

Bronchial thermoplasty in severe asthma: food for thoughts

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Asthma is a complex inflammatory disorder of the airways characterized by airway hyper-responsiveness and variable, reversible, airflow obstruction. Bronchial thermoplasty (BT) is a new modality for treating asthma. It targets airway smooth muscles (ASM) by delivering a controlled specific amount of thermal energy (radiofrequency ablation) to the airway wall through a dedicated catheter. The use of bronchial thermoplasty has been widely discussed for its potential in the treatment of asthma, since it seems to be able to reduce the symptoms of asthma. The definitive study for BT (AIR2 trial) employed a randomized, double-blind, sham-controlled design and enrolled 288 subjects with severe persistent asthma from 30 US and international centers. The results of the AIR2 trial demonstrated clinically significant benefits of BT compared with the sham group at one year post-treatment, including an improvement in asthma-related quality of life, 32% reduction in severe exacerbations, 84% reduction in emergency department visits for asthma symptoms, and a 66% reduction in time lost from work/school/other daily activities because of asthma symptoms. Pre-clinical work showed that ASM is reduced after BT by at least 3 years after treatment. The recent article from the AIR2 trial study group analyses the long-term safety and effectiveness of BT in patients with severe persistent asthma and demonstrates the 5-year durability of the benefits of BT in the control of symptoms and safety. It supports the

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evidence that reduction in asthma attacks, ER visits, and hospitalizations for respiratory symptoms are maintained for at least 5 years. There is a pressing need to understand the underlying mechanism(s) of BT and how the delivered heat is translated into clinical benefit. This necessitates additional investigation to identify disease and patient characteristics that would enable accurate phenotyping of positive responders to avoid unnecessary procedures and risks.

KEY WORDS: Bronchial diseases, therapy - Asthma - Inflammation.

Asthma is a complex chronic inflammatory disorder of the airways characterized by airway hyper-responsiveness (AHR) and variable airflow obstruction. Although advances in clinical and basic research over the past 30 years have led to the development of effective treatments and disease

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management guidelines^{1, 2} difficult-to-treat asthma continues to affect 5% to 10% of adults.³ Despite extensive therapies, in fact, patients with difficult-to-treat asthma continue to experience repeated symptoms, including potentially life-threatening exacerbations⁴ accounting for a disproportionately high share of asthma-associated morbidity and mortality.

In recent years, a novel non-pharmacological approach to severe asthma has been proposed, which has raised curiosity, interest and even excitement. Bronchial thermoplasty (BT) has indeed the potential to revolution the traditional treatment for asthma. The most recent document from an ERS/ATS task force published very recently⁵ includes, for the first time, BT among the possible treatments for severe asthma. BT is by no doubts a new modality for treating asthma, not just technically but also conceptually. It is appropriate for adult patients with severe persistent asthma that is not controlled with maximal medical treatment. It targets ASM by delivering a controlled specific amount of thermal energy (radiofrequency ablation) to the airway wall through a dedicated catheter. While BT shows great promise in reducing the symptoms of an asthma attack, we should never forget that it cannot be regarded as a cure for the disease. In this respect, BT cannot be envisaged as a substitute for medical adherence or a life style choice of refusing medicinal treatment. BT should be considered as the ultimate choice in asthmatic patients in whom all potential treatments (including anticorpal agents) have failed.

In this review article, we review the findings of the paper from Wechsler et al.,⁶ who provide evidence of long-term safety and effectiveness of BT in severe asthmatic patients 5 years after treatment.

All of the conducting airways down to the level of the respiratory bronchioles are lined with smooth muscles, the mass of which increases in asthma due to hyperplasia and hypertrophy.^{7, 8} An increase in the amount of ASM typically occurs in the lungs of patients with asthma. This increased ASM mass has the potential to increase the ma-

gnitude of airway responsiveness and constriction in response to external stimuli. The excessive and inappropriate constriction of ASM is recognized as a predominant feature of asthma, and therefore makes the ASM a key target for drug therapy. Although current medications are reasonably successful in controlling inflammation and contraction of ASM in the majority of patients with asthma, some patients with severe persistent asthma continue to suffer from excessive bronchoconstriction. In this respect, reduction of ASM theoretically helps to reduce the ability of the airways to narrow in response to a trigger, thereby providing a therapeutic benefit for patients with severe asthma.

It has been proposed that some organs in the human body, such as the appendix, most body hair, wisdom teeth and external ear muscles appear to lack any known function, perhaps even causing medical problems. In this perspective, ASM has been mentioned among this category, that is, an organ with no essential physiologic function that can lead to serious medical problems. Although fascinating, this hypothesis raises doubts and controversies. The function of smooth muscle in the airway wall has been speculated on for many years, with no convincing and definite conclusions. In an interesting debate on this topic, Seow and Fredberg⁹ commented that there is no known disease entity or physiologic deficit associated with loss of ASM. They further suggested that perhaps ASM was a vestigial remnant of its common embryologic origin with the gastrointestinal system, having no modern function. Theoretically, ASM contraction should protect the lung parenchyma from inhalation of potentially dangerous particles that can accidentally penetrate in the bronchial tree. In his extensive review article,¹⁰ Macklin could not imagine that such a system was there for no physiologic purpose, stating that "Organized as it is, into a very complex system, this muscle would seem of the utmost functional importance—in fact quite indispensable in respiration." Mitzner¹¹ examined ten possible roles of ASM and made clear that none of those potential functions is essential to normal lung

physiology. If this is true, then ASM should be treated in the same way an inflamed appendix is treated. In this scenario, airway inflammation would of course still be present, but would lose the ability to translate inflammatory signals into ASM contraction, thus minimizing the occurrence of asthmatic symptoms.

Recent observations in asthma suggest that bronchial smooth muscle is infiltrated by inflammatory cells including mast cells. Such an infiltration may contribute to airway remodelling that is partly due to an increase in smooth muscle mass. Whether muscle increase is the result of smooth muscle cell hypertrophy remains controversial and has not been studied by ultrastructural analysis. A specific role is played by stem cell factor (SCF), produced by ASM¹² which exerts its biological activities via interaction with c-kit, its cognate receptor present on human mast cells and induces histamine release from these cells.¹³ In asthma, airway myositis is characterized by a direct interaction between ASM cells and mast cells and lymphocytes. Smooth muscle remodelling is present, including cell hypertrophy and abnormal extracellular matrix deposition moulding.¹⁴

BT is performed via fiberoptic bronchoscopy in 3 separate procedures in which all accessible airways located beyond the mainstem bronchi (an average of 3-10 mm in diameter) with the exception of the right middle lobe are treated. The delivery of energy during bronchial thermoplasty uses continuous feedback to tightly control the degree and time of tissue heating to decrease ASM mass without airway perforation or stenosis.

With regard to patient selection, candidates for BT are adults with severe persistent asthma who require regular maintenance medications of inhaled corticosteroids (>1000 µg/day beclomethasone or equivalent) and a long-acting beta agonist (≥100 µg/day salmeterol or equivalent). These patients would have received add-on therapies such as leukotriene modifiers, omalizumab, and oral corticosteroids 10 mg/day or less. These patients should be on stable

maintenance asthma medications according to accepted guidelines,¹⁵ they need to have a prebronchodilator FEV₁ of 60% or more of predicted, and have a stable asthma status (FEV₁ within 10% of the best value, no current respiratory tract infection, and no severe asthma exacerbation within the preceding 4 weeks).

Early work in BT tested its mechanism of action and effect in a canine model. Danek et al. applied bronchial thermoplasty on the airways of 11 healthy dogs and found persistent and significant reduction in treated airway responsiveness to local methacholine (MCh) provocation.¹⁶ More importantly, these investigators performed necropsy and histological examination of the untreated and treated airways at various time points, up to 3 years, and found persistent ASM reduction in the treated airways with no evidence of regeneration. The thermal injury was limited to the bronchial wall and the immediate peribronchial region, and the extent of ASM reduction correlated with the improvement in airway hyper-responsiveness.

The first feasibility and short-term safety study on human airways was performed in 2005 in eight patients without asthma scheduled for surgical resection for proven or suspected lung cancer. Subjects underwent BT to the lobe to be removed 2 to 3 weeks before surgery. The treated airways were re-examined at the time of surgery and exhibited mild erythema, edema, or blanching within 2 weeks of the treatment. Histological examinations of resected airways showed an average of 50% reduction in the smooth muscle mass of the treated airways compared with non-treated airways. None of the patients experienced adverse events or change in medical care. This study paved the way to clinical studies in patients with asthma.

The first study evaluating BT in asthma enrolled 16 patients with stable mild to moderate asthma and found a significant reduction in airway hyperresponsiveness for up to 2 years after the procedure but no change in lung function. Short-term adverse events were common but were mainly mild and consisted of airway inflammation

that either resolved spontaneously or required a temporary increase in asthma medications. Chest computed tomography performed 1 and 2 years after the procedure did not show evidence of bronchiectasis, bronchial wall thickening, or other parenchymal changes. BT was then studied in a randomized, controlled, multicenter trial that enrolled 112 patients with moderate to severe persistent asthma.¹⁷ There was an improvement in asthma symptoms but no reduction in airway hyperresponsiveness or change in FEV₁. Again, the major adverse event was mild airway inflammation in the post-procedure period; however, subjects who underwent BT in this study had a higher hospitalization rate. Given the non-blinded design and lack of a sham arm in this study, its findings were limited because of a possible placebo effect.

In 2007, a small randomized study enrolled 32 patients with severe symptomatic asthma (refractory asthma) in an attempt to establish the safety of BT in this population.¹⁸ Patients were receiving higher doses of inhaled corticosteroids and oral prednisone than in previous studies. Seven hospitalizations due to worsening asthma symptoms occurred, during the treatment period, in 4 of 15 BT subjects. Lobar collapse occurred in two subjects, with one requiring bronchoscopic aspiration of mucous plugs. Persistent improvement in asthma symptoms and decrease in rescue medication use were seen in the BT group up to the 1-year follow-up period of the study.

The definitive study for BT employed a randomized, double-blind, sham-controlled design and enrolled 288 subjects with severe persistent asthma from 30 US and international centers.¹⁹ The study maintained a double-blind design by having an unblinded bronchoscopy team that performed the procedure and a blinded assessment team that measured blinded patients' responses in the post-treatment period. Overall, there was a statistically significant improvement in the quality of life from baseline values in the BT group compared with the sham group. The most impressive findings of this study were in terms of secondary outcomes,

in which BT subjects experienced a significant reduction in severe exacerbations, emergency department visits, and days missed from work or school in the post-treatment period. The short-term adverse events were similar to other trials and included airway inflammation and upper respiratory infections. A higher hospitalization rate post-BT was noted, as well as rare events of lower respiratory infection, segmental or lobar collapse, and one episode of massive hemoptysis (the latter requiring bronchial artery embolization).

In April 2010, the US Federal Drug Administration (FDA) approved BT for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting β -agonists. The FDA has required additional post-approval studies to include a continuation of the AIR2 trial with longitudinal data on the durability of effectiveness of BT at 5 years and a new prospective open-label, single-arm, multicenter study in the United States to demonstrate durability of treatment effect and safety out to 5 years from treatment.²⁰ The long-term safety of BT beyond one year has been evaluated in each of the BT clinical trials in patients with asthma. Long-term follow-up data are available at 5 years from the Feasibility Study,²¹ at 5 years from the AIR Extension Study,²² at 5 years from the RISA Extension Study,²³ and at 2 years in the AIR2 Trial.²⁴ In all, including the 2-year follow-up from the AIR2 trial, more than 700 years of follow-up data have been accumulated. Each of these longer term studies shows consistency over time in the safety profile for the BT treated patients during post-treatment follow-up in the percent of subjects reporting respiratory adverse events, the number of respiratory adverse events per subject, and the number of hospitalizations and emergency room visits due to respiratory symptoms per subject. Furthermore, lung function has remained stable, with no deterioration in FEV₁ over time and CT scans at 5 years in the Feasibility Study confirmed no negative long-term effects related to the procedure. Thus the long-term safety and

maintenance of asthma control of BT has been established.

The results of the AIR2 trial demonstrated clinically significant benefits of BT compared with the sham group at one year post-treatment, including an improvement in asthma-related quality of life, 32% reduction in severe exacerbations, 84% reduction in emergency department visits for asthma symptoms, and a 66% reduction in time lost from work/school/other daily activities because of asthma symptoms.

The current paper supports the evidence that reduction in asthma attacks, ER visits, and hospitalizations for respiratory symptoms are maintained to at least 5 years. These benefits were observed during clinical studies where patients continued to take their standard maintenance asthma medications which included combinations of inhaled corticosteroids and long-acting bronchodilators. The persistence of BT's effectiveness at 5 years suggests that BT has a disease-modifying effect, although this has not been confirmed by histology. The clinically meaningful improvements, combined with the consistent and stable long-term safety, confirm BT as an important new treatment option for patients with severe asthma whose condition is poorly controlled despite using high-dose inhaled corticosteroids and long-acting bronchodilators.

In last decades the role of pulmonologist has changed, from treatment of tuberculosis and other infectious diseases to intensive care skills, through rehabilitation and endoscopy, towards surgical competences. In fact, many diseases need a multidisciplinary approach with specific knowledge and expertise. Obstructive lung diseases have now many therapeutical opportunities, other than pharmacological. For example, end stage COPD is one of the main indications for lung transplantation, although a period of 20 years was needed to correctly define the patient's selection.^{25, 26}

With respect to lung volume reduction surgery, a period of 15 years occurred before the identification of the correct phenotype to undergo thoracic surgery, that is, the upper lobe highly heterogeneous

emphysema.^{18, 27} More recently, in the field of fibrobronchoscopic positioning of endobronchial valves multicentric studies have arisen faster with the first clear definition of patients: heterogeneous emphysema without collateral ventilation to be defined by HRCT study on fissures or flow detection instruments.²⁸⁻³⁰ Other endobronchial devices (coils, glues and vapor) are now under multicentric investigation studies.

Now we are witnesses of an intriguing challenge: the attempt to manage an inflammatory disease by fiberoptic thermal approach. The new question that calls for an answer, much more important than just following a guideline is whether an interventional approach to large airways is appropriate in an ubiquitous chronic inflammatory bronchial disease.

The effect of BT could be attributed to the theory that "pacemakers" within the proximal airways control ASM contractility and that BT ablates these controlling centers, leading to the distal effect.³¹ Such procedures would obviously not involve surgical excision but may possibly involve pharmacologically targeting ASM with a directed toxin, genetically impairing the contractile apparatus of ASM, or by a physicochemical disruption of the airway wall. Future therapies directed to this goal may provide alternative and effective treatments for asthma.

Subjects with severe asthma that were randomized to the sham-control group in the AIR2 Trial exited from the study at 1 year post-BT, because requiring these subjects to refrain from exploring alternative treatment options for their condition for an additional 4 years was deemed unethical. Therefore, findings are limited by lack of a comparator sham-controlled group beyond year 1. However, the use of a non-inferiority model designed to show that one group is no less different at a given time than a certain amount from the same group at a different time allows for the comparisons of the outcomes of the BT group at year 1 with outcomes in subsequent years.

Although studies have shown that the inflammation in the small airways is a prominent contributor to the pathophysiology of

asthma,³¹⁻³³ significant airflow obstruction and resistance occurs in the first 8 generations of the airway, indicating that the larger airways are greatly involved in the disease process of asthma.³⁴ The difference in the primary outcomes of the study fell below the clinically meaningful change in AQLQ score of 0.5 or greater. In addition, the improvement in AQLQ score in the sham group was greater than expected, possibly due to the placebo effect of bronchoscopy by itself, the enthusiasm for a new technology on the part of enrolled subjects, or simply because of the better medical care that patients usually receive during the course of a clinical trial. Thus, diminished efficacy of the intervention was appreciated when the placebo arm became more invasive. There was no difference between the two groups in morning peak flow, rescue medication use, or FEV₁. Data on the long-term safety of BT are evolving. The first report combined data from the first three human trials mentioned previously and demonstrated clinical, functional, and radiographic stability over a 3-year period after BT; the second report monitored 45 of the 52 BT subjects enrolled in the AIR Trial and found no increase in the rate of clinical complications or reduction in FEV₁ over a 5-year period post-BT. The persistence of effectiveness of BT at 2 years post-treatment has been documented in the AIR2 extension trial: 92% of patients in the intervention group in the AIR2 Trial were evaluated during the second year after BT and found to have the same rate of respiratory events in year 2 as in year 1. This follow-up study did not compare outcomes in the sham group, which is necessary to make an accurate assessment of sustained improvement of this intervention. There are also studies in progress in which airway biopsy is performed to directly evaluate the airway structural changes associated with thermoplasty.

There is a pressing need to understand the underlying mechanism(s) of BT and how the delivered heat is translated into clinical benefit. Ongoing and future studies should attempt to obtain endobronchial biopsies from treated areas with close examination

of alterations in anatomical structures and inflammatory markers. Prior histological data of BT effects on the airways had come from animal models or subjects who did not carry the diagnosis of asthma.³⁵ Finally, clinical trials on BT demonstrated that a favorable clinical response was not uniform among patients with asthma. This necessitates additional investigation to identify disease and patient characteristics that would enable accurate phenotyping of positive responders to avoid unnecessary procedures and risks.

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