Commentary: Cerebral protection during pediatric circulatory arrest, from bench to bedside

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Mechanism of nuclear factor κ B action.

Central Message

DHCA upregulated 124 genes, strongest in inflammatory signaling. NF- κ B binding sites were prominently enriched in promoters of most upregulated genes, a potential therapeutic target being investigated.

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In their investigation reported in this issue of the *Journal*, Tu and colleagues¹ studied the transcriptional changes in an animal model of neonatal deep hypothermic circulatory arrest (DHCA).¹ This contribution provides insights into the mechanisms of neurologic injury during DHCA and areas to develop therapeutic interventions.

Increasing data suggest that DHCA is associated with poor neurodevelopmental outcomes, particularly when it extends beyond 41 minutes,^{2,3} as the onus shifts from survival to long-term quality of life in the repair of complex congenital defects. Strategies to minimize the impact of DHCA continue to be studied. Antegrade cerebral perfusion was introduced to maintain brain oxygen delivery during neonatal arch surgery,^{4,5,6} providing more time for the surgeon to perform an optimal repair while minimizing neurologic injury.

The mechanisms of injury during DHCA are complex. Apoptosis plays a crucial role in neuronal cell death after DHCA.⁷ The process starts within a few hours after reperfusion and continues for several days. Ischemia has also been linked to excessive neuronal stimulation and hyperactivity, initiating a cascade leading to neuronal cell death through excitotoxic overstimulation, mainly by glutamate.⁸ The neonatal brain is particularly at risk and does not appear to be uniformly hurt during DHCA; the neocortex, hippocampus, and striatum are more vulnerable.^{9,10}

Tu and colleagues¹ found that 124 genes were upregulated, while 74 genes were downregulated, in the striata of newborn piglets subjected to 2 hours of cardiopulmonary bypass, 30 minutes of DHCA at 18°C, and 6 hours of recovery. Inflammatory signaling was the strongest response, with upregulation of chemokine ligands CXCL10, CXCL9, and CCL2 relative to sham controls. These could play a role in recruiting inflammatory cells and further brain damage in the later stages.

Tu and colleagues¹ also found that nuclear factor κ B (NF- κ B) binding sites were prominently enriched in the

promoters of close to two-thirds of the upregulated genes. NF- κ B is a powerful transcription factor family that controls expression of cytokines, chemokines, and cell survival proteins in response to stress (Figure 1). Multiple pharmacologic agents inhibiting NF- κ B signaling are being investigated in cancer¹¹ and stroke^{12,13} treatment, and NF- κ B inhibition may be of interest to avoid neurologic injury in DHCA by limiting apoptosis and inflammation.

This study has limitations that invite further investigation: the sham controls did not undergo cardiopulmonary bypass, making it difficult to understand whether gene upregulation or downregulation was a response to DHCA and cardiopulmonary bypass or just cardiopulmonary bypass. Tu and colleagues¹ chose one duration of DHCA and early time point, in the hopes of identifying genes upregulated early after DHCA that may have a major downstream impact. It would be interesting to understand how these changes in transcription vary with duration of DHCA or over time, providing windows of opportunity for intervention. Furthermore, operations performed with DHCA have become less frequent, with 59% of patients undergoing arch repair having antegrade cerebral perfusion and only 32% having DHCA in a recent review of the STS Congenital Database.¹⁴ The variations in transcriptome need to be confirmed in this perfusion strategy.

FIGURE 1. Mechanism of nuclear factor κ B (NF- κ B) action. The NF- κ B heterodimer consists of Rel and p50 proteins as an example. Extracellular signals activate I κ B kinase (IKK), which phosphorylates I κ B α . This results in ubiquitination, dissociation of I κ B α from NF- κ B. The activated NF- κ B is translocated into the nucleus, where it binds to specific sequences of DNA. The DNA/NF- κ B complex then recruits other proteins, such as coactivators and RNA polymerase, which transcribe downstream DNA into messenger RNA (mRNA). (Reproduced from Boghog2 under Creative Commons license, http://en.wikipedia.org/w/index.php?title=Image%3ANFKB_mechanism_of_action.png.)

Tu and colleagues¹ deposited their genomics data in Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>), which is open for public review. This is an excellent practice, for which they are to be commended.

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