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Long-term Outcomes

Monitoring the brain before, during, and after cardiac surgery to improve long-term neurodevelopmental outcomes

Nancy S. Ghanayem,[1,2,6] Michael E. Mitchell,[4,5,6] James S. Tweddell,[4,5,6] George M. Hoffman[2,3,6]

[1]*Department of Pediatrics,* [2]*Division of Critical Care,* [3]*Department of Anesthesia,* [4]*Department of Surgery, Division of Cardiothoracic Surgery, Medical College of Wisconsin;* [5]*Herma Heart Center at Children's Hospital of Wisconsin and* [6]*Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America*

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INNOVATION IN SURGICAL AND MEDICAL management of cardiac disease has generated a dramatic improvement in operative survival. Along with these favourable results in terms of survival is the heightened awareness of neurologic complications, which often become evident beyond the early postoperative period. A large, multicentre prospective study found serious neurologic injury occurs in about one-twentieth of patients after myocardial revascularization in adults.[1] More subtle evidence of persistent cognitive decline and functional impairment has been shown to occur in over two-fifths of such patients.[2] Acute neurologic abnormalities are reported in up to one-fifth of infants and children who undergo cardiac surgery.[3–6] Lasting impairments in cognitive, motor, and expressive functioning have been reported in up to three-fifths of children who have undergone complex cardiac surgery during infancy.[7] Specifically, gross and fine motor delays, visual-spatial problems, language deficits and long-term emotional and behavioural problems have been found.[8–13]

Risk factors for cerebral injury

Recent investigation of neurologic injury associated with congenital cardiac disease has led to a growing realization that neurologic abnormalities are multifactorial in nature. Previously, neurologic injury was regarded as an intraoperative phenomenon and the result of cardiopulmonary bypass, deep hypothermic circulatory arrest, inadequate cooling, blood gas management and haemodilution.[3,8,9,14–16] More recent data support the notion that the risk of neurologic impairment extends beyond the operating room for the infant or child with congenital cardiac disease. Genetic syndromes and polymorphisms, structural malformations, abnormalities in the flow of blood, and microcephaly have also been identified prior to surgery, and have variably been associated with neurologic impairment and global developmental delay.[9,12,17–20] Significantly, preoperative neuroimaging has identified abnormal cerebral metabolism, ischaemia, and periventricular leukomalacia, all of which potentially influence neurodevelopment independent of the risks associated with cardiac surgery.[21–24]

In contrast to the aforementioned aetiologies for neurologic dysfunction are commonly encountered modifiable risk factors that can lead to either global or focal ischaemic cerebral injury. These risks factors represent physiologic vulnerability that is potentially amendable to alterations in perioperative strategies. Management of these patients should be targeted at preventing hypoxia, embolisation, hyperthermia, hypotension, and hypocarbia not only as a means of reducing mortality, but also with a clear goal of minimizing the potential for cerebral injury.

Monitoring the brain

To date, our ability to prevent neurologic abnormalities during the perioperative period is limited by the multifactorial nature of cerebral injury, and lack of tools to identify physiologic vulnerability. Over recent decades, various monitoring modalities have been used for real-time detection of cerebral hypoxia, abnormalities of perfusion, and electrophysiological

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Correspondence to: Nancy S. Ghanayem MD, Cardiac Intensivist, Assistant Professor, Pediatrics (Critical Care), Associate Medical Director, PICU, Children's Hospital of Wisconsin, Medical College of Wisconsin, 9000 West Wisconsin Avenue, Milwaukee, Wisconsin 53122, United States of America. Tel: +1 414 266 3396; Fax: +1 414 266 3563; E-mail: NGhanayem@aol.com

derangements. Currently, near infrared spectroscopy, venous oximetry, transcranial Doppler, and continuous electroencephalography are applied in the perioperative period for the purpose of identifying risk factors for brain injury.

Venous oximetry

Prior to the adoption of near infrared spectroscopy for perioperative monitoring, continuous venous oximetry from the superior caval vein was used in our institution for postoperative management after the Norwood operation. From our early experience with venous oximetry, we reported an anaerobic threshold for systemic delivery of oxygen that occurs when venous saturation approaches 30 percent.[24] We recently investigated the critical threshold at which point neurologic function might be compromised. In a small pilot study of preschool aged children, venous saturation that approached 40 percent was the best haemodynamic predictor of late neurologic dysfunction, particularly in visual motor integration and behavioural functioning (Fig. 1).[25] The benefit of venous oximetry over other more commonly employed modalities is likely related to the technique providing a better measure of cerebral economy in the use of oxygen. Although these early data are encouraging in identifying periods of vulnerability to the brain, use of continuous venous oximetry is limited by the invasive technology, making it less feasible than currently available noninvasive monitors.

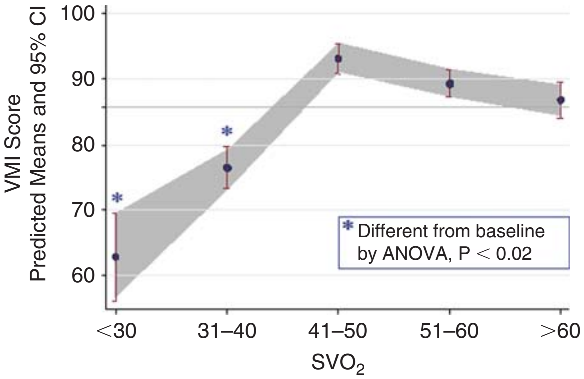

Figure 1.
The visual motor integration (VMI) score was modelled as a function of hourly haemodynamic data and cardiopulmonary bypass parameters. The model reveals the effect of systemic venous oxygen saturation (SVO_2) *on outcome, with a break point systemic venous oxygen saturation of 40 percent and less. In this cohort, prolonged circulatory arrest, venous oximetry, mean arterial blood pressure and arterial partial pressure of carbon dioxide accounted for almost four-fifths of the variance in a composite neurodevelopmental outcome score (data not shown).*

Near infrared spectroscopy

Near infrared spectroscopy provides a real-time window into regional oxygenation of the cerebral tissues, and has been validated with jugular venous saturation.[26,27] This non-invasive technology provides a venous-weighted approximation of the saturation of oxygen in the haemoglobin within tissue.[28] Modern renditions of this technology use modifications of Beer's equation, and the differential absorption of different wavelengths of light by haemoglobin as it associates with oxygen. Photons are injected into the forehead, scattered through tissues and return to exit the skin after following a banana-shaped reflectance path. Currently, only the Somanetics INVOS device is approved by the Food and Drug Administration for monitoring of the oxygen in the tissues of the brain. This specific device utilizes a source-detector distance of 4 centimetres, and measures the oxyhaemoglobin saturation of the cerebral tissues 2 centimetres beneath the skin. Subtraction of the shallow light path from the deep light path will approximate the oxygenation of the brain, while eliminating contamination from extracranial tissues such as the skin and skull. Factors which influence cerebral oxyhaemoglobin saturation include cerebral blood flow, haemoglobin, arterial oxygen saturation, arterial partial pressure of carbon dioxide, and cerebral metabolic rate.

Baseline cerebral oxyhaemoglobin saturation: Near infrared spectroscopy has been extensively studied in animal models and in clinical applications over the past few decades. Data is increasingly reported as to normative and pathologic cerebral oxyhaemoglobin saturations in adults and children. Healthy adults have been found to have a mean cerebral oxyhaemoglobin saturation of 70 percent, while adults subjected to cardiac surgery have a mean baseline cerebral oxyhaemoglobin saturation of 65 percent.[29] Baseline cerebral oxyhaemoglobin saturations in the infant and older children have been less well described. Early work by Kurth et al.[30] described baseline values in infants and children with various congenital cardiac lesions. Healthy children, and those with acyanotic disease, had baseline saturations similar to the adult population, whereas those patients with cyanosis had mean values between 47 and 57 percent.[30] Recently, Fenton et al.[31] reported similar findings that were physiologic specific rather than lesion specific. Patients with clinically evident left-to-right shunts with and without cyanosis had lower baseline cerebral oxyhaemoglobin saturations than those patients without left-to-right shunting, regardless of arterial saturation of oxygen. Within this series, perioperative mortality was highest in patients with both left-to-right shunting and cyanosis, with a mean baseline cerebral oxyhaemoglobin saturation in the nonsurvivors of 47 percent, compared to 65 percent in survivors.[31]

Critical threshold: Less well defined in infants and children are the critical cerebral oxyhaemoglobin saturations at which cerebral hypoxia results in adverse neurologic outcomes. In adults who underwent automated internal cardiac defibrillator testing with induced ventricular fibrillation, abnormal electroencephalography was associated with cerebral hypoxia, and corresponded to cerebral oxyhaemoglobin saturations of 47 percent.[32] A similar, lower ischaemic threshold was observed in piglets subjected to circulatory arrest. In this animal model, the critical threshold for cerebral oxyhaemoglobin saturation was defined by production of lactate, electroencephalographic changes, and depletion of adenosine triphosphate.[33] The study by Kurth et al.[30] of cerebral oxyhaemoglobin saturation during deep hypothermic circulatory arrest noted a nadir at 60 to 70 percent below baseline; and if sustained greater than 40 minutes, there was no additional uptake of oxygen by the brain, supporting previous work which found adverse neurologic sequels after prolonged periods of circulatory arrest.[16,34,35] Sakamoto et al.[36,37] identified similar findings in the animal model with variations in cooling, haematocrit and temperature, and found behavioural and histologic abnormalities if the nadir for cerebral oxyhaemoglobin saturation was sustained greater than 25 minutes at conditions of higher temperature, lower haematocrit, and with alpha stat blood gas management.

Clinical evidence: Over the past decade, near infrared spectroscopy has become a common intraoperative neuromonitor in many adult cardiothoracic centres. Clinical studies in adults subjected to cardiac surgery have shown that a decline in cerebral oxyhaemoglobin saturation greater than 20 percent from baseline, or absolute oxyhemoglobin saturation less than 50, corresponds to long-term cognitive decline, frontal lobe injury, increased incidence of stroke, prolonged mechanical ventilation, and prolonged hospitalization.[38–40] A landmark study by Austin et al.,[5] that investigated intraoperative neurophysiologic monitoring modalities in children undergoing cardiac surgery, found that cerebral oxyhaemoglobin desaturation accounted for almost three-fifths of events felt to place the brain at risk. Patients who underwent interventions to improve upon cerebral dysoxia had significantly fewer neurologic complications when compared to those patients with cerebral oxyhaemoglobin desaturation who were not intervened upon. Only three-tenths of patients did not manifest concerning neurophysiologic events and had a neurocomplication incidence of 7 percent, similar to the group of patients who had management altered based upon cerebral oxyhaemoglobin desaturation.

Clinical application: Application of near infrared spectroscopy has predominantly been in the operating room. Variations in bypass strategy alone, which include cooling, temperature, haematocrit, blood gas management, and duration of deep hypothermic circulatory arrest, have been shown to have profound effects on cerebral oxygen saturations. Each of these parameters represents a modifiable neuroprotective strategy. Real-time assessment of such neuroprotection, however, remains challenging. To date, near infrared spectroscopy is the most feasible technology. As explained above, in the study of Austin et al.,[5] desaturation of cerebral oxyhaemoglobin accounted for the majority of neurophysiologic abnormalities, and was often associated with perfusion imbalance, and less commonly with depth of the anaesthetic. The surgeon was directly involved with one-quarter of the interventions, which included repositioning of the aortic or venous cannulas, or the vascular clamp. The perfusionist intervened in over half the detected events through alterations in pump flow or perfusion pressure. The anaesthesiologist was responsive to the remainder of events through correction of problems with the airway, adjustment in depth of anaesthesia, and treatment with anticonvulsant agents.[5] These data support the notion that near infrared technology in the operating room benefits multiple aspects of intraoperative care, and that it requires attention from the cardiac team rather than a single individual.

The pattern of intraoperative oxygenation of the cerebral tissues during the first stage of palliation for hypoplastic left heart syndrome has been previously reported by Hoffman et al.[41] (Fig. 2). These data show cerebral oxygenation remains at risk after

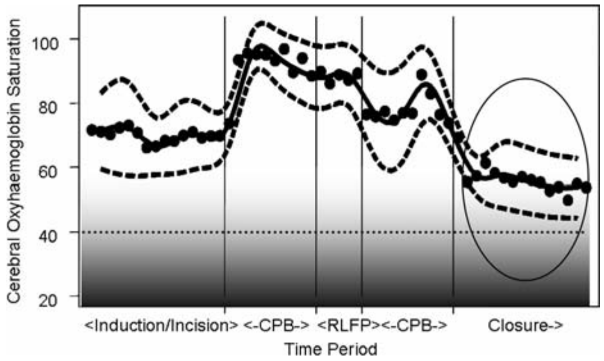

Figure 2.
Changes in cerebral oxyhaemoglobin saturation during the Norwood operation for hypoplastic left heart syndrome. CPB represents cardiopulmonary bypass and RFLP represents regional low-flow perfusion to head via the brachiocephalic artery at 18 degree Centigrade. The highlighted oval area after separation from bypass identifies the potentially critical fall in cerebral oxyhaemoglobin saturation that extends into the early postoperative period.

separation from cardiopulmonary bypass despite avoidance of circulatory arrest. The post-bypass vulnerability of cerebral oxygenation extends to the early postoperative period, prompting routine use of near infrared spectroscopy in the intensive care unit for postoperative care. Use of near infrared spectroscopy in the postoperative period has more clearly illustrated that cerebral oxygenation is increasingly responsive to changes in partial pressure of oxygen and arterial blood pressure for several hours subsequent to the completion of bypass. Hence, such monitoring has led to avoidance of hypocapnia, augmentation of blood pressure, and finally, treatment of anaemia as means to maintain cerebral oxyhaemoglobin saturation greater than 50 percent, a target which is above reported critical thresholds in adult and animal models. Dent et al.[23] recently reported a similar threshold in infants who underwent hypothermic bypass with antegrade cerebral perfusion. They found that sustained cerebral oxyhaemoglobin saturation less than 45 percent for greater than 180 cumulative minutes predicted the frequency of new ischaemic lesions as revealed by magnetic resonance imaging.

The use of near infrared spectroscopy at our institution has extended to the preoperative neonate with complex congenital cardiac disease, especially those with hypoplastic left heart syndrome. Historically, management of these infants included targeting arterial saturation in order to optimize systemic delivery of oxygen. In particular, common practices often reduced the fraction of inspired oxygen to subatmospheric levels. In a study of such patients just prior to staged palliation, Ramamoorthy et al.[42] compared 17 percent to 21 percent inspired oxygen. Although there was not a significant difference in arterial saturation, cerebral oxyhaemoglobin saturation was significantly lower with the hypoxic mixture, calling into question not only the effectiveness of a hypoxic gas mixture for circulatory balance, but also the safety of this strategy. At our institution, preoperative management of patients with hypoplastic left heart syndrome is, in large part, guided by continuous near infrared spectroscopy initiated at admission, and has made the use of nitrogen as a means of controlling circulation obsolete. As a result, preoperative cerebral oxyhaemoglobin desaturation is routinely avoided.

Transcranial Doppler

Transcranial Doppler is able to determine real-time differences in cerebral blood flow, and quantify the aggregate microembolic high-intensity transient signals (Companion III, Nicolet Vascular, Madison, WI). A 2 megaHertz probe held in place over the closed eyelid with a custom fixation device is used to insonate the intracranial carotid artery. The flow-velocity spectral envelope is trended throughout the case, and stored digitally for subsequent analysis. The device also quantifies the aggregate microembolic high-intensity transient signals, and reports with characteristic audio clicking representing each event. Moderate hypoperfusion is typically associated with a greater than 60 percent reduction in peak velocity, while severe hypoperfusion leads to a greater than 80 percent decline. Production of high-intensity transient signals at a rate of greater than 1 per minute is considered to be clinically significant.

Clinical evidence: Transcranial Doppler has predominantly been used as a research modality better to understand cerebral blood flow in response to cardiopulmonary bypass with either continuous cerebral perfusion or deep hypothermic circulatory arrest.[43–46] Carbutti et al.[47] documented a single case of acute ischaemic stroke after cardiac arrest, with retrospective documentation of asymmetrical cerebral blood flow using systematic postoperative transcranial Doppler recording. Fearn et al.[48] found that both transcranial Doppler measurements and high-intensity transient signals predicted poor attention at one week and memory loss, respectively. Abu-Omar et al.[49] found that microembolization, as detected by transcranial Doppler, was higher in patients undergoing on-pump coronary artery bypass grafting as opposed to off-pump surgery, and that increased number of high-intensity transient signals correlated with increased abnormalities on functional magnetic resonance imaging.

Clinical application: As an intraoperative tool, transcranial Doppler is able to diagnose perturbations in perfusion based on real time changes in the signal waveform. For example, inflow obstruction is immediately apparent as decreased peak Doppler flow signal, and is typically the result of malposition of the arterial cannulas, obstruction of the arterial line, changes in perfusion pressure, or changes in flows through the pump. Outflow obstruction is immediately recognized by decreased diastolic flow signal, and indicates obstruction to venous drainage from the head, typically problems with the superior caval venous cannula, kinking of the venous line, post snaring a large left sided superior caval vein, or after constructing a high pressure cavopulmonary anastomosis. Reversal of flow is visualized by waveform below baseline and can be used to quantify flow during retrograde cerebral perfusion. Flow asymmetry is readily detected, and is often the result of malposition of cannulas, or specific surgical manipulations.

In addition to changes in flow signal, transcranial Doppler provides continuous monitoring for embolic events, as indicated by high-intensity transient signals (Fig. 3). Transcranial Doppler is able to distinguish air from particulate matter embolization, based

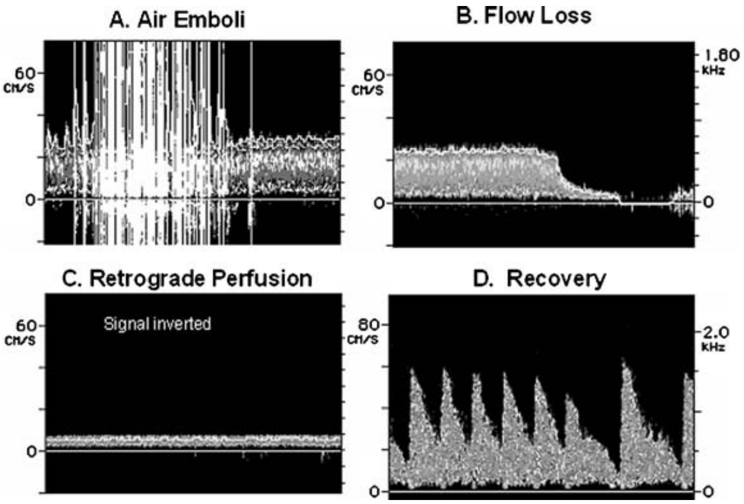

Figure 3.
Changes in the flow-velocity spectrum in the right middle cerebral artery associated with air embolism as detected by transcranial Doppler. The sudden appearance of high-intensity transient signals (intense, white, full-scale vertical deflections) is suggestive of gas bubbles (A). A transient loss of the flow-velocity signal occurred during hypothermic circulatory arrest (B). Establishment of retrograde cerebral perfusion through the superior caval vein was documented by a low-velocity signal of opposite direction (C). This retrograde flow is shown. The signal has been inverted to facilitate automatic velocity measurement and trending. After removal of cerebral air, effective pulsatile antegrade flow was restored (D). Data from Yeh et al.[54]

on the nature and frequency of the signal. This data is readily communicated to the surgeon by way of an audio signal or clicking sound, with each click representing a single high-intensity transient signal. This information is particularly valuable during de-airing manoeuvres at the conclusion of the case. Such high-intensity transient signals during dissections at reoperations are often the first indication of an injury to the left atrium, rapid recognition and treatment of which can prevent significant neurologic impairment.

Electroencephalography

Continuous quantitative electroencephalography is able to compare perfusion-related changes in neocortical synaptic activity as measured with quantitative. Two-channel bipolar recordings (A-1050, Aspect Medical, Newton, MA) are obtained using self-adhesive silver-silver chloride electrodes attached to the scalp overlying frontal and central cortical regions bilaterally. Fourier analysis of the electroencephalogram is used to generate a series of numeric descriptors, including median and 95 percent spectral edge frequencies, total power and suppression ratio. Mild cerebral ischaemia involving the cortex is typically associated with a sudden decrease of greater than 50 percent in both frequency indexes and increase in power. Moderate ischaemia produces further declines in frequency, and an increasing suppression ratio, this being the fraction of each minute with an isoelectric "flat-line" electroencephalogram. Severe ischaemia is characterized by a profound decrease in power, and a near-maximal suppression ratio.

Clinical evidence: Not surprisingly, a relationship exists between perioperative seizures and late neurodevelopmental morbidity.[3,50,51] Gaynor et al.[52] reported an incidence of electrographic seizures in one-tenth of patients who underwent hypothermic arrest in the absences of clinical seizures. These data would support findings by Helmers et al.,[53] namely that the incidence of electrical seizures following paediatric open heart surgery was 3 times the incidence of clinically detected seizures. Early recognition of electrical seizures through perioperative continuous monitoring could allow for potentially neuroprotective interventions, such as augmenting the depth of anaesthesia, administering anticonvulsant therapy or altering bypass strategies such as rates of flow, management of blood gases, or temperature.

Clinical application: Intraoperative electroencephalography is continuously interpreted by a neurophysiologist or trained anaesthesiologist, and provides real-time confirmation of neurophysiologic states. Ischaemia is confirmed by slowing of the electroencephalogram, and is directly addressed by increasing flows through the pump flows, or adjusting the position of cannulas. Cooling for a planned period of circulatory arrest is continued until the electroencephalogram is flat-line, rather than for a pre-determined time point (Fig. 4). Successful rewarming after circulatory arrest is accompanied by successful return of electrical activity. Subclinical seizure activity detected perioperatively is treated with anticonvulsant medication, and results in immediate evaluation of an aetiology for the seizure. Despite the reported contributions of continuous electroencephalography in the perioperative period, routine use of this technology is complicated. It remains

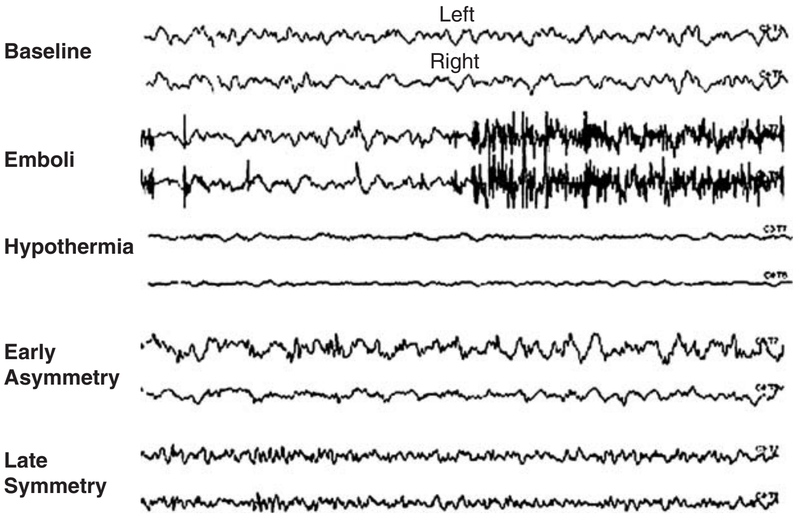

Figure 4.
Responses of cortical synaptic function to embolization, cooling, and gradual improvement in cortical perfusion and oxygenation. Waveform pairs were obtained from left and right frontotemporal derivations, respectively. The initially symmetric preinsult pattern was disrupted with high-frequency artifact, coincident with the appearance of ultrasonographic evidence of gaseous emboli in the flow-velocity spectrum shown in Figure 3. Rapid cooling to 26 degree Centigrate for neuroprotection suppressed synaptic activity and produced a near-flatline electroencephalogram. Oxygen imbalance in the right hemisphere (near infrared spectroscopy data not shown) was associated with a new electrical asymmetry as well. Both the amplitude and median frequency of the right hemispheric waveform are decreased. The following day, restoration of symmetric high-frequency electrical activity has occurred. Data from Yeh et al.[54]

challenging due to difficulty in interpretation from electrical signal interference and anaesthetic effects.

Multimodality monitoring

A growing number of centres are recognizing the power of multimodality monitoring during open heart operations in children. By combining near infrared spectroscopy with transcranial Doppler and electroencephalography, the cardiac team is provided with immediate recognition and with increased specificity of potentially modifiable events. Substantial literature supports the concept that injury to the nervous system is multifactorial, encompassing not only macro- and microembolisation, but also hypo- or hyperperfusion and imbalance of oxygen.[1,2] Interventional neurophysiology has shown that each of these pathophysiologic processes is detectable and alterable.[38] Simple and slight adjustments in the position of the patient or the perfusion cannula, blood pressure, arterial tension of carbon dioxide, or level of anaesthesia, are often all that is needed to prevent injury. As a result of these studies, those who now provide neuromonitoring for cardiac surgery have three distinct goals: to identify strategies associated with lower levels of neurophysiologic risk, to identify those risks in individual patients, and to guide treatment before irreversible injury ensues.

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