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Detection and prevention of neurologic injury in the intensive care unit

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Survivors of repairs of complex congenital cardiac malformations in infancy have an increased risk of permanent abnormalities in motor, cognitive, expressive, and behavioral functioning. These functional deficits are expressions of complex interactions of environment, including prolonged hospitalization and conditioned child–parental behaviours, alterations of social environment, the effects of physical limitations, biological influences including genetic determinants, prenatal injury, and acquired reversible and irreversible neuronal injury.[1,2] The magnitude of the problem is large, with incidence dependent upon the measures used for assessment. Overt postoperative neurologic signs have been recorded in up to one-tenth of postoperative infants and children, with double that rate found in those with abnormalities of the aortic arch.[3] A decreased potential for development, based upon parent-sibling models, has been estimated to occur in one-third of survivors.[4,5] Evidence of injury is provided by magnetic resonance imaging in up to one-third of patients preoperatively, and between half and nine-tenths postoperatively, although most of these early postoperative changes will disappear.[5] Although recent changes in perioperative management are likely to reduce such neurologic injury, their significance remains high.

Assessment in the intensive care unit

Assessment of potential neurologic injury is important in the intensive care unit, because conditions which cause permanent or transient neurologic dysfunction have been identified in the perioperative period, and treatment or prevention of these conditions is likely to reduce the incidence of prolonged neurologic disability in survivors.[6] Extensive investigation has elucidated much of the pathophysiology of intraoperative injury, and intensive monitoring has allowed the development of strategies to reduce exposure to known risk factors. The incidence of late postoperative cognitive dysfunction is inadequately explained, however, by intraoperative factors alone. Many of the conditions associated with neurologic injury are present not only in the operating room, but before and after. Identification of conditions associated with neurologic injury in the perioperative period opens the window for interventions explicitly targeted to prevent or reduce neurologic injury.

Multiple modalities are available for postoperative assessment of brain injury. The sensitivity of the clinical examination, when not obscured by medication, has been reported by neurologists to be as high as 100 percent in a neonatal medical unit, a figure unlikely to be realized in the postoperative cardiac unit. Electroencephalography may achieve a predictive value of 80 percent for later neurodevelopmental abnormality, but confounding effects of medications limit the utility of this measure.[7] Biochemical indicators of neuronal injury, such as the glial derived protein S100B,[8] cranial ultrasound, computed tomography, and magnetic resonance imaging, may all identify injury. Functional imaging with magnetic resonance spectroscopy, and isotope uptake scans, provides activity information, but, as snapshots, do not indicate reversibility or clinical severity. While each of these modalities offers a unique view on cerebral structure or function, none offers a continuous indicator of a pathophysiologic process associated with injury. At this time, the best continuous window into processes likely to result in cerebral injury appears to be near-infrared spectroscopy.

This technique can be used to assess the relative saturation of haemoglobin in cerebral capillaries, thus

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approximating a venous-weighted measure of tissue oxygenation. The measure is regional, not global, and sources of variation include the location of the probe, local cerebral activity, and individual differences. Despite these limitations, indexes of brain oxygenation derived from the technique have been related to impaired cerebral oxidative metabolism when regional saturations of haemoglobin approach 40 percent.[9] Assessment of cerebral brain oxygenation in this fashion has been related to biochemical[10] and histologic[11] markers of brain injury. Abnormalities in cerebral autoregulation detectable by near-infrared spectroscopy have been associated in premature infants with germinal matrix haemorrhage and periventricular leukomalacia, lesions typically resulting from hypoxic or ischaemic cerebral injury.[12] Thus, near-infrared spectroscopy can detect, albeit imperfectly, ischaemic conditions likely to induce neuronal injury. Perhaps more importantly, the measure is continuous, real-time, and non-invasive, factors that facilitate its use in children to help guide ongoing therapy.

Abnormal neurologic function in the intensive care unit may result solely from the sedative effects of drugs, and stereotypic responses to surgical trauma. Behavioural withdrawal and reduced responsiveness, however, present nearly universally in postoperative patients, may also indicate prior intraoperative injury now manifesting as systemic dysfunction, potentially reversible neuronal dysfunction resulting from ongoing pathophysiology, or the spectrum of irreversible, reversible, and potential injuries related to modifiable and non-modifiable risk factors. In animal models, the incidence of altered cerebral blood flow and metabolism far exceeds the incidence of detectable early behavioral abnormalities, emphasizing the inadequacy of clinical signs in identification of injury.[13] Identification of conditions likely to cause neuronal injury affords the opportunity to interrupt the pathway of physiologic risk from reversible dysfunction to irreversible injury, both by identifying patients in need of specific intervention, and by providing information about the efficacy of interventions.

Known pathophysiology of perioperative ischemic injury

Pathophysiologic mechanisms accounting for neurologic injury in the operating room include inadequate periods of cooling,[14] prolonged circulatory arrest,[15] strategies for management of cardiopulmonary bypass which reduce cerebral blood flow, profound hypotension, extreme anemia, hyperthermia after cardiopulmonary bypass,[16] and embolic phenomenons. In children, global ischaemic mechanisms seem to predominate over other mechanisms as the major cause of injury to the central nervous system.[17] Strategies in children which favourably impact the relationship of the supply of, and demand for, oxygen for the brain, such as adequate cooling prior to circulatory arrest,[18] pH-stat blood gas management,[19,20] control of aorto-pulmonary runoff,[21] limited duration of circulatory arrest,[22] higher haematocrit during cardiopulmonary bypass,[11,23] avoidance of hyperthermia,[16] and continuous perfusion versus techniques of circulatory arrest,[24] have generally been associated with improved neurologic outcome. Intraoperative management directed at preventing cerebral desaturation detected by near-infrared spectroscopy probably reduces the incidence of acute postoperative neurologic abnormalities.[25]

Although the limits of safety for deep hypothermic circulatory arrest continue to be debated, models of cellular oxygen kinetics indicate that cerebral metabolism will become substrate-limited at about 40 minutes of circulatory arrest at 18 degrees centigrade,[15] that uptake of oxygen from haemoglobin ceases after a maximum of 40 minutes,[9] that cerebral oxygenation is better preserved during arrest in neonates than in infants and children,[26] that profound hypothermia may interfere with the use of oxygen despite an adequate supply,[27] and that recovery of cerebral metabolism is impaired after circulatory arrest compared to profound hypothermia alone.[28,29] The impaired recovery of cerebral metabolism following circulatory arrest is partially manifested by altered autoregulation, since extraction during hypoxia and hypotension are impaired following circulatory arrest.[30] This cerebrovascular lesion, present for up to six hours after arrest,[31] may be partially reversed by blockade of the thromboxane A2 receptor[32] and modified ultrafiltration,[33] suggesting that microvascular occlusion and oedema may play a role in impaired recovery of cerebral blood flow and metabolism after circulatory arrest. Increased heterogeneity in microvascular flow-metabolism coupling has been suggested as the functional consequence of the cerebrovascular lesion.[34] Further data indicate that cortical oxygenation is preserved better with pH-stat than alpha-stat management prior to circulatory arrest,[35] and that strategies to increase cerebral delivery of oxygen after circulatory arrest ameliorate injury.[17] Collectively, these data have provided significant insight into the mechanisms of ischaemic cerebral injury during cardiopulmonary bypass, and imply that even with metabolic suppression from hypothermia, physiologic risk occurs both during and after a period of circulatory arrest.

Strategies to avoid interruption of cerebral perfusion have been facilitated by improvements in techniques used for perfusion. Pigula et al.[36] demonstrated the technical feasibility of continuous regional perfusion at low rates of flow during neonatal repair of the aortic arch in patients with hypoplastic left heart syndrome,

speculating that the technique would reduce the risk of cerebral injury related to circulatory arrest.[36] While their speculation may be correct, ischaemic cerebral injury may still result from inadequate flow of blood to the brain during cardiopulmonary bypass, and during periods of circulatory inadequacy both before and after the time spent in the operating room.

Changes in regional oxygenation detected using intraoperative and postoperative near-infrared spectroscopy

We systematically evaluated both cerebral and somatic perfusion using near-infrared spectroscopy during the Norwood procedure for hypoplastic left heart syndrome using a pH-stat high-haematocrit hypothermic perfusion strategy, including near-continuous regional perfusion of the brain at low rates of flow.[37] The pattern of tissue oxygenation is shown graphically in Figure 1. Regional perfusion at low flows was an effective strategy in maintaining cerebral oxygenation during repair of the aortic arch, and recovery of somatic oxygenation was rapid during whole-body reperfusion. Our data indicated, nonetheless, that cerebral oxygenation remained at risk following separation from cardiopulmonary bypass despite avoidance of circulatory arrest. Although absolute regional thresholds for saturation of oxygen are not known for individual patients, data from Kurth et al.[38] indicates that the oxidative metabolism providing cortical cellular energy is limited at regional values for saturation of oxygen in the range from 35 to 44 percent.[38] Using a cutoff for saturations of oxygen of 50 percent, our data indicated a progressively increasing risk of cerebral desaturation in the period between weaning from cardiopulmonary bypass and transfer to the intensive care unit (Fig. 2).

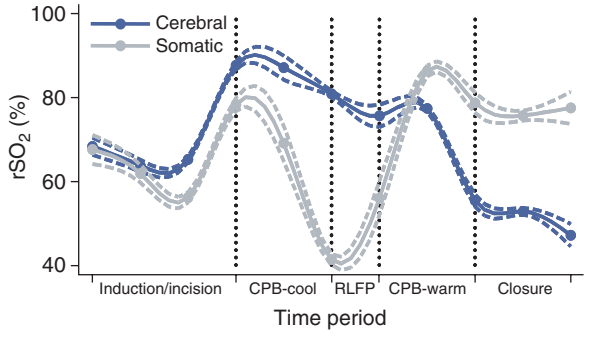

Figure 1.
Changes in cerebral and somatic regional saturations of oxygen during phases of Norwood repair in neonates with hypoplastic left heart syndrome. CPB-cool: cooling on cardiopulmonary bypass; RLFP: regional low-flow perfusion to head via the innominate artery at 18 degrees centigrade; CPB-warm: warming on cardiopulmonary bypass. Data from Hoffman et al.[37]

These results have driven us to extend the use of monitoring with near-infrared spectroscopy first to the postoperative unit, and more recently to the preoperative unit, in attempts to detect and treat conditions associated with cerebral hypoxia. The early postoperative period is typically characterized by reduced cardiac output, and the superimposition of altered cerebral autoregulation during this period results in a high risk of cerebral hypoperfusion. In Figure 3, we show the trend in regional cerebral saturation of oxygen in nine infants after the Norwood procedure, which mirrors the trend in global economy for oxygen as indicated by venous saturations of oxyhaemoglobin.

Strategies to increase cerebral oxygenation

Postoperative myocardial dysfunction, and systemic-pulmonary runoff in patients with mixing physiology,

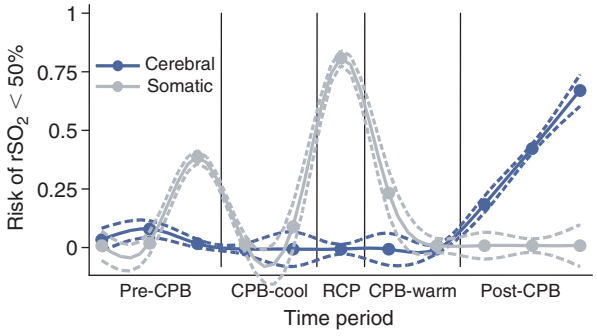

Figure 2.
The risk of regional saturations of oxygen decreasing to less than 50 percent during phases of Norwood repair. CPB-cool: cooling on cardiopulmonary bypass; RLFP: regional low-flow perfusion to head via the brachiocephalic artery at 18 degrees centigrade; CPB-warm: warming on cardiopulmonary bypass. Data from Hoffman et al.[37]

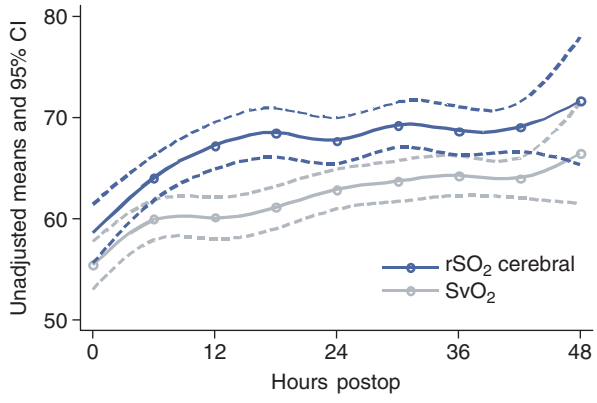

Figure 3.
Average trends in regional cerebral saturations of oxygen (rSO_2) and venous oxyhaemoglobin saturation for the first 48 hours after the Norwood repair in nine neonates. Data from Hoffman et al.[39]

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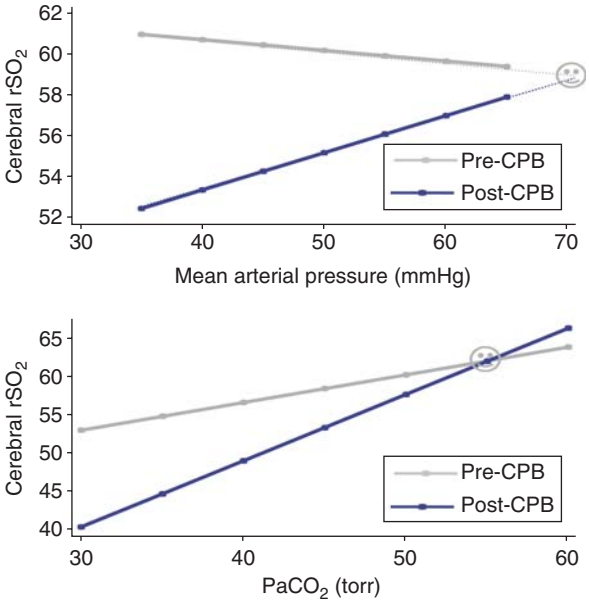

Figure 4.
Predicted values for regional cerebral saturations of oxygen (rSO_2) from a multiple linear model constructed from data obtained during the Norwood procedure. Variables held constant include haematocrit of 40 percent, arterial oxygen saturation of 80 percent, and temperature of 37 degrees centigrade. Cerebral oxygenation is more responsive to changes both in arterial blood pressure and partial pressure of carbon dioxide. Data from Hoffman et al.[37]

Table 1. Interventions to increase cerebral oxygenation.

Physiologic factor	Intervention
Increase cerebral perfusion pressure	Increase arterial blood pressure
	Increase systemic vascular resistance
	Increase cardiac output
	Reduce central venous pressure
Increase arterial oxygen content	Transfuse red cells
	Raise arterial partial pressure of oxygen
Reduce cerebral vascular resistance	Raise arterial partial pressure of carbon dioxide
Reduce cerebral metabolic rate	Control hyperthermia
	Sedation

make interventions to raise systemic vascular resistance less physiologically rational. Using the technique of multiple linear modeling, we showed that cerebral oxygenation was more sensitive to changes both in arterial partial pressure of carbon dioxide and blood pressure subsequent to regional cerebral perfusion at low rates of flow (Fig. 4). The intervention that best increases cerebral perfusion without increasing afterload, therefore, is deliberate induction of hypercapnia when alveolar ventilation is controlled. Other interventions to raise regional cerebral saturations of oxygen are summarized in Table 1.

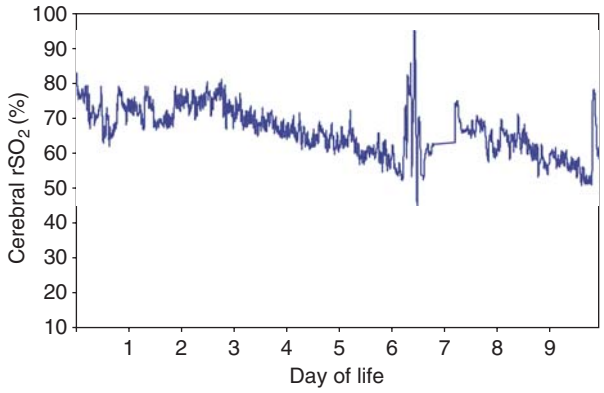

Figure 5.
The regional cerebral saturation of oxygen for a neonate with hypoplastic left heart syndrome was continuously obtained using near-infrared spectroscopy for the first ten days of life. The Norwood procedure was performed on the sixth day of life. Management was successful in avoiding periods of cerebral desaturation.

Extended monitoring with near-infrared spectroscopy in patients at high risk for cerebral ischaemia has shown that multiple brief periods of cerebral desaturation are commonplace. Currently, we attempt to monitor all neonates with hypoplastic left heart syndrome from the time of admission to discharge from hospital, aiming to intervene should measures of regional saturation of oxygen in the brain reduce to less than 50 percent, thus hoping to avoid conditions associated with ischaemic injury. The record of one such patient is displayed in Figure 5, revealing no periods of severe cerebral desaturation. We are currently testing the hypothesis that continuous availability of a measure of cerebral oxygenation will alter multiple aspects of treatment, and thereby reduce the occurrence of ischaemic brain injury in this population known to be at high risk.

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