

Bronchial thermoplasty in severe asthma in Australia

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Key words

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Abstract

Background: Bronchial thermoplasty (BT) is an approved bronchoscopic intervention for the treatment of severe asthma. However, limited published experience exists outside of clinical trials regarding patient selection and outcomes achieved.

Aims: To evaluate the effectiveness and safety of BT in patients with severe asthma encountered in clinical practice.

Methods: This is a retrospective analysis of the first 'real world' data from Australia. The following outcomes were measured prior to, and 6 months following BT: spirometry, Asthma Control Questionnaire-5 (ACQ-5) score, reliever and preventer medication use and exacerbation history.

Results: Twenty patients were treated from June 2014 to December 2015 at three university teaching hospitals. All subjects met the European Respiratory Society/American Thoracic Society definition of severe asthma. Mean pre-bronchodilator forced expiratory volume in 1 s was $62.8 \pm 16.6\%$ predicted (range: 33–95%). All patients were being treated with high dose inhaled corticosteroids, long-acting beta₂ agonists and long-acting muscarinic antagonists. Ten patients (50%) were taking maintenance oral prednisolone. Most subjects also required at least one of montelukast (65%), omalizumab (30%) and methotrexate (20%). ACQ-5 improved from 3.6 ± 1.1 at baseline to 1.6 ± 1.2 at 6 months, $P < 0.001$. Short-acting reliever use decreased from a median of 8.0–0.25 puffs/day, $P < 0.001$, and exacerbations requiring corticosteroids also significantly reduced. Five of 10 patients completely discontinued maintenance oral corticosteroids. Ten patients with a baseline forced expiratory volume in 1 s of $<60\%$ predicted significantly improved from $49.2 \pm 9.6\%$ to $61.8 \pm 17.6\%$, $P < 0.05$. Only two procedures required hospitalisation beyond the planned overnight admission.

Conclusion: BT is a safe procedure which can achieve clinical improvement in those with uncontrolled symptoms and severe airflow obstruction.

Introduction

Severe asthma can be defined using European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines.¹ It is present in patients confirmed to have asthma and taking high doses of inhaled corticosteroids and a second controller, such as a long-acting beta₂ agonist, and yet still being poorly controlled defined by one of four criteria being present, namely: (i) poor symptom control; (ii) frequent severe exacerbations requiring oral corticosteroids; (iii) at least one hospitalisation in the

previous year; or (iv) pre-bronchodilator forced expiratory volume in 1 s (FEV₁) $<80\%$ predicted. Bronchial thermoplasty (BT) is a new bronchoscopic intervention which can be used in the management of patients with severe asthma.

One of the histological hallmarks of asthma is airway smooth muscle (ASM) hypertrophy, which causes bronchoconstriction.^{2,3} BT involves the delivery of radio-frequency energy to distal airways of 3–10 mm in diameter, by a catheter electrode inserted through a flexible bronchoscope.⁴ The thermal energy generated causes ASM atrophy without damaging the superficial mucosa. This has been demonstrated in preclinical studies, and confirmed histologically in human airways.^{5–7} Canine studies have shown a sustained decrease in airway responsiveness to methacholine,⁸ in addition to improved airway dimensions after treatment.⁹ Given

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that ASM receives neural innervation, BT may also lead to functional denervation,¹⁰ with early research finding decreased amounts of nerve products on biopsy.¹¹ Finally, the inflammatory pathway has also been implicated, whereby bronchoalveolar lavage post-BT contains decreased inflammatory mediators, including TGF β 1.¹²

Three randomised controlled trials have examined the treatment effects of BT. Both the AIR¹³ and AIR2¹⁴ studies included participants with pre-bronchodilator FEV₁ of $\geq 60\%$ predicted, and demonstrated improved symptom control, quality of life scores and reduced exacerbations. However, in the AIR2 trial there was a large placebo effect, with improvement in 64% of patients treated with the sham procedure, and this weakened the magnitude of the treatment effect in the intervention arm. The RISA trial demonstrated significant improvements in rescue medication use, quality of life scores, and pre-bronchodilator FEV₁ in a small cohort of 15 patients with FEV₁ of $\geq 50\%$ predicted.¹⁵ Other than an expected increase in asthma symptoms during the immediate recovery period post-BT, no long-term adverse events or deaths have been reported. In all three trials, follow up of 5 years has been reported in the intervention arm, and has demonstrated sustained low symptom scores, infrequent exacerbations and stable lung function.^{16–18} However, no comparative follow-up data were reported in the placebo arm beyond 12 months.

Clinical trial data, however, is not the same as ‘real world’ data and the objective of this report is to evaluate how this new therapy is being used in actual clinical practice in Australia, what outcomes are being achieved in terms of improvement to quality of life, lung function and medication requirement, and what adverse effects are being observed as a result of the procedure.

Methods

Study subjects

The hospital medical records of consecutive patients undergoing BT between June 2014 and December 2015 at three Australian centres were reviewed retrospectively. No patients were excluded from analysis. All three hospitals were university teaching hospitals, two publicly funded and one not-for-profit private hospital. These hospitals were the first centres in each of the three Eastern Australian States to offer BT. Each subject had been selected for treatment at the individual discretion of the proceduralist/author. All patients were under the care of a respiratory physician prior to referral to the proceduralist.

The baseline characteristics of the patients were collated, including age, gender, body mass index, medication usage, exacerbation history, spirometry, and the disease specific quality of life tool, the Asthma Control Questionnaire score (ACQ-5).¹⁹ The ACQ-5 was chosen as it was collected routinely at all sites. It is an established evaluation tool in asthma that is sensitive to change, and practical to use.²⁰ The following outcomes were sought from the records at follow-up assessments: ACQ-5 score, reliever and preventer medication use, exacerbation history and spirometric parameters. Follow-up assessments were conducted at two time points after the final BT procedure, namely: (i) early follow up at 6–10 weeks (the timing varied between sites); and (ii) 6 months post-BT. For the purposes of analysis, the primary outcome measures were pre-specified as: (i) change in ACQ-5; and (ii) change in FEV₁ from baseline to the 6-month post-treatment assessment.

Spirometry was conducted in accredited respiratory laboratories by trained scientists, according to ERS/ATS standards.²¹ The predicted equations used at all sites were ERS 1993 Quanjer.²²

Procedure

BT was performed by experienced bronchoscopists, trained in using the Alair Bronchial Thermoplasty System (Boston Scientific, Mascot, NSW, Australia), using the Olympus BF Q190 bronchoscope (Olympus Australia, Melbourne, Vic., Australia) and conducted according to the published technique.⁴ All bronchoscopies were performed under general anaesthesia, with an anaesthetist present. Consistent with the standard protocol, each patient was treated in three sessions, at 3–4 weeks apart. The right lower lobe was treated first, followed by the left lower lobe, and then both upper lobes during the final bronchoscopy. By convention, the right middle lobe was not treated. The number of radiofrequency actuations delivered was recorded for each patient. Prednisolone was prescribed for three days prior, and continued for three days post-procedure. All patients were electively admitted to hospital overnight immediately following the procedure.

Analysis

SPSS version 24 (IBM corporation, New York, NY, USA) was used for all statistical analyses. All analyses include all 20 subjects unless otherwise stated. Normally distributed grouped data are reported as mean \pm standard deviation whilst median (interquartile (IQR) range) is used for non-normally distributed data. A paired *t*-test

was used to compare baseline and 6-month measurements of ACQ-5 and FEV₁, while a Wilcoxon signed-rank test was used for data relating to salbutamol puffs, exacerbation frequency and prednisolone usage. Statistical significance was taken at $P < 0.05$ for a two-tailed test. Subgroup analyses were exploratory and data driven. The association between change (6 months – baseline) in either ACQ-5 or FEV₁ and the corresponding baseline value was examined using correlation (Pearson) and univariate linear regression. We adjusted the change values for the influence of regression to the mean using the statistical approach outlined by Kelly and Price.²³ An adverse event was recorded for any patient requiring readmission to hospital for any cause from the time of the first BT treatment to the post-treatment 6-month assessment, or for any patient requiring admission beyond the planned hospital stay post each treatment.

Ethical considerations

Approval to collate and audit data as part of quality assurance was provided at each institution (Peninsula Health, Macquarie University, Royal Brisbane and Women's Hospital). Each participant was assigned a unique study-specific identifier number, so that no individually identifiable data were disclosed. Specific permission to use the ACQ-5 in this project was sought from its author, Elizabeth Juniper.

Results

Baseline characteristics

Twenty patients, 13 females and 7 males, completed treatment and 6 months follow up. A mean of 203 ± 53 total activations per patient (range: 121–305) were delivered. The mean age was 53.0 ± 11.6 years (range: 27–69 years.) The mean body mass index was 27.8 ± 6.2 (range: 22.0–46.9, $n = 19$). Eighteen patients were never-smokers, two were ex-smokers with ≤ 10 pack years. The mean FEV₁ was $62.8 \pm 16.6\%$ predicted

(range: 33–95%). Ten (50%) cases had FEV₁ of $< 60\%$ predicted, and four cases FEV₁ $< 50\%$ predicted. The forced expiratory ratio was $64.1 \pm 11.7\%$. The mean change in baseline FEV₁ after administration of salbutamol was $14.5 \pm 13.6\%$ (range: 0–46.7%). Mean IgE level was 148.1 ± 143.9 kU/L, and mean eosinophil count was $0.4 \pm 0.4 \times 10^9/L$.

All subjects were understood by their treating respiratory physician to be adherent to high doses of inhaled corticosteroids, mean beclomethasone equivalent dose of 2215 ± 395 mcg daily (range: 2000–3000 mcg). Ten patients (50%) required maintenance oral prednisolone, median dose 10 mg per day (IQR 7.4–15 mg). All patients (100%) were taking long-acting beta₂ agonists and long-acting muscarinic antagonists. Additional preventative therapy included leukotriene receptor antagonists (65%), omalizumab (30%) and methotrexate (20%).

Despite this treatment, symptom control was poor. Patients used a median of 8.0 salbutamol puffs daily for reliever therapy (IQR 4–14). The mean ACQ-5 score was 3.5 ± 1.1 (range: 1.4–5.6), where a value of < 0.75 indicates well-controlled asthma. In the 12 months prior to treatment, there was a median 4.5 exacerbations requiring prednisolone per patient (IQR 2.25–8.0), and a median of two hospital admissions per patient (range: 0–20).

Every patient met the ERS/ATS definition for severe asthma by fulfilling at least one of four criteria.¹ Specifically, 19 (95%) cases had ACQ-5 scores > 1.5 ; 19 (95%) cases had ≥ 2 prednisolone courses in the previous year; 18 (90%) cases demonstrated a baseline pre-bronchodilator FEV₁ $< 80\%$ predicted and 13 (65%) cases had been hospitalised for asthma at least once in the previous year.

Primary outcomes

Quality of life

The ACQ-5 improved from 3.5 ± 1.1 at baseline to 1.6 ± 1.2 at 6 months, $P < 0.001$ (Table 1). Seventeen (85%) cases achieved an improvement in ACQ-5 greater than the minimal clinically significant difference of ≥ 0.5 units.¹⁹ Whereas only 1 patient had an ACQ-5 of < 1.5 prior to treatment, 12 (60%) achieved this at 6 months after treatment.

In order to assess the timeframe of improvement in ACQ-5, the baseline results were compared to the early results (6–10 weeks) and then the 6-month results. Using analysis of variance, the overall effect was statistically significant, $P < 0.001$. *Post hoc* comparison of baseline with 6–10 weeks was statistically significant (Bonferroni correction), $P < 0.001$, whilst there was no significant further change thereafter.

Table 1 Summary of results

Outcome	Baseline	6 months post	<i>P</i> value
ACQ-5 score	3.5 ± 1.1	1.6 ± 1.2	< 0.001
FEV ₁ % predicted	62.8 ± 16.6	68.1 ± 17.4	NS
Exacerbations/6 months	2.25 (2.85)	0.0 (1.75)	< 0.001
OCS dose (mg) $n = 10$	10.0 (7.6)	1.5 (5.6)	< 0.005
Salbutamol puffs/day	8.0 (10.0)	0.25 (2.0)	< 0.001

Mean \pm SD, median (IQR). ACQ-5, Asthma Control Questionnaire score; FEV₁, forced expiratory volume in 1 s; IQR, interquartile; NS, not significant; OCS, oral corticosteroid dose; SD, standard deviation.

Using raw values, a negative correlation was demonstrated between change in ACQ-5 and baseline ACQ-5 ($r = -0.696$). However, when the Kelly correction was applied to change in ACQ-5, there was no longer evidence of an association – the estimated correlation coefficient was small ($r = -0.046$) and not statistically significant. This suggests that BT is equally effective across the range of baseline ACQ-5 values from 1.4 to 5.6.

Spirometry

Overall, mean FEV₁ did not significantly change after treatment (Table 1). However, patients were divided into two equal subgroups based on their baseline pre-bronchodilator FEV₁, in order to compare the treatment response between the more and less severely impaired patients. The two groups consisted of those with an FEV₁ $\geq 60\%$ predicted, similar to the AIR trials,^{13,14} 10 cases, mean FEV₁ $76.3 \pm 9.0\%$ (range: 63.8–95%), and those with more severe obstruction with an FEV₁ $< 60\%$, 10 cases, mean FEV₁ $49.2 \pm 9.6\%$ (range: 33–58.3%). The results of these comparisons are shown in Table 2. Subjects with a low FEV₁ demonstrated statistically significant improvement in FEV₁ post-BT, whereas this was not observed in the group with better baseline lung function, $P < 0.05$. However, both groups showed similar significant improvement in ACQ-5.

At baseline, nine patients had reversibility in FEV₁ of $\geq 15\%$ following inhaled bronchodilator, whilst 10 patients had $< 15\%$ reversibility. Results were unavailable for one case. Whilst there was a marked difference in baseline reversibility between the two groups ($25.3 \pm 11.9\%$ vs $4.7 \pm 4.4\%$), both groups showed statistically significant improvements in ACQ-5 following

Table 2 Comparison of FEV₁ subgroups

Subgroup	Baseline FEV ₁ %	6 months FEV ₁ %	Baseline ACQ-5	6 months ACQ-5
FEV ₁ $< 60\%$, $n = 10$	49.2 ± 9.6	$61.8 \pm 17.6^*$	3.2 ± 1.0	$1.3 \pm 0.9^{**}$
FEV ₁ $\geq 60\%$, $n = 10$	76.3 ± 9.0	74.5 ± 15.4	3.8 ± 1.1	$1.9 \pm 1.5^{**}$

* $P < 0.05$. ** $P < 0.001$. ACQ-5, Asthma Control Questionnaire score; FEV₁, forced expiratory volume in 1 s.

Table 3 Baseline bronchodilator responsiveness as a predictor of outcome

Subgroup	Δ FEV ₁ post-BD	Baseline ACQ-5	6 months ACQ-5
BD response $< 15\%$	4.7 ± 4.4	3.7 ± 1.1	$1.4 \pm 1.3^*$
BD response $\geq 15\%$	25.3 ± 11.9	3.2 ± 1.4	$1.8 \pm 1.2^*$

* $P < 0.05$. ACQ-5, Asthma Control Questionnaire score; FEV₁, forced expiratory volume in 1 s; BD, bronchodilator; Δ , change.

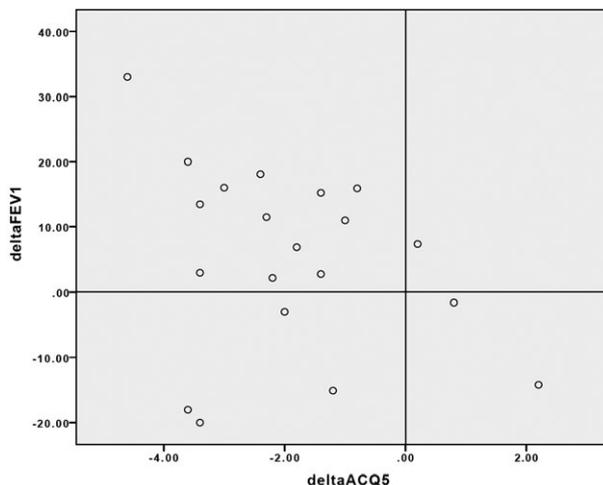


Figure 1 Relationship between change in ACQ-5 and change in FEV₁ % predicted after bronchial thermoplasty. ACQ-5, Asthma Control Questionnaire score; FEV₁, forced expiratory volume in 1 s.

treatment (Table 3). This suggests that the presence of bronchodilator responsiveness at baseline need not be a selection criterion for BT.

The relationship between change in ACQ-5 and change in FEV₁ is presented in Figure 1. Thirteen (65%) cases showed improvement after BT in both ACQ-5 and FEV₁.

Secondary outcomes

Rescue medication

Daily reliever salbutamol usage, in 16 subjects where paired data were available, improved from a median of 8.0 puffs per day (IQR 4–14) at baseline to 0.25 puffs per day (IQR 0–2) at 6 months post-BT, $P < 0.001$ (Table 1). Eight patients (50%) no longer required any daily rescue medication.

Exacerbations

In the 12 months prior to treatment, every patient had at least one exacerbation requiring oral corticosteroids, and the median annual rate was 4.5 per patient. For statistical comparison, the exacerbation rate per patient in the 12 months prior to treatment was halved to reflect a time period equal to the 6 months of follow-up post-treatment, thus becoming 2.25 exacerbations per patient per 6 months. During the 6 months follow-up period, 11 patients (55%) had not experienced any exacerbations at all, and the median group exacerbation rate was 0 exacerbations per patient (IQR 0.0–1.75), $P < 0.001$.

Oral corticosteroids

Ten patients were prednisolone dependent at baseline with a median daily dose of 10 mg per day (IQR 7.4–15 mg). At 6 months follow up, 5 patients had ceased prednisolone altogether, and the median daily dose for the group of 10 patients decreased to 1.5 mg per day (IQR 0–5.6 mg), $P < 0.005$. Every patient was on less prednisolone than at baseline. None of the other 10 patients had needed to commence oral corticosteroids in the interim.

Adverse events

There were no deaths, and no cases of pneumothorax, pneumonia, bronchiectasis, invasive ventilation or cardiac arrhythmia in this series of 60 procedures. Only one case required hospitalisation beyond the planned admission. This patient had a baseline FEV₁ of 82% predicted, was prednisolone dependent (minimum dose 10 mg), and taking methotrexate. Following her second treatment, she was monitored in the intensive care unit for an exacerbation of asthma, without assisted ventilation being required. After the third procedure, she again had an extended admission, this time requiring non-invasive ventilation in intensive care unit, before safe discharge back home. Her ACQ-5 decreased from 4.8 at baseline to 1.4 at 6 months. Her prednisolone dose at the 6-month assessment was 2 mg – reported to be the lowest dose in 20 years.

Discussion

This case series provides insight into the application of BT in real world clinical practice. The patients being selected for this therapy were highly symptomatic, requiring very frequent use of reliever medication, despite very high doses of inhaled corticosteroids and two long-acting bronchodilators. Half the patients required maintenance oral corticosteroid therapy and many were also taking third-line medications, such as montelukast, omalizumab, methotrexate and azathioprine. Despite this extensive treatment, exacerbations remained frequent and lung function remained obstructed. The implication is that BT is being offered to patients as an end of the line rescue therapy, other options having been already exhausted. It is reassuring to observe that BT is not being offered to GINA stage 1–4 asthmatics where more conventional therapy would be more appropriate.

This degree of severity would have excluded most of these patients from BT treatment based on existing guidelines. For example, 65% of our patients experienced >3 oral corticosteroid-requiring exacerbations in the previous 12 months, which was an exclusion

criterion in the AIR2 trial.¹⁴ Furthermore, an FEV₁ < 60% predicted excluded participation in the AIR¹³ and AIR2¹⁴ trials, and this represented 50% of our cohort. To our knowledge, this is the largest group of patients of this severity to be evaluated for and treated with BT.

Despite the severity of disease, BT was well tolerated and safe in these cases. Adverse events were minimal, and the incidence of infections was not increased in those on long-term prednisolone or other immunosuppression. Out of a total of 60 bronchoscopies, only 2 (3.3%) were associated with prolonged admissions, within the same patient. This adverse event rate is similar to the AIR2 trial's serious adverse event rate of 3.1%.¹⁴

Significant improvement in several important clinical parameters has been demonstrated in this series, showing BT to be an effective rescue therapy with valuable benefits for this group of end-stage patients. The mean ACQ reduction of -1.9 ± 1.7 , or four times the minimally significant clinical difference of 0.5, compares favourably to the improvement in ACQ-5 observed in clinical trials (-1.2 ± 1.0 in AIR, -0.82 ± 0.95 in AIR2 and -1.04 ± 1.03 in RISA).^{13–15} Consistent with the marked improvement in ACQ-5, a dramatic reduction in the requirement for daily reliever medication occurred, with 50% of subjects requiring no relievers at all at follow up. In the 6 months post-procedure, the asthma exacerbation rate markedly diminished, as did the prednisolone requirement in steroid-dependent patients, with 5 of 10 such patients ceasing completely. This result is very similar to the RISA trial, where four of eight patients post-BT discontinued maintenance oral corticosteroids.¹⁴

This case series demonstrates that equally positive outcomes are obtainable in patients with a baseline FEV₁ less than the usually accepted lower limit for treatment of 60% predicted pre-bronchodilator. With a mean FEV₁ of $49.2 \pm 9.6\%$ predicted, the FEV₁ < 60% predicted subgroup has the lowest published baseline FEV₁ ever to receive BT, yet significant improvements in FEV₁ were observed in these patients. Furthermore, the improvement in ACQ-5 in this group was equivalent to those with a preserved FEV₁. This argues against the view that patients with more severe airflow obstruction could have fixed, irreversible airflow obstruction unresponsive to BT. This concept is further supported by the observation that the degree of baseline bronchodilator responsiveness did not appear to influence the outcome of BT in this study.

It must be acknowledged that this is a retrospective uncontrolled case series. Its value lies in demonstrating the types of patients being selected for BT, and the outcomes that can be achieved in the real clinical world. At this stage, only 6 months post-treatment follow-up data

are available, but as these patients complete longer periods of observation and assessment, further data will be reported. The subgroup analyses must be regarded as exploratory and will require verification when larger patient cohorts, such as international registries, are examined. The positioning of BT as a therapy for severe asthma is still under scrutiny and may well be altered with the arrival of a new wave of biological agents directed at the interleukin pathway.

Conclusion

This study demonstrates use of BT in the real clinical world as a rescue therapy for patients at the most severe end of the disease spectrum, who are poorly controlled despite maximisation of other available treatments. In this group of patients, BT can be delivered not only safely, but also effectively, with demonstrable improvements in clinical outcomes.

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