

Advancements in Asthma Therapy: Bronchial Thermoplasty

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INTRODUCTION

Asthma remains increasingly prevalent worldwide, with the highest rates reported in countries such as the United Kingdom, United States of America, Canada, New Zealand and Australia. An estimated 235 million people are affected by this disease and it is projected to grow to more than 325 million by 2025 [1]. Its chronicity imposes a significant burden on health care costs with repeated emergency room visits and hospital admissions. The WHO estimates it is responsible for 250,000 deaths worldwide.

Most asthmatics remain somewhat controlled however, between 5%-10% of asthmatics have severe, difficult to control disease. The international European Respiratory Society (**ERS**)/ American Thoracic Society (**ATS**) guidelines [2] defines these asthmatics as those who require high dose inhaled corticosteroids (**ICS**), coupled with an additional controller medication and possibly also oral, systemic corticosteroids. While these guidelines offer a convenient method of classifying severity of asthma, we must acknowledge that it is in fact a heterogeneous condition which encompasses many sub-phenotypes [3].

With improved understanding of the pathophysiologic mechanisms, or endotypes, that drive these phenotypes, therapeutic options have expanded from bronchodilators and anti-inflammatories to include biologic interleukin inhibitors to target eosinophilic pathways [4] and airway smooth muscle modulation.

Bronchial Thermoplasty (**BT**) has emerged as a non pharmacological means of reducing airway smooth muscle (**ASM**) with radiofrequency energy applied to airways via a bronchoscopic procedure. Although seemingly straight forward, this therapy has yet to establish universal utility. The available evidence from clinical trials have generated much discussion and debate making this a reasonable option but in a select group of asthma suffers.

PATHOGENESIS

Our understanding of the pathological mechanisms that underpin the development and sustenance of asthma has certainly grow over the past few decades however, the more we learn, the more intricacies we uncover.

Increased airway smooth muscle (**ASM**) mass due to cellular hyperplasia and hypertrophy is a well-documented finding in severe asthmatic airways [5]. With reduced airway hyperresponsiveness and bronchoconstriction being the targeted goal of common inhaled pharmacological therapies, BT is believe to offer a non pharmacological therapy to achieve a similar overall effect. A number of small sample human studies have shown at least a 50% reduction in ASM mass after BT in severe asthmatics [6,7]. This effect, however, is not universal and there still remain some asthmatics who do not have a significant reduction in ASM after BT [8].

The effect of BT is not limited to ASM reduction. Bronchial biopsies examined 3 months after BT, show a significant reduction in sub-epithelial basement membrane thickening and a reduction in sub-mucosal nerves [9]. There is also some suggestion that ASM also plays a pro-inflammatory and immunomodulatory role in perpetuating the inflammatory cycle that plagues asthmatics [10]. Thus, by reducing the ASM mass, ASM orchestrated cytokine secretion and inflammatory cell migration, is potentially reduced.

BACKGROUND & HISTORY

Bronchial Thermoplasty was commercially developed after a few early studies determined its ability to reduce ASM and airway hyperresponsiveness to methacholine. The premise was that ASM contraction is a major contributor to bronchoconstriction and the subsequent morbidity that affects asthmatics. It was an initial canine study that reported a 50% reduction in bronchoconstriction of BT treated airways challenged with topical methacholine [11,12]. In this study, histologic bronchial airway biopsies were also examined. Samples were taken periodically upto 3 years after BT and they depicted a marked reduction in ASM. Over time, a thin layer of mature collagen was reported to replace the lost ASM but no ASM regeneration was noted.

The first human study to emulate these findings was performed in non-asthmatics awaiting lung resection for suspected or proven lung cancer [13]. At this time high energy radiofrequency for ablation of lung cancer was a therapeutic option however, low energy radiofrequency therapy technology was not in mainstream use. Eight patients underwent BT during their routine pre-op bronchoscopy 1 to 3 weeks prior to surgery. The segment or lobe that was due to be removed underwent BT and subsequent histological analysis. ASM at sites treated with BT at 65°C revealed an average ASM reduction of approximately 50% but with a rather broad range of reduction - 16% to 71%. These patients had no adverse effects reported and all continued onwards to complete their planned surgeries. Although completed in a small number of patients, the consistency of reported ASM reduction and lack of significant adverse effects paved the way for more extensive clinical BT trials to be published.

THE PROCEDURE

Bronchial Thermoplasty can only be administered with the Alair BT System that was developed by Asthmatx Inc., a subsidiary of Boston Scientific, Marlborough, MA, USA. It is comprised of a radio frequency controller unit and a catheter, which has an expandable network of four longitudinally arranged electrodes at the tip, which can be deployed by compression of the handle at the proximal end.

The Alair catheter is single-use disposable catheter that is fed through the working channel of a flexible bronchoscope that has an outer diameter of less than 5.0mm and a working channel of at least 2.0mm in diameter. Bronchoscopes with an outer diameter greater than 5 mm are generally not preferred as they would limit access to the distal airways [14]. The Alair catheter is connected to the radio frequency controller unit, which permits the delivery of 460 kHz, low power, monopolar radiofrequency energy to the bronchial airway. The resistance generated by the distal electrodes' contact of the bronchial walls results in the conversion of the radiofrequency energy into thermal energy. This is delivered when the operator steps on the foot pedal.

The BT system is calibrated to ensure that each activation of the foot pedal delivers the same amount of thermal energy (a maximum of 120 J) at 65°C for no more than 10 seconds. The distal electrodes have temperature sensing components which provide feedback to the system to ensure this is achieved. They also sense when the electrodes are incompletely in contact with the surrounding bronchial walls and do not allow administration of an activation. To complete the electrical circuit, an adhesive gel return electrode pad is applied to the patient and connected to the radio frequency controller unit.

Normally, BT is administered in series of 3 sessions, with each session being 3 weeks apart. The purpose of this is to allow for any post procedural irritation, inflammation or respiratory symptoms to abate. The first session usually begins in the right lower lobe, followed by the left lower lobe and then both the right and left upper lobes. The right middle lobe is avoided for a theoretical concern of developing right middle lobe syndrome [12]. The concern is that the long

length and narrow diameter of the right middle lobe bronchus may make it more prone to chronic injury and hence, no data currently exists on BT of this area.

A crucial part of BT is the planning stage. Immediately after radiofrequency energy is applied to the airways, there is seldom a clearly visible remnant of mucosal discoloration, distinct demarcation or bleeding to help identify treated airways. For this reason, a systematic, preplanned approach is vital to prevent retreatment of airways and skipping over untreated airways. A distal to proximal segmental bronchi approach, with a superior to inferior sub segmental approach is one suggested approach [14].

Once the desired sub segment has been identified, the bronchoscope is advanced as far into the sub segment as possible. This will typically be an airway 3 to 10 mm in diameter. The Alair catheter is then introduced through the working channel of the bronchoscope and directed to a visible portion of the distal airway. Here, the distal tip electrodes are expanded up to the point of complete circumferential airway contact. With appropriate positioning confirmed under bronchoscopic visualization, the foot pedal is pressed and an activation is delivered. The system also provides an audible notification of completion of the activation. The Alair catheter handle is then released to collapse the electrode network. Then, using the 5mm markings visible on the distal end of the Alair catheter, the catheter is withdrawn 5mm and positioned within the airway to administer another activation. This cycle is repeated until all the planned airways have been treated. Depending on the patient's anatomy, each session usually consists of 30 to 70 activations on average and this can take from 30 to 60 minutes to complete. It can be completed under either general anesthesia or under moderate sedation.

Upon completion of the procedure, spirometry is repeated and those with an FEV1 at least 80% of their preprocedure value are considered to have met a parameter for discharge.

Many centers practice administration of a 5 day prophylactic course of oral corticosteroids, such as prednisone 50mg daily, over the three days leading up to the procedure, the day of the procedure and then the following day to help alleviate post procedure airway inflammation. Some centers also routinely administer an anticholinergic – typically glycopyrrrolate and nebulized β_2 agonist just prior to the procedure.

As per the manufacturer's requirements, training is necessary before administration of BT. This comes in a variety of options including computer –based simulation models or hands-on training with the bronchoscopy team.

The current recommendations, on which patients would be eligible for BT, are extrapolated from the inclusion and exclusion criteria stipulated in the three major BT clinical trials [15-17]. As noted in Table 2, the inclusion and exclusion criteria in these studies varied.

Table 1: outlines these eligibility criteria.

Age 18 – 65 years old ambulatory adults
Not smoked in the past 1 or more years and < 10 pack year smoking history
Not been admitted to ICU or intubated for asthma in the past 24 months
Suitable candidate for bronchoscopy as per local practiceguidelines
Prebronchodilator FEV1 ≥ 60% and ≤ 85% predicted
Methacholine PC20 < 8 mg/ml
Asthma Quality of Life Questionnaire (AQLQ) score of 6.25 or less
No evidence of other respiratory diseases including emphysema, vocal cord dysfunction, mechanical upper airway obstruction, cystic fibrosis or uncontrolled obstructive sleep apnea
Stable asthma symptoms(no unscheduled visits or change to medications within 6 weeks prior to BT)
Requirement ofinhaled corticosteroids(ICS): at least 200 µg beclomethasone or equivalent per day, and long-acting b2-agonist (LABA): at least 100 µg salmeterol or equivalent per day
Demonstration of worsening of asthma after 2-week LABA withdrawal
None of the following: ≥ 3 hospitalizations for asthma in previous year, ≥ 3 LRTI in previous year, ≥ 4 steroid pulses for asthma in previous year

It is important to note that, there is no clinical data currently available to address the safety and efficacy of BT in patients who fall outside these parameters. Currently BT is contraindicated in those areas which have been previously been treated with BT. Contraindications also exist for those with a pacemaker, defibrillator or implantable electronic device.

EVIDENCE FOR PRACTICAL APPLICATION

BT was approved by the Food and Drug Administration (**FDA**) in April 2010. The indication was for patients aged 18 years or older who had severe, persistent asthma that was not-well controlled on inhaled corticosteroids and a long acting b2 agonist. This approval was based on evidence accumulated from three main clinical trials: Asthma Control the Year After Bronchial Thermoplasty (**AIR**) [16], Safety and Efficacy of Bronchial Thermoplasty in Symptomatic, Severe Asthma (**RISA**) [18] and Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma (**AIR-2**) [11]. Table 2summarizes these three trials.As is evident in Table 1, all three trials had a few differences in their patient populations, primary outcomes and study criteria, which innevitably makes it challenging to draw clear cut, generalized solutions.

Overall though, all three trials reported increased adverse events during the treatment period in the BT arms. Most of these events were mild and post treatment, the patients in the BT groups had improvements in their asthma symptoms.

Table 2: Overview of the pivotal initial BT Trials. LABA = long acting b2-agonist, AHR = airway hyperresponsiveness, AQLQ= Asthma Quality of Life Questionnaire. LRTI = lower respiratory tract infection, FEV1 = forced expiratory volume in the 1st second.

Trial	Design	Control	BT	Inclusion Criteria	Spirometric Criteria	Additional Criteria	Exclusion Criteria	Primary Outcome
AIR	Randomized controlled trial	56	56	Moderate to severe persistent asthma	FEV1 60%-85% predicted, AHR (PC20 < 8 mg/mL),	Stable symptoms for preceding 6 weeks, Worsening asthma symptoms when LABA withdrawn	Respiratory infection in preceding 6 weeks, ≥ 3 LRTI requiring antibiotics in previous year	Frequency of mild exacerbation
RISA	Randomized controlled trial	17	15	Severe persistent asthma	FEV1 ≥50% predicted, AHR			Safety
AIR-2	Randomized, double-blind, sham-controlled trial	101	196	Severe persistent asthma	FEV1 > 60% predicted, AHR (PC20 < 8 mg/mL), AQLQ ≤ 6.25	Stable dose of inhaled steroid and LABA for ≥ 4 weeks	Life-threatening asthma, Chronic sinus disease, Use of immunosuppressants (eg. Prednisone ≥ 10mg/day, β-adrenergic blocking agents, or anticoagulants, ≥ 3 hospitalizations for asthma in previous year, ≥ 3 LRTI in previous year, ≥ 4 steroid pulses for asthma in previous year	Change in AQLQ

The AIR Trial was the first randomizedcontrol trial (**RCT**) [16] for BT. The AIR trial found that at the 3 and 12 month post-BT mark, patient’s showed significant improvements in their Asthma Quality of Life Questionnaire (**AQLQ**) and Asthma Control Questionnaire (**ACQ**). Asthma symptom-free days were also significantly increased however this effect did not persist beyond the 3 month follow up mark. Patients who received BT in addition to standard therapy were found to have 50% fewer mild asthma exacerbations after BT but the rate of severe exacerbations, remained unchanged. The lack of blinding in this trial certainly confounds the interpretation of its results but certain parameters showed a significant improvement, which placebo alone may not have been able to achieve.

The RISA trial followed, and was again an unblinded RCT [18] but this time, looking at just severely symptomatic asthma patients. Approximately half of the patients in each arm were on daily oral corticosteroids to control their asthma. Again, AQLQ and ACQ scores significantly improved and persisted upto the 52 week mark. Rescue inhaler use was also significantly reduced. There was an initial 15% increase in the prebronchodilator Forced Expiratory Volume in the first second (**FEV1**) notable in the BT patients at 22 weeks but this was not statistically significant at the 52 week mark.

The final trial and most extensive trial was AIR-2. This is the only double-blind, sham-control RCT in BT patients. Just like a regular BT session, the sham group also underwent 3 sessions of bronchoscopy, Alair catheter electrode deployment into the airway but without radiofrequency energy delivery. The primary outcome measure was change in AQLQ. The AQLQ is a 32 point questionnaire that generates numeric value, of which an increase of 1 indicates moderate improvement in quality of life and if greater than 1.5; a large improvement [19]. The AQLQ did in fact improve by 1.35 ± 1.10 in the BT group, but it also improved by 1.16 ± 1.23 in the sham group. Interpretation of the AQLQ is an area of contention. Whether to look at it as an aggregate score, which would lead to the conclusion that this was a negative study or whether to analyze it in the context of the portion of patients who achieved the minimally important clinical difference continues to be debated [20]. Looking at the secondary outcomes, the BT group patients had 84% less presentations to the emergency room, a reduction in hospitalizations, 32% fewer severe exacerbations and fewer days off from work or school.

Applicability of the AIR-2 findings to “real world”, day-to-day practice requires some deliberation. Typically, severe asthmatics are perceived to be those requiring daily oral corticosteroids, in addition to their inhaler regimes. Just 2.7% of the enrolled patients were on oral corticosteroids. The exclusion criteria of those with frequent hospitalizations also limits the applicability of the AIR-2 data to this subset of severe asthmatics. The weight of placebo effect in the sham group was an important finding as this would certainly have to be accounted for in future BT studies.

SAFETY & COMPLICATIONS

The most commonly observed adverse effect of BT is a transient increase in respiratory symptoms. These include wheeze, cough, chest tightness or pain, symptoms of upper respiratory tract infection, sore throat and discolored sputum. They tend to manifest within 24 hours of the procedure and abate over the ensuing week. Of note, these complaints are rather indifferent to those that can be reported after routine bronchoscopy. As a consequence, it is challenging to tease out which risks of BT relate to the procedure itself versus the general risk of flexible bronchoscopy.

All three of the major clinical BT trials published 5 year follow up data [17,21,22]. Reassuringly, all the patients who could be followed up continued to have sustained reductions in their emergency room presentations, hospitalizations and asthma exacerbations. Patients who consented for extended follow up after their participation in the AIR trial, underwent annual pulmonary function testing, methacholine challenge testing and chest radiography. Interestingly, although not seen at the 1 year mark, BT treated patients had an increase in their PC20 from baseline, which reflects a reduction of their airways' hyper responsiveness. In the largest group of patients- 162 post BT from the AIR-2 trial [21], there were also no incidences of intubation and mechanical ventilation, pneumothorax, cardiac arrhythmias or deaths. Additionally, there was no significant change in prebronchodilator FEV1 values. Further comparative interpretation of the

extended AIR-2 trial data is limited because outcomes of the patients in the sham group were not reported [23].

More severe adverse effects, requiring hospitalization were noted at 3.4% by the AIR2 investigators however, none of these patients required chest tube placement or intubation and mechanical ventilation. Case reports of unusual complications such as bronchial artery pseudoaneurysm and hemorrhage [24]; of which there was 1 somewhat similar reported case of hemoptysis in AIR2 trial have been reported.

More long term concerns for development of parenchymal, restrictive interstitial disease have been questioned but yet to be convincingly shown. An extended follow up study of 45 BT patients and 24 control patients from the AIR trial [17] failed to show any significant changes in annual pulmonary functioning testing (which included lung volumes, bronchoprovocation testing and DLCO) or chest xrays. Similar outcomes in pulmonary function stability were reported in the extended 4 year follow up of the 14 BT patients who were originally enrolled in the RISA trial [22] and the 162 patients who were longitudinally followed for a total of 5 years after the AIR2 trial [21].

Assuming that the effects of BT remained localized to the airways greater than 3 mm in diameter, it would seem less likely that BT would affect the more distal interstitium and alveolar airways. Despite this logic, a small 10 patient cohort that underwent standardized BT (without any activations in the right middle lobe), were interestingly found to have a 48.7% ASM mass reduction in the untreated right middle lobe in 7 of the 10 patients [25]. This would suggest that there are additional, yet to be uncovered effects imposed within the airways by BT.

COST PERSPECTIVE

Whilst the targeted population for BT only comprises 5% - 10% of all asthmatics, prospectively followed asthma cohorts have identified that this percentage of patients are responsible for a significant portion (upto 50%) of the overall economic burden of asthma care [26,27]. It is therefore prudent to explore all resources capable of limiting this burden. In 2013, the total cost of asthma exceeded \$20.7 billion in the USA (Nih. Asthma info. 2013. Available from: <http://www.nhlbi.nih.gov.ezp.slu.edu/health-pro/resources/lung/naci/asthma-info/>).

One approach is to determine the cost effectiveness of BT however, a limited number of studies have looked at this. A group of investigators from Boston Scientific, assessed how the cost effectiveness for standard therapy alone compared with the addition of BT for poorly controlled severe persistent asthmatics [28]. They found an incremental cost-effectiveness ratio (**ICER**) of \$ 5,495 for BT however, some of the cost inputs seem to have been overestimated.

More recently, a study examined the 10 year cost-effectiveness of BT for individuals with severe uncontrolled asthma [29]. This study conservatively looked at the cost-effectiveness of BT in improving quality of life (**QOL**) for patients with severe uncontrolled asthma. Using

patient demographics from the AIR2 Trial and costs data abstracted from the Healthcare Cost and Utilization Project (**HCUP**), coupled with average Medicare reimbursement rates, this group concluded that Treatment with BT resulted in 6.40 quality adjusted life-years (**QALYs**) and \$7512 in cost compared to 6.21 QALYs and \$2054 for usual care. The incremental cost-effectiveness ratio for BT at 10 years was \$29,821/QALY, which can still be regarded as cost effective at the willingness-to-pay (**WTP**) of \$50,000/QALY.

As listed in the 2016 GINA guidelines, BT (evidence level B) shares the same add on therapy, Step 5 category asomalizumab (evidence level A), mepolizumab in those with severe eosinophilic asthma (evidence level B) and tiotropium (evidence level B). It is therefore of interest to look at a cost effectiveness study comparing standard therapy, omalizumab therapy and BT in U.S. patients with moderate - severe allergic asthma [30]. In comparison to standard care and omalizumab, BT requires a rather high willingness-to-pay (WTP) of \$80,000/QALY to be cost effective. Additionally however, despite its significant clinical improvements, omalizumab was not deemed cost effective when compared to standard therapy.

The high initial cost of BT has limited its coverage by many health insurance plans and hence, patient's access to it. With the multitude of approvals and recommendations from various medical societies, some insurers have started more readily approving BT however, a substantial portion still require case-by-case review before approval.

With its relatively new position as an approved therapy for certain adult populations of asthmatics, medical societies have now been issuing guidance on the use of BT. The 2014 international ERS/ATS guidelines on severe asthma [2] recommend that BT should be performed for severe asthmatics in the clinical trial setting under the approval from a local Institutional Review Board (**IRB**). GINA, the Global Initiative for Asthma, have given BT a B grade level of evidence for use in uncontrolled asthmatics at Step 5 of its therapy ladder. The 2014 British Thoracic society (**BTS**) guidelines have given BT a grade A recommendation stating that "Bronchial thermoplasty may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy". The American College of Allergy, Asthma, and Immunology (**ACAAI**) issued a statement encouraging insurers to provide coverage for BT in carefully selected patients with severe, persistent asthma who have persistent burden of disease, asthma exacerbations, emergency department visits or hospitalizations despite maximal medical treatment. Similarly, the American College of Chest Physicians (**ACCP**) and has also published statements to encourage healthcare insurers to cover BT for certain asthmatics.

THE FUTURE DIRECTIONS OF BT

Gaining a better understanding of which asthmatic phenotypes are most likely to benefit from BT is an area of inevitable interest [31]. Advanced imaging techniques such as, hyperpolarized xenon 129 or helium 3 lung MRI with CT are being utilized to investigate this further [32]. The combined MRI and CT imaging modality provides a quantitative value of ventilation in each

bronchopulmonary segment, which in turn has implications on how many segments are affected and how many can be potentially spared the need for treatment [33].

With airway remodeling being the pivotal pathological change in asthmatic airways, identification of those regions disrupted by extracellular matrix (**ECM**) deposition may also help direct BT therapy [34]. Fibered confocal fluorescence endomicroscopy is a modality that has been shown to successfully identify; in vivo, the fragmented elastic ECM fibers that are deposited in asthmatic airways [36] and hence serve as a potential BT target. Similarly, optical coherence tomography (**OCT**), which is more commonly used in ophthalmology for retinal imaging, has also been utilized to perform real time visualization of abnormalities in the epithelium of the airways [37].

Part of the approval agreement issued by the FDA for BT required completion of another post approval study to assess durability and safety of BT in the intended patient population. AIR2 was one, and the ongoing, multicenter Bronchial Thermoplasty in Severe Persistent Asthma (**PAS2**) Trial is the other. The targeted primary end point in PAS2 is severe asthma exacerbations over a 5 year follow up period of approximately 300 patients [38]. This study will obviously serve to fortify our understanding of BT and its long term safety profile.

Another area of ongoing work is analysis of the variables that could help us determine the specific predictors of response to BT. One study looked at 42 patients over 12 months and found that those who had less air trapping on multi-detector CT trended towards a better response to BT [39]. Those who required more prednisone bursts during the year prior to BT and those who carried a diagnosis of asthma for a shorter period of time before BT, had a better improvement in their AQLQ and ACT scores after BT. The future of BT efficacy seems to lie in the realm of a more phenotypic approach with classification of patients in terms of their glucocorticoid responsiveness, atopic status, comorbidities and reversibility of airway obstruction.

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