Ischemic Preconditioning for Neuroprotection of Infants Undergoing Cardiopulmonary Bypass for Correction of Congenital Heart Disease

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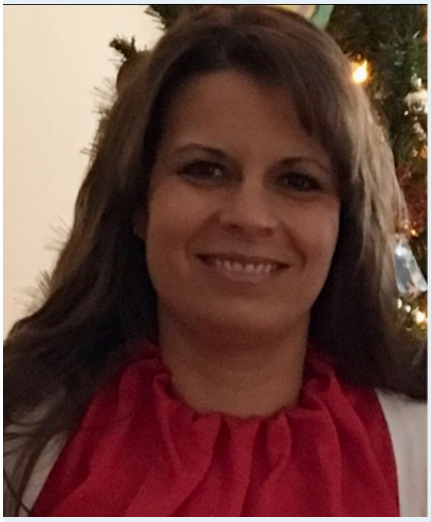

Neonates with congenital heart defects (CHD) are at increased risk of neurological injury due to various etiologies. Delayed or abnormal brain development increases that risk, as well as periventricular leukomalacia, which is the most common neuropathologic lesion found in preterm infants. It is associated with 20% of full-term infants with CHD and increases to greater than 50% post-surgery. This suggests an increased risk of white brain matter injury and possible delayed brain development. An immature brain increases the risk of micro emboli, oxidative stress, inflammation, and hemodynamic disturbances when theses infants are placed on cardiopulmonary bypass (CPB). One study showed a 10% risk of stroke in neonates with CHD and most occurring preoperatively.[1] Neonates with CHD also have unique hemorrhagic events due to hemosiderin deposits and an increased risk of air emboli or thromboembolism from either the cardiac lesion itself, the palliative surgical procedure, or the repair surgery. Postoperative conditions may lead to neurologic complications such as hyper coagulopathies, residual right-to-left shunts, low cardiac output syndrome, chronic cyanosis, and arrhythmias.[1]

As many as 50% of children with congenital heart defects will have neuropsychological defects by school age that affect the children, as well as their families. These neurological deficits may manifest as attention disorders or academic issues that lead to social and economic difficulties. These insults to the brain may not occur in surgery alone, but may occur in utero, the immediate post-natal period, or postoperatively. If a patient requires multiple operations, this may increase their risk of brain injury.[1]

Multiple neuroprotective interventions are in place to protect neonates undergoing CPB for CHD. Perioperative interventions that target prevention of neuronal cell damage, minimize cerebral oxygen demand, and optimize blood flow are taken prior to infants arriving in the operating room. Techniques in the operating room include deep hypothermic circulatory arrest (DHCA), continuous low flow CPB (as an alternative to DHCA), temperature-corrected (Ph-stat) blood gas management strategies during patient cooling, protocols for hemodilution, hypothermia, and rewarming during CPB. Pharmacologic therapies used to provide neuroprotection include anesthetic gases, methylprednisolone, and allopurinol but are not clinically proven to improve outcomes. These intraoperative strategies have been modified for over twenty years despite long term neuroprotective improvements.[1] Since the current strategies are not showing consistent, long term improvements, more must be done. Ischemic preconditioning is one method of interest.

"Preconditioning is a phenomenon in which prior exposure to sublethal insults results in up-regulation of endogenous defense mechanisms which then protect the organ system from subsequent lethal insults".[2, p.14]

Numerous animal studies have been conducted to measure the effects of ischemic preconditioning. One study using twelve newborn piglets that were subjected to ischemic preconditioning demonstrated a decrease in cardiac apoptosis and overall preservation of cardiac performance. Cardiac performance was measured by ejection fraction, cardiac index, and

stroke volume.[3] Since ischemic preconditioning was beneficial in a cardiac model, the technique was applied to protection in organs such as the brain.

Neurologic ischemic preconditioning was first introduced in a canine model in 1986.[4] A study using newborn pigs subjected them to 8% oxygen and 92% nitrogen for 3 hours. 24 hours later the piglets were exposed to hypoxic-ischemic events be breathing 5% 02, and at the same time manipulating the mean arterial pressure (MAP) to less than or equal to their baseline for 10 minutes. The results showed an increase in mRNA expression of the hypoxia-induced factor 1 alpha (HIF-1a) and its target gene, vascular endothelial growth factor (VEGF), which started at 0 hours and continued to rise for seven days.[5] This signified that hypoxia-conditioning provided protection against hypoxic ischemic injury in the newborn piglet and correlated with the pathophysiology of an asphyxiated human neonate. This HIF factor is a transcription factor that promotes hundreds of genes when hypoxia occurs. Some increase production of nitric oxide (NO), erythropoietin (EPO), glucose transporters, and angiogenesis. Anaerobic glycolysis and mitochondrial function preservation are all enhanced by the HIF 1a as well.[1]

The results of these studies were encouraging, and the discovery of remote ischemic preconditioning allowed the protective actions of ischemic preconditioning to be utilized in humans.[1]

Remote ischemic preconditioning was first demonstrated in 1993[4] and is achieved by applying a blood pressure cuff to the leg or arm to induce ischemic preconditioning to a distant target such as the brain or heart. Four cycles of ischemia lasting 5 minutes are then followed by 5 minutes of reperfusion. The exact mechanism of action is unknown. Neuroprotective benefits are thought to be derived from activation of mechanisms for cell survival, increased cerebral blood flow, and attenuation of neuroinflammation. Many hurdles regarding remote ischemic preconditioning continue to exist, such as the safety of producing limb ischemia with and without cooling therapy while on bypass. There is debate on the number and duration of ischemic cycles required to provide protection. Also unknown are what are the detrimental effects and the exact protective mechanisms.[6] However, clinical trials showed cerebral infarct was reduced by 70% in hypoxia-ischemic conditioned neonatal rats[7] and currently there is a clinical trial in progress for "Neuroprotective Effects of Remote Ischemic Preconditioning (RIPC) During Infant Cardiac Surgery".[8]

Neonates with CHD undergoing cardiopulmonary bypass continue to have increased risk of neurological vulnerabilities without significant improvements in neuroprotective techniques over the years. Neurologic ischemic preconditioning techniques are showing promising results in multiple animal studies with remote ischemic preconditioning providing benefits for many organs. Currently, there is a clinical trial in progress to determine the effects of ischemic preconditioning on neuroprotection in infants undergoing cardiac surgery, and there is hope that improvements in neuroprotection will be clinically demonstrated, furthering much needed advances in neuroprotection for neonates with CHD undergoing CPB.

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