

*“Kids are made to heal.
Their bodies are more resilient,
more adaptive,
and far more able to withstand acute stress.”*

Newman K. *Healing Children.*

New York, Scribner; 2016.

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**“Multimodal Neuromonitoring and Cerebral Autoregulation Assessment
in Neonatal and Pediatric Intensive Care”**

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SECTION I - Multimodal Neuromonitoring in Pediatric Critical Care

Chapter 1. Neurologic assessment in Pediatric Critical Care: a multi-modal approach

1.1 Brain Health and Neurological Risk in Pediatric Critical Illness

Contemporary pediatric neurocritical care is grounded in the recognition that neurological injury during critical illness emerges through dynamic and interacting physiological processes rather than as a single, static event. International consensus statements on multimodal neuromonitoring emphasize that no individual measurement can adequately characterize cerebral function in critically ill patients and that optimal neurological care depends on the integrated interpretation of signals reflecting cerebral perfusion, oxygenation, electrical activity, pressure dynamics, and metabolism. This conceptual framework, initially developed within adult neurocritical care, has enabled earlier recognition of secondary brain injury and supported the adoption of physiology-guided interventions aimed at preventing irreversible damage. (1) As these principles have matured, increasing attention has been directed toward their applicability in pediatric critical care. The developing brain differs fundamentally from the adult brain in terms of metabolic demand, vascular regulation, and susceptibility to systemic disturbances. In addition, neurological assessment in children is frequently confounded by sedation, mechanical ventilation, neuromuscular blockade, and developmental immaturity. Consequently, pediatric neurocritical care has progressively incorporated continuous neuromonitoring strategies to elucidate how systemic instability, disease-specific processes, and therapeutic interventions influence cerebral physiology during critical periods of brain development.

Over the past two decades, advances in pediatric intensive care have led to substantial improvements in survival among critically ill neonates and children. As mortality has declined, the definition of successful intensive care has evolved from short-term survival toward preservation of long-term neurological and neurodevelopmental health. (Fig.1) This shift reflects growing recognition that critical illness, even when not primarily neurological in origin, may exert lasting effects on brain development and function. (2)

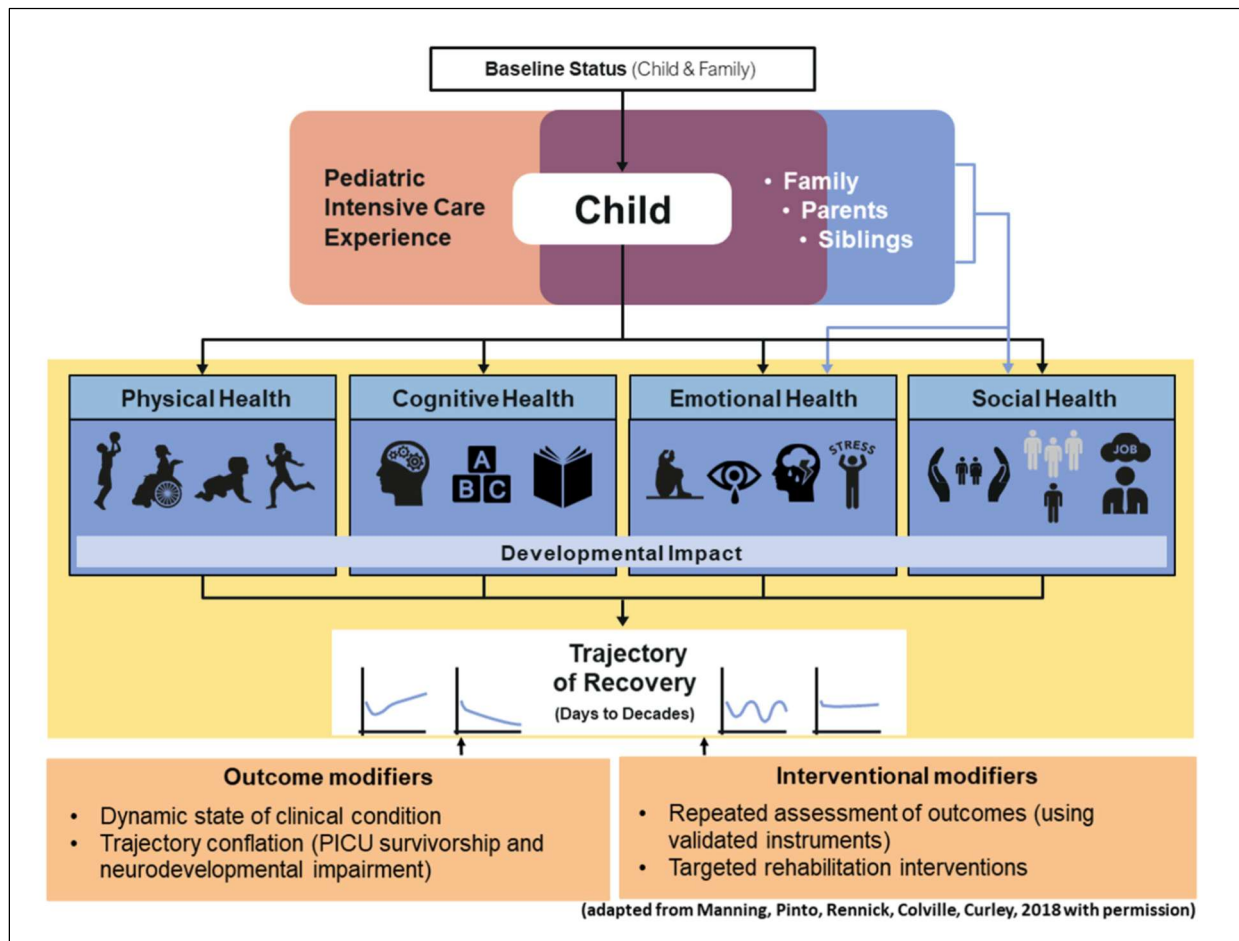


Fig. 1 Adapted from: Brown KL et al. Intensive Care Med, 2022 (original from Manning et al, 2018)

Epidemiological studies indicate that primary neurological disorders account for approximately 11–16% of pediatric intensive care unit admissions across North America, Europe, and Australia. These include conditions such as severe traumatic brain injury, cardiac arrest, stroke, central nervous system infections, and hypoxic-ischemic brain injury. However, multicenter investigations, including the PANGAEA study, have demonstrated that a substantially larger proportion of critically ill children are exposed to secondary neurological insults arising from hypoxemia, hemodynamic instability, systemic inflammation, metabolic derangements, and iatrogenic factors. Even in the absence of overt structural injury, such exposures have been associated with acute encephalopathy, delirium, and longer-term cognitive and behavioral sequelae. (3)

Within this broader framework, the concept of Post-Intensive Care Syndrome in pediatrics (PICS-p) has provided a unifying model for understanding the long-term consequences of pediatric critical illness. PICS-p encompasses persistent impairments across physical, emotional, cognitive, and social domains and affects both children and their families. Importantly, neurodevelopmental consequences may not be evident at hospital discharge and often emerge only as developmental demands increase with age, underscoring the importance of early identification of neurological risk and structured longitudinal follow-up. (4)

1.2 Developmental Considerations and High-Risk Pediatric Populations

Neurological risk during critical illness is not uniformly distributed across pediatric populations. Neonates and young infants, in particular, exhibit unique developmental characteristics that modulate cerebral physiology and influence susceptibility to injury. Among these groups, infants with complex congenital heart disease (CHD) represent one of the most extensively studied populations with respect to adverse neurodevelopmental outcomes.

Up to 20% of children undergoing congenital heart surgery experience neurological morbidity, reflecting the combined influence of pre-existing abnormalities in brain development and perioperative physiological stressors. A growing body of evidence indicates that many infants with critical CHD demonstrate altered brain maturation already in utero, including delayed cortical folding, impaired white matter microstructure, and reduced cerebral growth. These findings are attributed to a convergence of genetic factors, abnormal fetal circulation, chronic hypoxemia, and impaired cerebrovascular regulation. (5)

Studies of fetal cerebral physiology have shown that fetuses with severe CHD frequently exhibit reduced cerebral oxygen consumption and adaptive cerebral vasodilation, consistent with chronic alterations in oxygen delivery and utilization. These prenatal adaptations may preserve short-term cerebral perfusion but appear insufficient to support normal brain maturation, thereby establishing a substrate for subsequent injury. (6)

The perioperative period introduces additional challenges. Cardiopulmonary bypass is associated with ischemia-reperfusion injury, embolic phenomena, inflammatory activation, and fluctuations in cerebral perfusion and oxygenation. Postoperative low cardiac output syndrome, together with exposure to sedative, anesthetic, and vasoactive agents, further perturbs cerebral homeostasis. Consequently, even in the setting of successful cardiac repair, long-term neurodevelopmental impairments remain common, particularly in executive function, processing speed, attention, and visuospatial abilities. (7)

Other neonatal populations share comparable developmental constraints. Premature infants exhibit immature autonomic and vascular regulatory mechanisms, rendering cerebral blood flow highly sensitive to changes in arterial pressure, carbon dioxide tension, and oxygenation. This instability contributes to the risk of intraventricular hemorrhage, white matter injury, and later cognitive or motor impairment. Similarly, infants with hypoxic–ischemic encephalopathy experience profound disturbances in cerebral perfusion and autoregulatory capacity, which are closely linked to secondary energy failure and evolving abnormalities on neuroimaging.

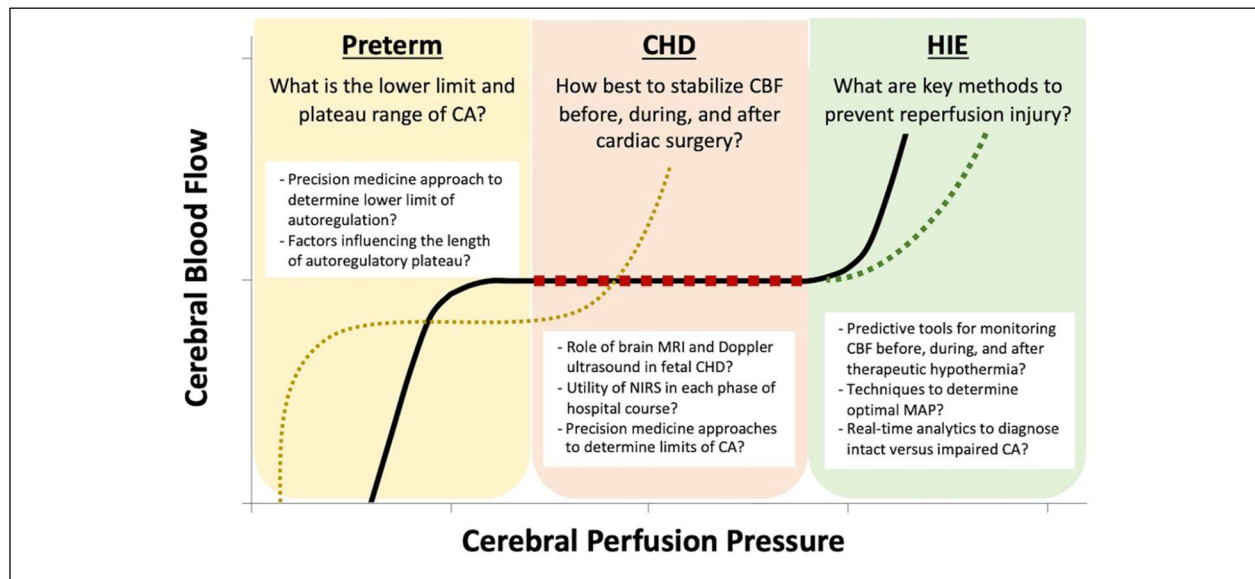


Fig.2 Adapted from: Leon RL, et al. Front Pediatr, 2022.

Collectively, these observations highlight that early life represents a period during which disturbances in cerebral perfusion, oxygen delivery, or autoregulatory function may have enduring consequences. Recognition of these developmental considerations is essential for guiding neuromonitoring strategies and informing neuroprotective approaches tailored to high-risk pediatric populations. (8)

1.3 Clinical Neurological Assessment and Structural Neuroimaging

Accurate neurological assessment remains a cornerstone of pediatric critical care; however, obtaining a reliable bedside examination is intrinsically challenging in critically ill children. Sedation and analgesia, invasive and noninvasive mechanical ventilation, neuromuscular

blockade, and fluctuating systemic physiology can obscure level of consciousness, tone, brainstem reflexes, and spontaneous motor activity. In addition, pre-existing neurodevelopmental conditions, postoperative states, and intercurrent metabolic derangements may further reduce the specificity of clinical signs. Importantly, neurological deterioration in the PICU often presents with subtle and nonspecific changes in behavior, arousal, pupillary reactivity, or ventilatory drive, rather than with discrete focal deficits. Serial examinations may also be affected by variability in examiner expertise, differences in documentation practices, and shifts in staffing, all of which can reduce sensitivity for early detection of evolving injury.

Standardized instruments, including the pediatric modified Glasgow Coma Scale, AVPU scale, and pediatric FOUR score, provide structured approaches to neurological assessment and facilitate communication across teams. Nonetheless, these tools retain important limitations in intubated patients, in infants and young children with limited language mediated responses, and in patients with developmental immaturity or baseline disability. In this context, more comprehensive bedside tools designed for longitudinal screening have gained increasing relevance. The Serial Neurologic Assessment in Pediatrics (SNAP) was developed to improve consistency of assessments across providers and to enhance recognition of clinically meaningful neurological change in the PICU environment. In validation work, SNAP demonstrated feasibility, strong interrater reliability, and high protocol adherence when implemented by critical care nurses, supporting its potential role as a standardized framework for serial surveillance in populations where the conventional examination is constrained. (9)

Structural neuroimaging provides essential complementary information by defining anatomical injury patterns, supporting time sensitive decision making, and informing prognostication. Computed tomography remains indispensable for rapid identification of intracranial hemorrhage, mass effect, hydrocephalus, and other lesions that may require urgent intervention, particularly in traumatic brain injury and acute neurosurgical emergencies. Magnetic resonance imaging offers superior sensitivity for diffuse axonal injury, posterior fossa pathology, ischemia, white matter abnormalities, and a range of inflammatory, infectious, or metabolic disturbances, thereby refining diagnostic accuracy and strengthening mechanistic interpretation. However, CT and MRI provide episodic snapshots of a dynamic pathophysiological process and are limited by practical considerations that are especially relevant in the PICU. These include the need for intrahospital transport, the risks introduced by physiologic instability, the requirement for MRI compatible monitoring and support equipment, and the competing demands of scanner availability. CT also entails exposure to ionizing radiation, reinforcing the importance of stewardship and indication-based use.

Current practice further illustrates that the timing, frequency, and modality of neuroimaging are often heterogeneous and influenced by institutional resources and clinical context. For example,

multicenter data in pediatric in hospital cardiac arrest demonstrate substantial site level variation in the selection and timing of neuroimaging modalities, and highlight associations between imaging utilization and factors reflecting illness severity and concurrent neurodiagnostic monitoring. (10)

Similarly, in severe pediatric traumatic brain injury, survey-based evidence indicates that MRI is frequently obtained during acute hospitalization despite limited consensus regarding optimal timing and sequence composition, underscoring the persistent gap between technological capability and evidence-based standardization. Advanced MRI techniques, including arterial spin labeling, diffusion tensor imaging, susceptibility weighted imaging, and MR spectroscopy, can provide added physiological and microstructural insight, but they remain constrained to discrete time points and are not universally available in routine care. (11)

Accordingly, structural imaging should be conceptualized as an anchoring modality that defines anatomical substrates of injury, supports differential diagnosis, and contextualizes physiological data. In contemporary PICU practice, the highest clinical value is often achieved when neuroimaging is integrated with serial standardized bedside examinations and continuous multimodal neuromonitoring, rather than positioned as a substitute for longitudinal physiologic assessment. This integrated approach enables clinicians to reconcile structural injury patterns with evolving cerebral physiology, refine individualized risk assessment, and strengthen clinical decision making across the trajectory of critical illness.

1.4 Multimodal Neuromonitoring as a Physiological Framework

In response to the limitations of clinical examination and episodic imaging, pediatric neurocritical care has increasingly embraced a multimodal, physiology-centered approach to neuromonitoring. Multimodal neuromonitoring refers not merely to the concurrent use of multiple devices but to the integration of diverse physiological signals into a coherent interpretation of cerebral function.

As will be discussed in detail in the subsequent chapters of this work, contemporary pediatric intensive care practice incorporates a broad array of invasive and noninvasive neuromonitoring techniques. Continuous electroencephalography enables real-time assessment of cortical electrical activity and supports the detection of electrographic seizures in the absence of overt clinical correlates. Near infrared spectroscopy provides bedside, noninvasive monitoring of cerebral oxygenation and, when integrated with correlation-based analytical approaches, permits assessment of cerebrovascular autoregulation. Advanced hemodynamic monitoring supplies essential information on systemic perfusion and cardiovascular support, while

transcranial Doppler ultrasonography and automated pupillometry offer complementary insights into cerebral blood flow dynamics and brainstem function, respectively. Laboratory parameters and circulating biomarkers further augment these modalities by capturing metabolic, inflammatory, and injury-related processes that influence cerebral physiology. (2)

Central to this framework is recognition that neurological injury evolves over time and is strongly influenced by systemic physiology. (Fig.3)

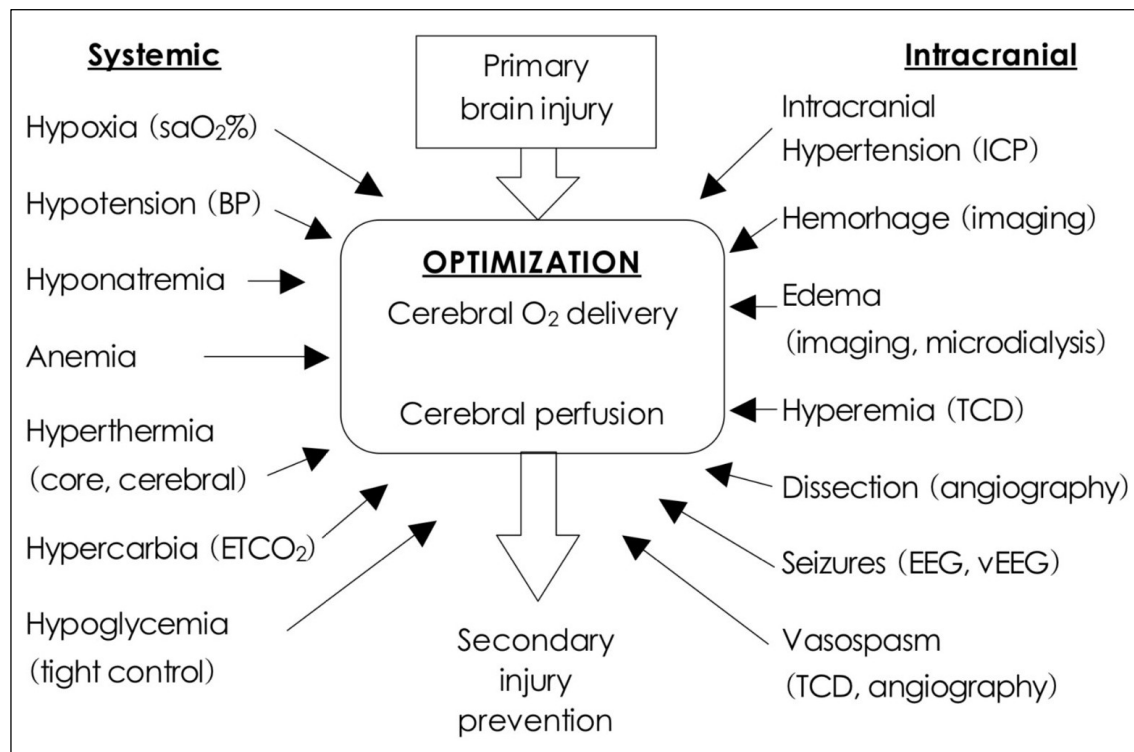


Fig.3 Adapted from: Glickman SG, et al. J Neurocrit Care, 2008.

Continuous multimodal monitoring enables early identification of maladaptive trends, such as impaired autoregulation, declining oxygen delivery, or emerging electrical instability, often preceding overt clinical deterioration. This approach supports individualized, physiology-guided management strategies that move beyond fixed thresholds toward patient-specific targets for blood pressure, ventilation, oxygen delivery, sedation, and extracorporeal support.

International consensus statements emphasize that the value of neuromonitoring lies not in the presence of individual devices but in the integration, interpretation, and clinical response to multimodal data streams. (12)

1.5 Current Limitations and the Need for Individualized Physiological Targets

Despite technological advances and increasing adoption, several challenges limit the impact of neuromonitoring in pediatric critical care. There is no universally accepted framework defining which patients should undergo specific monitoring modalities, at what time points, or according to which clinical criteria. As a result, practice varies widely across institutions and healthcare systems.

Cerebrovascular autoregulation monitoring exemplifies both the promise and the current translational limitations of advanced neuromonitoring in pediatric critical care. Cerebral autoregulation represents a fundamental physiological mechanism that maintains relatively stable cerebral blood flow across a range of cerebral perfusion pressures, thereby protecting the brain from ischemic injury during hypoperfusion and from vascular and metabolic stress during hyperperfusion. Over recent decades, substantial investigative efforts have focused on defining the systemic blood pressure ranges and clinical conditions over which the cerebral vasculature dynamically adapts intracranial hemodynamics to preserve perfusion, particularly in vulnerable populations such as children with congenital heart disease, traumatic brain injury, and survivors of cardiac arrest. (13 - 15)

Observational and exploratory prospective studies have consistently demonstrated associations between impaired autoregulation, deviations from individualized optimal perfusion pressures, and adverse neurological outcomes across multiple disease states. These findings highlight the strong physiological plausibility and clinical appeal of autoregulation informed management strategies and have driven significant technological advances in continuous monitoring techniques. Contemporary approaches now permit real time estimation of autoregulatory function using multimodal signal acquisition and correlation based or model driven analytical frameworks in both intraoperative and intensive care settings. Importantly, these developments have also contributed to a more refined understanding of secondary brain injury mechanisms, emphasizing the dynamic and individualized nature of cerebrovascular vulnerability during critical illness.

Despite these advances, the translation of cerebral autoregulation monitoring into routine clinical decision making remains limited. To date, proposed interventions aimed at optimizing autoregulatory status have not demonstrated consistent or robust clinical benefit. Several factors likely contribute to this gap, including heterogeneity in monitoring methodologies, variability in analytical assumptions and thresholds, limited standardization across platforms, and challenges in accurately capturing autoregulatory behavior under rapidly changing physiological conditions.

Most critically, high quality interventional trials designed to test autoregulation guided therapeutic strategies are scarce, and existing studies have been insufficient to support outcome driven recommendations. (16)

In parallel, important infrastructural barriers persist. Many pediatric intensive care units lack integrated systems capable of synchronizing, analyzing, and displaying multimodal physiological data in real time. Consequently, clinicians are often required to manually synthesize high frequency data streams, increasing cognitive burden and limiting timely recognition of clinically meaningful patterns. While advanced analytics and machine learning-based approaches offer promising solutions to these challenges, their implementation remains largely confined to research environments and has not yet been incorporated into standardized clinical workflows.

Finally, the absence of consistent long term neurodevelopmental follow up further limits the ability to link acute autoregulatory disturbances with meaningful patient centered outcomes. Although initiatives focused on pediatric core outcome sets represent important progress toward harmonized assessment, validated tools and structured longitudinal follow up pathways remain inconsistently applied. Addressing these gaps will require coordinated clinical development efforts, improved methodological standardization, and rigorously designed trials that evaluate whether physiology guided, autoregulation informed management strategies can meaningfully improve both short term neurological stability and long-term neurodevelopmental outcomes.

Chapter 2. Multi-modal Neuromonitoring at the bedside: tools and techniques

2.1 Intensive Care Unit Monitoring: Standards and Open Debate

Despite substantial advances in clinical assessment and neuroimaging, significant gaps remain in the ability to continuously characterize cerebral physiology in critically ill children. These limitations underscore a broader challenge in contemporary intensive care, namely the reliance on isolated physiological targets to guide therapy in systems characterized by marked interindividual variability and rapid temporal change. Within this context, monitoring strategies aimed at supporting individualized care have gained increasing attention. Hemodynamic monitoring represents a central component of this paradigm, as systemic perfusion is a prerequisite for adequate cerebral blood flow and oxygen delivery, yet it provides only a partial representation of cerebral physiological status.

In current pediatric intensive care practice, arterial blood pressure remains the most commonly used indicator of circulatory adequacy. However, consensus statements emphasize that the evidence supporting specific blood pressure thresholds in children is limited and largely

extrapolated from expert opinion rather than outcome driven trials. Developmental variability in cardiovascular physiology, age dependent differences in vascular tone and cardiac output, and technique related measurement limitations all complicate the interpretation of arterial pressure values. Moreover, arterial blood pressure alone does not reliably reflect systemic oxygen delivery or regional perfusion, particularly at the level of the brain.

Recent consensus documents from international pediatric critical care societies have explicitly cautioned against the use of arterial blood pressure as an isolated therapeutic target. Instead, blood pressure should be interpreted within a broader clinical and physiological context that includes markers of systemic perfusion and cardiovascular performance such as lactate concentration, capillary refill time, venous oxygen saturation, and echocardiographic indices. Importantly, noninvasive brain-specific monitoring modalities, including near infrared spectroscopy, are increasingly recognized as complementary tools that may provide insight into the cerebral consequences of systemic hemodynamic disturbances. (17)

Despite this multimodal framework, defining optimal perfusion goals in critically ill children remains challenging. Randomized studies evaluating specific blood pressure or perfusion targets are scarce, and the relationship between systemic hemodynamics and cerebral perfusion is highly variable across disease states. This uncertainty is particularly relevant in neurologically vulnerable populations, in whom cerebral perfusion pressure and cerebrovascular reserve are critical determinants of outcome. In such settings, interventions aimed at normalizing systemic hemodynamic variables may fail to address ongoing cerebral hypoperfusion or hyperemia.

Collectively, these considerations highlight the limitations of single parameter hemodynamic monitoring and reinforce the need for approaches that more directly interrogate cerebral physiology. This need provides the conceptual transition from conventional intensive care monitoring toward multimodal neuromonitoring strategies that integrate systemic and brain specific signals to better characterize cerebral perfusion and vulnerability.

2.2 Multimodal Monitoring Tools to Define Cerebral Perfusion Status

Cerebral perfusion is governed by complex interactions among systemic hemodynamics, intracranial pressure, cerebrovascular resistance, autoregulatory capacity, oxygen delivery, and metabolic demand. No single physiological variable can adequately capture these interactions, particularly in the developing brain. As a result, reliance on isolated metrics risks oversimplifying a highly dynamic and individualized process.

Multimodal neuromonitoring seeks to address this limitation by combining complementary techniques that provide information on different aspects of cerebral physiology. Rather than replacing traditional monitoring, this approach builds upon existing standards by contextualizing systemic variables within brain specific measurements. In adult neurocritical care, multimodal monitoring has demonstrated utility in detecting evolving secondary brain injury and in supporting physiology informed therapeutic adjustments. Pediatric applications, although less mature, suggest similar potential. (18)

Infants and children exhibit distinctive neurophysiological characteristics that increase susceptibility to perfusion related injury. These include limited intracranial compliance, developmental immaturity of cerebrovascular autoregulation, and relatively high cerebral metabolic requirements. Together, these features narrow the margin of safety for both hypoperfusion and hyperperfusion and limit the reliability of systemic surrogates of cerebral blood flow. Multimodal approaches are therefore particularly relevant in pediatric populations, where individualized assessment of cerebral perfusion status is essential.

In this framework, multimodal neuromonitoring is best understood not as a collection of independent technologies, but as an integrated strategy aimed at capturing the dynamic interplay between systemic and cerebral physiology. The following sections describe the principal modalities currently used at the bedside and their respective contributions to the assessment of cerebral perfusion, oxygenation, autoregulatory function, and neural integrity.

2.2.1 Intracranial Pressure Monitoring

Intracranial pressure (ICP) monitoring remains a cornerstone of pediatric neurocritical care, particularly in conditions characterized by reduced intracranial compliance and risk of secondary brain injury. Persistent intracranial hypertension is consistently associated with unfavorable outcomes in pediatric traumatic brain injury and other acute neurological disorders, reflecting the central role of pressure mediated reductions in perfusion and tissue oxygenation. Beyond a single numerical value, ICP monitoring provides clinically actionable information regarding intracranial compliance, the evolution of cerebral edema, and the risk of herniation, while also enabling temporal correlation with systemic interventions, ventilatory changes, and sedation adjustments. (Fig.4)

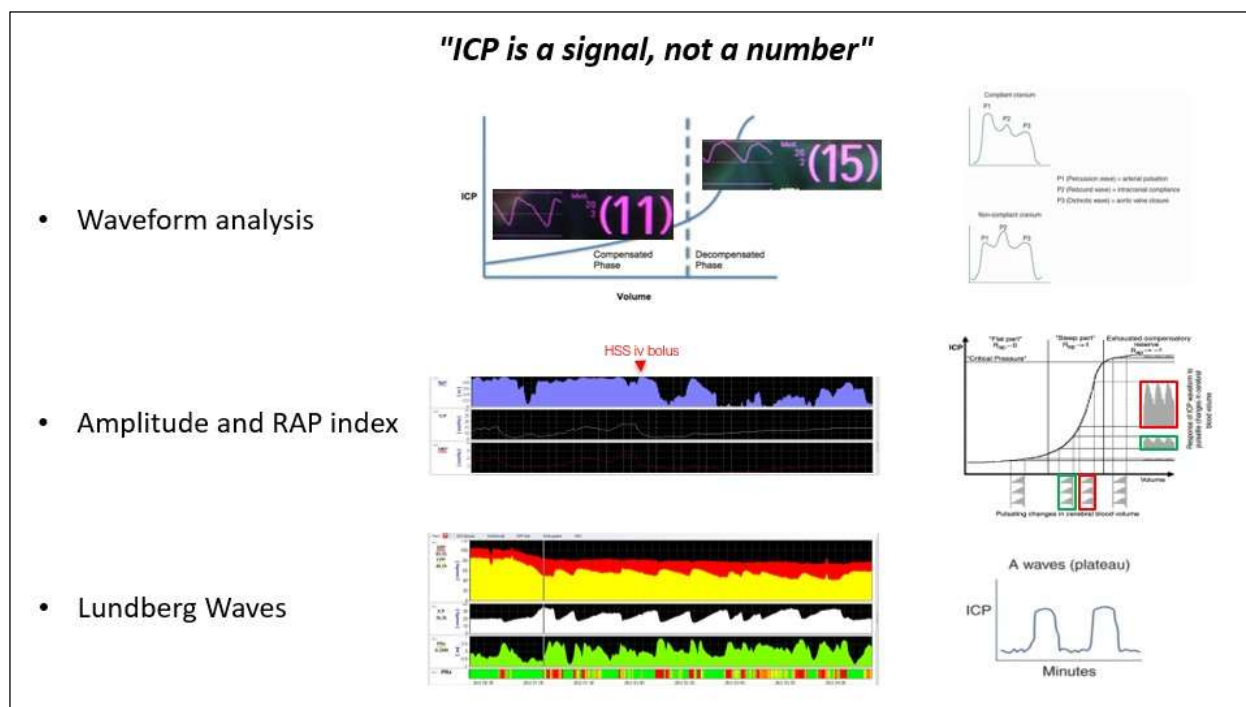


Fig.4 Pezzato S, ESPNIC Neurocritical Care Masterclass. 1st Edition, 2021.

At the bedside, ICP is most commonly measured via an intraparenchymal probe or an external ventricular drain (EVD). Intraparenchymal devices provide reliable continuous readings with limited infection risk but do not allow therapeutic cerebrospinal fluid drainage. EVDs offer the advantage of both measurement and drainage, but require meticulous leveling to an anatomical reference point, consistent attention to waveform quality, and strict infection prevention protocols. When available, inspection of ICP waveform morphology and trends, rather than isolated thresholds alone, can support assessment of deteriorating compliance and evolving intracranial dynamics. ICP data are most informative when interpreted in relation to systemic physiology, particularly arterial blood pressure, ventilation, and venous congestion, which can all modulate intracranial blood volume and pressure. (19)

Cerebral perfusion pressure (CPP), calculated as the difference between mean arterial pressure and intracranial pressure ($CPP = MAP - ICP$), is widely used as a pragmatic surrogate for the driving pressure of cerebral blood flow. However, its application in children remains constrained by limited high level evidence supporting age specific targets and by the developmental variability of cerebrovascular physiology. While pediatric traumatic brain injury guidelines suggest minimum CPP values, the optimal CPP likely differs across age groups and disease contexts, and may evolve over time within the same patient. Infants and young children may be particularly susceptible to perfusion disturbances due to high cerebral metabolic requirements and developmental immaturity of autoregulatory mechanisms, complicating extrapolation from adult paradigms.

Increasing evidence supports the concept that CPP should not be treated as a fixed threshold, but rather as a dynamic parameter best interpreted alongside indices of cerebrovascular autoregulation and tissue oxygenation. This physiology informed framing aligns with the broader rationale for multimodal neurologic monitoring, namely the need to detect early secondary injury and tailor targets to an individual patient's evolving physiological profile. Nevertheless, while associations between low CPP exposure and worse outcomes are strong, interventional evidence demonstrating that CPP manipulation based on individualized targets improves patient centered outcomes remains limited, underscoring the need for cautious interpretation and prospective validation. (20)

2.2.2 Near Infrared Spectroscopy

Near infrared spectroscopy (NIRS) is a noninvasive bedside modality that provides continuous estimation of regional cerebral oxygen saturation through differential light absorption by oxygenated and deoxygenated hemoglobin. NIRS is widely applied in neonates and children at risk of cerebral hypoxia, including during congenital heart surgery, extracorporeal membrane oxygenation, and selected neurocritical care contexts such as traumatic brain injury and post cardiac arrest care. Its principal value in contemporary practice often lies in trend monitoring, as sustained or abrupt reductions in cerebral saturation may precede overt hemodynamic deterioration and may prompt timely reassessment of ventilation, oxygen delivery, hemoglobin concentration, and systemic perfusion. (21)

At the bedside, NIRS sensors are placed on the frontal scalp, with attention to skin integrity, probe adherence, and artifact sources such as motion, ambient light, or changes in scalp perfusion. Interpretation requires awareness that NIRS reflects a mixed venous weighted compartment and is influenced not only by cerebral blood flow, but also by metabolic demand, arterial oxygen content, and venous drainage. Clinical factors such as evolving scalp edema, increased skull thickness, and interindividual differences in tissue characteristics, including skin pigmentation, can affect absolute readings and reinforce the primacy of longitudinal trend interpretation over isolated thresholds.

NIRS has also been used as an indirect surrogate of cerebral blood flow, forming the basis for correlation-based autoregulation indices and oxygenation reactivity metrics. In this framework, changes in NIRS derived cerebral oxygenation are examined in relation to arterial blood pressure to infer the pressure passivity of cerebral oxygenation, and to estimate ranges of arterial pressure associated with preserved autoregulatory function. While these approaches are physiologically appealing and increasingly feasible at the bedside, they rely on assumptions that oxygenation changes are predominantly flow mediated, which may not hold under conditions of rapidly changing metabolism or edema. Moreover, actionable thresholds for cerebral saturation values

remain insufficiently established across pediatric diagnoses. Accordingly, NIRS is best interpreted as a complementary signal that can provide early warning of cerebral oxygenation imbalance, especially when integrated with systemic markers of oxygen delivery, arterial blood pressure, and, when present, intracranial pressure. (22)

2.2.3 Continuous Autoregulation Monitoring

Continuous monitoring of cerebrovascular autoregulation provides insight into the brain's capacity to maintain relatively stable blood flow across fluctuations in perfusion pressure. This mechanism is central to protecting the brain from secondary injury caused by hypoperfusion and hyperperfusion, and it is particularly relevant in pediatric critical care, where autoregulatory capacity may be developmentally immature or impaired by acute brain injury, systemic inflammation, hypoxemia, or metabolic disturbances. The conceptual logic aligns with the broader multimodal monitoring paradigm, in which real time physiological surveillance supports timely detection of evolving vulnerability and individualized adjustment of therapeutic targets. However, while associations between autoregulatory impairment and poor outcome are increasingly reported, interventions designed to optimize autoregulation status have not yet demonstrated consistent outcome benefit, and translation into routine protocolized care remains limited.

In clinical research and in selected specialized settings, two parallel approaches are commonly employed: an invasive method derived from ICP dynamics and a noninvasive analogue derived from NIRS. The ICP-based Pressure Reactivity Index quantifies the moving correlation between slow wave fluctuations in mean arterial pressure and ICP. A positive correlation suggests pressure passivity, consistent with impaired autoregulation, whereas negative values indicate preserved vasoreactivity. When PRx is examined across a range of CPP values, it may yield an autoregulatory curve and permit estimation of an optimal CPP at which autoregulatory function appears most efficient. (23) Pediatric studies suggest that a greater burden of time spent below the lower limit of autoregulatory function may be associated with unfavorable outcomes, raising the hypothesis that individualized CPP targeting could reduce secondary injury. (24)

A noninvasive analogue uses NIRS derived regional cerebral oxygen saturation as a surrogate signal, generating indices such as the Cerebral Oximetry Index through correlations between arterial blood pressure and NIRS saturation. Positive values suggest impaired autoregulation and pressure dependent oxygenation, whereas near zero or negative values suggest preserved coupling. By mapping these indices across observed arterial pressures, an individualized optimal arterial pressure range may be derived. At the bedside, these analyses require synchronized high-quality signals, careful artifact management, and an appreciation that oxygenation signals may reflect changes in flow, metabolism, or venous drainage. In settings where invasive monitoring is

not feasible, NIRS based autoregulation monitoring offers a practical, lower risk approach to continuous physiological characterization, but it should be used with appropriate caution, particularly in unstable patients with rapidly changing physiology. (25)

Autoregulation metric	Input signals	Calculation	Interpretation	Comment
Autoregulation index (ARI)	ABP, Fv	Compares the CBF response to changes in ABP with those predicted from a parametric model with 10 different 'strengths' of autoregulation [110]	ARI = 0 absent autoregulation, ARI = 9 perfect autoregulation	Moderately complex signal processing required
Flow index (Mx, Sx, Dx)	ABP (CPP), Fv	Pearson correlation between CPP and mean Fv (300-s window of 10-s averages). Sx and Dx calculated with systolic and diastolic flow velocity, respectively	Impaired autoregulation = higher Mx, Dx, and Sx	Simplistic yet prognostically relevant
Transfer function (phase, gain, coherence)	ABP, Fv	Derived from the transfer function of fast Fourier transform of ABP and Fv signals. Phase is the shift required to align Fv and ABP signals, gain the transmission from ABP to Fv, and coherence the statistical association between ABP and Fv	Impaired autoregulation = low phase, high gain, high coherence	Moderately complex signal processing. Some prognostic relevance
TOx, COx, THx, HVx	ABP (CPP), NIRS oxygenation	Pearson correlation between 30 consecutive 10-s means of ABP and tissue oxygenation (or total haemoglobin for THx and HVx)	Impaired autoregulation = higher TOx, COx, THx, HVx	Correlated with TCD methods but allows for longer term monitoring
TOIHRx	HR, NIRS oxygenation	Correlation between 30 consecutive 10-s means of HR and NIRS oxygenation	?Higher TOIHRx = impaired autoregulation	Used in preterm infants. Further comparisons with standard autoregulation indices required
Transfer function (phase, gain, coherence)	ABP, NIRS oxygenation	Derived from the transfer function of fast Fourier transform of ABP and oxygenation signals. Phase is the shift required to align oxygenation and ABP signals, gain the transmission from ABP to NIRS oxygenation, and coherence the statistical association between ABP and NIRS oxygenation	Impaired autoregulation = low phase, high gain, high coherence	Moderately complex signal processing
PRx	ABP, ICP	Correlation between 30 consecutive 10-s means of ABP and ICP	Higher PRx = impaired autoregulation	Robust measure for long monitoring periods. Simplistic and prognostically relevant
PAx	ABP, amplitude of ICP	Correlation between 30 consecutive 10-s means of ABP and ICP	Higher PAx = impaired autoregulation	Similar to PRx, may allow better estimate of pressure reactivity when the "pressure-volume" compensatory curve is flat, i.e. at low ICP
ORx	CPP (ABP), P _b TO ₂	Correlation between 30 consecutive 10-s means of ABP and P _b TO ₂	High ORx = impaired autoregulation	Further validation required

ABP arterial blood pressure, *ARI* autoregulatory index, *CBF* cerebral blood flow, *COx* cerebral oximetry index, *CPP* cerebral perfusion pressure, *Dx* diastolic flow index, *Fv* flow velocity, *HR* heart rate, *HVx* haemoglobin volume reactivity index, *ICP* intracranial pressure, *Mx* mean flow index, *ORx* oxygen reactivity index, *PAx* pressure amplitude index, *P_bTO₂* pressure of brain tissue oxygen, *PRx* pressure reactivity index, *Sx* systolic flow index, *NIRS* near-infrared spectroscopy, *TCD* transcranial Doppler, *THx* total haemoglobin reactivity index, *TOIHRx* total oxygenation heart rate index, *TOx* total oxygenation reactivity index

Fig 5. Adapted from: Donnelly J, et al. Crit Care. 2016

Together, invasive and noninvasive autoregulation metrics illustrate how multimodal monitoring can operationalize the concept of individualized physiological targets. (Fig.5) They also exemplify the current translational gap in pediatric neurocritical care, where promising physiological insights and observational associations have not yet been matched by high level evidence demonstrating benefit from autoregulation guided therapeutic algorithms.

2.2.4 Electroencephalography

Electroencephalography (EEG) represents a core component of multimodal neuromonitoring in pediatric neurocritical care, providing continuous, noninvasive assessment of cerebral electrical activity with high temporal resolution. Acute brain disorders account for a substantial proportion of pediatric intensive care unit admissions, and the developing nervous system is particularly vulnerable not only to primary neurological insults but also to secondary injury arising from systemic illness. Neurological dysfunction during pediatric critical illness frequently manifests as seizures, encephalopathy, or disorders of consciousness, with etiologies including ischemia, hemorrhage, cerebral edema, metabolic derangements, infection, and inflammation. Although the neurologic examination remains foundational, its reliability in the intensive care setting is often compromised by sedation, analgesia, neuromuscular blockade, and critical illness itself, limiting the timely detection of evolving cerebral dysfunction. In this context, EEG provides an indispensable window into brain function that complements clinical assessment and other physiological monitoring modalities.

Continuous EEG (cEEG) enables uninterrupted acquisition of cortical electrical activity and has become the reference standard for electrographic surveillance in critically ill infants and children. From a technical perspective, EEG recordings reflect the summation of excitatory and inhibitory postsynaptic potentials generated predominantly by superficial cortical neurons, requiring spatially synchronous neuronal activity over several square centimeters to produce signals detectable at the scalp. In the pediatric ICU, cEEG is typically acquired using scalp electrodes arranged according to the International 10–20 System, with modified or reduced montages employed in neonates and young infants to account for head size and to mitigate the risk of skin injury during prolonged monitoring. Bedside implementation requires careful attention to electrode integrity, skin inspection, artifact recognition, and synchronization with video recording, which is essential for correlating electrographic findings with clinical events and for distinguishing cerebral activity from movement or equipment-related artifact.

The principal clinical indications for cEEG in the PICU include seizure detection, assessment of background activity, neuroprognostication, and identification of new or evolving brain injury. Seizure monitoring is the most common indication, as critically ill children have a high incidence of electrographic seizures, many of which lack overt clinical correlates. Sedation and neuromuscular blockade frequently obscure motor manifestations, rendering cEEG essential for accurate diagnosis. Importantly, seizure burden, rather than seizure presence alone, has emerged as a key determinant of outcome, with higher electrographic seizure burden independently associated with worse neurodevelopmental outcomes. These observations have informed updated definitions of electrographic status epilepticus and underscore the need for

timely detection and judicious treatment, while also highlighting the potential risks associated with aggressive antiseizure therapy in a physiologically fragile population. (26)

Beyond seizure detection, cEEG provides critical information regarding background cerebral activity, which serves as a global marker of brain function. Background features such as continuity, frequency composition, organization, reactivity, and sleep–wake cycling are routinely evaluated and are increasingly recognized as powerful prognostic indicators across multiple pediatric conditions. In children who remain comatose after cardiac arrest, for example, specific EEG background categories demonstrate high specificity for unfavorable neurological outcomes, while the presence of sleep features and reactivity is associated with recovery. Similar applications have been described in acute liver failure, inflammatory encephalopathies, and immune effector cell–associated neurotoxicity, where EEG background correlates with clinical severity and trajectory. At the bedside, serial assessment of EEG background allows clinicians to detect subtle deterioration or recovery that may precede changes in examination or imaging.

A major interpretative challenge in ICU EEG is the characterization of rhythmic and periodic patterns that fall along the ictal–interictal continuum. These electrographic patterns, which include periodic discharges and rhythmic delta activity, often lack definitive evolution or clinical correlation but are associated with an increased risk of seizures and worse outcomes. Their clinical significance lies in the unresolved question of whether they represent epiphenomena of acute brain injury or contribute independently to secondary neuronal damage through increased metabolic demand. Experimental and clinical data demonstrating frequency-dependent increases in cerebral blood flow and metabolism during such patterns suggest that even subthreshold rhythmic activity may exacerbate injury under vulnerable conditions. Consequently, interpretation of these patterns requires careful integration of EEG features, clinical context, and other neuromonitoring signals, rather than reliance on frequency criteria alone.

Given the large volume of data generated by cEEG and the limited availability of continuous expert interpretation, quantitative EEG (qEEG) techniques have emerged as an important adjunct in pediatric neurocritical care. qEEG transforms raw EEG signals into time-compressed, trend-based visualizations that summarize amplitude, frequency, rhythmicity, and hemispheric asymmetry. These displays facilitate bedside surveillance by allowing clinicians to rapidly identify seizures, changes in background activity, or evolving focal abnormalities over hours rather than seconds.

Commonly used qEEG trends include amplitude-integrated EEG (aEEG), suppression ratio, spectral power displays, alpha-to-delta ratios, and asymmetry indices, each providing complementary insight into cerebral function. (Fig. 6)

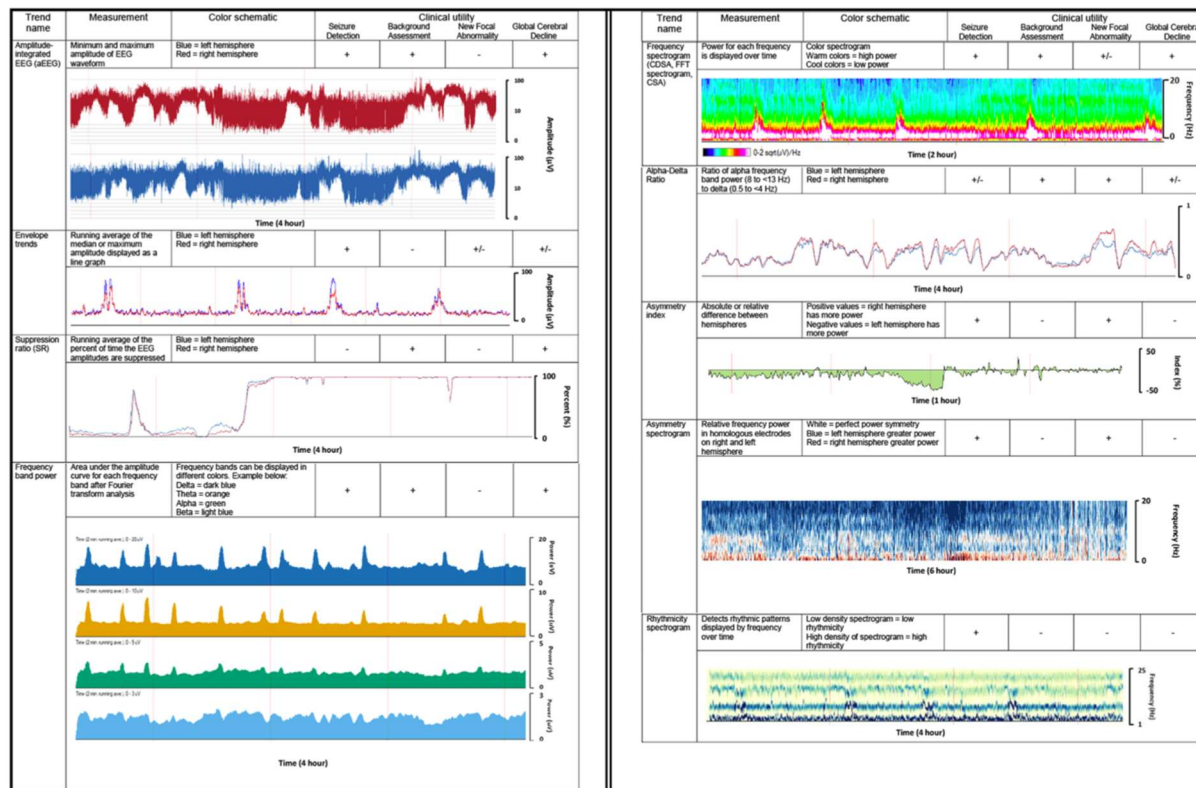


Fig.6 Adapted from: Benedetti GM et al. Neurocrit Care, 2023.

At the bedside, qEEG enhances situational awareness and may support earlier recognition of neurologic deterioration, including impending intracranial hypertension, hypoperfusion, or herniation. Studies in pediatric populations suggest that qEEG changes may precede clinical decline by several hours, offering a potential window for intervention.

In many settings, aEEG is also increasingly used to assess response to antiseizure medications and anesthetic infusions, particularly in refractory status epilepticus, by providing objective, time-locked measures of seizure burden and background suppression. (Fig. 7) However, aEEG remains dependent on validation against raw EEG, and false positives, artifact susceptibility, and limited age-specific normative data necessitate cautious interpretation.

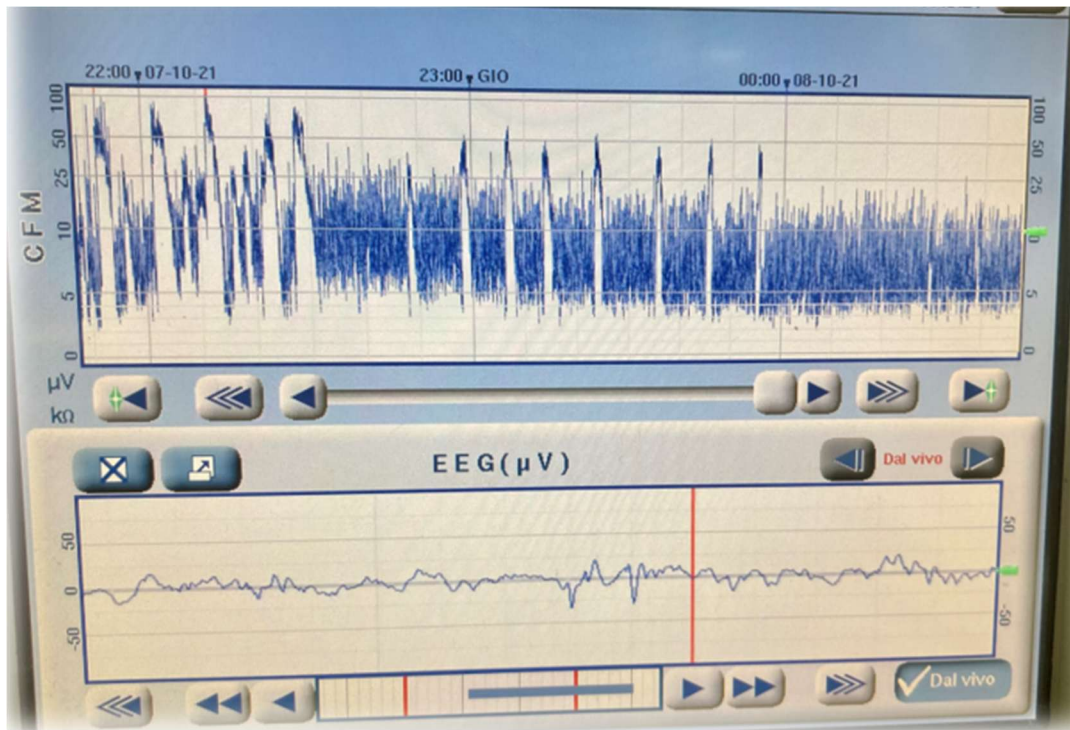


Fig.7 Pediatric ICU Internal Educational Material. Pezzato S, IRCCS Istituto G. Gaslini, 2025.

Despite its growing clinical role, EEG-based monitoring has important limitations. cEEG is resource intensive, requiring specialized technologists, expert interpretation, and robust data infrastructure. Spatial resolution is limited by scalp electrode placement, rendering small or deep lesions potentially undetectable. EEG findings are often nonspecific and may be influenced by medications, metabolic disturbances, or systemic physiological changes. qEEG, while efficient, is not yet standardized across platforms, lacks validated pediatric thresholds for many applications, and should not be used in isolation for clinical decision making. Integration of EEG with other neuromonitoring modalities, including intracranial pressure, cerebral oxygenation, autoregulation indices, and systemic hemodynamics, is therefore essential to maximize interpretative accuracy.

In summary, EEG occupies a central role within multimodal neuromonitoring by providing continuous, high-resolution insight into cerebral function that is otherwise inaccessible in the critically ill child. cEEG remains the gold standard for seizure detection and background assessment, while qEEG offers scalable tools for real-time bedside surveillance and trend recognition. When interpreted within an integrated physiological framework, EEG-based monitoring contributes to early detection of secondary brain injury, individualized therapeutic adjustment, and informed prognostication, while ongoing research seeks to refine its clinical application and outcome relevance in pediatric neurocritical care.

2.2.5 Automated Pupillometry

Quantitative pupillometry provides standardized, objective assessment of pupillary size and reactivity, addressing the substantial interobserver variability associated with manual examination. Automated infrared devices quantify constriction velocity, latency, dilation dynamics, and derived composite scores such as the Neurological Pupil Index. In pediatric neurocritical care, deterioration in pupillary reactivity may reflect evolving intracranial hypertension, impending herniation, or global cerebral ischemia, and pupillometry may therefore offer an early warning signal of brainstem dysfunction when the clinical examination is limited by sedation or neuromuscular blockade. (27)

At the bedside, pupillometry is typically performed as a brief point of care assessment using a handheld device that delivers a standardized light stimulus and captures dynamic pupil responses. Its practical advantages include rapid acquisition, repeatability, and ease of trending over time. (Fig.8) Interpretation, however, requires contextualization, as pupil dynamics can be influenced by medications, ocular pathology, and ambient conditions. Pediatric normative values and age-related physiological variability remain areas of ongoing development, and pupillometry should not be treated as a standalone surrogate for intracranial pressure. (28)

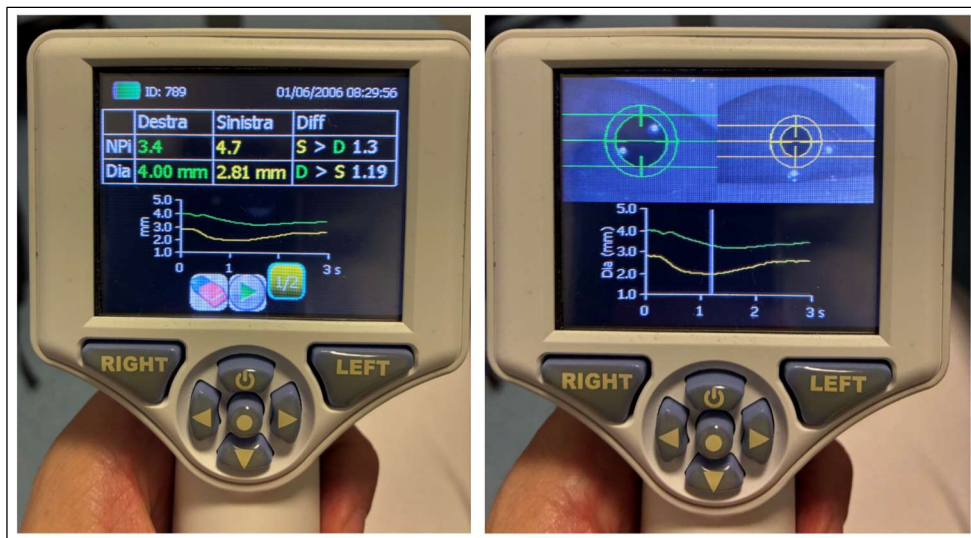


Fig.8 Pediatric ICU Internal Educational Material. Pezzato S, IRCCS Istituto G. Gaslini, 2025.

Within a multimodal framework, it is best used as a complementary measure that supports systematic surveillance of brainstem function and may trigger escalation of evaluation, including imaging, ICP assessment, or reassessment of systemic physiology.

2.2.6 Transcranial Doppler Ultrasound

Transcranial Doppler (TCD) ultrasonography is a noninvasive bedside technique that enables real-time assessment of cerebral hemodynamics through measurement of blood flow velocity waveforms in the major intracranial arteries. In pediatric neurocritical care, TCD is increasingly recognized as a valuable component of multimodal neuromonitoring, particularly in clinical contexts in which neurological examination is unreliable and invasive monitoring is unavailable or contraindicated. Expert consensus initiatives in pediatric intensive care emphasize that TCD should be regarded as a complementary physiological tool, contributing to the interpretation of cerebrovascular status rather than serving as an isolated determinant of therapeutic decision-making. (29)

In the pediatric intensive care unit, TCD is typically performed using low-frequency phased-array probes applied through established acoustic windows, most commonly the transtemporal approach for insonation of the middle cerebral artery. In infants and young children, open fontanelles frequently provide excellent acoustic access, facilitating high-quality and reproducible recordings. The technique is portable, repeatable, and well suited for serial assessments, allowing clinicians to track temporal changes in cerebral blood flow velocity in response to disease evolution or therapeutic interventions. (Fig. 9)

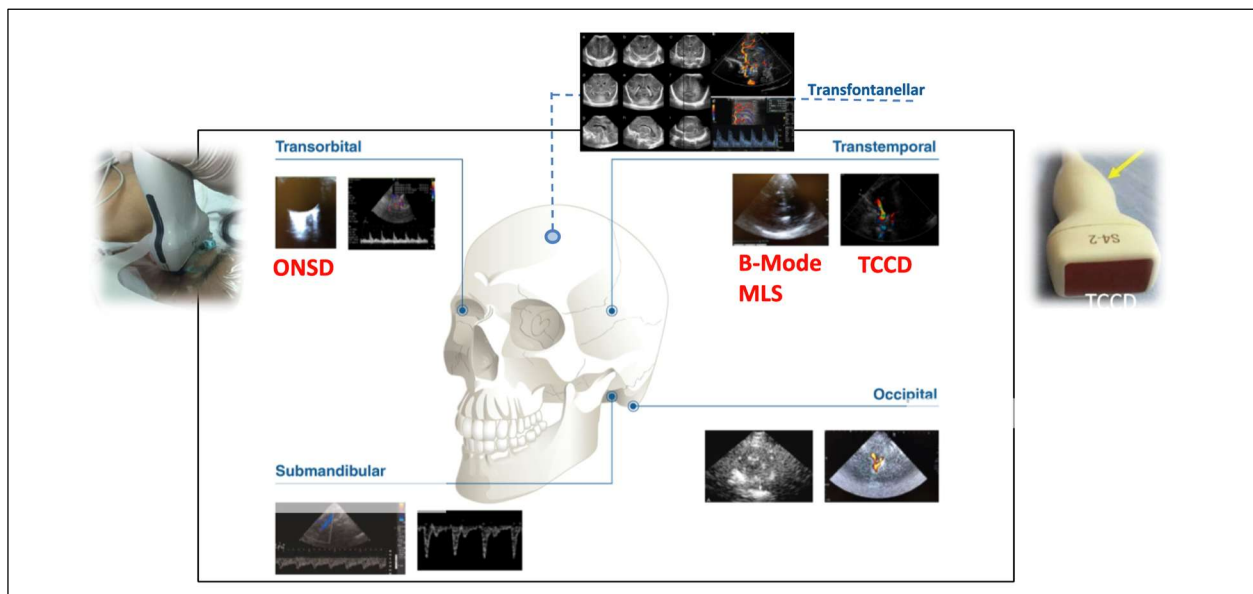


Fig.9 Modified from: Robba C et al. Intensive Care Med, 2019.

TCD provides indirect information on cerebral blood flow by measuring the velocity of erythrocytes within large basal arteries. Flow velocity is influenced by cerebral perfusion pressure, cerebrovascular resistance, arterial carbon dioxide tension, blood viscosity, and cardiac output. As a result, TCD is particularly useful for identifying dynamic cerebrovascular phenomena, including vasospasm, hyperemia, hypoperfusion, and alterations in vascular tone. In pediatric populations, TCD has been applied across a wide range of conditions, including traumatic brain injury, intracranial hypertension, stroke, central nervous system infection, metabolic encephalopathies, and extracorporeal life support.

Among the parameters derived from TCD waveforms, the pulsatility index (PI) is widely used to characterize the pulsatile nature of cerebral blood flow. (Fig. 10) PI is calculated from systolic, diastolic, and mean flow velocities and reflects the combined influence of distal cerebrovascular resistance, arterial compliance, intracranial pressure dynamics, and venous outflow conditions. In pediatric critical care, elevated PI values may be observed in association with increased cerebrovascular resistance, reduced intracranial compliance, or evolving intracranial hypertension, whereas lower PI values may reflect vasodilation, hyperemia, or impaired autoregulatory vasoconstriction.

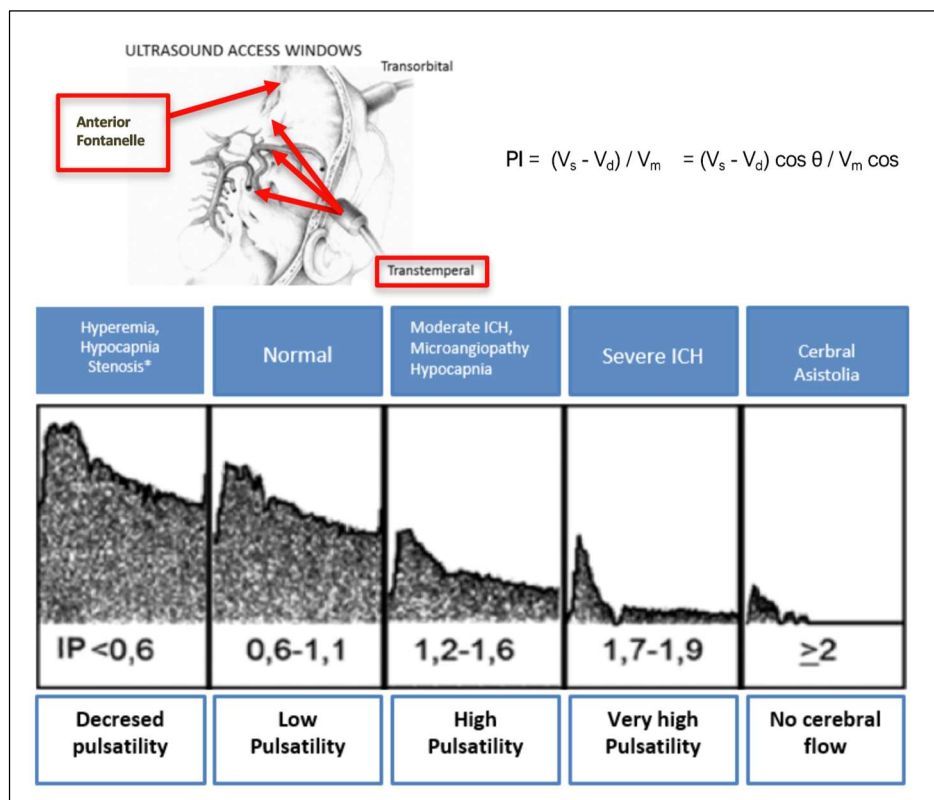


Fig.10 Modified from: Alvarez-Ferandez JA, et al. Rev Neurol, 2011.

Importantly, consensus guidance highlights that PI should not be interpreted as a surrogate for absolute intracranial pressure. The relationship between PI and intracranial pressure is complex and influenced by multiple physiological and technical factors, including age, vessel diameter, insonation angle, arterial carbon dioxide levels, heart rate, and systemic hemodynamics. For this reason, fixed PI thresholds are not recommended for clinical decision-making. Instead, PI is best understood as a trend-based parameter, with longitudinal changes providing greater clinical insight than isolated measurements. (30)

Serial assessment of PI may therefore contribute to the detection of evolving cerebrovascular dysfunction, particularly when interpreted in conjunction with other neuromonitoring modalities. Progressive increases in PI over time may suggest worsening cerebrovascular compliance or rising intracranial pressure, while abrupt changes may accompany acute hemodynamic perturbations or therapeutic interventions. When integrated with arterial blood pressure, cerebral oxygenation metrics, and indices of autoregulatory function, PI can enhance the physiological interpretation of cerebral perfusion status at the bedside. Within a multimodal neuromonitoring framework, TCD complements both invasive and noninvasive techniques by offering real-time information on cerebral hemodynamics without adding procedural risk. While its physiological rationale is strong and its feasibility well established, high-level evidence supporting TCD- or PI-guided therapeutic algorithms remains limited. Accordingly, current expert consensus supports the use of TCD as an adjunctive monitoring tool that informs clinical reasoning, supports individualized assessment, and guides further diagnostic evaluation, rather than as a standalone trigger for protocolized interventions in pediatric neurocritical care.

2.2.7 Optic Nerve Sheath Diameter (ONSD) Assessment

Ultrasound assessment of the optic nerve sheath diameter (ONSD) has gained increasing attention as a noninvasive bedside method for the evaluation of intracranial pressure dynamics in critically ill children. The physiological basis of this technique relies on the anatomical continuity between the intracranial subarachnoid space and the optic nerve sheath, such that elevations in intracranial pressure are transmitted along the optic nerve, resulting in distension of the perioptic cerebrospinal fluid space. (Fig. 11) In the pediatric intensive care unit, where invasive intracranial pressure monitoring may be delayed, contraindicated, or unavailable, ONSD measurement represents a pragmatic adjunct to the assessment of intracranial hypertension.

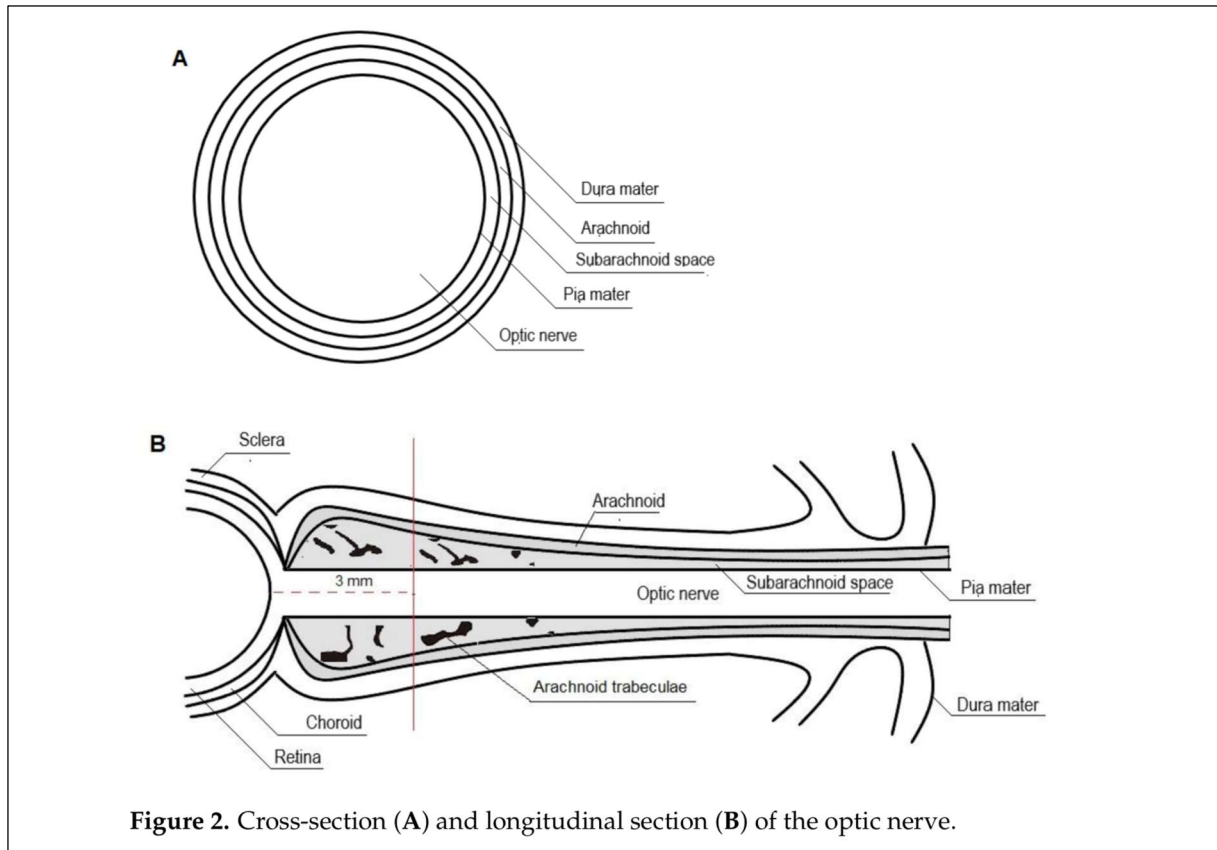


Fig.11 Adapted from: Cannata et al. Diagnostics (Basel), 2022.

ONSD evaluation is performed using a high-frequency linear ultrasound probe applied gently over the closed eyelid. After appropriate coupling gel is applied, the optic nerve is visualized in the axial plane as a hypoechoic tubular structure extending posteriorly from the globe, surrounded by echogenic orbital fat. Standardized measurement is obtained approximately three millimeters posterior to the globe, a location that has been shown to be most sensitive to pressure-related changes. (Fig. 12) To improve reliability, measurements are typically repeated and averaged, and bilateral assessment is often performed. The technique is rapid, repeatable, and feasible at the bedside, even in hemodynamically unstable patients or those requiring advanced life support.

(31)

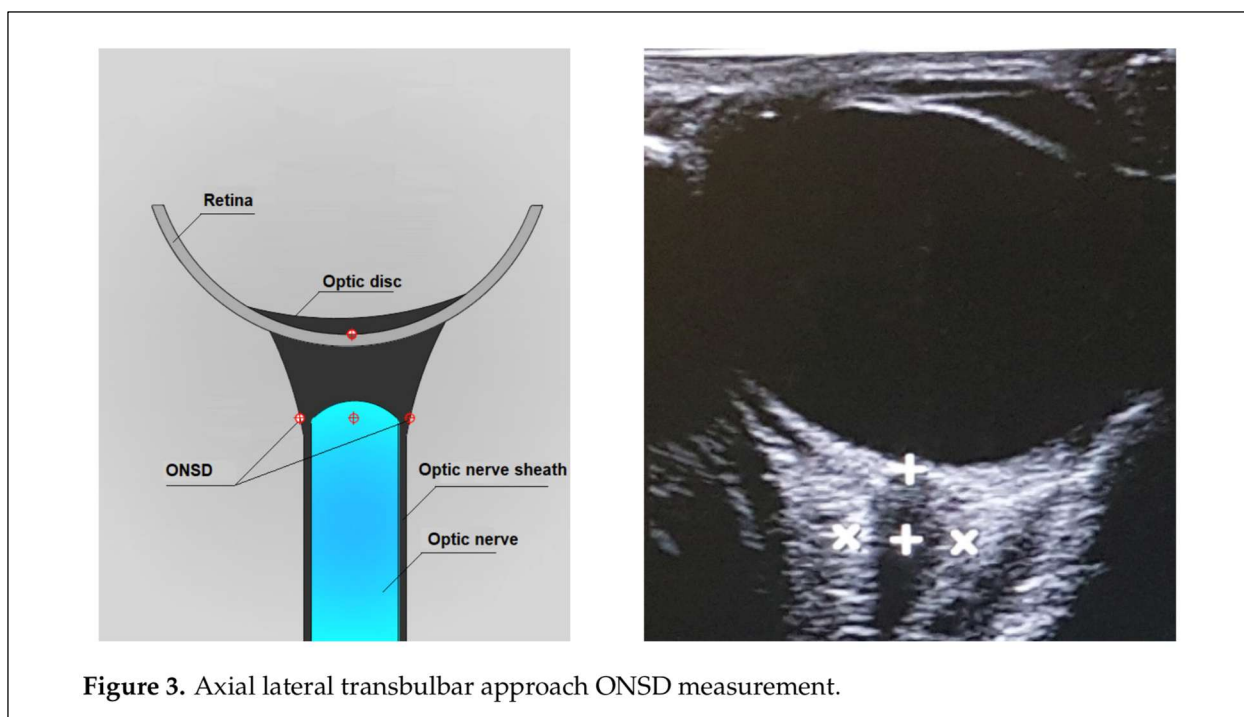


Fig.12 Adapted from: Cannata et al. Diagnostics (Basel), 2022.

Accumulating pediatric data support an association between increased ONSD and clinically relevant intracranial hypertension across a range of neurological and systemic conditions. Importantly, recent prospective pediatric studies have demonstrated that ONSD values differ significantly between children with and without raised intracranial pressure and that serial measurements track dynamic changes over time. (Fig.13)

Table 3 ONSD cut-off values for detecting ICP at various thresholds using age at 1 year as a dichotomy point		
ICP (in mmHg)	Age threshold (in years)	ONSD cut-off value (in mm)
≥20	Overall	5.50
	≥1	5.75
	<1	5.16
≥15	Overall	5.30
	≥1	5.49
	<1	4.97
≥10	Overall	5.04
	≥1	5.20
	<1	4.30
≥5	Overall	5.00
	≥1	5.10
	<1	N/A

Fig.13 Adapted from: Padayachy LC et al. Childs Nerv Syst, 2016.

Interpretation of ONSD measurements in children requires careful consideration of age-related anatomical variability. (32,33) Absolute sheath diameter values increase with age, and pediatric-specific reference ranges vary across studies, limiting the applicability of uniform cut-off thresholds. Furthermore, individual factors such as chronic intracranial pathology, optic nerve disease, orbital abnormalities, or previous neurosurgical intervention may influence baseline measurements and should be considered when interpreting results.

From a clinical perspective, ONSD assessment is best suited for early risk stratification, bedside reassessment, and monitoring of trends in patients at risk for intracranial hypertension. Its value is particularly evident in situations where transport for neuroimaging is unsafe, invasive monitoring is not immediately available, or frequent reassessment is required to evaluate response to therapy. However, ONSD provides no direct information regarding cerebral perfusion, intracranial compliance, or regional pressure gradients and cannot distinguish among the underlying mechanisms driving intracranial pressure elevation.

Within a multimodal neuromonitoring framework, optic nerve sheath diameter assessment can be integrated with transcranial Doppler ultrasonography to support a more comprehensive, physiology-driven characterization of intracranial dynamics. In this context, we collaborated with Robba and colleagues to investigate the combined use of optic nerve sheath diameter and transcranial Doppler-derived parameters, demonstrating that optic nerve sheath diameter outperformed flow-based indices and may enhance noninvasive assessment of intracranial pressure in this setting. (34) When interpreted alongside Doppler findings and broader clinical data, optic nerve sheath diameter contributes to an integrated understanding of cerebral physiology, particularly in scenarios where invasive monitoring is not available. (Fig.14)

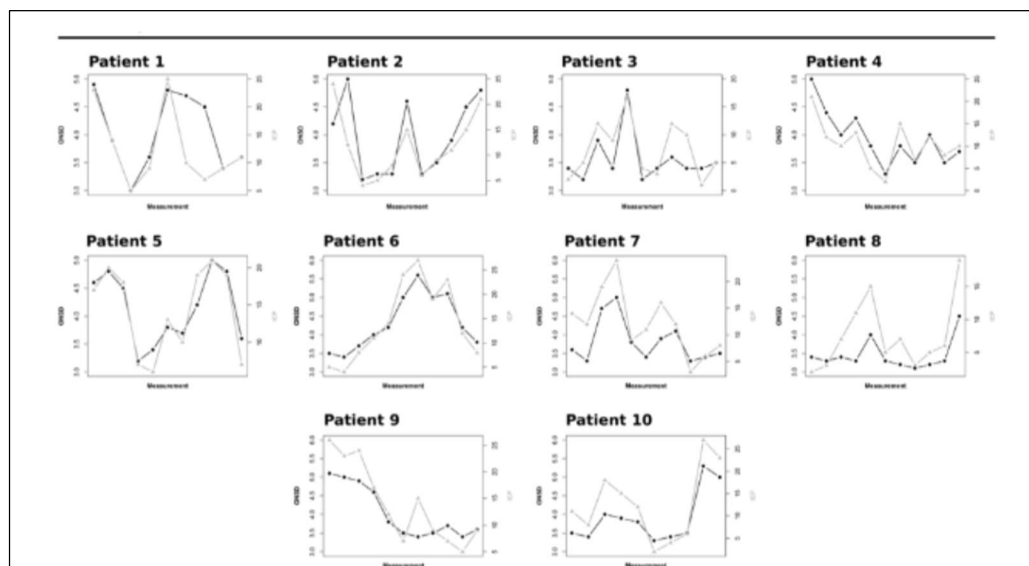


Fig.14 Adapted from: Robba et al. Childs Nerv Syst, 2020.

Nevertheless, while its diagnostic performance for detecting raised intracranial pressure is promising, high-level evidence demonstrating improved outcomes through ONSD-guided management remains limited. Current evidence therefore supports its role as an adjunctive monitoring tool that informs clinical judgment rather than a standalone trigger for protocolized intervention in pediatric neurocritical care.

2.2.8 Brain Tissue Oxygenation and Emerging Techniques

Brain tissue oxygen tension monitoring provides focal assessment of oxygen diffusion at the tissue level and can identify cerebral hypoxia that may not be apparent from systemic oxygenation or perfusion measures. While pediatric experience remains more limited than adult practice, low PbtO₂ values have been associated with unfavorable outcomes in observational studies, supporting its physiological relevance. In selected specialized centers, PbtO₂ monitoring is used to tailor oxygen delivery, ventilation targets, and perfusion strategies, often in combination with ICP and CPP monitoring. The emerging adult interventional literature suggests that PbtO₂ guided therapy can reduce cerebral hypoxia burden, but pediatric outcome based evidence and standardized interventional pathways remain insufficient. (35)

At the bedside, PbtO₂ requires placement of an invasive probe within brain parenchyma, often during neurosurgical procedures or alongside ICP monitoring. Interpretation is inherently regional, reflecting the probe location and local tissue conditions, which necessitates careful correlation with imaging and clinical context. Beyond absolute values, the temporal burden of hypoxia and responsiveness to interventions may offer the most actionable information, particularly when integrated with indices of autoregulation and perfusion pressure.

Cerebral microdialysis provides near real time sampling of extracellular metabolites, offering insight into cerebral energy balance and metabolic crisis through analytes such as glucose, lactate, and pyruvate. Pediatric use remains confined to highly specialized centers, and evidence supporting routine clinical integration is still limited. Nonetheless, the technique provides a mechanistically rich complement to hemodynamic and oxygenation data, and may detect metabolic deterioration before structural changes become evident.

Emerging approaches include invasive cerebral blood flow monitoring, intracranial EEG in selected contexts, and evolving neuroimaging strategies such as portable or low field MRI. (36) (Fig.15)

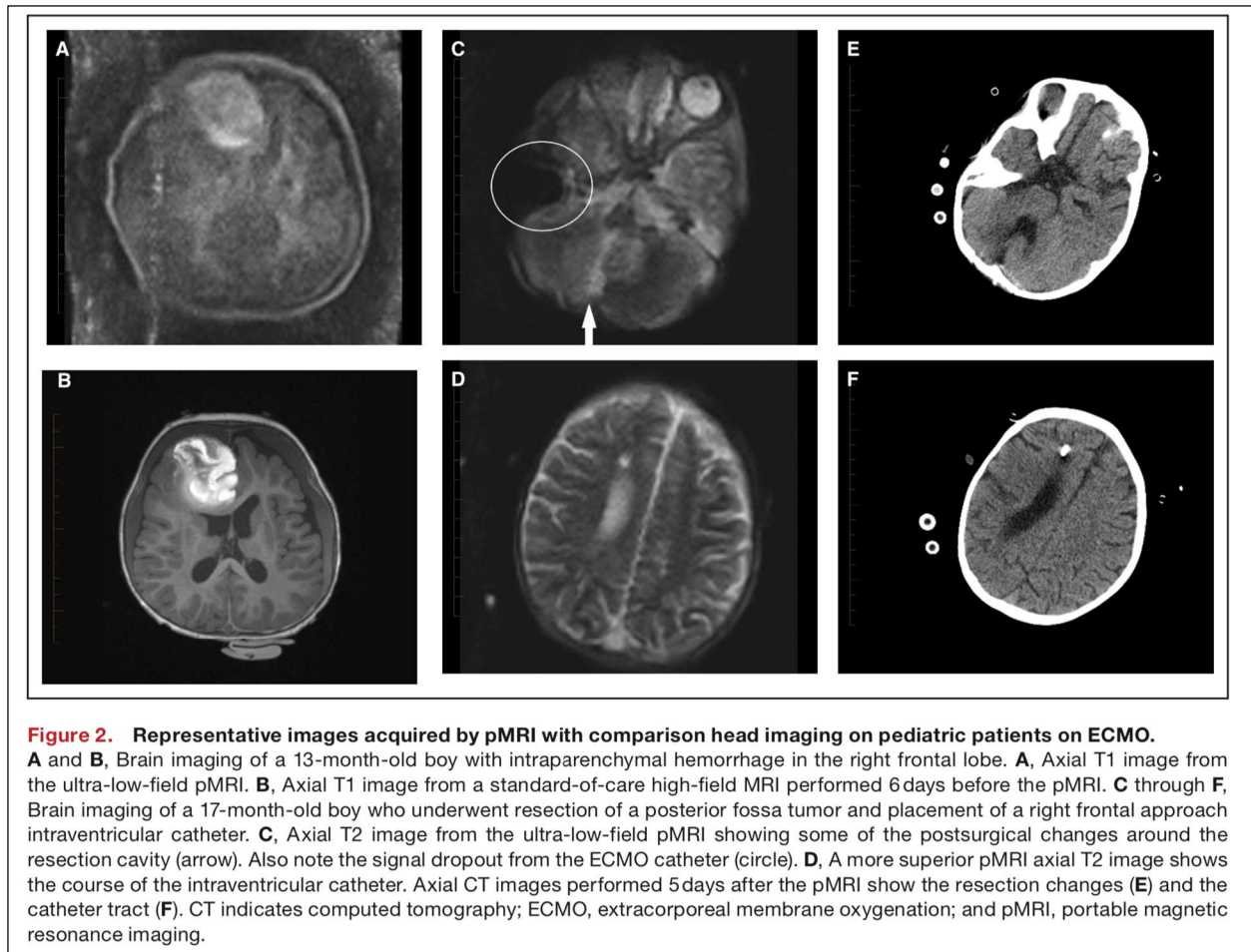


Fig.15 Adapted from: Wallisch JS, et al. J Am Heart Assoc, 2025

These modalities offer enhanced spatial and mechanistic resolution but are limited by invasiveness, resource requirements, and interpretative complexity. More broadly, advances in biomedical engineering and computing have enabled synchronized multimodal data acquisition, quantitative trending, and early forms of decision support. However, integrated platforms capable of real time synchronization and interpretation remain uncommon in pediatric practice, and implementation is constrained by the need for specialized personnel, standardized processes for artifact management and interpretation, and outcome based validation.

Future clinical development will likely depend on establishing reliable workflows that link multimodal physiological signatures to actionable therapeutic strategies and to meaningful long term neurological outcomes.

SECTION II – Cerebral Autoregulation monitoring in critically-ill patients

Chapter 1. Physiology of Cerebral Blood Flow Autoregulation

1.1 Basic Concepts of Cerebral Hemodynamics and Metabolism

Cerebral autoregulation reflects a complex interplay among perfusion pressure, vascular resistance, intracranial mechanics, and metabolic demand. A detailed understanding of the physiological foundations of cerebral blood flow and intracranial dynamics is essential for interpreting cerebrovascular behavior in health and disease, and for appreciating the unique vulnerabilities of the developing brain. More specifically, cerebrovascular autoregulation refers to the intrinsic capacity of the cerebral vasculature to maintain relatively stable blood flow across a range of perfusion pressures through dynamic modulation of cerebrovascular resistance. This compensatory behavior gives rise to an autoregulatory plateau, within which cerebral blood flow is buffered against pressure fluctuations, whereas beyond these limits autoregulatory reserve is progressively exhausted and flow becomes increasingly pressure dependent. (Fig. 16)

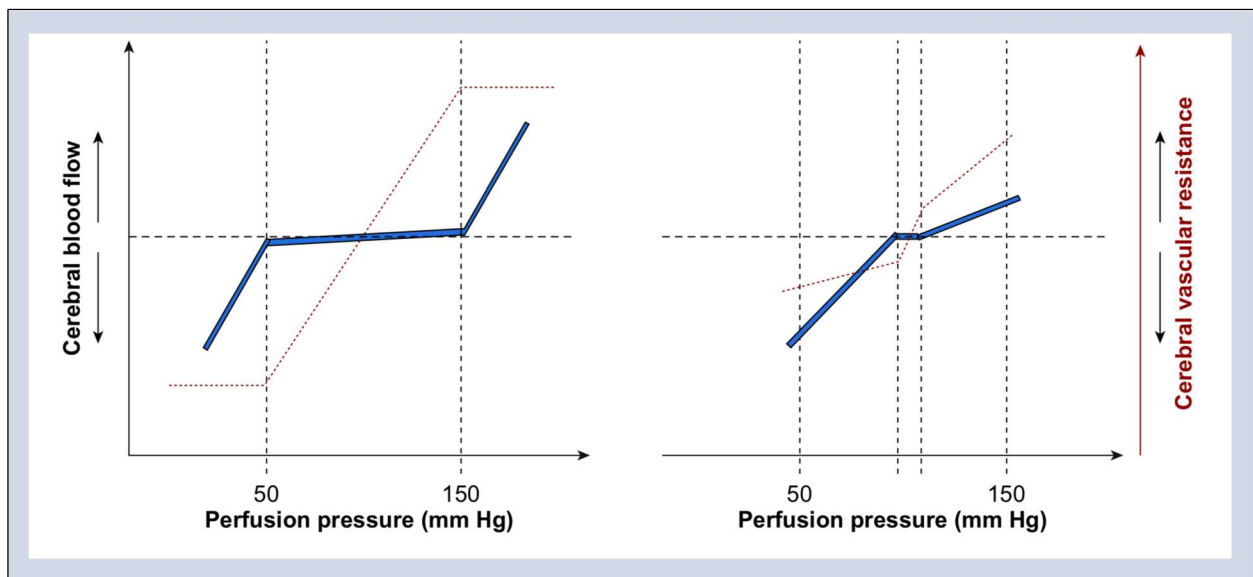


Fig.16 Adapted from: Vu EL, et al. Br J Anaesth. 2024.

1.1.1 Cerebral Blood Flow and Brain Metabolism

Cerebral blood flow exists to meet the metabolic requirements of neural tissue, which relies almost entirely on aerobic pathways for energy production. The brain consumes a

disproportionate share of the body's resources, using approximately one fifth of total oxygen uptake and a similar proportion of glucose turnover despite representing only a small fraction of total body mass. These demands are quantified by the cerebral metabolic rate of oxygen and the cerebral metabolic rate of glucose, both of which reflect the energetic cost of maintaining ionic gradients, supporting synaptic transmission, and sustaining the electrophysiological activity that underlies cognition and consciousness. Because neurons have negligible reserves of oxygen or glucose, momentary reductions in substrate delivery can disturb membrane potentials and impair cellular function, while more prolonged deficits result in irreversible injury.

The maintenance of cerebral metabolism depends on the tight regulation of cerebral blood flow. This regulation is achieved through an integrated system of vascular, neural, and glial mechanisms that adjust blood flow in proportion to changing metabolic needs. A central feature of this regulation is neurovascular coupling, the process through which neuronal activity initiates localized increases in blood flow. When regional synaptic activity intensifies, glutamatergic signaling and associated intracellular calcium changes within astrocytes activate biochemical pathways that influence both arteriolar smooth muscle and endothelial cells. These interactions produce vasodilation in the corresponding vascular territories and increase blood flow to regions of increased metabolic demand. Through this mechanism, the neurovascular unit ensures that $CMRO_2$ and CMR_{glu} are matched by proportional increases in substrate delivery. (37)

The neurovascular unit consists of neurons, astrocytes, endothelial cells, pericytes, and vascular smooth muscle. These elements form a coordinated network capable of translating neuronal activity into vascular responses. Astrocytes channel metabolic and neurotransmitter signals to nearby vessels, endothelial cells modulate vascular tone through the release of nitric oxide and other mediators, and pericytes influence capillary diameter and local resistance. Vascular smooth muscle responds to these signals by altering arteriolar tone and adjusting regional blood flow accordingly. Perturbations in any component of this unit, whether due to developmental immaturity, inflammation, hypoxia, or critical illness, weaken the relationship between metabolic demand and flow and increase the susceptibility of neural tissue to injury.

Cerebral blood flow is also shaped by systemic variables such as carbon dioxide tension, oxygen content, hematocrit, and autonomic influences. Carbon dioxide acts as a potent regulator because changes in pH alter smooth muscle tone, producing rapid adjustments in vascular resistance. Sustained hypoxemia elicits vasodilation in an attempt to increase oxygen delivery, though this compensatory mechanism has limited capacity. Variations in hematocrit influence both oxygen carrying capacity and blood viscosity, with consequences for flow distribution. These systemic influences interact with metabolic and cellular mechanisms to form a dynamic environment in which cerebral blood flow continually adapts to preserve metabolic homeostasis.

In summary, cerebral blood flow reflects the integration of systemic pressures, metabolic demands, and neurovascular control mechanisms that work together to maintain adequate delivery of oxygen and glucose. The precise regulation of $CMRO_2$ and CMR_{glu} through neurovascular coupling represents a fundamental principle of cerebral physiology and provides the basis upon which autoregulatory mechanisms operate to preserve brain function during physiological stress and critical illness.

1.1.2 Intracranial Dynamics and the Monro-Kellie Principle

Cerebral hemodynamics must be understood within the constraints imposed by the intracranial environment. The skull forms a rigid, non-distensible compartment that contains brain tissue, cerebrospinal fluid, and intracranial blood. According to the Monro Kellie principle, the total volume of these components remains nearly constant after closure of the cranial sutures. Any increase in one component must be balanced by a compensatory decrease in another in order to maintain stable intracranial pressure. (38) (Fig 17b)

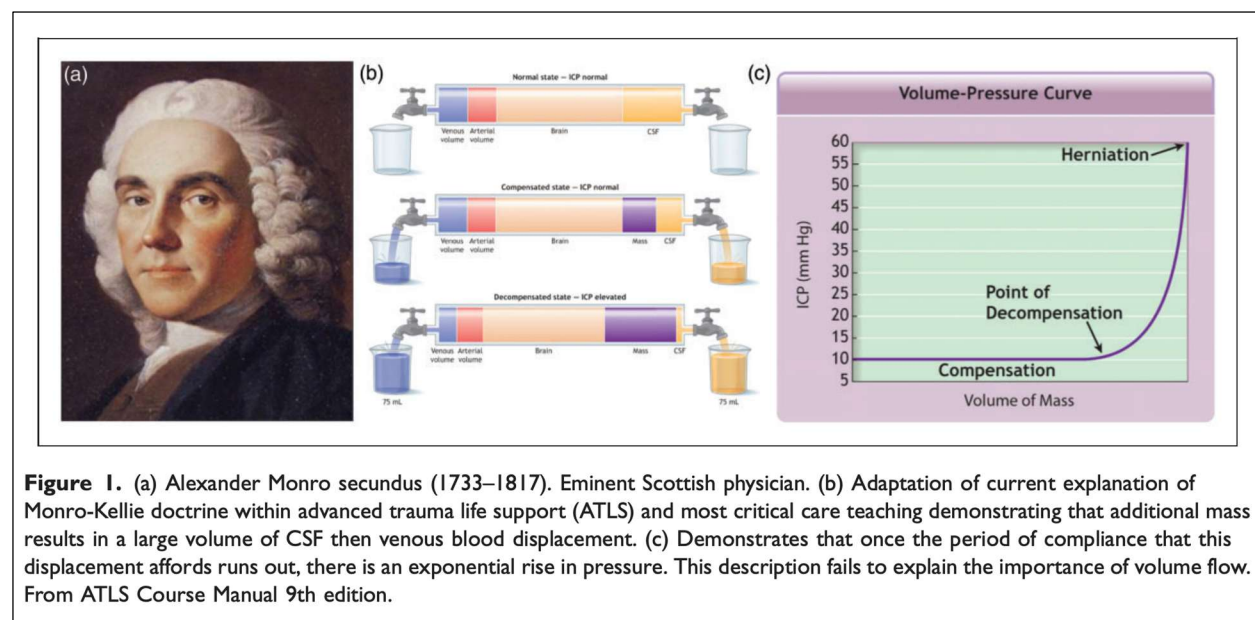


Fig.17 Adapted from: Wilson MH, et al. J Cereb Blood Flow Metab. 2016

Intracranial pressure therefore reflects the dynamic equilibrium among these intracranial constituents. When compensatory mechanisms are intact, small increases in intracranial volume are accommodated by displacement of cerebrospinal fluid into the spinal subarachnoid space or by reductions in venous blood volume. Once these compensatory reserves become exhausted, intracranial pressure rises steeply in response to even minimal additional volume. This non-linear pressure volume relationship is a defining feature of intracranial mechanics. (Fig 17c)

Fluctuations in intracranial pressure occur rhythmically as a result of cardiac pulsatility, respiratory variations, and slower vasogenic oscillations. These oscillations arise from physiological changes in arterial inflow and venous outflow that modify intracranial blood volume. Slow waves of intracranial pressure are particularly relevant for the assessment of autoregulation because they reflect the degree to which changes in arterial pressure are transmitted into the intracranial compartment. When autoregulation is intact, adjustments in cerebrovascular resistance minimize the transmission of arterial pressure oscillations into intracranial pressure. When autoregulation is impaired, arterial and intracranial pressures fluctuate in parallel. (39)

The relationship between intracranial pressure and cerebral perfusion pressure is central to cerebral blood flow regulation. Because cerebral perfusion pressure equals mean arterial pressure minus intracranial pressure, any increase in intracranial pressure reduces the effective driving force for perfusion. When intracranial pressure rises sufficiently, cerebral perfusion pressure may fall below the threshold needed to maintain adequate blood flow. Conversely, reductions in intracranial pressure increase cerebral perfusion pressure and may unmask previously autoregulated regions of the circulation.

Intracranial compliance plays a key role in shaping these interactions. Compliance describes the capacity of the intracranial compartment to accommodate changes in volume for a given change in pressure. High compliance allows volume changes to occur with minimal alterations in pressure, while low compliance amplifies the effect of volume changes. Conditions such as cerebral edema, mass lesions, or impaired cerebrospinal fluid circulation reduce compliance and increase the brain's susceptibility to pressure mediated injury.

These intracranial dynamics form the structural and mechanical context within which cerebral autoregulation operates. The interaction of systemic pressure, intracranial pressure, and vascular resistance determines cerebral perfusion pressure and influences the capacity of autoregulatory mechanisms to maintain stable flow. A comprehensive understanding of the Monro Kellie principle and intracranial compliance is therefore essential for interpreting cerebrovascular physiology in both healthy and critically ill patients. (40)

1.2 Determinants of Cerebral Blood Flow

The regulation of cerebral blood flow reflects the interaction among systemic cardiovascular forces, intracranial mechanical constraints, and intrinsic properties of the cerebrovascular bed. Modern physiological models describe these influences as three interconnected components. The cardiovascular component provides the perfusion pressure that drives flow. The intracranial pressure component opposes this driving force and shapes the effective perfusion gradient. The cerebrovascular component determines resistance to flow through adjustments in vascular tone.

Together, these components establish the cerebral blood flow that supports metabolic demands under both stable and pathophysiological conditions. (25) (Fig.18)

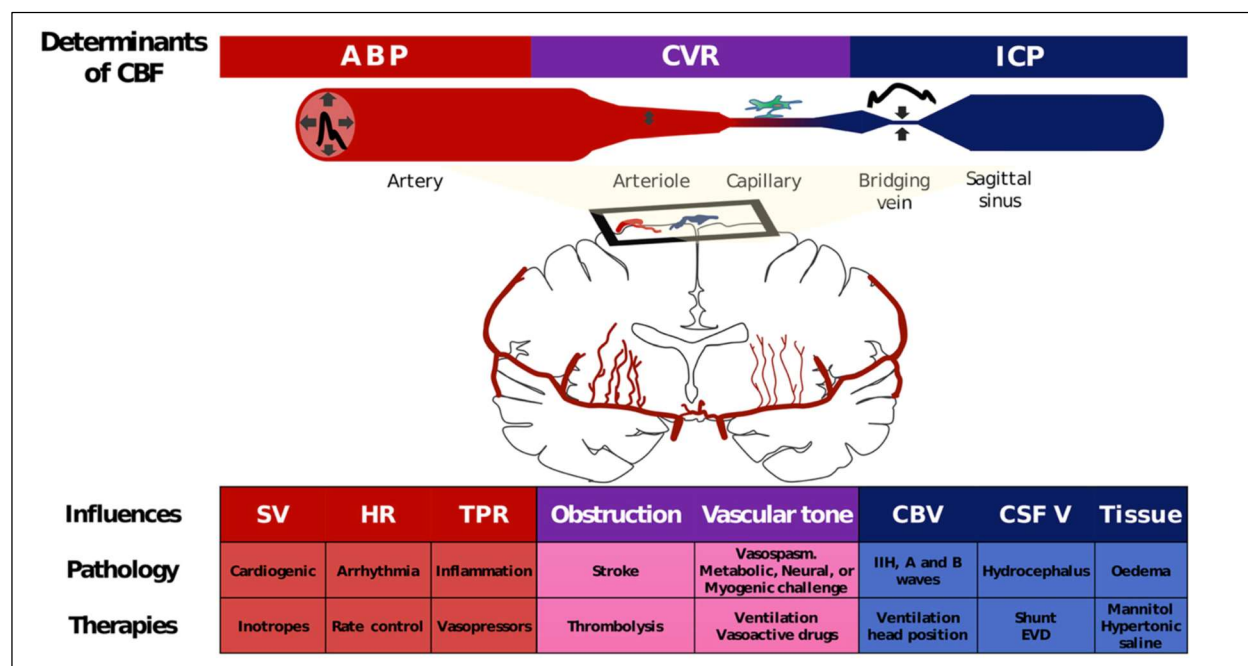


Fig.18 Adapted from: Donnelly J, et al. Crit Care. 2016.

1.2.1 The Cardiovascular Component

The cardiovascular system determines the arterial pressure that serves as the primary driving force for cerebral perfusion. Mean arterial pressure governs the inflow pressure at the level of cerebral arteries, while cardiac output, systemic vascular resistance, autonomic activity, and circulating blood volume influence the stability of this pressure over time. Variations in mean arterial pressure produce corresponding fluctuations in cerebral perfusion pressure unless compensated by adjustments in intracranial pressure or cerebrovascular resistance.

Several systemic variables modify the ability of mean arterial pressure to support cerebral perfusion. Carbon dioxide tension exerts a powerful effect on cerebral blood flow through pH mediated changes in smooth muscle tone. Hypercapnia produces vasodilation and augments flow, while hypocapnia induces vasoconstriction and decreases flow. Oxygen content also modulates perfusion. Significant hypoxemia triggers vasodilation in an effort to increase oxygen delivery, though this response has limits when oxygen tension becomes critically low. Hematocrit influences cerebral blood flow both through changes in viscosity and changes in arterial oxygen content. Higher viscosity impedes flow but increases the concentration of oxygen carried per unit of blood volume. Lower viscosity facilitates flow but reduces oxygen carrying capacity.

Autonomic influences provide additional modulation. Sympathetic activity can constrict large cerebral arteries during periods of stress, potentially shielding the microcirculation from excessive pressure. In contrast, parasympathetic and sensory innervation exert subtler effects on basal tone. These mechanisms, although secondary to metabolic and endothelial pathways within the cerebrovascular bed, participate in maintaining the overall stability of mean arterial pressure and its effectiveness as a perfusion source.

The cardiovascular component therefore establishes the potential energy available for perfusion. Its interaction with intracranial and cerebrovascular mechanisms determines whether cerebral blood flow remains adequate across a range of physiological and pathological states.

1.2.2 The Intracranial Pressure Component

Cerebral perfusion pressure is defined by the difference between mean arterial pressure and intracranial pressure. Intracranial pressure therefore acts as an opposing force to cerebral perfusion. Because the intracranial compartment is enclosed within the rigid cranial vault, the volume and pressure relationships within it follow the principles previously outlined by the Monro Kellie doctrine. Cerebrospinal fluid, venous blood, and brain tissue share a restricted space in which any increase in one element must be compensated by a decrease in another to maintain a stable pressure environment.

Intracranial pressure varies continuously in response to cardiac pulsations, respiratory influences, and slower vasogenic oscillations that reflect changes in intracranial blood volume. These oscillations can be transmitted from arterial pressure fluctuations unless they are buffered by intact autoregulatory mechanisms. When autoregulation is functional, increases in arterial pressure provoke compensatory vasoconstriction that limits the entry of blood into the intracranial space, thereby minimizing changes in intracranial pressure. When autoregulation is impaired, arterial and intracranial pressures fluctuate in parallel, indicating that cerebrovascular resistance no longer adjusts appropriately.

The relationship between intracranial pressure and cerebral blood flow is shaped by intracranial compliance. High compliance permits the accommodation of volume changes with minimal changes in pressure, while low compliance amplifies pressure responses to small variations in volume. Conditions such as cerebral edema, space occupying lesions, or impaired cerebrospinal fluid absorption reduce compliance and increase the likelihood that fluctuations in vascular volume will produce significant increases in intracranial pressure. When intracranial pressure rises sufficiently, cerebral perfusion pressure may fall below the lower limit of autoregulation, resulting in pressure dependent decreases in flow and increased risk for ischemic injury.

Intracranial dynamics therefore determine the degree to which systemic arterial pressure can effectively drive cerebral blood flow. The interaction of intracranial pressure with mean arterial pressure establishes the net perfusion pressure available to the cerebrovascular bed.

In pediatric patients, however, these compensatory mechanisms are developmentally constrained by age-dependent anatomical and physiological factors, including increased neural axis compliance, resulting in reduced buffering capacity and greater vulnerability to perturbations in intracranial volume and pressure. (41) (Fig.19)

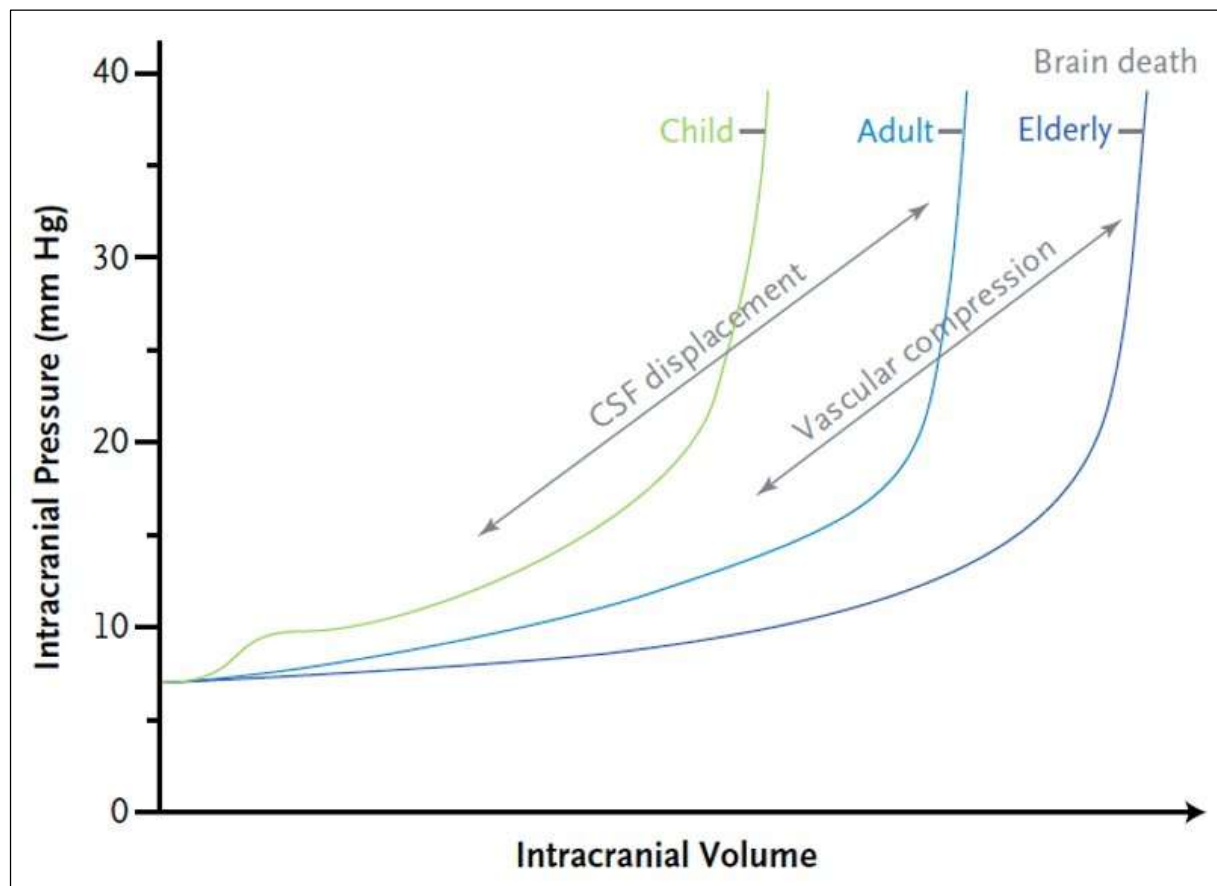


Fig. 19 Adapted from: Shapiro K, et al. J Neurosurg. 1982

1.2.3 The Cerebrovascular Component

Cerebrovascular resistance represents the intrinsic capacity of cerebral vessels to modulate blood flow through changes in arteriolar tone. This component integrates the myogenic, metabolic, endothelial, and neurogenic influences that determine vascular diameter. It is the most adaptable of the three components and the one most directly responsible for real-time regulation of flow. (42)

Four classical mechanisms have been proposed to account for the regulation of cerebrovascular autoregulation. (Fig 20)

1. The myogenic mechanism is activated by changes in intraluminal pressure. When pressure increases, vascular smooth muscle depolarizes and contracts, leading to vasoconstriction that stabilizes flow. When pressure decreases, smooth muscle relaxes and vessels dilate. This rapid response is essential for dynamic autoregulation and operates primarily within resistance vessels.
2. Metabolic regulation adjusts vascular tone according to local cellular activity. Increased CMRO₂ or accumulation of metabolites such as adenosine, potassium ions, or carbon dioxide signals a need for increased flow and induces vasodilation. Conversely, reduced metabolic activity decreases the need for perfusion and permits a relative increase in tone. Neurovascular coupling, described earlier, is the mechanism that links synaptic activity with regional perfusion through astrocytic and endothelial intermediaries.
3. Endothelial cells contribute to resistance regulation by releasing nitric oxide, prostacyclin, endothelin, and other mediators that influence vascular smooth muscle. These mediators respond to both mechanical signals, such as changes in shear stress, and biochemical signals, such as inflammatory cytokines. Endothelial function is therefore a major determinant of the cerebrovascular response during both physiological activation and pathological stress.
4. Neurogenic influences arise from autonomic innervation. Although the cerebral circulation is relatively protected from direct sympathetic control under normal conditions, sympathetic activation can constrict large arteries and modify baseline tone in circumstances of severe hemodynamic challenge. Neurogenic inputs therefore serve as an additional modulator of the systemic to cerebral interface.

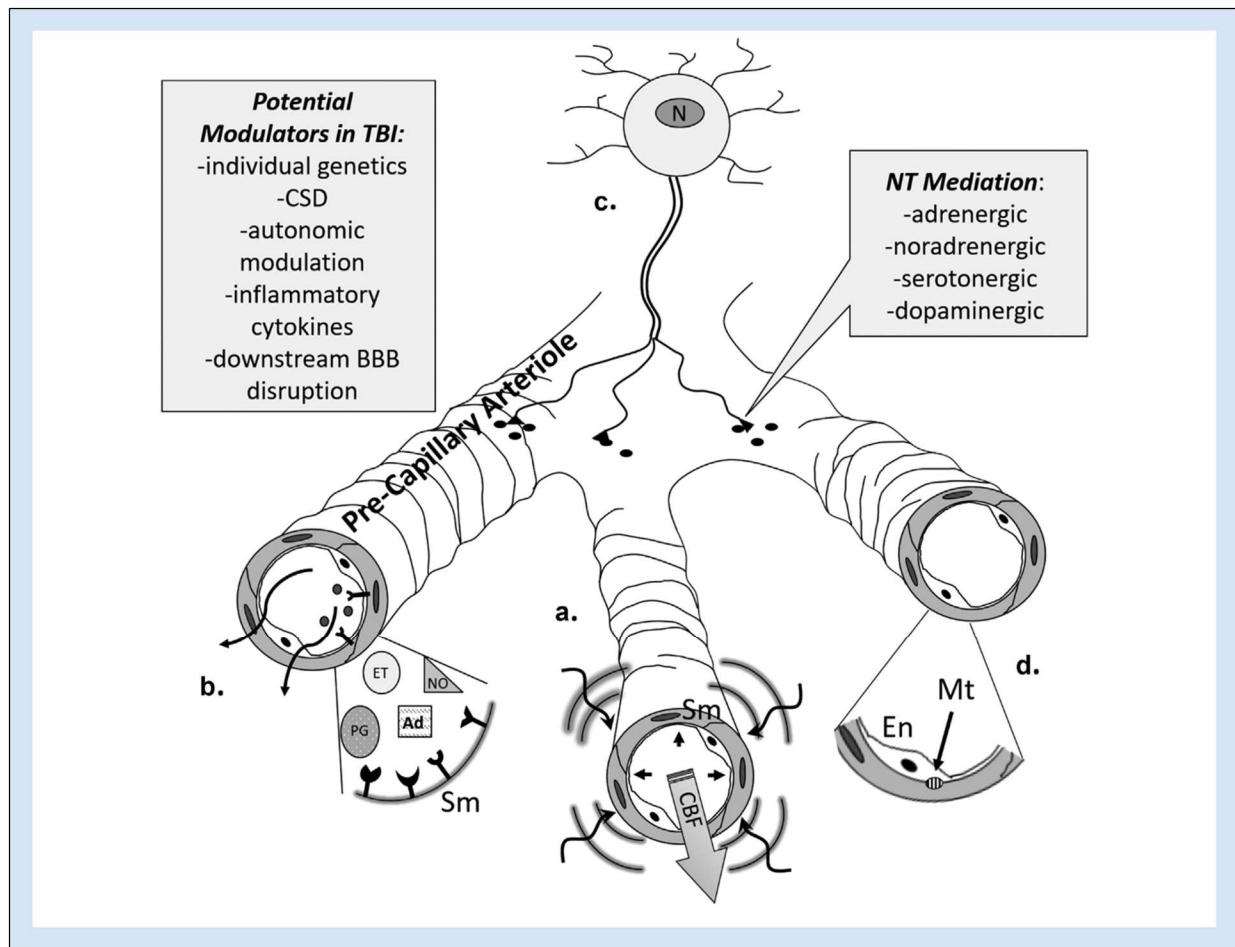


Fig.20 Adapted from: Zeiler FA, et al. Br J Anaesth. 2020.

Together, these regulatory pathways determine cerebrovascular resistance. The cerebrovascular component is the primary determinant of how changes in perfusion pressure translate into changes in cerebral blood flow. When resistance adjusts appropriately, cerebral autoregulation is preserved. When resistance fails to adjust, blood flow becomes increasingly dependent on pressure.

Chapter 2. Continuous Cerebral Autoregulation monitoring in clinical practice

2.1 Methods for assessment of CBF regulation in clinical practice

Assessment of cerebral blood flow regulation in clinical practice has progressed from intermittent physiological measurements to continuous multimodal strategies capable of capturing the dynamic behavior of the cerebrovascular system. These developments have been shaped by the growing understanding of autoregulatory physiology and by advances in bedside monitoring technology that permit real time examination of the relationship between arterial pressure and cerebral blood flow surrogates. Contemporary approaches seek to identify whether spontaneous fluctuations in perfusion pressure are appropriately buffered by vascular reactivity or whether cerebral blood flow varies passively with pressure, indicating impaired autoregulation. (25)

Among the earliest clinical methods used to examine cerebrovascular reactivity, transcranial Doppler ultrasonography has long been considered the reference standard for the non-invasive assessment of dynamic cerebral blood flow regulation. Transcranial Doppler provides beat-to-beat measurements of blood flow velocity in the major intracranial arteries and allows direct evaluation of cerebrovascular responses to spontaneous or induced changes in perfusion pressure. Its high temporal resolution and ability to track slow-wave oscillations render it uniquely suited to autoregulation research. However, despite its physiological strengths, transcranial Doppler has important practical limitations that restrict its use in many clinical settings. Continuous monitoring requires stable fixation of the probe, a condition that is difficult to maintain reliably in agitated or critically ill patients. Moreover, suitable acoustic windows are not always available, particularly in infants and children, in whom skull thickness and fontanelle closure vary with development. Operator dependency, the requirement for uninterrupted insonation, and the technical challenges associated with prolonged recordings further limit its feasibility. As a consequence, although transcranial Doppler remains the gold standard for evaluating dynamic cerebrovascular reactivity, it satisfies the practical requirements of continuous bedside monitoring only in selected clinical environments. (43)

The widespread availability of high-resolution physiological data at the bedside has transformed the assessment of cerebral autoregulation. Digital acquisition of beat-to-beat arterial pressure, intracranial pressure, cerebral oxygenation, and other physiological signals has enabled the development of sophisticated online and offline analytical tools. Over the last two decades, dedicated monitoring platforms and software systems have been developed to analyze slow-wave interactions among physiological variables that reflect cerebrovascular responsiveness (44).

Modern analytical frameworks apply correlation methods, moving-window analyses, frequency-domain techniques, and coherence metrics to extract autoregulatory information previously inaccessible in routine clinical practice. Continuous, high-fidelity processing of physiological signals represents a major conceptual and technological advance, enabling near real-time visualization of cerebrovascular behavior. The maturation of these technologies has driven a substantial expansion of intracranial pressure-based autoregulation monitoring. Continuous arterial and intracranial pressure recordings allow derivation of vascular reactivity indices, most notably the pressure reactivity index (PRx), which quantifies the relationship between slow pressure oscillations and cerebrovascular responses. Automated software for continuous calculation and trend visualization has facilitated its adoption, shifting autoregulation monitoring from an experimental tool toward routine use in clinical research and specialized intensive care units (Fig. 21)

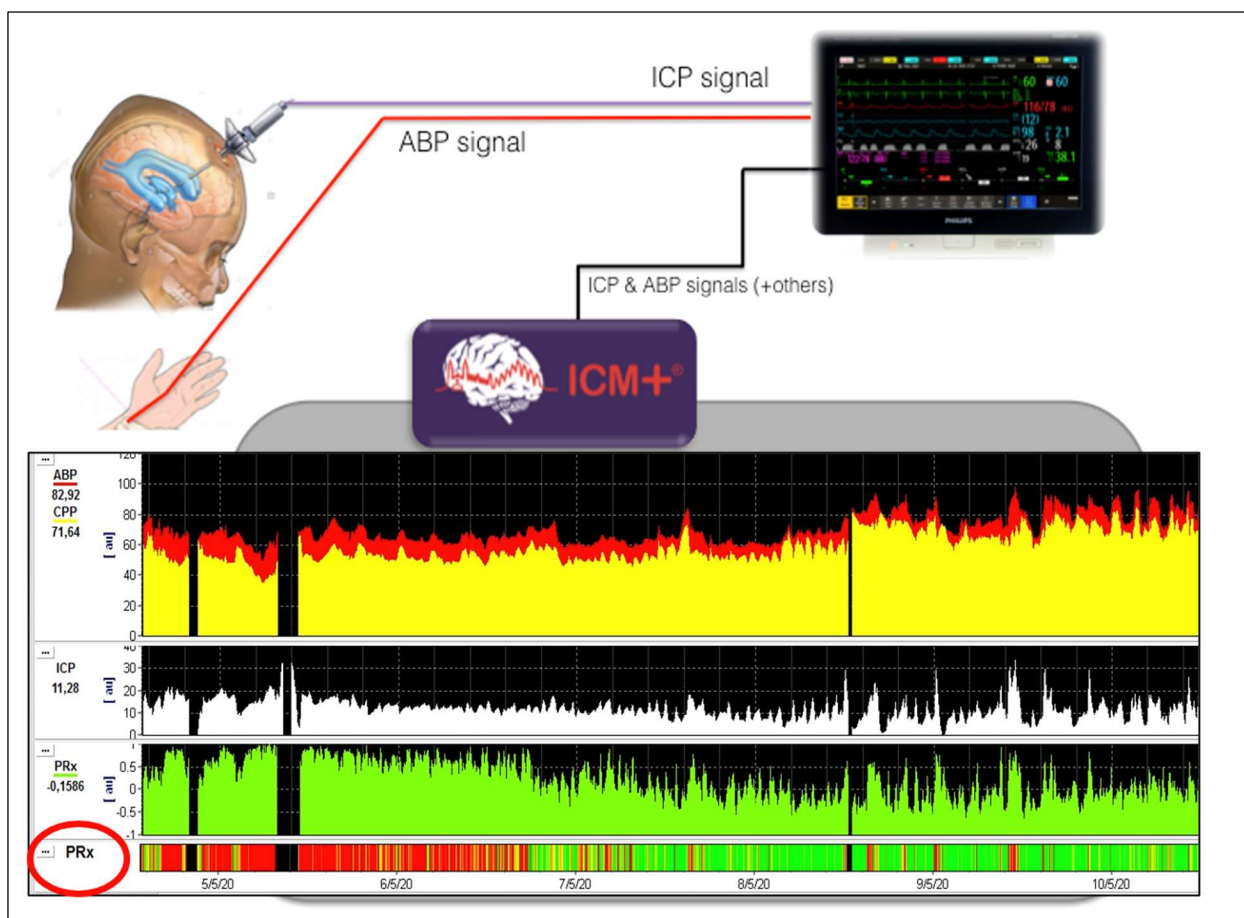


Fig.21 Pediatric ICU Internal Educational Material. Pezzato S, IRCCS Istituto G. Gaslini, 2025.

At the same time, non-invasive optical modalities have broadened the scope of autoregulation assessment beyond settings where invasive monitoring is available. Near infrared spectroscopy (NIRS) provides a continuous measure of regional cerebral oxygenation that correlates with changes in cerebral blood volume and, indirectly, with cerebral blood flow. By analyzing the relationship between arterial pressure and regional oxygen saturation across the slow wave frequency range, it is possible to derive indices of autoregulation analogous to those obtained from intracranial pressure. NIRS-based autoregulation metrics have shown promising concordance with pressure-based indices in several studies and have demonstrated feasibility in a wide range of clinical contexts. Because near infrared spectroscopy does not require invasive monitoring, its application extends to patient populations in which intracranial pressure monitoring is not indicated or is contraindicated. This includes neonates, infants, children, and adults undergoing major surgery or experiencing conditions that place them at risk for cerebral hypoperfusion. (45)

Taken together, these advancements have redefined how cerebral blood flow regulation is assessed at the bedside. Although transcranial Doppler remains the physiological gold standard for dynamic flow measurement, its practical limitations necessitated the development of alternative continuous methods. High resolution physiological data streams and advanced signal processing software have enabled continuous, automated evaluation of cerebrovascular reactivity using both invasive and non-invasive signals. Intracranial pressure-based techniques have matured into robust clinical tools, while NIRS-based approaches are expanding the reach of autoregulation monitoring into settings where invasive instrumentation is not available. These methodological innovations form the basis for contemporary autoregulation assessment and set the stage for the ICP based and NIRS based monitoring strategies described in the sections that follow. (46)

2.2 ICP-based autoregulation monitoring using Pressure Reactivity index (PRx)

Continuous cerebrovascular reactivity monitoring using intracranial pressure has become a central method for assessing autoregulatory function in acute brain injury. The pressure reactivity index is the most widely validated correlation-based metric derived from simultaneous recordings of arterial blood pressure and intracranial pressure. It quantifies the direction and magnitude of the relationship between slow-wave fluctuations in these signals and provides a surrogate for the state of cerebrovascular pressure reactivity.

The physiological foundation of the pressure reactivity index is the principle that functioning autoregulation produces compensatory changes in cerebrovascular resistance in response to

changes in arterial pressure. When arterial pressure increases, vasoconstriction limits the entry of blood volume into the intracranial compartment and attenuates associated changes in intracranial pressure. When autoregulation is impaired, this compensatory mechanism is lost and intracranial pressure varies passively with arterial pressure.

The pressure reactivity index is calculated as a moving Pearson correlation coefficient between thirty consecutive ten second mean values of arterial pressure and intracranial pressure, corresponding to a five-minute analysis window. (Fig. 22) This sampling strategy isolates slow-wave components in the frequency range relevant for autoregulation, typically below 0.05 Hertz. Negative or near zero pressure reactivity index values indicate that increases in arterial pressure are not transmitted into intracranial pressure, reflecting intact pressure reactivity. Progressively positive values indicate a pressure-passive state in which intracranial pressure follows arterial pressure, consistent with impaired autoregulation. (42)

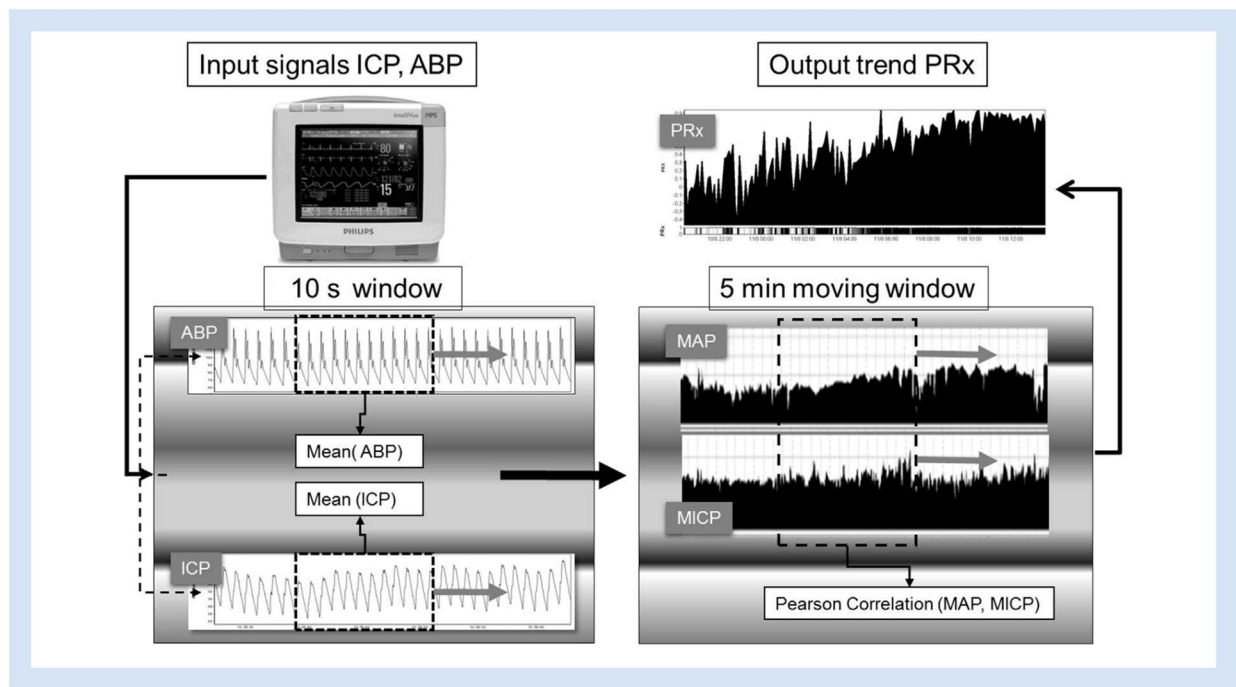


Fig.22 Adapted from: Zeiler FA, et al. Br J Anaesth. 2020.

Advances in high-resolution physiological waveform acquisition and bedside computational capabilities have enabled the continuous calculation of the pressure reactivity index. Dedicated automated software platforms perform real-time signal filtering, artifact rejection, and moving-window correlation analyses, allowing the index to be trended longitudinally and integrated with other physiological variables to characterize dynamic changes in cerebrovascular status. Multiple studies in both adult and pediatric populations have demonstrated that sustained elevations in

the pressure reactivity index are associated with intracranial hypertension, impaired compensatory reserve, metabolic crisis, and unfavorable clinical outcomes in severe traumatic brain injury. Collectively, these findings support the role of the pressure reactivity index as a robust physiological biomarker of cerebrovascular dysfunction.

The pressure reactivity index has also provided the methodological basis for computation of optimal cerebral perfusion pressure. By plotting the pressure reactivity index against cerebral perfusion pressure over extended time periods, a U-shaped curve can be generated in which the nadir identifies the perfusion pressure associated with the most favorable vascular reactivity. This individualized target represents the optimal pressure at which autoregulation appears most effective. The optimal cerebral perfusion pressure framework has been evaluated in several large cohorts and is increasingly used in research protocols investigating individualized perfusion targets. (47)

Despite its utility, pressure reactivity index monitoring has limitations. Accurate calculation depends on clean arterial and intracranial pressure waveforms. Catheter artifacts, dampened transduction systems, or abrupt signal perturbations can produce erroneous correlations. The index assumes that intracranial pressure fluctuations primarily reflect changes in cerebral blood volume, an assumption that may be altered in conditions with markedly reduced intracranial compliance. Furthermore, the method requires invasive intracranial pressure monitoring, restricting its applicability to patient populations with indications for ventriculostomy or intraparenchymal monitoring.

In pediatric populations, intracranial pressure monitoring is used less frequently than in adults, limiting the number of patients in whom pressure-reactivity index can be applied. Young and colleagues highlight that developmental differences in vascular reactivity and intracranial compliance may influence index behavior, although available pediatric reports indicate that pressure reactivity index patterns are physiologically interpretable and generally concordant with adult data. Broader applications will require further validation and integration with multimodal monitoring strategies. (48)

Overall, the pressure reactivity index is a robust and widely used method for continuous autoregulation assessment in acute brain injury. It provides a quantitative measure of cerebrovascular pressure reactivity, captures transitions between intact and impaired states, and supports individualized hemodynamic management frameworks based on optimal cerebral perfusion pressure. Its limitations are primarily related to the need for invasive monitoring and sensitivity to signal quality, but within appropriate clinical contexts it remains the most extensively validated intracranial pressure based autoregulatory metric.

2.3 NIRS-based autoregulation monitoring using Cerebral Oximetry index (COx)

Near infrared spectroscopy has emerged as a practical alternative for autoregulation monitoring in clinical contexts where invasive intracranial pressure monitoring or continuous transcranial Doppler insonation is not feasible. Near infrared spectroscopy provides continuous regional cerebral oxygen saturation, which reflects the relative balance between cerebral oxygen delivery and consumption. Because cerebral oxygen saturation varies with changes in cerebral blood volume and flow, and because slow-wave oscillations in arterial pressure can partially modulate these variables, near infrared spectroscopy signals can be used as indirect markers of cerebrovascular reactivity. (45) The cerebral oximetry index is the most widely described correlation-based autoregulation metric derived from near infrared spectroscopy. It is computed as a moving Pearson correlation coefficient between slow wave-induced fluctuations in mean arterial pressure and near infrared spectroscopy regional cerebral oxygen saturation. (Fig. 23) The analytical framework parallels that of the pressure reactivity index, but substitutes intracranial pressure with a non-invasive optical surrogate. Continuous recordings are typically processed using ten second mean values over a five-minute sliding time window to isolate the frequency range relevant for autoregulatory behavior, usually between 0.05 and 0.003 Hertz. (49)

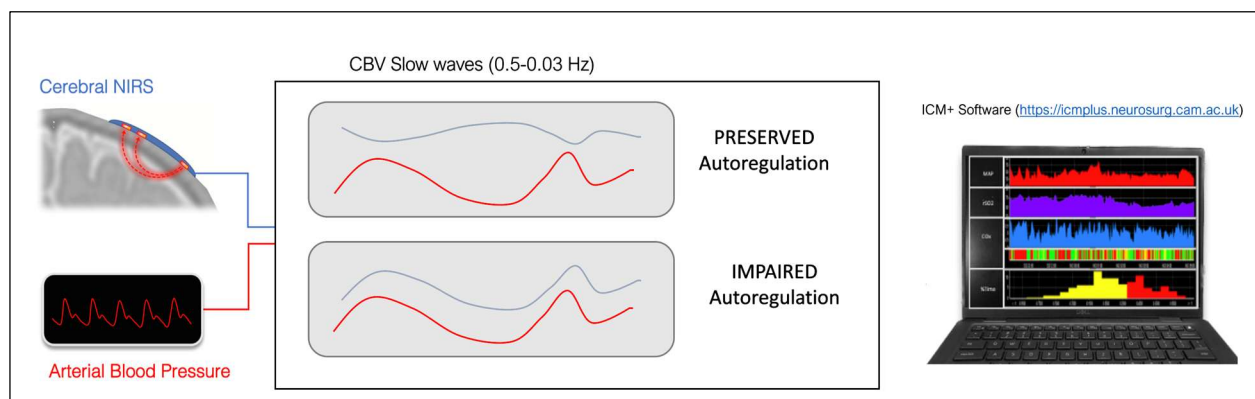


Fig.23 Pezzato S, Pediatric ICU Internal Educational Material. IRCCS Istituto G. Gaslini, 2025.

The physiological assumption underlying the cerebral oximetry index is that intact autoregulation attenuates the effect of arterial pressure fluctuations on cerebral blood flow and cerebral blood volume, resulting in minimal changes in cerebral oxygen saturation. When autoregulation is impaired, cerebral blood flow becomes pressure dependent and regional cerebral oxygen saturation varies directly with arterial pressure. Accordingly, cerebral oximetry index values near zero or negative indicate preserved autoregulatory function, whereas progressively positive values reflect increasing degrees of pressure-passivity. (Fig.24)

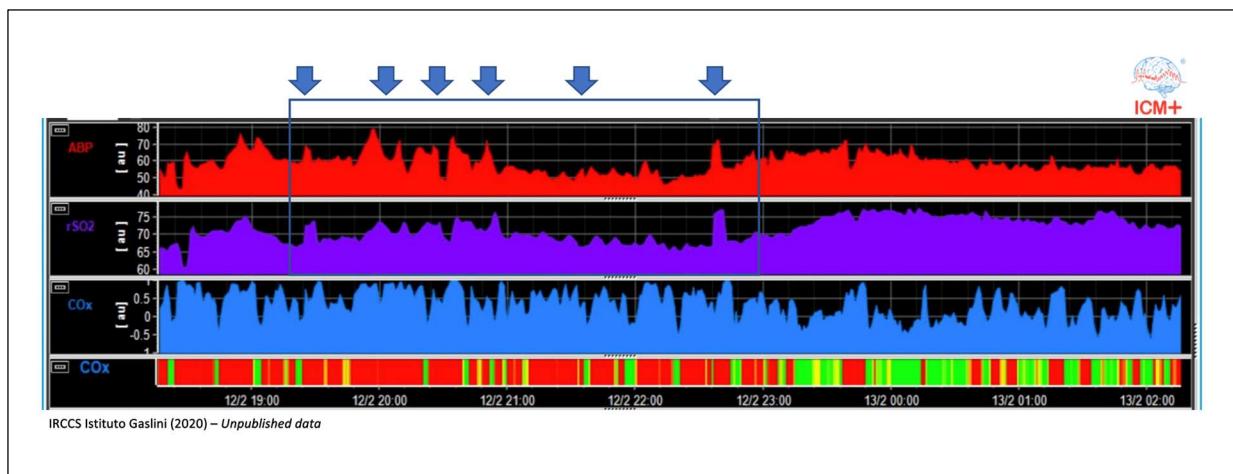


Fig.24 Pezzato S, Pediatric ICU Internal Educational Material. IRCCS Istituto G. Gaslini, 2025.

In one of their seminal studies, Brady and colleagues demonstrated strong concordance between the cerebral oximetry index and the pressure reactivity index under controlled conditions, and showed that the cerebral oximetry index is capable of detecting transitions between intact and impaired autoregulation. The noninvasive nature of near-infrared spectroscopy enables prolonged monitoring without the risks associated with intracranial instrumentation, making the cerebral oximetry index particularly well suited to clinical settings in which invasive monitoring is unavailable or contraindicated. (50)

NIRS-based autoregulation methods offer several advantages. The sensors are easy to apply, require minimal calibration, and provide stable recordings even in patients who cannot tolerate prolonged transcranial Doppler insonation. The technique is applicable to populations with open fontanelles, structural cranial abnormalities, or conditions in which intracranial pressure monitoring is not clinically indicated. Continuous monitoring can be performed during surgery, extracorporeal membrane oxygenation, or hemodynamic instability, providing data that may help identify periods of vulnerability to cerebral hypoperfusion.

However, important methodological considerations must be acknowledged. Near-infrared spectroscopy measures a composite signal from arterial, capillary, and predominantly venous compartments; consequently, cerebral oxygen saturation may be influenced by extracerebral tissues, scalp perfusion, oxygen extraction, and systemic oxygenation. (51) These factors introduce noise and may reduce the specificity of the cerebral oximetry index, with additional degradation from patient movement, probe displacement, or ambient light. Moreover, near-infrared spectroscopy does not directly measure cerebral blood flow, and interpretation of cerebral oximetry index values relies on physiological assumptions linking blood flow, blood volume, and oxygen saturation. (52)

Despite these limitations, cerebral oximetry index monitoring represents a promising method for expanding autoregulation assessment to a broader range of clinical environments. It enables clinicians to investigate cerebrovascular reactivity even in the absence of invasive intracranial pressure measurements and provides a foundation for determining individualized optimal mean arterial pressure targets.

Overall, the cerebral oximetry index (COx) offers a clinically feasible and physiologically grounded approach to continuous non-invasive autoregulation monitoring. While invasive methods remain the reference standard in specific contexts, near infrared spectroscopy-based approaches are increasingly recognized as complementary tools that can provide meaningful cerebrovascular information across a wide spectrum of critically ill patients.

2.4 Optimal Cerebral Perfusion Pressure (CPP_{opt}) Determination based on PR_x

The determination of optimal cerebral perfusion pressure has become a central application of continuous cerebrovascular reactivity monitoring and is based on the established relationship between the pressure reactivity index and cerebral perfusion pressure. Continuous calculation of the pressure reactivity index allows investigators to map vascular reactivity across a broad range of spontaneous perfusion pressures, and this mapping forms the foundation of the optimal cerebral perfusion pressure construct. The method involves binning cerebral perfusion pressure values, typically in five millimeters of mercury increments, and computing the average pressure reactivity index for each bin over moving temporal windows. When these paired values are plotted, the pressure reactivity index commonly displays a characteristic U-shaped relationship across the cerebral perfusion pressure spectrum. (Fig. 25)

At low cerebral perfusion pressure values, the pressure reactivity index is elevated, indicating pressure-passive flow due to exhausted vasodilatory reserve. As cerebral perfusion pressure increases toward a physiologically favorable range, the pressure reactivity index decreases toward zero, reflecting improved vasomotor responsiveness and more effective autoregulatory control. At higher cerebral perfusion pressures, the pressure reactivity index rises again as vasoconstrictive capacity becomes limited. The nadir of this parabolic relationship corresponds to the cerebral perfusion pressure at which cerebrovascular reactivity appears maximal and is defined as the optimal cerebral perfusion pressure. (53) Continuous curve fitting and iterative recalculation of this nadir allow dynamic tracking of optimal cerebral perfusion pressure over time and that deviation from this individualized target is associated with higher intracranial pressure burden, worsening metabolic dysfunction, reduced brain tissue oxygenation, and unfavorable neurological outcomes in traumatic brain injury. (54)

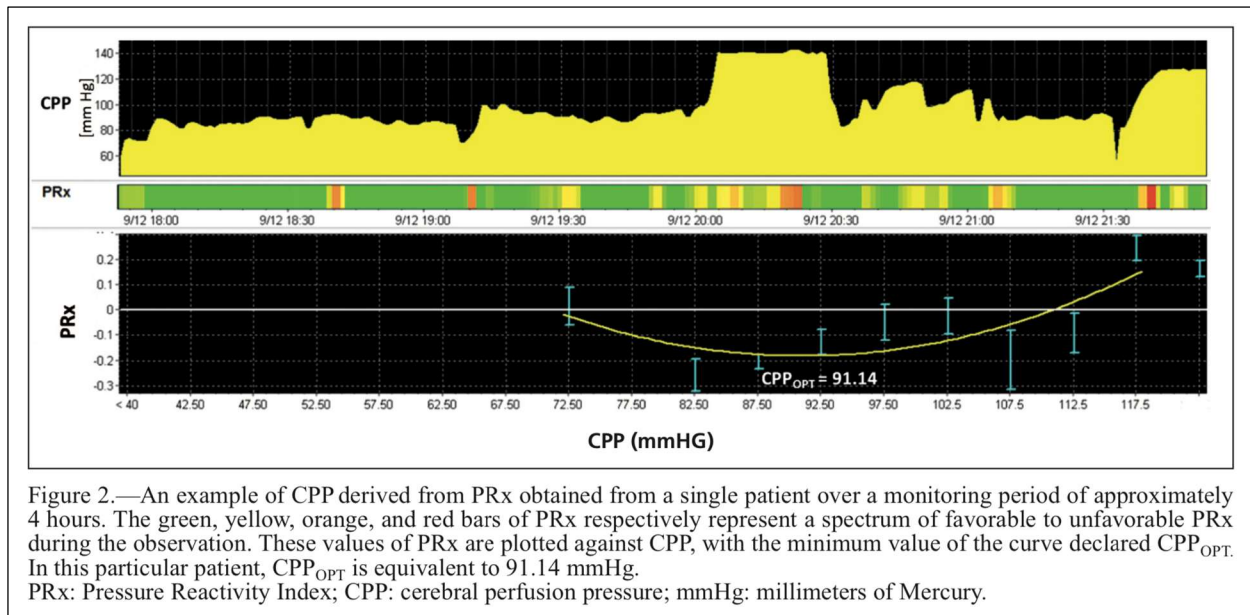


Fig 25 Adapted from: Calviello LA, et al. Minerva Anestesiol 2017.

The optimal cerebral perfusion pressure framework therefore represents a physiologically grounded strategy for individualized hemodynamic management, although its accuracy depends on artifact-free pressure recordings, robust signal processing, and preserved assumptions regarding the relationship between intracranial pressure, cerebral blood volume, and autoregulatory status. Moreover, its generalizability in pediatric populations remains limited by age-dependent differences in autoregulatory range and intracranial mechanics, underscoring the need for further validation before widespread clinical adoption.

2.5 Optimal Mean Arterial Pressure (MAPopt) determination based on COx

The determination of optimal mean arterial pressure using NIRS-based autoregulation monitoring extends the logic of pressure reactivity index derived optimal cerebral perfusion pressure into a fully noninvasive framework that is applicable across a broad range of clinical populations, particularly where invasive intracranial pressure monitoring is not feasible. The method relies on the cerebral oximetry index, a correlation-based metric that quantifies the degree to which slow-wave fluctuations in regional cerebral oxygen saturation covary with corresponding fluctuations in mean arterial pressure. Continuous near infrared spectroscopy recordings and arterial pressure waveforms are processed into ten second averaged segments over a five-minute moving window to isolate the frequency band most relevant for autoregulatory behavior.

As with optimal cerebral perfusion pressure analysis, mean arterial pressure values are grouped into pressure bins, and the mean cerebral oximetry index for each bin is computed to construct a curve describing the relationship between vascular reactivity and systemic pressure. (Fig. 26)

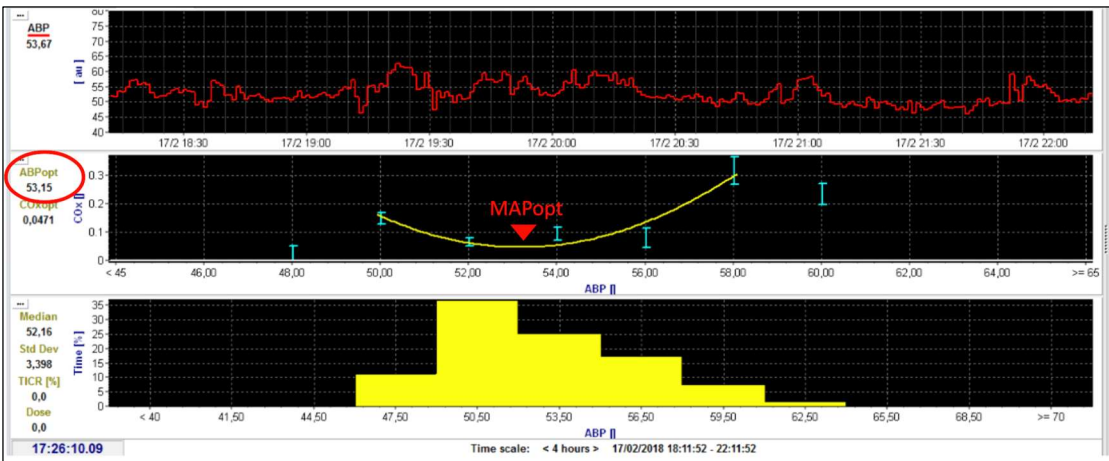


Fig.26 Pediatric ICU Internal Educational Material. Pezzato S, IRCCS Istituto G. Gaslini, 2025.

Brady and colleagues first demonstrated that this curve often exhibits a U-shaped configuration, analogous to the pressure reactivity index–cerebral perfusion pressure relationship, with higher cerebral oximetry index values at low and high mean arterial pressures indicating pressure passivity and a central nadir identifying the pressure range of most effective autoregulation. This nadir defines the optimal mean arterial pressure, representing a noninvasive arterial pressure target that best supports stable cerebrovascular reactivity. (55) (Fig. 22)

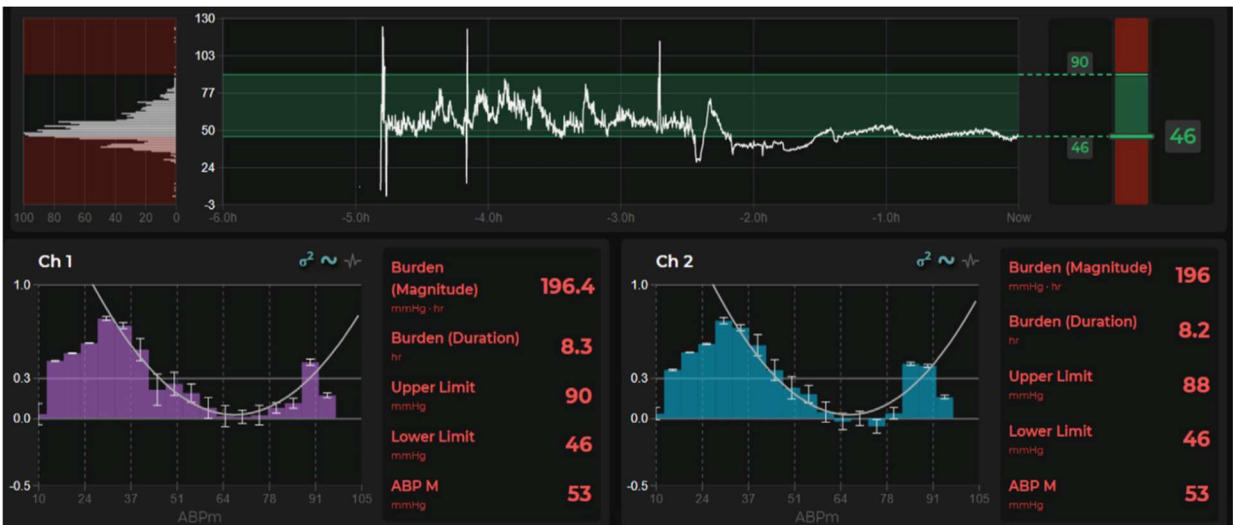


Fig.22 Adapted from: Vu EL, et al. Br J Anaesth. 2024.

At the same time, interpretation requires caution because near infrared spectroscopy signals derive predominantly from the venous compartment and are susceptible to contamination by extracerebral tissue, scalp perfusion, changes in oxygen extraction, and motion-related artifacts. (51) These influences can degrade the specificity of the cerebral oximetry index or distort the shape of the MAP-COx autoregulation curve, thereby affecting the accuracy of optimal mean arterial pressure estimation. Nevertheless, the framework provides a practical and physiologically coherent method for tailoring hemodynamic management to individual cerebrovascular conditions using a noninvasive monitoring modality.

SECTION III – Advancing Cerebral Autoregulation Monitoring in Pediatric Critically-ill Patients

Chapter 1. PRx Monitoring in Pediatric Severe Traumatic Brain Injury

1.1 Background

Severe traumatic brain injury (TBI) represents one of the most significant causes of death and long-term disability in childhood, with global incidence estimates ranging between 47 and 280 cases per 100,000 children per year. Despite improvements in trauma systems and critical care, morbidity remains substantial: nearly two-thirds of children who survive moderate or severe TBI experience persistent functional, cognitive or behavioral impairments. The enduring impact of TBI on neurodevelopment, academic performance and psychosocial integration underscores the importance of timely and effective neuroprotective strategies during the acute phase of care. (56)

The pathophysiology of pediatric TBI is complex and evolves over time. Primary mechanical injury initiates a cascade of secondary insults that may include cerebral edema, impaired autoregulatory capacity, metabolic crisis, excitotoxicity and inflammatory responses. (Fig. 23) Among these mechanisms, the development of intracranial hypertension occupies a central role. Rising intracranial pressure (ICP) reduces cerebral perfusion pressure (CPP), thereby threatening cerebral blood flow and oxygen delivery to metabolically vulnerable tissue.

In children, this process is further complicated by age-dependent anatomical and physiological characteristics. Greater brain water content, higher baseline cerebral metabolism and differences in cranial compliance influence both the manifestations of intracranial hypertension and the brain's tolerance to fluctuations in perfusion. These features contribute to the increased susceptibility of younger children to derangements in cerebrovascular control following TBI. (57)

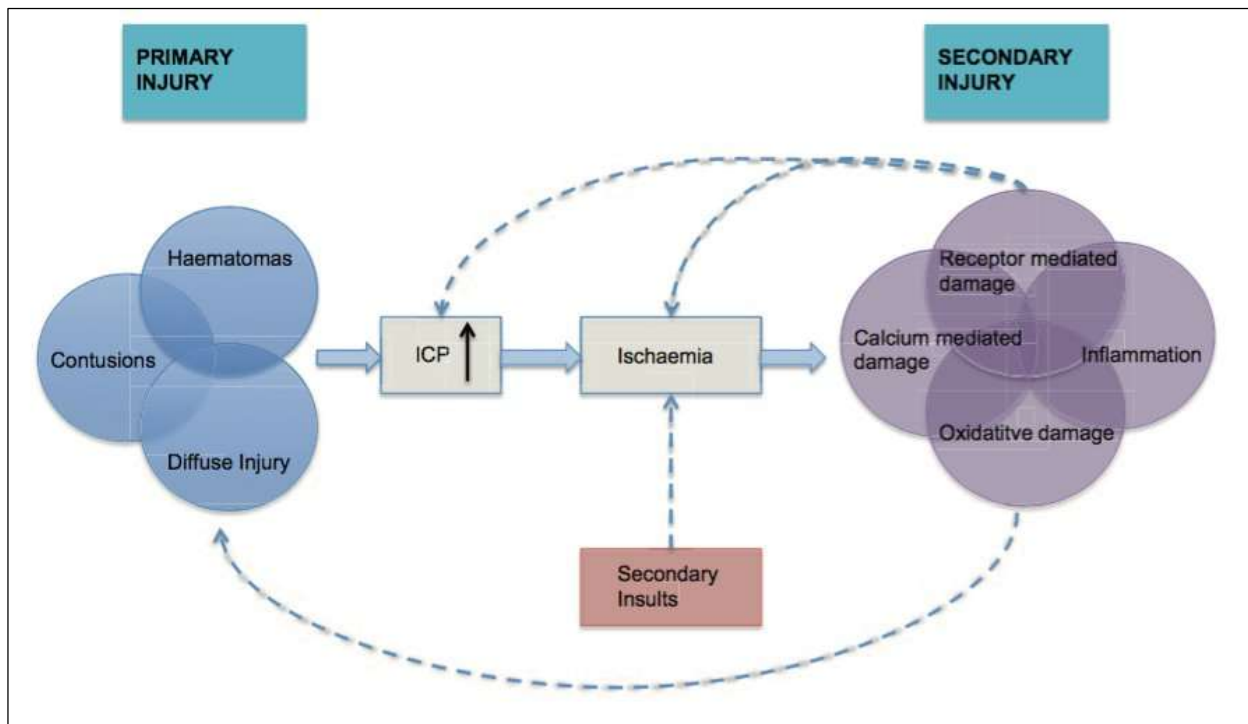


Fig.23 Adapted from: Piper I, et al. 2014.

Contemporary management in pediatric neurocritical care therefore places strong emphasis on minimizing secondary brain injury through the prevention and treatment of intracranial hypertension. Standard approaches target an ICP less than 20 mmHg and a CPP between 40 and 50 mmHg, thresholds that stem largely from retrospective studies and expert consensus rather than high-level, age-specific evidence. However, the applicability of these fixed cut-points across the broad pediatric age range has been questioned. Developmental changes in cerebral perfusion, skull compliance and autoregulatory responsiveness result in considerable inter-patient variability, suggesting that uniform ICP and CPP thresholds may be suboptimal for many patients. Moreover, intracranial hypertension may represent only one facet of secondary injury; fluctuations in perfusion pressure, loss of vascular reactivity and episodic insults of varying intensity and duration can also influence outcome yet remain undetected by static threshold-based monitoring.

These limitations highlight a critical gap in current pediatric TBI management: existing strategies rely primarily on coarse physiological targets that may not reflect the dynamic cerebrovascular physiology of the injured pediatric brain. Although maintaining adequate CPP and controlling ICP remain cornerstones of care, these metrics alone cannot capture the moment-to-moment interaction between arterial pressure, intracranial dynamics and cerebral blood flow regulation.

(58)

1.2 International Guidelines and Clinical Practice

1.2.1 Evolution and Structure of Contemporary Guidelines

The contemporary management of pediatric severe traumatic brain injury is anchored in the Brain Trauma Foundation Guidelines, most recently updated in 2019.(59) These guidelines consolidate the available evidence and propose a tiered clinical framework whose overarching aim is the prevention of secondary brain injury. Their structure reflects a physiologically grounded, stepwise escalation of care that begins with the establishment of baseline neuroprotective measures, proceeds through first-tier interventions targeting intracranial pressure, cerebral perfusion pressure and brain tissue oxygenation, and culminates in second-tier therapies for refractory cases. Although conceived as a decision-support tool rather than a rigid protocol, the guidelines have become a widely adopted reference point in pediatric neurocritical care, providing clinicians with a shared conceptual foundation and facilitating consistency across institutions. The accompanying flowchart, presented in both the text and graphical summary of the guidelines, visually articulates this treatment hierarchy by linking physiological thresholds with corresponding interventions and recommending reassessment after each therapeutic step.

Baseline management establishes the physiological conditions necessary for the prevention of secondary injury. This includes adequate sedation and analgesia to reduce agitation and metabolic demand, lung-protective mechanical ventilation to avoid both hypoxia and excessive hypocapnia, normothermia, maintenance of fluid and electrolyte balance with particular attention to serum sodium, and early nutritional support. Once these foundational elements are in place, first-tier therapies aim to correct deviations from the three core parameters identified by the guidelines: intracranial pressure, cerebral perfusion pressure and brain tissue oxygen tension, where monitored. The recommended treatment threshold for intracranial pressure is 20 mmHg sustained for at least five minutes, while cerebral perfusion pressure should be maintained at a minimum of 40 mmHg, with higher targets considered in older children. Management options include external ventricular drainage, hyperosmolar agents, vasopressor therapy, neuromuscular blockade and optimization of ventilation and oxygenation strategies. When brain tissue oxygen monitoring is available, a minimum threshold of 10 millimeters of mercury is advised, and the guidelines outline appropriate corrective actions. (Fig.24)

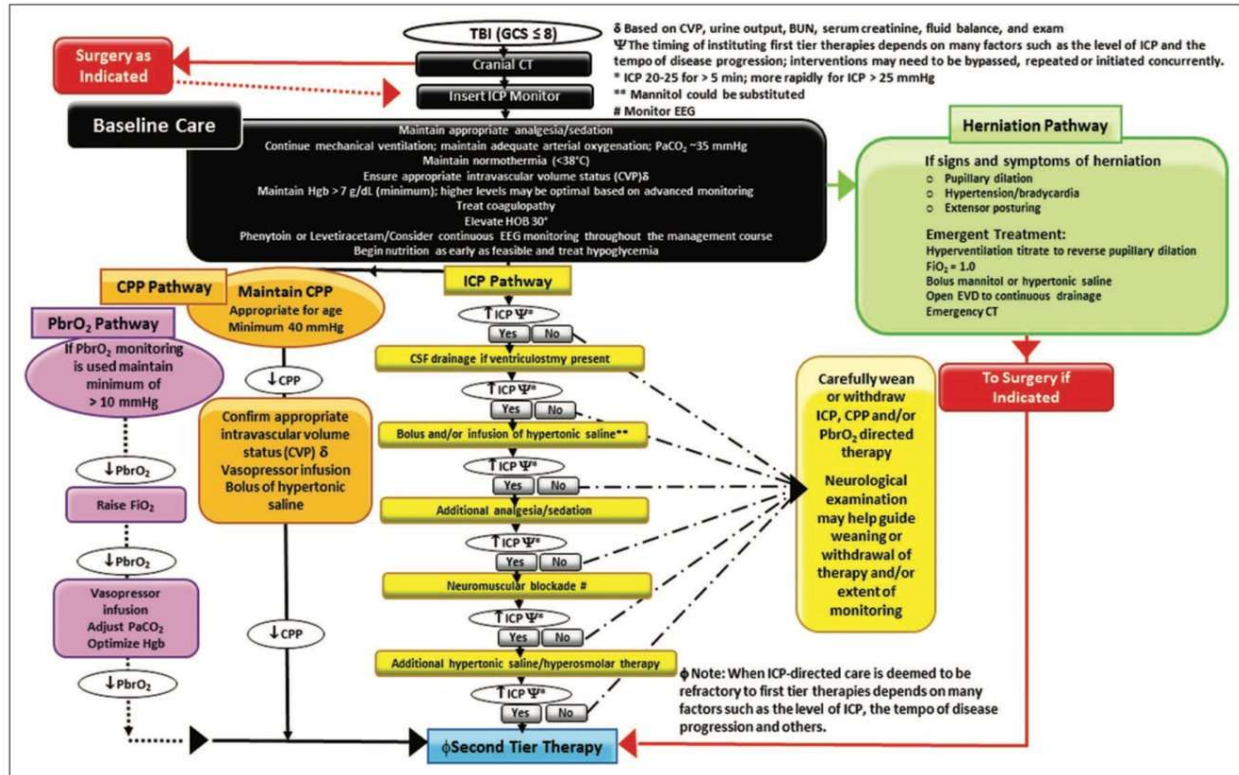


Fig.24 Adapted from: Kochanek PM, et al. *Pediatr Crit Care Med*, 2019.

Second-tier therapies are reserved for clinical scenarios in which intracranial hypertension persists despite optimized first-tier management, or when cerebral perfusion and oxygen delivery remain inadequate despite correction of systemic and intracranial physiological derangements. These interventions are inherently more invasive and carry a higher risk of complications, and therefore are typically implemented within a multidisciplinary decision-making framework. Therapeutic options at this stage include decompressive craniectomy, high-dose barbiturate therapy for metabolic suppression, intensified hyperosmolar strategies, controlled hyperventilation aimed at short-term reduction of intracranial pressure, and controlled moderate hypothermia applied under carefully selected conditions.

Escalation to second-tier therapies is accompanied by a strong recommendation to reassess the intracranial compartment with repeat neuroimaging to identify evolving structural lesions, mass effect, or secondary injury patterns that may influence treatment selection. In parallel, the integration of advanced neuromonitoring technologies (including PRx monitoring) is encouraged to better characterize cerebral physiology, including cerebral perfusion, oxygenation, and metabolic status. Multimodal data may help distinguish potentially reversible physiological disturbances from irreversible injury, support individualized therapeutic targets, and guide ongoing titration of high-risk interventions in this critically ill population. (Fig. 25)

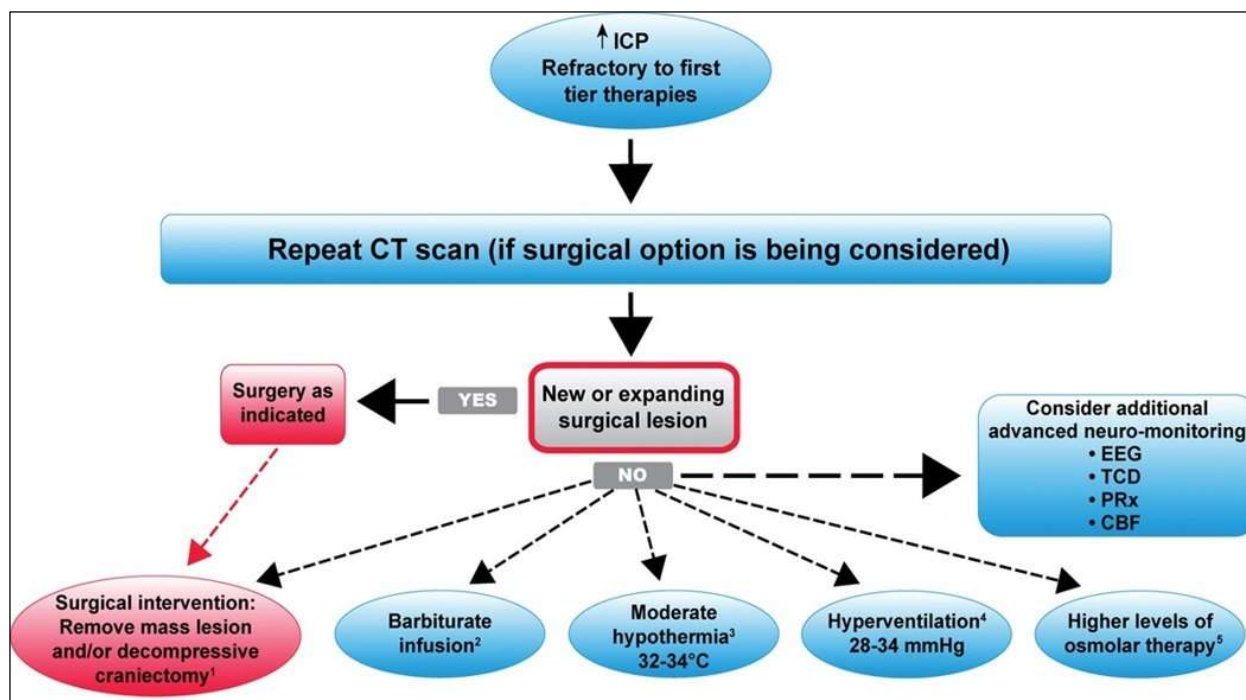


Fig.25 Adapted from: Kochanek PM, et al. *Pediatr Crit Care Med*, 2019.

1.2.2 Clinical Application and Limitations of the Guideline Framework

Although the guidelines have played a central role in promoting structured and physiologically informed management, several limitations constrain their application in contemporary practice. Many recommendations are supported by low-quality evidence and reflect consensus rather than definitive, age-specific clinical data. The often-cited thresholds for intracranial pressure and cerebral perfusion pressure represent minimum acceptable values rather than optimal targets, yet in daily practice they are frequently applied as rigid cut-points. This is problematic in pediatrics, where developmental differences in cranial compliance, vascular responsiveness, and metabolic demand create substantial inter-patient variability. A uniform threshold approach therefore risks both undertreatment and overtreatment, depending on the child's individual physiology. (60)

Consistent with findings from a large, multicenter, international observational study of severe TBI in adults, investigators from high-volume, leading centers have emphasized that, although the algorithm is useful for guiding escalation of care, it does not sufficiently capture the dynamic and evolving physiology of the injured pediatric brain. The interactions between therapies are nonlinear and context dependent. Vasopressor support, osmotherapy or ventilatory adjustments can have markedly different effects on cerebral blood flow depending on the integrity of autoregulation, the presence of intracranial hypertension or evolving edema, yet the guidelines offer little explicit guidance for interpreting these interactions.

Furthermore, the flowchart provides a linear sequence of interventions that may not align with the fluctuating temporal pattern of secondary injury, which often develops in cycles of deterioration and partial recovery. The complexity of bedside decision-making is therefore underestimated by the simplified structure of the guideline algorithm. (61)

1.2.3 The Gap Between Guideline Recommendations and Physiology-Informed Care

Despite sustained efforts to standardize the management of pediatric severe traumatic brain injury, current guideline frameworks remain insufficiently aligned with the dynamic and heterogeneous pathophysiology of the injured developing brain. As underscored in recent comprehensive reviews, including that by Figaji, the pediatric evidence base remains limited, resulting in a scarcity of strong recommendations and continued reliance on simplified, threshold-based management strategies. Although these guidelines provide an essential structure for clinical decision-making and escalation of care, they do not adequately account for the temporal evolution of secondary injury mechanisms or the substantial inter-individual variability that characterizes pediatric cerebrovascular and metabolic physiology. (58)

This limitation becomes particularly evident when pediatric practice is considered in the context of insights derived from large contemporary adult datasets. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study has demonstrated that neurological outcome in severe TBI is more closely associated with the burden and duration of physiologic derangements, such as intracranial hypertension, than with isolated threshold excursions. These findings challenge static management paradigms and emphasize the importance of continuous, high-resolution physiological assessment. However, despite the influence of CENTER-TBI in reshaping conceptual approaches to adult neurocritical care, its central insights regarding dynamic injury physiology have not yet been systematically incorporated into pediatric treatment algorithms. (62)

A critical gap in current pediatric guidelines is the absence of structured integration of advanced physiologic monitoring into therapeutic pathways. While the potential value of modalities such as brain tissue oxygen monitoring, transcranial Doppler ultrasonography, and indices of cerebrovascular autoregulation is increasingly acknowledged, these tools remain adjunctive rather than foundational within guideline-directed care.

Consequently, clinicians lack formalized strategies for interpreting multimodal physiologic data or for translating continuous, high-resolution signals into individualized therapeutic targets. This shortcoming persists despite growing pediatric evidence demonstrating that impaired autoregulation, cerebral hypoxia, and evolving intracranial dynamics are independently associated with outcome and cannot be reliably inferred from intracranial pressure or cerebral

perfusion pressure thresholds alone. Collectively, these considerations indicate that the current paradigm of severe pediatric TBI management has reached a critical juncture. Fixed, population-derived thresholds are insufficient to capture the complexity and temporal variability of evolving brain injury, and continued reliance on static parameters of risks, obscuring clinically relevant trajectories of secondary insult. A transition toward individualized, physiology-informed management is therefore warranted, incorporating cerebrovascular reactivity metrics such as the PRx as a mechanistically grounded means of characterizing the dynamic interaction between arterial pressure and intracranial dynamics in real time. (63)

1.3 Cerebral Autoregulation Monitoring: Current Evidence and Knowledge Gap

1.3.1 Foundations of Cerebrovascular Reactivity and Relevance to Pediatric TBI

Cerebrovascular autoregulation plays a pivotal role in limiting secondary brain injury by maintaining the stability of cerebral blood flow despite fluctuations in cerebral perfusion pressure. Seminal work by Marek Czosnyka and colleagues established the methodological and conceptual foundations of pressure reactivity assessment. (64) This foundational contribution catalyzed a major expansion of the original concept, subsequently led by the Brain Physics Laboratory at the University of Cambridge, which over more than three decades has pioneered and subsequently developed developed the most widely used advanced neuromonitoring software in the field, while also coordinating, fostering, and disseminating autoregulation research through an extensive international collaborative network. (65, 44)

This body of work has demonstrated that cerebrovascular reactivity indices, derived from continuous correlations between intracranial pressure and arterial blood pressure, provide dynamic and physiologically meaningful insights into cerebrovascular function that extend beyond those obtainable from static measurements of intracranial pressure or cerebral perfusion pressure alone. These principles are particularly relevant in pediatric traumatic brain injury, where the injured brain is characterized by pronounced developmental variability in intracranial compliance, cerebrovascular tone, and metabolic demand. As comprehensively reviewed by Figaji and colleagues, cerebral physiology in children undergoes rapid and non-linear maturation across early life, with age-dependent differences in baseline intracranial pressure, arterial blood pressure, cerebral blood flow, and cerebrovascular reactivity that fundamentally distinguish pediatric patients from adults. In this context, the application of uniform intracranial pressure or cerebral perfusion pressure thresholds fails to accommodate this physiological heterogeneity and may inadequately reflect the true risk of secondary brain injury.

Consequently, a substantial proportion of children may experience episodes of impaired cerebral perfusion or pressure-passive cerebral blood flow that remain undetected when conventional threshold-based monitoring strategies are applied. (20)

Continuous assessment of cerebrovascular autoregulation therefore offers a more nuanced characterization of the evolving cerebrovascular environment, capturing dynamic interactions between pressure, flow, and vascular reactivity, and may provide a physiology-informed framework to support individualized neuroprotective strategies in pediatric traumatic brain injury.

1.3.2 Evidence from Recent Multicenter and Large-Scale Cohort Studies

Early investigations into cerebrovascular autoregulation in pediatric severe traumatic brain injury, conducted by independent authors prior to 2020, established the feasibility and potential clinical relevance of continuous autoregulation monitoring using PRx-based metrics. Initial single-center studies demonstrated that the PRx could be reliably calculated in critically ill children and was associated with survival and neurological outcome. (Fig, 26a and 26b) Although limited in size, these early cohorts consistently showed that children with favorable outcomes exhibited lower PRx values and spent a greater proportion of time with intact autoregulation, whereas prolonged exposure to impaired autoregulation was linked to mortality and poor functional recovery. Importantly, these studies suggested that autoregulatory failure could occur despite apparently acceptable intracranial pressure or cerebral perfusion pressure values, highlighting a limitation of conventional threshold-based management and providing the physiological rationale for more individualized approaches to hemodynamic support. (48)

	Survivors (n = 7)		Non-survivors (n = 5)		P-value
	Median	IQR	Median	IQR	Mann-Whitney
ICP (mm Hg)	13.07	3.23	21.64	42.90	0.003
%time ICP > 20 mm Hg	9.73	9.84	60.47	67.40	0.003
MAP (mm Hg)	77.07	17.69	93.00	24.23	0.11
CPP (mm Hg)	63.42	8.10	61.11	38.62	0.91
CPPopt (mm Hg)	63.68	8.94	66.45	18.70	0.48
PRx (a.u.)	0.02	0.19	0.39	0.62	0.02
RAP (a.u.)	0.64	0.27	0.46	0.43	0.11
%time CPPopt available	55.96	13.84	43.48	28.32	0.02
Duration (hours)	75.3	22.3	82.3	61.8	0.87
%time CPPopt available	55.96	13.84	43.48	28.32	0.02
%time CPP-CPPopt < -10 mm Hg	4.70	5.68	15.17	30.74	0.04
%time CPP-CPPopt -10 to 10 mm Hg	90.68	12.64	70.61	21.78	0.02
%time CPP-CPPopt > 10 mm Hg	5.09	10.03	11.62	16.9	0.76

Fig.26a Adapted from: Young AM, et al. PLoS One,2016.

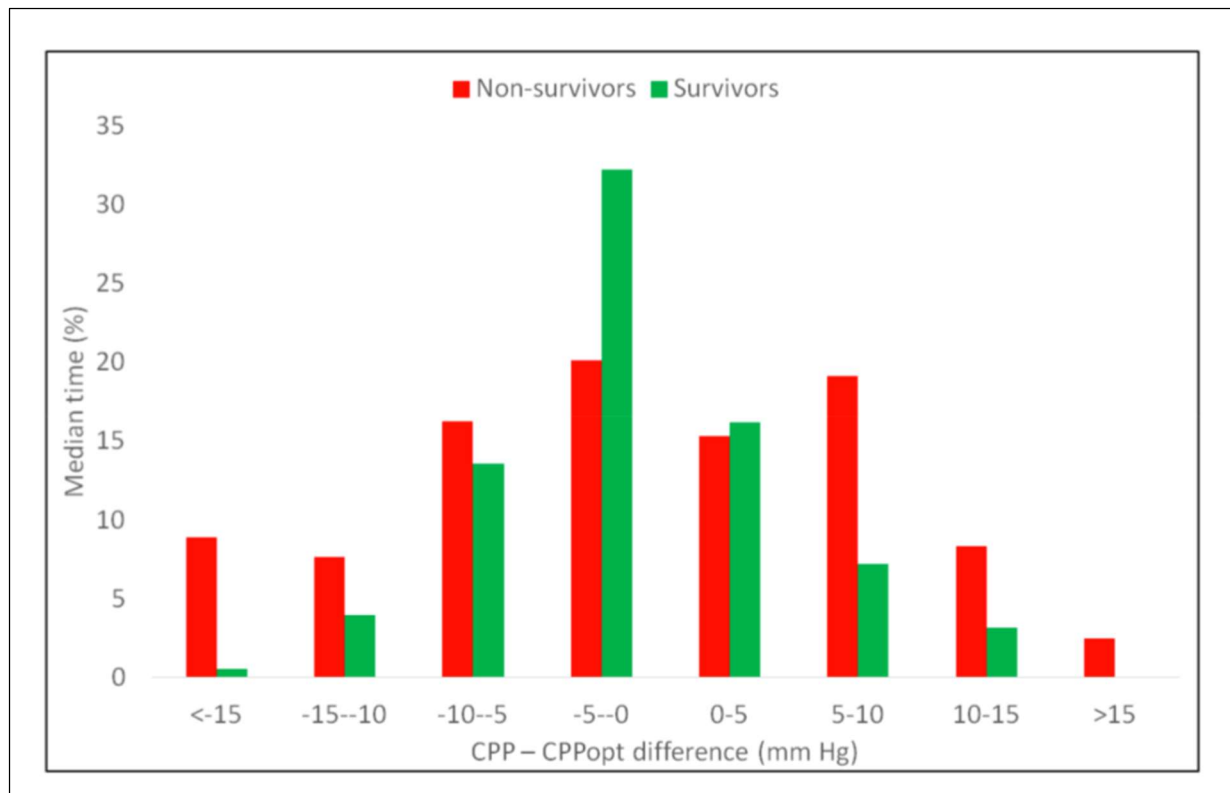


Fig.26b Adapted from: Young AM, et al. PLoS One,2016.

Building on this, a large single-center investigation from the Cape Town group has recently provided a major advance in scale, resolution, and statistical robustness. This retrospective cohort included 196 children with severe traumatic brain injury and analyzed more than 28,000 hours of high-frequency physiological data. In this population, PRx demonstrated a strong and independent association with both mortality and unfavorable neurological outcome. (66)

Children with poor outcomes exhibited persistently elevated PRx values throughout the early post-injury period, and a PRx threshold near 0.25 showed optimal discrimination for mortality. Crucially, the prognostic value of PRx remained significant after adjustment for intracranial pressure, cerebral perfusion pressure, age, and injury severity, and persisted even when analyses were restricted to periods in which intracranial pressure remained within conventionally acceptable ranges. (Fig. 27) These findings reinforced the concept that impaired autoregulation represents a distinct pathophysiological dimension of secondary brain injury that is not adequately captured by standard monitoring variables.

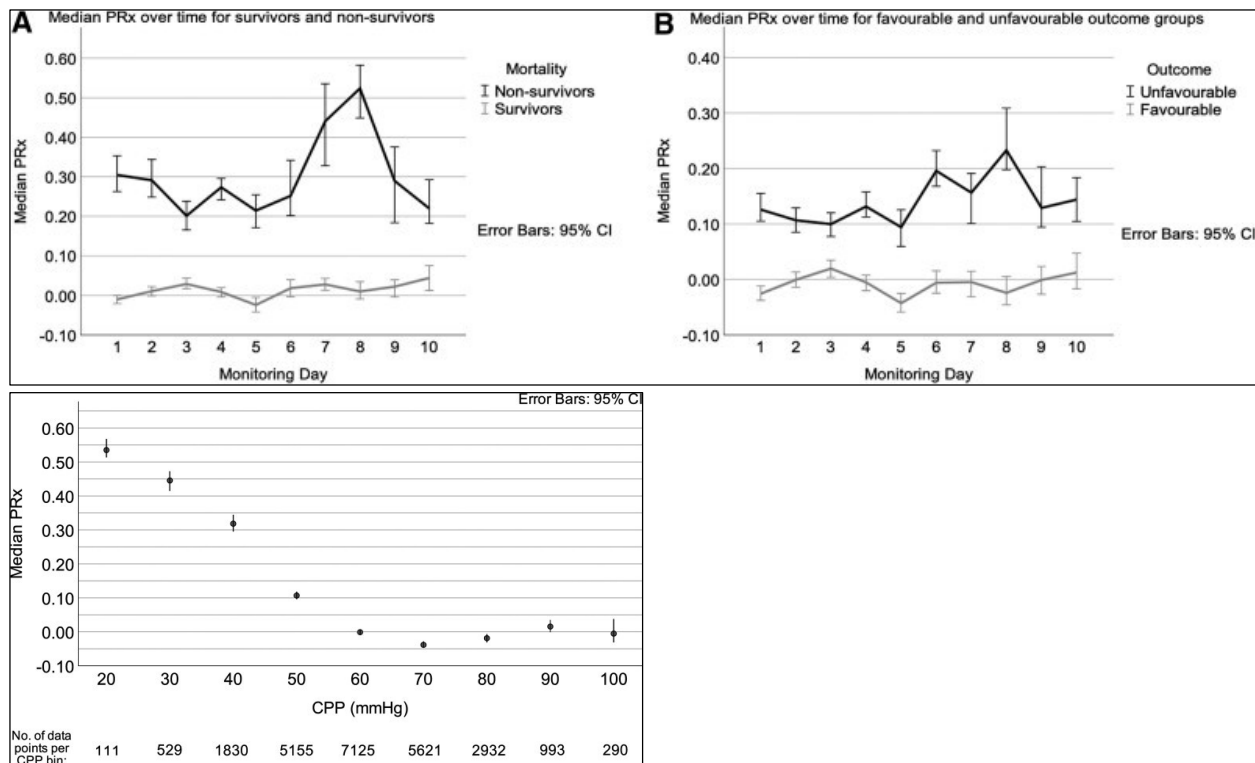


Fig.27 Adapted from: Smith CA et al. Crit Care Med. 2023

Extending and validating earlier single-center findings at scale, the STARSHIP study represents the most rigorous evaluation of cerebrovascular autoregulation in pediatric traumatic brain injury to date and constitutes a landmark contribution to the field. As the first prospective, multicenter observational study dedicated to PRx in children, STARSHIP enrolled 135 patients across ten pediatric intensive care units and paired high-resolution, time-synchronized physiological data with standardized twelve-month neurodevelopmental outcomes. (67)

The study confirmed that impaired autoregulation, reflected by elevated PRx values, was strongly associated with mortality and unfavorable functional outcome, independent of intracranial pressure, cerebral perfusion pressure, pupillary status, injury severity, and center-level effects. (Fig. 28) Distinct outcome-related thresholds were identified, with PRx values approaching 0.5 associated with mortality and values near zero associated with favorable recovery. In addition, temporal analyses demonstrated that clinical improvement was paralleled by progressive normalization of PRx over the first days following injury, supporting the biological plausibility of PRx as a dynamic marker of cerebrovascular recovery rather than a static risk indicator.

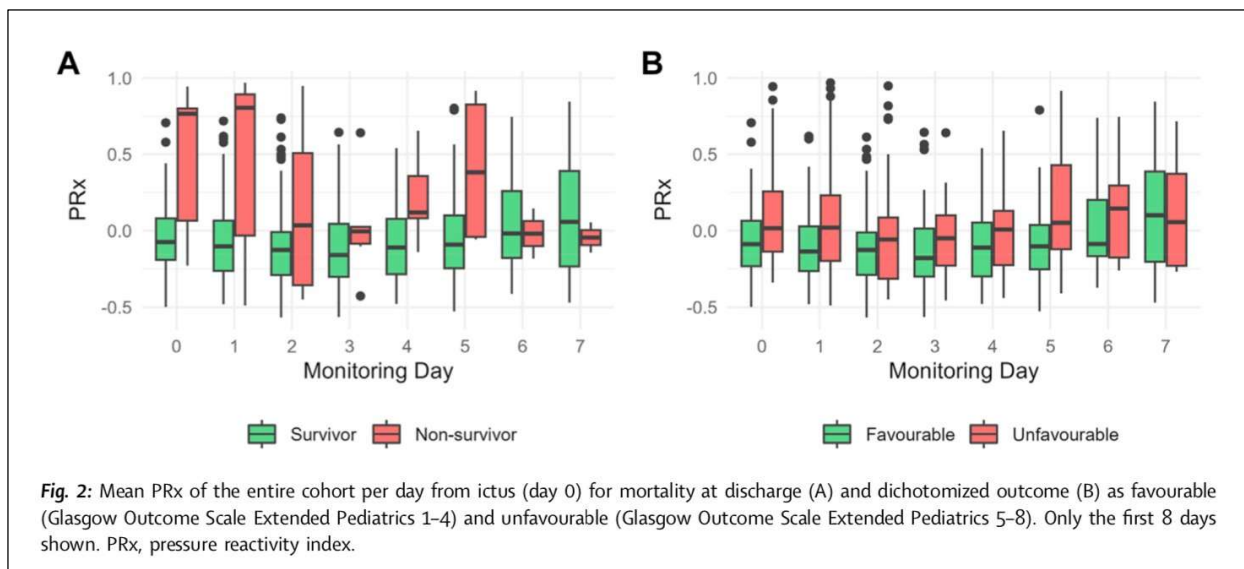


Fig.28 Adapted from: Agrawal S, et al. EClinicalMedicine, 2025.

1.3.3 Emerging Insights from Contemporary Evidence

The STARSHIP and Cape Town cohorts collectively demonstrate that cerebrovascular dysregulation is a key determinant of outcome after pediatric traumatic brain injury and that PRx provides prognostic information beyond traditional physiological measurements. These studies highlight that autoregulatory status is dynamic, evolving over days, and that early improvements in PRx are associated with better trajectories of recovery.

They also show that autoregulation impairment can exist independently of intracranial hypertension, suggesting that cerebrovascular dysfunction constitutes a parallel mechanism of secondary injury. Despite these advances, important questions remain. Neither study evaluated treatment strategies guided by PRx-informed targets, leaving the therapeutic implications of autoregulation monitoring untested. Furthermore, thresholds associated with outcome varied across cohorts, reflecting biological heterogeneity and suggesting that optimal perfusion targets may differ between patients and evolve over time. The evidence therefore moves the field beyond establishing the importance of autoregulation toward defining how cerebrovascular physiology should inform clinical management.

Addressing these gaps will require prospective interventional studies and large-scale data resources capable of integrating autoregulation metrics with outcomes, such as those developed within the KidsBrainIT consortium described below.

1.4 The KidsBrainIT Research Project: Aims and Methods

1.4.1 Rationale and Conceptual Framework

The KidsBrainIT initiative was developed to address a central challenge in the management of pediatric severe traumatic brain injury: the absence of validated, age-specific cerebral perfusion pressure targets and the limited availability of high-resolution physiological data needed to refine them. While adult neurocritical care research has demonstrated the feasibility and clinical relevance of autoregulation-based metrics such as PRx and CPPopt, the translation of these methodologies to children has been constrained by small sample sizes, heterogeneous monitoring practices, and the lack of a unified data infrastructure. The original KidsBrainIT concept paper articulated this need clearly, noting that validated CPPopt thresholds for children do not exist and that progress in the field requires a coordinated effort to collect standardized, high-fidelity bedside data across multiple centers. (68) The goal was to replicate and extend the success of the adult BrainIT program by creating a dedicated pediatric platform capable of supporting physiology-driven analyses of secondary brain injury and individualized perfusion targets. (69)

1.4.2 Aims of the Collaboration and Study Design

The collaboration was established with three interrelated objectives. The first was to create a multicenter, multidisciplinary and multinational pediatric brain monitoring consortium capable of prospectively collecting high-frequency physiological, clinical and outcome data from children with severe traumatic brain injury. The second was to use this central anonymized repository to support current and future hypothesis-driven analyses, including the examination of cerebrovascular autoregulation and optimal perfusion targets. The third was to test the working hypothesis that children who spend a greater proportion of their monitored time within individualized, model-derived CPPopt ranges experience improved clinical outcomes and better tolerance to intracranial hypertension. These aims reflected an explicit commitment to a precision-medicine approach, aligning pediatric neurocritical care with advances already seen in adult monitoring research.

KidsBrainIT was established as a prospective, observational cohort study enrolling children aged two to less than sixteen years who sustained life-threatening accidental brain injury requiring intensive care monitoring. The initial research network comprised seven pediatric intensive care units in the United Kingdom, together with additional centers in Spain, Belgium, and Romania, and was subsequently expanded to include further regions. (Fig.29) All participating centers adhered to a standardized protocol for data collection, anonymization, and secure transfer to the central KidsBrainIT databank.

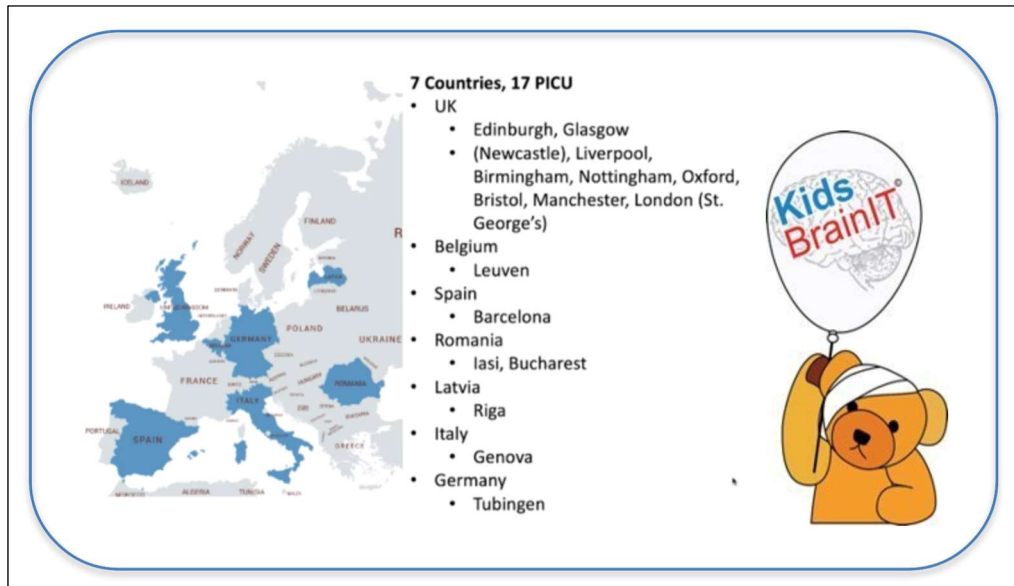


Fig.29 Modified from: KidsBrainIT Study Protocol supplementary material, 2022.

1.4.3 Physiological and Clinical Data Collection

A core feature of the project is the systematic collection of high-resolution physiological data recorded as part of routine clinical care. Arterial blood pressure, intracranial pressure and, when available, additional neuromonitoring signals were captured at minute-level resolution using either networked bedside monitoring systems or mobile data-harvesting devices in units without integrated digital infrastructure. Data extraction occurred after PICU discharge to ensure capture of the complete monitoring period. All physiological data underwent pseudo-anonymization at the local site, with identifying information removed and unique study numbers assigned before secure transfer to the central databank. Clinical data, including demographics, injury characteristics, Glasgow Coma Scale scores, pupillary responses, radiological findings and key treatment interventions, were collected using standardized electronic proformas designed to ensure harmonization across sites.

1.4.4 Outcome Assessment and Neuroimaging Data

Long-term outcomes were assessed through structured telephone interviews conducted at six and twelve months post-injury, using validated tools to capture global and functional recovery. Outcome data were also pseudo-anonymized and linked to physiological and clinical data through unique identifiers. Where available, postoperative MRI studies performed as part of clinical care were catalogued using a standardized template to permit longitudinal evaluation of lesion evolution. These neuroimaging data are intended to support future analyses exploring associations between autoregulation metrics, secondary injury burden and structural outcomes.

1.4.5 Analytic Framework and Computational Methodology

Data within the KidsBrainIT databank support a wide array of physiological analyses, including artifact removal, secondary insult quantification, computation of autoregulation indices such as L_{Ax} and P_{Rx} and estimation of CPP_{opt} through multiwindow adaptive models developed by collaborators in Leuven, Belgium. The consortium also applies dynamic autoregulation assessment tools such as DATACAR and generates ICP dose-response profiles to examine the interaction between intracranial pressure, autoregulatory capacity and outcome. These analyses create a physiologically rich, temporally resolved portrait of secondary brain injury that goes beyond traditional reliance on summary measures and threshold-based metrics.

1.4.6 Pilot Evidence Supporting CPP_{opt}-Guided Management

Pilot analyses performed prior to the launch of the full cohort provided preliminary support for the CPP_{opt} concept in children. These early studies demonstrated that CPP_{opt} varies meaningfully over time within individual patients and differs across age groups, with median values near sixty-nine millimetres of mercury for children aged two to six years, sixty-eight for ages seven to eleven years and seventy-two for adolescents. Moreover, children who survived and those with favorable functional outcomes spent significantly greater proportions of time within their calculated CPP_{opt} ranges. These findings underscore the potential clinical value of individualized CPP targets and provided the scientific rationale for the KidsBrainIT prospective validation effort.

1.4.7 Positioning KidsBrainIT in the Broader Research Landscape

The KidsBrainIT project represents a pivotal shift in pediatric neurocritical care research, providing for the first time the scale and methodological harmonization necessary to evaluate autoregulation-guided management strategies. By combining high-frequency monitoring, standardized clinical metadata and long-term outcomes across an international network, the collaboration creates a unique platform for interrogating the mechanisms of secondary injury and testing data-driven hypotheses at scale. In subsequent sections, this chapter will examine the first major analytical outputs of the KidsBrainIT consortium, including work on the visualization of intracranial pressure burden and cerebral perfusion insult intensity, which illustrate the transformative potential of high-resolution data in reshaping our understanding of childhood brain trauma.

1.5 Results

The results of the KidsBrainIT research program presented in this chapter focus on two complementary aspects of secondary brain injury after pediatric traumatic brain injury. The first focuses on intracranial pressure and characterizes the tolerance of the pediatric brain to the cumulative burden of intracranial hypertension. The second explores cerebral perfusion pressure and defines the perfusion thresholds associated with favorable recovery, including individualized targets derived from autoregulation monitoring. Together, these studies provide an integrated framework for understanding how pressure and perfusion dynamics influence outcome in childhood brain trauma.

1.5.1 Intracranial Pressure and Time Burden in Pediatric TBI

The KidsBrainIT analysis of intracranial pressure offers a detailed and quantitative assessment of how both the magnitude and temporal characteristics of intracranial hypertension influence clinical outcome following pediatric traumatic brain injury. Leveraging high-frequency, minute-by-minute physiological monitoring, the study reconstructed the longitudinal profile of intracranial pressure and quantified the cumulative burden imposed on the injured brain. This analytical framework demonstrates that neurological outcome is more strongly associated with the overall intracranial pressure burden than with the occurrence of isolated hypertensive excursions. Children with unfavorable outcomes accrued substantially greater exposure to intracranial pressure values exceeding approximately 20–25 mmHg, with this excess burden predominantly arising from prolonged periods of elevation rather than brief, self-limiting episodes. Conversely, children with favorable outcomes were characterized by transient intracranial pressure fluctuations that resolved promptly, resulting in a comparatively limited cumulative burden. (70)

Within the KidsBrainIT cohort of 104 children with severe traumatic brain injury undergoing invasive intracranial pressure monitoring, increasing duration of exposure to intracranial pressure above 20 mmHg was significantly associated with unfavorable outcome, whereas short-duration elevations demonstrated a weaker and less consistent relationship with prognosis. Importantly, the analysis further suggested that intracranial pressure values within the conventionally accepted range of 10–20 mmHg should not be considered uniformly innocuous when sustained over time, particularly in the presence of impaired cerebral autoregulation. A central contribution of this study is the demonstration that its findings closely reproduce and extend the seminal observations of Güiza and colleagues. (61) The 2015 study provided evidence in support of the concept that the pressure–time dose of intracranial hypertension, rather than isolated threshold violations, was the principal determinant of outcome. (Fig. 30)

The KidsBrainIT analysis validates this concept within a purely pediatric cohort and substantially refines it. (Fig. 31)

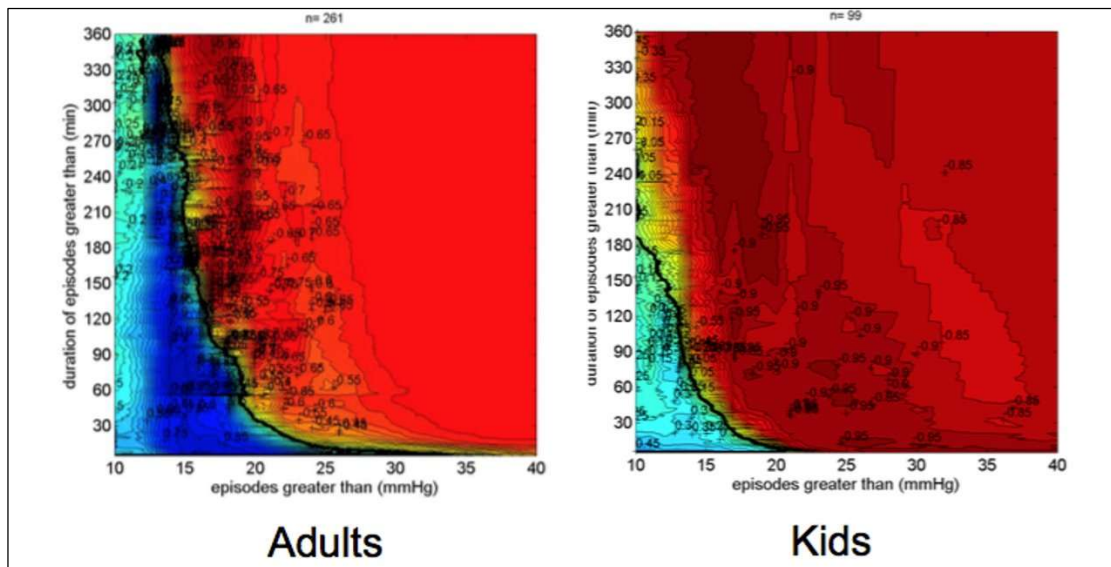


Fig.30 Adapted from: Güiza, et al. Intensive Care Med. 2015.

The chart shows the visualization of the univariate correlation between the Glasgow Outcome Score (GOS) and the average amount of intracranial cerebral (ICP) events per GOS category, N = 99. ICP events are denoted by the colored dots in the graph, defined by an intensity threshold (x-axis) maintained for a certain duration (y-axis). A negative association of a CPP event with GOS is color coded as dark red, which gradually transitions toward dark blue for positive correlations. The zero correlation line, that is, the transition curve, is highlighted in black.

This reduced tolerance likely reflects developmental differences in cranial compliance, cerebrovascular regulation and metabolic vulnerability of the immature brain. While in adult cohorts the injurious intracranial pressure dose often accumulated at higher pressure levels or over longer durations, the KidsBrainIT visualizations indicate that comparatively modest but sustained elevations exert a disproportionate effect in children. This provides strong empirical support for the long-held clinical impression that the pediatric brain is particularly sensitive to intracranial hypertension.

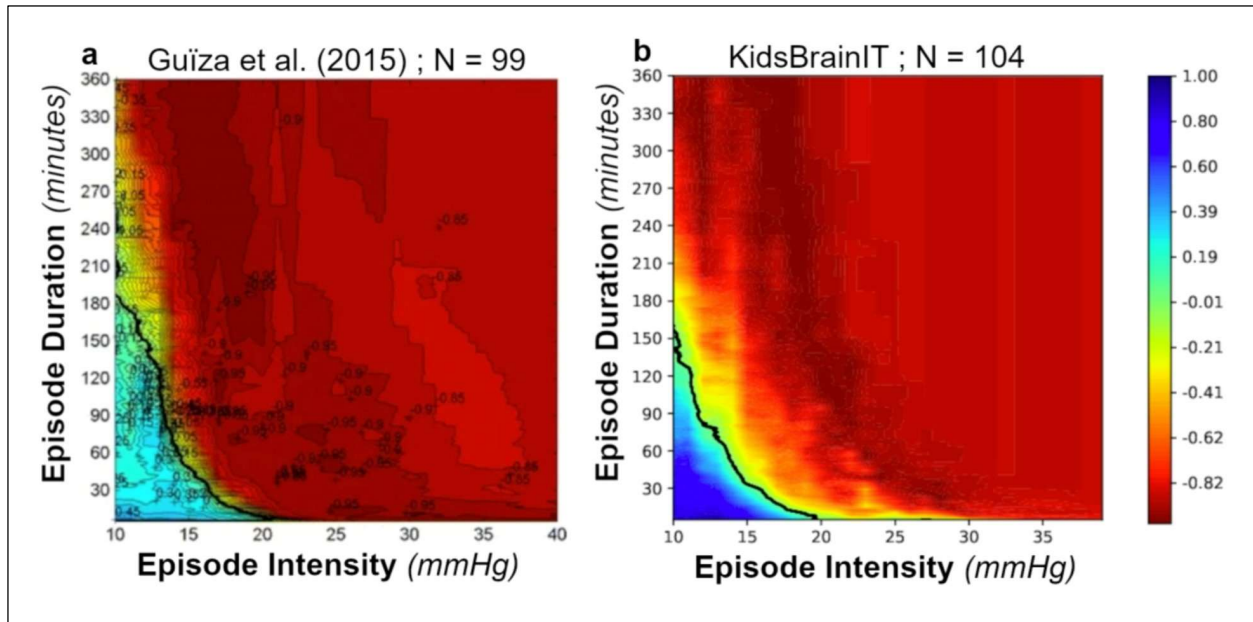


Fig.31 Reproduced from: Kempen B, et al. J Neurotrauma, 2024.

The strengthened concordance between the two studies also underscores the robustness of burden-based approaches to intracranial pressure assessment. The KidsBrainIT data reveal that the harmful impact of intracranial hypertension in children arises not only from the absolute level reached but also from the cerebral autoregulatory status .

These findings further underscore that the clinical impact of intracranial pressure cannot be interpreted in isolation from cerebral perfusion pressure. By incorporating color-coded visualizations of the univariate relationship between six-month Glasgow Outcome Scale scores and the average burden of intracranial pressure insults across predefined cerebral perfusion pressure thresholds of ≤ 50 , 60, and 70 mmHg, the analysis demonstrated that intracranial pressure elevations were consistently associated with worse outcome when occurring in the context of critically reduced cerebral perfusion pressure. Specifically, at cerebral perfusion pressure values below approximately 50 mmHg, the dose–response relationship between intracranial pressure burden and outcome became uniformly adverse, a pattern observed in both adult and pediatric traumatic brain injury. (Fig. 32) The present study represents the first independent validation of this interaction in childhood brain trauma, confirming that when cerebral perfusion pressure is critically compromised, intracranial pressure ceases to function as an isolated predictor of outcome and instead reflects a coupled failure of pressure–flow regulation.

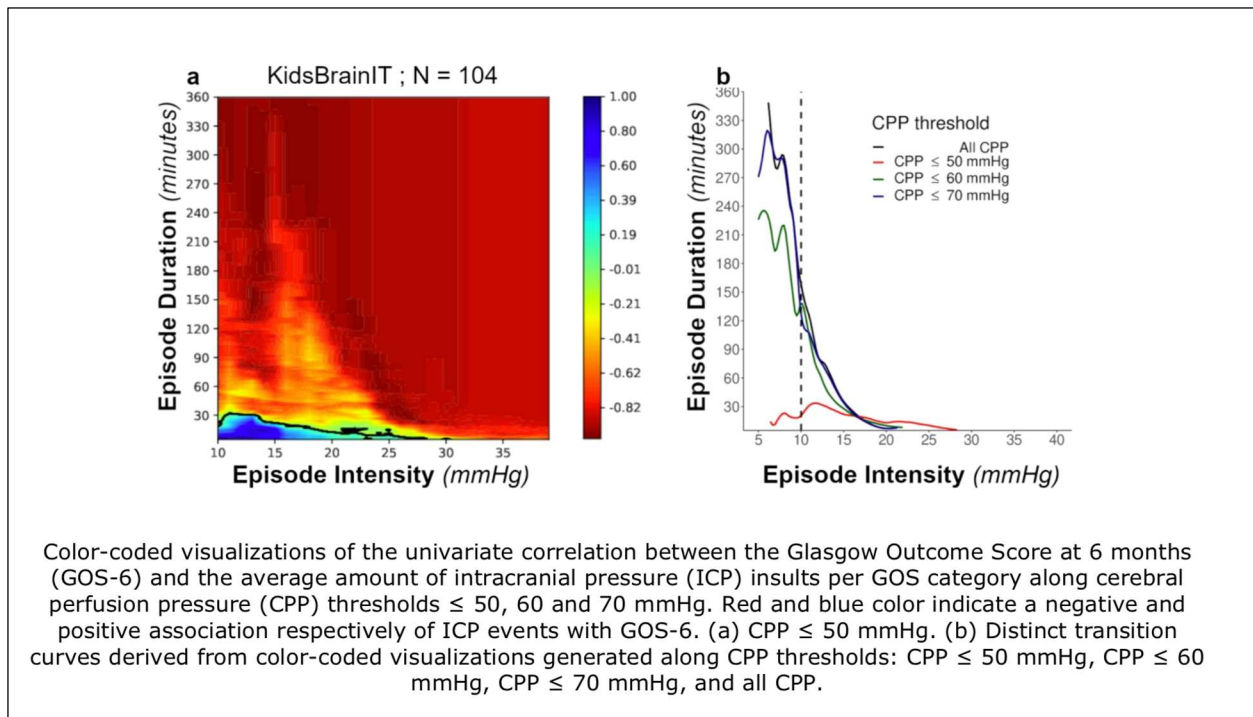


Fig.32 Adapted from: Kempen B, et al. J Neurotrauma, 2024.

Importantly, this study further demonstrated for the first time that pediatric patients with pressure-passive cerebrovascular reactivity experience worse outcomes even in association with intracranial pressure events occurring within the 10–20 mmHg range. These pressure levels are traditionally regarded as physiologically innocuous, as they fall well within conventionally accepted normal limits, and no prior investigations have systematically examined their potential pathological relevance in pediatric traumatic brain injury.

Crucially, this observation was made using the low-frequency autoregulation index (LAX), a cerebrovascular reactivity metric derived from the continuous correlation between slow oscillations of intracranial pressure and arterial blood pressure. LAX enables classification of individual intracranial pressure events according to whether cerebrovascular reactivity is preserved (active vasoreactivity) or impaired (pressure-passive vasoreactivity), thereby embedding each pressure exposure within its physiological context.

As illustrated in the vasoreactivity-stratified burden analysis, episodes of pressure-passive reactivity contributed disproportionately to cumulative exposure, even at modest intracranial pressure amplitudes. (Fig. 33) This observation challenges the prevailing assumption that low-range intracranial pressure values are universally benign and highlights the need to reinterpret “normal” pressure ranges through a physiological rather than purely numerical lens.

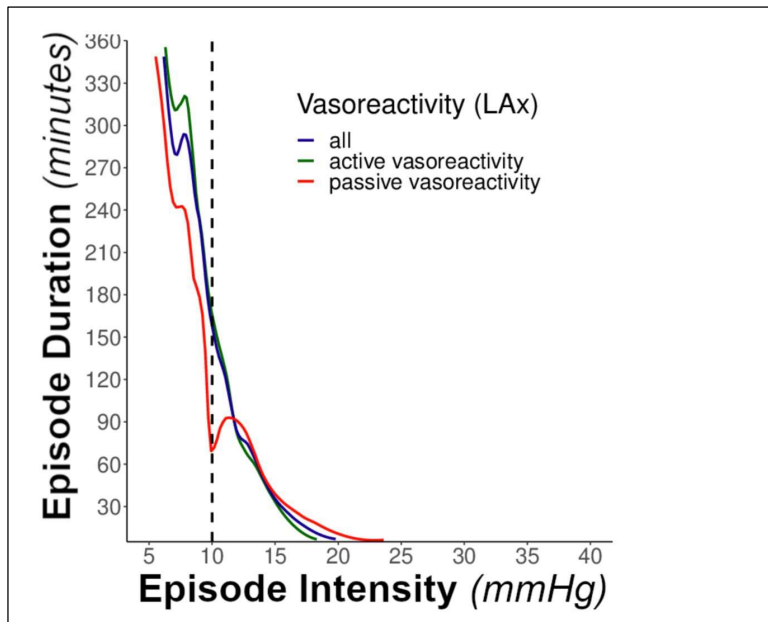


Fig.33 Adapted from: Kempen B, et al. J Neurotrauma, 2024.

These insights confirm that intracranial pressure is best conceptualized as a dynamic physiological process whose adverse effects depend on its interaction with time and with the brain's capacity to restore homeostasis.

The replication of this conceptual framework across independent cohorts reinforces the need for burden-based monitoring strategies in pediatric neurocritical care and provides the empirical foundation for integrating pressure time dose metrics into future clinical decision-making.

1.5.2 Impact of Cerebral Perfusion Pressure Insult Intensity and Duration

The KidsBrainIT investigation of cerebral perfusion pressure applied a burden-based analytical framework to systematically examine the combined effects of CPP insult intensity and duration on neurological outcome following pediatric traumatic brain injury, based on the same cohort. (Fig. 34)

Table 2 Patient characteristics summarized along GOS-6 (n = 104)					
GOS-6	GOS-6				
	1 (n = 10)	2 (n = 4)	3 (n = 25)	4 (n = 31)	5 (n = 34)
Summated GCS					
Median (IQR)	3.50 (3.00, 5.75)	6.50 (5.25, 7.00)	23; 6.00 (3.00, 7.00)	29; 6.00 (4.00, 9.00)	32; 7.00 (3.00, 9.50)
Motor GCS					
Median (IQR)	9; 1.00 (1.00, 2.00)	2.50 (1.00, 4.00)	21; 1.00 (1.00, 3.00)	23; 3.00 (1.00, 5.00)	25; 2.00 (1.00, 5.00)
Age (Years)					
Median (IQR)	10.50 (4.75, 12.00)	8.50 (3.75, 13.25)	7.50 (5.00, 11.00)	10.33 (6.00, 13.29)	10.00 (6.17, 12.75)
Pupil reactivity, n (%)					
None; N (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)
One; N (%)	1 (11)	1 (25)	3 (12)	2 (7)	1 (3)
Two; N (%)	8 (89)	3 (75)	21 (88)	28 (93)	29 (94)
CPP monitored time (days)					
Median (IQR)	3.56 (2.06, 4.44)	3.04 (2.50, 11.67)	4.58 (1.75, 8.40)	4.97 (3.23, 6.76)	3.92 (1.29, 4.81)
% valid CPP monitored time					
Median (IQR)	68.87 (47.25, 90.92)	88.90 (75.08, 95.15)	84.44 (71.08, 96.05)	97.59 (79.31, 99.05)	69.26 (36.54, 96.90)
GOS-6 ranges from 1 (death) to 5 (good outcome). The numbers preceding a semicolon reflect the total amount of patients of the GOS subpopulation that who had the respective variable available					
CPP cerebral perfusion pressure, GCS Glasgow Coma Score, GOS-6 Glasgow Outcome Score at 6 months, IQR interquartile range					

Fig.34 Adapted from: Kempen B, et al. Neurocrit Care. 2025

Utilizing minute-by-minute physiological recordings obtained during the acute phase of critical illness, the study generated the first pediatric CPP dose-response visualization, characterizing the univariate association between CPP insult profiles and six-month Glasgow Outcome Score. The resulting three-dimensional, color-coded plots delineated a distinct transition curve separating CPP insult patterns associated with favorable outcome from those linked to poor neurological recovery. Analogous to previously reported adult data, the pediatric CPP dose-response exhibited a non-linear, exponential configuration, indicating that progressively lower CPP values were tolerated only for increasingly shorter durations. Favorable outcome trajectories were characterized by confinement within a restricted region of the CPP intensity-duration space, whereas unfavorable outcomes were associated with deeper and more sustained hypoperfusion episodes. (71)

A principal finding of the analysis was the identification of a CPP range associated with relatively preserved outcome, herein referred to as a “safe” CPP zone, extending approximately between 56 and 89 mmHg. (Fig. 35a) CPP values below approximately 56 mmHg were consistently associated with unfavorable outcome irrespective of exposure duration, whereas CPP values within and above this range demonstrated a graded tolerance that diminished as the duration of exposure increased. Importantly, the lower boundary of this empirically derived CPP zone exceeds the minimum CPP targets recommended by the 2019 Pediatric Brain Trauma Foundation guidelines, which advocate maintaining CPP between 40 and 50 mmHg. (59)

These findings indicate that current guideline thresholds may inadequately capture the lower limit of CPP required to support cerebral perfusion in a substantial subset of pediatric patients, thereby permitting clinically relevant hypoperfusion despite apparent guideline adherence.

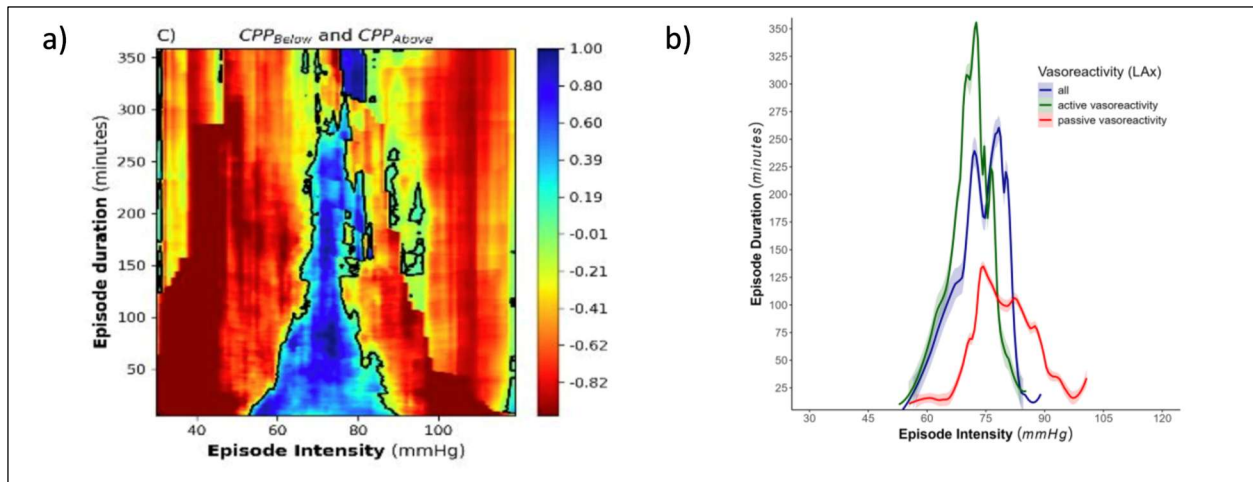


Fig.35 Adapted from: Kempen B, et al. Neurocrit Care. 2025

The analysis further demonstrated that CPP tolerance is strongly modulated by cerebrovascular reactivity status. Stratification of CPP dose-response plots by autoregulatory state revealed a pronounced contraction of the CPP range compatible with favorable outcome under conditions of pressure-passive cerebrovascular reactivity. (Fig. 35b) In this context, both the intensity and duration of CPP insults that could be tolerated were markedly reduced, whereas preserved autoregulation was associated with a broader CPP range compatible with recovery. These observations underscore the physiological dependence of CPP requirements on the integrity of autoregulatory mechanisms and provide quantitative support for individualized, autoregulation-informed CPP targets rather than uniform perfusion thresholds.

Finally, the interaction between CPP and ICP further refined the interpretation of CPP burden. When CPP events were examined in relation to concurrent intracranial pressure, CPP dose-response plots demonstrated that episodes associated with intracranial pressure ≥ 20 mmHg were uniformly linked to poor outcome across all CPP intensities and durations. (Fig. 36) This finding suggests that intracranial hypertension may dominate outcome risk once a critical threshold is exceeded, likely reflecting a global failure of intracranial compliance and cerebrovascular regulation. Nevertheless, this observation should not be interpreted as diminishing the relevance of CPP management during periods of elevated intracranial pressure. Rather, it highlights the interdependent nature of CPP and ICP as coupled physiological variables whose combined burden determines secondary brain injury risk.

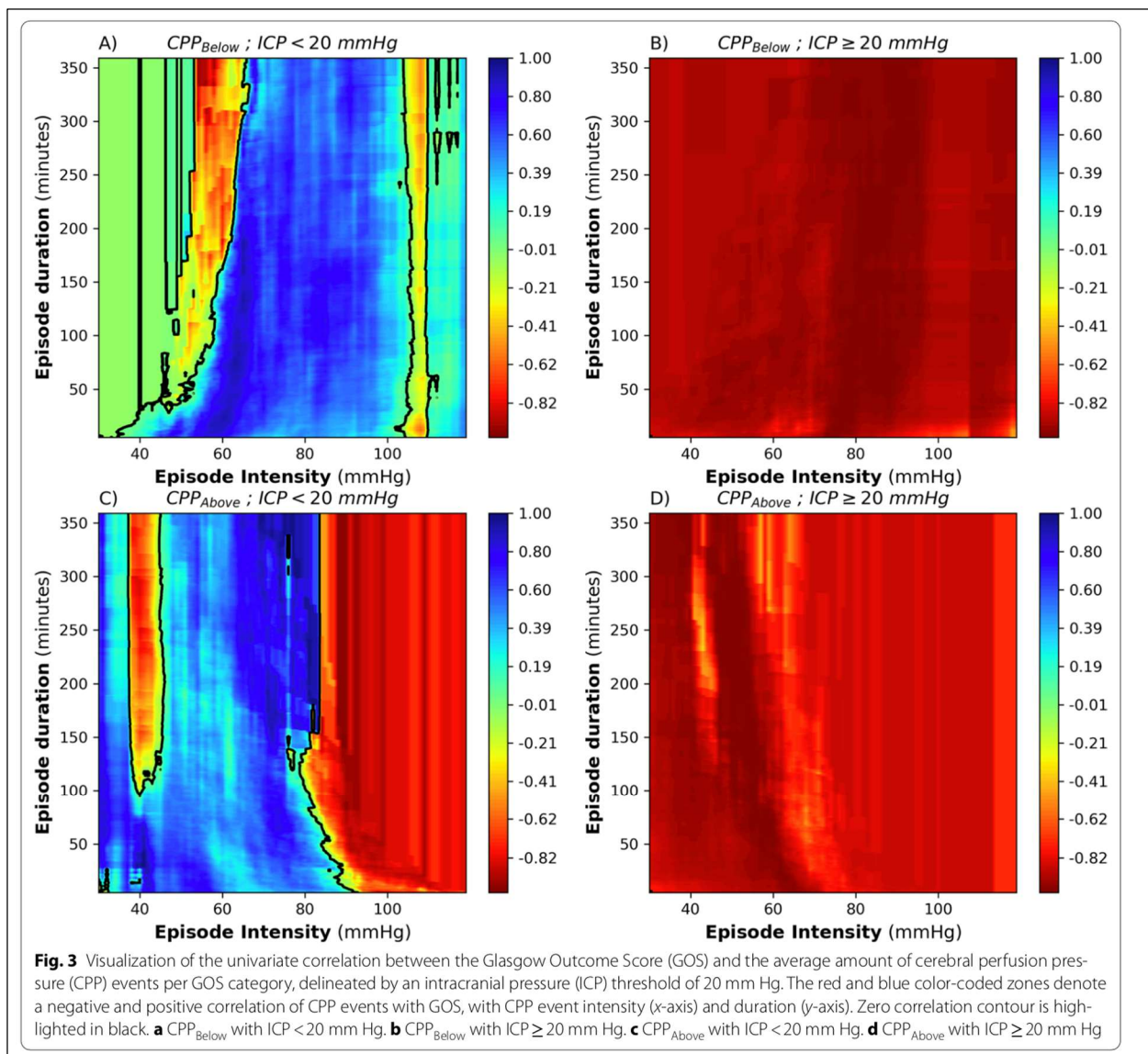


Fig.36 Adapted from: Kempen B, et al. Neurocrit Care. 2025

In aggregate, the KidsBrainIT CPP dose-response analysis provides the first pediatric evidence that cerebral perfusion pressure should be conceptualized as a dynamic, dose-dependent physiological signal shaped by intensity, duration, autoregulatory state, and intracranial pressure context. By demonstrating that the lower CPP limit associated with favorable outcome exceeds current guideline recommendations, and that CPP tolerance varies substantially across individuals, this work establishes a robust physiological foundation for the development of CPP-guided, autoregulation-informed therapeutic strategies in pediatric neurocritical care

1.6 PRx Monitoring Implementation in Neurocritical Care: Future Perspectives

The accumulating evidence from recent large-scale pediatric studies demonstrates that cerebrovascular autoregulation is a central determinant of outcome after severe traumatic brain injury and that indices such as PRx capture dimensions of physiological vulnerability that are not reflected in intracranial pressure or cerebral perfusion pressure alone. The findings from STARSHIP and KidsBrainIT, together with the detailed burden-based analyses of intracranial pressure and cerebral perfusion presented in this chapter, collectively support the view that static thresholds are insufficient to guide neuroprotective strategies in children. These studies show that autoregulation impairment is common, that it evolves over time, and that deviations from individualized perfusion targets derived from PRx analyses are strongly associated with poor recovery. Implementing PRx monitoring in clinical care therefore represents an important step toward a physiology-informed model of pediatric neurocritical management.

Future integration of PRx into bedside care requires a shift from threshold-based decision frameworks to strategies that interpret cerebrovascular physiology as a dynamic process. Autoregulation guided cerebral perfusion pressure targets, particularly individualized CPP_{opt} values, offer a promising alternative to current guideline recommendations that rely on fixed ranges. The demonstration in KidsBrainIT that optimal perfusion pressure values cluster around levels higher than those endorsed by present guidelines, together with the STARSHIP finding that excursions below CPP_{opt} predict outcome more reliably than excursions below fixed thresholds, underscores the potential of individualized CPP targets to enhance neuroprotection. A key future direction is the formal evaluation of CPP_{opt} guided therapy in prospective interventional studies, which will determine whether maintaining cerebral perfusion pressure within autoregulation informed ranges improves survival and long-term neurological function.

A second important development is the transition from descriptive to predictive use of autoregulation metrics. High resolution physiological datasets now allow modelling of temporal patterns in PRx, including early trajectories that distinguish between favourable and unfavourable outcomes. These insights could be used to develop real time alerts that identify periods of heightened cerebrovascular vulnerability, enabling clinicians to intervene preemptively. Time dependent visualisation tools developed within the KidsBrainIT consortium also offer a way to contextualize PRx within the broader physiological environment, linking changes in autoregulation to evolving intracranial pressure burden, perfusion deficits, ventilatory adjustments or sedative interventions. As these analytic frameworks become more mature, they have the potential to support continuous risk assessment and dynamic adaptation of treatment plans. (72)

Another priority for future implementation is the harmonization of monitoring platforms. Although PRx can be calculated from signals that are widely available in modern intensive care units, substantial variability still exists in signal resolution, artefact handling and data storage practices. The multicenter KidsBrainIT infrastructure provides a blueprint for standardized signal acquisition and processing, which is essential for translating autoregulation monitoring from research settings to routine care. Developing user-friendly clinical interfaces, integrating autoregulation indices into electronic medical records and ensuring compatibility with diverse bedside monitoring systems will be critical steps toward widespread adoption. Finally, the incorporation of PRx into multimodal neuromonitoring strategies represents an important frontier. Cerebral autoregulation does not occur in isolation but interacts with intracranial pressure dynamics, systemic physiology, metabolic demands and structural injury patterns. Future approaches may combine PRx with near infrared spectroscopy, brain tissue oxygenation, continuous electroencephalography or advanced imaging biomarkers to provide a multidimensional view of cerebral health. Such integrated platforms could offer actionable insights on when to escalate or de-escalate therapy and could help personalize treatment thresholds according to evolving patient specific physiology. (46)

Chapter 2. NIRS-based Cerebral Autoregulation Monitoring in Pediatric Cardiac Surgery

2.1 Neurodevelopmental Outcome in Congenital Heart Defects

2.1.1 Background

Over the past several decades, substantial advances in surgical techniques, perioperative management, and intensive care have led to marked improvements in survival following surgery for congenital heart disease (CHD). Refinements in cardiopulmonary bypass strategies, myocardial protection, anesthetic management, and postoperative critical care have collectively reduced early postoperative morbidity and mortality. In contemporary high-volume centers, early postoperative mortality is now typically stabilized in the range of 2–3%, even for complex lesions, such that the vast majority of individuals born with CHD survive into adolescence and adulthood and increasingly into later adult life. (Fig. 37)

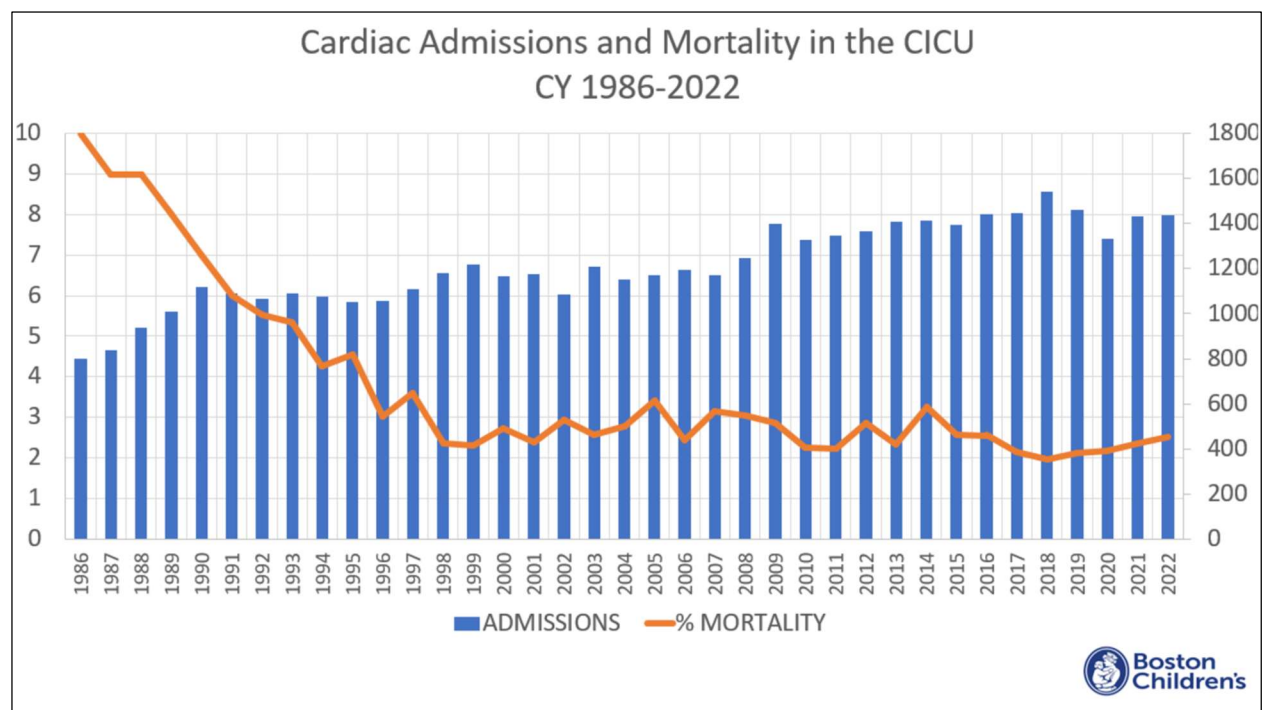


Fig.37. Courtesy of Munoz R, 2024.

As mortality has declined, attention has shifted toward long-term functional outcomes. Neurodevelopmental impairments have emerged as one of the most prevalent and consequential morbidities in this population, particularly among children with complex lesions. (Fig. 38)

Large longitudinal cohorts consistently demonstrate that approximately half of children with complex CHD exhibit at least one neurodevelopmental deficit, typically mild in isolation but frequently occurring in combination. Affected domains include cognition, language, motor skills, attention, executive function, visual-spatial processing, and academic achievement, often necessitating rehabilitative therapies, specialized education, and prolonged neurodevelopmental follow-up. (73)

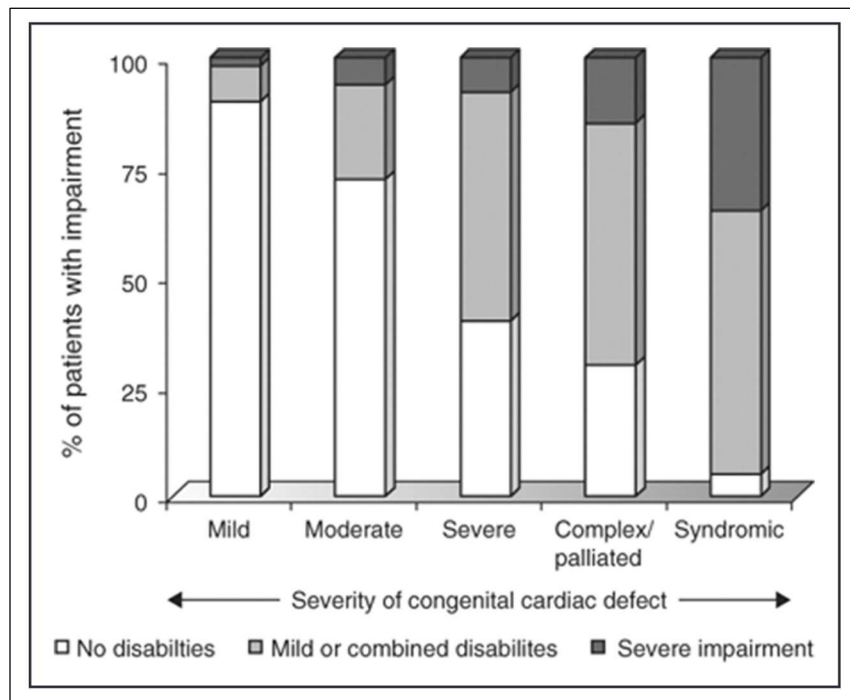


Fig.38 Adapted from: Wernovsky G, et al. *Cardiol Young*, 2006 .

Contemporary literature emphasizes that neurological vulnerability in CHD is not confined to the perioperative period. Rather, it reflects the cumulative impact of genetic susceptibility, altered fetal and neonatal physiology, delayed brain maturation, perioperative instability, and superimposed brain injury. Advances in fetal and neonatal neuroimaging, electroencephalography, and near-infrared spectroscopy (NIRS) have demonstrated that abnormalities in white matter maturation, cortical development, connectivity, and cerebral metabolism are common even before surgical intervention.

This evolving paradigm supports the concept of CHD as a disorder affecting both the heart and the developing brain, with neurodevelopmental outcome determined by a continuum of prenatal, perioperative, and postnatal exposures rather than a single injurious event. (74) (Fig. 39)

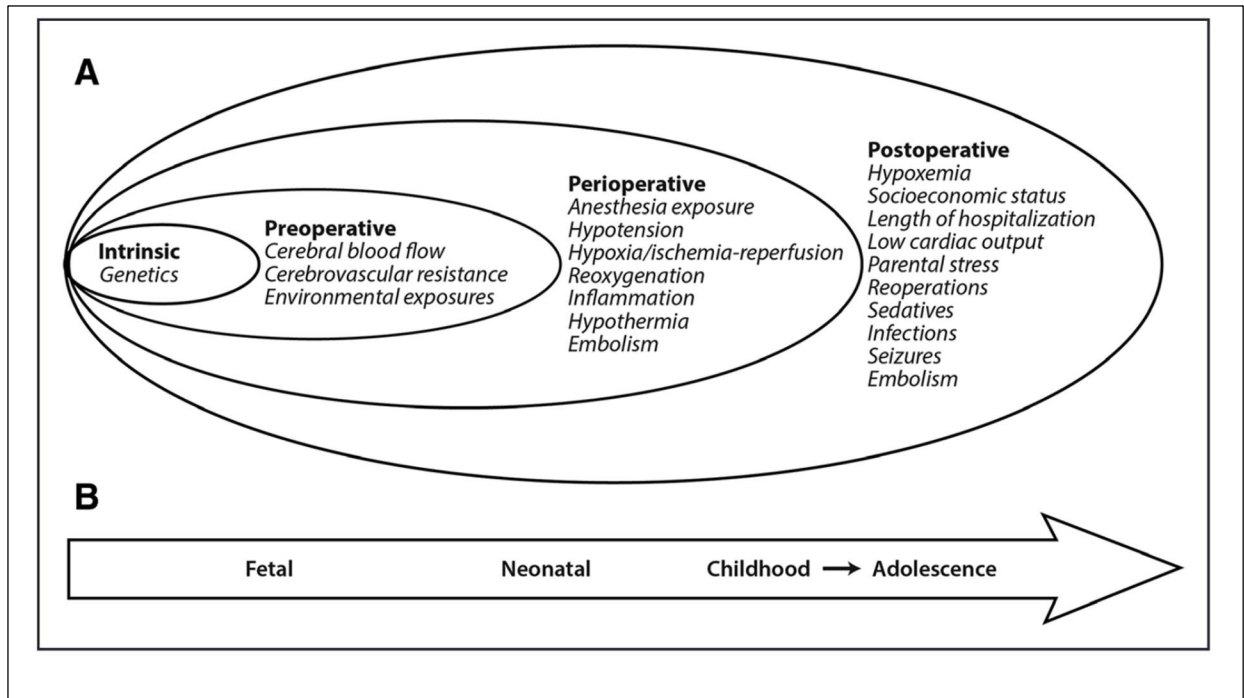


Fig.39 Adapted from: Morton PD, et al. Circ Res, 2017.

2.1.2 Preoperative Factors

Preoperative determinants of neurodevelopmental outcome include intrinsic vulnerability of the developing brain, genetic influences on cardiac and neural development, and disturbances in cerebral perfusion and oxygen delivery present during fetal life or early infancy.

Fetal neuroimaging studies consistently demonstrate reduced total brain volume, impaired cortical folding, and delayed white matter maturation beginning in the third trimester in several forms of complex CHD. Altered cerebrovascular resistance and abnormal fetal circulatory streaming reduce cerebral oxygen and substrate delivery, contributing to what Wernovsky and Licht have conceptualized as *congenital brain disease*, present in nearly half of neonates with complex CHD. These abnormalities largely represent non-modifiable risk factors rooted in cardiac anatomy, placental function, and fetal hemodynamics. (75)

Microcephaly, observed in approximately 20–25% of newborns with complex CHD, serves as a marker of impaired prenatal brain growth and is strongly associated with later neurodevelopmental impairment. (76) Diffusion tensor imaging and magnetic resonance spectroscopy demonstrate that reduced fractional anisotropy, abnormal neuronal metabolites, and delayed myelination are detectable before surgery. These early deviations reflect disrupted oligodendrocyte maturation and white matter network formation, processes that are particularly vulnerable during late gestation. (Fig. 40)

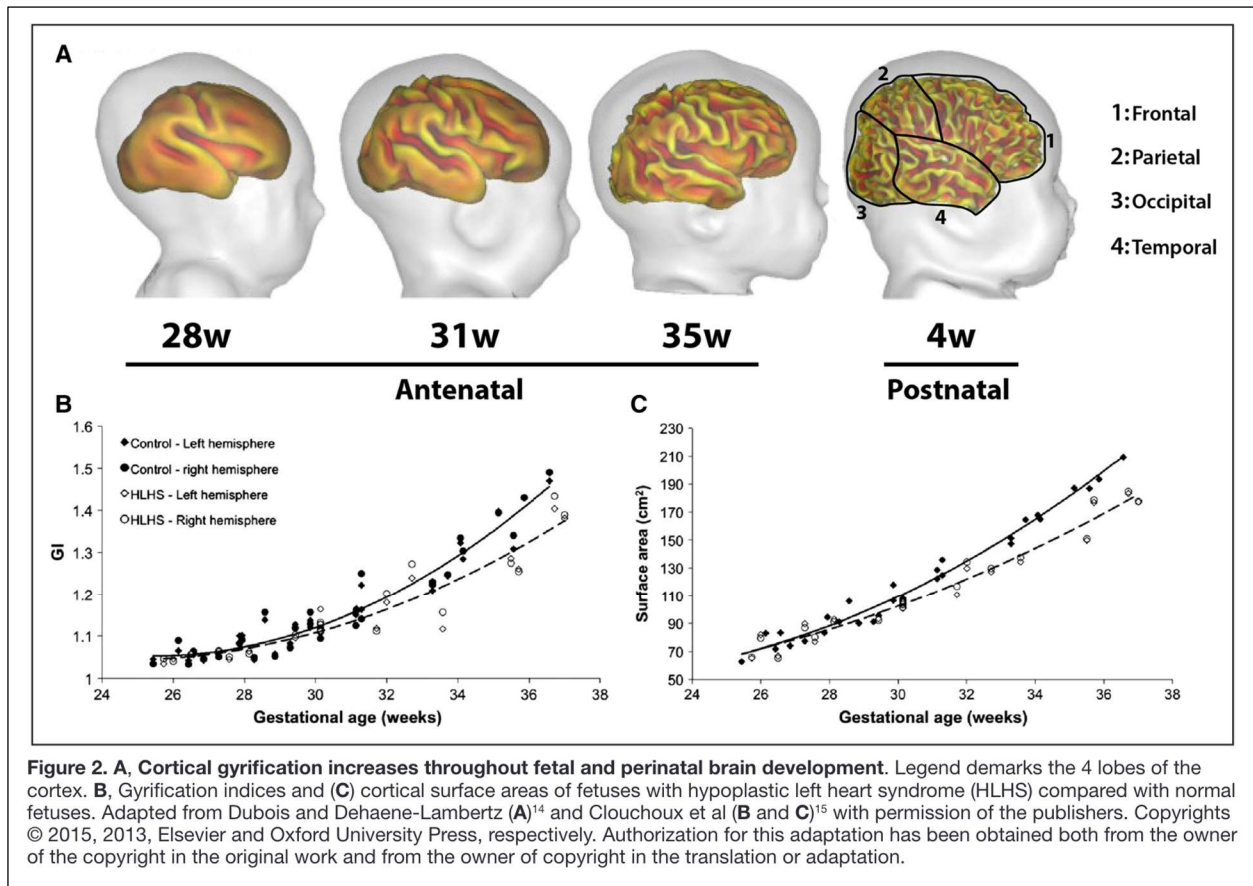


Fig.40 Adapted from: Morton PD, et al. Circ Res, 2017.

Genetic factors further modulate risk. Variants of apolipoprotein E, especially the $\epsilon 2$ allele, have been independently associated with poorer psychomotor performance, reduced head growth, and behavioral difficulties following infant cardiac surgery. In addition, de novo mutations affecting chromatin remodeling, transcriptional regulation, and neurodevelopmental pathways contribute to shared cardiac–neural phenotypes. While largely unmodifiable, these genetic determinants provide important prognostic and mechanistic insights. (5)

Modifiable preoperative factors also exist. Instability in cerebral oxygen delivery, profound hypoxemia in select lesions, low cardiac output states, and diastolic steal related to a patent ductus arteriosus may exacerbate pre-existing vulnerabilities. Observational studies demonstrate that progressive declines in preoperative cerebral oxygen saturation are associated with increased risk of postoperative white matter injury, suggesting that optimized preoperative stabilization and cerebral oxygenation monitoring may mitigate secondary injury. (77)

2.1.3 Intraoperative Factors

Intraoperative conditions during cardiopulmonary bypass (CPB) and, when employed, periods of circulatory arrest represent some of the most intensively studied contributors to neurological outcome in children undergoing surgery for congenital heart disease. This focus reflects the fact that, in contrast to prenatal and genetic determinants, intraoperative variables are at least partially modifiable and therefore constitute a key target for neuroprotective strategies. The conduct of CPB influences multiple physiological parameters relevant to cerebral integrity, including cerebral perfusion pressure, oxygen delivery, inflammatory activation, metabolic balance, and temperature regulation. Perturbations in these tightly coupled processes may impose additional stress on an already vulnerable developing brain.

Several intraoperative mechanisms have been implicated in perioperative brain injury. Hypothermia alters cerebral metabolic demand and blood flow regulation; hemodilution reduces oxygen-carrying capacity; non-pulsatile flow may impair microvascular perfusion; and particulate or gaseous emboli can result in focal ischemic injury. In addition, reperfusion following periods of low-flow or circulatory arrest may exacerbate cellular injury through oxidative stress and inflammatory cascades. The systemic inflammatory response triggered by blood contact with the extracorporeal circuit further contributes to endothelial dysfunction, increased capillary permeability, and cerebral edema, potentially compounding the risk of neurological injury. (75)

Among modifiable intraoperative variables, hematocrit during CPB has been most consistently linked to neurodevelopmental outcome. Randomized clinical trials have demonstrated that excessive hemodilution is associated with worse early neurodevelopmental performance, with hematocrit values below approximately 24% during bypass linked to lower psychomotor development scores at one year of age. Subsequent analyses have identified an inflection point beyond which further increases in hematocrit do not confer additional benefit, but these findings have nonetheless driven a widespread shift toward higher hematocrit targets during neonatal and infant CPB. (78)

Blood gas management strategies during hypothermic bypass have also been extensively investigated. Although pH-stat management enhances cerebral blood flow during cooling by promoting cerebral vasodilation, randomized trials and longitudinal follow-up studies have failed to demonstrate consistent long-term neurodevelopmental advantages over alpha-stat management. Importantly, the impact of blood gas strategy appears to vary according to cardiac diagnosis, age at repair, and baseline cerebral vulnerability, underscoring the complexity of extrapolating a single “optimal” intraoperative approach across heterogeneous patient populations. (79)

The use of deep hypothermic circulatory arrest has been the subject of sustained debate. Available evidence indicates a nonlinear relationship between arrest duration and neurological outcome. Prolonged uninterrupted arrest is associated with increased risk of adverse outcomes, whereas shorter periods may have limited or inconsistent effects and, in certain anatomical or technical contexts, may be preferable to prolonged low-flow perfusion that increases exposure to the inflammatory burden of CPB. Long-term follow-up from the Boston Circulatory Arrest Study demonstrates that children with transposition of the great arteries exhibit subtle but persistent deficits in executive function, visuospatial processing, and academic achievement regardless of intraoperative strategy, highlighting that surgical technique alone does not fully account for later neurodevelopmental outcomes. (80)

Taken together, these findings emphasize that intraoperative management represents an important but partial contributor to neurological outcome. While optimization of bypass strategies can reduce avoidable injury, the influence of intraoperative factors is constrained by substantial pre-existing brain vulnerability and postoperative physiological exposures. This perspective reinforces the need to interpret intraoperative neuroprotection within a broader, cumulative risk framework rather than an isolated determinant of long-term neurodevelopment.

2.1.4 Postoperative Factors

The postoperative period represents a critical window during which additional, largely modifiable physiological disturbances may compound pre-existing brain vulnerability and intraoperative stress. Following separation from cardiopulmonary bypass, the recovering brain remains highly sensitive to fluctuations in cerebral perfusion, oxygen delivery, metabolic balance, and inflammatory activation. Neurological injury during this phase is often secondary in nature, arising from cumulative or repetitive insults rather than a single catastrophic event.

Hemodynamic instability is common in the early postoperative course, particularly in neonates and young infants with complex congenital heart disease. Episodes of systemic hypotension, low cardiac output syndrome, impaired cerebrovascular autoregulation, and altered arterial carbon dioxide tension can compromise cerebral blood flow and oxygen delivery at a time when metabolic demand may be increased. Importantly, impaired autoregulation may render cerebral perfusion pressure-dependent, such that even modest reductions in mean arterial pressure can result in cerebral hypoperfusion. Conversely, excessive vasoconstriction or hypocapnia may further reduce cerebral blood flow despite apparently adequate systemic hemodynamics. (81)

Near-infrared spectroscopy has provided important insights into postoperative cerebral oxygenation. Observational studies demonstrate that early postoperative cerebral hypoxia, particularly within the first 24–48 hours following surgery, is associated with prolonged intensive care unit stays, increased need for extracorporeal life support, and worse neurodevelopmental performance in early childhood. These findings suggest that postoperative cerebral oxygenation may serve as a clinically relevant surrogate marker of neurological risk and highlight the importance of continuous monitoring during this vulnerable period. (82)

Neurological complications, most notably seizures, are also prevalent following infant cardiac surgery. A substantial proportion of postoperative seizures are clinically silent and detectable only through continuous electroencephalographic monitoring. The occurrence of postoperative seizures has been linked to adverse neurodevelopmental outcomes later in childhood, particularly affecting executive function, attention, and behavioral regulation. These observations support the routine use of electroencephalography in high-risk patients to enable early detection and timely intervention, potentially mitigating secondary brain injury. (83)

In parallel, systemic inflammatory responses initiated by cardiopulmonary bypass may persist into the postoperative period and interact with cerebral vulnerability. Exposure of blood to the extracorporeal circuit triggers cytokine release, complement activation, and endothelial dysfunction, processes that may increase blood–brain barrier permeability and exacerbate white matter injury in the immature brain. Postoperative complications such as infection, low cardiac output, and prolonged mechanical ventilation may further amplify inflammatory and metabolic stress. (84)

Postoperative neuroprotective care therefore centers on meticulous physiological management aimed at minimizing secondary insults. Strategies include maintaining adequate and stable perfusion pressure, optimizing oxygen delivery and ventilation to avoid extremes of hypoxia or hypocapnia, judicious use of sedative and vasoactive agents, and integration of multimodal neuromonitoring to guide individualized hemodynamic targets. Within this framework, the postoperative period emerges as a key opportunity for intervention, with the potential to attenuate cumulative neurological injury and improve long-term neurodevelopmental outcomes.

2.1.5 Clinical Implications for Perioperative Physiological Monitoring

Neurodevelopmental outcome in congenital heart disease reflects the interaction between pre-existing brain vulnerability and superimposed perioperative physiological disturbances. Although genetic and prenatal factors establish baseline risk, secondary neurological injury frequently arises from potentially modifiable alterations in cerebral perfusion, oxygen delivery, and metabolic balance during surgery and postoperative recovery.

These considerations highlight the importance of perioperative monitoring strategies focused on real-time assessment of cerebral physiology.

Neuroimaging, particularly brain magnetic resonance imaging, provides essential information on delayed maturation and acquired injury, thereby defining the structural substrate of neurological risk. However, MRI offers a static assessment and cannot capture transient physiological insults. Continuous bedside physiological monitoring complements imaging by providing dynamic insight into cerebral homeostasis during periods of hemodynamic instability, when timely intervention may reduce secondary injury. (5)

In this context, perioperative neuromonitoring is best viewed as a tool for identifying high-risk physiological states rather than predicting long-term outcome in isolation. Monitoring approaches capable of detecting impaired autoregulation, pressure-passive perfusion, and mismatches between oxygen supply and demand are particularly relevant in neonates and infants with complex congenital heart disease. The following sections therefore examine near-infrared spectroscopy and NIRS-based cerebral autoregulation assessment as practical methods for physiology-guided surveillance during the perioperative period.

2.2 Cerebral NIRS Monitoring in Pediatric Cardiac Surgery: State of the Art

2.2.1 Introduction

Over the past decade, near-infrared spectroscopy (NIRS) has emerged as a key modality within the broader framework of non-invasive multimodal neuromonitoring. Its increasing adoption reflects a growing recognition that patients without primary brain injury may nevertheless be exposed to secondary neurological insults across a wide range of clinical scenarios, including anesthesia, surgery, and critical illness. (21) In this setting, early detection of cerebral hypoxia and impaired cerebral homeostasis may offer an opportunity for timely intervention and potential mitigation of neurological complications. NIRS provides continuous, bedside estimates of regional cerebral tissue oxygen saturation, offering a non-invasive surrogate of the balance between cerebral oxygen delivery and metabolic demand. Unlike many established neuromonitoring techniques (such as intracranial pressure monitoring, jugular bulb oximetry, or transcranial Doppler ultrasonography) which are invasive, operator-dependent, or intermittent, NIRS allows for real-time monitoring without significant procedural risk. This unique combination of safety, availability, and temporal resolution has facilitated its application in clinical environments where brain-focused monitoring has traditionally been absent.

Historically, cerebral oxygenation monitoring was primarily developed and validated in patients with acute brain injury, where prevention of secondary ischemic insults represents a cornerstone of neurocritical care. However, contemporary evidence increasingly supports the concept that cerebral hypoxia, dysregulated perfusion, and impaired autoregulation may occur even in the absence of overt neurological disease. (85)

Conditions such as major surgery, systemic inflammation, circulatory failure, respiratory insufficiency, and exposure to anesthetic and vasoactive agents can all perturb the cerebral oxygen cascade, rendering the brain vulnerable despite preserved systemic parameters. In this evolving paradigm, NIRS has been proposed as a pragmatic tool to extend cerebral monitoring beyond traditional neurocritical care settings, complementing standard hemodynamic and respiratory surveillance. Rather than serving as a diagnostic instrument for focal brain injury, cerebral oximetry is increasingly viewed as an early warning system capable of identifying global or regional disturbances in cerebral oxygenation before the onset of irreversible injury.

2.2.2 Principles and Technological Foundations

NIRS is based on the capacity of near-infrared light, typically within the 600–1000 nm wavelength range, to penetrate biological tissues and undergo absorption and scattering by oxygen-dependent chromophores, primarily oxyhemoglobin and deoxyhemoglobin. By analyzing changes in light attenuation as photons traverse extracranial tissues, skull, and superficial cerebral cortex, NIRS devices estimate the relative proportion of oxygenated hemoglobin within the interrogated volume, expressed as regional cerebral oxygen saturation (rSO_2). (Fig. 41)

Because the sampled signal is venous-weighted assuming to reflect approximately 70–75 % venous and 25–30 % arterial blood in commercially available monitoring tools, it provides an integrated measure of the balance between cerebral oxygen supply and consumption rather than a direct measure of perfusion or metabolism.

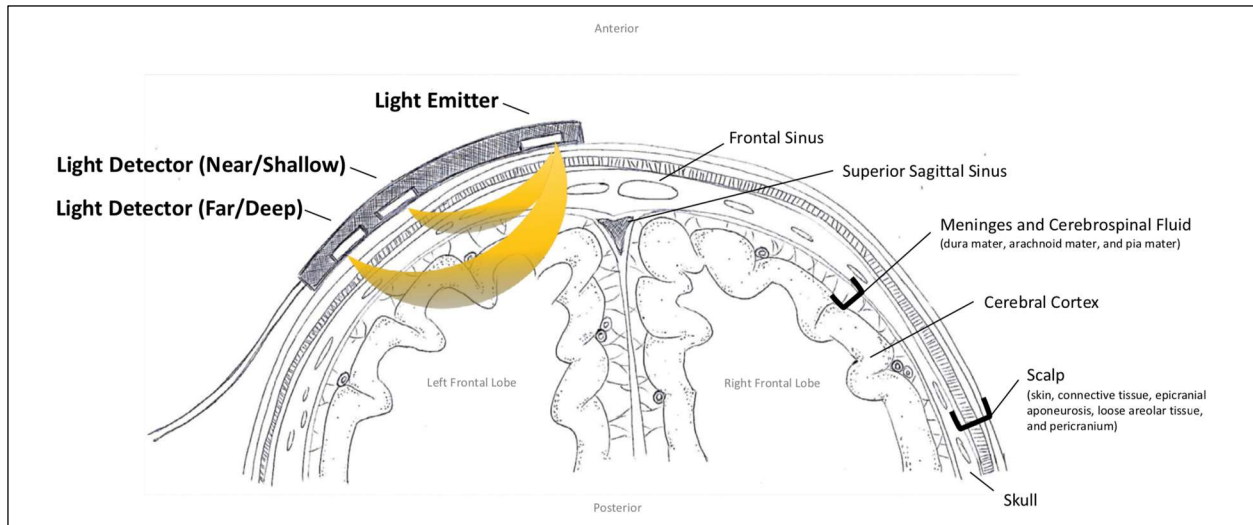


Fig.41 Adapted from: Zaleski KL, et al. J Cardiothorac Vasc Anesth, 2020.

Most bedside cerebral oximeters employ continuous-wave NIRS technology, which measures relative changes in chromophore concentration using the modified Beer-Lambert law and assumes a constant optical path length. While this approach enables practical bedside application, it precludes direct quantification of absolute tissue optical properties and introduces variability related to anatomical and physiological differences across patients. (Fig. 42)

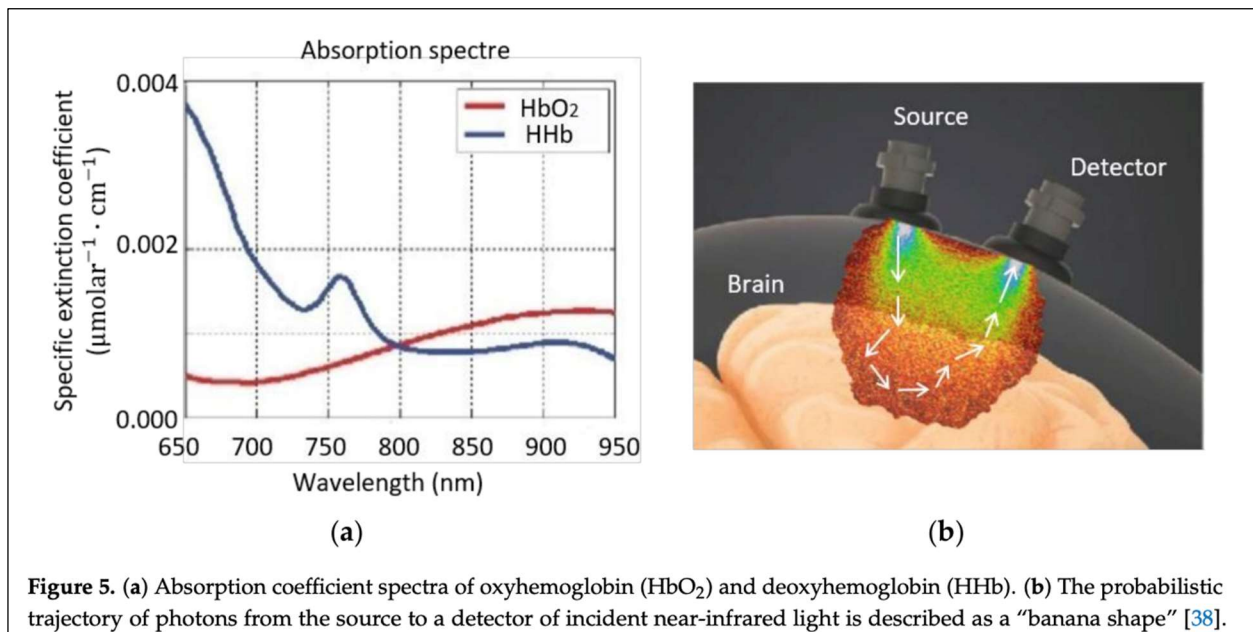


Figure 5. (a) Absorption coefficient spectra of oxyhemoglobin (HbO₂) and deoxyhemoglobin (HHb). (b) The probabilistic trajectory of photons from the source to a detector of incident near-infrared light is described as a “banana shape” [38].

Fig.42 Adapted from: Roldan M, et al. Sensors, 2021.

More advanced optical techniques, including spatially resolved spectroscopy, frequency-domain and time-domain near-infrared spectroscopy, and diffuse correlation spectroscopy, allow a more quantitative assessment of tissue oxygenation, cerebral blood volume, and microvascular blood flow by incorporating photon pathlength modeling and dynamic flow-sensitive measurements. (Fig. 43) These approaches offer important theoretical advantages over conventional continuous-wave NIRS, particularly in their ability to disentangle absorption and scattering effects and to provide metrics that more closely reflect underlying cerebral physiology.

However, their translation into routine clinical practice in pediatric cardiac surgery remains limited by substantial technical complexity, high acquisition and maintenance costs, and non-trivial logistical constraints related to probe positioning, calibration, and intraoperative workflow integration. As a result, their use is currently largely restricted to specialized research environments rather than widespread bedside implementation. (77, 86)

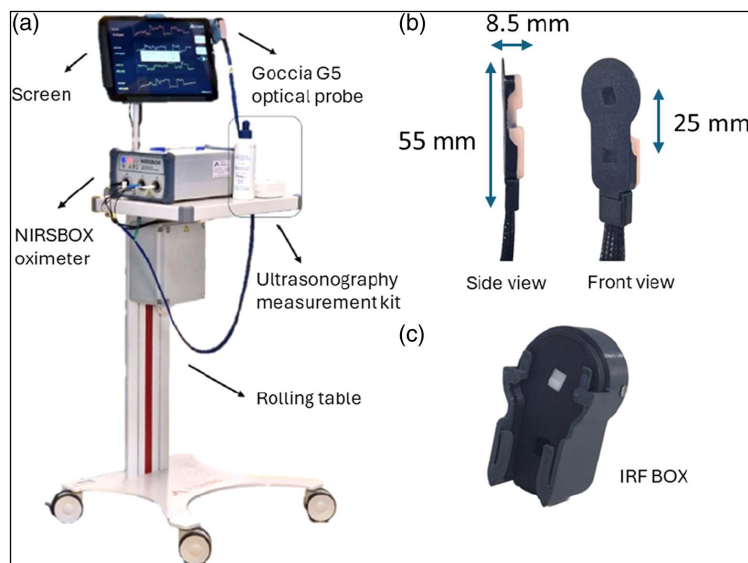


Fig.43 Adapted from: Calcaterra V, et al. Neurophotonics, 2024.

In routine practice, NIRS sensors are positioned on the forehead to interrogate the frontal lobes, supplied predominantly by branches of the anterior and middle cerebral arteries. This location facilitates reproducible placement and minimizes interference from hair, but inherently restricts monitoring to a regional cortical territory. Consequently, ischemic events affecting deeper brain structures or posterior circulation regions may not be detected. In addition, the NIRS signal is influenced by extracranial tissues, hemoglobin concentration, arterial oxygen saturation, cerebral blood volume, and metabolic rate, underscoring that rSO_2 represents an integrative physiological signal rather than a direct measure of cerebral blood flow or oxygen delivery. (87)

2.2.3 Interpretation of Cerebral Saturation Values

Normative values and clinically relevant thresholds for cerebral oxygen saturation in adults are influenced by baseline cerebrovascular physiology, comorbid conditions, and the clinical context in which monitoring is applied. In healthy adult subjects, resting frontal cerebral saturation values typically range between approximately 60% and 75%, although substantial inter-individual variability exists. Baseline values may be lower in older patients or in those with chronic cardiovascular, pulmonary, or cerebrovascular disease, reflecting reduced cerebral perfusion reserve, impaired oxygen delivery, or altered vascular reactivity. (88)

Rather than relying on universal absolute thresholds, most studies emphasize the importance of relative changes from an individual baseline. Reductions in cerebral saturation of 10–20% from baseline, or sustained absolute values below approximately 50%, have been associated in observational studies with increased risk of perioperative neurological complications, including delirium, postoperative cognitive dysfunction, and stroke. (Fig. 44) However, these thresholds should be interpreted cautiously, as definitive injury limits for cerebral tissue oxygenation in adults have not been established and are likely to vary according to the duration of desaturation, regional vulnerability, and the integrity of cerebral autoregulatory mechanisms.

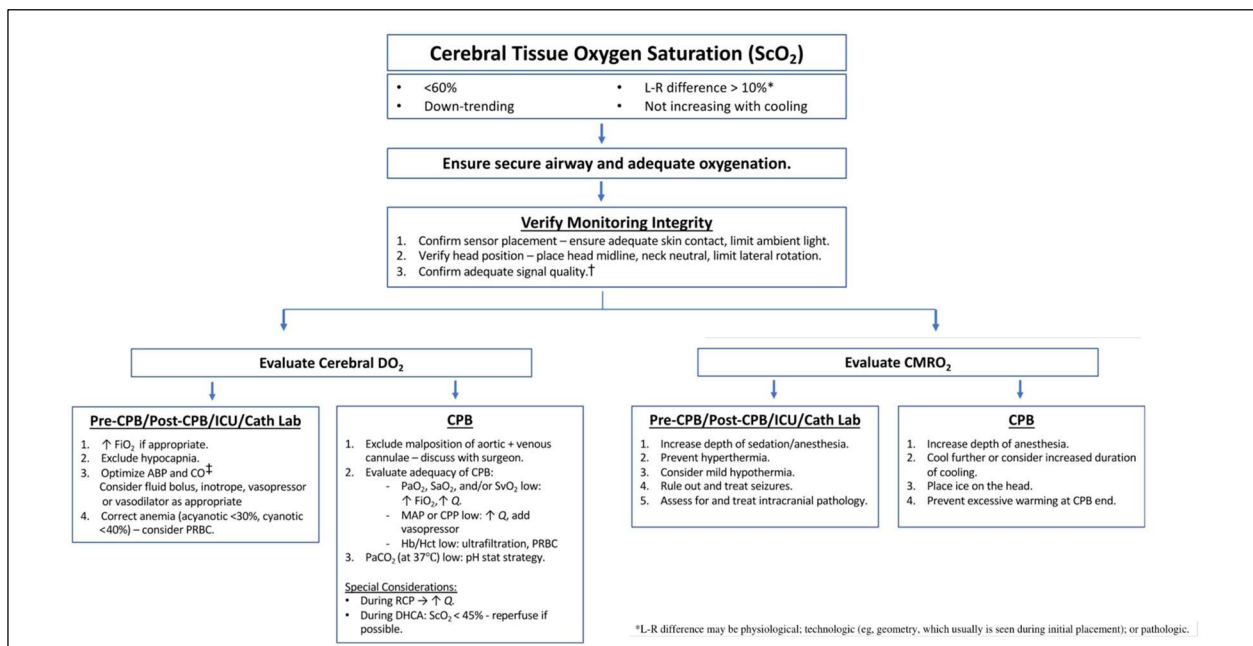


Fig.44 Adapted from: Zaleski KL, et al. J Cardiothorac Vasc Anesth, 2020.

Physiological interpretation of cerebral saturation values requires careful consideration of factors that influence the NIRS signal independently of cerebral blood flow. Extracranial contamination from scalp and skull blood flow, variability in arterial-to-venous weighting across devices, and changes in hemoglobin concentration, arterial oxygen saturation, carbon dioxide tension, temperature, and anesthetic depth all modulate cerebral oxygenation measurements. (87) In particular, hypercapnia and hypocapnia exert potent effects on cerebral blood flow, while anemia and hemodilution alter oxygen-carrying capacity without necessarily reflecting changes in perfusion.

Commercial NIRS systems demonstrate a mean precision of approximately 5%, with wide limits of agreement between devices. (89) As a consequence, absolute values are not directly interchangeable across platforms, and interpretation should prioritize intra-patient trends over time rather than isolated point measurements. Within this framework, cerebral oximetry is best understood as a dynamic physiological signal that reflects the integrated balance between oxygen delivery and consumption, and whose clinical value lies in trend analysis and contextual integration with systemic hemodynamic and respiratory parameters.

2.2.4 Clinical Applications and Evidence in Pediatric Cardiac Surgery

Pediatric congenital heart disease represents the clinical context in which near-infrared spectroscopy has been most extensively applied, both in research and routine practice. The widespread adoption of NIRS in this population reflects the high prevalence of neurodevelopmental impairment among survivors of congenital heart surgery and the recognition that perioperative disturbances in cerebral oxygen balance may contribute to acute brain injury and long-term neurological sequelae. As emphasized by Zaleski and Kussman, the primary rationale for cerebral NIRS in this setting is not diagnostic localization of brain injury, but the enhancement of physiological understanding and the early detection of potentially correctable perturbations in cerebral oxygen delivery and consumption. (88)

Early observational studies demonstrated that intraoperative cerebral desaturation events are common during pediatric cardiac surgery, particularly during cardiac manipulation, caval cannulation, initiation of cardiopulmonary bypass, and periods of altered flow or hematocrit. Importantly, decreases in cerebral oxygen saturation were often observed before changes in electroencephalography, highlighting the sensitivity of NIRS to early disturbances in cerebral oxygen balance. In the landmark study by Austin and colleagues, incorporation of cerebral oximetry within a multimodal neuromonitoring strategy was associated with a lower incidence of neurological sequelae when NIRS-detected abnormalities triggered timely intervention, most frequently related to cannula malposition or inadequate pump flow. (90)

Subsequent studies have explored associations between perioperative cerebral oxygenation and a range of outcomes, including magnetic resonance imaging–detected white matter injury, low cardiac output syndrome, postoperative morbidity, and neurodevelopmental performance at short- and mid-term follow-up. (91) Several of these investigations reported that prolonged post–cardiopulmonary bypass cerebral saturation values below approximately 45–50% were associated with adverse neurological or clinical outcomes (Fig. 45). However, other studies failed to demonstrate independent associations after adjustment for surgical complexity, underlying diagnosis, or baseline physiological status. Notably, baseline cerebral saturation has itself emerged as a potentially important marker of vulnerability, with lower preoperative values associated with increased risk and, in some studies, poorer neurodevelopmental outcomes.

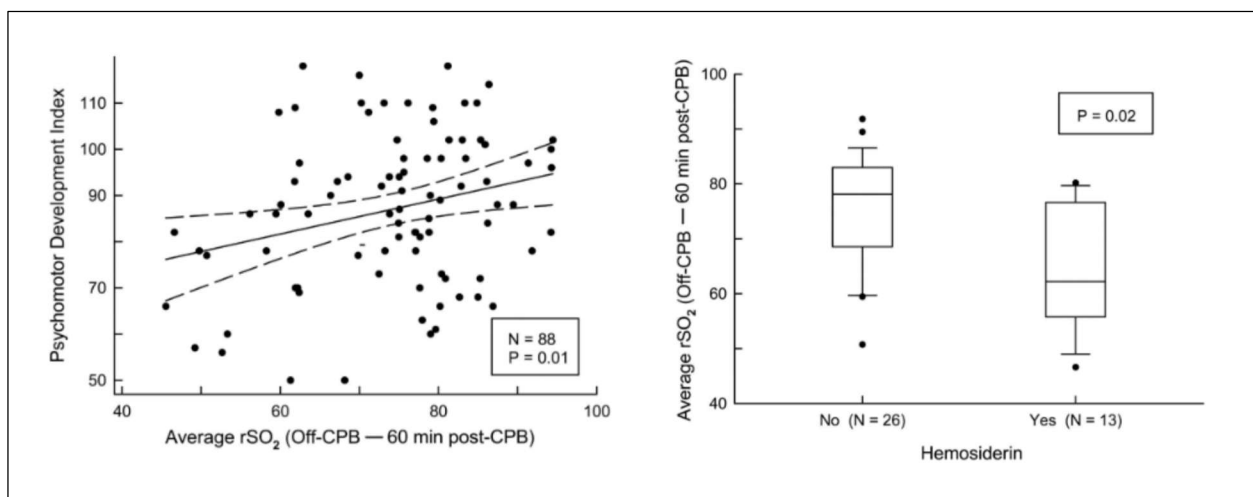


Fig.45 Adapted from: Kussman BD, et al. Circulation, 2010.

Beyond cerebral monitoring, multisite NIRS has been applied to assess somatic oxygenation, particularly in neonates and infants undergoing complex procedures such as stage I palliation for hypoplastic left heart syndrome. In this context, the somatic–cerebral saturation difference has been proposed as a surrogate marker of systemic perfusion and redistribution of blood flow, with reductions toward zero or negative values associated with low cardiac output states, biochemical shock, and increased mortality risk in early postoperative periods. (92) However, evidence supporting somatic NIRS remains less consistent than for cerebral monitoring, and clinically actionable thresholds have not been clearly established.

Despite extensive observational literature, no randomized controlled trials in pediatric congenital heart disease have been specifically designed to test whether NIRS-guided management improves neurological or clinical outcomes. The only pediatric randomized trials incorporating NIRS-guided interventions have been conducted in preterm infants in the neonatal intensive care setting and failed to demonstrate reductions in brain injury or improvements in neurodevelopment. Consequently, while NIRS is widely used and physiologically informative, its impact on outcome modification in pediatric cardiac surgery remains unproven. (93)

2.2.5 Limitations of Current Technology and Evidence

Several technological and methodological limitations complicate the use of NIRS in pediatric cardiac surgery. NIRS sensors interrogate only a small region of the frontal cortex, and thus may miss focal or posterior injuries. The lack of a universally accepted gold standard for calibration further complicates interpretation, as commercial devices rely on fixed arterial-to-venous weighting ratios that may not reflect true physiological variation. Factors such as hypercapnia, hypothermia, hemodilution, and altered cerebral autoregulation during cardiopulmonary bypass challenge the assumptions underlying NIRS algorithms and may influence the accuracy of readings. (94)

At the level of the literature, small sample sizes, single-center designs, heterogeneity in surgical diagnoses, and the absence of standardized NIRS-based treatment algorithms contribute to inconsistent findings and limit the strength of outcome associations. The multifactorial nature of neurodevelopmental outcomes in children with congenital heart disease further complicates attempts to isolate the independent effect of perioperative cerebral desaturation from other preoperative and intraoperative determinants.

2.2.6 Emerging Applications: Toward Multimodal Integration

Beyond conventional tissue oxygenation monitoring, NIRS has shown promise as a noninvasive tool for estimating cerebrovascular autoregulation at the bedside. By quantifying moving correlations between cerebral saturation and arterial blood pressure, the cerebral oximetry index can identify periods when cerebral perfusion becomes pressure passive. Early studies in pediatric cardiac surgery demonstrate the feasibility of this approach and suggest associations between impaired autoregulation, hypotension, and elevations of brain injury biomarkers such as glial fibrillary acidic protein. Although implementation remains limited by technical complexity and a lack of outcome-driven thresholds, autoregulation-guided perfusion management represents one of the most promising future directions for NIRS-based monitoring. (55)

Advanced optical techniques, including hybrid frequency-domain NIRS and diffuse correlation spectroscopy, allow simultaneous estimation of cerebral blood flow and oxygen metabolism. These methods have shown encouraging correlations with MRI-derived measures of oxygen extraction, cerebral blood flow, and metabolic rate. They also reveal physiological states that are not evident from saturation alone, such as uncoupling of cerebral blood flow and metabolism during deep hypothermic bypass. Although not yet feasible for routine clinical use, these technologies illustrate the potential of NIRS to evolve from a trend-monitoring tool into a comprehensive hemodynamic and metabolic monitoring platform. (77, 95, 96).

2.3 NIRS-based Cerebral Autoregulation Monitoring: Current Evidence and Knowledge Gap

2.3.1 Principles of NIRS-based Autoregulation Monitoring

Monitoring cerebral autoregulation requires simultaneous measurement of arterial blood pressure and a surrogate of cerebral blood flow or blood volume, along with an analytical method to quantify the relationship between these two signals. Near-infrared spectroscopy provides a practical and noninvasive tool for this purpose, offering continuous measures of cerebral oxygen saturation or total hemoglobin as proxies for cerebral hemodynamics. When autoregulation is intact, cerebral blood flow is maintained despite fluctuations in arterial pressure. When autoregulation is impaired, changes in arterial pressure produce corresponding changes in NIRS signals, reflecting pressure-passive cerebral blood flow. These relationships can be used to identify the lower limit of autoregulation, which represents the arterial pressure below which cerebral perfusion begins to decrease. NIRS-based indices such as the cerebral oximetry index and the hemoglobin volume index have been validated in experimental piglet models, demonstrating accuracy comparable to invasive gold-standard methods such as intracranial pressure monitoring and laser Doppler flowmetry. (50)

2.3.2. Technical Methodologies of NIRS-based Autoregulation Monitoring

Analytical methods for cerebral autoregulation can be broadly categorized into frequency domain and time domain approaches. Both rely on spontaneous fluctuations in arterial pressure but differ in how they characterize the relationship between blood pressure and NIRS-derived measures.

Frequency domain approaches use transfer function analysis to quantify coherence, gain, and phase between arterial pressure and cerebral signals. These methods require stable physiological conditions and adequate temporal resolution of spontaneous oscillations. Although theoretically robust, experimental work showed that frequency domain metrics often perform less sensitively than correlation or phase-based approaches in identifying the lower limit of autoregulation. Their reliance on longer data windows and more complex computation limits their feasibility in the rapidly changing physiological environment of infant cardiac surgery. (55)

Time domain methods, which are more commonly used clinically, focus on slow oscillations in arterial pressure that occur every thirty seconds to several minutes. These slow waves effectively engage autoregulatory mechanisms and allow autoregulation to be characterized by moving correlation windows. (49) The cerebral oximetry index, which calculates a correlation coefficient between mean arterial pressure and regional cerebral oxygen saturation, is the most widely applied index in infants. (45)

When autoregulation is impaired, the correlation becomes positive, and when autoregulation is intact, the correlation approaches zero or becomes negative. Thresholds around 0.3 to 0.4 have been used to delineate pressure-passive behavior, and these values have been supported by validation studies showing strong agreement with invasive measures of autoregulatory failure. Liu et al. reported that COx thresholds near 0.35 optimally identified the lower limit of autoregulation in cardiac patients undergoing CPB-requiring surgery. (97) (Fig. 46a and 46b)

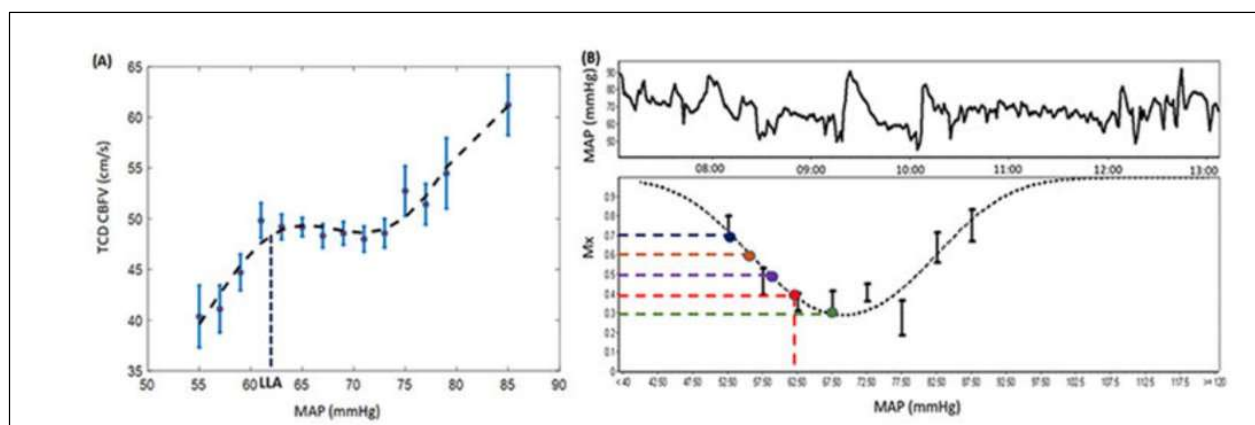


Fig.46a. Adapted from: Liu X, et al. Crit Care Med, 2021.

Root-mean squared and mean value of difference between lower limit of autoregulation defined by Lassen curves and different cerebral autoregulation thresholds.

CA threshold	Mx (n=47)		COx (n=46)		HVx (n=45)	
	RMS of difference	Mean $\pm$ SD of difference	RMS of difference	Mean $\pm$ SD of difference	RMS of difference	Mean $\pm$ SD of difference
0.1	12.91	-7.20 $\pm$ 11.30	11.56	-9.25 $\pm$ 9.52	9.97	-7.06 $\pm$ 7.22
0.15	13.73	-6.38 $\pm$ 12.76	8.63	-6.60 $\pm$ 6.18	8.02	-4.68 $\pm$ 6.65
0.2	13.81	-6.16 $\pm$ 12.82	7.17	-4.70 $\pm$ 5.42	6.84	-2.87 $\pm$ 6.33
0.25	12.05	-2.72 $\pm$ 12.15	8.28	-2.66 $\pm$ 5.43	7.05	-2.51 $\pm$ 6.69
0.3	12.88	-2.49 $\pm$ 13.00	6.46	-1.93 $\pm$ 6.31	6.01	-0.60 $\pm$ 6.07
0.35	10.33	-2.28 $\pm$ 10.31	5.81	-0.51 $\pm$ 5.10	6.30	0.34 $\pm$ 6.38
0.4	9.06	-1.15 $\pm$ 9.18	8.50	-1.45 $\pm$ 8.04	6.28	2.21 $\pm$ 5.95
0.45	8.77	0.64 $\pm$ 8.91	8.37	-0.72 $\pm$ 7.95	7.15	3.97 $\pm$ 6.02
0.5	9.29	1.06 $\pm$ 9.36	8.16	1.49 $\pm$ 7.50	8.36	5.22 $\pm$ 6.61
0.55	8.83	1.99 $\pm$ 8.72	9.02	3.42 $\pm$ 7.79	9.72	6.51 $\pm$ 7.30
0.6	9.47	3.73 $\pm$ 8.81	10.01	5.10 $\pm$ 7.96	11.43	8.26 $\pm$ 7.99
0.65	9.85	4.74 $\pm$ 8.74	11.41	7.51 $\pm$ 8.69	13.37	10.02 $\pm$ 8.95
0.7	11.89	5.86 $\pm$ 10.47	11.01	8.41 $\pm$ 7.18	11.67	9.60 $\pm$ 6.73
0.75	12.24	7.42 $\pm$ 9.86	11.89	9.90 $\pm$ 6.67	12.03	10.17 $\pm$ 6.52
0.8	12.53	8.48 $\pm$ 9.34	13.32	11.59 $\pm$ 6.64	13.43	11.58 $\pm$ 6.91
0.85	15.74	11.72 $\pm$ 10.66	14.87	13.19 $\pm$ 6.96	15.15	13.25 $\pm$ 7.45
0.9	15.38	12.22 $\pm$ 9.48	16.49	15.02 $\pm$ 6.90	17.31	15.54 $\pm$ 7.75

CA = cerebral autoregulation; COx = cerebral oximetry index; HVx = hemoglobin volume index; Mx = mean flow index; RMS = root mean square (unit: mmHg).

Fig.46b. Adapted from: Liu X, et al. Crit Care Med, 2021.

The hemoglobin volume index (HVx) offers an alternative and complementary measure by correlating mean arterial pressure with total hemoglobin concentration derived from NIRS isosbestic wavelengths. This index reflects changes in cerebral blood volume and provides insight into vascular tone. In experimental models, hemoglobin volume indices have been performed as well as or better than oxygenation-based measures for identifying autoregulatory failure. Despite this promise, they remain less commonly used clinically. (98)

Both COx and HVx require multi-minute data segments, often on the order of fifteen minutes, to generate stable and interpretable estimates of the autoregulatory state. This temporal requirement can pose challenges during cardiac surgery, where rapid transitions occur during bypass initiation, cooling, rewarming, and separation from bypass. Recent efforts to accelerate autoregulation estimation include co-trending methods and the controlled induction of oscillatory arterial pressure changes, yet these innovations have not been extensively tested in infants. Together, these methodological considerations highlight both the potential and current limitations of NIRS-based autoregulation monitoring in pediatric cardiac surgery.

2.3.3. Clinical Evidence in Neonates and Infants

Clinical studies investigating autoregulation monitoring in infants remain limited but consistently demonstrate substantial interindividual variability in autoregulatory capacity. Data from a prospective observational study shows that the lower limit of autoregulation could be identified in approximately seventy seven percent of infants undergoing cardiac surgery. The mean lower limit was around forty-two millimeters of mercury, but individual values ranged widely from twenty to fifty-five millimeters. This variability suggests that fixed blood pressure thresholds may be inadequate for protecting the brain and supports the concept of individualized blood pressure targets based on autoregulation monitoring. (13)

Despite feasibility, a major limitation is the lack of evidence that autoregulation-guided management improves neurological outcomes. No completed neonatal or infant trial has shown that identifying the lower limit of autoregulation reduces postoperative white matter injury, seizures, or neurodevelopmental impairments. In contrast, randomized trials in adults have demonstrated that autoregulation-guided blood pressure management reduces the burden of hypotension below the autoregulatory threshold and improves selected neurological outcomes such as postoperative delirium. While encouraging, these findings cannot be directly applied to infants because of substantial developmental and hemodynamic differences. (99)

2.3.4 Challenges Unique to the Infant Population

Infants undergoing cardiac surgery present unique physiological challenges that complicate autoregulation-guided care. Postoperative low cardiac output syndrome is common, and management often requires reducing systemic vascular resistance to improve cardiac output. These interventions may lower arterial pressure to values below the individual lower limit of autoregulation, placing the brain at increased risk of hypoperfusion. Balancing the competing needs of brain perfusion and cardiac output is therefore complex and may limit the ability to target autoregulatory thresholds safely. (100)

Outcome assessment also presents challenges. While postoperative MRI can quantify white matter injury, no intervention has yet demonstrated reduction of these lesions. (75) Neurological examinations are insensitive in neonates, and measures such as delirium are not applicable. Electrographic seizures occur in approximately ten percent of neonates after cardiac surgery and are strongly associated with later neurodevelopmental outcomes, making seizure burden an attractive short-term outcome measure. Nevertheless, detecting differences in seizure incidence requires large multicenter studies. Long-term neurodevelopmental assessments remain the gold standard but require many years of follow-up.

2.3.5 Knowledge Gap and Future Directions

Current evidence supports the physiological validity and feasibility of NIRS-based autoregulation monitoring in infants, yet major gaps remain. These include limited understanding of the clinical significance of autoregulation indices, lack of standardized analytic pipelines, uncertain links to neurological outcomes, and challenges of balancing cerebral protection with systemic hemodynamics. Furthermore, approaches validated in neonates have not been systematically extended to older infants, despite similar vulnerabilities in the first year of life. (13)

Bridging these gaps requires well-designed clinical studies that assess the accuracy, feasibility, and safety of autoregulation-guided care and evaluate outcomes such as MRI-defined brain injury, electrographic seizures, and long-term neurodevelopment. As described in the following sections, the research program developed in this thesis aims to advance this field by extending autoregulation monitoring to the entire infant population, characterizing autoregulatory behavior across the perioperative continuum, and evaluating its potential role in precision hemodynamic management.

2.4 Current Research and Project's Contribution

2.4.1 Introduction

Over the 2023-2025 period, a coordinated research program was developed to advance the understanding of cerebral physiology in infants undergoing open-heart surgery and to evaluate the feasibility and clinical relevance of perioperative NIRS-based cerebral autoregulation monitoring. This program builds upon the growing recognition that infants with congenital heart disease are exposed to significant hemodynamic instability during anesthesia, cardiopulmonary bypass, and early postoperative recovery, conditions that place them at elevated risk for cerebral hypoperfusion and oxygen supply-demand mismatch. Improving neurological outcomes therefore requires tools capable of characterizing cerebral perfusion in real time and guiding individualized hemodynamic strategies.

2.4.2 Rationale and Conceptual Framework

The central hypothesis of this research program is that continuous monitoring of cerebral autoregulation, integrated within a multimodal neuromonitoring framework, can enable individualized cerebral hemodynamic management and reduce the risk of acute neurological injury in critically ill infants. Despite major advances in pediatric and neonatal intensive care, the definition and clinical significance of hypotension in this population remain incompletely resolved.

Commonly used blood pressure thresholds are largely derived from expert consensus, vary across guidelines, and show limited correlation with cerebral perfusion or neurological outcomes. This uncertainty is particularly pronounced in neonates and young infants, in whom developmental immaturity of cardiovascular and cerebrovascular control mechanisms leads to substantial interindividual variability in tolerance to systemic blood pressure fluctuations. (101)

In clinical practice, cerebral near-infrared spectroscopy has become an important adjunct for monitoring cerebral oxygenation and has contributed meaningfully to the detection of gross alterations in cerebral oxygen balance. However, conventional use of NIRS provides only indirect and often nonspecific information regarding cerebral perfusion. Reductions in regional cerebral oxygen saturation may reflect a range of physiological states, including changes in oxygen delivery, extraction, or metabolic demand, and do not reliably discriminate between compensated perfusion changes and clinically relevant hypoperfusion. As a result, isolated NIRS thresholds may lack specificity for identifying periods in which cerebral blood flow becomes pressure dependent and the brain is at highest risk of injury. (88)

Continuous cerebral autoregulation monitoring addresses these limitations by directly interrogating the dynamic relationship between systemic arterial pressure and cerebral oxygenation signals. Autoregulation indices derived from the correlation between invasive arterial blood pressure and NIRS measurements provide a quantitative estimate of cerebrovascular reactivity over time. When processed using advanced signal-analysis platforms such as ICM+ (Cambridge Enterprise, University of Cambridge, Cambridge, UK <https://icmplus.neurosurg.cam.ac.uk/>) these indices allow identification of individualized blood pressure ranges over which autoregulation is preserved and enable detection of periods during which cerebral perfusion becomes pressure passive. In this framework, hypotension is no longer defined by a fixed numerical threshold but is instead contextualized as a patient-specific physiological state associated with impaired autoregulatory capacity.

By moving beyond population-based blood pressure targets and nonspecific oxygenation metrics, autoregulation-guided monitoring offers a path toward precision hemodynamic management in neonatal and pediatric critical care. This individualized approach provides a physiologically grounded basis for tailoring interventions and represents a critical step toward reducing avoidable cerebral hypoperfusion and improving neuroprotective strategies in vulnerable infant populations.

2.4.3 Structure of the Collaborative Program

The core research activity described in this thesis was developed within a dedicated collaboration between IRCCS Istituto Giannina Gaslini in Genova, Italy and the Children's National Hospital

Heart Center in Washington, DC, with the specific aim of advancing perioperative cerebral autoregulation monitoring in infants with congenital heart disease undergoing open-heart surgery. (Fig. 47) This partnership was designed to address the unique vulnerability of the developing brain during cardiopulmonary bypass and early postoperative recovery, periods characterized by profound and often rapid hemodynamic perturbations.

The collaboration enabled the systematic acquisition of high-resolution intraoperative and postoperative physiological data, including invasive arterial blood pressure and cerebral near-infrared spectroscopy signals, collected under standardized clinical and technical protocols. By leveraging the complementary clinical volumes, technical infrastructure, and research expertise of the two institutions, this program facilitated the development of one of the largest existing datasets focused on cerebral autoregulation dynamics in infant cardiac surgery. The joint effort further integrated advanced signal-processing and analytical methodologies, allowing continuous computation of autoregulation indices and individualized perfusion targets using dedicated monitoring software.

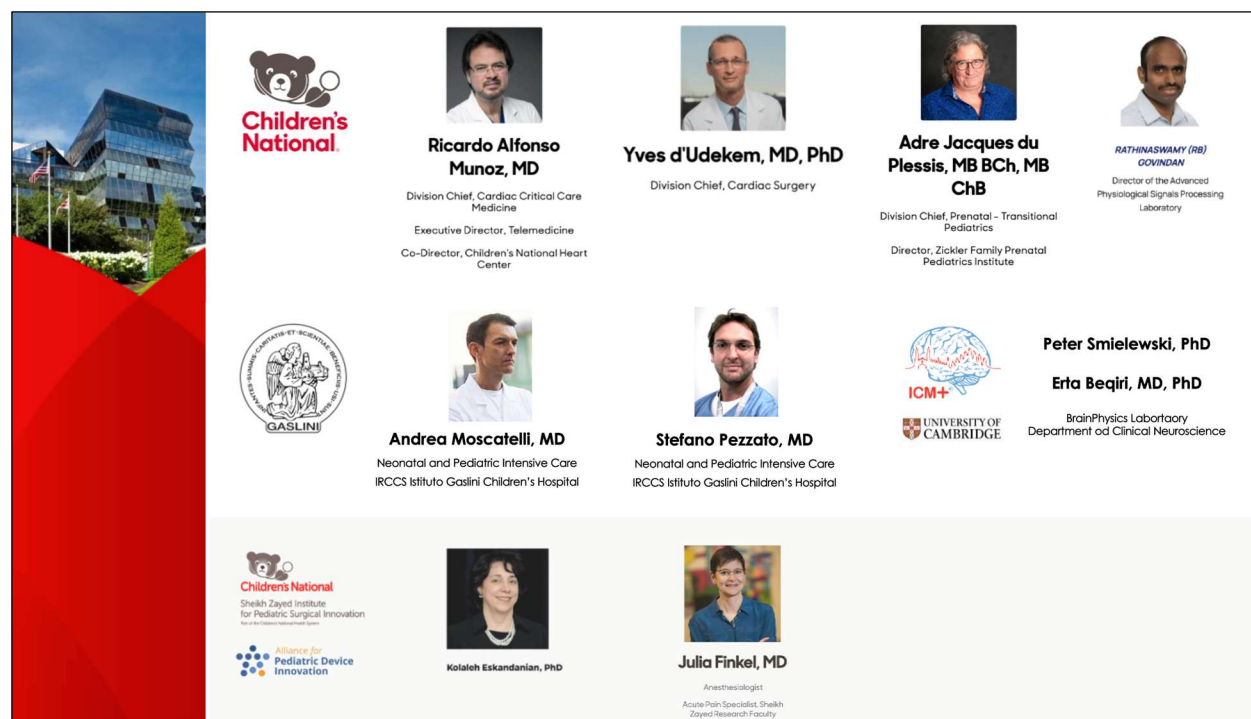


Fig 46. Overview of key roles within the collaborative research project with Children's National Hospital.

Beyond data generation, this collaborative framework fostered close interaction between clinicians, biomedical engineers, and data scientists, ensuring that methodological development remained tightly aligned with clinically relevant questions. As a result, the partnership with the Children's National Hospital Heart Center provided both the scale and the multidisciplinary expertise required to translate cerebral autoregulation monitoring from a research tool into a clinically meaningful approach for individualized perioperative neuroprotection in congenital heart disease.

2.4.4 Contribution to Research on Perioperative monitoring in Congenital Heart Defects

The core contribution of this work lies in the perioperative assessment of cerebral autoregulation in infants undergoing open-heart surgery. A major achievement of the collaboration between Gaslini and Children's National Hospital was the development of one of the largest existing databases of high-resolution intraoperative physiological recordings from infants supported with cardiopulmonary bypass, currently comprising $n=185$ patients. For more than half of these infants, early postoperative brain magnetic resonance imaging is available, providing a unique opportunity to examine the relationships among autoregulation metrics, cerebral perfusion physiology, and early neurological outcomes. Data processing and analysis were performed using ICM+, enabling continuous computation of autoregulation indices and the estimation of individualized optimal perfusion pressures (manuscript currently under submission). In parallel, a prospective observational study was initiated to characterize cerebral autoregulation during the first seventy-two hours after neonatal cardiac surgery. To date, seventy-three neonates have been enrolled at Children's National Hospital and ten at Gaslini. Continuous invasive blood pressure and NIRS signals were extracted from the CICU Data Warehouse at Children's National and from direct ICM+ acquisition at IRCCS Gaslini. These signals were processed into standardized HDF5 and .icmp formats through a collaborative workflow involving data scientists, biomedical engineers, and clinical researchers. This study aims to link postoperative autoregulatory behavior with neurological complications including seizures, abnormal neuroimaging, and adverse clinical events. The ongoing integration of quantitative EEG metrics will enable investigation of relationships between CO_x dynamics and patterns of cerebral electrical activity. (NCCA Study Protocol, Children's National IRB approval ID: STUDY00000475)

2.4.5. Integration of Artificial Intelligence and Predictive Analytics

A complementary line of investigation within this research program has focused on the application of artificial intelligence to real-time risk prediction in the pediatric cardiac intensive care unit. This work was developed through a dedicated collaboration with the CICU Command Center team at Children's National Hospital and aimed to leverage high-frequency, multimodal physiological data routinely collected at the bedside.

Within this framework, machine-learning models were designed to integrate hemodynamic, neuromonitoring, and clinical data streams in order to anticipate episodes of physiological deterioration, including hemodynamic instability and neurological complications. (102)

These efforts are closely aligned with the institution's broader strategic initiatives in digital health, data integration, and predictive analytics, and emphasize the translation of advanced computational methods into clinically relevant insights. Importantly, this research provides a methodological foundation for the future incorporation of cerebral autoregulation metrics into AI-assisted clinical decision support systems. By combining individualized autoregulation information with data-driven predictive models, this approach has the potential to enhance early risk stratification and support precision hemodynamic management in critically ill pediatric cardiac patients.

2.4.6 Scientific Output and Contribution to the Field

The research program has resulted in peer-reviewed publications and conference presentations, including original studies on postoperative and intraoperative autoregulation monitoring, scoping reviews on pediatric autoregulation physiology, and multicenter analyses of cerebral perfusion and outcome in traumatized and critically ill children. These outputs have contributed to establishing the feasibility of autoregulation monitoring in infants, characterizing the prevalence of impaired autoregulation in high-risk populations, and advancing the methodological framework required for its clinical implementation.

2.4.7. Ongoing and Emerging Research Directions

Two major funded initiatives are currently in development.

The first is a Gaslini-led research project (PI: Dr. Moscatelli A) aimed at integrating conventional and advanced time-domain NIRS technologies to improve identification of cerebral malperfusion and to correlate autoregulation impairment with biomarkers of neurological injury such as glial fibrillary acidic protein.

The second is an NIH R21 grant application (PI: Dr. Yves d'Udekem) focused on AI-assisted intraoperative autoregulation monitoring in infants undergoing open-heart surgery. This proposal seeks to develop methods that combine COx dynamics with machine-learning algorithms to enhance the detection of autoregulatory failure and to guide arterial pressure management. Both initiatives aim to accelerate the translation of physiologic monitoring innovations into clinically actionable strategies for perioperative neuroprotection.

2.5 Preoperative CAR Monitoring in Neonates with Congenital Heart Disease

2.5.1 Introduction

Preoperative cerebral autoregulation monitoring in neonates with congenital heart disease has emerged as an important area of investigation, motivated by evidence that cerebrovascular vulnerability begins before surgery and may contribute to the high prevalence of preoperative brain injury observed in this population. Recent studies performed with novel biomedical optical techniques have demonstrated that a substantial proportion of neonates with critical congenital heart disease exhibit impaired autoregulation even prior to operative intervention. (77)

These abnormalities appear to reflect the combined effects of abnormal fetal circulation, transitional hemodynamic instability, and lesion-specific alterations in cerebral perfusion physiology. (Fig. 47)

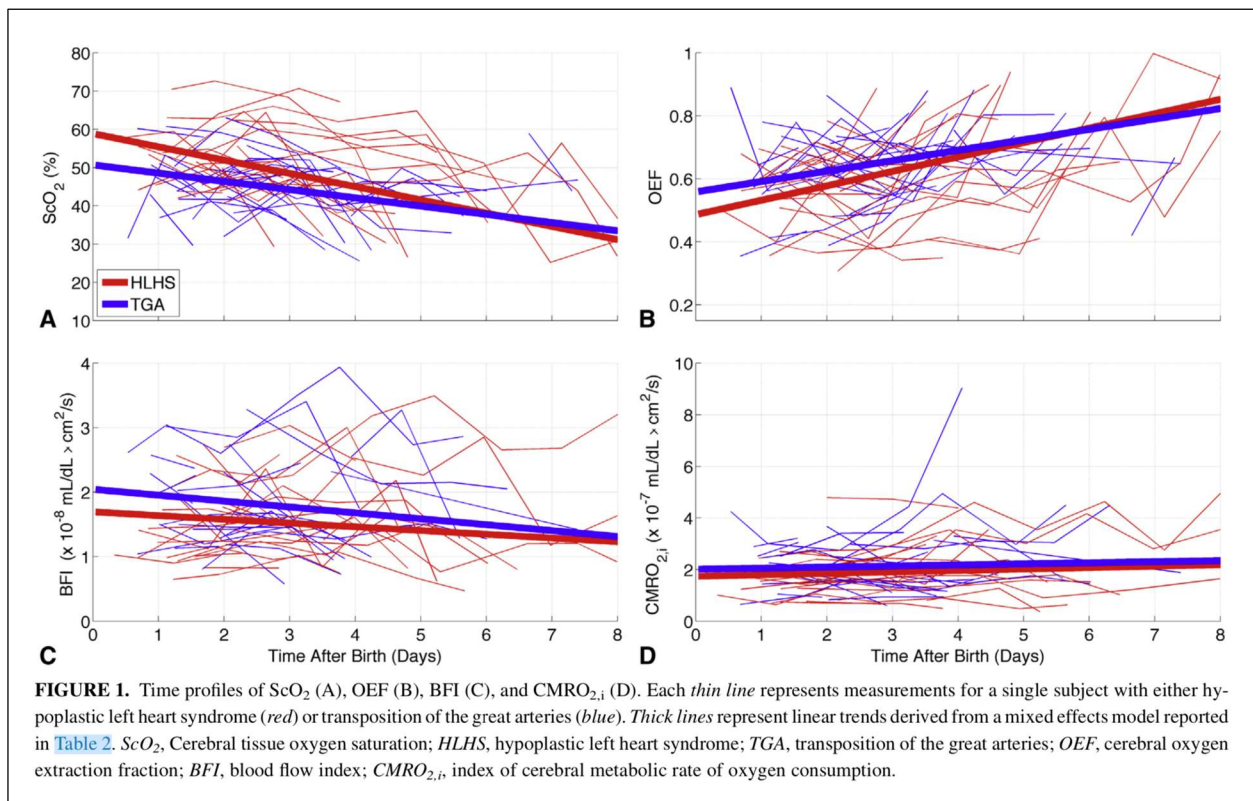


Fig.47 Adapted from: Lynch JM, et al. J Thorac Cardiovasc Surg, 2018.

2.5.2 Recent Evidence from Preoperative Monitoring Studies

Observational studies consistently report considerable interindividual variability in autoregulatory capacity, with some neonates demonstrating robust pressure reactivity while others spend a significant proportion of time in a pressure-passive state. Additionally, several centers have found associations between impaired preoperative autoregulation and markers of acute brain injury, including MRI-detected white matter injury and abnormal neurological examinations. However, these findings remain heterogeneous and, in some cases, inadequately powered, underscoring the need for standardized monitoring protocols and larger multicenter investigations. (103)

Across studies, continuous NIRS-based autoregulation monitoring has proven feasible and capable of revealing clinically meaningful patterns that would not be detectable through static cerebral saturation values alone. Nevertheless, the evidence base remains limited, with most studies enrolling small cohorts, using retrospective designs, or relying on heterogeneous analytic thresholds. (104)

2.5.3 Physiologic Interpretation of Preoperative Impairment

Impaired autoregulation in the preoperative period may reflect both structural and functional vulnerability. Neonates with congenital heart disease frequently exhibit reduced cerebral oxygen delivery due to diminished systemic output or mixing physiology, and these conditions may lower the autoregulatory plateau or narrow the range over which autoregulation is preserved. The transitional circulation itself, particularly in ductal-dependent lesions, introduces rapid changes in systemic and cerebral perfusion that can precipitate pressure-passive states. Moreover, the immature cerebrovascular bed of the neonate exhibits limited vasomotor reserve, which may predispose certain infants to autoregulatory failure even in the absence of overt hemodynamic compromise. (77)

2.5.4 Preliminary Preoperative Data from Children's National Hospital

Within this evolving landscape, our group contributed one of the first comparative evaluations of preoperative cerebral autoregulation in neonates with hypoplastic left heart syndrome (HLHS), initially presented as preliminary work at the 2024 PCICS Annual Meeting (*see below*).

Cerebral Autoregulation Monitoring with Cerebral Oxymetry Index in Neonates with Hypoplastic Left Heart Syndrome Undergoing Bilateral Pulmonary Artery Banding vs Primary Norwood Procedure: Single-Center Preliminary Data.

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Children's National



Gaslini
CURIAMO I BAMBINI

This retrospective observational study examined two distinct cohorts undergoing different initial strategies for single-ventricle palliation: the traditional primary Norwood procedure and bilateral pulmonary artery banding (bPAB) as the first stage of the rapid two-stage Norwood (RTSN) approach, as proposed by Wernovsky and colleagues.

The RTSN strategy is based on the recognition that the immediate postnatal period in hypoplastic left heart syndrome is characterized by profound circulatory maldistribution, driven by the rapid postnatal decline in pulmonary vascular resistance and the resulting preferential increase in pulmonary blood flow at the expense of systemic perfusion.

Early bPAB, performed within the first 24–48 hours of life, is intended to promptly limit pulmonary overcirculation and redirect the combined cardiac output toward the systemic circulation, thereby preserving oxygen delivery to critical end organs, including the brain, myocardium, kidneys, and gastrointestinal tract. By stabilizing systemic blood flow during the transitional circulation, this approach seeks to reduce the progressive decline in cerebral and systemic perfusion observed prior to surgical intervention and to limit the need for intensive preoperative measures aimed at manipulating pulmonary and systemic vascular resistances. Deferral of the Norwood procedure beyond the immediate neonatal period allows cardiopulmonary bypass and complex arch reconstruction to be undertaken in a more physiologically stable infant, potentially mitigating the cumulative burden of early postoperative low cardiac output, end-organ injury, and prolonged hospitalization. In contrast, the traditional primary Norwood strategy exposes neonates to cardiopulmonary bypass and myocardial ischemia during a phase of marked physiological vulnerability, when susceptibility to neurological, renal, and intestinal injury is greatest (105) (Fig. 48)

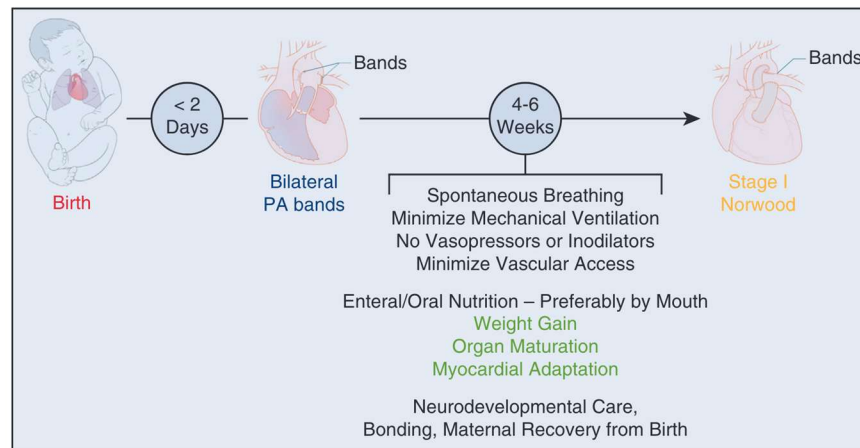
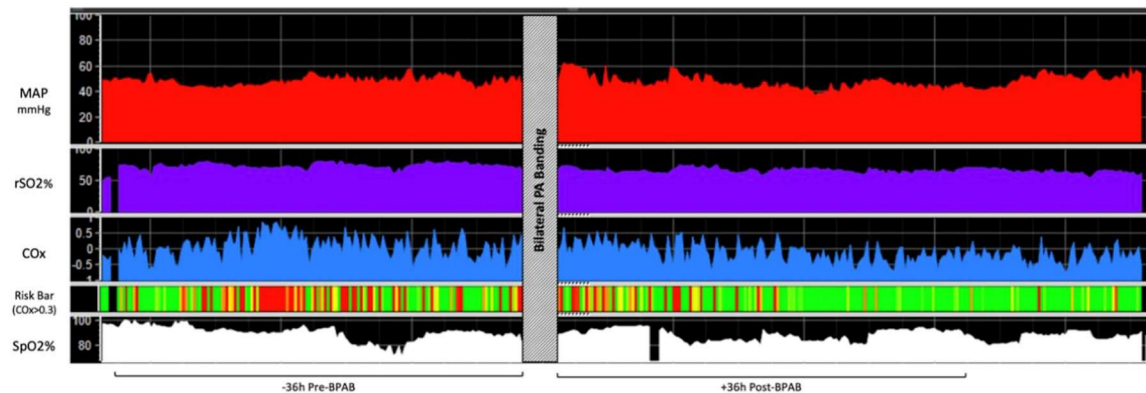


FIGURE 1. Proposed management strategy for neonates with hypoplastic *left* heart syndrome and standard risk profile. For high-risk patients, a hybrid approach is recommended (stent as neonate, comprehensive stage 2 at age 4-6 months). PA, Pulmonary artery.

Fig 48. Adapted from: Wernovsky G, et al. JTCVS Open, 2023.

In parallel with this cohort-based analysis, our work on this topic also included the presentation of a detailed case report at the 12th World Congress of Pediatric Critical Care Societies (WCPCCS) in 2023, which highlighted the application of preoperative and perioperative cerebral autoregulation monitoring in a high-risk neonate with HLHS. This case provided qualitative, physiology-driven insight that complemented the cohort findings and reinforced the biological plausibility of the observed group-level patterns. (Fig. 49)

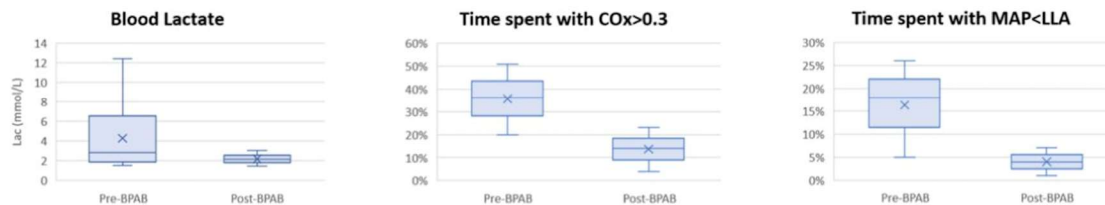
Figure A.



Perioperative Cerebral Oximetry index continuous monitoring.

Red solid-boxes from risk-bar represent cerebral autoregulation impairment (less frequent after BPAB).

Figure B.



Preoperative *versus* Postoperative tendencies of blood lactates levels, and cerebral autoregulation metrics. Calculations are based on 36-hours time windows before/after rBPAB.

Fig 49. Adapted from: Pezzato S, et al. Presented at the 12th WCPCCS, Washington DC, 2023.

In the preliminary dataset from CNH analysed, preoperative monitoring demonstrated that neonates awaiting bPAB and those awaiting primary Norwood did not differ meaningfully with respect to baseline mean arterial pressure, cerebral regional oxygen saturation (rSO₂), or the proportion of time spent with impaired cerebral autoregulation. Importantly, no deterioration in autoregulatory metrics was observed following bPAB, suggesting that this early intervention does not adversely affect cerebrovascular reactivity during the preoperative stabilization phase. In contrast, postoperative autoregulatory profiles differed substantially between the two surgical strategies. The seven neonates in the primary Norwood cohort underwent surgery at a median age of 5 days of life, whereas the nine neonates in the rapid two-stage Norwood cohort received bPAB at a median age of 2 days. Baseline patient characteristics are summarized below. (Fig. 50)

Parameters	Primary Norwood (n=7)	bPAB for RTSN (n=9)	P-Value
Female, n (%)	4 (57)	5 (55)	1
GA at birth, weeks	39 (38-39)	38 (38-38)	0.14
Birth weight, Kg	3.2 (3.10-3.55)	2.9 (2.6-3.4)	0.06
Age at surgery, days	5 (4-5.5)	2 (2-3)	<0.01
CPB duration, min	191 (150-213)	N/A	-
SCP duration, min	51 (49-64)	N/A	-
MAP, mmHg	52.9 (52.2-54.7)	47.9 (47.5-49.8)	0.34
rSO ₂ , %	51.2 (49.3-59.2)	62.7 (61.8-65.7)	0.07
SpO ₂ , %	83.6 (79.3-86.9)	87.12 (86.0-87.95)	0.28
Time COx>0.3, %	39.0 (28.1-40.9)	19.7 (17.5-27.3)	0.01
Time MAP<LLA, %	10.2 (4.9-12.6)	1.7 (0.7-2.9)	0.03
Time MAP>ULA, %	9.7 (7.4-19.3)	3.6 (2.4-5.1)	0.04
ULA-LLA, mmHg	12.6 (11.9-16.9)	16.4 (15.2-19.3)	0.2

Fig 50. Adapted from: Pezzato S, et al. Presented at the 2024 PCICS Annual Meeting, San Diego, CA.

Comparison of postoperative monitoring following the two procedures revealed no significant differences in mean arterial pressure or rSO₂ between cohorts. However, the proportion of time spent with impaired autoregulation (COx > 0.3) was markedly higher in the primary Norwood cohort compared with the bPAB cohort (39.0% [28.1–40.9] vs 19.3% [17.5–27.3]). Similarly, exposure to arterial pressures below the lower limit of autoregulation was greater following primary Norwood (10.2% [4.9–12.6] vs 1.7% [0.7–2.9]). Within-subject analysis of physiological monitoring before and after bPAB revealed no significant changes in mean arterial pressure, rSO₂, or autoregulation indices, further supporting the cerebrovascular tolerability of this intervention (Fig.51)

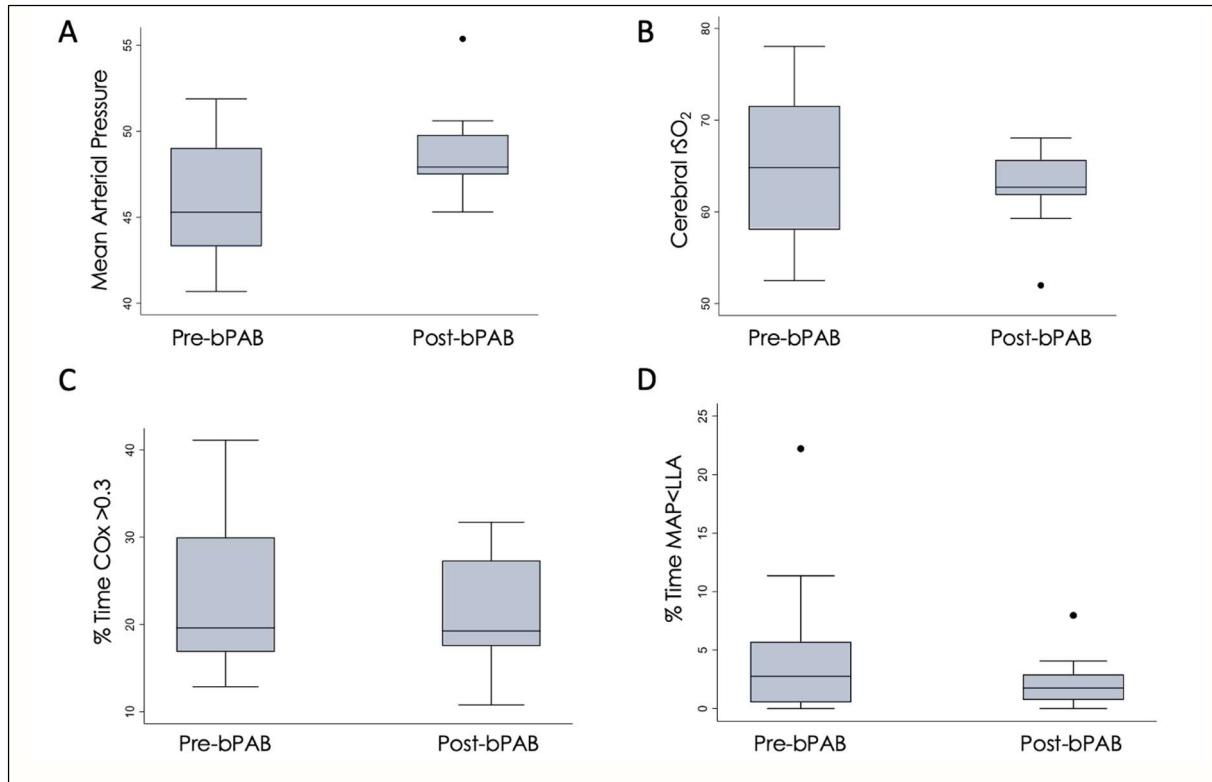


Fig 51. Adapted from: Pezzato S, et al. Presented at the 2024 PCICS Annual Meeting, San Diego, CA

These findings support the concept that rapid bilateral pulmonary artery banding may mitigate the risk of inadequate cerebral oxygen delivery by reducing exposure to pressure-passive cerebral perfusion during a critical period of neurodevelopmental vulnerability. While exploratory and limited by sample size, this work provides early physiological evidence that staged palliation strategies may confer differential cerebrovascular effects, warranting further investigation in larger prospective studies.

2.5.5 Implications for the Field and Directions for Future Research

Taken together, recent studies and our preliminary findings indicate that substantial physiological variability exists during the preoperative phase, which may influence susceptibility to postoperative neurological injury. The existing literature highlights the need for improved characterization of preoperative cerebrovascular physiology and suggests that targeted preoperative interventions, as well as optimization of surgical timing, may help preserve cerebral autoregulatory capacity during a critical window of neurodevelopmental vulnerability.

Our group's results add to this emerging evidence by demonstrating the feasibility of continuous NIRS-based autoregulation monitoring to compare surgical strategies and by suggesting that early bilateral pulmonary artery banding may attenuate postoperative cerebrovascular stress. Although these observations require confirmation in larger cohorts, they provide a compelling rationale for expanding preoperative neuromonitoring efforts and for integrating autoregulation-derived metrics into clinical decision-making regarding surgical timing and early palliation strategies.

The potential relevance of cerebral autoregulation monitoring in informing surgical strategy and timing was further highlighted in a dedicated scientific session at the 12th World Congress of Pediatric Critical Care Societies (WCPCCS) in 2023, including a focused event on “*Rethinking HLHS*” hosted by Children’s National Hospital, during which our data were presented and discussed by the leadership of the institutional neuro-cardiac critical care program, underscoring growing interest in this approach as a potentially modifiable determinant of perioperative neurological risk. (*see below*)

“We All Want Progress, But We Are Resistant To Change”
Challenging Current Dogma - Hot Topics
Presented by Children’s National Heart Institute, Washington DC, USA,
In Collaboration with



8th World Congress of
Pediatric Cardiology
and Cardiac Surgery

August 29th, 2023, 7:00 p.m. - 9:00 p.m., Walter E. Washington Convention Center 147AB

8:25 p.m. Fixing the Heart is Necessary But Insufficient; A Good Neurodevelopmental Outcome Is THE Most Important Outcome for our Patients and Families



The Brain of the Child with CHD: 21st Century Update - [Catherine Limperopolous, Ph.D.](#)



NeuroCardiac ICU Care and Cerebral Autoregulation - [Ricardo Muñoz, M.D.](#)



The Brain Will Tell us When To Operate on the Heart - [Daniel Licht, M.D.](#)

2.6 Intraoperative Monitoring in Infants Undergoing Open-Heart Surgery

2.6.1 introduction

The intraoperative period represents one of the most critical phases of physiological vulnerability for infants with congenital heart disease undergoing surgical repair. Cardiopulmonary bypass profoundly alters the determinants of cerebral perfusion through rapid and often non-physiological changes in arterial blood pressure, temperature, hematocrit, blood viscosity, acid–base balance, and systemic vascular resistance. These perturbations occur in the context of an immature neurovascular system and a developing brain characterized by limited vascular redundancy and heightened susceptibility to ischemic injury, particularly within watershed white matter regions. As a result, the ability of the cerebral circulation to buffer fluctuations in systemic pressure may be compromised at precisely the time when hemodynamic instability is most pronounced. (96)

Within this setting, arterial blood pressure is actively manipulated to balance competing physiological goals, including optimization of pump flow, myocardial performance, and systemic oxygen delivery. However, as highlighted in contemporary reviews of neonatal cardiac surgery, including the work by Spilka and colleagues, blood pressure targets used intraoperatively are largely empirical and not informed by patient-specific cerebral perfusion physiology. The lower limits of cerebral autoregulation during cardiopulmonary bypass are unknown in neonates and infants, and substantial interindividual variability is expected. Consequently, strategies aimed at supporting cardiovascular performance may inadvertently expose the brain to periods of pressure-passive perfusion and hypoperfusion injury. (13)

For these reasons, the operating room has emerged as a uniquely important environment for the application of continuous cerebral autoregulation monitoring. Unlike postoperative care, where hemodynamic changes may evolve more gradually, intraoperative management is characterized by abrupt transitions related to initiation and weaning of bypass, cooling and rewarming, and changes in anesthetic depth. Continuous autoregulation monitoring during these phases offers the opportunity to identify periods in which cerebral blood flow becomes dependent on arterial pressure and to define individualized perfusion targets that may enhance neuroprotection. (106) Importantly, near-infrared spectroscopy–based autoregulation indices, derived from the dynamic relationship between arterial pressure and cerebral oxygenation signals, are particularly well suited to the cardiac operating room, where monitoring must be non-invasive, continuous, and hands-free.

2.6.2 Pilot Evidence from Neonates Undergoing Cardiopulmonary-Bypass

Building on the seminal intraoperative studies by Brady, Easley, and colleagues, who first demonstrated the feasibility of using NIRS-derived indices such as HVx (107) and COx (108) to track cerebrovascular reactivity during pediatric cardiopulmonary bypass and identified characteristic increases in pressure passivity during cooling and rewarming, our recently published pilot study offers one of the first focused contemporary assessments of cerebral autoregulation exclusively in term neonates across the full trajectory of bypass. (109)

High-resolution arterial pressure and cerebral NIRS signals were then retrospectively analyzed using standardized ICM+ pipelines to compute the cerebral oximetry index across pre-CPB, on-CPB, and post-CPB periods. The analysis demonstrated a clear disruption of cerebrovascular reactivity during bypass, with COx values increasing from near-zero preoperative levels to markedly impaired values during CPB. Although a partial recovery was observed after rewarming and separation from bypass, COx did not return to baseline, indicating persistent vulnerability in the immediate postoperative period. The percentage of time with COx values above 0.3 was greatest during the post-cardiopulmonary bypass phase, indicating that the transition from bypass to spontaneous circulation represents a period of heightened vulnerability to impaired cerebral autoregulation and potential brain hypoperfusion.

This finding underscores the critical importance of meticulous mean arterial pressure management during this phase, when cerebrovascular reactivity may be particularly compromised. The observation that the greatest burden of autoregulatory impairment occurred after CPB suggests that this interval warrants heightened vigilance by the entire perioperative team to avoid excursions in arterial pressure outside the autoregulatory range. (Fig. 52a and 52b)

Table 2 Evolution of intraoperative variables related to cerebral perfusion (MAP, rSO ₂ , Temp, pCO ₂) and corresponding values of metrics used to describe cerebral autoregulation (mean COx, Time COx >0.3)				
Parameter	Pre-CPB	During CPB	Post-CPB	p value
MAP, mmHg	45.1 (40.3-48.8)	43.8 (40.1-48.9)	64.9 (56.8-68.7)	<0.01
rSO ₂ , %	50.3 (41.2-56.5)	80.8 (67.6-85)	55.3 (44.0-61.2)	<0.01
SpO ₂ , %	92.4 (87.3-94.3)	99.2 (98.8-99.9)	98.8 (85.3-99.8)	<0.01
FTOE	0.43 (0.36-0.45)	0.17 (0.09-0.3)	0.44 (0.38-0.52)	<0.01
Temp, °C	34.2 (33.9-35.2)	29.8 (28.9-31.7)	35.2 (34.8-35.7)	<0.01
pCO ₂ , mmHg	43.0 (39.0-50.4)	37.8 (37.2-38.5)	40.1 (36.3-46.9)	0.01
pO ₂ , mmHg	53.4 (45.4-55.7)	651.4 (620.4-664.9)	215.0 (46.3-312.0)	<0.01
COx	0.02 (-0.08 to 0.13)	0.34 (0.18-0.43)	0.26 (0.05-0.38)	<0.01
Time COx>0.3, %	39.2 (33.3-43.4)	51.8 (39.6-59.6)	56.3 (40.1-63.8)	<0.01

Fig. 52a Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth, 2025.

A composite MAP-COx plot generated from the cohort enabled estimation of a lower limit of autoregulation around 35 mmHg and an optimal pressure near 47 mmHg. These values are lower than those reported in studies of older children, reinforcing the need for age-specific considerations when defining hemodynamic targets.

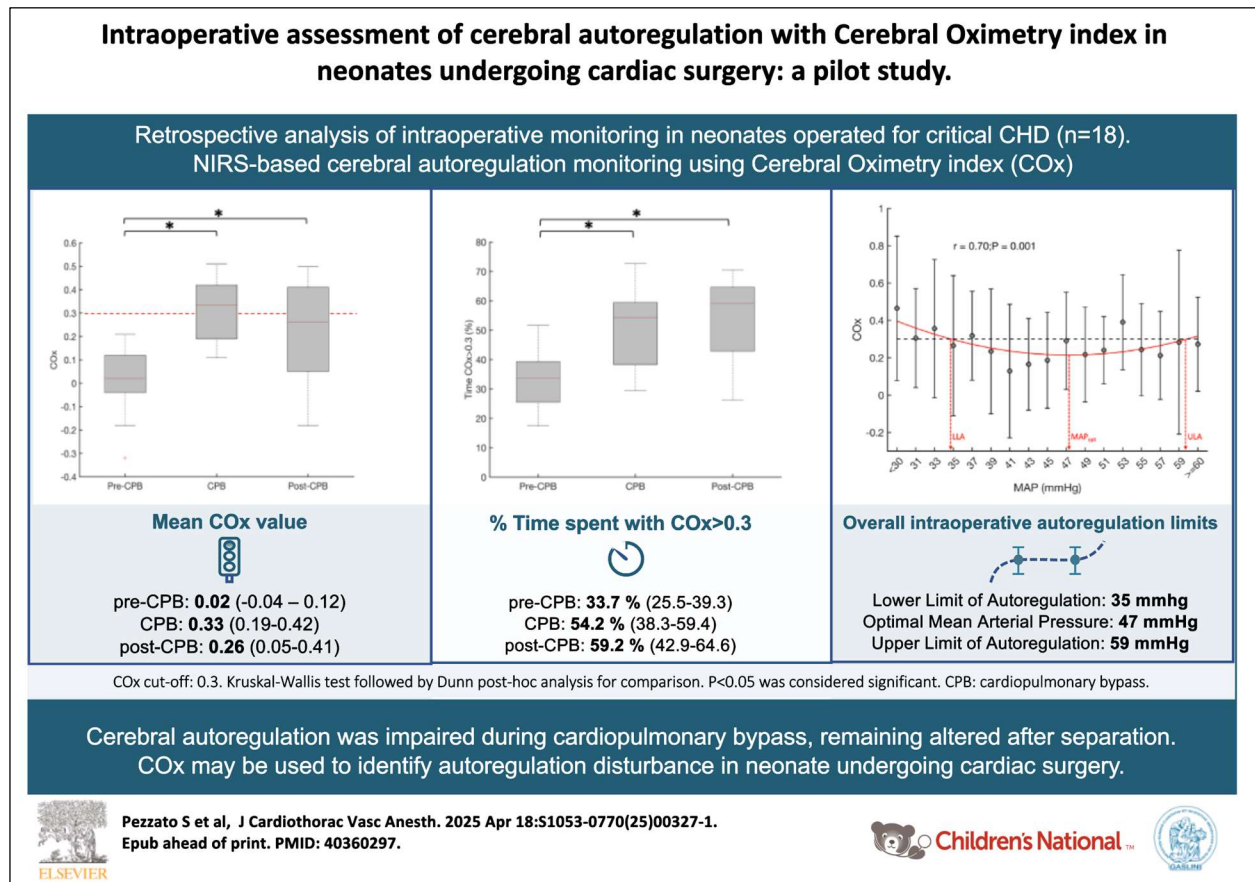


Fig. 52b Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth, 2025.

Interestingly, the temporal evolution of COx across the three surgical phases mirrors the pattern previously reported by Brady et al. (108) in a cohort characterized by different patient demographics and surgical conditions. Concordant findings were also described in a contemporary work by Bourgoin et al. (110) (Fig. 53)

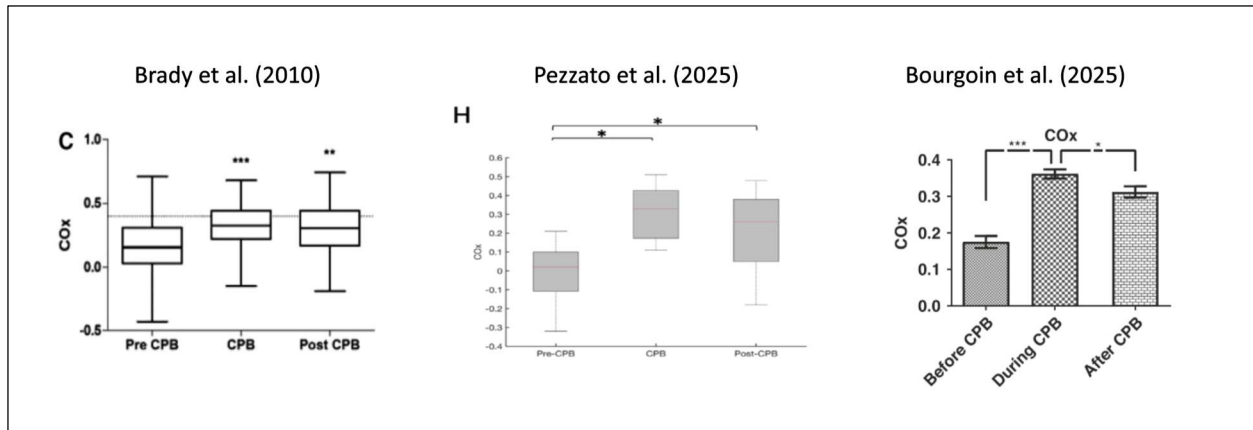


Fig. 53 Pezzato S, IRCCS Istituto G. Gaslini, 2025.

Notably, the study from Easley and colleagues (107) study further showed that this autoregulatory disruption was paralleled by elevations in serum glial fibrillary acidic protein, supporting its association with subclinical cerebral hypoperfusion. In the present investigation, a comparable phase-dependent pattern in COx was observed despite divergent trends in mean arterial pressure and cerebral oxygen saturation across surgical phases.

The estimated lower limit of autoregulation in this cohort (35 mmHg) was lower than that reported by Brady et al. (42 mmHg) and Easley et al. (40 mmHg). We hypothesize that these differences may be attributable, at least in part, to the younger median age at surgery in the present study (6 days of life) compared with the older cohorts examined in the aforementioned investigations.

2.6.3 Methods and Validation Strategy for Intraoperative Data Processing

To support robust intraoperative cerebral autoregulation analysis in neonatal cardiac surgery, a dedicated methodological framework for physiological data acquisition, harmonization, and processing was developed and formally validated. This effort was motivated by the recognition that autoregulation monitoring relies on subtle relationships between arterial blood pressure and cerebral oxygenation signals, and that variability in data sampling rates, storage formats, and preprocessing strategies can substantially influence derived autoregulation metrics. In the context of pediatric cardiac surgery, where prospective high-resolution data acquisition is logistically complex and patient numbers are limited, ensuring methodological consistency and scalability is particularly critical.

The methodological work underlying this section focused on comparing cerebral autoregulation indices derived from high-frequency arterial blood pressure waveforms with those obtained from low-resolution numeric data routinely archived by institutional clinical data warehouses. In current intraoperative and intensive care practice, arterial pressure signals may be stored either as high-fidelity waveforms sampled at ≥ 100 Hz or as mean arterial pressure values sampled at substantially lower frequencies. While high-resolution waveforms represent the reference standard for signal analysis, they are not always available for large retrospective cohorts. The validation strategy therefore aimed to determine whether low-resolution datasets, when processed appropriately, can reliably characterize cerebral autoregulation using the cerebral oximetry index.

A standardized data acquisition and processing pipeline was established to retrieve invasive arterial blood pressure and near-infrared spectroscopy signals from the clinical monitoring infrastructure at Children's National Hospital. Custom data extraction tools were developed to interface with the institutional data warehouse and convert heterogeneous raw signals into a unified format suitable for advanced signal analysis.

All physiological data were stored in HDF5 containers, enabling structured organization, reproducibility, and compatibility with established neurophysiological analysis platforms. (111) Autoregulation analysis was performed using the ICM+ software environment, applying consistent filtering, artifact handling, and correlation-based computation of the cerebral oximetry index across datasets. (Fig. 54)

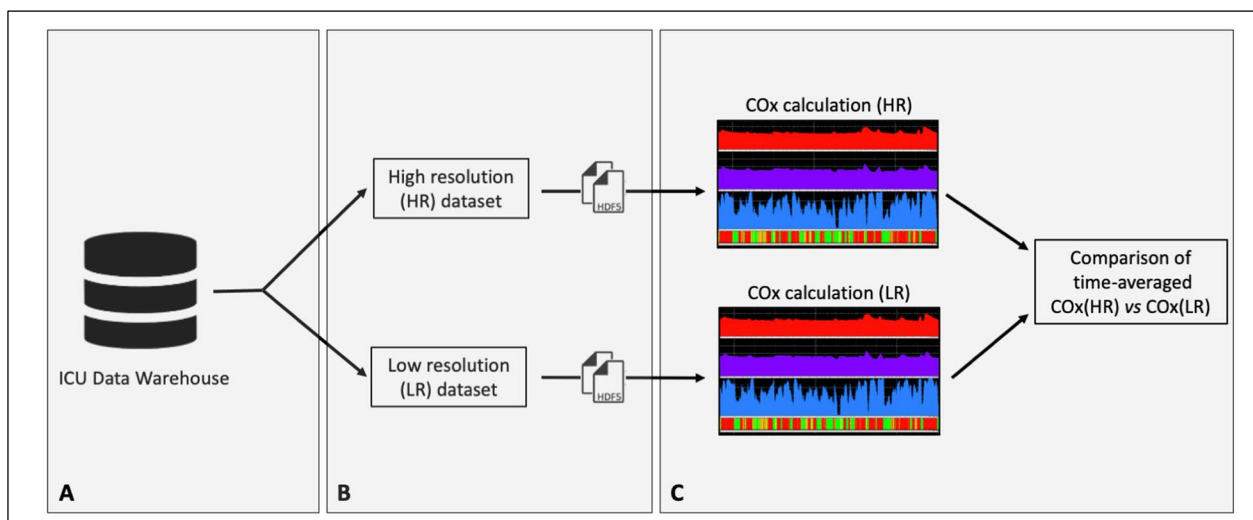


Fig. 53 Pezzato S and Govindan RB, Advanced Physiological Signal Process Lab, Perinatal Pediatrics Institute, Children's National Hospital, 2025.

Validation was achieved by directly comparing autoregulation metrics derived from high-resolution arterial pressure waveforms with those computed using low-resolution mean arterial pressure values for the same patients and time windows.

This approach allowed isolation of the effect of sampling resolution and signal preprocessing on autoregulation characterization, while controlling for patient-specific physiology and clinical context. Concordance between datasets was assessed using correlation and agreement metrics, demonstrating that low-resolution data, when appropriately processed, can yield cerebral autoregulation indices closely aligned with those obtained from high-frequency waveforms.

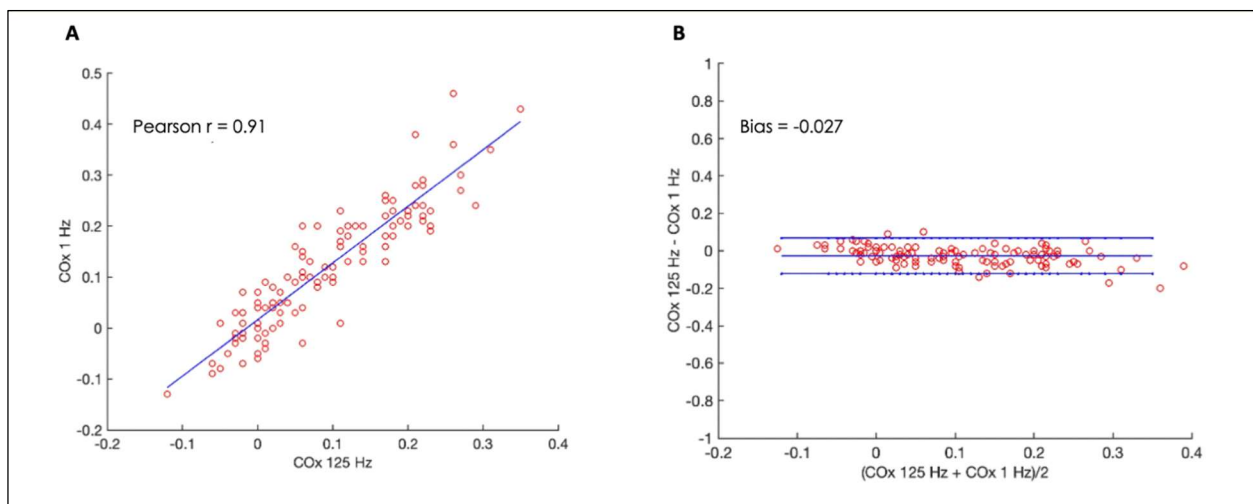


Fig.53 Pezzato S and Govindan RB, Advanced Physiological Signal Process Lab, Perinatal Pediatrics Institute, Children’s National Hospital, 2025.

This methodological contribution, described in detail in a standalone validation manuscript to be submitted to a journal focused on clinical monitoring and computing, provides an essential foundation for the broader research program presented in this thesis. By demonstrating the feasibility of reliable autoregulation analysis using routinely archived clinical data, this work enables retrospective investigation of large perioperative cohorts and facilitates cross-institutional studies without the need for bespoke bedside acquisition systems. Moreover, the standardized data pipeline developed through this effort supports future integration of autoregulation metrics into automated analytics and decision-support frameworks, bridging the gap between high-resolution physiological research and real-world clinical data infrastructures.

2.6.4 Evidence from Other Centers

Over the last few years, independent prospective work from other European centers has substantially strengthened the evidentiary basis for NIRS-derived cerebral autoregulation (CAR) monitoring during neonatal and infant congenital heart surgery, shifting the field from feasibility demonstrations toward cohort-level characterization of intraoperative patterns and early clinical correlates. A particularly important contribution is the prospective observational program led by Bourgoin and colleagues in Nantes, developed in close methodological continuity with the Cambridge ICM+ ecosystem. In a large single-center cohort of infants <100 days undergoing open-heart surgery with cardiopulmonary bypass (CPB), the authors applied continuous COx monitoring defined as a moving correlation between slow-wave mean arterial pressure (MAP) and cerebral regional oxygen saturation (rSO₂), and systematically analyzed three operative epochs (pre-CPB, during CPB, post-CPB). (110)

Their results show a reproducible, population-level signature of CAR disruption triggered by CPB initiation, with mean COx increasing from pre-CPB values (≈ 0.17) to higher levels during CPB (≈ 0.36), followed by only partial recovery after CPB (≈ 0.32). (Fig. 55) Importantly, this was not simply an epiphenomenon of overt desaturation, as rSO₂ was relatively controlled across time periods while COx worsened during CPB, reinforcing the concept that autoregulation monitoring provides information that is not captured by conventional cerebral oximetry trends alone. Beyond describing global patterns, this same study provides one of the most detailed contemporary demonstrations that CAR-derived hemodynamic metrics can be computed at scale in the intraoperative setting. Using MAP-binned COx analysis and a U-shaped fit approach, individualized MAPopt determination was feasible in a high proportion of patients (reported feasibility $\sim 83\%$ pre-CPB, $\sim 75\%$ during CPB, and $\sim 68\%$ post-CPB), while lower and upper limits of autoregulation (LLA/ULA) were variably identifiable, with feasibility declining during CPB—an important pragmatic signal about data richness, MAP dispersion, and methodological constraints under non-pulsatile flow. The authors also explored determinants of disrupted autoregulation during CPB, identifying age at surgery and average hematocrit during CPB as statistically associated factors, suggesting that both developmental physiology and CPB-related blood rheology may modulate cerebrovascular reactivity. Critically, they moved the discussion toward “actionability” by linking the *dose* of MAP below the LLA during CPB to early systemic perfusion surrogates, including postoperative lactate and creatinine changes, thereby framing CAR monitoring as potentially relevant for overall perfusion management in this setting.

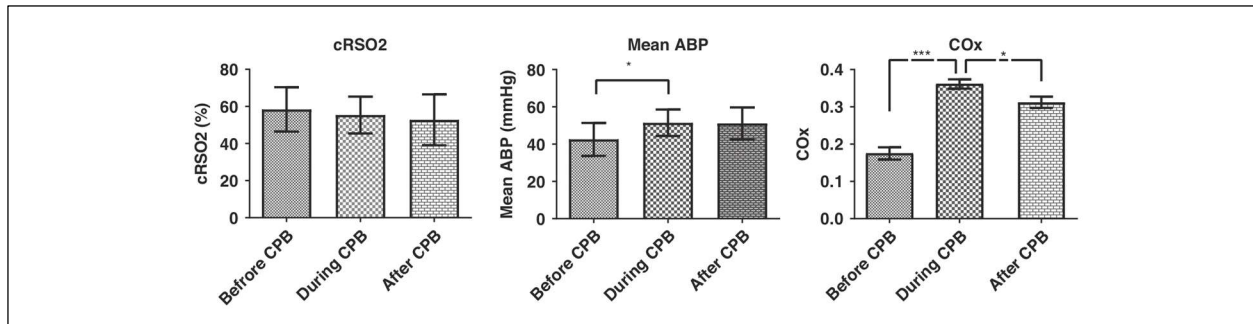


Fig.55 Adapted from: Burgoin P, et al. *Pediatr Res*, 2025.

A second, closely related prospective study conducted in Nantes further refined this line of investigation by explicitly testing the association between intraoperative cerebral autoregulation derived perfusion metrics and postoperative brain injury detected on magnetic resonance imaging. (112)

In a cohort of 38 neonates monitored using the same integrated near infrared spectroscopy and arterial blood pressure acquisition with ICM+ based analysis, the initiation of cardiopulmonary bypass was again associated with a marked disruption of autoregulatory function, with mean COx values increasing from approximately 0.16 in the pre CPB phase to approximately 0.39 during CPB, thereby supporting cross study reproducibility of this physiological pattern. A key methodological advance of this study was the application of a structured MRI severity scoring framework to stratify injury burden and examine mechanistic relationships. Neonates with moderate to severe MRI defined brain injury spent a significantly greater proportion of time below their individualized lower limit of autoregulation during CPB compared with those without detectable injury, whereas exposure above the upper autoregulatory limit did not demonstrate a similar association. (Fig. 56)

These findings are consistent with a biologically plausible hypoperfusion mediated pathway contributing to perioperative brain injury in a subset of neonates with congenital heart disease. Importantly, they extend the role of cerebral autoregulation monitoring beyond descriptive physiological characterization toward an outcome linked framework capable of informing individualized arterial pressure targets defined by patient specific MAPopt, lower limit of autoregulation, and upper limit of autoregulation, rather than reliance on fixed, population-based thresholds.

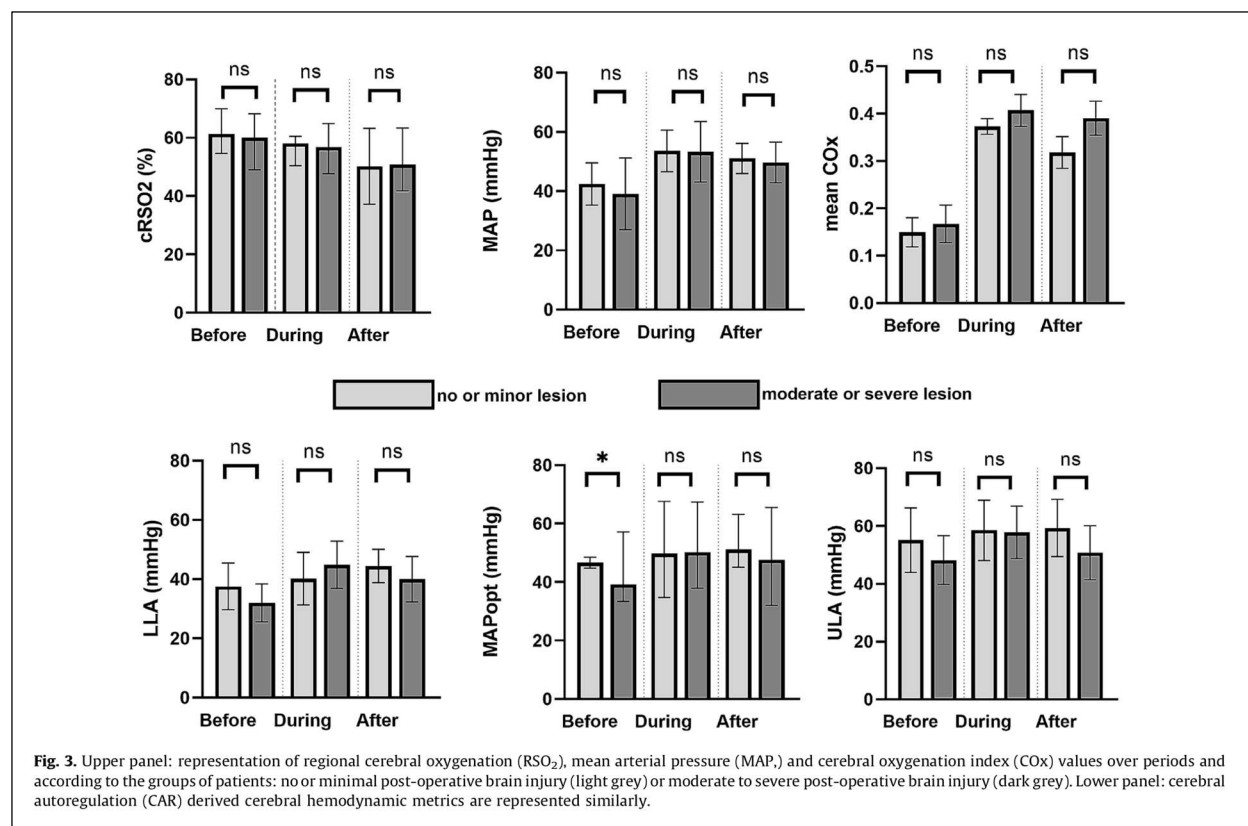


Fig.56. Adapted from: Burgoin P, et al. Anaesth Crit Care Pain Med, 2025.

Taken together, these two studies help clarify the emerging evidence base in three clinically relevant respects. First, they consistently demonstrate that cardiopulmonary bypass, particularly at its initiation and under non-physiologic conditions, is associated with measurable impairment of cerebrovascular reactivity in neonates and young infants, even when conventional intraoperative targets such as cerebral oxygen saturation, pump flow, and standard perfusion parameters appear adequately controlled.

Second, they show that cerebral autoregulation derived metrics including MAPopt and the lower and upper limits of autoregulation can be obtained in a substantial proportion of patients, although feasibility varies across operative phases, representing an important limitation for real time clinical implementation. Third, they provide early evidence that exposure to mean arterial pressure below the lower limit of autoregulation during cardiopulmonary bypass is associated with clinically meaningful outcomes, ranging from systemic perfusion surrogates to MRI defined brain injury, thereby supporting the rationale for interventional studies that target reduction of hypotension burden below the lower limit of autoregulation rather than reliance on fixed mean arterial pressure thresholds.

Finally, it is worth noting that parallel work using Doppler-based cerebral blood flow velocity monitoring provides convergent support for the central concept that intraoperative cerebrovascular stability is frequently compromised in this population, while also highlighting complementary strengths and limitations of different monitoring modalities. In a pilot study using continuous transfontanellar Doppler (NeoDoppler) during infant cardiac surgery with CPB, Leth-Olsen and colleagues demonstrated high-quality recordings for most of the monitoring period and reported a high proportion of time spent with impaired dynamic autoregulation based on a MAP–flow velocity correlation index (mean flow index). (113) They also observed a consistent reduction in time-averaged cerebral blood flow velocity during CPB and the ability to capture rapid hemodynamic events.

While this approach differs from NIRS-based COx (measuring a more direct flow surrogate rather than oxygenation), it supports the broader mechanistic premise that autoregulatory buffering is often insufficient during surgical stress and that real-time indices linking pressure to cerebral flow/oxygenation surrogates may enable more individualized perfusion management.

2.6.5 Exploring CAR monitoring for Early Detection of Neurologic Injury

Beyond cohort-based analyses, the potential clinical relevance of intraoperative cerebral autoregulation monitoring is further illustrated by our published case report describing an infant who developed an acute intracranial complication during surgical repair of interrupted aortic arch. (114) This case provides a concrete example of how continuous NIRS-based autoregulation indices may identify evolving cerebrovascular compromise at a stage when conventional monitoring parameters remain nonspecific or only minimally abnormal.

In the high-risk patient described, continuous computation of the cerebral oximetry index revealed a marked and sustained increase in COx during the post cardiopulmonary bypass phase, consistent with a transition toward pressure passive cerebral perfusion. (Fig. 57) Importantly, this unilateral impairment of autoregulation occurred in the absence of profound systemic hypotension or sustained reductions in absolute cerebral oxygen saturation, with rSO₂ values remaining within ranges that would not typically prompt immediate clinical concern if interpreted in isolation. On the contralateral side, the cerebral oxygenation signal was lost during the same interval despite exclusion of technical or sensor related issues. (** in Fig 57)

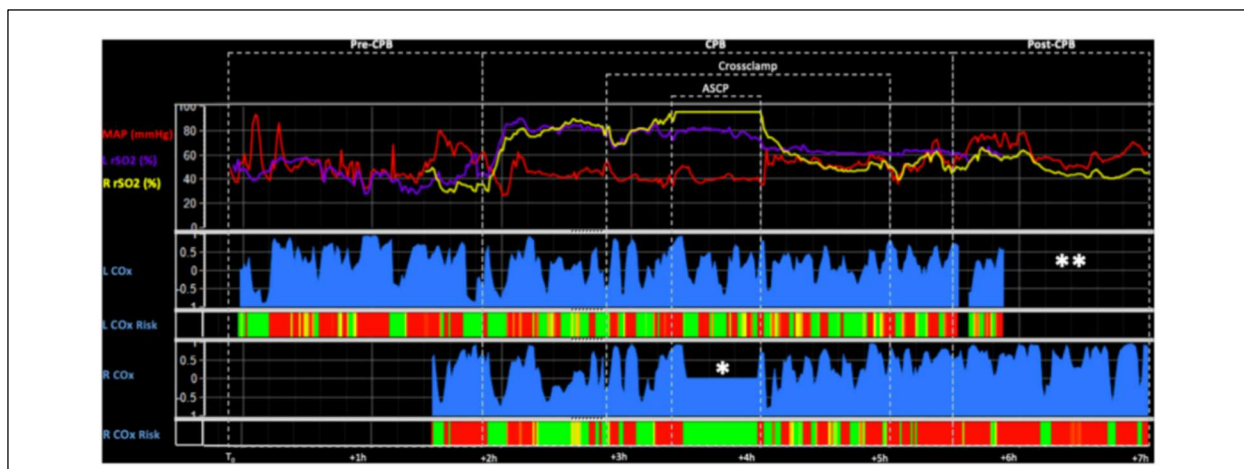


Fig. 57 Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth, 2025.

Subsequent clinical assessment in the Cardiac Intensive Care Unit revealed new-onset anisocoria approximately two hours after surgery. Bedside cranial ultrasonography demonstrated findings consistent with a rapidly expanding subdural hematoma with significant midline shift, later confirmed by computed tomography. (Fig. 58)

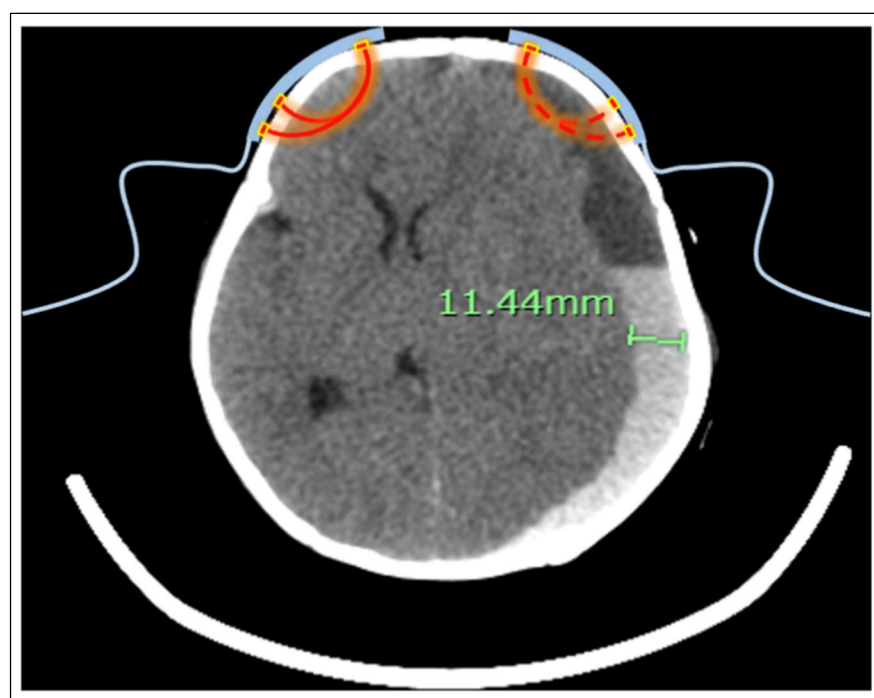


Fig. 58 Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth. 2025.

Importantly, retrospective review of the intraoperative autoregulation tracings indicated that profound and sustained impairment of cerebral autoregulation had been present several hours before the onset of overt neurological signs, suggesting that continuous autoregulation monitoring may have raised earlier diagnostic suspicion of an evolving intracranial process. This temporal dissociation implies that autoregulatory failure preceded clinically apparent deterioration and may represent an early physiological marker of focal intracranial pathology. Retrospective analysis further demonstrated that the period of maximal COx elevation coincided with the interval immediately following separation from cardiopulmonary bypass, a phase characterized by dynamic alterations in cerebral perfusion pressure and venous drainage.

This case illustrates several important conceptual points. First, it demonstrates that CAR monitoring may detect early cerebrovascular instability not readily apparent through standard hemodynamic variables or absolute NIRS thresholds. Second, it suggests that autoregulation indices may be sensitive to asymmetric or evolving intracranial processes, such as acute hemorrhage, which alter the pressure-flow relationship locally before systemic manifestations become evident. Third, it reinforces the vulnerability of the immediate post-CPB period, during which autoregulatory failure may persist despite apparent normalization of temperature, oxygenation, and arterial pressure.

Although single-case observations cannot establish diagnostic performance or clinical efficacy, this report provides proof of concept that continuous autoregulation monitoring can function as an early physiologic “warning signal” for acute neurologic complications in infants undergoing complex cardiac surgery.

2.6.6 The Expanding CNH -Gaslini Intraoperative Autoregulation Dataset

Building on the pilot findings and supported by validated methodological tools, a substantially larger intraoperative cohort is currently under analysis, consisting of approximately 195 infants undergoing CPB-supported open-heart surgery at Children’s National Hospital between 2023 and 2025. This dataset integrates high-resolution arterial pressure recordings, cerebral NIRS signals, bypass circuit parameters, gas exchange metrics, and temperature data. Extensive preprocessing pipelines have been developed using MATLAB and ICM+, enabling automated artifact detection, slow-wave extraction, COx computation, and phase-specific stratification. The goals of this large-scale analysis are to characterize autoregulation dynamics across CPB phases, quantify exposure to pressure-passive cerebral perfusion, identify determinants of individualized lower limits of autoregulation, and evaluate associations with postoperative MRI abnormalities and acute neurologic events. The size and granularity of this cohort make it uniquely positioned to generate robust physiologic insights and to define normative autoregulatory patterns that may inform future interventional studies.

2.6.7 Preliminary results from the CNH-Gaslini Study

Preliminary analyses were conducted using data derived from the prospectively acquired CNH–Gaslini intraoperative physiological database. For the purpose of this investigation, patients presenting with evidence of preoperative brain injury, those supported with extracorporeal membrane oxygenation immediately before or after surgery, and cases with incomplete or technically inadequate physiological recordings were excluded. After application of these criteria, the final analytical cohort comprised 182 subjects.

All surgical procedures were performed according to standardized institutional protocols for pediatric cardiac surgery. Anesthesia was provided using a balanced regimen combining volatile anesthetics and intravenous agents, with dosing adjusted according to patient age, cardiac physiology, and surgical phase. Cardiopulmonary bypass (CPB) was established using bicaval venous cannulation and non-pulsatile flow, with pump flow rates targeted to achieve an indexed cardiac output consistent with pediatric perfusion standards. Hematocrit was maintained within predefined institutional ranges, and a pH-stat strategy was adopted during hypothermic perfusion. In patients undergoing aortic arch repair, antegrade selective cerebral perfusion was employed when indicated, with controlled flow rates and predefined arterial pressure targets, as previously described.

Physiological monitoring was continuous throughout the intraoperative period and included invasive arterial blood pressure obtained from indwelling arterial catheters, regional cerebral oxygen saturation (rSO_2) measured by near-infrared spectroscopy (NIRS) sensors placed on the frontal scalp, and peripheral oxygen saturation (SpO_2) measured by pulse oximetry. Measurements of arterial oxygen saturation (SaO_2), partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and Hematocrit (Hct) were provided continuously during CPB, while Arterial blood gas analyses were performed intermittently as part of routine intraoperative management before and after CPB. Core temperature was continuously monitored using rectal probes when available, or esophageal probes when rectal measurements were not recorded.

All signals were time-synchronized and archived in digital format, enabling high-resolution off-line analysis using dedicated processing pipelines consistent with previously published methodologies. (109) (Fig. 59)

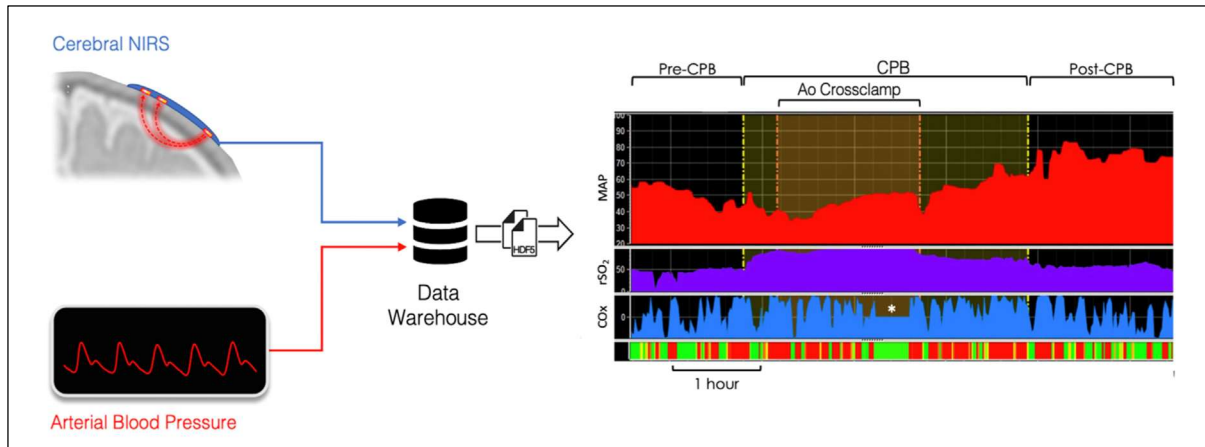


Fig.59 Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth. 2025.

Cerebral autoregulation was quantified using the cerebral oximetry index (COx), calculated as the moving linear correlation coefficient between mean arterial pressure and rSO_2 over predefined time windows. Within this framework, COx values near zero or negative indicate preserved cerebrovascular reactivity, whereas progressively positive values reflect increasing pressure-passive cerebral perfusion and impaired autoregulation.

To complement autoregulation assessment with information on cerebral oxygen metabolism, cerebral fractional tissue oxygen extraction (FTOE, also referred to as cFTOE) was calculated. FTOE is defined as the relative difference between arterial oxygen saturation and cerebral venous-weighted oxygen saturation, normalized to arterial saturation, according to the formula: $FTOE = (SpO_2 - rSO_2) / SpO_2$. Physiologically, FTOE represents a non-invasive surrogate of the balance between cerebral oxygen delivery and cerebral oxygen consumption. Because NIRS-derived rSO_2 predominantly reflects the venous compartment, FTOE increases when cerebral oxygen extraction rises, either as a compensatory response to reduced oxygen delivery or as a consequence of increased metabolic demand not matched by adequate perfusion. Conversely, a decrease in FTOE reflects reduced oxygen extraction, which may occur in the context of improved oxygen delivery, reduced metabolic demand, or both. Experimental and clinical validation studies have demonstrated that NIRS-derived FTOE correlates closely with directly measured fractional oxygen extraction, supporting its use as a continuous bedside marker of cerebral oxygen utilization. (115-117) A recent systematic qualitative review synthesizing data from over 3,500 neonates has reinforced the physiological relevance of FTOE as an integrative marker reflecting cerebrovascular, metabolic, respiratory, and hemodynamic influences on cerebral oxygenation. Across diverse clinical settings, increased FTOE has been consistently associated with conditions characterized by impaired oxygen delivery, pressure-dependent cerebral perfusion, or

compromised autoregulatory capacity, whereas stable or decreasing FTOE has been observed in states of adequate cerebral perfusion and oxygen supply. (118) FTOE calculation was also included in our pilot study focused on intraoperative monitoring.. (109) (Fig. 60)

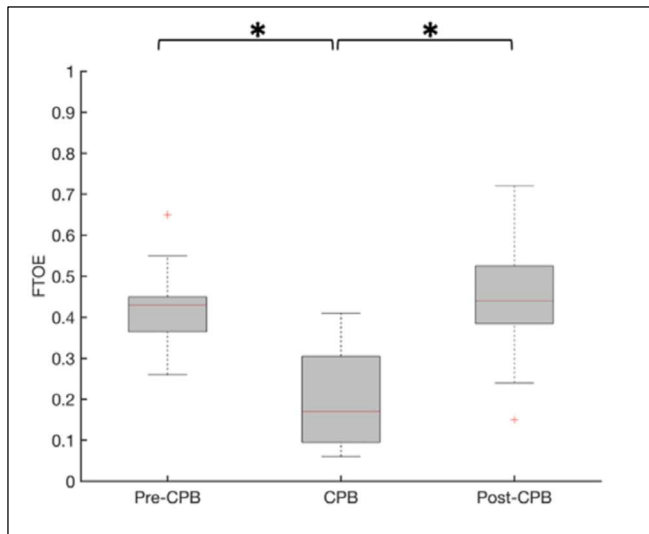


Fig. 60 Adapted from: Pezzato S, et al. J Cardiothorac Vasc Anesth, 2025.

Building upon these established concepts, an exploratory analysis was conducted introducing a novel composite metric defined as a FTOE-weighted oximetry index (FOx), aimed at integrating information on cerebrovascular pressure reactivity with contemporaneous cerebral oxygen extraction. The rationale underlying this approach is that impairment of cerebral autoregulation becomes clinically most relevant when it is accompanied by increased oxygen extraction, indicating a physiologically meaningful imbalance between cerebral oxygen delivery and metabolic demand. This pragmatic approach represents an alternative to conventional determination of the lower limit of autoregulation (LLA) based on the U-shaped curve on the MAP/COx plot for identifying clinically unacceptable MAP values.

Although LLA-based approaches provide valuable individualized perfusion thresholds, their real-time intraoperative implementation is constrained by technical limitations, including the requirement for prolonged and physiologically stable data acquisition windows. Such constraints reduce feasibility during rapidly evolving surgical phases and limit bedside applicability for proactive hemodynamic management. (13)

While exploratory in nature, this approach is conceptually aligned with contemporary views of cerebral hemodynamics as an interaction between vascular reactivity and metabolic demand and may provide a useful adjunct for future goal-directed intraoperative management strategies in high-risk pediatric cardiac surgery.

The results of this work are presented with an initial focus on the clinical characteristics of the study population and the surgical procedures performed, providing essential context for the interpretation of the subsequent physiological analyses. Following the same definition of Acute neurologic Event (ANE) used in our previous works, subjects diagnosed with any hypoxic or ischemic neurologic complication and/or seizures during the first seven postoperative days were assigned to the ANE+ group. (Fig. 60 and 62)

Characteristics of Patients	Total, n=182	ANE-, n=170 (93.4%)	ANE+, n=12 (6.6%)	P-value
Age at surgery, days, median (IQR)	90 (29-152)	95 (30-154)	62.5 (16.5-90.5)	0.097
Neonatal surgery, n (%)	58 (31.9)	53 (31.2)	5 (41.7)	0.525
Weight at surgery, kg, median (IQR)	4.4 (3.5-5.9)	4.5 (3.5-5.9)	3.6 (3.2-4.8)	0.113
Main Diagnose, n (%)				0.445
Septal Defects	64 (35.2)	62 (36.5)	2 (16.7)	
RVOT obstructions	45 (24.7)	41 (24.2)	4 (33.3)	
Single Ventricle lesions	27 (14.8)	24 (14.2)	3 (25)	
Left-sided/Aortic lesions	19 (10.4)	16 (9.4)	3 (25)	
d-Transposition of the Great Arteries	13 (7.1)	13 (7.6)	0	
Anomalous Pulmonary Venous Return	6 (3.4)	6 (3.5)	0	
Defects of aortopulmonary septation	4 (2.2)	4 (2.3)	0	
Others ¹	4 (2.2)	4 (2.3)	0	
Associated syndrome, n (%)	56 (30.8)	55 (32.3)	1 (8.3)	0.109
Trisomy 21	32 (57.1)	31 (56.4)	1 (100)	
DiGeorge	10 (17.8)	10 (18.1)	0	
Heterotaxy	3 (5.4)	3 (5.5)	0	
VACTERL	3 (5.4)	3 (5.5)	0	
CHARGE	2 (3.6)	2 (3.6)	0	
Others ²	6 (10.7)	6 (10.9)	0	
Preop bPAB, n(%)	18 (9.9)	15 (8.8)	3 (25)	0.101
Preop BAS, n(%)	18 (9.9)	16 (9.4)	2 (16.7)	0.337
Preop Cardiac Arrest, n(%)	4 (2.2)	4 (2.3)	0	1.000
Preop ECMO³, n(%)	4 (2.2)	4 (2.3)	0	1.000

¹Other diagnosis: Arch Obstructions (n=2), Cardiac tumor (n=1), Coronary Artery Anomalies (n=1)

²Other associated syndrome: Wolf-Hirschhorn S (n=1), Coffin-Lory (n=1), SOP dysplasia (n=1), Deletion Ch.17p11.2 (n=1), Ellis-van Crevelde (n=1), White-Sutton (n=1)

³Only if ECMO was successfully discontinued before surgery

Fig.61 Baseline characteristics of patients in the overall cohort, according to the ANE– and ANE+ status.

Characteristics of Surgery	Total, n=182	ANE-, n=170 (93.4%)	ANE+, n=12 (6.6%)	P-value
STAT category, n(%)				0.141
1	37 (20.3)	37 (21.8)	0	
2	97 (53.3)	89 (52.3)	8 (66.7)	
3	10 (5.5)	10 (5.9)	0	
4	20 (11)	19 (11.2)	1 (8.3)	
5	18 (9.9)	15 (8.8)	3 (25)	
Number of CBP-requiring surgery, n(%)				1.000
First surgery	164 (90.1)	153 (90)	11 (91.7)	
Second surgery	17 (9.3)	16 (9.4)	1 (8.3)	
Third surgery	1 (0.6)	1 (0.6)	0	
Cerebral NIRS monitoring side, n(%)				0.500
L + R	153 (84.1)	144 (84.7)	9 (75)	
L	26 (14.3)	23 (13.5)	3 (25)	
R	3 (1.6)	3 (1.8)	0	
CPB duration, minutes, median (IQR)	141 (106-194)	140 (106-192)	167 (114-202)	0.330
Aortic Cross-clamping duration, minutes, median (IQR)	81 (53-109)	79 (53-109)	95 (73-113)	0.313
DHCA/Selective Cerebral Perfusion duration, minutes, median (IQR)	0 (0-0)	0 (0-0)	0 (0-17)	0.155
Postoperative Delayed Sternal Closure, n (%)	47 (25.8)	41 (24.1)	6 (50)	0.081
Postoperative ECMO/ECLS, n (%)¹	3 (1.6)	1 (0.6)	2 (16.7)	0.012

¹ Post-cardiotomy ECMO excluded; support started at any point over the first postoperative week.

Fig.62 Characteristics of procedures performed in the entire cohort, stratified by ANE- and ANE+ status.

2.6.8 Intraoperative Cerebral Hemodynamic patterns

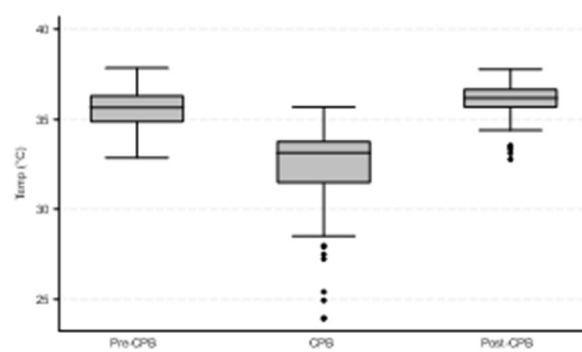
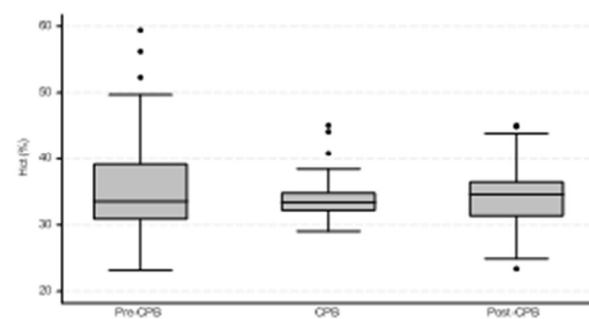
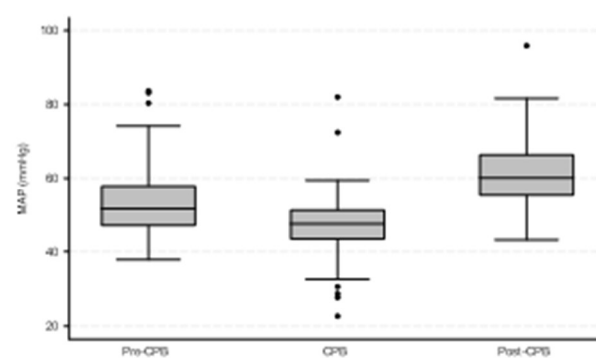
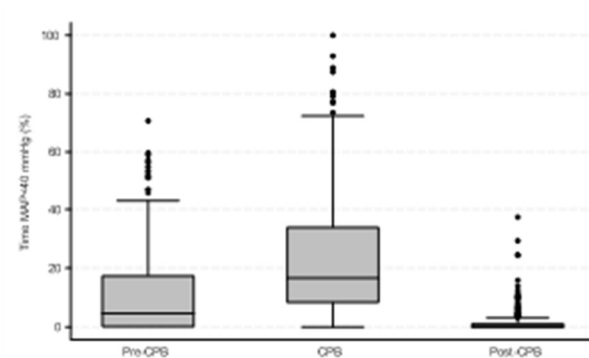
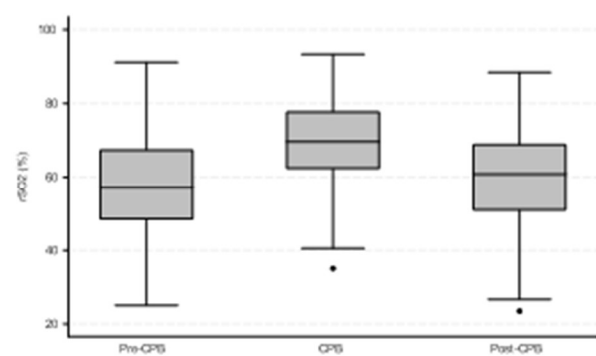
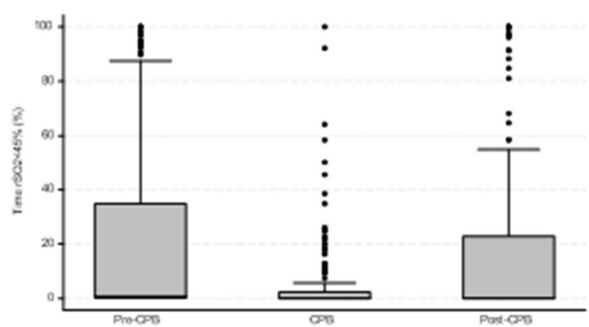
Intraoperative cerebral autoregulation was quantified using the cerebral oximetry index (COx), calculated as the moving linear correlation coefficient between mean arterial pressure (MAP) and cerebral regional oxygen saturation (rSO₂) over predefined time windows. Within this framework, COx values close to zero or negative indicate preserved cerebrovascular reactivity, whereas progressively positive values reflect increasing pressure-passive cerebral perfusion and impaired autoregulation.

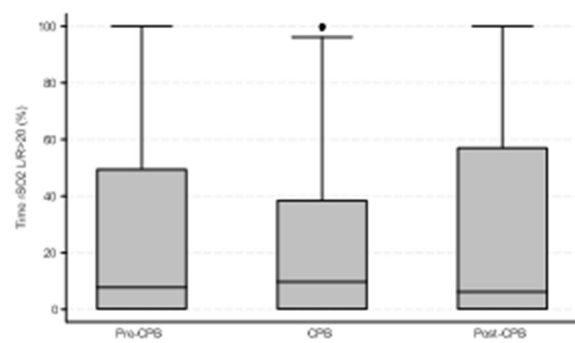
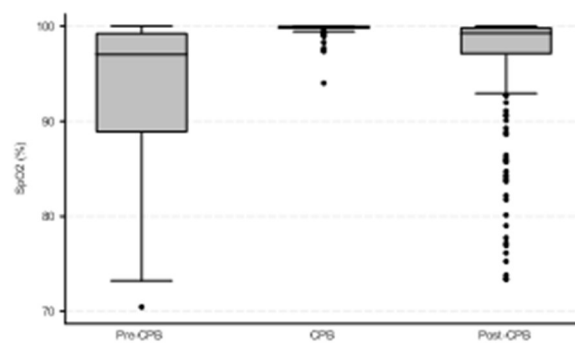
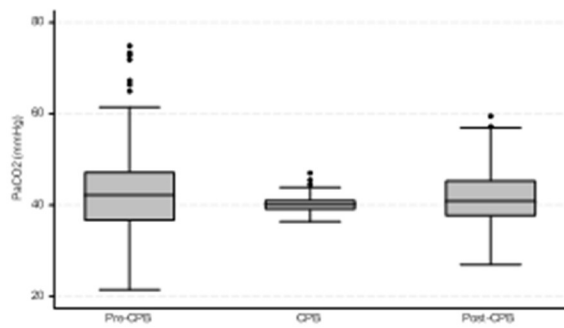
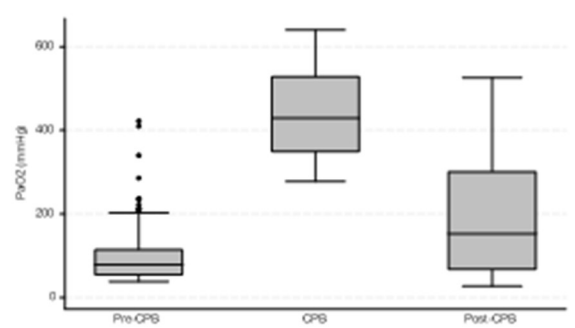
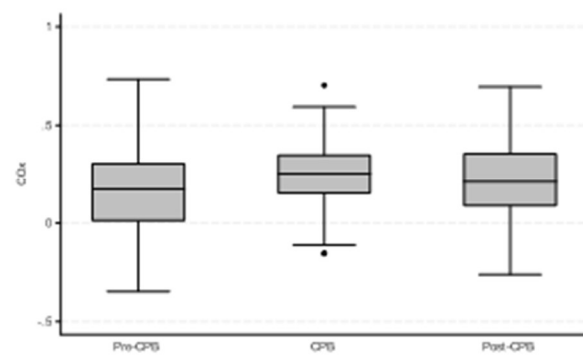
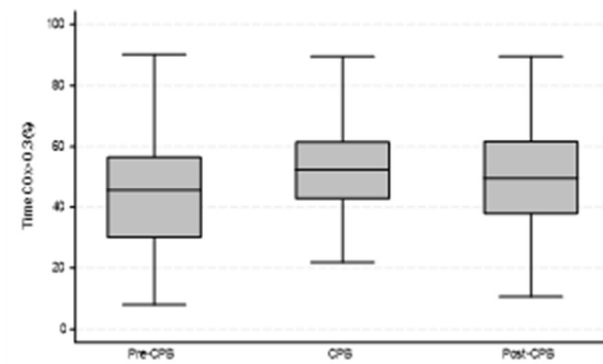
To complement autoregulation assessment with information on cerebral oxygen metabolism, cerebral fractional tissue oxygen extraction (FTOE) was calculated as the relative difference between arterial oxygen saturation and cerebral venous-weighted oxygen saturation, normalized to arterial saturation. From a physiological perspective, FTOE serves as a noninvasive surrogate of the balance between cerebral oxygen delivery and consumption potentially accounting for patient-specific differences in absolute values of rSO₂, particularly due to cyanotic CHD.

Significant differences were observed across phases for MAP, cerebral oxygenation, indices of cerebral oxygen extraction, and autoregulation metrics, underscoring the marked physiological heterogeneity encountered during pediatric cardiac surgery. In particular, CPB was characterized by lower MAP values, increased exposure to hypotension, higher cerebral oxygen saturation, reduced FTOE, and higher CO_x values, consistent with altered cerebral perfusion and oxygen utilization during nonpulsatile extracorporeal circulation.(Fig. 63)

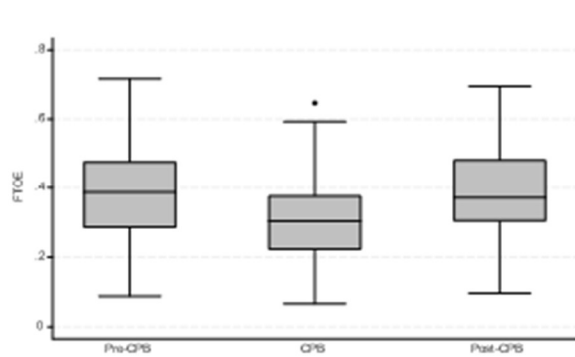
Parameter n=182	Pre-CPB	CPB	Post-CPB	P Value
Duration, mins	129 (103 - 159)	141 (106 - 194)	112.5 (88 - 139)	<0.001
Temp, °C	35.7 (34.9 - 36.3)	33.1 (31.5 - 33.8)	36.2 (35.7 - 36.7)	<0.001
MAP, mmHg	51.5 (46.9 - 57.9)	47.5 (43.3 - 51.3)	60.1 (55.1 - 66.5)	<0.001
Time MAP<40 mmHg, %	4.6 (0 - 17.6)	16.5 (8.3 - 33.9)	0 (0 - 1.2)	<0.001
rSO ₂ , %	57.1 (48.3 - 67.5)	69.59 (62.3 - 77.8)	60.8 (50.9 - 68.9)	<0.001
Time rSO ₂ <45%, %	0.7 (0 - 35)	0 (0 - 2.48)	0 (0 - 22.9)	0.002
Time rSO ₂ L/R>20, % (n=153)	7.9 (0 - 49.7)	9.8 (0 - 38.7)	6.31 (0 - 57.1)	0.475
SpO ₂ , %	97 (88.8 - 99.3)	99.9 (99.8 - 100)	99.3 (97.1 - 99.9)	<0.001
PaO ₂ , mmHg	78.7 (53.6 - 115)	429.1 (348.4 - 529.1)	153 (66.1 - 302)	<0.001
PaCO ₂ , mmHg	42.2 (36.6 - 47.3)	40.2 (39.0 - 41.1)	40.8 (37.6 - 45.4)	0.074
Hct, %	33.5 (30.8 - 39.2)	33.3 (32.1 - 34.9)	34.5 (31.3 - 36.5)	0.150
FTOE	0.39 (0.28 - 0.48)	0.30 (0.22 - 0.38)	0.37 (0.3 - 0.48)	<0.001
Time FTOE>0.5, %	2.39 (0 - 31.9)	1.0 (0 - 8.2)	1.73 (0 - 41.5)	0.007
CO _x	0.17 (0.01 - 0.31)	0.25 (0.15 - 0.35)	0.21 (0.09 - 0.36)	0.018
Time CO _x >0.3, %	45.5 (29.8 - 56.7)	52.5 (42.5 - 61.7)	49.6 (37.7 - 61.9)	0.002
FO _x	0.06 (0 - 0.11)	0.08 (0.05 - 0.11)	0.08 (0.03 - 0.14)	0.076
Time FO _x >0.15, %	35.0 (20 - 45.9)	34.3 (20.7 - 44.8)	40.7(26.4 - 54.4)	0.021

Fig.63 Evolution of intraoperative physiologic variables and derived metrics characterizing cerebral autoregulation and oxygen extraction across CPB-related surgical phases.

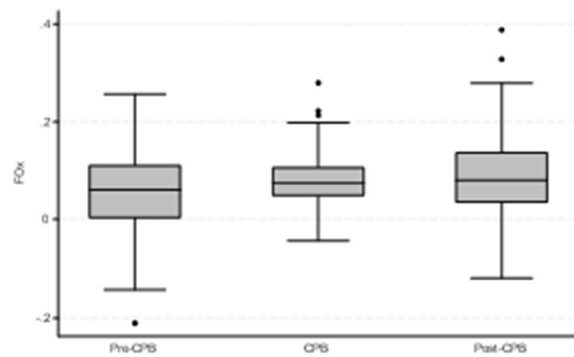
A**B****C****D****E****F**

G**H****J****K****L**

M



N



Parameter	Pre-CPB vs CPB	CPB vs Post-CPB	Pre vs Post-CPB	Total
Duration, mins	0.0039 (0.012)	<0.001	<0.001	<0.001
Temp, °C	<0.001	<0.001	<0.001	<0.001
MAP, mmHg	<0.001	<0.001	<0.001	<0.001
Time MAP<40 mmHg, %	<0.001	<0.001	<0.001	<0.001
rSO ₂ , %	<0.001	<0.001	0.0128 (0.038)	<0.001
Time rSO ₂ <45%, %	<0.001	<0.001	0.3536 (0.7030)	0.002
Time rSO ₂ L/R>20, % (n=153)	0.2207 (0.527)	0.1115 (0.299)	0.6495 (0.957)	0.475
SpO ₂ , %	<0.001	<0.001	<0.001	<0.001
PaO ₂ , mmHg	<0.001	<0.001	<0.001	<0.001
PaCO ₂ , mmHg	0.0008 (0.002)	0.0067 (0.020)	0.5211 (0.890)	0.074
Hct, %	0.0111 (0.033)	0.1378 (0.359)	0.2088 (0.505)	0.150
FTOE	<0.001	<0.001	0.8994 (0.9990)	<0.001
Time FTOE>0.5, %	<0.001	<0.001	0.4504 (0.834)	0.007
COx	<0.001	0.0539 (0.153)	0.0079 (0.024)	0.018
Time COx>0.3, %	<0.001	0.0238 (0.070)	0.0073 (0.022)	0.002
FOx	0.0085 (0.025)	0.2768 (0.622)	0.0012 (0.004)	0.076
Time FOx>0.15, %	0.8672 (0.998)	0.0005 (0.001)	0.0033 (0.010)	0.021

Fig.64 Distribution of intraoperative physiological variables and cerebral autoregulation metrics, shown as box-and-whisker plots. Boxes represent the interquartile range, with the median indicated by the central line. Group comparisons were performed using the Kruskal–Wallis test followed by Dunn’s post hoc analysis. The accompanying table summarizes all pairwise comparisons, with corrected *p* values reported where applicable. A *p* value < 0.05 was considered statistically significant.

Owing to the availability of high-resolution core temperature recordings in this dataset, temperature dynamics were further leveraged to delineate distinct phases of the hypothermic CPB strategy. Specifically, the cooling phase was defined as the interval from CPB initiation to attainment of target core temperature; the plateau phase corresponded to the period during which hypothermia target was maintained; and the rewarming phase encompassed the remaining CPB duration required to restore normothermia up to CPB discontinuation. (fig. 65)

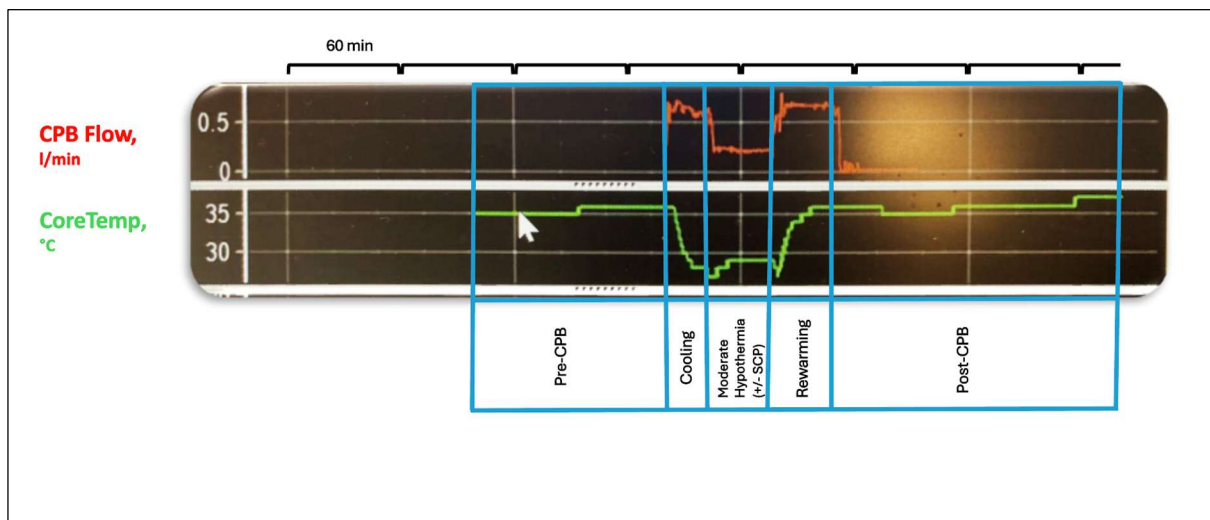
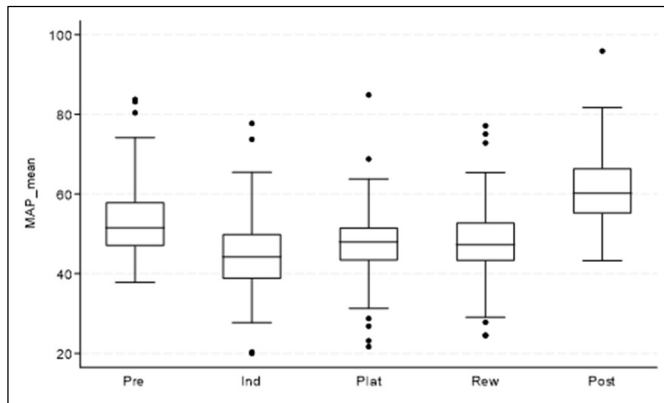


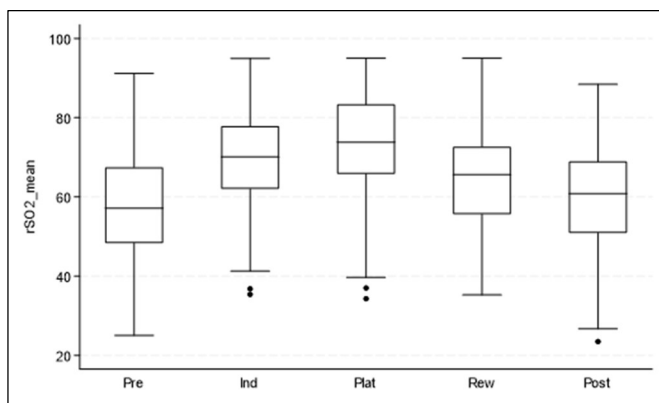
Fig.65 Pezzato S, IRCCS Istituto G. Gaslini, 2025.

Below are presented the box plots illustrating the evolution of systemic physiological variables and derived cerebral hemodynamic metrics across the resulting five surgical phases (pre-CPB, CPB induction, hypothermic plateau, rewarming, and post-CPB). This phase-resolved analysis highlights dynamic shifts in cerebral autoregulation, oxygen extraction, and combined indices across the intraoperative course, providing a more granular depiction of cerebrovascular stress during hypothermic cardiopulmonary bypass. (Fig. 66)

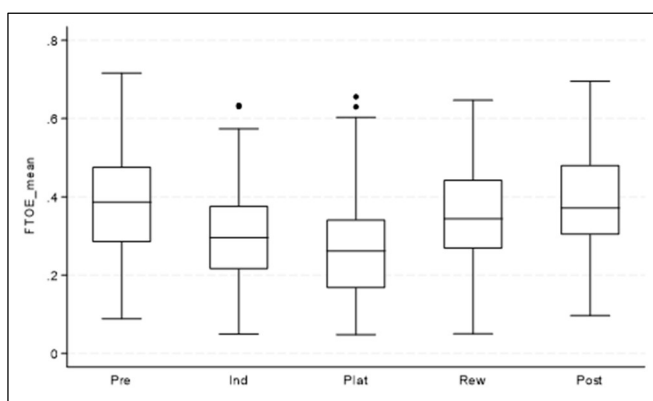
A



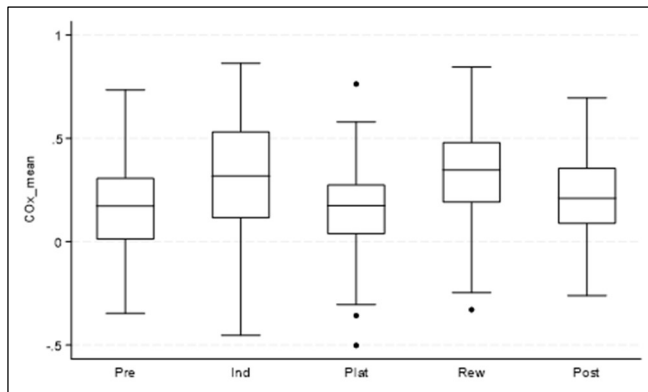
B



C



D



E

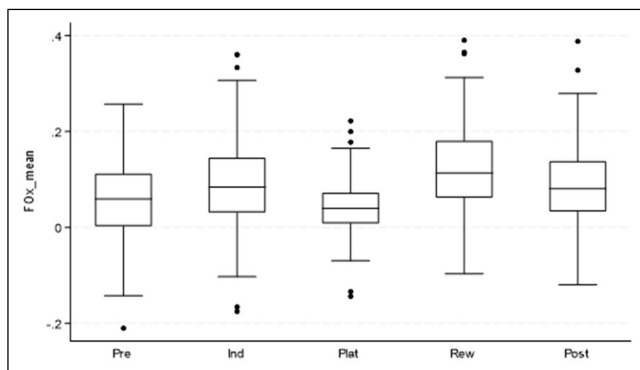


Fig.66 Distribution of intraoperative physiological variables and cerebral autoregulation metrics for each phase of the hypothermic CPB. Values are reported as median and interquartile range. Group comparisons were performed using the Kruskal–Wallis test followed by Dunn post hoc analysis. The table summarizes all pairwise comparisons, with corrected p values reported where applicable. A p value < 0.05 was considered statistically significant.

2.6.9 Cerebral Hemodynamic metrics and early neurological outcome

To explore the relationship between intraoperative cerebral hemodynamics and early postoperative neurological injury, intraoperative physiological metrics were examined in relation to findings on the first postoperative brain magnetic resonance imaging. Brain MRI represents the earliest available structural assessment of neurological injury in this population and provides an anatomically grounded outcome measure against which intraoperative physiological exposures can be contextualized.

Postoperative MRI was available in 96 of 182 patients (52.7%). Among these, newly acquired white matter injury (WMI) was identified in 21 cases (21.9%). Acute neurological events (ANE) were observed in 12 patients (6.6%) and were associated with a higher likelihood of undergoing postoperative MRI (83.3% vs 50.6% in ANE– patients, $P = 0.028$). The median interval between surgery and MRI did not differ significantly between groups. Notably, WMI was more frequently detected in patients with ANE (50.0%) compared with those without ANE (18.6%, $P = 0.038$). The distribution of WMI severity, assessed using the quantitative pediatric stroke (QPS) score, did not differ significantly between groups. (Fig. 67)

Brain MRI assesement	Total, n=182	ANE-, n=170 (93.4%)	ANE+, n=12 (6.6%)	P-value
Preoperative MRI performed, n(%)	59 (32.4)	55 (32.3)	4 (33.3)	1.000
Postoperative MRI performed, n(%)	96 (52.7)	86 (50.6)	10 (83.3)	0.028
Surgery-to-MRI interval days, median (IQR)	12 (8-26)	12 (8-27)	13 (12-23)	0.262
New WMI detected n (%)	21/96 (21.9)	16/86 (18.6)	5/10 (50)	0.038
WMI QPS score, n (%)				0.072
1	6 (28.6)	6 (37.5)	0	
2	11 (52.4)	7 (43.8)	4 (80)	
3	3 (14.3)	3 (18.7)	0	
4	1 (4.7)	0	1 (20)	

Fig.67 Summary of brain MRI findings in the entire cohort, stratified by the presence or absence of acute neurological events (ANE– vs ANE+).

Early neurological outcome was therefore defined based on the presence or absence of newly identified WMI on the first postoperative MRI, the most prevalent pattern of perioperative cerebral injury in neonates and infants with congenital heart disease. Intraoperative cerebral hemodynamic metrics, including mean arterial pressure, cerebral regional oxygen saturation (rSO₂), fractional tissue oxygen extraction (FTOE), cerebral oximetry index (COx), and the composite FOx metric, were summarized across predefined intraoperative phases and compared according to MRI findings.

Exploratory phase-resolved and exposure-based analyses revealed biologically plausible, phase-dependent patterns that were not apparent from global summary metrics. As illustrated in the heatmap below infants with postoperative white matter injury exhibited higher intraoperative COx values, a greater proportion of time spent above the autoregulatory impairment threshold, and increased exposure to pressure-passive cerebral perfusion, with the most pronounced differences observed during cardiopulmonary bypass and hypothermic phases. (Fig. 68) These infants also demonstrated higher fractional tissue oxygen extraction and a greater proportion of time spent above predefined FTOE thresholds, consistent with an increased reliance on oxygen extraction to meet cerebral metabolic demand during periods of altered or hemodynamically unstable perfusion.

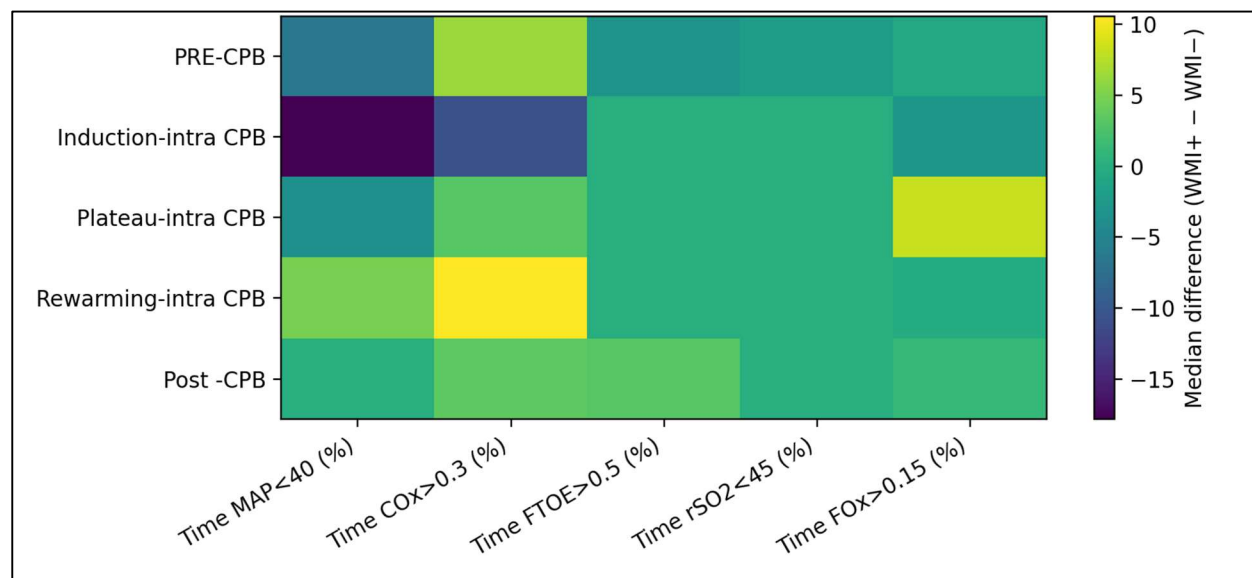


Figure 68. Phase-specific differences in intraoperative exposure burden between infants with and without postoperative white matter injury. Median differences (WMI+ – WMI-) in time beyond physiological thresholds are displayed as a heatmap, ordered by physiological domain. Positive values indicate greater exposure in the WMI+ group.

In contrast, when global intraoperative metrics were considered, no single parameter demonstrated a robust or statistically significant association with the presence of postoperative white matter injury. Median values of mean arterial pressure, absolute cerebral oxygen saturation, and systemic oxygenation were comparable between subjects with and without MRI-detected injury. These findings underscore the limited sensitivity of static or phase-averaged systemic parameters for capturing cerebral vulnerability during complex surgical conditions. Notably, the FOx metric, which combines information on impaired autoregulation and increased oxygen extraction, was consistently higher in infants with postoperative white matter injury across intraoperative phases. This finding supports the concept that cerebral vulnerability may be greatest when pressure-passive perfusion coincides with increased metabolic stress, rather than during isolated disturbances in perfusion or oxygenation alone.

These associations should be interpreted cautiously. The observational design of the analysis precludes causal inference, and postoperative white matter injury reflects the cumulative impact of prenatal brain immaturity, intraoperative exposures, and postoperative physiological disturbances. Moreover, MRI captures structural injury at a single time point and may not fully reflect dynamic or evolving physiological insults occurring during surgery. Nevertheless, the observed relationships suggest that intraoperative cerebral hemodynamic metrics, particularly those integrating cerebrovascular reactivity and oxygen extraction, provide complementary physiological information that may be relevant to early neurological outcome. Integrating such metrics with postoperative neuroimaging may therefore enhance mechanistic understanding of perioperative brain injury.

2.7 Postoperative CAR Monitoring in the Cardiac Intensive Care Unit

2.7.1 Rationale and Patterns of Postoperative Cerebrovascular Reactivity

The early postoperative period following neonatal cardiac surgery is characterized by profound hemodynamic, metabolic, and inflammatory perturbations that challenge the immature cerebrovascular system. During this phase, conventional systemic parameters such as mean arterial pressure and absolute cerebral oxygen saturation provide limited insight into the integrity of cerebrovascular control. Continuous monitoring of cerebral autoregulation offers a complementary physiological perspective, enabling real-time assessment of the coupling between systemic hemodynamics and cerebral perfusion, consistent with observation recently proposed by our research group in pediatric patients supported by ECMO. (119-120)

Recent studies have demonstrated that impaired cerebrovascular reactivity, assessed using near-infrared spectroscopy-based autoregulation indices, is common following congenital heart disease surgery. (121) Neonates and young infants frequently spend substantial proportions of the early postoperative period in pressure-passive states, particularly within the first 24–48 hours after cardiopulmonary bypass. This temporal pattern overlaps with the well-recognized nadir in postoperative cardiac output and heightened vasoactive support requirements, suggesting that impaired autoregulation may represent a critical mechanism linking perioperative physiological stress to neurological vulnerability.

Across the studied cohort, postoperative cerebral autoregulation demonstrates dynamic temporal evolution rather than fixed or uniform impairment. Exposure to arterial pressures below the lower limit of autoregulation is most pronounced during the first postoperative day, whereas exposure above the upper limit tends to increase during subsequent phases of recovery as systemic vascular resistance and arterial blood pressure rise. These observations underscore the importance of continuous, time-resolved physiological monitoring, as averaged or intermittent measurements may fail to capture clinically meaningful fluctuations in cerebrovascular control.

2.7.2 Evidence from Recent Studies in Postoperative CHD

Beyond neonatal cohorts, several groups have recently explored postoperative CAR monitoring in broader pediatric cardiac populations. In a contemporary retrospective study, Tabone and colleagues demonstrated the feasibility of continuously estimating individualized optimal mean arterial pressure and autoregulatory limits using NIRS-derived metrics during the first 48 hours after cardiac surgery in children of varying ages. Employing a weighted multi-time-window approach, the authors showed that autoregulation indices could be calculated for the majority of monitored time, even during periods of early postoperative instability. (122)

Notably, children in that cohort spent approximately one quarter of the monitored time outside their individualized autoregulatory range, irrespective of age group. Although no association was observed between autoregulatory impairment and postoperative delirium, the study provided important methodological validation for continuous autoregulation monitoring in the cardiac intensive care unit and reinforced the concept that fixed blood pressure thresholds may not adequately reflect individual cerebrovascular requirements. The study support the feasibility of postoperative CAR monitoring, demonstrating the high prevalence of pressure-passive cerebral perfusion after cardiac surgery, and providing a framework for individualized physiological assessment. At the same time, they highlight the need for disease-specific neonatal cohorts, higher temporal resolution, and integration with neurological outcome measures to clarify the clinical significance of autoregulatory impairment.

2.7.3 Postoperative Autoregulation and Acute Neurological Events

Within this evolving field, our retrospective cohort study focused specifically on neonates undergoing cardiac surgery and represents the largest neonatal dataset to date employing continuous COx-based autoregulation monitoring over the first 72 postoperative hours. The cohort included 28 neonates, of whom 21 had transposition of the great arteries and 7 had hypoplastic left heart syndrome. (123) Cerebral autoregulation was quantified using the cerebral oximetry index (COx), calculated as a moving correlation between slow-wave fluctuations in mean arterial pressure and cerebral regional oxygen saturation, with impaired autoregulation defined as COx > 0.3. (Fig. 69 and 70)

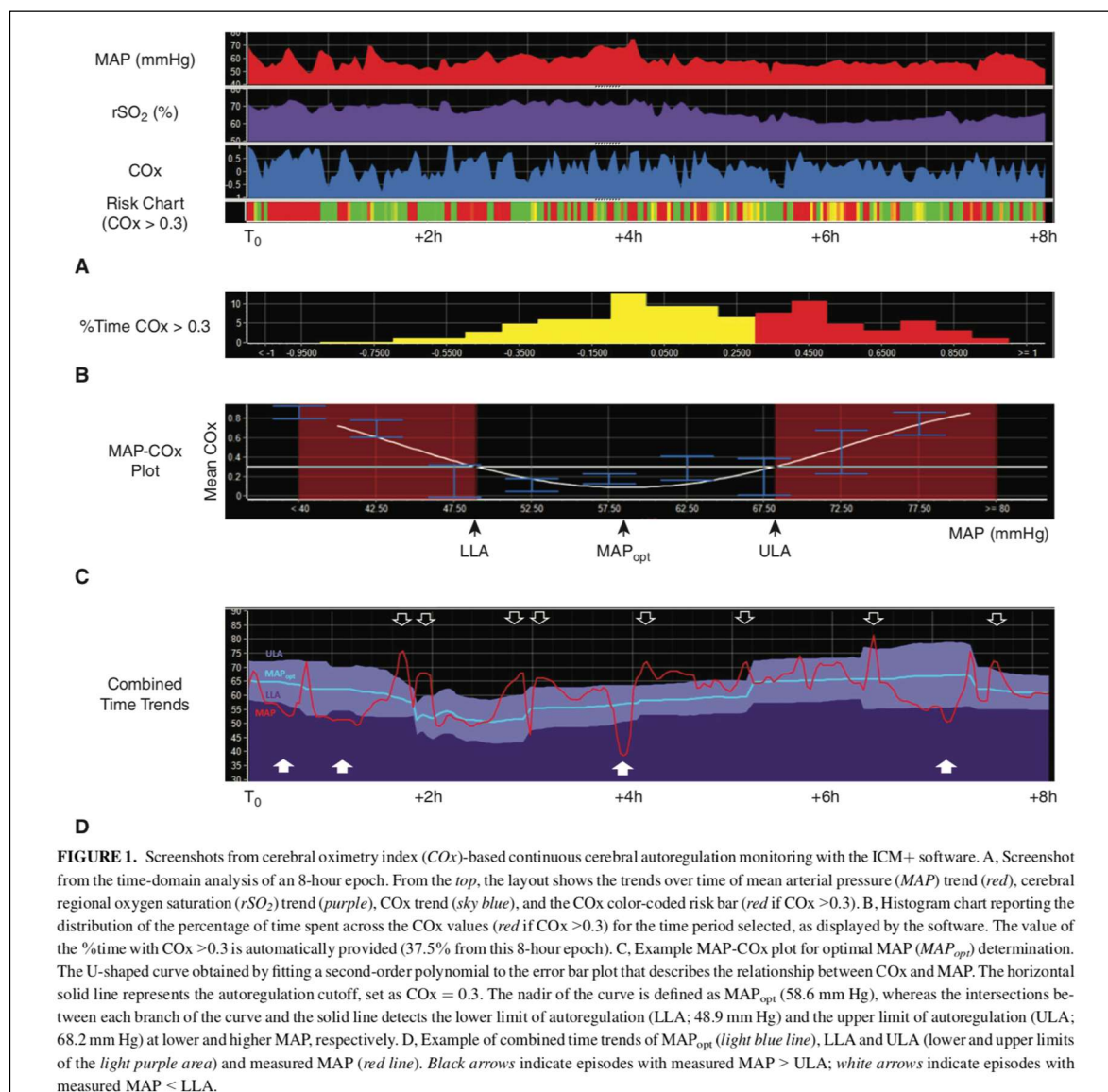


Fig.69 Adapted from: Pezzato S, et al. J Thor Cardiovasc Surg, 2024.

Characteristic	Total (N = 28)	ANE– (N = 21)	ANE+ (N = 7)	P value
Male sex, n (%)	22 (78.6)	17 (80.9)	5 (71.4)	.622
Apgar score at 5 min, median (IQR)	N = 18; 8 (8-9)	N = 12; 9 (8-9)	N = 6; 8 (8-8)	.239
Gestational age, wk, median (IQR)	39 (38-39)	39 (38-39)	38 (38-39)	.417
Birth weight, kg, median (IQR)	3.3 (3.1-3.6)	3.4 (3.1-3.7)	3.1 (3-3.3)	.156
Main diagnosis, n (%)				
HLHS	7 (25)	5 (23.8)	2 (28.6)	1.000
TGA	21 (75)	16 (76.2)	5 (71.4)	
Preoperative BAS, n (%)	15 (53.6)	11 (52.4)	4 (57.1)	1.000
Preoperative ECMO, n (%)	2 (7.1)	2 (9.5)	0	1.000
Age at surgery, d, median (IQR)	5 (3-7.5)	5 (3-8)	3 (2-7)	.260
CBP duration, min, median (IQR)	209.5 (186.5-249.5)	209 (169-254)	210 (187-217)	.866
Cross-clamping, min, median (IQR)	108 (82-135)	117 (82-139)	94 (71-119)	.383
DHCA/ASCP, min, median (IQR)	0 (0-13)	0 (0-9)	0 (0-49)	.745
Intraoperative MAP, mm Hg, median (IQR)	N = 19; 49 (46.8-54.9)	N = 14; 49.6 (46.8-55.1)	N = 5; 48.2 (47.4-49)	.444
Intraoperative mean rSO ₂ , %, median (IQR)	N = 19; 69.5 (63-71.7)	N = 14; 65.9 (61.4-70.8)	N = 5; 71.7 (69.5-75.5)	.156
Postoperative open chest, n (%)	21 (75)	16 (76.2)	5 (71.4)	1.000
Postoperative ECMO, n (%)	7 (25)	4 (19)	3 (42.9)	.318
Dead at ICU discharge, n (%)	5 (17.9)	3 (14.3)	2 (28.6)	.574

Fig.70 Adapted from: Pezzato S, et al. J Thor Cardiovasc Surg, 2024.

Impaired cerebral autoregulation was common across the cohort. Over the first 72 postoperative hours, the median percentage of time spent with COx > 0.3 was 31.6% (21.1–38.3%), indicating that nearly one third of the early postoperative period was characterized by pressure-passive cerebral perfusion. Autoregulation metrics did not differ significantly between cardiac diagnostic subgroups, despite expected differences in baseline oxygenation, supporting the interpretation that COx-derived indices primarily reflect cerebrovascular reactivity rather than absolute cerebral oxygen saturation. (Fig. 71).

Parameter	Whole cohort, median (IQR)	TGA (N = 21), median (IQR)	HLHS (N = 7), median (IQR)	P value
MAP, mm Hg	55.0 (52.9-57.4)	55.7 (53.5-57.9)	54.1 (50.5-54.6)	.208
rSO ₂ , %	67.3 (62.2-76.4)	70.1 (66.4-78.1)	57.3 (52.0-63.5)	<.001
SpO ₂ , %	97.7 (91.9-99.2)	98.8 (97.4-99.2)	82.8 (78.4-89.9)	<.001
%time MAP <40 mm Hg	0 (0-0.9)	0 (0-0.7)	0.3 (0-8.1)	.189
%time rSO ₂ <40%, min	0 (0-0.1)	0 (0-0)	2.3 (0-15.9)	.001
Mean COx	0.08 (0-0.16)	0.08 (0-0.16)	0.09 (0.05-0.2)	.612
%time COx >0.3, min	31.6 (21.1-38.3)	30.2 (21.7-36.8)	31.7 (20.4-42.1)	.499
MAPopt, mm Hg	54.8 (52.9-57.9)	55.6 (53.3-58.4)	53.8 (48.5-55.3)	.296
LLA, mm Hg	48.0 (42.8-49.6)	48.1 (42.5-49.7)	48.0 (43.1-48.4)	.669
ULA, mm Hg	64.2 (60.1-66.1)	64.5 (62.2-66.3)	59.1 (53.8-65.9)	.140
ΔMAPopt, mm Hg	−0.5 (−1.4 to 0.8)	−0.5 (−1.6 to 0.6)	0.2 (−1.3 to 0.8)	.353
%time MAP < LLA, min	7.8 (4.2-13.5)	6.9 (4.2-13.6)	9.1 (6.9-13.4)	.499
%time MAP > ULA, min	7.4 (4.6-14.6)	7.6 (4.6-14.3)	7.0 (4.6-26.6)	.959
LAr, mm Hg	15.6 (13.4-20.0)	16.2 (14.2-19.6)	12.7 (10.6-20.7)	.189

Fig.71 Adapted from: Pezzato S, et al. J Thor Cardiovasc Surg, 2024.

Seven neonates (25%) experienced an acute neurological event, defined a priori to include ischemic or hemorrhagic stroke, clinical or electrographic seizures, or brain death occurring within the first postoperative week. When autoregulatory profiles were compared between neonates with and without acute neurological events, consistent and statistically significant differences emerged. Neonates with neurological events exhibited a higher three-day median) and a greater proportion of time spent with impaired autoregulation (39.4% [32.7–42.1%] vs 29.2% [20.4–33.3%]; $P = .017$). (Fig. 72)

Parameter	Whole Cohort, median (IQR)	ANE– (N=21), median (IQR)	ANE+ (N=7), median (IQR)	<i>P</i> value
MAP, mm Hg	55.0 (52.9–57.4)	54.6 (52.7–57.0)	55.7 (53.5–58.1)	.640
rSO ₂ , %	67.3 (62.2–76.4)	66.8 (60.9–76.1)	67.8 (63.5–80.7)	.717
SpO ₂ , %	97.7 (91.9–99.2)	97.4 (94.0–99.1)	99.0 (89.9–99.2)	.499
%time MAP <40	0 (0–0.9)	0 (0–0.9)	0 (0–1.1)	.566
%time rSO ₂ <40%	0 (0–0.1)	0 (0–0.1)	0 (0–1.4)	.848
Mean COx	0.08 (0–0.16)	0.07 (0–0.1)	0.16 (0.12–0.2)	.035
%time COx >0.3	31.6 (21.1–38.3)	29.2 (20.4–33.3)	39.4 (32.7–42.1)	.017
MAP _{opt} , mm Hg	54.8 (52.9–57.9)	54.9 (52.7–57.3)	54.8 (53.8–59.3)	.717
LLA, mm Hg	48.0 (42.8–49.6)	48.0 (42.5–49.6)	48.3 (43.1–52.2)	.559
ULA, mm Hg	64.2 (60.1–66.1)	64.1 (60.2–65.9)	64.3 (59.1–66.3)	.917
ΔMAP _{opt} , mm Hg	–0.5 (–1.4–0.8)	–0.5 (–1.5–0.6)	0.6 (–0.8–1.2)	.353
%time MAP < LLA	7.8 (4.2–13.5)	6.9 (3.5–9.1)	13.3 (7.6–16.6)	.048
%time MAP > ULA	7.4 (4.6–14.6)	7.1 (4.0–10.2)	14.3 (5.5–22.0)	.228
LAr mm Hg	15.6 (13.4–20.0)	16.2 (14.3–20.3)	14.1 (10.6–17.6)	.126

Fig.72 Adapted from: Pezzato S, et al. J Thor Cardiovasc Surg, 2024.

Individualized autoregulatory limits were derived using a weighted multi–time–window approach applied to MAP–COx relationships. Infants with acute neurological events spent a significantly greater proportion of time with mean arterial pressure values below the lower limit of autoregulation (13.3% [7.6–16.6%] vs 6.9% [3.5–9.1%]; $P = .048$), indicating prolonged exposure to pressure–passive hypoperfusion. In contrast, median postoperative MAP and cerebral oxygen saturation values did not differ between groups, underscoring the limited sensitivity of conventional monitoring parameters for identifying cerebrovascular vulnerability. Temporal analysis revealed that divergence in autoregulatory behavior was most pronounced during the first postoperative day. On postoperative day 1, neonates with acute neurological events spent a significantly greater proportion of time with COx > 0.3 (38.3% [27.8–41.0%] vs 26.3% [22.3–30.2%]; $P = .036$), whereas differences attenuated on subsequent days. This timing aligns with the period of maximal hemodynamic instability following neonatal cardiopulmonary bypass. (Fig. 73)

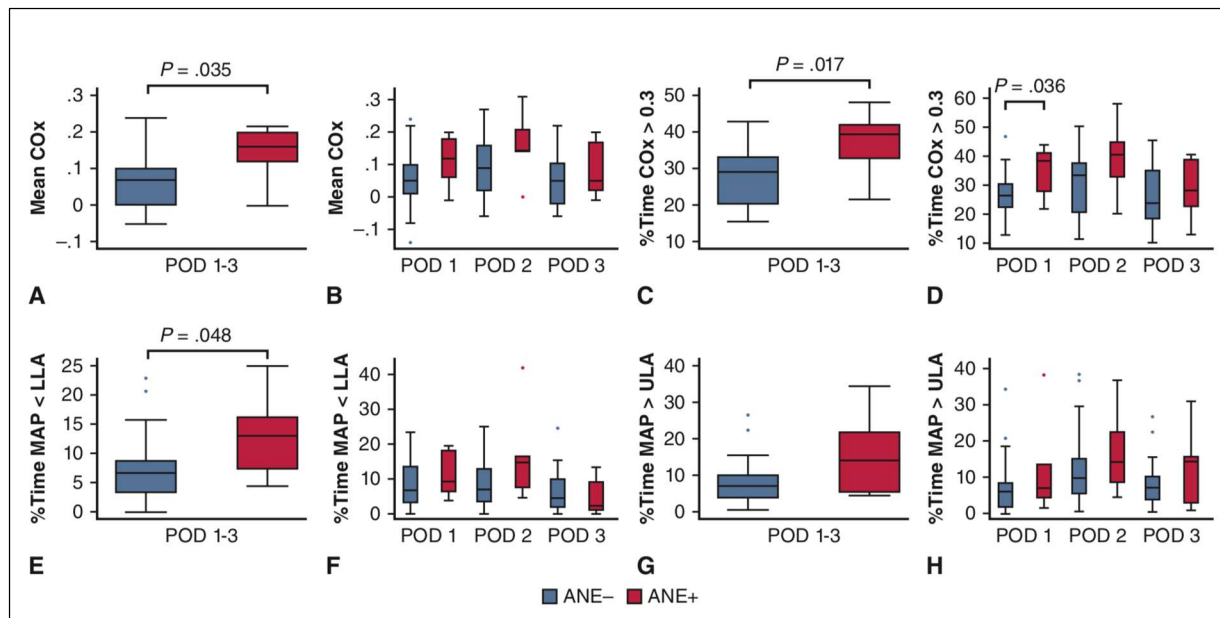


Fig.73 Adapted from: Pezzato S, et al. J Thor Cardiovasc Surg, 2024.

Importantly, the observational nature of the study precludes causal inference. Autoregulatory impairment cannot be interpreted as a direct cause of neurological injury, nor can neurological injury be excluded as a contributor to subsequent autoregulatory dysfunction. Rather, these findings indicate that impaired cerebrovascular reactivity identifies a physiological state in which the developing brain may be particularly susceptible to secondary injury during the early postoperative period.

From a translational perspective, these results support the hypothesis that the immediate postoperative phase represents a critical window of neurological vulnerability. By identifying periods of pressure-passive cerebral perfusion that are otherwise clinically silent, COx-based monitoring may facilitate earlier recognition of infants at heightened neurological risk. These observations provide a strong rationale for prospective studies designed to test whether maintaining arterial pressure within individualized autoregulatory limits can mitigate neurological injury, while emphasizing that such strategies remain hypothesis-generating and unproven.

The relationship between postoperative cerebral autoregulation and structural brain injury was further examined in this work using postoperative brain magnetic resonance imaging. MRI was available for the majority of the cohort and was systematically reviewed for evidence of newly acquired brain injury, with particular emphasis on white matter injury, which represents the most common pattern of perioperative cerebral damage in neonates with congenital heart disease.

When global autoregulation metrics were compared across MRI findings stratified according to the Quartered Point System category (124) (Fig. 74), no statistically significant association was identified between mean COx values and either the presence or severity of white matter injury. The absence of a robust association likely reflects both the limited sample size and the complex, multifactorial nature of perioperative white matter injury, which arises from the interplay of preexisting brain immaturity, intraoperative physiological and perfusion related exposures, and postoperative hemodynamic stress. (Fig. 75)

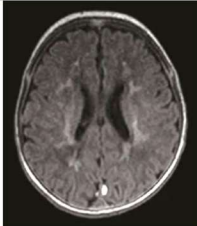
<i>Quartered Point System (QPS)</i>			
Category	Quartered point system	QPS questions (if yes, one point for each)	
None	0	Is PVL present?	
Mild	1	Is there PVL in all four quadrants?	
Moderate	2-3	Are there three or more lesions in one quadrant?	
Severe	4	Are any of the lesions greater than 5 mm?	
PVL, periventricular leuk		PVL, periventricular leukomalacia.	

Fig.74 Modified from: McCarthy A, et al. *Pediatr Res*, 2015.

TABLE 4. Postoperative physiologic parameters and cerebral autoregulation metrics in the whole cohort according to the first postoperative MRI					
Parameter	QPS category, median (IQR)				P value
	None (N = 8)	Mild (N = 4)	Moderate (N = 7)	Severe (N = 2)	
MAP, mm Hg	54.95 (51.14-59.61)	55.99 (53.10-58.62)	56.60 (55.37-56.97)	58.04 (53.46-62.63)	.9475
rSO ₂ , %	73.46 (62.57-77.11)	66.43 (63.62-72.62)	70.11 (64.76-86.75)	73.22 (65.75-80.68)	.8962
Mean COx	0.07 (0.00-0.09)	0.09 (0.00-0.20)	0.08 (0.05-0.16)	0.11 (0.00-0.21)	.7676
%Time COx >0.3	29.72 (22.49-32.14)	28.62 (18.47-37.37)	32.71 (27.99-39.37)	34.93 (21.72-48.14)	.6971
%Time MAP < LLA	6.36 (3.82-9.10)	12.02 (1.47-22.20)	7.55 (4.92-13.61)	15.03 (4.56-25.51)	.8220
White matter injury severity was stratified according to the QPS scoring system, and the nonparametric Kruskal-Wallis test was applied. QPS, Quartered point system; IQR, interquartile range; MAP, mean arterial blood pressure; rSO ₂ , cerebral regional saturation of oxygen; COx, cerebral oximetry index; LLA, lower limit of autoregulation; MRI, magnetic resonance imaging.					

Fig.75 Adapted from: Pezzato S, et al. *J Thor Cardiovasc Surg*, 2024.

Despite the absence of definitive statistical significance, important trends were observed. Neonates with postoperative white matter injury demonstrated higher mean COx values, a greater proportion of time spent with COx above the impairment threshold, and increased exposure to mean arterial pressure values below the lower limit of autoregulation during the early postoperative period. These findings are biologically plausible and consistent with the hypothesis that impaired cerebrovascular reactivity may contribute to an environment permissive to secondary injury, even if its effects are not uniformly captured by dichotomized MRI outcome measures. Importantly, MRI provides a structural snapshot of injury, whereas autoregulation monitoring reflects dynamic physiological processes that may precede, accompany, or exacerbate tissue damage.

Taken together, these observations highlight the complementary roles of postoperative neuroimaging and continuous physiological monitoring. While MRI defines the anatomical burden and spatial distribution of brain injury, cerebral autoregulation metrics provide insight into the evolving cerebrovascular conditions under which injury may occur. Integrating these modalities may therefore enhance mechanistic understanding and improve risk stratification, supporting the development of physiologically informed models of postoperative neurological vulnerability in neonates undergoing cardiac surgery.

2.7.4 Insights from the Ongoing CNH-Gaslini Prospective Observational Study

Building on the methodological framework and physiological insights derived from the present study, the CNH–Gaslini collaboration has expanded postoperative cerebral autoregulation monitoring within a larger prospective dataset developed under an Institutional Review Board–approved observational protocol entitled *“Non-invasive Continuous Cerebral Autoregulation (NCCA) Monitoring in Neonates with Congenital Heart Disease after Cardiac Repair Surgery.”* (Children’ National IRB approval ID: STUDY00000475) (Fig. 76)

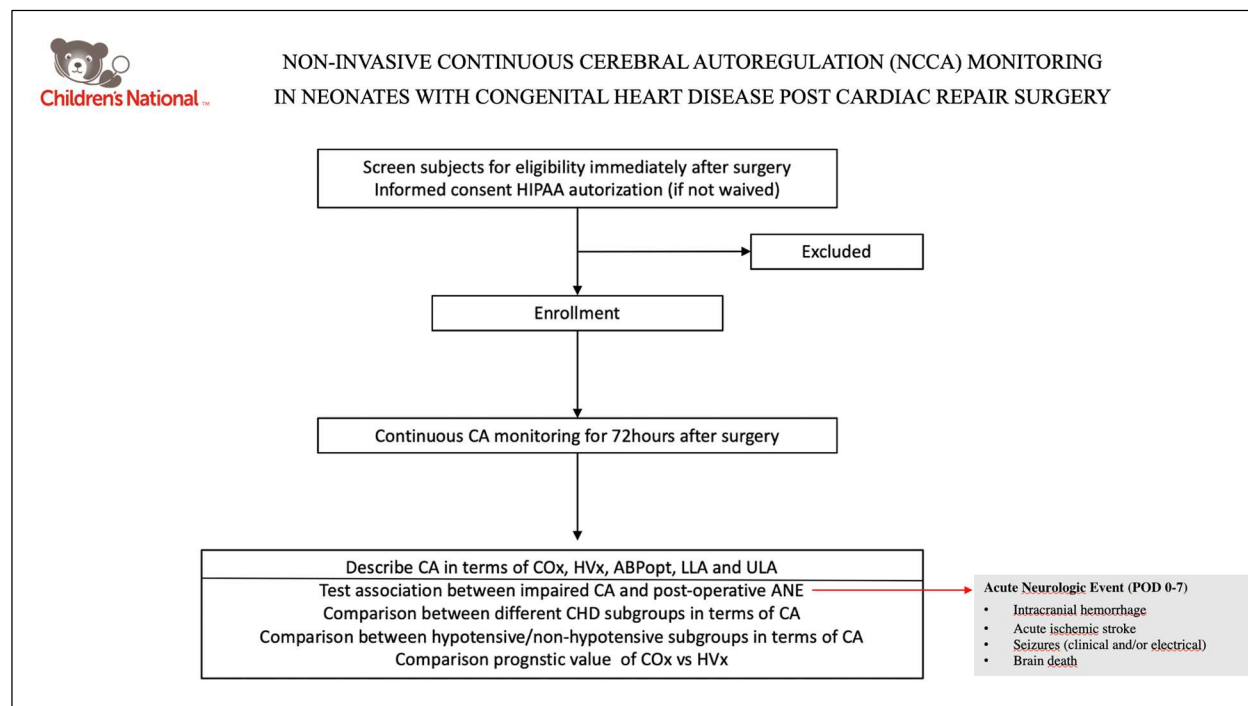
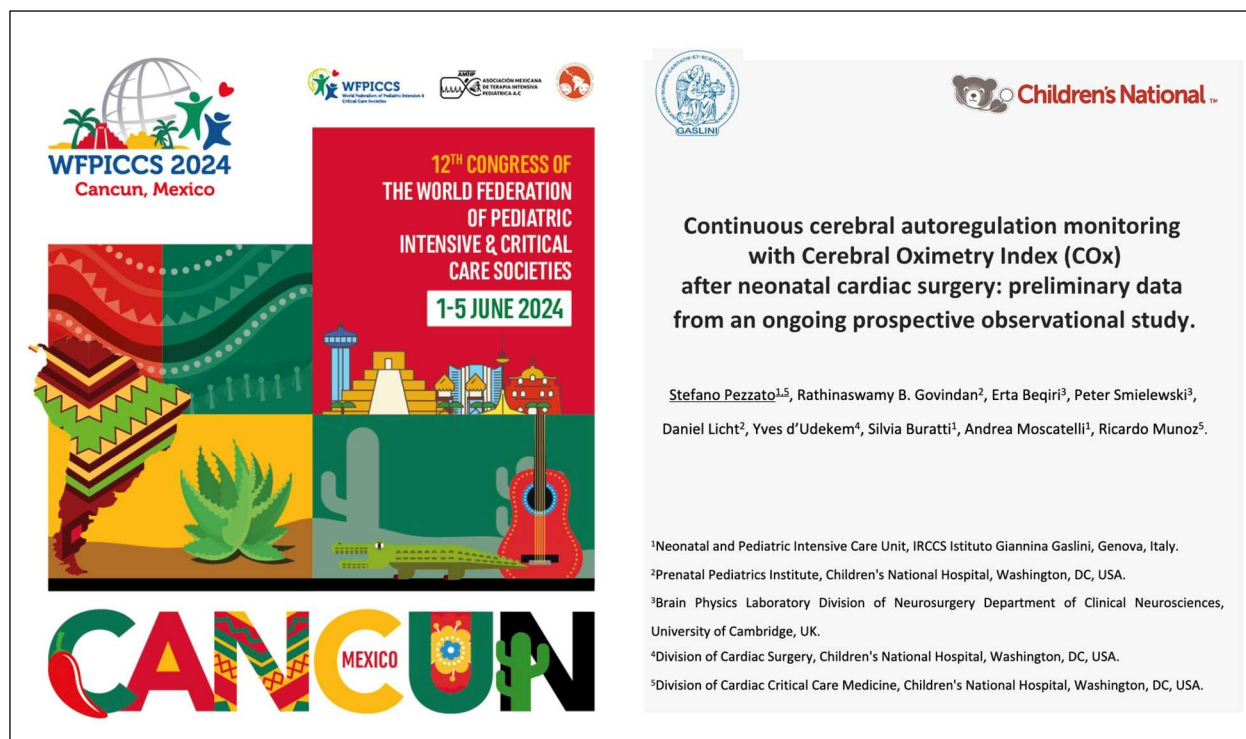


Fig.76 Pezzato S, Children National Hospital, 2023.

This expanded CNH-Gaslini cohort currently includes more than eighty neonates who underwent cardiac surgery between 2023 and 2025 and provides a substantially greater sample size for the evaluation of preliminary signals observed in earlier analyses. The increased cohort size, together with a harmonized analytic pipeline, will enable lesion-specific analyses, characterization of

distinct postoperative autoregulatory trajectories, and integration with multimodal neurological assessments. These include electroencephalography, cranial ultrasound, brain magnetic resonance imaging, and biochemical markers of neuronal injury. As the dataset continues to mature, it is expected to support the development of more refined models linking postoperative hemodynamic physiology to early neurological outcomes and may ultimately inform the design of future interventional studies evaluating whether autoregulation-guided blood pressure management improves neuroprotective care in this vulnerable population.

Preliminary results from an interim analysis of this cohort were presented at the 12th WFPICCS Congress of the World Federation of Pediatric Intensive and Critical Care Societies (June 1–5, 2024, Cancún, Mexico).



The interim analysis included the first 25 neonates enrolled in the NCCA study, all of whom were term infants undergoing surgery for critical congenital heart disease at a median postnatal age of 7 (interquartile range 5–29) days. Cerebral autoregulation was quantified using the cerebral oximetry index (COx), calculated according to the same methodology employed in the pilot study conducted at the same center. We described the evolution of the proportion of time spent within intact cerebral autoregulation during the first 72 postoperative hours, based on 12-hour epochs. (Fig 77)

Interim analysis, n=25	
Gestational Age	39 (37-39) weeks
Birth weight	3.15 (3-3.3) Kg
CHD physiology	20 biventricular repair, 80% 5 single-ventricle S1P 20%
Age at surgery	7 (5-29) days of life
CPB duration	168 (153-210) mins

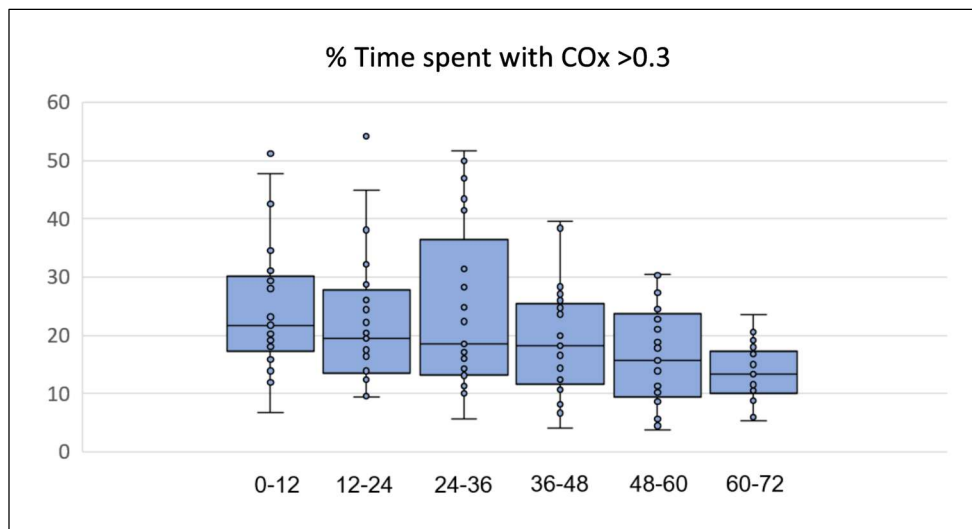


Fig.77 Pezzato S, Children National Hospital, 2023.

Early neurological outcome was assessed using the first postoperative brain MRI, which was available in 21 of 25 subjects (84%). Outcomes were dichotomized based on the presence or absence of newly identified white matter injury (WMI), as determined by review of the formal radiological report. Among the 7 subjects (33%) classified as WMI-positive, preliminary analyses suggested a higher proportion of time spent with impaired autoregulation ($COx > 0.3$) and a greater percentage of time with mean arterial pressure values below the estimated lower limit of autoregulation. These observations are exploratory in nature, and statistical significance will be formally evaluated upon completion of enrollment and analysis of the full cohort. (Fig. 78)

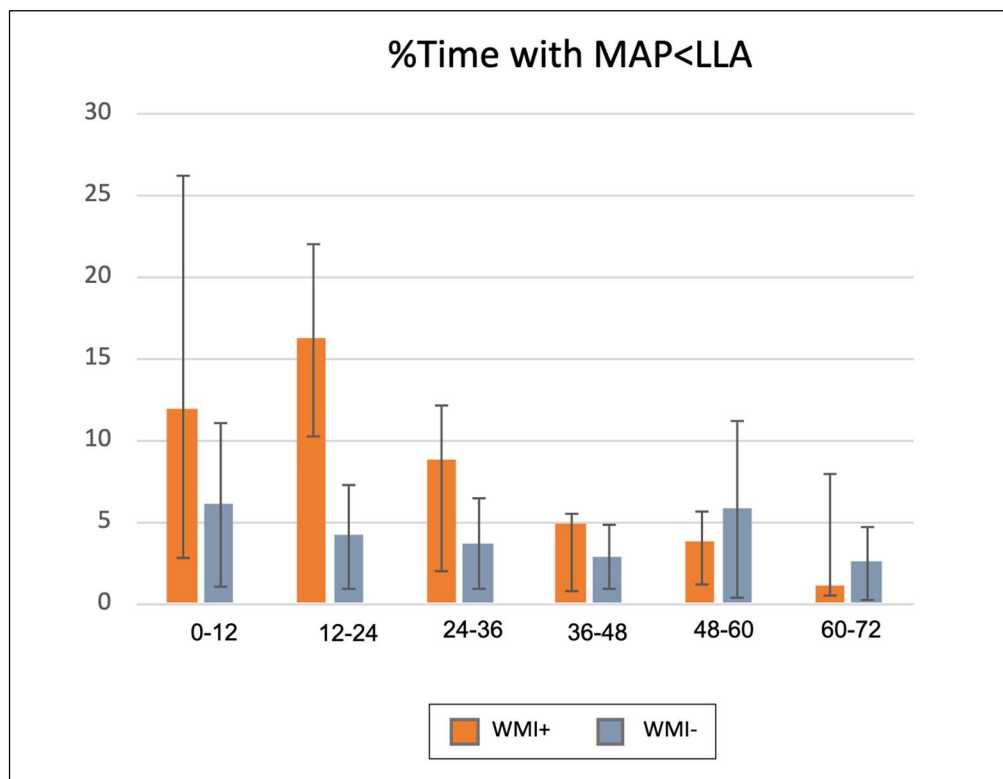
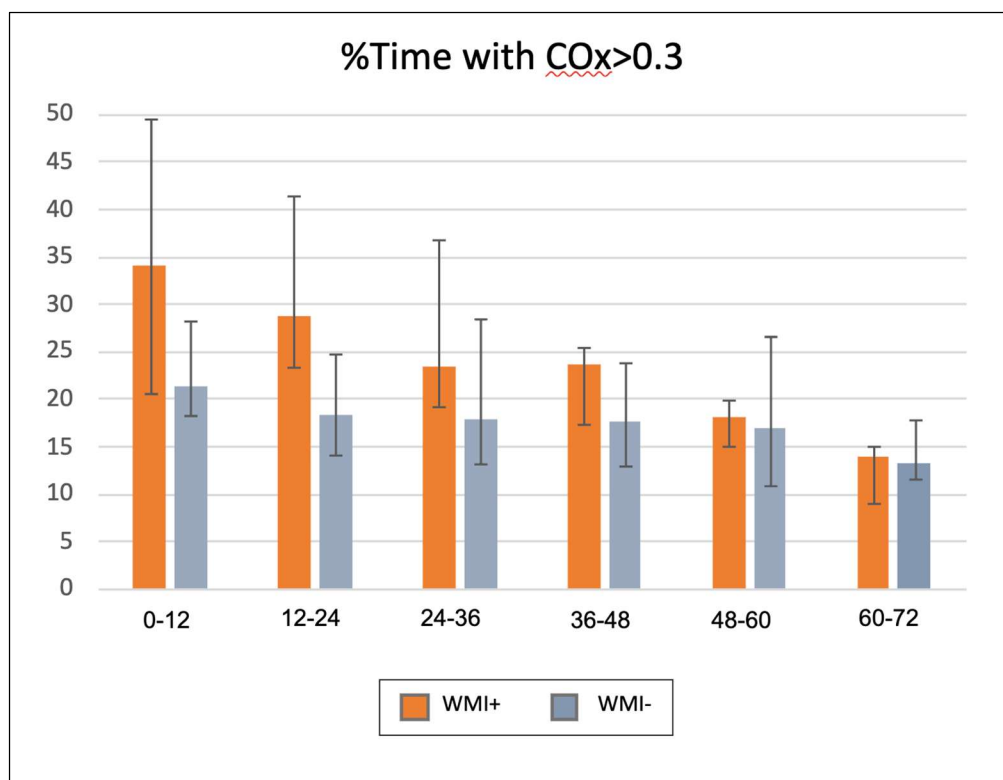


Fig.78 Pezzato S, Children National Hospital, 2023.

2.8 Cerebral Autoregulation Monitoring in patients supported by ECMO

2.8.1 Neurologic Outcomes in Neonatal and Pediatric ECMO

Extracorporeal membrane oxygenation (ECMO) is a lifesaving intervention for neonates and children with severe, potentially reversible cardiac or respiratory failure and can be delivered using different configurations that have distinct implications for cerebral hemodynamics and neurological risk. The two principal modes are veno-venous (VV) ECMO, primarily used for respiratory support, and veno-arterial (VA) ECMO, which provides combined cardiac and respiratory support. VV ECMO preserves native cardiac output and pulsatile cerebral blood flow, whereas VA ECMO partially or completely replaces systemic circulation, often resulting in non-pulsatile flow, altered cerebral perfusion pressure, and asymmetric cerebral blood flow depending on cannulation strategy. (125) (Fig.79)

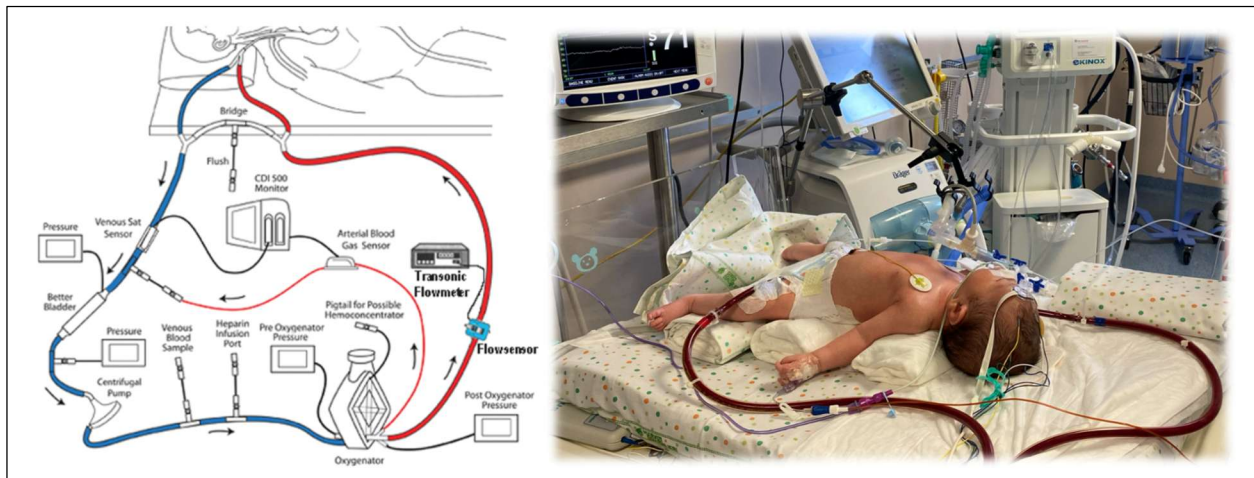


Fig.79 Modified from: Lequier L, et al. *Pediatr Crit Care Med*, 2013. Picture: IRCCS Istituto Gaslini, 2022.

These physiological differences are clinically relevant, as different ECMO indications are associated with distinct burdens of neurological morbidity and mortality, with acute brain injury reported in up to 25% of pediatric patients. Neurological complications during ECMO contribute not only to increase in-hospital mortality but also to long-term neurodevelopmental impairment among survivors. (126) (Fig. 80)

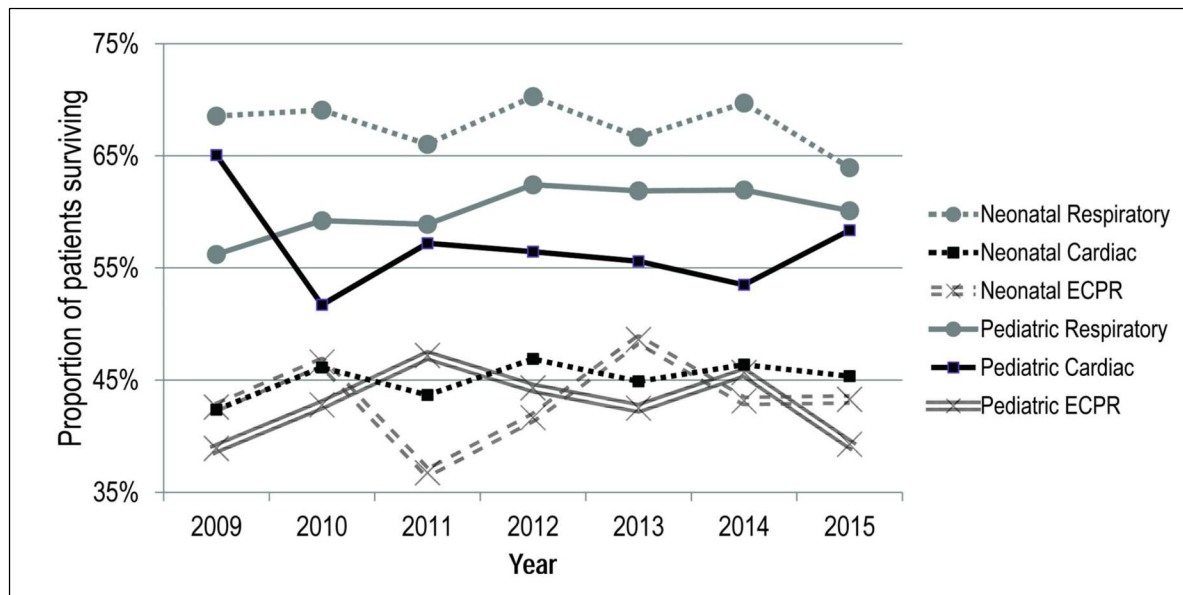


Fig.80 Adapted from: Barbaro RP, et al. ASAIO J, 2017.

The spectrum of neurological complications observed during ECMO includes seizures, intracranial hemorrhage, and ischemic brain injury, each reflecting distinct but often overlapping pathophysiological mechanisms. Seizures are among the most common manifestations, with electrographic seizures detected in up to one quarter of children when continuous electroencephalography is employed. Importantly, the majority of these events are subclinical, underscoring the limited sensitivity of clinical examination alone in this population. Seizures typically occur early after ECMO initiation and are frequently associated with underlying structural injury, metabolic disturbances, or antecedent hypoxic–ischemic insults.

Intracranial hemorrhage remains one of the most feared complications of ECMO, reflecting the complex interaction between anticoagulation requirements, altered cerebral hemodynamics, and vascular fragility. Reported rates range from approximately 4% to 16%, with large hemorrhages often associated with poor survival. Ischemic brain injury, occurring in 2–17% of pediatric ECMO patients, may present as global hypoxic–ischemic injury or focal arterial ischemic stroke related to thromboembolic phenomena or impaired cerebral perfusion. These complications are reported more frequently in patients supported with VA ECMO compared with VV ECMO, reflecting the combined effects of non-pulsatile flow, altered cerebral autoregulation, and the risk of arterial embolization associated with the extracorporeal circuit and arterial cannulation.(127)(Fig.81).

Parameter	Incidence	Contributing factors	Monitoring strategies ^a
Seizure	11–23%	Preexisting conditions, ischemic or hemorrhagic injury, metabolic disturbances	Clinical examination, EEG, plasma biomarkers
Intracranial hemorrhage	4–16%	Blood pressure, anticoagulation, ischemic injury	Clinical examination, neuroimaging, EEG, TCD, cerebral oximetry, plasma biomarkers
Ischemic injury (including arterial ischemic stroke and global hypoxic-ischemic injury)	2–17%	Preexisting conditions, blood pressure, inflammation, hypercoagulability	Clinical examination, neuroimaging, EEG, TCD, cerebral oximetry, plasma biomarkers

ECMO, extracorporeal membrane oxygenation, EEG, electroencephalography, TCD, transcranial Doppler

Fig.81 Modified *from*: Felling RJ, et al.. Neurocrit Care, 2023.

Survivors of ECMO frequently exhibit persistent neurodevelopmental sequelae, including cognitive impairment, motor dysfunction, behavioral abnormalities, and reduced health-related quality of life. Across published cohorts, adverse neurological outcomes have been reported in 10–60% of survivors, depending on age, indication for ECMO, injury burden, and duration of follow-up. These data emphasize that neurological injury during ECMO is not merely an acute complication but a determinant of lifelong outcome.

Despite this high burden of neurological morbidity, contemporary practice patterns reveal substantial variability in both neuromonitoring during ECMO and neurodevelopmental follow-up after hospital discharge. An international, multinational European survey conducted by the EuroELSO Neurological Monitoring and Outcome Working Group highlighted marked heterogeneity in neuromonitoring strategies across ECMO centers. Less than half of responding centers reported routine neuromonitoring for all ECMO patients, while a substantial proportion relied on selective monitoring or bedside clinical examination alone. Among centers employing neuromonitoring, near-infrared spectroscopy was the most frequently used modality, followed by electroencephalography, transcranial Doppler ultrasonography, and circulating biomarkers of brain injury. Pediatric centers more commonly utilized cranial ultrasound, although monitoring frequency and protocols varied widely. (128)

Equally striking variability was observed in post-ECMO neurological assessment and follow-up. Routine neurological evaluation prior to hospital discharge was performed in fewer than half of centers, and only a small minority reported structured, longitudinal neurodevelopmental follow-up programs. Importantly, the majority of surveyed centers expressed strong agreement that ECMO survivors would benefit from standardized, longitudinal neurodevelopmental surveillance. These findings underscore a critical gap between the recognized neurological risk associated with ECMO and the systematic implementation of monitoring and follow-up strategies needed to mitigate long-term morbidity.

2.8.2 Multimodal Neuromonitoring during ECMO

Neurological assessment during ECMO is inherently challenging, as sedation, neuromuscular blockade, metabolic derangements, and the severity of the underlying illness frequently preclude reliable bedside neurological examination. Consequently, contemporary neurocritical care during ECMO relies on multimodal neuromonitoring strategies that integrate structural imaging, cerebral hemodynamic assessment, and physiological monitoring to detect neurological injury and assess cerebral vulnerability. While these approaches have significantly improved the recognition of neurological complications, they remain limited in their ability to support proactive neuroprotective strategies. (127)

Structural neuroimaging remains a cornerstone of neurological surveillance during ECMO. Cranial ultrasound is widely used in neonates because of its portability and safety and is commonly performed serially during the early ECMO course; however, its sensitivity for ischemic injury, posterior fossa lesions, and subtle hemorrhagic abnormalities is limited. Computed tomography offers greater sensitivity for acute intracranial hemorrhage and is frequently employed in older children, but its use is constrained by radiation exposure and the risks associated with intrahospital transport of critically ill patients on extracorporeal support. Importantly, both modalities are inherently episodic and generally detect injury only after structural damage has already occurred. In this context, emerging applications of bedside ultra-low-field MRI have recently been proposed as a potential strategy to enable safer, earlier, and more comprehensive neuroimaging in ECMO-supported patients. (36)

Physiological monitoring modalities offer complementary information but are similarly constrained by their retrospective or injury-confirmatory nature. Continuous electroencephalography plays a central role in detecting seizures and assessing global cortical function during ECMO, revealing that a substantial proportion of seizures are electrographic and clinically silent. (129) Changes in EEG background activity may correlate with impaired cerebral perfusion or evolving injury; however, such alterations often reflect established or ongoing cerebral dysfunction rather than impending injury. Moreover, EEG abnormalities lack specificity with respect to underlying hemodynamic mechanisms and are influenced by sedation, metabolic disturbances, and systemic illness.

Cerebral blood flow monitoring techniques, including transcranial Doppler ultrasonography, provide noninvasive insight into cerebral blood flow velocity and pulsatility and may raise suspicion for altered cerebrovascular resistance, embolic phenomena, or impaired autoregulation. Nevertheless, transcranial Doppler is typically applied intermittently, and observed abnormalities are often interpreted after neurological injury has already developed or when physiological instability is well established.

Near-infrared spectroscopy has emerged as a practical bedside tool for continuous monitoring of regional cerebral oxygenation during ECMO. Associations between cerebral desaturation, large deviations from baseline oxygenation, and adverse neurological outcomes have been consistently reported. However, static cerebral oxygenation thresholds primarily function as warning signals of compromised cerebral oxygen delivery or utilization and do not, in isolation, provide actionable guidance for individualized hemodynamic management. As with other modalities, abnormal NIRS values frequently reflect a downstream consequence of systemic or cerebral derangements rather than an early, modifiable physiological state.

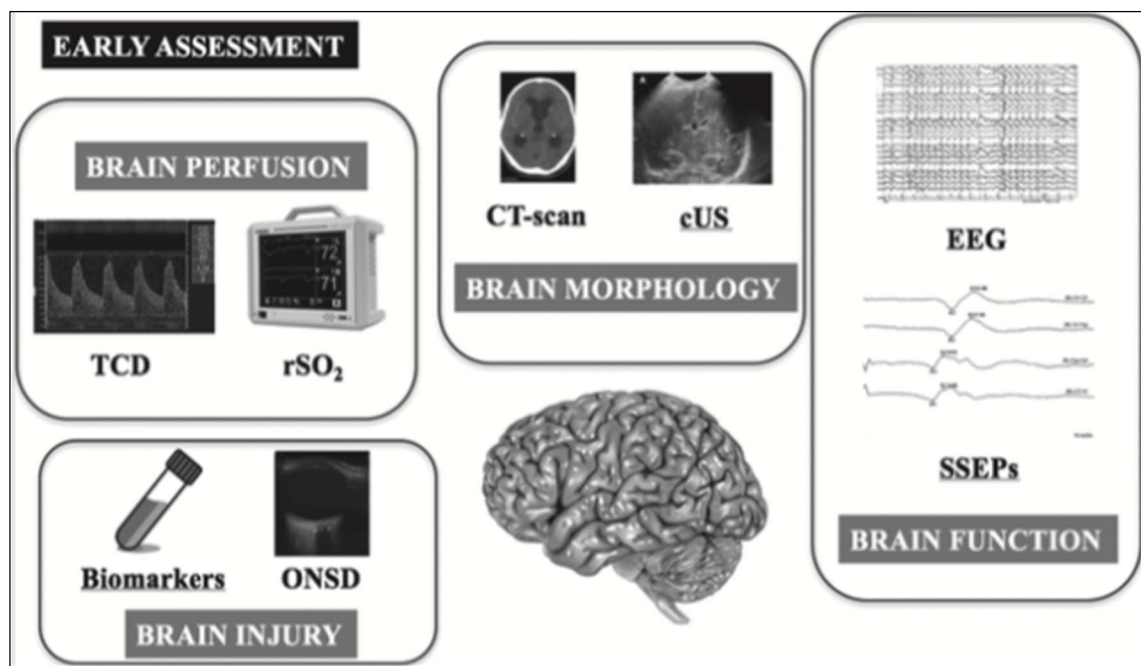


Fig.82 Modified *from*: Lorusso R, et al.. Minerva Anesthesiol, 2017.

Collectively, current neuromonitoring modalities during ECMO are predominantly reactive, identifying neurological injury or severe physiological compromise after pathological processes are already underway. While they improve detection and prognostication, they offer limited support for proactive neuroprotection, individualized perfusion targeting, or true goal-directed cerebral hemodynamic management. This limitation is particularly relevant in the ECMO population, where cerebral perfusion is profoundly influenced by ECMO mode, cannulation strategy, non-pulsatile flow, carbon dioxide handling, and rapid changes in systemic hemodynamics.

These constraints highlight a critical gap between neurological risk recognition and actionable bedside decision-making. Addressing this gap requires monitoring approaches that move beyond injury detection toward continuous characterization of cerebrovascular function, enabling clinicians to identify vulnerable physiological states and intervene before irreversible brain injury occurs. In this context, dynamic assessment of cerebral autoregulation represents a promising framework for transforming neuromonitoring during ECMO from a surveillance tool into a platform for precision-guided neuroprotection.

2.8.3 NIRS-based cerebral autoregulation monitoring during ECMO

Near-infrared spectroscopy (NIRS)-based cerebral autoregulation monitoring represents a promising approach to overcome the intrinsic limitations of conventional neuromonitoring during ECMO by enabling continuous, physiology-driven assessment of cerebrovascular function. Unlike structural imaging or electrophysiological monitoring, which primarily detect established injury or late manifestations of cerebral dysfunction, autoregulation monitoring aims to characterize the dynamic relationship between cerebral perfusion pressure and cerebral blood flow, thereby identifying periods of cerebral vulnerability before irreversible damage occurs.

Building on the widespread availability of NIRS in pediatric intensive care units, cerebral autoregulation can be assessed using correlation-based indices that exploit slow-wave fluctuations in regional cerebral oxygen saturation as a surrogate for cerebral blood flow. In this framework, the cerebral oxygenation index (COx) quantifies the degree of pressure passivity by measuring the moving correlation between mean arterial pressure and NIRS-derived cerebral oxygenation. When autoregulation is preserved, cerebral blood flow remains relatively independent of pressure changes and COx values remain low or negative; conversely, elevated COx values indicate pressure-passive cerebral circulation and impaired autoregulation. (119)

(Fig.83 and 84)

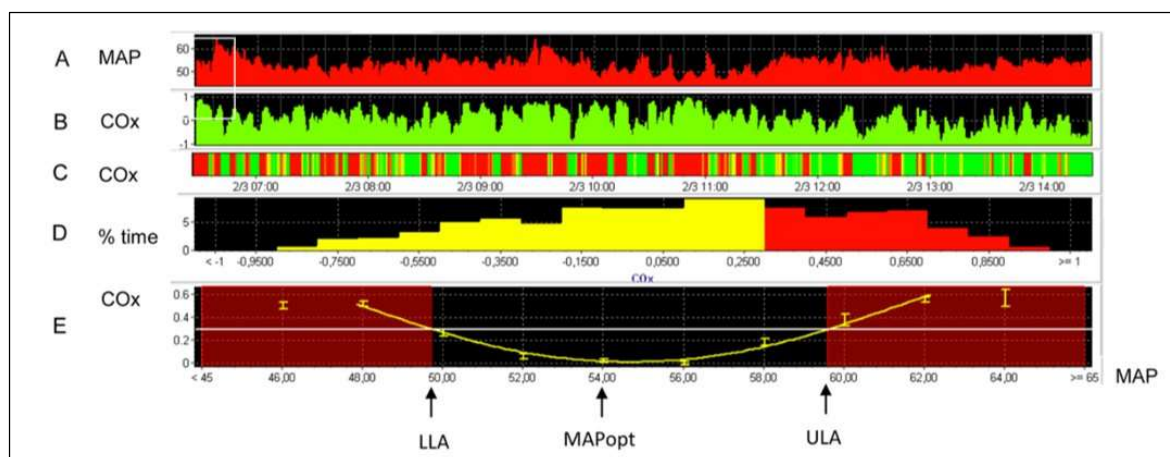


Fig.83 Modified from: Joram N, et al. Neurocrit Care, 2020.

In a prospective pilot study conducted in neonatal and pediatric patients supported by ECMO, continuous NIRS-based autoregulation monitoring was shown to be feasible using routine bedside signals integrated through high-resolution data acquisition platforms. COx values, as well as derived estimates of optimal mean arterial pressure (MAPopt) and the lower and upper limits of autoregulation, could be identified for the majority of monitoring time. Importantly, autoregulatory impairment was most pronounced during the first 24 hours following ECMO initiation, a period that coincides with the highest incidence of acute neurological events. Children who experienced acute neurological complications demonstrated significantly higher mean COx values and spent a greater proportion of time outside the individualized autoregulatory range, both below the lower limit and above the upper limit of autoregulation.

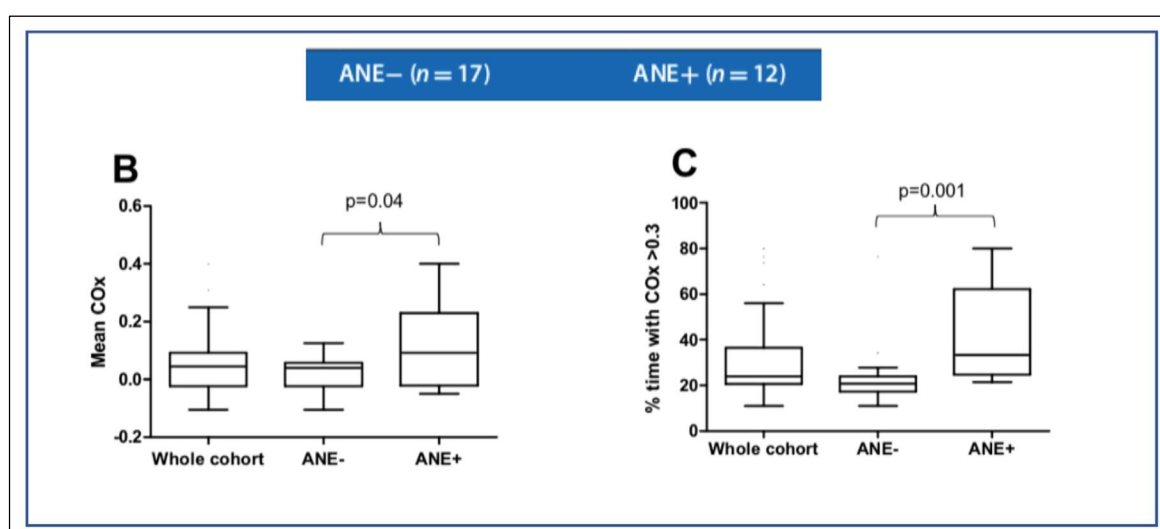


Fig.83 Modified from: Joram N, et al. Neurocrit Care, 2020.

These findings provided early evidence that impaired cerebral autoregulation is not merely an epiphenomenon of critical illness during ECMO, but rather a measurable physiological state associated with neurological injury risk. Notably, autoregulation monitoring captured cerebral vulnerability during a time window when conventional neuromonitoring modalities are least informative and when clinical management is most dynamic.

Subsequent work further explored the mechanistic determinants of autoregulatory instability during ECMO by examining the interaction between arterial blood gas parameters and cerebral autoregulation metrics. This analysis demonstrated a complex, non-linear relationship between arterial carbon dioxide tension and autoregulatory function, strongly modulated by blood pressure level and particularly evident during the early phase of ECMO support. Variations in PaCO₂ were associated with shifts in both the lower and upper limits of autoregulation, effectively altering the width and position of the autoregulatory plateau. These effects were most pronounced within the first 24 hours of ECMO, reinforcing the concept that early post-cannulation management represents a critical period for cerebral hemodynamic stability. (120)

Importantly, these observations highlight that cerebral autoregulation during ECMO is not static but dynamically influenced by modifiable clinical variables, including carbon dioxide and oxygen management. In contrast to static cerebral oxygenation thresholds, autoregulation monitoring provides individualized, patient-specific information regarding the tolerance of the cerebral circulation to blood pressure fluctuations under varying metabolic conditions. (Fig. 84)

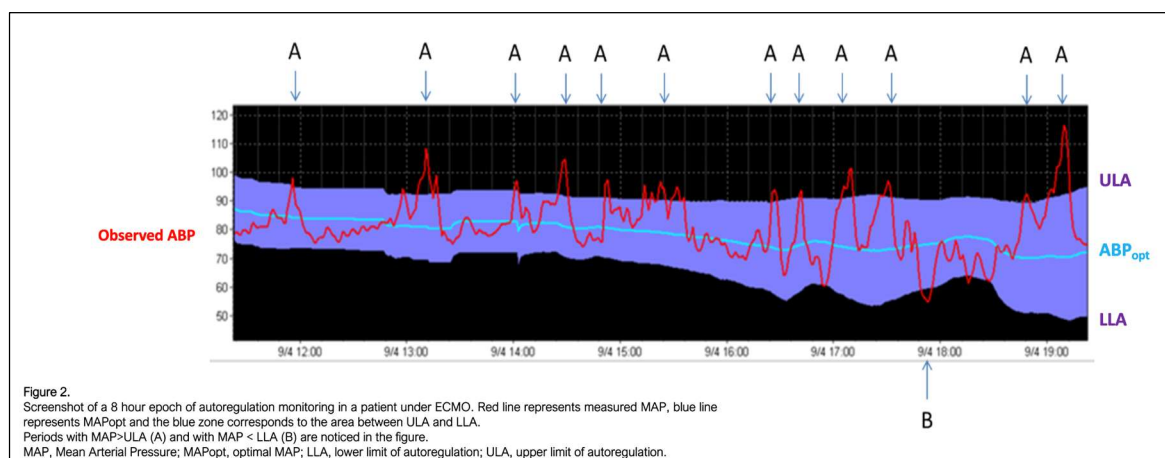


Fig.84 Modified *from*: Joram N, et al. Neurocrit Care, 2020.

NIRS-based cerebral autoregulation monitoring represents a conceptual shift in neuromonitoring during ECMO, from retrospective injury detection toward real-time identification of physiological vulnerability and individualized cerebral perfusion targets. By characterizing pressure passivity and defining patient-specific limits of autoregulation, this approach has the potential to support proactive neuroprotective strategies and goal-directed hemodynamic management.

Children supported by ECMO constitute a particularly fragile and high-risk subset within the broader population of critically ill neonatal and pediatric patients, in whom profound alterations in systemic hemodynamics, gas exchange, and cerebrovascular physiology converge to amplify susceptibility to autoregulatory failure and neurological injury. In this context, ECMO provides a unique and extreme clinical model in which the principles of cerebral autoregulation monitoring can be rigorously tested, refined, and ultimately generalized to neonatal and pediatric intensive care populations, as synthesized in recent scoping analyses of autoregulation monitoring across critical care settings. (131) (Fig.85)

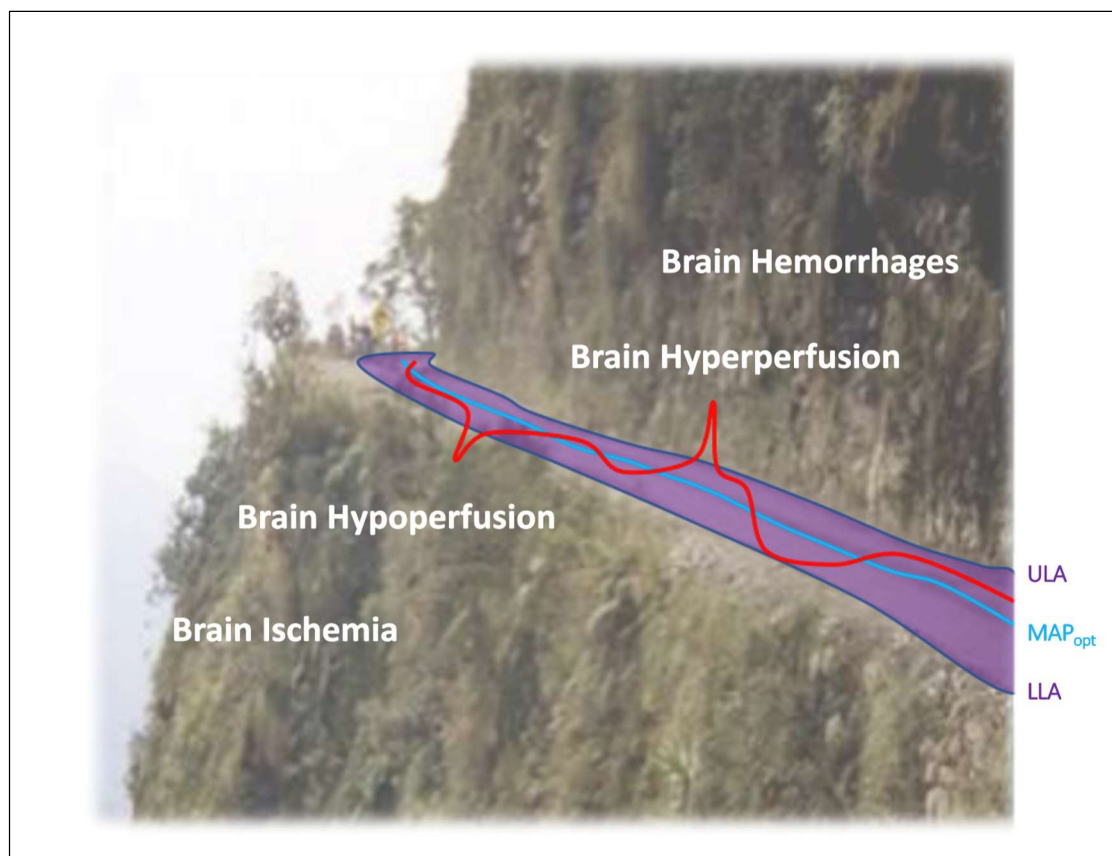


Fig.85 Pezzato S, Children National Hospital educational material, 2023.

2.8.4 Current Research Project in neonatal and pediatric ECMO

Building on preliminary evidence linking cerebral autoregulation impairment to neurological injury during extracorporeal membrane oxygenation, an ongoing collaborative research effort led by the Nantes University Hospital (ECMOX2 Study) was designed to systematically investigate cerebrovascular autoregulation in pediatric patients supported with ECMO. The study was developed to address the critical gap between observational neuromonitoring and mechanistic understanding of neurological vulnerability in this high-risk population .

ECMOX2 is a prospective, multicenter, international, non-interventional physiology study conducted across four European pediatric ECMO centers, with centralized data analysis performed in collaboration with the Brain Physics Laboratory at the University of Cambridge. The primary rationale of the study is that impaired cerebral autoregulation represents a key, measurable pathophysiological mechanism underlying acute neurological events during ECMO and may differ according to ECMO configuration and systemic management variables. (Fig. 86)

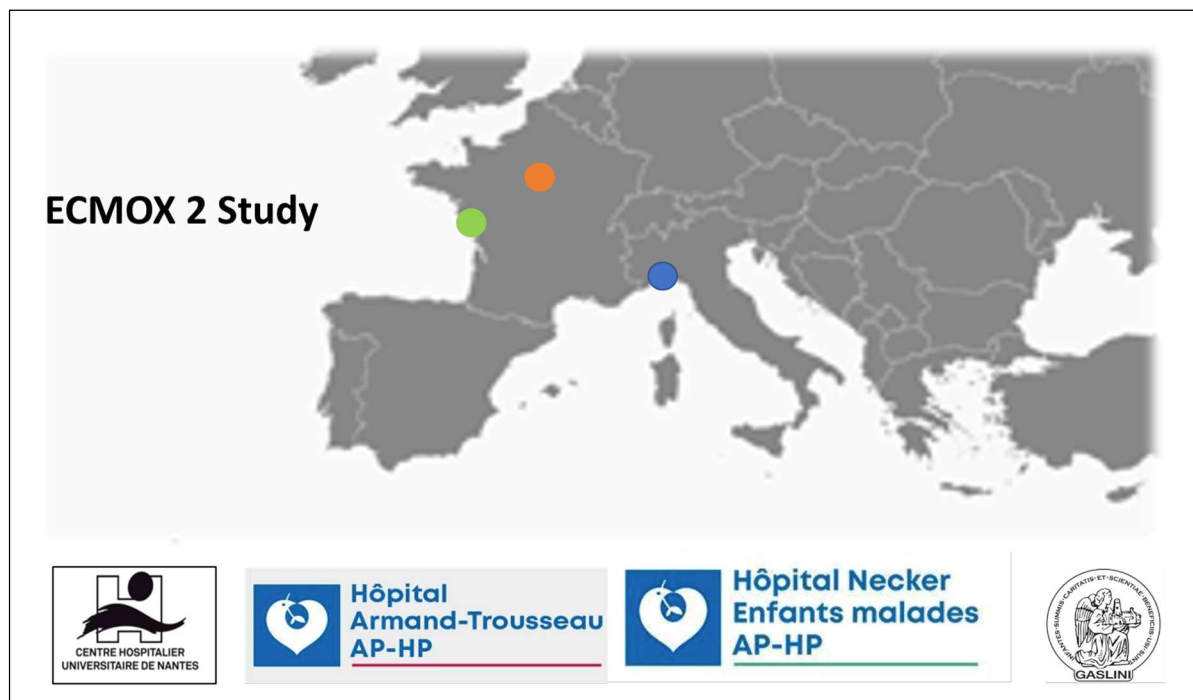


Fig.85 Pezzato S, IRCCS Istituto G. Gaslini, 2022.

The primary objective of ECMOX2 is to evaluate the association between cerebral autoregulation impairment (quantified using NIRS-derived correlation indices) and the occurrence of acute neurological events during ECMO support. Secondary objectives include the assessment of factors influencing autoregulation (such as arterial carbon dioxide tension, sedation level, ECMO settings, and cannulation type), comparison between veno-arterial and veno-venous ECMO, and the relationship between autoregulation metrics and neurological outcome at hospital discharge.

Eligible participants include all patients younger than 18 years supported with veno-arterial or veno-venous ECMO for respiratory or hemodynamic indications, including extracorporeal cardiopulmonary resuscitation. Patients are excluded if cerebral autoregulation monitoring is available for less than four hours or if parental consent is not obtained. The study does not alter clinical management and relies exclusively on routinely acquired physiological signals, which are recorded and analyzed offline.

At the time of writing, nine patients have been enrolled at IRCCS Istituto G. Gaslini. Data acquisition has been completed at the four enrolling centers, and data processing and analysis are ongoing. This study represents a critical step toward validating cerebral autoregulation monitoring as a physiologically meaningful biomarker in pediatric ECMO and provides a foundation for future investigations aimed at translating autoregulation assessment into individualized, goal-directed neuroprotective strategies

Conclusion

This doctoral work has explored the evolving role of multimodal neuromonitoring as a unifying physiological framework for the care of critically ill infants and children in the pediatric intensive care unit. By integrating high-resolution physiological signals across systemic, cerebral, and metabolic domains, multimodal monitoring offers the opportunity to move beyond static thresholds and protocolized targets toward a dynamic, patient-specific understanding of cerebral perfusion and vulnerability to secondary brain injury. Within this context, cerebral autoregulation emerges as a central construct linking cardiovascular physiology, cerebrovascular control, and neurological outcome across diverse pediatric disease states.

Through complementary lines of investigation, this thesis examined cerebral autoregulation using both invasive and noninvasive monitoring approaches in two high risk pediatric populations. In children with severe traumatic brain injury, intracranial pressure-based autoregulation monitoring provided mechanistic insight into pressure volume compensation and cerebrovascular reactivity. It also clarified the association between autoregulatory failure and secondary brain injury, underscoring the limitations of fixed cerebral perfusion pressure targets. In parallel, in neonates and infants undergoing cardiac surgery for congenital heart disease, near infrared spectroscopy-based autoregulation monitoring demonstrated reproducible, phase dependent impairment across the perioperative period. Clinically meaningful associations were identified between specific physiological derangements, including exposure to mean arterial pressure below individualized autoregulatory thresholds, and markers of brain injury.

Collectively, these findings support the view that cerebral autoregulation is a dynamic and context-dependent process rather than a binary phenomenon, with behavior that varies across time, developmental stage, and underlying disease. They further indicate that individualized perfusion targets derived from continuous autoregulation monitoring may provide greater physiological specificity than population-based thresholds, particularly during periods of increased vulnerability.

Looking forward, the translation of autoregulation monitoring from research settings to routine clinical practice will require prospective validation, integration with multimodal data streams, and the development of real-time decision support tools capable of guiding individualized hemodynamic management. Advances in signal processing, data integration, and machine learning are likely to further enhance the interpretability and clinical utility of these approaches. In this evolving landscape, the convergence of multimodal neuromonitoring and precision physiology holds promise for advancing neuroprotective strategies in pediatric critical care, with the overarching goal of improving survival while supporting optimal long term neurodevelopmental outcomes in vulnerable children.

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