

Mini-symposium: Upper Airway Abnormalities

## Paediatric Tracheomalacia

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## EDUCATIONAL AIMS

- To distinguish congenital tracheomalacia from acquired tracheomalacia.
- To define respiratory mechanics that affect airway compliance.
- To describe the formation and maturation of the paediatric central airway
- To describe advantages and disadvantages of the various methods of diagnosing paediatric tracheomalacia
- To understand the current available treatment strategies for paediatric tracheomalacia.

## ARTICLE INFO

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## SUMMARY

Intrathoracic tracheomalacia is characterized by increased compliance of the central airway within the thorax. This leads to excessive dynamic collapse during exhalation or periods of increased intrathoracic pressure such as crying. Extrathoracic tracheomalacia involves dynamic collapse of the airway between the glottis and sternal notch that occurs during inhalation rather than exhalation. The tone of the posterior membrane of the trachea increases throughout development and childhood, as does the rigidity of the tracheal cartilage. Abnormalities of airway maturation result in congenital tracheomalacia. Acquired tracheomalacia occurs in the normally developed trachea due to trauma, external compression, or airway inflammation. Although tracheomalacia can be suspected by history, physical examination, and supportive radiographic findings, flexible fiberoptic bronchoscopy remains the “gold standard” for diagnosis. Current treatment strategies involve pharmacotherapy with cholinergic agents, positive pressure ventilation, and surgical repair.

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## INTRODUCTION

Collapsibility of the central airways is an important cause of obstruction in childhood respiratory conditions such as tracheomalacia, bronchomalacia, and tracheobronchomalacia. This review will focus on tracheomalacia. Malacia refers to “softness” of a tissue, typically a bone or cartilage. In the case of the airway, “softness” refers to an increase in airway compliance and an excessive tendency for the airway to collapse when pressure is

applied across it. While the normal airway changes shape during the respiratory cycle, children with tracheomalacia or bronchomalacia have excessive dynamic collapse of the central airway that results in clinical symptoms [1].

Extrathoracic dynamic airway collapse causes inspiratory symptoms including stridor, a prolonged inspiratory phase and low lung volumes. Intrathoracic airway narrowing, whether generalized or localized, causes expiratory problems including wheezing, barking cough, a prolonged expiratory phase, and impaired secretion clearance. Symptoms are worse during periods of increased respiratory effort [2]. Children with intrathoracic tracheomalacia can also experience recurrent bacterial bronchitis, cyanotic spells, apnea, and difficulty weaning from respiratory support [3,4].

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## AIRWAY DEVELOPMENT

To understand paediatric tracheomalacia, it is first necessary to understand the development and structure of the airway. Airway formation is one of the earliest events in lung development. The trachea is derived from the embryonic endoderm. By the third week of gestation, the endoderm develops into the foregut [5]. An outpouching of the foregut develops during the fourth week of gestation and will give rise to all of the conducting airways. The trachea develops from the more proximal ventral foregut endoderm while the oesophagus arises from the dorsal foregut endoderm. The separation of the two structures is complete by the end of the fourth week of gestation [6]. Improper foregut separation of the trachea from the oesophagus results in congenital abnormalities such as laryngotracheoesophageal clefts, tracheo-oesophageal fistulae (TOF), and esophageal atresia (EA) that are associated with tracheomalacia [5,6].

In addition to the separation from the oesophagus, the airway must develop from a single lumen into the more than  $10^{20}$  conducting airways found in the mature lung. The trachea and main bronchi form during the fourth week of gestation. Lobar bronchi can be identified in five-week old fetuses, and segmental bronchi are present by the sixth week. By 16 weeks, the branching pattern of the conducting airways is complete [7].

While the first half of gestation is devoted to developing and increasing the number of airways, the second half is characterized by airway maturation and remodeling. The airways increase in length and diameter and also become less collapsible and distensible during the latter half of gestation. The rigidity of the airways is derived from cartilage, connective tissue, and muscle. Thus, the observed five-fold maturational decrease in airway compliance over the last third of gestation [8] must be explained by developmental changes in these structures.

The trachea is comprised of sixteen to twenty C-shaped, cartilaginous rings anteriorly supporting a fibroelastic membrane posteriorly. Tracheal cartilage is first identified at the seventh week of gestation and formation of new cartilage continues centripetally, following the branching patterns of the airways, until the fetus is about 25 weeks gestation [7].

Immature tracheal cartilage is hypercellular with little extracellular matrix. Throughout development, there is change in the mucoprotein composition that confers increasing strength to the cartilage [7]. In premature infants, the tracheal rings are smaller and more compliant; however, with increasing age, the length, area, and thickness increases [9]. There is also an increase in the quantity of tracheal cartilage with a proportional increase in airway smooth muscle, so that the cartilage: muscle ratio remains constant throughout infancy [9]. The geometry of the tracheal rings also changes during development. In premature animal models, the free ends of the cartilage are thin and easily deformed; however, with maturation the cartilaginous ends begin to abut one another forming a nearly complete ring which provides increased support to the posterior membrane [9]. In children with TOF, the natural formation of tracheal cartilage is altered such that there is a decreased length of the cartilaginous rings and an increased muscle: cartilage ratio. The abnormal tracheal structure occurs at the site of the TOF but often extends beyond the fistula and may encompass the entire length of the trachea [10].

There is increased production of glycosaminoglycans throughout gestation, which confers additional rigidity to the developing tracheal cartilage [9]. The characteristics of the glycosaminoglycans achieve their final properties by 25 weeks of gestation. Thereafter, the airways continue to stiffen due to increased amounts of cartilage [11]. The cartilage is the primary structural support of the trachea that allows it to withstand a collapsing transmural pressure and maintain luminal stability and airway patency [7,12].

The posterior membrane, or pars membranacea, contains the trachealis muscle, which also changes throughout development. There is an age related increase in the passive tone, contractility, size, and length of the trachealis [13]. The increased contractility of the trachealis is, in part, due to the increased expression of myosin heavy chains throughout gestation [14].

The net effect of the age related changes to the tracheal rings and posterior membrane is an increase in radius, cross-sectional area, and circumference of the trachea and a decrease in tracheal compliance [15]. Weakness of either the cartilage or posterior membrane results in increased tracheal compliance and possible compromise of the tracheal lumen during the respiratory cycle [16].

## TRACHEAL MECHANICS

The trachea is a dynamic structure that changes size and shape cyclically during respiration. The presence and extent of central airway collapse depend not only on how rigid the airway is but also on the magnitude of pressure applied across it, or the transmural pressure ( $P_{TM}$ ) across the tracheal wall. The  $P_{TM}$  is defined as intraluminal pressure minus the pressure outside of the trachea: in the extrathoracic trachea, the outside pressure will be atmospheric pressure ( $P_{TM} = P_{LUM} - P_{ATM}$ ), while the pressure outside of the intrathoracic trachea is pleural pressure ( $P_{TM} = P_{LUM} - P_{PL}$ ).

### *Intrathoracic Trachea*

During inspiration, both the pleural and airway lumen pressure in the intrathoracic trachea are subatmospheric; however, the  $P_{PL}$  is more negative than the  $P_{LUM}$ . This results in a positive  $P_{TM}$  for the intrathoracic trachea. The net effect is to expand the intrathoracic trachea and increase the volume of the intrathoracic airways. However, during exhalation, the opposite is true. The  $P_{PL}$  and  $P_{LUM}$  become more positive and exceed atmospheric pressure during forceful exhalation. Because of resistive forces, airway pressure drops between the alveolus and the mouth. Thus, the  $P_{PL}$  exceeds  $P_{LUM}$  in the trachea; therefore, the  $P_{TM}$  is negative. As a result the intrathoracic trachea tends to narrow and decrease in volume during exhalation (Figure 1A & 1B) [17,18].

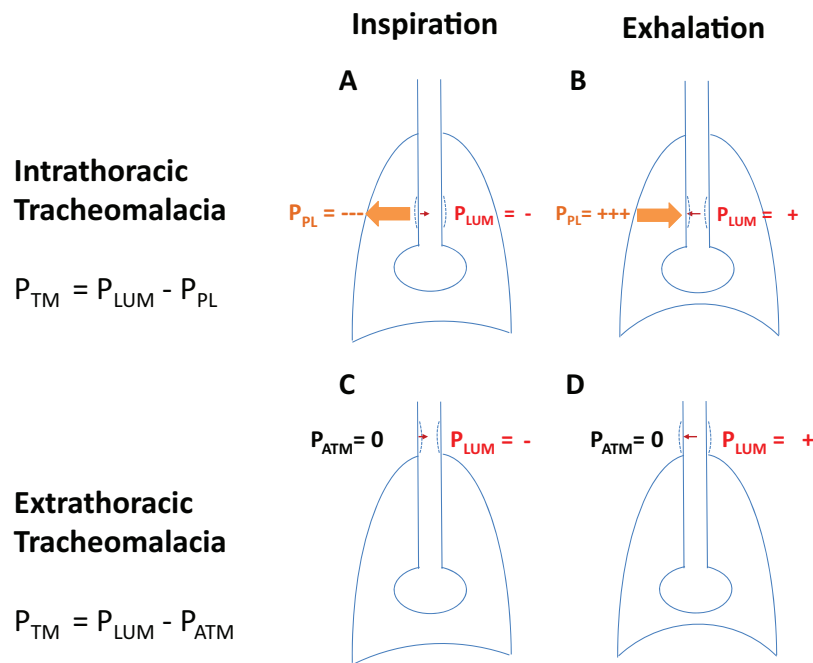
Patients with obstructive respiratory illness such as asthma or bronchopulmonary dysplasia (BPD) often use accessory muscles to exhale, thus elevating  $P_{PL}$ . Additionally, these patients have increased peripheral airways resistance, resulting in an exaggerated pressure drop from the alveolus to the mouth. This, in turn, lowers  $P_{LUM}$  and accentuates the  $P_{TM}$  difference, which can cause airway collapse even though airway compliance is normal.

### *Extrathoracic Trachea*

The dynamic properties of the extrathoracic trachea are reversed throughout the respiratory cycle when compared to the intrathoracic trachea. The atmospheric pressure is considered to be zero. Thus, during inspiration, when  $P_{LUM}$  is negative, the  $P_{TM}$  is negative, resulting in narrowing of the extrathoracic trachea. Conversely, during exhalation, the  $P_{LUM}$  exceeds  $P_{ATM}$ ; hence,  $P_{TM}$  is positive and will cause the extrathoracic trachea to expand. (Figure 1C & 1D) [18].

During tidal breathing, the magnitude of changes in  $P_{TM}$  is relatively small; thus, the normal trachea is able to resist the swings in pressure with minimal deformity. However, during forceful respiratory maneuvers such as coughing, crying, or exertion, there is a large change in  $P_{TM}$  that can result in airway collapse and deformation of the tracheal lumen [18].

Airway collapse occurs in patients with tracheomalacia because the airway wall itself is excessively compliant and so will narrow



**Figure 1.** **A.** During inspiration,  $P_{LUM}$  is less negative than  $P_{PL}$ , creating a positive intrathoracic  $P_{TM}$  that maintains airway lumen patency. **B.** During exhalation,  $P_{LUM}$  is less than  $P_{PL}$ , creating a negative intrathoracic  $P_{TM}$  that collapses the airway. **C.** During inspiration,  $P_{LUM}$  is less than  $P_{ATM}$ , creating a negative extrathoracic  $P_{TM}$  and extrathoracic airway collapse. **D.** However, during exhalation,  $P_{LUM}$  exceeds  $P_{ATM}$ , creating a positive extrathoracic  $P_{TM}$  and a patent extrathoracic airway.

even when exposed to a normal  $P_{TM}$ . Most commonly, the collapse is the result of invagination of the posterior membrane, but some forms of tracheomalacia can result in flattening of the anterior cartilaginous wall as well [17,18].

### CONGENITAL AND ACQUIRED TRACHEOMALACIA

Tracheomalacia can be categorized as congenital or primary tracheomalacia, and acquired or secondary tracheomalacia. Congenital tracheomalacia was first described by Holinger *et al* in 1952 [19] and later defined as weakening of the tracheal wall due to abnormal formation or maturation of the airway. The abnormal development leads to softening of the cartilaginous rings and/or decreased tone of the trachealis. In turn, structural and mechanical alterations result in excessive collapse of the airway and change in the shape of the lumen [17,18]. Congenital tracheomalacia occurs in approximately 1:2100 children and is the most common congenital tracheal abnormality [3]. Some authors reported a male to female predominance of tracheomalacia [20], yet others found no difference between sexes [17].

While congenital tracheomalacia can occur in isolation, it has also been associated with other airway anomalies such as laryngomalacia, bronchomalacia, and large laryngeal clefts [20,21]. Abnormal division of the foregut, as seen in TOFs, is also often associated with congenital tracheomalacia. Proximal EA with a distal TOF is the most common congenital anomaly associated with congenital tracheomalacia [10]. Congenital tracheomalacia can additionally be seen in conjunction with several syndromes involving craniofacial anomalies, chromosomal defects, mucopolysaccharidase deficiencies, and inherited connective tissue disorders [14].

Acquired, or secondary tracheomalacia occurs in the normally developed trachea after some insult such as trauma, external compression, positive pressure ventilation, infection, or inflammation. Tracheotomy is perhaps the most common cause of acquired extrathoracic tracheomalacia and affects at least 10% of the patients undergoing the procedure. Trauma to the cartilaginous rings results

in increased compliance at or just superior to the stoma; however, pressure necrosis and inflammation due to mechanical friction can result in dynamic collapse at the distal end of the tracheostomy tube or at the site of the cuff. Chest trauma as seen in crush injuries from steering wheels in motor vehicle collisions can result in damage to the trachea and subsequent intrathoracic tracheomalacia [22,23].

Acquired intrathoracic tracheomalacia is also particularly common in premature neonates who develop bronchopulmonary dysplasia (BPD). The preterm airway is much more compliant than the airway of the term infant or child, and so it is highly prone to deformation and injury when exposed to positive pressure ventilation [24–26]. Morphologic changes in the trachea after even brief exposure to positive pressure ventilation include overdistention of the airway (tracheomegaly), decreased thickness of the cartilage and muscle components, and histopathological changes such as epithelial necrosis and inflammation [27]. As a result, infants with BPD are prone to develop tracheomalacia. In infants with BPD who underwent flexible bronchoscopy for suspected lower respiratory tract abnormalities, the prevalence of tracheomalacia was estimated to be at least 16% [28]. However, because reports only include symptomatic infants, the true incidence of tracheomalacia in this population is not known.

External compression can also result in loss of tracheal wall integrity and increased tracheal compliance. The earliest reports of secondary tracheomalacia were described in the 1930s and 1940s and were associated with vascular compression of the central airways, i.e., by a vascular ring [29,30]. Later, Gross and Neuhauser noted that this type of deformity of the airways persisted even after the vascular compression was alleviated [31]. Although compression of the trachea is typically associated with vascular abnormalities, external compression can also occur by the axial skeleton as seen in severe scoliosis and pectus excavatum or by space occupying lesions such as goiter, tumors, and cysts [14].

The natural history of tracheomalacia has not been rigorously studied. However, it has been our experience that symptoms associated with isolated congenital tracheomalacia and tracheomalacia associated with positive pressure ventilation tend to

resolve or improve significantly over the first two years of life. On the other hand, tracheomalacia related to foregut malformation or external compression tends to persist later into childhood.

## DIAGNOSIS OF TRACHEOMALACIA

Despite the frequency of tracheomalacia, a standardized set of diagnostic criteria has yet to be defined. The clinical correlates of airway collapsibility can be evaluated by history and physical examination, pulmonary function testing, tracheograms, bronchograms, fluoroscopy [22], multi-detector computed tomography (MDCT) [32], dynamic magnetic resonance imaging [33], and direct bronchoscopy [4,34].

Clinically, patients present with symptoms such as shortness of breath, dyspnea, cough, apnea, and cyanotic spells, particularly during periods of activity. On physical examination, homophonous or monophonic wheezing with intrathoracic tracheomalacia and stridor with extrathoracic tracheomalacia can also be identified [3]. Excessive collapse of the central airways results in an ineffective cough and impaired ability to expel airway secretions. As a result, these children are at increased risk of secondary infections, especially during viral illnesses [35]. Pulmonary function testing in older children classically shows a reduction in peak expiratory flow (Figure 2A); however, this is not a specific finding and is variably present in patients with tracheomalacia [3,36]. Similar studies of pulmonary function in infants with tracheomalacia require sedation of the infant, and are not commonly performed. Taken together, history, physical examination, and pulmonary function testing have a positive predictive value of 74% and negative predictive value of 52% for detecting airway malacia [3].

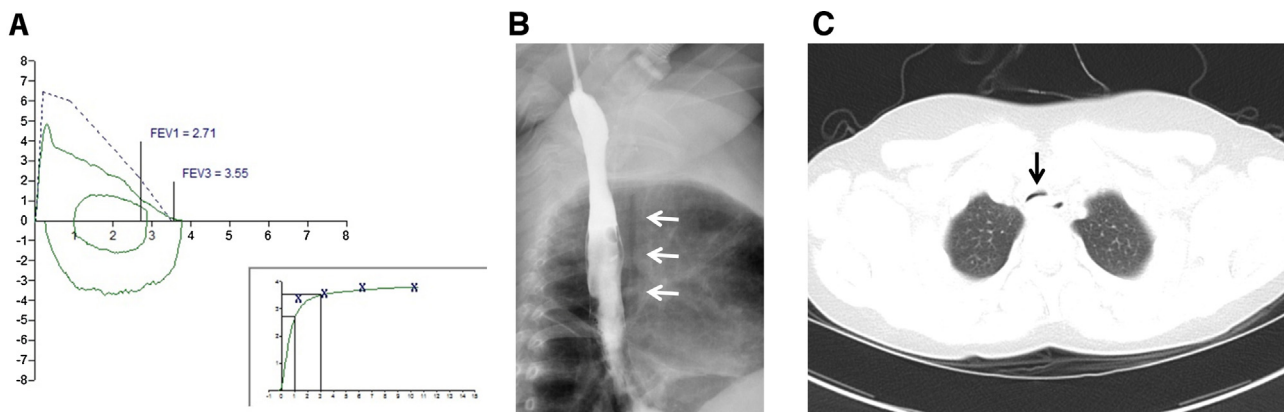
Because of the limitations of clinical evaluation and pulmonary function testing, radiography and endoscopy are often utilized in the evaluation of central airways collapse; all of these techniques are highly dependent on the child's breathing effort. Studies such as tracheograms, bronchograms, and fluoroscopy are not able to quantify the airway cross-sectional area (CSA) but instead reflect changes in the anterior-posterior (AP) diameter (Figure 2B). Notably, however, during periods of crying the AP diameter can decrease by up to 50% in the normal infant trachea [18]. While we are unaware of any studies that formally validate tracheograms and bronchograms, fluoroscopy is a highly specific (97–100%) but poorly sensitive (23.8%–62%) test for evaluating tracheomalacia [37,38].

The advances in MDCT allow quantitation of airway size during different phases of the respiratory cycle. There are currently three MDCT techniques for evaluating tracheal

collapse: paired end-expiratory and end-inspiratory studies, end-inspiratory and dynamic end-expiratory studies, and cine cough studies. In paired end-expiratory and end-inspiratory MDCT studies, the tracheal lumen is compared at end inhalation to the lumen size at end exhalation during a tidal breath. Because changes in airway CSA are small during tidal breathing, this method lacks sensitivity to detect less severe cases of tracheomalacia (Figure 2C). An alternative is dynamic expiratory MDCT. This method measures tracheal CSA at end inspiration and requires that a patient exhale forcefully during imaging. The forceful exhalation results in increased transmural pressure and is more sensitive for detecting tracheomalacia. Cine cough MDCT is similar to dynamic expiratory MDCT. The tracheal lumen is compared at end inhalation and during a cough. This results in a rapid, large increase in transmural tracheal pressure, which in turn can cause a large magnitude of central airways collapse. While this method is more sensitive for detecting tracheomalacia, a normal tracheal CSA can decrease by up to 70% during a cough, resulting in an increased rate of falsely positive evaluations [39].

A limitation of the MDCT method is the need for imaging during both inhalation and exhalation. Dual-phase imaging effectively doubles the dose of radiation and is particularly concerning in the paediatric population, which is more susceptible to the adverse effects of ionizing energy. Recent studies in children have shown that radiation exposure can be reduced by up to 23% while maintaining adequate diagnostic yield [40]. An additional challenge is the need for young children to participate in the methods required for MDCT techniques. This makes these techniques unfeasible in infants. Because movement artifact can make imaging difficult to interpret, young children are often sedated for MDCT, which minimizes changes in transmural pressure and can mask tracheomalacia. These children are also typically intubated for airway protection, and the presence of an endotracheal tube can severely distort the shape of the trachea and perturb tracheal mechanics. Lastly, there is no standardized method to account for axial movement of the trachea during forceful expiratory maneuvers to ensure that the airway is evaluated at the same level throughout the respiratory cycle.

Although advances in radiography can be useful in identifying central airways collapse, direct visualization of the airway with either flexible or rigid bronchoscopy remains the “gold standard” for the diagnosis of tracheomalacia. Flexible bronchoscopy obviates the need for general anesthesia and is the preferred modality for direct visualization and dynamic assessment of the central airways. By avoiding general anesthesia, patients are able to breathe spontaneously, thus allowing for assessment of dynamic



**Figure 2.** A. Flow-volume curve of a patient with tracheomalacia demonstrates decreased peak expiratory flow. B. Fluoroscopy with oral contrast of a patient with TOF and severe tracheomalacia demonstrates marked AP narrowing throughout the entire trachea during exhalation (white arrows). C. Chest CT of a patient with severe tracheomalacia reveals narrowing of the tracheal lumen and decreased AP diameter (black arrow).

airway collapse during tidal breathing or forced expiratory maneuvers. Additionally, flexible bronchoscopy results in less mechanical distortion of the airway than rigid bronchoscopy or endotracheal intubation [41]. Bronchoscopy also allows for the evaluation of additional airway pathology and the ability to sample airway secretions, which is not possible with other modalities.

In patients with congenital tracheomalacia, endoscopy typically reveals widening of the posterior membrane with collapse anteriorly or invagination during exhalation (Figure 3A). This results in a “fish mouth” appearance of the airway. In more severe cases, the airway may be entirely occluded, resulting in a “crescent” or “comma” shape (Figure 3B). While patients with congenital tracheomalacia typically have invagination of the posterior membrane, patients with tracheomalacia due to external compression often demonstrate flattening of the anterior tracheal cartilage as well [42].

Currently, there are no standardized criteria for establishing the diagnosis of tracheomalacia endoscopically. Most authors agree that >50% narrowing of the airways is diagnostic of tracheomalacia; however, classification of the severity of tracheomalacia is not well defined [43]. The degree of expiratory effort is not factored into the evaluation, so a poorly sedated child can demonstrate significant airway collapse merely because of a large (collapsing) transmural pressure applied across the airway wall. Assessment of the degree of airway narrowing is typically based on a semi-quantitative approximation made by the bronchoscopist during visual inspection. More recently, efforts have been made to quantify tracheal collapse accurately using the color histogram method. This technique objectively identifies the airway lumen and determines cross sectional area by accounting for the magnification and distortion of the bronchoscopic image [42]. Endobronchial ultrasound can also be used to determine airway caliber and can additionally evaluate the layers of the airway wall [44,45]. Despite the myriad of endoscopic appearances and lack of diagnostic standardization, there is high inter and intra-rater reliability for diagnosing tracheomalacia via bronchoscopy [38,46].

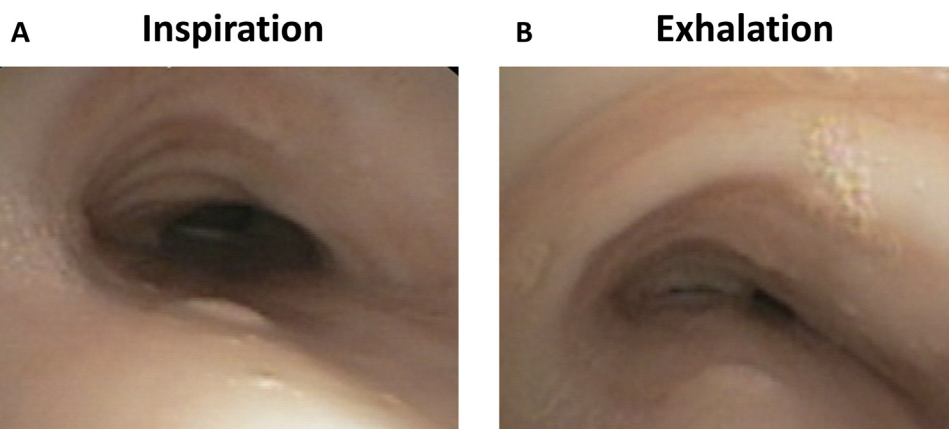
Another challenge in the diagnosis of tracheomalacia is that current methods only evaluate the change in cross-sectional area without taking the applied transmural pressure into account. Without knowing both the change in pressure and change in CSA, tracheal compliance cannot be accurately determined. A technique to evaluate tracheal compliance bronchoscopically has been described in excised lamb tracheae and *in vivo* in a newborn lamb model; however, this method has not yet been adapted to clinical practice [47,48].

## TREATMENT

Treatment of tracheomalacia in the pediatric patient depends on the etiology and severity of the airway collapse. Tracheomalacia is often self-limited and will resolve or become asymptomatic by the second year of life without intervention [17,35]. For patients who are symptomatic of central airways collapse, available treatments include pharmacotherapy, positive pressure application, and surgery.

Pharmacotherapy is directed at increasing the tone of the trachealis muscle, as its contraction has been shown to decrease tracheal compliance [49]. Type 2 and 3 muscarinic receptors play important roles in governing airway smooth muscle tone. Muscarinic agonists such as bethanechol and methacholine directly stimulate airway smooth muscle and improve airway mechanics in children with tracheomalacia [36]. Methacholine by inhalation is used in a laboratory setting to establish the effectiveness of bronchoconstrictor therapy; its short duration of action and the need to dilute it to a dose that provides effect without excessive airway narrowing makes it unsuitable for chronic outpatient use. Bethanechol is a cholinergic agonist that is administered enterally and has a long history of use in children, initially as a therapy for gastroesophageal reflux [50]. When used in a dosing regimen of 0.1 mg/kg/dose 3–4 times per day, it can increase trachealis tone and is unlikely to induce bronchospasm even in children with coexistent airway hyperreactivity. In low doses, inhaled ipratropium bromide blocks presynaptic muscarinic receptors (M2) whose job it is normally to provide feedback inhibition to limit acetylcholine release in the neuromuscular junction. This prolongs acetylcholine release and stimulates smooth muscle contraction. At higher doses, the M3 antagonistic effects predominate, relaxing airway smooth muscle and increasing tracheal compliance [51]. Similarly, beta agonists such as albuterol can also decrease the tone of airway smooth muscle and should be used with caution in patients with collapsible central airways.

Patients with tracheomalacia can also be treated with positive airway pressure. Continuous positive airway pressure (CPAP) provides distending intraluminal pressure which stents open the airway during expiratory maneuvers. CPAP improves respiratory mechanics by decreasing expiratory resistance and increasing lung volume and maximal expiratory flow in patients with central airway collapse [52,53]. CPAP can be provided via non-invasive ventilation or via invasive ventilation with either endotracheal intubation or tracheostomy placement. Invasive ventilation can have the added benefit of supporting the malacic tracheal segment with the artificial airway.



**Figure 3.** A. Endoscopic view of the distal trachea during inspiration in a patient with severe tracheomalacia that demonstrates a patent lumen with widening of the posterior membrane. B. During exhalation the lumen is nearly completely occluded and demonstrates a “comma” shape.

Surgical intervention is occasionally necessary to alleviate symptoms and sequelae of tracheomalacia. Aortopexy is the mainstay of surgical interventions in paediatric intrathoracic tracheomalacia and can provide symptomatic relief. While patients demonstrate clinical improvement, the collapsible segment of the airway remains [54]. More recently, tracheomalacia associated with TOF has been treated using slide tracheoplasty [55]. This technique removes the affected portion of the airway and can be an attractive method for treatment of short segments of severe tracheomalacia. In adult patients, silicone stents have been used to stabilize the airway with improvement in respiratory symptoms [56]; however, airway stents are infrequently used in paediatric patients due to the tendency for stents to migrate. While surgical interventions can improve symptomatic tracheomalacia, these methods should be reserved for the most severe cases.

## CONCLUSIONS

Tracheomalacia is characterized by an increase in tracheal compliance and inability to maintain airway lumen patency, especially during periods of increased respiratory effort. Primary tracheomalacia is fairly rare; however, secondary tracheomalacia is becoming increasingly common with advances in neonatal care and the successful treatment of sicker and more immature neonates with positive pressure ventilation.

## CONFLICTS OF INTEREST

Neither author has any conflicts of interest to disclose.

## FUTURE DIRECTIONS FOR RESEARCH

It will be important to:

- Develop standardized diagnostic criteria that evaluate change in cross sectional area of the trachea in the context of the applied transmural pressure.
- Provide more accurate characterization of tracheomalacia which will allow for improved understanding of its natural history and proposed treatments.
- Moving forward, it will be important to develop standardized diagnostic criteria that evaluate change in CSA in the context of the applied transmural pressure.

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