

TITLE PAGE

Bronchial Thermoplasty: A non pharmacological approach

Review Article

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ABSTRACT:

Asthma is a chronic inflammatory disorder of the airway characterized by the episodic symptoms of breathlessness, wheezes and cough. Even with the use of maximum anti-asthmatic pharmacological treatment sometimes it remains uncontrolled. For such patients bronchial thermoplasty is the new mode of treatment. It is the radiofrequency ablation of the airway smooth muscle with the help of flexible fiberoptic bronchoscope. It reduces the smooth muscle mass of the bronchial wall and decreases its contractility. Bronchial thermoplasty causes improvement in quality of life and cause reduction in the emergency room visit and exacerbation due to asthma. Long term safety has been established by various prospective studies.

Key Words: Asthma; anti-asthmatic; smooth muscle; quality of life

No need for human trial permission as it is a review article.

All the authors have seen the article and given permission for publication.

Introduction:

Asthma is the chronic inflammatory disorder of the airway affecting 300 million people worldwide. It is characterized by the episodic symptoms of breathlessness, wheezes and cough. These symptoms wax and wane over time. Its prevalence ranges from 1 to 18% of the population in different countries and is severe in 10% of the population¹. According to World Health organization 15 million disability years are lost due to asthma. Asthmatics typically have hyperresponsive and chronically inflamed airway along with airway remodeling. This airway remodeling at times used to be extensive. Wall thickness has been measured in resected lung specimen² and by radiological imaging³. Increased thickness is due to contributions from each of cellular influx⁴, increased vascularity⁵, edema and collagen matrix deposition⁶ and smooth muscle hyperplasia and hypertrophy⁷. The functional consequences of remodeling may include measureable loss of dynamic distensibility or effective rigidity, persistence of bronchial hyper-reactivity even after removal of antigen, reduced lung function with fixed airflow obstruction causing lack of responsiveness to bronchodilator medication, the accelerated fall in lung function seen in chronic asthma and increased risk of asthma mortality.

Airway Smooth Muscle (ASM):

Airway smooth muscles are considered to be the vital cause for the difficulties in breathing during an acute attack of asthma. For this reason all the efforts have been made to hamper the shortening of the airway smooth muscle and are the target for the therapeutic research related to the asthma. Beta 2 Adrenergic blockade has been used for the acute relaxation of the ASM contraction. In moderate to severe asthma β_2 antagonist are been used with anti-inflammatory

agents. Number of new inflammatory inhibitors has been available for those patients who do not respond to the conventional therapy⁸. Serious asthma exacerbations still occur despite the attempt to control the inflammatory pathway in patients with mild asthma⁹. Patients with severe asthma every now and then are poorly responsive to all form of therapy. Viral respiratory infections, environmental allergens, exercise, occupational chemicals or allergens, drugs, emotions, food, change in weather or various comorbid conditions like sinusitis etc are the triggers for the asthma which finally leads to the contraction of ASM.

It is well known that nearly all of the airway resistance occurs in bronchi larger than 2 mm in diameter¹⁰. In the patients of asthma the entire bronchial tree even larger airway with cartilage participates in airway constriction during asthmatic attack.

In the last decade it has been questioned whether ASM have any physiological function or not. It is considered as “The appendix of the Lung¹¹” whose sole contribution is the potential to cause problem. Seow and Friedberg¹² also pointed out that there is no disease entity or physiological deficiency associated with loss of ASM. They also commented that ASM was perhaps a vestigial remnant of its common embryologic origin with the gastrointestinal system. Mitzner¹¹ in his famous work summarizes roles for airway smooth muscles have appeared in the literature. These possible roles consist of the following: (1) peristalsis to assist exhalation, (2) peristalsis to assist mucus propulsion, (3) peristaltic contraction in the fetal lung to generate fluid pressure, (4) promoting lymphatic and venous flow, (5) ventilation/perfusion matching, (6) protecting the peripheral lung, (7) protecting airway structure, (8) stabilizing airways, (9) enhancing the effectiveness of cough, and (10) optimizing anatomic dead space volume. Finally they concluded that none of these potential functions of airway smooth muscle are essential to normal lung physiology. If airways smooth muscles are eliminated then the airways might enlarge

slightly due to loss of basal tone without having any physiologic consequences. Mitzner¹¹ concluded that the evidence strongly suggest that airway muscle is indeed like a vestigial organ analogous to the appendix with no known purpose other than to cause serious medical problems. He suggested if there were a way to treat airway smooth muscle like an inflamed appendix that is to effectively cut it out, then asthma like appendicitis could be cured.

Understanding of asthma pathophysiology makes us to use the bronchodilator along with corticosteroids as first line of treatment. But inability to treat moderate to severe asthmatic make the way for the introduction of other treatment modalities like leukotriene antagonists and omalizumab, an anti-immunoglobulin E (Anti IgE). Despite of it, asthma remains poorly controlled in a substantial group of population. These subgroups of patients are classified as difficult to control asthma or severe asthma¹³. They have high morbidity and mortality consuming large proportion of health resources allocated to them. For difficult to control asthma the novel approach has been advised known as Bronchial Thermoplasty (BT). It is the radiofrequency ablation of the airway smooth muscles causing the reduction in ASM contractility and quantity. This is the non-pharmacological treatment for asthma whose efficacy and its technique is well studied and discussed in various publications. In April 2010, the U.S. Federal Drug Administration (FDA) approved Bronchial Thermoplasty for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with conventional treatment (inhaled corticosteroid and long acting β_2 agonists).

Bronchial Thermoplasty: Procedural Aspect.

Three bronchoscopic sessions are required for the bronchial thermoplasty, at 2 to 3 weeks interval. In the first two sessions right lower lobe and left lower lobes are treated while the last

combines both the upper lobes of the lung. Bronchial thermoplasty is not performed in right middle lobe because of the long, narrow and acute take off angle from main bronchus making it vulnerable for stenosis after procedure due to post procedural inflammation leading to right middle lobe syndrome. During each bronchoscopic session, previously treated segments are examined for adequate healing. Non healing of the previously treated segment may lead to the postponement of the procedure.

The Alair system (Asthmatx. Inc., Sunnyvale, CA) is used to perform bronchial thermoplasty. It delivers a specific amount of radiofrequency (RF) through a catheter (Single-Use Only, disposable device). This catheter is deployed under direct vision through the 2.0 mm channel of the flexible bronchoscope. This catheter has an expandable basket with four electrodes attached to its end to transmit the heat to the respiratory mucosa. The Alair RF Controller is designed to provide controlled delivery of RF energy to the Alair Catheter. The Controller is used with a footswitch that allows the operator to start and stop the delivery of RF energy.

Indication for Use: The Alair Bronchial Thermoplasty System is indicated

- Patients 18 years-65 years
- Patients with severe asthma
- Patients whose asthma is not well tolerated with inhaled corticosteroids and long acting beta agonists.

Patients Selection: Patients is to be selected by a team of asthma expert and the bronchoscopist. Sometimes the same person can be responsible for both the procedure. Patients are to be selected according to the Asthma Intervention Research (AIR) 2 trial¹⁴ i.e. he should be stable in terms of asthma status (their post bronchodilator FEV1 is within 15% of baseline values) and there should

be no respiratory tract infection or asthma exacerbation within last 14 days. Other contraindications for BT includes; presence of implantable electronic device (pacemakers, internal defibrillator), sensitivity to drug used in bronchoscopy (atropine, lidocaine and benzodiazepines) and presence of coagulopathy. Asthmatics previously treated with BT should not be treated in the same areas.

Patients are given 50 mg of prednisone for 5 days beginning 3 days before the procedure to attenuate the post procedural inflammation. Procedure is performed under conscious sedation along with supplemental oxygen.

Procedure: The bronchoscope is fixed at the desired position, most distal branch of the targeted airway. The BT catheter is inserted through the working channel of bronchoscope to treat the most distal visible part of bronchus and opens its electrode basket to come in sufficient contact with airway wall. Radiofrequency generator is activated through controller to deliver thermal energy (65 °C) for approximately 10 sec. After that the bronchoscopist collapses the electrode and retracts the catheter by 5 mm to start the next application. Bronchi involved in this procedure are of diameter between 3 mm to 10 mm. Meticulous charting is to be done to avoid the overlapping of the procedure. Each session of BT procedure needed 40-60 activation extending the procedure approximately to 60 minutes.

Due to the risk of adverse outcome caution should be taken in patients with post bronchodilator FEV1 <65%, presence of respiratory diseases like emphysema, upper airway obstruction, cystic fibrosis etc., use of steroid in excess of 10mg/day for asthma, requirement of short acting β_2 agonist puffs >12/day, presence of serious comorbid conditions and pregnancy. Precautions are also required if there is history of intubation and ICU admission within last 24 months for asthma.

The general consensus is that only interventional bronchoscopist with advanced bronchoscopy skills and high bronchoscopy volume should perform BT to ensure the best outcome in the asthmatic patients. Training can be obtained through structured courses with curricular and practical portions. Simulation, via advanced software technology, has been validated as a tool for training and performance measurement for simple bronchoscopic tasks and can be valuable adjunct training tool if developed for advanced procedure as BT¹⁵.

MECHANISM OF BRONCHIAL THERMOPLASTY

Bronchial thermoplasty is the procedure that delivers controlled thermal energy at 65 °C to airway between 3 and 10 mm via bronchoscope under direct visualization. Firstly it reduces the airway smooth muscle mass which is the major characteristic occurring due to remodeling of the severe asthmatic airways. Other possible mechanism which has been postulated includes decreased secretion of inflammatory mediators by ASM cell and changes to the epithelium of airways, the nerve endings or the function of the inflammatory cells that infiltrate the bronchial mucosa¹⁶.

STUDIES OF BRONCHIAL THERMOPLASTY:

Animal Studies: Bronchial Thermoplasty was first tested in Dogs by Darek¹⁷ et al. They applied different temperatures to the lungs of dog divided into treated and untreated area. The animal models were evaluated over 3 years and histological examination was done at weeks 6, 12 and 157. **They noted blanching at the site of the treatment and histology showed the epithelial disruption at treated site. But there was no charring at the treatment site and subsequently re-growth was seen. The only morphological disruption at the treated site was seen in ASM which was replaced by loose connective tissue. All other tissue element remained intact or returns to normal as assessed on histological examination. There was no stricture of the**

airways, generalized fibrosis beyond the boundaries of the ASM resulting from the

treatment. They found that when airways were treated at 65 and 75 °C of radiofrequency, showed significant reduction in response to Methacholine (Mch) as compared to control airways. However, there was no such response in airways treated at 55 °C. They concluded that application of radiofrequency energy to the airways can reduce airway responsiveness to Mch for atleast 3 years in dogs by reduction of airway smooth muscle contractility.

In another animal study Brown¹⁸ et al used Computed tomography to quantify the effect of methacholine on treated and untreated groups. They found that dose response curve to methacholine challenge was shifted upwards at all points, concluding that treated group have significantly larger luminal area as compared to untreated group at all points. In another study by Brown¹⁹ et al also concluded that reducing the amount of functional smooth muscle with bronchial thermoplasty leads to increased airway size in both the relaxed and contracted status over an inflation pressure of normal range. The results of these studies were very promising and led to belief of applying it in humans to control asthma.

Short term Human Studies: Pioneer study done to assess the feasibility and general safety of the bronchial thermoplasty in human airways was done by Miller²⁰ et al. It was the prospective study done in nine patients who were planned to undergo lung resection for lung cancer. In these patients (eight patients) bronchial thermoplasty was performed during routine pre-operative bronchoscopy upto 3 weeks prior to surgery. BT was performed in the lung segments that were planned to be removed. All patients tolerated the procedure well; there was no adverse consequence as a result of treatment. Treated airways were again examined through bronchoscope at the time of resection and thereafter histological examination was done. Airway narrowing observed in two patients examined at 5 days and 13 days after treatment. In none of

the airways scarring was noted. Histological examination showed reduction in ASM mass. This study paved the way for the further studies to be conducted in human's asthmatic airways.

A prospective observational study was performed by Cox²¹ et al. This was the first study of bronchial thermoplasty in patients with mild to moderate asthma. This study had only treatment group and no control group. These patients were evaluated at baseline, 12 weeks, 1 year and 2 year. Numerous adverse effects were noted with the treatment, most of them were mild occurring immediately after the procedure. However all subjects were discharged at the end of the planned 6-h observation period. No subject required post-procedure admission to the hospital. The FEV1 was higher at 12 weeks, 1 year and year than the baseline but was not statistically significant. In addition airway hyper-responsiveness was decreased significantly at the end of 2 years. There was significant improvement in the symptom free period from the baseline. Chest CT was performed which did not show any evidence of bronchiectasis, bronchial wall thickening or other parenchymal changes at the end of 1-2 years. Because of the non-blinded design and lack of sham arm in this study, its finding were considered limited because of possible placebo effect.

The Asthma Intervention Research Trial (AIR)²² was the first multicenteric trial of Bronchial Thermoplasty. It was non blinded randomized trial conducted at 11 centers in 4 countries. The aim of the trial was to evaluate the effectiveness and safety of bronchial thermoplasty in the patients of non-smoker moderate to severe asthma (FEV1 60-85% of predicted and methacholine PC20 < 80mg/ml). Study included the persons of 18 to 65 years of age requiring daily therapy with inhaled corticosteroid equivalent to a dose of 200 microgram or more of beclomethasone and LABA (dose of 100 microgram of salmetrol or equivalent) to maintain

reasonable asthma control and these subjects withdrawal of LABA resulted in a worsening of asthma control. This study enrolled 112 subjects who are divided into two equal groups and were randomly assigned treatment with BT with inhaled corticosteroids plus LABA or to treatment with inhaled LABA plus corticosteroids. Treatment was done in three sessions over 9 weeks after that attempt was made to discontinue their long acting beta agonists at 3, 6 and 9 months after the procedure without exacerbations. Three bronchoscopic procedures were performed in BT group using ALAIR system at a interval of approximately 3 weeks. These patients were monitored for one year and various parameters were analyzed in the studies included frequency of mild and severe exacerbations, peak expiratory flow rate, use of rescue medication, spirometry, methacholine challenge results, adverse effect, degree of asthma control and corresponding health related quality of life score. Patients treated with BT showed 407 adverse events as compared compared to 106 adverse events in the control group. Most of these events occurred within 1 day of treatment and resolved within 7 after the onset of the event. BT treated cases showed more hospitalization as compared to control group as compared to two hospitalizations in the control group. In the BT treated patients four subjects required six hospitalization for asthma, one for left lower lobe collapse and one for pleurisy. Subjects treated with BT as compared to subjects not receiving treatment showed 10 fewer asthma attack (mild exacerbation) per year and they needed 400 fewer puff of their rescue medication (two less canister). BT treated subjects showed 86 more days completely free of symptoms and showed significant improvement in asthma control and quality of life. There was significantly more improvement in morning peak flow at 3,6, and 12 months from baselines in treatment group than in control group. Post hoc analysis showed patients requiring more beclomethasone (>1000 microgram) obtained greater benefit as compare to other studied population in the AIR trial.

The RISA (Research in Severe Asthma)²³, a multicenteric trial was conducted in eight centers worldwide to evaluate the BT treatment in symptomatic severe asthma patients. Thirty two subjects of 18-65 years of age group included in the study were symptomatic despite treatment with high dose asthma controller medication i.e. >750mg/day of inhaled fluticasone or equivalent, >100 µg/day of salmetrol or equivalent of LABA (Long Acting β2 Agonist) and could also be taking upto 30 mg/day of oral prednisolone along with other controller medications. Out of 32 patients, 15 asthmatics were subjected to bronchial thermoplasty along with standard medications and rest of the 17 patients received usual care. BT group patients underwent three procedures at least 3 weeks apart. After treatment subjects entered a 16 weeks steroids stable phase (weeks 6-12), a 14 week steroid wean phase (week 22-36) and a 16 week reduced steroid phase (week 36-52). During the treatment period BT group had more adverse events as compared to control group. BT group patients had seven hospitalizations in four patients while there was no hospitalization in the control group. Five of seven hospitalizations in the BT group were for exacerbations of asthma and two for partial collapse of a left lower lobe of the lung. There was no significant difference in the adverse event between groups. Treated subjects had clinically and statistically significant improvements over baseline in rescue medication use, prebronchodilator FEV1% predicted, and AQLQ (*Asthma Quality of Life Questionnaire*) and ACQ (*Asthma Control Questionnaire*) scores in the stable steroid (6-22) phase of this study. Persistent improvement in the asthma symptoms and decrease in use of rescue medication were seen in BT group upto 1 year.

The AIR-2 trial¹⁴ was randomized, double blind, sham controlled clinical trial conducted in six countries. All the eligible subjects were adults (18–65 years of age) diagnosed with asthma

who required regular maintenance medications of inhaled corticosteroids (ICS >1,000 µg/d beclomethasone or equivalent) and a long-acting β₂-agonist (LABA ≥100 µg/d salmeterol or equivalent) however medications were also allowed, including leukotriene modifiers, omalizumab (if used for at least 1 year prior), and oral corticosteroids (OCS) 10 mg/d or less.

All randomized subjects were scheduled to undergo three bronchoscopy procedures performed 3 weeks apart. The BT and the sham bronchoscopy were performed by a group of team who were not present at the clinical evaluation of the subjects and the clinical evaluations were performed by another group of researchers. BT was performed by delivering radiofrequency (RF) energy to the airway using the Alair Bronchial Thermoplasty System (Asthmatx Inc., Sunnyvale, CA).

Control group subjects in this study underwent three sham bronchoscopy procedures, each separated by at least 3 weeks. The sham bronchoscopy procedures involved necessary medication for conscious sedation and bronchoscopy that mimicked the BT treatment. No RF frequency was delivered when the Alair catheter was deployed into the airways through the bronchoscope. The sham RF controller produced audio and visual signals that were indistinguishable from the active RF controller. Five hundred and eighty subjects were screened for this study, of these 297 were randomized to the BT group (196 subjects) or the sham control group (101 subjects). Primary outcome in this study showed significantly higher AQLQ score at 6,9, and 12 months than at the baseline and showed significantly higher scores in comparison to sham group. Secondary endpoint measures of morning PEF, symptom-free days, symptom score, ACQ, and rescue medication use showed an improvement over baseline in the BT and sham groups, although the differences between the groups were not statistically significant. The thermoplasty group showed significantly fewer exacerbations and emergency visit and in the

post treatment period as compared to the sham treatment group. There were more adverse events in BT group as compared to sham group during the treatment period.

Long Term Study Human Studies:

Pavord et al²⁴ followed the subjects of RISA trial for 5 years and they found rate of adverse events per year as 1.4, 2.4, 1.7, and 2.4 respectively in year 2 to 5 years after BT. Subjects treated with BT also showed reduction in emergency room visit for respiratory symptoms in 1 to 5 years as compared to year before BT. There was no deterioration in lung function for 5 years after BT making the conclusion that it is safe for 5 years in severe asthma patients. In another follow up study forty five of 52 treated and 24 of 49 control group subjects participated in AIR1 Trial were selected for long-term follow-up of 5 years and 3 years respectively²⁵. The rate of respiratory adverse events in the BT group (AEs/subject) remained stable in years 2 to 5 following BT. The Control group data was collected for 2 and 3 years showed non-significant difference in respiratory events as compared to BT group. The absence of complications in the long term follows up also make the BT safer in asthmatics.

Long term follow up of AIR2 trial was conducted for 2 years which showed proportion of subjects experiencing severe exacerbation was 23% as compared to 30.9% in year one²⁶.

Wechsler²⁷ et al studied the BT treated subjects from AIR2 trial annually for 5 years to assess the long term safety of BT and its durability of its treatment effect. They assessed the outcomes after BT by measuring severe exacerbations, adverse events, health care use, spirometric data and high resolution computed tomography scans. Only 162 patients of 190 BT treated subjects from the AIR2 trial completed 5 years of follow up. Result showed reduction in severe exacerbation and emergency department visits in each of the year 1 to 5 as compared to those observed in 12 months before BT treatment. There was no change in respiratory adverse events and respiratory

related hospitalization in the years 2 through 5 compared with the first year after BT. Spirometric variable remains stable in terms of FEV1 between years 1 and 5 after BT, despite reduction in average daily inhaled corticosteroids dose. No structural abnormalities were noted in lung from baseline to 5 years after BT. Study finally concluded that BT is an effective and safe therapy in the long run also.

Conclusion:

Bronchial thermoplasty is the radiofrequency ablation of airway smooth muscle with the help of flexible bronchoscope. It is the new therapeutic option which has to be used with pharmacologic options in the treatment of uncontrolled severe asthma. Bronchial thermoplasty has showed significant improvement in the quality of life, decrease in emergency room visit and exacerbation along with decrease in steroid use. This improvement is not short term but it is also seen to be long term. However the future studies are needed to know the post BT histological alteration in asthmatic airways by using endobronchial biopsies. There is also need to know the asthmatics phenotypes that get maximum benefits from BT as no uniform improvement has been seen among asthmatics. Though thermoplasty treated patients has showed great number of adverse effect in the form of worsening of upper respiratory symptoms (cough, wheezing, and chest tightness) and infection of the upper respiratory tract, majority of them used to be mild and transitory occurring during the first week. They usually need conventional medications for treatment.

It is the high cost of procedure which has raised the eyebrow over the procedure. Despite the increase in direct cost of BT, the treatment of asthmatics with either BT or omalizumab in addition to standard care may not help the clinicians to meet the need of a greater number of

patients, but also decreases the emergency room visits and hospitalization and make savings in the long run²⁸.

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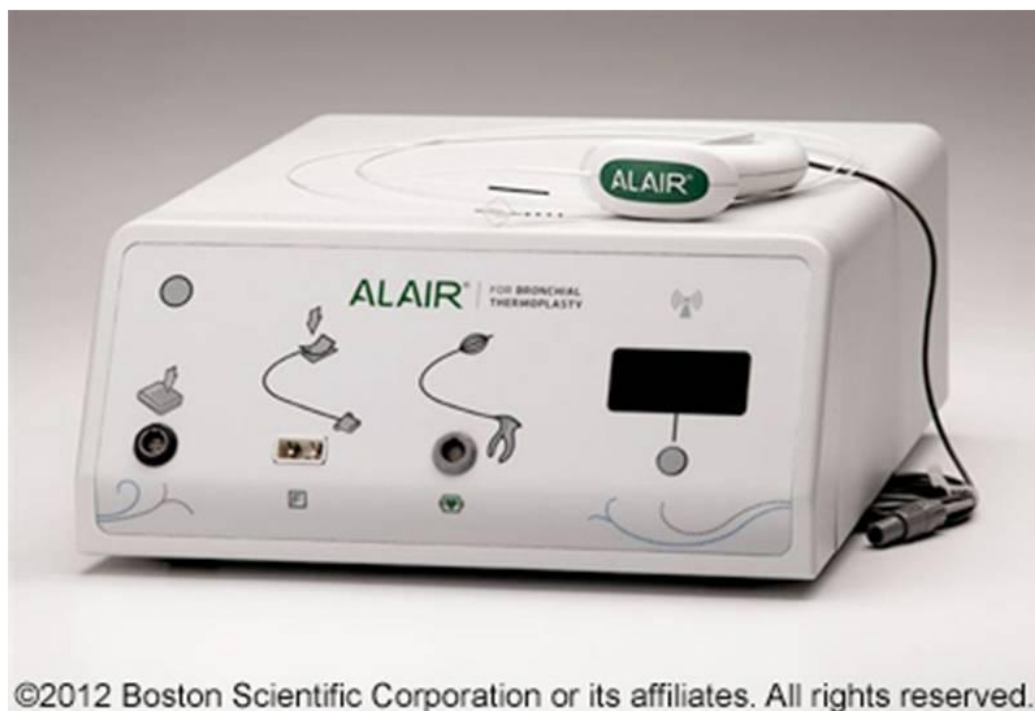


Fig 1: Alair Radiofrequency Generator with catheter.

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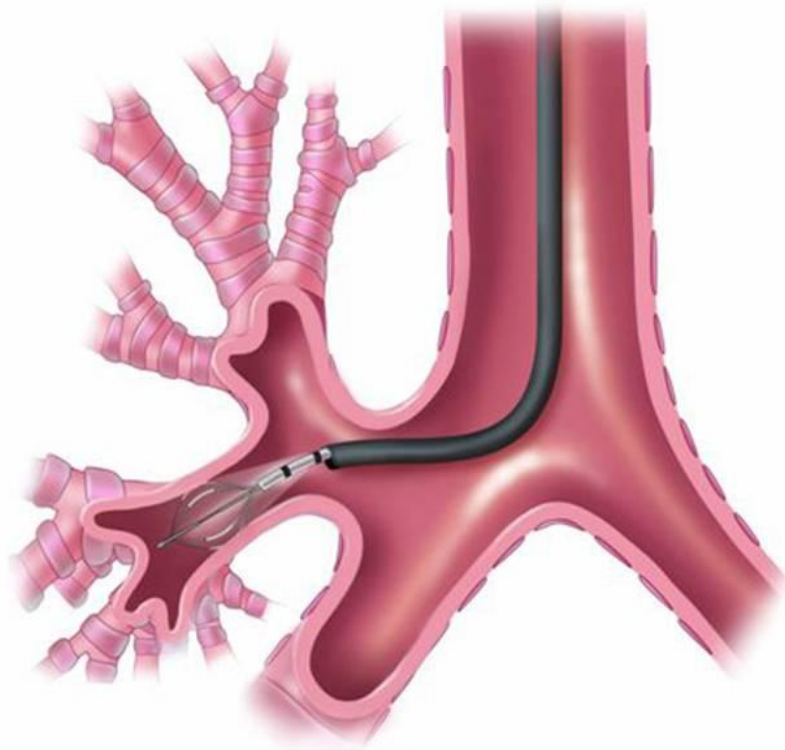


Fig. 2: Alair Bronchial Thermoplasty Catheter

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Fig 3: Alair Catheter in Airway

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