Neuronal Death Occurs in the Brain of Preterm Lambs Managed by Conventional Ventilation for 3 Days

Jeremy Alvord (MJ Dahl, A Shumway, DM Null, RH Lane, KH Albertine)  
Department of Pediatrics, University of Utah

Background: Preterm birth followed by prolonged mechanical ventilation often results in chronic lung disease (CLD) of prematurity. Associated with lung injury is brain injury. The molecular pathways that are affected in the brain of preterm neonates during the evolution of CLD are unclear. On the other hand, animal models of intratracheal growth retardation have shown that apoptosis is greater in the brain of postnatal rat pups with intrauterine growth retardation compared to controls (Ko et al, AJP:2004). A marker of apoptosis is expression of downstream targets of p53, such as caspase-3.

Hypothesis: Apoptosis of neuronal cells in the brain is enhanced during the evolution of CLD.

Methods: Preterm lambs (~132d gestation) were managed by conventional mechanical ventilation (CV) or nasal continuous positive airway pressure (nCPAP) for 72h (n=4/group). We used nCPAP as the positive control (gold-standard) for lung outcome in chronically ventilated preterm lambs (Albertine et al, Pediatr Res:2004). Brain tissue was analyzed for caspase-3 protein abundance (immunoblot analysis) and topographic distribution (immunohistchemistry).

Results: Immunoblot analysis showed that caspase-3 protein abundance in brain tissue homogenates from preterm lambs was greater in the CV group compared to the nCPAP group at 72h. Immunohistchemistry showed that caspase-3 protein was localized in more Purkinje cells in the cerebellum in the CV group compared to the nCPAP group at 72h.

Conclusion: Our results show that markers of apoptosis (caspase-3 protein abundance and immunolocalization) are more prevalent in the brains of preterm lambs that are managed by CV compared to nCPAP. We conclude that CV contributes to attrition of neurons during the first few days of life support with a ventilator. [Supported by CHRC, HL62875, HL56401, T35 HL07744]