CME CREDIT

EDUCATIONAL OBJECTIVE: Readers will describe the indications for bronchial thermoplasty

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Bronchial thermoplasty: A new treatment for severe refractory asthma

ABSTRACT

Bronchial thermoplasty was recently approved for treating severe refractory asthma that is not well controlled by high-dose inhaled corticosteroids and long-acting bronchodilator therapy. This article reviews its indications, evidence of efficacy, and protocols.

KEY POINTS

Bronchial thermoplasty involves the application of radiofrequency energy to the airways distal to the mainstem bronchi down to airways as small as 3 mm in diameter.

Treatments are done in three separate sessions, with careful monitoring before and after for respiratory complications that can occur in severe asthma. Airway complications and asthma exacerbations can occur up to 6 weeks after the last procedure, thus requiring close patient follow-up.

In clinical trials, including a randomized trial in which the control group underwent sham thermoplasty, bronchial thermoplasty had an acceptable safety profile while improving asthma quality-of-life scores, symptoms, and health care utilization.

Asthma now has a new treatment, but it isn't for everybody. Called *bronchial thermoplasty*, it is reserved for patients whose asthma is severe and refractory, as it involves three sessions of bronchoscopy, each lasting up to 1 hour, during which the smooth muscle layer is methodically ablated from the airway using radiofrequency energy.[1,2]

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The US Food and Drug Administration (FDA) has approved bronchial thermoplasty,[3] and although it does not cure asthma or completely eliminate its symptoms, patients with severe asthma that was not well controlled with medical therapy who underwent this procedure in clinical trials subsequently had fewer symptoms, enjoyed better quality of life, and needed less intensive health care (such as emergency room visits) than patients who did not undergo the procedure.[4–6]

Here, we present an overview of the pathophysiology of severe refractory asthma and the clinical trials of bronchial thermoplasty, its current protocols, and the status of this new treatment.

WHAT IS SEVERE REFRACTORY ASTHMA?

Asthma is a chronic inflammatory condition of the airways characterized by episodic symptoms of breathlessness, cough, and wheezing, which can wax and wane over time. Approximately 8.2% of the general population is affected.[7]

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Our understanding of the pathophysiology of asthma has improved over the past 20 years, and with the publication of clinical guidelines from the National Asthma Education and Prevention Program in 1991,[8] 1997,[9] and 2002,[10] outcomes have improved. Most people with asthma can control their symptoms if they adhere to anti-inflammatory therapies and avoid triggers. Yet 5% to 10% of asthma patients have severe refractory disease, and asthma accounts for nearly half a million hospitalizations every year.[11]

The latest guidelines, published in 2007, emphasize the importance of assessing the severity of asthma, including the patient's impairment (symptoms and limitations) and risk (likelihood of exacerbations).[12]

Workshop consensus definition of severe refractory asthma

A consensus group convened by the American Thoracic Society[13] defined asthma as severe and refractory if the patient meets at least one of the following major criteria:

- Takes oral corticosteroids continuously or nearly continuously (> 50% of year)
- Takes high-dose inhaled corticosteroids.

In addition, the patient must meet at least two minor criteria, ie:

- Takes a controller medication such as a long-acting beta-agonist, theophylline, or a leukotriene antagonist every day
- Takes a short-acting beta agonist every day or nearly every day
- Has persistent airway obstruction, ie, a forced expiratory volume in 1 second (FEV_1) less than 80% of predicted, or a peak expiratory flow that has a diurnal variability greater than 20%
- Has one or more urgent care visits for asthma per year
- Needs three or more oral corticosteroid "bursts" per year
- Has prompt deterioration when the dose of oral or inhaled corticosteroid is reduced by 25% or less
- Has had a near-fatal asthma event in the past.

Compared with people with mild asthma, people who have severe refractory asthma tend to be older, have fewer allergies, and make more use of intensive and urgent health care.[14]

Asthma accounts for nearly half a million hospitalizations every year

Asthma is due to both inflammation and bronchoconstriction

The pathophysiology of asthma involves both chronic airway inflammation and bronchoconstriction, the latter characterized by a greater response to methacholine. Histologic findings include excessive mucus secretion, epithelial cell injury, and smooth muscle hypertrophy. These changes can lead to persistent airflow obstruction that can be difficult to control with medical therapies.[12]

Bronchoconstriction can be reversed temporarily with bronchodilators, but no long-lasting therapy to reduce it has been available until now. Bronchial thermoplasty targets this gap in asthma management.

STUDIES OF BRONCHIAL THERMOPLASTY

Radiofrequency ablation has been used to treat other medical conditions such as lung cancer and cardiac arrhythmias.[15,16] Its use to treat asthma by eradicating smooth muscle cells from the airway wall began with studies in animals.[1] Later, studies were done in people without asthma,[2] then in patients with mild to moderate asthma,[17] and finally in patients with moderate to severe refractory asthma.[4–6]

These studies helped clarify which type of patients would be appropriate candidates and the outcomes to be anticipated, including adverse events.

Early studies

Danek et al,[1] in a study in nonasthmatic dogs, found that thermoplasty at 65°C or 75°C (149°F or 167°F) attenuated the airway's response to methacholine up to 3 years after treatment. As early as 1 week after treatment, airway smooth muscle was seen to be degenerating or absent, and the effect was inversely proportional to airway responsiveness.

Adverse effects of the procedure were cough, inflammatory edema of the airway wall, retained mucus, and blanching of the airway wall at the site of catheter contact. Three years later, there was no evidence of smooth muscle regeneration.

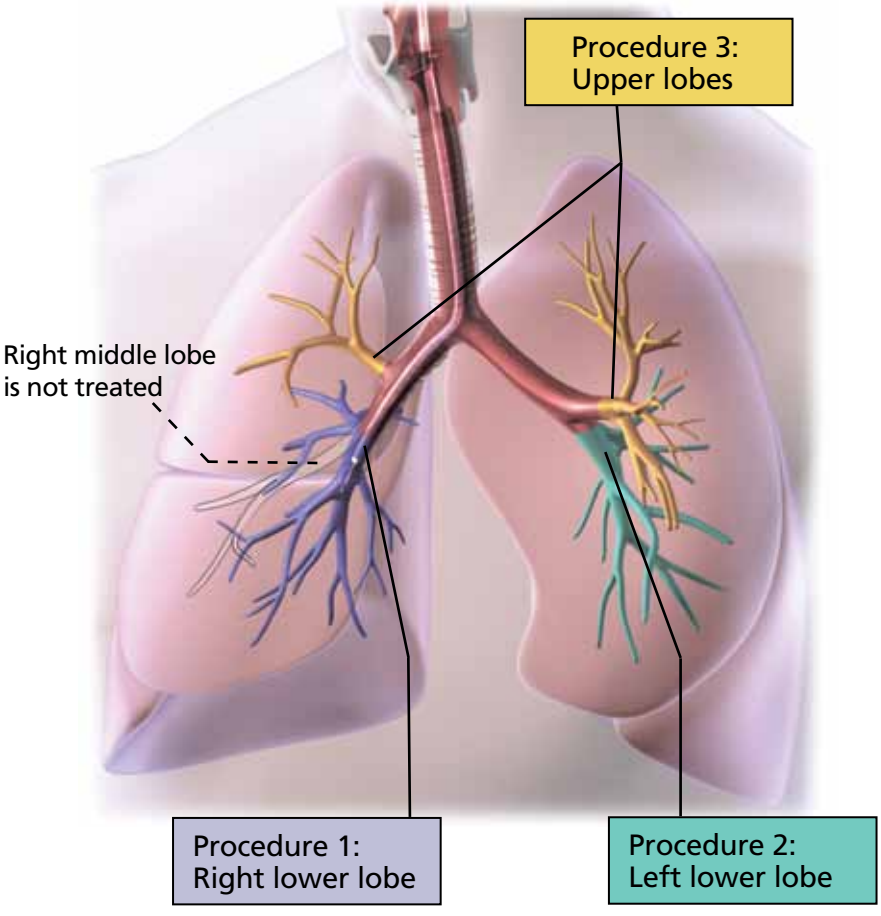
Miller et al[2] next performed a feasibility study in eight patients, mean age 58 ± 8.3 years, who were scheduled to undergo lung resection for lung cancer. Five to 20 days be-

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Bronchial thermoplasty for severe refractory asthma

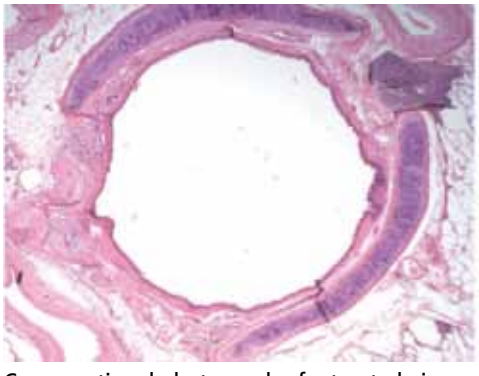
Bronchial thermoplasty involves delivery of radiofrequency energy to the airway wall, which ablates the smooth muscle layer, lessening bronchoconstriction and improving symptoms.

Treatments are done in three separate procedures, with meticulous mapping of the areas treated. The right lower lobe is treated in the first procedure, the left lower lobe in the second, and the two upper lobes in the third. The right middle lobe is not treated.

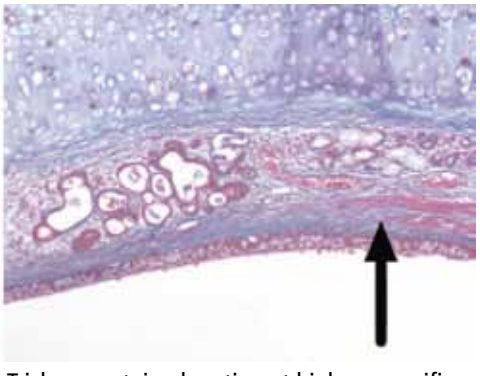




The thermoplasty device within the airway with the electrodes deployed.



Cross-sectional photograph of a treated airway from a patient with lung cancer resected 20 days after treatment. Magnification: 40x.



Trichrome-stained section at higher magnification (400x). Airway smooth muscle is largely absent to the left of the arrow.

PHOTOMICROGRAPHS FROM MILLER JD, COX G, VINCIC L, LOMBARD CM, LOOMAS BE, DANEK CJ. A PROSPECTIVE FEASIBILITY STUDY OF BRONCHIAL THERMOPLASTY IN THE HUMAN AIRWAY. CHEST 2005; 127:1999-2006. REPRODUCED WITH PERMISSION FROM THE AMERICAN COLLEGE OF CHEST PHYSICIANS.

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FIGURE 1

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fore surgery, the investigators performed thermoplasty at 55°C or 65°C (131°F or 149°F) in three to nine sites per patient, 1 cm from known tumors but within areas to be resected. There were no significant adverse events such as hemoptysis, respiratory infections, or excess bronchial irritation.

Bronchoscopy was done again at the time of resection; findings were generally unremarkable, with some airway narrowing and linear blanching. Bronchoscopy done earlier (within 5 days after thermoplasty) was more likely to show retained mucus or airway narrowing. Histologic findings in the resected and treated lungs ranged from normal to focal necrosis with inflammatory (noninfectious) pneumonitis of the parenchyma. Airway smooth muscle alterations were noted in about 50% of the area treated with 65°C (FIGURE 1).[2]

A pilot study in mild to moderate asthma

Cox et al[17] performed the first study of bronchial thermoplasty in patients with mild to moderate asthma. This was a prospective observational study in 16 patients who were younger than the patients in the previous study, with an average age of 30 years (range 24–58). They were given prednisone 30 or 50 mg the day before the procedure and on the day of the procedure. Three treatments were done, 3 weeks apart. The right middle lobe was not treated because the bronchus leading to it is relatively long and narrow, raising concern about damaging it.[18]

A major criterion for severe refractory asthma is oral or high-dose inhaled corticosteroid treatment

Results. The most frequent side effects were symptoms of airway irritation such as cough, dyspnea, wheezing, and bronchospasm. The mean time to onset was less than 1.7 days, and the mean time to resolution was 4.6 days after the most recent procedure. None of the patients needed to be hospitalized in the immediate postprocedure period.

In the 2 years after the procedure, there were 312 adverse events, mainly mild. Three (1%) of the adverse events were reported as severe, but they were deemed not related to the procedure. Yearly computed tomographic scans of the chest showed no structural changes such as bronchiectasis in the parenchyma or bronchial wall.

The FEV_1 was higher at 12 weeks and at 1 year after thermoplasty than at baseline but was not significantly different from baseline at 2 years.

At baseline, the patients reported that 50% of their days were symptom-free; this increased to 73% at 12 weeks ($P = .015$).

In addition, airway hyperresponsiveness decreased significantly, and the effect persisted over 2 years. The provocative concentration of methacholine that caused a 20% reduction in FEV_1 (the PC_{20}) was:

- 0.92 mg/mL at baseline (95% confidence interval 0.42–1.99)
- 4.75 mg/mL at 12 weeks (2.51–8.85)
- 5.45 mg/mL at 1 year (1.54–19.32)
- 3.40 mg/mL at 2 years (1.35–8.52).

Limitations of this study include the relatively small number of patients enrolled and their relatively stable asthma.

The AIR trial: A randomized trial in moderate or persistent asthma

The first large multicenter trial of bronchial thermoplasty, the Asthma Intervention Research (AIR) trial,[4] was prospective and randomized but not blinded. The aim was to determine whether bronchial thermoplasty would improve asthma control after long-acting beta agonists were discontinued.

Patients could be enrolled if they were 18 to 65 years old, had moderate or persistent asthma, and needed to take an inhaled corticosteroid (beclomethasone [Qvar] 200 µg or more or an equivalent drug) and a long-acting beta agonist (salmeterol [Serevent] 100 µg or more or an equivalent drug) every day. They also needed to have FEV_1 values of 60% to 85% of predicted and airway reactivity (PC_{20} < 8 mg/mL), and their asthma had to have been stable for 6 weeks.

At baseline, the long-acting beta agonist was withdrawn temporarily; the final criterion for entry was that their asthma had to become worse when this was done.

Then, 112 patients were randomized to receive either bronchial thermoplasty with medical care (inhaled corticosteroids and long-acting beta agonists) or usual care, ie, medical therapy alone. Treatments were done in three sessions over 9 weeks, followed by attempts to discontinue their long-acting beta agonists at 3, 6, and 9 months after the procedure without exacerbations.

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An exacerbation was defined as at least one of the following for 2 consecutive days: a reduction of peak flow by 20% of baseline average, the need for more than three additional puffs of rescue inhaler, or nocturnal awakenings caused by asthma symptoms. The patients kept a daily diary of their symptoms and rescue inhaler use, and they completed the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ).

Results. The number of mild (but not severe) exacerbations per week was significantly lower at 3 and 12 months than at baseline in the thermoplasty group, with 10 fewer mild exacerbations per patient per year, but was unchanged in the control group. There were significantly greater improvements in morning peak flow at 3, 6, and 12 months from baseline in the treatment group than in the usual-care group. Rescue medication use was also significantly less at 3 and 12 months. Symptom scores, AQLQ scores, and ACQ scores were all significantly better than at baseline as well.

Not surprisingly, in this cohort with unstable asthma, there were 407 adverse events in the treatment group and 106 adverse events in the control group. Most of these occurred within 1 day and resolved within 7 days after the procedure. There were more hospitalizations in the treatment group as well, for reasons that included exacerbations of asthma, collapse of the left lower lobe, and pleurisy.[4]

Therefore, this trial found that thermoplasty improved asthma symptoms within 3 months and that the effect lasted 1 year, with an encouraging reduction in the number of mild exacerbations. However, it was not blinded, and there is a strong placebo effect in asthma. Needed was a randomized trial in which the control group would undergo a sham treatment.

The RISA trial: A randomized trial in severe asthma

The Research in Severe Asthma (RISA) trial[5] included patients with more severe asthma than those in the AIR trial. Entry criteria were:

- Taking high doses of an inhaled corticosteroid (> 750 µg of fluticasone or its equivalent per day)
- Taking prednisone (≤ 30 mg/day)
- An FEV_1 of at least 50% of predicted without a bronchodilator
- A positive methacholine test.

Seventeen patients were randomized to undergo bronchial thermoplasty, and another 17 were randomized to receive medical treatment.

After a 2-week run-in period, the thermoplasty patients underwent three treatments, performed 3 weeks apart. For the next 16 weeks, the corticosteroid doses were kept stable in both groups, followed by a 14-week corticosteroid-weaning phase and then a 16-week reduced-corticosteroid phase. During this time, attempts were made to decrease the oral or inhaled corticosteroid doses according to a protocol (eg, a 20%–25% reduction every 2–4 weeks) unless there were mild exacerbations lasting more than 7 days.

Results. There were more adverse events in the thermoplasty group than in the medical management group in the treatment period, including seven hospitalizations for exacerbations of asthma and a partial collapse of the left lower lobe. There were no significant differences in adverse events between groups in the posttreatment period (up to 6 weeks after the last treatment). Forty-nine percent of the events were mild in each group; 10% of the events were severe in the thermoplasty group vs 4% in the control group.

In the AIR2 trial, patients underwent bronchial thermoplasty or sham thermoplasty

During the steroid-stable phase, patients in the thermoplasty group used rescue inhalers significantly less than those in the control group, and their prebronchodilator FEV_1 and AQLQ and ACQ scores were better. The differences in rescue inhaler use and questionnaire scores remained significant at 1 year.

Comment. As expected, serious adverse events occurred more often in patients with severe asthma in the treatment group than in the control group. However, 1 year after the procedure, the adverse-event rates were similar in the treatment and control groups, suggesting that this procedure can be safely performed in similar patient populations. Although there was significant potential for a placebo effect, these patients with severe persistent asthma showed significant improvement in clinical measures of asthma compared with the control group.

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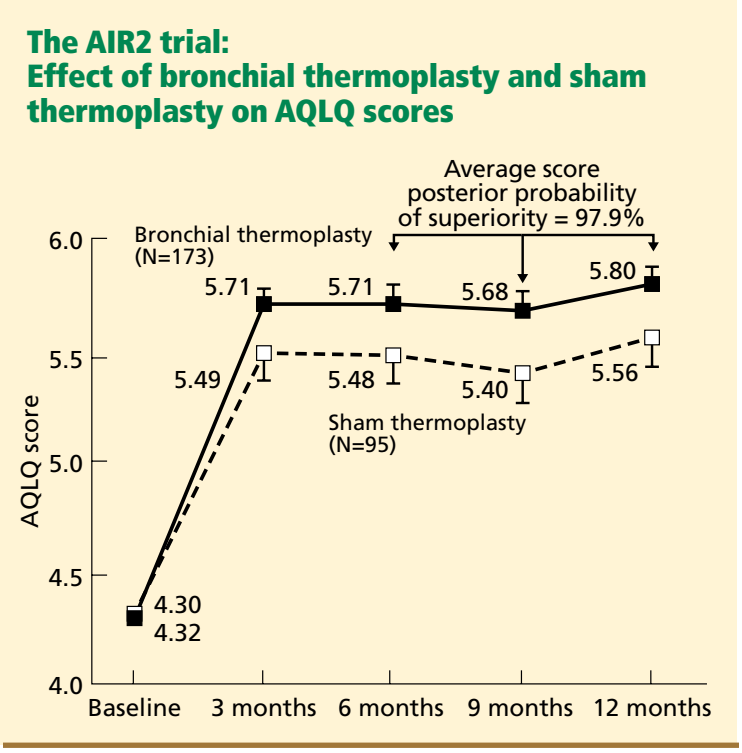


FIGURE 2. Mean Asthma Quality of Life Questionnaire (AQLQ) scores during 12 months after treatment with bronchial thermoplasty or sham bronchial thermoplasty. Possible scores range from 1 (worst) to 7 (best). A change of 0.5 points is considered clinically meaningful.

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AIR2: A randomized, double-blind trial

The latest trial of this new therapy in severe asthma was the AIR2 trial.[6] A major difference in its design compared with the earlier ones was that the control group underwent sham thermoplasty, allowing the trial to be truly double-blinded. (The bronchoscopy team knew which patients got which treatment, but the patients and the study physicians following them did not).

The primary outcome was the change in AQLQ score from baseline at 6, 9, and 12 months. Secondary outcomes included absolute changes in the asthma control scores, symptom scores, peak flows, rescue medication use, and FEV_1.

The randomized groups (196 patients in the thermoplasty group and 101 in the sham treatment group) were well matched, and more than 80% in each group met the American Thoracic Society criteria for severe refractory asthma.

Results. At baseline, the mean AQLQ score was 4.30 in the thermoplasty group and 4.32 in the sham thermoplasty group. This rose after treatment in both groups: at 6 months it was 5.71 in the thermoplasty group and 5.49 in the sham thermoplasty group. The thermoplasty group had significantly higher AQLQ scores at 6, 9, and 12 months than at baseline, and also significantly higher scores than the sham treatment group (FIGURE 2).[6]

On the AQLQ, a change of more than 0.5 is considered clinically meaningful. Interestingly, there was a significant and clinically meaningful improvement in AQLQ in 64% of the sham treatment group, highlighting the placebo effect in asthma treatment.[19] However, a larger proportion (79%) of the treated group had a clinically meaningful improvement on the AQLQ than in the sham treatment group.

The thermoplasty group also had significantly fewer severe exacerbations in the posttreatment period (> 6 weeks after treatment) compared with the sham treatment group (0.48 vs 0.70 exacerbations per patient per year, posterior probability of superiority 96%). There was a significant 84% risk reduction in emergency department visits in the treatment group (FIGURE 3).[6]

Adverse events occurred in both groups; however, during the treatment phase, 16 patients in the bronchial thermoplasty group needed to be hospitalized for respiratory symptoms including worsening asthma, atelectasis, lower respiratory tract infections, decreased FEV_1, and an aspirated tooth. One episode of hemoptysis required bronchial artery embolization. In contrast, only two patients in the sham treatment group needed hospitalization.

Therefore, this trial showed that patients with severe asthma treated with bronchial thermoplasty had a long-term improvement in quality of life and needed less health care.[6]

Translating these trials into practice

To summarize, these clinical trials showed that bronchial thermoplasty was feasible, was relatively safe, and produced better clini-

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cal outcomes in patients with severe asthma when medical therapies did not control their symptoms.

In practice, patient selection is likely to be important. A key question will be, Does the patient truly have severe refractory asthma, or is the patient not taking his or her medication? Adherence to therapy should be evaluated.

In addition, patients need to be observed and monitored closely during and after the treatment period, as airway complications and asthma exacerbations can occur up to 6 weeks after the last procedure. About 80% of all study patients had multiple symptoms of asthma and other symptoms in the treatment period. Rarely did these symptoms result in hospitalization, but they were more common in the treatment group in the AIR2 trial.

Long-term studies have evaluated the duration of effect and the safety of bronchial thermoplasty, and outcomes appear favorable.[20,21]

WHY DOES IT WORK?

The role of airway smooth muscle in asthma is yet to be fully elucidated. The trials outlined here showed that although asthma is a disease of the airways, including the small airways, treatment of airways 3 mm or larger improves asthma symptoms, quality of life, and health care utilization.[6] Thus, the role of airway smooth muscle in asthma and as a target of therapy has not previously been fully realized.[21]

Early investigations into the mechanisms of airflow obstruction and airway resistance found that 75% of postnasal resistance occurs in the first six to eight generations (ie, branchings) of the airways, indicating that larger airways are involved.[22] (The number of generations varies depending on the size of the person but it typically is 10 to 12.) Findings from the study in dogs introduced the idea that smooth muscle alterations contributed to the changes in airway resistance, and that subtle changes in airway smooth muscle could clinically benefit asthma patients.[1]

The speculated purpose of the airway smooth muscle layer is to support the airway, allow gas exchange, propel mucus for clearance, defend the airway, enhance cough, and promote lymphatic flow. However, the airway smooth muscle layer may also be vestigial. In asthma, airway smooth muscle adds to bronchoconstriction and hyperresponsiveness, and has a role in mediating inflammation and airway remodeling.[21] No definitive studies have shown that eliminating airway smooth muscle greatly inhibits normal airway function.[18]

What exactly does thermoplasty do to the smooth muscle? Studies in smooth muscle from cows showed that high temperatures directly disrupt the actin-myosin interaction, likely through denaturation of motor proteins.[23] This immediate loss of muscle cell function is not likely to be the result of apoptosis, autophagy, or necrosis, or mediated by heat-shock proteins, in view of the relatively

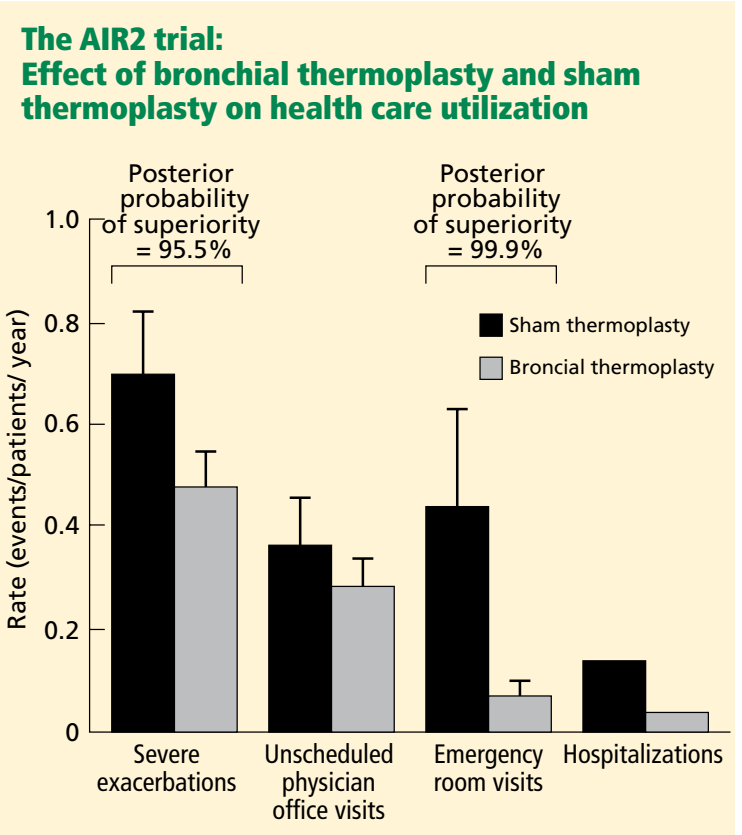


FIGURE 3. Health care utilization in the 12 months after real or sham thermoplasty. All values are means ± the standard error of the mean. Severe exacerbations are exacerbations requiring treatment with systemic corticosteroids or doubling of the inhaled corticosteroid dose.

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quick muscle response and lack of progressive changes. Tissue responsiveness is substantially reduced a few seconds after application of 60°C of heat and is subsequently abolished within 5 minutes after treatment.[23]

The intervention appears to be dose-dependent. Responsiveness to cholinergic stimulation is lessened by treatment, and the desired effect is seen within seconds and does not progress.

Therefore, we can surmise that disruption of myosin function is likely the mechanism of the therapeutic effect, breaking the cascade of airway smooth muscle spasm. Now that we know about the airway smooth muscle as a possible target of therapy, and that it may play only a vestigial role, we can think about other therapies that focus on it.[18,23]

BRONCHIAL THERMOPLASTY PROTOCOLS

Patients are assessed before and on the day of the procedure to make sure their disease is stable (ie, their postbronchodilator FEV_1 is within 15% of baseline values, and they have no evidence of asthma exacerbation or active infection), similar to the protocol used in the AIR2 trial,[6] before proceeding with the treatment.

Why does the airway even *have* a smooth muscle layer?

Patients are given 50 mg of prednisone 3 days before and again on the day of the procedure. Nebulized albuterol (2.5–5.0 mg) is given before the patients undergo screening spirometry and again before the procedure. If the preprocedure FEV_1 is lower than 15% below baseline, we postpone the procedure to another day.

The procedure is performed with the patient under moderate conscious sedation, typically using fentanyl (Sublimaze), midazolam (Versed), and topical lidocaine in a monitored environment. The bronchoscope is inserted via either the mouth or nose, and supplemental oxygen is provided.

Thermoplasty is performed with the Alair system (Asthmatx, Inc., Sunnyvale, CA), which delivers a specific amount of radiofrequency (thermal) energy through a dedicated catheter. The catheter is deployed through a 2.0-mm channel of a flexible bronchoscope, starting in distal airways as small as 3 mm in diameter and working proximally to sequentially treat all airways to the mainstem lobar bronchi. The sites treated are meticulously recorded on a bronchial airway map to ensure that treatment sites are not skipped or overlapped (**FIGURE 1**).

An array of four electrodes is manually expanded to make contact with the airway walls; each electrode has 5 mm of exposed wire. As the energy is delivered, the control unit measures electrical resistance converted to thermal energy and turns off the current when an appropriate dosage is given. This thermal energy is what is responsible for altering the airway smooth muscle.

A full course of treatment requires three separate bronchoscopy sessions, each separated by 2 to 3 weeks. The left lower lobe and the right lower lobe are treated in separate procedures, and then both upper lobes are treated in a third procedure to minimize any respiratory symptoms. Each procedure usually requires 50 to 75 activations of the device and takes up to 60 minutes.

After each procedure the patient should be observed for 3 to 4 hours, and spirometry should be repeated to make sure the FEV_1 (percent predicted) is within 20% of the baseline value. An additional 50-mg dose of prednisone is prescribed for the day after the procedure.[24]

FDA CLEARANCE AND LONG-TERM FOLLOW-UP

The FDA approved the Alair device for treating severe refractory asthma in early 2010.[3] The indications for it are based on the study populations in the published trials. Patients can be evaluated for this treatment if they have well-documented severe persistent asthma not well controlled on inhaled corticosteroids and long-acting beta agonists and have no significant contraindications to bronchoscopy.

As part of the conditions of approval, the FDA required a postapproval study based on the long-term follow-up of the AIR2 trial. They specifically wanted to compare patients who have desirable long-term outcomes and those in whom any treatment effect wanes with time. Since we have only a few years of follow-up data, we still do not know all the possible late effects of the treatment; we have an opportunity to learn more.

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Another question that needs to be studied is whether thermoplasty will help other forms of bronchospastic lung disease, such as chronic obstructive pulmonary disease.

A second postapproval study will be a prospective, open-label, single-arm, multicenter study conducted in the United States to assess the treatment effect and short-term and long-term safety profile of thermoplasty in asthma.

As experience with the procedure increases, we will be better able to characterize which patients may benefit from it. In addition, the knowledge gained by the longer-term study of airway smooth muscle function alterations will potentially drive the discovery of other innovative therapies for severe asthma.

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