

## Review

## Bronchial Thermoplasty in the Treatment of Asthma

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## ABSTRACT

Despite the numerous guidelines and treatments available for asthma, the disease remains poorly controlled in some patients, who remain symptomatic, are a considerable burden on the health system, and account for most of the hospitalizations due to asthma.

Bronchial thermoplasty is a novel experimental therapeutic option that consists of delivering radiofrequency-generated heat to the airways via a catheter inserted in the bronchial tree through a flexible bronchoscope to reduce smooth muscle quantity and contractility. The first investigations were conducted using an animal model. Subsequently, 2 randomized clinical trials designed to evaluate the safety and efficacy of thermoplasty in patients with moderate to severe asthma with a 1-year follow-up period showed the procedure to be safe, with mostly transient adverse effects and several clinical benefits. Although results from ongoing clinical trials are still awaited, thermoplasty may become an innovative therapeutic approach to asthma.

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## Termoplastia bronquial en el tratamiento del asma

## RESUMEN

A pesar de las normativas y tratamientos existentes, una proporción de pacientes con asma permanecen sintomáticos, están mal controlados y son causa de un mayor impacto sanitario e ingresos por asma.

La termoplastia bronquial es una novedosa opción terapéutica en fase experimental, que consiste en la aplicación de calor generado por radiofrecuencia, mediante un catéter que se introduce en el árbol bronquial con broncoscopia flexible, para reducir la cantidad y contractilidad del músculo liso. En una fase inicial se utilizó un modelo experimental animal. Posteriormente, 2 ensayos clínicos aleatorizados han examinado la seguridad y eficacia de la termoplastia en pacientes con asma moderada-grave tras un año de seguimiento. Los resultados muestran que es un procedimiento seguro, con efectos adversos en general transitorios, y que comporta algunos beneficios clínicos. A la espera de nuevos datos que ofrecerán ensayos clínicos en curso, la termoplastia se ha constituido como una posible e innovadora aproximación terapéutica del asma.

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## Palabras clave:

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Termoplastia bronquial

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Músculo liso bronquial

Hiperreactividad bronquial

Ablación

## Introduction

Bronchial smooth muscle plays a central role in bronchial obstruction in patients with asthma. Indeed, the first treatment step in such patients—and particularly when they have symptoms—is the use of bronchial dilators ( $\beta_2$ -adrenergic agonists) to relax this muscle.<sup>1</sup> Furthermore, smooth muscle hypertrophy and hyperplasia are part

of the bronchial remodeling processes associated with chronic asthma, treatment resistance, and the progressive loss of lung function seen in certain patients with asthma.<sup>2,3</sup>

Asthma is a very common disease, with a prevalence of 3% to 5% in the general population. Advances in our understanding of its pathophysiology and in the efficacy of treatments such as inhaled corticosteroids and bronchodilators, however, have been made in the past 20 years. The application of these advances, in combination with adherence to diagnostic and treatment guidelines, has had a positive impact on both asthma morbidity and mortality.<sup>4</sup> Furthermore, patients with moderate and severe asthma have

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benefited from the introduction of new, effective treatments such as leukotriene antagonists and omalizumab, an antiimmunoglobulin E (IgE) monoclonal antibody.<sup>1</sup> Another notable advance made in the treatment of asthma has been the development, implementation, and dissemination of international asthma management guidelines based on disease severity and level of control. There is also a growing awareness among health care professionals of the importance of correctly evaluating asthma, educating patients and their families, and ensuring proper use of treatment.

Despite these efforts, however, asthma remains a poorly controlled disease in a substantial proportion of patients, and as such, is still a common reason for emergency room visits. Asthma attacks in these patients can be very severe. Furthermore, between 3% and 6% of patients with asthma respond poorly to treatment, including oral corticosteroid therapy, and therefore continue to experience symptoms and diminished quality of life. This subgroup of patients are a major public health burden and account for most hospital admissions due to asthma. The pathogenic mechanisms underlying these forms of refractory asthma have yet to be fully elucidated. It is therefore clear that new treatments are required to improve the outlook of certain patients with asthma.

### **Principles of Bronchial Thermoplasty and the Role of Bronchial Smooth Muscle**

Bronchial thermoplasty is an innovative procedure consisting of the delivery of controlled radiofrequency-generated heat via a catheter inserted in the bronchial tree through a flexible bronchoscope to reduce bronchial smooth muscle mass and contractility. The procedure offers several benefits for patients with asthma, namely a reduction in bronchial hyperreactivity, exacerbations, and treatment needs, and an improvement in lung function and quality of life.

The bronchial wall contains smooth muscle with contractile capacity. In patients with asthma, this muscle can contract in response to a range of stimuli including irritants, allergens, exercise, drugs, methacholine, and histamine. It is known that most of the airway resistance occurs in bronchi larger than 2 mm in diameter. In a patient with asthma, however, airway narrowing probably affects the entire bronchial tree as even large airways with cartilage can become severely constricted.<sup>5,6</sup>

Another important aspect to consider is the role played by bronchial smooth muscle in humans. One possible role, on both a functional and structural level, is a protective one. The partial closure of the bronchi in response to the inhalation of a toxic or irritant agent, for example, would act as a defense mechanism, reducing the amount of harmful substances that reach and are deposited in the alveoli. Structurally, this constriction would help to prevent excessive bronchial dilation, particularly when there is an increase in pressure. The smooth muscle is also believed to favor peristalsis, contributing for example to fetal circulation, the passage of exhaled air, and mucosal, blood, and lymph secretions. Smooth muscle has also been associated with the maintenance of the ventilation-perfusion balance, cough reflex, and the regulation of the volume of the dead space (to ensure that it does not compromise gas exchange by becoming too large or increase airflow resistance by becoming too small). Nonetheless, no studies to date have demonstrated that the smooth muscle plays a vital role in the above-mentioned functions. Neither have any studies reported an association with impaired smooth muscle function or indeed the absence of smooth muscle. This muscle may, therefore, have little or even no functional capacity and may might simply be an embryonic remnant shared by the respiratory and digestive systems. This interesting scientific controversy is discussed in an article by Mitzner<sup>7</sup> entitled "Airway smooth muscle. The appendix of the lung."

There is, nonetheless, ample evidence that the smooth muscle plays a pathologic role in asthma.<sup>8</sup> Absence or blockade of the

bronchial smooth muscle might, therefore, offer clinical benefits in situations where contraction and/or hypertrophy of the muscle causes symptoms, as is the case with asthma. It is currently accepted that airway inflammation—a primary event in asthma—induces hypertrophy and hyperreactivity of this muscle. The mere activation of the smooth muscle, might, however, act as an inflammatory stimulus that exacerbates the inflammatory response through autocrine mechanisms activated by membrane mechanoreceptors. It would be interesting to investigate this hypothesis further within the context of a treatment aimed at reducing bronchial smooth muscle.

### **Bronchial Thermoplasty**

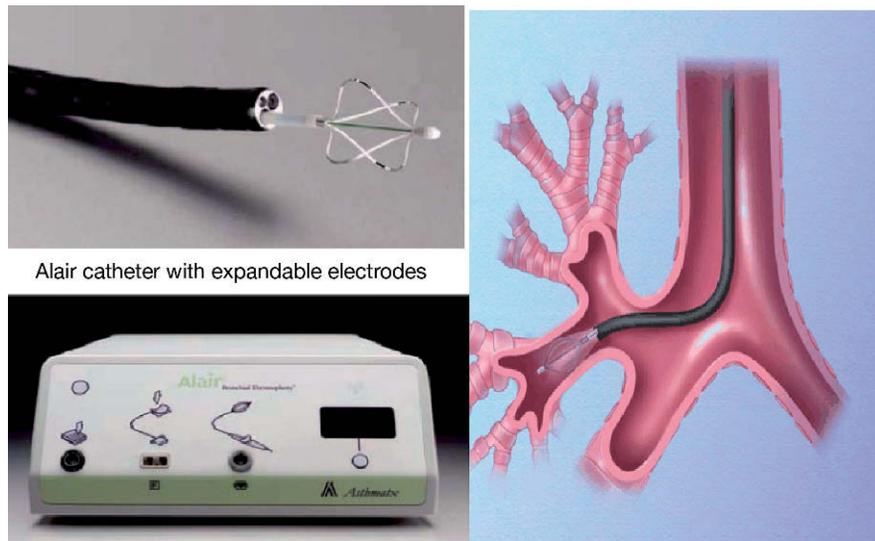
Radiofrequency is the portion of the electromagnetic spectrum that lies between 3 Hz and 300 GHz. Radiofrequency waves are used by a wide range of technologies such as telecommunications and microwave ovens, and in medicine, this portion of the electromagnetic spectrum has been used in a range of applications for years. One of the most illustrative examples of the efficacy of this technique is the treatment of arrhythmias via radiofrequency catheter ablation of aberrant conduction or accessory pathways of the heart. The device used to generate thermal energy in bronchial thermoplasty procedures (Alair System; Asthmatx Inc., Sunnyvale, California, USA; www.asthmatx.com) is connected to a probe or catheter to which it delivers heat. The catheter, which is inserted into the bronchial tree through a flexible bronchoscope, has 4 expanding electrodes that transmit heat to the respiratory mucosa (Figure 1).

The procedure is performed in 3 sessions separated by 3-week intervals.<sup>10</sup> The first session is used to treat the right lower lobe, the second to treat the left lower lobe, and the third to treat the 2 upper lobes (Figure 2). The middle lobe is not treated given the increased risk of mucus accumulation and atelectasis in the posttreatment period. The fact that this lobe has a somewhat longer and horizontal lobular bronchus might contribute to the development of this adverse effect. It is important that the procedure is performed by an experienced bronchoscopist. Careful patient selection/preparation and anesthetic management are also critical.

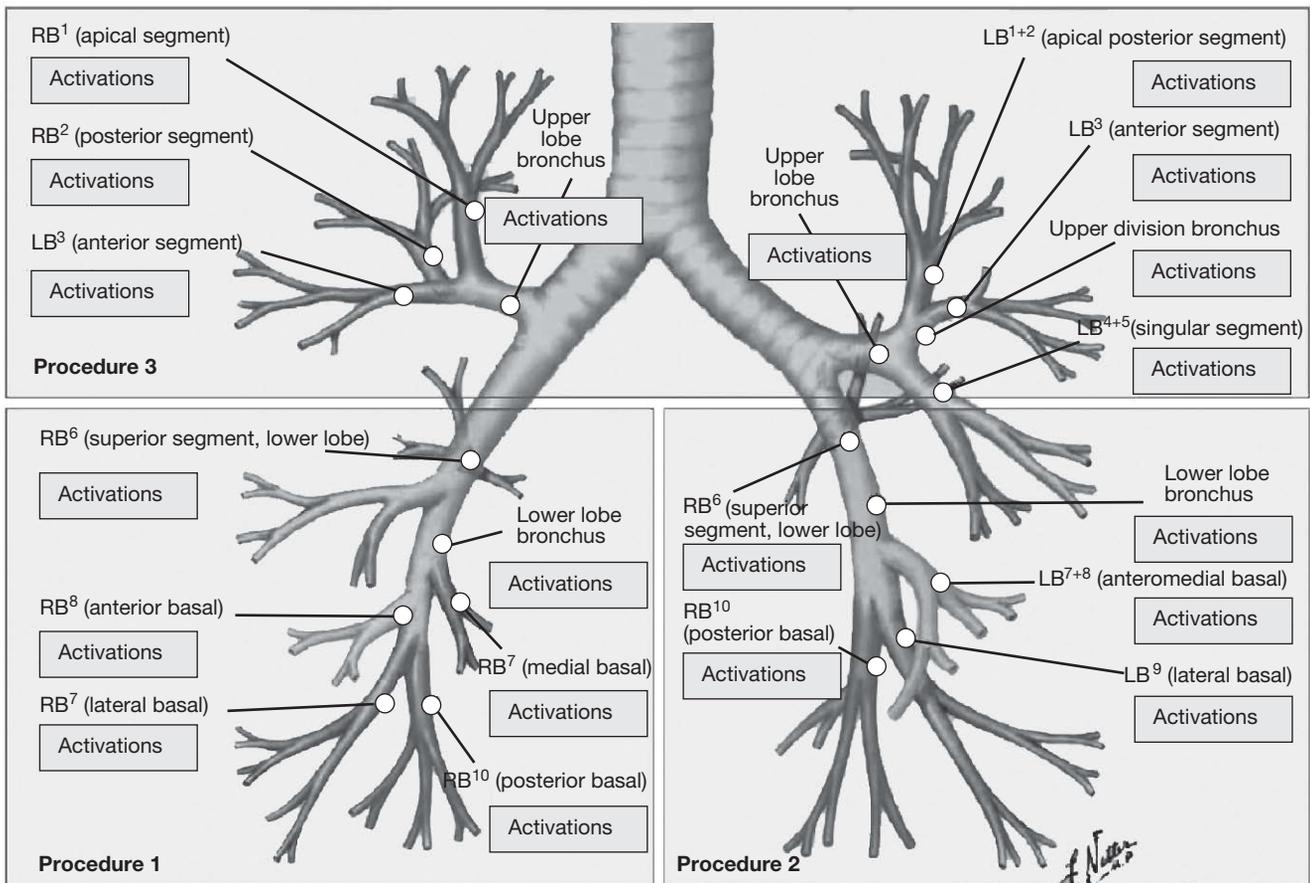
Once the bronchoscope has been placed in the airways, the catheter is advanced through the working channel until the distal end, fitted with the electrodes, reaches in the working area and opens to come in contact with the bronchial wall (Figure 3). The bronchoscopist then activates the radiofrequency generator using a pedal to deliver thermal energy (at a temperature of 65 °C) to the contact area for approximately 10 seconds. On completion, the electrodes immediately retract and the catheter is withdrawn 0.50 cm. The process is then repeated successively in adjacent proximal sites, starting with the smaller bronchi. The treatment is applied to all bronchi with a diameter of between 3 mm and 10 mm that are visible to the bronchoscopist. The aim is to systematically treat all the lung segments following a standardized protocol. There are approximately 40 effective activations during each session, which lasts for approximately 45 to 50 minutes. Because of the length of the sessions, the procedure is normally performed by more than 1 bronchoscopist. It can take place in a bronchoscopy or operating room and requires a flexible bronchoscope with a working channel of at least 2 mm. Appropriate anesthesia, ie, that ensures sedation but does not interfere with ventilation, is also required.

### **Preliminary Investigations**

Bronchial thermoplasty was first tested in dogs,<sup>11-13</sup> with the results forming the basis for later studies involving humans. In these early canine models, different application temperatures were tested and the lung was divided into treated and untreated areas. The animals were evaluated and monitored over 3 years, with histologic examination at weeks 6, 12, and 157. A temperature of 65 °C was



**Figure 1.** Thermoplasty catheter, radiofrequency generator, and system inserted in bronchi, which are visualized through a flexible bronchoscope. (Photographs courtesy of Asthmatx Inc.)



**Figure 2.** Map of bronchi from a thermoplasty protocol. RB indicates right bronchus; LB, left bronchus. (Source: Adapted from Tschumperlin et al<sup>9</sup>).

observed to reduce the mass of bronchial smooth muscle by approximately 50%, and this effect was still present after 3 years of follow-up. It is important to point out that thermoplasty does not eliminate all smooth muscle in the treatment zone and that with time epithelial regeneration and restoration of the bronchial wall structure occurs. Lasting changes, however, are observed in the

smooth muscle tissue, which is partly replaced by loose connective tissue (Figure 4). No serious side effects were observed in these early studies and tolerance was good. In addition, a correlation was observed between the mass of smooth muscle treated and improvements in methacholine-induced bronchial hyperreactivity. Finally, high-resolution computed tomography was used to analyze

the effect of thermoplasty on bronchial diameter and airway compliance (Figure 5).

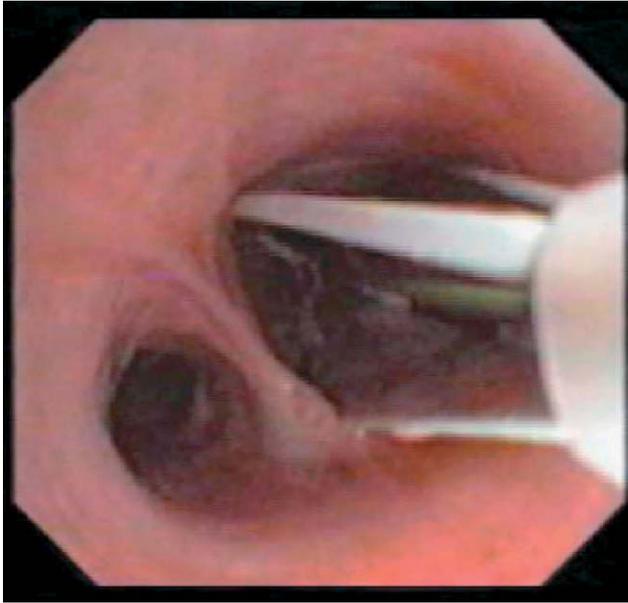
Miller et al<sup>14</sup> published the findings of the first study designed to test the feasibility and safety of thermoplasty in humans. The study consisted of performing thermoplasty in 9 patients without asthma who were scheduled for surgical resection for lung cancer. The treatment was applied during routine bronchoscopy between 5 and 21 days before resection. The treatment was limited to bronchial areas of the lobe or lung chosen for resection. No significant treatment-related adverse effects, new symptoms, or unscheduled medical visits were observed. When the treated areas were examined by bronchoscopy in the operating room moments before the thoracotomy, there was evident redness and edema of the mucosa, airway narrowing, and mucus hypersecretion in some patients, in particular in those who had been recently treated. There was no ulceration and examination of histologic sections revealed a reduction in the amount of bronchial smooth muscle and nonspecific inflammatory changes in the bronchial epithelium. It is also noteworthy that the changes observed were limited to the bronchial wall.

A later study examined the safety of the procedure and its impact on lung function and bronchial hyperreactivity 2 years after

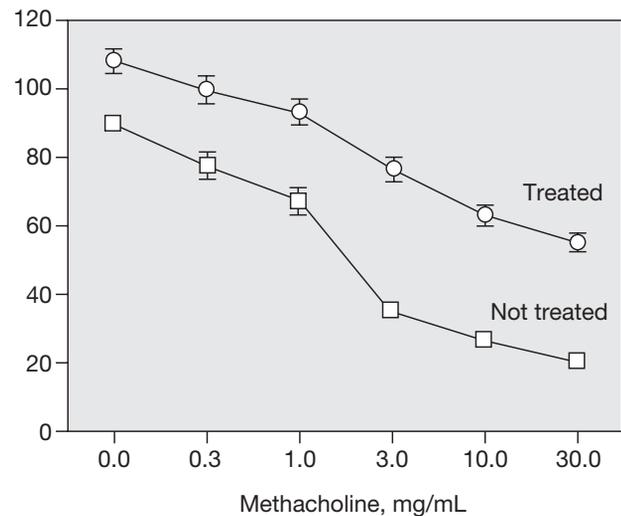
treatment in a group of 16 patients with mild or moderate asthma.<sup>15</sup> The study had just 1 treatment group and no control group. Although numerous adverse effects were associated with the treatment (cough, dyspnea, wheezing, bronchospasm, fever, chest discomfort, mucus hypersecretion, hemoptysis, and throat irritation), most of these were mild and occurred only in the days immediately following the procedure. As far as efficacy is concerned, the treatment significantly improved bronchial hyperreactivity, with a doubling in the concentration of methacholine needed to cause a 20% fall in forced expiratory volume in 1 second (FEV<sub>1</sub>) from baseline (PC<sub>20</sub>). Improvements were also recorded in peak expiratory flow and the percentage of symptom-free days. No changes were observed in FEV<sub>1</sub>.

### Clinical Trials With Bronchial Thermoplasty

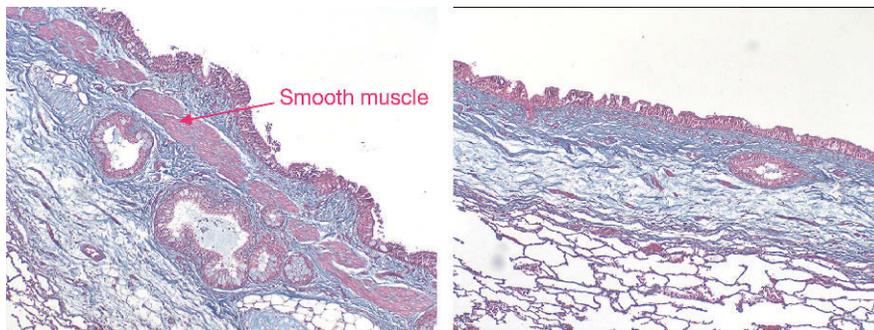
The first results to be published from a clinical trial evaluating bronchial thermoplasty were from the AIR (Asthma Intervention Research) study,<sup>16</sup> involving nonsmokers with moderate or severe asthma (FEV<sub>1</sub>, 60%-85% of predicted; methacholine PC<sub>20</sub>, < 8 mg/mL) who were receiving combined therapy with inhaled corticosteroids (> 200 µg/day of beclomethasone or equivalent) and in whom the



**Figure 3.** Bronchoscopic image of thermoplasty catheter with deployed electrodes in contact with the bronchial wall. (Courtesy of Asthmatx Inc.)



**Figure 5.** Maximum bronchial diameter measurements from a canine model after the administration of incremental doses of methacholine. The measurements were taken by high-resolution computed tomography in bronchi treated and not treated with thermoplasty. (Source: Adapted from Brown et al.<sup>11</sup>)



**Figure 4.** Histologic sections of the bronchial wall showing the airway surface before (left) and 12 weeks after (right) thermoplasty treatment at 65 °C (trichromic staining, ×100). The elimination of the smooth muscle in the treated area is evident. The rest of the epithelium, the mucus glands, and the subepithelial region are normal. (Courtesy of Asthmatx Inc.)

withdrawal of long-acting  $\beta_2$ -adrenergic agonists (LABAs) resulted in a worsening of asthma control. The study enrolled 112 patients aged between 18 and 65 years from 11 centers in 4 countries. The patients, divided into 2 groups of 56, were randomly allocated to a control group, which continued with the standard treatment (inhaled corticosteroids and LABAs), and a treatment group, which received bronchial thermoplasty in addition to the standard treatment regimen. Excluding patient withdrawals and protocol violations, the final analysis included 47 control patients and 49 treatment patients. The following parameters were analyzed: frequency of mild and severe exacerbations, peak expiratory flow, use of rescue medication, spirometry, symptoms, methacholine challenge results, adverse effects, degree of asthma control, and corresponding health-related quality of life. The patients were monitored for a year. Outcomes were measured during the year—throughout which the patients were taking inhaled corticosteroids—and also before and after LABA therapy was withdrawn.

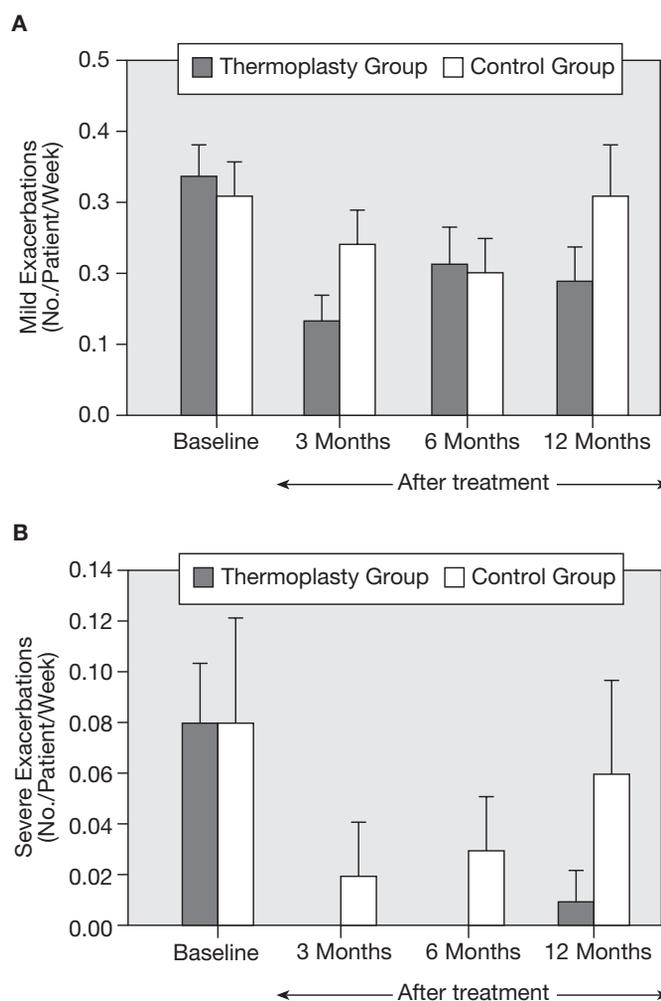
The only significant differences between the 2 groups in terms of adverse effects were observed in the 6 to 7 days following the procedure. Specifically, the thermoplasty group experienced a greater incidence of—generally mild—respiratory complications (dyspnea, wheezing, productive cough, chest pain, respiratory infections). One patient in this group developed atelectasis of the left lower lobe, but this resolved after 2 days of medical treatment. There were 6 hospitalizations in the thermoplasty group and 2 in the control group. There were no significant differences between the groups in terms of either the number of complications or lung function impairment in the follow-up period. Furthermore, there were no signs of long-term complications such as stenosis or bronchiectasis in the thermoplasty group.

The efficacy analysis for the thermoplasty group showed a reduction in the number of mild exacerbations at 1 year follow-up (0.18 vs 0.31 per patient per week,  $P=.03$ ) and a nonsignificant trend toward a reduction in severe exacerbations (Figure 6). As far as the effect of treatment on lung function was concerned, peak expiratory flow improved by 39 L/min, while FEV<sub>1</sub> and methacholine PC<sub>20</sub> showed a favorable, albeit nonsignificant, trend. Improvements were also noted in the thermoplasty group in terms of the percentage of symptom-free days, symptom severity, and questionnaire-assessed asthma control and quality of life. There were no differences in nighttime awakenings.

The second clinical trial—the results of which were published by Pavord et al<sup>17</sup>—was called RISA (Research in Severe Asthma) and was also a multicenter, randomized, controlled study. It was designed to evaluate the safety and efficacy of thermoplasty in patients with severe, symptomatic asthma despite conventional treatment. It studied nonsmokers with asthma (prebronchodilator FEV<sub>1</sub> of over 50% of predicted, methacholine PC<sub>20</sub> of less than 4 mg/mL, or postbronchodilator FEV<sub>1</sub> of over 12%) who were aged between 18 and 65 years and experienced symptoms (assessed using a symptoms scale and use of rescue medication) despite treatment with inhaled corticosteroids (> 750  $\mu$ g/day of fluticasone or equivalent), LABAs (> 100  $\mu$ g/day of salmeterol or equivalent), or other asthma medication (up to 30 mg/day of oral corticosteroids).

Thirty-two patients were evaluated: 15 in a thermoplasty group and 17 in a control group. Follow-up in both groups was complex and consisted of 3 phases. In the first phase, which lasted 16 weeks (weeks 6-22) a stable dose of corticosteroids was maintained; in the second phase (weeks 22-36), attempts were made to gradually taper down this dose according to an established protocol; and in the third phase (weeks 36-52), the minimum effective dose of corticosteroids obtained in phase 2 was maintained.

The safety results were identical to those seen in the AIR study, with a temporary worsening of respiratory symptoms in the thermoplasty group during the days immediately following the procedure. The majority of adverse effects were mild or moderate,

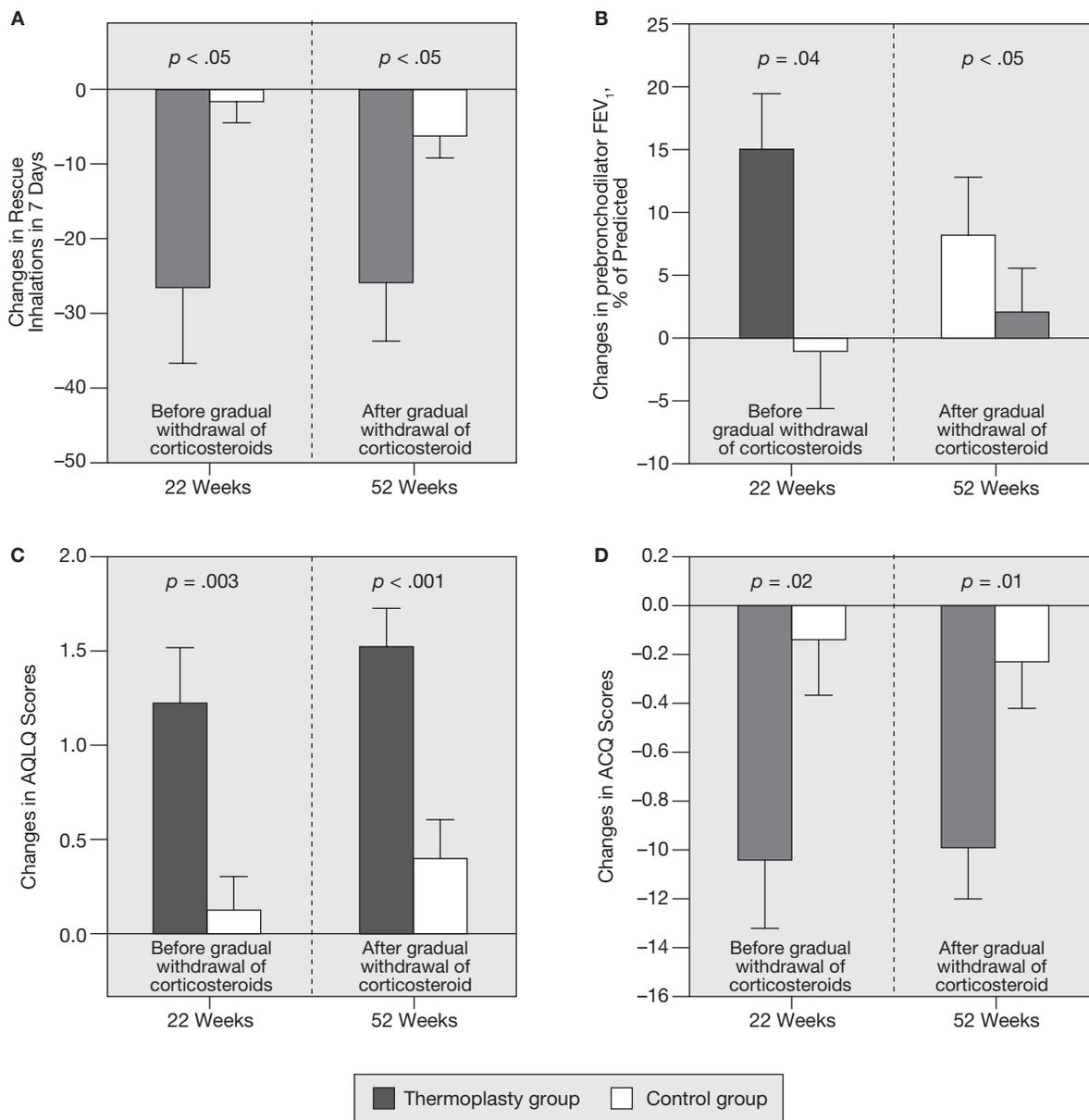


**Figure 6.** Number of mild (A) and severe (B) exacerbations by patient and week. Numbers are expressed as mean (SEM) values at different time points when the patients were receiving inhaled glucocorticosteroids alone. \*Statistical significance. (Source: Adapted from Cox et al<sup>15</sup>).

although in the treatment phase, there were 7 hospitalizations in the thermoplasty group (in 4 of 15 patients) and none in the control group. Furthermore, 1 of the patients who received thermoplasty required an additional bronchoscopy to aspirate secretions caused by a mucus plug. At 22 weeks, the thermoplasty group presented significant improvements with respect to the control group in terms of prebronchodilator FEV<sub>1</sub>, use of rescue medication, health-related quality of life, and asthma control. These differences were maintained in the last 2 cases at 52 weeks (Figure 7). There were no differences between the study and control group in terms of corticosteroid dose reduction in phase 2 of the study.

## Conclusions and Considerations

The reduction in bronchial smooth muscle contractility and mass achieved by applying heat directly to the airway surface is a novel approach to treating asthma. It has drawn much interest in the scientific community and might be a treatment option for cases of severe, poorly controlled asthma, and/or refractory asthma. Furthermore, the results obtained so far are encouraging enough to warrant continued efforts aimed at increasing our understanding of the mechanisms underlying severe asthma and deepening our knowledge of the possible physiological role of bronchial smooth muscle and its role in the pathogenesis of asthma.



**Figure 7.** Changes in efficacy at 22 weeks (stable corticosteroid dose phase) and 52 weeks (tapered corticosteroid dose phase) in the study by Cox et al.<sup>16</sup> Mean (SEM) changes with respect to baseline. FEV<sub>1</sub> indicates forced expiratory volume in 1 second; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire.

A, number of rescue inhalations in 7 days; B, forced expiratory volume in 1 second (% of predicted) before bronchodilation; C, health-related quality of life score (Asthma Quality of Life Questionnaire; scale of 1 to 7, where 7 is the best possible score); D, asthma control score (Asthma Control Questionnaire; scale of 0 to 6, where 0 is the best possible score).

The results of clinical trials conducted to date on bronchial thermoplasty have shown that the procedure is quite safe, with mainly transient adverse effects, and that it offers certain clinical benefits a year after treatment in patients with severe asthma. Nonetheless, these studies have evaluated the procedure in a limited number of patients (n=80) and have not employed a sham bronchoscopy group. Furthermore, not all the variables analyzed showed significant improvements and long-term safety and efficacy have yet to be evaluated. There are also doubts about whether or not to extend the applications of the procedure, which is currently limited to central bronchi, accessible by bronchoscopy, with a diameter of greater than 3 mm. This limitation could explain why no improvements have been noted in certain lung function parameters as extensive parts of the bronchial tree are affected in patients with asthma.

A rigorous multicenter, double-blinded clinical trial (AIR-2) is currently underway with 270 patients randomized to a thermoplasty or sham bronchoscopy group.<sup>18</sup> The results of this trial will provide valuable information for better evaluating the safety and efficacy of bronchial thermoplasty. Until these results are available, however, bronchial thermoplasty deserves consideration as a novel treatment option which, although currently in the experimental phase, may soon become an option for certain patients with severe, poorly controlled, or refractory asthma.

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