

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

Johsuke Hara (✉ [hara0728@staff.kanazawa-u.ac.jp](mailto:hara0728@staff.kanazawa-u.ac.jp))

Kanazawa University Hospital

**Kenta Yamamura**

Kanazawa University Hospital

**Tamami Sakai**

Kanazawa University Hospital

**Takafumi Kobayashi**

Kanazawa University Hospital

**Noriyuki Ohkura**

Kanazawa University Hospital

**Satoshi Watanabe**

Kanazawa University Hospital

**Yuichi Tambo**

Kanazawa University Hospital

**Takashi Sone**

Kanazawa University Hospital

**Hideharu Kimura**

Kanazawa University Hospital

**Miki Abo**

Kanazawa University Hospital

**Kazuo Kasahara**

Kanazawa University Hospital

**Seiji Yano**

Kanazawa University Hospital

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## Short Report

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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 12 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. Six 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.

## 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].

Capsaicin evokes cough via transient receptor potential vanilloid 1 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]. In bronchial asthma, CRS to irritant stimuli has been a controversial topic. 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 [6] 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 [7]. 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 [8]. However, the study was limited by a short follow-up period ( $\leq 2$  years). In this study, we examined whether increased CRS could predict the clinical effect of BT in 12 patients at least 2 years after receiving their final BT treatments. In addition, we investigated the influence of BT on CRS.

## 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, 58 years old male patient died within 2 years of treatment and was therefore not available for long-term follow-up. Thus, this study included 12 patients (43–78 years old, 2 male and 10 female) who could be evaluated for determining the efficacy of BT after 2 years of receiving the treatments. Nine cases investigated in the previous study [8] 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).

### **Patient assessment**

Patient were assessed before the first BT session and 2 years (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) [9], 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. 9 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  $\geq 5$  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  $\pm$  standard deviation. C5 is expressed as the geometric mean  $\pm$  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

Ten patients had scores of  $\geq 1.5$  on the ACQ-6 indicating poor control of bronchial asthma. Six patients were defined as “BT responders,” and six as “BT nonresponders,” based on their clinical parameters as described in section 2.3. There were no significant differences in the baseline characteristics and clinical data including C5 of BT responders and nonresponders (Table 1). 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 total J-LCQ ( $p < 0.05$ ) and C5 ( $p < 0.05$ ) (Figure) 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.

## Discussion

We reexamined whether increased CRS could predict the clinical effect of BT in 12 cases. Patients were assessed before receiving treatment (baseline) and at least 2 years after the final BT treatment. Moreover, 6 of the 12 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 [8]; 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 ( $\leq 2$  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 [10]. We need to carefully follow-up the patients received BT over long time because optimal predictors of BT response are still unknown [10, 11].

Our results showed that BT desensitized cough CRS to capsaicin, a phenomenon particularly remarkable in patients who responded to BT. Moreover, decreased CRS was accompanied by improved LCQ scores. To the best of our knowledge, this is the first report to demonstrate BT desensitized CRS in consecutive case series. Several studies have demonstrated that denervation in the airways may contribute to the clinical efficacy of BT [12–14]. 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.

Our study has several limitations. First, it was a single-center retrospective study that included only 12 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, we clearly showed that BT desensitizes CRS to capsaicin. Our results may support the denervation effect of BT.

## Declarations

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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.

### Conflict of interest

The authors declare no conflict of interest.

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## Tables

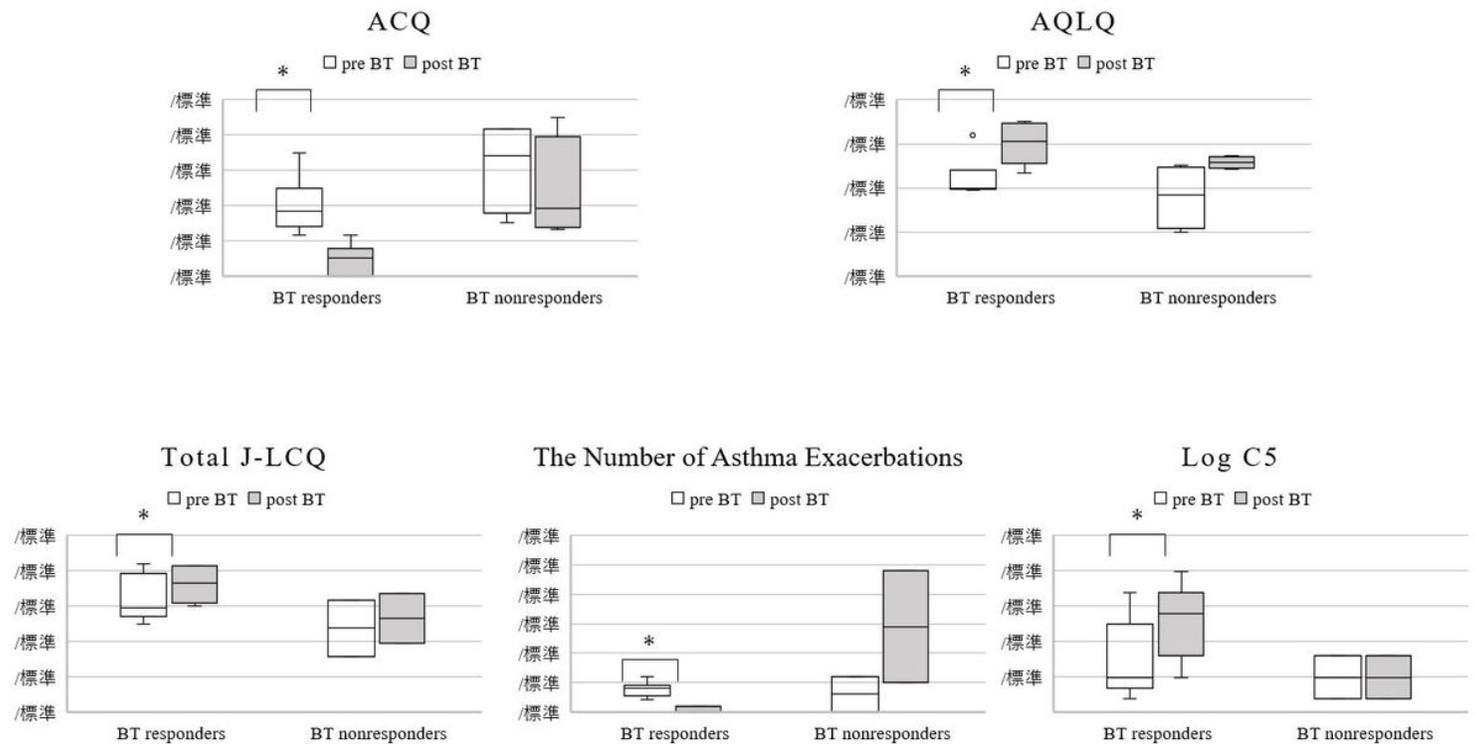
**Table 1** Baseline characteristics in bronchial thermoplasty (BT) responders and nonresponders.

	BT responder (n = 6)	BT non-responder (n = 4)
Age (years)	69.5 ± 6.3	55.2 ± 12.0
Sex (percentage of men)	0%	33.3%
BMI (kg/m <sup>2</sup> )	24.5 ± 3.9	23.5 ± 5.0
Disease duration (years)	23.8 ± 12.0	38.0 ± 18.2
Smoking status (Current/Former/Never) (pack-years)	(1/3/2) (8.0 ± 8.6)	(1/1/2) (5.6 ± 9.7)
Blood eosinophils (µL)	73.3 ± 28.0	518.3 ± 454.0 *
Total serum IgE (IU/mL)	47.7 ± 33.4	359.8 ± 414.5
Perennial allergens (positive percentage)	50%	50%
Treatment (% treated)		
high dose ICS/LABA	83.3%	100.0%
LAMA	66.7%	25.0%
LTRA	83.3%	75.0%
Theophylline	83.3%	75.0%
maintenance OCS	66.7%	50.0%
Pre-bronchodilator FEV <sub>1</sub> (%predicted)	83.9 ± 15.6	95.4 ± 19.7
Pre-bronchodilator FEV <sub>1</sub> /FVC ratio	65.1 ± 7.8	75.2 ± 5.2
Post-bronchodilator FEV <sub>1</sub> /FVC ratio	64.0 ± 8.1	79.8 ± 8.1*
Reversibility to beta-2 agonist (mL) (%)	(113.3 ± 121.6) (8.6 ± 11.2)	(147.5 ± 79.3) (6.3 ± 3.7)
FeNO (ppb)	14.7 ± 8.9	74.0 ± 65.9
C5 (µL)	3.4 ± 1.2	0.6 ± 0.7
ACQ-6	2.0 ± 0.8	3.1 ± 1.3
AQLQ	4.4 ± 1.0	3.6 ± 1.5
Total J-LCQ	16.0 ± 3.3	11.9 ± 5.6
No. of asthma exacerbations requiring systemic CS	3.8 ± 1.3	4.5 ± 3.1
The total number of activations	100.8 ± 11.3	99.5 ± 15.4

\* $P < 0.05$  compared with BT responder group

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  $\geq 5$  coughs; CS, corticosteroid; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; J-LCQ, The Japanese version of the Leicester Cough Questionnaire; LAMA, long-acting muscarinic receptor antagonist; LCQ, Leicester Cough Questionnaire; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid

## Figures



**Figure 1**

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  $\geq 5$  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