animal studies and exploring possible pharmacologic therapy for children with CHD. Going forward, further integration with neuroscience research will be helpful in designing experiments to determine the complex cellular events underlying brain injury. Hopefully, the knowledge gained will lead to treatment to protect immature brains during pediatric cardiac surgery. As the present report and recent studies indicate, animal studies show great promise in elucidating the cellular etiologies of disturbed brain development in the CHD population and establishing new approaches for improvement of neurologic development.

References

Commentary: A miracle product, applied early and often

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Publications about nitric oxide (NO) topped 6000 per year through the early 2000s, describing actions in cardiovascular biology, cancer, immunology, and neurology. NO-mediated endothelial dysfunction underlies a broad array of diseases, and NO is a putative miracle product to the rescue. As some applications of NO in congenital heart surgery are maturing toward standard-of-care status, new clinical applications are emerging, some effective and some remaining good news only for piglets and rats.

Checchia and colleagues showed a reduction in serum inflammatory markers and myocardial injury and shorter mechanical ventilation and intensive care unit stay in pediatric patients undergoing tetralogy of Fallot repair who had NO delivered to the CPB circuit. A randomized prospective trial of children undergoing cardiopulmonary bypass (CPB) at...
moderate hypothermia shows that NO administered to the oxygenator during pediatric CPB reduces low cardiac output postoperatively by attenuating ischemia reperfusion injury, mitigating the generation of oxygen-free radicals.3

In the brain, microglia are involved with vascular morphogenesis and maintenance and neuroprotection but also neurodestruction and apoptosis. Much remains unknown about the responsible signaling pathways.4 Kajimoto and colleagues,5 in this issue of the Journal, explore NO, CPB, and the brain, showing a significant reduction of degenerating and apoptotic hippocampal neurons in the NO group compared with untreated piglets, in a model of 30 minutes of deep hypothermic circulatory arrest. Spectacular 3-dimensional images of a reduction in activated microglia with NO administration accompany the data to tell a compelling story of microglia standing down from an otherwise-destructive stance.

Hypothermia itself contributes to the magnitude of the inflammatory response to CPB in the brain.6,7 Cerebrovascular autoregulation is normal at normothermia, impaired at moderate hypothermia, and absent at deep hypothermia, at which point autoregulation is pressure-passive.8 Deep hypothermia is associated with hippocampal damage from deranged cerebrovascular autoregulation, damage felt to occur largely during reperfusion and rewarming. Further, the degree of hypothermia during CPB is correlated with an increase in circulating glial fibrillary acidic protein, a biomarker of brain injury and a predictor of neurodevelopmental abnormalities.9 Most current practices use little or no deep hypothermia.

Kajimoto and colleagues5 add enthusiasm for NO applied early and often, and more evidence that what is good for the extracranial organs is good for the brain. Compelling as these data are to the piglet under conditions of deep hypothermia, they may or may not translate to clinical validity. There are several established reasons for administering NO during CPB, and mitigating microglia-mediated brain damage may be among them, but the idea will be more compelling if the data uphold relevance at modest hypothermia or normothermia, the climate of modern clinical practice.

References