

# Bronchial Thermoplasty: a safe treatment for patients with severe asthma?

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## Abstract

Many patients with asthma can be managed with appropriate pharmacological treatment. However, some patients with more severe asthma continue to have uncontrolled symptoms. In these patients, a relatively novel treatment, bronchial thermoplasty, may be considered. Bronchial thermoplasty involves the application of a heat probe to the airways, where it is thought to cause thermal ablation of airway smooth muscle. NICE guidelines for this procedure are currently being updated, and it is thought that with new guidelines in place bronchial thermoplasty will become more routinely offered throughout the UK. Early trials have shown clear benefits of the procedure but less is known about its safety in humans. An understanding of the risk involved is of paramount importance if we are to offer this to our patients.

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## 1. Introduction

Bronchial thermoplasty is a non-pharmacological treatment for severe asthma that involves the application of heat (65°C) to the airway wall using a bronchoscopically applied heat probe [1]. The mode of action is unclear however trials in animals and humans have demonstrated a reduction in airway smooth muscle [2, 3, 4, 5], and hypertrophy of airway smooth muscle cells has been found in non-fatal and fatal cases of asthma [6]. A canine study has also reported a reduction in airway responsiveness [2] which could be explained by a reduction in airway smooth muscle, but other unknown mechanisms may also exist. The NICE guidelines for bronchial thermoplasty are currently being updated, with a wide consultation on the use of this procedure in the UK [7]. There is huge potential for benefit of bronchial thermoplasty in asthmatic patients, however there have been some reports of poor adverse outcomes following the procedure, including a case of heat-induced necrosis [8]. If this procedure is to be made more available to patients, then an understanding of the risk involved is extremely important.

## 2. Early Clinical Trials in Humans

An initial study [3] assessed the feasibility of bronchial thermoplasty in the human airway. This involved eight participants scheduled for lung resection as a treatment for cancer. Participants received bronchial thermoplasty in the 3 weeks before lung resection, where only bronchi within the lobe to be resected were treated. No adverse outcomes were reported as a result of treatment, however participants were not followed for sufficient time to assess for long-term adverse events. Additionally, one should note that all participants were smokers with a 20+ pack-year history. Three participants had COPD, one emphysema, and another had a positive TB skin test. The architecture of participants' lungs may not be representative of patients that will be candidates for bronchial thermoplasty.

The Asthma Intervention Research (AIR) [9] and Research in Severe Asthma [10] trials were two of the first randomised controlled trials to investigate bronchial thermoplasty in patients with asthma. In both trials, participants were split into active (to receive bronchial thermoplasty) and control groups and were monitored in two defined timeframes: the treatment and post-treatment periods. The treatment period lasted between 6-9 weeks and was defined as the period during which participants actively received bronchial thermoplasty (three procedures at intervals of

approximately three weeks). The post-treatment period was defined as the follow-up period during which participants did not receive active treatment. This distinction was made as early side effects could be expected in the active treatment group, for example due to bronchial irritation associated with bronchoscopy [11].

The AIR trial involved 112 participants that were normally managed with inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs). Participants were monitored for 6-9 weeks in the treatment period, and then to a total of 12 months in the post-treatment period. Adverse events were actively solicited via clinic visits, phone calls, and searching daily diaries that participants were asked to keep. The active treatment group reported 407 adverse respiratory events in the treatment period, compared to 106 in the control. There was a similar distribution of 'mild', 'moderate' and 'severe' events between groups, with the most frequently reported events dyspnoea, wheezing and cough. In the post-treatment period, the proportion of adverse respiratory events was similar between groups.

Similar results were obtained in the Research in Severe Asthma (RISA) trial [10], which involved 32 participants. As in AIR, participants were aged 18-65 and required ICS and LABAs for adequate asthma control, however a proportion also had more severe disease for which they were taking oral corticosteroids. Adverse respiratory events were monitored via clinic visits and phone calls. The active treatment group reported 136 respiratory adverse events in the treatment period, compared to 57 in the control. In the active treatment group, most respiratory adverse events were worsening of asthma symptoms, and included dyspnoea, wheeze and cough as reported in the AIR trial. However, more serious events were also reported in the active group, including 7 hospitalisations, 5 of which were due to exacerbations. There was no difference between groups in the post-treatment period.

Both studies reported transient worsening of asthma symptoms post-bronchial thermoplasty. Most respiratory adverse events occurred within 1 day of the procedure and resolved within a week, which suggests that whilst symptoms are likely related, they are mostly temporary. However, neither the AIR or RISA trials were blinded, and so there is an increased likelihood of a placebo effect from treatment. A randomised sham-controlled trial, such as AIR2 [12], is gold-standard in preventing this.

### 3. Prevention of the Placebo Effect: AIR2

AIR2 is a multicentre, randomised, double-blind and sham-controlled trial that sought to assess the effectiveness and safety of bronchial thermoplasty in 288 adult participants [12]. Participants required ICS and LABAs for adequate asthma control, and were allowed to be taking additional medications, including oral corticosteroids. The sham group were given procedures that mimicked real bronchial

thermoplasty treatment, with identical audio and visual stimuli produced without releasing energy. Patients were evaluated at the end of the treatment periods, as well as at 3, 6, 9 and 12 months, where adverse events were actively solicited. Subjects were also asked to keep diaries for parts of the study. During the treatment period, both groups saw an increase in adverse respiratory events, but with more events reported in the active group compared to the sham control (85% vs. 76%). Interestingly, the significant increase in the sham control group suggests that many adverse respiratory events may be attributable to the bronchoscopy procedure rather than the application of radiofrequency energy, however this distinction will not however affect clinical practice. The severity of adverse respiratory events did differ more so between groups, with the active treatment group reporting more than double (3.1%) the proportion of severe cases compared to the control (1.5%). This is mirrored in the number of hospitalisations between groups, with 19 hospitalisations occurring in the active treatment group (16 participants) and 2 in the control (2 participants). Reasons for hospitalisation in the active treatment group included worsening of asthma, lower respiratory tract infections and haemoptysis. The reason for hospitalisation in both sham control patients was due to worsening asthma symptoms. In line with previous trials, most respiratory adverse events occurred within one day of the procedure and resolved within a week. This was also the case for adverse events that required hospitalisation, with over half (10 in 19) of all hospitalisations in the active group occurring on the day of procedure. In the post-treatment period, fewer adverse respiratory events were reported in the active treatment group compared to the control. There was a 36% risk reduction in participants reporting worsening of asthma symptoms in the active group compared to the control, and an 84% risk reduction in ED visits. As with previous trials, this suggests that most adverse respiratory events are transient and resolve quickly. The risk reduction in symptoms and ED visits demonstrates the efficacy of the treatment.

The patient with haemoptysis in AIR2 was managed with bronchial artery embolization, but the cause of haemoptysis and any association with the procedure is unclear. Little is known about the effect that bronchial thermoplasty may have on the pulmonary vasculature, but there has been one reported case of bronchial artery pseudoaneurysm [13] occurring post-procedure. Bronchial artery pseudoaneurysm is considered a rare event, and so it is difficult to understand the factors that increase the likelihood of one occurring. As the cause of haemoptysis in the patient in the AIR2 trial was not investigated in the study, it is more uncertain whether bronchial thermoplasty may be included within these risk factors.

#### 4. Bronchial thermoplasty: safe in the long term?

All clinical trials considered so far have published results of participants at 1 year of follow-up. This informs us of the short-term risk associated with bronchial thermoplasty but does not tell us anything about the long-term safety of the procedure and potential adverse respiratory outcomes. Many of the participants in initial trials consented for continued follow-up, which provides additional information.

AIR2 continued to monitor 162 of 190 (85.3%) of the actively treated group for a total follow-up of 5 years [14]. Respiratory adverse events and related hospitalisations remained unchanged in years 2-5 compared with the first year after bronchial thermoplasty, with more common adverse respiratory events (incidence  $\geq 3\%$ ) being asthma symptoms, cough and wheeze. Additionally, 93 participants in this group had HRCT imaging at both baseline and 5 years follow-up, with images compared by an independent blinded radiologist. They found no structural abnormalities attributed to the procedure.

Similar results were obtained in 5-year follow-up of participants involved in AIR and RISA [15, 16]. In the extended AIR trial, 45 of 52 participants that received bronchial thermoplasty were followed to a total of 5 years, and 24 of 49 participants in the control group were followed to 3. Adverse respiratory events were solicited during annual evaluations and via review of medical charts. In both years 2 and 3 where the control group was monitored, there was no significant difference in the rate of respiratory adverse events or number of emergency room visits between groups. In the active treatment group, the rate of respiratory adverse events remained stable when they were followed to 5 years, which is supportive that bronchial thermoplasty is a safe procedure when considered in the long-term. Whilst these results are encouraging, the method of collecting information annually makes participants susceptible to recall bias. Transient or less severe respiratory events are more likely to be forgotten.

In the extended RISA trial [16] a similar method of annual evaluation was used for the 14 out of 15 active treatment participants that consented to follow-up. The rate of respiratory adverse events was unchanged in years 2-5 post-bronchial thermoplasty and was reduced compared to the first year after treatment. There were no incidences of pneumothorax, intubation, mechanical ventilation, cardiac arrhythmias or death as a result of the procedure. Respiratory adverse events were typical of asthma.

It should be noted that no trial continued to monitor the control group for the same duration as the bronchial thermoplasty group. In RISA and AIR2, the control group were not followed at all during the extended period of years 2-5, and in AIR the control group were only followed to year 3. This limits our ability to make a comparison of safety outcomes between the active and control groups.

#### 5. Bronchial Thermoplasty in 'Real Patients'

Results from AIR, RISA and AIR2 trials are supportive that bronchial thermoplasty is a safe procedure with predominantly transient and non-severe side effects. However, all of these trials have strict inclusion and exclusion criteria that limit which participants are included. There is concern that participants involved in these trials may not reflect 'real' patients that would receive this treatment.

NICE guidelines suggest that bronchial thermoplasty should be used for adults with severe asthma [7], defined as "asthma that requires treatment with high dose ICS plus a second controller to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy" [17]. AIR included participants requiring daily LABAs  $\geq 100\mu\text{g}$  and ICS  $\geq 200\mu\text{g}$  or equivalent. This ICS dose is low-dose, so AIR included participants that did not meet the ERS/ATS definition of severe asthma. Similarly, some of the trials had strict inclusion and exclusion criteria that eliminated participants with particularly severe asthma. Participants in AIR were required to have had stable asthma in the 6 weeks before the trial, and in AIR2 participants were excluded if they had frequent asthma-related hospitalisations. Severe asthma is classically associated with persistent symptoms and increased health care utilisation.[18] In both AIR and AIR2, participants were required to have an FEV1  $\geq 60\%$  predicted, though in a phenotypic study to characterise severe asthma, nearly half had a baseline FEV1  $< 60\%$  [18]. Through only including participants with stable asthma and with strict FEV1 criteria, many participants are eliminated from trials that may be future candidates for bronchial thermoplasty.

In 2015, some of the first results were published on bronchial thermoplasty in 'real life' patients compared to clinical trials [19]. 10 patients from the Difficult Asthma Service in Glasgow were selected for bronchial thermoplasty and compared to 15 patients that had been recruited to clinical trials at the same centre. The clinic patients were not excluded based on asthma exacerbations and had FEV1 predicted values of 45-96%, meaning that patients were included with lung function poorer ( $< 50\%$ ) than that required for all clinical trials at the centre. Patients were evaluated during the treatment and post-treatment periods. Adverse respiratory events reported by patients were similar to those in clinical trials [9, 10, 11], with most events reported being transient worsening of asthma symptoms.

The ongoing PAS2 trial [20] is a similar study that compares the results of 190 'real-world' patients with AIR2. Compared to AIR2, more PAS2 participants experienced severe exacerbations (74% vs. 52%) and hospitalisations (15.3% vs. 4.2%) in the 12 months before bronchial thermoplasty, therefore representing a population with much poorer asthma control. Participants were evaluated during the treatment period, and in the post-treatment period

which currently extends to 3 years. During the treatment period, the percentage of participants requiring hospitalisation or prolonged hospitalisation was comparable between PAS2 (13.3%) and AIR2 (8.4%) trials. However, subjects in the PAS2 trial were significantly more likely to experience severe exacerbations and ED visits compared to AIR2. During the post-treatment period, the rate of respiratory adverse events was similar between trials.

These results suggest that patients with poorer asthma control may be more likely to experience severe exacerbations in the treatment period compared to those with more stable asthma. The procedure of bronchoscopy is associated with complications, including exacerbation of obstructive airway disease [11]. Patients with more severe asthma may be at higher risk of complications from bronchoscopy in bronchial thermoplasty due to a higher baseline for obstructed airway disease.

## 6. Conclusion

The results of clinical trials show that bronchial thermoplasty is safe in the short and long-term to 5 years. This is supported by a 2014 systematic review [21] of AIR, RISA and AIR2 trials that showed whilst the bronchial thermoplasty group had an increased risk of respiratory adverse events during the treatment period (RR 3.50), most events were mild or moderate and resolved within one week. There was no significant difference in the risk of adverse events in the post-treatment period. One can conclude that bronchial thermoplasty therefore has a reasonable safety profile, but we should continue to be aware of and investigate more severe adverse respiratory events that may be associated with the procedure. Similarly, an understanding of the long-term safety of bronchial thermoplasty beyond 5 years will become apparent with continued monitoring of patients involved in clinical trials. NICE advocate making patients aware that the long-term safety of this procedure is not well understood [14].

Furthermore, much is unknown about which patients will benefit most from bronchial thermoplasty and how the procedure should be applied in clinical practice. Notably is a case in which bronchial thermoplasty produced no improvement in asthma symptoms but caused dangerous exacerbations in a patient with severe asthma [22]. Additionally, among chest physicians there have been concerns about the effectiveness of bronchial thermoplasty in patients with asthma and concomitant bronchiectasis. Further evaluation is required to understand which patients are suitable candidates for the procedure.

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