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 exhaled 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, FEV1: forced expiratory volume in 1 second, FOT: forced oscillation technique, fR: breathing frequency, FVC: forced vital capacity, ICS: inhaled corticosteroid, LABA: long-acting β2 agonist, LAMA: long-acting muscarinic antagonist, Pco2: 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, V5': minute ventilation, Vex: expiratory tidal volume, Vin: 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; $T_e$: expiratory time; $T_i$: inspiratory time; $T_i/T_{tot}$: inspiratory duty cycle; $V_e$: minute ventilation; $V_{ex}$: expiratory tidal volume; $V_{in}$: inspiratory tidal volume.
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 ($V_{ex}$) 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 $V_{ex}$, ($V_{tin}-V_{ex}$) remained high from rest through exercise (Fig. 1c). These findings implied the presence of air remaining in the lung obtained before BT. In addition, before BT, the ratio of inspiratory time to total respiratory cycle time (i.e., $Ti/T_{tot}$) 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 $V_{ex}/$ 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 ($P_{e}CO_2$) 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 Vr-vex increased linearly without a plateau during exercise (Fig. 1a); this was likely related with the low air remaining in the lung after expiration. The VrIn-Vrex 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 (FEV₁) of < 60% predicted than with a baseline FEV₁ of ≥ 60% predicted (10). However, in the present study, the baseline FEV₁ 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 Vrin-Vrex 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 Vrex appeared and the Vrex increased linearly during exercise (Fig. 1a). Of note, after BT in the good responder, although the VrIn/Ti, Vrex/Te, and V′c decreased (Figs. 1e-1g), the level of PrcCO₂ was relatively higher at peak exercise than before BT, that is, the exertional wasted ventilation was decreased after BT (Fig. 1h). Taken together, V′c 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 PrcCO₂ 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 BT in and Vrex might be variable. However, the VrIn and Vrex 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.

**REFERENCES**

1. Castro M, Cox G: Asthma outcomes from bronchial thermoplasty in the AIR2 trial. Am J Respir Crit Care Med 184: 743-744, 2011
2. Chupp G, Laviolette M, Cohn L, McEvoy C, Bansal S, Shifren A, Khatri S, Grubb GM, McMullen E, Strauven R, Kline JN: Long-term outcomes of bronchial thermoplasty in subjects with severe asthma: a comparison of 3-year follow-up results from two prospective multicentre studies. Eur Respir J 50: pii: 1700017, 2017
3. Laveneziana P, Lotti P, Coli C, Binazzi B, Chiti L, Stendardi L, Duranti R, Scano G: Mechanisms of dyspnoea and its language in patients with asthma. Eur Respir J 27: 742-747, 2006
4. Wechsler ME, Laviolette M, Rubin AS, Fiterman J, Lapa e Silva JR, Shah PL, Fius E, Olivenstein B, Thomson NC, Niven RM, Pavord ID, Simoff M, Hales JB, McEvoy C, Sibos D, Holmes M, Phillips M, Erzurum SC, Hanania NA, Sumino K, Kraft M, Cox G, Sterman DH, Hogarth K, Kline JN, Mansur AH, Louie BE, Leeds WM, Barbers RG, Austin JH, Shargill NS, Quiring J, Armstrong B, Castelo M: Bronchial thermoplasty: Long-term safety and effectiveness in patients with severe persistent asthma. J Allergy Clin
5. Miki K, Maekura R, Hiraga T, Hashimoto H, Kitada S, Miki M, Yoshimura K, Tateishi Y, Fushitani K, Motone M: Acidosis and raised norepinephrine levels are associated with exercise dyspnoea in idiopathic pulmonary fibrosis. Respirology 14: 1020-1026, 2009

6. Puente-Maestu L, Palange P, Casaburi R, Laveneziana P, Maltais F, Neder JA, O'Donnell DE, Onorati P, Porszasz J, Rabinovich R, Rossiter HB: Use of exercise testing in the evaluation of interventional efficacy: an official ERS statement. 47: 429-460, 2016

7. Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14: 377-381, 1982

8. Busacker A, Newell JD, Jr., Keefe T, Hoffman EA, Granroth JC, Castro M, Fain S, Wenzel S: A multivariate analysis of risk factors for the air-trapping asthmatic phenotype as measured by quantitative CT analysis. Chest 135: 48-56, 2009

9. Schroeder JD, McKenzie AS, Zach JA, Wilson CG, Curran-Everett D, Stinson DS, Newell JD, Jr., Lynch DA: Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. AJR Am J Roentgenol 201: W460-470, 2013

10. Hall CS, Castro M: Predicting response to bronchial thermoplasty in patients with severe uncontrolled asthma: An elusive goal 24: 11-12, 2019

11. Ishii S, Iikura M, Shimoda Y, Izumi S, Hojo M, Sugiyama H: Evaluation of expiratory capacity with severe asthma following bronchial thermoplasty. Respirol Case Rep 7: e00387, 2019

12. Konietzke P, Weinheimer O, Wielputz MO, Wagner WL, Kaukel P, Eberhardt R, Heussel CP, Kauczor HU, Herth FJ, Schuhmann M: Quantitative CT detects changes in airway dimensions and air-trapping after bronchial thermoplasty for severe asthma. Eur J Radiol 107: 33-38, 2018