

Bronchial Thermoplasty

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INTRODUCTION

As per the GINA 2016 report, asthma is defined as a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory flow limitation.

Out of the patients diagnosed with asthma about 3-4% continues to have symptoms despite being on maximal recommended therapy. This subset of patients is believed to have severe asthma.

As per the ERS/ATS guidelines of 2014, severe asthma is defined as asthma which requires treatment according to GINA guidelines for steps 4-5, i.e. high dose inhaled corticosteroids + long acting bronchodilators or leukotriene modifiers/ theophylline for the previous year or systemic corticosteroids for more than 50% of the previous year.

The severe asthma is said to be uncontrolled is defined by at least by one of the following;

- 1) Poor symptom control: ACQ>1-5, ACT<20.
- 2) Frequent severe exacerbations: 2 or more bursts of systemic corticosteroids for > 3days in one year.
- 3) Serious exacerbations: At least one hospitalisation, ICU stay or requiring mechanical ventilation.
- 4) Airflow limitation: After appropriate bronchodilator withhold, FEV1 < 80% predicted when FEV1/FVC is less than normal.

Some of the newer therapeutic options available for this patient population include Omalizumab (more beneficial in allergic subtype and with elevated IgE levels) and anti-IL5 monoclonal antibodies like mepolizumab and reslizumab.

Bronchial thermoplasty was added to these modalities when it was FDA approved on April 27, 2010 for use in patients with severe persistent asthma which is uncontrolled.

This chapter will provide a review of Bronchial Thermoplasty including those trials which led to the above mentioned approval.

MECHANISM OF ACTION

Bronchial thermoplasty (**BT**) aims to reduce the airway smooth muscle (**ASM**) mass with the goal of diminishing bronchial constriction and ameliorating asthma symptoms. The reduction in ASM is accomplished by delivering controlled thermal energy to the airway walls during a series of three bronchoscopies. The British Thoracic Society guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults recommends BT as a possible treatment option in selected patients with severe asthma already on maximal therapy.

Role of Airway Smooth Muscle in Asthma

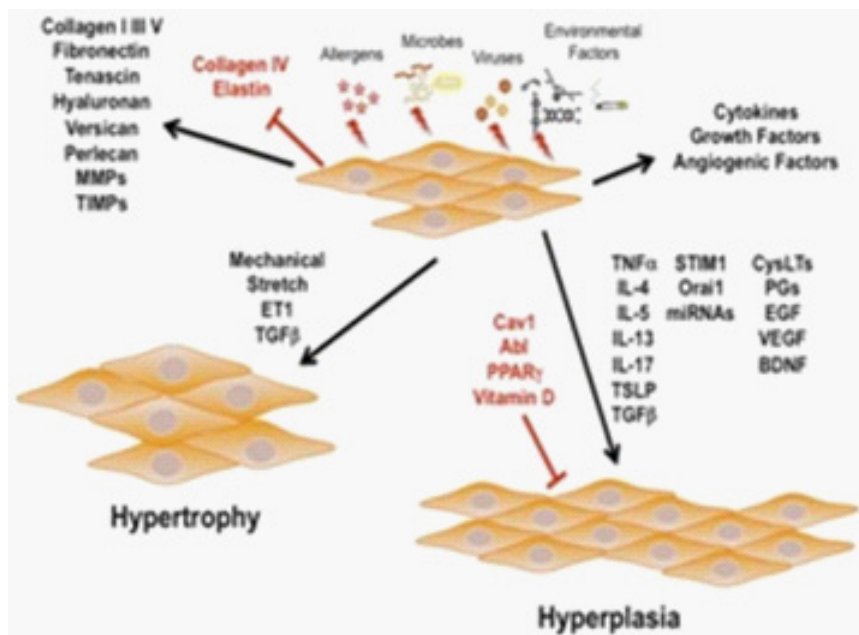
The chronic asthmatic's airway is characterized by extensive remodeling, with proliferation of mucous glands, increased vascularization, and hypertrophy of airway smooth muscle (**ASM**). In an acute asthma attack, there may be a variety of triggers, both infectious and noninfectious; but it is the downstream cascade of events that results in the activation and contraction of airway smooth muscle.

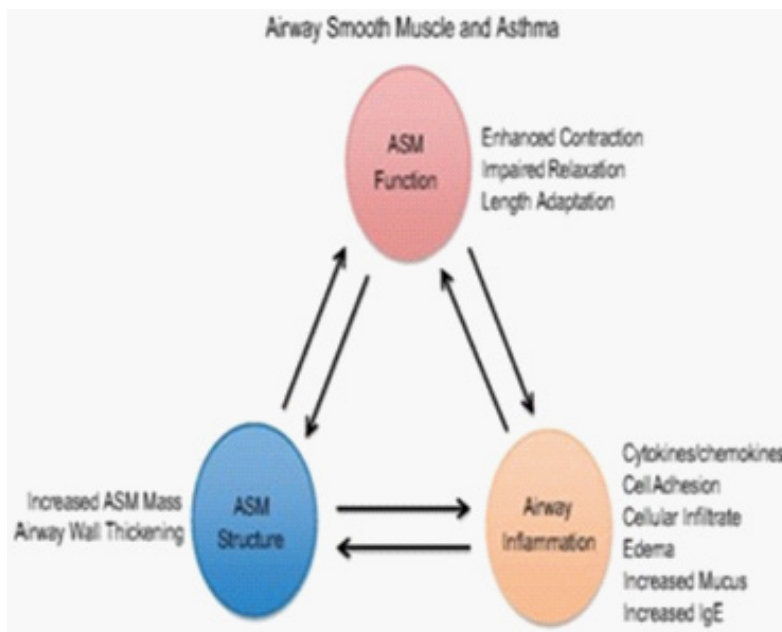
The precise role of the smooth muscles in the airways has been a subject of much debate. The airway smooth muscle has been described as a vestigial organ and, instead of having an authentic physiologic purpose, is involved in pathologic responses. According to rat and murine studies, ASM originates with the lung bud from the primitive foregut and is present in the proximal airway at 5 to 6 weeks of human gestation. ASM has been postulated to have several different functions in the respiratory system, including peristalsis to assist mucus clearance and exhalation, promotion

of lymphatic and venous flow, airway structure protection, increasing the effectiveness of cough, and optimizing dead space volume. Yet none of these functions appear to be absolutely essential to normal lung physiology. Consequently, ASM has been called the “appendix of the lung”.

In those patients with severe asthma, the spiral bundles of ASM increase both in number and in size, spread to infiltrate the larger airways, and can reach the respiratory bronchioles and alveolar ducts. The involvement of more proximal bronchi augments the total airway resistance as 75% of the postnasal resistance to airflow in the human bronchial tree occurs within the first six to eight generations of airways, which are more than 3 mm in size. Consequently, decreasing the bulk of ASM would logically result in a decrease in bronchospasm and ultimately respiratory failure in severe, acute asthmatic attacks.

In asthma, the airway smooth muscle is the main effector of bronchoconstriction in response to various stimuli, including several inflammatory mediators. The smooth muscle can also promote inflammation by producing a variety of cytokines and chemokines such as CXCL10 (IP-10) and fractalkine that participate in an autocrine loop. Mast cells perpetuate this inflammatory cascade as they have been shown to associate with airway smooth muscle in patients with asthma. Upon activation and degranulation, they also produce a number of cytokines and mediators such as IL-4 and leukotriene B₄ that can contribute to airway hyperresponsiveness and promote the increase in airway smooth muscle mass. Therefore, airway smooth muscle is an active participant in the inflammatory response and contributes to asthma exacerbations.





How Bronchial Thermoplasty Works?

Bronchial thermoplasty is a procedure that delivers controlled thermal energy at 65 degree C to airways between 3 and 10 mm diameter via a bronchoscope under direct visual guidance. There are a number of possible mechanisms of action that alone, or in combination, might explain the beneficial effects of bronchial thermoplasty.

Because an increase in airway smooth muscle (**ASM**) mass is one of the major characteristics of airway remodelling in severe asthma patients, the first and most well documented mechanism of action concerns reduction in the bronchial wall smooth muscle. A reduction in ASM mass after bronchial thermoplasty has been observed experimentally in a canine model and in non-asthmatic human lobectomy specimens examined between 1 and 3 weeks after bronchial thermoplasty; and the finding that the reduction in airway smooth muscle is directly related to the decrease in airway responsiveness provides indirect evidence that the beneficial effects of bronchial thermoplasty may be due to a decrease in airway smooth muscle mass.

A second mechanism might involve altering the airway function by reducing contractility of airway smooth muscle or stiffening the airway wall. The effects of the application of various temperatures on in vitro contraction of bovine bronchial smooth muscle have been examined. Acetylcholine-induced contraction of bronchial smooth muscle was inhibited at temperatures exceeding 55 degree C, while relaxation mediated by a β_2 agonist was not affected, suggesting that bronchial thermoplasty may alter the contractile properties of ASM cells. Interactions between actin and myosin were also very sensitive to temperature, and changes occurred in the absence of any histological signs of necrosis or apoptosis.

Other potential mechanisms of action include reduced secretion of inflammatory mediators by ASM cells and/or alteration to the epithelium of the airways, the nerve endings or the function of the inflammatory cells that infiltrate the bronchial mucosa.

Responsive Phenotypes

Asthma exists in multiple phenotypes and current selection criteria for BT is based on severity and not on phenotype. There has also been a trial evaluating use of biomarkers to predict response to BT. Histology has also been used to help identify different asthma phenotypes and thus help in identifying those who may respond to different medical therapies. One study looked into the role of endobronchial biopsy as part of initial evaluation and after the procedure to evaluate for response. Performing biopsies, on the other hand, is not practical or safe enough to be considered part of the overall evaluation.

We might imagine that the patients who benefit the most from bronchial thermoplasty would be those who have greater airway hyper reactivity as demonstrated by response to β_2 agonists, response to methacholine challenge or tendency to frequent exacerbations. In the same way, we might think that bronchial thermoplasty would be even more effective in those where smooth muscle contraction plays an important role in their disease; however, there are no clinical data to support this assumption. Similarly, there is little evidence that the inflammatory phenotype is relevant to clinical response. Likewise, the presence or absence of allergies by self-report or other predisposing factors does not seem to be a factor that can predict response to bronchial thermoplasty.

The lack of a consistent improvement in lung function following bronchial thermoplasty might be explained by the procedure targeting larger airways > 3 mm in diameter that do not greatly affect FEV1 measurements, although the benefits in AQLQ scores and exacerbations suggest that larger airways have an important role in these clinical outcomes in severe asthma.

THE PROCEDURE

Equipment

Bronchial thermoplasty is delivered by the Alair bronchial thermoplasty system. The Alair Bronchial Thermoplasty System consists of the Alair Catheter and the Alair Controller System.

Alair Catheter is a SINGLE-USE ONLY, disposable device. The Catheter delivers energy from the Controller to the desired site in the airway and relays temperature feedback to the Controller. The catheter has a basket electrode at the distal end which can be progressively expanded and retracted by a handle-grip control. The catheter has markings at 5 mm to facilitate endobronchial spacing of treatment activations.

Alair Controller System consists of Alair Radiofrequency (**RF**) Controller, footswitch and patient return electrode. The Alair RF Controller provides controlled delivery of RF energy to the Alair Catheter. The Controller delivers low-power, temperature controlled RF energy to the airway at a predetermined temperature setting for a predetermined time period.

Footswitch: The Controller is used with a footswitch that allows the operator to start and stop the delivery of RF energy.

Patient Return Electrode: The patient return electrode is used to complete the return path for the electrical current.

Bronchoscope requirements: The Catheter is designed to be used with high-frequency compatible flexible bronchoscopes that have a minimum 2.0mm working channel, and maximum 5.0mm outer diameter.

Patient Preparation

- Administer prophylactic prednisone or equivalent at a dosage of 50 mg/day for the 3 days before the procedure, the day of the procedure and the day after the procedure to minimize post procedure inflammation.
- Perform the pre-procedure spirometry on the day of procedure. Pre-procedure FEV1 value should be >/85% of the patient's recent value when stable.
- Patients should hold anticoagulants, antiplatelet agents and NSAIDS before the procedure.

Postpone the procedure if any of the following conditions apply:

- Prescribed prednisone was not taken on the 3 days before bronchoscopy.
- SpO2 is less than 90% on room air.
- Increase in asthma symptoms in last 48 hours requiring more than 4 puffs/day on average of rescue bronchodilator over pretreatment usage.
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma (up or down) in the past 14 days.
- Active respiratory infection, active allergic sinusitis, or other clinical instability.

Procedure:

- Bronchial thermoplasty should be performed only at facilities equipped to handle respiratory emergencies including respiratory failure requiring intubation.

The course of treatment is intended as a single, once per lifetime treatment and is not repeated.

- It is an outpatient procedure delivered over three bronchoscopy sessions spaced at approximately one month intervals, one for each lower lobe and one for both upper lobes.
- Right middle lobe is not treated because of the potential susceptibility of the right middle lobe to transient obstruction as a result of inflammation or edema. (Right Middle Lobe Syndrome).
- Nebulised salbutamol is administered prior to the bronchoscopy. In some settings anti-secretory agents such as glycopyrrolate or atropine are also given.

- It is conducted under moderate sedation or light general anesthesia. Patients are sedated usually with a combination of a short acting benzodiazepine and an opiate. Administration of effective topical anaesthesia before and during the bronchoscopy is very important due the significant mechanical and thermal irritation caused by the procedure.
- Patients are positioned in recumbent or semi-recumbent position and the scope is inserted via nose or mouth.
- The area to be treated is first inspected to plan the sequence of treatment.

The approach should be systematic to avoid missing or retreating bronchi, with consideration given to treating the most accessible bronchi first.

Following treatment planning, the bronchoscope is placed in the distal aspect of the airway being treated and the Alair catheter is advanced under visual guidance. The electrode array is then expanded to make contact with the airway wall, and the footswitch is depressed to deliver radiofrequency energy for 10 s. If electrode contact is inadequate the unit will alarm and abort the treatment. Care must be taken to avoid over-expansion of the catheter array which tends to invert the electrodes, progressive but gentle squeezing of the catheter handle until the electrodes are just touching the airway wall is most effective. After activation of the catheter the operator relaxes the handle, collapsing the electrodes slightly away from the airway wall and the bronchoscope operator then moves the bronchoscope and catheter 5 mm proximally. This sequence is repeated until the full length of each airway has been treated. The sites of the various activations are recorded on a suitable airway map.

An experienced team will typically complete each treatment session in ~45 min.

At the start of the second and third procedures, the airways treated in the previous procedure are carefully inspected for persisting inflammation or infection and if this were present, delay of treatment should be considered.

Post-procedure care

Recommended post-procedure assessments:

- 1) 4 hour recovery/monitoring period following each procedure.
- 2) Spirometry, breath sounds and vital signs (heart rate, blood pressure, temperature, respiratory rate, pulse oximetry) prior to discharge. Criteria for discharge include a post-bronchodilator FEV_1 within 80% of the pre-procedure value and that the patient is feeling well.

Indications:

- 1) Patients with severe persistent asthma not well controlled despite high dose ICS and LABA or oral corticosteroids.

- 2) Patients between 18-70 years old.
- 3) Post-bronchodilator FEV1 more than 55% of predicted.

Contra-indications:

- 1) Presence of a pacemaker, internal defibrillator or other implantable electronic devices.
- 2) Known sensitivity to medications required to perform bronchoscopy including lidocaine, atropine and benzodiazepines.
- 3) Patients previously treated in the same area.
- 4) Active respiratory infection.
- 5) Asthma exacerbation or changing dose of systemic corticosteroids for asthma in last 14 days.
- 6) Known coagulopathy.

Precautions:

- 1) Postbronchodilator FEV1<65% of predicted.
- 2) Concurrent respiratory disease including emphysema, vocal cord dysfunction, cystic fibrosis, bronchiectasis and obstructive sleep apnea.
- 3) Use of SABA in excess of 12 puffs a day within 48 hours of bronchoscopy.
- 4) Use of oral corticosteroids in excess of 10 mg a day for asthma.
- 5) Increased risk for adverse events associated with bronchoscopy or anesthesia.
- 6) Intubation for asthma or intensive care unit admission for asthma within the previous 24 months.
- 7) Any of the following within the past 12 months –

Four or lower respiratory tract infections.

Three or more hospitalizations for respiratory symptoms.

Four or more oral corticosteroid pulses for asthma exacerbation.

EFFICACY

Several trials have evaluated the efficacy and safety of Bronchial Thermoplasty, some of which were followed for 5-years for extended safety data. We will review the major ones here:

1) One of the first trials to examine the impact of BT was published by Cox et al. in 2006. It was a nonrandomized, prospective study in which 16 patients from two investigational sites were treated with Bronchial Thermoplasty and followed for 2 years to evaluate its effect and safety. All subjects demonstrated improvement in airway hyperresponsiveness. The mean PC20

increased by 2.37 +/- 1.72 ($p < 0.001$), 2.77 +/- 1.53 ($p = 0.007$) and 2.64 +/- 1.52 ($p < 0.001$) at 12 weeks, 1 year and 2 year post-procedure respectively. Statistically significant improvements were also seen in mean percentage of symptom-free days and in morning and evening peak flows at 12-weeks post treatment.

2) AIR trial – 112 subjects who had been treated with inhaled corticosteroids and long-acting beta2-adrenergic agonists (LABA) and in whom asthma control was impaired when the LABA were withdrawn to either bronchial thermoplasty or a control group. Statistically significant improvements were noted in BT group compared to control group at 12 months in morning peak expiratory flow, scores on the AQLQ and ACQ, percentage of symptom-free days and symptom scores.

45 out of 52 treated and 24 out of 49 control group subjects participated in long-term follow-up of 5 years. The improvement in the lung functions and the subjective scores were maintained throughout the 5 years along with no increase in adverse events reported.

3) RISA trial – Trial was conducted in eight sites in 3 countries. After a 2-week run in period, a total of 32 subjects were randomized to control group (17) or to treatment with BT group (15). After treatment period, subjects entered a 16-week steroid stable phase followed by a 14-week steroid wean phase and 16-week reduced steroid phase. Improvements were noted in decreased SABA use and percentage change from baseline in prebronchodilator FEV1 in BT group compared with control group at 12 weeks. There were also significant improvements noted in subjective markers like ACQ and AQLQ scores.

14 out of 15 randomised to BT group provided consent for 5-year follow-up. Annual examinations were conducted at the end of years 2-5. The number of adverse events was largest in the first year at 8.4 per patient per year followed by 1.4, 2.4, 1.7 and 2.4 in subsequent years. Number of ER visits and hospitalisations was reduced along with no significant changes found in maintenance asthma medication use, serial chest radiographs and PFTs over 5-year time.

4) AIR-2 trial – Randomized, double-blind, sham-controlled clinical trial at 30 sites in 6 countries. Subjects were randomized in a 2:1 ratio to BT or a sham group and were then evaluated 6 weeks after the last procedure followed by 3, 6, 9 and 12 months. 580 patients were screened for the trial with eventual randomisation of 288 into 190 for BT and 98 in sham control group. Mean change in AQLQ score in Intention-To-Treat population was greater in BT groups than in the sham group. There was also a 32% reduction in the rate of severe exacerbations in the BT group along with improvement noted in morning PEF, symptom-free days, symptom score, ACQ and rescue medication use which were not statistically significant.

162 out of 190 BT treated subjects from AIR-2 trial completed 5 years of follow-up. Number of severe exacerbations and ED visits were less in the BT group. There was no change in respiratory adverse events and respiratory-related hospitalisations.

ADVERSE EFFECTS

1) In the first trial by Cox et al in 2006, around 155 adverse events were reported that were thought to be procedure-related. The majority of these were mild (130/155), with the remaining events being moderate (25/155) and no severe side effect reported. The major events in decreasing frequency included cough (21%), dyspnea (12%), wheezing (11%), bronchospasm (10%), fever (9%), chest discomfort (8%) and mucus production (5%). The mean time to onset was 1.7 days and mean time to resolution was 4.6 days. 58% of them resolved spontaneously within 1 week while the remaining 42% were managed with medications.

2) In the AIR trial, a total of 407 adverse events were reported, out of which 69% were mild, 28% were moderate and 3% were severe. Majority of the side effects observed were in the treatment period (0-6 wks) as well as post-treatment period (6-12 wks) were dyspnea, wheezing, cough, chest discomfort, night awakenings with nasal congestion.

In the 5-year follow-up of the AIR trial, the rate of respiratory adverse events were higher in both BT and control groups as they were recorded individually but they remained stable from years 2-5 when multiple symptoms were recorded as a single event.