

Bronchial Thermoplasty: A New Treatment Paradigm for Severe Persistent Asthma

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Abstract Patients with severe asthma represent only a minority of the total asthma population; however, they account for the majority of the mortality, morbidity, and health care-related cost of this chronic illness. Bronchial thermoplasty is a novel treatment modality that employs radiofrequency energy to alter the smooth muscles of the airways. This therapy represents a radical change in our treatment paradigm from daily repetitive dosing of medications to a truly long-term and potentially permanent attenuation of perhaps the most feared component of asthma—smooth muscle-induced bronchospasm. A large, multicentered, double-blinded, randomized controlled trial employed the unprecedented (but now industry standard for bronchoscopic studies) approach of using sham bronchoscopy as a control. It demonstrated that bronchial thermoplasty is safe, improved quality of life, and decreased frequency of severe exacerbations in the treatment group compared to the control group. Although the mechanism of action of bronchial thermoplasty is not currently completely understood, it should be considered as a valid and potentially valuable option for patients who have severe persistent asthma and who remain symptomatic despite inhaled corticosteroids and long-acting beta-2 agonists. Such patients should however be carefully evaluated at

centers with expertise in managing severe asthma patients and with physicians who have experience with this promising new treatment modality.

Keywords Bronchial thermoplasty · Severe asthma · Refractory asthma · Airway smooth muscle · Radiofrequency energy

Introduction

The approval of bronchial thermoplasty (BT) by the Food and Drug Administration (FDA) on April 27, 2010, marked a new era in the treatment of asthma. This novel approach represents the first and only potentially permanent treatment for asthma. BT represents a radical change in our treatment paradigm from daily repetitive dosing of medications to a truly long-term and potentially permanent attenuation of the perhaps the most feared component of asthma, smooth muscle-induced bronchospasm. Based on randomized controlled trials, it improves symptom control and reduces exacerbations. Although its mechanism of action is believed to be the result of smooth muscle reduction and consequent reduction in bronchoconstriction, its effects have not been completely elucidated and remain an area of continued study. While further investigations and long-term follow-up are ongoing, BT represents a truly unique and novel asthma treatment.

BT requires technical expertise and training, but patient selection and pre- and postprocedural management are equally important. Consequently a sound understanding of the fundamentals of asthma is key to a successful BT program. In this review, a brief overview of severe asthma epidemiology, pathophysiology, and severity rating will be discussed. More importantly, an in-depth review of the

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preclinical and clinical BT trials and FDA-established guidelines for performance of BT will be provided.

Asthma Overview

Epidemiology

Asthma is a debilitating, chronic inflammatory disease that is characterized by airway hyperresponsiveness and remodeling of airways. It is a global problem, affecting about 300 million individuals, with a prevalence of 1–18% [1]. In 2008, asthma accounted for 14.2 million missed workdays and 10.5 million missed school days in the USA [2]. In the previous year, there were 1.75 million asthma-related emergency department visits and 456,000 asthma hospitalizations [2]. Indeed, asthma continues to weigh heavily on health care resources and utilization.

Much of the morbidity, mortality, and economic burden of asthma are primarily attributed to the estimated 5–10% of asthmatics with severe or difficult to control disease [3]. Patients with refractory asthma have the greatest impairment in their lifestyle and account for a disproportionate use of health care resources through unplanned primary care physician visits, hospital admissions, and emergency department visits [3, 4].

Definition of Severe Asthma

In 2000, the American Thoracic Society (ATS) sponsored a workshop on refractory asthma that developed a consensus definition based on major and minor criteria. They proposed that the terms “severe asthma,” “steroid dependent and/or resistant asthma,” “difficult to control asthma,” “poorly controlled asthma,” “brittle asthma,” and “irreversible asthma” be encompassed under the broader term refractory asthma [5]. Nevertheless two terms, refractory asthma and severe asthma, predominate the medical literature without a clear common use consensus. In this review we will consider them to be synonymous but will use only the term severe asthma for the sake of clarity.

For patients to qualify as having severe asthma, they must meet one of two major criteria [the use of high-dose inhaled corticosteroids (ICS) and/or the need for frequent oral corticosteroids] and two of seven minor criteria (see Table 1). The 2010 update of Global Initiative for Asthma recognized that asthma severity is dynamic and underscored that the classification of asthma should be based upon the severity of the underlying disease and responsiveness to treatment. Therefore, asthma severity should be currently classified on the basis of the intensity of treatment required to achieve good asthma control [6–8].

Pathophysiology of Asthma

In the severe asthmatic, the airways behave like a chronic wound, with ongoing inflammation and repair. The reparative process is mediated by the increased production and release of a wide range of growth factors that promote remodeling and vascularization [9]. The epithelial mesenchymal unit (EMU) in severe asthma is thought to play a role in epithelial dysfunction. Epithelial damage alters the set point for communication between the bronchial epithelium and the underlying mesenchymal cells that leads to myofibroblast activation, an increase in mesenchymal mass and promotion of structural changes in the airway wall. These changes lead to thickened and stiffer airways [10]. However, the relationship between morphologic changes in refractory asthma and hyperresponsiveness has not been completely elucidated [4]. It is believed that the changes that occur in the airway smooth muscles likely play an important role and are key to this altered response.

The Airway Smooth Muscle

The chronic asthmatic’s airway is characterized by extensive remodeling [11], with proliferation of mucous glands, increased vascularization, and hypertrophy of airway smooth muscle (ASM) [12]. In an acute asthma attack, there may be a variety of triggers, both infectious and noninfectious; but it is the downstream cascade of events that results in the activation and contraction of airway smooth muscle [12].

The airway smooth muscle has been described as a vestigial organ and [13], instead of having an authentic physiologic purpose, is involved in pathologic responses. According to rat and murine studies, ASM originates with the lung bud from the primitive foregut and is present in the proximal airway at 5 to 6 weeks of human gestation [14]. ASM has been postulated to have several different functions in the respiratory system, including peristalsis to assist mucus clearance and exhalation, promotion of lymphatic and venous flow, airway structure protection, increasing the effectiveness of cough, and optimizing dead space volume. Yet none of these functions appear to be absolutely essential to normal lung physiology [12]. Consequently, ASM has been called the appendix of the lung [13].

In those patients with severe asthma, the spiral bundles of ASM increase both in number and in size, spread to infiltrate the larger airways, and can reach the respiratory bronchioles and alveolar ducts [15]. The involvement of more proximal bronchi augments the total airway resistance as 75% of the postnasal resistance to airflow in the human bronchial tree occurs within the first six to eight generations of airways, which are more than 3 mm in size [16].

Table 1 The ATS definition of severe or refractory asthma requires one or two major and two minor criteria (adapted from [5])

Major characteristics

Control to a level of mild to moderate asthma is achieved through:

Continuous or more than 50% use of oral corticosteroids

Use of high-dose ICS

Beclamethasone dipropionate >1,260 µg/day or >40 puffs/day (42 µg/inhalation)

Budesonide >1,200 µg/day or >20 puffs/day (84 µg/inhalation)

Flunisolide >2,000 µg/day or >6 puffs/day

Fluticasone propionate >880 µg/day or >8 puffs/day (110 µg/inhalation), >4 puffs/day (220 µg/inhalation)

Triamcinolone acetonide >2,000 or >20 puffs/day

Minor characteristics

Daily use of a controller medication in addition to ICS: long-acting β-agonist, theophylline, or leukotriene agonist

Asthma symptoms that require daily use or near daily use of a short-acting β-agonist

Persistent airway obstruction with FEV₁ <80% predicted, and a diurnal PEF variability of >20%

One or more urgent care visits for asthma per year

Three or more oral steroid bursts per year

Immediate decline with <25% reduction in oral or inhaled corticosteroid dose

Near fatal asthma event in the past

Consequently, decreasing the bulk of ASM would logically result in a decrease in bronchospasm and ultimately respiratory failure in severe, acute asthmatic attacks.

Scientific Rationale for Bronchial Thermoplasty

Preclinical Studies

The original data on BT emanate from a canine study in 2004 that involved the delivery of controlled radio-frequency energy into the airways of anesthetized mongrels. Danek and colleagues [17] used the Alair® System, consisting of a 460-kHz, low-power, monopolar radiofrequency (RF) generator and a four-electrode basket catheter passed through a bronchoscopic channel, to deliver RF energy to the bronchial walls of airways 3 mm in size and larger, for 10 s, at various temperatures (55°C, 65°C, and 75°C). Posttreatment airway responsiveness to locally applied methacholine and examination of bronchial histology for up to 3 years posttreatment were performed.

Their study demonstrated that the airways treated in the 65°C and 75°C groups were significantly less responsive to methacholine challenge compared to control airways (Fig. 1; $p < 0.001$ for both temperatures). Histology revealed unaltered ASM in control airways; but where RF energy was applied, ASM was degenerative, completely absent, or replaced by fibroblasts (Fig. 2) [17]. A statistically significant inverse relationship between airway hyperresponsiveness and the percentage of airway circumference containing altered ASM was also demonstrated ($p < 0.001$).

Dogs tolerated the procedure well, and there were no documented adverse clinical events. Grossly, the treated airways did not develop constriction or distortion of the lumen [17]. The investigators noted a spectrum of blanching of the surfaces of the bronchial wall at the point of catheter contact with the higher temperature settings (65°C and 75°C). However, by the sixth week of survey, all bronchial walls were normal in appearance without retained mucus.

In 2005, two other preclinical studies were published on BT [18, 19]. Brown et al. [18] examined airway distensibility in canines that underwent the procedure at a temperature setting of 75°C. They demonstrated that the treated airways had a significant increase in dimensions at any degree of lung inflation up to 5 weeks following treatment, whether the airway smooth muscle was relaxed or contracted with methacholine [18]. The measured compliance of these airways was not altered by the procedure, therefore implying that treated airways behave similar to normal, healthy bronchi in response to deep inspiration [20].

In the second study by the same authors, computed tomography (CT) was used to evaluate bronchial dimensions in response to inhaled methacholine postapplication of RF energy at a temperature of 75°C. The dose–response curve of the treated airways to methacholine was noted to have shifted upwards at weeks 2 and 4 posttreatment, indicating a significantly decreased sensitivity to the challenge ($p < 0.001$) [19]. The investigators surmised that there was no significant damage to the treated airway submucosa, which contains blood vessels responsible for the removal of a locally acting, topically delivered medication. They reasoned that if bronchial vessels were damaged by treatment, then there should be an increased

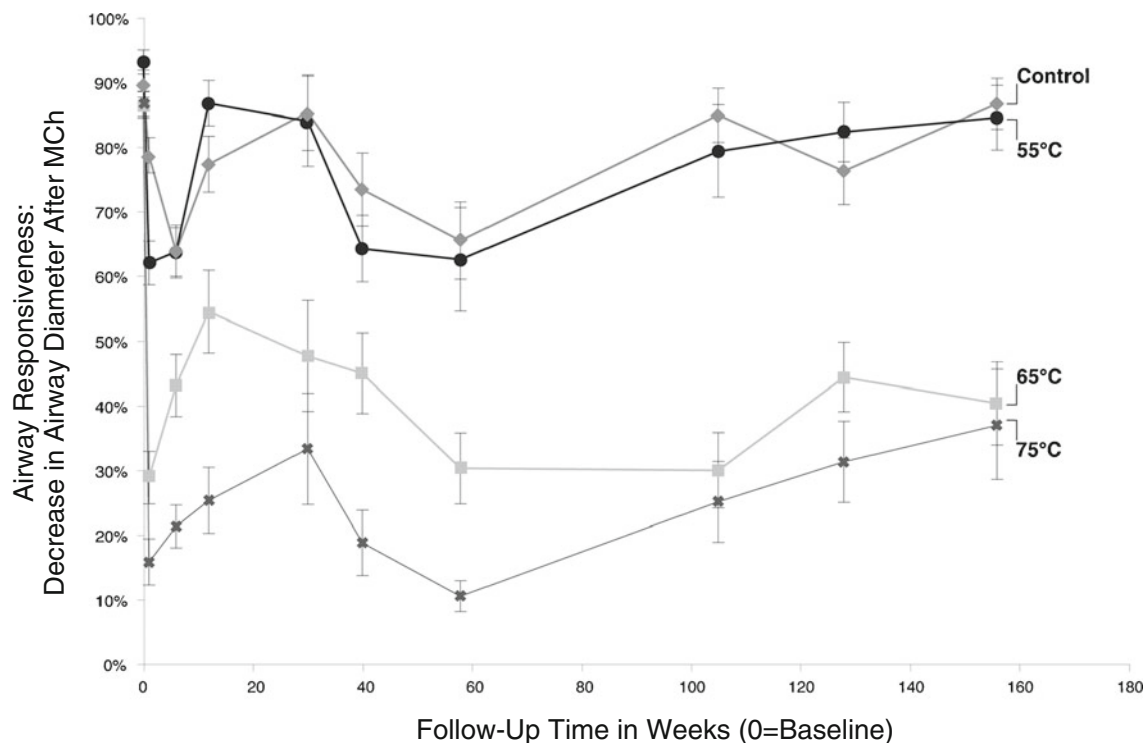


Fig. 1 Mean airway responsiveness—percent change in diameter after local methacholine (*MCh*) challenge in dogs treated at various temperatures. Control airways and those treated at 55°C show a stable response to *MCh* over time. The 65°C treated airways show a statistically significant reduction in response to *MCh* compared to the

reactivity to methacholine as this is a direct airway muscle constrictor, and its removal from the immediate vicinity would have been impaired (Fig. 3).

Studies in Human Subjects Using Bronchial Thermoplasty

The incipient clinical investigation of BT in human subjects was a prospective feasibility study that involved nine

control airways at eight out of nine follow-up times ($p \leq 0.039$, except at 12 weeks where it was not significant). The 75°C treated airways showed a statistically significant reduction in response to *MCh* at all posttreatment follow-up times ($p \leq 0.001$) [17]

patients who were nonasthmatics but were to undergo elective lung resection for a proven or suspected lung cancer [21]. These patients underwent RF application at a temperature setting of 55°C to 65°C, in the segment of the lung that was to be removed, 3 weeks prior to their scheduled surgery. They were followed for a period of up to 20 days after treatment. The same Alair® System and technique was used as in the canine studies to apply RF

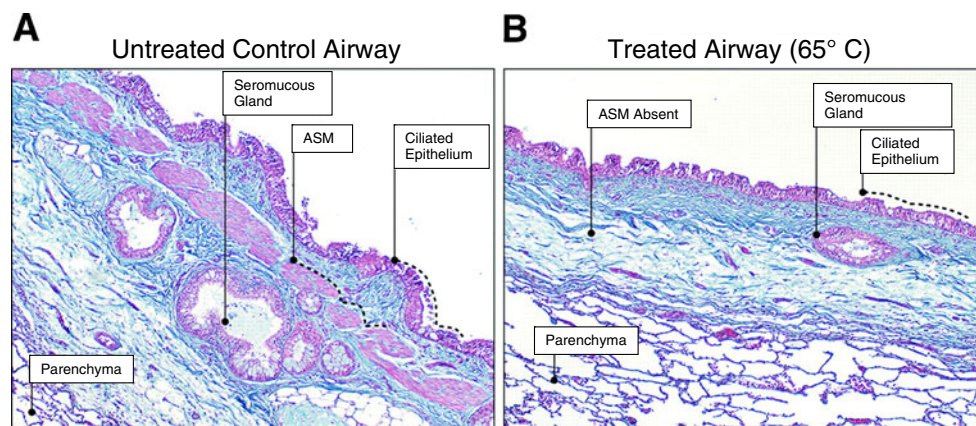


Fig. 2 Histopathologic features of an untreated control airway (**a**) and an airway treated with RF energy at 65°C (**b**), 12 weeks posttreatment (trichrome stain, original magnification $\times 100$). Airway smooth muscle (*ASM*) in the untreated airway is normal, and *ASM* in the airway

treated at 65°C is absent. *ASM* is reduced throughout the circumference of the treated airway (**b**) and present in amounts similar to that shown throughout the circumference of the untreated airways (**a**) [17]

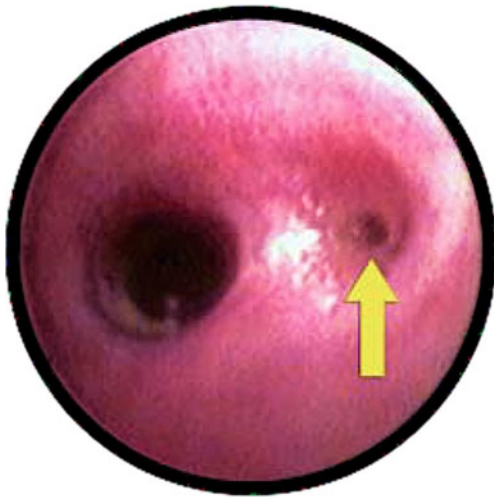
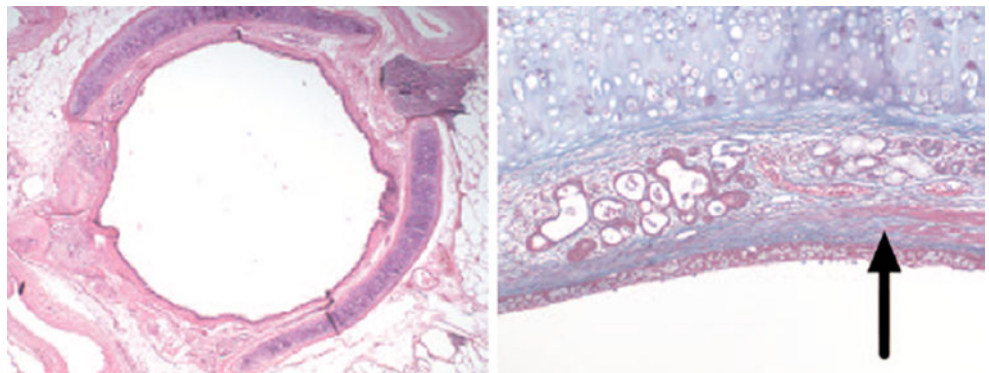


Fig. 3 This demonstrates a canine airway that has been treated with BT (*left*) did not constrict after local administration of methacholine. In contrast to the airway on the right that has not been treated with BT, showing remarkable bronchoconstriction after methacholine ([12] reproduced with permission)

energy for 10 s to airways 3 mm in diameter or larger and >1 cm from the known tumor site. The patients tolerated the procedure well, without signs of bronchial irritation, respiratory tract infection, unscheduled hospitalization, or unscheduled primary care physician visits. One patient treated at 65°C showed a 25–50% narrowing of three of his treated bronchi along with mucus plugging in one. Upon microscopic examination, it was found that on average, about 50% of the treated airways contained altered ASM. One third of the patients had normal airway epithelium, while the rest showed a range of sloughing and regenerative epithelium (Fig. 4) [21]. A noninfectious pneumonitis, characterized by patchy accumulation of inflammatory cells, was observed in the peribronchial region of 27% of patients who received treatment at 65°C, while focal necrosis was found in 25% of those examined. This study demonstrated that use of the Alair® System in humans is safe and that alteration of human ASM occurs with radiofrequency application to the airways.

Fig. 4 A section of the airway from one of the subjects of the first human feasibility study after being treated with BT at 65°C. *Left* an airway in cross section stained in hematoxylin–eosin. *Right* trichrome stained at higher magnification. ASM is largely absent to the left of the arrow ([21] reproduced with permission)



The first study to involve asthmatic patients focused primarily on the safety and feasibility of BT, and was a nonrandomized prospective trial that enrolled 16 patients, 18 years of age or older, with stable mild to moderate asthma [22]. They were premedicated with corticosteroids prior to the procedure and underwent BT under general anesthesia in three sessions, 3 weeks apart. Bronchi greater or equal to 3 mm in diameter in both upper lobes and both lower lobes (the right middle lobe was spared) were treated. Posttreatment evaluations were performed at 12 weeks, 1 year, and 2 years thereafter, with a methacholine challenge performed at 12 weeks to evaluate airway hyperreactivity (AHR).

The most frequently reported adverse events in the study were cough (21%), dyspnea (12%), and wheezing (11%) [22]. Overall, adverse events were predominantly described as “mild” (74%), there were no reported emergency room visits or hospitalization, and no supplementary steroids were required. Severe adverse events occurred in three subjects but were considered not related to the procedure [22]. Symptom-free days ($p=0.015$), peak expiratory flow rates (morning peak flow $p=0.01$, evening peak flow $p<0.007$) and AHR were also improved.

Randomized Studies in Asthmatics with Bronchial Thermoplasty

The Asthma Intervention Research (AIR) trial was the first open-label, randomized clinical trial for BT. One hundred twelve patients, with moderate to severe asthma previously treated with ICS and long-acting β_2 -adrenergic agonists (LABA) and whose asthma control was impaired when LABA were withdrawn, were randomized to either a control or a treatment group [23]. The subjects in this study required at least 200 μg of beclomethasone equivalent and a LABA (at least 100 μg of salmeterol or its equivalent) to maintain asthma control. Inclusion criteria were a prebronchodilator FEV₁ between 60% and 85% of predicted, AHR with a provocative concentration of methacholine required to lower the FEV₁ by 20% (PC₂₀)

of less than 8 mg/ml, and stable asthma 6 weeks prior to enrollment in the study. The BT group underwent bronchoscopy using the Alair® System at 3-week intervals, while those in the control group were also seen at 3-week intervals for spirometric measurements, clinical assessment, and received systemic corticosteroids equivalent to that of the BT group. All patients were followed up 2 weeks after each treatment visit, and after the last treatment at 6 weeks, 3 months, 6 months, and 12 months. At each of 3, 6 and 12 months interval, patients were taken off their LABA, a potential confounder in their study, for 2 weeks and outcomes were assessed [23].

The primary outcome measure of this trial was the change in the rate of mild exacerbations between baseline and posttreatment [23]. Secondary outcomes included: changes in peak expiratory flows (PEF), the frequency of rescue inhaler use, number of symptom-free days, and improvement in scores on the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ).

The average number of exacerbations during the 2-week LABA withdrawal periods at 3, 6, and 12 months during which subjects were treated with ICS alone was significantly reduced in the BT group but was unchanged in the control group ($p=0.005$) [23]. There were approximately 10 fewer mild exacerbations per subject per year in the treatment group. There was no difference in severe exacerbation at 12 months after the last study treatment. The BT group had no significant change in FEV₁ or PC₂₀ but did demonstrate improved morning PEF, better scores on ACQ and AQLQ, higher percentage of symptom-free days, and less rescue medication use.

Patients in the AIR trial were followed up in a long-term safety study by Thomson et al. [24]. Only half of the patients in the original control group participated in this 5-year posttreatment extension study. Nevertheless, in this long-term follow-up study, there were essentially no changes in the rate of respiratory events of patients in the BT group in years 2 through 5, post-BT. Furthermore, their FEV₁ and forced vital capacity remained stable over a period of 5 years.

The second randomized, nonblinded clinical study to evaluate the effects of BT in symptomatic, severe asthma was the Research in Severe Asthma trial that was conducted in three countries, with eight investigational sites. It assessed the safety (primary endpoint) of BT by monitoring adverse events and pulmonary function. Efficacy was determined by measuring secondary endpoints that included alterations in corticosteroid doses, frequency of use of rescue inhaler, peak expiratory flow rates, forced expiratory volume in 1 s (FEV₁), and provocative concentration (of methacholine) causing a 20% fall in FEV₁ (PC₂₀).

Thirty-four patients who had uncontrolled, severe asthma—defined as requiring high-dose inhaled corticosteroids

(>750 µg fluticasone propionate per day or its equivalent) and LABA with or without oral prednisone, leukotriene modifiers, or theophylline [25]—were randomized either to a control group (medical management) or a treatment group (BT). The subjects had a prebronchodilator FEV₁ of more than 50% predicted, documented airway hyperresponsiveness by methacholine challenge, or reversible bronchoconstriction within the last 12 months as evidenced by at least a 12% increase in FEV₁ 30 min after inhalation of a short-acting β_2 -agonist. Patients underwent a 16-week steroid stable phase, a 14-week steroid wean phase where they attempted to be weaned off oral corticosteroids, and a 16-week reduced steroid phase after BT or medical management.

Results of this trial demonstrated that the BT group had more adverse respiratory events after the initial treatment period. Wheezing, cough, chest discomfort, dyspnea, productive cough, and discolored sputum [25] were the most frequently observed symptoms. However, patients in the treatment group did not note any increase in adverse events with successive treatments. Seven hospitalizations occurred during the treatment period for the BT group for asthma exacerbation and one for a left lower lobe atelectasis. There was a reduction in the use of short-acting β_2 agonists from baseline compared to the control group, as well as an improvement in the prebronchodilator FEV₁% predicted in the treatment group. It should be noted that this trial had patients with more severe asthma, requiring higher doses of ICS and with lower mean FEV₁% predicted compared to patients in the AIR trial.

The first human, randomized, double-blinded, sham bronchoscopy (SB)-controlled clinical trial was AIR2. It demonstrated the efficacy of BT in severe asthma. A total of 288 adult patients were randomized (2:1) to either BT or SB. All of the patients had asthma which was classified as severe, necessitating a regular maintenance ICS (>1,000 µg/day of beclomethasone or its equivalent) and a LABA (at least 100 µg/day of salmeterol or its equivalent). Additional medications, including leukotriene inhibitors, omalizumab, and 10 mg or less per day oral prednisone, were allowed into the study. All subjects were required to be on stable asthma medications for at least 4 weeks and have an AQLQ of 6.25 or lower, a prebronchodilator FEV₁ of more than 60% predicted, a methacholine PC₂₀ of less than 8 mg/ml, at least 2 days of asthma symptoms during a 4-week baseline period and a nonsmoker for at least 1 year with less than 10 pack years smoking history [26]. The bronchoscopy team was unblinded in this trial, while the assessment team was blinded. However, a large proportion of patients assigned to the BT group were able to correctly guess their treatment assignment ($p=0.011$) after the first bronchoscopy. The subjects were evaluated 6 weeks after the last treatment period, with the posttreatment period extending from 6 to

52 weeks after the last procedure. Clinical evaluations were performed at 3, 6, 9, and 12 months.

The primary outcome in this study was the difference between study groups in AQLQ score change from baseline to the average of the 6-, 9-, and 12-month scores (integrated AQLQ) [26]. Secondary outcomes were identified as changes in AQLQ, ACQ scores, percentage of symptom-free days, symptom scores, rescue medication use, morning PEF and FEV₁.

In an intention-to-treat analysis, the mean change in the integrated AQLQ score of subjects in the BT group was significantly greater than in the SB group, with a larger proportion of subjects in the BT group (79%) compared with the SB group (64%) having clinically meaningful improvement in AQLQ score of 0.5 or greater [26]. A reduction in severe exacerbations and days lost from work, school, and other activities due to asthma was also seen in the BT group compared to the controls during the posttreatment period [26]. On the other hand, there was no significant change in the other secondary outcome measures including the morning PEF, symptom-free days, ACQ score, and rescue medication use.

As in the AIR study, more early respiratory events occurred in the BT group (85%) than in the SB group (76%), with the majority of these occurring within 1 day of the bronchoscopy and resolution within 7 days. However, by 6 to 52 weeks posttreatment, there were fewer respiratory events reported in the BT group than in the SB group, with a 36% risk reduction in those patients reporting worsening of asthma in the BT group compared to the SB group [26]. A long-term safety follow-up phase of the AIR2 trial (up to 2 years posttreatment) demonstrated that reductions in rates of severe exacerbations, respiratory adverse events, ED visits, and hospitalizations for respiratory symptoms were maintained for up to 2 years post-BT [27].

Currently, there are no studies evaluating the histological changes in the airways after BT in humans with severe asthma [28]. Posttreatment alterations in airway smooth muscles, inflammation, and potential effects on distal airways in asthmatics remain uncharacterized. Despite this limitation, patients with severe asthma who have not achieved good control despite appropriate treatment should be considered for this procedure. The long-term effects of BT on airways will take many years to characterize and are the subject of ongoing study.

Bronchial Thermoplasty Procedure

Overview

BT was approved by the FDA for the treatment of patients with severe persistent asthma, ages 18 years or older, whose

symptoms are not well controlled with ICS and LABA. In conjunction with the FDA, patient selection, procedural and management guidelines have been developed and disseminated by the manufacturer, Asthmatx, a subsidiary of Boston Scientific. BT is a complex procedure requiring the bronchoscopist and bronchoscopy team to undergo specific training, proctoring, and certification. We will detail the BT equipment, accessory function and operation, as well as review the above-mentioned guidelines.

Patient Selection

Patients should have asthma symptoms that are not controlled despite regularly scheduled ICS and long-acting beta-2 agonist and have an FEV₁ $\geq$ 65% of predicted. While omalizumab, montelukast, and tiotropium bromide are allowed, they are not required as a severity indicator. Conversely, chronic systemic corticosteroids, frequent exacerbations and hospitalizations can be contraindications as markers of asthma severity and an increased risk of procedural complication. Not all patients with severe persistent asthma are good candidates for BT. What is not commonly appreciated is that BT candidates in fact represent the less severe end of the severe asthmatic patient.

A detailed history and physical examination should be obtained for all patients being considered for the procedure. Patients are generally selected according to the severity of their disease and lack of control despite adherence to nationally accepted treatment guidelines. Specific guidelines including indications, contraindications, and precautions for this procedure were developed by the manufacturer in conjunction with the FDA and are based on the major clinical trials (Table 2). Ruling out confounding and treatable factors is an essential part of the evaluation (Table 3). Patients should be on stable asthma medications and have stable asthma status without active infection or exacerbation or changing dose of systemic corticosteroids in the preceding 14 days. They should also not have unstable comorbidities which could preclude them from tolerating the bronchoscopic procedure (e.g., untreated obstructive sleep apnea, serious cardiovascular disease, epilepsy, and uncontrolled diabetes) [29]. While aspirin is listed as a precaution, in general, it is considered safe for bronchoscopic procedures.

Preprocedure Patient Management

Patients should be reevaluated for stability approximately 1 week prior to their scheduled procedure. They should be started on daily prednisone at 50 mg for the 3 days prior to the procedure, the day of the procedure, and the day following. On the day of the procedure, patients should once again be assessed for stability and as to whether they

Table 2 Indications, contraindications, and precautions for bronchial thermoplasty

Indication

Patients with severe persistent asthma not well controlled despite inhaled corticosteroids and long-acting beta-2 agonists

Patients 18 years and older

Contraindications

Known sensitivity to required medications for bronchoscopy

Presence of an internal pacemaker or other implantable devices

Patients previously treated with the Alair System in the same area

Active respiratory infection

Asthma exacerbation or changing dose of systemic corticosteroid for asthma (up or down) in the preceding 14 days

Inability to stop taking anticoagulants or antiplatelet agents before the procedure

Precautions

Postbronchodilator FEV1 <65% of predicted

Other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis, or uncontrolled obstructive sleep apnea

Use of short-acting bronchodilator in excess of 12 puffs per day within 48 h of bronchoscopy (excluding prophylactic use for exercise)

Use of oral corticosteroids in excess of 10 mg per day for asthma

Increased risk for adverse events associated with bronchoscopy or anesthesia, such as pregnancy, coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension

Intubation for asthma or ICU admission for asthma within the prior 24 months

Any of the following within the past 12 months:

Four or more lower respiratory tract infections

Three or more hospitalizations for respiratory symptoms

Four or more oral corticosteroid pulses for asthma exacerbation

can tolerate the procedure. A postbronchodilator spirometry should be performed and be at least 85% of the pretreatment baseline to insure stability of disease and to provide a baseline for postprocedure comparison. Premedication with an inhaled short-acting β_2 agonist (albuterol),

an antisialogogue (glycopyrrolate), and anxiolytics should be administered.

While most of the procedures in the clinical trials were performed under moderate sedation, many institutions now employ deeper sedation that may involve securing the patient's airway by means of endotracheal intubation or a laryngeal mask airway to facilitate spontaneous ventilation or to provide short-term positive pressure ventilation during the procedure. Topical anesthesia of the upper airway is achieved with application of 1% or 2% lidocaine. Patients should be monitored as per moderate or deep sedation institutional protocols.

Table 3 Evaluation of confounding factors in patients with severe asthma (adapted from [5])

Consideration of other diagnoses in the work up of cough, dyspnea, and wheeze:

Chronic obstructive pulmonary disease

Cystic fibrosis

Vocal cord dysfunction and other mechanical upper airway obstruction

Obstructive sleep apnea

Churg–Strauss syndrome

Cardiac disease

Allergic bronchopulmonary aspergillosis

Investigation and identification of concomitant disorders that may exacerbate asthma:

Allergen skin tests for atopy and allergic rhinitis

CT scan of the sinuses for sinus disease

24-h esophageal monitoring for gastroesophageal reflux disease

Chest radiograph to identify pulmonary infiltrates, interstitial lung disease, or bullous lung disease

Eosinophil count, immediate hypersensitivity testing for *Aspergillus*, IgE level

Bronchial Thermoplasty Equipment and Procedure

The Alair[®], which is the only FDA-approved system, is employed in the procedure of BT. It consists of an RF controller and a bronchial catheter that has a four-electrode basket. The RF controller delivers low-power RF energy to the airways at a predetermined temperature (65°C) over a set period of time (10 s). A footswitch allows the operator to actuate the delivery of RF energy. The Alair[®] catheter is a sterile, single-use catheter that can be accommodated by the 2-mm working channel of a standard 5-mm flexible bronchoscope. The four-electrode basket has heating and temperature-sensing components that provide feedback control to the system.

When an airway to be treated is identified, the basket is opened with a handheld trigger to allow the four electrode arms to make contact with the airway wall circumferentially [30]. The footswitch is activated, and the RF energy is delivered for the specified time and temperature. With actuation, distinct tones are heard signaling the progression of a successful, or termination of an unsuccessful treatment. After successful application, the basket is contracted and the catheter is pulled back one black line (5 mm). The basket is then reexpanded, and the process is repeated. In this fashion, bronchi 3 mm in diameter or larger are treated distally to proximally, in 5-mm nonoverlapping increments.

The lower lobes and both upper lobes are treated in three separate sessions, while the right middle lobe is spared due to the theoretical concerns for obstruction and atelectasis in the setting of its long and narrow airway. These sessions are usually carried out 3 weeks apart [29]. The right lower lobe is usually treated on the first session, the left lower lobe on the second, and both upper lobes on the third (Fig. 5).

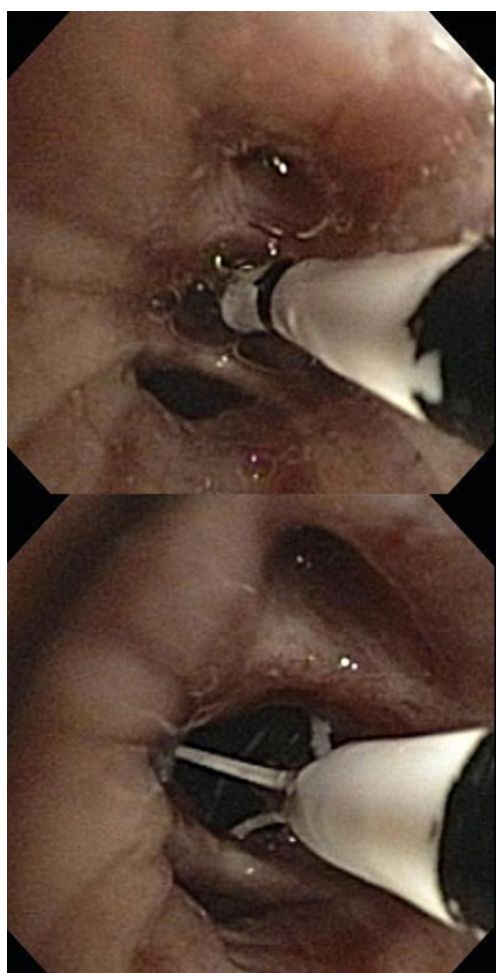


Fig. 5 Images of the Alair® Catheter being applied to a subject's airway. Image courtesy of Dr. Ken Yoneda

A systematic approach, starting from the most distal airways to the more proximal, is recommended to ensure that all accessible airways are carefully identified and treated only once [29]. The number and location of actuations should be recorded at the treatment completion of each bronchial segment. A session of BT may involve 30 to 90 activations and takes approximately 50 min to complete but varies based on the lobes being treated and individual patient anatomy [30].

Postprocedure Management

Recovery lasts between 2 and 4 h depending on the modality of sedation employed and the patient's response to treatment. Physical examination with close attention to the patient's vital signs and breath sounds and spirometry are done prior to discharging the patient. Serial spirometry is performed, and patients are not discharged home until their postbronchodilator FEV1 is 80% of their preprocedure postbronchodilator baseline. An airway clearance device, such as an acapella device, to assist in clearance of airway secretions is useful in managing postprocedure secretions. Patients should be called after 24 h, 48 h, and 7 days following the procedure. They should be evaluated in the clinic approximately 2 weeks after the procedure to evaluate their recovery and status for subsequent procedures.

Conclusion

Patients with difficult to control asthma should be rigorously and methodically evaluated to identify factors that prohibit optimal management with standard modes of therapy. These factors and issues should then be thoughtfully addressed to help control their disease. Inability to stabilize asthma symptoms despite regularly scheduled ICS and LABA should then lead to consideration of BT.

Since FDA approval in April 2010, BT has been implemented in clinical practice at more than 55 global sites [31]. BT is a novel and promising procedure that appears to be safe and effective in improving quality of life and reducing exacerbations in patients with severe persistent asthma. Long-term safety studies up to 2 to 5 years posttreatment did not show any increase in exacerbations, respiratory events, and hospitalizations [27].

Our knowledge regarding the mechanism of action of BT is incomplete, and its ultimate effect on inflammation, epithelial function, airway innervation, vascular supply, and mucus production has not fully been realized [31]. Likewise, data on effects on lung function, control of symptoms, and health care utilization beyond 5 years posttreatment remain an ongoing area of study. Nevertheless, the clinical evidence including a double-blinded,

sham-controlled trial demonstrating improvement in quality of life scoring and severe asthma exacerbations, and the 5-year stability data are compelling. While postapproval studies are ongoing, BT should be considered a novel, yet accepted treatment for severe persistent asthma.

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