Central Airway Issues in BPD

Erik Hysinger[1]

[1]Cincinnati Children's Hospital Medical Center

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Abstract

While there is a very large focus on the abnormalities of parenchymal lung development and extensive efforts to minimize alveolar damage with "gentle ventilation" and non-invasive respiratory support for neonates with bronchopulmonary dysplasia (BPD), there is relatively little consideration for the implications of central airway disease in this patient population. There are significant changes in the structure and conformation of the central airway during the last half of gestation, and premature birth disrupts this natural developmental process. Arrest of maturation results in a smaller airway that is more compliant, easier to deform, and more susceptible to damage. Consequently, neonates with BPD are prone to developing central airway pathology, particularly for patient that require intubation and positive pressure ventilation. Central airway disease can be divided in dynamic and fixed airway obstruction and results in increased respiratory morbidity in neonates with chronic lung disease of prematurity.

Title: Central Airway Issues in Bronchopulmonary Dysplasia

Author: Erik B. Hysinger MD

Institution: Cincinnati Children's Hospital Medical Center

Address: 3333 Burnett Ave, Cincinnati, OH 45229

Phone: 513-803-3674

Fax: 513-636-4615

Email: Erik.Hysinger@cchmc.org

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Abstract

While there is a very large focus on the abnormalities of parenchymal lung development and extensive efforts to minimize alveolar damage with "gentle ventilation" and non-invasive respiratory support for neonates with bronchopulmonary dysplasia (BPD), there is relatively little consideration for the implications of central airway disease in this patient population. There are significant changes in the structure and conformation of the central airway during the last half of gestation, and premature birth disrupts this natural developmental process. Arrest of maturation results in a smaller airway that is more compliant, easier to deform, and more susceptible to damage. Consequently, neonates with BPD are prone to developing central airway pathology, particularly for patiens that require intubation and positive pressure ventilation. Central airway disease can be divided into dynamic and fixed airway obstruction and results in increased respiratory morbidity in neonates with chronic lung disease of prematurity.

Central Airway Development

To understand central airway pathology in neonates with BPD, it is first necessary to understand the developmental changes of the airway that occur throughout gestation. By the 3rd week of gestation, the endoderm develops into the foregut.(1) An outpouching of the foregut forms during the 4th week of gestation and will ultimately give rise to the conducting airways. The trachea and main bronchi are formed by the end of the 4th week of gestation,(2) and by 16 weeks, what once was a single lumen has branched into the more than 10^{20} conducting airways, similar to the fully developed lung.(3)

In addition to increasing the numbers of conducting airway, the basic structure of the trachea is developed during the first half of gestation. The trachea is composed of 16 to 20 cartilaginous rings anteriorly and a muscular membrane posteriorly. The first deposits of tracheal cartilage form during the 7th week of gestation, and the formation of new cartilage continues, following the branching of the airways, until about 25 weeks' gestation.(3)

While the first half of gestation is primarily devoted to developing the structure and increasing the numbers of conducting airways, the airway matures and remodels throughout the latter half of gestation. This maturation results in increased dimensions of the trachea and components of the tracheal wall, changes in the geometry of the tracheal rings, and alterations in the chemical properties of tracheal cartilage and smooth muscle. Throughout gestation the length and thickness of tracheal cartilage increases, and there is a proportionate increase in the length and thickness of airway smooth muscle. Consequently, the ratio of cartilage to muscle is constant. The net result is a larger, more robust airway as gestation progresses.(4) In addition to the changes in the amount of airway cartilage and smooth muscle, the geometric relationships of airway cartilage and smooth muscle also change during gestation. In preterm-sheep, the free ends of airway cartilage are thin and easy to deform; however, with increasing gestational age the relationship changes such that the cartilage nearly abuts.(4) This provides increased support to the posterior membrane and makes the airway less compliant.

As structure changes throughout the second half of gestation to result in an airway that is less susceptible to dynamic collapse, properties of airway smooth muscle and tracheal cartilage also mature, conferring further strength to the developing trachea. In animal models passive stress of airway muscle increases three-fold in the term vs preterm trachea.(5) Furthermore, myosin expression is upregulated throughout gestation, (6, 7) which may explain the increased contractile force of mature tracheal smooth muscle in response to chemical stimuli. (8, 9) Maturational changes in tracheal cartilage also serve to increase strength of the airway wall. At 24 weeks' gestation, the airway cartilage resembles pre-cartilage, and changes in the mucoproteins will not result in a mature appearance until near term corrected age. (3) With increasing age, there is also increased expression of glycosaminoglycans in tracheal cartilage with decreased water content, resulting in increased tracheal stiffness. (4, 10, 11)

The combination of structural and conformational changes of tracheal cartilage and smooth muscle results in a larger, less compliant trachea throughout development that is more resistant to damage and difficult to deform in response to positive pressure. (12) While mechanical ventilation has limited impact on the adult airway, there can be changes in the dimensions and mechanical properties of the neonatal airway. Positive pressure results in an increased radius and cross-sectional area of the trachea and decreased thickness of the airway cartilage and smooth muscle. Further, application of pressure to the premature airway can cause changes in the relationship of the cartilage and smooth muscle as well as epithelial damage.(13) Consequently, immature airways that are exposed to mechanical ventilation have increased resistance and collapsing compliance, making the airway more difficult to inflate.(14) This collapsed airway results in marked increased tracheal work of breathing in neonates.(15)

Failure of the natural developmental progression of the premature trachea and frequent need for positive pressure ventilation predisposes neonates with BPD to central airway pathologies. Central airway disease can be divided into two main categories: 1) dynamic airway obstruction and 2) fixed airway obstruction.

Dynamic Airway Obstruction

Tracheomalacia, Bronchomalacia, and Tracheobronchomalacia

The central airway is a dynamic structure that changes both size and shape during the respiratory cycle. The extent of airway collapse depends both on the rigidity of the airway and the pressure applied across the airway wall. The airway of neonates with BPD, does not undergo the natural maturation process and is hence less rigid, and this propensity to collapse can be exacerbated by damage to the trachea from positive pressure ventilation, which is frequently necessary in the management of BPD. Further, patients with BPD have increased airway resistance and often utilize accessory muscles for exhalation, which can increase transmural airway pressure for the intrathoracic airway. Consequently, dynamic pathologies such as tracheomalacia (TM), bronchomalacia (BM), and tracheobronchomalacia (TBM) are quite common in this population.

Historically, the diagnosis of TBM in neonates has required either direct visualization with bronchoscopy (Fig 1A & 1D) or imaging with ionizing radiation such as fluoroscopy or computed tomography(Fig 1B & 1E) (16-21) and is defined based on the percent of airway collapse during spontaneous respiration. There is currently no widely accepted, standardized method for the evaluation of TBM; however, most experts agree that dynamic collapse during quiet breathing by more than 50% is abnormal.(22) Unfortunately, relying solely on airway collapse does not take the pressure applied across the airway into account when evaluating airway dynamics. Lack of a standardized technique and inability to account for patient effort may in part contribute to variability in the diagnosis of TBM, which can be seen in neonates, even under the same sedation.(23) In an effort to obtain and objective, purely quantitative measure and avoid radiation and the need for sedation, ultrashort echo-time (UTE) MRI with respiratory gating has been recently been utilized to evaluate TM in neonates with BPD (Fig 1C & 1F).(24, 25) While this technique exposes neonates to minimal risk and permits evaluation of airway dynamics in entire patient populations, UTE MRI is not yet widely available.

Because most methods for assessing airway dynamics expose children to sedation, ionizing radiation, or both, these evaluations are only performed in select patients. Thus, the true prevalence of TBM in BPD is unknown; however, the prevalence is estimated to be between 10-48%.(16-20) Further, infants with severe BPD are more likely to develop TBM and have greater variability and severity of dynamic collapse than children with mild or moderate premature lung disease.(25)

Dynamic collapse of the central airways is correlated with increased respiratory morbidity in patients with BPD, both during the neonatal period and toddler years. Clinically, patients with TBM can present with mild symptoms such as cough, wheezing, noisy breathing or more severe symptoms such as cyanotic spells and inability to wean respiratory support.(26, 27) Neonates with BPD and TBM are treated for longer periods of time with invasive mechanical ventilation an undergo more surgical interventions such as tracheotomy and gastrotomy during the initial hospitalization.(17, 21) The net impact for patient with BPD and TBM is to be hospitalized for three weeks longer than patients with BPD alone, which is similar to the impact of necrotizing enterocolitis. At the time of hospital discharge, patients with TBM are more likely to be technology dependent and treated with multiple pharmacologic therapies.(17) Following discharge, infants with TBM have a more than 60% increased frequency of rehospitalization during the first year of life.(28) Despite the marked impact of central airway collapse during the neonatal and toddler periods, no studies have assessed the implications of dynamic central airway obstruction in BPD nor the natural progression of airway dynamics throughout childhood.

Typically, TBM is self-limited and thought to resolve by the second year of life without intervention.(29, 30) Treatment depends on the severity and location of airway collapse and, more importantly, the severity of clinical symptoms. While no studies have rigorously evaluated therapeutics for TBM in patients with BPD, treatment strategies for TBM in general include pharmacotherapy, positive pressure ventilation, and surgical intervention.

Pharmacotherapy is primarily aimed at increasing trachealis tone and decreasing tracheal compliance. Treatment with cholinergic agents such as bethanechol reduce tracheal compliance in neonatal animal models (31)

and improve respiratory mechanics and symptoms in infants and children with TBM.(32, 33) Inhaled ipratroprium bromide in low doses blocks type 2 muscarinic receptors, which potentiate acetylcholine activity in the neuromuscular junction and stimulate contraction of tracheal smooth muscle; however, antagonistic effects of type 3 muscarinic receptors dominate at high doses and result in relaxation of airway smooth muscle, which could exacerbate tracheal collapse.(34) Similarly, treatment with albuterol relaxes airway smooth muscle and can impair respiratory mechanics in infants with TBM in the absence of known lung disease, (32) but, in patients with severe BPD, nearly two-thirds of patients have a positive bronchodilator response based on pulmonary function testing during the neonatal period. (35) Consequently, albuterol can be considered with caution for treatment in patients with BPD, even those with known TBM.

Non-invasive continuous positive airway pressure (CPAP) is frequently used for respiratory support in neonates with BPD, and may have added benefits in the management TBM. CPAP serves as a pneumatic stent which decreases airway resistance, reduces respiratory work, and raises lung volumes in infant with TBM. (15, 36, 37) Positive airway pressure can also be provided invasively via an endotracheal tube or tracheostomy tube, and the artificial airway can bypass the collapsible segment of airway.

Because dynamic collapse is typically identified throughout the airway rather than in a focal segment of the trachea; (16) prolonged positive pressure may be necessary to manage both the proximal TM and more distal BM as well as the parenchymal lung disease. Consequently, tracheotomy is the primary surgical intervention for treatment of dynamic airway obstruction in patients with BPD. Aortopexy involves pulling the aorta anteriorly off of the trachea and has historically been used to treat focal TM in children. While aortopexy results in symptomatic relief in a majority of children, the benefits seem to be related to creating more space in the tracheal lumen by relieving vascular compression rather than treating the TM. (38) More recently, posterior tracheopexy has shown promise in treating TM in children. By suturing the posterior membrane of the trachea to the anterior longitudinal ligament of the spine, posterior tracheopexy can prevent dynamic collapse of the trachea and improve severe symptoms such as the need for mechanical ventilation and cyanotic spells in infants with esophageal atresia.(26, 39) Despite the improvement in other diseases, the efficacy of aortopexy and posterior tracheopexy has yet to be established for the management of patients with BPD and TBM.

Tracheobronchomegaly

Exposure to positive pressure ventilation results in deformation of the trachea related to airway barotrauma.(40) Although the precise mechanism is unknown, airway barotrauma may result in disruption of the muscle-cartilage junction, alterations in the arrangement in the fibers of the airway cartilage and smooth muscle, or thinning of the airway cartilage.(41) The deformation of the airway predisposes pre-mature animals to developing tracheomegaly.(42) Similarly, exposure to invasive positive pressure ventilation in extremely pre-term infant results in increased tracheal diameter and volume. Though the degree of tracheomegaly is typically fairly mild, cases may be extreme (**Fig.** 2A-C). Further, the tracheal enlargement appears correlated with the duration of exposure to positive pressure and persists even after extubation. (43) Currently, the impact of tracheomegaly on outcomes in BPD is entirely unknown; however, a greater tracheal volume increases anatomic dead space and could impair gas exchange. Similarly, there are no current treatment options targeted at treatment of tracheomegaly.

Fixed Airway Obstruction

Subglottic Stenosis

Although congenital subglottic stenosis is rare, acquired subglottic stenosis is common in neonates with BPD. The cricoid is the narrowest portion of the pediatric airway; as a result the cricoid is the most likely area to be damaged in neonates requiring intubation.(44) Multiple factors predispose children to developing subglottic stenosis including duration of intubation, multiple intubation attempts, traumatic intubation, nasal vs oral intubation, endotracheal tube composition, and inadequate sedation.(45-48) However, the most important factor is the relative size of the endotracheal tube to the patient's airway.(46) The endotracheal tube exerts pressure of the airway mucosa that can exceed capillary filling pressure, particularly with cuffed endotracheal

tubes. (49, 50) Within two hours, pathologic changes of the airway mucosa related to intubation can occur, and the alterations of the airway mucosa progress with longer periods of intubation.(51, 52) Damage to the airway related to endotracheal intubation can eventually lead to tissue necrosis and scar formation that manifests as subglottic stenosis

Post-intubation subglottic stenosis develops in 0.9-8.3% of intubated neonates; however, because of the small airway size, prolonged intubation, and multiple intubation attempts, the risk of subglottic stenosis in BPD is likely higher than other neonatal populations. (48, 53) As with TBM, the diagnosis of subglottic stenosis depends on imaging techniques that expose neonates to the ionizing radiation and/or direct visualization with bronchoscopy; thus, the true incidence of subglottic stenosis in BPD is unknown. Subglottic stenosis can be suspected based on airway plain films or computed tomography; (54, 55) however, definitive diagnosis is made by bronchoscopy. Subglottic stenosis is classified using the Myer-Cotton grading scale, which determines the largest endotracheal tube that permits an air leak at 20 cm H_2O. The severity of subglottic stenosis is defined as grade 1 (<50% narrowed), grade 2 (51-70% narrowed), grade 3 (71-99%narrowed), and grade 4 (no detectable lumen) (**Fig.**3B-E).(56)

As the severity of subglottic narrowing increases, airway resistance and respiratory work increases exponentially. Clearly, the extent of the stenosis is the primary driver, but the length of the stenotic segment and the location of the stenosis in relationship with the glottis also impacts airway resistance. (57, 58) The narrowing and increased airway resistance most commonly manifests with biphasic stridor and increased respiratory effort. Indeed, neonates with subglottic stenosis may not tolerate extubation and are at high risk of undergoing tracheotomy. (20, 59)

Management of subglottic stenosis in neonates with BPD should focus on prevention. Recent efforts have increased the use of nasal CPAP at birth rather than intubation to minimize the risk of the development of BPD.(60, 61) If neonates are adequately supported non-invasively, acquired subglottic stenosis does not develop. Non-invasive positive airway pressure can also be utilized to minimize the risk of extubation failure, thereby reducing the risk of airway trauma related to multiple intubations.(62) In the event that endotracheal intubation is necessary, an endotracheal tube that leaks at less than 20-25 cm H_2O minimizes the risk of developing subglottic injury;(63) unfortunately, this may not be feasible to adequately support gas exchange and respiratory comfort in patients with particularly severe lung disease. For patients who require prolonged intubation, adequate sedation that minimizes agitation may also limit the development of subglottic stenosis. (47)

If a neonate with BPD does develop subglottic stenosis treatment options include non-operative measures, endoscopic intervention, open airway surgery, and tracheotomy. Non-operative treatments include downsizing to a smaller endotracheal tube that permits an air-leak at 20-25 cm H20 combined with topical steroid and antibiotic drops delivered via the endotracheal tube. An oral endotracheal tube can be replaced with an nasal tube to minimize mucosal trauma related to movement of the tube along the axis of the airway.(44) Even if non-operative measures do not prevent the need for surgical management, reduction of airway edema and inflammation may aid operative intervention.

For patients with grade 1 or grade 2 subglottic stenosis, balloon dilation is the mainstay of endoscopic intervention. Balloon dilation is a minimally invasive technique that involves inflating a high pressure, non-compliant airway balloon in the narrowed segment of the airway and is generally safe and well-tolerated; however, multiple dilations are often needed for a successful outcome. (64, 65) While endoscopic balloon dilation is successful at avoiding tracheotomy in a majority of pediatric patients with mild subglottic stenosis, balloon dilation is frequently inadequate for more severe stenoses.(64-66) Infants that are born premature or have multiple medical comorbidities appear to be at increased risk of failed endoscopic balloon dilation and are more likely to need invasive surgical interventions.(66)

Surgical options available for the management of subglottic stenosis in neonates with BPD include cricoid split, laryngotracheal reconstruction with cartilage grafting, and tracheotomy. Anterior cricoid split was first described in 1980 for aiding extubation in premature infants with isolated subglottic stenosis. The operation

involves a small neck incision over the cricoid and a vertical incision in the anterior airway from the lower thyroid cartilage to the upper two tracheal rings. The endotracheal tube is left in place, and the airway is allowed to heal by secondary intention. In highly selective patients, anterior cricoid split is successful in facilitating extubation.(67) In more severe cases, modifications to this technique include the placement of a cartilage graft using thyroid ala or costal cartilage to close the airway and a posterior cricoid split with or without a posterior cartilage graft.(68, 69) In the event that a cartilage graft is used, the operation is referred to as laryngotracheal reconstruction, which is highly successful for appropriately selected patients, even with severe subglottic stenosis.(69, 70) For infants that are likely to need prolonged mechanical ventilation for parenchymal lung disease or those who are not candidates for airway reconstruction, tracheotomy can be pursued to bypass the stenotic segment.

Posterior Glottic Stenosis

Like subglottic stenosis, posterior glottic stenosis results from scarring of the airway related to damage from endotracheal intubation.(71) While subglottic stenosis can occur concurrently, posterior glottic stenosis is a distinct entity. (72) Patients typically have inspiratory stridor following extubation and/or fail to tolerate extubation. As the vocal cords are fixed and unable to move, posterior glottic stenosis is often confused for bilateral vocal cord paralysis. It is therefore important to distinguish the portions of the airway that are involved. Bogdasarian classified posterior glottic stenosis into four types. Type I is vocal process adhesion. Type II is posterior commissure stenosis. Type III is posterior commissure stenosis with unilateral cricoarytenoid ankylosis, and Type IV is posterior commissure stenosis with bilateral cricoarytenoid ankylosis.(73) Whited divided the condition into Type I with scarring in the interarytenoid plane and type II with banding between the vocal processes.(74) Posterior cartilage grafting is very successfully for alleviating posterior glottic stenosis in children and can allow return of vocal cord motion. (70-72)

Granulation

Airway granulation is commonly encountered in infants with BPD who are treated with prolonged intubation or tracheotomy and can occur throughout the airway.(16, 20, 67, 75) Granulation tissue of the trachea an lobar bronchi result from a malpositioned endotracheal tube or suction trauma. Patients may demonstrate minimal symptoms if the granulation tissue is small, but more severe granulation can create airway stenosis that results in air trapping and respiratory distress or complete airway occlusion that results in atelectasis.(75, 76) A properly positioned artificial airway and appropriate endotracheal suction depth can both prevent and treat traumatic granulation tissue in the trachea and bronchi in majority of patients.(75) In more severe cases, treatment with topical steroids and antibiotics drops can be effective (**Fig.** 4A-D). A variety of endoscopic techniques have been described for management of tracheal and bronchial granulation tissue including electrocautery, argon laser, cryotherapy, and balloon dilation, though none of these techniques have been rigorously studied in neonates.(75-79)

Conclusion

In patients with BPD, the natural maturation of the airway does not occur resulting in a small, highly compliant structure that is prone to collapse and injury. Further, neonates with BPD are often exposed to prolonged periods to invasive mechanical ventilation and multiple intubations, which leads to airway damage. Consequently, both dynamic and fixed central airway pathologies are common in this patient population and are associated with increase respiratory morbidity. Future work is needed to develop targeted therapies for dynamic airway pathology and improve prevention of fixed airway lesions.

Figure 1 : Bronchoscopic, chest computed tomography, and ultrashort echo-time magnetic resonance images of three neonates with bronchopulmonary dysplasia and tracheomalacia during inhalation (A, B, and C and exhalation (D, E, and F)

Figure 2: Chest radiograph, chest computed tomography, and bronchoscopic images of a neonate with bronchopulmonary dysplasia and marked tracheobronchomegaly.

Figure 3: An endoscopic image of a neonate with bronchopulmonary dysplasia and a normal subglottis

(A). Endoscopic images of four neonates with BPD and grade 1 (B), grade 2 (C), grade 3 (C), and grade 4 (D) subglottic stenosis.

Figure 4: Bronchoscopic images of the carina (A) and right main bronchus (B) in a neonate with bronchopulmonary dysplasia and severe suction trauma. Bronchoscopic images of the carina (C) and right main bronchus (D) in the same patient following seven days of treatment with topical ciprofloxacin/dexamethasone applied via the endotracheal tube.

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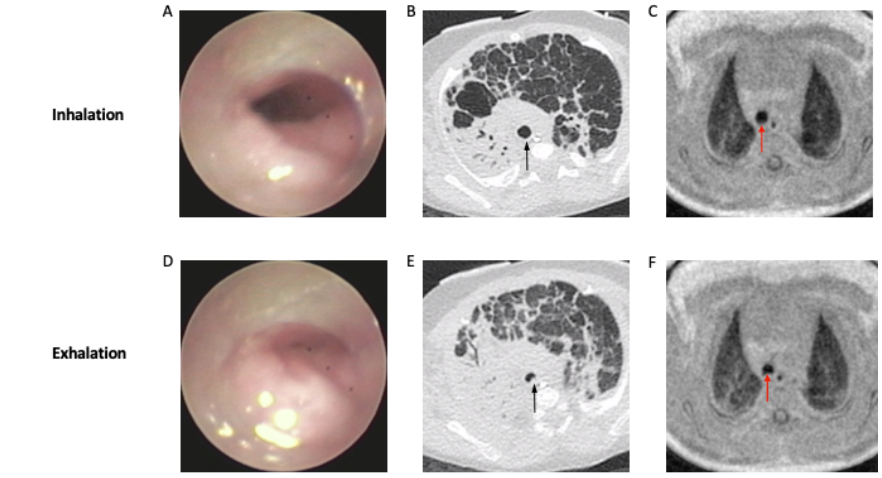

Figure 1

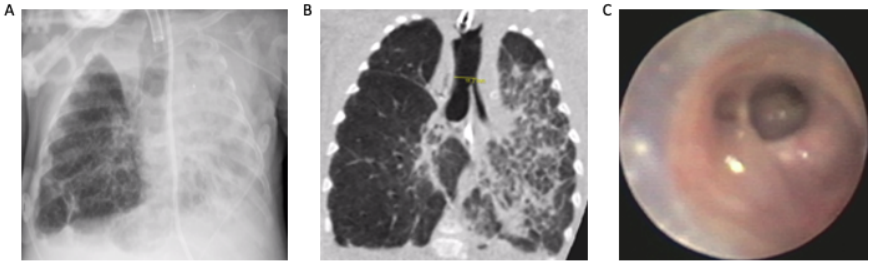

Figure 2

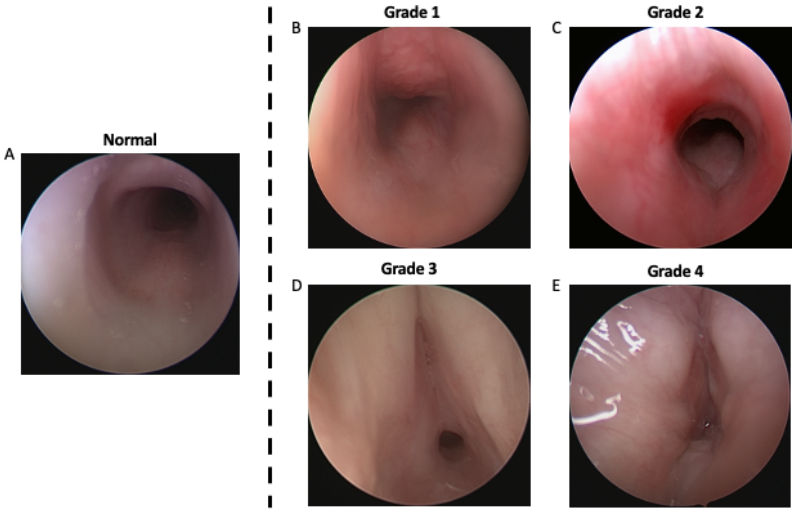

Figure 3

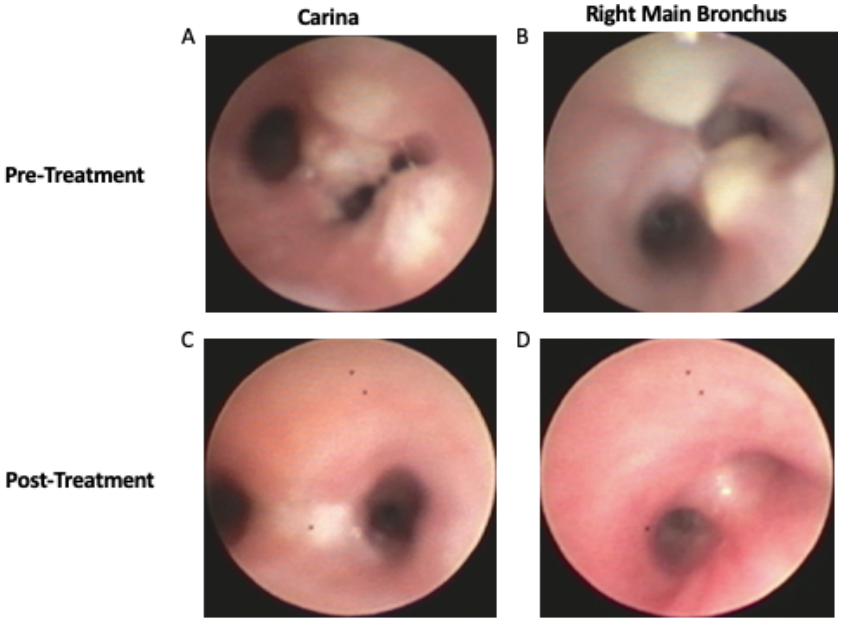

Figure 4