CASE REPORT

The therapeutic effects of bronchial thermoplasty evaluated by cardiopulmonary exercise testing : a case series

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Abstract : Bronchial thermoplasty (BT) had been reported to improve the symptoms of severe asthma. However, the exertional responses of BT based on the mechanisms have not been elucidated. A 57-year-old man and a 60-year-old woman underwent BT due to intractable severe asthma. We evaluated the therapeutic effects of BT using cardiopulmonary exercise testing (CPET). After BT, the exercise time during CPET substantially prolonged reducing exertional dyspnea in the former (good), but not in the latter (poor). In the good responder, the high air remaining in the lung after expiration (i.e., inspiratory tidal volume minus expiratory tidal volume) during CPET decreased after BT. In contrast, in the poor responder, the high air remaining after expiration during exercise was not obtained before BT. Further investigations are necessary to confirm that the presence or absence of the exertional wasted ventilation on CPET may be informative to evaluate the therapeutic effects of BT. J. Med. Invest. 67 : 386-390, August, 2020

Keywords **:** *dynamic hyperinflation, dyspnea, expiration, inspiration, tidal volume*

INTRODUCTION

Bronchial thermoplasty (BT) is one of the effective treatments that had been reported to improve the symptoms of severe asthma (1-4). However, the mechanisms of symptomatic improvement and the effects of BT on resting respiratory function have not been elucidated. In the present case series, we evaluated whether the results obtained from cardiopulmonary exercise testing (CPET) in 2 severe asthmatics could reflect the therapeutic effects of BT. Two patients were defined as either a good responder or poor responder based on the exertional response (i.e., dyspnea and exercise time) during CPET.

CASE REPORT

In both patients, BT was performed in 3 treatment sessions on different segments of the lung. Each treatment was performed approximately 3 weeks apart. Before and after BT, both patients underwent symptom-limited exercise tests using CPET system (Marquette CASE series T 2001, GE Healthcare, Tokyo, Japan ; Aero monitor AE310S, Minato Medical Science Co., Ltd, Osaka, Japan) with multistep increments for the treadmill (Sheffield or the modified Sheffield protocol) (5, 6). Both patients used a similar treadmill protocol before and after BT. The ventilatory values (Fig. 1) were measured on a breath-by-breath basis and were presented as 30-second averages at rest, 1 minute and 3-minute intervals during exercise, and at the end of exercise. During CPET, dyspnea was measured with the modified Borg scale (7). The subjects rated their dyspnea at rest, every minute during exercise, and at peak exercise. Written informed consent in Japanese was obtained from the 2 patients, who were also included the main observational study of the National Hospital Organization Osaka Toneyama Medical Center (approval number, 1713). The main study was registered in the University Hospital Medical Information Network (UMIN000027662).

1. GOOD RESPONDER

Clinical course

A 57-year-old man visited our hospital due to poor control of asthma, which was diagnosed at 30 years old after being triggered by a cold (Table 1). Since then, he had been consulting a local physician and had been taking inhaled corticosteroids (ICS), long-acting β2 agonist (LABA), long-acting muscarinic antagonist (LAMA), and theophylline. He would take oral corticosteroids several times a year due to repeated asthma attacks. Based on his history, he was considered to have an intractable severe asthma. Chest computed tomography (CT) showed severe bronchial thickening. Therefore, BT was performed, and after 1 year, he remained free from asthma attacks or need for oral steroids and had improved activities of daily living.

Abbreviation List : ACT : asthma control test, BMI : body mass index ; BT : bronchial thermoplasty ; CPET : cardiopulmonary exercise testing ; CT : computed tomography ; FeNO : fractional nitric oxide concentration in exhaled breath ; FEV_1 : forced expiratory volume in 1 second ; FOT : forced oscillation technique ; f_R : breathing frequency ; FVC : forced vital capacity ; ICS : inhaled corticosteroid ; LABA : long-acting β2 agonist ; LAMA : long-acting muscarinic antagonist ; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide ; R5 : the resistance at 5 Hz ; R20 : the resistance at 20 Hz ; Te : expiratory time ; Ti : inspiratory time ; Ti/Ttot : inspiratory duty cycle ; V'_E : minute ventilation ; $V_T$ex : expiratory tidal volume ; $V_T$in : inspiratory tidal volume.

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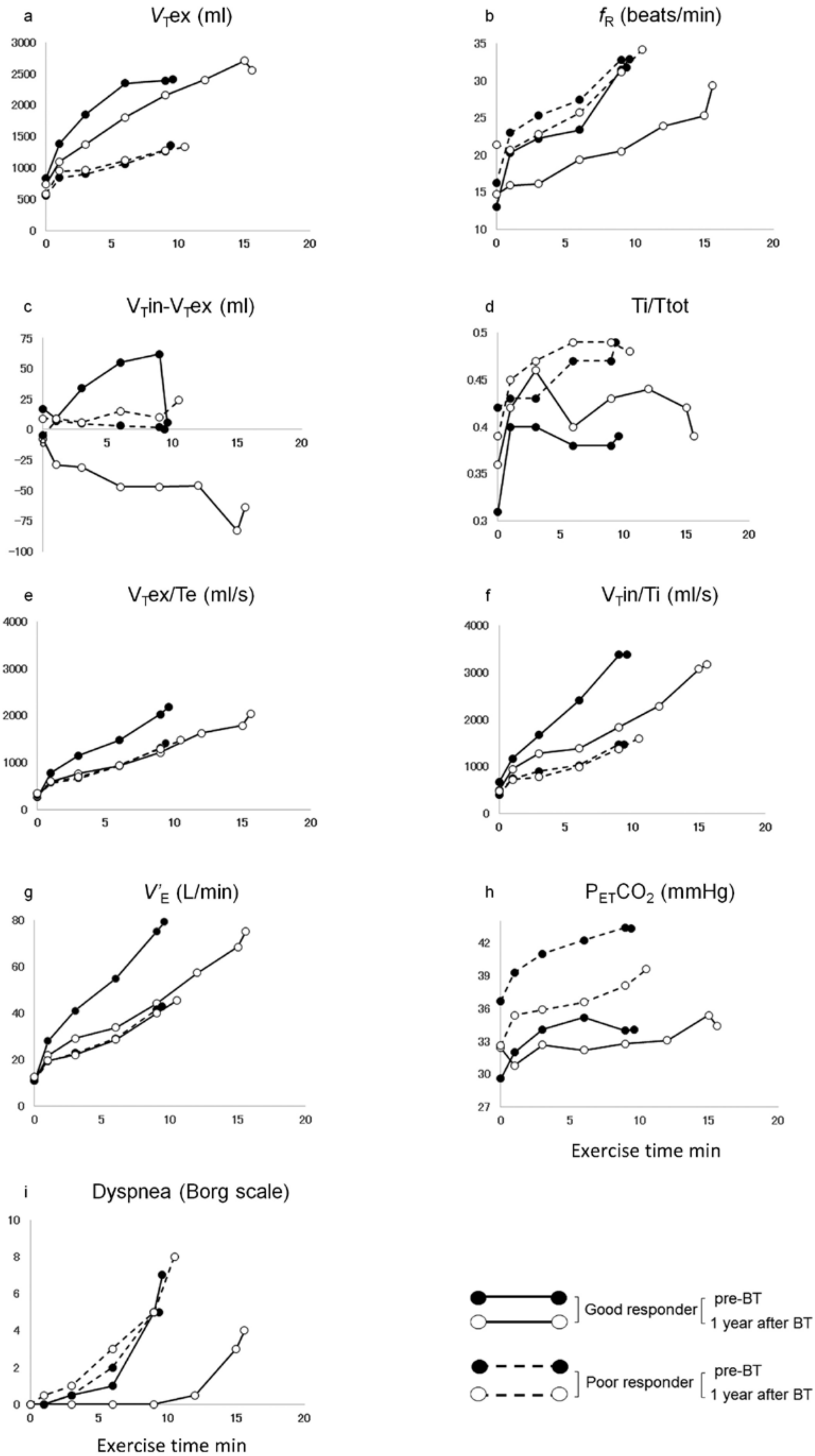

Figure 1. The therapeutic effects of BT, based on cardiopulmonary exercise testing.
BT : bronchial thermoplasty ; f_R : breathing frequency ; Te : expiratory time ; Ti : inspiratory time ; Ti/Ttot : inspiratory duty cycle ; V'_E : minute ventilation ; $V_T$ex : expiratory tidal volume ; $V_T$in : inspiratory tidal volume.

Table 1. Comparison of clinical features between a good responder and a poor responder

	Good responder	Poor responder
Age (years)	57	60
Sex	male	female
Body weight (kg) ; BMI (kg/m^2)	72 ; 25.5	79.2 ; 33.5
Disease duration (years)	28	22
Comorbidity	Eosinophilic sinusitis	Hypertension
Smoking history	Never smoker	Ex-smoker (20 pack-year)
Pre-evaluation		
Peripheral eosinophil (% ; /μL)	7.1 ; 460	0.2 ; 207
Total IgE (IU/mL)	256	108
Specific IgE (U_A/mL)	House dust, 0.97	Orchard grass, 0.97
	Mite, 1.18	
FeNO (ppb)	68	99
Treatment at pre-evaluation	ICS, LABA, LAMA	ICS, LABA, LAMA
	Theophylline	Macrolide antibiotics
	Macrolide antibiotics	Leukotriene antagonists
	Leukotriene antagonists	Oral corticosteroid 7 mg/day
Biological therapy	None	None
BT		
Activation count, total (first/second/third)	98 (12/26/60)	134 (34/37/63)
Response after BT		
Resting pulmonary function (pre-BT/1 year after BT)		
FEV_1 (L)	2.63/2.38	1.65/1.78
%FEV_1 (%)	76.2/70.8	80.5/86.4
FEV_1/FVC (%)	51.2/46.5	68.4/70.6
FOT (pre-BT/1 year after BT)		
R5 ex (cmH_2O/L/s)	3.83/2.42	7.18/8.81
R5 in (cmH_2O/L/s)	1.96/1.66	2.85/2.71
R20 ex (cmH_2O/L/s)	2.77/2.00	5.35/5.79
R20 in (cmH_2O/L/s)	1.80/1.68	3.62/2.85

BMI : body mass index ; BT : bronchial thermoplasty ; FeNO : fractional nitric oxide concentration in exhaled breath ; FEV_1 : forced expiratory volume in 1 second ; FOT : forced oscillation technique ; FVC : forced vital capacity ; ICS : inhaled corticosteroid ; LABA : long-acting β_2 agonist ; LAMA : long-acting muscarinic antagonist ; R5 : the resistance at 5 Hz ; R20 : the resistance at 20 Hz.

Exertional conditions before BT

In the good responder before BT, the variables related to the expiratory flow limitation during exercise confirmed that 1) the expiratory tidal volume (V_{Tex}) reached a plateau after 6 minutes of exercise (Fig. 1a) ; 2) immediately after the plateau, the respiratory frequency (f_R) increased (Fig. 1b) ; and 3) the difference between inspiratory tidal volume (V_{Tin}) and V_{Tex}, (V_{Tin}-V_{Tex}) remained high from rest through exercise (Fig. 1c). These findings implied the presence of air remaining in the lung after expiration obtained before BT. In addition, before BT, the ratio of inspiratory time to total respiratory cycle time (i.e., Ti/Ttot) decreased after 6 minutes of exercise, as demonstrated by the prolonged expiration (Fig. 1d). Given the short inspiratory time in the good responder, the V_{Tin}/inspiratory time (Ti) exceeded the V_{Tex}/e expiratory time (Te) during exercise, both of which placed burden on inspiratory breathing (Figs. 1e and 1f). The partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was lower in the good responder than in the poor responder. This implied that before BT, the good responder had insufficient expired carbon dioxide during exercise, although the minute ventilation (V'_E) was relatively high at peak exercise (Figs. 1g and 1h). As a result of this wasted ventilation before BT, the good responder was out of breath after 6 minutes of exercise (Fig. 1i).

2. POOR RESPONDER

Clinical course

A 60-year-old woman visited our hospital due to poor control of asthma, which was diagnosed at 38 years old after being triggered by hay fever (Table 1). She had been on triple treatment with ICS, LABA, LAMA, and macrolide antibiotic. However, she would have repeated asthma attacks triggered by hay fever and periodically took oral corticosteroid, which she needed at a dose of at least 7 mg/day but could not be increased further due to the drug reaction of leg cramps. CT showed bronchial thickening, which was less severe than that in the good responder. BT was performed, but, after 1 year, it did not lead to symptomatic improvement or dose reductions in her drug regimens.

Exertional conditions before BT

Before BT in the poor responder, the V_{Tex} increased linearly without a plateau during exercise (Fig. 1a) ; this was likely related with the low air remaining in the lung after expiration. The V_{Tin}-V_{Tex} was low, and almost remained flat during exercise (Fig. 1c).

DISCUSSION

In asthmatics, achievement of efficient ventilation, especially during expiration, would lessen the exertional dyspnea. In the good responder whose exercise time during CPET prolonged reducing exertional dyspnea after BT, the high exertional air remaining in the lung after expiration during CPET before BT decreased after BT. In contrast, in the poor responder whose exercise time and exertional dyspnea during CPET did not improve after BT, the high exertional air remaining after expiration was not confirmed before BT.

The effective ventilation is necessary to reduce dyspnea, especially during exercise, in respiratory diseases including asthma (8, 9). Langton *et al*. reported that the improvement in gas trapping obtained by BT in severe obstructed patients was greater with a baseline forced expiratory volume in 1 second (FEV_1) of < 60% predicted than with a baseline FEV_1 of ≥ 60% predicted (10). However, in the present study, the baseline FEV_1 levels in both the good and poor responders were maintained at more than 70%. Nevertheless, in the good responder, CPET was able to quantify the air remaining in the lung after expiration during exercise (i.e., wasted ventilation), regardless of the good pulmonary function at rest. Physiological conditions during exercise rather the resting pulmonary function might be informative to evaluate the effects of BT.

The changes in the exertional conditions at 1 year after BT were compared between the good responder and the poor responder as shown in Fig 1. Compared with the therapeutic responses in the poor responder, the V_{Tin}-V_{Tex} in the good responder remained low from rest through exercise (Fig. 1c) after BT, that is, the air remaining after expiration dramatically decreased. After BT, in the good responder, the plateau of V_{Tex} disappeared and the V_{Tex} increased linearly during exercise (Fig. 1a). Of note, after BT in the good responder, although the V_{Tin}/Ti, V_{Tex}/Te, and V'_E decreased (Figs. 1e-1g), the level of $P_{ET}CO_2$ was relatively higher at peak exercise than before BT, that is, the exertional wasted ventilation was decreased after BT (Fig. 1h). Taken together, V'_E was optimal throughout exercise and became almost half at isotime, when exercise was stopped before BT (Fig. 1g). In contrast, after BT in the poor responder, the level of $P_{ET}CO_2$ decreased during exercise (Fig. 1h). Thus, the effective ventilation obtained after BT reduced the ventilatory demand. Ishii *et al*. (11) demonstrated a decrease in expiratory capacity followed by improvement in static lung hyperinflation using expiratory chest CT imaging in asthmatics after BT ; this shared the mechanism shown in the present case report. Furthermore, Konietzke *et al*. (12) reported a decrease in air trapping after BT determining the quotient of mean lung attenuation in expiration vs. inspiration by quantitative chest CT, and explained the response with the effective ventilation obtained from a decrease in airway obstruction. These findings suggested that BT can improve wasted ventilation, especially in asthmatic patients who have high air remaining in the lung after expiration before BT, thereby, improving exertional dyspnea and extending exercise time from 9 minutes to 16 minutes (Fig. 1i).

LIMITATIONS

First, the difference between V_{Tin} and V_{Tex} might be variable. However, the V_{Tin} and V_{Tex} were measured with an unaffected breath during CPET, and then the obtained values might have reflected the natural breathing pattern during exercise. Second, assessment of dynamic inspiratory capacity by the forced inspiration technique during CPET or measurement of the residual volume may give more helpful information.

CONCLUSION

This case series implied that BT could decrease the exertional air remaining in the lung after expiration and produced the benefits during exercise, especially in asthmatic patient who had high expiratory flow limitation before BT. Further investigations are necessary to confirm whether the exertional wasted ventilation on CPET might be an informative parameter to reflect or predict the therapeutic effects of BT.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

FINANCIAL DISCLOSURE STATEMENT

The authors do not have financial relationships to disclose.

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