# Brain Injury in Chronically Ventilated Preterm Neonates

## Collateral Damage Related to Ventilation Strategy

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**KEYWORDS**

• White matter injury • Gray matter injury • Bronchopulmonary dysplasia
• Neonatal chronic lung disease

**KEY POINTS**

- Brain injury is a frequent comorbidity in chronically ventilated preterm infants. However, the molecular basis of the brain injury remains incompletely understood.
- This article focuses on the subtle (diffuse) form of brain injury that has white matter and gray matter lesions, without germinal matrix hemorrhage–intraventricular hemorrhage, posthemorrhagic hydrocephalus, or cystic periventricular leukomalacia.
- This article synthesizes data that suggest that diffuse lesions to white matter and gray matter are collateral damage related to ventilator strategy.
- Evidence is introduced from the 2 large-animal, physiologic models of evolving neonatal chronic lung disease that suggest that an epigenetic mechanism may underlie the collateral damage.

### INTRODUCTION

The brain of chronically ventilated preterm infants is vulnerable to injury during the days, weeks, or months of ventilation support with oxygen-rich gas that are necessary to keep them alive.[1] Familiar lesions are germinal matrix hemorrhage–intraventricular hemorrhage, posthemorrhagic hydrocephalus, or periventricular leukomalacia, particularly with parenchymal cysts.[2] These gross histopathologic lesions are not the focus of this article. This article focuses on more subtle diffuse lesions that lead to abnormal neural function and subsequent suboptimal neurodevelopmental outcome.

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Diffuse lesions to white matter and gray matter are recognized among chronically ventilated preterm infants.[3] Diffuse white matter lesions within the first week of life are characterized histopathologically at autopsy as palely stained and soft regions of degeneration of white matter and thinning of the corpus callosum. Gray matter lesions also occur.[4] Gray matter lesions are characterized by diffuse neuronal loss in deeper cerebral cortical layers, the hippocampus, thalamus, globus pallidus, and cerebellar Purkinje cell layers in the dentate nucleus.[4] A mixture of diffuse white and gray matter lesions presumably contributes to subtler delays and/or deficits in neurodevelopment and impairments in motor skills, learning disabilities, attention deficit/hyperactivity disorders, and/or anxiety disorders in former preterm children.[3,5]

Subtler adverse neurodevelopmental outcomes affect the health and quality of life of the survivors and their families. The outcomes also increase the cost for health care borne by the families and society. Therefore, diffuse brain injury in chronically ventilated preterm neonates is a significant national public health issue.

In spite of increasing recognition of diffuse lesions to white matter and gray matter in chronically ventilated preterm infants, the molecular basis of the lesions remains incompletely understood. This article synthesizes data that suggest that ventilator strategy leads to collateral white and gray matter lesions. Evidence is introduced later to suggest that an epigenetic mechanism may underlie the collateral damage.

## PREMATURITY AS THE SETTING FOR COLLATERAL DAMAGE TO THE BRAIN

Prematurity contributes to about a third of all infant deaths in the United States.[6] Mortality is greatest among infants born at or before 25 weeks of gestation (http://www.nichd.nih.gov/about/org/cdbpm/pp/prog_epbo/epbo_case.cfm).

Infants born prematurely are at risk of acute respiratory distress or failure because the future gas-exchange regions of the lung are not developed structurally. The relative or absolute absence of surfactant contributes to collapse of the distal airspaces (atelectasis), which contributes to functional mismatch of ventilation and perfusion that impairs gas exchange.[7]

Two treatments are used routinely for anticipated preterm birth and subsequent respiratory distress. One treatment is antenatal corticosteroid administration to the mother who is in premature labor. The objective of administering antenatal corticosteroids is to stimulate production of endogenous surfactant in the fetus.[8] The other treatment is postnatal surfactant replacement to the preterm infant.[9] The intended consequence of these treatments is to reduce surface tension and thereby increase lung compliance and gas exchange.[10–13] Preterm infants with larger surfactant pools are likely to be supported by nasal continuous positive airway pressure (nasal CPAP). The rationale for using nasal CPAP is to avoid or minimize endotracheal intubation and positive pressure ventilation support.[14–17] However, when nasal CPAP is insufficient, the remedy is endotracheal intubation and positive pressure ventilation using an oxygen-rich gas mixture. High inflation pressure and mean airway pressure may be necessary to recruit the collapsed distal airspaces to achieve ventilation and oxygenation targets. Infants who do not recover from acute respiratory distress and require prolonged positive pressure ventilation with oxygen-rich gas are predisposed to develop neonatal chronic lung disease (also called bronchopulmonary dysplasia [BPD] or the so-called “new” BPD).[18,19]

## VULNERABILITY OF THE IMMATURE BRAIN IN CHRONICALLY VENTILATED PRETERM NEONATES

Vulnerability for collateral damage to the brain is related in part to the width of the developmental window and the types of developmental processes that occur within