

Original Article

Predicting the Response to Bronchial Thermoplasty

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What is already known about this topic? Little is known about which patients are most suitable for bronchial thermoplasty.

What does this article add to our knowledge? This study evaluates the outcomes of 77 Australian patients with asthma and finds that those with the greatest response to treatment were most severely affected at baseline regarding asthma control and exacerbation frequency.

How does this study impact current management guidelines? Bronchial thermoplasty should be particularly considered for patients with asthma with high levels of risk and impairment.

BACKGROUND: Although it is established that not all patients respond to bronchial thermoplasty (BT), the factors that predict response/nonresponse are largely unknown.

OBJECTIVES: To identify baseline factors that predict clinical response.

METHODS: The records of 77 consecutive patients entered into the Australian Bronchial Thermoplasty Registry were examined for baseline clinical characteristics, and outcomes measured at 6 and 12 months after BT, such as change in the Asthma Control Questionnaire (ACQ) score, exacerbation frequency, the requirement for short-acting beta-2 agonist (SABA) medication and oral corticosteroids, and improvement in spirometry.

RESULTS: This was a cohort of patients with severe asthma: aged 57.7 ± 11.4 years, 57.1% females, 53.2% of patients taking maintenance oral steroids, 43% having been treated with an mAb, mean FEV₁ of $55.8\% \pm 19.8\%$ predicted.

RESULTS: BT resulted in an improvement in the ACQ score from 3.2 ± 1.0 at baseline to 1.6 ± 1.1 at 6 months ($P < .001$).

Exacerbation frequency in the previous 6 months reduced from 3.7

± 3.3 to 0.7 ± 1.2 ($P < .001$). SABA requirement reduced from 9.3 ± 7.1 puffs/d to 3.5 ± 6.0 ($P < .001$), and 48.8% of patients were weaned completely off oral steroids. A significant improvement in FEV₁ was observed. Using multiple linear regression models, baseline ACQ score strongly predicted improvement in ACQ score ($P < .001$). Patients with an exacerbation frequency greater than twice in the previous 6 months showed the greatest reduction in exacerbations (-5.3 ± 2.8 ; $P < .001$). Patients using more than 10 puffs/d of SABA experienced the greatest reduction in SABA requirement (-12.4 ± 10.5 puffs, $P < .001$).

CONCLUSIONS: The most severely afflicted patients had the greatest improvements in ACQ score, exacerbation frequency, and medication requirement. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Asthma; Bronchial thermoplasty; Predictive factors

INTRODUCTION

Bronchial thermoplasty (BT) is an endoscopic treatment for severe asthma, using radiofrequency energy delivered to the airway smooth muscle. Its current role, as recommended by the Global Initiative for Asthma, is in patients with severe uncontrolled asthma who are not suitable for biologic therapy.¹ Its efficacy and safety have been demonstrated in long-term follow-up studies of randomized cohorts.²⁻⁴ However real-world case series demonstrate that although BT is effective in many, the magnitude of the response is variable, and some patients are nonresponders.⁵⁻⁸

The key to maximizing clinical response lies with the accurate selection of patients to treat. The characteristics of the responding population, however, are still relatively undefined, and there are no established phenotypes or biomarkers to indicate optimal suitability for BT.⁸ A multicenter study suggested that early onset atopic asthma was associated with a more favorable response.⁹ Proceduralist technique has also been suggested as an influence, with a higher number of radiofrequency

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No funding was received from any source by any author in relation to this work.
Conflicts of interest: The authors declare that there are no commercial associations that create a conflict of interest and need disclosure.

Received for publication July 21, 2019; revised October 6, 2019; accepted for publication October 22, 2019.

Available online ■■

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2213-2198

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<https://doi.org/10.1016/j.jaip.2019.10.034>

Abbreviations used

ACQ- Asthma Control Questionnaire

BMI- Body mass index

BT- Bronchial thermoplasty

OCS- Oral corticosteroid

SABA- Short-acting beta-2 agonist

activations having been found to be associated with improved symptom control.¹⁰

A new treatment paradigm for severe asthma has arrived in the form of individualized therapy, yet the available evidence in guiding selection for BT is still lacking. In this study, we aimed to identify baseline characteristics that will help predict improved clinical response to BT.

METHODS**Setting**

Patients were drawn from the Australian Bronchial Thermoplasty Registry—a voluntary collaboration between Australian university teaching hospitals performing BT. Four centers were participating during this study. The registry was established in 2014 with the aim of auditing surgical outcomes. Patients are selected for BT at the discretion of the treating proceduralist, but are required to meet the European Respiratory Society/American Thoracic Society definition of severe asthma.¹¹ Patients are referred to a center from other respiratory physicians once all other treatment avenues such as mAbs have been explored. On the basis of Australian sales of the Alair Radiofrequency Catheter (Boston Scientific, NSW, Australia), the authors estimate that the registry enrolled 60% of cases performed in Australia between 2014 and 2018. Participating sites agree that all cases performed at that institution must be included, and that data are entered prospectively. Each patient gives consent to data collection, and data are shared in the registry in a deidentified fashion, and with the approval of the local Ethics Committee. Smaller subsets of this registry have been previously published.^{6,12}

Independent variables

The baseline data collected for each patient include age, sex, body mass index (BMI), medication usage, exacerbation history, biomarkers (IgE and blood eosinophil count), and the 5-item Asthma Control Questionnaire (ACQ) score.¹³ All patients have spirometry performed in accredited respiratory laboratories by experienced scientific staff, and conforming to European Respiratory Society/American Thoracic Society standards.¹⁴ Tests are conducted in the mornings, before any bronchodilator therapy and before the initiation of any additional periprocedural oral steroid treatment. The predicted equations used are taken from the Global Lung Initiative.¹⁵ The single breath diffusion capacity for carbon monoxide is also measured and the gas transfer per lung unit calculated and expressed as a percentage of predicted. An exacerbation is defined as the requirement for the introduction of oral corticosteroids (OCSs) for 3 consecutive days in a steroid-naïve patient, or an increase by 10 mg from baseline dose for patients taking maintenance oral prednisolone.

Outcome measures

Follow-up study assessments are performed independently of the proceduralists by experienced clinical research nurses at each site, and at the agreed time points—6 weeks, 6 months, and 12 months postprocedure. Outcome measures include (1) ACQ score, (2)

TABLE I. Baseline characteristics Australian BT Registry

Parameter	Australia	North America ⁷	P
n	77	190	
Age (y)	57.7 ± 11.4	45.8 ± 11.4	<.001
Sex: female (%)	57.1	61.6	NS
BMI (kg/m ²)	29.8 ± 6.4	32.5 ± 7.7	<.01
FEV ₁ (% predicted)	55.8 ± 19.8	79.6 ± 13.1	<.001
SABA (puffs/d)	9.3 ± 7.1	2.4 ± 1.5	<.001
Inhaled steroid (μg/d)*	1963 ± 830	2301 ± 807	<.005
Daily oral steroid (%)	53.2	18.9	<.01
Prednisolone dose (mg/d)	12.1 ± 7.5	9.1 ± 2.7	<.001
Exacerbations (per annum)	7.3 ± 6.6	1.6 ± 1.2	<.001
Symptom score	ACQ: 3.2 ± 1.0	AQLQ: 4.2 ± 1.3	

AQLQ, Asthma Quality of Life Questionnaire; NS, not statistically significant.

Values are mean ± SD unless otherwise indicated.

*Beclomethasone equivalent dose.

exacerbation frequency, (3) requirement for short-acting beta-2 agonist (SABA) reliever, (4) requirement for maintenance OCSs, and (5) spirometry. The change in ACQ score 6 months posttreatment is used as the primary outcome measure.

Statistical analysis

The baseline data were collated and compared with the North American registry data.⁷ The treatment outcomes at 6 and 12 months postprocedure were summarized. Best responders and worst responders in terms of ACQ score improvement were identified. A receiver-operating characteristic curve was derived using the accepted minimal clinically significant change in ACQ score of 0.5 to define responders and nonresponders to BT.¹³ Sensitivity and 1 – specificity were plotted for baseline ACQ score. Multiple regression models were used to assess the relationships between baseline data and the outcome variables measured by 2 time points, and a mixed-effect model was used to analyze the associations between baseline measures and ACQ score change over 3 time points. Statistical analysis tools used were SPSS version 25 (IBM corporation, New York, NY) and R 3.6.0 (R Core Team, Vienna, Austria). Grouped data are reported as either mean ± SD, or, median (interquartile range). Statistical significance was taken throughout as $P < .05$. P values are quoted whenever less than .10; otherwise, not significant is used.

RESULTS**Study population**

Baseline data were available for 80 consecutive patients entered into the registry between June 2014 and December 2018. Three patients were excluded from analysis owing to the absence of follow-up data at 6 months (primary end point). Complete follow-up data were available for the remaining 77 patients at the 6-month reassessment. The data for 66% of patients were available at 12 months—12 patients still waiting to complete 12-month follow-up, and 14 patients from regional centers being lost to follow-up.

TABLE II. Outcomes after BT in the Australian Registry

Outcome	Baseline	6 mo	12 mo	P 0-6 mo	P 6-12 mo
ACQ score	3.2 ± 1.0	1.6 ± 1.1	1.6 ± 1.2	<.001	NS
Exacerbations/6 mo	3.7 ± 3.3	0.7 ± 1.2	0.9 ± 1.5	<.001	NS
SABA (puffs/d)	9.3 ± 7.1	3.5 ± 6.0	4.2 ± 6.2	<.001	NS
OCS dose (mg/d) (n = 41)	12.1 ± 7.5	5.0 ± 6.8	4.2 ± 6.9	<.001	NS
FEV ₁ (% predicted)	55.8 ± 19.8	60.0 ± 20.7	60.6 ± 21.0	<.05	NS

NS, Not statistically significant.

Values are mean ± SD unless otherwise indicated.

The baseline data from these 77 patients were compared with the North American postmarketing PAS2 registry⁷ and the results are summarized in Table I. The Australian patients were significantly older, more obstructed, more likely to be using maintenance OCSs, and were more prone to exacerbations than the North American cohort.

Additional baseline lung function data included a forced expiratory ratio of 54.4% ± 14.1%, mean bronchodilator reversibility of 14.6% ± 15.7%, and mean gas transfer per lung unit of 95.9% ± 21.6% predicted. In this cohort of patients, 75% were never smokers and there were no current smokers. The mean blood eosinophil count was 300 ± 300 cells/μL, and the median IgE was 100 (28,201) IU/mL. All patients were treated with dual long-acting bronchodilators, and 33 patients (43%) had been treated with an mAb for asthma.

Response to treatment

The outcomes following BT assessed at 6 and 12 months after treatment are presented in Table II. Significant improvements in all outcome parameters were observed 6 months after treatment, with particularly marked effects evident in relation to ACQ score and exacerbation frequency. A small but significant improvement in FEV₁% predicted was also observed. These improvements were maintained at the 12-month reassessment. To provide predictive guidance to proceduralists, the likelihood of a response was calculated across a range of outcome measures, and these are presented in Table III. The average quantum of radiofrequency treatment per patient was 208 ± 54 activations.

Predicting the improvement in ACQ score

The group of 77 patients was divided into tertiles on the basis of change in ACQ score 6 months after BT. The first group of poorer responders was defined by an improvement in ACQ score of less than 1.0 (n = 21). The second group of typical responders (n = 33) was defined by an ACQ score improvement of 1.0 to 2.0, whereas the third group of super responders (n = 23) comprised patients whose ACQ score improved by more than 2.0. These 2 groupings were then compared by 1-way ANOVA across a range of baseline variables to uncover baseline characteristics that might predict response to BT. The results are presented in Table IV. These data suggested that baseline ACQ score influenced delta ACQ score, with higher baseline scores predicting greater improvement after therapy.

Therefore, the relationship between baseline ACQ score and delta ACQ score was explored graphically (Figure 1). The Pearson correlation coefficient for this relationship was $r = -0.537$ ($P < .001$). The data suggest that more severely symptomatic patients at baseline have more to gain from BT. The area under the receiver-operating curve was 0.71 (95% CI, 0.56-0.87; $P = .008$), indicating that there was a 71% chance of

TABLE III. Likelihood of response to BT in the Australian Registry

Parameter	n	6-mo response rate (%)
ACQ score improvement by ≥0.5 points	77	84.4
ACQ score at baseline ≥1.5 and improvement to <1.5	75	52.0
Exacerbations at baseline >0 and reduced by 50% after treatment	66	92.4
SABA at baseline >0 and reduced by 50% after treatment	71	80.2
Maintenance OCS at baseline and reduced by 50% after treatment	41	70.7
Maintenance OCS at baseline and reduced to 0 after treatment	41	48.8

predicting response to BT based entirely on baseline ACQ score. The cutoff point of ACQ score = 2.7 maximized the balance of sensitivity (0.682) and specificity (0.727). An alternative cutoff point of 2.5 was more sensitive (0.742) but less specific (0.545).

A linear mixed model was then established to evaluate the effect of all baseline variables on ACQ score change, over 3 time points—baseline, 6 weeks, and 6 months. The following variables were found to have no impact on ACQ score change: age, sex, BMI, smoking history, exacerbation frequency, SABA usage, OCS dose, inhaled steroid dose, biomarkers, and activations. Baseline ACQ score remained strongly significant (β coefficient, 0.51; $P < .001$), even when correcting for the potential influence of regression to the mean.¹⁶ A small but statistically significant effect was also observed from baseline FEV₁ (β coefficient, 0.01; $P < .001$). The overall variance in delta ACQ score explained by this model was 46.5%.

Frequent exacerbators

The Australian registry offered an opportunity to look at frequent exacerbators because almost 50% of patients in the Australian registry would have been excluded from the North American studies^{7,17-19} on the basis of the mean exacerbation rate of 3.7 ± 3.3 exacerbations in the previous 6 months. Therefore, the study cohort was divided into tertiles of baseline exacerbation frequency. The highest tertile of greater than 2 exacerbations in the previous 6 months represented all 37 patients who would have been excluded from the North American studies. The middle group comprised 20 patients with 2 exacerbations in the previous 6 months, whereas the lowest tertile

TABLE IV. BT responder analysis using delta ACQ score

Delta ACQ response	<1.0	1-2	>2.0	P*
n	21	33	23	—
Delta ACQ score	-0.1 ± 0.7	-1.5 ± 0.3	-3.0 ± 0.6	—
Baseline ACQ score	2.5 ± 0.8	3.2 ± 1.0	3.8 ± 0.7	<.001
ACQ score 6 mo	2.3 ± 1.1	1.7 ± 0.9	0.8 ± 0.6	<.001
Age (y)	57.0 ± 1.9	58.2 ± 12.6	53.1 ± 9.9	NS
Sex: female (%)	47.6	51.5	78.3	NS†
BMI (kg/m ²)	29.8 ± 6.7	29.6 ± 5.1	30.5 ± 8.1	NS
FEV ₁ (%predicted)	52.7 ± 18.0	51.0 ± 15.2	63.8 ± 22.7	NS
Blood eosinophils (cell/μL)	408 ± 291	292 ± 285	310 ± 265	NS
IgE (IU/mL), median (IQR)	112 (142)	144 (364)	48 (118)	NS
Inhaled steroid (μg/d)	1970 ± 698	1967 ± 887	1992 ± 864	NS
Exacerbations/6 mo	2.25 ± 2.4	3.9 ± 3.8	4.5 ± 2.9	NS
SABA (puffs/d)	6.8 ± 4.7	9.0 ± 6.7	12.1 ± 8.9	.07
Activations	214 ± 66	201 ± 51	212 ± 44	NS

IQR, Interquartile range; NS, not significant.

Values are mean ± SD unless otherwise indicated.

*Two-way ANOVA.

† χ^2 .

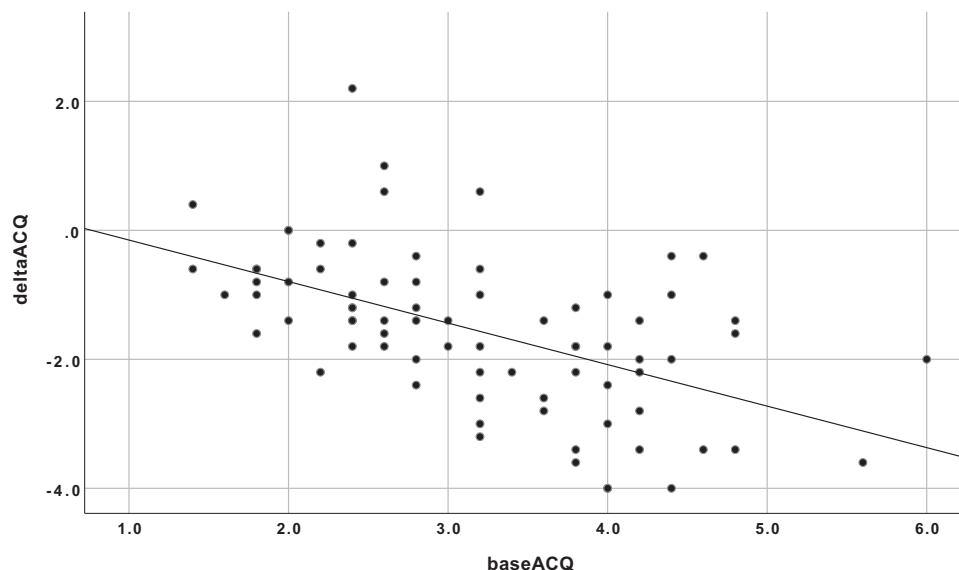


FIGURE 1. The relationship between baseline ACQ score and change in ACQ score after BT.

included patients experiencing less than 2 exacerbations ($n = 20$). The results are presented in Table V. The 3 groups were similar in age, sex, BMI, baseline FEV₁, baseline eosinophil count, and radiofrequency activations. The more frequent the baseline exacerbation rate, the higher the baseline ACQ score ($r = 0.42$; $P < .001$). All 3 patient groups improved to the same average ACQ score posttreatment. Similarly, all 3 groups improved to the same low exacerbation rate at the 6-month follow-up visit. The higher the baseline exacerbation rate, the greater the magnitude of the improvement.

SABA usage and outcomes

Consistent with more severe disease, the baseline usage of short-acting reliever medication was substantially greater in this registry than in the North American registry (Table I). We

therefore sought to evaluate patient outcomes across the spectrum of SABA usage. To achieve 3 similar tertiles, a frequency distribution of baseline SABA usage was examined, and this suggested cutoff points of fewer than 6 puffs/d and more than 10 puffs/d. These groups were similar in most baseline parameters (Table VI). The posttreatment mean ACQ score results were near identical in each group. The reduction in SABA usage after BT was significantly greater in the high SABA users.

Prediction of OCS weaning

There were 41 patients taking maintenance OCS treatment at baseline in a mean dose of 12.1 ± 7.5 mg/d. At the 6-month follow-up, in 20 patients the oral steroids had been completely ceased. The mean baseline prednisolone dose in those 20 patients was 9.5 ± 4.7 mg/d, compared with 15.1 ± 8.9 mg/d in the

TABLE V. The effect of baseline exacerbation rate on BT outcomes

Baseline exacerbation rate in 6 mo	<2.0 (low)	2 (medium)	>2.0 (high)	P*
n	20	20	37	—
Exacerbation rate/6 mo	0.6 ± 0.5	2.0 ± 0.0	6.2 ± 3.0	—
Age (y)	58.5 ± 10.3	60.4 ± 9.4	55.9 ± 12.7	NS
Sex: female (%)	55	65	57	NS†
BMI (kg/m ²)	28.9 ± 5.5	30.7 ± 7.6	29.8 ± 6.3	NS
Eosinophils (cells/μL)	306 ± 211	305 ± 298	344 ± 307	NS
Activations	223 ± 63	199 ± 55	204 ± 46	NS
ACQ score baseline	2.6 ± 0.9	3.3 ± 0.9	3.5 ± 1.0	<.005
ACQ score 6 mo	1.6 ± 1.0	1.7 ± 0.9	1.6 ± 1.2	NS
FEV ₁ baseline (%predicted)	56.5 ± 20.2	48.2 ± 15.5	59.5 ± 20.1	NS
FEV ₁ 6 mo (%predicted)	58.4 ± 20.0	54.7 ± 16.9	63.6 ± 22.5	NS
FEV ₁ delta	0.3 ± 6.8	6.5 ± 13.0	4.1 ± 16.9	NS
Exacerbations 6 mo	0.5 ± 1.4	0.5 ± 0.6	1.0 ± 1.2	NS
Exacerbations delta	−0.3 ± 1.4	−1.5 ± 0.6	−5.3 ± 2.8	<.001

NS, Not statistically significant.

*Two-way ANOVA.

† χ^2 .**TABLE VI.** Baseline SABA usage and response to BT

Baseline SABA usage (puffs/d)	<6 (low)	6-10 (medium)	>10 (high)	P*
n	23	33	21	—
SABA (puffs/d)	2.3 ± 1.7	8.2 ± 1.2	18.8 ± 5.7	—
Age (y)	60.3 ± 10.2	57.3 ± 13.0	55.4 ± 9.7	NS
Sex: female (%)	39	67	67	NS†
BMI (kg/m ²)	28.4 ± 4.6	29.2 ± 6.9	32.3 ± 6.8	NS
Oral steroids (mg/d)	3.8 ± 4.5	7.0 ± 8.2	8.6 ± 10.5	NS
ACQ baseline	2.9 ± 0.9	3.1 ± 1.0	3.7 ± 1.0	<.05
ACQ 6 mo	1.7 ± 1.1	1.5 ± 1.0	1.7 ± 1.2	NS
FEV ₁ baseline (%predicted)	54.7 ± 15.7	61.4 ± 19.9	49.5 ± 21.4	NS
FEV ₁ 6 mo (%predicted)	55.5 ± 18.4	64.1 ± 17.9	58.3 ± 25.6	NS
FEV ₁ delta	0.8 ± 9.1	2.6 ± 14.3	8.7 ± 16.8	NS
SABA 6 mo (puffs/d)	1.0 ± 2.3	3.0 ± 4.0	6.4 ± 8.9	<.01
SABA delta (puffs/d)	−1.2 ± 2.6	−5.6 ± 3.7	−12.4 ± 10.5	<.001

NS, Not statistically significant.

Values are mean ± SD unless otherwise indicated.

*Two-way ANOVA.

† χ^2 .

group in which steroids could not be ceased altogether ($P < .05$). Comparing these 2 groups across a broad range of other baseline characteristics showed no significant differences. Examined from the point of view of baseline oral prednisolone dose, patients taking less than or equal to 10 mg/d prednisolone ($n = 25$) had a 56% chance of being completely weaned from steroids. Patients taking more than 10 mg/d oral prednisolone had a mean baseline prednisolone dose of 19.3 ± 7.0 mg, a mean reduction in prednisolone by -11.6 ± 7.2 mg/d, but only a 38% chance of being completely weaned from oral steroids.

The group of 41 patients treated with maintenance OCSs at baseline was compared with the 36 steroid-naïve patients in terms of response to BT. There were no statistically significant differences between the 2 groups of patients in relation to improvement in ACQ score and FEV₁, and reduction in exacerbations and SABA usage (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Prediction of FEV₁ improvement

The relationship between the change in FEV₁ %predicted observed 6 months after BT and the baseline FEV₁ %predicted is plotted in Figure 2. It appeared that the patients whose FEV₁ improved after BT had a baseline FEV₁ of less than 60% predicted. A linear regression model was then used to evaluate the effect of all baseline variables on change in FEV₁ at 6 months. This analysis initially suggested that baseline FEV₁ had a negative effect ($\beta = -0.26$; $P < .01$) on the change in FEV₁. However, after correcting for the effect of regression to the mean, this significant relationship disappeared ($\beta = -0.02$; $P > .05$). No other baseline variables had any predictive effect on change in FEV₁.

The effect of baseline eosinophil count

BT is being increasingly used where patients are not suitable for biological therapy owing to a noneosinophilic phenotype.⁸ Therefore, a group of 38 patients was identified whose baseline

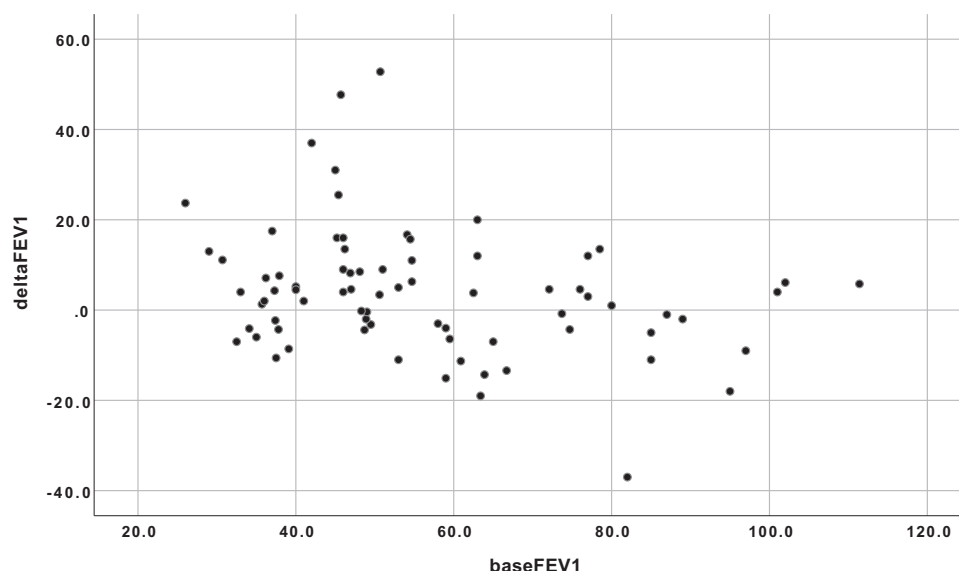


FIGURE 2. The relationship between baseline FEV₁ and change in FEV₁ after BT.

blood eosinophil count was less than 300 cells/mL, and the outcomes in this group were compared with those in 39 patients with a baseline eosinophil count of greater than or equal to 300 cells/ μ L. These results are presented in Table E2 in this article's Online Repository at www.jaci-inpractice.org. There were no significant differences in outcomes between the 2 groups. The table suggested a trend toward greater improvement in FEV₁ after BT in patients with higher baseline eosinophils, but when this was examined further, there was no significant correlation between the 2 variables ($r = 0.18$; $P = .13$).

Age older than 65 years

Patients older than 65 years were excluded from the randomized controlled trials of BT¹⁷⁻¹⁹ and the North American registry.⁷ Therefore, the outcomes in 22 patients in this study whose age was greater than 65 years were compared with those in 55 patients who were 65 years or younger. These results are presented in Table E3 in this article's Online Repository at www.jaci-inpractice.org, which shows that despite a mean age of 70.9 ± 4.3 years, outcomes in older patients measured by improvement in ACQ score, FEV₁, and exacerbation frequency were not significantly different from those in younger patients.

Other key baseline variables

Participants in this registry exhibited a range of BMI values from 19 to 51 kg/m². There was no relationship demonstrated between baseline BMI and change in ACQ score after BT ($r = 0.04$; $P = .75$), demonstrating that there is no loss of efficacy of the radiofrequency treatment in obese patients.

There were no statistically significant differences observed between the 32 males and 45 females in responses to BT measured by improvement in ACQ score, exacerbation frequency, FEV₁%predicted, reduction in oral steroid dosing, or requirement for SABA.

In relation to the effects of cigarette smoking, patients were divided into 58 never smokers and 19 ever smokers. The mean pack-year history in the ever smokers was 13.9 ± 10.4 years. The mean gas transfer per lung unit in the ever smokers was $83.5\% \pm 24.1\%$ predicted, compared with $99.9\% \pm 19.3\%$ predicted in

the never smokers ($P < .01$). There was no significant difference between the 2 groups in improvement in ACQ score after treatment (never smokers delta ACQ score = 1.5 ± 1.2 , ever smokers delta ACQ score = 1.9 ± 1.3 ; $P = .19$).

In this registry study, no relationship was observed between activations administered and treatment response measured by delta ACQ score ($r = 0.03$; $P = .8$). However, 88% of patients received radiofrequency treatment in excess of 140 activations, which has previously been suggested as a threshold necessary to achieve effect.¹⁰

The ACQ score at 6 weeks posttreatment as a success predictor

The ACQ score at 6 weeks following completion of treatment was measured in every subject. The mean value was 2.0 ± 1.2 , representing a partial improvement on baseline values but an incomplete improvement when compared with the 6-month average of 1.6 ± 1.2 ($P < .001$; partial eta squared, 0.627). The presence or absence of improvement at 6 weeks was then used to predict success or failure of treatment at the 6-month assessment. Patients who had experienced an improvement in ACQ score of 0.5 (minimal clinical significant difference) by the 6-week assessment had a 96% chance of being responders at 6 months. On the other hand, in 22 patients the ACQ score had not improved by 0.5 at the 6-week assessment, and in these patients, the probability of improvement by 6 months was 59%. Therefore, in 9 of the 11 cases (80%) who had not responded to BT treatment by 6 months, measured by ACQ, this was evident at the 6-week mark.

DISCUSSION

The patient group in this registry had more severe asthma than previously published in relation to BT. They had more severe airflow obstruction, a higher exacerbation frequency, a higher requirement for both SABA and oral steroids, and a higher symptom burden (ACQ). This is evident in Table 1 where the Australian registry data are compared with the North American data, but it is also evident when comparing this registry data with

the baseline characteristics of patients in the 3 randomized controlled trials.¹⁷⁻¹⁹ Despite this severity, or perhaps because of it, strong outcomes were observed in terms of reduction in exacerbation frequency, reduction in medication requirement (both SABA and oral steroids), and improvement in symptoms. These data show that patients who might previously have been considered too severe to undergo BT, owing to a high exacerbation frequency, or high SABA usage, or high oral steroid requirement, can expect positive improvement as a result of BT.

This analysis set out to examine factors predictive of success in BT. The consistent theme emerging is that more severe patients can expect a greater magnitude of improvement. This was particularly evident in relation to baseline ACQ score, but also was evident in frequent exacerbators and high SABA users. The receiver-operating curve data suggest that, if using the ACQ score as the sole criterion on which to make decisions regarding BT, the best separation between responders and nonresponders is achieved at an ACQ score of 2.7. This is consistent with the Asthma Intervention Research 2 trial data, which also suggested that patients with a higher baseline ACQ score had a higher chance of response to treatment.¹⁸ It is perhaps not surprising that this is so. BT targets airway smooth muscle, causing it to atrophy,^{20,21} and the airway smooth muscle layer has been shown to be more hypertrophied the more severe the asthma.²² Furthermore, when the effects of BT have been simulated in a lung model, the greatest response has been evident in the most severely affected patients with asthma.²³

It is of interest that of the 3 randomized controlled trials of BT, only 1, the Research in Severe Asthma (RISA) trial,¹⁹ showed improvement in FEV₁ after BT. The RISA trial enrolled patients with a lower baseline FEV₁% predicted (mean, 62.9 ± 12.2) compared with the Asthma Intervention Research trial (72.7% ± 10.4%)¹⁷ and Asthma Intervention Research 2 trial (77.8 ± 15.7).¹⁸ In this respect, the RISA trial population is more similar to the Australian registry data, where the baseline FEV₁ was 55.8% ± 19.8% predicted. In the Australian data, as in the RISA trial, a small improvement in FEV₁ was observed after BT. Again, this is consistent with the notion that more severely affected patients with asthma seem to do better after BT. The mechanisms that might explain this observation in relation to FEV₁ are speculative, but we have previously demonstrated that BT leads to a reduction in lung hyperinflation, and that this effect is greatest in the most obstructed patients.²⁴ The reduction in residual volume that is observed after BT suggests a reopening of previously closed small airways, and this in turn has been demonstrated in magnetic resonance imaging studies evaluating improvements in ventilation homogeneity after BT.²⁵ These effects are also consistent with the predictions made by Donovan in a mathematical model of the human asthmatic lung based on multiple histological airway sections.²³

The observation that BT is best suited to the most severe patients with asthma fits nicely with the niche that BT seems to be finding for itself in clinical practice, namely, as a treatment of last resort, when other options have already been deployed.⁸ This appears to be supported by the clinical usage of BT in this registry. The fact that patients with a low eosinophil count at baseline respond equally well to BT is reassuring for those patients not suitable for anti-IL-4/5 or anti-IL-5-receptor mAb therapy.

It is also reassuring to observe that in clinical practice, the inclusion and exclusion criteria used in the original randomized controlled trials can be widened to incorporate a larger spectrum

of the target population. The finding that (1) older patients and (2) patients with asthma with a smoking history also respond to treatment is important, because these groups might have been assumed to have more fixed airflow obstruction and potentially less response to therapy. The finding that the radiofrequency treatment is not dampened by morbid obesity is also of importance to procedural clinicians.

In this patient cohort, there was no relationship observed between radiofrequency activations administered and the response measured by improvement in ACQ score. At first glance, this might appear to contradict our previous work on this subject.⁶ However, we have deliberately embraced using a high number of activations in all our patients to maximize treatment effectiveness (eg, by using a thinner bronchoscope).²⁶ As a result, 88% of patients in this registry were treated with more than 140 activations, which we have previously estimated to be a minimum requirement to achieve a reduction in ACQ score by 0.5.⁶ This therefore dilutes the ability of this registry data to show an effect of this parameter. In fact, a peculiar limitation of the data contained in this registry is that most patients (80%-90%) responded to BT. This makes it more difficult to identify the factors contributing to nonresponse, and the detailed analysis of outcomes of other clinical registries, such as the Global BT Registry, is eagerly awaited.²⁷

CONCLUSIONS

In this registry of Australian patients undergoing BT, the greatest magnitude of improvement was observed in the most severely afflicted patients at baseline—those with the highest ACQ score, highest exacerbation frequency, or highest usage of SABA.

Acknowledgments

We thank Peninsula Health and Monash University for supporting this research work. We particularly thank our nursing and laboratory staff for their dedicated support in patient assessments.

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ONLINE REPOSITORY

TABLE E1. Response to BT in steroid-requiring vs steroid-naïve patients

Parameter	Steroid-naïve	Steroid maintenance	P
n	36	41	
Oral steroid dose (mg/d)	0 ± 0	12.1 ± 7.5	—
Age (y)	58.7 ± 18.9	54.5 ± 20.2	NS
Sex: female (%)	61.1	56.1	NS
BMI (kg/m ²)	29.1 ± 6.2	30.5 ± 6.6	NS
Baseline ACQ score	2.9 ± 0.8	3.4 ± 1.1	<.05
FEV ₁ (%predicted)	58.7 ± 18.9	54.5 ± 20.2	NS
SABA (puffs/d)	8.5 ± 7.2	10.2 ± 6.9	NS
Exacerbations/6 mo	3.2 ± 2.9	4.2 ± 3.5	NS
Delta ACQ score	−1.4 ± 1.3	−1.7 ± 1.1	NS
Delta FEV ₁	4.5 ± 14.5	3.2 ± 13.7	NS
Delta SABA (puffs/d)	−5.7 ± 7.5	−6.3 ± 7.5	NS
Delta exacerbations/6 mo	−2.5 ± 8.4	−3.5 ± 3.2	NS

NS, Not statistically significant.

Values are mean ± SD unless otherwise indicated.

TABLE E2. The effect of baseline blood eosinophils on BT outcomes

Parameter	Eosinophils ≥300 cells/μL	Eosinophils <300 cells/μL	P
n	39	38	
Blood eosinophils (cell/ mL)	540 ± 220	100 ± 80	—
Age (y)	56.0 ± 12.0	59.4 ± 10.6	NS
Sex: female (%)	48.7	68.4	.08
BMI (kg/m ²)	29.1 ± 5.9	30.6 ± 6.8	NS
Baseline ACQ score	3.1 ± 1.0	3.3 ± 1.0	NS
FEV ₁ (%predicted)	55.6 ± 18.4	56.0 ± 21.3	NS
SABA (puffs/d)	9.4 ± 6.1	9.2 ± 8.1	NS
Exacerbations/6 mo	3.8 ± 3.6	3.5 ± 3.0	NS
Oral steroid dose (mg/d)	7.0 ± 9.1	5.8 ± 7.1	NS
Delta ACQ score	−1.5 ± 1.3	−1.7 ± 1.1	NS
Delta FEV ₁	+6.6 ± 15.2	0.9 ± 12.2	.07
Delta PNL (mg/d)	−4.7 ± 6.8	−2.1 ± 6.5	NS
Delta exacerbations/6 mo	−3.1 ± 3.6	−2.8 ± 2.8	NS

NS, Not statistically significant; PNL, prednisolone.

Values are mean ± SD unless otherwise indicated.

TABLE E3. Outcomes in older patients after BT

Parameter	Age ≤ 65 y	Age > 65 y	P
n	55	22	
Age (y)	52.4 ± 8.7	70.9 ± 4.3	—
Sex: female (%)	58	59	NS
BMI (kg/m ²)	29.8 ± 6.6	29.9 ± 6.0	NS
Activations	212 ± 56	196 ± 45	NS
ACQ score baseline	3.3 ± 1.1	2.9 ± 0.7	<.05
ACQ score 6 mo	1.7 ± 1.2	1.5 ± 0.9	NS
ACQ score delta	−1.6±1.3	−1.4±1.1	NS
Exacerbation baseline (per 6 mo)	4.2 ± 3.5	2.4 ± 2.2	<.05
Exacerbation 6 mo (per 6 mo)	0.9 ± 1.2	0.4 ± 0.9	NS
FEV ₁ baseline (%predicted)	58.2 ± 21.1	49.8 ± 14.5	.051
FEV ₁ 6 mo (% predicted)	62.6 ± 22.1	53.7 ± 15.1	.050
FEV ₁ delta	3.8 ± 15.5	3.9 ± 9.8	NS

NS, Not statistically significant.

Values are mean ± SD unless otherwise indicated.