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Bronchial Thermoplasty

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Perspective

Bronchial thermoplasty

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Asthma is a chronic inflammatory disease that affects 300 million people worldwide. Its prevalence ranges from 1% to 18% of the population in different countries.[1] The World Health Organization has estimated that 15 million disability-adjusted life years are lost annually due to asthma. Worldwide deaths from asthma are estimated at 250 000 per year. Furthermore, asthma is a major cause of absence from work in many countries, including United States.[2]

The prevalence of asthma has increased over the last ten years around the world. One of the suggested explanations to this increment is the western lifestyle hypothesis in countries that are going through a transition from a more traditional to a more modern lifestyle, as has been described in China.[3] The prevalence of asthma in China is 2.1%,[4] which results in an addition of 20 million asthmatics. Prevalence varies from region to region in China, for example, in Jinan it is reported as 1.1%, which is less than most western countries; however, asthma control is below the goals established by the Global Initiative for Asthma.[5] The case fatality in China reported by GINA is 36.7/100 000.

The management of patients with asthma can be challenging since patient population is diverse when it comes to phenotypes and endotypes.[6,7] Furthermore, the overlapping of asthma with other obstructive pulmonary diseases makes it difficult for targeted therapy. The cornerstone in the management includes the use of inhaled corticosteroids, to keep asthma under clinical control. Although, different populations, like Chinese, might have a better response to one steroid compared to another.[8] Other commonly used medications include anti-leukotrienes, anti-immunoglobulin E and methylxanthines. Further therapies have been tried to target different steps in the inflammatory cascade seen in asthma.[9,10] Recently, studies in the management of airway smooth muscle (ASM) have demonstrated that this can be an excellent target to control asthma. Bronchial thermoplasty is one of the most recent therapies that targets airway smooth muscle.

AIRWAY SMOOTH MUSCLE

There has been major progress in the field of ASM biology over the last few years. ASM has been identified to play a significant role in the pathogenesis of obstructive airways diseases.[11] Further research is underway evaluating immunomodulation and airway remodeling of ASM.[12]

Alterations in the excitation-contraction coupling within the myocytes of ASM has been demonstrated in patients with asthma compared to normal subjects.[13] This may promote airway hyperresponsiveness in asthma and other obstructive diseases. Furthermore, *in vitro* studies have shown that ASM secrete chemokines such as CXCL10 and fractalkine, as well as cytokines that are important in the autocrine loop, perpetuating airway inflammation and angiogenesis, that contribute to an already complex immunomodulatory role.[14] Multiple studies have identified an increase in the ASM mass in patients with asthma. This occurred by either hypertrophy and/or hyperplasia of myocytes.[15,16] These changes also contribute to hyperresponsiveness and bronchoconstriction of airways.

BRONCHIAL THERMOPLASTY

Bronchial thermoplasty (BT) is a new approach for the management of severe asthma that specifically targets ASM to reduce its mass in order to control airway hyperresponsiveness; effect that is seen even by high resolution computed tomography.[17] This is accomplished by bronchoscopic delivered radiofrequency ablation to the airway walls.[18] The actin-myosin interaction chain is disrupted by the high temperatures generated by the high frequency alternating current. Through denaturation of the motor proteins, disruption of the ASM spasm cascade is accomplished.[19,20] In previous studies, BT has already shown to have long term effects with the reduction of ASM mass in healthy dogs and humans.[21,22]

Other contributing mechanisms of bronchial thermoplasty include modification of the extracellular matrix (leading to fixation of the airway structure) and reduction in mucous gland hyperplasia.[23] BT also leads to ablation of

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"pacemakers" found in large and medium-size airways. The additive effects of decreased hyperreactivity is reflected in the reduction of downstream modulatory effect in small and medium-size airways, which have been hypothesized to contribute in the pathophysiology of asthma.[24,25]

BRONCHIAL THERMOPLASTY: TECHNIQUE

BT is performed via fiberoptic bronchoscopy, with the patient under moderate sedation in an outpatient setting. It requires three separate bronchoscopic procedures (at two to three weeks intervals), in which all the visualized airways distal to the mainstem bronchi (down to three mm) are treated, with the exception of the right middle lobe. The first two sessions are dedicated to treat each lower lobe separately, and the third session targets both upper lobes.

The thermal energy utilized in BT is delivered via the Alair system (Boston Scientific, Natick, MA, USA), which consists of a radiofrequency (RF) electrical generator (controller) and a single-use, long, flexible catheter with an expandable electrode array attached at one end and a deployment handle at the other (Figures 1 and 2). The electrode array expands to contact the airway walls and then activated to deliver RF energy for ten seconds each time (Figure 3). If improper contact occurs between the array and the airway walls the system signals the operator. As AF energy is oscillatory electrical current, the patient is connected to the Alair controller through an electrode to create a closed circuit. A flexible bronchoscope with a 2.0 mm working channel is required for the procedure. As in any airway procedure with the transfer of energy, oxygen supplementation to the patient should be reduced to less than 40% fraction of inspired oxygen to minimize the risk of ignition during activation. The number of activations required per procedure varies due to anatomical differences in patients as well as operator experience with 40 to 110 activations occurring per lobe.

Contraindications to BT include presence of an implantable electronic device, hypersensitivity to the drugs used during the bronchoscopy, and severe comorbidities that increase the risk of adverse events (Table 1). The previous studies performed with BT did not include patients who had three or more hospitalizations for asthma, three or more lower respiratory tract infections, and four or more episodes of oral corticosteroids use for asthma exacerbations in the previous year.[26-28] Patients undergoing BT should be treated with a 5-day course of prednisone (50 mg/d), beginning two days before the procedure. This has been found to decrease the airway inflammation caused by BT and the subsequent minor post procedure morbidities.

BRONCHIAL THERMOPLASTY: SAFETY AND EFFICACY

After multiple studies in canines with the use of BT demonstrating reduction in the airway responsiveness to local methacholine provocation,[21,29] and persistent histologic reduction in the ASM mass,[21] the first feasibility study in human airways was performed by Miller et al[22] in eight non-asthmatic patients who underwent lobectomy for lung cancer. This study showed a reduction in 50% of the ASM mass of the treated airways, with no adverse effects.

Cox et al[30] found a significant reduction in airway hyperresponsiveness (for up to two years) in sixteen patients with mild to moderate asthma who underwent BT. Adverse events included airway inflammation that required a temporary increase in asthma medications.

Since these studies, three randomized, controlled trials have been performed with the use of BT: the Asthma Intervention Research (AIR) study, Research in Severe Asthma (RISA) study, and the AIR2 trial.[26-28] The AIR trial[26] randomized 112 patients with moderate to severe asthma to BT and control. At twelve months, there were significant improvements in the morning peak expiratory flow, scores on the Asthma Quality of Life Questionnaire (AQLQ), and Asthma Control Questionnaire (ACQ) in the BT group compared to control. However, there was no significant difference in airway responsiveness and forced expiratory volume in 1 second (FEV_1) between both groups. Adverse effects were more common in the BT group during the first six weeks after the treatment, which included dyspnea, wheezing, cough, and night awakenings; however,

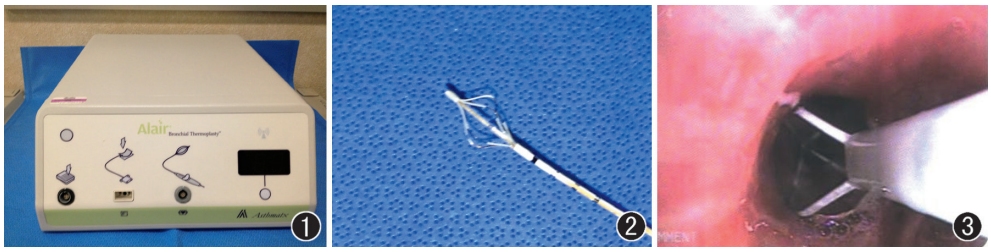

Figure 1. Asthmatx AF Controller (Alair System).
Figure 2. Bronchial thermoplasty catheter with electrodes in open position.
Figure 3. Alair catheter opened in airway with electrodes approximating the airway wall.

Table 1. Indications and contraindications of bronchial thermoplasty

Indications	Contraindications
Adults with severe persistent asthma[41] defined by:	Presence of implanted electronic device
Daily symptoms	Hypersensitivity to the drugs used during bronchoscopy
Nightime symptoms more than 7 days per week	Severe medical conditions that will increase the risk of adverse events during bronchoscopy
Use of short-acting beta 2-agonists several times per day to relieve symptoms	
FEV1 <60% predicted; FEV1/FVC reduced >5%	

there was no significant difference in the treatment and control groups during the period of six weeks and twelve m onths post treatment.

In 2007, the RISA trial[27] enrolled 32 patients with refractory severe asthma who were on high doses of inhaled steroids and oral prednisone. The BT group again demonstrated a significant reduction in the use of rescue medication as well as improvement in AQLQ and ACQ compared to control up to 1 year. It was also possible to reduce the dose of oral steroids in the bronchial thermoplasty group, although this was not statistically significant. The bronchial thermoplasty treated group had post-procedure morbidities, which included seven hospitalizations due to worsening asthma (four patients) and lobar collapse (two patients) that required bronchoscopy for suctioning of secretions. In order to minimize the subjective effect over the improvement of the AQLQ (primary outcome in the AIR2), the AIR2 trial was performed.[28] This was a randomized, double-blind, sham-controlled study of 288 subjects with severe persistent asthma (defined by the Severe Asthma Working Group[31]) on high-dose of inhaled corticosteroids. However, patients with FEV_1 post-bronchodilator of less than 65% were excluded, as well as patients with four or more asthma exacerbations requiring systemic steroids, or three or more upper respiratory infections in the previous year. Excluding these criteria changes the definition of severe asthma.

The AIR2 trial did show a significant difference in improvement of AQLQ in the BT group compared to the sham group. There was also a significant improvement of AQLQ in the sham group, which was unexpected and persisted during the initial twelve months of follow-up. The treated group had a significant reduction in severe exacerbations (32% reduction vs. sham), unscheduled office visits (23% reduction vs. sham), emergency department visits (84% reduction vs. sham), hospitalizations (73% reduction vs. sham), as well as a statistical reduction in days missed from work or school in the BT group for the fifty-two weeks follow-up post-treatment. Short-term adverse effects related to BT in this study included airway inflammation and upper respiratory infections, which were similar to previous BT studies.

There are several studies providing data regarding long-term effects of BT. Thomson et al[32] found an absence of clinical complications (respiratory events, hospitalizations and emergency department visits) over a period of five years post BT in forty-five patients treated in the AIR trial. Despite the improved clinical condition of patients, there was no change in the lung capacity over the same period of time. Castro et al[33] followed the BT-group patients from the AIR2 trial for two years and found the same rate of respiratory events compared to the first year post treatment, however no comparison with patients with the sham-group occurred. The AIR2 study's five years follow-up is currently closing worldwide, with long-term data hopefully available in 2014.

The United States Federal Drug Administration (FDA) approved the use of BT in 2010 for the treatment of severe persistent asthma in patients 18 years and older (Table 1), with different centers already reporting their favorable experiences,[34,35] as well as developing histological grading systems[36] that can be used in the future. However, the routine use of this therapy has not been spreading as quickly as it is still recognized by most medical insurance companies in the United States as experimental and is therefore not paid for. Besides, further questions will need to be answered before this technique continues to spread worldwide,[37] like the long-term effects and the specific population that BT can have a significant impact on,[38,39] knowing that failure can also happen.[40]

CONCLUSIONS

Given the high prevalence of asthma worldwide, as well as its social and economical impact, further investigations regarding new therapies for asthma are needed. BT is a novel therapy that targets ASM in an attempt to reduce its mass and decrease hyperresponsiveness of the airways. BT consists of applying radiofrequency ablation, through flexible bronchoscopy, to the ASM. Multiple blinded controlled randomized studies have demonstrated the effectiveness and safety of bronchial thermoplasty. BT is a complex bronchoscopic procedure. To maximize safety and effectiveness, the procedure should be performed at centers with experience in complex airways procedures. Further studies assessing long-term effects of BT and in which subgroups therapy will have the most impact are still pending or needed.

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