Review Article

Thermal ablation for asthma: current status and technique

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Abstract: Bronchial thermoplasty (BT) is a novel technique used in the treatment of severe asthma. A catheter is advanced through the bronchoscope and directed radiofrequency waves are applied to the segmental bronchi to reduce airway smooth muscle mass. Several randomized clinical trials demonstrate improvement in quality of life and reduction in exacerbation rates after treatment. BT is a safe and cost effective treatment option for severe asthma which is refractory to medical treatment. Further studies are needed in order to better describe the mechanism of action and the asthma subphenotype that was best benefit from this treatment.

Keywords: Asthma; bronchial thermoplasty (BT); reactive airway disease; asthma exacerbation; pulmonary function

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Introduction

Asthma is a chronic condition in which patients experience airway inflammation and airway muscle contraction leading to symptoms of dyspnea, wheezing, coughing and chest tightness. It is one of the most common chronic conditions with estimated worldwide prevalence of 235 million (1). Severe and difficult to treat asthma is defined as asthma that requires treatment with high-dose inhaled corticosteroid (ICS), a second controller medication, and/or systemic steroids. The standard approach to care occurs in a stepwise fashion with maintenance medications such as ICS and long acting B2 receptor agonists (LABAs). In specific populations' medications omalizumab, mepolizumab and oral corticosteroids (OCS) are effective (2). Although difficult to estimate, the prevalence of severe asthma has been estimated to occur in 5–10% of asthmatics in the United States. Approximately 80% of the $56 billion in health care costs attributed to asthma is incurred by severe or poorly controlled asthma (3). Majority of the costs are from emergency department visits and hospitalizations. Management continues to present a challenge for physicians. Bronchial thermoplasty (BT) is an endoscopic therapy which is the only nonpharmacological intervention approved by the US Food and Drug Administration. It is approved for patients >18 years of age whose asthma is not well controlled despite ICS and LABA therapy (4). BT delivers controlled thermal energy into the airway wall in three separate bronchoscopic procedures. Despite the existence of several large clinical trials, BT efficacy and the appropriate patient population is uncertain.

The procedure

BT is a therapeutic intervention for patients with severe persistent asthma uncontrolled by ICS and LABA. In severe asthma, airway smooth muscle undergoes cellular hypertrophy and hyperplasia, resulting in angiogenesis

and extracellular matrix formation (5). This causes airway narrowing, increased airway resistance and leads to the symptom syndrome of asthma: wheezing, dyspnea and chest tightness. Although the specific mechanisms of action for BT is not clear, it is generally understood that BT delivers thermal energy and directly targets the airway smooth muscles with the goal of reducing the airway smooth muscle mass (6,7).

The thermal energy is delivered using the Alair BT System (Boston Scientific, Natick, MA, USA) which consists of a radiofrequency controller and catheter (8). The procedure is typically done under general anesthesia, however, can be performed using moderate sedation. Standard airway examination is performed prior to the treatment, with particular attention paid to previously treated lobes and the lobe undergoing current treatment. Mucous should be suctioned to ensure adequate visualization and airway wall contact during the treatments. The catheter is inserted through a compatible diagnostic bronchoscope with a minimum 2 mm working channel. A diagnostic bronchoscope is preferred due to better visualization of the airways. The distal tip of the catheter contains an expendable four electrode basket, which is sequentially deployed in the airways (9). The catheter itself is marked at 5 mm increments. The catheter is connected to the radiofrequency controller, the patient is grounded with a grounding pad to complete the electrical circuit, and the catheter is advanced into the distal airways. The RF controller delivers thermal energy at temperature of 65 C for 10 seconds. Each activation is delivered via a footswitch pedal. During the activation, the basket is expanded to ensure proper contact with the airway wall. When the wires contact the airway wall, monopolar radiofrequency energy is applied and converted to heat. The energy disrupts normal airway smooth muscle resulting in destruction and atrophy. Once the activation is delivered the basket is collapsed, and the catheter is withdrawn 5 mm to the next site of treatment. Each bronchus is treated at the sub-segmental and segmental levels and along its entire visible length. Each activation targets a 5 mm section of the bronchus between 3 to 10 mm in diameter. The sequence of treatment begins in the peripheral bronchus and moving proximally. A given airway is only treated once.

The entire BT treatment is divided into three separate sessions. This allows shorter procedure time and minimizes the risks associated with diffuse airway irritation. The first two sessions target the right lower lobe and left lower lobe separately while the final procedure targets the bilateral upper lobes. The right middle lobe is excluded due to the theoretical risk of causing stenosis of the narrower right middle lobe airway resulting in bronchiectasis or right middle lobe syndrome (9). Each session takes 30–45 minutes with approximately 30–40 activations per session. The duration and number of activations can vary depending on experience level of the bronchoscopist and patient's airway anatomy. Patients are given OCS (typically 40–50 mg daily) for 3 days prior to the procedure, the day of the procedure, and 1 day following the procedure to minimize post-procedure airway inflammation.

Efficacy of BT

To this day there are three randomized controlled trials evaluating efficacy and safety of BT in patients with mild to moderate asthma. The Asthma Intervention Research Trial (AIR) was the first randomized controlled trial comparing BT and conventional therapy (10). It investigated 112 with moderate to severe asthma who required treatment with ICS and LABA. The study matched 56 patients who received BT and conventional therapy with 56 patient who received conventional therapy alone. Before the intervention of interest patients received maintenance therapy for four weeks: ICS and LABA for first two weeks, followed by withdrawal of LABA for two additional weeks. Maintenance therapy was restarted during the intervention period. Patients were followed at 6 weeks, and 3, 6 and 12 months. LABA therapy was again withheld at 3 months follow up. The primary outcome was the average frequency of mild exacerbations during LABA withdrawal. The Research in Severe Asthma (RISA) Trial was an unblinded, randomized, controlled trial of 34 patients with symptomatic, severe, asthma despite being on high dose ICS and LABA therapy (15 patients received BT and conventional therapy and 17 patients received only conventional therapy) (11). The second AIR (AIR-2) trial, was the largest study conducted (12). It was a sham-controlled, randomized, double-blinded clinical trial with 297 patients. The patients had uncontrolled asthma despite high-dose ICS and LABA; 190 patients were treated with BT and conventional therapy, 98 patients received sham thermoplasty (every step of the procedure except actual RFA) and conventional therapy. The primary outcome was a change in mean Asthma Quality of Life Questionnaire (AQLQ) score from pre-treatment baseline.

Quality of life

In the AIR trial, the BT patients had statistically significant greater improvements in Asthma Control Questionnaire (ACQ) and AQLQ scores. This effect was appreciated at the 3, 6 and 12 month follow up. In the RISA trial the BT group, despite reduction in maintenance therapy, had statistically significant improvements in the AQLQ and ACQ scores. This difference persisted at 52 weeks. The AIR-2 trial was a negative study, although the improvement from baseline AQLQ scores was slightly greater in the BT group (1.35±1.10 compared with 1.16±1.23) it did not reach statistical significance. When analyzed as a proportion of the patients achieving the minimally important difference in AQLQ (>0.5), a significant larger number of patients in the BT group had improvements in scores with net benefit in AQLQ in the BT group of 76% *vs.* 57% in the sham group.

Asthma control

The AIR trial reported improvement in ACQ scores at 12 months in patients who received BT; specifically increase in symptoms free days and less use of rescue medications. It should be noted that subjective changes experienced by participants were clinically relevant regardless of group allocation, suggesting a Hawthorne effect. In RISA, the BT group demonstrated improvement in ACQ score, reduced use in SABA and more symptom free days. This difference persisted despite the reduction in medication following the steroids weaning phase. The changes from baseline ACQ scores in AIR 2 did not reach statistical significance (BT 2.13±0.87 to 1.31±0.94 *vs.* sham from 2.09±0.90 to 1.32±0.91).

Asthma exacerbations

The AIR trial reported a statistical significant difference in number of mild exacerbation between the BT and control groups at 12 months of follow up. Participants in the BT group showed a decrease from 0.35±0.32 exacerbations per participant/wk at baseline to 0.18±0.31 exacerbations per participant/wk 12 months post procedure. The control group increased from baseline of 0.28±0.31 exacerbations per participant/wk to 0.31±0.46 exacerbations per participant/wk at 12 months post procedure. In contrast, there were no statistical differences in the number of severe exacerbations per participant per week. Although the BT group had 50% less exacerbations following treatment, the exacerbations were counted during the 2-week period of abstinence from LABA, before treatment, then at 3, 6, and 12 months. In AIR 2 the rate of severe exacerbations per participant per year was significantly lower in the BT group (26.3% of BT group participants *vs.* 39.8% sham group participants). BT-treatment group demonstrated superiority with 32% less severe exacerbations, fewer days lost from work/school, fewer hospitalizations and 84% fewer Emergency Department visits.

Lung function

In AIR the pre-bronchodilatory FEV1 percentage predicted did not change significantly between groups. The airway hyperresponsiveness (amount of provocation concentration that caused a 20% decrease in FEV1) was decreased in BT group, however, this was not statistically significant. Although the RISA trial showed a statistical significant improvement in pre-bronchodilator FEV1% (14.9±17.4) *vs.* control group (–0.9±22.3) at 22 weeks, this difference did not persist at 52 weeks. AIR 2 trial found no statistical difference in FEV1 improvements between the BT-treatment group and sham procedure group.

Effect on corticosteroid therapy

The RISA trial demonstrated a decrease in OCS and ICS use by 63.5% and 28.6% in the BT group respectively. In the control group OCS and ICS use fell by 26.2% and 20% respectively. Quality of life and asthma symptom scores remained significantly improved in the 4 months following steroids wean phase.

Long term efficacy

The RISA and AIR 2 trials analyzed long-term safety data up to 5 years in patients who underwent BT therapy. In the RISA long term safety trial, data was available for 14 of the 15 participants in the BT-treatment group (13). When compared to the year prior BT-treatment the RISA group had fewer adverse respiratory events, decreased hospitalization and emergency department visits and unchanged pre and post bronchodilator FEV1. Similar to the RISA trial, the AIR 2 extension study did not include the sham group in their follow up (14). Of the 190 BT-treatment participants, 162 were assessed from year 1 through 5. Compared to the year before BT therapy, the rate of exacerbations decreased by 48%, there were 78% fewer emergency department visits and there was no change

in pre-bronchodilator FEV1 at 5 years. Additionally, a decrease in use of ICS, LABA, ICS/LABA maintenance therapy was demonstrated (17%, 12% and 9% respectively), while 7% of the patients no longer required maintenance therapy at 5 years. Of the 93 high-resolution computed tomography (HRCT) of the chest performed, 82% were radiographically normal or improved from baseline. Only three participants had evidence of new or increased bronchiectasis.

Safety

Adverse events have been described in each of the three studies. AIR BT-group participants had more adverse respiratory events and hospitalizations immediately following the procedure, by 6 weeks there was no difference between the groups (10). The BT group had a total of 407 adverse events, of which 69% were mild, 28% were moderate and 3% severe. The most commons symptoms were dyspnea, wheezing and discomfort. Of the six hospitalizations observed in the BT-group, three were for asthma, one for lower lobe collapse and one for pleurisy. In the AIR trial control group there was total of 106 adverse events observed, of which 69% were mild, 30% moderate and 1% severe. In the RISA trial, here was an increase in respiratory adverse events in the treatment period in the BT-group, however, there was no difference between groups in the post-treatment period (11). Most of the events occurred within 1 day of the bronchoscopy and resolved within a week of the procedure. The most common respiratory event was wheezing, cough, chest discomfort, dyspnea and productive cough. The AIR-2 trial demonstrated an increase in asthma symptoms and slight increase risk in hospitalizations in the BT-group (12). The symptoms resolved within 7 days of the procedure, however, 3.4% of them led to admission following bronchoscopy. The risk of hospitalization resolved within 24–48 hrs of the procedure; of the 19 hospitalizations observed in the BT-group, most were for worsening asthma. One patient presented with significant hemoptysis from the right upper lobe 1 month following the last session and required bronchial artery embolization.

Overall, the patients experienced few complications from the procedure (15). The observed adverse events were often mild and did not require invasive intervention and largely included transient worsening of baseline symptoms. As with any procedures, it is important to periodically re-assess long term clinical safety data, specifically, the chronic affects of BT on the airway wall. The risks of sedation and bronchoscopy itself should be considered (16). Flexible bronchoscopy is relatively safe, however, changes in airway resistance can occur during the procedure and can result in exacerbation of obstructive disease resulting in worsening asthma symptoms (17). Major complications such as bleeding, infection, respiratory depression and pneumothorax occur in less than 1% of the cases, with mortality rate reported between 0% and 0.04% (18).

Selecting the right patient

Studies of BT in adults with asthma have addressed a broad range of asthma severity. Most participants presented with poor asthma control and evidence of airway obstruction, however, maintenance therapy dosing and degree of airway obstruction has been variable with some patients being on maintenance OCS. The difference in disease characteristics between AIR, RISA and AIR-2 make recommendations on patient selection for BT in clinical practice challenging. We think it is reasonable to follow the guidelines set by the Global Initiative for Asthma (GINA) and maximize medical therapy before offering BT (19).

Benefits of BT in very severe asthmatics have not been fully explored. Although the AIR and AIR 2 trials enrolled patients with moderate to severe asthma, patients with severe airflow obstruction, frequent exacerbations or who required more than 10 mg/day of OCS were excluded. The RISA trial enrolled patients with more severe airflow obstruction, mean FEV1 less than 63% in BT group, however, patients with FEV1 less than 50% were excluded. It stands to reason that very severe asthmatic with greater degree of airflow obstruction would benefit from BT therapy, however, additional studies evaluating the safety of BT in this patient population are needed.

Identifying patients who would benefit from BT has been a challenge. In an attempt to develop predictors of BT response, one study evaluated lung function variables, asthma control, quality of life, health-care use and demographic data in 42 patients at baseline and 12 months following BT (20). Investigators analyzed baseline multi-detector CT of the chest and measured percentage of air trapping. The study demonstrated that shorter duration of asthma, severe exacerbations, decreased quality of life and higher baseline OCS dose predicted response to BT. Less air trapping on MDCT correlated with BT response. Additional studies are needed to further explore specific phenotypes of BT responders.

The contraindications to having BT performed include age younger than 18 years, presence of implantable devices such as internal defibrillator or pacemaker, sensitivity to medications administered during the procedure such as lidocaine and benzodiazepines and previous BT therapy (16,17). The procedure should be delayed in patients with recent upper respiratory infections, asthma exacerbation, coagulopathy, or inability to stop anticoagulants. Additionally, the location of airway obstruction is paramount in selecting the appropriate patients for BT therapy. BT is effective in central airway obstruction as evidenced in its success in patients with asthma. Diseases of peripheral airway obstruction, such as chronic obstructive airway disease and bronchiolitis, involve small airways and alveoli, and are not reached by BT. Patients with small airway disease would not see the improvement in quality of life or reduction in exacerbations from BT therapy and should not be offered this therapy.

Cost effectiveness

The high initial cost of BT may limit access due to lack of insurance coverage. Cost effectiveness was evaluated with a model based analysis which compared cost effectiveness of standard therapy with cost effectiveness of BT in addition to standard therapy in severe asthmatics. A 5-year cost was projected for each treatment and included quality-adjusted life, cost of physician office visits, emergency department visits, hospitalizations and cost of controller medication (21). The BT estimate included physician office visits and procedure costs. The study reported cost effectiveness of BT to be US$5,459 per quality-adjusted life year. A more recent study assessed the 10-year cost-effectiveness of BT for patients with severe uncontrolled asthma to be US$29,821 per quality-adjusted life year (22). When compared to the anti-IgE antibody therapy, omalizumab, a recent study demonstrated BT to be a potentially more cost effective option. The study compared standard therapy, BT and omalizumab and demonstrated the discounted 5-year costs and quality adjusted life years were US$15,400 and 3.08, US$28,100 and 3.24, and US$117,000 and 3.26, respectively (23). The study concluded that there is at 67% chance that BT is more cost effective compared to omalizumab and standard therapy at the willingness to pay (WTP) of US $100,000 per quality adjusted life years. These studies suggest that BT could be a cost effective option in the right patient population.

Conclusions

BT is a novel, safe and cost effective treatment for patients with severe, poorly controlled asthma. Large randomized clinical trials have demonstrated an improvement in quality of life and a reduction in overall health care usage with this treatment. The largest advantage is demonstrated in reduction of exacerbations and hospitalizations following treatment. BT therapy is a good option as add on therapy in carefully selected patients. The exact asthma phenotype that would benefit from this treatment is yet unclear. More research needs to be done to determine the ideal asthma patient that would benefit from BT, with particular attention on the effect of intervention in patients with most severe disease.

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Footnote

Conflicts of Interest: Dr. Krmisky is a consultant with intellectual property right with Gala Medical. And other authors have no conflicts of interest to declare.

References

1. World Health Organization (WHO). Asthma Fact sheet N°307. Updated November 2013. Available online: http://www.who.int/mediacentre/factsheets/fs307/en/
2. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
3. Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. J Allergy Clin Immunol 2012;130:332-42.e10.
4. Dombret MC, Alagha K, Boulet LP, et al. Bronchial thermoplasty: a new therapeutic option for the treatment of severe, uncontrolled asthma in adults. Eur Respir Rev 2014;23:510-8.
5. Solway J, Irvin CG. Airway smooth muscle as a target for asthma therapy. N Engl J Med 2007;356:1367-9.

6. Dyrda P, Tazzeo T, DoHarris L, et al. Acute response of airway muscle to extreme temperature includes disruption of actin-myosin interaction. Am J Respir Cell Mol Biol 2011;44:213-21.
7. Chakir J, Haj-Salem I, Gras D, et al. Effects of Bronchial Thermoplasty on Airway Smooth Muscle and Collagen Deposition in Asthma. Ann Am Thorac Soc 2015;12:1612-8.
8. Boston Scientific Corporation. Bronchial themoplasty. Available online: https://btforasthma.com/how-it-works, accessed June 6, 2016.
9. Mayse ML, Laviolette M, Rubin AS, et al. Clinical pearls for bronchial thermoplasty. J Bronchology Interv Pulmonol 2007;14:115-23.
10. Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. N Engl J Med 2007;356:1327-37.
11. 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;176:1185-91.
12. 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;181:116-24.
13. Pavord ID, Thomson NC, Niven RM, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. Ann Allergy Asthma Immunol 2013;111:402-7.
14. Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. BMC Pulm Med 2011;11:8.
15. Dunn R, Wechsler ME. Reducing asthma attacks in patients with severe asthma: The role of bronchial thermoplasty. Allergy Asthma Proc 2015;36:242-50.
16. Pratt S. Anesthesia for bronchoscopy. In: Ernst A. editor. Introduction to Bronchoscopy. New York: Cambridge University Press, 2009:59-60.
17. Waxman A. Flexible bronchoscopy: indications, contraindications, and consent. In: Ernst A. editor. Introduction to Bronchoscopy. New York: Cambrdige University Press, 2009:82.
18. de Blic J, Marchac V, Scheinmann P. Complications of flexible bronchoscopy in children: prospective study of 1,328 procedures. Eur Respir J 2002;20:1271-6.
19. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). Available online: http://www.ginaasthma.org, accessed on June 12, 2016.
20. Sherikonda K, Sheshadri A, Koch T, et al. Predictors of bronchial thermoplasty response in patients with severe refractory asthma. Am J Respir Crit Care Med 2014;189:A2429.
21. Cangelosi MJ, Ortendahl JD, Meckley LM, et al. Cost-effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma. Expert Rev Pharmacoecon Outcomes Res 2015;15:357-64.
22. Zein JG, Menegay MC, Singer ME, et al. Cost effectiveness of bronchial thermoplasty in patients with severe uncontrolled asthma. J Asthma 2016;53:194-200.
23. Zafari Z, Sadatsafavi M, Marra CA, et al. Cost-Effectiveness of Bronchial Thermoplasty, Omalizumab, and Standard Therapy for Moderate-to-Severe Allergic Asthma. PLoS One 2016;11:e0146003.

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