

Bronchial Thermoplasty A Nonpharmacologic Therapy for Severe Asthma



Fayez Kheir, MD, MSc^{a,b}, Adnan Majid, MD^{a,*}

KEYWORDS

• Bronchial thermoplasty • Asthma • Bronchoscopy • Airway smooth muscles

KEY POINTS

- Severe asthma accounts for substantial morbidity and increased health care use.
- Bronchial thermoplasty is a novel therapeutic modality that targets airway smooth muscles in patients with severe asthma and chronic airflow obstruction.
- Current evidence suggests that bronchial thermoplasty is effective in reducing asthma exacerbations and emergency department visits, and improving quality of life.
- Long-term studies have demonstrated that bronchial thermoplasty is safe and has sustained clinical benefits when used to treat patients with severe asthma.

INTRODUCTION

Asthma is characterized by nonspecific airway hyperreactivity, and chronic inflammation and intermittent respiratory symptoms of breathlessness, wheeze, and cough triggered by infection, environmental allergens, or other stimuli. It affects more than 25 million people in the United States.¹ Asthma treatment aims at (1) reducing inflammation with inhaled corticosteroids (ICS), (2) relaxing airway smooth muscle (ASM) with inhaled bronchodilators, (3) minimizing exposure to allergic triggers, (4) modifying the allergic response, (5) addressing confounding comorbidities, such as anxiety, rhinosinusitis, vocal cord dysfunction, obesity, and gastroesophageal reflux disease, as well as smoking, and (6) patient education. Despite these measures, around 5% to 10% of patients will have persistent symptoms.^{2,3} Unfortunately,

such patients will have substantial morbidity and mortality and increased health care use, as well as decreased quality of life.⁴

According to the recent guidelines of European Respiratory Society and American Thoracic Society, severe asthma is defined as asthma that requires treatment with high-dose ICS as well as a second controller, including the possible use of systemic corticosteroids; symptoms can be either controlled or uncontrolled with such therapy.² It is important to recognize that severe asthma represents a heterogeneous group of multiple phenotypes and, thus, treatment is tailored according to the underlying pathophysiologic mechanism(s) contributing to such illness.⁵ Omalizumab is a monoclonal antibody targeting IgE that might lead to better asthma control in patients with a predominant allergic phenotype.⁶ Monoclonal antibodies against interleukin-5 have also shown

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^a Division of Thoracic Surgery and Interventional Pulmonology, Beth Israel Deaconess Medical Center, Harvard Medical School, 185 Pilgrim Road, Deaconess -201, Boston, MA 02215, USA; ^b Division of Pulmonary Diseases, Critical Care and Environmental Medicine, Tulane University Health Sciences Center, Tulane Medical Center, 1430 Tulane Avenue, New Orleans, LA, 70112 USA

* Corresponding author.

E-mail address: amajid@bidmc.harvard.edu

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substantial benefit in patients with the eosinophilic asthma phenotype, whereas antibodies against interleukin-4 α and 13 have shown promise in patients with T2 allergic severe asthma phenotype.⁶ Bronchial thermoplasty (BT) is a relatively new technique aiming at reducing ASM that potentially might lead to improving quality of life and reducing exacerbations in patients with severe asthma. This review focuses on BT and how clinicians could potentially select the appropriate patient for such treatment.

BRONCHIAL THERMOPLASTY: ROLE IN SEVERE ASTHMA

Chronic airflow obstruction in severe asthma is probably due to increased airway wall thickness from airway remodeling caused by various mechanisms, such as epithelial thickening, subepithelial fibrosis, smooth muscle hypertrophy, inflammatory cell infiltration, and goblet cell hyperplasia.^{7,8} BT is a novel approach aiming to target ASMs in an attempt to help reverse airway remodeling. This aim is achieved by delivering controlled thermal radiofrequency (RF) energy to the airway walls causing a reduction in ASM contractility and quantity. Based on preclinical as well as large clinic trials, the US Food and Drug Administration approved BT for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well-controlled despite treatment with ICS and long-acting bronchodilators in April 2010.

BRONCHIAL THERMOPLASTY DEVICE

BT is delivered by the Alair Bronchial Thermo-plasty System (Boston Scientific, Natick, MA) and consists of a RF controller and a disposable catheter with an expandable 4-arm array at its distal tip inserted through the working channel

(2 mm) of a bronchoscope and is marked at 5-mm increments (Fig. 1). The smaller diameter of the diagnostic bronchoscope is preferred over the larger therapeutic bronchoscope, allowing more thorough visualization and treatment of the distal tracheobronchial tree. The controller is used with a footswitch that initiates the delivery of RF thermal energy. The electrical energy (18 W) applied for 10 seconds and delivered through the electrodes is converted into heat (up to a prespecified temperature of 65°C) when met with tissue resistance. A return electrode is placed on the patient’s back or thigh and connects to the RF controller, thereby completing the circuit. BT is delivered in a systematic fashion to airways located beyond the mainstem main bronchi and are on average 3 to 10 mm in diameter because airway resistance occurs in bronchi larger than 2 mm in diameter, causing airway constriction during asthma exacerbation.⁹

BRONCHIAL THERMOPLASTY TECHNIQUE

BT should always be performed by an experienced bronchoscopist and is done in a series of 3 bronchoscopic sessions separated by at least 3 weeks, which allows shorter procedure times and decreases the risks associated with widespread irritation of the airways in patients with severe asthma. BT can be performed either under moderate sedation with benzodiazepine and opioids or under general anesthesia, depending on the preference of the bronchoscopist, anesthesiologist, and institution. Although there are no head-to-head studies comparing both types of anesthesia, at our institution we perform BT under general anesthesia with a laryngeal mask airway because it provides comfort (less coughing) with less desaturation during the procedure, which might impact the number of activations delivered. The first session targets the right lower lobe, the second

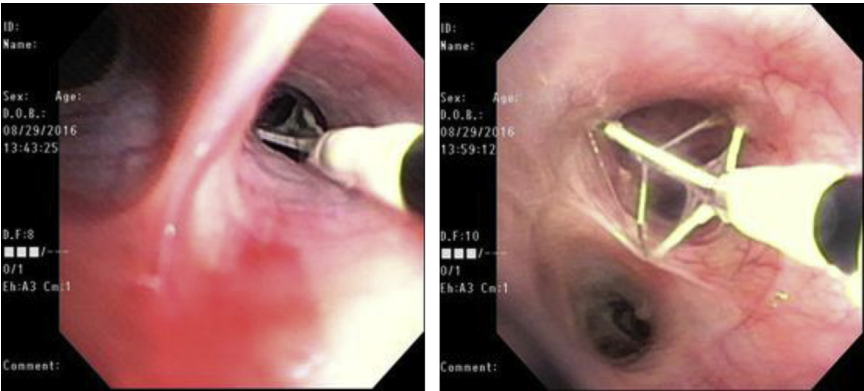


Fig. 1. The catheter is placed distally (left), electrode array expanded (right) and controller then activated.

session targets the left lower lobe, and the final procedure targets both bilateral upper lobes. The right middle lobe is not treated during BT owing to concerns over causing stenosis to this typically long, narrow bronchus and potentially increasing the risk for chronic injury owing to postprocedural inflammation leading to right middle lobe syndrome.^{10,11}

Each BT procedure takes about 30 to 60 minutes, depending on the experience of the bronchoscopist, the type of bronchoscope (we prefer using the Olympus diagnostic bronchoscope BF-P190 [Olympus American Medical, Bridgeport, CT] with an outer diameter of 4.2 mm and 2.0 WC), and the patient's individual bronchial anatomy, because this factor dictates the number of activations that are delivered. The procedure begins with a standard examination of all airways, with particular attention to the lobe being treated. Any mucous should be cleared, because it will impair visualization once BT begins. During subsequent bronchoscopic session, previously treated segments are examined thoroughly for adequate healing to ensure there is no residual inflammation, scarring, or excessive mucous production, because this factor might lead to the postponement of the procedure. Topical 1% lidocaine is important to minimize cough and should be used generously, but not to exceed the toxic limit of 7 to 9 mg/kg.

Airways are treated with thermal energy in a methodical fashion. We typically start with the distal to proximal airway, starting moving from the lateral segment to the medial segment, because this methods will allow the bronchoscopist to systematically target all bronchi in the specified lobe. In this fashion, all airways will be adequately targeted without retreating same airway in error. Large lobar segmental airways are typically the last airways to be treated during a session. Each bronchus is treated in its entire visible length. The bronchoscopist advances the RF catheter tip until it is barely visible at the distal end of the airway, which is at the third to fourth generation of airway before the respiratory bronchiole level. The 4-arm array basket is expanded using a handle to ensure adequate contact with the airway wall, then expanded, and the footswitch depressed, signaling the RF controller to deliver an appropriate amount of thermal energy to the airway. Once an activation is delivered, the basket is collapsed and the catheter is withdrawn 5 mm at a time as indicated by markings on the catheter. This maneuver will allow adequate treatment of the airway without overlap. In general, each treatment session consists of 40 to 70 activations of thermal energy.

PATIENT SELECTION

The US Food and Drug Administration approved BT in 2010 for patients with:

1. Severe asthma with over 18 years of age;
2. Asthma is not well-tolerated with ICS and long-acting beta-agonists;
3. Stable in terms of asthma status with post-bronchodilator forced expiratory volume in 1 second (FEV₁) is within 15% of baseline values;
4. No respiratory tract infection or asthma exacerbation within the last 14 days;
5. Absence of implantable electronic device (pacemakers, internal defibrillator);
6. No sensitivity to drug used in bronchoscopy (atropine, lidocaine, and benzodiazepines);
7. Absence of coagulopathy; and
8. Nonsmoker for 1 year or former smoker with less a than 10 pack-year history.

PATIENT MANAGEMENT

Before the Procedure

1. Systemic oral corticosteroids (prednisone 50 mg) for 3 days before the procedure, the day of the procedure, and 1 day after the procedure to alleviate airway inflammation that may occur (we increase to 60 mg prednisone if FEV₁ < 60% predicted).
2. Inhaled bronchodilator (nebulized albuterol and ipratropium bromide) and nebulized lidocaine are given immediately before bronchoscopy to provide topical anesthesia and improve patient comfort.
3. Oxygen saturation should exceed 90%.
4. An antisialagogue (0.4–0.6 mg atropine intravenously or intramuscularly or 0.2–0.4 mg glycopyrrolate intravenously or intramuscularly) is used to minimize secretions during the procedure and should be administered 15 to 30 minutes before the procedure.
5. Obtain postbronchodilator peak flow (if post-bronchodilator FEV₁ is not readily available).

After the Procedure

1. Short-acting β_2 -agonists.
2. There is a 2- to 4-hour recovery and monitoring period after each procedure.
3. Monitor patient until their postbronchodilator FEV₁ or peak flow is at least 80% of the preprocedure value.
4. Obtain a chest radiograph.
5. Prednisone 50 mg for at least 1 day after the procedure. Some patients might need a prednisone taper for a few days.

Most patients will have increased symptoms (cough, wheeze, chest tightness) during the first 24 to 72 hours after the procedure, but the symptoms typically resolve within 1 week.

Criteria for hospital admission include persistently diminished lung function ($<80\%$ of baseline), oxygen saturation of less than 90% , persistent tachycardia, hypotension, significant hemoptysis (>50 mL/4 h), or altered mental status.

Patients discharged should be followed by telephone at 24 hours, 48 to 72 hours, and 1 week after the procedure and should be seen in the clinic before the subsequent treatment.

BRONCHIAL THERMOPLASTY EVIDENCE

So far, 3 randomized controlled trials support the use of BT for patients with moderate to severe asthma. The Asthma Research Intervention (AIR)¹² trial enrolled patients with moderate to severe, persistent asthma. There was a significant reduction in the rate of mild exacerbations (without reduction in severe exacerbations) and an increase in morning peak expiratory flow rate among patients receiving BT. Furthermore, there was significant improvement in symptom-free days, asthma control, and quality of life in the BT group compared with the control group at 3 and 12 months.

The Research in Severe Asthma (RISA) trial¹³ was a randomized, multicenter trial for patients with severe asthma that demonstrated a clinically significant increase in prebronchodilator FEV₁, and an improvement in asthma control and quality of life at 22 weeks after BT. However, a significant limitation of the AIR and RISA trials was the placebo effect; neither trial was blinded.

The AIR2 trial¹⁴ was a sham-controlled, randomized, multicenter trial that showed an improvement in quality of life, severe exacerbations, decrease in days lost from work, and decrease in emergency department (ED) visits compared with the sham group for up to 12 months. However, the sham group had also improvement in their quality of life, and the difference between Asthma Quality of Life Questionnaire (AQLQ) among both groups was less than 0.5 unit (less than the minimum clinically important difference). This finding has created a lot of debate regarding the efficacy of BT. It is important to realize that the clinical difference on the AQLQ instrument reflects within-group changes, but cannot meaningfully be applied to detect between-group differences.¹⁵ Furthermore, the improvement in the control arm could be attributed to the increased attention given to participants during a clinical trial.

To summarize, 3 clinical trials showed improvement in asthma symptoms compared with the

control group after BT, albeit with an increase in the number of adverse events in the BT group during the treatment period. Importantly, all these trials included patients with evidence of variable airflow obstruction but with an FEV₁ of 50% or more of the predicted value and fewer than 3 exacerbations per year. Extrapolation of clinical benefits of BT beyond this population should be interpreted with caution.

LONG-TERM OUTCOMES AND SAFETY

Although the 3 randomized clinical trials of BT showed marked improvements in asthma-related quality of life and a decrease in the number of exacerbations, the longevity of such findings were not assessed in those trials. Furthermore, concerns regarding the long-term effects of thermal injury on lung function and airway stenosis remain unknown. Recently, the long-term follow-up of patients enrolled in the AIR, RISA, and AIR2 trials have been published to address such questions.^{16–18}

From the cohort of the AIR trial (56 in each arm), 45 patients from the BT group and 24 patients from the control group were followed for a total of 5 and 4 years, respectively. Although patients who underwent BT had similar rates of respiratory adverse events, oral corticosteroid bursts, hospitalizations, and ED visits as compared with the control group, they showed marked improvements in airway hyperresponsiveness for 3 consecutive years after BT. Furthermore, there were no changes in pulmonary function tests or airway structural changes on serial chest imaging.¹⁶

From the RISA trial, 14 of 15 patients in the BT arm and none from the control arm were followed for a total of 5 years. There was a significant decrease in hospitalization and ED visits when compared with the year before BT. Also, pulmonary function tests showed no deterioration over the follow-up period.¹⁷

From the AIR2 trial, 162 of 190 patients who received BT were followed for up to 5 years after treatment. There was a reduction in severe exacerbations (around 30% for each year of the 5-year follow-up period as compared with 51.6% in the year before BT), and ED visits. In addition, among those treated with BT, nearly 30% of patients were able to decrease their ICS dosage by 50% or more. Similar to the long-term follow-up of previous trials, there was no change in pulmonary function tests. Furthermore, high-resolution computed tomography (HRCT) images were followed in 93 patients and did not show significant structural changes, except for 1 patient who had new bronchiectasis after BT. However, it is unclear whether

this finding was related treatment or to the progression of severe asthma. Also, in patients who achieved a minimal clinically important difference in AQLQ scores after BT had lower rates of severe exacerbations, ED visits, and hospitalizations as compared with those who did not. This finding might help predict which patients will derive the most long-term benefit after BT.¹⁸ Furthermore, 2 ongoing clinical trials (NCT01350336 and NCT02104856) will assess the proportion of patients experiencing severe exacerbations after BT and will hopefully confirm the long-term benefits of such therapy.

To summarize, long-term studies showed that BT seems to have acceptable long-term safety as well as sustained improvements in quality of life, airway hyperresponsiveness, severe exacerbations, and ED visits without deterioration in lung function tests.

BRONCHIAL THERMOPLASTY IN VERY SEVERE ASTHMA

Large clinical trials of BT have excluded patients with very severe asthma (defined as patients with an FEV₁ of <50%, intensive care unit admissions in the previous year or regular steroid treatment of >10 mg/d) owing to concerns of safety and airway injury. However, such a population is attractive for BT treatment because they have the highest use of health care resources as well as probably being more resistant to steroids and less likely to be an allergic or atopic phenotype.^{5,19,20}

In a case series of 8 patients with very severe asthma and a mean FEV₁ of 52% of predicted (5 patients with mean FEV₁ of 37% of predicted), there were no severe adverse events, significant decreases in FEV₁, or clinical deterioration. There were 9 overnight hospitalizations after a total 24 BT procedures performed. Long-term follow-up in this cohort showed 5 patients with significant clinical improvement and 3 with no clinical change.^{21,22} Another published small cohort of 22 patients (14 with very severe asthma) showed that 17% had severe complications in very severe group as compared with 4.3% in less severe group after BT treatment. However, BT reduced ED visits and provided improvement in quality of life.²³ In another recently published small case series of 10 patients with an FEV₁ of less than 60% predicted, there was significant improvement of FEV₁ from 49.2 ± 9.6% to 61.8 ± 17.6% as well as quality of life 6 months after BT. One patient required prolonged hospitalization beyond the usual planned overnight admission after each BT procedure.²⁴

BRONCHIAL THERMOPLASTY COST EFFECTIVENESS

Few studies have assessed the long-term cost effectiveness of BT. Zafari and colleagues²⁵ suggested that there is a greater than 60% chance that BT becomes cost effective relative to omalizumab and standard therapy at the willingness to pay of \$100,000 per quality-adjusted life-year in patients with moderate-to-severe allergic asthma projected over a 5-year period. Another study showed that BT is cost effective as compared with standard therapy at a willingness to pay of \$50,000 per quality-adjusted life-year projected over a 10-year period in patients with severe asthma.²⁶ Another model-based analysis compared the estimated cost effectiveness of standard therapy for severe asthma with the cost effectiveness of BT in addition to standard therapy projected over a 5-year period. These investigators concluded that BT is a cost-effective treatment option for patients with poorly controlled, severe, persistent asthma.¹ However, a recent study in Singapore demonstrated that BT is not cost effective as compared with standard therapy, likely because of the low costs of hospitalization and ED visits.²⁷ It seems that such therapy might reduce overall costs; however, continued follow-up of patients who underwent BT beyond 5 years as well as further comparative studies with other therapies are needed to confirm such efficacy.

BRONCHIAL THERMOPLASTY ADVERSE EVENTS

The most common adverse events after BT is temporary worsening of respiratory-related symptoms such as dyspnea, wheezing, cough, and upper respiratory tract infections. They usually occur within 1 day of BT and abate within 1 week. Severe complications requiring hospitalizations are infrequent, and occurred in up to 8.4% during treatment, 3.3% at 1 year after BT, and 4.2% at 2 years after BT in the AIR2 trial.^{14,28} So far, there has not been evidence that BT can cause bronchiolitis obliterans, pulmonary emphysema, airway scarring, or stricture.^{14,28}

Furthermore, the reported incidence of bronchiectasis in BT is 0.2% per year.¹⁴ This finding is similar to the observed incidence seen in patients with severe asthmatics on medical therapy alone arguing that BT does not cause bronchiectasis.^{29,30} One case report showed bronchial wall thickening 7 days after BT in the same region of treatment in an asymptomatic patient that completely resolved when a repeat computed

tomography scan of the chest was done 40 days later.³¹ Another case of hemoptysis requiring hospitalization and bronchial artery embolization occurred in AIR2 trial¹⁴ and a case of right hemothorax with bronchial artery pseudoaneurysm requiring embolization 3 days after BT.³²

WHEN SHOULD BRONCHIAL THERMOPLASTY CONSIDERED IN ASTHMA THERAPY?

To date, there are no comparative trials to evaluate BT and biologic agents in patients with severe asthma and more studies are needed to identify which asthma phenotype will have the greatest response, and whether BT should be implemented earlier or reserved as a last option in the treatment of severe asthma. One study evaluated the predictors of BT response in 42 patients. Demographics, lung function test, AQLQ, asthma control, health care use, and HRCT were recorded at baseline and 12 months after therapy. Patients with a;shorter duration of asthma, frequent exacerbations in the

year before treatment, lower quality of life, and higher oral corticosteroid dose predicted response to BT. In addition, patient with less air trapping (ie, less small airway disease) on HRCT tended to respond better to BT.³³

Before considering BT for patients with severe asthma (Fig. 2), it is important to consider the following:

- 1. Review adherence to therapy of high-dose ICS and long-acting beta agonist combinations as well as inhaler technique (through an asthma educator nurse).
- 2. Screen for environmental factors and allergen that might be modified or removed from the patient’s surroundings.
- 3. Screen for other contributing diseases such as vocal cord dysfunction, postnasal drip, and gastroesophageal reflux disease.
- 4. Perform dynamic HRCT chest scans to assess for interstitial lung disease, emphysema, bronchiectasis, airway trapping, and

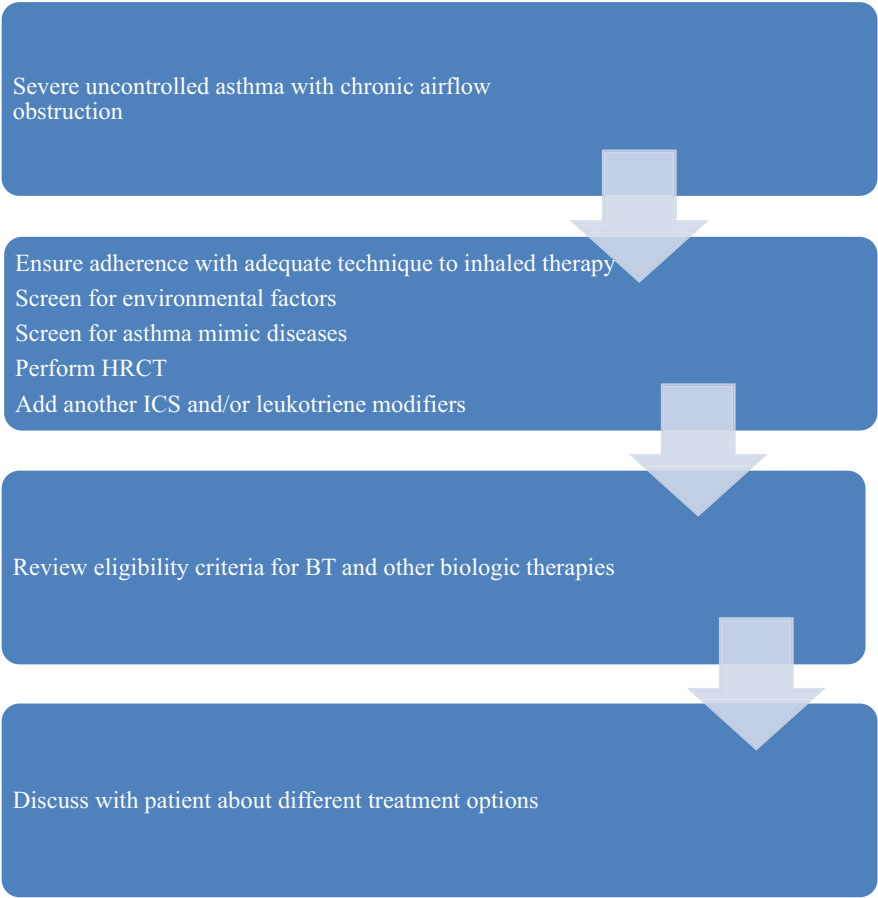


Fig. 2. Proposed algorithm before considering bronchial thermoplasty (BT). HRCT, high-resolution computed tomography; ICS, inhaled corticosteroids.

tracheobronchomalacia that would contribute to patient respiratory symptoms.

5. Consider adding second ICS and/or leukotriene modifiers
6. Consider anti-IgE treatment (omalizumab) in patients with a predominant allergic component (IgE > 30kU/l) or anti-interleukin 5 (mepolizumab) in patient with a predominant eosinophilic component (blood eosinophils >300–400 cells/ μ L).

BRONCHIAL THERMOPLASTY AND IMAGING

Few reports have addressed whether changes occur in the endobronchial lumen and airway walls after BT. One report used 3-dimensional airway analysis software and showed dilation of the bronchial lumen and decreased bronchial wall thickness before and after BT sessions.³⁴ Another report evaluated optical coherence tomography (OCT), a minimally invasive imaging technique for visualizing airway wall structures with near-histologic resolution, in 2 patients with severe asthma before and after BT.³⁵ In the patient who responded to BT, there was thickened airway wall without evidence of inflammation in the epithelial layer at baseline, as well as remarkable reduction in airway wall thickness that persisted for 2 years after BT as shown on OCT, which translated to clinical improvement in respiratory symptoms as compared with the patient who did not respond to BT. This observation generated a hypothesis to assess whether OCT can predict which population will benefit from BT. Currently, there are ongoing trials assessing the usefulness HRCT (NCT01185275), MRI (NCT01832363), and OCT (NCT02975284) to identify the phenotypes of patients that would be best treated with BT.

BRONCHIAL THERMOPLASTY AND IMMUNOMODULATION

Previous studies have demonstrated that BT reduces ASM few weeks after treatment. Besides ASM, BT seems to reduce (1) subepithelial fibrosis,³⁶ (2) concentrations of transforming growth factor- β 1, chemokine (C-C motif) ligand 5 and eosinophils in the bronchoalveolar lavage,³⁷ as well as (3) nerve cell receptors³⁸ as a component of airway remodeling. There are several ongoing studies (NCT02225392, NCT01974921, NCT01839591, ISRCTN94263922) evaluating the molecular, cellular, and histopathologic changes that should provide a better understanding of the underlying mechanism by which BT improves asthma control.

BRONCHIAL THERMOPLASTY AND PATHOLOGY

Few studies have assessed the histopathologic changes that occur in the airways after BT treatment. In a recent study, Pretolani and colleagues³⁹ assessed different bronchial structures of 15 patients with severe asthma who had BT with bronchial biopsy before and 3 months after therapy. They found a remarkable reduction in ASM, neuro-endocrine epithelial cells, and bronchial nerve endings that was associated with an improved clinical outcome of fewer exacerbations and ED visits, as well as improvement in quality of life. Another study showed decrease in ASM on biopsy and inflammatory cytokines on bronchoalveolar lavage 6 weeks after BT.³⁷ In another cohort study of 17 patients, ASM and collagen deposition were reduced significantly after BT treatment.³⁶ These studies suggest that sustained ASM reduction is associated with clinical benefit from BT. However, it remains unknown whether ASM regenerate after BT or which mechanism leads to persistent ASM hypertrophy or hyperplasia in nonresponders to BT.^{40,41}

Gordon and colleagues⁴² reported a histologic grading system to assess inflammation and structural remodeling on endobronchial biopsy in patients with severe persistent asthma. As compared with controls, patients with severe asthma have goblet cell hyperplasia, intraepithelial eosinophils, intraepithelial lymphocytes, and prominent smooth muscle. Such a grading might help clinicians to decide which patients might benefit from BT or biological targeted therapies.

SUMMARY

BT is regarded as a novel approach with a high safety profile and sustained effect in carefully selected patients with severe asthma and chronic airflow obstruction targeting ASM, which leads to airway remodeling. BT has demonstrated significant improvements in the quality of life, decrease in emergency room visits and exacerbations, as well as decreases in steroid use in a carefully selected population. However, questions regarding the mechanism leading to improvement in asthma symptoms after BT as well as predictors and optimum phenotypic response of such therapy remain to be answered.

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