

Recent advances in bronchial thermoplasty for severe asthma: a narrative review

Senquan Wu^{1#}^, Shaomei Li^{2#}, Ping Zhang¹, Nianxin Fang¹, Chen Qiu³

¹Department of Respiratory and Critical Care Medicine, Dongguan People's Hospital, Dongguan, China; ²Department of Hematology and lymphoma, Dongguan People's Hospital, Dongguan, China; ³Department of Respiratory and Critical Care Medicine, Shenzhen People's Hospital, Shenzhen, China

Contributions: (I) Conception and design: S Wu, S Li, C Qiu; (II) Administrative support: P Zhang, C Qiu; (III) Provision of study materials or patients: S Wu, S Li ; (IV) Collection and assembly of data: S Wu, S Li; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

"These authors have contributed equally to this work.

Correspondence to: Chen Qiu. Department of Respiratory and Critical Care Medicine, Shenzhen People's Hospital, 1017 Dongmen North Road, Luohu District, Shenzhen 518000, China. Email: qiuchen@email.jnu.edu.cn.

Background and Objective: Severe asthma refers to asthma that requires step 4 or 5 therapy recommended by Global Initiative for Asthma (GINA) to prevent it from becoming uncontrolled or remaining "uncontrolled" despite this therapy. The poor treatment effect of severe asthma has been perplexing clinicians, which reduces the quality of life (QoL) of patients with asthma, and increases the mortality of such patients, so improving the therapeutic effect of severe asthma is an urgent problem to be solved in the clinic. Bronchial thermoplasty (BT) is a new non-drug therapy for severe asthma that is difficult to control with medications. It has been approved for clinical practice in China and the United States. The article aims at providing a new treatment option for patients with severe asthma that is poorly controlled by medications, thus improving the QoL in these patients.

Methods: An extensive literature search was performed in the PubMed database, with "bronchial thermoplasty" as the key term. The full texts of all potentially relevant articles were obtained, and relevant information was extracted.

Key Content and Findings: We find that BT is suitable for patients with severe asthma poorly controlled by medications.

Conclusions: This paper reviews the mechanism of action, procedure, safety and effectiveness, adverse effects and complications, problems, and prospects of BT, with an attempt to guide the practical application of this technique.

Keywords: Severe asthma; bronchial thermoplasty (BT); review

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Introduction

Background

Airway smooth muscle (ASM) plays an indispensable role in airway structure and immune modulation and

is involved in asthma exacerbations and chronic airway remodeling (1). Bronchial thermoplasty (BT) is a new nondrug therapy targeting the ASM. In BT, a radiofrequency (RF) ablation probe is inserted into the patient's bronchus through a bronchoscope; RF energy is applied to the

[^] ORCID: 0000-0002-1090-6610.

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	October 2021 to February 2022
Databases and other sources searched	All from the PubMed database
Search terms used (including MeSH and free text search terms and filters)	Bronchial thermoplasty
Timeframe	February 2008 to October 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	The full-texts of English articles relevant to bronchial thermoplasty were obtained
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	All relevant information was extracted by all authors, including the mechanism of action, procedure, safety and effectiveness, adverse effects and complications, problems, and prospects of bronchial thermoplasty
Any additional considerations, if applicable	No additional consideration

airway wall to reduce the quantity and function of the ASM, thus preventing or alleviating asthma exacerbations. It is indicated in patients with severe asthma who remain symptomatic despite good compliance and adequate treatment with high-dose inhaled corticosteroids (ICS) and long-acting beta antagonists (LABA). In addition, the efficacy of BT in the treatment of severe asthma can be maintained for a long time. The effectiveness of BT for severe asthma has been well established, and this treatment has been approved by the China Food and Drug Administration (CFDA) and the US Food and Drug Administration (FDA) for the clinical treatment of severe asthma. However, the clinical role of BT remains controversial because the mechanism of action has not been fully elucidated, and its adverse effects and complications cannot be ignored., The pathogenesis of severe asthma and the working principle of BT are elucidated in detail to make BT better understood by readers, as well as the research progress of BT's operating procedures, indications and contraindications, safety and efficacy, adverse reactions and complications, existing problems and prospects.

Objectives

To provide a new treatment option for patients with severe asthma poorly controlled by medications, thus improving the quality of life (QoL) in these patients. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups. com/article/view/10.21037/atm-22-580/rc).

Methods

The literature search was extensive in the PubMed database, with "bronchial thermoplasty" as the key term. The full texts of all potentially relevant articles were obtained, and relevant information was extracted. The mechanism of action, procedure, safety and effectiveness, adverse effects and complications, problems, and prospects of BT were reviewed (*Table 1*).

Discussion

Mechanism of action

ASM is considered to be the target of neurogenic stimulation and inflammatory cytokines in severe asthma (2). BT is a new intervention measure for the treatment of asthma by delivering controllable thermal energy (65 °C) to the airway wall, which led to a continuous decrease in ASM quantity, thereby relieving symptoms and improving the QoL of asthmatic patients (3). The mechanism of action of BT remains incompletely elucidated, and the mechanism of action of BT can not be fully explained by the denaturation and destruction of the smooth muscle layer alone (4,5). Some recent studies have suggested that BT treatment in patients with severe asthma results in a reduction in ASM mass, neuroendocrine epithelial cell count, reticular basement membrane thickness, and bronchial nerve endings, thereby improving airway stenosis and reducing bronchial hyperresponsiveness (6-9). Thus, BT may exert its clinical effects through multiple mechanisms.

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In asthma, ASM at as a critical role in airway remodeling. Thickening of the ASM layer around airways has been found in autopsy specimens, which is mainly caused by ASM hypertrophy and hyperplasia. James *et al.* further found that ASM cell hypertrophy occurred in the large airway in both severe and non-severe asthma cases, while ASM cell proliferation was only found in the airway of severe asthma cases, and they also found that the proliferation and hypertrophy of ASM cells in patients with severe asthma contributed to angiogenesis and extracellular matrix formation, leading to airway necrosis and increased airway resistance. These pathophysiological mechanisms offered a theoretical basis for treating severe asthma with BT (10).

ASM contraction is a crucial effector of bronchial contraction. ASM may plays an important role in airway hyperresponsiveness (AHR) because of the increased sensitivity and response to bronchoconstrictive stimuli in asthma patients (11). In addition to changes in the ASM mass, contraction, and gene expression profile observed in asthma patients, ASM is also considered a rich source of inflammatory cytokines and chemokines (12,13). ASM cells can induce AHR by releasing pro-inflammatory cytokines and chemokines to promote ASM contraction or altering ASM relaxation (14). Thus, in asthmatics, ASM is involved in multiple pathophysiological alterations of the asthmatic airway in various ways, from airway inflammation to airway mechanics.

Neuromodulation is also involved in bronchoconstriction and inflammation of the human airway, which is innervated by cholinergic, non-cholinergic, adrenergic, and nonadrenergic nerves. Cholinergic nerve is composed of the parasympathetic nerve, which can send signals to the muscarinic receptor (M receptor) by releasing acetylcholine. M receptor widely exists in inflammatory and airway structural cells, including ASM and mucous gland. This parasympathetic signal mediates the process of bronchial contraction, mucus hypersecretion, inflammation, and airway remodeling (15-17). Therefore, blockade of M receptors with inhaled anticholinergics (e.g., tiotropium bromide) is effective in clinical settings and has been approved to treat patients with poorly controlled asthma. Facciolongo et al. performed endobronchial biopsies on 12 severe asthma cases at baseline (T0), 1 month (T1), 2 months (T2), and 12 months (T12) after BT, along with the investigations using immunohistochemistry. The research showed that the nerve fibers of epithelium and ASM decreased earlier and lasted for 1 year after BT. Therefore, it can be proposed that the nerve ablation effect of BT is helpful to mediate the treatment of severe asthma (18).

Operating procedure and its principles

Clinically, BT operates through an Alair system, including an Alair RF controller, a footswitch, a reflux electrode, and an Alair catheter. The Alair catheter requires the bronchoscope with inner diameter ≥ 2 mm and outer diameter ≤ 5 mm to be sent to the distal bronchus with a diameter ≥ 3 mm. The distal end of the catheter is equipped with four expandable electrodes, which dilate to form a basket contact with the airway wall. The RF energy generated by the RF controller *in vitro* is converted into thermal energy through the catheter electrode and transferred to the bronchial wall. The target temperature is 65 °C for 10 seconds. By heating the bronchial wall, the ASM cells keep a persistent reduction in quantity, thereby reducing the extent of airway contraction during asthma attacks and reducing the frequency and severity of asthma attacks (19).

It is recommended that BT be performed by an experienced bronchoscopist, which facilitates truncation of the operating time and reduces risk. The whole process of the BT operation is three times, each at least 3 weeks apart. Depending on the capabilities of the bronchoscopist, anesthesiologist, and medical institution, BT can be operated under general anesthesia, or under moderate sedation using benzodiazepines and opioids. In a prospective cohort trial performed by d'Hooghe et al., moderate sedation with propofol and remifentanil was feasible and safe. It resulted in high satisfaction rates of both patients and bronchoscopists (20). Conventionally, the first procedure is done in the right lower lobe, the second procedure in the left lower lobe, and both upper lobes are in the final session. Current recommendations do not prescribe BT for the right middle lobe due to the relatively elongated and narrow bronchus, and BT may increase the risk of chronic injury and lead to right middle lobe syndrome due to postoperative inflammation (21). However, in 2019, Eisenmann et al. argued that BT, including the right middle lobe bronchus, could also improve lung function and QoL in patients with severe asthma (22).

Indications and contraindications

The indications approved by CFDA for BT in treating asthma are severe persistent asthma patients over 18 years old who remain symptomatic despite adequate treatment of high-dose ICS and LABA. The contraindications include: (I) absolute contraindications: (i) patients with implanted pacemakers, defibrillators, or other electronic devices; (ii) patients with acute myocardial infarction within 6 weeks; (iii) Patients with the severe cardiopulmonary disease who cannot tolerate bronchoscopy; (iv) allergic reactions to anesthetic agents required in bronchoscopy; (v) patients with uncorrectable coagulation dysfunction; and (vi) patients who have already completed BT; (II) relative contraindications: (i) patients unable to discontinue anticoagulants or antiplatelet drugs due to other medical conditions; (ii) those with uncontrolled asthma resulting in severe impairment of pulmonary function; (iii) history of a near-fatal asthma attack; and (iv) other uncontrolled comorbidities (19).

In 2010, BT was approved for the treatment of severe asthma patients meeting the following criteria by the US FDA: (I) aged 18 years or older; (II) remain uncontrolled on ICS and LABA; (III) a change of below 15% of the baseline value in post-bronchodilator forced expiratory volume in 1 second (FEV₁); (IV) in recent 2 weeks without respiratory infections and asthma attacks; (V) without implanted electronic devices (e.g., pacemakers or defibrillators); (VI) no allergy to drugs (e.g., atropine, lidocaine, and benzodiazepines) used in bronchoscopy; (VII) without coagulation disorders; and (VIII) non-smokers or smokers who have quit smoking for 1 year or who have smoked less than 10 pack-years previously.

Safety and effectiveness

In 2019, Langton et al. used computed tomography (CT) scanning to measure airway volume in post-BT patients and found that BT increased luminal airway volume on the treated side compared to control lungs. The authors thus suggested an essential link between the ASM atrophy demonstrated pathologically, and the improvement in symptoms observed clinically (6,23). In 2019, Seeley et al. conducted a prospective study of 25 patients with severe persistent asthma. The main result was the change of Mini Asthma Quality of Life Questionnaire (mini-AQLQ) 1 year after BT treatment, and the secondary result was the change of asthma drug use 1 year after BT. The results showed that 88% of the patients showed significant improvement in mini-AQLQ and reduced drug use 1 year after BT treatment (24). Konietzke et al. performed quantitative CT to detect changes in airway dimensions and air-trapping after BT for severe asthma, and their results suggested that BT can significantly reduce airway stenosis and air

retention in patients with severe asthma, which might be directly due to a reduction in ASM mass and neurological alterations. In addition, the reduction in air trapping also suggested a beneficial effect of BT on the peripheral airways without immediate treatment (25,26). Goorsenberg et al. used optical coherence tomography (OCT) to evaluate the acute airway effects of BT in severe asthma; it was found that the acute effects extended beyond the targeted ASM layer and the distal section of directly BT-treated airway areas, suggesting that BT might also affect smaller distal airways (26). The effectiveness and safety of BT were also validated by O'Reilly et al. in long-term follow-up after BT treatment for severe persistent asthma (27). Chupp et al. also validated the long-term efficacy of BT for severe asthma in 2 prospective multicenter studies of patients with severe asthma followed up for up to 3 years (28).

In summary, many clinical studies have demonstrated the safety and long-term effectiveness of BT from different perspectives, including respiratory function imaging, quantitative CT measurements, OCT, pathological studies, pulmonary function tests, QoL scores, and long-term follow-up.

Adverse reactions and complications

Although BT has provided a fresh perspective on treating severe asthma, there are concerns about the adverse effects and complications associated with BT. Studies have shown that patients treated with BT had a significantly higher incidence of adverse events during treatment compared to controls, with most adverse events (e.g., acute exacerbation of bronchial asthma, hypoxemia, bronchospasm, minor bleeding, pneumonia, and non-ischaemic chest pain) occurring after BT (29-31). More severe events have also been reported. According to Research in Severe Asthma (RISA), 4/15 (27%) of BT patients were hospitalized at least once during treatment, while no hospitalization occurred in the control group; these hospitalizations in the BT group were due to asthma exacerbations or partial collapse of a lower lobe of the lung, occurring 1 to 2 days after BT. In the Asthma Intervention Research 2 (AIR2), 8.4% of BT patients required hospitalization during treatment, mainly for asthma exacerbation or segmental atelectasis, compared to 2% in the control group; however, there was no significant increase in the incidence of adverse events and improvement in respiratory symptoms in the BT group later in treatment (3). Data from another large multicenter clinical study showed a high rate of adverse events after BT, with 11.2% of patients experiencing post-

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BT complications, some of which resulted in emergency respiratory readmission (32).

To date, there is no evidence that BT causes bronchiolitis, occlusive bronchitis, emphysema, or airway scarring/stenosis. A study reported that the incidence rate of bronchiectasis in a BT group was 0.2% per annum (3), and it has been argued that BT does not cause bronchiectasis (33,34). There are four common acute radiological abnormalities on chest CT after BT, including peribronchial consolidations with surrounding ground-glass opacities (94%), atelectasis (38%), partial bronchial occlusions (63%), and bronchial dilatations (19%). However, these acute changes do not have a long-term impact on clinical prognosis and outcomes and are mostly transient (35). Other rare complications have also been reported, such as plastic bronchitis (36) and bronchial artery pseudoaneurysm (37) after BT.

Problems and prospects

The exact mechanism of action of BT has still not been fully elucidated. BT aims to reduce the quality of ASM, which is one of the critical features of airway remodeling. However, the mechanism of BT is more complex than the simple reduction of ASM quality. More research is warranted further to investigate the impact of BT on airway pathophysiology. Several mechanisms of action of BT have been proposed, including a reduction in ASM mass and function and structural/functional alterations of airway epithelial cells, neural or extracellular matrix components, and inflammatory cells.

In addition, the role of BT in the management of severe asthma is not yet fully defined. Compared with other treatments such as biologics, it is unclear which subtypes of severe asthma should be treated with BT. It is currently applied mainly in patients with severe non-eosinophilic asthma or as a second-line option for patients who have failed to respond to biologics.

Langton *et al.* found the improved Asthma Control Questionnaire (ACQ) score after BT was associated with more activations (38). However, in any study, the cumulative number of activations performed during 3 BT sessions was not associated with histological changes on bronchial biopsy (6). Some authors have proposed that the number of RF activations during BT is not associated with severe adverse events after BT (39). In contrast, others have concluded that an increased number of RF activations during BT results in a more significant number of serious adverse events. Thus, there is consensus on the impact of BT's activations on treatment outcome and adverse events. In addition, whether the right middle lobe of the lung can be treated with BT remains controversial.

Summary

The BT method offers a new treatment option for severe asthma, and many clinical studies have confirmed its safety and therapeutic efficacy. Although many adverse effects and complications have been noted, mainly in the early stage, the long-term prognosis is good. In addition, the exact mechanism of action of BT has not been fully elucidated, and its role in the treatment of severe asthma is worthy of further investigation.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-580/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm. amegroups.com/article/view/10.21037/atm-22-580/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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