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Bronchial Thermoplasty Attenuates Cough Reflex Sensitivity in Severe Asthma : A Single-Center Retrospective Study with 2-year Follow-up

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Abstract : Despite the relatively short follow-up period in our previous study, we had reported that increased cough reflex sensitivity (CRS) may predict the efficacy of bronchial thermoplasty (BT) for treating asthma. Herein, we examined whether CRS predicts the efficacy of BT 2 years after the final BT treatment. We also investigated the influence of BT on CRS. We reviewed 10 patients 2 years after their final BT treatment. CRS, asthma-related symptoms, asthma exacerbations, and cough-related quality of life were assessed at baseline and 2 years after BT. Five patients responded positively to BT (BT responders) and their asthma control improved. No significant difference in CRS at baseline was detected between the BT responders and nonresponders. In contrast, BT responders exhibited significant improvements in CRS 2 years after BT. CRS at baseline could not predict the BT efficacy after 2 years. This is the first report demonstrating BT desensitized CRS in consecutive case series. J. Med. Invest. 70 : 271-275, February, 2023

Keywords **:** *bronchial asthma, bronchial thermoplasty, cough reflex sensitivity, cough-related quality of life*

INTRODUCTION

Bronchial thermoplasty (BT) is a nonpharmacological treatment for patients with asthma. Treatment with BT can improve asthma-specific quality of life (QOL) (1) and reduce severe asthma exacerbations (1, 2), emergency room visits (1, 2), and days missing work or other activities due to asthma (1). Possible mechanisms of action for BT involve changes in the structure and / or function of airway smooth muscle, epithelial cells, glands, extracellular matrix components, nerves, and / or inflammatory cells. However, optimal predictors of BT response and certain mechanism of action have not been identified.

Capsaicin evokes cough via transient receptor potential vanilloid 1 (TRPV1) activation, which in turn results in neurogenic inflammation, including airway contraction, airway edema, airway secretions, and cough via peptides. The capsaicin cough reflex sensitivity (CRS) is thought to reflect airway nerve dysfunction and be associated with the pathogenesis of asthma (3, 4). Increased CRS to inhaled capsaicin is a fundamental feature of atopic cough (5). The CRS to capsaicin or irritant stimuli in patients with asthma has been controversial (6, 7). Recently, Kanemitsu *et al*. reported that CRS to inhaled capsaicin was associated with worse clinical outcome in patients with severe asthma (3). Drake *et al*. reported that airway innervation and substance P expression were higher in patients with moderate asthma than in those with mild intermittent asthma and healthy subjects and that increased innervation was associated with increased irritant sensitivity (8) in human airway tissues. These findings suggest that remodeling and functional changes in airway nerves result in resistant cough in some patients with asthma. In a recent case study reported that BT reduced CRS to inhaled capsaicin in a patient with severe asthma (9). To the best of our knowledge, there is no reports to demonstrate BT desensitized CRS in consecutive case series.

We previously reported that increased CRS to capsaicin may be a predictor of BT responder (10). However, the study was limited by a short follow-up period (≤2 years). In this study, we examined whether increased CRS could predict the clinical effect of BT in 10 patients at least 2 years after receiving their final BT treatments. In addition, we investigated the influence of BT on CRS.

PATIENTS AND METHODS

Patients

The medical records of 13 consecutive patients with asthma who underwent three BT treatment sessions at Kanazawa University Hospital between January 2016 and June 2019 were retrospectively reviewed. All patients were diagnosed with severe persistent asthma according to the Japanese guidelines for adult asthma 2020. Overall, 6 patients received maintenance oral corticosteroid. Among these cases, 1 patient died within 2 years of treatment and was therefore not available for long-term follow-up. And 2 patients with current smoking were exclude. Thus, this study included 10 patients (42–75 years old, 4 male and 6 female) who could be evaluated for determining the efficacy of BT after 2 years of receiving the treatments. Seven cases investigated in the previous study (10) were reexamined in the present study. All patients provided written informed consent to participate in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board of Kanazawa University Hospital (Approval date : March 14, 2017 ; Approval number : 2380, UMIN : 000026578). There was no change in smoking habits of former smokers during study period.

Patient assessment

Patient were assessed before the first BT session and 2 years

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(between 24 months and 25 months) after the last BT treatment. Asthma symptoms, asthma medication, exacerbation requiring treatment with systemic corticosteroids, asthma control using the Asthma Control Questionnaire (ACQ)-6, asthma-specific health-related QOL using the Asthma Quality of Life Questionnaire (AQLQ), cough-related QOL using the Japanese version of the Leicester Cough Questionnaire (J-LCQ) (11), global evaluation of treatment effectiveness (GETE), pulmonary function (including reversibility to beta-2 agonists and fractional exhaled nitric oxide [FeNO]), and CRS to capsaicin were evaluated at baseline and 2 years after the last BT treatment. 7 patients who participated in both earlier study and the current study underwent this same set of tests. FeNO was measured using an electrochemical analyzer (NIOX MINO or VERO ; CHEST, Tokyo, Japan). The cough threshold to capsaicin was defined as the lowest concentration of capsaicin that elicited ≥5 coughs (C5). The number of asthma exacerbations requiring systemic corticosteroids in the one-year period from 1 to 2 years after the final BT treatment was recorded for each patient.

Response criteria

BT responders were defined as patients who showed improvement greater than the minimal important difference (MID) on the ACQ-6, improvement greater than the MID on the AQLQ (0.5 units for both instruments), improvement in the number of asthma exacerbations per year, and a score of good/excellent on the GETE. Patients who did not meet these criteria were defined as BT nonresponders.

Statistical analysis

Data values and numbers (percentages), excluding C5, are expressed as mean ± standard deviation. C5 is expressed as the geometric mean ± geometric standard error of the mean. Logarithmically converted C5 values were used in analyses. The Mann–Whitney U-test was used for between-group analyses and the Wilcoxon signed-rank test was used for paired analyses. The Fisher's exact probability test was used for between-group analyses. A two-sided p-value <0.05 was considered significant.

RESULTS

Eight patients had scores of ≥1.5 on the ACQ-6 indicating poor control of bronchial asthma. Five patients were defined as "BT responders," and five as "BT nonresponders," based on their clinical parameters as described in response criteria. No significant differences were observed in the baseline characteristics and clinical data including C5 of BT responders and nonresponders (Table 1). In the BT responders, one had reduced their OCS dose and two had completely discontinued OCS use, and four patients reduced their ICS dose (Table 2). In addition to significant improvements in ACQ-6, AQLQ, and the number of asthma exacerbations, which were included in the definition of a "responder," significant improvements in C5 ($p < 0.05$) and tendency to improve in J-LCQ ($p = 0.080$) were also observed in the BT responders 2 years after the last BT treatment compared with baseline. Conversely, no significant improvements were detected in the BT nonresponders, 2 years after the last BT (Figure).

DISCUSSION

We reexamined whether increased CRS could predict the clinical effect of BT in 10 cases. Patients were assessed before receiving treatment (baseline) and at least 2 years after the final BT treatment. Moreover, 5 of the 10 patients responded positively to BT. However, CRS did not predict response to BT. In contrast, patients who responded to BT exhibited desensitization of CRS to capsaicin accompanied by improvement of cough-related QOL after BT.

We previously reported that increased CRS to capsaicin might predict positive BT response (10) ; however, we were unable to confirm similar results in this study. Two patients with increased CRS, who were initially considered BT responders, experienced exaggerated asthma symptoms as well as worsened QOL and symptom control 1 year after their last BT treatments. These differences may be attributed to the short follow-up period (≤2 years) in our previous report, and the administration of systemic steroids with BT may have masked the true therapeutic effect of BT. We postulate based on these cases that follow-up periods of <2 years do not accurately reflect the therapeutic effects of BT. Severe asthma exacerbation, hospital emergency department visits, AQLQ and ACQ more worsened during 1 year than that of during 2 years in long-term (>10 years) prospective, follow-up study (12). We need to carefully follow-up the patients received BT over long time because optimal predictors of BT response are still unknown (12, 13).

Our results showed that BT desensitized CRS to capsaicin, a phenomenon particularly remarkable in patients who responded to BT. Moreover, decreased CRS was accompanied with a tendency to improve in LCQ scores. To the best of our knowledge, this is the first report to demonstrate BT desensitized CRS in consecutive case series. Several recent reports have shown that the involvement of CRS and severe asthma. CRS to inhaled capsaicin was significantly increased in asthma, especially non-atopic women and correlated with severity and poor control but was independent of airway hyperresponsiveness (AHR) and FeNO (4). The increased CRS to capsaicin during the stable phase of asthma, independent of airflow obstruction, contributed to poor asthma control and frequent exacerbations, especially in non-atopic cases (3, 14). Nocturnal cough refractory to ICS in asthma was associated with increased AHR and daytime cough with increased CRS (15). Sensory neuropathy resulting in CRS enhancement may be an important therapeutic target in severe, especially non-type 2 asthma (14). One report showed that BT reduced CRS refractory to high-dose ICS, LABA and LTRA in a severe asthma case study (9). Several studies have demonstrated that denervation in the airways may contribute to the clinical efficacy of BT (16-19). The denervation effect of BT may have decreased CRS and improved asthma control as a result of the amelioration in sensory neuropathy. In our study, the cough reflex desensitization to capsaicin observed in BT responders is consistent with that of previous reports on airway denervation effects of BT.

We do not know why BT showed denervation effects in half of our cases. Especially in the three female patients with strongly heightened CRS, BT failed to improve C5 at all. These patients did not differ in their background or number of activations. We think that the effects of BT on receptors (TRPV1, TRPV4, transient receptor potential ankyrin 1, acid- sensing ion channel and ATP receptors), ion channel expression and lipid mediators involved in the regulation of CRS should be investigated.

Our study has several limitations. First, it was a single-center retrospective study that included only 10 patients. Second, there were few male patients in the study ; therefore, differences in efficacy due to sex could not be evaluated. Third, the appropriate period to judge the effects of BT could not be determined. To confirm our findings, larger studies are necessary.

In conclusion, while our results showed that increased CRS to capsaicin does not predict a positive response to BT, it was evident that BT desensitizes CRS to capsaicin. Our results can support the denervation effect of BT.

Table 1. Baseline characteristics in bronchial thermoplasty (BT) responders and nonresponders.

	BT responder (n = 5)	BT non-responder (n = 5)
Age (years)	67.8 ± 6.3	62.2 ± 8.9
Sex (percentage of men)	0%	40.0%
BMI (kg/m^2)	24.7 ± 3.3	23.3 ± 4.0
Disease duration (years)	23.0 ± 13.2	36.0 ± 16.1
Smoking status (Current/Former/Never)	(0/3/2)	(0/2/3)
(pack-years)	(8.0 ± 8.4)	(0.7 ± 1.1)
Blood eosinophils (μL)	72.9 ± 31.3	468.8 ± 431.5
Total serum IgE (IU/mL)	56.6 ± 28.2	323.0 ± 419.1
Perennial allergens (positive percentage)	60%	40%
Treatment (% treated)		
high dose ICS/LABA	80.0%	60.0%
LAMA	60.0%	60.0%
LTRA	80.0%	100.0%
Theophylline	80.0%	40.0%
maintenance OCS	60.0%	40.0%
Pre-bronchodilator FEV_1 (% predicted)	85.1 ± 16.7	87.4 ± 22.6
Pre-bronchodilator FEV_1/FVC ratio	63.0 ± 6.7	70.1 ± 9.4
Post-bronchodilator FEV_1/FVC ratio	64.0 ± 8.1	71.3 ± 11.2
Reversibility to beta-2 agonist (mL)	(96.0 ± 127.4)	(70.0 ± 78.4)
(%)	(7.9 ± 12.4)	(2.8 ± 3.5)
FeNO (ppb)	16.4 ± 8.8	57.5 ± 59.8
C5 (μL)	1.0 ± 1.6	1.5 ± 1.5
ACQ-6	1.7 ± 0.4	2.2 ± 1.3
AQLQ	4.5 ± 1.1	4.1 ± 1.7
Total J-LCQ	15.4 ± 3.3	12.8 ± 5.7
No. of asthma exacerbations requiring systemic CS	3.8 ± 1.5	6.0 ± 1.0
The total number of activations	112.0 ± 18.0	149.4 ± 47.3

Abbreviations : ACQ-6, Asthma Control Questionnaire-6 ; AQLQ, Asthma Quality of Life Questionnaire ; C5, Cough threshold defined as the lowest concentration of capsaicin that elicited ≥5 coughs ; CS, corticosteroid, FeNO, fractional exhaled nitric oxide ; FVC, forced vital capacity ; ICS, inhaled corticosteroid ; J-LCQ, The Japanese version of the Leicester Cough Questionnaire ; LABA, long-acting beta-2 agonist ; LAMA, long-acting muscarinic receptor antagonist ; LCQ, Leicester Cough Questionnaire ; LTRA, leukotriene receptor antagonist ; OCS, oral corticosteroid

Table 2. The treatment details 2 years after the last BT in bronchial thermoplasty (BT) responders and nonresponders.

	BT responder (n = 5)	BT non-responder (n = 5)
Treatment (% treated)		
high dose ICS/LABA	20.0%	80.0%
LAMA	40.0%	60.0%
LTRA	60.0%	100.0%
Theophylline	20.0%	40.0%
maintenance OCS	20.0%	40.0%

ICS, inhaled corticosteroid ; LABA, long-acting beta-2 agonist ; LAMA, long-acting muscarinic receptor antagonist ; LTRA, leukotriene receptor antagonist ; OCS, oral corticosteroid

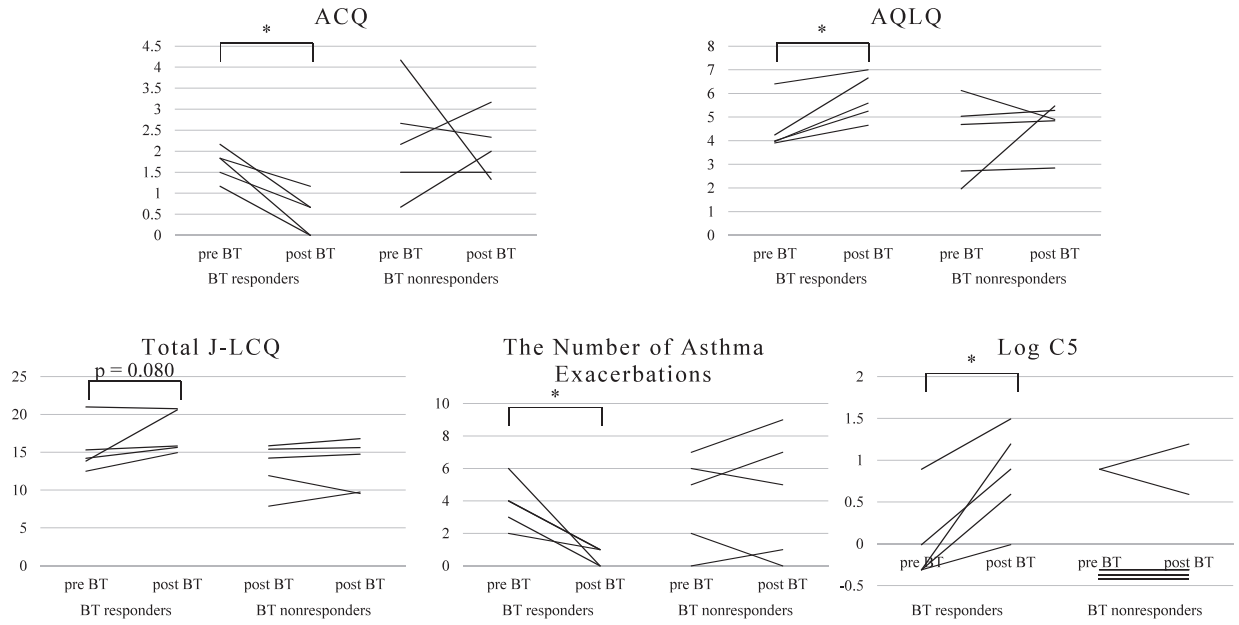

Figure. Changes in ACQ-6 scores, change in AQLQ scores, changes in the number of asthma exacerbations requiring systemic corticosteroids, changes in total J-LCQ scores and changes in C5 in BT responders and nonresponders pre- and post-BT
ACQ-6, Asthma Control Questionnaire-6 ; AQLQ, Asthma Quality of Life Questionnaire ; BT, Bronchial thermoplasty ; C5, Cough threshold defined as the lowest concentration of capsaicin that elicited ≥5 coughs ; J-LCQ, The Japanese version of the Leicester Cough Questionnaire.
open bar, baseline ; shaded bar, 2 years after the last BT
* $P < 0.05$ compared with baseline

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CONTRIBUTIONS

JH designed the study and collected the data and wrote the manuscript. JH, KY, TS, TK, NO, SW, YT and MA performed the BT treatment. JH, TS, and HK performed the statistical analysis. JH, KK and SY performed the interpretation of the results. All authors read and approved the final manuscript.

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