

Bronchial thermoplasty: Where there is smoke, there is fire

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ABSTRACT

Bronchial thermoplasty (BT) is the first nonpharmacologic interventional therapy approved by the U.S. Food and Drug Administration in 2010 for severe asthma. This approval was based on randomized sham-controlled trial called Asthma Intervention Research (AIR) 2 published in 2010. BT involves the application of radiofrequency energy to airways with an aim to selectively ablate airway smooth muscle. BT is currently marketed for patients with "severe" asthma. Most practicing clinicians apply this severity category to patients with oral corticosteroid dependence, frequent exacerbations, or a significantly reduced forced expiratory volume in 1 second along with a poor quality of life. Did the patients studied in the AIR-2 trial have these clinical features? Was there a reduction in severe asthma exacerbation achieved in the intervention group? Did any of the primary or secondary end points in the AIR-2 trial show a positive signal? There continues to be controversy regarding patient selection and primary outcome. Its efficacy in the management of the patient with difficult-to-manage asthma is uncertain. This review covered pertinent aspects of BT, the design and results of the AIR-2 trial, and provides the practicing allergist with a comprehensive overview of this therapy.

(Allergy Asthma Proc 36:251–255, 2015; doi: 10.2500/aap.2015.36.3857)

What Is Bronchial Thermoplasty?

Bronchial thermoplasty (BT) is a bronchoscopy-based intervention for asthma that involves the application of radiofrequency (RF) energy to *visible* proximal airways. A special catheter designed to deliver RF pulses is advanced down to the level of visible segmental and subsegmental airways. Sequential RF pulses are applied in a methodical fashion to cover all visible airways of each lobe of the lung. The therapy is typically performed in three outpatient treatment sessions. Both upper lobes are treated in the first session, followed by a separate session for each of the lower lobes. The right middle lobe is not treated. Airways that have been previously treated with BT cannot be re-treated. In addition, patients with pacemakers, defibrillators, or other implanted medical devices are not eligible for BT. The RF energy pulse selectively ablates airway smooth muscle (ASM) in treated airways. Early animal and human studies documented selective loss of ASM without significant fibrosis or epithelial injury.¹ The selective ablation of ASM is thought to reduce airway hyperresponsiveness, airway obstruction, and asthma symptoms.¹ The distal airways (<2–3 mm in diameter) account for ~10% of the total airway resistance in normal healthy subjects. However, in patients with asthma, distal airway inflammation and mucus hypersecretion may result in these smaller air-

ways being the predominant site for airflow limitation, increased resistance, and airway hyperresponsiveness.² BT does not treat these smaller airways and thus has no impact on distal airway resistance and inflammation.

Overview of the AIR-2 Trial

BT was approved by the U.S. Food and Drug Administration in April 2010 for adult patients (18 years and older), "whose severe and persistent asthma is not well-controlled with inhaled corticosteroids and long-acting β -agonist medications."³ This approval was primarily based on the results of the pivotal AIR-2 trial, which was a high-quality multicenter (multinational) double-blind, sham controlled, randomized clinical trial. Subjects with severe asthma were randomized on a 2:1 basis to receive either BT or sham thermoplasty.⁴ The subjects in the sham group underwent bronchoscopy and the BT procedure in three separate sessions similar to the intervention group. The only difference was that no RF energy was delivered during the sham procedure.

A total of 288 adult patients were analyzed, of which 190 subjects underwent BT and 98 subjects underwent sham thermoplasty (2:1 randomization). Severe asthma in this study was defined by the use of high-dose inhaled corticosteroids and a second controller for maintenance therapy ($\geq 1000 \mu\text{g/day}$ of beclomethasone or an equivalent, and $\geq 100 \mu\text{g/day}$ of salmeterol or an equivalent) for at least 4 weeks. Subjects with moderate airflow obstruction (prebronchodilator forced expiratory volume in 1 second [FEV_1] $\leq 60\%$) were excluded. In addition, the subjects who required for $\geq 10 \text{ mg}$ of prednisone a day for control were excluded. As a result, only seven subjects in the BT

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The authors have no conflicts of interest to declare pertaining to this article
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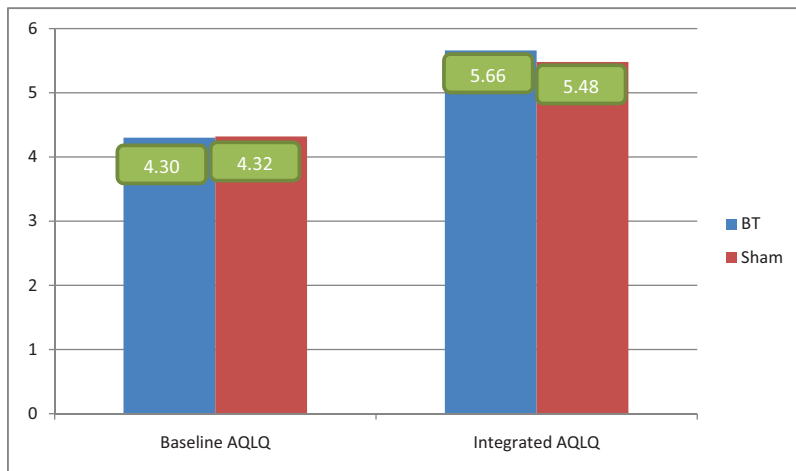


Figure 1. AQLQ values: Baseline and integrated AQLQ (average of the 6-, 9-, and 12-month AQLQ scores).

group and one subject in the sham group were on chronic oral corticosteroids (mean dose, 6.4 mg in the BT group). Also excluded were subjects with three or more hospitalizations or lower respiratory tract infections or four or more oral corticosteroid pulses within the previous year. Thus, subjects with asthma and with frequent exacerbations were specifically excluded from this study. This is interesting because current marketing of BT specifically highlights the reduction in asthma exacerbations as a benefit of BT. Blinding of the study participants in the trial was of concern, with more subjects in the thermoplasty arm able to correctly guess their treatment allocation after the first bronchoscopy procedure.⁴

What Was the Primary End Point of the AIR-2 Trial?

The primary end point of the AIR-2 trial was an improvement in the asthma quality of life questionnaire (AQLQ) score from baseline to 12 months. The baseline AQLQ score (before thermoplasty) was compared with the average of the 6-, 9-, and 12-month AQLQ scores after thermoplasty (integrated AQLQ).

Some Background About the AQLQ

The AQLQ is an asthma-specific quality-of-life (QOL) scale, with higher values denoting a better QOL.⁵ The AQLQ has 32 items in 4 domains: activities (12 items), asthma symptoms (11 items), emotional function (5 items), and environmental exposure (4 items). Every QOL scale has a minimal clinically important difference (MCID), which allows the clinician to determine if the numeric change in the QOL scale before and after the intervention is of clinical importance and/or significance. The MCID for the AQLQ scale was determined to be 0.5 (range, 0.42–0.58), with higher scores (a greater positive change) indicating improved asthma-related QOL.^{5,6} For example, if a subject's AQLQ increased from 4.5 to 5, it would mean

that he or she experienced a slight improvement in his or her asthma-related QOL. An AQLQ score increase of 1 (range, 0.77–1.51) would indicate a moderate improvement, whereas an improvement of ≥ 1.5 would indicate a large improvement in asthma-related QOL.

The Trial Failed to Reach the Primary End Point

The AQLQ score improved by 1.16 ± 1.23 in the sham group (a moderate improvement) and by 1.35 ± 1.10 mean (SD) in the thermoplasty group (also a moderate improvement), with a difference in AQLQ scores between the two groups of only 0.19 (Fig. 1).⁴ The difference of 0.19 between the two groups did not achieve statistical significance in the AIR-2 trial.⁴ Moreover, 0.19 is only approximately one-third of the MCID of 0.5. Thus, it would fair to say that the QOL improvement seen in patients who received BT was no different from those who received a sham procedure. This lack of improvement in the primary end point was pointed out in detail in a follow-up Letter to the Editor⁷ by the investigators who had written the original commentary that accompanied the AIR-2 trial.⁸

What About Individual AQLQ Domains and Subgroup Analysis?

It has been argued that a greater proportion of subjects in the BT group achieved an improvement of ≥ 0.5 compared with the sham group, thus proving a beneficial effect of BT.⁹ This is a specious argument for a number of reasons. First, if enough patients in the BT group had really improved compared with the sham group, then the change in the individual AQLQ scores would have resulted in a real statistical difference between the two groups in their overall AQLQ scores. An analogy would be to say that a new antihypertensive agent is beneficial because more subjects in the intervention group achieved a ≥ 5 mm/Hg reduction in their blood pressure; however, what if the two groups showed no statistical difference in their overall blood

Table 1 Health care utilization and asthma symptoms in the posttreatment period

	BT	Sham
Hospitalizations	5 subjects (6 admissions) (including 1 subject had 2 admissions)	4 subjects (12 admissions) (including 1 subject with 9 admissions)
ED, visits/subject/y	0.07 (13 visits)	0.43 (42 visits)
Subjects who reported worsening of asthma, %	27	43

pressure responses? Would we still say that the new agent is beneficial in lowering blood pressure? In a similar fashion, the posttreatment AQLQ score in the AIR-2 trial was no different between the sham and BT groups. This aggregate response takes into account all individual subject responses in the two arms. Although a larger proportion of patients in the BT group achieved a ≥ 0.5 improvement in their AQLQ score, *not enough of them* achieved that improvement for the overall groups to show a statistical difference. This is the whole point of statistical testing.

The second reason is the clinical significance of an AQLQ MCID threshold of 0.5. Recall that an AQLQ improvement of 0.5 equates to subjects saying that their asthma is “a little better” or “somewhat better.” On the self-reported scale used for the development of the MCID, this was just one category better than the subject saying that his or her asthma was “almost the same, hardly any better at all.”⁵ One must also remember that, in the AIR-2 trial, more patients in the BT group were able to correctly guess their treatment allocation group, which raised a question about a placebo effect in QOL reporting.⁴ Thus, an AQLQ score cutoff of 0.5 equates to a weak signal regarding any improvement in asthma-related QOL. When one considers that the difference in AQLQ score between the two groups in the AIR-2 trial was only 0.19, it becomes quite apparent that QOL did not improve at all in the BT group.

Also, none of the secondary end points achieved statistical significance.⁴ The two groups did not differ in clinically important end points, such as FEV₁ (both before and after bronchodilator), asthma control questionnaire scores, total symptom scores, morning peak expiratory flow, and rescue medication use. If BT were truly effective, one would have expected many of these variables to also show a positive signal, especially the asthma control questionnaire and symptom scores.

What About Emergency Department Visits and Hospitalizations in the AIR-2 Trial?

The AIR-2 trial claimed a reduction in unscheduled physician office visits, emergency department (ED) visits, and hospitalizations (Table 1). A look at Table 1 would make one realize that these three outcomes are

all interrelated. For example, a patient who was hospitalized due to severe asthma was also more likely to have visited the ED and also be classified as having had a severe asthma exacerbation. This is an important point because there seems to be at least one outlier in the sham group (with 9 hospitalizations) who may have skewed the overall data toward thermoplasty. This subject likely contributed to all three end points by having multiple ED visits and multiple severe asthma episodes in addition to the subject's hospitalizations. Another critical point is that the AIR-2 trial *specifically excluded* subjects with frequent exacerbations or repeated hospitalizations, which brings into question its marketing as a treatment for patients with frequent exacerbations and hospitalizations. Health care utilization was a planned outcome measurement for this study and study design.

How Is the AIR-2 Trial Different From the Previously Published Trials of BT?

The AIR-2 trial is the only double-blind, sham controlled, randomized controlled trial available for BT. The other trials of BT in human subjects were not sham controlled.^{10–12} This is extremely important because any invasive procedure (such as BT) is likely to produce a strong placebo response in subjects with asthma.¹³ The robust AQLQ score improvement seen in the sham thermoplasty arm of the AIR-2 trial is further proof of the potential power of the placebo response.

Why Is a Sham Controlled Trial So Important in Asthma?

Asthma is a clinically defined entity with vast inter-subject variability in disease perception, disease severity, and QOL. The placebo effect was elegantly shown in a recent trial by Wechsler *et al.*¹³ They showed that subjective improvement in asthma does not necessarily correlate with objective improvements in lung function. In their study, they administered either albuterol (active arm) or a dummy (placebo arm) inhaler to subjects in a blinded fashion, and they found that the subjects in both arms experienced symptomatic relief in their asthma symptoms regardless of whether they

had received an active (albuterol) or a dummy inhaler.¹³ However, when objective testing was performed, only the subjects who received albuterol demonstrated an improvement in the FEV₁.¹³ Thus, this study demonstrates the powerful effect that a placebo intervention can have on subjective assessment of asthma symptoms and QOL. This concept is extremely important when one assesses the evidence regarding thermoplasty.

The AIR-2 trial is the only sham controlled randomized trial of thermoplasty ever performed. The AIR-2 trial was preceded by the AIR trial¹¹ and the research in severe asthma trial,¹² both of which had no sham control arms. Thus, the results of these two previous trials need to be interpreted with a great deal of caution given the strong potential for a placebo effect in the thermoplasty arm. Combining data from these trials with the AIR-2 trial is not advisable given the different study design and lack of follow-up data in the sham controlled arm of the AIR-2 trial. The U.S. Food and Drug Administration approval process regarding thermoplasty also deserves some comment here, and this topic has been addressed in more detail elsewhere.¹⁴

Do the AIR-2 Postapproval Studies Provide Any Useful Information Regarding Efficacy?

Two postapproval studies have reported on safety and efficacy after thermoplasty.^{15,16} The biggest shortcoming of these reports is the lack of any information regarding the sham control arm. One should again recall that the sham control arm had a substantial improvement in AQLQ score (1.16), which was similar to the BT group. How can one assess the relative merits of BT over a sham procedure if no follow-up was ever carried out in the sham group? It is quite conceivable that the subjects in the sham group maintained their improved AQLQ score over time and did quite well over time. How can we compare rates of asthma exacerbations or hospitalizations when the control group is lost to follow up? The only way to address persistent effectiveness in an interventional study is to provide data in both the control and the intervention arms.

An analogy to this situation would be a sham controlled trial of a new RF ablation device to convert atrial fibrillation into sinus rhythm. If the investigators were to report on 5-year outcomes only for the patients undergoing the RF procedure and not on the patients undergoing the sham procedure, then how would one know whether the real ablation was any better than the sham procedure in maintaining patients in a sinus rhythm? This is especially important in a disease such as asthma in which strong placebo effects can play an important role in asthma symptom perception. In fact, 5-year follow-up data from the first thermoplasty study (The AIR trial),¹⁷ showed no difference in exac-

erbation rates, ED visits, hospitalizations, FEV₁, or oral corticosteroid usage between the BT and control groups. Interestingly, during years 1 and 2, there was a nonsignificant trend toward increased hospitalizations in the BT arm! Thus, reporting follow-up outcomes only in the thermoplasty arm in the AIR-2 trial is without any meaning and does not inform the clinician regarding the benefits or risks associated with thermoplasty. This is even more relevant given a recent publication about a patient whose thermoplasty failed and was later found to have no reduction in ASMs in the airway sites where thermoplasty had been previously performed.¹⁸ The overall concerns regarding thermoplasty are reflected in the cautionary position of the American Thoracic Society/European Respiratory Society Severe Asthma Task Force.¹⁹ The task force mentions in its report that thermoplasty be performed only in the context of an institutional review board approved independent systematic registry or a clinical study. The report also mentions having very low confidence in the currently available estimates of the effects of BT in patients with severe asthma.¹⁹

Practical Questions

Would My Steroid-Dependent Patient With Asthma Benefit From BT?

The AIR-2 trial did not include a sufficient number of patients who were on chronic oral corticosteroids. In fact, only seven patients (3.7%) in the BT arm and one patient in the control arm were reportedly on prednisone. The mean dose of oral steroids for those in the BT arm was 6.4 mg. Thus, we do not have any randomized controlled evidence to support the claim that BT works in patients who are chronically dependent on oral corticosteroids.

My Patient With Asthma Has a Prebronchodilator FEV₁ Value of 50%: Will He or She Benefit From Thermoplasty?

The mean pre- and postbronchodilator FEV₁ of the subjects in the BT arm were 77.8 and 86.1, respectively.⁴ These values did not change after treatment. Thus, patients with an FEV₁ of 50% were not included in the AIR-2 trial, and we do not have sham controlled evidence regarding the short-term or long-term safety (or efficacy) of BT in patients with severe obstruction.

Will My Patient With Elevated Exhaled Oral Nitric Oxide and Immunoglobulin E Levels Benefit From Thermoplasty?

No phenotyping data were reported as part of the AIR-2 trial. Thus, we do not have any information about specific patient subgroups that might have benefited (or have been harmed) by BT. In an era in which an increasing number of biologic agents are being de-

veloped for specific asthma phenotypes, it is unfortunate that no such information is currently available with regard to thermoplasty.

CONCLUSION

BT does not meet the burden of proof required to incorporate this procedure into routine clinical practice. The pivotal AIR-2 trial did not show improvements in any of the primary or secondary end points. More importantly, data from the AIR-2 Trial should not be conflated with previous thermoplasty studies due to a lack of a sham thermoplasty arm in those studies. BT requires further study and cannot be recommended at this time for the treatment of severe asthma.

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