

# A Case Series of Patients Undergoing Bronchial Thermoplasty a Second Time for Severe Asthma

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**Abstract:** Bronchial thermoplasty is a treatment option for patients with severe asthma. We report a case series of 6 patients who underwent bronchial thermoplasty on two separate occasions for poorly controlled asthma. The repeat procedures were well tolerated with no unexpected complications. One patient developed a focal area of mild bronchiectasis on imaging 6-months after repeat treatment, but this was not felt to be clinically relevant. Individual responses to repeat bronchial thermoplasty were varied, with some patients showing great improvement after treatment, whereas others did not. This series highlights the safety and feasibility of performing repeat ablation on previously ablated airways, as well as the potential clinical benefit in a select group of patients.

**Keywords:** Asthma, mechanism of action, pathophysiology, treatment failure

## Introduction

Asthma is a common disease characterized pathologically by the increased thickness of the airway smooth muscle layer (ASM). ASM plays a crucial role in bronchoconstriction, and correlates with worsening asthma severity.<sup>1</sup>

Bronchial thermoplasty (BT) is a treatment option for severe asthma and has been shown to improve clinical outcomes for at least 10 years.<sup>2,3</sup> BT utilizes radiofrequency ablation to shrink the ASM, reducing airway hyperresponsiveness<sup>4-6</sup> and the response to bronchodilators,<sup>7-9</sup> with histological changes shown to persist for up to 2.5 years<sup>10</sup> and perhaps even longer.<sup>11</sup>

About 20–40% of the patients fail to respond to BT, although the mechanism remains unknown.<sup>2,8,12-14</sup> Given that the ASM is the primary target of BT, one possible explanation is that BT failed to reduce the ASM. Mathematical modelling and a small number of studies suggest a causal relationship between the degree of ASM ablation and clinical improvements.<sup>12,15,16</sup> If this is true, there might be a potential role for re-treatment in patients who fail to respond to BT.

To our knowledge, there are no reports of repeat BT in the published literature. In this series, we document our initial experience of 6 patients with severe asthma who underwent repeat BT. We highlight the safety and feasibility of repeat BT, and describe three different outcomes using the following 3 cases (from the 6 listed in Tables 1 and 2). Repeat BT was approved by the Peninsula Health Human Research Ethics Committee and included permission to publish the cases. All patients have provided written informed consent for their data to be published.

## Cases

### Case N2

A 62-year-old male had poorly controlled atopic asthma despite being treated with fluticasone propionate/formoterol 250/10 mcg 2 puffs twice daily, ciclesonide 160 mcg 2 puffs daily, glycopyrronium 50mcg daily, prednisolone 10 mg daily, and omalizumab. Pre BT, Asthma Control Questionnaire (ACQ) was 2.6, with an average reliever use of 5 nebulized salbutamol (5 mg)/day, and 12 exacerbations in the last 12 months. Forced expiratory volume in 1 second (FEV1) was 46% predicted, with a 75% bronchodilator response (BDR). BT was undertaken with 238 activations and resulted in a significant reduction in

**Table 1** Demographic and Clinical Characteristics for Patients N1-3 at Baseline, After Initial BT and After Repeat BT

<b>Patient N1</b> 50y female Atopic	<b>Initial BT</b> (183 activations)								<b>Repeat BT</b> (200 activations)	
Interval (months)	Baseline	6	12	24	36	42 <sup>‡</sup>	48 <sup>§</sup>	54 <sup>¶</sup>	Baseline	12
ACQ	2.4	1.8	0.4	0.4	1	2.8	0.6	2.8	3.4	1
OCS (mg/day)	0	0	0	0	0	0	0	0	0	0
SABA (puff/day)	12	2–4	2–4	2–4	2–4	8–10	2–4	6–8	4–8	<1
Exacerbations*	6	1	1	2	2	3	2	3	8	2
FEV1%	87	86	88	86	61	–	90	45	102	95
FeNO	10	11	11	<5	11	–	17	5	8	10
Medications <sup>†</sup>	Budesonide/formoterol 400/12 mcg 2 puffs twice daily, ciclesonide 160 mcg 2 puffs daily, grass-pollen immunotherapy									
<b>Patient N2</b> 62y male Atopic	<b>Initial BT</b> (238 activations)							<b>Repeat BT</b> (363 activations)		
Interval (months)	Baseline	6	12	24	36	48**		Baseline	12	
ACQ	2.6	2	2	2	2.4	2.4		2.4	1.8	
OCS (mg/day)	10	5	5	5	5	5		5	5	
SABA (nebulizer/day)	4–5	2–3	2–3	2–3	2–3	4–5		4–6	2–3	
Exacerbations*	12	1	2	4	6	8		12	3	
FEV1%	46	46	47	29	42	–		32	67	
FeNO	18	20	18	20	22	–		28	10	
Medications <sup>†</sup>	Fluticasone propionate/formoterol 250/10 mcg 2 puffs twice daily, ciclesonide 160 mcg 2 puffs daily, glycopyrronium 50mcg daily, prednisolone 10mg daily, omalizumab									
<b>Patient N3</b> 31y female Eosinophilic	<b>Initial BT</b> (198 activations)					<b>Repeat BT</b> (230 activations)				
Interval (months)	Baseline	6 <sup>#</sup>	12	18	24**	Baseline	12			
ACQ	2.2	1.6	1.6	3	2.6	2.4	1.2			
OCS (mg/day)	12.5	10	5	5	5	5	5			
SABA (puff/day)	12	8	8	8	12	16	8			
Exacerbations*	2	0	0	2	2	5	0			
FEV1%	49	44	–	–	48	50	75			
FeNO	79	107	–	–	70	62	123			
Medications <sup>†</sup>	Budesonide/formoterol 200/6 mcg 2 puffs twice daily, ciclesonide 160 mcg 1 puff twice daily, tiotropium 2.5mcg 2 puffs daily, prednisolone 12.5mg daily, theophylline 200mg daily, mepolizumab									

**Notes:** \*Number of OCS-requiring exacerbations in the preceding 12 months for baseline assessments, and between timepoints for interval assessments. <sup>†</sup>Medications at time of initial BT. Depending on the assessment timepoint, mepolizumab, benralizumab, and dupilumab may not have been available for use in Australia. <sup>‡</sup>Omalizumab commenced. <sup>§</sup>Underwent Nissen fundoplication for reflux disease. <sup>¶</sup>Omalizumab switched to dupilumab, inhalers changed to fluticasone furoate/umeclidinium/vilanterol 200/62.5/25 mcg. <sup>#</sup>Mepolizumab ceased due to patient preference. <sup>\*\*</sup>Patient declined the offer to switch biologic therapy and instead requested for repeat BT as BT had been the most impactful treatment in his/her asthma history.

**Abbreviations:** ACQ, Asthma Control Questionnaire; BT, bronchial thermoplasty; FEV1%, forced expiratory volume in 1 second; OCS, oral corticosteroids; SABA, short acting  $\beta$ -agonist.

**Table 2** Demographic and Clinical Characteristics for Patients N4-6 at Baseline, After Initial BT and After Repeat BT

<b>Patient N4</b> 50y female Atopic	<b>Initial BT</b> (152 activations)					<b>Repeat BT</b> (170 activations)	
Interval (months)	Baseline	6	12	24 <sup>‡</sup>	48	Baseline	12
ACQ	2.4	4.6	3.8	3.4	2.4	2.6	2.3
OCS (mg/day)	0	0	0	10	7.5	7.5	10
SABA (puff/day)	4	0	7	6	4	4	2
Exacerbations*	5	2	2	12	5	5	1
FEV1%	64	50	51	–	55	57	61
FeNO	–	–	–	–	–	19	24
Medications <sup>†</sup>	Budesonide/formoterol 200/6 mcg 2 puffs twice daily, omalizumab						
<b>Patient N5</b> 37y male Eosinophilic	<b>Initial BT</b> (117 activations)			<b>Repeat BT</b> (180 activations)			
Interval (months)	Baseline	6	12	Baseline	12		
ACQ	6	4.2	4.2	4.2	3.8		
OCS (mg/day)	50	37.5	25	50	23		
SABA (puff/day)	16+	16+	16+	16+	16+		
Exacerbations*	20	6	6	6	4		
FEV1%	34	30	32	23	37		
FeNO	–	–	–	25	27		
Medications <sup>†</sup>	Furoate/vilanterol 200/25 mcg daily, umeclidinium 62.5mcg daily, ciclesonide 160 mcg 2 puffs twice daily, prednisolone 50mg daily, mepolizumab.						
<b>Patient N6</b> 38y female Atopic	<b>Initial BT</b> (190 activations)				<b>Repeat BT</b> (220 activations)		
Interval (months)	Baseline	6	12	24 <sup>§</sup>	Baseline	12	
ACQ	4.4	2.4	4	4.2	4.2	4.2	
OCS (mg/day)	10	10	10	10	10	10	
SABA (puff/day)	14–16	6–8	14	14–16	16–20	16	
Exacerbations*	6	1	2	6	6	8	
FEV1%	63	44	57	68	58	53	
FeNO	–	–	–	–	15	16	
Medications <sup>†</sup>	Fluticasone propionate/salmeterol 250/25 mcg two puffs twice daily, tiotropium 2.5mcg two puffs daily, prednisolone 10mg daily and omalizumab						

**Notes:** \*Refers to the number of OCS-requiring exacerbations in the preceding 12 months for baseline assessments, and between timepoints for interval assessments.

<sup>†</sup>Medications at time of initial BT. Depending on the assessment timepoint, mepolizumab, benralizumab, and dupilumab may not have been available for use in Australia.

<sup>‡</sup>Omalizumab switched to benralizumab after re-endotyping. <sup>§</sup>Omalizumab changed to mepolizumab after re-endotyping; fluticasone propionate/salmeterol changed to fluticasone furoate/vilanterol 200/25 mcg twice daily.

**Abbreviations:** ACQ, Asthma Control Questionnaire; BT, bronchial thermoplasty; FEV1%, forced expiratory volume in 1 second; OCS, oral corticosteroids; SABA, short acting  $\beta$ -agonist.

ACQ (defined as a  $\geq 0.5$  point reduction<sup>17</sup>), exacerbation frequency, and a 50% decrease in maintenance oral corticosteroid (OCS). FEV1 fluctuated over time, with ongoing large BDR. Three years later, the patient reported increasing asthma symptoms and more frequent exacerbations. Re-endotyping showed no change and the patient requested for repeat BT as he felt it had the greatest impact on his asthma control in his entire asthma history. Assessments before repeat BT showed an ACQ of 2.4, with an average reliever use of 6 nebulized salbutamol (5 mg) a day, and 12 exacerbations in the last 12 months. FEV1 was 32% predicted with a 166% BDR. Repeat BT was performed with 363 activations and resulted in a substantial decrease in exacerbation frequency and reliever use, as well as significant improvements in ACQ and FEV1 at 12-month follow-up. A summary of his clinical course can be found in [Table 1](#).

## Case N5

A 37-year-old male with eosinophilic asthma remained highly symptomatic despite receiving treatment with fluticasone furoate/vilanterol 200/25 mcg daily, umeclidinium 62.5 mcg daily, ciclesonide 160 mcg 2 puffs twice daily, prednisolone 50 mg daily, and mepolizumab. Prior to BT, he had an ACQ of 6, average reliever >16 puffs/day, 20 exacerbations in the last 12 months, and FEV1 34% predicted with no BDR. BT was performed with 117 activations. Although improvements in ACQ, maintenance OCS, and exacerbation frequency were observed, the patient continued to be highly symptomatic with an ACQ of 4.2, maintenance prednisolone of 25 mg, and an average of 1 exacerbation per month at 12-month follow-up. Six months later, the FEV1 had fallen to 23.4% predicted and prednisolone was at 50 mg daily. Due to the ongoing high symptom burden, excessive prednisolone requirement, and low number of activations during the initial BT, the patient underwent repeat BT with 180 activations. Follow-up 12-months post showed a non-significant reduction in ACQ from 4.2 to 3.8, with accompanying decreases in exacerbations, maintenance prednisolone, and an improvement in FEV1. A summary of his clinical course can be found in [Table 2](#).

## Case N6

A 38-year-old female with severe atopic asthma was being treated with fluticasone propionate/salmeterol 250/25 mcg two puffs twice daily, tiotropium 2.5mcg two puffs daily, prednisolone 10 mg daily, and omalizumab. Despite this, the patient was highly symptomatic with an ACQ of 4.4, average reliever 14–16 puffs/day, and 6 exacerbations in the preceding 12 months. FEV1 was 63.4% predicted with 27% BDR. BT was undertaken with 190 activations. This led to a 6–12-month improvement in asthma control (reduced ACQ, reliever use, and exacerbation frequency), which gradually worsened by 24-months. This prompted a change in the patient medications — fluticasone propionate/salmeterol was replaced with fluticasone furoate/vilanterol 200/25 mcg twice daily, and omalizumab was switched to mepolizumab (after re-endotyping). Nonetheless, the patient suffered from ongoing poor asthma control over the next 12 months with an ACQ of 4.2, an average reliever of 16–20 puffs/day, and 6 exacerbations in the intervening period. FEV1 was 57.7% predicted with 12.4% BDR. Repeat BT was undertaken with 220 activations. No change in asthma control was observed at 12-months. A summary of her clinical course can be found in [Table 2](#).

## Discussion

This is the first series describing repeat BT in patients with severe asthma, and highlights the safety and feasibility of performing further ablation on previously ablated airways. We also describe positive outcomes in a subset of patients who have regressed after initial treatment.

All patients in this series were non-smokers and had a diagnosis of severe asthma as defined by the European Respiratory Society/American Thoracic Society,<sup>18</sup> and underwent BT as part of their clinical care. All patients were severely affected by their disease, as evidenced by high symptoms burden, frequent exacerbations, and persistent lung function impairment despite being on GINA step 4–5 treatment, with 4 out of 6 patients requiring maintenance OCS.

After the initial BT, each patient experienced a different degree of improvement, but ultimately, all of them deteriorated albeit at varying timepoints. Individual response following repeat BT was also highly variable, with patients N1-3 clearly deriving benefit, while improvements were marginal (N4,5) or absent in the others (N6).

The reasons for these observations remain unclear. Low tissue activations may have contributed to treatment failure, eg in patient N5 whom only had 117 activations on initial BT. This is much lower than the 140 activations recommended

in one study,<sup>19</sup> and less than the 151 activations (average) in the AIR2 trial.<sup>2</sup> Given repeat BT with 180 activations only resulted in a marginal improvement, low tissue activations may not be the sole reason for his treatment failure.

Another explanation is that in standard BT, airways are treated at 65°C, the temperature shown to be the most effective in reducing ASM whilst minimizing collateral damage.<sup>20</sup>

Subsequent real-world data showed an approximately 50% reduction in ASM in patients post BT, a finding that correlates with clinical outcomes.<sup>10</sup> Whether this magnitude of reduction is sufficient to elicit a beneficial response in patients with a thicker ASM remains unclear. Additionally, impaired reduction in ASM has been found in some patients after routine BT, raising the possibility of ASM resistance to thermal ablation, and the need for higher temperatures to achieve successful ablation.<sup>12,16</sup> In addition to shrinking the ASM, BT has also been shown to cause sloughing of the airway epithelium on optical coherence tomography immediately after treatment.<sup>21</sup> This recovers by 6-weeks, with evidence of increased epithelial integrity on histological biopsies at 3 months.<sup>22</sup> Concerns over airway wall scarring have not been substantiated,<sup>23</sup> and was not observed in any of our patients on serial chest computed tomography (CT).

Given that the ASM plays a crucial role in bronchoconstriction, it follows that a reduction in ASM post BT should accompany a decrease in bronchial reactivity. This, however, has not been consistently demonstrated in clinical studies. For example, the response to methacholine was mitigated by BT in,<sup>4-6</sup> but not in.<sup>8,24</sup> Similarly, the response to bronchodilator therapy after BT was reduced in,<sup>7-9</sup> but unaffected in.<sup>12,13,25</sup> In this case series, individual bronchodilator responsiveness was not observed to decrease after initial or repeat BT.

The role of the airway epithelium must also be considered. Epithelial damage from external insults (viruses, allergens, pollutants, BT etc.) stimulates the release of epithelial cytokines such as thymic stromal lymphopoietin, interleukin (IL)-33 and IL-25. These cytokines trigger a downstream inflammatory cascade that is abnormally perpetuated in asthmatics, ultimately leading to epithelial dysfunction, mucus hypersecretion and plugging, ASM hypertrophy and hyperplasia, and airway hyperresponsiveness (collectively known as airway remodelling).<sup>26,27</sup> While none of our six patients showed evidence of mucus hypersecretion or plugging on serial chest CT, ASM regrowth from persistent airway inflammation and remodelling may explain the clinical trajectory in patients N1-N3 ie regrowth of the ASM after initial BT (treatment failure), and its successful re-ablation during repeat BT (restoration of asthma control). This phenomenon has previously been described in a single case report.<sup>28</sup>

The downregulation of the airway inflammatory cascade has recently been associated with clinical improvements post BT.<sup>29</sup> In a small study involving 23 patients with severe asthma, BT responders, defined as those with <3 exacerbations in the 12 months post BT, were found to display a significantly different immunological profile than partial responders. In brief, responders had a higher incidence of atopy, blood eosinophilia, and serum IgE levels at baseline compared to partial responders. Twelve months post BT, blood eosinophil and IgE levels were exclusively reduced in responders, and associated with significant improvements in asthma control and quality of life. Importantly, 93% of the responders had previously failed to improve with omalizumab, suggesting a role for BT in this group of patients. Interestingly, both responders and partial responders had similar reductions in ASM, highlighting the impact of BT in attenuating the T2-high response. Of note, several other studies have also found significant correlations between patients with a T2-high endotype and clinical improvements post BT.<sup>8,30</sup>

All patients in this series had a T2-high endotype and were receiving asthma biologics throughout their initial and repeat BT with the exception of patients N1 and N3 (Patient N1 commenced asthma biologic 42 months after initial BT and was switched 12 months later; Patient N3 was receiving treatment with an asthma biologic prior to initial BT but ceased 6-months later due to lack of perceived efficacy). Despite this, all patients had poorly controlled asthma and a variable response to BT. Whether BT was successful in reducing the T2-high response in these patients remains uncertain.

Given the lack of airway biopsies and immune-profiling, these mechanisms remain speculative and require confirmation in future studies. Moreover, it is likely that a combination of factors, including some yet to be identified, are ultimately involved in determining treatment response/failure in BT.

All repeat BT procedures were generally well tolerated, with no unexpected periprocedural complications. Additionally, no major CT abnormalities were identified on serial scans taken before initial and repeat BT, and 6-months after repeat BT. Although patient N2 developed a localized area of mild bronchiectasis after repeat BT, this was not felt to be clinically relevant, as similar findings have been reported after standard BT.<sup>3</sup>

## Conclusion

In conclusion, we present the first series describing the use of repeat BT in severe asthma, highlighting the safety and feasibility of such an approach, as well as the potential clinical benefit in a select group of patients. Further studies are needed to elucidate the mechanism of treatment response/failure and long-term safety of this approach.

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