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REVIEW

Central Airway Collapse, an Underappreciated Cause of Respiratory Morbidity

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Abstract

Dyspnea, cough, sputum production, and recurrent respiratory infections are frequently encountered clinical concerns leading patients to seek medical care. It is not unusual for a well-defined etiology to remain elusive or for the therapeutics of a presumed etiology to be incompletely effective. Either scenario should prompt consideration of central airway pathology as a contributor to clinical manifestations. Over the past decade, recognition of dynamic central airway collapse during respiration associated with multiple respiratory symptoms has become more commonly appreciated. Expiratory central airway collapse may represent the answer to this diagnostic void. Expiratory central airway collapse is an underdiagnosed disorder that can coexist with and mimic asthma, chronic obstructive pulmonary disease, and bronchiectasis. Awareness of expiratory central airway collapse and its spectrum of symptoms is paramount to its recognition. This review includes clear definitions, diagnostics, and therapeutics for this challenging condition. We performed a narrative review through the PubMed (MEDLINE) database using the following MeSH terms: *airway collapse*, *tracheobronchomalacia*, *tracheomalacia*, and *bronchomalacia*. We include reports from systematic reviews, narrative reviews, clinical trials, and observational studies from 2005 to 2020. Two reviewers evaluated potential references. No systematic reviews were found. A total of 28 references were included into our review. Included studies report experience in the diagnosis and/or treatment of dynamic central airway collapse; case reports and non-English or non-Spanish studies were excluded. We describe the current diagnostic dilemma, highlighting the role of dynamic bronchoscopy and tracheobronchial stent trial; outline the complex therapeutic options (eg, tracheobronchoplasty); and present future directions and challenges.

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Dyspnea, cough, sputum production, and recurrent respiratory infections are frequently encountered clinical concerns leading patients to seek medical care. When attributable to a specific etiology, such as chronic bronchitis, bronchiectasis, or asthma, appropriate therapies can dramatically mitigate or even resolve these symptoms. However, it is not unusual for a well-defined etiology to remain elusive or for the therapeutics of a presumed etiology to be incompletely effective. Either of these scenarios should prompt consideration of central airway pathology as the etiology of or a contributor to clinical manifestations.

Over the past decade, recognition of dynamic central airway obstruction or collapse during respiration has been associated with multiple respiratory symptoms but remains incompletely understood.[1] Identifying expiratory central airway collapse (ECAC) requires consideration of the diagnosis followed by appropriate testing. The uncertainties of this condition make identification and investigation challenging.[2,3] Presently

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ARTICLE HIGHLIGHTS

- Expiratory central airway collapse (ECAC) is an underdiagnosed disorder that can coexist with and mimic asthma, chronic obstructive pulmonary disease, and bronchiectasis. Awareness of ECAC and its spectrum of symptoms is paramount to its recognition.
- The term *ECAC* comprises 2 pathophysiologic entities: excessive dynamic airway collapse of the posterior membrane and tracheobronchomalacia.
- Dynamic flexible bronchoscopy under light or moderate sedation remains the most reliable test to confirm and assess the severity of ECAC, and it is still considered the criterion standard.
- Corrective surgery with tracheobronchoplasty may be beneficial for many patients; however, given the surgical morbidity, stent trial to assess clinical improvement is still recommended before surgery.

there is no consensus definition or nomenclature; this pathology has been addressed with several names, contributing to diagnostic inconsistency. Furthermore, these patients often present with multiple comorbidities, such as chronic obstructive pulmonary disease (COPD), bronchiectasis, asthma, gastroesophageal reflux disease, vocal cord dysfunction, obstructive sleep apnea, and laryngopharyngeal reflux, which manifest with similar symptoms challenging appropriate allocation to an attributable etiology.[1,4,5] It is important to highlight that they will often coexist with ECAC and these conditions are not mutually exclusive. To obtain this review article, we performed a narrative review through the PubMed (MEDLINE) database using the following MeSH terms: *airway collapse*, *tracheobronchomalacia*, *tracheomalacia*, and *bronchomalacia*. We include reports from systematic reviews, narrative reviews, clinical trials, and observational studies. Two reviewers (D.A.-T. and S.F.-B.) evaluated potential references. No systematic reviews were found. A total of 28 references were included into our review. Included studies report experience in the diagnosis and/or treatment of dynamic central airway collapse; case reports and non-English or non-Spanish studies were excluded. Here, we review the current understanding of ECAC diagnosis and therapy, highlighting tips to promote appropriate consideration of the diagnosis during evaluation by both specialists and generalists.

The term *ECAC* comprises 2 pathophysiologic entities: excessive dynamic airway collapse (EDAC) and tracheobronchomalacia (TBM).[4,6-8] The "E" in ECAC has been described as both *expiratory* and *excessive* without consistency.[2,3,9,10] Although this ambiguity may contribute to confusion, both terms describe the same pathologic entity. Excessive dynamic airway collapse refers to an excessive forward displacement of the posterior membranous portion of the tracheal wall due to weakness and atrophy of the longitudinal elastic fibers.[6] Excessive dynamic airway collapse should be used only to describe an abnormality in the posterior membranous portion of the airway that bulges into the lumen during expiration.[1,4,11,12] Abnormal motion of the anterolateral or cartilaginous portion of the tracheobronchial wall is termed as *TBM*.[1,8] Tracheobronchomalacia can be subdivided into cartilaginous or circumferential (or concentric). Cartilaginous TBM implies a weakness of the lateral (sabersheath) or anterior (crescent) cartilaginous wall.[1] Cartilaginous TBM leads to splaying of the end of the tracheal cartilage, increasing the transverse diameter, and decreasing the anteroposterior diameter. Circumferential, or concentric, TBM is a combined anterior and lateral airway wall collapse usually associated with inflammatory conditions, such as relapsing polychondritis.[6,13,14] Figures 1 and 2 illustrate these differences.

During forced expiration, there can be a physiologic anteroposterior diameter narrowing of 50% (±20%).[8,10,12] The degree of collapse that constitutes pathology is uncertain and needs to be defined in the context of clinical findings.[1,5] Some studies have found a threshold of 70% collapse as

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the minimum to define pathology and greater than 90% identifies those for whom aggressive treatment such as tracheobronchoplasty (TBP) is more likely to be beneficial.[1,4,9] The evidence of increasing the threshold for ECAC from 50% to 70% is based on a single-center observational study of 51 healthy volunteers aged between 25 and 75 years with no risk factors for ECAC. In this study, the average ECAC was around 55% with an SD of 20%. The 70% cutoff is approximately 1SD higher than that in those normal controls.[15]

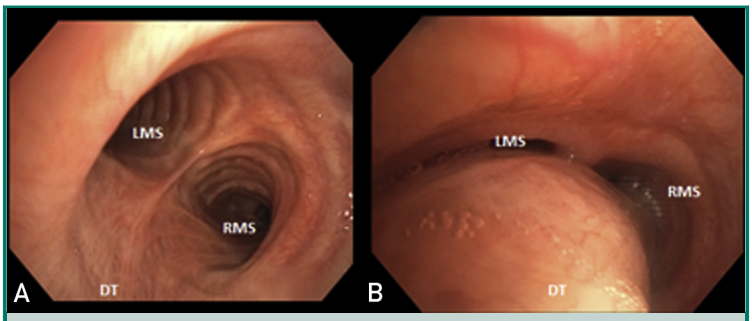

FIGURE 1. Inspiration and expiration views of the distal trachea. A, DT, LMS, and RMS on inspiration. B, DT, LMS, and RMS on forced expiration exhibiting severe EDAC. DT = distal trachea; EDAC = excessive dynamic airway collapse; LMS = left main stem; RMS = right main stem.

ANATOMY AND PHYSIOLOGY

The anterior wall of the trachea is formed by 14 to 20 C-shaped cartilaginous rings, and the posterior wall is composed of the trachealis muscle. On inspiration, the average adult tracheal length is 10 cm, with a normal anteroposterior diameter of 2.2 to 2.9 cm in men and 1.9 to 2.6 cm in women. The transverse diameter ranges from 2.7 to 3.4 cm in men and from 2.2 to 2.6 cm in women.[16] It is currently theorized that large airway collapse is due to increased airway resistance, decreased lung elastic recoil, and increased pleural pressure. Collectively, these factors increase luminal airflow velocity and decrease pressure, creating a stress on luminal integrity and leading to smooth muscle fatigue. As perpetuating factors, weakening of the smooth muscle tone, reduced elastic recoil, and greater narrowing lead to greater transmural pressure gradient, resulting in ECAC.[5]

EPIDEMIOLOGY AND ETIOLOGY

The true prevalence of ECAC is unknown; although increasingly recognized, it is likely grossly underdiagnosed. An overall prevalence of 13% has been suggested, with an increase to 37% in those with COPD and other airway diseases.[6,12]

The etiology of ECAC is uncertain, but small airway obstruction, chronic inflammation, trauma or previous tracheostomy, relapsing polychondritis and other autoimmune diseases, COPD, asthma, obesity, and gastroesophageal reflux disease have been linked to the development of ECAC.[6,17] Notably, inhaled corticosteroids, commonly used in various airway diseases, have been postulated to have a causative role.[17] Hypothesized contributors to TBM include secondary injuries, such as infiltrative disorders, prolonged tracheal ischemia, or inhalation of toxins.[12]

DIAGNOSIS

The clinical manifestations of ECAC are so common and nonspecific that diagnosis is often delayed. To reach its diagnosis, a high index of suspicion is needed as intensification of therapy, for more common diseases such as COPD or asthma fails to improve the patients' clinical status.[4,6,13] The lack of progress with a specific treatment for a presumed etiology should prompt consideration for the alternative or additive diagnosis of ECAC. It has various pulmonary presentations, and the most commonly described in the literature are chronic bronchitis, chronic cough, dyspnea, and difficulty clearing secretions.[18] Their exact frequency is unknown, as ECAC may coexist with other respiratory diseases, which may contribute to the presenting symptoms.

The potential pathophysiologic source of these presentations is merely hypothesized; however, it is thought to be multifactorial in nature. Chronic cough in these patients tend to be paroxysmal described as "seal-like barking," and it is thought to be influenced by the excessive vibration of the posterior tracheal wall against the anterolateral borders of the tracheobronchial tree.[19] In

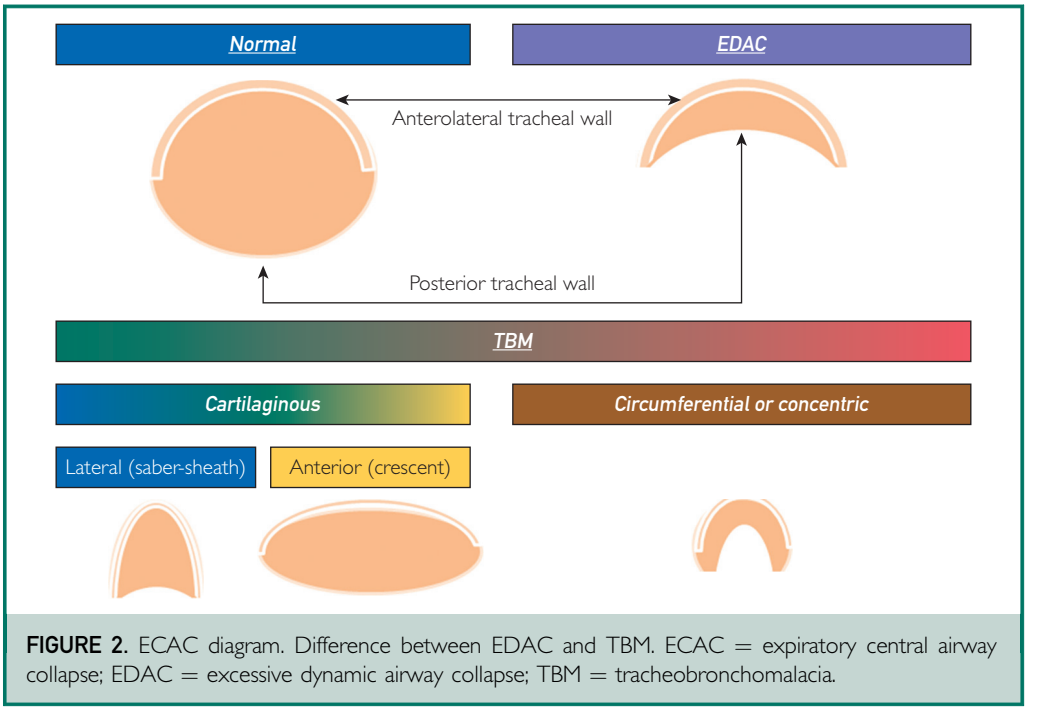

FIGURE 2. ECAC diagram. Difference between EDAC and TBM. ECAC = expiratory central airway collapse; EDAC = excessive dynamic airway collapse; TBM = tracheobronchomalacia.

addition, the poor airway secretion clearance precipitated by the mechanical collapse fails to expectorate retained airway secretions and perpetuates chronic airway inflammation and impaired mucociliary clearance.[10] The etiology of dyspnea is indeed more challenging as often these patients may have no substantial airflow limitation noted in the pulmonary function test. It is also thought to be multifactorial, with air trapping and hyperinflation at the moment of forced expiration thought to be the main contributing factors. It is hypothesized that this happens mainly on exertion due to increased luminal airflow velocity.[5] Deconditioning may also play a significant role as these patients' quality of life is often limited and their ability to exercise is impaired. Expiratory central airway collapse may cause only exertional symptoms, leading to an erroneous diagnosis of exercise-induced asthma.[5] Expiratory central airway collapse may also

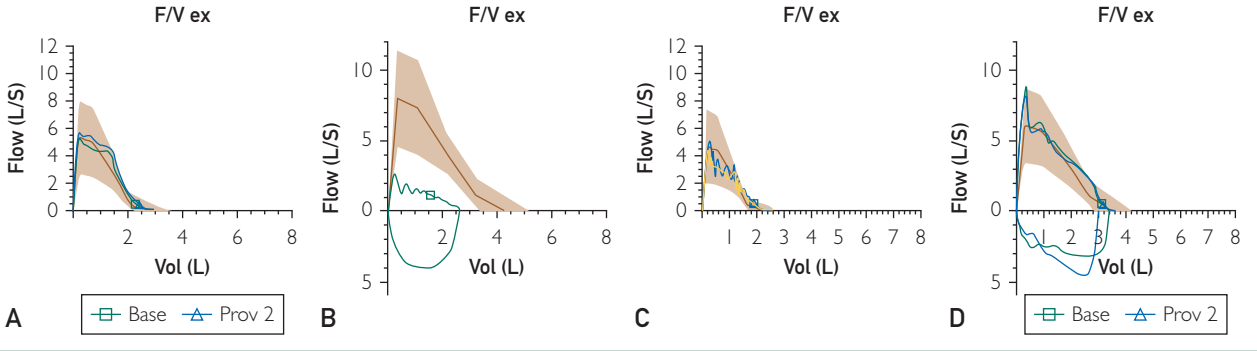

FIGURE 3. Patterns associated with the expiratory flow-volume loop in patients with ECAC. A, Biphasic expiratory curve. B and C, Flow oscillations or "serrated" pattern. D, Notching of the expiratory flow-volume loop. ECAC = expiratory central airway collapse; F/V ex = flow/volume expiratory time; Prov 2 = provocation test.

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complicate ventilation during surgery of procedures performed under conscious sedation or become manifest after extubation or tracheostomy decannulation.[11,12]

Pulmonary function tests may reveal obstructive (44%) or restrictive (17.8%) changes, but are normal in 20% of patients with ECAC.[6,13] Helpful clues during these tests include reduced maximum forced expiratory flow, a biphasic expiratory curve, flow oscillations, and notching, but these are not universally present.[10,18,20-22] Examples of these abnormalities are presented in the flow-volume loops in Figure 3.

Dynamic computed tomography of the chest with images obtained at end inspiration and during forced expiration is increasingly used to establish the presence of ECAC, but its utility is predicated on radiology expertise for both image collection and interpretation.[6,8,10,13] Dynamic computed tomography collapsibility index should be calculated at the same recommended areas as when performing the dynamic bronchoscopy assessment: cricoid level, mid-trachea, distal trachea, proximal left and proximal right main bronchi, and proximal bronchus intermedius. Different locations have also been proposed on the basis of experts' opinion: 1 cm above the aortic arch, 2 cm above the main carina, level of the left main stem take off, and level of right main stem take off. None of these approaches have been substantially studied, and there is no strong evidence for them to support either of them. From the images obtained, a *collapsibility index* can be determined as follows: (area at end inspiration−dynamic expiratory area/area at end inspiration)×100, in which both dynamic expiratory area and area at end inspiration values are calculated using the established algorithms.[12] Dynamic flexible bronchoscopy under light or moderate sedation remains the most reliable test to confirm ECAC and is still considered the criterion standard.[18,23] Throughout the procedure, the patient must be able to purposefully produce a forced expiration as the bronchoscopist evaluates each segment of the central airways.[12,24] Six areas should be intentionally and separately evaluated to visually assign a degree of collapsibility: cricoid level, mid-trachea, distal trachea, proximal left and proximal right main bronchi, and proximal bronchus intermedius.[24] These images are usually video recorded for further analysis. Disease severity is described as mild disease with collapse of 70% to 80%, moderate with collapse of 81% to 90%, and severe as collapse of 91% or higher.[4,18]

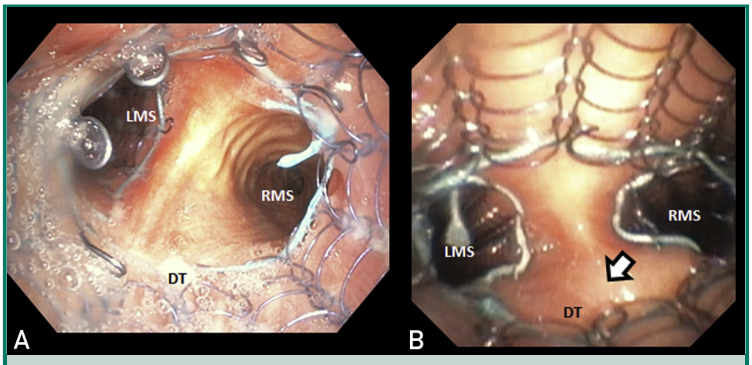

FIGURE 4. Distal trachea with metallic stents preventing dynamic airway collapse. A, DT, LMS, and RMS after stent placement. B, DT, LMS, and RMS after stent placement on expiration. The minimal collapse of the posterior wall (arrow) notably improved by metallic stents. DT = distal trachea; LMS = left main stem; RMS = right main stem.

STENT TRIAL

Corrective TBP surgery can be beneficial for many patients; however, some degree of certainty about its potential benefit for patients is required before it. This can be obtained through a stent trial. Before it, all respiratory comorbidities treatments should be optimized for at least 4 to 8 weeks, because up to 40% of patients will report substantial improvement in symptoms, even in the absence of airway stabilization. In addition, not treating the comorbidities may negatively affect the outcome of surgical central airway stabilization.[6] Commonly, airway stents are placed for a short period of time (5 to 10 days) to assess clinical improvement and help identify those patients who may benefit from surgery.[2,3] Subjective and objective evaluation of respiratory symptoms, health-related quality of life (St George's Respiratory Questionnaire and

cough quality of life), lung function (forced expiratory volume), exercise capacity (6-minute walk test), and functional status (Karnofsky Performance Scale) using validated scoring scales should be used before and during stenting.[6,23] In a recent case series, 73% of patients (31 of 42) underwent robotic TBP without antecedent stent trial.[4] The downside of this approach is that some patients may undergo a surgical procedure for a condition that may not be the main source of their symptoms. It has been described that around 20% of patients with severe and symptomatic disease will not improve with a stent trial.[8] Both uncovered self-expanding metallic stents and silicone tubular and Y stents have been used for stent trials before TBP. It is important to highlight that neither type of stent is an effective long-term solution for ECAC.[25] Uncovered self-expanding metallic stents (Figure 4) are more frequently used as they preserve mucociliary function and can be placed with relative simplicity; however, these stents may be difficult to remove secondary to granulation tissue in inflamed airways.[3,7] The use of silicone Y stents is complicated by cough, mucus plugging, foreign body irritation, and infection.[4,6,13,23,25] For these reasons, stents are maintained for only 5 to 10 days, with quantification of respiratory symptoms and functional status repeated before removal.[6,7] Up to 75% of patients selected for a stent trial exhibit an improvement in symptoms and are considered for further surgical intervention.[11] Recently, pneumatic stenting via nasal continuous positive pressure has been proposed as an alternative to diagnostic stent placement,[11,12] although some experts believe that this approach may overestimate the benefits of surgical stabilization.[3]

TREATMENT

Therapy for ECAC is determined by disease severity (degree of collapse and severity of symptoms) and comorbid conditions. Optimization of pulmonary status with attention to appropriate treatment of recurrent infections, maximization of medical therapy for concomitant airway diseases, and use of bronchial hygiene measures are critical to management. Maximal treatment of any potential alternative cause of symptoms for 4 to 8 weeks is recommended before diagnosing ECAC as the primary cause of symptoms. Mild-to-moderate cases can be treated with intermittent continuous or bilevel positive airway pressure.[5,6,8,10] In the United States, insurance coverage for positive airway pressure therapy for the indication of ECAC is not universal. Tracheobronchoplasty or surgical central airway stabilization by posterior mesh splinting should be considered for patients with severe disease.[2,3] The data that support TBP for severe ECAC cases are based on a prospective observational study and the retrospective analysis of a prospectively maintained database of a single institution.[25,26] Surgical planning for TBP requires distinguishing EDAC from TBM. In patients with EDAC, the transverse diameter of the airway is not excessively large; therefore, lateral downsizing of the trachea is less pronounced than in the technique for repairing TBM. When repairing EDAC, the posterior wall tension may be predominantly developed by suture placement to achieve axial tension.[6] Tracheobronchoplasty is performed by suturing a knitted polypropylene mesh to the posterior membrane of the trachea and bilateral main bronchi, with the goal of splinting the trachea to promote the development of normal rigidity and configuration with healing.[9,13] Tracheobronchoplasty is performed through a right posterolateral thoracotomy, with exposure of the intrathoracic trachea, bilateral main bronchi, and bronchus intermedius. The mesh is sutured to the posterior membrane in a partial thickness fashion to avoid entering the airway lumen. One case series of robotic TBP has reported promising results and favorable outcomes.[6] Bronchoscopic laser TBP with the application of endoluminal laser to the posterior tracheal wall to induce fibrosis and wall rigidity holds promise as a less invasive therapy; however, more clinical trials are needed to establish its real value.[11,27]

Tracheobronchoplasty is associated with a 1% mortality rate in appropriately selected

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adults with severe symptomatic ECAC when performed by an experienced airway surgeon and team. Perioperative adverse events occur in nearly half of patients, including respiratory failure or pneumonia. Tracheobronchoplasty can improve quality of life, exercise capacity, and respiratory symptoms.[6]

FUTURE RESEARCH DIRECTION

As recognition of ECAC improves, it is critical that clinical risk factors be identified and therapy refined. The ideal use of inhaled corticosteroids, portable pneumatic stenting devices, laser tracheoplasty, and robotic bronchoscopy, as well as stem cell therapy or other regenerative medicine techniques to strengthen the airway, alone or in conjunction with 3-dimensional bioprinting or even trachea transplant, may hold promise.[28]

CONCLUSION

Expiratory central airway collapse is an underdiagnosed disorder that can coexist with and mimic asthma, COPD, and bronchiectasis. Common manifestations include dyspnea, chronic cough, and recurrent respiratory infections. Dynamic flexible bronchoscopy is the diagnostic criterion standard, although dynamic forced expiratory computed tomography is also helpful when used with appropriate expertise. Optimization of bronchial hygiene, treatment of coexisting conditions, and use of positive airway pressure therapy are used in mild-to-moderate cases of ECAC. Definitive surgical treatment should be considered for those with severe disease, especially if a diagnostic stent trial reports quantified improvement. Less invasive interventions, such as robotic TBP or bronchoscopic laser therapy, offer promise as future therapies, expanding the spectrum of patients for whom intervention is indicated; however, further research is required to assess the safety, efficacy, and durability of these interventions.

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Abbreviations and Acronyms: **COPD** = chronic obstructive pulmonary disease; **ECAC** = expiratory central airway collapse; **EDAC** = excessive dynamic airway collapse; **TBM** = tracheobronchomalacia; **TBP** = tracheobronchoplasty

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