Bronchial Thermoplasty

33

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Introduction

Asthma is a chronic pulmonary disease characterized by recurrent episodes of bronchial hyperresponsiveness and airflow obstruction. During these episodes, patients experience coughing, wheezing, chest tightness, and dyspnea. The symptoms are typically reversible, either spontaneously or with treatment. These symptoms are the result of a number of pathophysiologic processes including airway remodeling characterized by airway epithelial injury, subepithelial fibrosis, excess mucus secretion, airway inflammation, and increased airway smooth muscle mass [1–3]. In a subgroup of patients with severe asthma, increased airway smooth muscle mass is thought to contribute considerably to persistent airflow obstruction that is difficult to manage, even with the maximal medical therapy [4]. Bronchial thermoplasty (BT) was developed to reduce airway smooth muscle mass in the treatment of severe persistent asthma.

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The Impact of Severe Asthma

Asthma is a major global health concern. Estimates suggest that almost 300 million people worldwide have asthma. In developed countries, the prevalence of asthma can exceed 15% [5]. While asthma is less prevalent in developing countries, the prevalence is increasing at an alarming rate [6]. Over 24 million people in the United States have asthma [7]. Poorly controlled asthma imposes a significant disease burden resulting in decreased quality of life, increased healthcare utilization, and significant economic burden [8]. There were nearly 13.6 million unscheduled physician office visits, 1.8 million emergency room visits, 450,000 hospitalizations, and 3600 deaths attributable to asthma in the United States in 2012 [7]. The estimated annual cost of asthma in the United States is approximately $56 billion, including $5.9 billion in indirect costs like lost work days, and $50.1 billion in direct costs such as medications and healthcare utilization [9].

Asthma is currently managed with the use of long-term controller medications, to achieve and maintain control of persistent asthma, and quick-relief medications to treat acute symptoms and exacerbations. Long-term controller medications include inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), muscarinic antagonists (LAMA), monoclonal antibodies (anti-immunoglobulin (Ig)E and anti-interleukin (IL)-5), and, in a subset of patients, chronic oral corticosteroids. Approximately 15–20% of asthmatic patients

J.P. Díaz-Jimenez, A.N. Rodriguez (eds.), *Interventions in Pulmonary Medicine*,
https://doi.org/10.1007/978-3-319-58036-4_33

have severe persistent asthma, defined by the presence of persistent asthma symptoms despite treatment with the best available medications [4]. The most severe asthmatic patients have refractory asthma. These patients constitute approximately 5–10% of all asthmatic patients and are defined by a requirement for treatment with high-dose inhaled corticosteroids plus a second controller medication or the need for continuous or near continuous (> 50% of year) oral corticosteroids [10]. Patients with severe persistent asthma present the greatest burden to the healthcare system [11], with refractory asthmatics having the most concentrated healthcare utilization including intensive care unit stays [4].

Limitations of Current Therapeutic Interventions

Although the current treatment of severe asthma has improved the level of asthma control, refractory asthmatics do not achieve disease control and have recurrent exacerbations requiring systemic corticosteroids [4]. Chronic oral corticosteroid use is associated with undesirable side effects ranging from mild annoyances to serious, irreversible organ damage. These side effects occur more frequently with higher doses and more prolonged treatment and include immunosuppression, adrenal suppression, growth retardation, osteoporosis, skin thinning, hypertension, cataracts, glaucoma, muscle weakness, and increased risk of infection. Short-term side effects include stomach upset, headache, dizziness, anxiety, agitation, trouble sleeping, fluid retention, weight gain, high blood pressure, hypokalemia, elevated cholesterol, and vision changes. There is, therefore, a critical need for additional therapeutic options for patients with corticosteroid-dependent asthma.

More recently, several biologic agents that target specific subsets of patients with severe asthma are either approved for use or undergoing clinical trials. Omalizumab, a monoclonal antibody to IgE, is FDA approved and is appropriate for patients with a predominant allergic component and severe uncontrolled asthma [12]. The most recent biologic therapies are antibodies to IL-5, mepolizumab and reslizumab, that are best suited for severe uncontrolled asthmatic patients with a predominant eosinophilic component [12]. Over the past decade, BT has been developed as a novel device-based approach for the treatment of severe persistent and refractory asthma.

The Rationale for Bronchial Thermoplasty

In normal airways, smooth muscle offers support, enables mucus clearance, enhances cough, and promotes lymphatic flow [13]. Chronic asthma is associated with a pathologic increase in airway smooth muscle mass [2, 14]. This excess airway smooth muscle constricts in response to asthma triggers resulting in airway hyperresponsiveness, bronchospasm, and severely reduced airflow, leading to difficulty breathing during asthma exacerbations. Early investigations into mechanisms of airflow obstruction and airway resistance demonstrated that 75% of airway resistance occurs in the first 6–8 generations of airways, indicating that larger airways are critically important [15]. Therefore, physical reduction of the increased airway smooth muscle mass of asthmatic patients, even in larger airways, could have significant conceivable benefits [16]. By reducing the amount of airway muscle present, the potential for bronchoconstriction may be reduced. The benefits of such an intervention might include less severe bronchoconstriction during exacerbations with fewer symptoms of airflow obstruction and less variability of disease [17]. BT provides a new approach for treating severe persistent and refractory asthma through a reduction in this excess airway smooth muscle mass, with the goal of providing long-term relief of asthma symptoms and reducing exacerbations.

Indications and Contraindications for Bronchial Thermoplasty

BT is currently only indicated for the treatment of severe persistent asthma in patients over the age of 18 whose symptoms are not well controlled with inhaled corticosteroids (ICS) and long-acting beta-2-agonists (LABA) [Alair

Table 33.1 Inclusion and exclusion criteria for bronchial thermoplasty

Inclusion criteria	• Males or females age 18 or greater • Patient has asthma and remains uncontrolled despite using regular maintenance medication for past 12 months that includes: • Inhaled corticosteroid (ICS) at a dosage greater than 1000μg beclomethasone per day or equivalent, AND long acting ß2-agonist (LABA) at a dosage of ≥100μg per day Salmeterol or equivalent • Other asthma medications such as long acting muscarine antagonist (LAMA), leukotriene modifiers, or biologic therapy, are acceptable • Asthma confirmed by: (a) b-agonist reversibility of FEV1 ≥ 12 % following 360mcg albuterol OR (b) 20% fall in forced expiratory volume in 1 second (PC20-FEV1) after a challenge with methacholine ≤ 8 mg/ml if not receiving an inhaled corticosteroid (ICS) or ≤ 16 mg/ml if receiving an ICS • FEV1 ≥ 50% predicted pre-bronchodilator • Patient is a non-smoker for 1 year or greater (if former smoker, less than 10 pack-years total smoking history)
Exclusion criteria	• Asthma exacerbation (ED visit, hospitalization, course of increased systemic steroids, or urgent health care visit for asthma) during the prior four weeks • Asthma exacerbation requiring hospitalization during the prior six weeks. • Chronic oral steroid therapy greater than 30 mg per day • Respiratory tract infection within past 4 weeks • Patient has a known sensitivity to medications required to perform bronchoscopy (such as lidocaine, atropine and benzodiazepines) • Patient has bleeding diathesis, platelet dysfunction, and thrombocytopenia with platelet count less than 125,000/mm2 or known coagulopathy (INR > 1.5) • Patient uses an internal or external pacemaker, cardiac defibrillator, or other implantable electronic device • Patient has clinically significant cardiovascular disease, including myocardial infarction, angina, cardiac dysrhythmia, conduction defect, cardiomyopathy, aortic aneurysm, or stroke

package insert, Boston Scientific, Marlborough, MA]. Patients are deemed appropriate based on inclusion and exclusion criteria from previous and current clinical trials of BT and accepted treatment guidelines for asthma [17, 18]. Table 33.1 outlines important patient selection criteria.

The Bronchial Thermoplasty Apparatus

BT is performed using the Alair Bronchial Thermoplasty System® (Boston Scientific, Marlborough, MA). The system is composed of two principle components (Figs. 33.1 and 33.2):

1. The Alair Controller System, which includes a radiofrequency (RF) controller, a footswitch, and a patient return electrode
2. The Alair catheter, which includes an expandable 4-arm array and an actuator

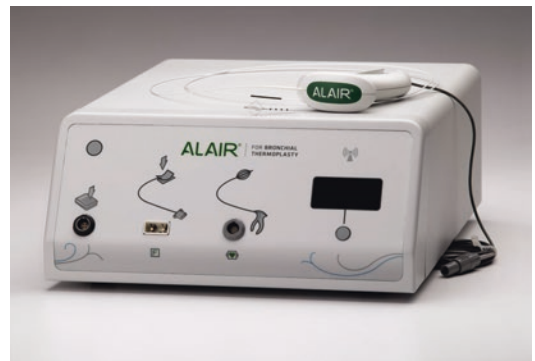

Fig. 33.1 The Alair radiofrequency controller with inputs for the footswitch (*right*), return electrode (*center*), and Alair catheter (*left*). The Alair catheter can be seen resting on the controller

The Alair catheter is a sterile, single-use device that is introduced into the airways through the working channel of an RF-compatible bronchoscope. The bronchoscope should ideally have an outer diameter of 4.9–5.2 mm and a working channel ≥2.0 mm [17]. The catheter has a distal 4-arm

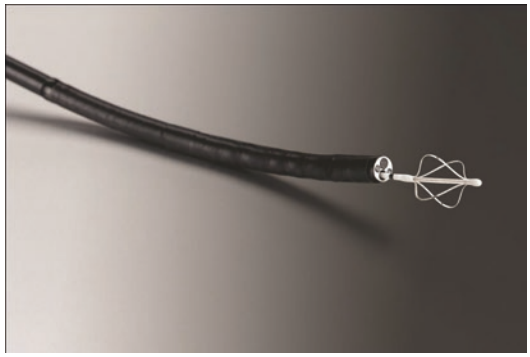

Fig. 33.2 The Alair catheter inserted through the working channel of the bronchoscope with the 4-arm array fully expanded

electrode wire array that expands to contact the airway wall when the proximal actuator is activated. The catheter is connected to the RF controller by a cable attached to its proximal end. The controller also has inputs for the footswitch and the patient return electrode. The footswitch allows the bronchoscopist to initiate delivery of RF energy. The return electrode completes the circuit, providing a pathway for the return of electrical current. This gel electrode is typically placed on the patient's chest or thigh. The RF controller delivers RF energy to the expanded 4-arm array in contact with the airway wall for a duration of 10 s. The RF controller utilizes sensory data from the catheter to limit current, power, voltage, time, and temperature of the RF energy delivered. This allows for the proper intensity and duration of RF energy to be applied while minimizing collateral airway damage. If the bronchoscopist determines that early termination of RF energy is needed, the footswitch can be pressed and released a second time to cease energy delivery [19]. The RF controller also safeguards against incorrect device setup. If any of the individual components are incorrectly connected, or the catheter electrodes fail to contact the airway wall, the device will not deliver RF energy.

Overview of the Bronchial Thermoplasty Technique

BT is performed under conscious sedation to a moderate level or general anesthesia. Visible airways distal to the main stem bronchi are treated by activation of the RF probe against nonoverlapping adjacent airway segments. Airways between 3 and 10 mm in diameter are systematically targeted, starting distally and moving proximally, being careful to avoid overlap with areas already treated [16, 19, 20]. Three sequential procedures are performed with a minimum interval of 3 weeks between each procedure. This allows for adequate healing of the airways between treatments and minimizes the likelihood of an asthma exacerbation [17]. Each treatment addresses a separate lobe, with the exception of the right middle lobe (RML). The RML remains untreated due to its narrow opening and the theoretical concern that inflammation related to the procedure may result in the development of RML syndrome [21]. However, recent experience suggests that the RML can be treated safely [22]. The right lower lobe is treated first, followed by the left lower lobe. Finally, both the right and left upper lobes are addressed in a single treatment. Each treatment takes approximately 45 min to 1 h to perform [16].

Pre-procedure Preparation

In order to facilitate successful BT, adequate pre-procedure preparation is essential. Pre-procedure preparations include (1) reassessing asthma stability and status on the day of each procedure; (2) administration of oral steroids (prednisone 50 mg daily) 3 days before, on the day of, and after each procedure; and (3) administration of inhaled bronchodilators, antisialagogues, anxiolytics, sedatives, and topical anesthetics to facilitate an uneventful procedure.

Clinical assessment of the patient on the day of the procedure is the first step in performing BT. The patient should have no contraindications to routine bronchoscopy. It is imperative to rule out current respiratory tract infections and ensure that the patient has not had a severe asthma exacerbation within 2 weeks of performing the procedure. Finally, the patient should be at baseline with respect to their asthma symptoms and pulmonary function testing performed on the day of the procedure by confirming that the patient's FEV_1 is within 15% of their baseline value [18, 23]. If any of the recommended criteria are not met, bronchoscopy should be postponed.

To reduce inflammation resulting from the application of thermal energy, patients are prescribed

oral corticosteroids (equivalent to 50 mg/day of prednisone) starting 3 days prior to the procedure, on the day of the procedure, and for one day following the procedure [17]. Patients on chronic oral steroids should be increased to the level used to treat their exacerbations. Antisialagogues are administered on the day of the procedure to reduce salivary and tracheobronchial secretions. At our institution, the antimuscarinic agent glycopyrrolate (0.2–0.4 mg IV/IM) is administered a minimum of 30 min prior to initiation of the procedure. Lastly, bronchodilators are administered prior to the procedure to help ameliorate bronchospasm. We make use of nebulized albuterol (2.5–5.0 mg), but albuterol may also be dispensed through a metered-dose inhaler (four to eight puffs) [24].

Maintaining adequate analgesia and proper sedation during BT is necessary because each procedure lasts for up to 1 h. At our institution sedation is accomplished with the combination of a short-acting benzodiazepine and a short-acting narcotic, specifically midazolam (Versed) and fentanyl (Sublimaze). Midazolam (1–2 mg IV initial bolus followed by repeated 1–2 mg IV doses) and fentanyl (50–100 mcg IV initial bolus followed by repeated 25–50 mcg IV doses) are administered alternately throughout the procedure. Sedation level is frequently reassessed during the procedure, and additional sedation is administered as needed. Benefits of this specific drug combination include familiarity with the drugs, rapid onset of action of both agents and their additive effects, convenient dose titration, and the ability to rapidly reverse either agent if needed [18]. Other agents including propofol have been utilized for sedation. Some centers have utilized general anesthesia administered with anesthesiologist assistance. Ultimately, the final decision on sedation is dependent on the physician performing the procedure and institution-specific guidelines.

In order to suppress the cough reflex during bronchoscopy, topical anesthetics are administered prior to and during the procedure. At our institution, anesthetization of the upper airway is achieved using 4 mL of 2% lidocaine nebulized through a mask prior to the procedure. Next, the posterior pharynx and laryngeal area are anesthetized with 5 mL of 1% lidocaine using a syringe with blunt-tip catheter directed over the back of the tongue. The bronchoscopy is initiated, and the bronchoscope is advanced to the level of the vocal cords, which are directly anesthetized with two to three 2 mL aliquots of 1% lidocaine delivered through the working channel of the bronchoscope. Finally, the trachea, carina, and each of the main stem bronchi are anesthetized with 2 mL aliquots of 1% lidocaine until the patient appears comfortable and exhibits minimal coughing. When the bronchoscope is advanced into the airway segments targeted for treatment, additional 2 mL aliquots of 1% lidocaine can be administered. During the procedure it may be necessary to administer additional targeted doses of lidocaine utilizing the intervals when the catheter is removed from the bronchoscope for suctioning. In our experience, the use of 1% lidocaine limits the potential for toxicity. While elevated levels of lidocaine have occurred, toxicity is rare. Lidocaine doses in the range of 400–600 mg (9 mg/kg) appear to be safe in asthmatic patients undergoing bronchoscopy as long as patients are monitored continuously for evidence of toxicity [25, 26]. Signs and symptoms of toxicity include lightheadedness, dizziness, headache, visual disturbances, metallic taste, muscular twitching, tremors, perioral tingling, auditory disturbances, seizures, or loss of consciousness [27].

Due to the length of the procedure and the level of sedation required, the use of an airway device may become necessary. An endotracheal tube (ET) can be used to maintain a patent airway and minimize the number of desaturations but runs the risk of irritating the asthmatic airways, potentially triggering bronchospasm. At our institution, a laryngeal mask airway (LMA) is used when performing BT. It does not enter the trachea, protects the upper airway, and provides comparable benefits to an ET tube. Ultimately the discretion of the bronchoscopist and their level of comfort with the various airway devices will determine which device is optimal.

Intra-procedural Technique

Pathway planning is performed at the beginning of each BT procedure. This is essential and guarantees that no targeted bronchopulmonary segments are missed during each procedure. It also ensures that each targeted segment is treated once, and only once, and that no overlapping ablations are performed. Pathway planning is accomplished by inspecting, identifying, and

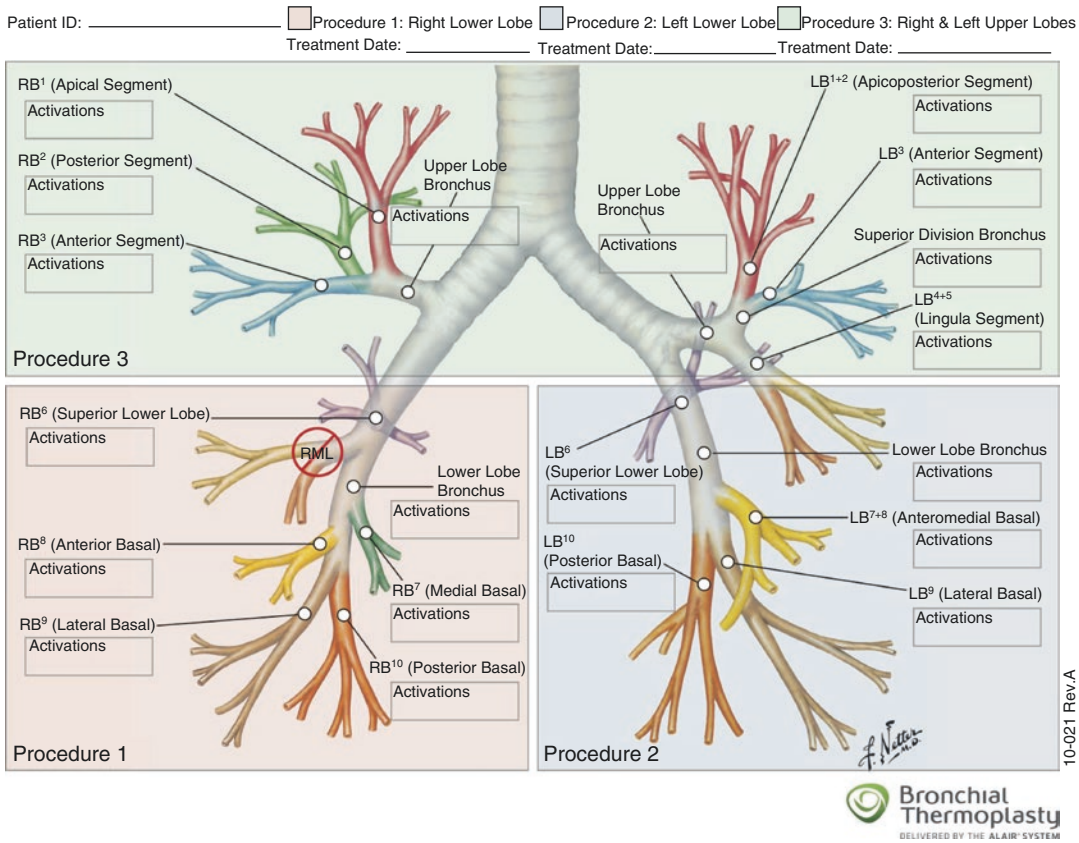

Fig. 33.3 Diagram of the tracheobronchial tree. The diagram can be used for mapping of the airways and thermoplasty planning prior to starting treatment. Activations performed during the procedure can be noted and recorded

mapping out the segments targeted for treatment. A systematic, methodical, and consistent approach is key, working from distal airways to proximal and from airway to airway across the lobe being treated to ensure that all accessible airways are identified and treated only once [17, 18]. Within each segment, subsegmental airways should also be identified and treated. We recommend moving from superior airways to those that are more inferior or from airways to the right of the field of view toward those to the left. Diagrams of the tracheobronchial tree can assist in both planning BT and documenting treated airway segments (Fig. 33.3).

Once planning is complete, RF ablation may be initiated. The bronchoscope is directed into the desired segment or subsegment of the lobe under visualization. The Alair catheter is deployed through the working channel of the bronchoscope into the targeted area under direct bronchoscopic visualization until the desired location is reached. The diameter of the non-expanded catheter is 1.5 mm and is used to determine the diameter of the targeted airways. Once the catheter tip is at the desired location, the actuator is gripped allowing the arms of the catheter array to expand into contact with the airway wall. The degree of pressure applied to the actuator is determined by visualization of the expanding array in more proximal airways, while resistance guides the bronchoscopist in more distal segments where visualization is not possible. Once all four electrode wires are firmly in contact with the airway wall (Fig. 33.4), the footswitch is depressed (activated) and released and RF energy is delivered automatically for approximately 10 s [17, 23]. The actuator is then released, partially collapsing the electrode array, and the catheter is retracted 5 mm proximally.

This distance corresponds to a set of black markings present on the distal end of the catheter just proximal to the electrode array. These markings guide withdrawal of the catheter during the BT ensuring that the electrode array is positioned adjacent to, but does not overlap, the previous activation site (Fig. 33.5). If contact with the airway walls is not adequate during an attempted activation, a different audible signal will be emitted from the RF controller notifying the bronchoscopist. In these instances, the array will need to be collapsed and the catheter will need to be repositioned prior to retreating that particular area. The airways are always treated from the smaller more distal subsegments all the way to the most proximal main lobar bronchi. The usual number of activations per treatment session varies, and the usual range for successful activations is between 50 and 100 per lobe.

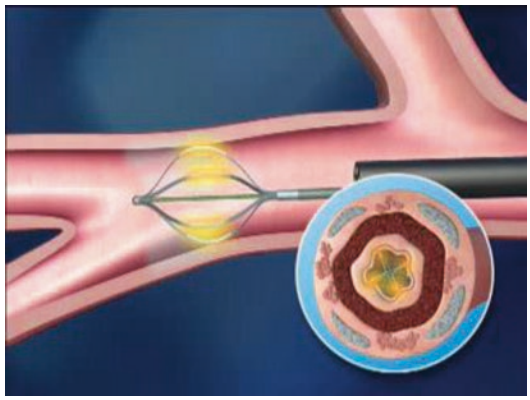

Fig. 33.4 Longitudinal and cross-sectional representation of an expanded Alair catheter making contact with the bronchial wall during activation

In our experience, and based on the manufacturer's recommendations, the following may assist when performing BT:

1. Be careful to ensure that the catheter does not kink or bend during insertion into the working channel of the bronchoscope as this can damage the catheter.
2. Avoid flexing the distal end of the bronchoscope when the catheter tip is in the working channel for the same reason.
3. Avoid deploying the catheter far beyond the view of the bronchoscope to ensure patient safety.

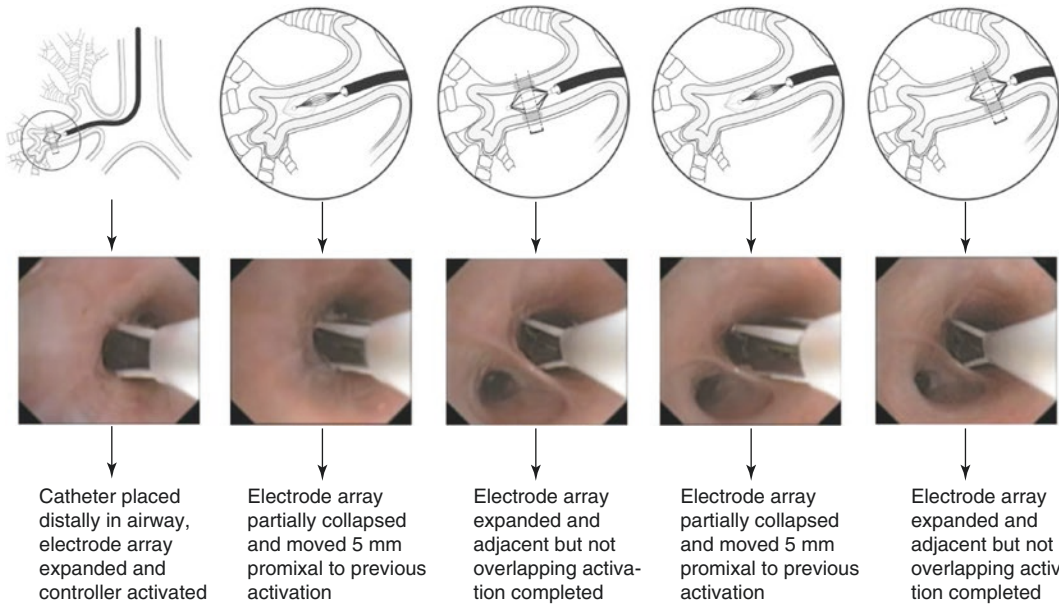

Fig. 33.5 Schematic and bronchoscopic views of the Alair catheter during sequential activations

4. Since most subsegments do not require full expansion of the catheter array for contact with the airway walls, avoid overexpanding the electrodes as this may cause inward deflection of the individual arms and loss of contact with the airway wall.
5. Accumulation of mucus or secretions in the airways or on the electrode array may require periodic catheter removal from the working channel for catheter cleaning and patient suctioning—at these times additional topical lidocaine can be administered to provide continued patient comfort.
6. The RF controller will automatically stop the RF signal if an abnormality is detected—if this happens repeatedly, the entire system should be checked for problems starting at the patient end and working backward to the controller [Alair package insert].

The technique for the second and third treatments is identical to the first with one important addition. Prior to initiating the second and third treatments, the lobe treated at the previous session must be inspected before starting pathway planning to evaluate for airway secretions or inflammation that may require suctioning or postponement of the current treatment.

Post-procedure Care

After BT is completed, normal post-bronchoscopy monitoring is performed, often in conjunction with institution-specific practice guidelines. Because of the increased doses of sedation required for the prolonged bronchoscopy, patients should be monitored for the presence of an intact gag reflex and tolerance for oral liquids on recovery from sedation. In addition, patients undergoing BT must have serial post-procedure FEV_1 tests performed after bronchodilator administration. In order to be discharged home, the post-procedure FEV_1 should be $\geq$80% of the pre-procedure *post-bronchodilator* value. Upon discharge, patients need to be advised of potential adverse events and reminded to take their remaining prophylactic steroid doses. Since patients undergoing BT have severe asthma, worsening of respiratory-related symptoms, including wheezing, dyspnea, chest discomfort, and cough, is not uncommon following the procedure [20, 28]. These typically occur within 1–2 days of treatment and resolve over 1 week with standard treatment with bronchodilators and systemic steroids. As a result, patients should be contacted at 24 h, 48 h, and 1 week post procedure to assess their respiratory status. Alternatively, very severe or labile asthmatics may be admitted overnight to the hospital for observation. Lastly, the patient should be assessed at a clinic visit 2–3 weeks after the procedure to determine whether they are stable for the next BT [23].

Possible Therapeutic Mechanisms of Bronchial Thermoplasty

The potential mechanisms of BT have been studied in a bovine tracheal smooth muscle model. Smooth muscle responsiveness is substantially reduced a few seconds after application of 60 °C heat and is eliminated by 5 min posttreatment [29]. The intervention appears to be dose-dependent, and the desired effect does not progress. The immediate loss of airway smooth muscle cell function in this model suggests that the high temperature disrupts actin-myosin interactions, possibly through denaturation of muscle motor proteins [29]. Identification of this airway smooth muscle target also introduces the possibility of other therapeutic interventions focusing on abolition of the smooth muscle spasm cascade [16, 29].

At least four clinical studies to date have demonstrated a significant reduction in airway smooth muscle in severe refractory asthmatic patients treated with BT [30–33]. The first study evaluated biopsies in ten patients 15 days before and 3 months after BT [33]. Following BT, smooth muscle decreased to 48.7–78.5%. Interestingly, a 50% decrease in smooth muscle was found in the RML which was not treated. Three subsequent studies, involving a total of 38 patients, have

demonstrated an approximately 50–60% reduction in smooth muscle mass following BT [30–32]. Furthermore, a decrease in nerve endings (9.5-positive nerves) [30], type I collagen [31], transforming growth factor-β1, CCL5, and eosinophils in BAL and an increase in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) have been found following BT [32]. Lastly, whole transcriptome gene expression analysis in 15 patients before and after BT has demonstrated a significant decrease in genes associated with T-cell activation, neuron homeostasis, and eosinophilic inflammation, suggesting a systemic response to BT [34].

Preclinical and Non-asthmatic Evidence for Bronchial Thermoplasty

Animal studies in non-asthmatic dogs demonstrated that the application of thermal energy to airway walls attenuated methacholine responsiveness for up to 3 years posttreatment [19]. Degeneration or lack of bronchial wall smooth muscle was seen as early as 1 week following treatment, and the extent of the smooth muscle changes was inversely proportional to bronchial responsiveness**.** No evidence of smooth muscle regeneration was noted over the 3 years of study. Adverse effects in these animals included cough, airway edema, increased mucus production, and blanching of airway walls at the sites of catheter contact.

The first human study of BT was a feasibility study in individuals undergoing targeted lung resection for lung cancers [35]. Eight individuals underwent BT to visible airways within the areas of the lung selected for resection. BT was performed at 3–9 treatment sites per patient, 5–20 days prior to scheduled lung resection. There were no significant adverse events, and at the time of resection, bronchoscopy was generally unremarkable. Only airway narrowing, excess mucus, or linear blanching was noted. The treated lung tissue showed airway smooth muscle changes at approximately 50% of the treated areas [35].

Clinical Evidence for Bronchial Thermoplasty in Asthmatic Patients

Since 2005, numerous human studies of BT in mild to moderate asthmatics, and later moderate to severe refractory asthmatics, have been performed to identify appropriate candidates, adverse events, and expected outcomes with BT [24, 28, 35, 36].

The first study of BT in mild to moderate asthmatic patients was a prospective observational study of 16 patients at 2 centers in Canada. It was a single-arm study designed to evaluate the safety of BT [20]. Patients were pretreated with prednisone, either 30 or 50 mg, on the day before and the day of the procedure, and the three BT treatments were spaced 3 weeks apart. The right middle lobe remained untreated. There were no hospitalizations following the procedures. The most common post-procedure side effects were cough, bronchospasm, wheeze, or dyspnea. Symptoms commonly started 2 days after the procedure and resolved within 5 days of treatment [20]. Over 2 years of follow-up, the majority of adverse events were mild, and no severe events were felt to be procedure-related. Improvement in peak flow rates at 3 months posttreatment demonstrated the early effectiveness of the procedure when compared to baseline, but there was no significant change in peak flows at 2 years of follow-up. Symptom-free days also increased significantly 3 months post-procedure. A significant decrease in airway hyperresponsiveness (measured by methacholine challenge) was maintained at 3 months, 1 year, and 2 years following the procedure. BT in this study was associated with a high level of patient satisfaction 14–36 months after treatment [37]. In addition, annual CT of the chest demonstrated no parenchymal or airway changes related to the procedure. However, the small number of subjects and their relatively stable asthma status limited the findings of this study [13].

The Asthma Intervention Research (AIR) trial was a multicenter, prospective, randomized, controlled, non-blinded study to evaluate the effectiveness and safety of BT in subjects with

moderate to severe asthma [28]. All subjects (56 BT group and 56 control group) were on standard asthma care, requiring ICS (≥200 mcg beclomethasone equivalent) and LABA to maintain asthma control. All subjects demonstrated impairment with LABA withdrawal. Subjects were randomized to either BT plus ICS and LABA (BT group) or to ICS and LABA alone (controls). Treatments occurred in three sessions over 9 weeks and were followed by attempts to discontinue LABA at 3, 6, and 9 months post-procedure. Acute exacerbations on ICS alone were the primary study endpoint. Daily diaries documenting symptoms and rescue inhaler use and Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were administered. Compared to the control group, the BT group experienced an increased number of adverse events during treatment period (up to 6 weeks after the last bronchoscopy). The events occurred largely within 1 day of BT and resolved on average 7 days after the onset. There were more hospitalizations in the BT group (four subjects required six hospitalizations) than in the control group (two hospitalizations) [28]. Reasons for hospitalization included asthma exacerbations, left lower lobe collapse, and pleurisy. Compared to control subjects, there was a significantly greater reduction in mild exacerbation rates at both 3 and 12 months in the BT-treated group (ten fewer mild asthma attacks per year). Severe exacerbations were lower in the BT-treated group compared to control subjects, but the difference did not achieve statistical significance. The BT group demonstrated significantly lower rescue medication use at 3 and 12 months (400 fewer rescue medication puffs). BT patients also had significant improvements in asthma control and quality of life (86 more asthma symptom-free days). Hospitalization rates for respiratory adverse events were low in the posttreatment period (between 6 and 52 weeks posttreatment) and did not differ between the two groups. The AIR study, however, was limited by its non-blinded design and a strong placebo effect in the control group and highlighted the need for a trial with a sham treatment arm [13].

The Research in Severe Asthma (RISA) trial was a multicenter, randomized, controlled clinical trial designed primarily to study the safety of BT in subjects with severe refractory asthma. Patients whose asthma was more severe than those in the AIR study were evaluated for procedure safety, changes in asthma symptoms, and daily medication use [24]. Subjects had to be symptomatic despite treatment with >750 mcg/day of fluticasone or equivalent and could also be taking oral corticosteroids (OCS) up to 30 mg prednisone/day. Thirty-two subjects were randomized to BT with ICS + LABA ± OCS ($n = 15$) or medical management with ICS + LABA ± OCS alone ($n = 17$). Following a 2-week run-in period, three BT treatments were performed 3 weeks apart. After treatment the study was divided into a 16-week corticosteroid-stable phase, followed by a 14-week corticosteroid wean phase, and finally a 16-week reduced corticosteroid extension phase. During the last 2 phases, attempts at decreasing oral steroid or ICS doses were made. During treatments there was a higher rate of hospitalization in the BT group (seven hospitalizations in four subjects) compared to controls (no hospitalizations). Reasons for hospitalization included asthma exacerbations and a partial left lower lobe collapse. However, during the 6-week posttreatment period, the BT group had a similar number of hospitalizations compared to controls and a lower number of hospitalizations when compared to baseline. During the corticosteroid-stable phase, the BT group demonstrated a significant reduction in rescue inhaler use (25 fewer puffs/week) and improvement in pre-bronchodilator FEV_1 (15.8% improvement). In addition, both AQLQ and ACQ scores improved. In the corticosteroid wean phase, all subjects in the BT group were able to initiate steroid weaning, while three subjects in the control group did not attempt steroid reduction at all. During the reduced corticosteroid extension phase, four of eight BT subjects were weaned completely off OCS through 52 weeks, compared to only one of seven control subjects. Although there was significant potential for placebo effect, BT-treated patients demonstrated significant improvement

in clinical asthma outcomes compared to the control group [24]. The study also demonstrated that BT could be safely performed in severe refractory asthmatic populations.

The most recent randomized controlled trial evaluating BT in severe asthmatics was the AIR2 trial [36]. AIR2 was a multinational, multicenter, randomized, double-blinded, and sham-controlled study. Sham procedures were identical to active procedures, and used an RF controller that provided audio and visual cues that mimicked the active controller, but did not deliver RF energy through the catheter. Neither subjects nor assessing physicians were aware of individual treatment assignments. AIR2 used a 2:1 randomization scheme (2 BT to 1 control subject) to randomize a total of 297 subjects (196 BT/101 sham) to 3 bronchoscopy procedures, separated by 3 weeks. All patients had severe asthma and were symptomatic despite management with ICS (>1000 μg/day beclomethasone or equivalent) and LABA (≥ 100 μg/day salmeterol or equivalent). The primary outcome was the difference in the change in AQLQ score between study groups from baseline measurements at 6, 9, and 12 months after the final BT treatment. During the treatment period, there was a higher rate of hospitalization for respiratory symptoms in the BT group (19 hospitalizations in 6 subjects) compared to controls (2 hospitalizations). Reasons for hospitalization included low $FEV_{1,}$ worsening asthma, segmental atelectasis, lower respiratory tract infections, an aspirated prosthetic tooth, and an episode of hemoptysis requiring bronchial artery embolization. Ten of the nineteen hospitalizations in the BT group occurred on the day of the procedure. However, in the 6-week posttreatment period, there was a significant 34% reduction in severe exacerbations in the BT group compared with the sham group. There was also a 66% reduction in days lost from work, school, or other daily activities due to asthma in the BT group.

The AIR2 BT group experienced improved quality of life compared to the sham group. This was demonstrated by a significant difference between the groups in average improvement in AQLQ score from baseline at 6, 9, and 12 months (posterior probability of superiority of 96.0%). To further determine the clinical significance of the data, the AQLQ data were categorized into the proportion of subjects in each group that achieved a significant and clinically meaningful improvement in AQLQ score of ≥0.5. While 64% of the sham group experienced improvements in AQLQ scores of ≥0.5, 79% of BT-treated subjects demonstrated the same. For the intention to treat population, the difference between the groups had a posterior probability of superiority of 99.6%, proving that the AQLQ score improvement in the BT group was superior to that in the sham group. However, the large percentage of sham subjects demonstrating improved AQLQ scores emphasizes the importance of the placebo effect in asthmatic populations.

During longer-term follow-up (>6 weeks after the last BT treatment), secondary endpoints also demonstrated clinically meaningful and statistically significant differences in favor of the BT group. These included reductions in asthma adverse events, emergency department visits for respiratory symptoms, and hospitalizations for respiratory symptoms. In addition, blinded evaluation of CT of the chest from 100 BT and 50 sham subjects did not reveal any parenchymal or airway changes related to the procedure. Overall, the AIR2 study demonstrated improved short- and long-term quality of life along with decreased healthcare utilization in severe refractory asthma treated with BT [36].

FDA Approval and Long-Term Follow-Up

In early 2010 the FDA approved the Alair Bronchial Thermoplasty System® for severe refractory asthma [Alair package insert,]. As part of the conditions of approval, the FDA required a post-approval study based on long-term follow-up of the AIR2 trial population. In addition, a second prospective, open-label, single-arm, multicenter, post-approval study (PAS2) is currently underway to assess the treatment effects and the short- and

long-term safety profiles of BT. Long-term follow-up data are available out to 5+ years from the lung cancer feasibility study [38], the AIR Extension Study [39], the RISA Extension Study [Asthmatx, Inc., personal communication], and the AIR2 trial. In AIR2 extension study, the average 5-year reduction in severe exacerbations and ED visits compared to the year prior to BT were 44% and 78%, respectively [40]. In addition, high-resolution CT images at 5 years demonstrated no structural abnormalities compared to baseline. These studies demonstrate the durability of the therapy without any obvious long-term structural consequences.

Future Directions

As with other new therapies for asthma, there is a need to identify which phenotypes will have an optimal response to BT with the fewest side effects. In an effort to elucidate which characteristics will predict a response to BT, 42 patients had baseline ACT, AQLQ, medication usage, demographic data, as well as pulmonary function testing analyzed and compared to repeat evaluation at periodic intervals for 12 months after BT [41]. In addition, baseline CT images were analyzed for wall area percentage and air trapping by automated software. A logistic regression model identified patients with a shorter duration of asthma and a higher number of severe exacerbations in the year prior to BT as potential responders. Prior studies have demonstrated that patients with severe asthma have heterogeneous ventilation defects that can be identified using hyperpolarized noble gas MRI [42, 43]. Currently, studies are ongoing utilizing this technology to identify high-yield targets for BT treatments, which may eliminate the need for multiple treatment sessions and associated complications [44].

Summary

In patients without significant contraindications to bronchoscopy, BT is a well-validated, FDA-approved therapeutic modality for the treatment of severe refractory asthma not well controlled on combination high-dose ICS and long-acting bronchodilator therapy. Clinical trials have demonstrated its efficacy and safety for improving quality of life, respiratory symptoms, and healthcare utilization in carefully selected patients with asthma. Patient selection is paramount and should be based on a careful evaluation by an asthma specialist. In addition, proper monitoring of patients both during and after the treatment period (up to 6 weeks after the last procedure) is mandatory. As experience with the procedure increases, we will further characterize the subsets of severe asthmatic patients obtaining maximal benefits from BT and, in doing so, improve outcomes while minimizing adverse events.

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