.

Routine assessment should include:

- hourly urine output monitoring,
- daily renal biochemistry,
- review of nephrotoxic medications,
- consideration of therapeutic drug monitoring when appropriate.

Particular attention should be paid during therapeutic hypothermia, when changes in renal clearance may significantly alter drug exposure.

9.1.4. Cooling Is Not a Physiological Steady State

Therapeutic hypothermia alters cardiovascular, renal, metabolic, and pharmacological physiology.

Bradycardia during cooling should be interpreted within the clinical context and should not automatically trigger intervention in otherwise stable infants.

Similarly, reductions in urine output or changes in serum creatinine should be interpreted cautiously during cooling and rewarming.

Clinical trends often provide more useful information than isolated measurements.

9.1.5. The Rewarming Phase Deserves Equal Vigilance

The period of rewarming is sometimes viewed as the conclusion of active neurocritical care.

In reality, important physiological changes continue to occur during this stage.

Clinicians should remain alert for:

- haemodynamic instability,
- seizure activity,
- worsening pulmonary hypertension,
- changes in urine output,
- increasing lactate concentrations.

Careful observation during rewarming may be as important as monitoring during the cooling phase itself.

9.1.6. Multimodal Monitoring Is Likely to Become Standard Practice

No single physiological parameter adequately reflects the complexity of HIE.

Increasingly, management decisions may rely upon integration of multiple sources of information including:

- clinical examination,
- invasive blood pressure monitoring,
- lactate trends,
- targeted echocardiography,
- cerebral NIRS,
- EEG monitoring,
- cardiac biomarkers,
- renal biomarkers.

The future of neonatal neurocritical care is likely to depend upon the interpretation of these physiological signals as an integrated system rather than as isolated variables.

Table 5. Therapeutic Interventions Targeting the Cardio-Renal-Brain Axis in Neonatal HIE

Domain	Intervention	Mechanism / Rationale	Key Clinical Considerations
Cardiac Support	• Volume optimization • Inotropes (e.g., dopamine, dobutamine) • Vasopressors (e.g., norepinephrine) • Pulmonary vasodilators (e.g., inhaled NO)	• Improve preload and stroke volume • Enhance myocardial contractility and cardiac output • Maintain systemic vascular resistance and perfusion • Reduce pulmonary vascular resistance and improve oxygenation	• Avoid both hypovolemia and fluid overload • Titrate to achieve perfusion targets (lactate, urine output, MAP) • Monitor for arrhythmias, hypotension • Consider echocardiography guidance
Renal Protection	• Maintain adequate renal perfusion • Avoid nephrotoxic drugs • Optimize fluid and electrolyte balance • Consider diuretics (if fluid overload) • Renal replacement therapy (RRT)*	• Preserve GFR and renal blood flow • Prevent further tubular injury • Maintain electrolyte and acid–base homeostasis • Remove toxins and excess fluid when indicated	• Monitor urine output hourly • Monitor serum creatinine, electrolytes • Adjust drug dosing for renal function • Early nephrology consultation in severe AKI
Neuroprotection & Neuro-management	• Therapeutic hypothermia (33–34°C) • Seizure control (phenobarbital, levetiracetam) • Optimize cerebral oxygenation and perfusion • Glucose management • Avoid hyperoxia and hypercarbia	• Reduce metabolic demand and limit secondary injury • Reduce excitotoxicity and neuronal damage • Maintain cerebral autoregulation and oxygen delivery • Prevent hypo-/hyperglycemia injury • Prevent oxidatvie stress and cerebral vasoconstriction	• Start cooling within 6 h of birth • Continuous EEG/aEEG monitoring • Use NIRS to guide cerebral oxygenation (rSO_2 55–85%) • Maintain normoglycemia (3.5–10 mmol/L) • Maintain $PaCO_2$ 40–60 mmHg
Systemic Support	• Maintain normothermia after rewarming • Optimize oxygenation and ventilation • Treat acidosis and coagulopathy • Infection prevention and control • Nutrition support (early parenteral, then enteral)	• Support overall homeostasis • Ensure adequate tissue oxygenation • Prevent further organ dysfunction • Reduce inflammation and secondary injury • Promote growth and recovery	• Gentle ventilation strategy • Target SpO_2 92–97% • Correct metabolic acidosis • Strict aseptic technique, early antibiotics if indicated • Individualize nutrition based on tolerance

Note: Management should be individualized based on severity of HIE, gestational age, comorbidities, and response to therapy. A multidisciplinary approach is essential for optimizing outcomes.

** Indications for RRT in neonates: severe AKI with fluid overload, refractory electrolyte abnormallities, severe acidosis, or uremic complications.*
Abbreviations: HIE, hypoxic-ischemic encephalopathy; GFR, glomerular filtration rate; AKI, acute kidney injury; RRT, renal replacement therapy; MAP, mean arterial pressure; rSO_2, regional cerebral oxygen saturation; aEEG, amplitude-integrated EEG; $PaCO_2$, arterial partial pressure of carbon dioxide.

Table 17. Suggested bedside assessment of the cardio-renal-brain axis in neonatal HIE

Domain	Assessment Tool	Suggested Frequency
Cardiovascular	Clinical perfusion assessment	Continuous
Cardiovascular	TnECHO	At admission and as clinically indicated
Cardiovascular	Lactate	Every 6–12 hours
Neurological	Neurological examination	Every 4–6 hours
Neurological	aEEG/EEG	Continuous during cooling
Neurological	Cerebral NIRS	Continuous if available
Renal	Urine output	Hourly
Renal	Serum creatinine and electrolytes	Daily
Renal	Renal biomarkers (where available)	According to local practice

9.1.7. A Change in Clinical Perspective

Perhaps the most important implication of the cardio-renal-brain axis is conceptual rather than technological.

The question facing the clinician is no longer simply:

"Has the infant met criteria for therapeutic hypothermia?"

but increasingly:

"Are we providing the physiological conditions required for cerebral recovery?"

This subtle shift in perspective may ultimately prove to be one of the most important developments in neonatal neurocritical care over the coming decade.

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