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Original article

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Bronchial thermoplasty guided by hyperpolarized gas MRI in adults with severe asthma: A one-year pilot randomized trial

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Take home message: In adults with severe asthma, MRI-guided BT reduced the number of radiofrequency activations and bronchoscopy sessions, and resulted in asthma quality-of-life and control improvements at 12-months that were non-inferior to standard whole-lung BT.

ABSTRACT

Patient-specific localization of ventilation defects using hyperpolarized gas magnetic resonance imaging (MRI) introduces the possibility of regionally targeted bronchial thermoplasty (BT) for the treatment of severe asthma. We aimed to demonstrate that BT guided by MRI to ventilation defects reduces the number of radiofrequency activations while resulting in improved asthma quality-of-life and control scores that are non-inferior to standard BT.

In a one-year, pilot randomized-controlled trial, 14 patients with severe asthma who were clinically eligible to receive BT, underwent hyperpolarized gas MRI to characterize ventilation defects and were randomized to MRI-guided or standard BT. Endpoints were improved Asthma Quality-of-Life Questionnaire (AQLQ) and Asthma Control Questionnaire (ACQ) scores, the proportion of AQLQ and ACQ responders and the number of radiofrequency activations and bronchoscopy sessions.

Participants who underwent MRI-guided BT received 53% fewer radiofrequency activations compared to those who had standard BT (p=0.003). At 12-months, the mean improvement from baseline was similar in both groups for AQLQ score (MRI-guided n=5, 1.8 [95% CI, 0.1 to 3.5], p=0.04; standard n=7, 0.7 [95% CI, -0.9 to 2.3], p=0.30) (p=0.25) and ACQ-5 score (MRI-guided n=5, -1.4 [95% CI, -2.6 to -0.2], p=0.03; standard n=7, -0.7 [95% CI, -1.3 to 0.0], p=0.04) (p=0.17). A similar proportion of participants in both groups achieved a clinically relevant improvement in AQLQ (MRI-guided, 80%; standard, 71%) and ACQ-5 scores (MRI-guided, 80%; standard, 57%).

Hyperpolarized gas MRI-guided BT reduced the number of radiofrequency activations, and resulted in asthma quality-of-life and control improvements at 12-months that were non-inferior to standard BT.

Key words: severe asthma, bronchial thermoplasty, magnetic resonance imaging, ventilation defects

INTRODUCTION

Variable airway narrowing and airflow obstruction due to airway smooth muscle (ASM) dysfunction are diagnostic features of asthma that contribute to symptoms and disease severity. Bronchial thermoplasty (BT) has been developed as a non-pharmacological procedure that is aimed at targeting the ASM component of asthma [1]. Histological studies confirm that local intraluminal delivery of radiofrequency energy to the walls of airways that are accessible by a bronchoscope results in reduced ASM mass [2-5]. BT of all accessible airways, performed over three bronchoscopy sessions, elicits a prolonged clinical benefit that has been confirmed in clinical trials [6-11] and real-world studies [11, 12]. Despite safety and efficacy profiles [6-11] sustained for 10 years or more [13], guidelines do not recommend BT and its clinical uptake has been slow mainly because it remains difficult to predict those patients who will respond to BT, the procedure requires endoscopy time and costs [14, 15] and involves risk of worsening asthma and other adverse events. Strategies that reduce the number of BT activations and bronchoscopy sessions, may help to curb some of these limitations.

In asthma, airway abnormalities are patient-specific, heterogeneously distributed, and tend to persist and reoccur in the same location over time [16]. Hence, it is possible that conventional BT may be treating airways that do not contribute to patient symptoms or disease severity. Patient-specific localization of focal airway abnormalities introduces the possibility of regionally targeted BT, which has the advantage of avoiding treatment of normal airways.

Focal ventilation defects visualized using hyperpolarized gas magnetic resonance imaging (MRI) have been shown to be the functional consequence of luminal narrowing [17] and obstruction by mucus and eosinophils [18, 19]. Related to the pathophysiology of ASM dysfunction, MRI ventilation defects respond in the anticipated direction following bronchoconstriction [20-22] and bronchodilation [20, 23]. They are also correlated with disease severity [24], and are predictive of asthma exacerbations [25] and control [26].

We and others [19, 27] postulated that by treating only those focal airway abnormalities that exhibit abnormal MRI ventilation, BT could be optimized. Pilot results of MRI-guided BT showed that after 3-months, there was no difference in Asthma Quality-of-Life Questionnaire (AQLQ) score improvements after a single-session of MRI-guided BT as compared to the conventional three-session approach [28]. We hypothesized that MRI-guided BT would result in a reduced number of radiofrequency activations, as well as bronchoscopy sessions. We also postulated that one-year after the end of therapy, AQLQ and Asthma Control Questionnaire (ACQ) score improvements would be similar for MRI-guided and standard whole-lung BT. Here we report the results of a 12-month, pilot randomized controlled trial comparing MRI-guided and standard BT in severe asthma.

MATERIAL AND METHODS

Study design and participants

We conducted a randomized controlled trial of hyperpolarized gas MRI-guided versus standard BT (1:1 allocation ratio) at two sites (London Health Sciences Centre/Western University and St. Joseph's Healthcare Hamilton/McMaster University) between 10/2014 and 11/2019 (ClinicalTrials.gov NCT02263794). Study participants were >18 years of age, with severe asthma that was poorly-controlled [29], and BT was prescribed as part of their clinical care. Written informed consent to ethics-board-approved protocols (University of Western Ontario Health Sciences Research Ethics Board (#104200), Hamilton Integrated Research Ethics Board (#14-642)) was obtained from all participants.

As shown in Figure 1, the trial was comprised of a pre-intervention period, an intervention period, and a post-intervention follow-up period of 12-months. During the pre-intervention period, all participants completed a study visit before (baseline, visit 1) and after receiving an oral corticosteroid burst (post-OCS burst, visit 2). During the post-intervention period, all participants were managed according to standard-of-care; follow-up visits were completed by phone or in person, 3- (visit 3), 6-

(visit 4) and 12-months (visit 5) after MRI-guided or standard BT was completed. On face-to-face visits, spirometry and hyperpolarized gas MRI were performed pre- and post-bronchodilator. The AQLQ and ACQ were completed for all phone-call and face-to-face visits. For post-bronchodilator measurements, four 100μg doses of *Novo-Salbutamol® HFA* (Teva Novopharm Ltd.) were delivered through a pressurized metered dose inhaler using an *AeroChamber Plus* spacer (Trudell Medical International).

Image acquisition and analysis

All imaging was completed at the Robarts Research Institute (Western University). ^{1}H and inhaled hyperpolarized gas (^{3}He and/or ^{129}Xe) MRI (3x3x15mm^{3}) were acquired within five minutes of one another using a 3T MR system (General Electric Health Care; Milwaukee, USA) as previously described [23]. For all acquisitions, participants were coached to inhale 1L of gas from functional residual capacity (FRC), and coronal slices were acquired under breath-hold conditions at FRC + 1L. Thoracic CT was performed at a similar lung volume using a 64-slice Lightspeed VCT system (General Electric Health Care; Milwaukee, USA) as previously described [23]. Quantitative MRI analysis was performed by a single trained observer who was blinded to intervention allocation (MM) using semi-automated segmentation and registration software to generate the MRI ventilation defect percent (VDP) at baseline [30]. The observer segmented each baseline MRI dataset twice (CV=14.9%; ICC=0.97, 95% confident interval, 0.93 to 0.99), and the mean VDP of the two rounds was reported.

Bronchial thermoplasty

BT was performed using the Alair Bronchial Thermoplasty System (Boston Scientific) by bronchoscopists (DGM and GC) with >10 years experience [6]. All participants received a 5-day oral corticosteroid burst (50mg of prednisone/day) prior to BT. Participants randomized to standard BT underwent three bronchoscopy procedures to treat all accessible airways as previously described [1, 31]. Those who were randomized to MRI-guided BT underwent up-to two bronchoscopy procedures to treat all accessible airway targets visually identified by the bronchoscopy team on hyperpolarized gas

MRI acquired at pre-intervention visits. As shown in Figure 2, bronchopulmonary segments were considered targets if they demonstrated characteristics of smooth muscle dysfunction; characterized by their spatial relationship to ventilation defects that were completely or partially reversible following bronchodilator inhalation [19] at one or both pre-intervention visits. The bronchopulmonary segment that spatially corresponded to a reversible ventilation defect was identified by the bronchoscopists based on their knowledge of the bronchopulmonary segmental anatomy. CT scans were available for review alongside the MRI as a structural aid, but they were not co-registered to the MRI or segmented to delineate the bronchopulmonary segments.

Outcomes

Our primary outcome was the change in AQLQ-score between baseline (visit 1) and follow-up visits completed 3- (visit 3), 6- (visit 4) and 12-months (visit 5) after BT. Secondary outcomes were change in ACQ-5 score, the percentage of participants achieving AQLQ and ACQ-5 score improvements ≥minimal clinically important difference (MCID, ≥0.5 [32, 33]), and the difference in the number of radiofrequency activations and bronchoscopy sessions between intervention groups. All participants were monitored for adverse events related to hyperpolarized gas MRI, and clinically for adverse respiratory events during the intervention period plus 6-weeks and post-intervention period (6-weeks to 12-months).

Statistical analysis

Since this was a pilot trial, we did not complete an a priori sample size calculation; based on our previous observation of differences in AQLQ and ACQ improvements between two groups of BT patients [34], we recruited 14 patients to this study. Data were tested for normality using the Shapiro-Wilk normality test and when data were not normal, non-parametric tests were performed. Baseline and follow-up AQLQ and ACQ-5 scores were compared using paired t-tests and Wilcoxon matched-pairs signed rank tests. The difference between groups for baseline demographics, clinical characteristics, the number of radiofrequency activations, and for the change in AQLQ and ACQ-5

scores between baseline and follow-up timepoints were evaluated using unpaired t-tests and Mann-Whitney U-tests. We also determined the proportion of participants in each group achieving AQLQ and ACQ-score improvements ≥MCID [32, 33], Fisher's exact tests were performed to determine if these proportions were statistically different. Data are expressed as mean ± standard deviation or mean [95% confidence interval (CI)]. Intent-to-treat (online supplement) and per-protocol analyses were performed. All statistical analyses were performed using GraphPad Prism 7.00 (Graphpad Software Inc., La Jolla, USA) or SPSS 23.00 (IBM Corporation, Armonk, USA).

RESULTS

Fourteen participants completed the pre-intervention period and were randomized to MRI-guided (n=6) or standard BT (n=8) (Figure 3). After randomization, two participants were excluded following one or more BT sessions; a single participant initiated anti-IL5 monoclonal antibody therapy, and the other was unable to complete BT due to the COVID-19 pandemic. In total, five participants who underwent MRI-guided BT and seven participants who underwent standard BT were included in the per-protocol analysis.

Baseline demographics and characteristics

Baseline demographics and clinical characteristics for participants in the per-protocol analysis are summarized in Table 1. The intervention groups were similar except for FEV_1, which was lower in the MRI-guided BT group, and FEV_1 reversibility, which was greater in the MRI-guided group. One participant (20%) in the MRI-guided BT group was OCS-dependent, whereas two participants (29%) in the standard BT group were OCS-dependent. Three participants (60%) in the MRI-guided BT group were receiving biologic therapy (omalizumab, n=1; mepolizumab, n=1; reslizumab, n=1) as compared to one participant (14%) in the standard BT group (mepolizumab, n=1). Airway inflammation (characterized using sputum cell counts) was controlled prior to BT for four participants (80%) in the MRI-guided BT group, and five participants (71%) in the standard BT group. In the remaining three

participants, airway inflammation was not characterized prior to BT, however their blood eosinophil counts were within the normal range. The burden of mucus plugging was low in both groups, with intraluminal plugging visualized on CT in three bronchopulmonary segments for one participant in each group.

Activation Outcomes

Participants who underwent MRI-guided BT received significantly (73±37, p=0.003) fewer radiofrequency activations than those who underwent standard BT (155±34). The median number of bronchopulmonary segments treated was 7 (minimum of 4, maximum of 10) in the MRI-guided group and 18 (minimum of 13, maximum of 18) in the standard BT group. For participants in the MRI-guided BT group, all target airways were treated in a single bronchoscopy session for three participants (4, 6 and 7 segments treated), while two participants required two bronchoscopy sessions to treat all targets (9 and 10 segments treated) (7 sessions in 5 participants or 47% of standard BT). Participants requiring two bronchoscopy sessions had more target airways identified by the bronchoscopist who also determined that treatment of all airway targets required two BT sessions. All participants in the standard BT group underwent three bronchoscopy procedures to treat all accessible bronchopulmonary segments (21 sessions in 7 participants or 100% of standard BT).

Asthma quality-of-life and control Outcomes

Figure 4 summarizes asthma quality-of-life and control outcomes at 3-, 6- and 12-months by intervention group. In Figure S1 (Supplementary Information), inter-individual changes in AQLQ and ACQ-5 scores are shown from baseline to 12-months post-BT. As shown in Figure 4A and Figure S1A, the mean change in AQLQ score from baseline to 12-months post-BT was 1.8 [95% CI, 0.1 to 3.5] (n=5, p=0.04) in the MRI-guided group and 0.7 [95% CI, -0.9 to 2.3] (n=7, p=0.30) in the standard BT group. The change in AQLQ score 12-months post-BT was not significantly different between the MRI-guided and standard BT groups (p=0.25). In addition, in the MRI-guided and standard-BT

groups, the improvement in AQLQ score was ≥MCID for 4 of 5 (80%) and 5 of 7 (71%) participants at 12-months respectively (p>0.99).

Similar outcomes were observed for ACQ-5. As shown in Figure 4B and Figure S1B, the mean change in ACQ-5 score from baseline to 12-months post-BT was -1.4 [95% CI, -2.6 to -0.2] (n=5, p=0.03) in the MRI-guided group and -0.7 [95% CI, -1.3 to 0.0] (n=7, p=0.04) in the standard BT group. The change in ACQ score 12-months post-BT was not significantly different between the MRI-guided and standard BT groups (p=0.17). In the MRI-guided and standard-BT groups, the improvement in ACQ-5 score was ≥MCID for 4 of 5 (80%) and 4 of 7 (57%) participants at 12-months respectively (p=0.58).

Adverse events

MRI and hyperpolarized gas inhalation were well tolerated by all participants. The total number of ^{3}He and ^{129}Xe doses was 125 in 12 participants. In total there were 14 mild adverse events after dose inhalation in five of 12 (42%) participants, all of which resolved within 2 minutes of onset without treatment. Six adverse events in 3 participants were related to the breath-hold maneuver ($SpO_2 \leq$ 85% for a few seconds after breath-hold) and eight adverse events in two participants (light headedness x 6 and tingling arms x 2) were also judged related to the breath-hold maneuver.

BT was well-tolerated by all but one participant who was in the standard BT group and required early termination of their first and third BT sessions due to bronchospasm and wheeze. The most frequently observed adverse respiratory events are summarized in Table 2 and hospitalizations for adverse respiratory events are detailed in Table S2 of the online supplement. During the intervention period (BT plus 6 weeks), there were two hospitalizations for adverse respiratory events in each group. In the MRI-guided group, two participants (2/5, 40%) required a total of two hospitalizations (one seven days after BT for 12 days; one within one day after BT for 3 days). In the standard BT group, one participant (1/7, 14%) required two hospitalizations (both within one day after BT, for 5 and 21 days). A similar proportion of participants in both groups were hospitalized for adverse respiratory

events during the post-intervention period, although hospitalizations were less frequent in the MRI-guided group (one participant (20%) required one hospitalization) than in the standard group (two participants (29%) required a total of four hospitalizations). The total duration of hospitalization was 20 days in the MRI-guided BT group and 41 days in the standard BT group.

DISCUSSION

For current and newly emerging asthma therapies, the assumption has been that airway abnormalities are homogenously distributed. Recent work has shown that asthma airway abnormalities are, in fact, regionally heterogeneous, and this observation can be exploited to guide therapies to only the abnormal airways. As BT targets all accessible airways with curative intent, this approach may offer potential advantages over standard BT.

In this pilot randomized controlled trial, MRI-guided BT resulted in clinically and statistically significant improvements in asthma-specific quality-of-life and control over 12-months. Despite receiving 53% fewer radiofrequency activations, four of five (80%) participants who underwent MRI-guided BT reported a clinically relevant AQLQ and ACQ-5 score improvement at 12-months. This response rate is similar to the AIR-2 trial (79%) [8] and the Australian Bronchial Thermoplasty Registry (84%) [12]. At 12-months, we also reported a mean AQLQ and ACQ-5 score improvement of 1.8 and -1.4 respectively, which was statistically significant and consistent with published trials [6-8]. Importantly, we made a number of observations that suggest these improvements were non-inferior to standard BT. First, the improvement from baseline in AQLQ and ACQ-5 scores were not statistically different between the intervention groups. Second, the proportion of AQLQ and ACQ responders were similar between intervention groups. Finally, despite our small sample size, the upper bound of the 95% CI [−1.8 to 0.4] around the difference between intervention groups with respect to ACQ-5 score improvement at 12-months was below the non-inferiority margin of 0.5 points.

Our observations support and complement the previous findings of Hall and colleagues [28], which also showed that >70% of MRI-guided BT participants reported a clinically relevant AQLQ-score improvement at 3-months. Whilst this previous work [28] was not designed to evaluate effectiveness of MRI-guided BT beyond 3-months, our trial confirmed that such improvements were durable 12-months post-BT. In both trials, outcomes were not related to the number of radiofrequency activations, contradicting the observations by Langton et al that fewer activations were associated with poor response following standard BT (34). It is important to highlight a number of methodological differences between the trials. First, different criteria were used to identify treatment targets on MRI. Hall et al [28] employed an MRI-CT co-registration and segmentation approach to quantify segmental VDP from up-to four baseline ^{129}Xe MRI scans and targeted the six bronchopulmonary segments with the largest mean VDP in a single bronchoscopy session. In contrast, we visually inspected the dynamic behaviour of ventilation defects in response to bronchodilator to identify targets. We did not impose an upper limit on the number of targets, which led to the treatment of 4-7 segments during a single procedure and some participants requiring two bronchoscopy sessions to complete MRI-guided BT. It is logical to assume that the aforementioned discrepancies in terms of the number and characteristics of treatment targets, also the approach to localize targets (automated imaging processing versus visual interpretation by bronchoscopist), may influence the efficacy of MRI-guided BT and highlights the need for mechanistic studies to optimize treatment decisions. An advanced CT-MRI registration and segmentation approach, similar to that employed by Hall and colleagues, would likely be a more repeatable and scalable means to localize treatment targets.

We must acknowledge a number of assumptions when identifying patient-specific airway targets. In the MRI-guided group, we elected to guide BT to airways that were spatially aligned with ventilation defects that improved following bronchodilator, which we believe reflected ASM dysfunction [19]. We prospectively planned to avoid treating airways that were spatially aligned to "persistent" or "bronchodilator non-responsive" ventilation defects because we previously showed that

these were the consequence of intra-luminal plugging due to inflammatory cells [19, 35] and/or mucus [18]. Importantly, there was a single protocol deviation in the MRI-guided group (S-11), for a participant with persistent lower lobe ventilation defects in whom the interventional specialist treated all ten lower lobe segments. Retrospective review of the chest CT revealed mucus plugs in two (RB6 and LB6) of the 10 bronchopulmonary segments that were treated. Our approach assumed: 1) adequate inhaled bronchodilator deposition to all segmental airways, and, 2) MRI ventilation defects that stem from intra-luminal plugging or other mechanisms not responsive to bronchodilator were not good targets for BT. While the optimal treatment target has not yet been established, our decision making was informed based on the primary mechanism of action of BT (reduced ASM mass [2-5]) and our understanding of the underlying contributions to MRI ventilation defects. Nevertheless, it is important to emphasize that bronchial biopsy [3] and modelling studies [36] suggest BT effects are not localized to the ASM or the site of radiofrequency delivery and may have effects on other structural cells such as the epithelium [37] or nerves [5, 38]. Pretolani et al observed reduced ASM area in the untreated right middle lobe for participants who underwent BT, suggesting that thermal injury may cross lobar divisions and affect adjacent lobes [3]. In addition, while BT directly treats only the large airways, Donovan et al provided evidence via a mathematical model that structural changes in the large airways leads to reopening of the smaller airways via a global flow redistribution mechanism [36]. Salem et al observed decreased MUC5AC and IL-13 expression one-year after BT [37], which challenges our assumption that ventilation defects distal to mucus plugs are not ideal targets for BT. It is unclear if BT would consistently normalize IL-13 activity and mucus in all patients and this requires further investigation.

There are a number of limitations to our pilot trial that should be considered. We acknowledge that the small sample size likely contributed to different clinical characteristics between intervention groups at baseline. At baseline, the MRI-guided group were treated with more biologics, had lower FEV_1 and greater bronchodilator reversibility. While AQLQ and ACQ-5 scores were similar between

the groups, we did not account for baseline differences in severity or lung function between the groups and cannot exclude that the standard-BT group would have shown better outcomes if it had consisted of "equally severe" asthmatics. We estimate that only 5-8% of all patients with severe asthma are optimal candidates for BT, therefore our small sample size is a consequence of the small number of patients clinically selected to receive BT at the study sites. During the study period, only two patients underwent BT outside of the study protocol. Moreover, our study was not blinded as we did not implement a sham procedure in the MRI-guided group to mimic standard BT of all airways. Therefore, both the participant and clinical team were aware of intervention allocation during the post-intervention period. This may be problematic given the subjective nature of our endpoints. Finally, treatment targets for all but one participant were identified on MRI using hyperpolarized ^{3}He gas, not ^{129}Xe gas. As the hyperpolarized gas community has now transitioned to the use of ^{129}Xe gas to reduce costs and improve accessibility to hyperpolarized gas MRI, documented biases between the gases [23, 39, 40] should be considered when generalizing our trial findings.

In summary, we completed a one-year pilot randomized controlled trial and observed that MRI-guided BT resulted in a reduced number of BT activations and bronchoscopy sessions, with clinically and statistically significant improvements in asthma control and quality-of-life at one year that were non-inferior to standard whole-lung BT. A patient-specific approach to BT offers advantages over standard BT in terms of reduced procedure time, cost, adverse events, and perhaps enabling BT in more severe patients with asthma.

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TABLES

Table 1. Baseline demographic and clinical characteristics

	MRI-guided BT (n=5)	**Standard BT** (n=7)	**Significance of Difference[*] (p)**
Age yrs	49±12	42±14	0.44
Female sex n (%)	4 (80)	5 (71)	N.D.
BMI kg/m^2	33±9	29±5	0.39
BMI ≥ 30 kg/m^2 n (%)	3 (60)	5 (71)	N.D.
Smoking history n (%)	1 (20)	2 (29)	N.D.
Blood eosinophils (x10^9/L)[†]	0.3 (0.0-0.6)	0.2 (0.0-0.7)	0.86
Sputum eosinophils %[†]	0.7 (0.0-1.5)[§]	0.2 (0.0-4.3)[‖]	0.90
ACQ-5 Score	2.8±1.1	2.7±1.1	0.88
AQLQ Score	3.4±1.6	4.0±1.1	0.48
FEV_1 Pre-BD $\%_{pred}$	44±8	83±23	**0.005**
FEV_1 Post-BD $\%_{pred}$	63±13	92±22	**0.03**
Reversibility of FEV_1 %[†]	51 (6-87)	11 (-3-35)	**0.04**
FEV_1/FVC Post-BD %	63±14	76±13	0.12
MRI VDP Pre-BD	11±9	13±17	0.76
MRI VDP Post-BD	6±6	8±11	0.76
Asthma Medications			
ICS dose µg/day[†‡]	1500 (1000-4000)	1000 (500-2000)	0.27
OCS dose mg/day[†]	0 (0-20)	0 (0-25)	0.84
OCS dependent n (%)	1 (20)	2 (29)	N.D.
Monoclonal antibody n (%)	3 (60)	1 (14)	N.D.
LABA n (%)	5 (100)	7 (100)	N.D.
LAMA n (%)	3 (60)	3 (43)	N.D.
LTRA n (%)	3 (60)	4 (57)	N.D.

Values are mean ± standard deviation except when indicated otherwise.

N.D.=not-determined; BMI=body mass index; ACQ-5=five-item asthma control questionnaire; AQLQ=asthma quality of life questionnaire; FEV_1=forced expiratory volume in one second; BD=bronchodilator; FVC=forced vital capacity; MRI=magnetic resonance imaging; VDP=ventilation defect percent; ICS=inhaled corticosteroid; OCS=oral corticosteroid; LAMA=long-acting muscarinic antagonist; LTRA=leukotriene receptor antagonist.

*Significance of difference ($p<0.05$) between groups determined using an unpaired t-test for parametric data or Mann-Whitney test for nonparametric data; [†]Median (minimum - maximum); [‡]fluticasone or equivalent; [§]n=4; [‖]n=6.

Table 2. Proportion of participants with adverse respiratory events

	MRI-guided BT	Standard BT
Intervention period plus 6 weeks		
SAE - Hospitalization*	**2/5 (40%)**	**1/7 (14%)**
Cough	4/5 (80%)	6/7 (86%)
Wheeze	3/5 (60%)	4/7 (57%)
Chest tightness	1/5 (20%)	4/7 (57%)
Consolidation/atelectasis/airspace opacity	2/5 (40%)	4/7 (57%)
Dyspnea	2/5 (40%)	3/7 (43%)
Chest discomfort	1/5 (20%)	3/7 (43%)
Bronchospasm	1/5 (20%)	3/7 (43%)
Hemoptysis	0/5 (0%)	3/7 (43%)
Productive cough	1/5 (20%)	3/7 (43%)
Decreased breath sounds	2/5 (40%)	2/7 (29%)
Sputum discolored	2/5 (40%)	0/7 (0%)
Infection	2/5 (40%)	1/7 (14%)
Fever	1/5 (20%)	1/7 (14%)
Night awakenings	0/5 (0%)	1/7 (14%)
Bronchospasm	0/5 (0%)	1/7 (14%)
Post-intervention period (6 weeks – 12 months)		
SAE - Hospitalization*	**1/5 (20%)**	**2/7 (29%)**
Cough	2/5 (40%)	4/7 (57%)
Dyspnea	3/5 (60%)	4/7 (57%)
Chest tightness	1/5 (20%)	4/7 (57%)
Wheeze	2/5 (40%)	3/7 (43%)
Productive cough	1/5 (20%)	3/7 (43%)
Infection	1/5 (20%)	3/7 (43%)
Chest discomfort	0/5 (0%)	2/7 (29%)
Night awakenings	0/5 (0%)	2/7 (29%)
Sputum discolored	1/5 (20%)	1/7 (14%)
Decreased breath sounds	1/5 (20%)	1/7 (14%)
Fever	0/5 (0%)	1/7 (14%)

BT=bronchial thermoplasty; SAE=severe adverse event.

FIGURE LEGENDS

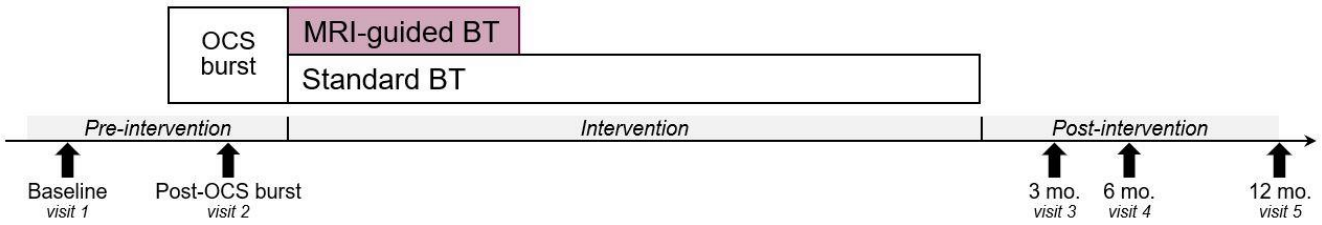

Figure 1. Study design

All participants completed two pre-intervention study visits before being randomized to MRI-guided or standard BT. For those participants randomized to MRI-guided BT, target airways were identified on inhaled hyperpolarized gas MRI acquired at baseline (visit 1) and following an OCS burst (visit 2). The post-intervention follow-up period was 12-months, with outcome assessment visits completed 3- (visit 3), 6- (visit 4) and 12-months (visit 5) after BT.

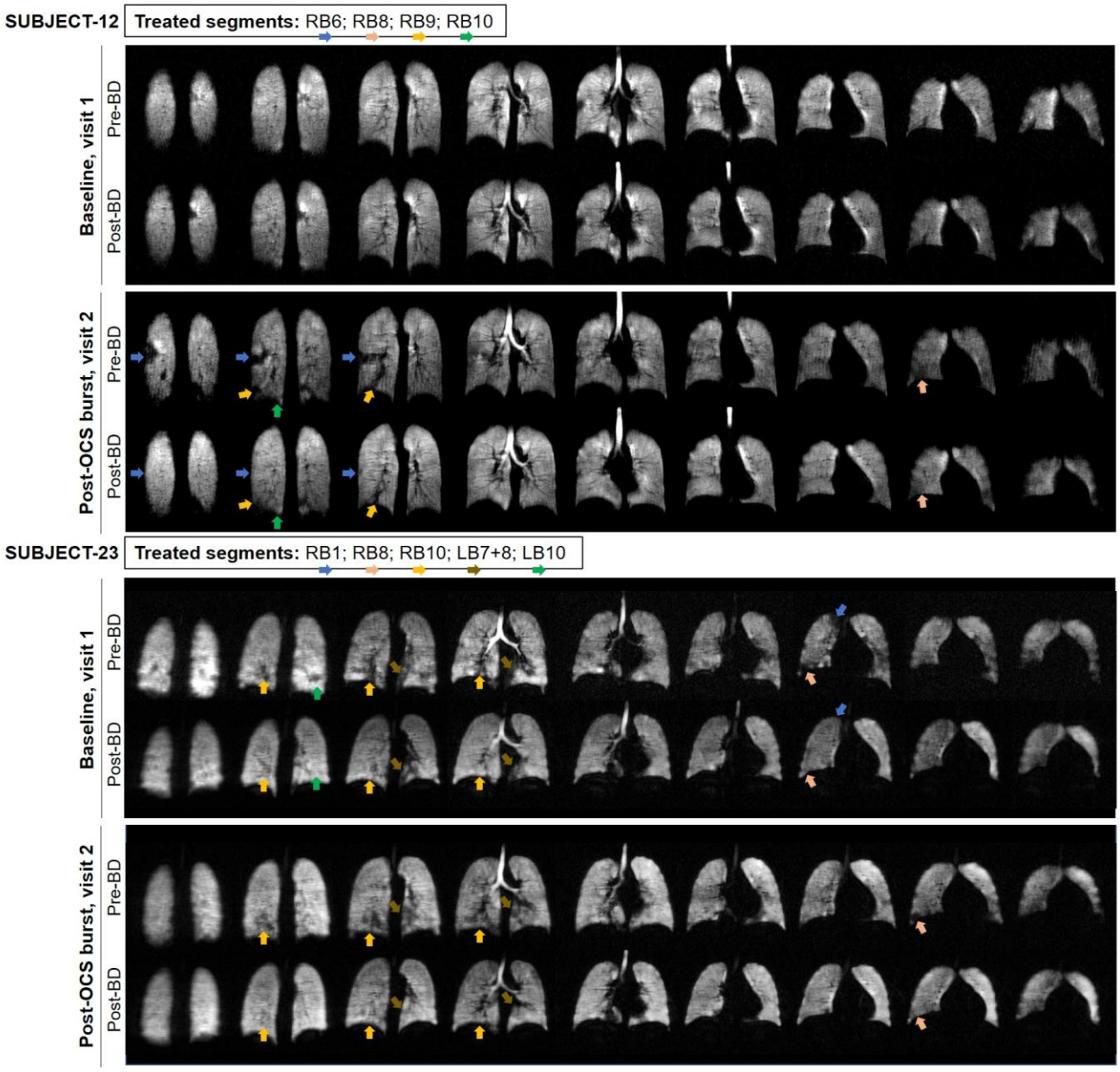

Figure 2. Representative examples of focal airway targets identified by inhaled hyperpolarized gas MRI.

Pre- and post-bronchodilator inhaled hyperpolarized gas MRI coronal slices acquired during the pre-intervention period at baseline (visit 1) and after receiving an oral corticosteroid burst (post-OCS burst, visit 2) for two representative participants with severe asthma. Arrows identify focal ventilation defects that were deemed targets by the bronchoscopist as they were completely or partially reversible

following bronchodilator inhalation at one or both pre-intervention visits. For subject-12, the RB6, RB8, RB9 and RB10 bronchopulmonary segments were treated during a single MRI-guided BT session. For subject-23, the RB1, RB8, RB10, LB7+8 and LB10 bronchopulmonary segments were treated during a single MRI-guided BT session.

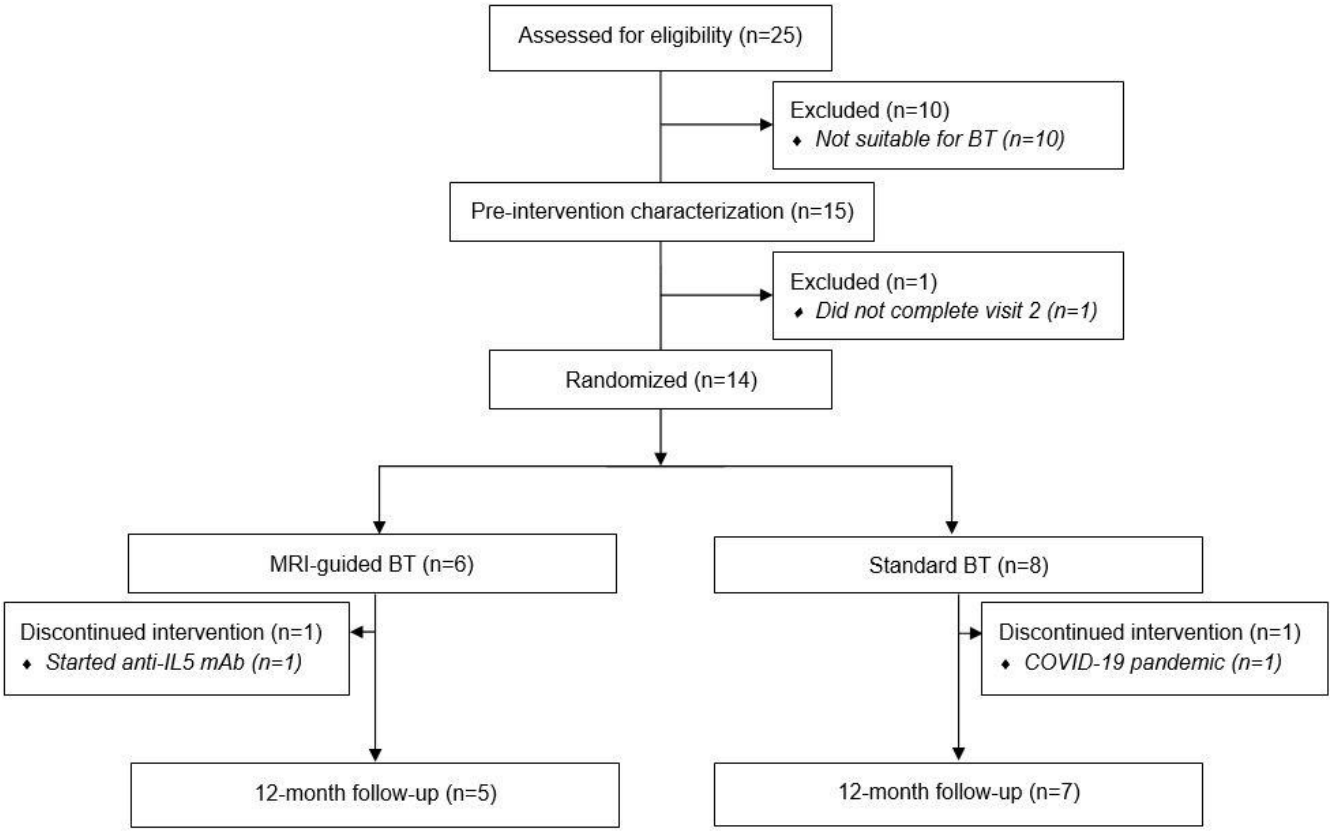

Figure 3. Consort diagram

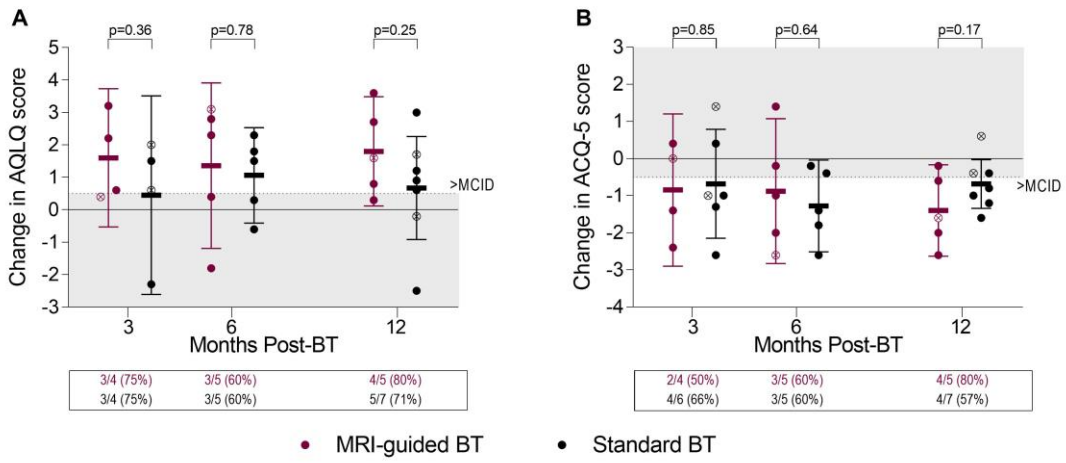

Figure 4. Change in AQLQ score (A) and ACQ-5 score (B) following MRI-guided *(maroon)* and standard *(black)* bronchial thermoplasty.

Bars show the mean change from baseline and 95% confidence intervals with individual values for all participants superimposed on the plot. Crossed and solid symbols represent participants who underwent BT at site 1 and site 2, respectively. The number and proportion of participants with an AQLQ score and ACQ-5 score improvement ≥ MCID are provided below each plot.

AQLQ=Asthma Quality of Life Questionnaire; ACQ-5=five-item Asthma Control Questionnaire; MCID=minimal clinically important difference.

ONLINE SUPPLEMENT

Bronchial thermoplasty guided by hyperpolarized gas MRI in adults with severe asthma: A one-year pilot randomized trial

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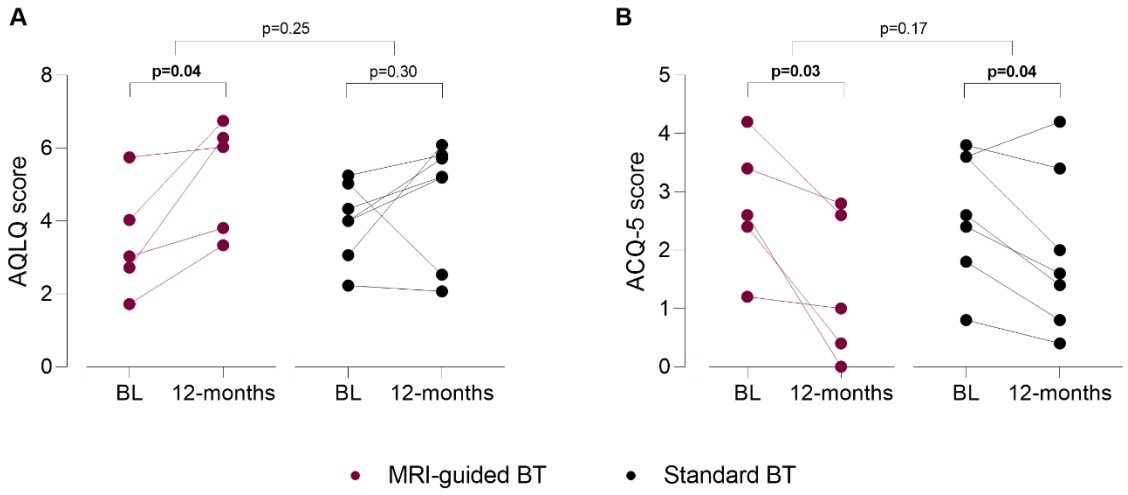
Figure S1- AQLQ (A) and ACQ-5 scores (B) at baseline and 12-months following MRI-guided *(maroon)* and standard *(black)* bronchial thermoplasty.



AQLQ=Asthma Quality of Life Questionnaire; ACQ-5=five-item Asthma Control Questionnaire; BL=baseline; BT=bronchial thermoplasty.

Table S1- Baseline demographic and clinical characteristics for intent-to-treat population

	MRI-guided BT (n=6)	**Standard BT** (n=8)	**Significance of Difference[*] (p)**
Age yrs	46±13	45±14	0.89
Female sex n (%)	5 (83)	5 (63)	N.D.
BMI kg/m^2	33±8	29±4	0.32
Smoking history n (%)	1 (17)	2 (28)	N.D.
Blood eosinophils (x10^9/L)[†]	0.3 (0.0-0.6)	0.2 (0.0-0.7)	0.77
Sputum eosinophils %[†]	1.3 (0.0-11.3)[§]	0.0 (0.0-4.3)[‖]	0.36
ACQ-5 Score	3.0±1.1	2.7±1.0	0.69
AQLQ Score	3.4±1.4	3.8±1.1	0.56
FEV_1 Pre-BD $\%_{pred}$	43±8	76±29	**0.02**
FEV_1 Post-BD $\%_{pred}$	65±12	85±29	0.14
Reversibility of FEV_1 %[†]	62 (6-94)	12 (-3-35)	**0.01**
FEV_1/FVC Post-BD %	63±12	71±18	0.36
Asthma Medications			
ICS dose µg/day[†‡]	1750 (1000-4000)	1250 (500-2000)	0.20
OCS dose mg/day[†]	0 (0-20)	0 (0-25)	>0.99
OCS dependent n (%)	2 (33)	3 (38)	N.D.
Monoclonal antibody n (%)	3 (50)	2 (25)	N.D.
LAMA n (%)	3 (50)	4 (50)	N.D.
LTRA n (%)	3 (50)	4 (50)	N.D.

Values are mean ± standard deviation except when indicated otherwise.

N.D.=not-determined; BMI=body mass index; ACQ-5=five-item asthma control questionnaire; AQLQ=asthma quality of life questionnaire; FEV_1=forced expiratory volume in one second; BD=bronchodilator; FVC=forced vital capacity; ICS=inhaled corticosteroid; OCS=oral corticosteroid; LAMA=long-acting muscarinic antagonist; LTRA=leukotriene receptor antagonist.

*Significance of difference ($p<0.05$) between groups determined using an unpaired t-test for parametric data or Mann-Whitney test for nonparametric data; [†]Median (minimum - maximum); [‡]fluticasone or equivalent; [§]n=5; [‖]n=7.

Table S2- Hospitalizations for respiratory adverse events following bronchial thermoplasty

Participant	Treatment Group	AE description	Days since BT	Duration of hospitalization (d)	Treatment of AE while in hospital
Intervention period plus 6 weeks					
006	MRI-guided BT	Dyspnea, fatigue, wheeze, productive cough, pleuritic chest pain; airway wall edema, mucus plugging, consolidation on CT	7 days after BT#1	12	Antibiotic + oral prednisone + chest physiotherapy + bronchoscopy washings + morphine
016	Standard BT	Cough, wheeze, bronchospasm, respiratory distress; opacities on CT	0 days after BT#2	5	High doses of bronchodilators + intravenous methyl prednisone + oral prednisone + lorazepam
		Cough, wheeze, chest tightness, bronchospasm, respiratory distress; opacities on CT	0 days after BT#3	21	High doses of bronchodilators + antibiotic + oral prednisone + non-invasive ventilation (BiPAP) + magnesium sulfate + ketamine + theophylline + Ativan
023	MRI-guided BT	Febrile, purulent sputum (yellow-green), consolidation/atelectasis on x-ray	0 days after BT#1	3	Antibiotic + oral prednisone
Post-intervention period (6 weeks – 12 months)					
012	MRI-guided BT	Shortness of breath	317 days after BT#1	5	High doses of bronchodilators + magnesium sulfate + intravenous methyl prednisone + oral prednisone
013	Standard BT	Asthma exacerbation	244 days after BT#3	3	Intubated and ventilated (2 days), nebulized salbutamol and atrovent, advair, intravenous methyl prednisone
		Asthma exacerbation	348 days after BT#3	4	Intubated and ventilated (12 hours), nebulized salbutamol and atrovent, advair, intravenous methyl prednisone
016	Standard BT	Respiratory distress	175 days after BT#3	4	High doses of bronchodilators + oral prednisone + non-invasive ventilation (BiPAP) + tamiflu
		Shortness of breath	350 days after BT#3	4	High doses of bronchodilators + oral prednisone

AE=adverse event; BT=bronchial thermoplasty.