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REVIEW

COMPETENCE IN INTERVENTIONAL PULMONOLOGY

Competence in bronchial thermoplasty

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ABSTRACT

Bronchial thermoplasty (BT) is an innovative non-pharmacological endoscopic treatment for patients with severe persistent asthma based on controlled heat release with a device called Alair™ Catheter (Boston Scientific, Natick, MA, USA). The Alair™ system is the first device that works by delivering radiofrequency or thermal energy to selectively reduce the amount of airway smooth muscle (ASM) in bronchi. Literature showed significant improvement in clinical outcomes such as symptom control, severe exacerbation rate, hospitalization, quality of life, and number of working or school days lost for asthma. Besides smooth muscle effects changes in inflammatory pattern after BT have been documented. Bronchial thermoplasty requires an experienced physician who had a proficiency training in bronchoscopy and had rigor, dexterity and a thorough knowledge of the airway anatomy. Furthermore, right selection of severe asthma patient is crucial in order to have best response after BT. This article reviews BT device description and how to perform the procedure. Criteria for right selection and management of patient before and after BT will be discussed.

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KEY WORDS: Bronchoscopy - Bronchial thermoplasty - Pulmonary medicine - Asthma.

Asthma, as defined in the Global INitiative for Asthma (GINA) 2018 document, is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1] It is a common chronic respiratory disease which affects in some countries up to 18% of the population. It is also a heterogeneous disease with different pathogenetic mechanisms and different clinical phenotypes. Patients with severe asthma represent 5-10% of all asthmatic population. Severe asthmatic (SA) patient is defined as a subject which requires continuous treatment with recommended medications for GINA step 4-5 or systemic corticosteroids (CS) for more of 6 months in the previous year, to achieve a clinical control or which remains "uncontrolled" despite this therapy. Uncontrolled asthma is defined as: 1) presence of poor symptoms control (with asthma control questionnaire or as defined by GINA guidelines); 2) frequent severe exacerbation (*i.e.*, 2 treatment with systemic CS) in the previous year; 3) at least one hospitalization for asthma; 4) persistent bronchial obstruction with a postbronchodilator FEV.1<80% predicted.[2] Under the definition of "severe asthma" are included several clusters with different clinical presentations, underlying pathophysiological characteristics and outcomes. These clusters are often called "asthma phenotypes." The most common phenotypes include: allergic, non-allergic (neutrophilic, eosinophilic or pauci-granulocytic), late-onset, asthma with fixed airflow limitation, asthma with obesity. Chronic airflow limitation in severe asthma (SA) is due to the increase in airway wall thickness from airway remodeling caused by epithelia thickening, subepithelial fibrosis, airway smooth muscle (ASM) hypertrophy, inflammatory cell infiltration and goblet cell hyperplasia.[2, 3] The treatments of SA patients include medications recommended by GINA for step 4-5. GINA

step 4 includes medium to high dose of inhaled CS (ICS) with a long acting beta-agonist (LABA), and/or the long acting antimuscarinic antagonist (LAMA) tiotropium, leukotriene receptor antagonist or theophylline. If the control is not achieved within GINA step 4, GINA step 5 includes ICS plus tiotropium, monoclonal antibodies anti-IgE, anti-interleukin 5 (anti-IL5) and, eventually, low dose of oral CS. It is from a decade, with the introduction in the clinical practice of monoclonal antibody anti-IgE, that the differentiation in phenotypes has assumed practical relevance. The recent availability of other new monoclonal antibody anti-interleukin 5 also extend the use of phenotyping asthmatic subjects. Anti-IgE can be considered in patients with a predominant allergic phenotype, and anti-IL5 in patients with a predominant eosinophilic phenotype.[4] However, to date, no strong relationship has been found between specific phenotypes and treatment response.[5] Although symptoms can be controlled in the majority of SA patients with a pharmacological approach, there is a substantial group of subjects who remains difficult-to-treat, symptomatic, with frequent access to emergency room and hospitalization. These patients are also responsible for a relatively large proportion of total resource expenditure for asthma.[6]

Bronchial thermoplasty (BT) is a recently developed innovative bronchoscopic treatment that aim to reverse the process of airway remodeling in patients with SA. The target is the ASM and is achieved by delivering controlled thermal radiofrequency (RF) energy to the airway small muscle causing a reduction in ASM contractility and quantity.[7] BT has been approved in 2010 by the US Food and Drug Administration for asthmatic patients aged 18 years and older "whose severe and persistent asthma is not well controlled with inhaled corticosteroids and long-acting beta agonist medication."[8] BT can be considered for SA patients with predominant chronic airflow obstruction or patients with unsatisfactory response to GINA step 5, particularly those who are not eligible for anti-IgE or anti-IL5.[9] It has also to be mentioned in this framework that Task Force on SA recommend that BT is performed only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study.[6]

Knowledge of the instruments and mechanism of action

Alair™ System

The Alair™ System (Asthmatx Inc., Sunnyvale, CA, USA) consist of two major components, as illustrated in Figure 1A, B:

• the Alair™ RF Catheter is a single-use device designed to be brought into position using a standard bronchoscope introduced through the nose or mouth. The catheter delivers controlled release radiofrequency energy over the entire length of the airway walls reached, with a pulse lasting ten seconds, causing a reduction of smooth muscle mass in the airways of asthmatic patients;

• Alair™ RF Controller is the energy generator to which is connected a foot switch to start an activation and an electrode that delivers radiofrequency which is transformed into heat on contact with bronchial mucosa. Thermoplasty Alair™ system allow the delivery of thermal energy temperature-controlled RF energy to the airway at a temperature of 65°C at an appropriate intensity and for a time sufficient to reduce the smooth muscle's mass in the airway, while limiting the long-term impact on surrounding tissue.[10]

The Alair™ Catheter needs standard flexible bronchoscope with a 4.9-5.2 mm outer diameter with a working channel of 2.0 mm. The electrode array is expanded to contact the airway walls and then activated to deliver RF energy over the 5 mm length of the exposed electrode. RF

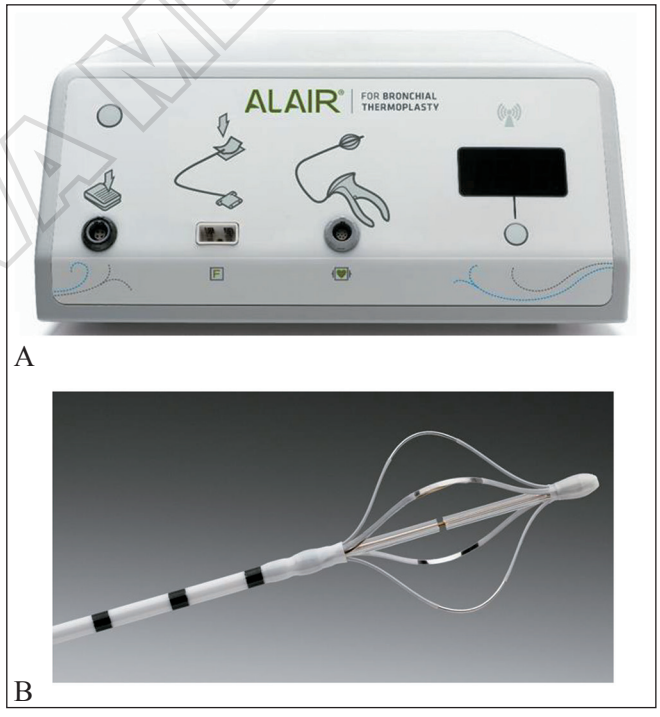

Figure 1.—A) Alair™ Radiofrequency (RF) Controller: designed to safely and accurately deliver precise, controlled RF energy through the catheter to the airway walls; B) Alair™ Catheter: a flexible tube with an expandable wire array at the tip to deliver therapeutic RF energy to the airway walls via a standard bronchoscope.

transfer energy from the electrode to the tissue where it is converted into thermal energy. The correct intensity and duration of energy delivery is regulated by the controller resulting in a reduction in the amount of airway smooth muscle, while limiting/minimizing collateral damage to other airway supporting structures.

Mechanisms of action

As we know BT can functionally inactivate smooth muscle cells of the bronchus, but this is not enough to fully explain the clinical effects on patients. After 3 months of BT, Aubier observed a selective down-regulation in ASM, neuroendocrine epithelial cells and nerve fibers, suggesting the involvement of multiple mechanisms through which BT can exert its effects.[11] It is worth remembering that severe-moderate asthma, concerning histological and pathological pathway, is characterized by an airway remodeling that involves epithelial abnormalities, increased basal membrane thickness, changes of the interstitial matrix, increased vascularization, hypertrophy of mucous glands and ASM hypertrophy/hyperplasia.[12, 13] Airway remodeling is known to be caused by chronic asthmatic inflammation. Indeed, inflammation is the main actor well known to be involved in pathogenesis of asthma. In particular, pro-inflammatory cytokines released at bronchial mucosal level, activate an inflammatory cascade that ends in deposition of extracellular matrix and smooth muscle tissue hyperplasia which leads to airway wall thickness.[14, 15] The ASM role in asthma is still under investigation, but Woodfruff has clearly demonstrated a hyperplasia of ASM in biopsies of mild to moderate asthmatic patients.[16] Moreover, it has been documented, in patients died for fatal asthma, a deposition of collagens and myofibroblasts,[17] suggesting modification of airway function caused by these molecules.[18] ASM seems to have also a pacemaker function for bronchial contractility through a nervous stimulus resulting in an increase of inflammatory pathway.[17] Although mechanisms of action of BT remains under investigation, based on what we have discussed before, it has been supposed that BT could improve asthma outcome through the release of thermal energy to large bronchi even if asthma is known to be a small airways disease. Indeed, literature reports reduction of ASM as a BT target.[19] More specifically ASM cells could have a role of pace-maker on the downstream bronchi.[20, 21] This hypothesis is supported by the assumption that destruction of ASM induced by BT act to nerve fibers interrupting central and local reflexes. These results on bronchial wall may be due to distribution in the large bronchi of a number of Transient Receptor Potential Vanilloid Type 1 (TRPV1) receptors and type-C unmyelinated fibers known to be heat sensitive.[19] TRPV1, also known as the capsaicin receptor, and the vanilloid receptor 1 are a subfamily of channel proteins that play an important role for cough in subjects with airway hyperresponsiveness (AHR).[22, 23] These channel proteins, when stimulated by irritant agents, switch on inducing stimulation of type-C unmyelinated fibers in bronchial mucosa by interrupting central and local reflexes responsible for the activation of bronchospasm in presence of bronchial hyperreactivity. Recently, it has been demonstrated a reduction of nerve fibers in epithelium and ASM. This result could explain the clinical improvement of patient underwent BT and support hypothesis previously suggested (Figure 2).[24]

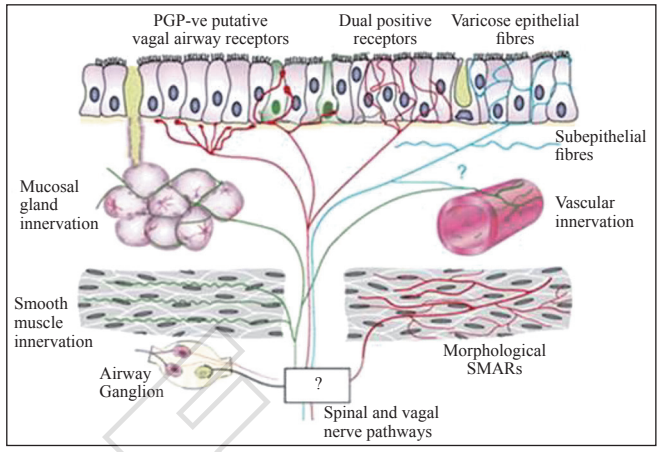

Figure 2.—Morphologic characterization of nerves in whole-mount airway biopsies.

Pretolani *et al.* carried out a study where they demonstrated that BT downregulates selectively structural abnormalities drive airway narrowing and bronchial reactivity, particularly ASM, neuroendocrine epithelial cells, and bronchial nerve endings.[25] In detail, in a cohort of 15 uncontrolled asthmatic patients that underwent BT, data showed a reduction in ASM area (median values before and after BT, respectively: 19.7 and 5.3%, P<0.001), subepithelial basement membrane thickening (4.4 and 3.9 μm, P<0.02), submucosal nerves (1.0, 0.7-1.3‰), ASM-associated nerves (452.6, 196.0-811.2) immunoreactive pixels per mm2 and 62.7, 0.0-230.3), and epithelial neuroendocrine cells (4.9 and 0.0/mm2, P<0.02).

Regarding the effects of BT on inflammation, there are different pathways involved. Doeing *et al*. demonstrated a reduction in T-cells and RANTES/CCL5 in Broncho-Alveolar Lavage (BAL) after 3 and 6 months of BT in 11 severe asthmatic patients, but not all patients showed

respiratory improvement after treatment.[26] BT's anti-inflammatory effect has been observed in a retrospective review of 15 consecutive patients. Study showed a statistically and clinically significant reduction in blood eosinophil counts after BT treatment.[27] Eosinophilia were also observed in bronchoalveolar lavage fluid of asthma patient after BT, but it should to be considered that this effect was probably determined by the OCS administered before the procedure.[26]

Indication of procedure and selection of patient

BT has been applied both to patients with moderate-to-severe asthma, refractory to the available optimal medical maintenance therapy, including biological drugs. The key selection criteria are provided in Table I. According to new subtypes of asthma, BT finds place in the treatment of T2-low subtype of asthma that is characterized by neutrophilic or paucigranulocytic airway inflammation and may consist of: obesity-related asthma, late-onset; asthma and chronic obstructive pulmonary disease overlap syndrome (ACO)/neutrophilic, late-onset; smoking-related asthma; paucigranulocytic, associated with smooth muscle. Pulmonologist need to perform a rigorous selection of patients candidate for BT, should follow a step-by-step assessment from difficult to severe asthma (Table I). Patients with severe steroid-resistant refractory asthma may also be selected for BT.[27] Moreover, BT was considered as a preferential treatment for patients who could not be addressed to other therapies, or who decided to perform a once-lifetime therapy.[28] Ideal BT candidate has daily symptoms as measured by asthma control test (ACT) and/or ACQ, and recurrent/frequent exacerbations, which results in a major burden on their quality of life as measured by an asthma-related quality-of-life questionnaire (*e.g.*, AQLQ).

Despite the availability of several monoclonal antibody for severe asthma treatment, we could address to BT a patient who is not eligible for bio-drugs or is a non-responder phenotype or unwilling to undergo therapies with an indefinite duration since BT consists of only 3 procedure. ERS/ATS guidelines currently recommend BT in adults with severe refractory asthma despite optimal therapy but only in the context of an "Institutional Review Board-approved independent systematic registry" or in a clinical study.[6] Similar recommendation is given by the latest Cochrane review, which also stresses the need for new studies to better understand BT mechanisms of action in the different asthmatic phenotypes and in patients with severe respiratory disturbances.[29] Following these indications, the Bronchial Thermoplasty Global Registry (BT Registry), a 2-year observational study that is expected to provide new and valuable data, is currently recruiting patients.

TABLE I.—*Indications BT.*

Inclusion criteria
1. Patient with severe persistent asthma uncontrolled found stable for at least 3 weeks
2. Patient receiving regular treatment with inhaled corticosteroids (beclomethasone >1000 mcg or equivalent) and LABA (salmeterol ≥100 mcg or equivalent)
3. AQLQ Score <6.25
4. FEV1 ≥50% predicted
5. Patients not smoking for at least one year
Exclusion criteria
1. Acute asthma life threatening
2. Concomitant respiratory diseases (*e.g.*, COPD or emphysema)
3. Use of ß-blocker drugs
4. Severe active infection in the last 2 weeks
5. Pacemaker, internal defibrillator or other implanted electronic device
6. Known sensitivity to medications used to perform bronchoscopy, including lidocaine, atropine and benzodiazepines
7. Currently known bleeding disorder is not well controlled
8. Inability to stop prior to the procedure taking anticoagulants, antiplatelet agents, aspirin or non-steroidal anti-inflammatory drugs
9. <18 years old
10. Pregnant women

TABLE II.—*Check-list for the procedure.*

On the day of the procedure
• Check asthma stable and no infection in the past 2 weeks.
• Check spirometry is above 55% predicted post salbutamol
• Check consent form signed for bronchoscopy.
• Nebulized salbutamol 2.5 mg
• Atropine 0.6 mg prior to procedure
• Sedation with midazolam, propofol and remifentanil in spontaneous breathing or as advised by anesthetist
• Local anesthesia of nose and throat
• Perform procedure
• Use 1-2 liters of oxygen during procedure
• Monitor oxygen saturation, ECG and blood pressure
• Ensure arrest trolley available
After procedure
• Monitor oxygen saturation, blood pressure and pulse every 15 minutes for the first hour and then every 30 minutes for the next 4 hours.
• Check asthma stable before sending home. To be checked by respiratory physician.
• Repeat spirometry [PFT lab]
• Instruction sheet, prescription for antibiotics if present sign of infection, asthma clinic appointment 2 weeks where next procedure will be booked if patient stable. Contact details of hospital center, prednisolone treatment
• Prescription for antibiotics if present sign of infection, asthma clinic appointment 2 weeks where next procedure will be booked if patient stable.

Core basic skills

Bronchial thermoplasty should only be performed by pulmonologists experienced in bronchoscopy and staff may be involve 2 trained endoscopy and nurses to handle the basket catheter and support the patient. Furthermore, it is crucial an experienced anesthetist in management of anesthesia/sedation protocol. Pulmonologist should have competence in flexible and rigid bronchoscopy and basic biopsy technique such as endobronchial biopsy, transbronchial biopsy, TBNA, ROSE, BAL and brushing. Pulmonologist must perform a proficiency training in the specific use of the Alair™ Bronchial Thermoplasty System.

Procedural steps

BT is performed via fiberoptic bronchoscope inserted through the nose or mouth. The procedure is usually performed with the patient under moderate sedation or light general anesthesia administered by an anesthesiologist. Usually, patient is hospitalized a day before procedure and discharged when patient is considered stable with an average duration of hospital stay of 3-4 days. Table II illustrates the check-list for the procedure. Patients are treated with 50 mg/day of prednisolone or equivalent for 5 days, starting treatment 3 days prior to the procedure. The procedure consists in the treatment of right lower lobe for first, left lower lobe during second session and right and left upper lobe in last session. Sessions are performed every three or four weeks. All accessible airways are treated with the exception of the right middle lobe, because of the theoretical concern of inducing right middle lobe syndrome. Before starting procedure bronchoscopist performs an inspection of the region of the lung that is to be treated and plans the order in which the airway segments are to be accessed and treated. The bronchoscopist reach the distal bronchi with the area to treat in clear view. The catheter is subsequently introduced in the working channel of the bronchoscope up

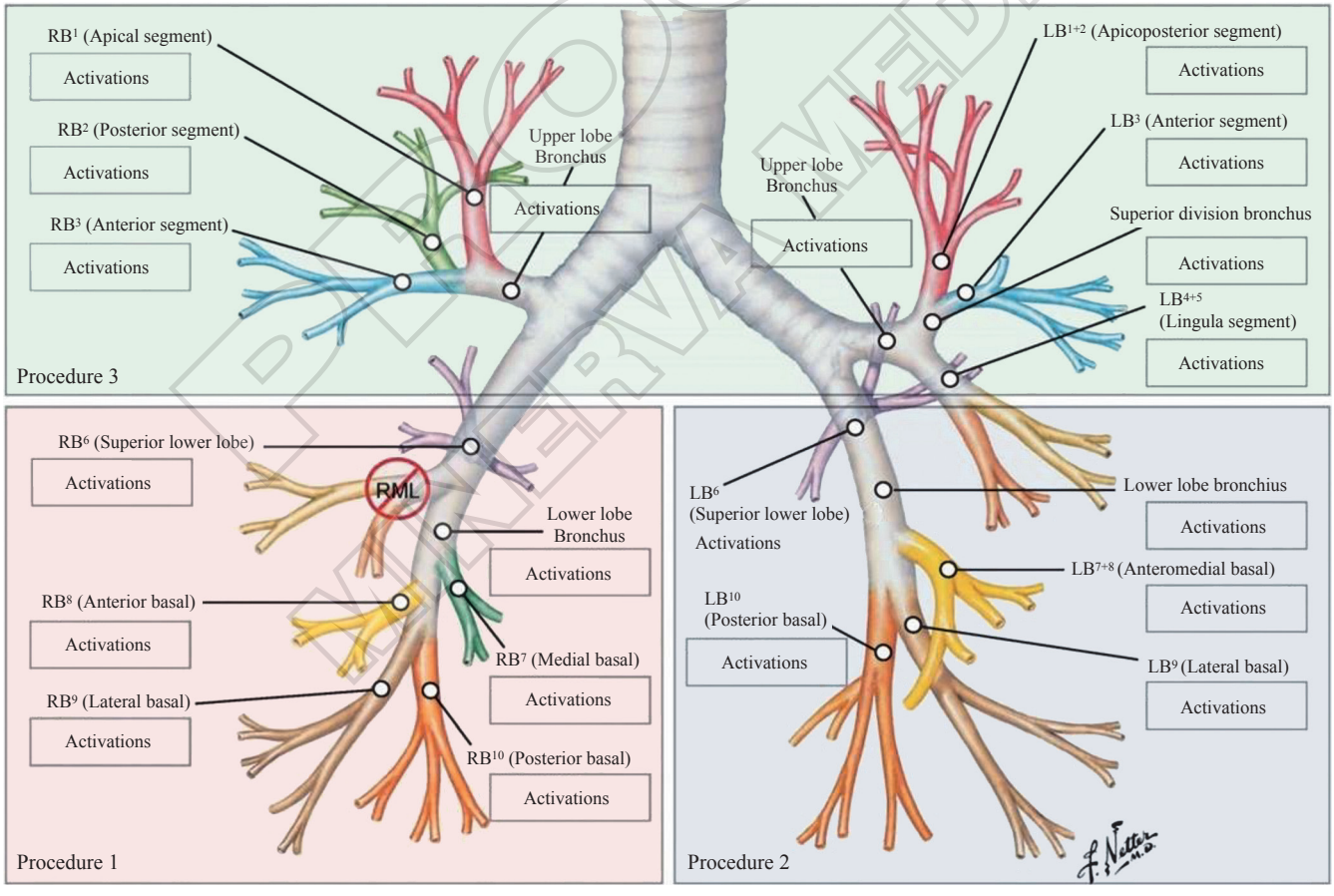

Figure 3.—BT is performed by a BT-certified pulmonologist in three outpatient visits, typically scheduled three weeks apart.

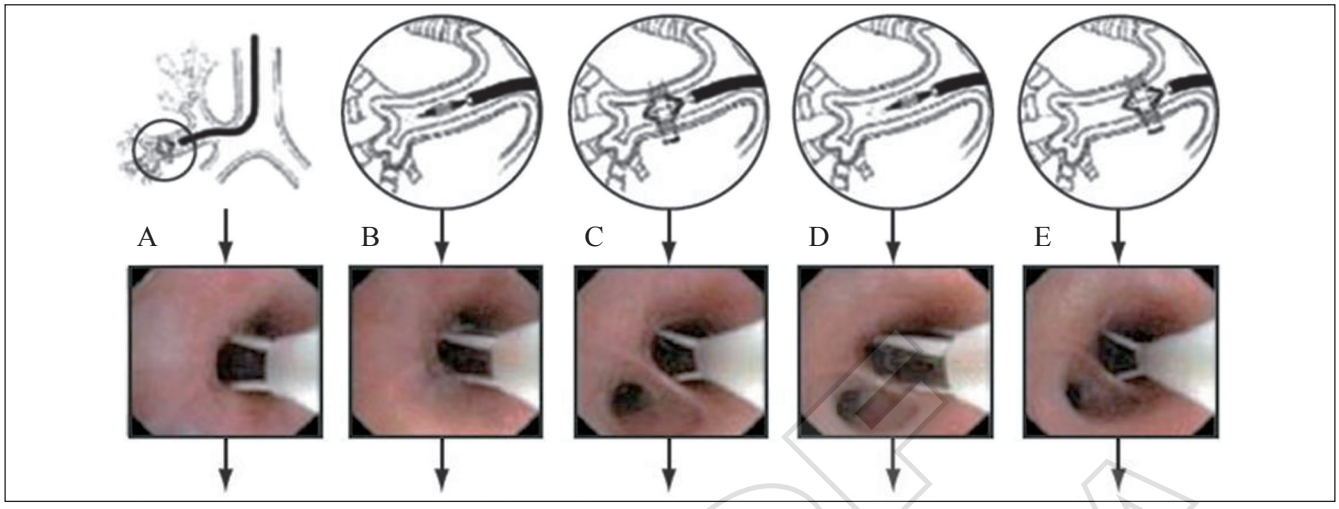

Figure 4.—Continuous activation with the catheter in the airway. A) Basket catheter inserted distally into the airway: electrodes expanded and generator activated; B) electrodes partially collapsed and retracted 5 mm distal to the previous activation; C) electrodes again expanded, with adjacent but not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

to first site to treat. Each bronchus is treated along its entire visible length, with each activation targeting a 5-mm section of bronchus between 3 and 10 mm in diameter, beginning at the periphery and moving proximally. Areas should not be retreated. On average treatment consists of ~30–70 activations per lobe (depending on the specific anatomy) and typically it takes 30-40 minutes to complete the procedure (Figure 3).

During this meticulous procedure, physician is supported by a partner with an airway mapping useful to register the area already treated. Bronchial thermoplasty requires close attention by the bronchoscopist to identify any marked effect on the bronchial mucosa except a transient blanching represented by a whitening of the mucosa. This makes it difficult to identify the treated bronchi (Figure 4).

During this endoscopic procedure may occur several events such as abundant secretions or uncontrollable cough, and bronchial mucosa of asthma patient is often friable and bloody due to hyperresponsiveness and chronic steroid therapy. This is why carrying out bronchial thermoplasty requires expertise not only in interventional pulmonology but also in asthma management. In addition, an accurate prescreening of patients seems to be crucial in order to select the appropriate patient to offer the best treatment possible.

Theoretical and practical training

The trainee is required to have an extensive and updated knowledge of severe asthma both concerning new endotyping and phenotyping of disease, as well as a competence in the management of severe asthma patients. Are recommended overview of asthma pathophysiology and knowledge of bronchial anatomy. Training should include a review of Alair™ System Catheter Directions for Use and Controller Operator's Manual, guided didactic instruction in computer simulation-based Bronchial Thermoplasty Learning Centre, detailed in-service training of the Alair™ System. Hands-on training with Alair™ System in a lung model prior to initial cases, proctoring of initial cases by Boston Scientific Health Care Industry Representative (HCIR). Ongoing support of cases is provideo when requested Physicians may undergo training through an accredited program of Alair™ delivery with Boston Scientific (the applicant) under the supervision of a qualified proctor. Training is provided free of charge. The service should only be provided by an interventional pulmonologist or a respiratory physician.

We also suggest the use of plastic and animal models to simulate the procedure. Moreover, good practical training on bronchial thermoplasty need to perform at least 5 supervised procedures, live session and clinical cases for problems discussion with emphasis on the strategy to be followed in different situations. To assess and manage complications that may occur before, during and after bronchial thermoplasty, it may be useful to elicit non-technical skill with simulation in a contest of multidisciplinary team with anesthetic physicians, nurses and pneumologists.

Quantitative e qualitative assessment

The final assessment includes:

- quantitative assessment:
  - Number of procedures, at least 3 procedures under supervision
- qualitative assessment:
  - MCQ
  - case-based questionnaires
  - DOPS
- outcome assessment: mortality, survival, complications, pulmonary function, quality of life, dyspnea scores, average duration of procedure: 30-45 minutes per session.[30, 31]

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