Bronchial thermoplasty in asthma*

Termoplastia brônquica em asma

Adalberto Sperb Rubin, Paulo Francisco Guerreiro Cardoso

Abstract

Currently available treatments for asthma provide satisfactory control of the disease in most cases. However, a significant number of patients do not respond to such treatments (i.e., do not achieve effective symptom relief). One novel approach to treating asthma is bronchial thermoplasty, in which the airway smooth muscle is specifically and directly treated. This procedure delivers radiofrequency energy to the airways in order to reduce smooth muscle-mediated bronchoconstriction. In this article, we present the thermoplasty technique, summarizing the results of the major randomized clinical trials of the procedure, as well as discussing its mechanisms of action and potential adverse effects. We also propose strategies for the future clinical use of this new treatment.

Keywords: Asthma/prevention & control; Asthma/therapy; Bronchoscopy.

Resumo

Os modernos tratamentos disponíveis para a asma proporcionam um bom controle da doença na maioria dos casos. Um número significativo de pacientes, no entanto, não responde a esses tratamentos, ou seja, não apresenta um alívio sintomático importante. A termoplastia brônquica é uma nova modalidade terapêutica, na qual a musculatura lisa das vias aéreas é especificamente tratada. Esse procedimento broncoscópico libera energia através de radiofrequência para as vias aéreas buscando a redução da broncoconstrição mediada pela musculatura lisa. Neste artigo, apresentamos a técnica da termoplastia, sumarizamos os resultados dos principais estudos clínicos randomizados do procedimento e discutimos seus mecanismos de ação e potenciais efeitos adversos. Também propomos estratégias para o futuro uso clínico desse novo tratamento.

Descritores: Asma/prevenção & controle; Asma/terapia; Broncoscopia.

Introduction

As a result of the considerable advances in the development of effective treatments, as well as in the formulation of guidelines for the management of asthma, most asthma patients easily achieve control of the disease.[1,2] However, a small but significant proportion of patients have persistent symptoms, pulmonary function changes, and frequent exacerbations, despite appropriate management. This subgroup of patients, who are classified as having difficult-to-control asthma, have high morbidity and mortality rates, as well as consuming a large part of the health resources allocated to this disease.[3]

Severe asthma is associated with a chronic inflammatory process and airway remodeling—bronchial wall thickening, glandular hyperplasia, increased mucoid secretion, increased vascularity, and airway smooth muscle (ASM) hypertrophy. The increase in muscle mass and the potentiation of ASM contractility in response to a variety of stimuli are of particular importance in the pathophysiology of asthma.[4] Many of the symptoms in asthma patients, especially in severe and difficult-to-control cases, are due to contraction of the ASM, which is hypertrophied in such patients.

One novel approach to treating difficult-to-control asthma, and whose main target is ASM, has recently been developed. The reduction in ASM contractility or ASM quantity, or a combination of the two, can alleviate symptoms and reduce the number of exacerbations in asthma patients.[5] This is the first non-pharmacological treatment for asthma, and its technique, as well as its efficacy, has been the subject of several publications and discussions within the medical scientific community.

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Bronchial thermoplasty

Concepts

The concept that, in asthma, variable airflow obstruction, which is responsible for most symptoms, is due to airway constriction and is mostly determined by ASM contraction in response to a variety of stimuli, has been well established for many years. All airways above the respiratory bronchioles are filled with ASM, whose contractility has the potential to reduce the caliber of the airways and, occasionally, to occlude them entirely. Many of the available treatments for asthma aim at preventing or reducing ASM contractility, reducing airflow limitation and therefore the occurrence of symptoms and exacerbations. Treatment with long-acting and short-acting β_2 agonists aims at relaxing ASM, and a large number of patients achieve symptom relief through the use of these drugs. Nevertheless, since many patients are refractory to this treatment and continue to have symptoms, it is important to search for novel approaches to preventing bronchospasm.[3]

The true function of ASM remains a subject of controversy.[5] Although most authors believe ASM to be a fundamental part of the bronchial structure, others maintain that it is only a vestige of embryogenesis. In asthma patients, ASM shows hyperplasia or hypertrophy, or a combination of the two, depending on the phenotype of the case, and is highly susceptible to stimuli, which results in bronchial hyperreactivity and airway contraction. In addition, ASM might be associated with the inflammatory process and might be an important contributor to bronchial remodeling. Studies have demonstrated that much of the airway resistance observed in asthma patients is associated with the constriction of airways larger than 2 mm in diameter. Based on these concepts, the search for a method for ablation of ASM in asthma patients would greatly contribute to disease control.

Mechanisms

The mechanism postulated by bronchial thermoplasty consists in the destruction or atrophy of ASM by releasing heat into the airways. This change has been observed in the airways of dogs, in which bronchial thermoplasty converts ASM to fibrous tissue. It is possible that other airway aspects, such as innervation, vascularization, inflammatory recruitment, epithelium, and mucus production, are also changed by heat, but no studies have confirmed this. Theoretically, any changes in these aspects could contribute to better disease control.

Method

Bronchial thermoplasty is a method for ablation of bronchial smooth muscle by radiofrequency thermal energy.[6] The equipment used, designated the Alair system (Asthmatx, Mountain View, CA, USA), consists of a bronchial catheter and a radiofrequency generator (Figures 1 and 2). The catheter is inserted through the working channel, measuring approximately 2 mm, of an ordinary (5 mm) bronchoscope and has an expandable basket with four electrodes at its end.

The catheter reaches the airway that is most distally visible through the bronchoscope. The basket is then expanded so that the four electrodes are in equal contact with the airway wall (Figure 3). The generator delivers 480 kHz of monopolar radiofrequency energy, generating and delivering heat through the electrodes, for a period of 10 s.

After each activation, the basket is retracted and the catheter is repositioned proximally by 5 mm, adjacent to the previous activation and carefully avoiding overlap (Figure 4). The complete treatment consists of three sessions at three-week intervals. The treatment involves completing a map in each session and follows a pre-determined sequence: first session, right lower lobe; second session, left lower lobe; and third session, right and left upper lobes. The middle lobe is never treated. On average, each session consists of 30-45 activations and lasts 30-60 min. The procedure can be performed under simple sedation (midazolam) or under general anesthesia (propofol). The procedure is considered technically correct when all airways distal to the main bronchi and with a caliber of 3-10 mm are treated (except the middle lobe).

Several recommendations on patient selection, preparation for the procedure, and follow-up after thermoplasty are necessary.[7] These recommendations are essential for the success and safety of the procedure (Chart 1).

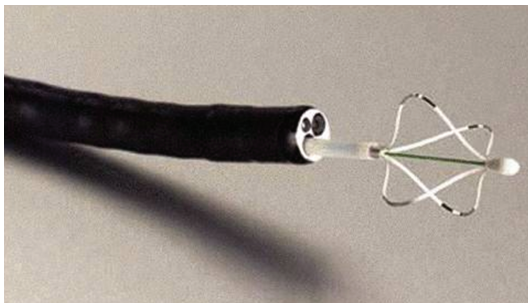

Figure 1 - Basket catheter (electrodes expanded).

Clinical experience

The first clinical trials of the bronchial thermoplasty technique were carried out in dogs.[8] In those trials, it was found to be more efficacious to deliver heat at a temperature of 75°C than at lower temperatures. Over three years of observation, the treatment was shown to reduce or eliminate ASM in the treated areas, without evidence of damage to the parenchyma, the epithelium, or the bronchial structure.

The first trial involving humans involved 9 patients requiring lobectomy due to lung cancer.[9] The lobe to be resected was treated for 1-3 weeks prior to surgery. In that pilot trial (bronchial thermoplasty at 65°C), effects similar to those observed in dogs were found in the histological analysis of the resected lobe. Subsequently, 16 patients with mild asthma were treated and monitored for two years. In that trial, there were only a few adverse effects, most of which resolved within a week. Clinical and functional improvement, including reduced bronchial hyperreactivity, occurred in the period. At this point, randomized trials, designed to confirm the clinical efficacy and the safety of bronchial thermoplasty in asthma patients, were initiated.

The Asthma Intervention Research (AIR) Trial[10] included 112 patients with moderate or severe asthma who were considered having been stable for six weeks before inclusion. The patients were randomized into two groups: conventional treatment group, in accordance with the Global Initiative for Asthma (GINA) recommendations; and conventional treatment + thermoplasty group. At the end of a one-year follow-up period, the group treated with thermoplasty showed a significant reduction in the number of exacerbations, an improvement in morning peak expiratory flow, an improvement in the scores of a quality of life and symptom questionnaire, an increase in the percentage of symptom-free days, and a reduction in the use of rescue medication. Although the patients treated with thermoplasty more often experienced adverse effects, such as dyspnea, cough, and wheezing, most such effects were mild in nature and resolved, on average, in less than one week. Nevertheless, there was an increase in the number of hospitalizations due to exacerbated asthma in the thermoplasty group. From the sixth week onward, the incidence of adverse effects was similar in the two groups. In a post hoc analysis, the patients who required higher doses of inhaled corticosteroids (> 1,000 µg of beclomethasone) obtained benefits from thermoplasty that were even superior to those observed in the total population studied, indicating that, in patients with more severe disease, thermoplasty could provide greater benefits. In that trial, there were no changes in bronchial hyperreactivity, nor was there any damage to the airways at the end of twelve months of treatment.

The Research in Severe Asthma (RISA) Trial[11] was designed to evaluate the efficacy and safety of thermoplasty in patients with severe persistent asthma. It included patients from 18 to 65 years of age who used high doses of inhaled corticosteroids (> 750 µg of fluticasone or equivalent), as well as long-acting β_2 agonists. Fifteen patients were randomized to undergo thermoplasty (in addition to conventional treatment), being compared with 17 patients considered as controls. Half of the patients in each group also used oral corticosteroids. An analysis at one year after inclusion revealed that, during the treatment period (up to six weeks after the last procedure), there was a high number of hospitalizations in the treated group (seven hospitalizations in 4 patients), whereas there were no hospitalizations in the control

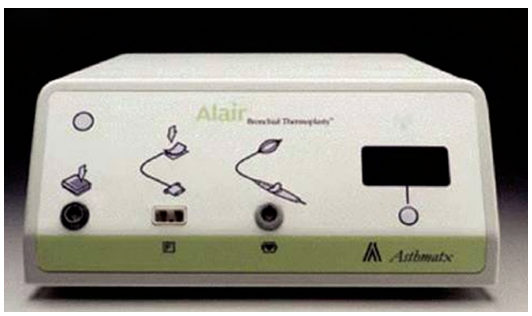

Figure 2 - Radiofrequency energy generator.

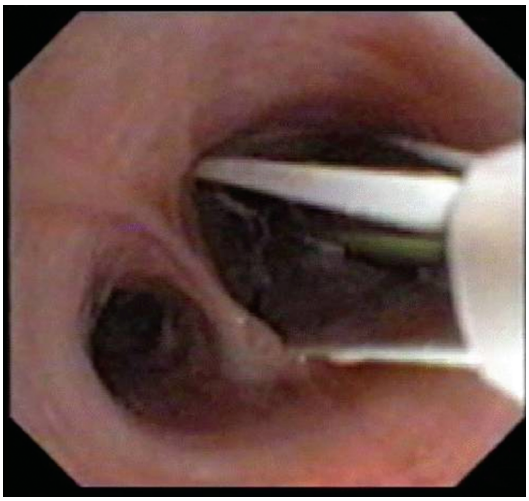

Figure 3 - Catheter with the basket expanded in the airway.

group. Of those seven hospitalizations, five were due to asthma exacerbation and two were due to lower lobe collapse, demonstrating a higher incidence of thermoplasty-related complications in patients with severe disease in comparison with previous trials. In addition, the occurrence of respiratory symptoms was higher among the patients submitted to thermoplasty. Between the end of treatment and the one-year mark, the incidence of adverse effects and hospitalizations was similar in the two groups. In the treated group, there were no ICU admissions, need for intubation, or deaths, whereas mechanical ventilation was required for one control group patient. As observed in previous trials, treated patients showed a clinical and statistically significant improvement in FEV_1, use of rescue medication, and asthma control scores—on the Asthma Control Questionnaire and the Asthma Quality of Life Questionnaire (AQLQ). The authors of the trial concluded that, although there was an increase in morbidity soon after treatment, the benefits of thermoplasty in patients with severe persistent asthma extended to one year and were significant, a finding that had been reported in the post hoc analysis of the AIR Trial.

Despite being well developed, neither the AIR Trial nor the RISA Trial was considered blind, since one group was treated and the other was not even sham-treated. Therefore, a third trial was developed. This new trial was designated the Asthma Intervention Research 2 (AIR2) Trial[12] and including a placebo group in which asthma patients were submitted to the procedure in a similar way but without activation or delivery of energy to the airways. The treatment and the sham bronchoscopy were performed by a group of researchers who were not present at the clinical evaluation of the patients, this analysis being performed by another group that did not have access to the randomization scheme. This randomized, double-blind, placebo-controlled

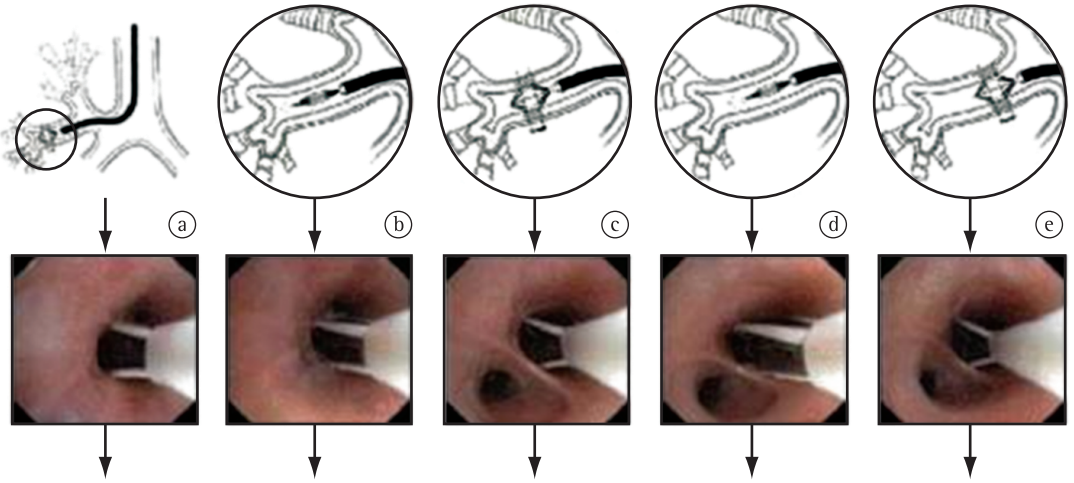

Figure 4 - Continuous activation with the catheter in the airway. In A, basket catheter inserted distally into the airway: electrodes expanded and generator activated; in B, electrodes partially collapsed and retracted 5 mm distal to the previous activation; in C, electrodes again expanded, with adjacent but not overlapping activation; in D, electrodes partially collapsed and retracted 5 mm distal to the previous activation; and in E, electrodes again expanded, with adjacent but not overlapping activation.

trial included patients from 18 to 65 years of age diagnosed with severe asthma and who, despite using high doses of inhaled corticosteroids, as well as long-acting β_2 agonists, remained symptomatic. In this multicenter trial, 196 patients were submitted to thermoplasty, whereas 101 underwent the placebo treatment. The primary outcome was the difference in changes in the AQLQ scores in relation to the baseline measurement at one-year follow-up between the two groups. Both groups showed a significant improvement in the AQLQ scores. However, in the thermoplasty group, 81% of patients achieved a score ≥ 0.5 (considered clinical improvement), compared with only 63% in the placebo group. Improvements were also found for the secondary outcomes, such as use of rescue medication, symptom score, number of symptom-free days, and morning peak expiratory flow, in the treated group, although the difference was not significant. In the post-treatment period, the number of severe exacerbations was significantly lower in the thermoplasty group than in the placebo group. A total of 558 activations were performed in the treated group, and there were no instances of pneumothorax, massive hemoptysis, intubation, mechanical ventilation, or death. Although the number of hospitalizations in the group submitted to thermoplasty was higher in the treatment period, there was a reduction in the number of hospitalizations and emergency room visits in this group between the end of treatment and the end of the first year of follow-up. The adverse effects observed in both groups after treatment were mainly a transitory increase in asthma symptoms, which resolved in approximately one week. The authors concluded that, in comparison with the sham-treatment group patients, symptomatic patients with severe asthma who were submitted to thermoplasty had a significantly better quality of life and fewer severe exacerbations. Together with the improvement in quality of life, patients treated with thermoplasty had a significantly lower incidence of severe exacerbations and less often required emergency room treatment. Patients with severe uncontrolled asthma are known to be responsible for most of the expenditures of and the visits to public health care facilities.[13,14] It is known that, in asthma patients, bronchoscopy can worsen symptoms and cause complications. Nevertheless, the improvement in the quality of life in patients submitted to thermoplasty, as well as the reduction in the number of emergency room visits, demonstrates that the benefits of the treatment compensate for its potential adverse effects. As previously demonstrated,[15,16] the improvement in quality of life is directly associated with the reduction in health-related expenditures in asthma.

Chart 1 - Selection criteria for bronchial thermoplasty.

- Adult with a documented diagnosis of asthma: FEV_1 reversibility; bronchial hyperreactivity; or pulmonary tuberculosis
- Former smoker (less than 10 pack-years) who has not smoked for one year or more
- Symptomatic, despite appropriate treatment (fluticasone, or equivalent, at a dose > 500 µg + long-acting β_2 agonists)
- Prebronchodilator $FEV_1 \geq 60\%$
- Fit to undergo bronchoscopy in accordance with the guidelines of the institution
- No history of hypersensitivity to drugs used during bronchoscopy (lidocaine, atropine, midazolam, fentanyl, and benzodiazepines, etc.)
- No internal pacemaker or neurostimulator
- No unstable comorbidities that could pose a risk to bronchoscopy (cardiovascular disease, epilepsy, insulin-dependent diabetes, sleep apnea, neoplasms, etc.)

Some doubts about the long-term safety of this treatment, such as the possibility of some tissue damage, atelectasis, or even bronchiectasis, remain. Recent data on safety involving the three large clinical trials—AIR Trial, RISA Trial and AIR2 Trial—have recently been published.[17] In three years of follow-up after those trials, there have been no clinical complications or deterioration of pulmonary function in patients submitted to thermoplasty, indicating a positive long-term safety profile for the procedure. An analysis of chest CT findings performed five years after treatment in 15 patients also revealed no significant anatomical changes, confirming the absence of late anatomical deformities.

Indications

Bronchial thermoplasty is still an experimental procedure, and recent studies are being evaluated in order to enable regulatory approval for its clinical use. Those studies indicate that the main use of thermoplasty will be in patients with

severe persistent asthma and difficult-to-control asthma, for whom, despite optimized treatment based on international guidelines (GINA), asthma control cannot currently be achieved.[18] The current selection criteria (Chart 1) involve patients with severe asthma who have a safety profile to be submitted to bronchoscopy, and this information is based on inclusion and exclusion criteria of clinical studies. There have yet to be any studies allowing the precise identification of the subgroups of patients with severe asthma who will gain the most benefit from the treatment. Individual analysis of cases included in the studies have demonstrated that, in some cases, there was a significant improvement of symptoms and asthma control, as well as a significant reduction in the use of medication and discontinuation of oral corticosteroid therapy.[19,20] It is essential that the bronchoscopist in charge of the procedure be technically proficient and possess knowledge about the management of asthma patients submitted to the test, especially about potential asthma-related complications. This bronchoscopist should receive appropriate training, under the supervision of an experienced professional.

Final considerations

Bronchial thermoplasty is the first non-pharmacological procedure specifically developed for the treatment of asthma patients. Although its preliminary results are promising and regulatory approval for its clinical use is expected soon, some questions remain to be more fully investigated.[21]

It is important to determine which subgroup of patients with severe asthma will benefit most from the treatment and in which patients the treatment should be contraindicated, due to low efficacy or potential adverse effects. There is a wide heterogeneity in relation to the expression of the inflammatory process and the physiological dysfunction in asthma patients, especially in severe cases that are refractory to conventional treatments. In principal, there seems to be no reason to suspect that thermoplasty can alter the inflammatory process. Therefore, its usefulness would be limited in patients with predominantly inflammatory disease, hypersecretion, and minimal involvement of the muscle component.[22] Although some authors defend the idea that the reduction or elimination of ASM would reduce the release of inflammatory mediators that exist within the muscle fibers,[23] this hypothesis has yet to be tested. In contrast, patients with predominantly "non-eosinophilic" disease, in which ASM dysfunction is more prominent, would benefit more from this treatment. Similarly, patients who are resistant to corticosteroids might be a target group for this novel technique.

In conclusion, bronchial thermoplasty opens a new phase in the search for adequate asthma control in patients with severe asthma. Over time, the use of this procedure in daily practice will define its role in the current guidelines for the treatment of patients with difficult-to-control asthma.

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