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Bronchial Thermoplasty: A Novel Therapy for Severe Asthma

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Synopsis

This article presents an overview of bronchial thermoplasty, a novel treatment for severe asthma. Within, the authors discuss the rationale for bronchial thermoplasty in severe asthma, current clinical evidence for the use of this procedure, clinical recommendations, and future directions.

Keywords

Bronchial thermoplasty; severe asthma; airway remodeling; airway smooth muscle

Introduction

Asthma is an airway disease characterized by chronic inflammation, bronchial hyperreactivity, and variable airflow obstruction triggered by a variety of stimuli, including allergens and infections. The prevalence of asthma has been steadily rising in the United States and in 2010 was estimated to affect 8.4% of the population, or 25.7 million people.¹ Health care costs from asthma in the United States are estimated at \$56 billion annually.²

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Every year, over 50% of asthma patients experience exacerbations of asthma, which are characterized by cough, wheezing, chest tightness, and dyspnea.³ These symptoms are usually reversible, either spontaneously or with treatment, yet those patients who experience frequent exacerbations may have an accelerated decline in lung function as compared to those who do not.⁴⁻⁶ Importantly, those with severe asthma, as defined by recent National Heart, Lung, and Blood Institute (NHLBI) guidelines, often experience the most frequent exacerbations and account for the majority of health care utilization costs in asthma.⁷

Typical pharmacotherapy for asthma includes short-acting β_2 agonists (SABA), long-acting β_2 agonists (LABA), leukotriene modifiers, inhaled corticosteroids (ICS) and oral corticosteroids (OCS). The ATS has defined patients with severe, refractory asthma as those who require OCS over 50% of the year or high-dose inhaled steroids with the goal of obtaining asthma control.⁸ However, for many patients, even this aggressive anti-inflammatory therapy may not be sufficient to achieve adequate control of symptoms. Currently, the only agent approved for add-on therapy for severe allergic asthma which is uncontrolled on inhaled or oral corticosteroids is the anti-IgE monoclonal antibody omalizumab. Omalizumab requires biweekly dosing for some patients, is expensive and provides control only in a subset of asthma patients with allergic disease. New therapies are needed to address the unmet need of patients with severe asthma for whom these therapies are not effective.

Airway Smooth Muscle in Asthma

The smooth muscle within the walls of airways, or airway smooth muscle (ASM), has been postulated to play a role in multiple normal processes in the healthy airway, including regulation of bronchomotor tone, immunomodulation, and extracellular matrix deposition, though some also claim that it is a vestigial structure without a real salutary function.⁹ However, ASM mass is considerably increased in asthma when compared to healthy controls and these same processes contribute to the chronic inflammation and airway remodeling present in severe asthma.¹⁰ In addition, there is substantial hypertrophy and hyperplasia of ASM cells in fatal asthma as compared with non-fatal asthma.¹¹ This increase in ASM mass contributes to the bronchoconstriction, airway inflammation, and airway remodeling seen in severe asthma. It follows that a reduction in ASM in patients with asthma would potentially alleviate the amount of bronchoconstriction present in the airway and perhaps decrease airway remodeling.

Radiofrequency energy has safely been used to treat a variety of clinical conditions, including lung cancer,¹² hepatocellular carcinoma,¹³ and cardiac conduction abnormalities.¹⁴ Early studies in canines showed that radiofrequency at low energies could be safely performed in large airways to reduce ASM mass.¹⁵ This intervention also reduced airway hyperresponsiveness (AHR) within one week, and the effect lasted up to three years. This rapid loss of sensitivity to cholinergic agents may be due to immediate disruption of actin-myosin filaments, though subsequent loss of ASM mass may be due to cellular necrosis or apoptosis.¹⁶ Large airways account for the majority of airway resistance in humans, and therefore pose a viable target for ablation of ASM in patients with asthma.¹⁷ The application of radiofrequency energy to ablate smooth muscle in the large airways of patients with asthma is called bronchial thermoplasty (BT) and is performed using the Alair Bronchial Thermoplasty System (Boston Scientific, Inc, Natick, MA).

The Alair Bronchial Thermoplasty System

The Alair Bronchial Thermoplasty System is comprised of the Alair Controller System (Figure 1), which includes the radiofrequency (RF) controller, a footswitch, and a return electrode, and the Alair Catheter (Figure 2), which contains an expandable 4-arm array and a

handle with depressible actuator. The flexible catheter is 1.5 mm in diameter, sterile, disposable, and designed to be introduced in the working channel of an bronchoscope (ideally 4.9–5.2 mm outer diameter) with a working channel of at least 2.0 mm. Larger bronchoscopes may preclude the access to smaller airways which should be treated.¹⁸ The distal tip of the catheter has an expandable 4-arm array which is designed to make contact with the walls of airways 3–10 mm in diameter. The proximal end of the catheter connects to the controller, which also has inputs for the return gel-electrode (typically placed on the patient's back or thigh) and the footswitch. The depressible actuator is located on the handle at the end of the catheter and controls expansion and collapse of the electrode array. Pressing and releasing the footswitch once triggers the delivery of RF energy through the electrode array on the catheter to the airway wall for 10 seconds, constituting an "activation". The Controller System monitors power, impedance, and duration and delivers an appropriate amount of RF energy to the airways.¹⁵ The bronchoscopist can also press and release the footswitch a second time to terminate the delivery of energy at any time.

Pre-Procedure Assessment

The FDA has approved the Alair bronchial thermoplasty system for the treatment of severe persistent asthma in patients 18 years and older (Alair Package Insert). Selection criteria are outlined in Table 1 and are adapted from inclusion and exclusion criteria from the AIR2 trial, discussed further below.²⁴ A thorough clinical assessment of the patient is imperative prior to performing BT. In order to perform BT safely, any potential patient must have stable asthma symptoms without an increase in rescue inhaler usage and no recent exacerbations or infections in the two weeks preceding the procedure. If a patient meets these criteria, he or she should receive prednisone at 50 mg/day for the three days prior to the procedure, the day of the procedure, and the day after the procedure to minimize inflammation after BT. On the day of the procedure, the patient's post-bronchodilator FEV₁ should be within 10% of his or her documented baseline and oxygen saturation should be greater than 90%.¹⁸

Prior to the procedure, patients should receive a short acting bronchodilator and an anti-sialogogue, typically atropine (0.4–0.6 mg IV/IM) or glycopyrrolate (0.2–0.4 mg IV/IM). Albuterol or another SABA should be administered by nebulizer (2.5–5.0 mg) or by metered-dose inhaler (4–8 puffs). A topical anesthetic should be used to numb the posterior pharynx and larynx prior to the procedure according to institutional practice.

Moderate sedation should be used during the procedure according to institutional guidelines. We prefer midazolam and fentanyl due to their rapid onset of action, ease of titration, and ease of reversal if necessary. Other institutions have used propofol, and some perform BT under general anesthesia. The amount of sedation given during BT can often be much higher than during typical bronchoscopy due to the fact that the procedure often lasts 45 minutes to one hour. During the procedure, topical anesthesia is paramount to suppress the cough reflex. We initially use three aliquots of 2 mL 1% lidocaine at the level of the vocal cords, followed by 2 mL aliquots of 1% lidocaine along the trachea, on the carina, and down each main stem bronchus. Additional 2 mL aliquots of 1% lidocaine are used as needed during the procedure to anesthetize treated airways. Oxygen supplementation should not exceed 40% FiO₂ to prevent the theoretical concern of airway ignition. The decision for managing the airway during BT is based on the preference of the bronchoscopist. We typically use no endotracheal tube or a laryngeal mask airway (LMA) in those with narrowing of oropharynx. Other institutions have used an endotracheal tube (ETT) and general anesthesia.

Performing Bronchial Thermoplasty

BT should be performed by an experienced bronchoscopist in conjunction with an asthma specialist. Airways are treated in three separate sessions, each three weeks apart: the right

lower lobe is treated in the first session, the left lower lobe in the second session, and both upper lobes in the final session. The right middle lobe is not treated due to concerns of airway collapse secondary to right middle lobe syndrome.¹⁹ In each session, the airway tree is carefully visualized, and the bronchoscopist devises a plan for systematically treating every visual airway in region being treated. In general, the bronchoscopist works from distal to proximal airways, and methodically works from a bronchopulmonary segment to immediate adjacent segments across the lobe until all visible airways that are 3 mm or greater in diameter are treated once and only once. Each activation is recorded on a diagram of the tracheobronchial tree (Figure 3). The lobar segmental airways are typically the last airways treated due to its ease of access. In the second and third sessions, the previously treated lobe is examined to ensure adequate healing from the previous session. If the previously treated airways are still inflamed or have copious mucous secretions, the BT session may need to be postponed and the secretions removed.

After the session has been meticulously planned, treatment of the airways with BT can commence. The catheter is inserted into the chosen airway and should always be kept in bronchoscopic vision. The bronchoscopist should take care not to kink the catheter, which could impede the deployment of the electrode array. Once the catheter has been positioned, the actuator is depressed until all four arms of the electrode array are visualized to be in contact with the airway wall (Figure 4). The bronchoscopist can then press and release the footswitch for the delivery of RF energy, and the Controller System will play an audible cue. Care should be taken not to over-expand the electrode array, which may cause an array arm to invert instead of expand. The array may be cleaned to remove any mucus that accumulates in order to facilitate positioning of the catheter. If the electrode array does not make adequate contact with the airway wall, the Controller System will play a different audible cue, advising the bronchoscopist to make subtle changes with array positioning to ensure adequate contact. If the array is dislodged (e.g. by a strong cough), the system will automatically abort the activation. Once the Controller System delivers the RF energy, the actuator may be released and the catheter drawn proximally 5 mm, as noted by the marks on the catheter shaft. Activations should be adjacent to each other along the airway but not overlapping (Figure 5). All planned airways are treated in this fashion until the session is complete. A typical session lasts 45 minutes to 1 hour, and involves up to 100 activations.

Post-Procedure Assessment

After the BT procedure is complete, the patient should be monitored as per normal institutional post-bronchoscopy guidelines. Patients may take longer to recover due to the greater amount of sedation typically required for BT, again due to the fact that BT often takes longer than typical bronchoscopy. Lung sounds should be auscultated immediately after the procedure and again prior to discharge. After patients recover from sedation, post-BT spirometry measurements are performed. Patients must have a post-bronchodilator FEV₁ of 80% of their pre-procedure measurement to be considered for discharge. Serial measurements are sometimes needed due to delayed recovery. Patients may need to be admitted for observation if recovery from BT is delayed (see Table 2 for criteria for hospital admission). Once patients are discharged after BT is performed, they should be notified that they may experience worsening symptoms of asthma and should take prednisone as prescribed. Patients often experience more coughing, wheezing, chest tightness and dyspnea in the 24–48 hours following BT, but these usually improve within 1 week after BT and can be treated with bronchodilators and if needed, systemic corticosteroids. A clinical provider should maintain close follow-up with the patient by phone at 24 hours, 48 hours, and 1 week to assess clinical symptoms. A clinic visit is typically scheduled 2–3 weeks after a BT treatment for follow-up as well as to assess clinically in anticipation of subsequent BT treatments.¹⁸

Clinical Evidence for Bronchial Thermoplasty

The first trial of BT in humans was done to determine the safety of the procedure in eight subjects who were scheduled to undergo lung resection for suspected or proven lung cancer.²⁰ All subjects tolerated the therapy well and proceeded to their planned surgery. One subject showed signs of airway narrowing but was asymptomatic. When the Alair system was used to apply a temperature of 65° C to the airways, a notable reduction in ASM was observed on histopathologic specimens. Subsequently, Cox and colleagues carried out a prospective, non-randomized feasibility study in 16 subjects with mild to moderate asthma to determine the safety of the procedure in this population.²¹ All subjects had stable asthma without recent infection or exacerbation of asthma symptoms. BT was safely performed in a similar fashion to the description above. One subject received only two treatments due to recurrent infections after the second treatment. Adverse events were common shortly after the procedure, including cough, dyspnea, wheezing, and bronchospasm. However, these symptoms resolved within 1 week of the procedure, and there were no hospitalizations or emergency room visits related to asthma exacerbation within 12 weeks of the first BT treatment. Lung function did not change significantly over two years, but AHR improved at 12 weeks, 1 year and 2 years as measured by methacholine bronchoprovocation challenge and subjects experienced more symptom free days at 12 weeks.

The Asthma Intervention Research (AIR) Trial was the first randomized, controlled trial of BT and enrolled 112 patients with moderate to severe persistent asthma, who were randomized to LABA plus ICS, or BT with LABA plus ICS.²² Subjects included were on LABA plus ICS prior to enrollment, had documented AHR and airway obstruction (pre-bronchodilator FEV₁ 60–85%), and stable asthma symptoms but had clear worsening of asthma symptoms as measured by the Asthma Quality of Life Questionnaire (AQLQ) if LABA therapy was withdrawn for 2 weeks. The primary outcome measured was mild exacerbation rate during periods of LABA withdrawal, as defined by reduction in morning peak expiratory flow (PEF), increased rescue medication use, or nocturnal asthma symptoms. The rate of mild exacerbations over one year in subjects in the BT arm was halved, while the rate of mild exacerbations in the control arm remained the same. Subjects who received BT were estimated to experience 10 fewer mild exacerbations within the first year, used less rescue medication, and had more symptom free days. There were more adverse events in the BT arm, usually worsening of asthma control with most occurring within 1 day of a BT treatment.

The Research in Severe Asthma (RISA) trial was a randomized, controlled trial in which subjects with severe persistent asthma on high-dose ICS with LABA and with AHR were randomized to receive BT or continue current therapy. Six weeks after treatment, subjects in both groups were maintained on stable doses of steroids for 16 weeks before entering a “wean phase” in which OCS and ICS doses were weaned at pre-determined time points over one year.²³ 4 of 8 subjects in the BT arm and 1 of 7 subjects in the control arm were weaned off OCS at one year. In addition, patients in the BT arm had improved asthma symptoms by the Asthma Control Questionnaire (ACQ) and AQLQ, and had decreased rescue medication use and increased pre-bronchodilator FEV₁ as compared with the control arm. Adverse events included lobar collapse in two patients in the BT arm requiring therapeutic aspiration of mucus.

The most recent and largest trial of BT to date is the Asthma Intervention Research 2 (AIR2) trial performed by Castro and colleagues.²⁴ In this study, 288 adults with severe asthma on ICS and LABA with a low AQLQ score, frequent symptoms, and documented AHR by methacholine bronchoprovocation were randomized to BT or a sham procedure. Importantly, the subjects included in AIR2 had to be on at least 1,000 µg/d of

beclomethasone or an equivalent ICS, which is a much higher required dose of ICS than in the original AIR trial (200 µg/d of beclomethasone or equivalent). In addition, subjects in AIR2 were all classified as severe asthmatics, as opposed to the original AIR which also included those with moderate disease.

The sham procedure in AIR2 was identical to the BT procedure with the exception that the Alair catheter did not deliver any RF energy when the foot pedal was depressed. 190 patients were randomized to BT and 98 patients were randomized to the sham procedure. Adverse events were similar in both groups, though more patients were hospitalized in the BT arm (8.4%) as compared to the sham arm (2%). Reasons for hospitalization included worsening of asthma, segmental atelectasis, lower respiratory tract infection, hemoptysis, and low FEV₁. Though both arms experienced significant improvements in quality of life as measured by AQLQ, 79% of subjects in the BT arm reported a clinically meaningful increase of 0.5 in AQLQ as compared with 64% in the sham arm. This highlights the strength of the placebo effect in patients with severe asthma in a proper sham-controlled trial, as has been documented in sham-controlled studies in other diseases as well.^{25,26} Importantly, in the year following BT or sham treatment, subjects in the BT arm had a 32% decrease in severe exacerbations, 66% decrease in days work/school days lost due to asthma symptoms, and an 84% risk reduction in emergency department visits.

The Alair Bronchial Thermoplasty System received FDA approval in 2010 for the treatment of severe, refractory asthma. A post-approval study is currently ongoing to measure treatment effect and safety. In addition, long-term follow-up data are available for several of the studies discussed above which demonstrate the safety and persistence of effect of BT.^{27–31} Five-year follow up data from the original AIR trial showed no increase in adverse events and stable lung function in those subjects who received BT.²⁸ Furthermore, two year follow-up from the AIR2 trial has showed that the decreased health care utilization and severe exacerbation rates in subjects with BT as compared with sham treatment were maintained between year 1 and year 2.³¹ Follow-up beyond year 2 is currently ongoing.

Conclusions

Bronchial thermoplasty is a novel treatment option for patients 18 and older with severe asthma for whom management with conventional pharmacotherapy has been ineffective in controlling asthma symptoms. The procedure should be performed by an experienced bronchoscopist in conjunction with an asthma specialist. Clinical studies have shown improved asthma symptoms, fewer severe exacerbations and decreased health care utilization with bronchial thermoplasty. Clinical experience has shown bronchial thermoplasty to be a safe and well-tolerated procedure that presents many potential benefits to patients with severe, refractory asthma.

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Key Points

- Traditional asthma controller medications are often unsuccessful in controlling the symptoms of patients with severe asthma.
- Bronchial thermoplasty presents a novel therapy in which radiofrequency energy is used to decrease bronchoconstriction by a reduction in airway smooth muscle.
- Current clinical evidence suggests that bronchial thermoplasty may be effective in reducing asthma exacerbations and improving asthma symptoms.
- Long term data suggests that bronchial thermoplasty is safe and a disease modifier with persistence of effect.

Figure 1.
The Alair Controller System

Figure 2.
The Alair Catheter with expandable 4-arm array. Black markings are measured at 5 mm intervals from the tip.

BT Procedure Lung Map

Figure 3.
Diagram of the tracheobronchial tree used for planning BT and recording activations.

Figure 4.
The Alair Catheter with deployed array in a subsegmental airway.

Figure 5. Schematic showing the method for performing adjacent activations in an airway.

Table 1

Inclusion and exclusion criteria for bronchial thermoplasty (Adapted from AIR2 Trial)

Inclusion Criteria	➤ Adults ages 18–65 ➤ Severe persistent asthma (symptoms throughout the day, symptoms most nights, SABA use several times per day, normal activities are extremely limited by disease) ➤ Currently using regularly scheduled high-dose ICS and LABA ➤ Positive methacholine bronchoprovocation test ($PC_{20} < 8\text{mg/ml}$) ➤ Pre-bronchodilator FEV_1 60% predicted at baseline OR post-bronchodilator $FEV_1 > 65\%$ predicted ➤ Non-smoker for at least 1 year OR < 10 pack year smoking history if current smoker
Exclusion Criteria	➤ History of life-threatening asthma requiring intubation ➤ ICU admission for asthma in past 24 months without intubation ➤ 3 hospitalizations for asthma exacerbations in the last 12 months ➤ >3 lower respiratory tract infections requiring antibiotics in the last 12 months ➤ >4 pulses of OCS in the last 3 months ➤ Known sensitivity to medications required to perform bronchoscopy ➤ Patients with a pacemaker, internal defibrillator, or other implantable electronic device.

Table 2

Hospital Admission Criteria (Adapted from PAS2 clinical guideline)

➤	Severe or persistent cough at end of monitoring period
➤	Failure of post-bronchodilator FEV ₁ to return to within 20% of pre-procedure level at end of monitoring period
➤	Persistent oxygen saturation <90% at end of monitoring period
➤	Persistent tachycardia >130 bpm at end of monitoring period
➤	Unexpected altered mental status during or after procedure
➤	Hemoptysis >50 ml during 4 hour post-recovery period
➤	Excessive requirement of bronchodilator during monitoring period
➤	Absence of companion or care-giver to assist on the day of treatment