ORIGINAL RESEARCH

Can the Number of Radiofrequency Activations Predict Serious Adverse Events after Bronchial Thermoplasty? A Retrospective Case-Control Study

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ABSTRACT

Introduction: Bronchial thermoplasty (BT) is a bronchoscopic procedure that involves the delivery of thermal radiofrequency energy to the bronchial wall for treating severe asthma. It has been suggested that too many radiofrequency activations could induce serious adverse events (SAEs) at an early stage. We aimed to examine the number of radiofrequency activations at each session and early lung function changes from baseline to determine whether these are related to SAEs.

Methods: We retrospectively investigated 13 consecutive patients who underwent three sessions each of BT for severe asthma from February 2015 to January 2016. Lung function tests were performed on the day before and after each BT procedure. Since we compared the number of activations and lung function changes from baseline after each session, a total of 39 sessions were reviewed. The relationship between the number of radiofrequency activations and each lung function change from baseline was also examined by linear regression analysis.

Results: A total of 10 SAEs (4 of pneumonia, 3 of atelectasis, 2 of bronchial asthma exacerbation and 1 of hemoptysis) were observed following the 39 BT sessions. When we compared sessions with and without SAEs, there were no differences in the number of activations (mean ± SD, 71.5 ± 28.6 times in sessions with SAEs; 66.5 ± 25.1 times in sessions without SAEs; $p = 0.772$) and lung function changes (mean changes in FVC/%FVC/FEV$_1$/%FEV$_1$/ %PEF from baseline; − 0.49 l/− 14.2%/− 0.36 l/− 11.7%/− 9.6% in sessions with SAEs; − 0.43 l/− 13.3%/− 0.34 l/− 12.1%/− 9.4% in sessions

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without SAEs; $p > 0.05$ for all the above). Increase in the number of activations correlated with decreased FEV_1 ($R^2 = 0.17$, $p = 0.0088$) and %FEV_1 ($R^2 = 0.11$, $p = 0.0357$).

Conclusions: Increase in the number of radiofrequency activations during BT is related to a decrease in FEV_1 and %FEV_1 from baseline. The number of radiofrequency activations, however, is not associated with SAEs after BT.

Keywords: Bronchial asthma; Bronchial thermoplasty; Lung function tests; Serious adverse events

PLAIN LANGUAGE SUMMARY

Bronchial thermoplasty (BT) is a bronchoscopic procedure that involves the delivery of thermal radiofrequency energy to the bronchial wall for treating severe asthma. BT is performed as three sessions at 3-week intervals. A previous in vitro study and a case report demonstrated that too much thermal energy caused irreversible epithelial cell necrosis. It might induce early serious adverse events (SAEs). This study evaluated the number of radiofrequency activations during successive BT sessions and early lung function changes from baseline to determine whether these are related to SAEs. We retrospectively investigated 13 consecutive patients (mean age, 55.2 years; 7 males) who underwent the BT procedure for severe asthma from February 2015 to January 2016 at the National Center for Global Health and Medicine (Tokyo, Japan). Lung function tests were performed on the day before and after each BT procedure. A total of 10 SAEs (4 of pneumonia, 3 of atelectasis, 2 of bronchial asthma exacerbation and 1 of hemoptysis) were observed following 39 BT sessions. Comparison of sessions with and without SAE indicated no difference in the number of activations (mean $\pm$ SD, 71.5 $\pm$ 28.6 times during sessions with SAEs; 66.5 $\pm$ 25.1 times during sessions without SAEs; $p = 0.31$) and lung function changes from baseline. Increase in the number of radiofrequency activations correlated with reduction in FEV_1 and %FEV_1.

Key Summary Points

Why carry out this study?

Bronchial thermoplasty (BT) is a novel bronchoscopic procedure that involves the delivery of thermal radiofrequency energy to the bronchial wall for treating severe asthma

It is hypothesized that too many radiofrequency activations could induce early serious adverse events (SAEs)

What was learned from the study?

When we compared BT sessions with and without SAEs, there was no difference in the number of radiofrequency activations (mean $\pm$ SD, 71.5 $\pm$ 28.6 times in sessions with SAEs; 66.5 $\pm$ 25.1 times in sessions without SAEs; $p = 0.77$)

Increase in the number of activations correlated with a decrease in FEV_1 ($R^2 = 0.17$, $p = 0.0088$) and %FEV_1 ($R^2 = 0.11$, $p = 0.0357$)

This study revealed that the number of radiofrequency activations is not associated with SAEs; further studies elucidating the predictive factors for SAEs are required to enhance patient safety

INTRODUCTION

Asthma remains an important health problem with significant morbidity, mortality and economic burden. Airway smooth muscle contraction and the resultant bronchoconstriction induce the many variable symptoms of asthma. Increased airway smooth muscle mass is a characteristic feature of asthma, especially among patients with severe asthma. Bronchial thermoplasty (BT) is a novel intervention that involves the delivery of thermal radiofrequency energy to the bronchial wall during a series of bronchoscopies, resulting in prolonged

reduction of airway smooth muscle mass. In previous clinical studies, treatment of patients with airways between 3 and 10 mm in diameter led to clinically meaningful reduction in muscle-mediated narrowing of the airway and to improvement of asthma symptoms [1–3].

The most common complications of BT are transient adverse respiratory events that occur a median of 1 day after the procedure and rarely require hospitalization [4]. Recently, however, serious adverse events (SAEs) involving the airways, which required prolonged hospitalization or threatened the patient's life, have been reported after the BT procedure [5–8]. Hence, it is necessary to determine early predictors of SAEs after BT to enhance patient safety.

Even a single radiofrequency activation can affect the bronchial mucosa and cause epithelial sloughing [9]. A previous in vitro study and a case report demonstrated that too much thermal energy caused irreversible epithelial cell necrosis [10, 11]. Several studies suggested that intense thermal stimulation of the bronchial mucosa could represent a strong boost for inflammation, with microvascular alteration being directly induced by the heat or through the release of chemical mediators causing mucosal exudation and edema [5, 12]. Since the number of activations is directly related to the amount of thermal energy, we hypothesized that the number of activations was related to SAEs in the early post-procedure stage. Generally, lung function tests are used to evaluate airway obstruction in persons with asthma. Hence, we hypothesized that early changes in lung function following BT might be useful to predict SAEs.

In this study, we aimed to examine the number of radiofrequency activations during each BT session and early lung function changes from baseline to determine whether these are related to SAEs following BT.

METHODS

Patients

We retrospectively investigated adult asthma patients aged 18 years or older who underwent three sequential BT procedures at the National Center for Global Health and Medicine, Tokyo, Japan, from February 2015 to January 2016. All of them performed lung function tests on the day before and after each BT procedure. As previously described [3], BT is indicated in patients aged > 18 years and with severe uncontrolled asthma despite high-dose inhalational corticosteroid therapy. The contraindications to BT include [3]: (1) presence of a pacemaker, internal defibrillator or other implantable electronic devices; (2) known sensitivity to the medications used during bronchoscopy; (3) previous treatment with BT at the same area; (4) active respiratory infection; (5) pulmonary emphysema or any cystic disease; (6) asthma exacerbation or change in the dose of systemic corticosteroids for asthma in the past 14 days; (7) known coagulopathy; (8) therapy with anticoagulants, antiplatelet agents and non-steroidal anti-inflammatory drugs before the procedure.

Study Design

We conducted a retrospective case-control study. Patient factors (age, sex, height, body weight, smoking status, nasal comorbidities, laboratory data, Global Initiative for Asthma treatment step, quality of life, medications and lung function tests) and BT procedure factors (number of radiofrequency activations, procedure time and time/activation ratio) were investigated from the patients' charts. SAEs were defined as undesirable adverse experiences occurring within 30 days after the BT procedure, as previously described [13]. They included death, life-threatening conditions, prolonged hospitalization, disability and conditions requiring intervention (e.g., antibiotics, systemic steroid, oxygen therapy and artificial ventilator). The primary aim of this study was to examine the number of radiofrequency activations during each session and early lung function changes from baseline following BT and to determine whether these are related to SAEs. The secondary aim was to evaluate the relationship between the number of activations and each lung function change from baseline. Each

treatment session was divided into two groups: the SAE group, which represented sessions with SAEs, and non-SAE group, which represented sessions without SAEs. This study followed the principles of the Declaration of Helsinki and was approved by the institutional review board of the National Center for Global Health and Medicine, Tokyo, Japan (approval no. NCGM-G-001801-00) on June 15, 2015. We verified that written informed consent was obtained before each patient's participation in this study.

Bronchial Thermoplasty

Using the ALAIR® device (Boston Scientific Japan, Tokyo, Japan), BT was performed in three sessions at 3-week intervals. The lower lobe bronchi were treated in turn during the first two sessions, beginning with the right bronchus in the first session and the left bronchus in the second session, and both upper lobe bronchi in the third BT procedure. The right middle lobe bronchus was not treated in order to avoid the theoretical risk of obstruction and right middle lobe syndrome. The system was adjusted to deliver a constant temperature of 65°C for 10 s at each treatment site from the small 3-mm bronchi to the lobar bronchi. The procedure was performed under intravenous sedation with midazolam. The patients underwent close clinical monitoring immediately after the BT procedure. If there were no SAEs, they were discharged a few days after the BT procedure. Prednisone (50 mg/day) was systematically administered orally from 3 days before the BT procedure to 1 day after each procedure.

Lung Function Tests

BT was performed as three sessions at 3-week intervals. We examined lung function tests by spirometry (Superior Spiro Discom-21 FXIII; Chest, Tokyo, Japan) on the day before (as baseline) and the day after each BT procedure. Differences between lung function on the day before and after BT were calculated as the change from baseline. A single experienced clinical technologist performed all the lung function tests with the patients in the seated position, the tests being performed at least twice to verify the stability of lung function values. For quantitative evaluation of airway status, the parameters of forced vital capacity (FVC), percent forced vital capacity (%FVC), forced expiratory volume in 1 s (FEV$_1$), percent forced expiratory volume in 1 s (%FEV$_1$) and percent peak expiratory flow (%PEF) were used. We used each prediction formula to predict the FVC value by Baldwin, FEV$_1$ value by Berglund and PEF value by Cherniack.

Statistical Analysis

Qualitative variables are shown as numbers and percentages. Quantitative variables are reported as mean values and SDs, unless otherwise indicated. We used Mann-Whitney U test to compare the treated lobes, mean number of activations, procedure time, time/activation ratio and lung function changes from baseline (FVC, %FVC, FEV$_1$, %FEV$_1$, %PEF) between sessions with and without SAEs. The transition of lung function among all bronchial thermoplasty sessions was compared using the paired t-test. The potential associations between the number of activations and lung function changes from baseline were assessed using Pearson's correlation coefficient (R^2). All tests were two-tailed. P values < 0.05 were considered significant. Data were analyzed statistically with JMP® 14.0.0 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study Population

Patient demographics and baseline characteristics are shown in Table 1. A total of 13 patients were investigated in this study. The patients were on several medications, including high-dose inhaled corticosteroids (mean beclomethasone-equivalent dose of 1700 μg/day), systemic steroids (39% of patients) and molecular targeted drugs (46% of patients). All patients used high-dose inhaled corticosteroids and long-acting beta-agonists.

Table 1 Patient demographics and baseline characteristics

Age (years)	55.2 ± 13.7
Sex, n (%)	
Male	7 (54%)
Female	6 (46%)
Height (cm)	160.9 ± 10.0
Body weight (kg)	58.0 ± 13.9
BMI	22.1 ± 3.6
Smoking status, n (%)	
Never-smoker	9 (69%)
Ex-smoker	4 (31%)
Nasal comorbidities, n (%)	9 (69%)
Peripheral eosinophils (/µl)	205.5 ± 229.9
IgE (IU/ml)	383.5 ± 586.9
FeNO (ppb)	48.4 ± 65.4
Disease duration (years)	30.0 ± 14.4
GINA treatment step, n (%)	
4	4 (31%)
5	9 (69%)
Exacerbations in previous year	6.3 ± 5.1
Baseline ACT score	19.0 ± 4.2
Baseline AQLQ score	4.8 ± 1.1
Systemic steroid use, n (%)	5 (38%)
Molecular target drug use, n (%)	6 (46%)
ICS dose (µg/day)	1700 ± 380
LABA use, n (%)	13 (100%)
LAMA use, n (%)	10 (77%)
LTRA use, n (%)	12 (92%)
Theophylline use, n (%)	10 (77%)

Unless otherwise indicated, values are presented as mean ± SD

BMI body mass index, *ICS* inhaled corticosteroids; ICS dose was calculated as the beclomethasone-equivalent dose, *IgE* immunoglobulin E, *FeNO* fractional exhaled nitric oxide, *GINA* Global Initiative for Asthma, *ACT* Asthma Control Test, *AQLQ* Asthma Quality of Life Questionnaire, *LAMA* long-acting muscarinic receptor antagonist, *LABA* long-acting beta agonist, *LTRA* leukotriene receptor antagonist

As previously described, systemic steroids were given in the perioperative period (from 3 days before to the day after procedure; total 5 days)[14]. This is consistent with the standard preparation before the BT procedure. Judging according to the Global Initiative for Asthma (GINA) treatment steps [15], all patients in this study were categorized as severe asthma patients (31% of patients: GINA step 4; 69%: GINA step 5). Quality of life associated with asthma remained relatively stable (mean baseline Asthma Control Test/Asthma Quality of Life Questionnaire scores, 19.0/4.8, respectively). This was considered the result of high-intensity pharmacologic treatment. We performed chest CT scans in all patients before the procedure, which did not demonstrate the notable changes in the patient's lungs (e.g., no emphysema, no cystic disease, no interstitial opacity, no bronchiectasis and no thickness of bronchi).

Early Lung Function Changes after BT

Table 2 demonstrates early lung function changes after the BT procedure. Evaluation of all BT procedures showed that all lung function parameters decreased after BT (mean change in FVC/%FVC/FEV$_1$/%FEV$_1$/%PEF from baseline, − 0.44 l/− 13.3%/− 0.35 l/− 12.2%/− 9.5%, respectively). Figure 1 shows the transition of lung function. Comparison of the first, second and third sessions indicated the most significant lung function change was at the third session. Although lung function decreased with each BT procedure, the change was temporary. Furthermore, lung function on the day before BT progressively improved with each BT procedure.

Comparison of SAE and Non-SAE Groups

A total of 10 SAEs (4 of pneumonia, 3 of atelectasis, 2 of bronchial asthma exacerbation and 1 of hemoptysis) were observed over the 39 BT sessions. Comparison of the SAE and non-SAE groups (Table 3) showed that hospital stay in the SAE group tended to be longer than that in the non-SAE group (p = 0.064). Two SAEs

Table 2 Early lung function changes evaluated on the day after bronchial thermoplasty

	Day before BT (baseline)	Day after BT	Change from baseline
First procedure at right lower lobe (13 sessions)			
FVC (l)	3.23 ± 1.13	2.83 ± 1.13	− 0.39 ± 0.39
%FVC (%)	95.0 ± 12.5	82.5 ± 15.7	− 12.5 ± 11.4
FEV_1 (l)	2.14 ± 1.03	1.85 ± 0.87	− 0.29 ± 0.26
$\%FEV_1$ (%)	74.5 ± 22.7	64.6 ± 20.5	− 10.0 ± 7.6
%PEF (%)	76.6 ± 20.9	67.7 ± 20.1	− 9.0 ± 8.0
Second procedure at left lower lobe (13 sessions)			
FVC (l)	3.29 ± 1.11	2.94 ± 1.01	− 0.36 ± 0.27
%FVC (%)	97.5 ± 12.0	86.6 ± 11.5	− 10.8 ± 7.7
FEV_1 (l)	2.21 ± 0.90	1.97 ± 0.77	− 0.25 ± 0.33
$\%FEV_1$ (%)	78.2 ± 19.5	69.2 ± 17.0	− 9.0 ± 9.9
%PEF (%)	78.1 ± 19.8	72.2 ± 19.5	− 6.0 ± 11.1
Third procedure at bilateral upper lobes (13 sessions)			
FVC (l)	3.41 ± 1.29	2.82 ± 1.05	− 0.59 ± 0.40
%FVC (%)	100.1 ± 11.8	86.6 ± 11.5	− 17.0 ± 9.1
FEV_1 (l)	2.45 ± 1.00	1.92 ± 0.83	− 0.53 ± 0.32
$\%FEV_1$ (%)	85.2 ± 17.1	67.1 ± 17.0	− 18.1 ± 7.6
%PEF (%)	82.2 ± 18.0	68.4 ± 17.8	− 13.9 ± 7.7
All procedures (39 sessions)			
FVC (l)	3.31 ± 1.16	2.86 ± 1.07	− 0.44 ± 0.37
%FVC (%)	97.4 ± 12.3	84.1 ± 13.7	− 13.3 ± 9.9
FEV_1 (l)	2.26 ± 0.98	1.91 ± 0.83	− 0.35 ± 0.33
$\%FEV_1$ (%)	79.2 ± 20.4	66.9 ± 18.4	− 12.2 ± 9.4
%PEF (%)	78.9 ± 20.0	69.4 ± 19.3	− 9.5 ± 9.6

Values are presented as mean ± SD unless otherwise indicated

BT bronchial thermoplasty, *FVC* forced vital capacity, *%FVC* percent forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *$\%FEV_1$* percent forced expiratory volume in 1 s, *%PEF* percent peak expiratory flow

occurred within 3 weeks of the first BT session, and four each occurred within 3 weeks of the second and third BT sessions. Asthma exacerbation was only seen within 3 weeks of the third BT session. In two cases, exacerbations of asthma were treated with additional bronchodilators and systemic steroids, and these patients needed longer hospitalization than those with the other adverse events. Three patients had complete atelectasis although the lung segment re-inflated without treatment, while four cases who developed pneumonia needed standard antibiotic therapy. One of the cases had a serious course with hemoptysis.
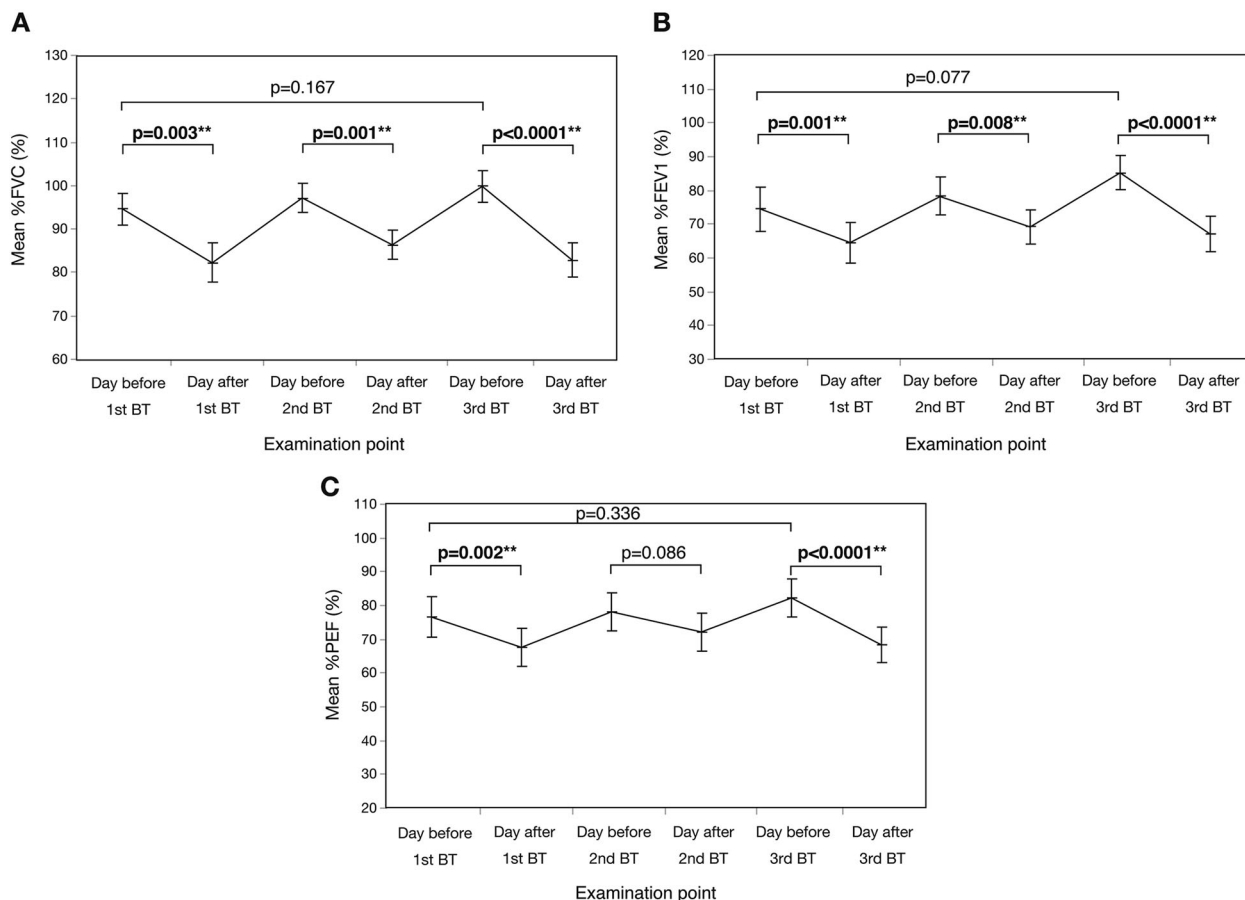
Fig. 1 Transition of lung function among all bronchial thermoplasty sessions. Mean value of lung function test at six examination points (day before and after 1st, 2nd and 3rd BT procedure) is demonstrated. **a** Mean percent forced vital capacity. **b** Mean percent forced expiratory volume in 1 s. **c** Mean percent peak expiratory flow. In all the lung function tests, most values significantly decreased after the bronchial thermoplasty (BT) procedure ($p < 0.05$ in all cases except **c**). There were no significant differences between values on the day before the first BT procedure and the day before the third BT procedure ($p > 0.05$ in all cases). The mean value of each session was compared using the paired t-test

During hospitalization, the subject had a small amount of bloody phlegm that was treated with a hemostatic agent, and the patient was subsequently discharged 8 days after the BT procedure. A few weeks after discharge, the subject was referred to the emergency department because of hemoptysis, and unconsciousness and was diagnosed with cerebral infarction, although the causal relationship with BT was unknown. There were no significant differences in the number of radiofrequency activations, procedure time or time-activation ratios between the two groups (mean number of activations/procedure time/time-activation ratio, 71.5 times/78.4 min/1.27 vs. 66.5 times/78.4 min/1.29, respectively, in the SAE and non-SAE groups, $p > 0.05$ for all values). There was also no significant difference in lung function change from baseline between the two groups (mean change in FVC/%FVC/FEV$_1$/%FEV$_1$/%PEF from baseline, $- 0.49$ l/$- 14.2\%$/$- 0.36$ l/$- 11.7\%$/$- 9.6\%$ vs. $- 0.43$ l/$- 13.3\%$/$- 0.34$ l/$- 12.1\%$/$- 9.4\%$, respectively, in the SAE and non-SAE groups, $p > 0.05$ for all values). Linear regression analysis of the changes in lung function from baseline, performed to evaluate the relationship between the number of activations and lung function

Table 3 Comparison between sessions with and without serious adverse events and details of the serious adverse events after bronchial thermoplasty

	SAE group N = 10	Non-SAE group N = 29	p value
Hospital stay (days)	10.1 ± 6.6	6.1 ± 1.7	0.064
Serious adverse event			
Pneumonia, n	4 (1 at the right lower lobe; 2 at the left lower lobe; 1 at the right upper lobe)	–	–
Atelectasis, n	3 (1 at the right lower lobe; 2 at the left lower lobe)	–	–
Asthma exacerbation, n	2 (2 at the bilateral upper lobe)	–	–
Hemoptysis, n	1 (unknown origin)	–	–
Treated lobe			
Right lower lobe, n (%)	2 (20)	11 (38)	0.315
Left lower lobe, n (%)	4 (40)	9 (31)	0.623
Bilateral upper lobes, n (%)	4 (40)	9 (31)	0.623
BT procedure			
Number of radiofrequency activations (times)	71.5 ± 28.6	66.5 ± 25.1	0.772
Procedure time (min)	78.4 ± 20.7	78.4 ± 22.1	0.936
Time/activation ratio	1.27 ± 0.70	1.29 ± 0.46	0.489
Lung function changes from baseline			
FVC (l)	− 0.49 ± 0.35	− 0.43 ± 0.38	0.479
%FVC (%)	− 14.2 ± 8.6	− 13.3 ± 10.5	0.618
FEV_1 (l)	− 0.36 ± 0.36	− 0.34 ± 0.33	0.847
$\%FEV_1$ (%)	− 11.7 ± 9.8	− 12.1 ± 9.5	0.785
%PEF (%)	− 9.6 ± 10.7	− 9.4 ± 9.5	0.898

Values are presented as mean ± SD unless otherwise indicated

All the results were analyzed using Mann-Whitney U test

BT bronchial thermoplasty, *SAE* serious adverse event, *FVC* forced vital capacity, *%FVC* percent forced vital capacity, *FEV_1* forced expiratory volume in 1 s, *$\%FEV_1$* percent forced expiratory volume in 1 s, *%PEF* percent peak expiratory flow

*p < 0.05

(Fig. 2), showed that FEV_1 and %FEV1 had a negative correlation with the number of activations. On the other hand, FVC, %FVC and %PEF did not have any correlation.

DISCUSSION

To the best of our knowledge, this is the first report assessing the relationship between the

number of radiofrequency activations and early SAEs after BT. We performed lung function tests to quantitatively evaluate morphologic airway changes to enable objective evaluation of the changes. Generally speaking, bronchial asthma exacerbation is involved with worsening lung function (FEV1 and PEF) [16], so lung function tests are suitable for assessment of asthmatic patients. Although Langton et al. focused on the number of activations as a predictor of treatment response [17], we hypothesized that this parameter could be a predictor of SAEs in the early stages after BT. Actually, in the present study, the number of activations was significantly related to the reduction in FEV_1 and %FEV_1 after the BT procedure (change in FEV_1, $R^2 = 0.171$, $p = 0.009$; change in %FEV_1, $R^2 = 0.114$, $p = 0.036$). The amount of FEV_1 reduction on the day after BT and the correlation between the number of activations and FEV_1 followed the same trend as in Langton's report [18]. In addition, both Langton's and our reports demonstrated that upper lobe treatment causes a greater decrease in FEV_1 than lower lobe treatment. Increase in the number of activations might affect edematous changes in the bronchial mucosa and around the bronchus [4, 9, 19]. According to previous in vitro research, administration of thermal energy at a temperature of 37–70 °C to cultured airway epithelial cells and airway smooth muscle cells can cause irreversible epithelial cell necrosis [10]. In this research, we concluded that not only the number of activations, but also lung function changes over a short period were not enough to predict SAE occurrence.

Our research group has previously reported on airway morphologic and functional changes after BT therapy. We studied asthma-related quality of life, lung function tests and the number of asthma exacerbations both 1 and 12 months after the third BT session in 12 Japanese patients. We found that %FEV_1 significantly improved a month after the third BT session (mean %FEV_1 before first BT session: 70.5%, mean FEV_1 a month after third BT session: 82.2%; $p < 0.05$) [20]. The report also confirmed that patients maintain the lung function improvement for a year (mean %FEV_1 within a year of the third BT session: 82.3%).

The reason why the BT procedure was capable of maintaining a sustained effect over a year in our study is that the total number of activations throughout BT in our institute was more than 1.3 times higher than in the AIR2 trial. Due to the larger number of activations, more peripheral airways could be treated. It was also previously reported that the number of activations could play a role in determining clinical response to treatment [17]. In the present study, %FEV_1 followed the same trend as in our previous report. Moreover, %FEV_1 tended to improve the day before the second BT procedure (mean %FEV_1 a day before first BT session: 74.5%, mean %FEV_1 a day before second BT session: 78.2%). After the first BT procedure, %FEV_1 decreased temporarily, although %FEV_1 on the day before the third BT procedure was better than that on the day before the first BT procedure (mean %FEV_1 on the day before third BT: 85.2%) (Fig. 1). Our findings were supported by the recent study by Ishii et al. conducted in a 68-year-old Japanese woman with severe asthma who underwent BT, which confirmed dilation of the bronchial lumen and decreased bronchial wall thickness by comparing the changes in the bronchial lumen and walls before BT and after the first and third sessions by three-dimensional (3D) airway analysis [21]. Previous studies demonstrated the occurrence of morphologic changes in airways right after the BT procedure. However, there is no proof that the changes are related to functional improvement. Our reports suggest that the BT procedure leads to an initial decrease in lung function, although repeated sessions lead to gradual dilatation of the bronchial lumen and a decrease in bronchial wall thickness.

Previous major clinical trials have proved the safety and efficacy of BT procedures [1–3]. Compared with the incidence of SAEs in previous clinical trials, including the AIR trial, AIR2 trial and RISA study (7.3%, 8.4% and 26.7%, respectively), adverse events occurred relatively frequently among elderly and adult patients with severe asthma in this study (25.6%). Apart from the number of activations, the differences between the above trials and the present study are asthma severity, age and study design. In terms of asthma severity, the AIR and AIR2 trials

A

R² 0.086
p=0.070

B

R² 0.037
p=0.244

C

R² 0.171
p=0.009*

D

R² 0.114
p=0.036*

E

R² 0.096
p=0.055
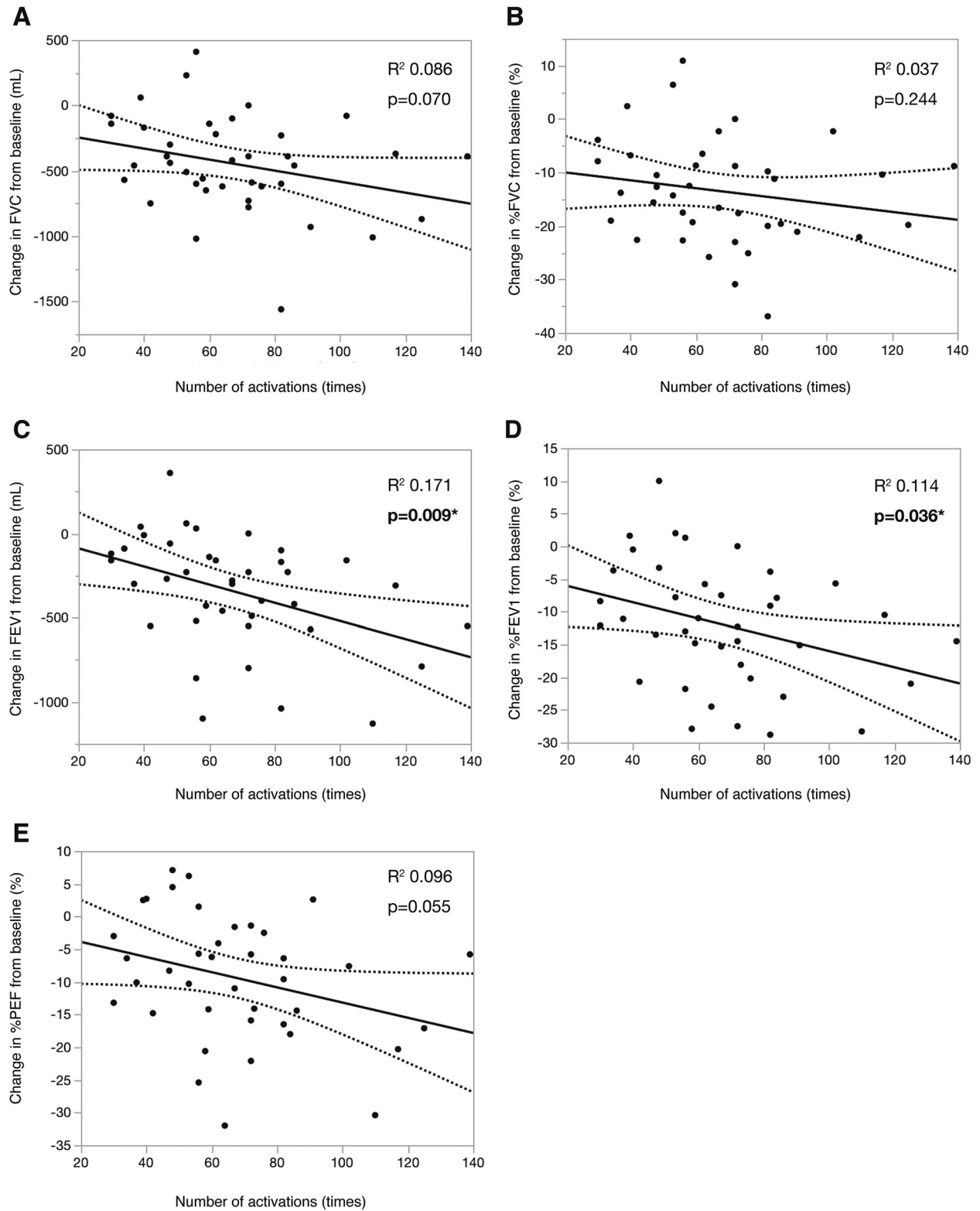
◄**Fig. 2** Correlation between the number of radiofrequency activations and lung function changes from baseline. Linear regression analysis was performed to evaluate the relationship between the number of activations and changes in lung function from baseline, using the following parameters: **a** forced vital capacity (FVC), **b** percent forced vital capacity (%FVC), **c** forced expiratory volume in 1 s (FEV$_1$), **d** percent forced expiratory volume in 1 s (%FEV$_1$) and **e** percent peak expiratory flow (%PEF). Increase in the number of activations correlated with a decrease in FEV$_1$ ($R^2 = 0.17$, $p = 0.0088$) and %FEV$_1$ ($R^2 = 0.11$, $p = 0.0357$). There were no significant correlations between the number of activations and FVC/%FVC/%PEF

targeted persons with moderate-to-severe persistent asthma. On the other hand, the present study and the RISA study targeted persons with severe asthma who were symptomatic despite maximal pharmacologic treatment. Asthma severity might affect SAE occurrence, although we could not assess the relationship between asthma severity and SAE occurrence because of the small number of subjects analyzed. Using two independent data sources, Burn et al. showed that there were more reports of re-admissions in the group who underwent the BT procedure in clinical practice (re-admission rate, 95% CI; 19.1%, 13.2–26.2) compared with the previous clinical trials. Further, they considered asthma severity and age as factors affecting the complication rate of BT. The average age of patients in the AIR trial, AIR2 trial, RISA study, Burn *et al*'s report and this study was 39.4 years, 40.7 years, 39.1 years, 42.6 years and 55.2 years, respectively [12]. Actually, the incidence of adverse events in elderly patients in the present study (25.6%) is slightly high compared with the other studies. The difference could be because this study reflects real-world data that were generated during routine clinical practice and enrolled many elderly and/or adult patients with severe asthma. Among the SAE group, additional needs for antibiotics or corticosteroid therapy were observed but significant prolongations of hospital stays were not observed (SAE group, 10.1 days; non-SAE group 6.1 days; $p = 0.064$) (Table 3). The previously reported treatments for adverse events after BT included

fibrin plug removal by bronchoscopy for atelectasis secondary to occlusion by the plug [5], chest tube insertion for pneumothorax after partial atelectasis [7] and bronchial artery thrombosis and intubation for bronchial artery aneurysm rupture [6]. Such adverse events are the leading causes of death without proper treatment. Since a significant therapeutic effect of BT has been reported, the number of eligible patients for BT are expected to increase. However, the determinant factors related to SAEs remain unclear. This study is the first step to proving whether the number of activations and changes in lung function after the BT procedure are related to SAEs. Future studies should consider asthma severity and include an age-matched population.

There are some limitations to our study. The retrospective study conducted at a single center with a small number of patients limits the weight with which we can interpret the results. The limited number of patients and practitioners could lead to bias in terms of observation of SAEs and treatment, so a larger multicenter study is warranted. In this study, we used lung function tests to assess the occurrence of SAEs. Many previous studies have used chest CT scans to evaluate the lung damage resulting from radiofrequency activation [4, 19]. While CT scans provide high spatial resolution that is especially beneficial in evaluation of fibrin plugs in the airway and airway thickness, diagnostic x-rays are problematic in terms of radiation exposure. Japan has the highest annual frequency of diagnostic x-rays among developed countries. Reportedly, the cumulative cancer risk is related to diagnostic x-ray exposure [22]. Since women of childbearing age might need to undergo the BT procedure, we recommend that frequent diagnostic x-rays should be avoided.

CONCLUSIONS

Increase in the number of radiofrequency activations is involved in a decrease in FEV$_1$ and %FEV$_1$ from baseline after BT. The number of activations, however, is not associated with SAEs after BT. Therefore, further studies elucidating the factors predictive of SAEs are

required to enhance patient safety after the procedure.

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Data Availability. The datasets generated and/or analyzed during the present study are available from the corresponding author on reasonable request.

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