

## Bronchial Thermoplasty in Patients with Severe Persistent Asthma: A Literature Review

Ghulam Mustafa Aftab <sup>a</sup>, Sana Rehman<sup>b</sup>, Mudassar Ahmad<sup>a</sup>, Ali Akram<sup>c</sup> and Amar Bukhari<sup>a</sup>

<sup>a</sup>Division of Pulmonary Disease and Critical Care Medicine, Saint Peters University Hospital, New Brunswick, New Jersey, USA; <sup>b</sup>Division of Internal Medicine Marshfield Clinic Health Center (Incoming Internal Medicine Resident); <sup>c</sup>Division of Internal Medicine the Wright Center

### ABSTRACT

The literature review aimed to see the safety and efficacy of bronchial thermoplasty in patients with severe asthma. We searched the online database, PUBMED, using bronchial thermoplasty and asthma as the key words and including trials from 2007 to 2021. Our review found that bronchial thermoplasty reduces asthma-related hospitalizations, emergency room visits and asthma exacerbations with sustained benefits for 5–10 years. This came at the expense of increased asthma-related adverse events, most commonly during the 7 days immediately after the procedure. Adverse events from 6 weeks after procedure to up to 5 years were similar between the bronchial thermoplasty group and the medication-only group. Bronchial thermoplasty is a safe and efficacious treatment modality for patients with severe asthma.

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## 1. Introduction

Asthma is associated with increased airway reactivity and chronic airway inflammation, which may cause remodeling of the airway; this is characterized by the thickening of the basement membrane and hypertrophy of the airway smooth muscles [1].

Within the USA, it is projected that more than 24 million people have asthma [2]; these patients are generally treated with drugs such as as-needed short-acting Beta agonists, inhaled corticosteroid (ICS), long-acting Beta-agonists (LABA) and biologics. Even with such medications, though, approximately 5% of patients having severe persistent asthma continue to experience symptoms [3]. For these patients, bronchial thermoplasty (BT) is an emerging treatment: it works by delivering radiofrequency energy to the different segments of the lung, thereby reducing the density of the airway smooth muscles.

## 2. Procedure description

Bronchial thermoplasty involves three separate treatment sessions, often conducted around three weeks apart. The procedure involves passing a catheter through the working channel in the bronchoscope; this catheter is then used to deliver radiofrequency ablation to the airways, that are 3–10 mm in diameter.

Patients are started on prednisone 50 mg 2–3 days prior to and until 1–2 days after the procedure. Both

pre-and post-procedure spirometry are performed to ensure that the post-procedure FEV1 is 80% of the pre-procedure FEV1 [4].

## 3. Candidates for BT

The general consensus is that BT is the preferred treatment for patients with non-allergic, non-eosinophilic uncontrolled asthma, who are already on ICS and LABA. BT may also be considered in allergic and eosinophilic uncontrolled asthma patients if patients fail, or are unable, to tolerate biologics [5].

Currently, ATS/ERS recommend BT be performed in patients with severe asthma after getting approval from an IRB, or in the context of a clinical trial [6]. Chest, in a statement in 2014, recommended that symptomatic patients with severe asthma, who are already on appropriate therapy, should be offered BT, and it should not be considered experimental [7]. FDA has approved BT for adults aged 18 or older with severe asthma that is not controlled on ICS and LABA.

## 4. Safety and efficacy of BT

Bronchial thermoplasty helps reduce episodes of asthma exacerbation, emergency room visits and hospital admissions. In the short-term, i.e., immediate post-procedure period, bronchial thermoplasty may

**CONTACT** Ghulam Mustafa Aftab  [MUSTAFA\\_AFTAB1@HOTMAIL.COM](mailto:MUSTAFA_AFTAB1@HOTMAIL.COM)  Division of Pulmonary Disease and Critical Care Medicine, Saint Peters University Hospital, 135 Somerset Street, Apt 1109, New Brunswick, NJ 08901.

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increase hospital admissions due to asthma exacerbation; however, in the long-term, adverse events associated with it are found to be similar to patients being treated with medications alone. The trials are summarized in Table 1.

#### 4.1. AIR trial

The first large randomized trial conducted was the Asthma Intervention Research trial. One hundred

**Table 1.**

Clinical Trials	Design and Objective	Population	Key Findings
AIR trial	Open label multicenter randomized control trial to assess the frequency of exacerbations in patients with severe asthma (on ICS and LABA) during the 2-week periods off LABA.	112 subjects were enrolled in the study with 56 were randomized each group Group 1: BT in addition to ICS and LABA Group 2: ICS and LABA alone.	There was a reduction in the number of episodes of mild asthma exacerbation in patients who underwent BT. At 12 months there was also a significant improvement in the AQLQ score. There were increased adverse events in immediate post procedure period however were similar 6 weeks onwards.
AIR 2 Trial	Double blind multi-center, randomized controlled which compared BT to a sham procedure. It assessed the treatment benefit and safety of BT in subjects who had symptoms on ICS and LABA	288 subjects were randomized 190 were included in the BT group and 98 in the sham group. Both groups underwent three bronchoscopic procedures.	The subjects in the BT group had a greater improvement in their AQLQ score compared to the sham group. In addition a greater number of subjects in the BT group had a significant improvement in the AQLQ score. There were increased adverse events in immediate post procedure period.
RISA Trial	Multicenter, randomized control trial to assess the safety and effectiveness of BT in subjects with severe asthma	32 adult subjects were randomized, 15 were randomized to BT in addition to medication use and 17 were randomized to the control group (medical management)	BT subjects had significant improvements in the

prebronchodilator FEV<sub>1</sub> [11% and asthma control questionnaire (ACQ) scores. There was also reduced use of rescue medications in the BT group. BT resulted in a transient increase in asthma related adverse events in the treatment phase

twelve subjects were enrolled. These subjects were on ICS and LABA. These subjects were randomized to either BT in addition to treatment with ICS and LABA or the control group that included treatment with ICS and LABA alone. Fifty-six subjects received BT and 56 received the standard of care. The study looked at the frequency of mild asthma exacerbations, during three scheduled periods, off LABA. These were 2-week periods scheduled at 3, 6 and 12 months. There was a reduction in the frequency of mild exacerbations in the BT group, as compared with baseline. At 12 months, improvement in the morning peak expiratory flow and asthma quality of life questionnaire (AQLQ) was seen. The need for the rescue medication decreased and there was an increase in the number of symptom free days, at 12 months, in subjects who had undergone bronchial thermoplasty. In the treatment phase and for 6 weeks post-treatment, there were increase in the respiratory-related adverse events, including hospitalization in the BT group compared to the control group. The adverse events were similar from 6 weeks to 12 months after treatment in both the groups [8]. As this was a non-blinded study and concerns that BT may have a placebo effect, there was need for a placebo control trial.

#### 4.2. RISA trial

In the Research in Severe Asthma (RISA) trial, symptomatic patients on treatment with high dose ICS, LABA and other medications which included oral corticosteroids (OCS) equivalent to prednisone of 30 mg or less were randomized to BT plus medical management or medical management alone. A total of 32 subjects were enrolled, 15 were randomized to the BT group and 17 to the control group. After the treatment phase the subjects had their doses of the ICS and OCS kept the same for the succeeding 16 weeks following which an attempt was made to wean subjects off inhaled and oral steroids during a specified time period of 14 weeks. Patients were then followed for an another 16-weeks (decreased steroid phase). BT resulted in increased asthma related adverse events in the treatment phase. Four out of the 15 subjects in the BT group were hospitalized compared to no hospitalization in the control group. Two subjects in the BT group experienced segmental collapse. There was no difference in the number of adverse events after the treatment phase. Following the initial increase in morbidity in the BT group, BT subjects used less of the rescue medication compared to the control subjects. There was also a significant improvement in the prebronchodilator FEV<sub>1</sub> – an improvement of 15.8% with 12% considered clinically significant, and asthma control questionnaire (ACQ) scores [9].

### 4.3. AIR 2 trial

In the AIR 2 study, the effectiveness of BT was compared to a sham procedure. It included subjects with severe asthma who were symptomatic on ICS and LABA. Two hundred eighty eight subjects were randomized, 190 were included in the BT group and 98 were included in the sham group [10]. Both groups underwent three bronchoscopic procedures. The primary end point was to evaluate a difference in the asthma quality of life questionnaire (AQLQ) scores, at baseline and the average of the 6, 9 and 12 months AQLQ score, between the sham group and the BT group. A safety analysis was also performed. The mean improvement in the AQLQ score in the BT group was greater, compared to the sham group. In addition, a greater number of subjects in the BT group had a clinically significant improvement in the AQLQ score compared to the sham group (79% vs 64%, respectively).

Results also indicated that there were more adverse respiratory events during the treatment period (time period from the first procedure to 6 weeks after the third bronchoscopic procedure) in the BT group compared to the sham group. Sixteen subjects were hospitalized in the BT group and 2 subjects in the sham group. Ten patients in the BT group were hospitalized for asthma exacerbation. Other reason for hospitalization in the BT group included atelectasis, lower respiratory tract infection and hemoptysis (requiring treatment with bronchial artery embolization). Most subjects recovered by day 7. The hospitalization in the sham group were for asthma exacerbation. None of the subjects developed pneumothorax and no one required intubation or mechanical ventilation. In the 6 weeks to 12 months after BT, the BT group experienced fewer asthma related adverse events. Emergency room (ER) visits and hospitalization were reduced in the post-treatment period. Subjects in the BT group missed 1.3 days of work or school per year per subject compared to 3.9 days in the sham group. Hence, BT in subjects with severe asthma improves the asthma related quality of life in the post-treatment period [10]. This comes at the price of increased adverse respiratory events in the treatment period. These adverse events are most common during the first 7 days post procedure.

### 4.4. Long-term follow up studies

A five year follow up study of the AIR 2 trial has been conducted to evaluate the safety and the long-term treatment benefits of BT. One hundred sixty two out of the 190 patients undergoing BT were included in the follow-up. The results showed that BT had long term treatment benefits demonstrated by a persistent

reduction in the number of patients having severe asthma exacerbation or ER visits. There was no increase in adverse respiratory events or hospitalizations [11]. The trials are summarized in Table 2.

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Table 2.

Long Term Follow up Studies	Design and Objective	Key Findings
Three Year Follow-up results from the AIR 2 and PAS 2 studies.	190 subjects in the PAS 2 trial compared with the AIR 2 trial. It was conducted to see the safety and long term treatment benefits of BT in real life settings.	Post BT in the PAS 2 trial there was a decrease in ED visits, hospitalizations and the dose of ICS. At 3 year follow up 39.9% subjects in PAS 2 experienced at least one severe asthma exacerbation, a 44.6% decrease in exacerbation prior to BT. This mirrored the results of the AIR 2 study.
AIR 2 5 years Follow up	162 out of the 190 patients undergoing BT were included in the follow up. It was conducted to see the safety and long term treatment benefits of BT.	The results showed that BT had long term treatment benefits demonstrated by a persistent reduction in the number of patients having severe exacerbation or Emergency Room visits. Adverse respiratory events or hospitalization due to a respiratory event were the same throughout year one to year five.
BT 10+	10 year or more follow up on subjects in the AIR trial, RISA trial and the AIR 2 trial undergoing bronchial thermoplasty. It was carried out to evaluate the sustained benefit and safety of BT 10 years or more post procedure. 192 subjects from the AIR trial, AIR 2 trial and RISA trial were included.	The rate of decrease in the ER visits, hospitalization and severe asthma exacerbation were maintained over the ten years post bronchial thermoplasty. High resolution CT scans of the participants from the AIR 2 were also evaluated to find any image changes. 13 subjects out of 97 had bronchiectasis out of which 6 developed bronchiectasis after bronchial thermoplasty treatment.
RISA Extension Study	A five year follow up of the RISA trial. 14 participants out of 15 who received bronchial thermoplasty participated in the study.	There was a decrease in hospitalization and ER visits for up to 5 years compared to the year before BT treatment.

(PAS 2) is currently ongoing. The first 190 subjects in the PAS 2 trial were compared with 190 subjects in the AIR 2 trial. PAS 2 trial is an open label, observational, multicenter study to show the effectiveness and safety of BT in the real world. Patients in the PAS 2 trial were on higher dose of ICS, were older, had a higher BMI and more likely to have been hospitalized or have an asthma exacerbation in the 12 months preceding the procedure. Post BT in the PAS 2 trial there was a reduction in ED visits, hospitalizations and the dose of ICS. At 3 year follow up 39.9% subjects in PAS 2 experienced at least one severe asthma exacerbation, a 44.6% decrease in exacerbation prior to BT. This mirrored the results of the AIR 2 study [12].

Five year follow up of the RISA trial showed sustained benefit. There was a decrease in hospitalization and ER visits for up to 5 years compared to the year before BT treatment. Hence, BT was deemed safe even after 5-year post-treatment [13].

BT 10+ is a 10 year or more follow up on subjects in the AIR trial, RISA trial and the AIR 2 trial undergoing bronchial thermoplasty. It evaluated the durability of treatment response and safety of bronchial thermoplasty 10 years or more post procedure. One hundred ninety-two subjects from the AIR trial, AIR 2 trial and RISA trial were included. The rate of decrease in the ER visits, hospitalization and severe asthma exacerbation were maintained over the ten years post bronchial thermoplasty. High-resolution CT scans of the participants from the AIR 2 were also evaluated to find any image changes. Thirteen subjects out of 97 had bronchiectasis out of which 6 developed bronchiectasis after being treated with BT. Overall, this study shows that the benefits of BT are persistent for 10+ years [14].

## 5. Effects of BT on bronchial responsiveness

It is hypothesized that BT decreases bronchial hyperresponsiveness by decreasing the airway smooth muscle mass and subepithelial basement membrane thickness. At the same time, it does not cause an increase in the production of inflammatory mediators.

In one study, 300 bronchial specimens were evaluated in 15 patients, with severe asthma, prior to BT treatment and 3 months after treatment. The effect of BT was studied on cellular level in terms of the measurement of airway smooth muscle area and subepithelial thickness. Bronchial thermoplasty led to improvement in asthma control and quality of life. At 3 months, this clinical benefit was associated with a reduction in the area of the airway smooth muscles, thickness of the subepithelial basement membrane (median values before and after BT, respectively, 4.4  $\mu\text{m}$  and 3.9  $\mu\text{m}$  respectively), and epithelial neuroendocrine cells

(median values before and after BT, respectively: 4.9/mm and 0.0/mm, respectively) [15].

In another study, Ichikawa et al. recruited 14 subjects with severe asthma who had a bronchial biopsy performed during the initial bronchoscopic procedure and 6 weeks after the initial BT procedure. The obtained sample was stained with antibodies for  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA). Results showed that alpha-smooth muscle actin was decreased post-BT. Biopsy specimens were also stained for a nerve marker, interleukin-17A (IL-17A), transforming growth factor-B1 (TGF B1) and a marker for blood vessels. The results showed that there was a reduction in PCP 9.5- a nerve marker. There was no impact on the production inflammatory markers- IL-17A and TGF B1. The number of blood vessels remained similar before and after procedure [16].

In the TASMA randomized trial 40 subjects with severe asthma were randomized to either receive immediate BT or to continue to receive standard of care followed by BT after six months. Endobronchial biopsy results after 6 months of treatment showed that there was a >50% reduction in the airways smooth muscle mass in the immediate BT treatment group compared to no change in the airway smooth muscle mass in the delayed BT treatment group [17]. Interestingly, even though it showed a decrease in airway smooth muscle mass however treatment response did not correlate with it. Response was better in patients with a higher IgE level.

## 6. CT chest changes after BT

Most changes on CT chest post BT are temporary and resolve or decrease spontaneously. AIR 2 trial showed that six participants developed bronchiectasis more than one year after BT treatment; however, it is important to further evaluate if bronchiectatic changes were due to BT treatment.

A study assessed the immediate changes after BT using non contrast CT chest at the time of enrollment in the study and after each BT session. Thirteen patients and a total of 38 treated lobes were evaluated. All 38 lobes on day 1 showed ground glass opacities and consolidations along the bronchi. There was involvement of an adjoining untreated lobe in 12 out of 38 (32%) cases. A one month follow up CT thorax was performed in 11 patients, having a total of 15 treated lobes. Opacities completely disappeared in 10 patients and decreased in 5 patients [18].

Other studies have shown similar findings. CXR and CT chest show changes post procedure however they resolve in almost all cases [19].

## 7. Conclusion

BT is an effective treatment modality in patients with severe asthma. It reduces asthma-related adverse



events and improves the quality of life of asthmatics. It is hypothesized that BT reduces airway hyperreactivity and narrowing by decreasing airway smooth muscle mass and neuroendocrine epithelial cells. It is well tolerated and safe. Even though there is an increase in respiratory adverse events, mostly during the first 7 days post-procedure, follow-up studies have shown it has a good safety profile.

In the future, more clinical trials are needed to find the ideal candidates for BT treatment and to compare the response of BT treatment in patients with Type 2 and non-Type 2 asthma.

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### ORCID

Ghulam Mustafa Aftab  <http://orcid.org/0000-0002-5467-2203>

### References

- [1] Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality; USA, 2005–2009. *2011*.
- [2] National Health Interview Survey, National Center for Health Statistics, CDC, 2018. Available from: <https://www.cdc.gov/nchs/fastats/asthma.htm>
- [3] World Allergy Organization. The management of severe asthma: economic analysis of the cost of treatments for severe asthma. *2017*.
- [4] Cárdenas-García J, Cheng G, Castro M. Bronchial thermoplasty: an update for the interventional pulmonologist. *2018*.
- [5] Blaiss MS, Castro M, Chipps BE, et al. Guiding principles for use of newer biologics and bronchial thermoplasty for patients with severe asthma. *Ann Allergy Asthma Immunol.* **2017**;119(6):533–540.
- [6] Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J.* **2014**;43(2):343–373.
- [7] American College Of Chest Physicians. Position statement for coverage and payment for bronchial thermoplasty. *Chest.* **2014** May 12 [cited 2015 Jan 17].
- [8] Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med.* **2007**;356(13):1327–1337.
- [9] Pavord ID, Cox G, Thomson NC, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med.* **2007**;176(12):1185–1191.
- [10] Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med.* **2010**;181(2):116–124.
- [11] Wechsler ME, Laviolette M, Rubin AS, et al. Bronchial thermoplasty: long-term safety and effectiveness in patients with severe persistent asthma. *J Allergy Clin Immunol.* **2013**;132(6):1295–1302.
- [12] Chupp G, Laviolette M, Cohn L, et al. Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. *Eur Respir J.* **2017**;50(2):1700017.
- [13] Pavord ID, Thomson NC, Niven RM, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. *Ann Allergy Asthma Immunol.* **2013**;111(5):402–407.
- [14] Chaudhuri R, Rubin A, Sumino K, et al. Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials. *Lancet Respir Med.* **2021**;9(5):457–466.
- [15] Pretolani M, Bergqvist A, Thabut G, et al. Effectiveness of bronchial thermoplasty in patients with severe refractory asthma: clinical and histopathologic correlations. *J Allergy Clin Immunol.* **2017**;139(4):1176–1185.
- [16] Ichikawa T, Panariti A, Audusseau S, et al. Effect of bronchial thermoplasty on structural changes and inflammatory mediators in the airways of subjects with severe asthma. *Respir Med.* **2019**;150:165–172.
- [17] Goorsenberg AWM, d’Hooghe JNS, Srikanthan K, et al. Bronchial thermoplasty induced airway smooth muscle reduction and clinical response in severe asthma. The TASMA randomized trial. *Am J Respir Crit Care Med.* **2021**;203(2):175–184.
- [18] Debray M-P, Dombret M-C, Pretolani M, et al. Early computed tomography modifications following bronchial thermoplasty in patients with severe asthma. *Eur Respir J.* **2017**;49:3.
- [19] d’Hooghe JNS, Van Den Berk IAH, Annema JT, d’Hooghe, Julia NS, et al. Acute radiological abnormalities after bronchial thermoplasty: a prospective cohort trial. *Respiration.* **2017**;94(3):258–262.