

Reducing asthma attacks in patients with severe asthma: The role of bronchial thermoplasty

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ABSTRACT

Asthma remains one of the most common diseases worldwide and results in significant societal health care costs and in morbidity and mortality to those afflicted. Despite currently available medications, 5–10% of patients with asthma have severe disease with debilitating symptoms and/or life-threatening exacerbations. Bronchial thermoplasty is a device-based therapy with proven efficacy in this subgroup of patients. Thus far, bronchial thermoplasty has been shown to reduce exacerbations and to improve important measures of asthma control. The purpose of this article is to review the pathophysiology of severe asthma, including the role of airway smooth muscle cells and the procedural aspects of bronchial thermoplasty, and to review the evidence behind this important therapy.

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Asthma remains one of the most common and costly diseases in the world, is a major public health concern in the United States, and is associated with significant morbidity and increased health care costs.¹ The prevalence of asthma has continued to increase over the past decade and affected 8.4% of the United States population in 2009.² Five to ten percent of the almost 26 million people living with asthma in the United States are estimated to have severe asthma.³ The impact of severe, uncontrolled asthma is very significant from an economic standpoint, with an estimated cost of asthma in the United States in 2007 of \$56 billion in direct costs and productivity losses^{1,4,5}; a large proportion of these costs are associated with patients with severe asthma.

Advances in pharmacologic asthma therapies have primarily been in improved delivery methods for inhaled corticosteroids and β -agonists, the mainstay of asthma management,⁶ or targeted therapies with select biologics that can be used only in a limited subset of patients.^{7–9} Less conventional options include the unapproved immunotherapy with methotrexate, cyclosporine, azathioprine, macrolides, antifungals, and immunoglobulin infusions¹⁰; however, the benefit of these therapies has not been demonstrated in well-designed trials. Despite the availability and success of asthma medications for a majority of patients with severe asthma, there is a subset of patients whose

asthma remains uncontrolled.¹¹ Data from the Severe Asthma Research Program¹² and from the The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimes study¹³ demonstrate that more than 50% of patients with severe asthma continue to seek emergency and/or urgent care, which indicates that many patients with severe asthma lack effective therapy to control their symptoms and minimize impairment. In the management of asthma, severe asthma represents the greatest unmet need in terms of understanding mechanisms, morbidity, health care costs, and effective treatment. Management of asthma continues to evolve, with a major goal of asthma management being to reduce asthma exacerbations,^{3,14} which, in and of themselves, have been shown to be predictors of future exacerbations.¹⁵

Bronchial thermoplasty (BT), a recently developed device-based therapy, provides a novel and more broadly applicable approach to treat severe asthma and has recently been added as a treatment option for those patients at step 5 of the Global Initiative for Asthma Guidelines classification.¹⁶ This review provides a brief overview of asthma pathophysiology, followed by the clinical evidence on the effectiveness and safety of BT in patients with severe asthma.

Pathophysiology of Asthma

Asthma is a chronic disease of both the large and small airways, and is characterized by bronchial hyperresponsiveness, airway inflammation, and airway remodeling. The pathogenesis of asthma is classically viewed as a T-helper (Th) 2 mediated disease marked by upregulation of Th2 specific cytokines (interleukin [IL] 4, IL-5, and IL-13) and predominantly eosinophilic airway inflammation in response to an allergen or irritant. It has now been recognized that asthma is a more heterogeneous disease that may be characterized

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by both eosinophilic as well as noneosinophilic phenotypes.¹⁷ Neutrophilic inflammation is thought to be mediated by Th1 and Th17 pathways, and may be predictive of a more-severe course.^{18,19} Regardless, the histopathology of severe asthma is typically marked by mucous cell hyperplasia, smooth muscle hypertrophy, and tissue infiltration with inflammatory cells. Chronic airway remodeling with subepithelial fibrosis is also seen in patients with asthma and may lead to irreversible airflow obstruction.²⁰ The bronchial hyperresponsiveness in patients with asthma is an excessive bronchoconstrictive response to various inhaled triggers that would have little effect on the airways of persons without asthma. There are both direct (histamine and methacholine) and indirect triggers (allergens, exercise, irritant dusts) of bronchial hyperresponsiveness.

Role of Airway Smooth Muscle in Asthma

Airway smooth muscle (ASM) is thought to play an important role in acute bronchial hyperresponsiveness and chronic airway remodeling. The airways of patients with severe asthma have long been noted to have an increased smooth muscle mass secondary to cellular hypertrophy and hyperplasia.²¹

The increased contractility of ASM in patients with asthma is thought to be secondary to exaggerated responses to contractile stimuli (e.g., acetylcholine, histamine, leukotriene, serotonin, bradykinin).²² The contractile stimuli signal through G-protein-coupled receptors leads to activation of phospholipase C and the generation of inositol triphosphate. Inositol triphosphate then binds to its receptor on the sarcoplasmic reticulum, which induces the release of calcium into the cytosol that binds with calmodulin. The calcium-calmodulin complex activates myosin light-chain kinase, which phosphorylates myosin and triggers contraction.²³ The mechanisms behind this exaggerated response seen in patients with asthma are unclear but may be secondary to increased myosin light-chain kinase expression, priming of smooth muscle cell *via* IL-13, or dysregulation of calcium homeostasis.^{23,24}

The increase in smooth muscle cell mass is an important contributor to airway remodeling and bronchial hyperresponsiveness. Although this increase is caused by both hypertrophy and hyperplasia, the mechanisms behind these well-recognized pathologic findings remain incompletely understood. In 2000, Johnson *et al.*²⁵ provided data that, when analyzed, indicated that ASM *in vitro* taken from patients with asthma had higher proliferation rates than healthy controls, although this was not supported by more recent data.²⁶ Mitogen-stimulated pathways may be upregulated in the airways of patients with asthma, and some have suggested that, in addition to the typical mitogens (tissue growth factor- β , fibroblast growth factor, etc.),



Figure 1. The Alair RF Controller (left) and expanded electrode array of the Alair Catheter (right).

inflammatory cytokines may serve as mitogens for ASM proliferation.²⁷ An alternative explanation of the hyperplasia seen in patients with asthma is that peripheral progenitor fibrocytes are recruited to the airways in patients with asthma. Peripheral recruitment of fibrocytes has been shown in mouse models, and, more recently, Schmidt *et al.*²⁸ and Saunders *et al.*²⁹ showed that, in patients with asthma, fibrocyte numbers were increased in both the airways and peripheral blood of patients with severe asthma. Although, the majority of the research has focused on hyperplasia, hypertrophy may actually be more common, except occasionally, in very severe fatal asthma.³⁰ Results of cell culture studies have implicated the involvement in the phosphoinositide 3-kinase, protein kinase-B mammalian target of rapamycin, p70^{S6} pathway in cell hyperplasia.³¹ Irrespective of the mechanisms behind the increased ASM mass, it is clearly an important pathologic feature of asthma and a significant contributor to its clinical consequences.

BT

BT is a procedure that delivers thermal energy to the airways during bronchoscopy to reduce excess ASM and limit the ability of the airways to constrict. Analysis of data from randomized controlled clinical trials has shown BT to increase the level of asthma control and improve the quality of life of patients with severe asthma.^{32,33}

The Procedure

BT is performed with the Alair Bronchial Thermoablation System (Boston Scientific Corp., Marlborough, MA), which comprises the Alair Radiofrequency (RF) Controller and the Alair Catheter (Fig. 1). The Alair catheter is a single-use, disposable device deployed under direct vision through the working channel (2.0 mm) of a high-frequency compatible flexible diagnostic bronchoscope (outer diameter, ≤ 5.0 mm). The 4-electrode array at the catheter tip is expanded to contact the airway walls and is activated to deliver RF electrical energy over the 5-mm length of the exposed electrodes, which heat the tissue to a temperature of 65°C. A thermocouple attached to one arm of the electrode array monitors the temperature at the tissue surface, as well as other parameters, to provide the necessary feedback to the RF Controller to carefully control the

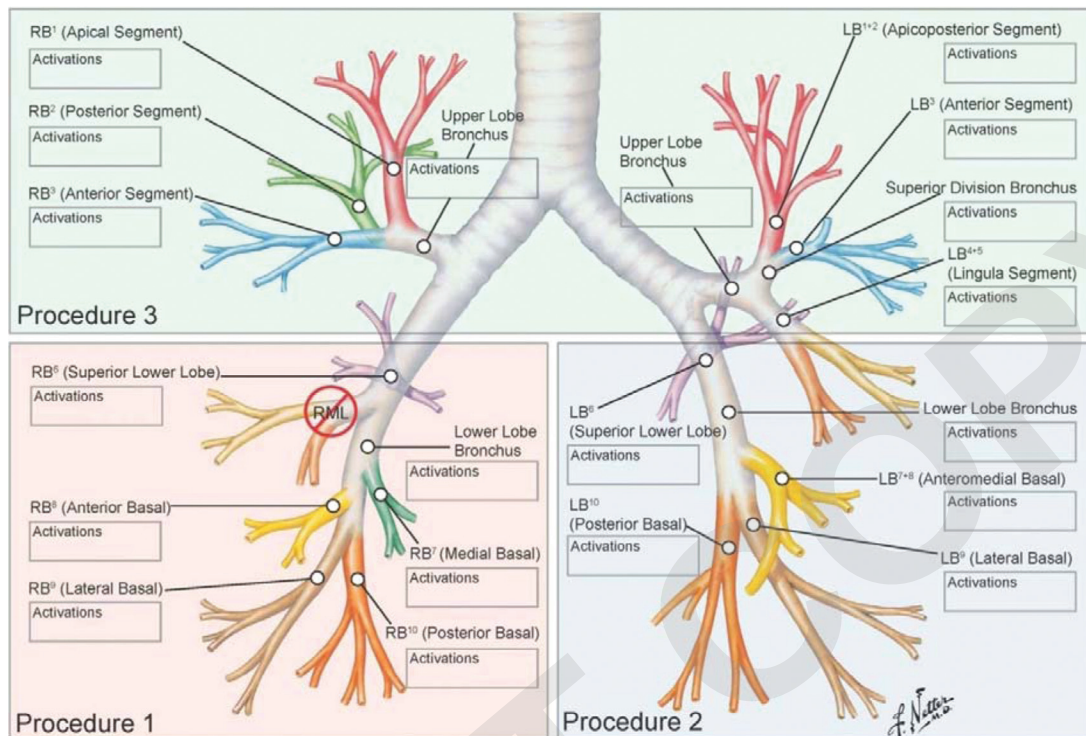


Figure 2. Map of the airways, showing sequence of treatments (Procedure 1, Right Lower Lobe; Procedure 2, Left Lower Lobe; Procedure 3, Right and Left Upper Lobes), and tracking of activations.

delivery of energy.³⁴ Five-millimeter-long contiguous activations are performed along the length of all accessible 3–10-mm-diameter airways, beginning from the distal end to the proximal end of the airways. The procedure is routinely performed with the patient under moderate sedation and typically takes <1 hour. A series of three procedures, each separated by at least 2–3 weeks are required to complete a full treatment, with a different lobe being treated during each session (right lower lobe in session 1, left lower lobe in session 2, and both the right and left upper lobes in session 3) the right middle lobe is not treated, based on theoretical concerns of middle lobe syndrome.³⁵ The lung map that identifies airways that can potentially be treated and documents the number of activations in the treated segments are depicted in Fig. 2.

Patient Selection

Careful patient selection and assurance of stability of the patient to undergo each of the three bronchoscopy procedures are key to performing the procedure successfully. The contraindications and precautions are listed in Table 1 (Alair directions for use).

Clinical Evidence

Clinical evidence for the safety and effectiveness of BT for the treatment of asthma has been collected over the course of 14 years, beginning in 2000, and has included three randomized clinical trials, one of which

was a sham-controlled, double-blind study.^{32,33,36,37} Key aspects of the randomized clinical trials are highlighted in Supplemental Table 1, followed by a more detailed description of the pivotal sham-controlled Asthma Intervention Research 2 (AIR2) Trial. Although the first two trials (AIR and Research In Severe Asthma) were not sham-controlled trials and, as such, may be prone to bias and/or the sham effect, the more recent and larger AIR2 Trial was a randomized sham-controlled trial that demonstrated efficacy of this novel therapy.

AIR2 Trial

The AIR2 Trial (pivotal trial for Food and Drug Administration approval) was a multicenter (30 centers in 6 countries), randomized, double-blind, sham-controlled trial that demonstrated effectiveness and safety of the BT with the Alair System in patients with severe asthma who were still symptomatic despite being managed on conventional therapy of high inhaled corticosteroids (doses of >1000 µg per day of beclomethasone or equivalent) and long acting β agonist (doses of ≥100 µg per day of salmeterol or its equivalent) with or without oral corticosteroids at a dose of ≤10 mg per day.³²

A total of 297 patients were enrolled in the study by using a 2:1 randomization scheme (two BT to one sham-control patients: 196 BT group, and 101 sham group). The subjects were allowed to have up to four exacerbation and/or two hospitalizations for asthma in

Table 1 **Contraindications and precautions for the Alair BT System***

Contraindications

Patients with the following conditions should not be treated:

The presence of a pacemaker, internal defibrillator, or other implantable electronic devices

Known sensitivity to medications required to perform bronchoscopy, including lidocaine, atropine, and benzodiazepines

Patients previously treated with the Alair System should not be re-treated in the same area(s); no clinical data are available that study the safety and/or effectiveness of repeated treatments

Patients should not be treated while the following conditions are present:

Active respiratory infection

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

Known coagulopathy

As with other bronchoscopic procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin, and nonsteroidal anti-inflammatory drugs before the procedure with physician guidance

Precautions

Caution should be taken in patients with the following conditions due to a potential increased risk of adverse events that may be associated with the procedure; patients with these conditions were not studied in the pivotal trial, and the safety of Alair treatment for such patients has not been determined:

Postbronchodilator FEV₁ of <65%

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

Use of short-acting bronchodilator in excess of 12 puffs per day within 48 hr 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; insulin-dependent diabetes; epilepsy; or other significant comorbidities, such as uncontrolled coronary artery disease, acute or chronic renal failure, and uncontrolled hypertension

Intubation for asthma or intensive care unit admission for asthma within the previous 24 mo

Any of the following within the past 12 mo:

I. Four or more lower respiratory tract infections

II. Three or more hospitalizations for respiratory symptoms

III. Four or more OCS pulses for asthma exacerbation

OCS = Oral corticosteroid; FEV₁¹, forced expiratory volume in 1 second.

*Derived from Alair—Directions for use (www.btforasthma.com).

the previous 12 months. The subjects with more-frequent exacerbations or hospitalizations were excluded for safety reasons. The treatment and sham procedures were performed by an unblinded bronchoscopy team, and all follow-up and assessment visits were conducted by a blinded assessment team. Sham procedures were performed identically to active procedures by using an RF controller that provided audio and visual cues that mimicked the active controller but did not deliver RF energy through the catheter.

The primary effectiveness end point was the difference between the study groups in the change in the Asthma Quality of Life Questionnaire (AQLQ) score from baseline and the average of the 6-, 9-, and 12-month assessments after the last bronchoscopy session. The BT group had improved quality of life compared with the sham group as demonstrated by the observed difference between the BT and sham groups in the

mean change in AQLQ score from baseline to the average of the 6-, 9-, and 12-month score; posterior probability of superiority (PPS) for the difference between the groups for the intention-to-treat population was 96.0% (BT superior to sham), and more patients in the BT group (79%) compared with those in the sham group (64%) achieved an improvement in the AQLQ score of ≥ 0.5 , the minimal important difference for AQLQ (PPS = 99.6% [BT superior to sham]).

The severe exacerbation rate and proportion of patients who experienced severe exacerbations were reduced in the BT group compared with the sham group, with a 32% reduction in the rate of severe exacerbations that required systemic corticosteroids in the BT group versus the sham group (0.48 versus 0.70 severe exacerbations per patient per year; PPS = 95.5%). During the posttreatment period, there was a 34% reduction in the proportion of patients who experienced

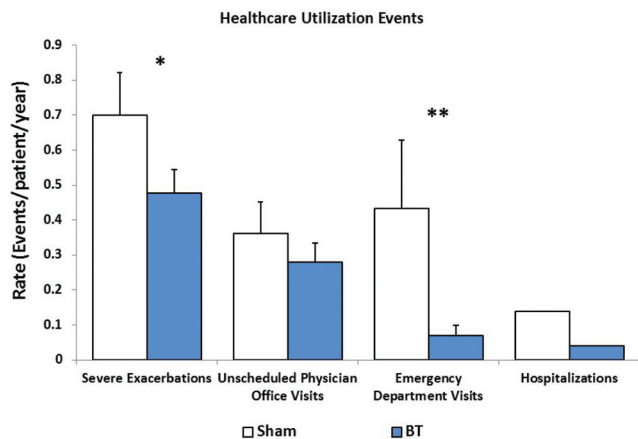


Figure 3. Annualized health care utilization events in the 12 months after sham or BT procedure. Values are mean $\pm$ SE. Severe exacerbations are defined as exacerbations that require treatment with systemic corticosteroids or doubling of the inhaled corticosteroid dose. *Posterior probability of superiority (BT-sham) = 95.5%. **Posterior probability of superiority (BT-sham) = 99.9%.

severe exacerbations (26.3% in the BT group and 39.8% in the sham group; PPS = 99.0%).

In addition, as shown in Fig. 3, clinically meaningful reductions also were observed in emergency department (ED) visits for respiratory symptoms, with the proportion of patients having ED visits for respiratory symptoms in the BT group (3.7% in the BT group compared with 15.3% in the sham group; PPS >99.9%). There also was a significant reduction in the proportion of patients with asthma (multiple symptoms) adverse events in the BT group compared with the sham group (PPS = 99.6%). Patients reported fewer days lost from work and/or school, or other daily activities due to asthma, with a 66% reduction in the BT group compared with the sham group during the 12-month period after BT (1.3 versus 3.9 days per year per patient; PPS = 99.3%). There was no deterioration (or significant improvement) in forced expiratory volume in 1 second (FEV₁) in either the BT or sham groups throughout the 12-month follow-up. Although there were improvements in the BT group over the sham group in other secondary end points, including the percentage of symptom-free days, the total symptom score, rescue medication use, Asthma Control Questionnaire, and morning peak expiratory flows, the differences between the groups were not statistically significant.

Safety Results

The AIR2 Trial involved 558 BT treatment bronchoscopy procedures in 190 patients and 292 sham bronchoscopy procedures in 98 patients. There were no serious complications such as pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias, or

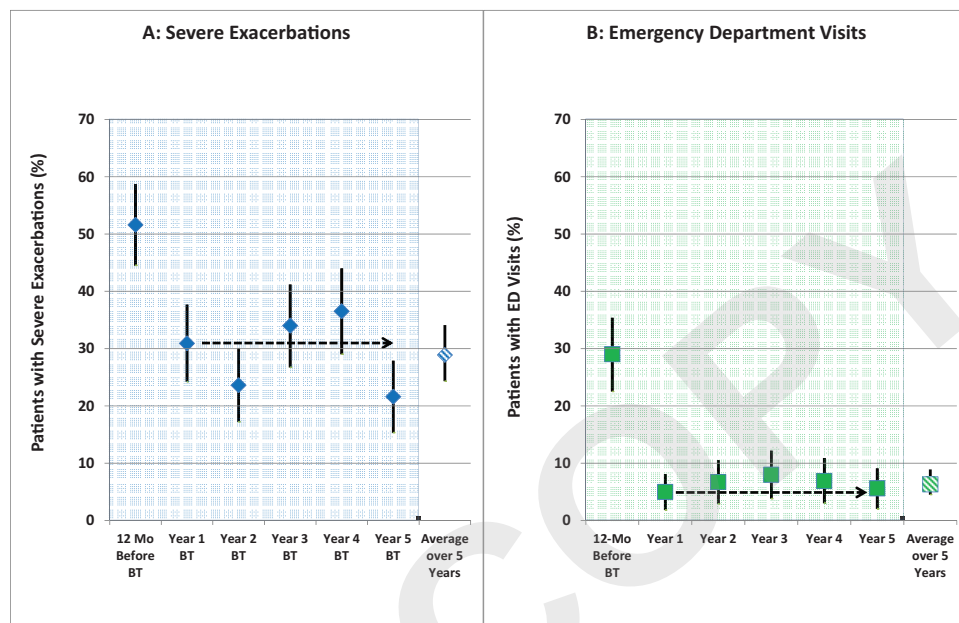
death as a result of BT treatment or the sham bronchoscopy. During the treatment period (from the first treatment through 6 weeks after the third treatment), there was a significant transient increase in respiratory adverse events in 84.7% of patients in the BT group compared with 75.5% patients in the sham group. Respiratory adverse events included asthma (multiple symptoms), upper respiratory tract infection; atelectasis; lower respiratory tract infection, wheezing, and hemoptysis; and anxiety. The median time to onset for respiratory adverse events after bronchoscopy was 1.0 day for the BT group (average, 5.9 days) and 1.0 day for the sham group (average, 7.2 days). Sixteen patients (8.4%) in the BT group required 19 hospitalizations (3.4% per bronchoscopy) for respiratory symptoms during the treatment period, which compared well with the hospitalization rate after bronchoscopy of >5% reported in the patients with severe asthma in the Severe Asthma Research Program.³⁸

Reasons for hospitalization included the following: in the BT group worsening of asthma (12 in 10 patients), segmental atelectasis (3 in 2 patients), lower respiratory tract infection (1 patient), low FEV₁ (1 patient), hemoptysis (1 patient, treated with bronchial artery embolization), and an aspirated prosthetic tooth (1 patient) compared with two patients in the sham group (both for worsening of asthma). All adverse events resolved with standard therapy. In the post-treatment period, 70% patients in the BT group experienced at least one respiratory adverse event compared with 80% in the sham group. Significantly fewer patients in the BT group (27.3%) reported an asthma (multiple symptoms) adverse event compared with 42.9% in the sham group (PPS = 99.7%), which represented a 36% risk reduction. There were no structural changes in the lung that were of a safety concern based on a blinded review of high-resolution computed tomography pairs (baseline and at 1 year after the procedures); there was no evidence of bronchial dilatation, bronchiectasis, bronchiolitis obliterans, or pulmonary emphysema in any of the patients treated with BT 1 year after treatment.

Durability of Effectiveness

Wechsler *et al.*³⁹ reported data from a 5-year follow-up of patients who received BT in the AIR2 Trial, which demonstrated the long-term benefits of BT to at least 5 years after a single BT treatment was performed during 3 separate procedures. As seen in Fig. 4, the proportion of patients who experienced one or more severe exacerbations in each of the years from year 2 to year 5 compared with year 1 after BT remained unchanged and met the prespecified noninferiority margin. In addition, the reduction in ED visits seen in the first year after BT was maintained to at least 5 years

Figure 4. Percentage of patients who experienced severe exacerbations (A) and ED visits (B) in the 5 years after BT. Values are point estimates with 95% upper and lower confidence intervals. The 365-day period that constituted year 1 began at 6 weeks after the last BT bronchoscopy. A noninferiority margin of 20% was used to demonstrate that the proportion of patients who experienced one or more severe exacerbations was not substantially worse during each of the subsequent valuation periods (i.e., the upper 95% confidence interval for the difference in proportions is less than 20%). Reproduced with permission from Wechsler, JACI 2014.



(Fig. 4). *Post hoc* comparison of the average reduction in the proportion of subjects who experienced severe exacerbations over a 5-year period compared with the 12 months before BT showed consistent, clinically meaningful improvements in both measures, with a 44% reduction in severe exacerbations and a 78% reduction in ED visits.

Long-Term Safety

The absence of an increase in respiratory adverse events in general and asthma (multiple symptoms) adverse events in particular over a 5-year period demonstrated the safety of BT over the long term. The long-term safety was supported further by the absence of any decrease in prebronchodilator FEV₁, the lack of an increase from the low baseline rate of hospitalizations, and the absence of any significant structural changes in the airways (from review of high-resolution computed tomography pairs) over the course of 5 years of follow-up. Over this 5-year period, 3 patients (3%) were noted to have increased or new bronchiectasis: one involved worsening of preexisting bronchiectasis; one involved mild bronchiectasis in two lobes, including the right middle lobe, which had not been treated with BT; and one involved bronchiectasis newly identified by means of high-resolution computed tomography.

The long-term safety data from the AIR2 Trial was consistent with the observations previously reported for the AIR and the Research In Severe Asthma trials.^{37,40} Each of these longer-term studies has shown consistency over time in the safety profile for the patients treated with BT during posttreatment follow up in the percentage of patients who reported respiratory

adverse events, the number of respiratory adverse events per patient, and the number of hospitalizations and ED visits due to respiratory symptoms per patient (Fig. 5).

DISCUSSION

Controlled clinical trials of BT have demonstrated persistent efficacy of this therapy in a reduction of severe exacerbations, health care utilization, days lost from school or work, and overall improvement in asthma quality of life.^{32,33,36} The most recent data from the long-term follow-up of patients treated with BT in the AIR2 Trial provided evidence that this improvement persists for at least 5 years.³⁹ A reduction in asthma exacerbations is an important benefit of BT because exacerbation frequency has been shown to correlate closely with quality-of-life measures in patients with asthma.⁴¹ BT can be delivered safely and effectively by pulmonologists experienced with bronchoscopy. Although there often is a transient worsening of asthma symptoms, most common of which are breathlessness, wheeze, cough, chest discomfort, night awakenings, and productive cough after the application of heat to the airways of these patients with severe asthma, the long-term benefits outweigh these risks.

Although corticosteroids have been the first-line treatment of choice for asthma for decades,⁴² the molecular mechanisms by which corticosteroids produce their effect are still being elucidated.⁴³ Not surprisingly then, although BT has been shown to be a safe and effective therapy in providing long-lasting asthma control, questions remain about its mechanism of action other than the demonstrated reduction in ASM and reduced methacholine-induced bronchoconstriction.³⁴

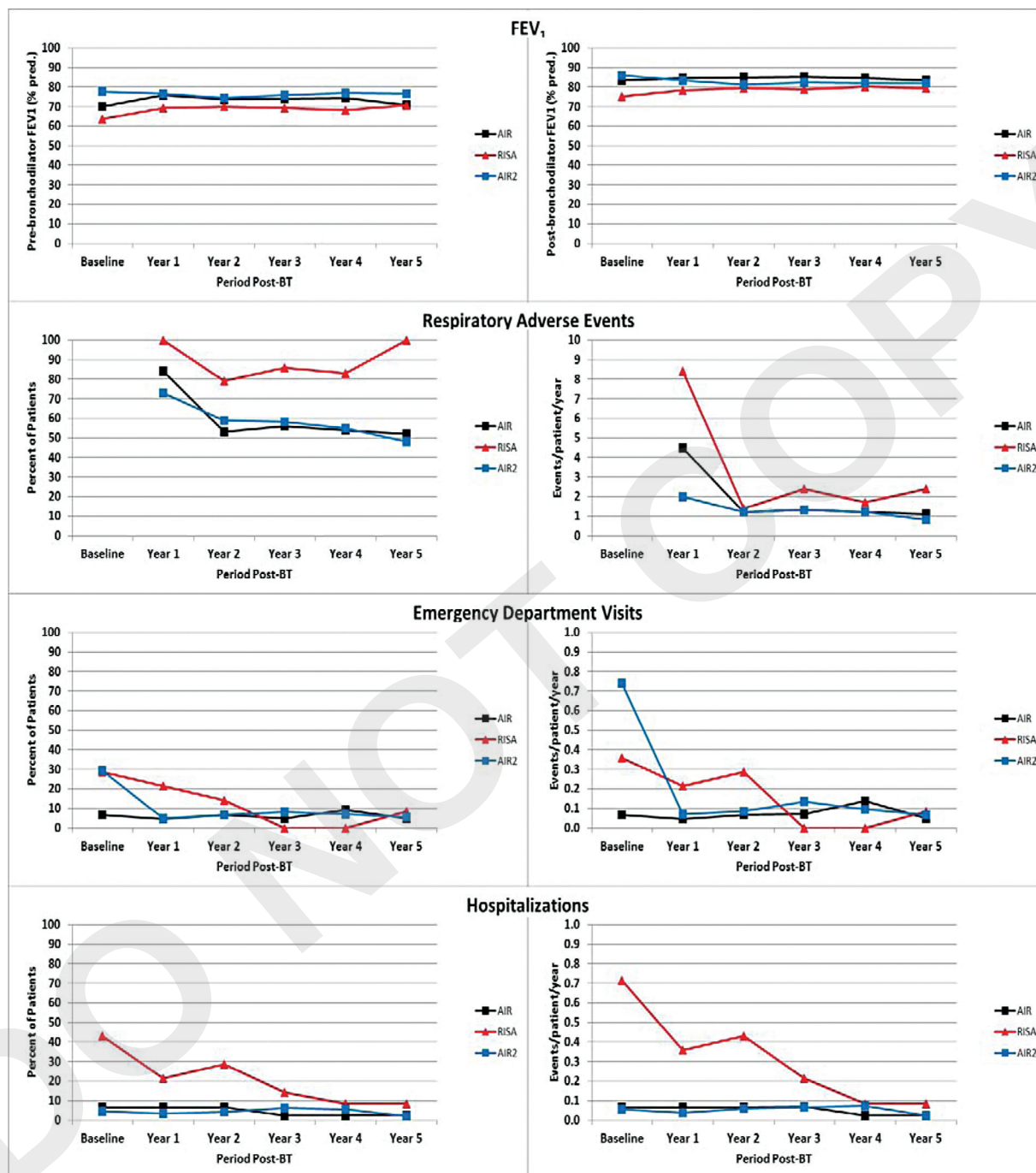


Figure 5. FEV₁ (percent predicted), respiratory adverse events, ED visits, and hospitalizations for respiratory events from the AIR Trial (black), Research In Severe Asthma Trial (red), and AIR2 Trial (blue) across 5 years after BT. The four graphs on the left represent the percentage of patients who experienced each type of event and the prebronchodilator FEV₁ values; whereas the four graphs on the right represent the postbronchodilator FEV₁ values and the event rates (events per patient per year). FEV₁ = forced expiratory volume in 1 second.

Although a number of ongoing studies are underway to better understand the mechanism by which BT works to impact asthma exacerbations, a recent French study of 10 patients confirmed that ASM was reduced in airways of patients who underwent BT.⁴⁴ Future and ongoing trials should also provide data that may help define the phenotypes of responding patients and po-

tentially improve the already favorable risk-benefit profile of BT.⁴⁵ As was the case for corticosteroids, continuing research to address these important questions should not stop physicians from making this important treatment option available to carefully selected patients who remain symptomatic despite being treated with the best available pharmacologic or bio-

logic therapies. In recognizing this unmet need, the most recent update from Global Initiative for Asthma Guidelines recommends BT as a preferred treatment option at step 5 when considering add-on therapy.¹⁶

Summary

BT is a novel device-based treatment of asthma that disrupts ASM.

- BT is a complementary treatment, and not a replacement, for current asthma reliever and controller medications
- BT is performed by a trained physician over three treatment sessions, during which controlled thermal energy is delivered with the Alair catheter to the airways *via* a bronchoscope to reduce excess ASM and to limit its ability to constrict the airways.
- Previous studies demonstrated safety and a compelling, persistent effect of increasing the level of asthma control and improve quality of life of patients with severe asthma for at least 5 years.
- BT is now recommended in international guidelines as a treatment option for patients with severe, uncontrolled asthma.^{16,46}
- Current and future studies that use imaging techniques, airway biopsies, and measures of exhaled bronchial condensate and exhaled nitric oxide will provide answers to many key questions regarding the mechanisms behind BTs therapeutic efficacy.

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