

## ORIGINAL ARTICLE

# Asthma Control during the Year after Bronchial Thermoplasty

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## ABSTRACT

**BACKGROUND**

Bronchial thermoplasty is a bronchoscopic procedure to reduce the mass of airway smooth muscle and attenuate bronchoconstriction. We examined the effect of bronchial thermoplasty on the control of moderate or severe persistent asthma.

**METHODS**

We randomly assigned 112 subjects who had been treated with inhaled corticosteroids and long-acting  $\beta_2$ -adrenergic agonists (LABA) and in whom asthma control was impaired when the LABA were withdrawn to either bronchial thermoplasty or a control group. The primary outcome was the frequency of mild exacerbations, calculated during three scheduled 2-week periods of abstinence from LABA at 3, 6, and 12 months. Airflow, airway responsiveness, asthma symptoms, the number of symptom-free days, use of rescue medication, and scores on the Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) were also assessed.

**RESULTS**

The mean rate of mild exacerbations, as compared with baseline, was reduced in the bronchial-thermoplasty group but was unchanged in the control group (change in frequency per subject per week,  $-0.16 \pm 0.37$  vs.  $0.04 \pm 0.29$ ;  $P=0.005$ ). At 12 months, there were significantly greater improvements in the bronchial-thermoplasty group than in the control group in the morning peak expiratory flow ( $39.3 \pm 48.7$  vs.  $8.5 \pm 44.2$  liters per minute), scores on the AQLQ ( $1.3 \pm 1.0$  vs.  $0.6 \pm 1.1$ ) and ACQ (reduction,  $1.2 \pm 1.0$  vs.  $0.5 \pm 1.0$ ), the percentage of symptom-free days ( $40.6 \pm 39.7$  vs.  $17.0 \pm 37.9$ ), and symptom scores (reduction,  $1.9 \pm 2.1$  vs.  $0.7 \pm 2.5$ ) while fewer puffs of rescue medication were required. Values for airway responsiveness and forced expiratory volume in 1 second did not differ significantly between the two groups. Adverse events immediately after treatment were more common in the bronchial-thermoplasty group than in the control group but were similar during the period from 6 weeks to 12 months after treatment.

**CONCLUSIONS**

Bronchial thermoplasty in subjects with moderate or severe asthma results in an improvement in asthma control. (ClinicalTrials.gov number, NCT00214526.)

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**M**ANY OF THE VARIABLE SYMPTOMS OF asthma are thought to be due to the contraction of airway smooth muscle, leading to bronchoconstriction.<sup>1,2</sup> Increased airway smooth-muscle mass is a characteristic feature of asthma, particularly in persons with severe or fatal asthma.<sup>3,4</sup> Bronchial thermoplasty is a novel intervention in which controlled thermal energy is delivered to the airway wall during a series of bronchoscopies, resulting in a prolonged reduction of airway smooth-muscle mass.<sup>5</sup> In previous studies, we determined the amount and duration of energy to be delivered that result in modest thermal injury.<sup>5,6</sup> The treatment in humans of airways between 3 and 10 mm in diameter led to clinically meaningful reductions in muscle-mediated narrowing of the airway and to the improvement of asthma symptoms.<sup>7,8</sup> We report the results of the yearlong randomized, controlled Asthma Intervention Research (AIR) Trial, which examined the efficacy and safety of bronchial thermoplasty as a treatment for moderate or severe persistent asthma.

## METHODS

### SUBJECTS

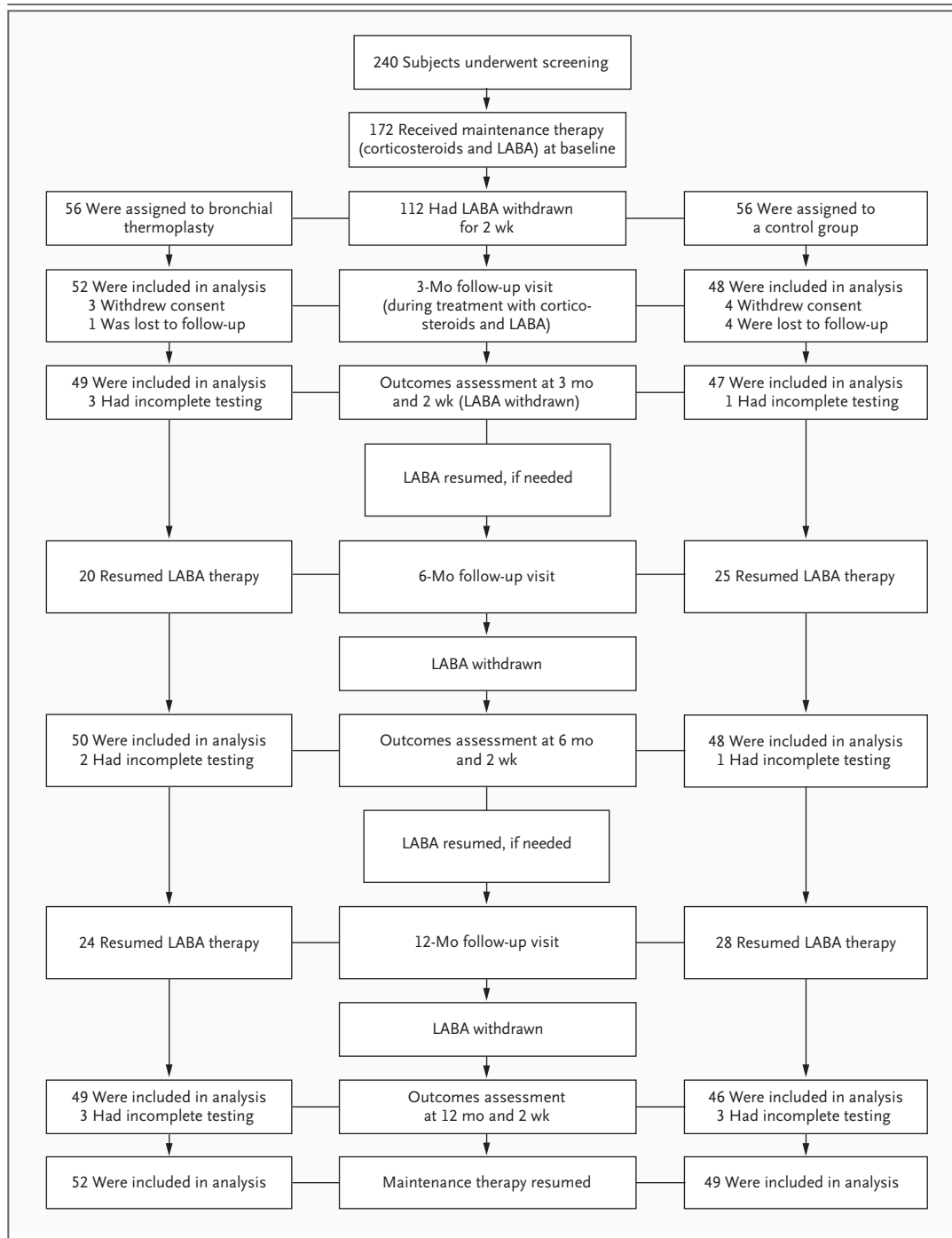
Persons 18 to 65 years of age were eligible for enrollment if they had moderate or severe persistent asthma, defined according to the guidelines of the Global Initiative for Asthma,<sup>9</sup> requiring daily therapy with inhaled corticosteroids equivalent to a dose of 200  $\mu\text{g}$  or more of beclomethasone and long-acting  $\beta_2$ -adrenergic agonists (LABA), at a dose of 100  $\mu\text{g}$  or more of salmeterol (Serevent, GlaxoSmithKline) or the equivalent, to maintain reasonable asthma control. Inclusion criteria were airflow obstruction, assessed as a prebronchodilator forced expiratory volume in 1 second ( $\text{FEV}_1$ ) of 60 to 85% of the predicted value, and airway hyperresponsiveness, defined by a provocative concentration of methacholine required to lower the  $\text{FEV}_1$  by 20% ( $\text{PC}_{20}$ ) of less than 8 mg per milliliter, as well as stable asthma during the 6 weeks before enrollment. Stable asthma was defined as an absence of unscheduled physician visits for asthma care, unchanged use of asthma medication for maintenance therapy, and stable use of rescue medication (4 puffs or fewer of a short-acting bronchodilator at a dose of 100  $\mu\text{g}$

per puff delivered by a metered-dose inhaler [albuterol or the equivalent]) during 24 hours for symptom relief.

One other criterion in addition to fulfilling the definition of moderate or severe asthma was worsening asthma control after abstinence from LABA at baseline for 2 weeks, documented by either an increase of at least 0.5 in the score on the Asthma Control Questionnaire (ACQ)<sup>10</sup> (on a scale of 0 to 6, with higher numbers indicating worse control), or a decline of 5% in the average morning peak expiratory flow (PEF) during the second week of abstinence, as compared with the mean morning PEF during the week immediately before LABA therapy was withdrawn. Subjects were excluded if they had had three or more lower respiratory tract infections requiring antibiotics during the previous 12 months or a respiratory tract infection within the previous 6 weeks.

### STUDY DESIGN

This randomized, controlled trial was conducted at 11 centers in four countries. During the 4-week baseline period, subjects continued to receive maintenance therapy with inhaled corticosteroids and LABA for the first 2 weeks, and LABA were then withheld for the next 2 weeks. Therapy with inhaled corticosteroids and LABA was resumed for the treatment period, which lasted for at least 6 weeks and usually no more than 9 weeks, with a subsequent 12-month follow-up period. The study design is shown in Figure 1. All subjects were seen in follow-up at 3 months while receiving treatment with inhaled corticosteroids and LABA. They were asked to refrain from using LABA after this point, unless they had a severe exacerbation (an event requiring treatment with oral corticosteroids, as judged by the investigator, or a decrease in the morning PEF, for 1 or more days, of more than 30% below the average baseline morning PEF recorded during the week immediately preceding withdrawal from LABA therapy), or if they were judged by the investigator to have poor asthma control that required the resumption of LABA. For those subjects whose asthma could be controlled without LABA, evaluations were performed after 6 and 12 months of treatment with inhaled corticosteroids alone. Subjects who needed to resume LABA therapy be-



**Figure 1. Study Design.**

Seven subjects (three in the bronchial-thermoplasty group and four in the control group) withdrew consent before the 3-month follow-up visit. Six subjects (two in the bronchial-thermoplasty group and four in the control group) withdrew consent for reasons unrelated to the study, and one subject in the bronchial-thermoplasty group refused to abstain from long-acting  $\beta_2$ -agonist (LABA) after the follow-up visit at 6 weeks. Inhaled corticosteroids alone were continued only if the treatment was tolerated. Visits 1 through 3 after baseline and the 6-week follow-up visit are not shown.

fore the visits at 6 and 12 months were evaluated at those assessment points after withdrawal from LABA therapy for 2 weeks.

The study protocol was approved by local or regional ethics review boards at all study sites before the enrollment of any subjects. All subjects provided written informed consent. The study began in November 2002, and the 12-month follow-up period was completed for all subjects by November 2005. An independent data and safety monitoring board oversaw the study.

#### RANDOMIZATION

Eligible subjects were assigned to treatment with inhaled corticosteroids plus LABA (control group) or to treatment with bronchial thermoplasty in addition to inhaled corticosteroids and LABA (bronchial-thermoplasty group) in blocks of four at each center. The randomization code was computer-generated centrally and provided to the study sites in separate envelopes. Investigators were unaware of the block size.

#### TREATMENT PERIOD

Subjects assigned to the bronchial-thermoplasty group underwent three bronchoscopy procedures performed with the use of the Alair system (Asthmatx) at intervals of approximately 3 weeks. During the procedure, they were under either general anesthesia or conscious sedation, as previously described.<sup>5,8</sup> A video showing part of an actual procedure is in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org). Control subjects had three treatment visits at intervals of 3 weeks for clinical review and spirometric assessment and received a systemic corticosteroid similar to that administered to subjects in the bronchial-thermoplasty group.

#### FOLLOW-UP PERIOD

All subjects in the two groups were seen 2 weeks after each treatment visit. After the last treatment visit (designated as time 0), clinic visits were scheduled at 6 weeks and at 3, 6, and 12 months. Subjects were contacted by telephone on days 1 and 7 after each treatment visit and monthly after the visit at month 3.

#### OUTCOME MEASURES

The primary outcome was the difference between the two groups in the change in the rate of mild exacerbations between baseline and later time

points. Exacerbations, ascertained from daily diaries in which subjects recorded events, were defined as at least one of the following occurrences on 2 consecutive days: a reduction in the morning PEF of at least 20% below the average value (based on the PEF recorded during the week immediately preceding the withdrawal of LABA at baseline), the need for more than three additional puffs of rescue medication exceeding the average use during the week immediately preceding the withdrawal of LABA at baseline, or nocturnal awakening caused by asthma symptoms.<sup>11</sup> Only events occurring during the 2-week periods of abstinence from LABA, according to the study protocol, at 3, 6, and 12 months were used to calculate the rates of mild and severe exacerbations.

All subjects kept a daily diary from the beginning of the baseline period to the visit at month 6, and for a 4-week period before the visit at month 12. The data recorded in the diaries were used to assess changes in the PEF, the use of rescue medication, the number of symptom-free days, and the symptom score. The symptom score was the total of the individual scores (on a scale of 0 to 3, with higher numbers indicating more frequent or more severe symptoms or both) for nighttime wheezing and cough and daytime wheezing, cough, breathlessness, and sputum production. These six individual scores were summed to yield a maximum possible score of 18. A symptom-free day was defined as a day during which the symptom score was 0 and there was no nighttime awakening. The ACQ consists of six questions and the measurement of prebronchodilator FEV<sub>1</sub>, and responses are scored on a scale of 0 to 6, with lower numbers indicating better asthma control. The minimal important change in the score is thought to be 0.5.<sup>12</sup> The Asthma Quality of Life Questionnaire (AQLQ) consists of 32 items covering asthma-related symptoms and limitations during the 2 weeks preceding administration of the questionnaire, and responses are scored on a scale of 1 to 7, with higher numbers indicating a better quality of life. The minimal important change in the score is thought to be 0.5.<sup>13</sup> For details of the outcome measures, see the Supplementary Appendix.

#### MONITORING ADVERSE EVENTS

At each visit and during each telephone call, subjects were asked by research staff about potential adverse events, and their daily diaries were exam-

ined by study personnel to ensure complete reporting of events. Adverse events were classified as respiratory or nonrespiratory events and were reported at baseline and for the treatment period and the post-treatment period.

#### STATISTICAL ANALYSIS

The statistical analysis was performed on an intention-to-treat basis and included those subjects who completed at least one bronchoscopy session or treatment visit. The study was powered to detect differences between the two groups in the change from baseline to later time points. There was no imputation of missing data. Frequencies of adverse events were compared with the use of Fisher's exact test. For continuous variables, statistical significance was determined with the use of Student's *t*-test, and for categorical variables, statistical significance was determined with the use of the Cochran–Mantel–Haenszel test. *P* values of less than 0.05 were considered to indicate statistical significance. Data are reported as means ( $\pm$ SD), and all reported *P* values are two-sided, unless otherwise indicated.

The study was designed with more than 90% power to detect a difference of eight mild exacerbations per subject per year between the two groups with the use of a two-tailed *t*-test. Exacerbation rates and secondary outcomes were analyzed on the basis of the change from the baseline period (the 2-week period during which the subjects were treated with inhaled corticosteroids alone) to the 2-week periods at 3, 6, and 12 months during which they were treated with inhaled corticosteroids alone (Fig. 1). For the analysis of the effects of bronchial thermoplasty in addition to usual care, at 3 months, the relevant baseline was treatment with inhaled corticosteroids plus LABA. Data for all subjects were included in the safety analyses.

The protocol was designed by a committee of academic authors and employees of the sponsor, with comment in specific areas from an advisory board. The database was managed and all analyses requested by the investigators were performed by QST Consultations. The manuscript was written by the corresponding author, with contributions from all coauthors and selected employees of the sponsor, and was reviewed by the external advisory board. The final manuscript was prepared by the corresponding author, without limitation by the sponsor. All the authors

vouch for the accuracy and completeness of the reported data.

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## RESULTS

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#### BASELINE CHARACTERISTICS OF THE SUBJECTS

Of 240 subjects who underwent screening, 68 did not fulfill all the entry criteria on assessment during the run-in period and 60 did not complete the phase of withdrawal from LABA (i.e., could not tolerate withdrawal, did not have deterioration, or withdrew consent). The remaining 112 subjects underwent randomization, and 56 subjects were assigned to each of the two study groups (Fig. 1). Outcomes for the effect of bronchial thermoplasty in addition to usual care were assessed at 3 months for 52 subjects in the bronchial-thermoplasty group and 48 control subjects; complete data after 12 months of follow-up were available for 52 subjects in the bronchial-thermoplasty group and 49 in the control group (Fig. 1). The baseline demographic characteristics of the two groups were similar (Table 1). For the statistical comparisons, baseline means were calculated only for subjects for whom follow-up data were available.

#### EXACERBATIONS

Twelve months after the last study treatment, the mean number of mild exacerbations in the bronchial-thermoplasty group was  $0.18 \pm 0.31$  per subject per week, as compared with  $0.35 \pm 0.32$  at baseline. The number of mild exacerbations in the control group was  $0.31 \pm 0.46$  per subject per week, as compared with  $0.28 \pm 0.31$  at baseline. The difference between the two groups in the change from baseline was significant at 3 months and at 12 months ( $P=0.03$  for both comparisons) but not at 6 months (Fig. 2). As compared with baseline, the average number of exacerbations during the 2-week periods at 3, 6, and 12 months when subjects in the two groups were treated with inhaled corticosteroids alone was reduced in the bronchial-thermoplasty group but was not significantly changed in the control group ( $-0.16 \pm 0.37$  vs.  $0.04 \pm 0.29$  per subject per week,  $P=0.005$  for the comparison between the groups). Analysis with the use of the Wilcoxon rank-sum method also showed a significant difference between the groups ( $P=0.01$ ). This finding can be extrapolated to approximately 10 fewer mild exacerbations per subject per year in the bronchial-thermoplasty group.

**Table 1. Demographic and Clinical Characteristics of Subjects Completing One or More Treatment Visits.\***

Characteristic	Bronchial-Thermoplasty Group	Control Group
No. of subjects	55	54
Age — yr	39.36±11.18	41.65±11.35
Sex — no. (%)		
Male	24 (44)	23 (43)
Female	31 (56)	31 (57)
Race or ethnic group — no. (%)†		
White	51 (93)	50 (93)
Black	3 (5)	2 (4)
Asian	1 (2)	2 (4)
PC <sub>20</sub> geometric mean — mg/ml (95% CI)	0.25 (0.16–0.40)	0.35 (0.23–0.52)
Prebronchodilator FEV <sub>1</sub> — % predicted	72.65±10.41	76.12±9.28
Dose of study medication — µg		
Inhaled corticosteroid — beclomethasone or the equivalent‡	1351±963	1264±916
Median	1000.00	1000.00
LABA — salmeterol or the equivalent§	111.3±35.9	105.8±30.8
Asthma severity — no.¶		
Moderate persistent	21	26
Severe persistent	34	28
Seasonal allergies present — no. (%)	34 (62)	35 (65)
Deterioration of asthma control after 2 weeks of abstinence from LABA — no. (%)		
Increase in score on ACQ of at least 0.5	17 (31)	12 (22)
Decline in morning PEF of at least 5%	15 (27)	14 (26)
Both increase and decrease	21 (38)	25 (46)
Neither increase nor decrease	2 (4)	3 (6)

\* Subjects in the bronchial-thermoplasty group were treated with bronchial thermoplasty, inhaled corticosteroids, and long-acting  $\beta_2$ -agonists (LABA), and those in the control group were treated with inhaled corticosteroids and LABA. Plus–minus values are means  $\pm$ SD. Percentages may not sum to 100 because of rounding. PC<sub>20</sub> denotes provocative concentration of methacholine required to lower the forced expiratory volume in 1 second (FEV<sub>1</sub>) by 20%, CI confidence interval, ACQ Asthma Control Questionnaire, and PEF peak expiratory flow.

† Race or ethnic group was self-reported.

‡ The dose of any other inhaled corticosteroid was converted to the equivalent dose of beclomethasone.

§ The dose of any other LABA was converted to the equivalent dose of salmeterol.

¶ For each subject, asthma was categorized as moderate and persistent or severe and persistent on the basis of the assessment of the subject's FEV<sub>1</sub> value and the frequency of symptoms with the dose of maintenance therapy, according to the 2004 guidelines of the Global Initiative for Asthma for these measures.<sup>9</sup>

|| Three subjects in the control group and two in the bronchial-thermoplasty group did not fulfill either of these criteria, and their inclusion in the study was considered a deviation from the protocol. There was no significant difference in the outcomes when these subjects were excluded.

Twelve months after the last study treatment, the mean number of severe exacerbations in the bronchial-thermoplasty group was  $0.01 \pm 0.08$  per subject per week, as compared with  $0.07 \pm 0.18$  at baseline. The number of severe exacerbations in the control group was  $0.06 \pm 0.24$  per subject per week, as compared with  $0.09 \pm 0.31$  at baseline.

The difference between the two groups in the change from baseline was not significant at any time point (Fig. 2).

Changes in the secondary outcomes (airflow, airway hyperresponsiveness, use of rescue medication, asthma symptoms, and scores on the AQLQ and ACQ) in the subjects receiving usual

care at 3 months and when LABA were withdrawn at 3, 6, and 12 months are shown in Figure 3. For further data on secondary outcomes, see the Supplementary Appendix.

#### HIGH-DOSE INHALED CORTICOSTEROIDS

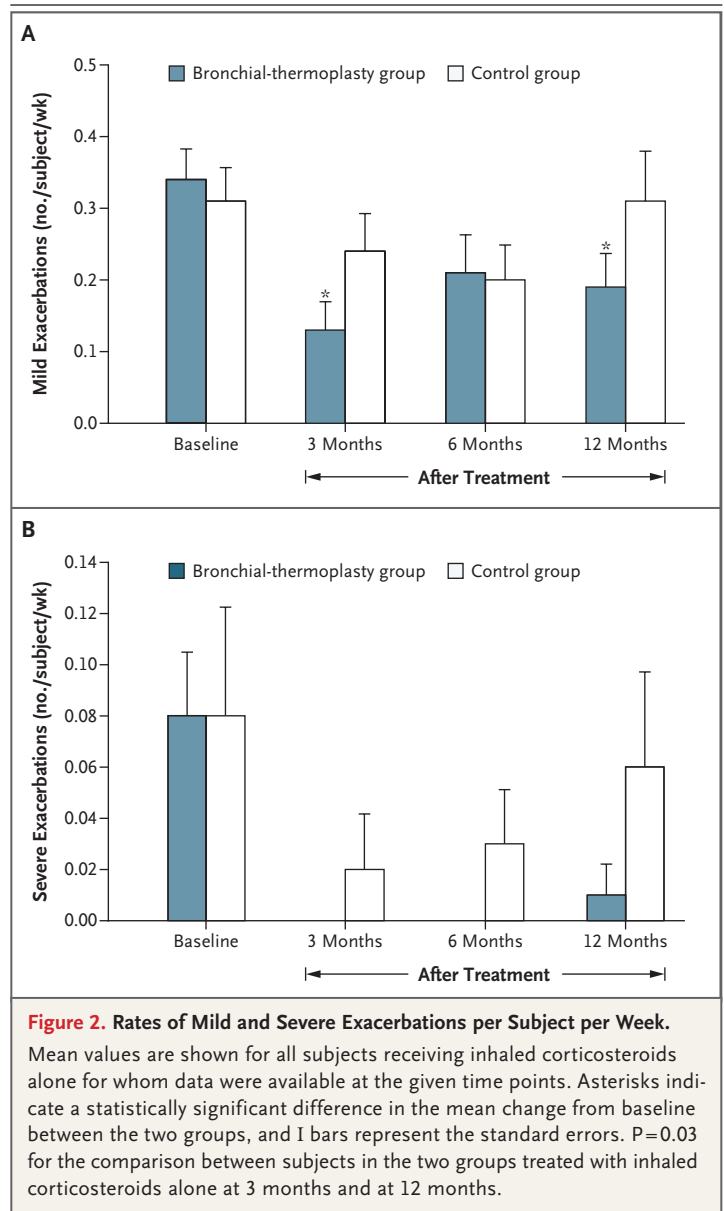
In a post hoc analysis, data for a subgroup of subjects requiring high maintenance doses of inhaled corticosteroids ( $>1000 \mu\text{g}$  of beclomethasone or the equivalent) at baseline were analyzed separately and showed greater differences between the control group and the bronchial-thermoplasty group. Data on this analysis are in the Supplementary Appendix.

#### ADVERSE EVENTS

There was an increase in adverse respiratory events in subjects undergoing bronchial thermoplasty immediately after the procedure, with a return to baseline values during the post-treatment period. During the treatment period, there were 407 adverse respiratory events, of which 69% were mild, 28% were moderate, and 3% were severe. In the control group there were 106 adverse respiratory events, of which 69% were mild, 30% were moderate, and 1% were severe. The most frequently observed adverse events during the treatment period are listed in Table 2. In the bronchial-thermoplasty group, the majority of the adverse events occurred within 1 day after the procedure and resolved an average of 7 days after the onset of the event.

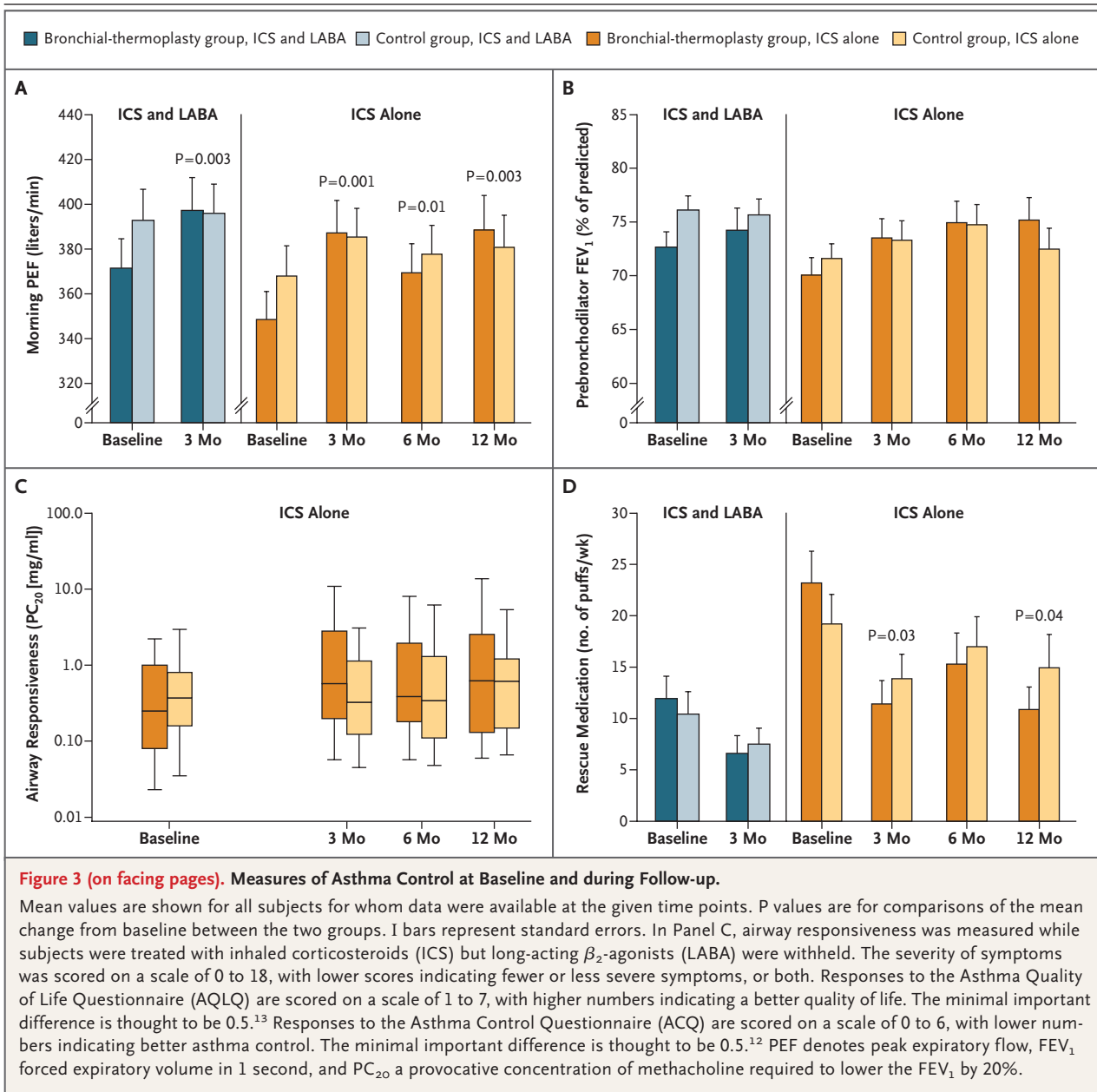
Hospitalizations for adverse respiratory events during the treatment period were more frequent in the bronchial-thermoplasty group (four subjects required a total of six hospitalizations) than in the control group (two subjects required one hospitalization each). Four of the hospitalizations of subjects in the bronchial-thermoplasty group were for exacerbation of asthma (one within 1 day after treatment, two 30 days after treatment, and one 85 days after treatment), one was for partial collapse of the left lower lobe (2 days after treatment), and one was for pleurisy (43 days after treatment).

During the post-treatment period, the proportion of subjects with adverse respiratory events was similar in the two groups (Table 2). The rate of hospitalization for respiratory events was low during this period and did not differ significantly between the two groups: three subjects in the bronchial-thermoplasty group required hospital-



ization — one for chest infection and two for asthma exacerbation — and two subjects in the control group required a total of three hospitalizations for increased asthma symptoms. There were no deaths during the study.

Although there were variations among the study centers in the size of the treatment effect and the number of adverse events, there was no obvious relationship between the investigators' experience with bronchial thermoplasty or the numbers of subjects treated and the outcomes or adverse events. One additional hospitalization for an adverse respiratory event occurred 14 months

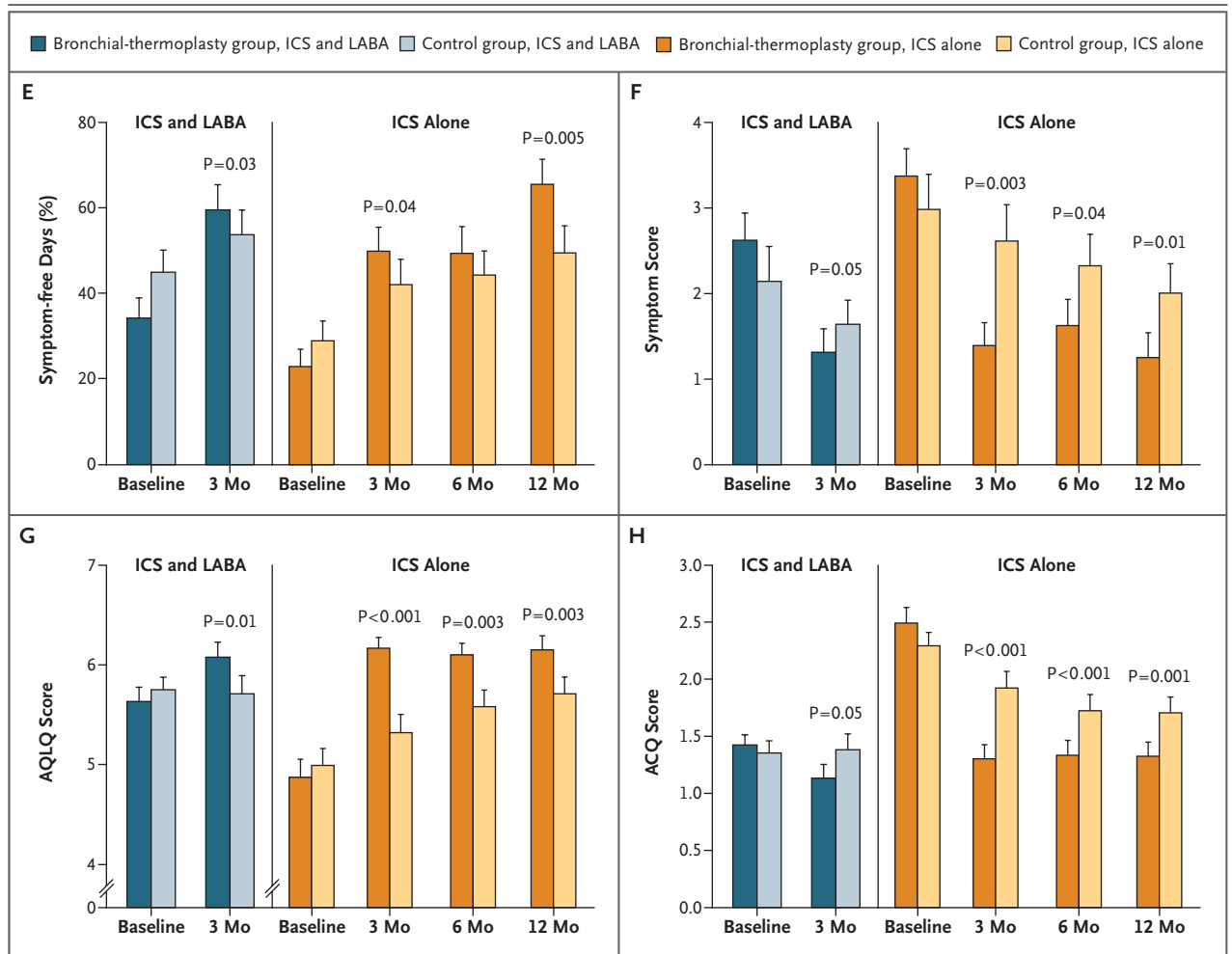


after bronchial thermoplasty in a subject who had undergone the procedure uneventfully and had completed the trial with normal spirometric values and good asthma control (score on the ACQ, 0.2; symptom score, 0), but who subsequently underwent resection for an abscess in a left upper lobe. Histologic examination did not reveal obstruction or any other potentially contributory abnormality in the airways as a result of thermoplasty. (For information on the follow-up in the

bronchial-thermoplasty group after completion of the study, see the Supplementary Appendix.)

## DISCUSSION

This randomized, controlled study examined the efficacy and safety of bronchial thermoplasty in subjects with moderate or severe persistent asthma. The study design was based on the hypothesis that if bronchial thermoplasty were beneficial,



then in subjects treated with bronchial thermoplasty, as compared with control subjects, asthma control would be improved when treatment with LABA was discontinued. Although the benefits of bronchial thermoplasty were obvious when LABA were withdrawn, they were also observed at 3 months, when all subjects in the two study groups were still receiving LABA (Fig. 3). Among subjects treated with inhaled corticosteroids alone, bronchial thermoplasty reduced the frequency of mild exacerbations at a rate equivalent to 10 exacerbations per subject per year and provided 86 additional symptom-free days per subject per year. These improvements were achieved during a period in which the use of rescue medication was reduced in the bronchial-thermoplasty group, as compared with the control group.

The effect of bronchial thermoplasty was evident 3 months after the procedure. The improve-

ments in objective and subject-centered outcomes did not diminish over the course of the study, and the outcomes assessed at 1 year showed the same degree of improvement as at 3 months. In a preliminary, nonrandomized study, we found that the benefits of bronchial thermoplasty persisted at 2 years.<sup>8</sup> Thus, although the duration of the effect of bronchial thermoplasty remains uncertain, in this study the benefit appeared to persist at 1 year.

Treatment with bronchial thermoplasty was associated with adverse events related primarily to worsening of asthma symptoms during the period immediately after treatment. Although the frequency of adverse events was similar in the two groups at 6 weeks to 1 year after bronchial thermoplasty, studies of larger numbers of patients and with a longer follow-up will be needed to rule out less common adverse events than those identified in this study.

**Table 2. Adverse Respiratory Events.\***

Event	Bronchial-Thermoplasty Group		Control Group		P Value†
	Frequency of Event	Subjects with Event <i>percent</i>	Frequency of Event	Subjects with Event	
<b>Treatment period plus 6 wk</b>					
Dyspnea	19.9	70.9	21.7	33.3	<0.001
Wheezing	17.0	61.8	7.5	13.0	<0.001
Cough	16.0	52.7	11.3	18.5	<0.001
Chest discomfort	10.3	47.3	18.9	20.4	0.004
Night awakenings	9.8	40.0	4.7	9.3	<0.001
Productive cough	8.6	40.0	8.5	11.1	<0.001
Upper respiratory tract infection	2.5	12.7	1.9	3.7	0.16
Bronchial irritation	2.0	9.1	0	0	0.06
Nasal congestion	2.0	12.7	10.4	11.1	1.00
Sputum discolored	1.7	10.9	0	0	0.03
Dry mouth	1.2	3.6	0	0	0.50
Abnormal chest sound	1.0	5.5	0	0	0.24
Bronchospasm	1.0	7.3	0	0	0.12
<b>Post-treatment period (6 wk–12 mo)</b>					
Dyspnea	22.1	49.1	26.4	53.8	0.70
Cough	15.4	38.2	13.0	36.5	1.00
Nasal congestion	9.6	27.3	10.1	26.9	1.00
Wheezing	9.6	29.1	8.7	23.1	0.52
Productive cough	9.2	23.6	7.7	23.1	1.00
Chest discomfort	6.7	21.8	8.2	13.5	0.32
Upper respiratory tract infection	6.3	18.2	2.9	5.8	0.07
Night awakenings	3.3	12.7	3.4	9.6	0.76
Pharyngolaryngeal pain	3.3	10.9	3.8	13.5	0.77
Nasopharyngitis	2.9	10.9	1.4	5.8	0.49
Respiratory tract congestion	2.5	9.1	1.0	3.8	0.44
Respiratory tract infection	2.5	9.1	5.8	17.3	0.26
Bronchitis	1.3	1.8	0	0	1.00
Throat irritation	1.3	3.6	1.0	3.8	1.00

\* Subjects were asked about adverse events at each office visit and during telephone calls. Only adverse events occurring in the bronchial-thermoplasty group at a frequency of 1.0% or greater are listed.

† For the comparison between the two groups of the number of subjects reporting an adverse event, P values were calculated with the use of Fisher's exact test.

The interpretation of our results is confounded by the nonblinded study design; this limitation is important, given that bronchial thermoplasty is a procedure that may increase the potential for a strong placebo effect.<sup>14-16</sup> However, the magnitude and persistence of the effects of the intervention observed are probably greater than what

could be attributed to placebo alone. For example, a within-group change of 0.5 in scores on the AQLQ is considered clinically significant,<sup>13</sup> and we found a between-group difference of 0.69 at 12 months. Of the outcomes reported, perhaps the two that are least susceptible to bias are the morning PEF, since it was measured daily for

most of the study period, and the number of mild exacerbations per subject per week, since these were counted after the study had ended by a statistician who reviewed the data in the daily diaries, according to predetermined criteria. The increase in the morning PEF value of 39 liters per minute from baseline to 12 months among subjects treated with bronchial thermoplasty (between-group difference, 31 liters per minute) exceeded the change seen in placebo groups in other trials involving patients with asthma (range, -22 to 17 liters per minute).<sup>17-21</sup> Our data showing potential beneficial effects of bronchial thermoplasty provide the basis for mounting a placebo-controlled trial involving the use of sham bronchial thermoplasty.

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#### APPENDIX

Members of the AIR Trial Study Group were as follows: **data and safety monitoring board** — W. Busse, R. Schellenberg, A.S. Slutsky (chair); **coinvestigators and study coordinators** — **Canada:** McMaster University: P. Nair, S. Goodwin, K. Currie; Montreal Chest Institute: J. Bourbeau, F. Houghton; London Health Science Centre: N. Patterson, S. Metha, J. Howard, L. MacBean; Laval University: S. Martel, L.-P. Boulet, L. Morel, L. Trépanier; **United Kingdom:** University of Glasgow: S. Bicknell, E. Livingston, J. Lafferty; University of Manchester: C. Prys-Picard, G. Fletcher; Newcastle University: B. Higgins, T. Small, B. Foggio; University of Leicester: M. Berry, D. Shaw, N. Sheldon; London Chest Hospital: N. Barnes (investigator), D. Watson; **Brazil:** Santa Casa: P.G. Cardoso, P.R.D. Soares; **Denmark:** Odense University Hospital: F. Rasmussen, H.M. Christensen, M. Olsén.

#### REFERENCES

- National Center for Health Statistics. Asthma prevalence, health care use and mortality, 2002. Atlanta: Centers for Disease Control and Prevention, 2002. (Accessed March 5, 2007, at <http://www.cdc.gov/nchs/products/pubs/pubd/hestats/asthma/asthma.htm>.)
- Doherty DE. The pathophysiology of airway dysfunction. *Am J Med* 2004;117: Suppl 12A:11S-23S.
- Woodruff PG, Dolganov GM, Ferrando RE, et al. Hyperplasia of smooth muscle in mild to moderate asthma without changes in cell size or gene expression. *Am J Respir Crit Care Med* 2004;169:1001-6.
- Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. *Am Rev Respir Dis* 1993;147:405-10.
- Cox PG, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. *Eur Respir J* 2004;24:659-63.
- Danek CJ, Lombard CM, Dungworth DL, et al. Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. *J Appl Physiol* 2004;97:1946-53.
- Miller JD, Cox G, Vincic L, Lombard CM, Loomas BE, Danek CJ. A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest* 2005;127: 1999-2006.
- Cox G, Miller JD, McWilliams A, Fitzgerald JM, Lam S. Bronchial thermoplasty for asthma. *Am J Respir Crit Care Med* 2006;173:965-9.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention: updated 2004. Bethesda, MD: National Institutes of Health, 2004. (NIH publication no. 02-3659.)
- Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902-7.
- Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11. [Erratum, *N Engl J Med* 1998;338:139.]
- Juniper EF, Svensson K, Mork A-C, Stahl E. Measurement properties and interpretation of three shortened versions of the Asthma Control Questionnaire. *Respir Med* 2005;99:553-8.
- Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol* 1994;47:81-7.
- Sackett DL. Biases in analytic research. *J Chronic Dis* 1999;32:51-63.
- Freed CR, Greene PE, Breeze RE, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med* 2001;344:710-9.
- Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med* 2002;347:81-8.
- Adkinson NF Jr, Eggleston PA, Eney D, et al. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997;336:324-31.
- Balon J, Aker PD, Crowther ER, et al. A comparison of active and simulated chiropractic manipulation as adjunctive treatment for childhood asthma. *N Engl J Med* 1998;339:1013-20.
- FDA new drug application for Flovent Rotadisk: manufactured by Glaxo-Wellcome. Rockville, MD: Food and Drug Administration, November 7, 1997. (No. NDA 20-549 and 20-770.) (Accessed March 12, 2007, at <http://www.fda.gov/CDER/foi/nda/97/020549ap.pdf>.)
- FDA New Drug Application (NDA) no. 21-077 for Advair Diskus, manufactured by GlaxoSmithKline, Inc., approved August 2000. Rockville, MD: Food and Drug Administration, 2000.
- FDA Biologics License Application (BLA) no. 103976 for Xolair Omalizumab, manufactured by Genentech, Inc., approved June 2003. Rockville, MD: Food and Drug Administration, 2003.

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