

Bronchial thermoplasty for asthma: A critical review of a new therapy

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ABSTRACT

Bronchial thermoplasty (BT) is a novel experimental procedure involving the application of controlled heat from a radiofrequency source to the airway wall as a means to reduce airway smooth muscle in the airway wall. After BT was shown to reduce airway smooth muscle in preclinical studies in dogs, clinical studies in humans revealed that BT resulted in a significant improvement in asthma outcomes including mild asthma exacerbations, asthma symptom-free days, asthma rescue medication use, and airway hyperresponsiveness as measured by methacholine PC₂₀. A second trial in humans revealed that BT was safe and effective in patients with severe asthma refractory to the current standard of care. While current trials are ongoing, BT holds promise as an exciting novel therapy in the management of patients with asthma.

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Key words: Asthma, bronchial thermoplasty, device, radiofrequency ablation, severe asthma, smooth muscle, thermal energy

Over 20 million Americans are affected by asthma. In the last 10 years, multiple novel therapies have been developed to treat asthma and new guidelines have been published and promulgated to educate physicians and asthmatic patients alike. Although removal of environmental allergic triggers and new formulations of inhaled corticosteroids (ICSs), long-acting β -agonists (LABAs), and leukotriene modifiers remain the cornerstone of asthma management, novel biological agents including omalizumab (anti-IgE) have been added to the armamentarium. However, despite these efforts, a large proportion of asthmatic patients remain poorly controlled with close to 2 million emergency room visits for asthma; 500,000 hospitalizations for asthma; and over 4000 deaths from asthma each year. Indeed, we spend over \$14 billion annually treating patients with asthma.

Clearly, there are several unmet needs in asthma and a critical need for innovative and effective therapies. This review focuses on bronchial thermoplasty (BT), a revolutionary new way to potentially treat asthma. A nonpharmacologic intervention, this exciting device-based therapy holds promise as a means to reduce both bronchoconstriction and asthma symptoms and to improve asthma-related quality of life.

BRONCHIAL THERMOPLASTY AND AIRWAY SMOOTH MUSCLE

The term “bronchial thermoplasty (BT)” describes a novel procedure involving the application of controlled heat from a radiofrequency (RF) source to the airway wall as a means to reduce airway smooth muscle in the airway wall. The rationale for this unique approach to treating asthma requires an appreciation of the role that airway smooth muscle plays in bronchoconstriction, an important manifestation of an asthma attack.

All airways in the lung to the level of the respiratory bronchioles are lined with smooth muscle that has the capacity to shorten in response to a variety of stimuli.¹ Indeed, if sufficiently stimulated (e.g., with methacholine or histamine), all airways in the lung (including cartilaginous ones) can narrow to complete closure.^{1,2} This is considered to be the primary mechanism leading to narrowing of the airways and the dyspnea that is manifest during an acute asthma attack. The role of airway smooth muscle in healthy as well as asthmatic patients has been well debated. One area of discussion revolves around the question of whether the large conducting airways or the small airways are more responsible for the airway narrowing and airflow obstruction during asthma attacks. Another debated area revolves around the functional importance of airway smooth muscle in the lungs. A variety of roles have been postulated for airway smooth muscle.^{3–6} However, none of these potential functions of airway smooth muscle has been shown to be essential to normal lung physiology, leading to the postulation that in humans, airway smooth muscle is indeed like a vestigial organ.⁵ Although a practical function for airway smooth mus-

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cle in normal healthy individuals remains elusive, it clearly has a pathological role in disease states such as asthma.^{4,5} Anatomic and histological observations of airways from patients with asthma have shown that there is hypertrophy of airway smooth muscle in the airway wall. Additionally, physiological measures have shown that the airways in these patients are hyperresponsive to parasympathomimetic agents. Although not clearly understood, the combination of structural, chemical, and physiological factors in this pathology contribute to the excessive narrowing of the airways. These considerations led to the hypothesis that if airway smooth muscle could be reduced, airway bronchoconstriction would be minimized with a resultant decrease in asthma symptoms. Stemming from this hypothesis was the notion that application of thermal energy could reduce or disrupt airway smooth muscle.

BT: DEVICE AND TECHNIQUE

The technique for BT, including the importance of bronchoscopy experience of the physician, careful patient selection, patient preparation, patient management, and postoperative follow-up, have recently been described in detail by Mayse *et al.*⁷ Briefly, the BT system uses a bronchoscope and includes a special catheter with an expandable electrode array on the tip (the Alair catheter; Fig. 1 A) and an RF controller that supplies energy *via* the catheter to heat the airway wall (Fig. 1 B). Once the bronchoscope is inserted in the airways, the catheter is passed through the bronchoscope and deployed with the electrode array open such that all sides of the array are in contact with the airway wall (Figs. 2 and 3). The bronchoscopist steps on a footswitch attached to the RF controller for ~10 seconds; this results in thermal energy being delivered to the treated airway during that time. The catheter is then repositioned so that other contiguous areas of the airway may be treated. All visible and reachable airways from 3 to 10 mm distal to the mainstem bronchi are treated with a series of contiguous activations. In the protocols used to date, three bronchoscopies were required to treat all airways in both lungs. Each procedure typically takes 30–45 minutes to complete, with one or two lobes treated at a time. Every segment is treated, but the size of the individual's airways and the diameter of the bronchoscope are limiting features. Usually, the airways are large enough so that one or two subsegments in each segment are able to receive a treatment. Although procedure duration is also limited by oral anesthesia, it is expected that with increased experience of the bronchoscopist, at most two bronchoscopies will be required to treat all of the airways.

PRECLINICAL STUDIES

The current approach and parameters of using RF energy to reduce airway smooth muscle were estab-

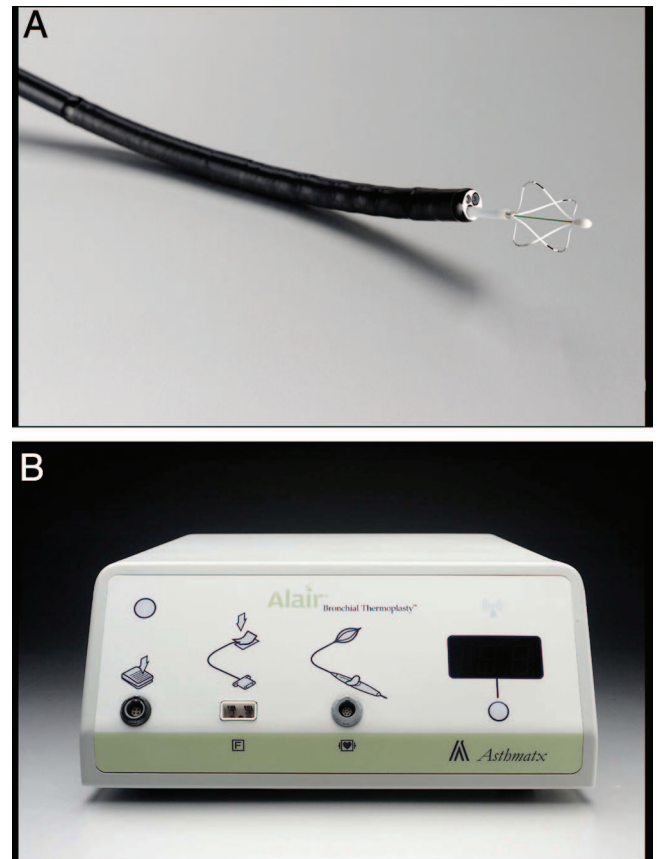


Figure 1. (A) The bronchial thermoplasty catheter; (B) the bronchial thermoplasty energy source.

lished from a series of preclinical studies conducted in dogs.^{8,9} Eleven dogs were studied after treatment of airways with the Alair System. In all dogs, the lungs were divided into four regions: upper left, lower left, upper right, and lower right. In each dog, each region was left untreated or received treatment at 55, 65, and 75°C. These treated dogs were followed out to 3 years,

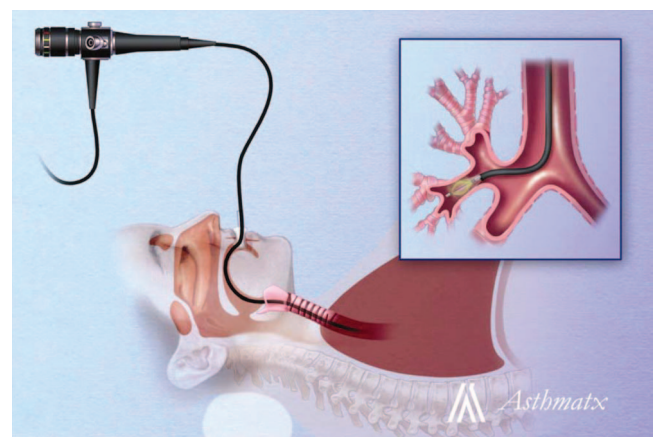


Figure 2. The Alair Bronchial Thermoplasty System by Asthmatx. The bronchial thermoplasty catheter may be deployed bronchoscopically to all visible airways.

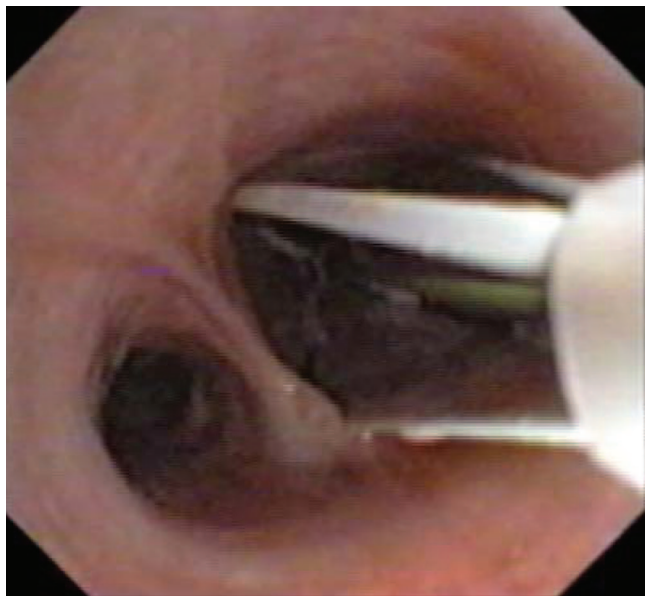


Figure 3. A bronchial thermoplasty catheter deployed in the airway of an asthmatic patient.

with death and detailed histological evaluations performed on two dogs at 12 weeks, and three dogs each at 6, 12, and 157 weeks, respectively. The temperature ranging study showed a consistent reduction of ~50% of the airway smooth muscle at 65°C, with the effect persisting out to 3 years.⁸ Although the replacement of the airway smooth muscle by connective tissue is shown in the histology in Fig. 4, it is important to note that BT reduced but did not completely eliminate airway smooth muscle. The parenchyma, epithelium, and mucous glands in the treated airways were normal and without significant change. This study also showed an inverse correlation between the amount of altered airway smooth muscle and the airway responsiveness to

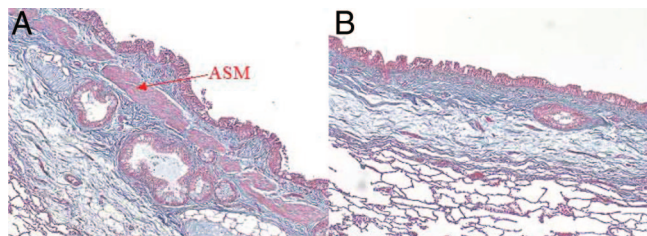


Figure 4. (A) Representative sections showing histopathological features of untreated control airway and (B) an airway treated with RF energy at 65°C, 12 weeks posttreatment (trichrome stain, original magnification, $\times 100$). Airway smooth muscle (ASM) in the untreated airway appears normal, and ASM in the airway treated at 65°C is absent. ASM is generally reduced throughout the circumference of the treated airway (B) and present in amounts similar to that shown throughout the circumference of the untreated airway (A). The parenchyma, epithelium, and mucous glands in the treated airway appear normal.

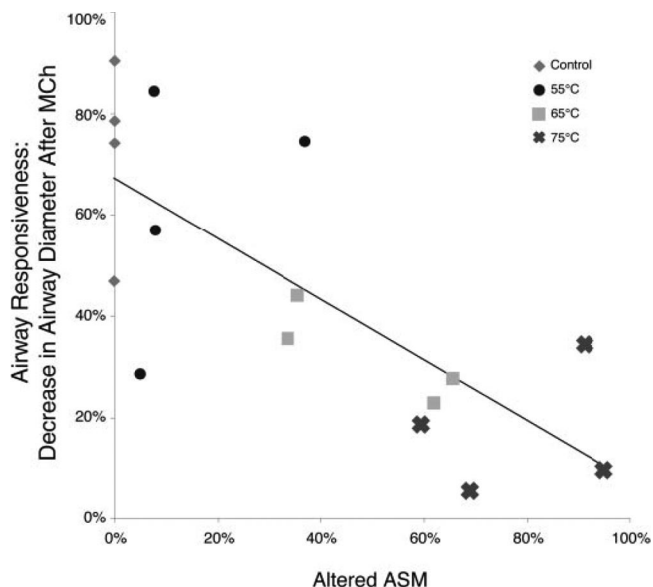


Figure 5. Inverse correlation between airway responsiveness (percent change in airway diameter after local MCh challenge) and percentage of airway circumference containing altered airway smooth muscle. Data are mean values for each histological time point and treatment temperature ($n = 16$) or untreated control ($n = 4$). Individual data ($n = 175$) also exhibit a statistically significant inverse correlation ($r = -0.72$; $p < 0.001$).

local methacholine challenge (Fig. 5), although this in itself did not indicate causality.

The dogs in the study tolerated the procedure well, with no adverse physiological or clinical observations made at any of the time points. The stability of the airway diameter and airway patency was maintained based on >900 blinded bronchoscopic evaluations of the airways performed over the course of the 3-year study.

CLINICAL STUDIES

Positive data from the initial dog studies led to the careful introduction and evaluation of this procedure in humans.^{9,10} As of May 2007, 284 patients have received BT. The initial proof of concept in humans was performed in a group of eight human subjects that planned to have surgery to remove lung tissue for cancer.¹¹ The ability of humans to tolerate this procedure led to the first evaluation of BT in a group of 16 patients with mild to moderate asthma. This single-arm study conducted at two clinical centers showed the tolerability of this procedure in patients with asthma as well as the effect of the procedure on improving both morning and evening peak expiratory flow (PEF) and symptom-free days.¹² Particularly interesting was the greater than two doublings in the methacholine PC₂₀ value after BT, a magnitude that is achieved with ICSs in steroid naive subjects. This effect

Table 1 Efficacy of inhaled corticosteroids with or without long-acting β -agonists

Efficacy for Patients while taking inhaled corticosteroids and long-acting β -agonists

Performed at 12 wk post-BT. BT group ($n = 55$) showed statistically significant improvements over control group ($n = 54$) in changes from baseline to 12 wk post-BT:

Morning PEF

Evening PEF

Percent symptom-free days

Symptom score

Percent of days when rescue medication was needed

AQLQ score

ACQ score

Efficacy for Patients while taking inhaled corticosteroids alone

Performed at 12 wk, 6 mo, and 12 mo post-BT. BT group ($n = 55$) showed statistically significant improvements over the control group ($n = 54$) in changes from baseline to later time points in:

Rate of mild exacerbations

Morning and evening PEF at 12 wk, 6 mo, and 12 mo

Percent symptom-free days at 12 wk, and 12 mo (not significant at 6 mo)

Symptom score at 12 wk, 6 mo, and 12 mo

Percent of days when rescue medication was needed at 12 wk (not significant at 6 mo, and 12 mo)

Total puffs of rescue medication used over 7 days at 12 wk and 12 mo (not significant at 6 mo)

AQLQ score at 12 wk, 6 mo, and 12 mo

ACQ score at 12 wk, 6 mo, and 12 mo

AQLQ = *Asthma Quality of Life Questionnaire*; ACQ = *Asthma Control Questionnaire*; BT = *bronchial thermoplasty*; PEF = *peak expiratory flow*.

was apparent at 12 weeks postprocedure and remained persistent up to 3 years.

Two additional multicenter randomized clinical trials have been completed in patients with moderate to severe asthma. Recently published data from both of these studies, the AIR trial and the RISA trial, provide insight into the outcomes that may be expected from BT^{13,14,17} and are discussed below. The first of these studies is discussed here based on previously published data. The second study will be mentioned briefly since detailed data are pending publication but have been described in abstract form.^{14,15}

The Asthma Intervention Research (AIR) Trial

The first randomized clinical study to evaluate the safety and efficacy of BT¹⁶ involved patients with moderate to severe persistent asthma meeting the following inclusion criteria: nonsmoking adults (aged 18–65 years), taking ICSs ($>200 \mu\text{g}$ of beclomethasone or equivalent) and LABAs, showing worsening of asthma on LABA withdrawal, prebronchodilator forced expiratory volume in 1 second (FEV₁) between 60 and 85% predicted, and showing airway hyperresponsiveness by MCh PC₂₀ $< 8 \text{ mg/mL}$. Subjects were excluded if they had a respiratory tract infection (recent, ≤ 6 weeks, or recurrent, ≥ 3 /year), change in maintenance asthma medications in

the last 6 weeks, or were using >4 puffs/24 hours of rescue medications (except for exercise) in the last 7 days. The effect of BT plus standard medical care was compared with standard medical care alone by assessing frequency of mild and severe exacerbations, PEF measurements, asthma symptoms, use of rescue medication, lung function assessed by spirometry, methacholine challenge, Asthma Quality of Life Questionnaire (AQLQ), and Asthma Control Questionnaire (ACQ). Evaluations were performed when patients were taking their ICSs and were on LABA (ON-LABA) and also when they are off their LABA (OFF-LABA). BT was performed using the regimen of three treatment procedures each separated by ~ 3 weeks. Follow-up of all subjects was up to 1 year. Details of the study design and efficacy and safety outcomes have been recently reported.¹³ Efficacy outcomes are summarized in Table 1. BT resulted in a significant decrease in mild exacerbations at 3 and 12 months compared with the control group and a trend toward a reduction in severe exacerbations. Although patients were taking ICS alone, the patients in the BT group showed improvements over the control group in the methacholine PC₂₀ doublings, although these changes did not reach statistical significance. Although BT resulted in a significant increase in asthma symptom-free

days, a significantly decreased asthma rescue use (400 fewer puffs/year compared with the control group), and a significant increase in asthma-free days and improvements in ACQs and morning PEF, there were no changes in the number of night awakenings or pre- and postbronchodilator FEV₁.

Safety Results

Adverse event profiles were compared for the peri- and postprocedure periods for the BT and control groups. Considering that BT was administered during a bronchoscopy procedure, it was expected that there would be more adverse events, particularly respiratory in nature, in the BT group compared with the control group and that the majority of these would present in the period immediately after the bronchoscopy. There was a transient increase in adverse events in the BT group in the peribronchoscopy period, but there was no difference in adverse events once the immediate postprocedure period was over. The distribution of severity of adverse events is comparable between the BT and control groups. Of the 407 adverse respiratory events in the BT group, 69% were "mild," 28% were "moderate," and 3% were "severe"; in the control group, there were 106 adverse events, of which 69% were mild, 30% were moderate, and 1% were severe. There was no increase in the rate of adverse events with subsequent BT procedures. Most frequently observed adverse events in the BT group are primarily respiratory in nature and the most frequently observed respiratory-related adverse events were dyspnea (18.7%), wheezing (17.0%), cough (16.0%), night awakening (9.8%), productive cough (7.9%), chest discomfort (5.7%), chest pain (4.7%), discolored sputum (2.5%), upper respiratory tract infection (2.5%), nasal congestion (2.0%), and bronchial irritation (2.0%). Respiratory-related adverse events occurred on average within 5.4 days of BT treatment (median time to onset was 1.0 day) and resolved on average within 6.6 days after onset. From a qualitative perspective, the adverse events reported after BT have been of the type usually reported after a bronchoscopy procedure in an asthma patient.

During longer-term follow-up (>6 weeks after the last BT treatment), the adverse event profile of BT group patients was similar to that of the control group. There has been no deterioration in the FEV₁ values after BT treatment. During the course of the study, there were six hospitalizations in the BT group and two hospitalizations in the control group related to respiratory symptoms during the treatment phase of the study. The most extreme adverse event in the BT group was a subject who was hospitalized because of a segmental collapse of the left lower lobe that occurred within 1 day of a BT treatment and resolved within 2

days with medical therapy. The hospitalization rates during the posttreatment period were comparable between the BT and control groups. The use of antibiotics for respiratory symptoms/respiratory infections was similar between the BT and control groups at baseline during the treatment period and in the posttreatment period. To date, there has been no evidence of airway stenosis or bronchiectasis in patients receiving BT.

Research in Severe Asthma Trial

The second randomized clinical study was designed to evaluate the safety of BT in patients with severe asthma refractory to the current standard of care.¹⁷ Secondary objectives were to evaluate whether asthma symptoms or medication levels can be reduced in this population of subjects after BT. The Research in Severe Asthma (RISA) Trial recruited patients that met the following inclusion criteria: nonsmoking adults (aged 18–65 years), taking ICSs (>750 µg of fluticasone MDI or equivalent) and LABA (at least 100 mg of salmeterol per day or equivalent) with or without oral corticosteroids at a dosage of ≤30 mg/day, prebronchodilator FEV₁ of >50% predicted, showing airway hyperresponsiveness by MCh PC₂₀ of <4 mg/mL for patients with prebronchodilator FEV₁ of >60% predicted or reversible bronchoconstriction during the 12 months before enrollment, as indicated by an increase in FEV₁ of at least 12% 30 minutes after 4 puffs of short-acting β₂-agonist, symptomatic despite medication with high-dose ICSs and LABA, by at least one of the following: use of rescue medication (short-acting β₂-agonist) at least 8 of the 14 days before enrollment or daytime symptoms at least 10 of the 14 days before enrollment. Patients were excluded if they had a respiratory tract infection (recent, ≤6 weeks, or recurrent, ≥3/year), change in maintenance asthma medications in the last 6 weeks, or were using >4 puffs/24 hours of rescue medications (except for exercise) in the last 7 days. The

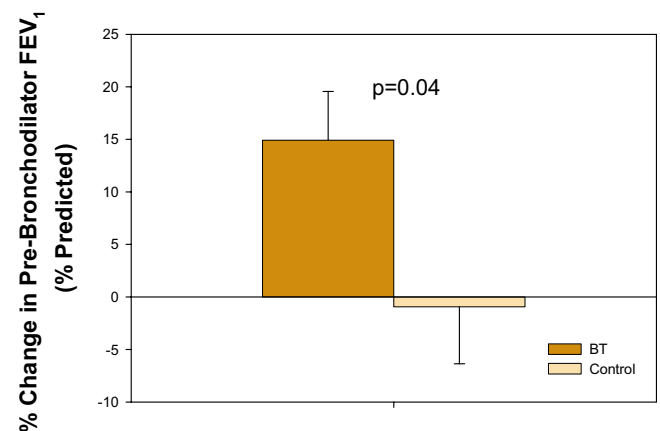


Figure 6. Improvement in lung function in patients receiving bronchial thermoplasty in the Research in Severe Asthma trial. BT = bronchial thermoplasty. (Ref. 17)

safety of BT plus standard medical care was compared with standard medical care alone by assessing adverse event in the peri- and posttreatment periods. As reported by Niven¹⁴ and Pavord,¹⁷ patients with severe asthma who received BT showed significant improvements in rescue medication use, FEV₁, Asthma Quality of Life Questionnaire score, and ACQ score. The newt improvement in FEV₁ of 16% was larger than that seen in the AIR trial (Fig. 6).

Data from this study show that BT treatment is associated with a greater acute risk in this population of subjects. The procedure was associated with an increase in respiratory-related adverse events and an increase in the rate of hospitalizations for respiratory symptoms during the treatment phase. However, the adverse event profile and hospitalization rate were similar between the BT group and control group in the posttreatment period. All adverse events resolved with standard medical care and subjects returned to their baseline prebronchodilator FEV₁ levels or better.^{14,15,17} A rigorous, sham-control, double-blind randomized clinical trial¹⁶ is currently underway in the United States and internationally to definitively evaluate the efficacy and safety of BT.

CONCLUSION

By reducing airway smooth muscle through controlled thermal treatment to the airway wall, BT is a novel way of treating asthma and holds promise as an option for difficult to treat or poorly controlled asthmatic patients. It is the first device-based treatment that has been shown to establish efficacy in asthma. Studies to date have indicated both safety and a compelling persistent effect in patients with asthma. While multicenter international trials are currently underway, BT offers an exciting opportunity to make a difference in an underserved asthma population and to help us all learn about the important role airway smooth muscle plays in this disease.

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