Use of MDCT to Assess the Results of Bronchial Thermoplasty

Matheus Zanon[1,2]
Débora L. Strieder[3]
Adalberto S. Rubin[1]
Guilherme Watte[1]
Edson Marchiori[4]
Paulo F. G. Cardoso[5]
Bruno Hochhegger[1,2,3]

OBJECTIVE. The purpose of this study was to evaluate the use of MDCT to assess response to bronchial thermoplasty treatment for severe persistent asthma.

MATERIALS AND METHODS. MDCT data from 26 patients with severe persistent asthma who underwent imaging before and after bronchial thermoplasty were analyzed retrospectively. Changes in the following parameters were assessed: total lung volume, mean lung density, airway wall thickness, CT air trapping index (attenuation < –856 HU), and expiratory-inspiratory ratio of mean lung density (E/I index). Asthma Quality of Life Questionnaire score changes were also assessed.

RESULTS. Median total lung volumes before and after bronchial thermoplasty were 2668 mL (range, 2226–3096 mL) and 2399 mL (range, 1964–2802 mL; $p = 0.08$), respectively. Patients also showed a pattern of obstruction improvement in air trapping values (median before thermoplasty, 14.25%; median after thermoplasty, 3.65%; $p < 0.001$] and in mean lung density values ± SD (before thermoplasty, –702 ± 72 HU; after thermoplasty, –655 ± 66 HU; $p < 0.01$). Median airway wall thickness also decreased after bronchial thermoplasty (before thermoplasty, 1.5 mm; after thermoplasty, 1.1 mm; $p < 0.05$). There was a mean Asthma Quality of Life Questionnaire overall score change of 1.00 ± 1.35 ($p < 0.001$), indicating asthma clinical improvement.

CONCLUSION. Our study showed improvement in CT measurements after bronchial thermoplasty, along with Asthma Quality of Life Questionnaire score changes. Thus, MDCT could be useful for imaging evaluation of patients undergoing this treatment.

Keywords: airway obstruction, asthma, asthmatic airway wall remodelling, bronchoscopy, MDCT

DOI:10.2214/AJR.17.18027

Received January 31, 2017; accepted after revision March 30, 2017.

[1]Medical Imaging Research Laboratory, LABIMED, Department of Radiology, Pavilhão Pereira Filho Hospital, Irmandade Santa Casa de Misericórdia de Porto Alegre, Av. Independência 75, Porto Alegre 90020160, Brazil. Address correspondence to M. Zanon (mhgzanon@hotmail.com).

[2]Department of Diagnostic Methods, Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil.

[3]Department of Radiology, Pontificia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil.

[4]Department of Radiology, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil.

[5]Heart Institute, Clinical Hospital of the University of São Paulo, São Paulo, Brazil.

AJR 2017; 209:752–756

0361–803X/17/2094–752

Asthma is a heterogeneous chronic respiratory disease characterized by airway inflammation and bronchial hyperresponsiveness from a variety of stimuli, which leads to airway smooth-muscle contraction. Asthma exacerbation is usually treated with long- and short-acting bronchodilator drugs. In some patients, however, excessive airway narrowing occurs and does not respond to conventional medication [1–4].

Bronchial thermoplasty (BT) is a nonpharmacologic intervention involving the application of low-energy radiofrequency to the airway wall during bronchoscopy. This treatment causes ablation of the airway smooth muscle because of the disruption of myosin function. In this manner, it reduces airway hyperresponsiveness, improving asthma symptoms [4–8]. Randomized clinical trials have shown that the procedure is safe and produces better clinical outcomes in patients with severe asthma that is refractory to medical therapies [7]. These trials assessed the effectiveness of BT on the basis of clinical findings, such as airflow, severity of asthma symptoms, number of symptom-free days, use of rescue medication, and Asthma Quality of Life Questionnaire (AQLQ) scores [4, 7, 8]. However, the literature contains few reports on the role of imaging in the assessment of the procedure's efficacy.

Thomen et al. [9] first used imaging for assessing changes in lung ventilation, function, and microstructure at the level of individual bronchopulmonary segments. They initially quantified pulmonary function in healthy patients and those with asthma using a combination of ^{3}He MRI and CT and then performed ^{3}He MRI again in patients who had undergone BT. They found that ventilation defects decreased as a function of time after treatment [9]. However, ^{3}He MRI is not available for routine use in radiology services, and it requires machines with special settings, implying a high cost [10].

MDCT, with images acquired at different lung volumes, is a modality that provides data on regional lung function, air trapping, and bronchial wall thickening [11–14]. It detects structural and ventilation abnormalities of asthma, which have been shown to be related to spirometric features [15–18]. The objective of this study was to evaluate the role of MDCT findings in the assessment of BT efficacy, which could help to provide a more efficient imaging-guided treatment of severe asthma.

Materials and Methods

Patients

This study was performed with the approval of the institutional review board of Irmandade Santa Casa de Misericórdia de Porto Alegre, and informed consent was obtained. We retrospectively evaluated the medical histories of adult patients (18–65 years old) from the same center who underwent BT between 2004 and 2014. Eligible subjects had to meet the Global Initiative for Asthma criteria for severe persistent asthma [2], which means asthma refractory to conventional therapy of inhaled corticosteroids (beclomethasone > 1000 µg/day or equivalent) and long-acting ß2 agonists (salmeterol ≥100 µg/day or equivalent). In addition, patients were included only if they had undergone CT at least once before and once 1 year after the procedure. Those who changed pharmacologic treatment after BT and before the second CT examination were excluded. All patients in the sample had participated in previous multicenter clinical trials [7, 8]. Subjects had undergone CT before and after BT as part of the study protocol. However, the primary outcomes assessed were differences in AQLQ scores and clinical findings before and after the procedure. To our knowledge, ours is the first study of automated quantitative CT analysis of patients with asthma who have undergone BT.

CT Settings

All subjects underwent paired inspiratory and expiratory chest CT with 16 × 0.625-mm collimation (LightSpeed 16 Slice Pro, GE Healthcare). CT examinations were conducted to measure total lung capacity (at full inspiration) and functional residual capacity (at the end of normal expiration). Scans were performed in the caudocranial direction, using a helical acquisition. Images were reconstructed with a slice thickness and interval of 0.625 mm to achieve near-isotropic voxels. Inspiratory images were acquired at 200 mAs and expiratory images were acquired at 50 mAs; all images were acquired at 120 kVp, using a pitch of 1.375. A standard reconstruction kernel was used to achieve medium-smooth images. A data matrix of 512 × 512 and an FOV from 35 to 45 cm were used. No CT dose modulation or IV contrast agent was used for this study.

CT Image Analysis

Inspiratory and expiratory CT images were evaluated using software (Advantage Workstation 4.6, GE Healthcare) designed for the assessment of segmented images from the chest wall, mediastinum, diaphragm, and airways. Automated segmentation of the right and left lungs from the chest wall and mediastinum was performed. Two radiologists blinded to whether the scan was obtained before or after BT and who had training in thoracic anatomy and in specific features of the software decided whether manual editing was necessary. Otherwise, lung lobe segmentation was mainly automated.

Because studies have shown that CT measures of airway diameter are directly proportional to the severity of asthma, airway disease was quantified using airway wall thickness (AWT) [16, 17]. Mean AWT values were calculated as the average of values for six segmental bronchi per subject. Airways were measured in cross section on transverse CT images in a lung window setting (level, –600 HU; width, 1600 HU), using Airway Inspector software (BWH and 3D Slicer contributors) [19]. The phase congruency edge–detection method was used to locate wall margins. Airways were excluded from measurement in the following situations: when airway wall circumference appeared to be discontinuous as a result of inadequate resolution; when the long- to short-axis ratio of an ellipse fitting the lumen exceeded 2; and when abutting soft tissues, such as vessels or lymph nodes, obscured more than one-half of the outer wall circumference [19, 20].

Total lung volume (TLV) and attenuation of all voxels included in the lung segmentation were calculated, and a mean lung density (MLD) histogram was created for each subject [18, 21, 22]. For air trapping assessment, end-expiratory CT data were used. These data were obtained using functional residual capacity or residual volume. CT air trapping was defined as the percentage of voxels on expiratory CT images with attenuation less than -856 HU, and the expiratory-inspiratory (E/I) index was obtained by division of MLDs from these protocols [11, 22]. Emphysema was defined using the percentage of low-attenuation (< –950 HU) areas on inspiratory CT [11].

Clinical Outcome Measures

BT effectiveness was also assessed clinically though AQLQ score changes from baseline to 12 months after the procedure. An AQLQ change in score of 0.5 was the minimal variation that indicated clinical improvement of asthma [8]. The four domains used to compose the AQLQ overall score (symptoms, activity limitation, emotional function, and environmental stimuli) were also analyzed individually, and changes from baseline to 12 months after BT were registered. A linear association was performed to correlate AQLQ score variations and imaging parameter changes. Secondary outcomes included changes in forced expiratory volume in the first second of expiration (FEV_1) and forced vital capacity (FVC).

Statistical Analysis

All results were analyzed using commercially available software (SPSS version 20, SPSS; Excel 2010, Microsoft). The Shapiro-Wilk test was used to assess data distribution. Two-tailed p values less than 0.05 were considered to indicate statistical significance. Analyses were performed using

TABLE 1: Demographic Characteristics of Study Subjects

Variable	Patients With Severe Asthma (n = 26)
Mean age ± SD (y)	41 ± 8
Patient sex, no. (%)	
Male	10 (38.4)
Female	16 (61.5)
Mean age (range) (y)[a]	
Male	43 (32–54)
Female	40 (28–51)
Methacholine PC20 (mg/mL)	
Geometric mean	0.27
95% CI	0.22–0.34
Mean FEV_1 before bronchodilator ± SD (% predicted)	78 ± 15.65
Inhaled corticosteroid dose (µg/day), mean (median)	1960.7 (2000)
Mean long-acting ß2 agonist dose ± SD (µg/day)	116.8 ± 34.39

Note—FEV_1 = forced expiratory volume in the first second of expiration, PC20 = provocative concentration causing a 20% fall in FEV_1.
[a]The t test showed no significant difference between male and female subjects.

mean values, SD, and quartiles for continuous variables and proportions for nominal data. The Mann-Whitney-Wilcoxon test was used for continuous variables, whereas the Fisher exact test was used for nominal variables. The TLV, E/I index, and air trapping percentages were expressed as medians and interquartile ranges, and MLD and AWT were expressed using mean values and SD. A paired *t* test was used to compare AQLQ scores from baseline to 1 year after the procedure. The Pearson correlation test was used for assessment of linear association between continuous variables. Coefficients were interpreted using the following parameters: 0.00–0.20 were considered very weak; ≥ 0.20–0.40, weak; ≥ 0.40–0.70, moderate; ≥ 0.70–0.90, strong; and ≥ 0.90, very strong [23].

Results

Thirty-two subjects were selected, but six did not fulfill the CT criteria (examinations before and 1 year after BT). The remaining sample consisted of 16 women (61.5%) and 10 men (38.5%) with a mean age of 41 ± 8 years. The mean interval between BT and the second CT examination was 12.5 months (range, 10.3–15.1 months). Table 1 gives baseline demographic characteristics of the study sample.

CT data are presented in a box-and-whisker plot in Figure 1. TLV, MLD, and air trapping percentage data were collected only from expiratory CT examinations. All cases had an increase in MLD and reduction in the E/I index and air trapping percentage. Median TLV after BT (2399 mL; range, 1964–2802 mL) was slightly lower than that before BT (2668 mL; range, 2226–3096 mL), but this difference was not statistically significant ($p = 0.08$). Significant improvement in median air trapping percentage was observed after BT (14.25% before treatment [interquartile range, 1.83–16.93%] vs 3.65% after treatment [interquartile range, 1.23–6.20%], $p < 0.001$; Fig. 2). In addition, MLD values showed a pattern of obstruction improvement (–702 ± 72 HU before treatment vs –655 ± 66 HU after treatment; $p < 0.01$). As estimated according to the MLD analysis, the median E/I index also decreased from 0.849 (interquartile range, 0.808–0.878) to 0.799 (interquartile range, 0.763–0.828; $p < 0.01$). Median AWT also decreased after BT (1.5 mm before treatment [range, 0.53–1.52 mm] vs 1.1 mm after treatment [range, 0.63–1.62 mm], $p < 0.05$; Fig. 3). In three patients, AWT reduction was minimal (< 0.05 mm). Mean dose-length product was 295.9 ± 115 mGy · cm (mean effective radiation dose, 4.14 ± 1.61 mSv).

Table 2 summarizes variations in imaging and AQLQ parameters. We found a mean AQLQ score change of 1.00 ± 1.35 ($p < 0.001$), whereas 65.4% of subjects achieved minimal important difference, (i.e., an AQLQ score change of 0.5 or greater). In four patients (15.4%), AQLQ score decreased after BT, despite improvement in imaging parameters (score variation range, 0.28–1.53). All four AQLQ domains means varied by more than 0.5, with all variations showing statistical significance except in the symptoms domain ($p = 0.025$). Using the Pearson correlation test to evaluate associations between AQLQ score changes and imaging parameter variations, a moderate correlation coefficient was observed between differences for the E/I index and those for the AQLQ symptoms, environmental stimuli, and overall scores (–0.41, –0.50, and –0.43, respectively). For other associations, correlation coefficients were weak or very weak and were not statistically significant. Although FEV_1 and FVC improved, the changes were not statistically significant ($p = 0.12$, $p = 0.35$, respectively).

Discussion

The study results found improvement in tomographic volumes and indexes 1 year after BT, represented by decreased TLV and E/I index and increased MLD. Nonetheless, no statistically significant TLV reduction was observed. Because asthma is a chronic obstructive airway disease characterized by prolonged expiration, the effectiveness of treatment could be reflected by decreased air trapping on CT. As expected, a significant reduction in air trapping was observed in the study period.

Variations in CT findings were accompanied by significant changes in mean AQLQ scores. This indicated that imaging modifi-

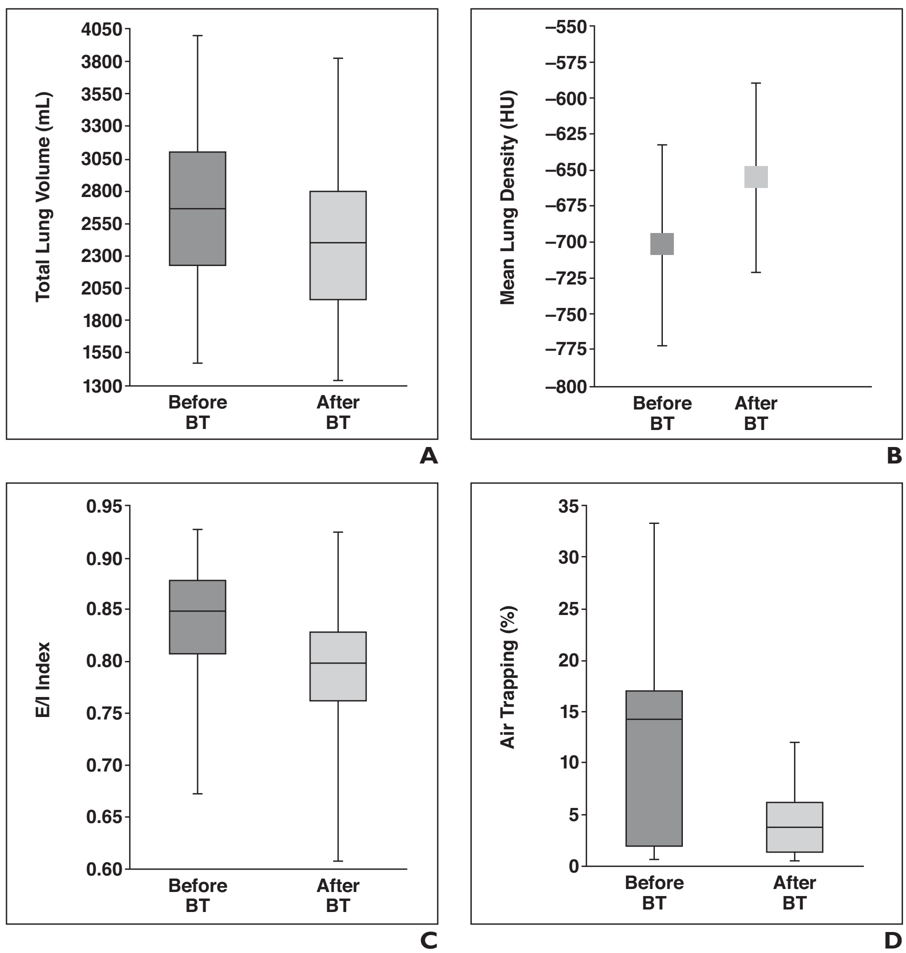

Fig. 1—Box-and-whisker plots obtained from analysis of CT data show improved respiratory pattern after bronchial thermoplasty (BT). Middle lines indicate medians; top lines, 75th percentiles; bottom line, 25th percentiles; and whiskers, 95% CIs.
A, Total lung volume before and after BT as obtained on expiratory CT ($p = 0.08$).
B, Mean lung density before and after BT as obtained on expiratory CT ($p < 0.01$).
C, Expiration-inspiration (E/I) index before and after BT ($p < 0.01$).
D, Air trapping before and after BT as obtained on expiratory CT ($p < 0.001$).

cations were supported by clinical improvement of asthma. Despite the fact that moderate correlation was observed only between E/I index variations and AQLQ changes, this effect does not imply causation. Perhaps correlations for other variables could be obtained with a larger sample [23].

In previous trials assessing the efficacy of BT for the treatment of severe asthma with a subjective, patient-centered primary outcome measure (AQLQ score), a reasonable placebo effect was observed [4, 7, 8]. Castro et al. [8] conducted the only double-blind study to date to our knowledge, using sham thermoplasty to avoid the placebo effect. The group receiving sham treatment showed 64% improvement in AQLQ score. Because imaging findings are not susceptible to the placebo effect, they may be useful for assessing the efficacy of BT.

Our data support the use of CT to assess the outcomes of BT. We found that MDCT data obtained before and after BT using inspiratory and expiratory protocols are useful for the characterization of an improved respiratory pattern. Notwithstanding methodologic differences between the studies, our results are compatible with those of previous reports and provide more evidence supporting the use of imaging in the evaluation of BT results [9]. Moreover, our exclusive use of MDCT provides an alternative to ^{3}He MRI, with greater accessibility and lower cost. However, CT is associated with risks and potential consequences of ionizing radiation from serial examinations, which should be considered especially in the management of asthmatic patients of a young age undergoing thermoplasty. Furthermore, Thomen et al. [9] assessed BT results from 40 to 104 days after treatment and patients who undergo bronchial thermoplasty often experience more exacerbations and adverse effects in the first 90 days after treatment [4, 7, 8]. In our study, this short-term masking of real BT-related improvement in asthma condition was avoided by including only data from CT examinations performed at least 1 year after the procedure.

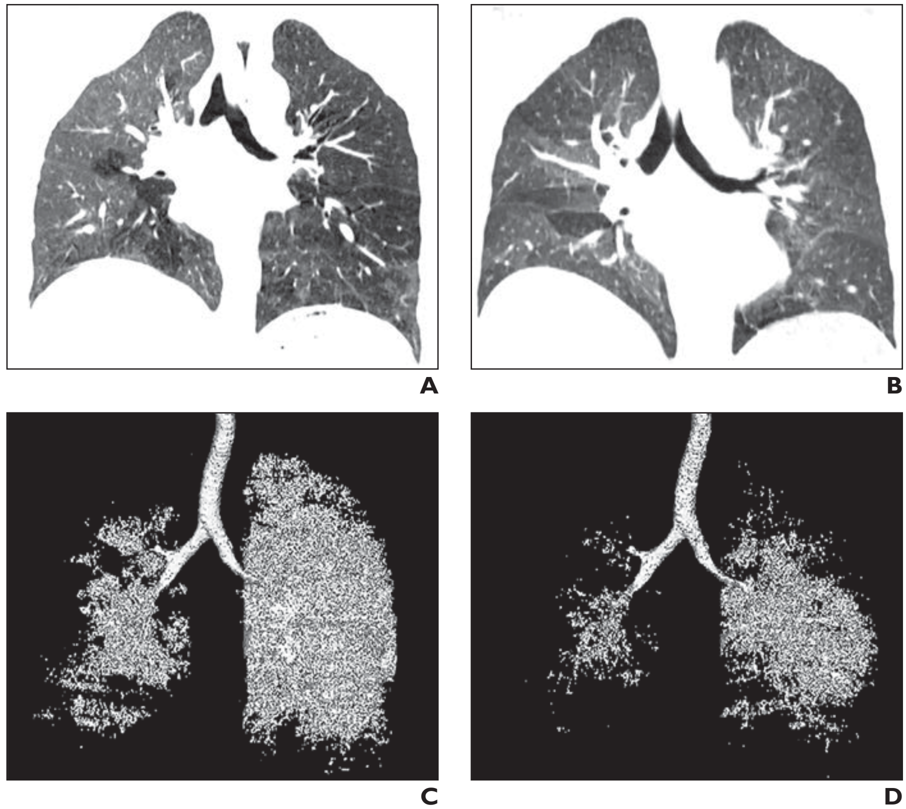

Fig. 2—37-year-old woman with severe persistent asthma.
A and **B**, Coronal CT image (**A**) obtained during expiration shows extensive areas of air trapping before bronchial thermoplasty, which are less pronounced on image obtained 12 months after procedure (**B**).
C and **D**, Three-dimensional CT image reconstructions show air trapping volumes (areas with densities < −856 HU) before (**C**) and after (**D**) bronchial thermoplasty.

Given the retrospective nature of this study, other prospective trials should be performed to collect more robust clinical evidence, ideally with bigger sample sizes and multicenter data, the lack of which was a major limitation of our study. Because some patients who underwent changes in medications after BT and before the second CT were excluded from the study, patients who did not respond to thermoplasty could have been excluded, representing a possible selection bias. In addition, CT is associated with multiple limitations. The measurement of lung attenuation varies substantially according to CT scanner model, reconstruction algorithm, and CT protocol parameters, including voxel size, tube voltage, and tube current–exposure time product [24]. CT attenuation values are also affected by variation in inspiratory and expiratory lung volumes and acquisition techniques. Further studies should also focus on using spirometer-controlled or controlled-ventilation CT to try to reduce this variable by standardizing degrees of inspiratory and expiratory efforts during the scan. However, strong correlations identified in previous

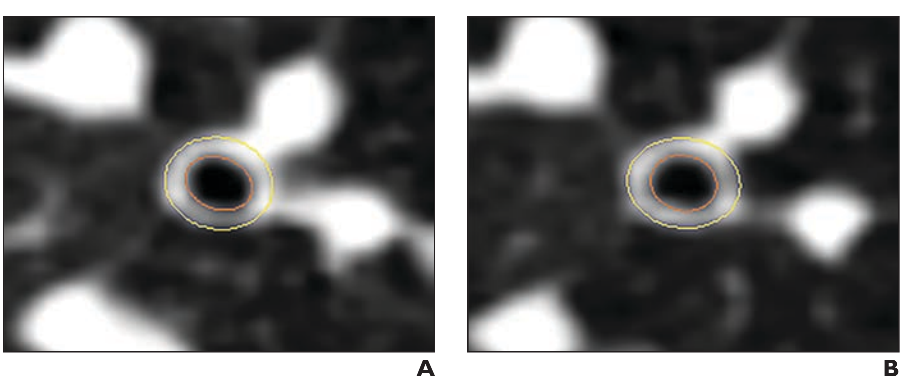

Fig. 3—40-year-old woman with severe persistent asthma. Images obtained using Airway Inspector software (BWH and 3D Slicer contributors). Yellow line represents outer edge of airway wall; orange line represents inner edge of airway wall.
A, Image obtained before bronchial thermoplasty using phase congruency method shows airway wall thickness (AWT) of 1.238 mm.
B, Image obtained after bronchial thermoplasty using phase congruency method shows AWT of 1.1679 mm. Difference in measurements was statistically significant.

TABLE 2: Variations Before and After Bronchial Thermoplasty

Parameters	Before Bronchial Thermoplasty	After Bronchial Thermoplasty	*p*
CT findings			
Median total lung volume (IQR) (mL)	2668.53 (2226–3096)	2399 (1964–2802)	0.08
Mean lung density ± SD (HU)	–702 ± 72	–655 ± 66	< 0.01
Median expiration/inspiration index (IQR)	0.85 (0.81–0.88)	0.80 (0.76–0.83)	< 0.01
Median air trapping (IQR) (%)	14.25 (1.83–16.93)	3.65 (1.23–6.20)	< 0.001
Mean airway wall thickness (range) (mm)	1.50 (0.53–1.52)	1.10 (0.63–1.62)	< 0.05
Mean AQLQ score ± SD	4.30 ± 1.14	5.30 ± 1.22	< 0.001
Subjects with change ≥ 0.5 in AQLQ score (%)	—	65.38	—
Symptoms domain	4.55 ± 1.24	5.26 ± 1.36	0.025
Activity limitations domain	4.50 ± 1.14	5.38 ± 1.32	< 0.001
Emotional functions domain	3.84 ± 1.58	5.39 ± 1.20	< 0.001
Environmental stimuli domain	3.88 ± 1.63	5.07 ± 1.52	< 0.01
FEV_1 (% predicted)	77.8 ± 16.53	84.00 ± 18.92	0.12
Forced vital capacity (L)	3.92 ± 0.83	4.03 ± 0.82	0.35

Note—Dash indicates not applicable. AQLQ = Asthma Quality of Life Questionnaire, IQR = interquartile range, FEV_1 = forced expiratory volume in the first second of expiration.

studies suggest that the variation from these technical factors is minimal [11].

In addition, further studies should try to evaluate other imaging modalities that have been used to assess airway changes after therapies such as BT, including optical coherence tomography and endobronchial ultrasound [25, 26].

Conclusion

This study showed that an improved respiratory pattern can be seen on MDCT after BT, a treatment of severe asthma that improves quality of life and reduces need for care in many patients. Although further studies with greater sample powers are needed, CT appears to be an option for the assessment of BT results that is considerably more accessible and less expensive than previously reported imaging methods.

References

1. Miller JD, Cox G, Vincic L, Lombard CM, Loomas BE, Danek CJ. A prospective feasibility study of bronchial thermoplasty in the human airway. *Chest* 2005; 127:1999–2006
2. Reddel HK, Bateman ED, Becker AA, et al. A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46:622–639
3. Hogg JC, Paré RC, Boucher RC, Michoud MC. The pathophysiology of asthma. *Can Med Assoc J* 1979; 121:409–414
4. Pavord ID, Cox G, Thomson NC, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med* 2007; 176:1185–1191
5. Gildea TR, Khatri SB, Castro M. Bronchial thermoplasty: a new treatment for severe refractory asthma. *Cleve Clin J Med* 2011; 78:477–485
6. Cox PG, Miller J, Mitzner W, Leff AR. Radiofrequency ablation of airway smooth muscle for sustained treatment of asthma: preliminary investigations. *Eur Respir J* 2004; 24:659–663
7. Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med* 2007; 356:1327–1337
8. Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med* 2010; 181:116–124
9. Thomen RP, Sheshadri A, Quirk JD, et al. Regional ventilation changes in severe asthma after bronchial thermoplasty with ^{3}He MR imaging and CT. *Radiology* 2015; 274:250–259
10. Liu Z, Araki T, Okajima Y, Albert M, Hatabu H. Pulmonary hyperpolarized noble gas MRI: recent advances and perspectives in clinical application. *Eur J Radiol* 2014; 83:1282–1291
11. Schroeder JD, McKenzie AS, Zach JA, et al. Relationships between airflow obstruction and quantitative CT measurements of emphysema, air trapping, and airways in subjects with and without chronic obstructive pulmonary disease. *AJR* 2013; 201:[web]W460–W470
12. Aliverti A, Pennati F, Salito C, Woods JC. Regional lung function and heterogeneity of specific gas volume in healthy and emphysematous subjects. *Eur Respir J* 2013; 41:1179–1188
13. Simon BA. Non-invasive imaging of regional lung function using X-ray computed tomography. *J Clin Monit Comput* 2000; 16:433–442
14. Fain SB, Gonzalez-Fernandez G, Peterson ET, et al. Evaluation of structure-function relationships in asthma using multidetector CT and hyperpolarized He-3 MRI. *Acad Radiol* 2008; 15:753–762
15. Laurent F, Latrabe V, Raherison C, et al. Functional significance of air trapping detected in moderate asthma. *Eur Radiol* 2000; 10:1404–1410
16. Kosciuch J, Krenke R, Gorska K, Zukowska M, Maskey-Warzechowska M, Chazan R. Airway dimensions in asthma and COPD in high resolution computed tomography: can we see the difference? *Respir Care* 2013; 58:1335–1342
17. Little SA, Sproule MW, Cowan MD, et al. High resolution computed tomographic assessment of airway wall thickness in chronic asthma: reproducibility and relationship with lung function and severity. *Thorax* 2002; 57:247–253
18. Ueda T, Niimi A, Matsumoto H, et al. Role of small airways in asthma: investigation using high-resolution computed tomography. *J Allergy Clin Immunol* 2006; 118:1019–1025
19. Estépar RS, Washko GR, Silverman EK, Reilly JJ, Kikinis R, Westin CF. Airway inspector: an open source application for lung morphometry. Applied Chest Imaging Laboratory website. acil.med.harvard.edu/files/acil/files/first_international_workshop_on_pulmonary_image_processing_2008_san_jose_estepar.pdf. Published 2008. Accessed June 21, 2017
20. Estépar RS, Washko GG, Silverman EK, Reilly JJ, Kikinis R, Westin CF. Accurate airway wall estimation using phase congruency. *Med Image Comput Comput Assist Interv* 2006; 9:125–134
21. Mets OM, Isqum I, Mol CP, et al. Variation in quantitative CT air trapping in heavy smokers on repeat CT examinations. *Eur Radiol* 2012; 22:2710–2717
22. Nishio M, Matsumoto S, Koyama H, Ohno Y, Sugimura K. Airflow limitation in chronic obstructive pulmonary disease: ratio and difference of percentage of low-attenuation lung regions in paired inspiratory/expiratory computed tomography. *Acad Radiol* 2014; 21:1262–1267
23. Mukaka MM. A guide to appropriate use of correlation coefficient in medical research. *Malawi Med J* 2012; 24:69–71
24. Sieren JP, Newell JD, Judy PF, et al. Reference standard and statistical model for intersite and temporal comparisons of CT attenuation in a multicenter quantitative lung study. *Med Phys* 2012; 39:5757–5767
25. Williamson JP, McLaughlin RA, Phillips MJ, et al. Using optical coherence tomography to improve diagnostic and therapeutic bronchoscopy. *Chest* 2009; 136:272–276
26. Soja J, Grzanka P, Sladek K, et al. The use of endobronchial ultrasonography in assessment of bronchial wall remodeling in patients with asthma. *Chest* 2009; 136:797–804