Review Article

Bronchial thermoplasty-an update

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Abstract:

Bronchial Thermoplasty is a procedure that involves the delivery of radiofrequency energy during bronchoscopy to airways in order to selectively ablate airway smooth muscles. Bronchial Thermoplasty was approved by the FDA in 2010 and remains the only device based non-pharmacological treatment approach for severe asthma. We appraise the trials leading to the approval of Bronchial Thermoplasty in light of the FDA approval process. Current international guidelines regarding use of Bronchial Thermoplasty and emering pharmacological options for severe asthma are reviewed.

Keywords:

AIR trial, AQLQ, Bronchial Thermoplasty, Severe Asthma

Clinicians continue to have questions with regard to the exact role of bronchial thermoplasty (BT) in the management of their severe asthma patient. A review of this topic is especially relevant given the availability of multiple new monoclonal antibody (mAb)-based therapies with excellent safety and efficacy in specific asthma phenotypes. Although the authors have previously published on this topic,[1,2] we believe that there is a definite value in providing an updated review of BT and its role (if any) in the management of the severe asthma patient.

What is Bronchial Thermoplasty?

BT involves the delivery of radiofrequency (RF) energy through bronchoscopy to all visible airways (except the right middle lobe) to selectively ablate airway smooth muscles (ASM). BT was approved by the Food and Drug Administration (FDA) in 2010 and remains the only device-based nonpharmacological treatment approach for severe asthma.[3] The BT catheter is passed through the working channel of the bronchoscope, and RF energy is delivered through an expandable wire array at the tip of the BT catheter. BT is typically performed in three sessions (1st session: Right lower lobe followed by the left lower lobe in the 2nd session and then both upper lobes in the 3rd session). During each session, airways are approached in a systematic fashion starting from the most distal visible airway in each subsegment and then moving proximally. The only part of the lung not treated with BT is the right middle lobe. Airways once treated with BT cannot be retreated.[4] The decreased ASM mass is postulated to reduce airway hyperresponsiveness and bronchial obstruction with improvement in asthma symptoms. The FDA approved BT for the treatment of severe persistent asthma in patients >18 years whose asthma is not well controlled with high-dose inhaled corticosteroids and long-acting beta-agonists.

Clinical Trials of Bronchial Thermoplasty

There have been three clinical trials of BT performed to date. The Asthma Intervention Research (AIR) trial was a randomized controlled trial (RCT) published in 2007. It was neither blinded or sham controlled. Individuals were randomized 1:1 to either BT or the control arm. The AIR trial demonstrated feasibility and safety of BT in human individuals.[5] The Research in Severe Asthma (RISA) trial was also

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published in 2007. This was a much smaller study of only 15 patients in the BT arm and 17 in control arm. This was also an open, 1:1 randomized control trial with no sham component.[6] The 3rd trial (AIR-2) published in 2010 was the pivotal trial and the primary evidence base for the FDA approval of BT.

A Critical Analysis of the Asthma Intervention Research Trial 2

Let us spend some time analyzing the AIR-2 trial which was a multicenter (multinational) double-blind, sham-controlled, randomized clinical trial. Participants with severe asthma were randomized on a 2:1 basis to receive either BT or sham thermoplasty.[7] Table 1 compares these 3 trials. Patients enrolled in AIR-2 were aged 18–65 years and needed to be on stable doses of inhaled corticosteroids (>1,000 mg/d of beclomethasone or equivalent and >100 mg/d of salmeterol or equivalent) for at least 4 weeks. Did the AIR-2 trial achieve its primary end-point? The Answer is a resounding NO (discussed in detail in the next paragraph). Did the AIR-2 trial achieve any meaningful secondary end-point? The answer again is NO. What about the supposed reduction in asthma exacerbations, emergency room (ER) visits, hospitalizations, and days lost from work in the BT arm of the AIR-2 trial? These analyses were done *post hoc* and were not part of the declared primary or secondary end-points of the AIR-2 trial. (More about this later).

Since the publication of AIR-2, there has been considerable critique of the reported results, and its application to clinical practice and these are summarized in Table 2. Let us start by again pointing out that the AIR-2 study *did not achieve* its primary end-point.[2] Let us take a closer look at this primary end-point, the Asthma Quality of Life Questionnaire (AQLQ) [Figure 1]. The AQLQ is a validated quality of life (QOL) tool in asthma patients and an increase in the AQLQ score correlates with improved asthma-related QOL. An AQLQ improvement of 0.5 is considered the minimal clinically important difference (MCID) and an increase of 0.5 in AQLQ correlates with the patient reporting that their asthma is "somewhat better" [Figure 1].[8] Similarly, a decrease in the AQLQ of 0.5 would correlate to the patient reporting their asthma as being "somewhat worse" [Figure 1]. Thus, it is easy to see why a change of 0.5 in the AQLQ was considered as the MCID because this correlates with patients reporting some small meaningful change in their asthma control. So what was the AQLQ difference between the sham and the BT arm in the AIR-2 trial? It was exactly 0.19, which is <50% of the AQLQ MCID of 0.5. A quick glance at Figure 1 will show that a difference of 0.11 in the AQLQ correlates with almost no change in asthma QOL. Thus, the AIR-2 trial failed to achieve its primary end-point which was to show a meaningful increase in the AQLQ among patients receiving BT.

What about the reported benefit in asthma exacerbations, ER visits, and days lost from work in the BT arm? It is very important to note that these end-points were not part of the original primary or secondary end-points of the trial and constitute a *post hoc* analysis. A very important fact to also point out is that AIR-2 trial *specifically excluded*

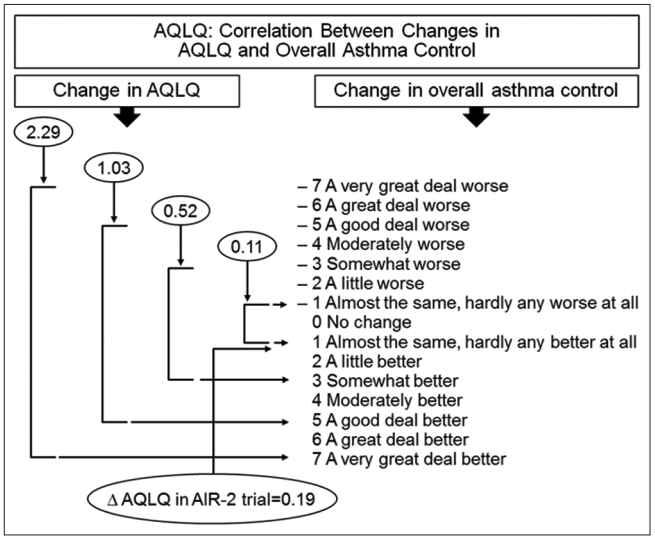


Figure 1: Correlation between change in Asthma Quality of Life Questionnaire and asthma severity

Table 1: Comparison of AIR, RISA, and AIR-2 trials

Trial	Year published	Study design	Number of patients	Randomization	Age (years)	Pre-BD FEV1 (% predicted)	ICS dose (mg/days) (beclomethasone or equivalent)	OCS dose (mg/days)	Primary endpoint
AIR	2007 (NEJM)	RCT	55 BT, 54 control	1:1 (BT: Control)	18-65	60-85	>200	0	Exacerbations
RISA	2007 (AJRCCM)	RCT	15 BT, 17 control	1:1 (BT: Control)	18-65	>50	>1500	<30	AQLQ
AIR-2	2010 (AJRCCM)	RCT/DB/sham controlled	196 BT, 101 control	2:1 (BT: Sham)	18-65	>60	>1000	<10	AQLQ

RCT=Randomized controlled trial, BT=Bronchial thermoplasty, FEV1=Forced expiratory volume-1 s, ICS=Inhaled corticosteroid, OCS=Oral corticosteroid, AQLQ=Asthma Quality of Life Questionnaire, BD= Bronchodilator, DB= double bind

Table 2: Problems with the AIR-2 trial

Inclusion criteria
Nonsevere asthmatic with
Very few patients on oral steroids (3.7%)
Pre-BD FEV1 >60% predicted
Patient phenotype (Th1/Th2 etc.): Not known
Statistical methods
Bayesian statistics
Univariate logistic regression
Primary end-point
AQLQ unchanged (except emotional component)
Secondary end-point
No change in airway hyperresponsiveness as measured by
FEV1 (pre- or post-BD)
Morning PEF
Percentage symptom-free days
Post hoc analysis
Unplanned analysis of health care utilization
Significant outlier effect
Rescue inhaler usage during and after the AIR-2 trial: Not reported
Characteristics of airway inflammation not assessed
Lack of
Bronchial biopsies
Induced sputum eosinophil counts
ENO
Lack of Sham group follow up
5 year report of treatment arm alone
No follow-up report on Sham arm
Peripheral airways treated with BT: No
Th2 mediated inflammation in asthma: Not addressed by bronchial thermoplasty

BT=Bronchial thermoplasty, ENO=Exhaled oral nitric oxide, FEV1=Forced expiratory volume-1 s, PEF=Peak expiratory flow, AQLQ=Asthma Quality of Life Questionnaire, BD=Bronchodilator

patients with frequent asthma exacerbations. Patients needing >10 mg of prednisone per day; having a history of three or more hospitalizations/lower respiratory tract infections or reporting four or more oral corticosteroids courses within the past year were excluded from the trial. Thus, the AIR-2 trial specifically excluded "frequent exacerbators" who are the very group of patients for whom BT is often considered in clinical practice. In addition, we have previously shown that all of these end-points are linked together. Thus, a patient going to the ER is likely to report a day lost from work as well as report an asthma exacerbation and also have a higher chance of being hospitalized. The problem with using such co-linear end-points is that a few outliers with severe asthma can alter the outcomes in all these end-points. For example, in the AIR-2 trial, one patient in the control arm had nine hospitalizations. It is very plausible that this patient also had a large number of ER visits, days lost from work, etc. Thus, a few outliers in either arm of the trial could have altered outcomes for or against BT in the AIR-2 trial.[9] It so happened that these outliers were in the control arm and thus could have contributed to the "efficacy" of BT in the AIR-2 trial.

Additional concerns surround the lack of other data commonly reported in asthma trials. For example, rescue inhaler use before and after BT was not included in the trial. The asthma in these patients was not phenotyped. We do not have any information regarding the eosinophil count or other markers such as exhaled oral nitric oxide in these subjects. In addition, in the long-term follow-up trials after BT published so far, there has been no follow-up published on the sham arm at all.[10] How can anyone judge the long-term safety or efficacy of BT when there is absolutely no long-term information available about the sham (control) arm of the AIR-2 trial. This has been previously pointed out.[1,2]

Furthermore, given that BT reduces ASM mass by RF ablation; one would expect to see decreased bronchial hyper-responsiveness and/or improvement in airway obstruction. However, none of the BT trials to date have showed a statistically significant improvement in airway hyperresponsiveness or forced expiratory volume-1 s (FEV1). An explanation for this might lie in the small airways which are untreated in BT and which are considered to be the source of considerable airflow resistance, mucous production, and inflammation in asthma patients. The small airways are not only difficult to reach by standard inhaled medications but also remain untreated in BT (which only treat large airways visible through the bronchoscope.

The Placebo Effect and Bronchial Thermoplasty

What about the placebo effect in the BT trials to date? It is crucial to point out that the AIR-2 trial is the only sham-controlled trial of BT ever published. Both the AIR and the RISA trials were not sham-controlled. Why is this important? An asthma study by Wechsler *et al*. elegantly pointed out the power of the placebo response in asthma. In that study, all blinded participants experienced symptomatic relief in their asthma symptoms regardless of whether they had received an active (albuterol) or a dummy inhaler.[11] However, when lung function testing was performed, only the participants who received albuterol demonstrated an actual improvement in their FEV1. Given the considerable subjective nature of asthma symptoms, this raises questions about whether the beneficial effects of BT reported in the AIR and RISA trial were the result of a placebo effect. This point was clearly demonstrated in the AIR-2 trial with the sham arm reporting a significantly improved AQLQ after sham BT (AQLQ increasing from 4.32–5.48 post BT). If one recalls the previous discussion about magnitude of increase in AQLQ; this increase of 1.16 in the sham arm would equate to patients reporting that their asthma was a "good deal better" after undergoing sham BT! Another important point to note here is that more

patients corrected guessed their treatment in the BT arm of the AIR-2 trial and this may have also lead to a more favorable reporting of their symptoms due to the placebo effect. Studies also show that the placebo effects remain unchanged in magnitude for a considerable period of time even after a single intervention such as BT.[12]

Adverse Effects of Bronchial Thermoplasty

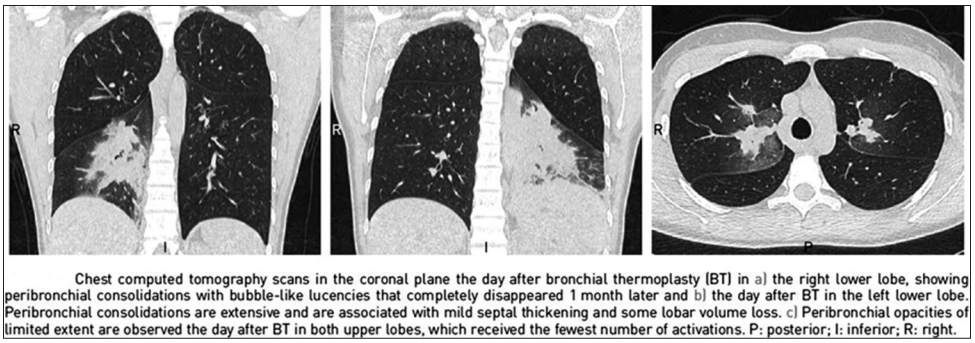
Recent reports have also highlighted adverse outcomes associated with BT[13,14] A recent report is alarming because it shows a high incidence of acute postoperative inflammation and pulmonary consolidations, extending far beyond the treated airways.[15]. One study reports computed tomography abnormalities extending beyond the BT-treated zones with involvement of the adjacent untreated lung lobe in one-third of cases [Figure 2].[16] Reports of reversible complete lobar collapse, asthma exacerbations, pulmonary abscess, pulmonary pseudoaneurysm, and massive hemoptysis requiring embolization have also been reported.[17-19] Thus, the long-term implications of this significant BT associated lung injury are uncertain but definitely raise significant concerns about the long-term safety of this procedure.

The Food and Drug Administration Device Approval Process and its Implications for Bronchial Thermoplasty

Clinicians often confuse the approval process for devices and drugs. The FDA gained statutory authority to regulate medical devices in 1976. Prior to that, medical devices were grouped together with other commercial nonmedical devices and regulated by individual state-based agencies. The FDA currently classifies devices into low-risk (Class I) devices such as bandages, stethoscopes, etc., medium-risk (Class II) devices such as peripheral vascular catheters etc., and high-risk devices (Class III) such as defibrillators, stents, BT, etc. Class III devices (including BT) typically have to go through a rigorous premarket approval process before they are allowed to be marketed. BT underwent which called pretypically by do not have a firm understanding of often confuse the Food and Drug Administration Modernization Act (FDAMA) modernization act also known as the FDAMA was passed in 1997. Since then, FDA has had different guidelines for drug and device approval. Under the FDAMA act, one or more clinical investigations are necessary for device approval. Simply stated, this new standard means that only one favorable trial is needed to bring a device into the market for consumer use. The approval of BT for human use was *based on a single pivotal study* under this FDA regulation. This is in contrast to FDA's rules of pharmacological therapy approval process which requires >1 well-controlled trial showing benefit of therapy and lack of long-term adverse events. The only time a single pivotal trial is valid for prescription drug approval is in the case of rare diseases and lack of possibility in conducting a second trial.[20] Asthma is hardly a rare disease and the AIR-2 trial did not even come close to achieving its primary end-point. This raises the very obvious question. Why are clinicians being encouraged to change their practice on the basis of a single trial that failed to achieve its primary end-point? BT may well be effective in a subset of asthma patients. To prove this, however, requires well conducted sham-controlled clinical trials of well-phenotyped asthma patients. This should be the benchmark for BT or any other intervention before it is accepted as an valid treatment option for asthma patients.

What are the Current Guidelines Regarding Bronchial Thermoplasty?

The European Respiratory Society (ERS) and American Thoracic Society (ATS) joint Task Force were the first to address the issue of BT in asthma in 2014. The ERS/ATS task force recommends that BT be performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry or a clinical study. The level of evidence was graded as very low-quality evidence indicating that the



Chest computed tomography scans in the coronal plane the day after bronchial thermoplasty (BT) in a) the right lower lobe, showing peribronchial consolidations with bubble-like lucencies that completely disappeared 1 month later and b) the day after BT in the left lower lobe. Peribronchial consolidations are extensive and are associated with mild septal thickening and some lobar volume loss. c) Peribronchial opacities of limited extent are observed the day after BT in both upper lobes, which received the fewest number of activations. P: posterior; I: inferior; R: right.

Figure 2: Immediate postbronchial thermoplasty computed tomography changes. Image adapted with permission

estimated effects of interventions are uncertain, and further research is likely to have an important impact on the resulting recommendations.[21] In 2014, the American College of Chest Physicians (ACCP) issued a position statement in response to problems faced by practicing clinicians for the coverage and payment for BT for severe persistent asthma patients. In the statement, BT was to be not considered experimental and was to be covered by insurance when offered to disabling severe persistent asthmatic patients.[22] The most updated guidelines we have available are from British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) and Global Initiative for Asthma (GINA), both published in 2016. Both recommend BT in severe asthmatics with need for further studies to demonstrate long-term safety and efficacy.[23,24] BTS/SIGN Grade A is for a well-conducted RCT. If the RCT results in high quality of evidence, with low risk of bias, this is considered 1 + and 1++ for level of evidence. GINA Grade B for level of evidence is granted for an RCT with a limited body of data. Expert Panel Report 3 Guidelines by National Asthma Education and Prevention Program and National Heart, Lung, and Blood Institute (NHLBI) have not been updated since 2007.[25] Table 3 summarizes the various societal consensus statements regarding BT in asthma, the level of evidence, and strength of the recommendation.[26]

What are the New Pharmacological Options for Severe Asthma?

Asthma is now recognized as a heterogeneous disease with varying phenotypes. With the advent of targeted therapies, asthma is becoming an increasingly phenotyped disease with potential for personalized medicine approaches.[27] Omalizumab was the first anti-immunoglobulin E to be approved for the treatment of asthma in 2003.[28] An indirect comparison of the BT posttreatment period to ongoing treatment with Omalizumab showed no significant differences in the risk for severe exacerbations.[29] In recent years, two new anti-interleukin 5 (anti-IL-5) mAb medicines have been approved for the eosinophilic phenotype of asthma. Numerous other targeted therapies for asthma are on the horizon.[30] Current and upcoming biological therapies for asthma are listed in Table 4. To date, BT has not been compared head to head to its biologic pharmacological counterparts approved for treatment of severe asthma. Another shortcoming of the AIR-2 trial is that phenotyping of asthma patients was not performed. Given the excellent safety and efficacy data of the IL-5 inhibitors in eosinophilic asthma, they are the preferred agent for refractory or severe eosinophilic asthma cases in our practice. The role of BT (if any) in the management of other asthma phenotypes is unclear and requires further study.

Conclusions

BT is the only FDA approved nonpharmacological treatment available for severe asthma patients. The only sham-controlled trial of BT (the AIR-2 trial) failed to achieve its primary end-point and has left many unanswered questions about the results reported in that trial. As a result, major societies including the ATS and the ERS recommend that BT be performed

Table 3: Current international society recommendations

Year	Society	Recommendation	Strength	Level of evidence
2007	EPR-3 guidelines by NAEPP and NHLBI[25]	BT was not addressed	N/A	N/A
2014	ERS/ATS task force[21]	BT be performed in adults with severe asthma only in the context of an Institutional Review Board approved independent systematic registry or a clinical study	Strong	Very low
2014	ACCP (chest)[22]	Chest believes that based on the strength of the clinical evidence, BT offers an important treatment option for adult patients with severe asthma who continue to be symptomatic despite maximal medical treatment and, therefore, should not be considered experimental	N/A	N/A
2016	BTS/SIGN[23]	BT may be considered for the treatment of adult patients who have poorly controlled asthma despite optimal therapy	Grade A	1+ and 1++
2016	The Saudi Initiative for Asthma by Saudi Thoracic Society[26]	In selected patients with moderate to severe persistent asthma, it has shown to improve various measures of asthma, including FEV1, quality of life, asthma control, exacerbations, and use of rescue medications	N/A	N/A
2016	GINA[24]	BT may be helpful in selected patients with severe asthma but more studies are needed to identify its efficacy and long-term safety in broader severe asthma population	N/A	Evidence B

GINA=Global Initiative for Asthma, SIGN=Scottish Intercollegiate Guidelines Network, BTS=British Thoracic Society, ACCP=American College of Chest Physicians, ATS=American Thoracic Society, ERS=European Respiratory Society, NHLBI=National Heart, Lung, and Blood Institute, NAEPP=National Asthma Education and Prevention Program, EPR=Expert panel report, BT=Bronchial thermoplasty, N/A=Not available, FEV1=Forced expiratory volume-1 s

Table 4: Current and upcoming biological therapies in asthma

Target	Medication	Clinical trial
Anti-IgE mAb	Omalizumab	Approved 2003
Anti-IL-5 mAb	Mepolizumab	Approved 2015
Anti-IL-5 mAb	Reslizumab	Approved 2016
Anti-IL-13 mAb	Lebrikizumab/ tralokinumab/ anrukinzumab	Phase 2/3
Anti-IL-4 receptor	Pascolizumab	Phase 2
CXCR2 antagonist	SCH527123	Phase 2
Anti CD4 mAb	Keliximab	Phase 2
Tyrosine kinase inhibitor	Masitinib	Phase 3
Anti-IL-2 IgG1 mAb	Daclizumab	Phase 2
Anti-TNF mAb	Infliximab/golimumab	Phase 2/3

IL=Interleukin, mAb=Monoclonal antibodies, TNF=Tumor necrosis factor, CXCR2=Cysteine-X-cysteine chemokine receptor-2

on in the context of an IRB approved study protocol. The safety of BT is also in question with recent reports of significant pulmonary parenchymal injury beyond treated airways. BT may be an effective treatment option in selected asthma phenotypes, but further sham-controlled studies are necessary to test those hypotheses. In the meantime, a growing number of targeted therapies with good efficacy are becoming available for specific asthma phenotypes.

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Conflicts of interest
There are no conflicts of interest.

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