Key points

- Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways, is a nonpharmacological intervention developed for the treatment of patients with moderate-to-severe asthma that is poorly controlled despite maximal therapy.

- Randomised controlled clinical trials of bronchial thermoplasty in patients with moderate and severe asthma have shown modest improvements in asthma quality of life and clinically worthwhile reductions in severe exacerbations and emergency department visits.

- The treatment involves three bronchoscopy sessions with repeated, precise and carefully recorded activations of a radiofrequency catheter within the medium and large airways.

- Bronchial thermoplasty causes short-term increases in asthma-related morbidity including increased admissions to hospital for asthma; follow-up data, to date, supports the long-term safety of the procedure.
How to: Bronchial thermoplasty in asthma

Educational aims

• To provide an overview on how to perform bronchial thermoplasty for the treatment of asthma
• To summarise the development, mode of action and evidence for the effectiveness of bronchial thermoplasty as well as its place in the management of asthma

Summary

Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways, is a nonpharmacological intervention developed for the treatment of moderate-to-severe asthma. The mode of action of bronchial thermoplasty is not established, but could be due to reduction in airway smooth muscle mass induced by thermal energy. Bronchial thermoplasty results in modest improvements in asthma quality of life questionnaire scores and clinically worthwhile reductions in severe exacerbations and emergency department visits in the year post-treatment, which may persist for up to 5 years.

The procedure involves systematic, controlled heating of the airways using dedicated radiofrequency equipment during a series of three bronchoscopy sessions. Bronchial thermoplasty causes short-term increases in asthma-related morbidity, including hospital admissions. Follow-up data, to date, supports the long-term safety of the procedure. Bronchial thermoplasty is a novel treatment option for selected patients with moderate-to-severe asthma that is poorly controlled despite maximal therapy.

Statement of Interest

The authors have all been investigators in the AIR, RISA and AIR 2 clinical studies and received institutional funding for research. N. Thomson has received grants and fees for lectures from Boston Scientific.
Background

Asthma is a chronic inflammatory disease of the airways that affects over 300 million people worldwide, and over 30 million children and adults in Europe. Patients with more severe asthma, which accounts for 5–10% of cases, experience considerable morbidity and generate high healthcare costs despite current therapies. Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways, is a nonpharmacological intervention developed for the treatment of moderate-to-severe asthma [1]. This article provides an overview on how to perform bronchial thermoplasty and summarises the development, mode of action and evidence for the effectiveness of bronchial thermoplasty as well as its place in the management of asthma.

Development and mode of action of bronchial thermoplasty

Airway remodelling in asthma includes an increase in airway smooth muscle mass [2], particularly in severe disease [3], which may contribute to impaired lung function, airway hyperresponsiveness and poor symptom control [4, 5]. Bronchial thermoplasty was developed as a nonpharmacological treatment to reduce the amount of airway smooth muscle by delivering radio frequency energy to the airways with the aim of improving clinical outcomes in asthma. In support of this hypothesis there are data indicating that bronchial thermoplasty treatment of airways >3 mm diameter, at a temperature of 65°C, reduces smooth muscle mass in experimental animals (fig. 1) [6] and in non-asthmatics undergoing lobectomy [7], as well as preliminary data suggesting that this effect may also occur in asthma [8]. In addition, bronchial thermoplasty treatment of canine airways decreases airway responsiveness to methacholine for at least 3 years post-treatment and increases airway size measured by computed tomography [6, 9, 10].

The mode of action of bronchial thermoplasty remains uncertain and, in particular, it is not clear if a reduction in the amount of airway smooth muscle accounts for its efficacy in the treatment of asthma. Several other mechanisms, either alone or in combination, could explain the beneficial effects of bronchial thermoplasty in the treatment of asthma. For example, bronchial thermoplasty might alter airway function by reducing contractility of airway smooth muscle [11] or by stiffening the airway wall [6] or by reducing the secretion of pro-inflammatory mediators from airway smooth muscle cells [5]. In addition, it is possible that bronchial thermoplasty might alter airway epithelial, neural or inflammatory cell function. A placebo effect may also contribute to some of the improvements in clinical outcome measures following bronchial thermoplasty [12–15].

Efficacy of bronchial thermoplasty

Evidence for the efficacy of bronchial thermoplasty in the treatment of asthma is based on
the results of three randomised controlled trials, two of which compared bronchial thermoplasty with usual care [13, 14] and one with a sham procedure [15], plus a systematic review and meta-analysis of these trials [16].

In the Asthma Intervention Research (AIR) trial 112 adults with moderate or severe asthma were randomised to bronchial thermoplasty treatment or usual care (control group) [13]. Bronchial thermoplasty reduced the rate of mild exacerbations compared with the control group and also resulted in improvements in morning peak expiratory flow (PEF), Asthma Quality of Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores at 12 months. In the Research in Severe Asthma (RISA) trial the safety and efficacy of bronchial thermoplasty was compared to usual care in 34 patients with severe asthma, half of whom were also taking oral prednisolone daily [14]. Bronchial thermoplasty resulted in improvements in ACQ scores and rescue medication use at 52 weeks, and although more subjects in the bronchial thermoplasty group weaned off oral corticosteroids the difference was not statistically significant compared with the usual care group. The AIR2 trial compared bronchial thermoplasty with a sham procedure in 288 adult subjects with severe asthma randomised to the active procedure in a ratio of two to one [15]. Bronchial thermoplasty resulted in improvements in AQLQ score compared with the sham group (1.35 for bronchial thermoplasty versus 1.16 for sham), with 79% of bronchial thermoplasty and 64% of sham participants achieving changes in AQLQ of $\geq 0.5$ (fig. 2a). In the post-treatment period (from the end of the treatment period up to 1 year post-treatment), there was a 32% reduction in severe exacerbations and 84% fewer emergency department visits with bronchial thermoplasty (fig. 2b). A systematic review and meta-analysis of the three trials concluded that bronchial thermoplasty improves AQLQ scores and PEF [16]. An observational follow-up study of 92% of patients who completed the AIR2 trial reported that the reduction in the proportion of subjects experiencing severe exacerbations and emergency department visits after bronchial thermoplasty is maintained up to 5 years (fig. 3). Severe exacerbations in year five after bronchial thermoplasty occurred in 22% of patients, compared with 31% in year one and 52% in the year prior to the intervention [17]. Compared with the 12 months before bronchial thermoplasty, the average reduction over the 5 years in the proportion of subjects with emergency department visits for respiratory symptoms was 78%. The decrease in rate of emergency department visits that was achieved after bronchial thermoplasty in year one was maintained out to 5 years [17].

Taken together, these clinical studies suggest that bronchial thermoplasty treatment results in a modest improvement in AQLQ scores and clinically worthwhile reductions in severe exacerbations and emergency department visits in the year after treatment and also suggest that these benefits may persist for at least 5 years. However, bronchial thermoplasty produces no consistent improvement in forced expiratory volume in 1 s (FEV1) or airway responsiveness.

**Patient selection**

**Assessment and management of difficult to control asthma**

It is important that patients are assessed at a specialist asthma clinic prior to consideration for bronchial thermoplasty. A systematic evaluation should be performed to identify patients with severe asthma and differentiate from those with difficult-to-treat asthma due to poor adherence, untreated comorbidities, dysfunctional breathing or psychological problems [18, 19]. Once it is established that the patient has severe refractory asthma and is receiving maximal therapy, bronchial thermoplasty is a potential treatment option.

**Selection criteria**

When selecting patients for this procedure caution is advised as efficacy and safety information is available only for patients who satisfied the inclusion criteria for the pivotal clinical trials of the procedure (see the box Eligibility criteria for bronchial thermoplasty used in pivotal clinical trials). In patients with severe asthma who fall outside these entry criteria, such as a post-bronchodilator FEV1 $< 65\%$ predicted, use of oral corticosteroids in excess of 10 mg per day for asthma or greater than four exacerbations of asthma in the past year, there is limited information on the safety of bronchial thermoplasty treatment and caution should...
be exercised in treating such patients. In the RISA study more severe patients, with FEV1 as low as 55% predicted post-salbutamol and higher daily doses of oral prednisolone (\(f30\) mg per day), were treated safely although the numbers in this study were small (n=15) [14].

Patient information about bronchial thermoplasty

The balance of risks and benefits of bronchial thermoplasty treatment should be discussed with patients being considered for the procedure. Patients should be given written information to take home to read and consider after a face to face discussion with the physician. Information sheets for patients being considered for bronchial thermoplasty are available online [23, 24].

Bronchial thermoplasty procedure

The procedure should be performed at facilities that are appropriately equipped to perform bronchoscopy and are equipped to handle respiratory emergencies. Respiratory physicians undertaking bronchial thermoplasty should be experienced in bronchoscopy. Training is required by the manufacturer and is available in different formats: didactic technical review of the equipment; bronchial thermoplasty

\[\text{Figure 2} \]
\text{a) Total Asthma Quality of Life Questionnaire (AQLQ) score over 12 months after treatment with bronchial thermoplasty (BT) in the per protocol population and b) mean ± SEM healthcare utilisation events during the post-treatment period. Severe exacerbations were defined as exacerbations requiring treatment with systemic corticosteroids or doubling of the inhaled corticosteroids dose. }^2 \text{: Posterior probability of superiority 97.9%; }^1 \text{: posterior probability of superiority 95.5%; }^*: \text{posterior probability of superiority 99.9%}. \text{Reproduced from [15] with permission from the publisher.}

\[\text{Figure 3} \]
\text{Severe exacerbations and emergency department (ED) visits in the 5 years after bronchial thermoplasty (BT). a) Proportion of subjects with severe exacerbations and b) severe exacerbation rates. c) Proportion of subjects with ED visits for respiratory symptoms and d) ED visit rates. Values are point estimates with 95% confidence intervals. The 365-day period constituting year 1 began at 6 weeks after the last bronchial thermoplasty bronchoscopy. Reproduced from [17] with permission from the publisher.}
computer-based simulator learning module; or model-based hands-on technical training with bronchoscopy team.

Equipment
The Alair bronchial thermoplasty system (Boston Scientific, Natick, MA, USA) comprises an Alair radiofrequency controller, an

Contraindications for bronchial thermoplasty

Patients with the following conditions should not receive bronchial thermoplasty treatment [22]:

- Presence of a pacemaker, internal defibrillator or other implantable electronic device
- Known sensitivity to medications required to perform bronchoscopy, including lignocaine, atropine and benzodiazepines
- Patients previously treated with bronchial thermoplasty should not be retreated in the same area(s), as no clinical data is available studying the safety and/or effectiveness of repeat treatments

Alair catheter with an expandable electrode array (fig. 4), a patient return electrode and a suitable flexible bronchoscope.

The Alair controller contains a radiofrequency generator and additional elements which regulate the energy applied to the airways to allow effective treatment without unwanted tissue damage. The controller is activated by a footswitch which triggers a timed period of radiofrequency energy delivered via the Alair catheter.

The Alair catheter is a single use catheter which is connected to the controller via an integral electrical cable. The catheter has a basket electrode at its distal end which can be progressively expanded and retracted by a handle-grip control. The catheter has markings at 5 mm intervals to facilitate endobronchial spacing of treatment activations.

The patient return electrode completes the electrical circuit. A CE-marked gel type electrode for adult use is suitable.

Treatment requires a radiofrequency compatible flexible bronchoscope with an insertion diameter of 4.9–5.3 mm and a working channel of at least 2 mm. Larger bronchoscopes are less suitable because of reduced flexibility and reduced access to the smaller, distal airways.
Pre-procedure patient preparation

Oral corticosteroids: administer prophylactic prednisolone or equivalent at a dose of 50 mg per day for the 3 days before the procedure, the day of the procedure and the day after the procedure to minimise post-procedure inflammation. This is the dose used in the clinical trials. Locally we use 40 or 50 mg prednisolone depending on the asthma severity and body weight, for 2 days prior to the procedure, the day of the bronchial thermoplasty and 2 days after the procedure. We provide patients with a further 5-days’ supply of prednisolone and advise them to use it only in the event of significant worsening of asthma symptoms post-procedure.

Pre-procedure spirometry: on the day of procedure, perform a post-bronchodilator FEV1 to assess the patient’s stability pre- and post-procedure. Pre-procedure FEV1 value should be ≥85% of the patient’s recent value when stable.

As with other bronchoscopy procedures, patients should stop taking anticoagulants, antiplatelet agents, aspirin and non-steroidal anti-inflammatory drugs before the procedure with physician guidance.

The procedure should be postponed if any of the following conditions apply [21]:

- Prescribed prednisolone was not taken on the days before bronchoscopy
- Arterial oxygen saturation measured by pulse oximetry <90% on room air
- Increase in asthma symptoms in last 48 h requiring >4 puffs per day on average of rescue bronchodilator over pretreatment usage
- Asthma exacerbation or changing dose of systemic corticosteroids for asthma in the past 14 days
- Active respiratory infection or active allergic sinusitis
- Any other reason for clinical instability

Bronchoscopic procedure

Bronchial thermoplasty can be delivered by outpatient flexible bronchoscopy under conscious sedation. However, the procedure is more protracted and more technically demanding than routine bronchoscopy and many other interventional bronchoscopy techniques [25, 26]. The combination of a technically challenging procedure applied to asthmatic subjects with capacity for abrupt alterations in airway conditions must be addressed by a clinical team with expertise in complex bronchoscopy and regular experience of severe asthma. Delivery of bronchial thermoplasty involves close cooperation between the bronchoscope operator and the catheter operator and these two individuals should have practiced the manoeuvres involved together, prior to the procedure.

Following a format established in the principal clinical trials, patients receive treatment over three bronchoscopy sessions spaced at approximately 1 month intervals, one for each lower lobe and one for both upper lobes (fig. 5). The right middle lobe has not been treated because of theoretical concerns about causing stenosis of the relatively long middle lobe bronchus leading to middle-lobe syndrome. Patients should be educated with regard to the practicalities of the procedure to reduce anxiety and facilitate cooperation.

The bronchoscopy must be performed in a facility equipped to deal with medical emergencies including potential treatment-related complications such as pneumothorax and haemoptysis. Before starting the bronchoscopy procedure the team checks correct assembly of the Alair system, including correct placement of the patient return electrode. The Alair catheter is checked with particular regard to smooth and symmetrical deployment of the catheter array and if the deployment is not satisfactory another catheter is chosen. Nebulised salbutamol is administered prior to bronchoscopy. In our practice, patients are given an anti-secretory
agent, such as glycopyrrolate or atropine, and are sedated, usually with a combination of a short-acting benzodiazepine (such as midazolam) and an opiate (such as alfentanil). Administration of effective topical anaesthesia before and during the bronchoscopy is of critical importance due to the significant mechanical and thermal irritation inherent to the procedure. As the procedures are significantly longer than standard diagnostic bronchoscopy, it is usually necessary to give further aliquots of sedation during the treatment. It is important the cumulative treatment is documented accurately and that clinical governance is in place with regard to complexities of these procedures.

The bronchoscope can be inserted via the nose or mouth with the patient in a recumbent or semi-recumbent position according to the team’s usual practice.

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. This allows maximum coverage of the airways in the event of mucosal oedema occurring when manipulating the catheter into less accessible bronchi. If mucosal oedema does start to limit access to the airways the authors find that this can be reduced by the application of small aliquots of dilute adrenaline (1:10,000, i.e. 0.1mg·mL⁻¹).

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 (fig. 6). 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. The system is only activated when the electrode array is within vision and throughout the procedure care must be taken to avoid damage to the distal airways. 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**

It is recommended that patients should be carefully monitored and discharged only after they are deemed to be stable, and have adequate lung function, mental status and are able to take liquids adequately. Patients are rarely required to stay overnight.

Recommended post-procedure assessments: 1) 4 h recovery/monitoring period following each procedure; and 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 FEV₁ within 80% of the pre-procedure value and that the patient is feeling well.

**Figure 5**

Map of the large airways used to record the number of activations undertaken in each segment during each bronchial thermoplasty procedure. Image courtesy of Boston Scientific Corporation.
Short-term adverse effects of bronchial thermoplasty

Bronchial thermoplasty is associated with a short-term increase in asthma-related morbidity, including increased hospital admission for asthma [13–15]. The main adverse effects in the treatment phase are wheeze, cough, chest discomfort, night awakening and discoloured sputum with most adverse events occurring in the first day after bronchoscopy and resolving within a week. In the AIR study there were more hospitalisations in the bronchial thermoplasty group in the treatment phase of the study (six hospitalisations in four subjects) compared with the control group [13]. The RISA trial of patients with severe asthma reported seven hospitalisations for respiratory symptoms in four subjects 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 [14]. In the pivotal AIR2 study during the treatment period 16 subjects (8.4%) required 19 hospitalisations in the bronchial thermoplasty group compared with two subjects (2.0%) in the sham group [15].

Other commonly reported side-effects were increased upper respiratory tract infection, headache and dyspepsia. Details of adverse events that occurred more commonly in the thermoplasty treated group compared to the sham treated group are presented in table 1.

Long-term safety

The long-term safety of bronchial thermoplasty up to 5 years post-procedure has been completed in patients with moderate-to-severe asthma included in the three randomised controlled trials and in those recruited to an observational trial in patients with mild asthma (table 1). The rate of respiratory adverse events was unchanged in years two to five following bronchial thermoplasty in the AIR trial [27], RISA trial [28] and AIR2 trial [17]. Lung function was stable and there was no increase in hospital admissions or emergency department visits for respiratory symptoms between years one and five (fig. 3). In addition, 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 [17].

**Place of bronchial thermoplasty in the management of asthma**

Bronchial thermoplasty is licensed for the treatment of asthma in Europe, the USA and many other countries worldwide. For example, in 2010 the US Food and Drug Administration approved bronchial thermoplasty for the treatment of severe persistent asthma in patients aged ≥18 years whose asthma is not well controlled with inhaled corticosteroids and long-acting β-agonists, the current standard of care treatment for

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**Table 1. Adverse effects of bronchial thermoplasty (BT)**

|                                | Treatment period | Post-treatment period |
|--------------------------------|------------------|-----------------------|
|                                | BT group         | Sham group            | BT group         | Sham group |
| Subjects n                     | 190              | 96                    | 187              | 96         |
| Average duration of period days| 84               |                       | 322              |            |
| Worsening of asthma            | 52               | 39                    | 27               | 43         |
| Upper respiratory tract infection| 20               | 11                    | 30               | 26         |
| Wheezing                       | 15               | 6                     | 4                | 3          |
| Chest pain                     | 14               | 13                    | 3                | 1          |
| Headaches                      | 14               | 9                     | 5                | 3          |
| Dyspnocia                      | 11               | 6                     | 2                | 1          |
| Chest discomfort               | 9                | 10                    | 2                | 1          |
| Lower respiratory tract infection| 8                | 2                     | 3                | 6          |
| Nasopharyngitis                | 5                | 7                     | 11               | 5          |
| Atelectasis                    | 5                | 0                     | 0                | 0          |
| Bronchitis                     | 4                | 2                     | 7                | 5          |
| Anxiety                        | 4                | 0                     | 1                | 2          |
| Dyspepsia                      | 4                | 2                     | 2                | 4          |
| Haemoptysis                    | 3                | 0                     | 1                | 2          |
| Acute sinusitis                | 3                | 2                     | 4                | 8          |
| Rhinitis                       | 2                | 0                     | 4                | 6          |
| Influenza                      | 4                | 2                     | 4                | 12         |
| Pyrexia                        | 4                | 2                     | 0                | 1          |
| Hypertension                   | 3                | 2                     | 3                | 3          |
| Urinary tract infection        | 1                | 1                     | 3                | 1          |

Data are presented as %, unless otherwise stated. "*: adverse events >3% frequency that were higher in the BT group compared with the sham treated group; †: the period from first treatment to 6 weeks after last treatment; ‡: the period from 6 weeks post-treatment to 12 months after last treatment.

Data from [21].
Future directions

- Longer term follow-up of treated patients is recommended. In the UK, all patients undergoing bronchial thermoplasty have demographic and procedure details recorded in the British Thoracic Society Difficult Asthma Registry.
- Studies to date have been unable to identify factors that predict a therapeutic response to bronchial thermoplasty. A prospective observational study of baseline clinical, physiological, biological and imaging predictors of response to bronchial thermoplasty in patients with severe refractory asthma is underway, with the aim of recruiting 190 subjects [31].
- Future studies need to determine the mechanisms accounting for the beneficial clinical response to bronchial thermoplasty, the long-term effects after 5 years, and the feasibility of repeating the procedure after 10 years or when the effect wanes in a patient who responds initially.

these patients [22]. In the European Union, the Alair bronchial thermoplasty system has a CE mark for the treatment of asthma in patients aged ≥18 years.

The Global Initiative for Asthma guidelines consensus recommendation is that bronchial thermoplasty is now a possible option in some countries for adults with uncontrolled asthma despite maximal therapy and review by an asthma specialist [29]. The recommendation adds that longer-term safety follow-up of larger numbers of active and control patients is required to assess effectiveness and that caution should be exercised in patient selection for the procedure [29]. 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) [30].

Conclusion

Bronchial thermoplasty, which involves the delivery of radio frequency energy to the airways, is a nonpharmacological intervention developed for the treatment of uncontrolled moderate-to-severe asthma. Bronchial thermoplasty reduces airway smooth muscle mass in experimental animals and produces long-lasting decreases in airway responsiveness to methacholine. The mode of action of bronchial thermoplasty in the treatment of asthma is not established. Randomised controlled clinical trials of bronchial thermoplasty in patients with moderate and severe asthma have shown modest improvements in asthma quality of life and clinically important reductions in severe exacerbations and emergency room visits. The procedure involves a systematic approach requiring expertise in complex bronchoscopic interventional procedures.

Bronchial thermoplasty is associated with short-term increases in asthma-related morbidity including increased hospitalisations for asthma. 5-year follow-up of patients recruited to randomised clinical trials of bronchial thermoplasty have reported no increase in respiratory-related adverse effects. Bronchial thermoplasty is a treatment option for patients with moderate-to-severe asthma who have poorly controlled disease despite maximal therapy.

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