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Review

Airway damage of prematurity: The impact of prolonged intubation, ventilation, and chronic lung disease

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SUMMARY

Over the past four decades, advances in neonatal intensive care have led to the survival of smaller and more immature infants. The improved survival of very low birth weight infants is associated with long term respiratory morbidity, most frequently in the form of bronchopulmonary dysplasia. In this review, we will discuss the pathogenesis, risk factor as well as management of commonly seen acquired airway disorders associated with prematurity, prolonged intubation and ventilation.

1. Introduction

Over the past four decades, advances in neonatal intensive care have led to the survival of smaller and more immature infants. The lungs of these extremely immature infants are both structurally and biochemically immature. Supplemental oxygen and ventilatory support are often essential for the survival of these immature infants. Unfortunately these therapies and interventions frequently cause lung and airway damage and result in the subsequent development of chronic lung disease of infancy or bronchopulmonary dysplasia (BPD). The incidence of BPD in very low birth weight (VLBW) infants ranges between 15% and 65% and this incidence increases as the gestational age (GA) decreases [1,2]. Along with interrupted alveolar development, infants with BPD also have airway abnormalities such as increased airway muscle thickening that result in long term impairment of lung function and the prolonged effects of prematurity on the developing lung and airways. In this review, we discuss the widely seen acquired airway disorders associated with prematurity, prolonged intubation, and ventilation.

2. Pathogenesis of acquired airway disorders in premature infants

The majority of VLBW neonates receive some forms of assisted ventilation, whether intubated or non-invasive respiratory support. Premature infants on assisted ventilation for long periods are subject to injury not only of the lungs, but also the entire respiratory tree.

2.1. Airway injury resulting from prolonged and/or repeated endotracheal intubation

The placement of endotracheal tube (ETT) is an integral part of our practice in newborn infants who require mechanical ventilation. Premature infants requiring prolonged ventilator support often experience prolonged and repetitive ETT placement due to failed planned extubation, unplanned extubation, plugged tube, or the need to upsize the tube with physical growth. Immediate complications of endotracheal intubation such as oral-pharyngeal abrasion and lacerations of the oropharynx, hypopharynx and larynx are well recognized. Cricoarytenoid joint fixation, granuloma formation and subglottic stenosis are relatively common longer term patterns of injury. Cricoarytenoid dislocation, arytenoid subluxation, esophageal perforation, tracheal rupture, and retropharyngeal abscess formation have all been reported in the newborns [3] (Fig. 1).

During prolonged intubation, the ETT exerts pressure and can cause ischemic necrosis in the contact area between the tube and

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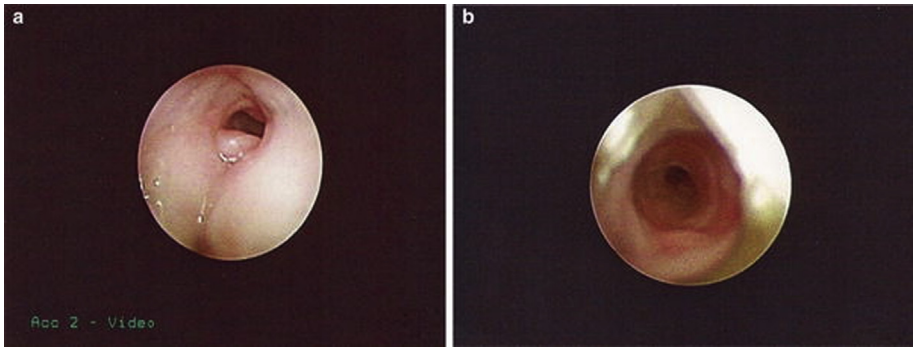

Fig. 1. Subglottic stenosis with infraglottic granuloma noted in a preterm infant after multiple failed extubations.

the laryngeal surface. The presence of a nasogastric tube in most of these infants, and the continued physiologic sucking and swallowing resulting in movement of the ETT against the glottis and subglottic mucosa, are compounding factors that contribute to upper airway injury in these infants.

Repeated endotracheal intubation itself has been identified as another major risk factor for airway injury. Downing et al. reported all but two infants who developed subglottic cysts had multiple intubations (6.4 ± 1.5 intubations) [4]. In animal models, repeated endotracheal intubation, even without mechanical ventilation, has been shown to cause significant tracheal trauma with reduction in the airway epithelial height, reduction in the percentage of basement membrane covered by the epithelium, and thinning of the mucosal wall [5].

2.2. Effects of mechanical ventilation on airway dynamics and function

Although the anatomical maturation of the fetal airways precedes alveolar development, the airways are immature at birth. Therefore the airways of premature infants are highly susceptible to damage before the maturational process is complete. Infants on ventilator support for a prolonged period of time are subject to injury of the entire respiratory tree including the upper airway, the large and small airways, as well as the lungs.

Although positive pressure respiratory support strategies, whether mechanical ventilation via ETT or non-invasively through nasal prongs or masks, are necessary to sustain the life of very preterm infants, positive airway pressure imposes physical forces on the immature airways and its effects have been implicated in the pathogenesis of diverse airway disorders [6]. The high pressure needed to ventilate relatively stiff lungs may cause marked airway deformation of the relatively compliant airways. Increased tracheal diameter, thinning of airway cartilage and smooth muscle, disruption of the muscle–cartilage junction, focal abrasion of the airway epithelium as well as changes in airway chondrocytes, and extracellular matrix expression have been observed in animals and pediatrics patients after positive pressure ventilation (PPV) [6,7]. These injuries may delay the growth and differentiation of the conducting airways and may affect the mechanical properties and pressure–flow relationships of the airway in preterm infants. Both the anatomical and functional changes in response to PPV may exacerbate the congenital weakness of the premature airway wall, resulting in further increased collapsibility and decreased resistance to deformation. Consequently, acquired tracheomegaly and tracheobronchomalacia (TBM) develop in some of the premature infants after prolonged PPV (Fig. 2).

2.3. Small airway disease associated with BPD

Survivors of BPD often have respiratory symptoms, and lung function impairments closely resemble those of asthmatic patients. Current data suggest that infants with established BPD mainly have obstructive rather than restrictive disease and that small airways are the primary contributor to the obstruction [8]. However, although BPD and asthma have some clinical and functional similarities, current data tend to suggest that these two obstructive lung diseases may not share the same type of airway inflammation. In a follow-up study at 6–8 years of age, Brostrom et al. found that all children with BPD showed some evidence of impaired lung function, but there was no evidence that atopy was associated with BPD [9]. Other studies have suggested that prematurity may be associated with neutrophilic airway inflammation and oxidative stress later in life rather than with eosinophilic inflammation as seen in children with asthma [10].

3. Incidence and risk factors of acquired airway disorders in premature infants

Subglottic stenosis (SGS) is a commonly seen injury secondary to endotracheal intubation of neonates. Although some studies have reported a trend towards decreased incidence [11], many studies report an incidence of around 11% in pediatric patients who have undergone endoscopic studies and an even higher incidence (13–37%) in preterm infants [12]. Factors that have been associated with the development of SGS in neonates include birth weight, gestational age, endotracheal tube size, route of intubation (nasal vs oral), trauma of intubation, the number of ETTs inserted, presence of infection, and length of intubation [13] (Fig. 1).

Acquired subglottic cysts after intubation have been described by several studies [4]. The estimated incidence of subglottic cysts is 1.9 per 100,000 live births. However, the true incidence of subglottic cysts in neonates is difficult to determine due to the selection bias of the studies. Downing et al. reported 11 cases (7.2%) in 153 premature infants who were intubated for ≥7 days over a 30-month period [4]. In another study, Halimi et al. identified 17 cases (9.3%) in 172 premature infants over a 10-year period [14]. The majority of subglottic cyst cases were reported in premature newborns with gestational age between 24 and 28 weeks.

Traumatic injury of the vocal cords due to short or long term intubation has been well recognized. Post-intubation laryngeal injuries have been reported in as many as 73% of patients; vocal cord avulsion in neonates leading to dysphonia has also been