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Research article

Quantitative CT detects changes in airway dimensions and air-trapping after bronchial thermoplasty for severe asthma

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ABSTRACT

Objectives: Bronchial thermoplasty (BT) can be considered in the treatment of severe asthma to reduce airway smooth muscle mass and bronchoconstriction. We hypothesized that BT may thus have long-term effects on airway dimensions and air-trapping detectable by quantitative computed tomography (QCT).

Methods: Paired in- and expiratory CT and inspiratory CT were acquired in 17 patients with severe asthma before and up to two years after bronchial thermoplasty and in 11 additional conservatively treated patients with serve asthma, respectively. A fully automatic software calculated the airways metrics for wall thickness (WT), wall percentage (WP), lumen area (LA) and total diameter (TD). Furthermore, lung air-trapping was quantified by determining the quotient of mean lung attenuation in expiration vs. inspiration (E/I MLA) and relative volume change in the Hounsfield interval −950 to −856 in expiration to inspiration ($RVC_{856\text{-}950}$) in a generation- and lobe-based approach, respectively.

Results: BT reduced WT for the combined analysis of the 2nd–7th airway generation significantly by 0.06 mm ($p = 0.026$) and WP by 2.05% ($p < 0.001$), whereas LA and TD did not change significantly ($p = 0.147$, $p = 0.706$). No significant changes were found in the control group. Furthermore, E/I MLA and $RVC_{856\text{-}950}$ decreased significantly after BT by 12.65% and 1.77% ($p < 0.001$), respectively.

Conclusion: BT significantly reduced airway narrowing and air-trapping in patients with severe asthma. This can be interpreted as direct therapeutic effects caused by a reduction in airway-smooth muscle mass and changes in innervation. A reduction in air-trapping indicates an influence on more peripheral airways not directly treated by the BT procedure.

1. Introductions

Adult bronchial asthma is a heterogeneous disease and characterized by chronic airway inflammation, and poorly controlled asthma usually leads to a significant reduction in quality of life. In patients with ongoing symptoms and uncontrolled asthma, bronchial thermoplasty (BT) is an interventional treatment option as recommended in the ERS/ATS guidelines [1]. Randomized controlled clinical trials have shown the procedure to be safe with significant clinical improvements in patients with refractory moderate to severe asthma [2–5]. Usually three separate bronchoscopies are performed with the right lower lobe treated first, followed by the left lower and then both upper lobes [6,7]. The middle lobe is spared to avoid middle lobe syndrome [6]. During BT, thermal energy (radiofrequency ablation) is delivered to the airway wall of subsegmental bronchi with a diameter of 3–10 mm (e.g. 3th–4th generation of airways) [7]. The aim is to reduce airway smooth muscle (ASM) mass, and presumably through alterations within the innervation pattern [8], a decrease in bronchoconstriction can be achieved [6,9,10]. Most trials assessed the effectiveness of BT based on clinical findings, such as airflow obstruction, severity of asthma symptoms,

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number of symptom-free days, use of rescue medication, and Asthma Quality of Life Questionnaire (AQLQ) scores. However, morphometric data on post-interventional airway changes are sparse. Quantitative computed tomography (QCT) has proven to deliver valuable morphometric data in studies of other lung diseases such as chronic obstructive pulmonary disease [11,12], cystic fibrosis [13,14] or asthma [15–17]. Bronchial wall thickness (WT) might be best suited to detect a possible response to therapy, however only around 60% of asthma patients showed thickened bronchial walls in CT [18]. We hypothesized that QCT may serve as a surrogate marker for therapy guidance and outcome for future studies and might help in understanding the therapeutic mechanism of BT by longitudinally assessing airway morphology.

2. Materials and methods

2.1. Patient population

This retrospective study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (S-646/2016). 17 patients were retrospectively recruited from a cohort of 21 patients who had been diagnosed with severe asthma and underwent BT (Table 1). The main inclusion criterion was the availability of at least one non-enhanced paired in- and expiratory CT scan before and within two years after BT in a time interval of 266 ± 219 d (Table 1). Pre-therapeutic CT-scan was performed for intervention planning and exclusion of other diagnosis than asthma. Post-therapeutic CT-scan was indication for various reasons such as follow-up of nodules, while no pneumonia was diagnosed at CT. Four patients were excluded due to non-evaluable CT data (e.g. administration of contrast agent), and for five patients expiratory CT was not available. For the control group, patients with severe asthma who underwent two CT scans within one and a half years were recruited. 11 patients were retrieved from a database search with CT in a comparable time interval of 266 ± 219 d (Table 1). Expiratory CT scans were not available for patients in the control group.

2.2. Bronchial thermoplasty

In all 17 patients BT was performed according to the standard protocol in 3 subsequent bronchoscopies. The right lower lobe is treated first, followed by the left lower and the both upper lobes [6,7]. The thermal energy was applied to the 2nd–4th airways generation.

2.3. CT acquisition and reconstruction

Non-enhanced CT (Somatom Definition AS64, Siemens Medical Solutions AG, Forchheim, Germany) was performed in supine position as recommended for asthma patients [19,20]. All patients were instructed and carefully monitored for a stable full inspiratory and normal end-expiratory breathing position before scanning. The used CT scanner underwent dedicated routine calibration for water every 3 months and for air daily. Scans were performed in caudocranial direction with a dose-modulated protocol using a reference of 120 kV/70 mA or 100 kV/117 mA (Caredose4D, Siemens Medical Solutions, Forchheim, Germany) at a collimation of 64 × 0.6 mm, and a pitch of 1.45. The reconstructed slice thickness was 1.0 mm with 0.825 mm increment with iterative reconstruction in a medium soft i40f algorithm as recommended for quantification of air-trapping and a sharp i70f algorithm for airway analysis [13,20,21]. All examinations were visually inspected for absence of significant motion artefacts and inclusion of all parts of the chest by a senior chest radiologist.

Table 1
Patient's baseline characteristics.

	Bronchial thermoplasty	Control
Number of subjects	17	11
Age [years]	55 ± 11	59 ± 12
Sex male/female	6/11	5/6
FEV1 [l/s]	1.43	2.17
FEV1 [%]	49.9	69.9
VC [l]	2.69	3.39
VC [%]	43.3	86.6
Tiffeneau [%] FEV1/FVC	63.47	61.99
RV [l]	3.46	3.31
RV [%]	172.82	156.94
Oral corticosteroids n [%]	12 (70.6)	6 (54.5)
ACT	9.5	8.2
6 MWT [m]	357	391

FEV1 = forced expiratory volume in 1 s, VC = vital capacity, RV = residual volume, ACT = Asthma Control Test, 6MWT = 6 min walk test. Percentage values refer to predicted values in spirometry.

2.4. Quantitative post-processing

The in-house software YACTA (version 2.7.1.3, programming by O.W.) segmented the airway tree and lung lobes fully automated on paired inspiratory and expiratory CT images, [13,14,19,22,23] and quantified airways and air-trapping parameters as previously shown [21,24–27]. Airway dimensions were normalized to lung volume as recommended by several studies, since the lung volume depends on height, body weight, and gender [28–30]. After fully automatic lobe segmentation, the lobe masks were reviewed by a radiologist and manually corrected for missegmentations, which was necessary in 12 out of 2 × 17 + 11 = 45 examinations.

Airways were assessed generation-based from 2nd to 7th generation for wall thickness (WT), wall percentage (WP), total diameter (TD) and lumen area (LA) using the parameter-free integral-based method [26]. Although YACTA is potentially able to evaluate deeper airways generations, e.g. 8th–10th, the complete analysis was, due to the increasing difficulty of segmentation of smaller airways generations, only available up to the 7th airways generation for all nearly patients (values for the 7th generation could not be determined in two patients). A standardised measure for WT was derived by plotting the square root of the airway wall area against the internal perimeter of the airway for every measured airway location. By using the regression line of this plot, the square root of the wall area for a 'theoretical airway' with an internal perimeter of 10 mm was determined and defined as Pi10 [31]. Pi10 values were determined for the whole airway tree and for all bronchi within the different lung lobes down to the 7th airways generation. Furthermore, average WP values were determined for the whole airway tree, right and left main bronchus (RMB and LMB), and all bronchi within the different lung lobes.

Total lung volume (TLV) was calculated for each patient. Air trapping was quantified by three different parameters: 1) $RVC_{856\text{-}950}$ which is defined as the difference between the expiratory and inspiratory lung volumes with attenuation between −856 and −950 HU divided by the total lung volume without emphysema. The index ranges from −1.0 to 0, greater values (closer to zero) mean more air trapping [32]. 2) E/I MLA which is the expiratory to inspiratory ratio of mean lung attenuation with a range from 0 to 1.0, greater values mean more air trapping [32]. 3) A1, 2 and 3 which use three thresholds for the definition of air-trapping, expressing the size of the defect areas as a fraction of the whole analysed parenchyma region. A1 represents defects on the basis of liberal criteria, (mild air-trapping), while A3 represent defects on the basis of stringent criteria as published previously (severe air-trapping) [33].

All variables were computed for total lung and respective for all lobes separately (i.e. right upper (RUL), middle (RML) and lower (RLL) lobe, as well as left upper lobe (LUL), lingula (LLi) and left lower lobe (LLL)) and exported as a structured report as well as in a dedicated database.

2.5. Clinical outcome measures

Body plethysmography with reference values according to Global Lung Initiative (GLI) [34], 6 min Walk Test (6MWT) and Asthma Control Test (ACT) were performed at baseline and during the time of the follow-up CT scan (Table 1). Medication prior to BT as well as at the time of follow-up was recorded.

2.6. Statistical analysis

All data were analysed using commercially available software (SigmaPlot,Systat Software GmbH, Erkrath, Germany). Data is given as mean ± standard deviation (SD) unless specified otherwise. Quantitative CT data were tested for changes after intervention with the Mann-Whitney-Wilcoxon signed rank test for paired measurements due to a non-parametric distribution. The clinical outcome measures were assessed with a paired *t*-test and the spearman rank order correlation coefficient r_s was calculated for QCT data vs. clinical outcome measures. A p-value of < 0.05 was considered statistically significant.

3. Results

3.1. Changes in airway dimensions before and after bronchial thermoplasty

In the control group, QCT did not reveal significant changes of the airway dimension during the observational period (Table 2). In the group of patients who had undergone BT, nearly all airway generations showed a tendency of reduction of WT and WP parameters after BT. The averaged WT decreased from 1.63 mm to 1.57 mm and WP from 57.94% to 55.82% (Fig. 1), which was significant for the combined analysis of the 2nd–7th airway generation for WT (−3.94%; p = 0.026) and WP (−3.67%; p < 0.001). The reduction of WT was more evident in smaller airway generations (5th–7th) than in proximal ones (2nd–4th), with even a slight increase by 0.48% observed in the 4th airway generation (Table S1). Looking at the individual patients the changes in WT were inhomogeneous. Only three patients showed reduced WT for all airways generations (e.g. 2nd–7th), while in most patients at least 1–2 airways generations showed a slight increase in WT. If the mean change in WT was calculated over all airways generations (e.g. 2nd–7th) for every individual patient, an increase in WT was noticed in five patients.

LA increased insignificantly from 39.63 mm up to 40.25 mm (+1.57%; p = 0.147). TD showed a non-significant increase in the combined assessment of the 2nd–7th airway generation from 9.50 mm up to 9.53 mm (+0.36%; p = 0.730) (Table 2). More specifically, TD increased in larger airway generations (2nd–4th), while it decreased in smaller airway generations (5th–7th) (Table S1).

The averaged WP values were reduced for the whole lung, the RMB and the LMB, and for all lung lobes. The bronchi in the lingula showed the highest and the bronchi in the middle lobe the lowest reduction. The averaged Pi10 values were decreased for the whole lung and the different lung lobes (Table S2).

Table 2
Airway dimensions in the treatment and the control group.

	Before	After	Δ	Δ%	p
BT					
WT [mm]	1.63 ± 0.49	1.57 ± 0.48	−0.06	−3.94	**0.026**
WP [%]	57.94 ± 10.51	55.82 ± 9.56	−2.13	−3.67	**0.001**
LA [mm^2]	39.63 ± 40.92	40.25 ± 40.53	0.62	1.57	0.147
TD [mm]	9.50 ± 3,67	9.53 ± 3.70	0.03	0.36	0.730
Pi10	0.34 ± 0.08	0.32 ± 0.10	−0.02	−5.89	**0.050**
Controls					
WT [mm]	1.75 ± 0.61	1.76 ± 0.53	0.01	0.73	0.933
WP [%]	55.68 ± 11.70	57.09 ± 8.97	1.42	2.33	0.797
LA [mm^2]	48.26 ± 46.47	42.90 ± 38.04	−5.35	−11.09	0.146
TD [mm]	10.47 ± 3.99	10.18 ± 3.59	−0.29	−2.73	0.230
Pi10	0.31 ± 0.10	0.32 ± 0.07	0.01	0.81	0.577

Mean and standard deviation for the aggregated the 2nd–7th airway generation for wall thickness (WT), wall percentage (WP), lumen area (LA) and total diameter (TD) as well as Pi10 for the whole airway tree before and after bronchial thermoplasty and the control group. Furthermore, mean differences **Δ** are given in absolute values and %. A p-value of < 0.05 was considered statistically significant (bold).

3.2. Changes in air-trapping before andafter bronchial thermoplasty

The mean lung volume (TLV) decreased by 68 cm^3 on average (−1.27%; p = 0.459) (Table 3), indicating a reduction of hyperinflation after BT. The most extensive decrease in volume was in the lower lobes with 28 cm^3 (−2.27%) for RLL and 56 cm^3 (−4.51%) for LLL (Table S3). All air trapping parameters decreased significantly for the whole lung, predominantly $RVC_{856\text{-}950}$ by −13.4% (p < 0.001) (Fig. 2) (Table 3). Accordingly, the lobe-based approach showed reduced air-trapping for $RVC_{856\text{-}950}$ in all lobes with a maximum of −29.29% for the LLL and a minimum of −10.33% for RLL (not significant for single lobes). E/I MLA, and A1-A3 showed comparable results (Table S3).

3.3. Changes in clinical parameters before and after bronchial thermoplasty

Twelve of the 17 treated patients required oral corticosteroids on a regular basis on top of the high dose inhaled corticosteroid and long acting beta-agonist combination inhalers. Seven patients had received omalizumab prior to thermoplasty. Medication prior to thermoplasty and until the follow up remained the same, although the dosage of oral steroids was adjusted in some patients depending on an exacerbation. Clinical changes six and twelve month after thermoplasty showed a tendency of improvement; however, the values were not significant (Table 4). FEV1 improved by 192 ml (−109 to + 494 ml 95% CI, p = 0.195), RV reduced by 237 ml (−919 to +445 ml, 95% CI, p = 0.472), ACT improved by 1.7 points (−1.8 to +5.2 95% CI, p = 0.313). The 6MWT showed a mean improvement by 36.7 m (−3.54 to +76.97 m, p = 0.070). Patients were able to reduce their oral cortisone dose by 5.58 mg (−22.6 to +11.4 mg, p = 0.497). There was no significant correlation between QCT data and clinical outcome measures.

4. Discussion

In the present study we analysed airway changes in 17 patients with severe asthma who had undergone BT and compared them with 11 patients who also had severe asthma but did not receive BT. After performing BT, there was a significant decrease in WT and WP. LA tended to increase insignificantly for the combined 2nd– 7th airways generations. TD increased insignificantly overall but showed an increase in larger airway generations (2nd–4th) and a decrease in smaller airway generations (5th–7th). Our observations are in line with data recently published by Ishii [35] and Zanon et al. [36], which both could show a decrease in WT in patients treated with BT.

However, generation-based evaluation was performed, in neither study, which would have been interesting considering the new findings by Facciolongo et al. [8], who describes a reduction of nerve fibres in epithelium and in airway smooth muscle one year after BT. This could explain the reduction in WT and the increase in LA in the distal airway generations (4th–7th), which are not directly treated by radiofrequency. Since it is believed that the main direct effects of BT are the reduction in overall airway smooth muscle mass and effects on the contractile properties of the airway smooth muscle [6,9], this phenomenon may also be explained by the hypothesis proposed by Debry et al., that “diffusion of energy” along the bronchial wall could lead to a decrease in airway smooth muscle mass in airway generations distal to

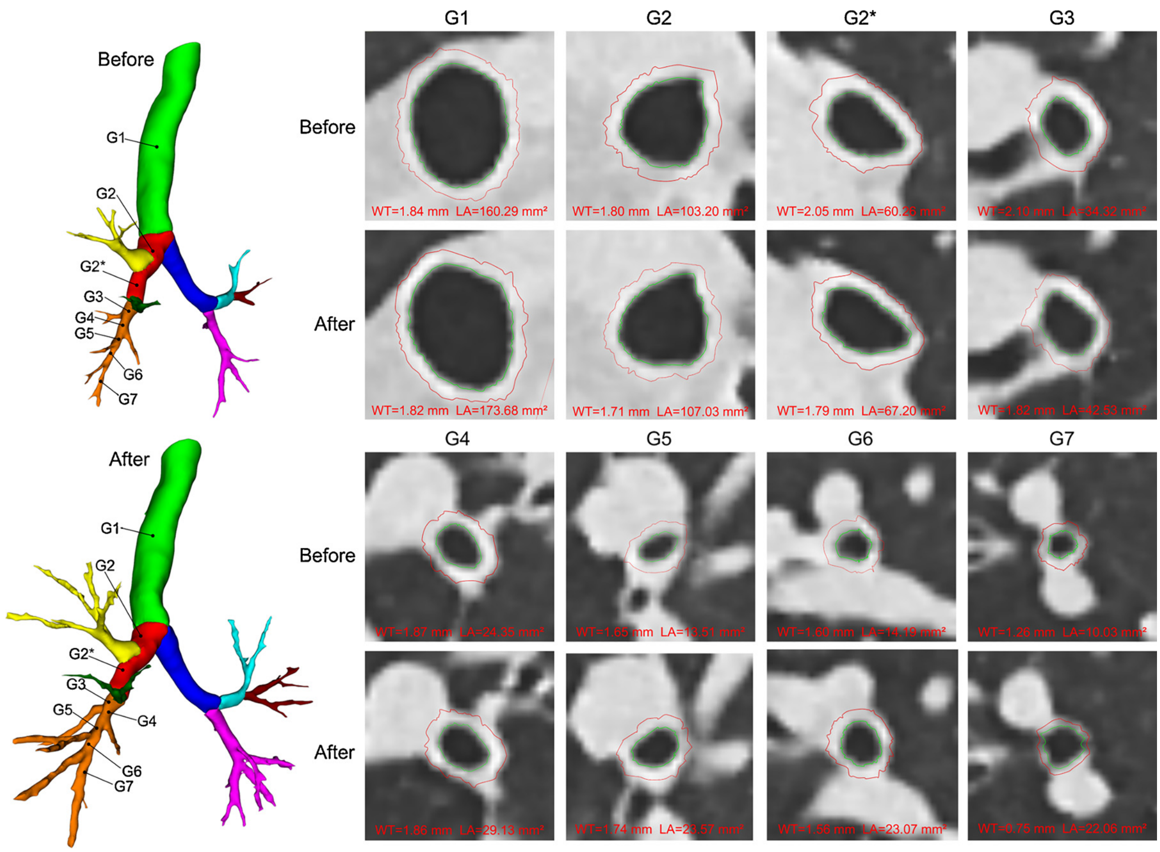

Fig. 1. Airway dimensions before and after bronchial thermoplasty and changes of clinical parameters. Representative images of one patient before (FEV1% = 39, vital capacity 1.2 l) and after bronchial thermoplasty (FEV1% = 48, vital capacity 1.4 l). Left panel: segmented airway tree before and after BT. Right panel: Orthogonal slices through airways, inner (green) and outer (red) wall borders as detected by YACTA are indicated. Wall thickness (WT) and lumen area (LA) are given in each panel for the individual airway generations displayed. Note the predominant decrease in WT in small airways.

Table 3
Changes in air-trapping before and after thermoplasty.

	Before	After	Δ	Δ%	p
TLV [cm^3]	5319 ± 1577	5251 ± 1540	−68	−1.27	0.459
$RVC_{856\text{-}950}$	−0.35 ± 0.16	−0.41 ± 0.19	−0.06	−13.35	< **0.001**
E/I MLA	0.94 ± 0.03	0.92 ± 0.04	−0.02	−1.77	< **0.001**
A1 [%]	81.81 ± 1.52	79.27 ± 2.69	−2.54	−3.11	< **0.003**
A2 [%]	68.63 ± 2.15	64.03 ± 4.53	−4.6	−6.71	< **0.001**
A3 [%]	29.87 ± 4.24	26.18 ± 10.26	−3.69	−12.37	< **0.001**

Means and standard deviations for total lung volume (TLV) and the air trapping parameters $RVC_{856\text{-}950}$, E/I MLA and A1-A3 for the treatment group. Also mean difference **Δ** and mean difference in % are given. A p-value of < 0.05 was considered statistically significant (bold).

treated airways [37]. However, according to the latest findings of Facciolongo et al. the impairment of neuronal innervation and a resulting bronchial dilatation seem more likely, comparable to the effect of bronchodilation after inhaling anticholinergic agents shown by Hasegawa et al. [38]. Another example for this theory is the targeted lung denervation (TLD), which acts by destroying the parasympathetic fibres in the main bronchi and hence reducing the amount of bronchoconstriction as seen with anticholinergic agents. TLD has been shown to improve FEV1 and SGRQ (St George Respiratory Questionnaire) in patients with COPD [39]. In our study the changes in WT after BT were inhomogeneous when looking at the airway generations within individual patients. Only three patients showed a reduced WT for all generations (e.g. 2nd–7th), while in most patients at least 1–2 airways generations showed a slight increase in WT. In addition, if the individual values for the 2nd–7th airway generation were averaged, WT increased in five patients after BT. These observations may open up new possibilities to distinguish responders from non-responders in the future. However, significantly more patients are needed for forming appropriate groups and correlate them with clinical parameters.

Interestingly, total diameter (TD) showed a significant decrease in the airway generations (5th–7th) after BT. The discovery apparently contradicts the statements made above but it seems possible that a direct destruction of the muscle cells is required to disturb the anatomical structure of the whole wall and to enlarge the total bronchial diameter. This possibility could be examined in a pathological study. However, our findings are supported by the fact that none of the airway parameters had a significant change in the untreated control group.

After BT, median TLV decreased non-significantly, showing volume reduction in both lower and the middle lobe with a slight volume increase in the upper lung regions. Air trapping was reduced significantly in the entire lung. Results from COPD genetic studies have shown that physiologic airway obstruction correlates with QCT air trapping indices [12,32]. Similarly, in asthmatic patients QCT-determined air trapping has been associated with increased disease severity [40]. Hyperinflation/emphysema in asthmatic patients has not been extensively studied, partly because this phenomenon may be highly variable in an individual and dependent on the actual clinical situation (stable vs. exacerbation). However, a few studies have suggested that emphysema in asthmatic patients is likely secondary to smoking [41]. Recently Debray et al. examined short-term pulmonary changes following BT showing early pulmonary hyperdensities in all treated lobes. These findings however were unrelated to clinical symptoms and decreased spontaneously after one month [37]. Zanon et al. showed a significantly reduced air trapping and non-significantly lower TLV after BT [36]. Compared to Zanon et al. in our study, the decrease in TLC was less

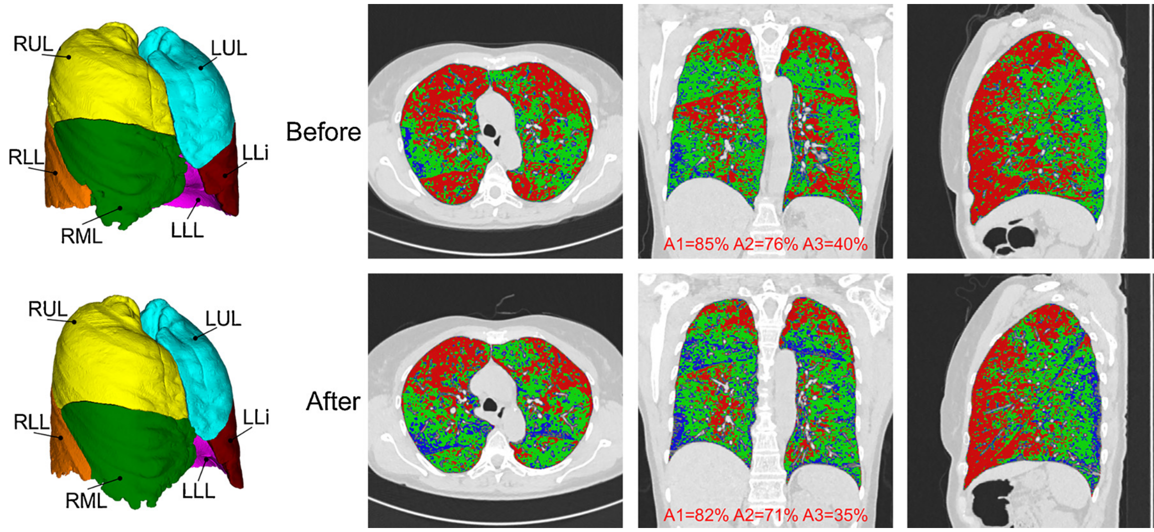

Fig. 2. Air-trapping before and after bronchial thermoplasty. Representative example of a patient before and after bronchial thermoplasty (BT) (same patient as in Fig. 1). Air trapping categorized in three grades (A1 (green) = moderate, A2 (yellow) = medium, A3 (red) = severe) and visualized on parameters maps before and after BT. After BT air trapping was reduced corresponding to changes in airway dimensions.

Table 4
Change in clinical parameters before and after bronchial thermoplasty.

	n	mean	Δ	p	95% condidence interval of the diff.	
					lower	upper
FEV1 [s]	16	1.35	0.19	0.195	−0.109	0.494
FEV [%]	16	1.67	7.18	0.115	−1.955	16.308
VC [cm^3]	16	1.26	0.22	0.226	−0.153	0.599
VC [%]	16	1.61	6.88	0.127	−2.181	15.946
Tiffenau	16	1.19	3.88	0.253	−3.058	10.823
RV [cm^3]	16	−0.74	−0.24	0.472	−0.919	0.445
RV [%]	16	−0.77	−11.59	0.451	−43.409	20.233
ACT	13	1.05	1.71	0.313	−1.812	5.240
6 MWT	13	1.97	36.71	0.070	−3.539	76.967
Cortison [%]	16	−0.67	−5.59	0.497	−22.619	11.443

FEV1 = forced expiratory volume in 1 s, VC = vital capacity, RV = residual volume, ACT = Asthma Control Test, 6MWT = 6-min walk test. Percentage values refer to predicted value.

striking (67 cm^3 vs. 269 cm^3). However, we could show a definite volume reduction in both lower lobes and the middle lobe, which may be explained by a higher lung compliance due to reduced air trapping. In supine position, there is an increased collapse of the lower lobes, while there is compensatory volume increase in upper lung regions. Furthermore, we could show a decrease in air trapping for RVC by ~13% after BT. The most evident explanation for the reduction in air trapping is an ameliorated ventilation of peripheral airways due to a decrease in airway obstruction. These findings are in line with the reduction in WT.

With regards to the clinical changes in our retrospective analysis, we were able to confirm previously published findings. As previously described, following BT, FEV1 and 6MWT did not increase to a statistically significant level. However, patients report less exacerbations as well as an improvement of their clinical symptoms and a higher quality of life (reference: AIR, RISA and AIR-2 trial). In our study all clinical parameters improved, however, not to a statistically significant level. This is most likely due to the small number of participants in the present retrospective study.

As this is a retrospective analysis, the BT treated and the control group show some differences with regards to OCS use and FEV1 in their baseline characteristics. This confirms previously published findings that in the 'real life experience' the patients receiving thermoplasty are on higher doses of OCS and show worse lung functions than the initial trial patients of the AIR-2 trial [42].

The limitations of our current study include the low numbers of patients as well as the retrospective approach resulting in different time delays of the CT scans in relation to the intervention. Variations in QCT data were accompanied by a tendency of improvement in clinical changes after BT; however, these changes were not significant. This indicates that changes in QCT may be linked to clinical improvement, the lack of statistical significance may be attributable to our small study population. Thus, future prospective studies with larger patient numbers and multicentre data are necessary to put the changes shown into a meaningful clinical context.

5. Conclusion

QCT was able to show post interventional changes in airway and lung parenchymal morphology in asthma patients treated with BT. A reduction in WT and a tendency to increased LA resulting in a decreased WP may be interpreted as direct therapeutic effects caused by a reduction in airway-smooth muscle mass and denervational changes. QCT could also show a significantly reduced air trapping in the entire lung. Larger scale prospective assessments will be necessary to assess long-term changes following BT and to relate QCT parameters to the clinical response.

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Role of the funding source

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of interest

The parts of the lobe segmentation algorithm that are used for the lobar labeling of the airways have been licensed to the company Imbio, LCC. There are no further patents, products in development or marketed products to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2018.08.007.

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