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Editorial

Cutting the Gordian Knot That Ties Intraoperative Conditions to Long-term Neurodevelopmental Outcomes in Children Undergoing Congenital Heart Surgery

SUBSTANTIAL PROGRESS has been made during the more than 80-year history of pediatric cardiac surgery. With improvements in surgical technique and patient survival, the focus has shifted to alleviating morbidity in young children requiring repair of complex congenital heart disease. Abnormal brain structural and functional outcomes are not infrequently observed in this vulnerable patient population; however, challenges remain to identify when they occur and how they relate to neurodevelopmental abnormalities. Contributing factors are probably multifactorial and may include preexisting conditions and syndromes, genetic abnormalities, sex, socioeconomic status, prolonged exposures to anesthetics and sedatives, acute or chronic impediments of oxygen and nutrient supply to the brain, inflammation, need for extracorporeal membrane oxygenation support, as well as prolonged periods of nonpulsatile perfusion on cardiopulmonary bypass (CPB) and deep hypothermic circulatory arrest (DHCA). Clinicians and researchers continue to explore novel noninvasive technologies, such as electroencephalograph (EEG) and near-infrared spectroscopy (NIRS), to continuously monitor brain function before, during, and after surgical repairs. Accordingly, for this month's edition of the ***Journal,*** Alkhatip and coworkers performed a systematic review of the literature reporting on the use of EEG to monitor brain function in children undergoing cardiac surgery with CPB and DHCA.[1]

More than 70 years ago, pioneering cardiac surgeries such as the systemic-to-pulmonary artery shunt for tetralogy of Fallot primarily aimed at palliation and prolongation of life.[2] Contemporary outcomes, however, are measured by the lack of physiologic abnormalities after surgical repair and the long-term quality of life, which is strongly correlated with neurodevelopmental outcomes.[3] In the 1960s, when CPB techniques were being developed, DHCA was first popularized by Kirklin et al.[4,5] This perfusion technique involves systemic cooling of the entire body to a temperature of less than 20 ˚C and complete cessation of the blood circulation. DHCA quickly became widely popular because it reduced exposure time to the more primitive CPB circuits in use at that time, provided a bloodless field unencumbered by CPB cannulae for the surgeon, and thereby facilitated increasingly complex repairs of intracardiac lesions and aortic arch defects. It was thought that hypothermia bestowed protection to nutrient-starved vital organs, most importantly the brain. However, as DHCA extended beyond 45-to-60 minutes, the technique's safety to prevent hypoxic-ischemic brain damage and subsequent adverse neurodevelopmental outcomes was called into question. Accordingly, alternative strategies, such as low-flow (LF) CPB and intermittent reperfusion during DHCA were introduced.[6,7] Although it seems intuitive to believe that full-flow or even LFCPB may lead to better neurodevelopmental outcomes than those observed after complete cessation of blood flow during DHCA, two randomized,controlled trials have failed to demonstrate significant differences in neurologic outcomes comparing these perfusion techniques.[8,9]

The pursuit of improving long-term neurologic outcomes in infants with complex congenital heart disease is intimately linked with the search for suitable, noninvasive, continuous bedside techniques to observe brain homeostasis and to guide neuroprotective strategies during pediatric cardiac procedures. However, "predicting" adverse neurologic outcomes is hampered by knowledge gaps in identifying the underlying mechanisms, associated brain structural correlates, and challenges in selecting suitable monitoring techniques. Monitoring of cortical electrical activity with an electroencephalogram, for example, currently is not routinely utilized in the operating room or the cardiac intensive care unit. When ubiquitously used under investigational conditions after neonatal cardiac surgery, postoperative electrographic seizure activity has been observed in approximately 10% of patients, even when full-flow CPB is

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used during surgery.[10] Although intuitively useful to potentially identify patients at risk for neurologic injury and in guiding cooling strategies,[11] outcomes data have yet to demonstrate any association of EEG monitoring with improved neurodevelopmental results. Continuous monitoring of the brain's oxygenation status using NIRS during full-flow CPB or oxygen depletion during DHCA requires further technologic advances and outcomes studies (personal communication, Daniel J. Licht, MD, 2021). Retrospective analyses have been unable to clearly link intraoperative events with postoperative neurodevelopmental abnormalities, which is compounded by the shortcomings of current monitoring technologies and lack of defined parameters that can predict long-term neurologic outcomes.

In this context, Alkhatip et al. performed a systematic review and meta-analysis of the available literature using EEG monitoring after cardiac surgery with CPB and DHCA in children. They identified 19 relevant studies, from 1990 to 2018, covering a wide range of surgical repairs, with postoperative follow-up varying from two days-to-ten years. The authors correctly identified and attempted to adjust for the heterogeneity of cardiac diagnoses and changes in CPB technology and DHCA management over this long period of time.

Significant findings included (1) a higher rate of seizures detected on EEG (14.9%) versus clinically observed (12.9%); these seizures were associated with increased neurologic abnormalities and delayed neurodevelopment outcomes. (2) longer DHCA times were associated with increased rates of EEG seizure activity and neurologic abnormalities, although a distinct time threshold for the safe use of DHCA or an increased risk for neurologic abnormalities could not be identified. (3) compared with LFCPB, patients undergoing DHCA were more likely to develop seizures, more frequently demonstrated neurologic abnormalities, and scored lower on neurodevelopmental tests. However, no outcome differences were found between DHCA and antegrade cerebral perfusion. Moreover, the authors pointed out the heterogeneity of perfusion conditions, such as cooling and warming durations, temperature targets, as well as pH management before and after DHCA, across studies.

The authors discussed the utility of EEG to verify isoelectricity prior to instituting DHCA. Importantly, one of the reviewed studies found that only 10% of neonates achieved isoelectric EEG during DHCA when cooled to 20.2 ˚C, suggesting that cerebral electrical activity and metabolism had not been minimized in a great majority of patients, putting them at risk for cerebral ischemia and abnormal neurologic outcomes.[12]

Although not within the scope of their meta-analysis, Alkhatip et al. discussed the benefits of combined monitoring of EEG and NIRS. Although EEG measures the demand side of the cerebral supply-demand balance by monitoring cerebral electrical activity, and hence metabolic and oxygen requirements, NIRS can quantify both cerebral oxygen supply and demand via monitoring cerebral blood flow and oxygenation. EEG provides superior temporal resolution and potentially can monitor across a larger area of the brain, whereas NIRS offers better localization. In piglet models instituting deliberate cerebral ischemia, NIRS was more sensitive than EEG in detecting ischemia.[13] In addition to cardiac surgery, NIRS also has been used to monitor cerebral oxygenation in premature infants and neonatal noncardiac surgery, in which the brain is also at risk for ischemia.[14,15]

In summary, the systematic review and meta-analysis by Alkhatip et al. emphasized that, although significant progress has been made in the past 30 years, additional efforts are needed to improve neurodevelopmental outcomes after complex cardiac surgeries. Surgical and CPB techniques have been improving; however, our ability to monitor the neurologic consequences of these changes is lacking. Technologies to monitor brain homeostasis, cerebral blood flow, rate of cerebral oxygen metabolism, and quantitative tissue oxygen saturations still are underdeveloped. Without further developing these technologies, it is not possible to evaluate intraoperative interventions, with DHCA representing only one of them, in real time to truly evaluate their effects on long-term neurologic outcomes.

Conflict of Interest

The authors do not report any conflicts of interest.

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