



Plethysmography-derived gas trapping lacks utility in predicting response to bronchial thermoplasty

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Shareable abstract (@ERSpublications)

This study examined whether measuring gas trapping by plethysmography could be used to predict response to bronchial thermoplasty; no association was found <https://bit.ly/3tJN1X8>

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Abstract

There is a paucity of literature on measurable baseline parameters predicting response and guiding selection for bronchial thermoplasty. This study examines whether baseline gas trapping, as assessed by plethysmography, is associated with a response to bronchial thermoplasty at 12 months.

43 consecutive patients with severe asthma (mean±sd age 57.6±13.3 years) were evaluated at baseline and 12 months post bronchial thermoplasty. Data collected at both time points included spirometry, body plethysmography and four clinical outcome measures, namely Asthma Control Questionnaire (ACQ) score, annual exacerbation frequency, maintenance oral corticosteroid requirement and short-acting β-agonist use.

At baseline, participants had severe airflow obstruction (forced expiratory volume in 1 s 49.1±15.8%) with marked gas trapping (residual volume (RV) 150.3±40.8%, RV/total lung capacity (TLC) 51.3±10.5%), poor symptom control (ACQ 3.3±1.0) and frequent exacerbations (median 4, interquartile range 8). 12 months after bronchial thermoplasty, significant improvements were observed in all four clinical outcome measures. However, baseline RV and RV/TLC were not significantly associated with changes in ACQ nor any other clinical outcome measure, and changes in RV and RV/TLC did not significantly correlate with a change in any clinical outcome measure.

Plethysmography-derived gas trapping does not demonstrate utility in predicting response and guiding selection for bronchial thermoplasty. An improvement in gas trapping was not associated with positive clinical outcomes, suggesting that this may not be the dominant mode of action of bronchial thermoplasty in generating clinical improvement.

Introduction

Bronchial thermoplasty is a bronchoscopic treatment modality for severe asthma (defined by the Global Initiative for Asthma as those patients whose symptoms are uncontrolled and require step 5 of controller treatment [1]). Bronchial thermoplasty involves the use of radiofrequency ablation delivered to bronchial smooth muscle, and this has been shown to increase airway cross-sectional lumen and reduce wall thickness [2–4].

While bronchial thermoplasty has been shown to be effective in groups of patients, the individual responses are variable. A proportion of patients fail to respond to bronchial thermoplasty, and there is a scarcity of literature on measurable baseline parameters predicting response and guiding selection for bronchial thermoplasty [5–7]. This poses challenges for the role of this treatment modality in the era of personalised medicine. Previous studies have demonstrated that more severe asthmatics have a better response, but baseline bronchodilator responsiveness and airway smooth muscle (ASM) mass have been shown not to be predictive of response [8, 9].



The pathophysiological mechanisms behind the success of bronchial thermoplasty are being increasingly elucidated. Previous studies have observed improvements in downstream airway calibre and gas trapping after treatment of proximal airways [10–12]. These smaller airways make a major contribution to the large cross-sectional area of the lung, but only represent 10% of the total resistance. This makes quantification of response by spirometry difficult [10]. While a number of studies have shown improvements in quality of life, exacerbations and symptoms with bronchial thermoplasty, the majority have not shown significant improvements in spirometry [13–15]. In contrast, measures of small airway function have shown improvements after the procedure. These include functional imaging modalities such as quantitative computed tomography (CT) and hyperpolarised magnetic resonance imaging (MRI), which have shown increases in distal airway volume and ventilation homogeneity [2–4, 12, 16, 17]. Similarly, physiological measures such as impulse oscillometry, inert gas washout and body plethysmography have also been shown to respond to bronchial thermoplasty [11, 18, 19]. In particular, there has been demonstrable improvements in plethysmography-derived residual volume (RV) as a measure of gas trapping in a number of studies [13, 19]. Gas trapping is a well-recognised feature in severe asthma, as in other obstructive airways diseases, and has adverse physiological effects on ventilation/perfusion (V'/Q') matching by increasing physiological dead space [20]. In addition, hyperinflation reduces pulmonary compliance and places the diaphragm at a mechanical disadvantage, resulting in an increased work of breathing [21]. In COPD, the greater the degree of gas trapping, the more responsive the patient is to interventional therapies such as lung volume reduction [22, 23]. Therefore, we wondered whether response to bronchial thermoplasty might be linked to the degree of gas trapping at baseline.

Plethysmography is a widely available, noninvasive, quick and cost-effective means of quantifying gas trapping. This study aims to evaluate whether baseline gas trapping, as determined by plethysmography, is predictive of response to bronchial thermoplasty at 12 months.

Methods

Participants

43 consecutive patients were prospectively recruited from a single Australian university teaching hospital, between October 2015 and January 2020. Patients were referred for bronchial thermoplasty by their treating respiratory physician if they were assessed to have uncontrolled symptoms despite treatment with high-dose inhaled corticosteroids, two long-acting bronchodilators, and if eligible, monoclonal antibody therapy. Participants were required to meet the definition of severe asthma in accordance with European Respiratory Society (ERS)/American Thoracic Society (ATS) criteria [24].

Assessments

Measurements at baseline and 12 months post bronchial thermoplasty were undertaken by experienced clinical research nurses. Data collection included age, gender, body mass index, smoking history and the five-item Asthma Control Questionnaire (ACQ) score [25], as well as exacerbation frequency (defined by the requirement for oral corticosteroids (OCS)), and medication usage including daily short-acting β_2 -agonist (SABA) frequency, inhaled corticosteroid dose and maintenance daily OCS requirement. For the purposes of categorising patients into responders and nonresponders, two outcome variables were used independently: 1) improvement in ACQ by the accepted minimal clinically significant difference of 0.5 units; and 2) improvement by $\geq 50\%$ in OCS-requiring exacerbation frequency [26].

Lung function testing, including spirometry and body plethysmography, was performed according to ERS/ATS standards in an accredited respiratory laboratory by experienced scientific staff [27–31]. Instruments were calibrated immediately before testing, and tests were completed in the morning prior to the administration of bronchodilators. Three reproducible repetitions of forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC) were performed. Static lung volumes were performed with functional residual capacity measurements within 5% of each other. Diffusing capacity of the lung for carbon monoxide corrected for alveolar volume (K_{CO}) was measured using the single-breath method. The predicted equations used were drawn from the Global Lung Initiative (2012 for spirometry and 2017 for diffusing capacity) and European Coal and Steel Community (1993) for all other measurements [32–34].

Procedure

Bronchial thermoplasty was performed by experienced bronchoscopists using the Alair Bronchial Thermoplasty System (Boston Scientific, NSW, Australia) and using the Olympus BF-P190 bronchoscope (Olympus Medical Systems, Tokyo, Japan). The technique used aligned with published methods [35]. The procedure was performed in three sessions 3–4 weeks apart, targeting each lower lobe then bilateral upper lobes. The right middle lobe was not treated.

Analysis

Stata BE (StataCorp, College Station, TX, USA) was used for all statistical analyses. Baseline characteristics are reported as mean \pm SD or median (interquartile range) for nonparametric data. In regards to group response to treatment, a paired t-test and Wilcoxon signed-rank test were used to determine significant changes in parametric and nonparametric parameters, respectively. Pearson's correlation coefficient was calculated to evaluate the association between bivariate, continuous, normally distributed data. Statistical significance was defined as $p < 0.05$ for a two-tailed test.

Ethics

This study was prospectively approved by the Peninsula Health human research ethics committee under the banner of clinical audit. Patients were enrolled only after informed consent had been obtained.

Results

Baseline characteristics

The baseline characteristics of the 43 patients studied are presented in table 1. This was a group of severe asthmatic patients with very marked airflow obstruction (FEV₁ 49.1 \pm 15.8% predicted), high ACQ scores (3.3 \pm 1.0) and frequent exacerbations (a median of four OCS-requiring exacerbations in the previous 12 months). Many patients (62.7%) were taking maintenance OCS, despite high-dose inhaled corticosteroids, long-acting β_2 -agonists (100%) and long-acting muscarinic agonists (100%). 29 (67.4%) patients were being treated with a monoclonal antibody prior to bronchial thermoplasty (n=7 omalizumab, n=19 mepolizumab/benralizumab, n=2 dupilumab, n=1 tezepelumab). These treatments were commenced >12 months prior to bronchial thermoplasty and were continued during the 12 months following bronchial thermoplasty. Exposure to tobacco was generally low (58% patients were never-smokers, 42% were ex-smokers, no current smokers). The mean \pm SD K_{CO} was 94.0 \pm 23.3% pred. The obstructed spirometry was accompanied by marked gas trapping as evidenced by the high residual volume (RV) (150.3 \pm 40.8% pred) and the elevated RV/total lung capacity (TLC) ratio of 51.3 \pm 10.5%.

Outcomes of treatment

Patients responded to bronchial thermoplasty with significant and substantive improvements in clinical outcomes 12 months post procedure, namely ACQ, annual exacerbation frequency and requirement for medication including both maintenance prednisolone and SABA (table 2). If the accepted minimal

TABLE 1 Baseline characteristics of participants

Participants	43
Age (years)	57.6 \pm 13.3
Female (%)	48.8
BMI (kg·m ⁻²)	31.3 \pm 7.3
Smoking (pack-years)	6.8 \pm 11.6
SABA (puffs·day ⁻¹)	10 (14)
LABA (%)	100
LAMA (%)	100
Inhaled steroid (beclomethasone μ g·day ⁻¹)	1730 \pm 941
Daily oral steroid (%)	62.7
Prednisolone dose (mg·day ⁻¹)	7 (15)
Monoclonal antibodies (%)	67.4
Exacerbations (per annum)	4 (8)
ACQ	3.3 \pm 1.0
Pre-bronchodilator FEV ₁ (% predicted)	49.1 \pm 15.8
Forced expiratory ratio (%)	50.4 \pm 11.3
Bronchodilator response FEV ₁ (%)	15.1 \pm 14.5
RV (% predicted)	150.3 \pm 40.8
TLC (% predicted)	104.7 \pm 17.4
RV/TLC (%)	51.3 \pm 10.5
K_{CO} (% predicted)	94.0 \pm 23.3
Blood eosinophil count (cells· μ L ⁻¹)	190 \pm 210
Serum IgE (IU·mL ⁻¹)	588 \pm 2324

Data are presented as n, mean \pm SD or median (interquartile range), unless otherwise stated. BMI: body mass index; SABA: short-acting β -agonist; LABA: long-acting β -agonist; LAMA: long-acting muscarinic antagonist; ACQ: Asthma Control Questionnaire; FEV₁: forced expiratory volume in 1 s; RV: residual volume; TLC: total lung capacity; K_{CO} : diffusing capacity of the lung for carbon monoxide corrected for alveolar volume.

TABLE 2 Response to bronchial thermoplasty at 12 months post procedure

	Baseline	12 months post bronchial thermoplasty	p-value
Symptom score (ACQ)	3.3±1.0	2.0±1.3	0.001
SABA (puffs·day ⁻¹)	10 (14)	2 (6)	0.001
Prednisolone dose (mg·day ⁻¹)	7 (15)	0 (10)	0.001
Exacerbations (per annum)	4 (8)	1 (3)	0.001
FEV ₁ (L)	1.43±0.63	1.51±0.70	0.140
FEV ₁ (% pred)	49.1±15.8	52.7±18.1	0.035
Vital capacity (L)	2.91±0.94	3.01±1.00	0.078
TLC (L)	6.01±1.43	5.95±1.42	0.338
TLC (% pred)	104.7±17.4	103.9±20.6	0.567
RV (L)	3.09±0.95	2.93±0.94	0.026
RV (% pred)	150.3±40.8	141.8±46.0	0.023
RV/TLC (%)	51.3±10.5	49.3±10.8	0.009

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. Bold type represents statistical significance. n=43. ACQ: Asthma Control Questionnaire; SABA: short-acting β-agonist; FEV₁: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume.

clinically significant difference in ACQ of 0.5 is used to classify response, 27 (63%) out of 43 patients would be classified as responders to treatment. The magnitude of the improvement in ACQ score was -1.3 ± 1.3 , or more than twice the minimal clinically important difference, and similar in magnitude to improvements seen in randomised controlled trials of monoclonal antibodies for asthma [36–39]. A reduction in OCS-requiring asthma exacerbations was observed in 75% of patients. Out of 27 patients using daily maintenance prednisolone at baseline, 37% had been completely weaned from oral steroids at 12 months post bronchial thermoplasty.

In relation to lung function, there was a small improvement in FEV₁ of $3.6\pm 10.7\%$ pred in raw terms at 12 months ($p=0.035$). Neither FVC nor TLC were altered by bronchial thermoplasty, but significant improvements were observed in measures of gas trapping (RV, RV%, RV/TLC).

The effect of gas trapping at baseline

The impact of baseline gas trapping on the response to treatment was assessed by plotting the baseline RV % pred against the change in ACQ 12 months after bronchial thermoplasty (figure 1a). A significant relationship was not identified ($r = -0.18$, $p=0.24$). This exercise was then repeated using the RV/TLC ratio on the x-axis (figure 1b), and again no significant relationship was evident ($r=0.09$, $p=0.55$). Furthermore, there were no significant relationships identified between baseline gas trapping measures and other outcome measures such as change in SABA use, daily OCS requirement and annual exacerbation frequency (table 3).

Relationship between change in gas trapping and outcome measures

Potential correlations were explored between the change in gas trapping measures 12 months after bronchial thermoplasty, with the change in clinical outcomes such as ACQ, SABA, OCS and exacerbation frequency. No significant correlations existed. However, as would be expected, change in RV% pred correlated with change in FEV% pred ($r = -0.33$, $p=0.03$), and so did change in RV/TLC ratio ($r = -0.53$, $p=0.003$).

Responder analysis

The study population was then divided into two cohorts based on the change in ACQ at 12 months post treatment, namely nonresponders with ACQ change <0.5 ($n=16$), and responders with an ACQ change ≥ 0.5 ($n=27$). The baseline characteristics of these two groups are compared in table 4. The table demonstrates that a clinician could not rely on any lung function parameter to predict or choose which patients would respond to bronchial thermoplasty.

This analysis was then repeated dividing the cohorts into responders and nonresponders based on a 50% reduction in OCS-requiring exacerbations in the year following bronchial thermoplasty compared to the year prior to bronchial thermoplasty. These results are shown in table 5. Again, we failed to identify baseline characteristics predictive of response.

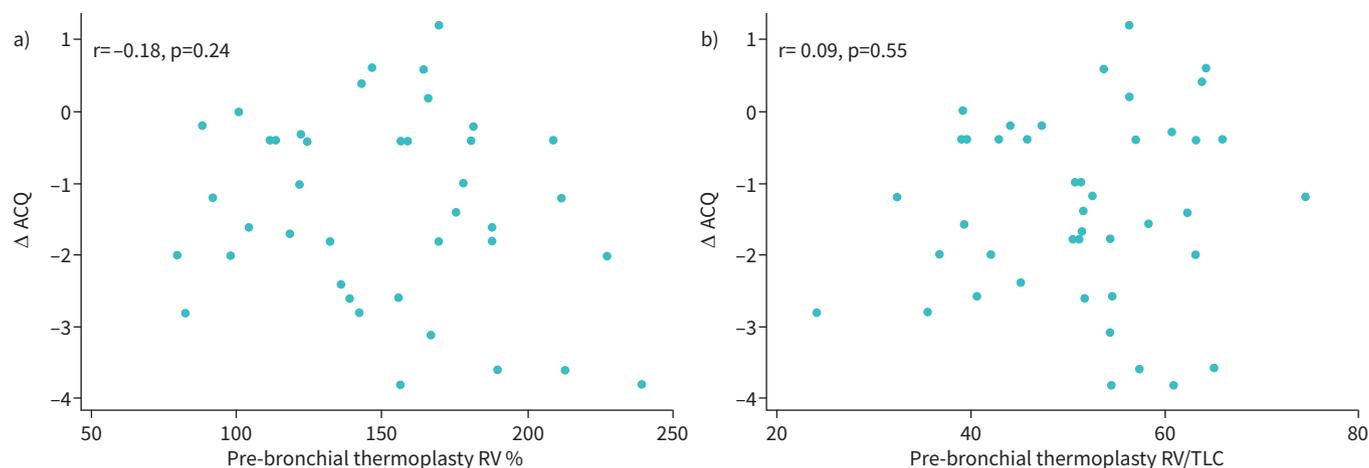


FIGURE 1 Baseline gas trapping versus change in Asthma Control Questionnaire (Δ ACQ). RV: residual volume; TLC: total lung capacity.

Discussion

The patients in this registry had severe asthma and demonstrated marked gas trapping at baseline. In line with previous studies, there was a group response to treatment across all outcome measures. There was also a small improvement in physiological measures of gas trapping following bronchial thermoplasty. Yet, despite this, measures of gas trapping were unhelpful in guiding selection for bronchial thermoplasty. Baseline gas trapping was not able to predict those patients who would respond to bronchial thermoplasty by way of four key clinical outcome measures (ACQ, annual exacerbation frequency, maintenance OCS requirement and SABA use). Nor was an improvement in plethysmography-derived gas trapping after bronchial thermoplasty associated with positive clinical outcomes.

How does this information help us in understanding the pathophysiological mechanisms whereby bronchial thermoplasty achieves a therapeutic effect? It is helpful to draw comparisons with lung volume reduction in COPD. Patients with COPD also commonly demonstrate significant baseline gas trapping [40]. Surgical and endoscopic techniques exist to reduce the degree of baseline gas trapping, either by removing or by deflating portions of the lung [41–43]. The greater the degree of baseline gas trapping, the higher the likelihood of success with these interventions [22, 23]. The greater the degree of improvement in gas trapping after treatment, the greater the improvement in clinical outcomes [23]. In contrast, in this study we observe that despite substantive improvements in clinical outcomes after bronchial thermoplasty, the improvements in gas trapping are modest and do not correlate with the clinical outcomes. Therefore, the conclusion must be that the improvement in gas trapping observed after bronchial thermoplasty is not the dominant mode of action in generating clinical improvement.

MRI studies demonstrate that bronchial thermoplasty leads to improvement in regional ventilation within the lung, and CT studies have demonstrated that bronchial thermoplasty leads to dilatation of narrowed asthmatic airways, particularly the small airways [2, 3, 16, 17]. Both sets of observations would be associated with a reduction in gas trapping. Hence, the data presented in this study would argue that these mechanisms may not play as important a part in clinical improvement after bronchial thermoplasty as first thought. Instead, one would have to conclude that the dominant effect of bronchial thermoplasty resided

TABLE 3 Correlation between baseline gas trapping and bronchial thermoplasty outcome (12 months)

	Pearson correlation coefficient			
	RV (%)	p-value	RV/TLC	p-value
Δ ACQ	-0.18	0.24	0.09	0.55
Δ SABA ($\text{puffs}\cdot\text{day}^{-1}$)	-0.05	0.73	0.14	0.37
Δ Prednisolone dose ($\text{mg}\cdot\text{day}^{-1}$)	0.006	0.97	0.04	0.79
Δ Exacerbations (per annum)	0.09	0.56	0.14	0.39

n=43. RV: residual volume; TLC: total lung capacity; Δ : change; ACQ: Asthma Control Questionnaire score; SABA: short-acting β -agonist.

TABLE 4 Baseline comparisons: nonresponders *versus* responders using change in Asthma Control Questionnaire score (Δ ACQ)

	Nonresponders (Δ ACQ <0.5)	Responders (Δ ACQ \geq 0.5)	p-value
Patients	16	27	
ΔACQ at 12 months	-0.03 \pm 0.5	-2.2 \pm 0.9	
Baseline characteristics			
Age (years)	56.4 \pm 13.2	57.3 \pm 13.6	0.872
Male/female	8/8	14/13	0.910
BMI (kg·m ⁻²)	30.2 \pm 7.5	32.4 \pm 7.5	0.22
Smoking history (pack-years)	0 (0)	1 (14)	0.040
ACQ	3.1 \pm 0.8	3.5 \pm 1.0	0.199
SABA (puffs·day ⁻¹)	8.5 (14)	10 (13)	0.604
Prednisolone dose (mg·day ⁻¹)	8.8 (15)	5 (15)	0.476
Exacerbations (per annum)	4 (7)	4 (7)	0.395
FEV ₁ (% pred)	47.2 \pm 10.9	50.3 \pm 18.1	0.534
TLC (% pred)	100 \pm 13	107 \pm 20	0.200
RV (% pred)	146 \pm 33	153 \pm 45	0.601
RV/TLC (%)	53 \pm 10	51 \pm 11	0.571

Data are presented as n, mean \pm SD or median (interquartile range), unless otherwise stated. BMI: body mass index; SABA: short-acting β -agonist; FEV₁: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume.

with the airways themselves and at the site of treatment rather than being a downstream effect. That is to say, the major action of bronchial thermoplasty must be a direct effect on the treated ASM, causing a direct improvement in airway calibre, as well as a reduced capacity to constrict when stimulated. This latter phenomenon would nicely explain why bronchial thermoplasty so reliably reduces asthma exacerbations, as seen in this study. This has been elegantly predicted by DONOVAN *et al.* [10] in a mathematical model of the effect of bronchial thermoplasty on the lung. If the major effect of bronchial thermoplasty is exerted directly on the ASM, then it is plausible that the difference between responders and nonresponders lies in differences in ASM characteristics between patients. This might, for example, include differences in the thickness of this layer and hence susceptibility to radiofrequency treatment. Optical coherence tomography, deployed down the bronchoscope, offers a potential method of evaluating ASM thickness *in vivo* and may potentially solve the riddle of nonresponse in bronchial thermoplasty [44].

TABLE 5 Baseline comparisons: nonresponders *versus* responders using change (Δ) in annual exacerbation frequency

	Nonresponders (Δ Exacerbations <50%)	Responders (Δ Exacerbations \geq 50%)	p-value
Patients	10	30	
ΔExacerbations at 12 months	-1 (2)	-4 (5)	
Baseline characteristics			
Age (years)	51.2 \pm 16.4	59.0 \pm 12.2	0.120
Male/female	3/7	16/14	0.200
BMI (kg·m ⁻²)	30.9 \pm 8.4	31.7 \pm 7.4	0.778
Smoking history (pack-years)	0 (4)	0 (10)	0.406
ACQ	3.6 \pm 0.9	3.4 \pm 1.0	0.499
SABA (puffs·day ⁻¹)	10.5 (16.5)	9 (14)	0.288
Prednisolone dose (mg·day ⁻¹)	17.5 (25)	5 (10)	0.143
Exacerbations (per annum)	5 (8)	4 (6)	0.623
FEV ₁ (% pred)	52.9 \pm 10.8	48.3 \pm 17.7	0.440
TLC (% pred)	98.7 \pm 15.2	105 \pm 18	0.331
RV (% pred)	135 \pm 35	152 \pm 43	0.261
RV/TLC (%)	48 \pm 10	52 \pm 11	0.230

Data are presented as n, mean \pm SD or median (interquartile range), unless otherwise stated. BMI: body mass index; ACQ: Asthma Control Questionnaire; SABA: short-acting β -agonist; FEV₁: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume.

The study method used here was of an observational cohort, which is a valid tool for evaluating potential exposure (gas trapping) and effect (clinical response) over time. However, it must be noted that the outcome assessments were not blinded, and that there was no control arm to describe patient improvement in the absence of bronchial thermoplasty. Nevertheless, the assessment of gas trapping using body plethysmography in this study did not provide useful additional information that would assist a clinician to choose the best candidates for bronchial thermoplasty. From a mechanistic point of view, this suggests that the downstream effects of bronchial thermoplasty on lung ventilation may be less important than previously thought, and that the more important effects may be the direct effects on the airways themselves.

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Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request.

Author contributions: A. Rajan performed all statistical calculations, managed the database and wrote the manuscript. K. Bennetts performed all lung function measurements. D. Langton designed the study, recruited all patients, performed all bronchial thermoplasty procedures and assisted with manuscript preparation.

Conflict of interest: None declared.

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