



Bronchial thermoplasty for severe asthma

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Purpose of review

Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways to reduce airway smooth muscle mass, has been recently introduced for the treatment of severe asthma. This review summarizes the preclinical development, efficacy and adverse effects of bronchial thermoplasty. In addition, the potential mechanisms of action and place in management of severe asthma are discussed.

Recent findings

The efficacy and adverse profile of bronchial thermoplasty has been assessed in three randomized controlled trials, the first two of which showed clinical benefits of bronchial thermoplasty compared with usual care in patients with moderate or severe asthma. The third trial reports the results of a comparison with sham bronchial thermoplasty in 288 adults with severe asthma. Bronchial thermoplasty improved asthma quality of life questionnaire scores compared with sham bronchial thermoplasty; in the posttreatment period, there were fewer severe exacerbations and emergency department visits. Bronchial thermoplasty causes short-term increases in asthma-related morbidity. Follow-up data to date support the long-term safety of the procedure.

Summary

Bronchial thermoplasty has a role in the management of patients with severe asthma who have uncontrolled symptoms despite current therapies. Future studies need to identify factors that predict a beneficial clinical response.

Keywords

asthma quality of life, bronchial thermoplasty, severe asthma

INTRODUCTION

The majority of adults with asthma have mild or moderate disease that can be controlled by inhaled corticosteroids alone or in combination with inhaled long-acting β_2 agonist (LABA) bronchodilators [1–3]. Five to 10% of patients have more severe asthma and often, despite maximal drug treatment, these individuals experience considerable morbidity and generate high healthcare costs [4]. There is an unmet need for new improved therapies for patients with severe asthma [5]. Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways to reduce airway smooth muscle mass, has been recently introduced for the treatment of severe persistent asthma. The review summarizes the preclinical development, efficacy and adverse effects of bronchial thermoplasty. In addition, the potential mechanisms of action and place in the management of severe asthma are discussed.

PRECLINICAL DEVELOPMENT

In experimental animals, bronchial thermoplasty has been shown to reduce airway smooth muscle

mass [6], increase airway size [7,8] and decrease airway responsiveness to methacholine [6–8]. In a canine model, Danek *et al.* [6] examined the effects of bronchial thermoplasty on airway responsiveness to methacholine and airway wall histology. Bronchial thermoplasty treatments, to airways more than 3 mm in diameter, controlled to 65°C and 75, but not 55°C, reduced airway responsiveness to local methacholine challenge for at least 3 years posttreatment (Fig. 1a). Airway smooth muscle mass was reduced at 12 weeks (Fig. 1b) and by 3 years, the airway smooth muscle was partially replaced by a thin layer of mature collagen. The histology of the lung parenchyma, epithelium and mucous glands in the airway was not altered by bronchial

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KEY POINTS

- Bronchial thermoplasty involves the delivery of radio frequency energy to the airways to reduce airway smooth muscle mass.
- Randomized controlled clinical trials of bronchial thermoplasty in patients with moderate and severe asthma have shown improvements in asthma quality of life and reduction in severe exacerbations and emergency room visits.
- Bronchial thermoplasty causes short-term increases in asthma-related morbidity including increased hospitalizations for asthma. Follow-up data to date support the long-term safety of the procedure.
- The mechanism of action of bronchial thermoplasty, although not established, may be explained by reduced amount or contractility of airway smooth muscle.
- Bronchial thermoplasty has a role in the management of severe asthma in patients with uncontrolled symptoms despite current therapies.

thermoplasty at 12 weeks posttreatment. Airways treated with bronchial thermoplasty have increased luminal area during exposure to inhaled methacholine at 4 weeks compared with untreated airways as assessed by high-resolution computed tomography [7]. In support of this finding, bronchial thermoplasty leads to increased airway size of canine lungs in both relaxed and contracted states over a normal range of inflation pressures [8]. Taken together, these preclinical studies support the concept that reducing the amount of functional smooth muscle with bronchial thermoplasty may have a beneficial effect in clinical outcomes in asthma.

BRONCHIAL THERMOPLASTY PROCEDURE

Bronchial thermoplasty can be delivered by outpatient flexible bronchoscopy under conscious sedation. The procedure is, however, more protracted and more technically demanding than routine bronchoscopy and many other interventional bronchoscopy techniques [9,10]. The 'Alair' Bronchial Thermoplasty system consists of a radio frequency generator and single-use catheters with an expandable electrode array. Treatment requires a radio frequency compatible bronchoscope with an insertion diameter of 4.9–5.2 mm and a working channel of at least 2 mm. Larger bronchoscopes are less suitable because of reduced access to distal airways.

In clinical trials thus far, patients have received three bronchoscopy sessions, one for each lower

lobe and one for both upper lobes (Fig. 2). The right middle lobe has not been treated because of concerns about inducing middle-lobe syndrome. Patients receive oral prednisolone for 3 days before, the day of and 1 day after the procedure. Nebulized albuterol is administered prior to bronchoscopy. Patients should be educated with regard to the practicalities of the procedure to reduce anxiety and facilitate cooperation. Patients are given an antisecretory agent and are sedated, usually with a combination of a short-acting benzodiazepine and an opiate. Administration of effective topical anesthesia is of critical importance due to the mechanical and thermal irritation inherent in the procedure. The authors have found the Enk Fiberoptic Atomiser Set (C-EFNS-100, William Cook Europe, Bjaeverskov, Denmark) to be particularly useful for the application and reapplication of topical lidocaine during bronchial thermoplasty.

The area to be treated is 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. This allows maximum coverage of the airways in the event of mucosal edema occurring when manipulating the catheter into less accessible bronchi. If mucosal edema does start to limit access to the airways, the authors find that this can be reversed by the application of small aliquots of dilute adrenaline (1:10 000) through the Enk Fiberoptic Atomiser Set.

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 catheter operator then expands the electrode array to make contact with the airway wall, activating a footswitch to deliver radio frequency energy for 10 s. If electrode contact is inadequate, the unit will alarm and abort the treatment. After each treatment, the catheter operator relaxes the handle, collapsing the electrodes slightly away from the airway wall, then moves the bronchoscope and catheter 5 mm proximally. This sequence is repeated until the full length of each airway has been treated. An experienced team will typically complete each treatment session in approximately 45 min.

After the procedure, the patients are monitored for at least 4 h and spirometry is performed prior to discharge. After the procedure, there is an increased incidence of asthmatic and infective symptoms, usually occurring within the first week. During this time, patients may require increased asthma treatment, antibiotics for infection or treatment for mucus plugging.

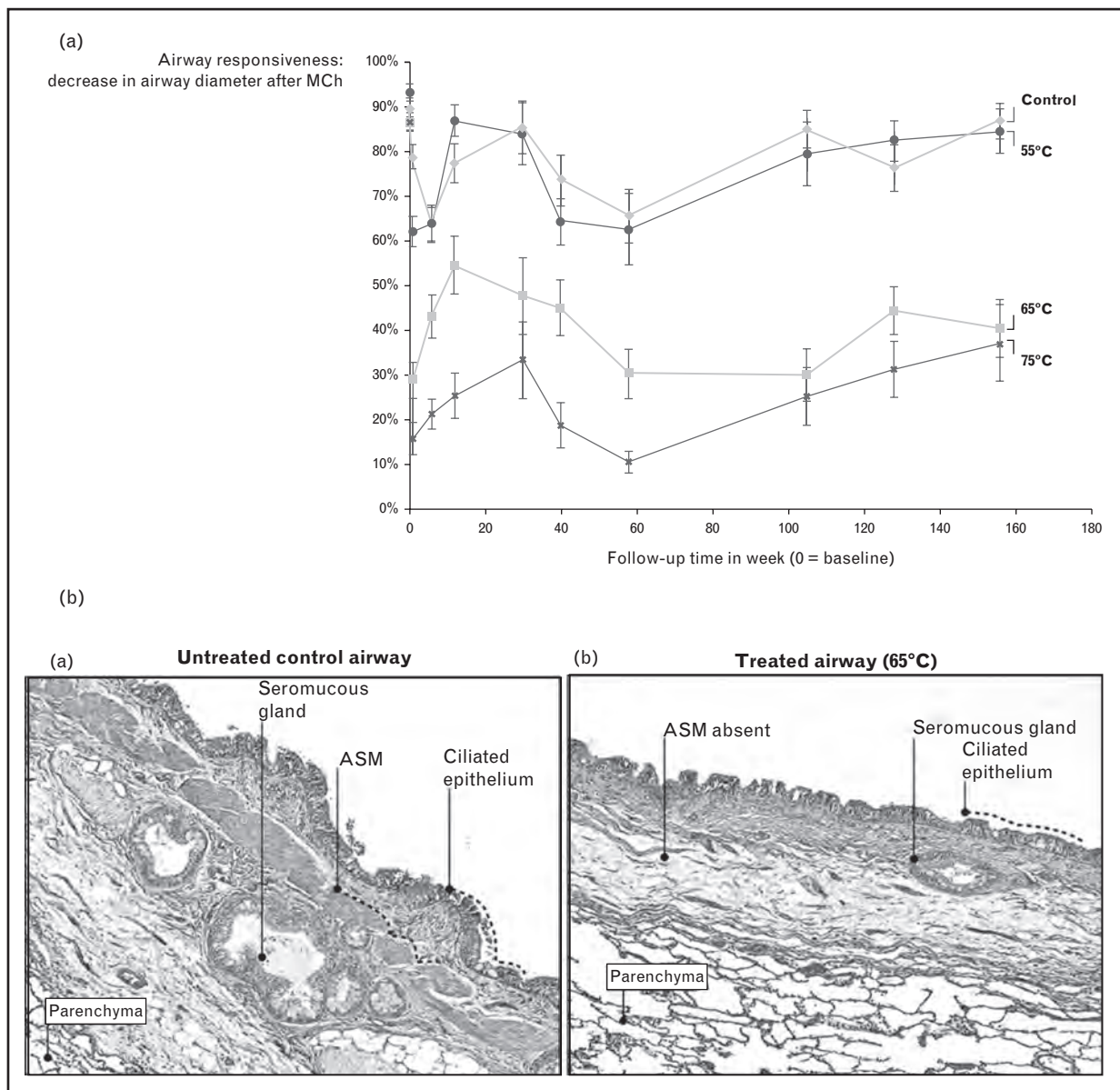


FIGURE 1. Effect of treatment with bronchial thermoplasty at different temperatures on airway responsiveness to methacholine and airway disorder in dogs. (a) Airway responsiveness [percentage change in diameter after local methacholine (MCh) challenge] in dogs treated with bronchial thermoplasty at different temperatures (55, 65 and 75°C) [6]. (b) Histological changes in untreated control airway (a) and an airway treated with radio frequency energy at 65°C (b), 12 weeks after treatment (trichrome stain, original magnification $\times 100$). Airway smooth muscle in the untreated airway is unchanged compared with the reduction in airway smooth muscle in the treated airway. Reprinted with permission of the American Physiological Society [6].

EFFICACY OF BRONCHIAL THERMOPLASTY IN SEVERE ASTHMA

An observational pilot study [11], in addition to demonstrating the safety of the procedure in 16 patients with mild-to-moderate asthma, also reported improvements in symptom-free days, morning peak expiratory flow (PEF) at 3 months after bronchial thermoplasty treatment and a reduction in airway hyperresponsiveness to methacholine that lasted for at least 2 years.

The main evidence for the efficacy of bronchial thermoplasty in the treatment of asthma is based on the results of three randomized controlled trials, one of which was sham controlled. The first randomized controlled study was the Asthma Intervention Research (AIR) 1 Trial [12^{***}]. One hundred and twelve patients aged 18–65 years with moderate or severe asthma were randomized to receive bronchial thermoplasty treatment or to continue their usual asthma drug therapy (control group). LABA

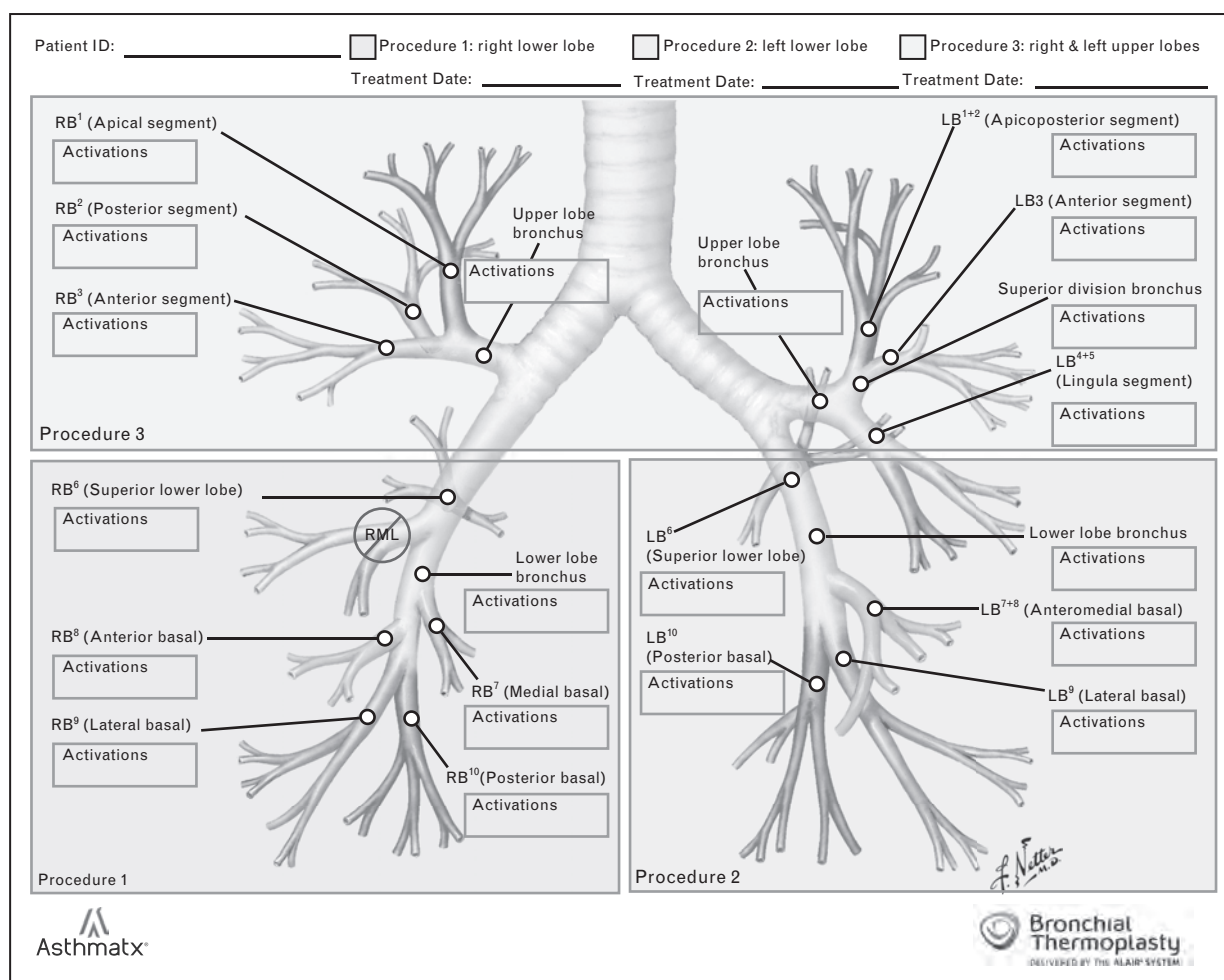


FIGURE 2. Map of the large airways used to record the number of activations undertaken in each segment during each bronchial thermoplasty procedure. Reprinted with permission of Boston Scientific.

therapy was discontinued for 2-week periods at baseline and after 3, 6 and 12 months. The primary outcome measure was the frequency of mild exacerbations (calculated from PEF measurements, rescue medication use and nocturnal awakening), during the periods of LABA withdrawal compared with baseline. In the bronchial thermoplasty group compared with the control group, the mean rate of mild exacerbations compared with baseline was significantly reduced. Secondary outcomes, including change in morning PEF, asthma quality of life questionnaire (AQLQ) and asthma control questionnaire (ACQ) scores also improved at 12 months. There was no difference in forced expiratory volume in 1 second (FEV₁) or methacholine responsiveness between the two groups.

The second randomized controlled study, the Research in Severe Asthma (RISA) trial [13[■]], examined the safety and efficacy of bronchial thermoplasty compared with usual care in 34 patients with severe asthma over a 12-month period.

All participants were taking high doses of inhaled corticosteroids (over 750 µg of fluticasone equivalent) and LABA therapy and half were also taking oral prednisolone daily. Improvements in ACQ scores and rescue medication use were present at 22 and 52 weeks following bronchial thermoplasty and in prebronchodilator FEV₁ at 22 weeks after treatment. More patients in the bronchial thermoplasty group weaned off oral corticosteroids, although the difference was not statistically significant compared with the usual care group.

The pivotal AIR2 trial reported the results of a comparison with sham bronchial thermoplasty in 288 adult patients with severe asthma [14[■]]. Bronchial thermoplasty resulted in improvements from baseline in the primary outcome measure, AQLQ scores compared with sham (bronchial thermoplasty, 1.35 versus sham, 1.16), with 79% of bronchial thermoplasty and 64% of sham patients achieving changes in AQLQ of 0.5 or greater (Fig. 3a). In the posttreatment period, the bronchial thermoplasty

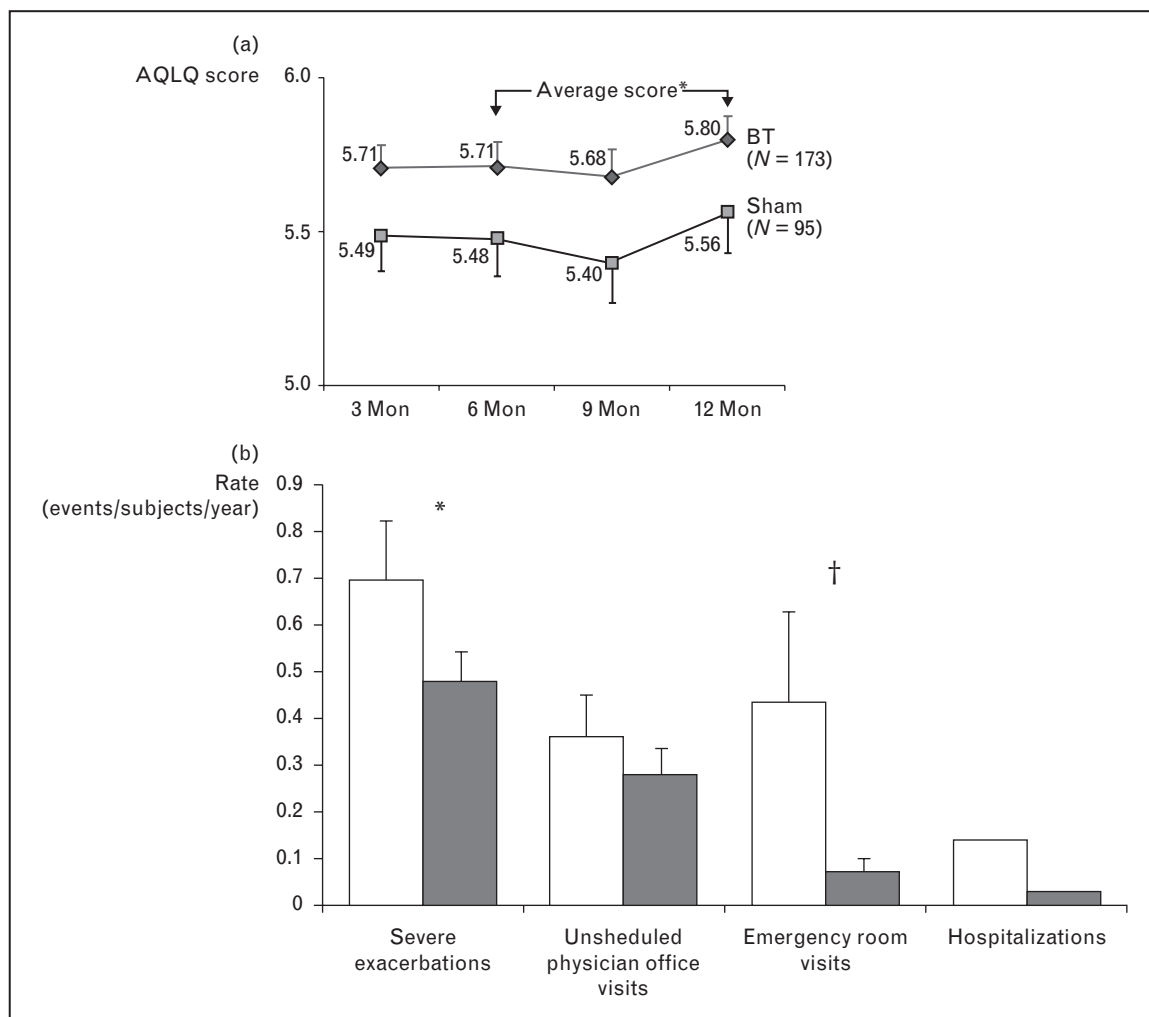


FIGURE 3. (a) Total asthma quality of life questionnaire (AQLQ) score over 12 months after treatment with bronchial thermoplasty and (b) healthcare utilization events during the posttreatment period. (a) Bronchial thermoplasty (BT) (diamonds) or sham control (squares) in the per protocol population. *Posterior probability of superiority is 97.9%. (b) Severe exacerbations (exacerbation requiring treatment with systemic corticosteroids or doubling of the inhaled corticosteroids dose), emergency department visits and hospitalizations occurring in the posttreatment period. Open bars, sham; shaded bars, BT. All values are mean $\pm$ SEM. *Posterior probability of superiority is 95.5%. †Posterior probability of superiority is 99.9%. Reprinted with permission of the American Thoracic Society [14²²].

group also experienced a 32% reduction in severe exacerbations and an 84% fewer emergency department visits (Fig. 3b). An observational follow-up study [15] of 92% of patients who completed the AIR2 trial reported that the reduction in the proportion of patients experiencing severe exacerbations after bronchial thermoplasty is maintained for at least 2 years; severe exacerbations in year 2 after bronchial thermoplasty was 23%, compared with 31% in year 1.

ADVERSE EFFECTS OF BRONCHIAL THERMOPLASTY

Bronchial thermoplasty causes a short-term increase in asthma-related morbidity, including increased

hospital admission for asthma [12²²,13²³,14²⁴]. The main adverse effects in the treatment phase are wheeze, cough, chest discomfort, night awakening and discolored sputum with most adverse events occurring within 1 day of the bronchoscopy procedure and resolving within a week. In the AIR1 study [12²²], there were more hospitalizations in the bronchial thermoplasty group in the treatment phase of the study (six hospitalizations in four subjects) compared with the control group. The RISA trial of patients with severe asthma [13²³] reported seven hospitalizations for respiratory symptoms in four patients in the bronchial thermoplasty group during the treatment period, five for asthma and two for partial lobar collapse, compared with no admission to hospital in this period for the control

group. In the AIR2 study during the treatment period [14²²], 16 patients (8.4%) required 19 hospitalizations in the bronchial thermoplasty group compared with two patients (2.0%) in the sham group.

Five-year follow-up of the safety of bronchial thermoplasty is either underway or completed in participants included in the four clinical trials. The first 16 patients with asthma who received bronchial thermoplasty in the feasibility study [11] have completed a 5-year follow-up for safety assessments. In this follow-up period, there were two severe respiratory adverse events (cold symptoms and bronchitis) and no respiratory-related hospitalizations. Comparison of computed tomography scans taken at baseline and annually for 5 years after bronchial thermoplasty showed no clinically significant changes in the airways such as bronchiectasis, parenchymal fibrosis or airway stenosis. Long-term 5-year safety data for patients recruited to the AIR1 trial [12²²] reported absence of clinical complications and maintenance of stable lung function [16²].

The rate of respiratory adverse events was stable in years 2–5 following bronchial thermoplasty and there was no increase in hospitalizations or emergency room visits for respiratory symptoms in years 2–5 compared with year 1. Spirometry values showed no deterioration over the 5-year period in the bronchial thermoplasty group. Similar results were obtained for the control group who were monitored for 3 years. A 5-year follow-up of patients recruited to the RISA study [13²] reported an absence of complications and stable lung function [17]. Patients participating in the long-term safety follow-up of the AIR2 [14²²] have shown stable lung function and no increase in respiratory adverse events, emergency department visits or hospitalizations for respiratory symptoms between years 1 and 2 [15].

MECHANISM OF ACTION OF BRONCHIAL THERMOPLASTY

Several possible mechanisms, either alone or in combination, could explain the beneficial effects of bronchial thermoplasty in the treatment of severe asthma, although to date, no specific mechanism of action has been established.

First, increased airway smooth muscle mass, which is a pathological feature of severe asthma [18], may contribute to impaired lung function and airway hyperresponsiveness [19,20]. The reduction in airway smooth muscle amount following bronchial thermoplasty found in experimental animals [6] and in humans undergoing lobectomy [21] and

the finding that the reduction in airway smooth muscle is directly related to the decrease in airway responsiveness [6] provides indirect evidence that the beneficial effects of bronchial thermoplasty may be due to a decrease in airway smooth muscle mass.

Second, bronchial thermoplasty could alter airway function by reduced contractility of airway smooth muscle [22²] or by stiffening the airway wall [6]. A recent study [22²] examining the effects of different temperatures on the contraction of bovine airway smooth muscle suggests that bronchial thermoplasty could reduce the contractile properties of airway smooth muscle. The contraction of airway smooth muscle to acetylcholine was inhibited at temperatures greater than 55°C, whereas relaxation with a beta₂-agonist was unaffected. Actin–myosin interactions were similarly temperature sensitive and preceded any histological evidence of necrosis or apoptosis. It remains to be established whether these acute effects *in vitro* can be translated to long-term reductions in airway contractility and if so, whether similar effects occur in humans.

Other potential mechanisms by which bronchial thermoplasty could impact on asthma control include reduced secretion of inflammatory mediators from airway smooth muscle cells [20] and/or alterations in airway epithelial, neural or inflammatory cell function. None of these pathways has been investigated in preclinical asthma models or in patients with asthma.

It is possible that a placebo effect may contribute to the improvements in clinical outcome measures following bronchial thermoplasty [23–25] reported in the nonblinded AIR1 and RISA trials [12²²,13²] and in the sham-controlled AIR2 trial [14²²]. In the AIR2 trial, sham bronchial thermoplasty was associated with a large increase in AQLQ scores, although the active intervention produced significantly larger changes in AQLQ scores and it was associated with a reduction in severe exacerbations and emergency room visits [14²²]. Taken together, the findings from the clinical trials of bronchial thermoplasty suggest that the treatment yields significant improvement for patients, although as with other treatments for asthma, some of this benefit may be due to a placebo effect [25].

The lack of a consistent improvement in lung function following bronchial thermoplasty might be explained by the procedure targeting larger airways more than 3 mm in diameter that do not greatly impact on 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.

PLACE OF BRONCHIAL THERMOPLASTY IN CLINICAL PRACTICE

In 2010, bronchial thermoplasty was approved by the US Food & Drug Administration (FDA) for the treatment of adults with severe persistent asthma that is not well controlled with inhaled corticosteroids and a LABA. The British Thoracic Society guideline for advanced diagnostic and therapeutic flexible bronchoscopy in adults recommends bronchial thermoplasty as a possible treatment option in selected patients with severe asthma already on maximal therapy, although its place in management remains to be established (grade A) [26]. The criteria currently employed for selecting patients for the procedure are based on those used in clinical trials [26].

Eligibility criteria for bronchial thermoplasty are

- (1) severe persistent asthma receiving high-dose combination inhalers ($>1000\text{ }\mu\text{g}$ beclomethasone equivalent) and LABA bronchodilators or oral corticosteroids,
- (2) patient with chronically poorly controlled asthma and considered compliant with their usual asthma medication,
- (3) adult aged 18–70 years,
- (4) postbronchodilator FEV₁ more than 55% predicted and
- (5) patient considered suitable for bronchoscopy.

Future research needs to identify factors that best predict a therapeutic response to bronchial thermoplasty. A prospective observational study [27] of baseline clinical, physiologic, biologic and imaging predictors of response to bronchial thermoplasty in patients with severe refractory asthma is underway (ClinicalTrials.gov Identifier: NCT01185275) with the aim of recruiting 190 participants.

CONCLUSION

Bronchial thermoplasty involves the delivery of radio frequency energy to the airways by flexible bronchoscopy with the aim of reducing airway smooth muscle mass and responsiveness in asthma. Preclinical studies show that bronchial thermoplasty reduces airway smooth muscle in experimental animals and in humans and produces long-lasting decreases in airway responsiveness to methacholine. Randomized controlled clinical trials of bronchial thermoplasty in patients with moderate and severe asthma have shown improvements in asthma quality of life and reduction in severe exacerbations and emergency room visits. Bronchial

thermoplasty is associated with short-term increases in asthma-related morbidity including increased hospitalizations for asthma. Future studies need to determine the mechanisms accounting for the beneficial clinical response to bronchial thermoplasty, the risk–benefit ratio of bronchial thermoplasty in different severities of asthma and the factors that predict a therapeutic response to the treatment. It will also be important to investigate whether less invasive techniques can be used to target airway smooth muscle.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 332).

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This small randomized controlled trial was undertaken in patients with very severe asthma, half of whom were oral corticosteroid dependent, and showed efficacy of bronchial thermoplasty in this patient group. Bronchial thermoplasty was associated with short-term increase in asthma-related morbidity, including increased hospital admission for asthma.

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This was a large multicenter randomized trial with a sham procedure as control and demonstrated an improvement of asthma-related quality of life with bronchial thermoplasty compared with sham control. The bronchial thermoplasty group had a reduced rate of severe exacerbation and emergency department visits in the postprocedure follow-up period of 1 year.

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