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RESEARCH ARTICLE

Response of individual airways in vivo to bronchial thermoplasty

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Abstract

Bronchial thermoplasty (BT) is a treatment for moderate-to-severe asthma, which generally improves quality-of-life scores but not conventional measures of lung function. Newer methodologies have begun to demonstrate the underlying physiological changes and elucidate the mechanism of action. We postulated that systematic, computed tomography (CT)-based assessment of the response of *individual* airways to BT is feasible, and our aim was to determine the distribution of these responses and the relationship with airway size. Twenty patients meeting the European Respiratory Society/American Thoracic Society (ERS/ATS) definition of severe asthma underwent BT and assessment including CT, Asthma Control Questionnaire (ACQ), and spirometry. Treatment was structured so that the left and right lungs are treated sequentially with a midtreatment assessment providing an internal control. Pairs of CT scans were analyzed using a new semiautomatic processing algorithm that matched individual segmented airways for quantitative comparison. Cross-sectional airway lumen area from matched airway pairs in treated lungs increased on average by 6.4% after BT ($P < 0.02$) but showed no change in the untreated lung. Matched airway length was also unchanged. Breakdown by airway size showed amplified response in more distal airways, with the smallest quintile of measured airways dilating by 13.2% ($P < 0.001$). ACQ improved from 3.5 ± 0.9 to 1.9 ± 1.2 ($P < 0.001$). These data show that the response to BT in individual airways can be assessed by CT and that dilation is heterogeneous and predominant in distal compared with proximal airways. A CT-based approach may further our understanding of the physiological changes in BT and aid in the development of refined and personalized versions of the therapy.

NEW & NOTEWORTHY CT scanning was used to evaluate the response of individual airways in patients undergoing bronchial thermoplasty. Airways dilated after treatment by 6.4% on average with substantial heterogeneity and a greater response in the most distal airways measured.

asthma; bronchial thermoplasty; bronchodilation; imaging

INTRODUCTION

Bronchial thermoplasty (BT) is a treatment for moderate-to-severe asthma in which radiofrequency energy is delivered directly to the targeted airways via bronchoscopy (1, 2). The goal is thermal ablation of the airway smooth muscle (ASM) layer, and hence permanently reduced capacity for bronchoconstriction in the treated airways (3, 4). BT has generally shown improvements in clinical measures of asthma control, such as the Asthma Control Questionnaire (ACQ) and exacerbation frequency, but changes in conventional measures of lung function have been modest or nonexistent (2, 5–7). This, along with the substantial placebo component to the quality-of-life score improvements (5), has led to some controversy regarding BT's efficacy and underlying mechanism of action [e.g., (8, 9)].

More recently, new measurements, such as quantitative computed tomography (CT)-based assessments (10, 11) and hyperpolarized gas MRI (12, 13), have begun to elucidate the physiological changes and mechanism of action behind BT. We have previously shown that CT-derived aggregate airway volume is increased following BT, and that these changes correlate significantly with improvements in ACQ and plethysmographically determined airway resistance (10, 14). Focal dilatation on CT has also been observed following BT (15), consistent with high-resolution CT measurements of airway dose-response in dogs (16). Although the changes in total airway volume provide clear physiological validation of BT's mode of action, many questions remain unanswered. Are these changes driven by airway length, caliber, or the number of airways measured? Do the airways dilate uniformly, and if not, what is the distribution of the response across proximal and distal airways?

To answer the above questions, we have developed a new method to systematically assess the response of *individual* airways derived from matched pairs of CT scans; together with a contemporaneously assessed untreated lung as a temporal control, this provides new knowledge on how airway size and anatomical location within the bronchial tree impact the response to BT. To the best of our knowledge,

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this is the first systematic measurement of the response of individual airways to BT in vivo. These findings were compared with previous theoretical predictions of BT's efficacy based on changes in ASM force production, helping not only to advance our understanding of the underlying process behind BT but also representing a first step toward predicting individual patient response.

METHODS

Participants

Participants were referred for BT from a tertiary hospital severe asthma clinic. Patients needed to be using inhaled triple therapy and have poorly controlled symptoms with frequent oral steroid requiring exacerbations to be considered for BT. All participants were required to meet the European Respiratory Society/American Thoracic Society (ERS/ATS) definition of severe asthma, and alternative respiratory conditions such as chronic obstructive pulmonary disease (COPD) or bronchiectasis had been excluded (17).

Setting and Procedure

All procedures were conducted under general anesthesia with patients routinely observed in hospital overnight postprocedure. For the purposes of this study, the scheduling of the BT procedures was altered in a novel way to achieve one treated lung (left side) and one untreated lung (right side) at the midtreatment assessment. A timeline for evaluation and procedures is shown in Fig. 1*A*. The left lower lobe was treated in the first BT session and then the left upper lobe in the second session. Imaging studies were conducted at

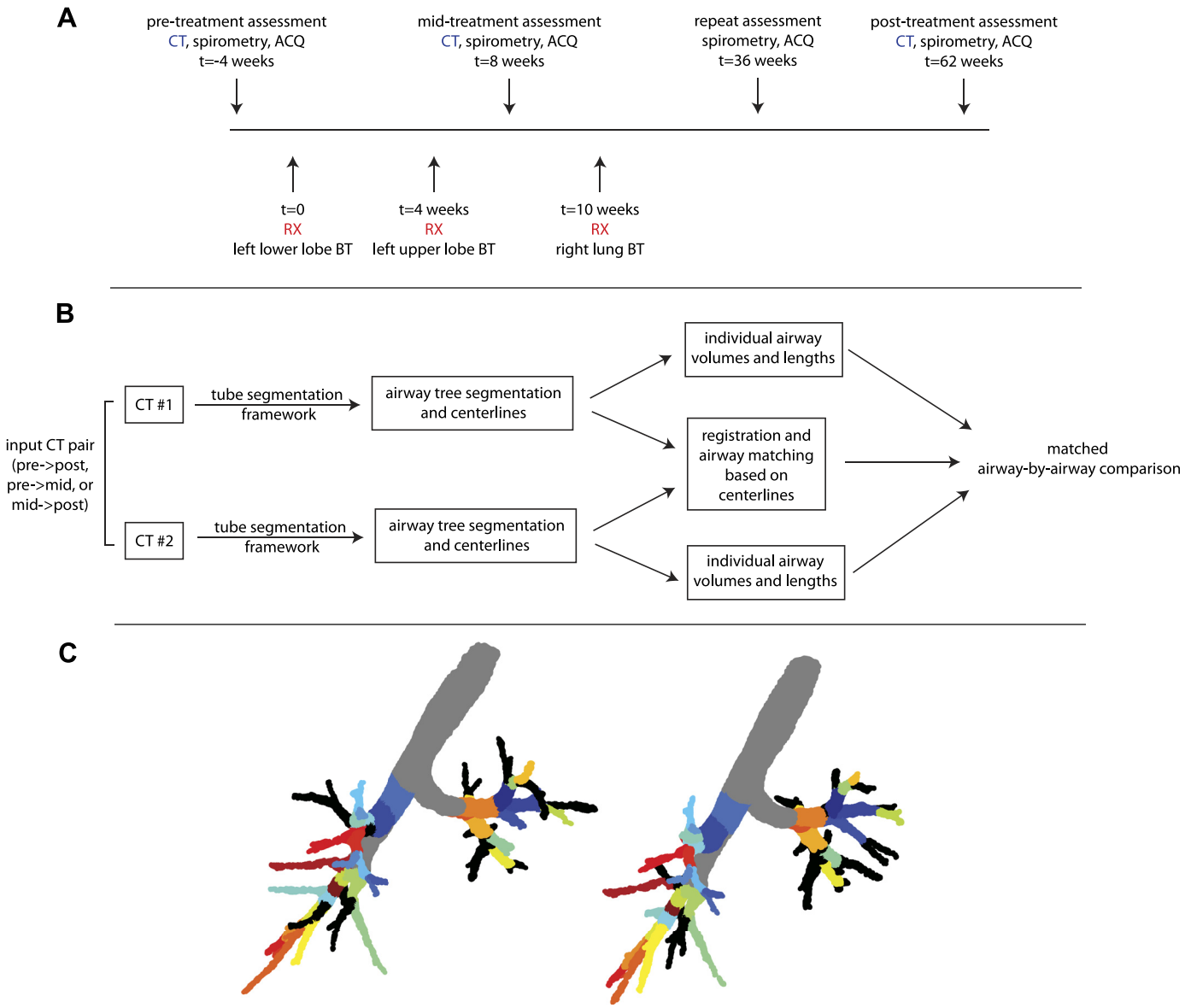

Figure 1. Illustration of methodology. *A*: treatment and assessment timeline. *B*: schematic illustration of image analysis method for a single pair of CT scans, repeated for all 56 scan pairs. *C*: example of resulting matched airway pairs, gray = unused, black = unmatched. ACQ, Asthma Control Questionnaire; CT, computed tomography.

baseline, and then again 4 wk after completion of BT treatment to the left lung, and before treatment of the right lung (which acted as a control). Following the second set of imaging, the right lower and upper lobes were treated together in the final BT session. Consistent with current guidelines, the right middle lobe was not treated. Imaging studies were then repeated 12 mo after completion of all BT procedures.

Clinical Measurements

The following data were recorded for all patients: age, gender, weight, height, asthma medication usage, asthma exacerbation history, lung function parameters, and the five-item ACQ (18). Written permission to use the ACQ was provided by its author, Elizabeth Juniper. Key clinical outcome parameters included changes measured at 6 and 12 mo in *1*) ACQ, *2*) prebronchodilator forced expiratory volume in 1 s (FEV1), *3*) short acting beta-agonist (SABA) usage (measured in puffs/day), *4*) daily maintenance of oral corticosteroid (OCS) dose (measured in mg/day of prednisolone), and *5*) the number of oral steroid requiring exacerbations of asthma reported in the previous 6 mo. Patient assessments were performed by experienced clinical research nursing and scientific staff and were conducted independently of the procedural team. Spirometry was performed using the Jaegar Masterscreen Body (Carefusion, Hoechberg, Germany), and tests were conducted in the morning, and having withheld bronchodilators since the previous evening. The laboratory equipment was calibrated on the morning of testing, and all tests were conducted to ERS/ATS standards (19). The single breath carbon monoxide diffusing capacity (DLCO) was also tested, and at least two acceptable maneuvers within 3 mL/min/mmHg of each other were required. The predicted value equations used were taken from the Global Lung Initiative (20).

Imaging

Noncontrast CT scanning was performed on a 128-slice Siemens Definition AS+ scanner with a helical slice thickness of 0.6 mm, rotation time of 0.6 s, detector coverage of 38.4 mm, and tube voltage of 100 kV. Scans were performed at full inspiration [total lung capacity (TLC)] and in a stable state, prebronchodilator, and before periprocedural oral steroid administration. As part of the baseline scanning, an emphysema score was determined by counting the percentage of intrapulmonary voxels with a density in the range of −1024 to −950 Hounsfield Units [divided by the total lung volume (21)].

Image Analysis

The image analysis process was semiautomatic and performed blind to both patient and treatment condition by the same operator. A schematic diagram of the analysis method is given in Fig. 1*B*. The airway tree was segmented from the CT source data using the tube segmentation framework (22) as implemented in CustusX v18.04 (23) (SINTEF Digital, Trondheim, Norway). Centerlines for the segmented airways were obtained concurrently. The process was almost fully automatic except for the determination of a segmentation "seed point" placed manually in the trachea for scans in which fully automatic segmentation failed (approx. 35% of scans). Segmentation of the airways other than the trachea was not sensitive to seed point placement, and the tracheal segmentation is not used in the analysis. After segmentation and centerlining, the analysis process was fully automatic.

Pairs of airway tree segmentations were registered by rigid transformation using the coherent point drift algorithm (24) as implemented in Matlab R2020a (Mathworks, Natick, MA). Airway centerlines were transformed according to the same rigid transformation, and then airways were matched according to the transformed centerlines. The deviation between two transformed centerlines was defined to be the 2-norm of the segment difference normalized by the average segment length; in essence this measures the relative difference between two centerlines.

Airway lumen volumes were determined by assigning points in the segmentation point cloud to the nearest airway centerline. This point cloud then defines the airway surface, and the convex hull was computed to find the airway lumen volume. Unmatched airways and airways with measured volumes greater than 2,000 mm^3, assumed to be more proximal than those receiving BT actuations, were not used in the analysis. Airway lengths were determined from the airway centerlines, and airway lumen average cross-sectional area is then determined by the ratio of the volume to the length.

The analysis process was repeated for all scan pairs. Eighteen patients completed their treatment and hence each had three scan pairs available for analysis: pre >mid, mid >post, and pre >post; totaling 54 scan pairs. Including two additional patients who only reached midtreatment (see RESULTS), a further two scan pairs were available i.e., 56 pairs in total. On average, each scan pair yielded 25–30 matched airway pairs (~50% of segmented airways were matched). For analysis purposes, airway generation was estimated from airway size using the data of (25) relating average lumen airway and airway generation.

Ethics

Prospective approval to undertake this study was provided by the Peninsula Health Human Research Ethics Committee, and no patient was enrolled without having given written informed consent.

Statistical Analysis

SPSS version 25 (IBM corporation, New York, NY) and Matlab R2020a were used for statistical analyses. Normally distributed data are reported as mean ± SD, and a *t* test was used; nonparametric data are reported as median [interquartile range (IQR)], and the sign test was used. Statistical significance was taken at $P < 0.05$. For comparison between model predictions and the data, a nonparametric regression smoother [Friedman's super smoother (26)] was used to visualize the trends.

RESULTS

Baseline Characteristics

Twenty consecutive patients with very severe asthma participated in this study, seven males, 13 females, age 56.0 ± 14.3 yr, body mass index (BMI) 32.9 ± 7.6 kg/m^2. The mean

Table 1. *Clinical response to BT (n = 18)*

Parameter	Baseline	6 Mo Post	12 Mo Post	*P*
ACQ score	3.5 ± 0.9	2.1 ± 1.3	1.9 ± 1.2	0.001
FEV1 (%predicted)	45.7 ± 14.0	50.4 ± 14.8	51.4 ± 15.6	0.065
SABA (puffs/day)	13.4 ± 9.9	5.9 ± 6.6	5.6 ± 6.6	0.001
OCS (mg/day)	14.3 ± 15.8	6.2 ± 7.9	5.5 ± 6.6	0.030
Exacerbations (per 6 mo)	2.6 ± 2.0	1.2 ± 1.8	1.2 ± 1.7	0.020

ACQ, Asthma Control Questionnaire; BT, bronchial thermoplasty; FEV1, 1-s forced expiratory volume; OCS, oral corticosteroid (prednisolone); *P*, analysis of variance repeated measures; SABA, short-acting beta agonist.

ACQ score was 3.5 ± 0.9. Seventeen of the 20 patients were being treated with maintenance oral prednisolone—group mean dose 15.3 ± 15.3 mg/day. All patients were using triple inhaler therapy with beclomethasone-equivalent inhaled steroid dose 1,750 ± 786 μg/day. The average daily requirement for SABA therapy was 13.4 ± 9.4 puffs/day. The frequency of OCS requiring exacerbations in the 6 mo before BT was 2.8 ± 2.1.

The mean prebronchodilator FEV1 was 44.5 ± 14.0% predicted, with an average improvement of 15.4 ± 16.1% after 400 μg salbutamol. The vital capacity was 70.9 ± 14.9% predicted, and the forced expiratory ratio was 52.2 ± 12.2%. Within the group, there were no active smokers, 12 never smokers, and six patients with a pack year history in excess of 10. The mean DLCO per unit lung volume was 94.2 ± 29.7% predicted, and the median CT emphysema score was 0.2% (IQR 0.01, 2.0). The median IgE was 18.5 (IQR 5, 250) International Units, and the median peripheral blood eosinophil count was 0.1 (IQR 0, 0.15) cells/μL.

Clinical Response to BT

Eighteen patients completed 12-month follow-up, and their clinical responses to BT are summarized in Table 1. Two patients had their treatment interrupted by the Covid-19 pandemic, and in those two patients, we have CT data before and after the left lung was treated, but the right lung treatment had not been completed at the time of writing. Significant, substantive and sustained improvements were observed in ACQ, exacerbation frequency, and the requirement for oral steroids and SABA. A trend toward improvement in FEV1% predicted was observed but did not reach statistical significance ($P = 0.065$).

Paired-Airway Image Analysis Results

The overall changes in matched airway measurements from 56 scan pairs (yielding 1,407 matched airway pairs) are shown in Fig. 2. Figure 2*A* shows the change in airway area. In the first panel (pre >mid), the mean airway area is seen to increase significantly after treatment of the left lung by 6.0% (SE 2.5%), whereas no significant change is observed in the untreated right lung. In the second or middle panel (mid >post), the effect of treating the right lung is observed, with no change to the left side. In the final panel (pre >post), the overall effect of treatment compared with baseline is observed. Corresponding measurements of airway length are shown in Fig 2*B*; no significant changes are present.

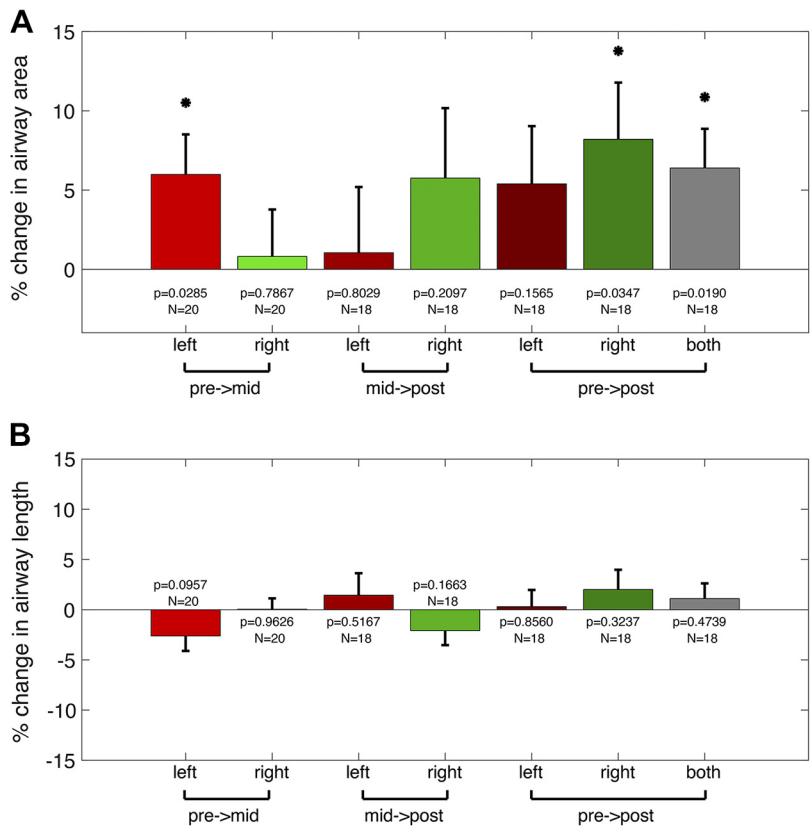

Figure 2. Results of matched airway analysis. *A*: change in airway cross-sectional lumen area. *B*: change in airway length. Mean ± SE, *$P < 0.05$. Between pretreatment and midtreatment assessments, the left lung is treated and the right remains untreated; between midtreatment and posttreatment, the right lung is treated. The pre >post pair assessment captures treatment of both sides.

The overall mean increase in airway area is 6.4% (SE 2.5%) for all airways once both lungs are treated ($P < 0.02$). However, it is possible that a mean increase of 6.4% is made up of a larger dilation in some airways with no dilation in others, or a stratified effect in airways of different sizes. To examine the regional distribution of response to BT, we examined the change in airway area (y-axis) by size of the airway (x-axis) for individual airways. In Fig. 3, the datapoints are additionally grouped into quintiles by baseline cross-sectional area, and the effect of BT on cross sectional area is examined at the three time points. Once again, no changes are demonstrated on the untreated control side. Following treatment, the greatest changes are observed in the most distal measured airways, and the least changes in the more proximal airways. In the final panel, with data from both lungs amalgamated, the mean increase in cross sectional area in the most distal airway quintile was 13.2% (SD 34.4%, $P < 0.001$).

To conceptualize exactly which locations of the bronchial tree were responding to BT, the data were regrouped by estimated airway generation [based on (25)], and this is shown in Fig. 4. The final panel summarizing the effects for treatment of both lungs shows no change in airway size for airway generations 4 and 5, a small increase in airway size for generations 6–9, and the greatest impact of BT is demonstrated in airway generations beyond 9—i.e., the most proximal airways measured in this study.

Comparison with Model Predictions

We have previously developed a theoretical model of BT that predicted that functional effects of BT will extend beyond the directly treated airways by means of airway interdependence driven by increased flow to downstream segments and parenchymal tethering (27). Figure 5 reproduces these predictions in comparison with the present measurements. As in Fig. 3, the axes are % change in airway cross-sectional area versus airway size, but here we show only a nonparametric regression [Friedman's super smoother (26)] rather than the individual airway data. Importantly, model predictions are dependent on the degree of ASM tone that may be present in a patient because ASM tone alters apparent luminal volume. Therefore, for any given reduction in muscle mass, BT will be more effective at increasing apparent luminal volume in individuals where bronchoconstriction

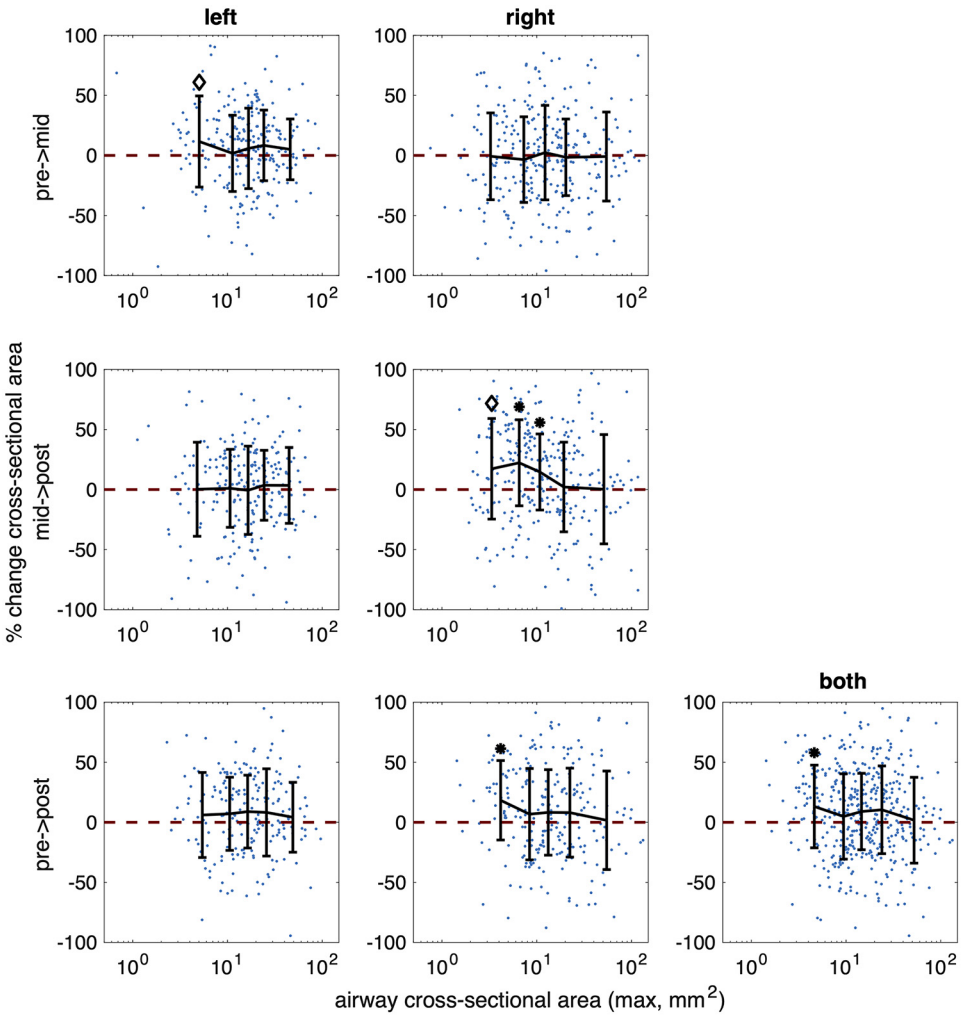

Figure 3. Individual airway measurements from matched CT pairs (blue dots), further broken down into airway size quintiles (black). The *top* row gives results for pretreatment and midtreatment matched scans; the *middle* row for midtreatment and posttreatment; and the *bottom* row for pretreatment and posttreatment. The left column gives results for the left lung (treated between pre- and midtreatment), the center column for the right lung (treated between mid and post), and the right column for both lungs combined. Note that the most proximal airways measured are likely to be treated in a relatively high proportion, while progressively more distal airways are potentially treated, but with a decreasing fraction of those measured airways having actually undergone direct treatment. Airway cross-sectional area given on the x-axis is the maximum area measured in the scan pair. *$P < 0.01$, diamond: $P < 0.05$. CT, computed tomography.

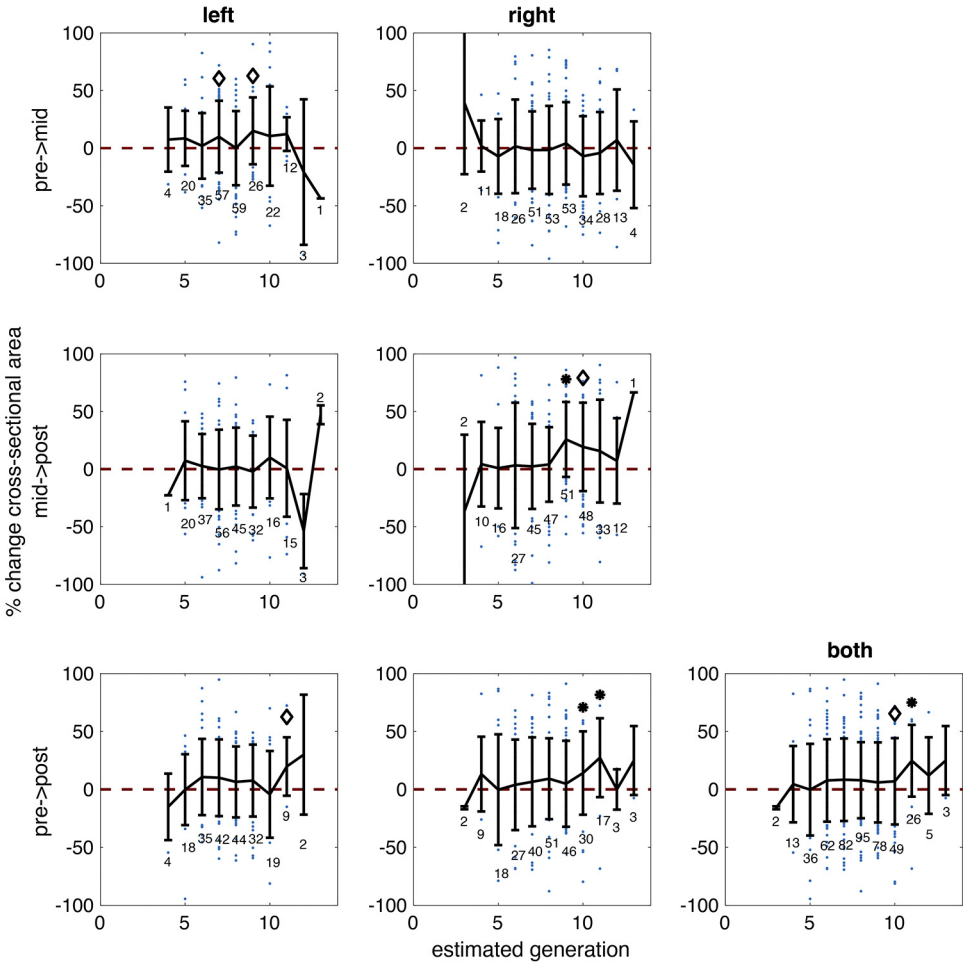

Figure 4. Individual airway measurements from matched CT pairs, now arranged by estimated airway generation. Layout as in Fig. 3, additionally with the number of measured airways in each estimated generation noted. CT, computed tomography.

due to activated and therefore shortened ASM is present. The model predictions therefore simulate a response to BT in the scenario where patients lack ASM tone altogether (red) or exhibit persisting ASM tone (yellow), which may be expected in a group of severe asthmatics. The predictions are compared with empirical CT-derived measurements (blue). The comparison indicates that CT-assessed response to BT is in good accordance with the predictions and that subjects are likely to exhibit at least some level of ASM tone since the empirical data lay within simulations that include or exclude residual ASM tone. The implications of these findings will be considered in the discussion.

DISCUSSION

CT-derived measurements of individual airway response to BT show that on average the cross-sectional area of the measured airways increases by 6.4% in response to BT ($P < 0.02$), but that there is no significant change in airway length. Moreover, the averages conceal substantial heterogeneity, and indeed some airways appear constricted in their posttreatment assessment, whereas others dilate much more than the average, as previously predicted (27). Perhaps most importantly, the response is not uniform across airway size: among those airways large enough to be assessed by CT, the more distal airways dilate more prominently, with the most distal quintile increasing in cross-sectional area by 13.2%. These findings help to demonstrate BT's underlying mechanism of action and also have implications for the design of improved therapies.

The implied level of prebronchodilator ASM tone in this cohort provide a useful datapoint in interpreting the overall results of BT trials: namely that quality-of-life improvements are shown consistently but not more traditional measures of lung function. We have previously predicted, by way of a theoretical model, that this apparent discrepancy can be explained by ASM tone. Specifically, BT-induced functional improvements in conventional measures of lung function are apparent only at relatively high levels of ASM tone (27), consistent with high-resolution CT observations in dogs (16). This offers a possible explanation of the observed results: high tone situations rarely occur in the clinical test environment due to safety concerns but do occur in uncontrolled situations outside of the clinic. Thus, it may be expected that improvements manifest only in measures that capture these uncontrolled situations, such as exacerbation frequency and quality-of-life scores, which are indeed the most consistent clinical observations.

Comparison of the observed airway response with those predicted in the absence and presence of tone (Fig. 5) helps

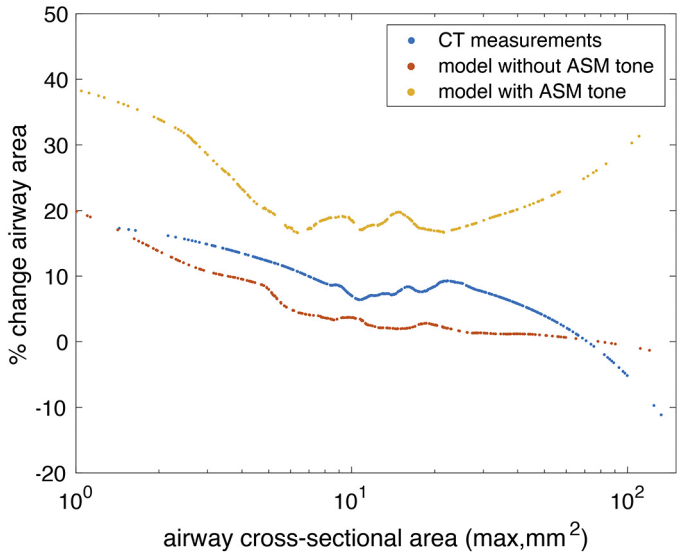

Figure 5. Comparison of airway response measurements with previous model predictions (27). CT measurements shown in blue, along with two model conditions: without ASM tone (red) and with ASM tone (yellow). Nonparametric regression by Friedman's super smoother (26). ASM, airway smooth muscle; CT, computed tomography.

to clarify this situation. In this simulation, the magnitude of tone included was relatively modest, equating to that which just exceeds the threshold of ASM contraction during a conventional bronchial challenge. The measurements lie cleanly between the tone and no-tone predictions, suggesting that this patient cohort, at the time of CT (prebronchodilator), had an intermediate level of tone. At this level of tone, functional improvements in conventional measures are predicted to be sufficiently small as to be difficult to detect reliably (27), and hence it is perhaps not surprising that the changes in FEV1 did not reach statistical significance. However, at increased levels of tone (i.e., perhaps accompanying an acute exacerbation), we predict that BT treatment will produce more pronounced airway dilation, concomitant with greater increases in function.

Comparison between measurements and predictions also suggests that the largest measured airways may not dilate as much as predicted. One potential explanation is that thermal ablation of the ASM is less effective in larger airways. We have assumed that BT is equally effective in all treated airways, and there is little information about how this efficacy might vary with airway size; indeed simply the average figure for ASM reduction is somewhat controversial (28, 29). However, a recent theoretical analysis suggests ASM ablation is highly sensitive to lumen size due to attenuated distribution of heat throughout the airway wall (30). Developments in polarization-sensitive optical coherence tomography (OCT) may soon allow much more detailed in vivo assessment of ASM reduction after BT and its dependence on airway size (31–33). OCT would also facilitate the measurement of total wall area, which we are unable to assess from CT for the more peripheral airways.

Throughout this manuscript we use the terms "proximal" and "distal" to refer to airways by their location within the airway tree; we do this both for the intuitive value in interpreting the data and also to avoid overuse of the relative terms "smaller" and "larger" in referring to airway size, change in airway size, and airway location. However, it should be noted that we have directly measured airway size and not anatomical location.

There seems little doubt that changes in airway volume after BT are due to radial expansion of the lumen without a shift in airway length. An additional consideration is the number of segmented airways. Changes in aggregate airway volume potentially include not just individual airway changes but also new or "recruited" airways, which appear in the airway tree segmentation after BT. In essence, these are airways that dilate from below the detection threshold to above it (see Fig 1*C*) and as such are not included in the matched airway analysis. Aggregate volume is thus in some sense a combination of the average matched airway change combined with the total airway count (34). We propose that airway recruitment contributes substantially to increased aggregate volume after BT, since the magnitude of airway dilation observed here accounts for only about one third of the increase reported previously where aggregate volume was also dependent on airway recruitment (14). Separate contributions of dilation and recruitment will in turn impact the relationship between airway changes and clinical outcomes. We have previously shown that aggregate airway volume changes correlate significantly with changes in ACQ (14); in contrast, the change in matched airway area in this study does not reach statistical significance in its relationship with the change in ACQ. It is likely that aggregate airway volume provides a stronger signal in this regard because it effectively combines both changes in individual airways as well as the additional "recruited" airways.

The CT-derived individual airway response exhibits substantial heterogeneity (see Fig. 3). Heterogeneity in the BT response is consistent with our earlier predictions, with some airways dilating substantially, whereas others exhibit little change or even contraction (27). The modeling predictions (and therefore patient data) are likely explained by airway-airway and airway-parenchyma interdependence where mechanical changes in one region impact another. However, there are other sources that contribute to heterogeneity after BT, especially on the untreated side. One factor is time: the scan pairs are separated by between 12 and 66 wk, depending on the assessment pairing. During this time, it is possible that there is natural variation in the airway state (even without treatment), especially in a group with severe asthma where asthma control may vary. Another source of heterogeneity is segmentation and matching error in the image analysis. That the airway area does not change on the untreated control side, and also that the airway length does not change, is reassuring that there is no significant systematic error; however, to the extent that some airways may be mismatched by the automatic process, these will contribute to the observed heterogeneity. The relative contributions of these factors could be disentangled in a follow-up study through the use of scan pairs with adequate control and variation of both the time separation of the scans and the disease state of the subject.

Finally, our findings have important clinical implications. The differential response between proximal and distal airways observed here suggests that a treatment emphasis in the more distal airways might be advantageous. In

combination with recent results trialing personalized BT using hyperpolarized MRI to target constricted airways and ventilation defects (12), this further suggests that refined, patient-specific versions of BT can deliver greater efficacy.

Conclusions

Analysis of individual airway response in BT is feasible and demonstrates that there is significant dilation of individual airways, and that this response is greater in the more distal measured airways. This further demonstrates that BT induces physiological changes that are not easily captured by traditional measurements of lung function. Comparison with previous predictions suggests that greater airway dilation and improvements in traditional measures of lung function will be apparent at higher levels of ASM tone.

DATA AVAILABILITY

The data sets used during the current study are available from the corresponding author on reasonable request.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

D.L., P.B.N., and G.M.D. conceived and designed research; D.L. performed experiments; D.L. and G.M.D. analyzed data; D.L., P.B.N., and G.M.D. interpreted results of experiments; G.M.D. prepared figures; D.L., P.B.N., and G.M.D. drafted manuscript; D.L., P.B.N., and G.M.D. edited and revised manuscript; D.L., P.B.N., and G.M.D. approved final version of manuscript.

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