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Effectiveness and Safety of Bronchial Thermoplasty in the Treatment of Severe Asthma with Smoking History: A Single-Center Experience

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Keywords
Asthma · Asthma and chronic obstructive pulmonary disease overlap · Bronchial thermoplasty · Chronic obstructive pulmonary disease · Smoking history

Abstract
Introduction: Bronchial thermoplasty (BT) improves asthma-related quality of life and decreases the number of asthma exacerbations. However, the effectiveness of BT in the treatment of severe asthma with smoking history is unclear because previous studies have excluded patients with smoking history of more than 10 pack-years. ***Objective:*** The aim of the study was to clarify the effectiveness and safety of BT for severe asthma with smoking history. ***Methods:*** We retrospectively reviewed patients who received BT and compared its effectiveness and safety with and without smoking history. ***Results:*** Seven patients were assigned to the smoking group and 9 to the nonsmoking group. Before BT, despite Global Initiative for Asthma step 4 or 5 treatment including oral corticosteroids (OCS) or monoclonal antibody drugs, most patients in both groups had asthma-related symptoms every day (85.7 vs. 77.8%; $p = 0.475$) and frequent asthma exacerbations. After BT, in the smoking group, 3 patients could discontinue or reduce OCS and all 3 patients treated with monoclonal antibody drugs could discontinue them. In the smoking group, 6 patients (85.7%) experienced a reduction in the rate of symptoms, of which 3 patients (42.9%) had a disappearance of symptoms, similar to the nonsmoking group. BT was effective in 5 patients (83.3%) in the smoking group and 6 patients (75.0%) in the nonsmoking group. There were no severe complications. ***Conclusions:*** BT was found to be effective and safe for treatment of severe asthma with smoking history. Our results suggest that BT may be a therapeutic option for asthma-chronic obstructive pulmonary disease overlap.

Introduction

Bronchial thermoplasty (BT) is a bronchoscopic procedure for treating severe asthma that delivers controlled thermal energy to the airway wall, resulting in a prolonged reduction in airway smooth muscle mass [1, 2]. Although previous randomized clinical trials reported that BT improved Asthma Quality of Life Questionnaire

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scores and reduced the number of severe asthma exacerbations, patients with a history of smoking of more than 10 pack-years were excluded from these studies. Thus, the effectiveness and safety of BT for the treatment of severe asthma with smoking history remain unclear.

Although both bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) are chronic airway inflammatory diseases, they are recognized as essentially distinct diseases because of the difference in their pathogenesis, pathophysiology, and clinical features. Some patients have clinical features of both BA and COPD, which was given the term "asthma-COPD overlap syndrome (ACOS)" by the Joint Committee of Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2014. GINA recommended the more appropriate term "asthma-COPD overlap (ACO)" in 2017 [3]. ACO reportedly accounts for 11.1–61.0% of patients with BA and is not a rare clinical condition [4, 5]. Generally, in the treatment strategy for ACO, the use of inhaled corticosteroids (ICS) and concomitant use of bronchodilators such as long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) are recommended. However, the national guidelines in each country do not include a recommendation of BT for the treatment of ACO [6, 7]. In the present study, we retrospectively investigated the clinical efficacy and safety of BT for the treatment of severe asthma with smoking history.

Methods

Patients and Settings

This retrospective study was performed at Kanagawa Cardiovascular and Respiratory Center in Yokohama, Japan. We retrospectively enrolled 19 patients who received BT in our center from September 2015 to August 2018. Participants were referred for BT by their treating respiratory physician if they had frequent symptoms despite optimized asthma therapy including high-dose ICS and long-acting bronchodilators. Of these patients, 16 patients who were evaluable for response 1 year after BT were divided into 2 groups on the basis of smoking status: patients with smoking history of more than 10 pack-years were assigned to the "smoking group," and the remaining patients were assigned to the "non-smoking group." The reason of the cut-off value of cigarette pack-years was that it is the exclusion criterion of previous randomized trials [1, 2]. Subsequently, we compared patient characteristics, treatment status, and any adverse events following BT. The Ethics Committee waived the requirement of obtaining patient consent because this was a retrospective study and high anonymity was ensured.

Treatment Protocol

Patients were treated with BT using the Alair system (Boston Scientific, Natick, MA, USA) under moderate sedation, as previously described [8]. Prednisolone (50 mg) was prescribed for 3 days before each BT procedure and continued for 2 days after the procedure. On the morning of the procedure, subjects were assessed for stability of their illness and absence of symptoms of respiratory tract infection. Each patient was treated in 3 sessions of BT at intervals of at least 3 weeks. The right lower lobe was treated first, followed by the left lower lobe and then both upper lobes during the final bronchoscopy [1, 8].

Assessment of Effectiveness and Safety

The clinical efficacy of BT was evaluated by assessing the frequency of asthma-related symptoms including coughing and wheezing, the number of emergency room visits and hospitalization due to asthma attack, and the dose of concomitant medication such as oral corticosteroids (OCS) and monoclonal antibody drugs 1 year after BT. In addition, efficacy was also evaluated by the physician's Global Evaluation of Treatment Effectiveness (GETE); patients were rated on a 5-point scale for the status of their asthma control [9].

The safety of BT was evaluated by the type, frequency, and severity of complications after BT. We investigated the type and frequency of adverse events after each session of BT. The severity of complications was determined as follows: mild, resolved spontaneously without additional drug administration; moderate, resolved with additional drug administration; or severe, resulted in clinical deterioration or sequelae despite additional treatment.

Statistical Analysis

Categorical data are presented as numbers (percentages) and compared using Fisher's exact test, and continuous data are presented as medians (interquartile ranges) and compared using the Mann-Whitney *U* test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [10], which is a graphical user interface for R version 3.2.2 (the R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Baseline characteristics before BT are shown in Table 1. Of the 19 patients who underwent BT in our hospital, 16 patients completed 3 BT procedures and were evaluable for response 1 year after BT. Of these patients, 7 were assigned to the smoking group and 9 to the nonsmoking group.

The median age was 54 years, and the smoking group was younger than the nonsmoking group (48 vs. 67 years; $p = 0.026$). The smoking group had a higher proportion of male patients, but not statistically significant (71.4 vs. 44.4%; $p = 0.358$). In the smoking group, 2 patients were current smokers, and 5 patients were past smokers. The type of asthma in most patients was atopic, and the nonsmoking group had significantly more allergic comorbidities, such as allergic rhinitis and atopic dermatitis (14.3

Table 1. Summary of clinical characteristics

	All (n = 16)	Smoking (n = 7)	Nonsmoking (n = 9)	p value
Characteristics				
Age, years	54 [48, 68]	48 [43.5, 53]	67 [53, 69]	0.026*
Sex (male/female)	9/7	5/2	4/5	0.358
Duration of disease, years	21 [11, 43.5]	17.5 [12.5, 28.5]	43 [6, 45]	0.420
BMI	24.9 [22.2, 27.7]	25.2 [23.2, 27.1]	24.6 [22.3, 29.3]	0.758
Smoking (pack-years)	1.3 [0, 11.4]	12.0 [10.6, 23.3]	0 [0, 0]	<0.001
Emphysema on computed tomography	1 (6.3%)	1 (14.3%)	0 (0%)	0.438
Type of disease (atopic/nonatopic)	11/5	6/1	5/4	0.308
Allergic complications	8 (50%)	1 (14.3%)	7 (77.8%)	0.041*
Diagnosis of ACO	6 (37.5%)	6 (85.7%)	0 (0%)	0.001*
Laboratory data				
WBC, μL^{-1}	6,885 [5,375, 9,388]	9,060 [6,310, 9,615]	6,040 [5,300, 9,150]	0.585
Eosinophil count, μL^{-1}	241.9 [38.9, 489.5]	398.4 [139.7, 792.7]	42.4 [6.9, 356.9]	0.549
Eosinophils, %	2.7 [0.8, 8.4]	8.1 [1.5–9.8]	0.8 [0.1, 5.5]	0.284
Total IgE, IU/mL	206.5 [77.7, 449.3]	333 [234, 461.5]	170 [66.4–205]	0.670
Respiratory function test				
% FVC	96.8 [91.2, 10.5]	93.1 [89.5, 96.8]	107 [92.7, 116]	0.041*
% FEV_1	60.5 [48.9, 67.2]	50.9 [33.3, 61.0]	62.3 [56.4, 67.7]	0.089
% FEV_1	75.9 [50.6, 83.3]	53.3 [38.0, 67.7]	80.1 [76.8, 92.6]	0.012*
Exhaled nitric oxide levels, ppb	32 [23, 80]	90 [48, 113.5]	24.5 [21.3, 29.0]	0.019*
Medication usage				
JSA step (1/2/3/4)	0/0/0/16	0/0/0/7	0/0/0/9	1.000
GINA step (1/2/3/4/5)	0/0/0/5/11	0/0/0/1/6	0/0/0/4/5	0.308
OCS, n (%)	8 (50.0)	4 (57.1)	4 (44.4)	1.000
OCS dosage, g/day	1.25 [0, 5]	2.5 [0, 5]	5 [0, 5]	0.698
Omalizumab	3 (18.8%)	2 (28.6%)	1 (11.1%)	0.55
Mepolizumab	2 (12.5%)	1 (14.3%)	1 (11.1%)	1.000
Treatment status				
Frequency of any symptoms (0/1/2/3)[a]	0/1/2/13	0/1/0/6	0/0/2/7	0.475
Exacerbations required corticosteroid (events/subject/year)	3 [1.75, 9]	5 [2, 14]	3 [1, 4]	0.531
Hospitalizations (events/subject/year)	0 [0, 0]	0 [0, 0.5]	0 [0, 0]	0.255
Emergency department visits (events/subject/year)	2.5 [0.75, 5.25]	5 [2, 13]	2 [0, 4]	0.141

Categorical data are presented as numbers (percentages) and were analyzed using Fisher's exact test. Continuous data are presented as medians (interquartile ranges) and were analyzed using the Mann-Whitney U test. A *p value of <0.05 was considered statistically significant. ACO, asthma-chronic obstructive pulmonary disease overlap; WBC, white blood cell; IgE, immunoglobulin E; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; JSA, Japanese Society of Allergology; GINA, Global Initiative for Asthma; OCS, oral corticosteroids. [a] 0: absent; 1: less than once a week; 2: more than once a week; 3: every day.

vs. 77.8%; p = 0.041). In the smoking group, 6 patients (85.7%) met the diagnostic criteria of ACO according to "The Japanese Respiratory Society Guidelines for the Management of ACO 2018" [11]. The remaining 1 patient in the smoking group was not diagnosed with ACO because of a slightly high forced expiratory volume in 1 s/forced vital capacity rate (73.7%).

Laboratory results, including white blood cell counts, eosinophil counts, and total immunoglobulin E, showed no differences between the 2 groups. In terms of respiratory function tests, significantly lower percentage-predicted forced vital capacity (p = 0.041), lower percentage-predicted forced expiratory volume in 1 s (p = 0.012), and higher exhaled nitric oxide (NO) levels (p = 0.019) were observed in the smoking group than in the nonsmoking group.

All patients required step 4 or 5 treatment according to the guidelines of GINA for severe asthma with high-

Table 2. Summary of the treatment outcomes 1 year after BT

	Smoking (n = 7)	Nonsmoking (n = 9)
Medication usage		
OCS (0/1/2/3)[a]	1/2/4/0	1/2/6/0
Monoclonal antibody drugs (0/1/2)[b]	3/0/0	1/0/2
Treatment status		
Frequency of any symptoms (0/1/2/3)[c]	3/2/1/1	5/0/3/1
Exacerbations required corticosteroids (events/subject/year)	4 [1, 4]	0.5 [0, 1]
Hospitalizations (events/subject/year)	0 [0, 0]	0 [0, 0]
Emergency department visits (events/subject/year)	1 [0, 2]	0 [0, 1]
GETE (1/2/3/4/5)[d,e]	4/1/0/0/1	4/2/0/2/0
Effectiveness[e]	5 (83.3%)	6 (75%)

Categorical data are presented as numbers (percentages), and continuous data are presented as medians (interquartile ranges). OCS, oral corticosteroids; GETE, Global Evaluation of Treatment Effectiveness; ABPM, allergic bronchopulmonary mycosis. [a]0: discontinuation; 1: dose reduction; 2: no change; 3: increase. [b]0: discontinuation; 1: no change; 2: addition. [c]0: absent; 1: less than once a week; 2: more than once a week; 3: every day. [d]1: excellent; 2: good; 3: moderate; 4: poor; 5: worsening of asthma. [e]1 patient each in both groups was unevaluable due to ABPM as complications after BT and the need for maintenance therapy of OCS.

dose ICS/long-acting beta-2 agonists and concomitant use of LAMA. In addition to these inhaled therapies, 6 patients (85.7%) in the smoking group and 5 patients (55.6%) in the nonsmoking group were treated with OCS or monoclonal antibody drugs. Despite the above treatment strategies, most patients in both groups had asthma-related symptoms every day (85.7 vs. 77.8%; p = 0.475) and required frequent emergency room visits and hospitalization during 1 year before BT, which physicians' assessment of their asthma control was similarly poor.

Effectiveness Outcome 1 year after BT

Table 2 shows the summary of treatment outcomes 1 year after BT. Three patients each in both groups were able to discontinue or reduce OCS (42.9 vs. 33.3%, respectively). Additionally, in the smoking group, all 3 patients who were treated with monoclonal antibody drugs before BT were able to discontinue them after BT. During the posttreatment period, in the smoking group, 6 patients (85.7%) experienced a reduction in the rate of asthma-related symptoms, of which 3 patients (42.9%) showed a disappearance of these symptoms, similar to the nonsmoking group.

In both groups, the numbers of asthma attack requiring systemic corticosteroid administration, emergency room visits, and hospitalizations were decreased after BT (Fig. 1). Although 1 patient in each group was not evaluable because of allergic bronchopulmonary mycosis as a complication after BT and the need for maintenance therapy of OCS, BT was effective in the remaining cases: 5 patients (83.3%) in the smoking group and 6 patients (75.0%) in the nonsmoking group.

Adverse Events

The adverse events of BT are presented in Table 3. The median length of stay for a single procedure of BT was 5–6 days in both groups. In the smoking group, 13 adverse events (61.9%) after BT were observed, which was similar to the nonsmoking group. In both groups, most of the complications, including atelectasis, asthma attacks, fever, and blood clots, occurred within 1 month after BT. As late complications, allergic bronchopulmonary mycosis was occurred in 1 patient in each group.

All complications after BT were defined as mild or moderate, which were resolved with observation or with administration of additional drugs such as OCS or antibiotic therapy. There were no severe complications of BT in each group.

Discussion

In this study, we retrospectively analyzed the effectiveness and safety of BT for severe asthma patients with smoking history. In previous randomized prospective

Table 3. Summary of the adverse events of BT

	Smoking (n = 21)[a]	Nonsmoking (n = 27)[a]
Length of hospital stay		
1st procedure, days	5 (3–11)	5 (3–13)
2nd procedure, days	5 (3–17)	5 (4–14)
3rd procedure, days	5 (3–14)	6 (4–13)
Complications		
Total	13 (61.9%)	15 (55.6%)
Early (within 1 month)	12 (57.1%)	14 (51.8%)
Atelectasis	4 (19.0%)	8 (29.6%)
Asthma attack	6 (28.6%)	1 (3.7%)
Fever/pneumonia	0 (0%)	3 (11.1%)
Bloody sputum	2 (9.5%)	1 (3.7%)
Others	0 (0%)	1 (3.7%): EP
Later (after 1 month∼)	1 (4.8%): ABPM	1 (3.7%): ABPM
Severity (mild/moderate/severe)[b]	7/6/0	7/8/0

Categorical data are presented as numbers (percentages). [a]Patients number ×3 procedures. [b]Mild: resolving spontaneously without additional drug administration; moderate: resolving by additional drug administration; severe: resulting clinical deterioration or sequelae despite additional treatment.

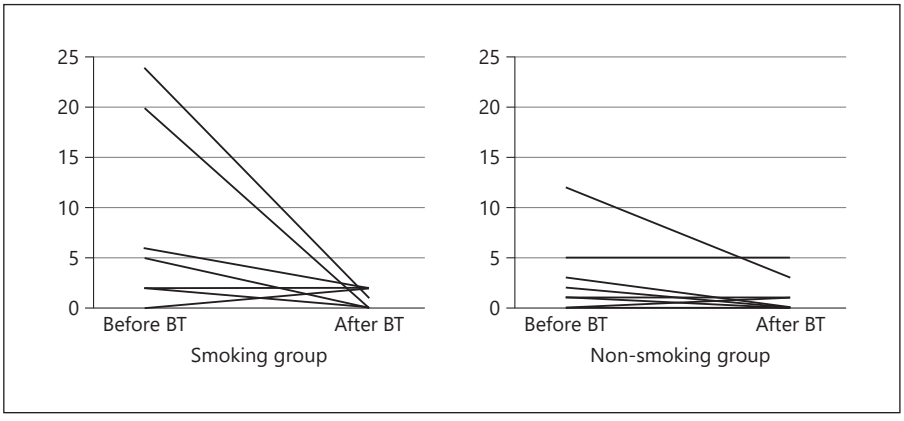

Fig. 1. Change of the number of emergency department visits in the smoking and nonsmoking groups. Most patients experienced a decrease in the number of emergency department visits after BT. The decrease in the number in the smoking group was similar to that in the nonsmoking group.

studies such as the AIR2 and PAS2 trials, BT reportedly improved asthma control and reduced the number of severe exacerbations and the dose of concomitant medications including OCS and monoclonal antibody drugs [1, 2]. In our study, BT was effective in the treatment of severe asthma, as seen in previous reports. Additionally, BT was found to be equally effective and safe in the smoking and nonsmoking groups, which suggests that BT might be effective for the treatment of severe asthma with smoking history.

Both BA and COPD are chronic inflammatory diseases with airway obstruction, and they often coexist, with a probability of 11.1–61.0% [4, 5]. Although BA and COPD have common pathological features including airway wall thickening with inflammatory cell infiltration, hyperplasia of submucosal glands, and airway remodeling induced by repeated injury and repair processes, there are many differences between the 2 diseases [12, 13]. Allergic inflammation in BA is driven by CD4+ T-helper 2 (Th2) lymphocytes, eosinophils, and mast cells, whereas CD8+ T-helper 1 (Th1) lymphocytes, neutrophils, and macrophages play a key role in the inflammation of COPD [14, 15]. Besides, in inhaled drugs, beta-2 agonists are the most effective bronchodilators in BA, whereas LAMA are more effective bronchodilators than beta-2 agonists in COPD [15]. In other words, in COPD, acetylcholine

(ACh) released from parasympathetic airway nerve fibers mediates smooth muscle tone, reflex bronchoconstriction.

In this study, we considered the following 2 hypotheses regarding the effectiveness of BT for the treatment of severe asthma with smoking history. The first hypothesis is that BT would affect the bronchial nerve. As mentioned above, ACh released from parasympathetic airway nerve fibers causes bronchoconstriction, mucus secretion, and bronchial vasodilation in COPD. In recent years, targeted lung denervation (TLD), which is a bronchoscopic radiofrequency ablation therapy, has reportedly been effective for the treatment of COPD [16, 17]. TLD durably disrupts parasympathetic pulmonary nerves to decrease ACh secretion, resulting in a decrease of airway resistance and mucous hypersecretion. A previous randomized double-blind trial (AIRFLOW trial) showed that TLD decreased the frequency of respiratory symptoms and exacerbations in patients with COPD [16]. On the other hand, it was also reported that BT has an effect on the bronchial nerve. Pretolani et al. [18] reported that BT selectively downregulated structural abnormalities not only in the airway smooth muscle but also in the neuroendocrine epithelial cells and bronchial nerve endings. Similarly, Ichikawa et al. [19] demonstrated a decrease after BT in the expression of protein gene product 9.5, a marker for neuroendocrine cells, that was confined to neural and neuroendocrine cells, suggesting that BT reduces airway innervation. Based on these findings, the effect on the bronchial nerve by BT might decrease ACh secretion, resulting in the reduction of the frequency of respiratory symptoms and exacerbations in COPD, similar to TLD.

The second hypothesis is that BT would induce immunomodulation and affect the inflammatory component of COPD in this study. As noted above, CD4+ Th2 lymphocytes and eosinophils mainly cause airway inflammation in BA, whereas CD8+ Th1 lymphocytes and neutrophils play a key role in the inflammation of COPD. Previous studies suggest that BT might have an immunomodulatory activity; in a small recent study, Marc Malovrh et al. [20] reported that the proportion of cytotoxic CD8+ Th1 lymphocytes in bronchoalveolar lavage fluid significantly decreased after BT. We believe that a decrease of CD8+ Th1 lymphocytes owing to an immunomodulatory effect of BT would result in an effect on severe asthma with smoking history. It is so difficult to explain how BT affects the component of COPD in ACO patients because there are limited reports of detailed mechanisms of BT. However, as seen from the above, not only an effect on asthma but also the action to bronchial nerve and immunomodulation of BT may have a favorable impact on the components of COPD.

This study has several limitations. First, this study was a small, retrospective study, which may have caused various biases. Some positive or negative results in this study may have been because of the inadequate power. Therefore, large-scale prospective studies are required to confirm our results. Second, significantly higher levels of exhaled NO in the smoking group before BT might have caused a bias. In general, exhaled NO increases in asthma and does not increase in COPD. In our study, the higher levels of exhaled NO in the smoking group suggest that patients in this group, as opposed to those in the nonsmoking group, may have a greater component of asthma. However, we believe that the higher levels of exhaled NO did not affect the results in our study because it reportedly could not predict the effect of BT in a previous study [21].

In conclusion, in the present study, BT was found to be also effective and safe for treatment of severe asthma with smoking history. Our results suggest that BT may be a therapeutic option for the treatment of ACO. Unfortunately, accurate efficacy and safety of BT to smokers have not been fully proven because of our limited cases. Further investigation is required to establish an optimal treatment strategy.

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Statement of Ethics

This retrospective study was approved by the institutional review board of the Kanagawa Cardiovascular and Respiratory Center (KCRC-19-0031). Because of the retrospective nature of the study, the review board waived the need for written informed consent from the patients.

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Author Contributions

R.O. was the primary investigator and had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the analysis. R.O., T.B., N.A., E.T, S.S., H.N., A.S., S.K., E.H., and T.O. were involved in data generation and analysis. R.O. and T.B. were involved in drafting the manuscript. All authors were responsible for the critical revision of the manuscript and approved the final manuscript.

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