

# What is the role of bronchial thermoplasty in the management of severe asthma?

Aoife O'Reilly  and Stephen Lane

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**Abstract:** Asthma is a common chronic inflammatory condition of the airways. Conventional therapy comprises inhaled corticosteroid and bronchodilators as well as trigger avoidance and management of comorbid conditions. A small group remain symptomatic despite these strategies and novel therapies have been developed. Bronchial thermoplasty is a nonpharmacological therapy which targets airway smooth muscle to improve asthma control. Clinical trials to date have shown the efficacy and safety of bronchial thermoplasty with a persistent effect on extended follow up. Questions remain regarding the exact mechanism of action of bronchial thermoplasty, the cost effectiveness of the procedure and the ideal criteria for patient selection.

**Keywords:** asthma, bronchial hyperresponsiveness, airway smooth muscle, bronchial thermoplasty, bronchoscopic procedure

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## Introduction

Asthma is a common condition affecting more than 235 million people worldwide. Asthma is caused by chronic inflammation of the large and small airways, resulting in airway hyper responsiveness, excessive mucous secretion and airflow obstruction. Patients present with intermittent wheeze, shortness of breath and cough triggered by infection, environmental allergens or other stimuli. The mainstay of therapy is inhaled corticosteroid to treat inflammation and inhaled bronchodilators to relax airway smooth muscle (ASM). Management also focuses on trigger avoidance, treatment of allergy and addressing contributing comorbidities such as rhinosinusitis, gastroesophageal reflux disease, obesity and smoking as well as patient education.<sup>1</sup> While the majority of patients achieve symptom control with these strategies, there remains a significant cohort with severe asthma estimated at 5–10% who are more difficult to treat. The group will have an increased morbidity and mortality associated with asthma, as well as more health care use and reduced quality of life.

In the last decade increasing knowledge of the pathophysiology of asthma and awareness of individual clinical phenotypes has led to the development of new treatments for asthma. Most new

therapies in development have been focused on modulating the inflammatory response. Anti-immunoglobulin E therapy with the monoclonal antibody omalizumab has been in use for several years and more recently the anti-interleukin (IL)-5 agents mepolizumab, reslizumab and benralizumab have become available for those with eosinophilic asthma. Biologic therapy targeting IL-4 and IL-5 have been of particular interest; several of these agents have yielded promising results, however they only appear effective in certain subgroups of patients with asthma. Bronchial thermoplasty (BT) is a novel nonpharmacological therapy which targets ASM in an effort to improve asthma control.

## Airway smooth muscle

While patients with asthma demonstrate reversible airflow obstruction due to airway inflammation and bronchial hyperresponsiveness, often this airflow obstruction is not fully reversible and many patients with asthma experience an accelerated and progressive loss of lung function over time. Histopathologic studies have shown that asthma is characterized by chronic inflammation with bronchial epithelial basal membrane thickening, epithelial desquamation, increased vascularization, smooth muscle hypertrophy and

Correspondence to:

**Aoife O'Reilly**  
Tallaght Hospital, Tallaght,  
Dublin 24, D24 NR0A,  
Ireland  
[aoife.oreilly1@gmail.com](mailto:aoife.oreilly1@gmail.com)

**Stephen Lane**  
Tallaght Hospital, Tallaght,  
Dublin, Ireland

hyperplasia, and mucous gland hypertrophy. The role of ASM has long been subject to debate. Many roles in normal function have been postulated, including immunomodulation, extracellular matrix deposition and regulation of bronchomotor tone, while some claim that it is a vestigial structure without an essential function.<sup>2</sup> ASM cells proliferate more rapidly in patients with asthma compared with healthy subjects, resulting in an increase in smooth muscle mass. Bronchial remodelling, in particular an increase in ASM, has been shown to be related to clinical and functional severity of asthma.<sup>3</sup> It has been shown that those with fatal asthma have an increased volume of smooth muscle compared with nonfatal asthma.<sup>4</sup> As a result, ASM has become a therapeutic target.

### Bronchial thermoplasty

BT is a minimally invasive therapeutic intervention for patients with severe refractory asthma. The technique involves the controlled delivery of endobronchial thermal energy in order to modify the structure of the airway wall by reducing the amount of smooth muscle using a device called the Alair Bronchial Thermoplasty System (Boston Scientific, Marlborough, MA, USA). It is performed in a series of three bronchoscopies at approximately 3-week intervals. The first two sessions treat the right lower lobe and left lower lobe separately and both upper lobes are treated in the final procedure. In the original trials the right middle lobe was not treated due to the risk of causing stenosis to this typically narrow bronchus. There have now been reports of centres treating the right middle lobe without complication<sup>5</sup> and indeed large ventilation defects have been shown in this lobe<sup>6</sup> so this may be beneficial. Thermal energy is delivered using a catheter introduced through the working channel of the bronchoscope. The distal tip contains an expandable four-electrode basket which is serially deployed in visible bronchial areas. Each procedure takes around 30-60 min and can be performed using local anaesthesia and conscious sedation. Dividing the treatment into three procedures allows for shorter procedure times and avoids the risks associated with widespread airway irritation in patients with severe asthma. The most common complications during the procedure include bronchoconstriction, mucous hypersecretion, and minor bleeding related to superficial trauma. Patients are given systemic corticosteroids and nebulized

bronchodilators prior to the procedure; afterwards they are monitored closely and may require treatment with bronchodilators in the immediate post-procedure setting.

### Review of data

The first randomized clinical trial (RCT) evaluating the efficacy of BT was published in 2006 by Cox and colleagues and included 16 patients with stable mild-moderate asthma. The primary objective of the study was to evaluate the safety of BT, which was well tolerated with only mild adverse events within 1 week of BT that resolved without treatment or when current medications were increased. Long-term safety assessment at 2 years showed no deterioration in respiratory health status. There were no changes in forced expiratory volume in 1 s (FEV1) or parenchymal alteration on chest computed tomogram (CT) at this assessment. They also reported a statistically significant improvement in airway hyperactivity, determined by methacholine provocation challenge which persisted at 2 years, an increase in peak expiratory flow rates and an increase in symptom-free days (47% *versus* 73%) ( $p = 0.015$ ).<sup>7</sup>

The Asthma Intervention Research (AIR) trial in 2007 was the first large-scale, multicentre, randomized controlled study of BT. One hundred and twelve patients with moderate to severe asthma were included. This study showed no difference in pulmonary function before and after BT, but there was a significant improvement in asthma symptoms, measured by symptom-free days, the Asthma Control Questionnaire (ACQ) scores ( $1.3 \pm 1.0$  *versus*  $0.6 \pm 1.1$ ,  $p = 0.003$ ) and the Asthma Quality of Life Questionnaire (AQLQ) scores ( $1.3\% \pm 1.0\%$  *versus*  $0.6\% \pm 1.0\%$ ,  $p = 0.005$ ), and there was a reduction in mild exacerbations ( $0.16 \pm 0.37$  *versus*  $0.04 \pm 0.029$  asthma attacks per week,  $p = 0.005$ ).<sup>8</sup>

Also published in 2007, the Research in Severe Asthma (RISA) trial showed the safety and efficacy of BT in symptomatic patients with severe uncontrolled asthma. Thirty-two patients were enrolled with uncontrolled asthma despite high-dose inhaled corticosteroid and long-acting  $\beta$  agonist, and other medications including oral prednisolone. Fifteen were randomized to BT and those who underwent the procedure showed significant improvements in ACQ, AQLQ and rescue medication use.<sup>9</sup> The treated group did

have an increase in respiratory adverse events in the treatment period but there was no difference between groups during the post-treatment period. The most frequently observed events were wheezing, cough, chest discomfort, dyspnoea, productive cough and discoloured sputum. Most of these adverse events occurred within 1 day of the procedure and resolved on average within a week.

These results were promising, however questions remained over the true efficacy of BT *versus* any potential placebo effect as the RISA and the AIR trials were unblinded. The AIR-2 trial was designed to answer these questions. This was a multicentre, randomized, double-blind, sham-controlled study of 288 subjects, 190 of whom underwent BT. In the group treated with BT a significantly greater proportion had a meaningful increase in the AQLQ score compared with those who underwent sham bronchoscopy (79% *versus* 64%). There was also a significant reduction in the number of exacerbations (32% risk reduction), emergency department visits (84% risk reduction) and days lost from school/work (66% risk reduction) in those treated with BT.<sup>10</sup> However, it is important to note that patients treated with sham bronchoscopy did have an increase in the AQLQ score compared with their prerandomization baseline; this placebo effect results in a small absolute difference between the groups.

These trials showed promising results with regard to quality of life and reduction in exacerbation frequency, but the longevity of findings and long-term safety was not assessed. Since then, follow-up data on these cohorts have been published.

A long-term evaluation of the patients treated with BT in the RISA study was performed, including 14 of the 15 patients. These were followed for a total of 5 years and showed a significant reduction in emergency visits and hospitalizations for asthma exacerbations and no deterioration in lung function.<sup>11</sup> Subjects in the AIR-2 trial were followed for an additional 4 years. A persistent reduction in severe exacerbations and emergency department visits was seen, demonstrating durability of the effects of BT up to 5 years. Reassuringly, no deterioration in lung function was noted and no significant structural changes were seen on CT.<sup>12</sup> One criticism that has been made of the study is that control patients who underwent sham bronchoscopy

were not followed up in the same way, so there is an absence of long-term comparative data.

### Patient selection for bronchial thermoplasty

Overall, data from controlled clinical trials have supported the efficacy of BT in the treatment of different phenotypes of asthma, but we have seen that not all patients with asthma respond to BT. Doeing and colleagues published a case report in which a patient who was poorly responsive to BT demonstrated no reduction of ASM on histology of endobronchial biopsies taken before and after the procedure.<sup>13</sup> This highlights the fact that the criteria for selection of the most appropriate patients who will likely benefit from BT remain unknown.

Proposed criteria based on currently available evidence include those with severe refractory asthma, FEV1 of at least 60%, unsuitable for or unwilling to commit to therapy with biological therapy.<sup>14</sup> Biologic therapy requires regular visits and potentially lifelong therapy; an advantage of BT is that it involves only three procedures. BT has been recommended in the Global Initiative for Asthma (GINA) guidelines as an add-on therapy at step 5,<sup>1</sup> but they highlight that the AIR-2 trial excluded patients with FEV less than 60%, frequent chest infections or sinus disease. They recommend that BT only be performed on adults with severe asthma in the context of an independent institutional review board approved systematic registry or a clinical study. BT is contraindicated in patients with a pacemaker, internal defibrillator or any implantable electronic device.

There have been smaller studies, including patients with lower baseline FEV1 values. In 2013, Doeing and colleagues published a case series of eight patients with fixed airflow obstruction (FEV1 between 52% and 37% predicted) in which BT was effective in five patients.<sup>15</sup>

A study from our group described a cohort of seven patients with severe asthma who underwent BT (FEV1 41–93%). They were assessed in a specialist asthma centre and management was optimized prior to BT. One year post therapy they were shown to have a significant improvement in Asthma Control Test (ACT) scores and a trend towards reduction in hospital admissions.<sup>16</sup> On extended follow up (mean 49.42 months), there was a trend towards improvement in ACT and

reduction in hospital admissions. There was also no significant change in lung function post BT.<sup>17</sup> These data provide support for the safety and efficacy of BT. Bicknell and colleagues published a study comparing the response to BT in patients from the same difficult asthma centre, either as part of a clinical trial or selected from the clinic as part of clinical service.<sup>18</sup> Clinical improvements occurred in 50% of the clinic patients compared with 73% of the research patients. Patients in the clinic group were noted to have greater baseline asthma severity, with 6 out of 10 at British Thoracic Society (BTS) Guidelines step 5 treatment compared with 2 of 15 of the research patients. Adverse events were similar to those reported in clinical trials. This indicates that the data on safety and efficacy obtained from carefully controlled trials may not be replicated in real-life practice, although the greater severity of asthma in the clinic group may provide an explanation for this.

Another important consideration is that of adherence to therapy. A recent study by Lee and colleagues assessed a group of 69 patients with difficult asthma; severe asthma criteria were fulfilled by 59 of these patients and 47 were eligible for novel therapies such as BT. Sixteen of this group had confirmed nonadherence using an electronic monitoring device and a further seven were felt to possibly be nonadherent.<sup>19</sup> Adherence rates demonstrated in this study are similar to those reported in other studies, and they showed that self-reporting of nonadherence was unreliable and poorly sensitive. Adherence to therapy and effective inhaler technique is of paramount importance and no patient should be considered for therapy such as BT without a thorough review of inhaler technique and adherence. Alternative diagnoses should be considered and investigated, and comorbid conditions such as allergic rhinitis, sinusitis, vocal cord dysfunction and gastroesophageal reflux disease should be treated. Ideally such work up should be carried out in a specialty asthma centre and any patients going forward for BT should be followed in a registry or as part of ongoing research.

### Mechanism of action

As mentioned previously, the function of ASM and its precise role in the pathogenesis of asthma remains poorly understood and by extension the underlying mechanisms that lead to improvements in asthma control in patients treated with

BT are unclear. While the favoured mechanism is ablation of the ASM layer, because BT treats only a small number of central airways there is ongoing debate regarding the precise mechanism of action. In the normal bronchial tree the greatest source of resistance to airflow is in the conducting airways at about the fourth generation,<sup>20</sup> therefore it is likely that narrowing in this area would cause a greater effect to overall airflow obstruction and treating more central airways should have a therapeutic effect. A recent study by Donovan and colleagues using lung specimens and novel computational methods has suggested that structural changes to treated airways lead to a reopening cascade in the small airways and alteration of lung-wide flow patterns causing an improvement in lung function.<sup>21</sup> An improvement in airway obstruction has been shown by Zanon and colleagues in a study in which multidetector computed tomography was performed on 26 patients with severe asthma who underwent BT. Median total lung volumes were reduced from 2668 ml (range 2226–3096 ml) to 2399 ml (range 1964–2802 ml;  $p = 0.08$ ) and median air trapping values also decreased from 14.25% to 3.65% ( $p < 0.001$ ). Median airway wall thickness was reduced from 1.5 mm to 1.1 mm ( $p < 0.05$ ).<sup>22</sup>

In a group of 10 patients studied by Pretolani and colleagues the authors found that BT was effective at reducing ASM volume in the treated lobes and unexpectedly they found that in 7 out of 10 patients there was a reduction in ASM volume in the untreated right middle lobe which decreased by an average of 48.7%.<sup>23</sup> This suggests that the clinical effect of BT may go beyond the treated areas. In a more recent study published by the same authors in 2017, a group of 15 patients were studied. Clinical effectiveness of BT was demonstrated at both 3 and 12 months and the histopathologic effects of BT were also studied.<sup>24</sup> A decrease in ASM area was shown at 3 months post BT from a median of 19.7% (25th–75th IQR, 16.2–21.8%) to 5.2% (25th–75th IQR, 3.7–9.8%;  $p < 0.001$ ). They also found there was a significant reduction in subepithelial basement membrane thickening and submucosal and ASM-associated nerve fibres. In the heat-untreated middle lobe they noted a trend toward decrease in submucosal and ASM-associated nerves.

These findings were supported by Facciologo and colleagues in 2018. This group studied a group of seven patients who underwent BT and had

biopsies taken at the end of each procedure and 12 months after BT.<sup>25</sup> A significant reduction of total nerve fibre scores was observed in the sub-mucosa and airways smooth muscle. These findings raise the possibility of nerve ablation being a possible alternative, or additional, mechanism of severe asthma control beside the known effect of BT on ASM.

Another study by Chakir and colleagues in 2015 also showed significant reduction in ASM from  $12.9\% \pm 1.2\%$  to  $4.6\% \pm 0.8\%$  at 3–14 weeks post treatment.<sup>26</sup> Additionally BT decreased type 1 collagen deposition underneath the basement membrane from  $6.8 \pm 0.3$  micron to  $4.3 \pm 0.2$  micron, showing that the effect of BT on asthmatic airways is not limited to the ASM.

As well as exacerbating airway constriction through hypertrophy and hyperplasia, ASM contributes to the inflammatory response through the production of cytokines and chemokines. In 2015 Denner and colleagues demonstrated a reduction in ASM by showing a reduction in smooth muscle actin in endobronchial biopsy specimens 6 weeks after BT. They also found a reduction in concentration in bronchoalveolar lavage (BAL) specimens of two inflammatory cytokines: transforming growth factor (TGF)- $\beta$ 1 and RANTES/CCL5, while there was a significant increase in tumour necrosis factor related apoptosis-inducing ligand (TRAIL).<sup>27</sup> TGF- $\beta$ 1 expression is markedly increased in asthmatic airways and has a complex role in asthma pathogenesis; it is involved in epithelial transformation, subepithelial fibrosis, ASM remodelling, mucus production and both surpassing and activating inflammatory cytokines. RANTES/CCL5 is a chemoattractant that recruits eosinophils that has been shown to account for 80% of TGF- $\beta$  expression in asthma. BAL RANTES incites eosinophil attraction and has been shown to correlate with the proportion of BAL eosinophils. The percentage of eosinophils in differential cell counts had decreased from  $4\% \pm 1\%$  to  $1\% \pm 0\%$  by week 3, and remained low at 6 weeks post BT. No significant changes were noted in other asthma-related cytokines IL-4, IL-5, IL-13 and IL-17. This study demonstrated clear changes in inflammatory editors after BT and points the way for further trials increasing our understanding of the mechanism of action of BT.

As with all procedures, there may be some variance between operators. A study by Langton and

colleagues included 24 patients undergoing BT performed by three different proceduralists. A significant relationship was shown between the number of activations per procedure and the improvement in ACQ-5.<sup>28</sup> The authors have suggested that a target of 140 activations or more should be delivered over the three procedures to achieve an improvement in ACQ-5 of 0.5 units or greater, though this will require further validation in larger studies.

There are ongoing studies in this area which will likely help identify new therapeutic targets and provide insights into the mechanisms of BT. It has become clear that there are several subphenotypes of asthma and trials of immunomodulatory agents have shown that these phenotypes respond differently to therapy. It is important that we develop our understanding of BT in order to better identify subsets of patients who will have the largest clinical benefit. Ongoing trials are assessing the utility of imaging and also evaluating the use of blood and sputum biomarkers to identify this subgroup.

### Pharmacoeconomics of bronchial thermoplasty

The cost effectiveness of BT has been studied in recent years. BT is a costly procedure but recent studies have shown that direct costs may be partially offset by the reduction in costs incurred by the health service due to reduction in emergency hospital admissions for acute exacerbations of asthma, the reduction of indirect costs and the effects of improved quality of life for patients. A study performed in Italy by Menzella and colleagues showed that the increase in direct costs incurred with BT was reduced by a long-term economic saving due to reduction in emergency hospital visits and hospitalizations due to the use of BT.<sup>29</sup> Zein and colleagues also found that BT is cost effective in patients with asthma at high risk of exacerbations.<sup>30</sup> However, a study carried out in Singapore found that BT is not cost effective compared with optimized asthma therapy and suggested a reduction in the cost of the procedure in order to make it more cost effective,<sup>31</sup> so cost effectiveness may differ based on local costs.

### Conclusion

BT is a novel therapy for patients with severe asthma. It is the only therapy that specifically

targets ASM, which has long been associated with severe asthma. Initial trials have shown promising results with regard to its safety and efficacy, but the mechanisms underlying these improvements remain poorly understood. The identification of patients most likely to benefit from this therapy is a crucial next step and will be of paramount importance in determining the role of BT in the management of asthma in the future.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

### ORCID iD

Aoife O'Reilly  <https://orcid.org/0000-0002-2026-2345>

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