Personalized interventions for tracheobronchomalacia

Tayfun Caliskan[1], Sarah Sungurlu[2], Septimiu Murgu[3]

[1]Pulmonary Division, Haydarpasa Sultan Abdulhamid, Training and Research Hospital, The University of Health Sciences, Istanbul, Turkey;
[2]Pulmonary Division, Swedish Covenant Hospital, Chicago, IL, USA; [3]The University of Chicago Medicine, Chicago, IL, USA
Correspondence to: Septimiu Murgu, MD, FCCP. Associate Professor of Medicine, Co-director of Bronchoscopy, Interventional Pulmonology
Fellowship Program Director, The University of Chicago Medicine, 5841 S Maryland Ave, MC 6076, Chicago, IL 60637, USA.
Email: smurgu@medicine.bsd.uchicago.edu.
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There are several bronchoscopic, thoracoscopic and open techniques for the treatment of severe tracheobronchomalacia (TBM). The publication by Huang *et al.* in this issue of the journal focuses on a novel modality as a step forward towards a more personalized therapy. It is necessary to be aware of the two types of expiratory central airway collapse (ECAC) defined as excessive airway collapse during expiration. It is either a result of cartilaginous weakening (TBM) or redundancy and inward bulging of the posterior membrane [excessive dynamic airway collapse (EDAC)] (1) (*Figure 1*).

Both EDAC and TBM are characterized by excessive narrowing of the airway lumen during exhalation, which leads to the reduction of the cross-sectional area (CSA) as seen on paired inspiratory-dynamic expiratory computed tomography or bronchoscopy (1). Patients with ECAC have impaired quality of life (QOL). For example, in a cohort of patients with COPD, asthma and chronic bronchitis, the prevalence of ECAC was 5% and was associated with worse respiratory QOL as measured by St. George Respiratory Questionnaire (SGRQ) (2). It remains unclear what degree of airway collapse is pathologic, especially for EDAC. Distinguishing TBM from EDAC becomes clinically relevant since there is no clear role for stent insertion or surgical interventions in EDAC (3).

Tracheomalacia (TM), characterized solely by the weakness of tracheal cartilaginous wall, is not a common entity and is usually due to either chronic compression from tumors, vascular structures or caused by inflammatory processes involving the airway cartilage. It can be diffuse [as seen in Ehlers-Danlos syndrome or Relapsing Polychondritis (RP)] or localized (cartilaginous injury post tuberculosis, radiation or post-tracheostomy/intubation) (4). Treatments for patients with malacia depend on the etiology, severity of symptoms, degree and extent of airway collapse. Non-invasive positive pressure ventilation (NIPPV) can be offered to patients who are not severely impaired and who do not have severe, complete collapse of the cartilaginous wall. NIPPV has been successfully applied in patients with RP (5).

For more symptomatic patients with severe malacia not responding to the treatment of the underlying disorder and NIPPV, open surgery or bronchoscopic stent insertion are two proposed treatment alternatives. As far as airway stenting is concerned, US Food and Drug Administration does not recommend metal stents if other alternatives are available (tracheal surgery or silicone stenting) (6). Silicone stents were shown to improve functional status and dyspnea immediately after intervention, but are associated with a high rate of complications including mucus plugs, migrations, and granulation tissues requiring repeat bronchoscopies (7,8). Because of the long-term issues with indwelling airway stents, in some centers silicone stents are used only as a bridge to membranous tracheoplasty (in order to assess improvement in symptoms once airway patency is restored by the stent) or as a definitive therapy in non-operative candidates (8).

Open or thoracoscopic surgical techniques are proposed options for patients with severe airway collapse due to TM that also have severe functional impairment (i.e., hospitalizations for pneumonia due to inability to raise
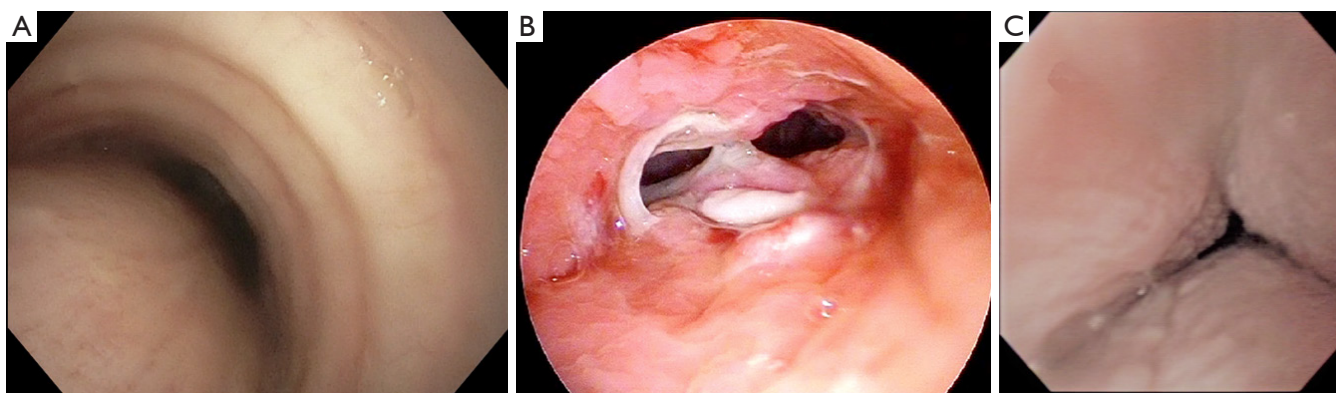
Figure 1 Three distinct forms of ECAC. (A) EDAC with posterior membrane bulging inwards in a patient with severe obesity; (B) crescent-type tracheomalacia with airway edema; (C) circumferential tracheomalacia in a patient with Relapsing Polychondritis. ECAC, expiratory central airway collapse; EDAC, excessive dynamic airway collapse.

secretions or hypercarbic failure). They offer the advantage of being a permanent solution without the need for an airway foreign object (i.e., airway stent). There are several established techniques including tracheobronchopexy, aortopexy, and external stabilization.

Direct tracheobronchopexy could be performed via thoracoscopy or thoracotomy for pediatric malacia and is achieved with either anterior suspension and/or posterior fixation (9). For posterior fixation, sutures are passed through the posterior membrane and secured to anterior spinal ligament. For anterior suspension, the airway wall is elevated by passing sutures through a tracheal ring and then secured to the sternum.

Aortopexy is an alternate surgical treatment for severe TM, which can also be performed either open or thoracoscopically. This procedure involves suturing the aorta to the sternum; the anterior tracheal wall is attached to posterior aortic wall via pre-tracheal fascia and therefore the tracheal lumen is opened. Outcomes with this procedure are variable. In a review of 40 articles reporting on patients who underwent aortopexy for pediatric TM, more than 80% of the patients improved, 8% showed no improvement, 4% had a worsening of their symptoms and 6% died. Complications were observed in 15% of patients and included pneumothorax, pleural effusion, atelectasis, pericardial effusion, phrenic nerve palsy, and bleeding (10).

It remains unclear whether bronchoscopic or open surgical techniques are better for patients suffering from TM although the efficacy and clinical outcomes of aortopexy versus tracheal stents were compared in pediatric patients (11). The authors concluded that both modalities

were effective in the management of TM. However, although aortopexy was associated with early perioperative complications, tracheal stents were associated with higher failure rate and more severe morbidity and mortality. This study generates a hypothesis that open surgery may be preferable for long-term and more sustained response for this disease process.

External stabilization offers a potential solution. One of the first approaches used a Marlex mesh splint reinforced with silastic rings which was sutured in place for a permanent tracheal splinting in pediatric patients with TBM (12). Tracheoplasty (aka tracheobronchoplasty) is a surgical procedure for diffuse TBM in which the membranous portion of the trachea is splinted from the thoracic inlet to the distal left mainstem bronchus and distal bronchus intermedius. It is performed via a right thoracotomy allowing the posterior airway to be exposed after the azygos vein is ligated. The posterior wall of the trachea is reefed to a sheet of acellular dermis (or polypropylene mesh) with a series of stitches from the thoracic inlet to the bottom of the trachea to restore the normal D-shaped airway morphology (13,14). This procedure was shown to improve respiratory symptoms, health-related QOL, and functional status in selected patients with severe symptomatic TBM (15). In one study of 63 patients, however, complications were not uncommon and included a new respiratory infection in 14 patients, pulmonary embolism in two, and atrial fibrillation in six; an additional six patients required reintubation, and nine received a postoperative tracheotomy; 47 patients required postoperative bronchoscopy for aspiration of

secretions. Two patients (3.2%) died postoperatively- one due to worsening usual interstitial pneumonia and the other of massive pulmonary embolism (16). Because of the morbidity and mortality described in previous attempts for external stabilization for TM, searching for safer alternatives is warranted.

In these regards, the surgical technique published by Huang *et al.* in this month's article is the first documented attempt for an external fixation using a personalized scaffold in an adult patient with TM. Previous reports address the use of external tracheal stabilization techniques in animals, but limitations included the restricted growth of the trachea due to the fixed-size implant and the premature splint degradation (17). Three-dimensional printing (3DP) has been used in various medical devices in the past, including many cases of pediatric TM, but has never been reported in adults (18-20). In their case report published in this issue, the authors developed a 270° open-ring scaffold that is bio-absorbable and meant to last for 24 months to maintain the native airway. It is composed of polycaprolactone, which over the 24 months degrades into H_2O and CO_2, causing fibrosis and hyperplasia of surrounding tissues allowing the malacic trachea to solidify. The scaffold was printed after the tracheal malacic segment was recreated using the patient's personal chest CT and bronchoscopy findings. The scaffold was inserted by a posterolateral thoracotomy and required the ligature of the azygos vein and bronchoscopy to choose optimal sites for suture placement. A pleural patch was placed around the 3DP scaffold to alleviate abrasion to surrounding organs. The patient was kept on a ventilator for 48 hours and discharged after two weeks. Follow-up after three months showed improvement in breathing, stable position of the scaffold and maintained tracheal patency on chest CT.

This case report demonstrates a personalized therapy for TM, with the added benefit of not leaving a permanent foreign body within the patient (i.e., airway stent). However, further investigations are warranted with similar techniques in more patients. Long-term follow-up will be necessary to evaluate complications, as well objective documentation of change in symptoms according to validated dyspnea, performance status or QOL scales. Also, to our knowledge, there are no published reports on 3DP biodegradable airway stents that could be inserted bronchoscopically for TM. If feasible, this procedure will preclude the need for thoracotomy and its associated morbidity. Thus, the use of personalized 3DP for TM remains to be defined. Potential therapies recently studied in animal models might include

tissue-engineering techniques with collagenous connective tissue membranes (bio sheets) as a potential tracheal substitute material (21,22). These will have to be validated in humans prior to implementation in practice.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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