ORIGINAL RESEARCH

Unraveling a Clinical Paradox: Why Does Bronchial Thermoplasty Work in Asthma?

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Abstract

Bronchial thermoplasty is a relatively new but seemingly effective treatment in subjects with asthma who do not respond to conventional therapy. Although the favored mechanism is ablation of the airway smooth muscle layer, because bronchial thermoplasty treats only a small number of central airways, there is ongoing debate regarding its precise method of action. Our aim in the present study was to elucidate the underlying method of action behind bronchial thermoplasty. We employed a combination of extensive human lung specimens and novel computational methods. Whole left lungs were acquired from the Prairie Provinces Fatal Asthma Study. Subjects were classified as control ($n = 31$), nonfatal asthma ($n = 32$), or fatal asthma ($n = 25$). Simulated lungs for each group were constructed stochastically, and flow distributions and functional indicators (e.g., resistance) were quantified both before and after a 75% reduction in airway smooth muscle in the "thermoplasty-treated" airways. Bronchial thermoplasty triggered global redistribution of clustered flow patterns wherein structural changes to the treated central airways led to a reopening cascade in the small airways and significant improvement in lung function via reduced spatial heterogeneity of flow patterns. This mechanism accounted for progressively greater efficacy of thermoplasty with both severity of asthma and degree of muscle activation, broadly consistent with existing clinical findings. We report a probable mechanism of action for bronchial thermoplasty: alteration of lung-wide flow patterns in response to structural alteration of the treated central airways. This insight could lead to improved therapy via patient-specific, tailored versions of the treatment—as well as to implications for more conventional asthma therapies.

Keywords: airway smooth muscle; airway hyperresponsiveness; ventilation heterogeneity; clustered ventilation defects

The underlying pathophysiology of asthma is poorly understood (1), and attempts to improve understanding of pulmonary structure and function are bedeviled by complexity in many forms. These range from the extent of the branching tree structure (2) and structural heterogeneity of the airways (3, 4) through to self-organized emergent phenomena such as spatial ventilation heterogeneity and clustered ventilation defects (5–9), all in the context of multiscale interactions (10, 11). Combined with variation in patient phenotypes, this leaves us with an insufficient understanding of the pathophysiology of asthma (12). Arguably, this failing is less acute for those whose asthma is well controlled by standard therapies, but for the minority in whom this is not the case, asthma can be fatal; this group accounts for the majority of the healthcare burden. This especially is where lack of a complete understanding of the complexity of the disease remains an impediment to effective therapy.

One recent addition to the arsenal of available therapies for asthma is bronchial thermoplasty (BT), approved by the U.S. Food and Drug Administration in 2010. BT delivers targeted thermal energy to the

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The uncompressed video is accessible from this article's supplementary material page.

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Clinical Relevance

More than 200 papers concerning bronchial thermoplasty (BT) have been published in the last 10 years. It is approved for treatment and known to be safe and effective over a 5-year time scale, with modest increases in quality-of-life scores and more substantial decreases in severe exacerbations and emergency department visits. However, the underlying mechanism of action is unknown and controversial; the small number of large airways treated directly is believed to be insufficient to explain the observed benefits, and several hypotheses have been advanced regarding treatment effects that may extend to a greater portion of the lung. In this study, we show that the observed benefits of BT can be explained by changes in whole-lung flow patterns induced by structural changes in the central BT-treated airways, providing a probable mechanism of action for BT. No other non–local airway changes are needed to explain the improvement. An improved understanding of the underlying mechanism of action may allow more informed patient selection for BT, patient-specific targeted versions of BT, and other novel therapies operating through a similar method of action.

central airways via bronchoscope and radiofrequency catheter, and it is considered in the treatment of patients with moderate to severe asthma who do not respond to conventional therapy. Although BT has been shown to increase quality-of-life scores and decrease severe exacerbations and emergency department visits (13), the mode by which these improvements occur is unclear (14, 15). The most likely direct mechanism is a reduction in airway smooth muscle (ASM) mass in the treated airways (16). Given that activation and contraction of the ASM are responsible for airway narrowing during acute events (17), this is an appealing hypothesis. However, BT treatment is restricted to a small number of large central airways, whereas asthmatic pathophysiology is widely believed to have a significant contribution from smaller airways (18, 19). Thus, local thermal ablation of ASM in a small number of central airways is believed by many to be insufficient to explain the observed benefits of BT. As a result, several hypotheses have been advanced by which the effects of BT may extend to tissues that were not directly treated, such as via changes in immunomodulation (20, 21) or neural control (22).

In the present study, we investigated the mechanism through which BT exerts its effects on respiratory function. We used extensive human lung specimens ($N = 2{,}339$ airways from 88 subjects) to construct structurally heterogeneous simulated human lungs for nonasthma (NA), nonfatal asthma (NFA), and fatal asthma (FA) populations. Within these simulated lungs, we employed an appropriate ventilation model and analyzed the resulting lung function (flow patterns and resistance) both before and after simulated BT. Our simulated BT protocol is matched to current clinical practice, and we assume that structural changes are restricted to directly treated airways, in which ASM undergoes a sustained long-term reduction.

Methods

Human Lung Specimens

Whole left lungs were acquired from the Prairie Provinces Fatal Asthma Study (23–26). Subjects were classified as follows: control ($n = 31$), with no history of asthma, wheeze, or other lung disease; NFA ($n = 32$), with death attributed to a nonrespiratory cause and with a confirmed history of asthma; and FA ($n = 25$), with death attributed to asthma with a confirmed history. The main bronchus and pulmonary artery were perfused simultaneously with glutaraldehyde (2.5% in 0.05 M phosphate buffer, pH 7.4, 350 mOsm with sucrose) at pressure heads of 20 and 40 cm H_2O, respectively, thus maintaining a capillary–alveolar pressure difference of 15–20 cm H_2O. Vascular perfusion was maintained for 2 hours, and bronchial perfusion was done overnight.

Three segmental bronchi, two from the lower lobe (LL) (anterior and posterior basal) and one from the upper lobe (apical), were isolated from lung parenchyma. Portions of airway (free from parenchyma) were acquired at nine equidistant levels from proximal to distal locations. This yielded 27 airways per subject. Samples were processed into wax blocks, sectioned (5 μm), and stained using the elastic trichrome technique. The area of the ASM layer and the total wall area were measured by point counting using a Nikon light microscope, drawing tube, and square lattice grid containing 240 points.

Mathematical Model

In this subsection, we provide an overview of the mathematical model. Full technical details are provided in the data supplement, including a flowchart for visualization. Below is an outline of the model process, which is repeated for each group (NA, NFA, and FA).

1. *Structural airway data*: We begin with the structural data for the group, acquired from human lung specimens as described above, using basement membrane perimeter, wall area, ASM area, and anatomical level (27) for each sampled airway.
2. *Statistical fit*: The structural data are used to fit distributions for basement membrane perimeter, wall area, and ASM area for each airway order (28).
3. *Simulated lung structure and function*: The steps outlined below are repeated 25 times to generate independent simulations via Monte Carlo simulation (29):
   a. Generate *synthetic lung and airway structure* using the fitted distributions for each airway order.
   b. Calculate *pre-BT flow* using the generated synthetic lung and airway structure (30, 31).
   c. Apply *simulated BT treatment* to the airway structure. Simulated BT protocols are based on current clinical practice (13), treating the LL bronchus, upper lobe bronchus, superior division bronchus, and LB1–LB10. Treated airways undergo a 75% reduction in ASM mass (16, 22, 32). Wall area is altered via ASM reduction, but we assume no other changes to the airway wall. Two variations in BT were also simulated: treating the LL only or an extended BT that treats airways one further generation distally. *See* the data supplement for details.
   d. Calculate *post-BT flow* using the BT-treated synthetic lung and airway structure.

e. Calculate *impedance* (i.e., resistance) using a standard circuit analog model (3, 4), and assess *dose response* by repeating flow and function calculations for different levels of agonist (methacholine) stimulus, related to ASM activation using human ASM data (33).

4. *Compute statistics for the group* using function and dose response across all simulated lungs.

Results

Dose–response curves for each group (NA, NFA, FA), both pre- and post-BT, are provided in Figure 1A wherein ASM activation increases with theoretical dose of agonist (methacholine) (33). In the absence of ASM activation, no significant improvement is observed after BT in any group; however, significant improvement is observed concomitantly with increases in either asthma severity or agonist dose.

Because the effect of our simulated BT is limited solely to changes in the ASM of the BT-treated (large) airways, the observed global improvement cannot be explained by more widely disseminated structural effects on other tissue types or in smaller airways, as has been postulated elsewhere (34). Indeed, further analysis demonstrates the method of action. Figure 1A shows statistics for each group, with 25 simulations per group; however, it is illustrative to examine individual simulated lungs more closely. Typical flow distributions are provided in Figure 1C (pre-BT) and Figure 1D (post-BT); visually, recruited areas are apparent, together with a decrease in spatial heterogeneity. The BT-induced change is quantified explicitly in Figure 1E, showing both the expected regions of flow increase and also paradoxical regions exhibiting decreased flow. Video 1 shows the evolution of the flow states for the simulation.

A similar pattern of change with BT was observed when we assessed the relationship between BT-treated airways

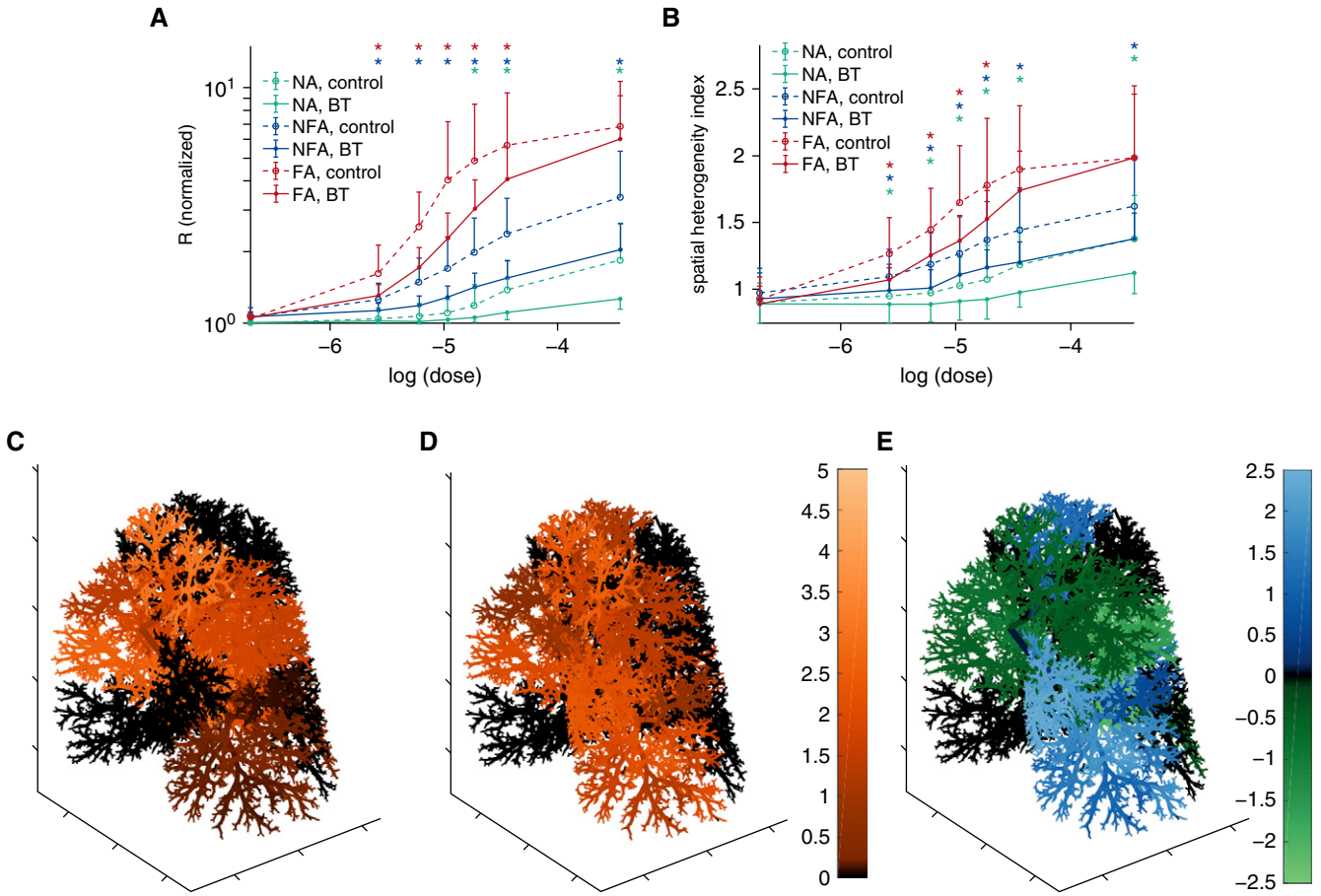
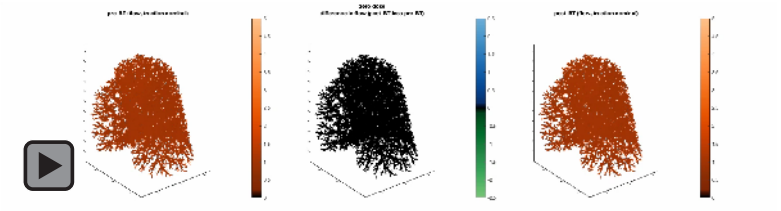


Figure 1. (*A*) Dose–response curves for respiratory resistance (R, normalized) as a function of agonist dose (logarithmic scale). Pre-BT control simulations (dashed line) and post-BT simulations (solid line) are provided for each group (FA, red; NFA, blue; NA, green). $n = 25$ simulations per group; error bars are SD. $^*P < 0.05$ via two-way ANOVA (post-BT vs. pre-BT). (*B*) Spatial heterogeneity index (*see* the data supplement) as a function of agonist dose. Pre-BT control simulations (dashed line) and post-BT simulations (solid line) are provided for each group (FA, red; NFA, blue; NA, green). $n = 25$ simulations per group; error bars are SD. $^*P < 0.05$ via two-way ANOVA (post-BT vs. pre-BT). (*C*) Pre-BT flow pattern for typical simulation [NFA at log(dose) −4.4]. The color bar to the right of *D* indicates the scale for both *C* and *D*, showing flow through each airway (normalized to nominal flow; *see* the data supplement). (*D*) Post-BT flow pattern for typical simulation [NFA at log(dose) −4.4]. Details as in *C*. (*E*) BT-induced flow pattern changes for typical simulation [NFA at log(dose) −4.4]. Color bar indicates the difference in flow (post-BT less pre-BT, normalized to nominal; *see* the data supplement). BT = bronchial thermoplasty; FA = fatal asthma; NA = nonasthma; NFA = nonfatal asthma.



Video 1. Illustration of the evolution of Figures 1C–1E.

and their subtended airways, with respect to both flow and lumen radius (Figure 2). Broadly, recruitment of new regions allows modest reduction in flow in previously hyperinflated areas. Furthermore, although BT-treated airways do dilate, untreated airways show a mixed contraction–dilation pattern, an effect recently demonstrated with synchrotron phase-contrast computed tomography (CT) (35). These results are typical, and other simulations show similar results.

To quantify this explicitly, we computed a spatial heterogeneity index that captures both overall heterogeneity and the extent to which flow is clustered (*see* the data supplement). We calculated this spatial heterogeneity index for all simulations, as shown in Figure 1B, indicating a systematic reduction in spatial heterogeneity due to BT that closely mirrors the dose–response curves. Thus, the central mechanism behind the effectiveness of BT as a treatment for asthma appears to be that central airway structural changes trigger global flow redistribution toward a more homogeneous and efficient flow configuration (e.g., reducing ventilation heterogeneity).

We also considered two BT variation therapies: treating the LL only or an extended BT in which one additional generation of airways is treated beyond current practice. These treatment regimes are illustrated in Figure 3A. Quantification of flow pattern differences for the typical simulation is provided in Figures 3B and 3C for LL-only and extended-BT treatments, respectively. Unsurprisingly, the LL treatment shows flow increases exclusively within the treated lobe, whereas the extended treatment shows effects across the entire lung. Dose–response curves are shown for LL-only and extended BT in Figures 3D–3F for the NA, NFA, and FA groups respectively. These data indicate that if BT were limited to LL-only treatment, there would still be significant improvement in most situations, though it would not be as effective as current clinical protocol. The extended BT shows improvements in function, increasing with severity of both disease and dose.

It is also interesting to examine the population-level distribution of responses. Previous work has suggested that BT response is related to the number of radiofrequency activations during BT treatment (36) and that nonresponders may not exhibit the same degree of ASM reduction (37). In our simulations, we found that 65% of the FA group displayed a significant response to BT, with the remainder showing essentially no change. In the other groups, 70% of the NFA group and 45% of the NA group also demonstrated a response. For LL-only BT, positive responders reduced to 59% (FA), 45% (NFA), and 25% (NA), whereas extended BT would increase the response rates to 71% (FA), 80% (NFA), and 50% (NA). In all simulations, the proportion of ASM ablated in the treated airways is fixed, suggesting that although inadequate radiofrequency activation during treatment would certainly contribute to nonresponse rates, there are also subpopulations that are intrinsically less susceptible to BT treatment owing to the structure of their airways.

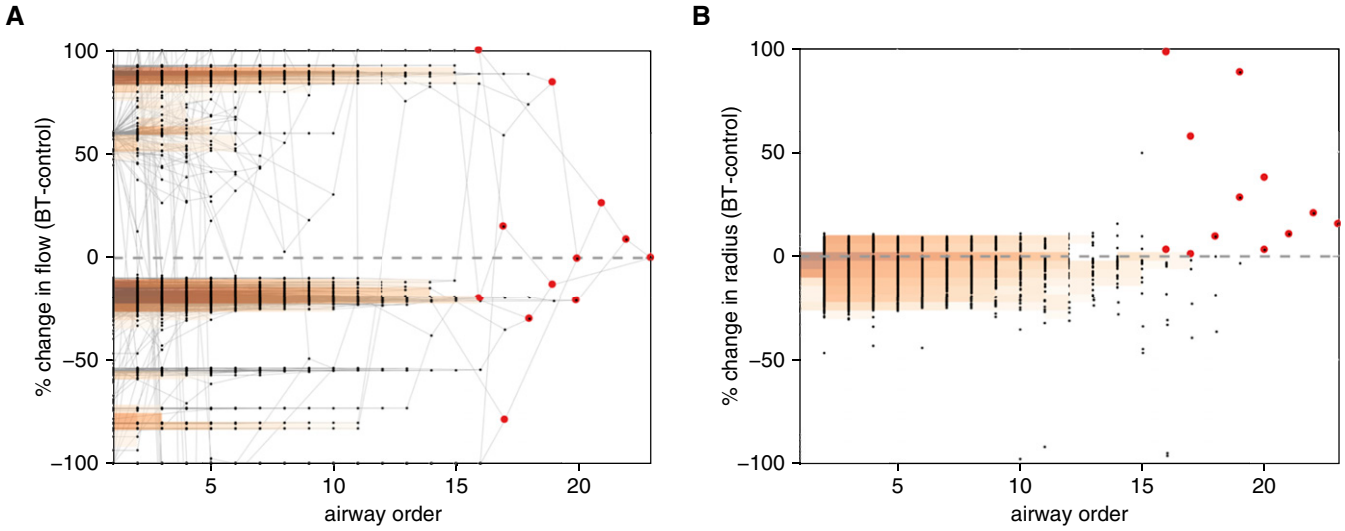


Figure 2. (*A*) Change in flow through individual airways for a typical simulation [NFA at log(dose) −4.4] as a function of airway order (28). Horsfield order begins at the respiratory bronchioles and increases progressively, moving up the airway tree. Red airways are BT treated; tree connectivity is indicated by gray lines, and orange back shading indicates point density. (*B*) Change in airway radius for individual airways for a typical simulation. Details as in *A*.

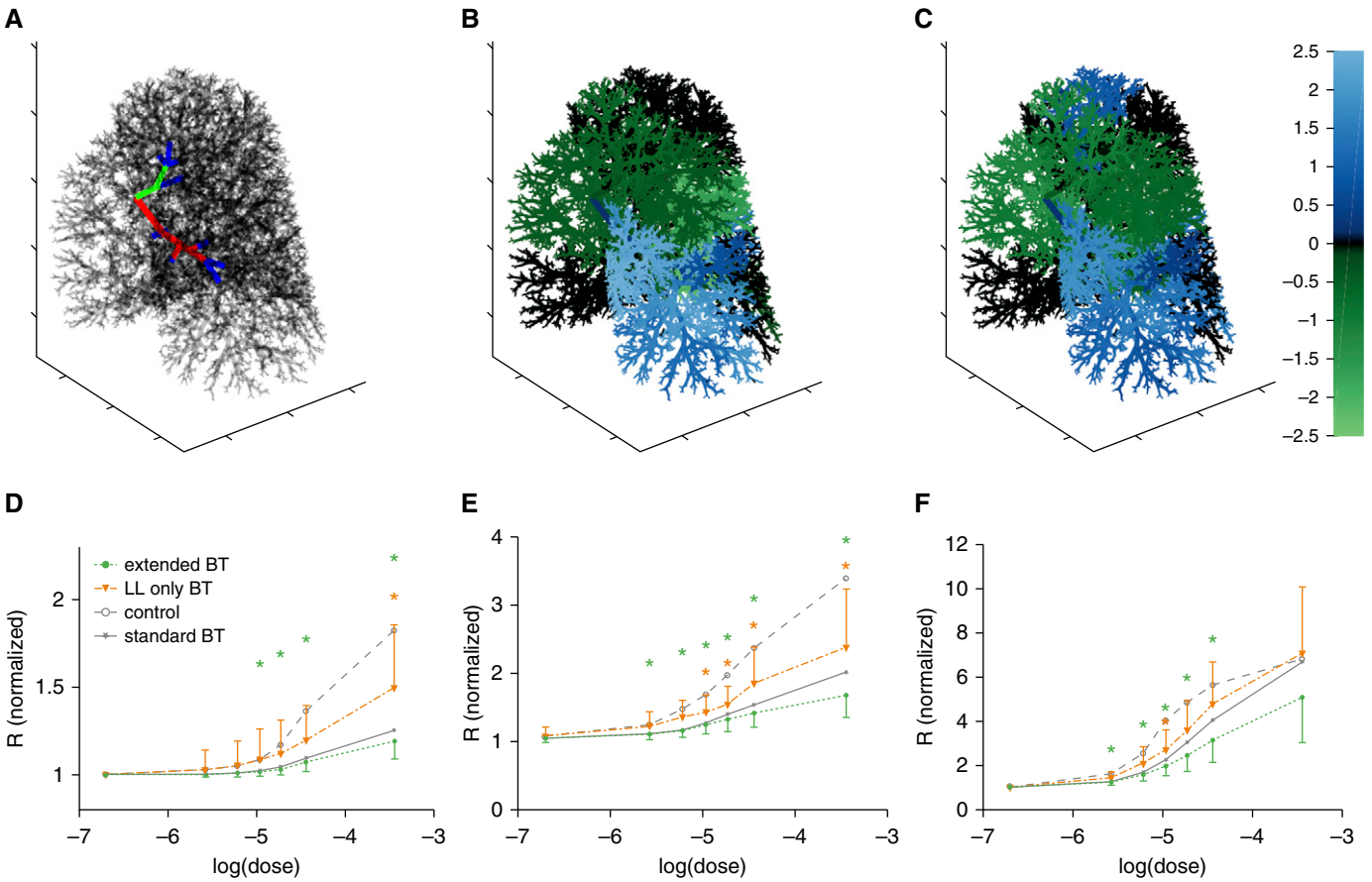


Figure 3. (*A*) Illustration of three BT protocols in a simulated human lung: lower lobe only (red), current clinical practice (red + green), and hypothetical "extended" BT (red + green + blue). (*B*) Lower lobe (LL)-only BT induced flow pattern changes for typical simulation [nonfatal asthma at log(dose) −4.4], normalized to nominal (*see* the data supplement). (*C*) Extended BT-induced flow pattern changes for typical simulation. Details as in *B*. (*D*) Dose–response curves for respiratory resistance (R, normalized) in the nonasthma group as a function of agonist dose (logarithmic scale). LL-only BT is indicated in orange and extended BT in green, with control (gray, dashed) and standard BT (gray, solid) repeated from Figure 1 (mean only) for reference. For each group, $n = 25$ simulations. Error bars are SD. $^*P < 0.05$ via two-way ANOVA (post-BT vs. pre-BT). (*E*) Dose–response curve for nonfatal asthma group. Details as *D*. (*F*) Dose–response curve for fatal asthma group. Details as in *D*.

Discussion

Our principal finding is that the probable underlying mechanism for BT is structural changes to the ASM in the BT-treated central airways leading to a reopening cascade in the smaller airways, in turn creating more homogeneous and efficient flow patterns. This mechanism predicts that although little functional difference is found in the absence of agonist challenge, the effect of BT is progressively greater with increasing agonist stimulation and asthma severity. These predictions are consistent with a suite of existing empirical results. Perhaps most important are the recent ^{3}He magnetic resonance imaging and CT results showing mixed post-BT regional ventilation changes; that is, post-BT regional ventilation shows both increases and decreases (38), exactly as predicted by the model.

Clinical trials vary in terms of the health parameters that are reported to improve post-BT. The AIR (Asthma Intervention Research) trial (39) showed significant improvement in quality-of-life questionnaire scores, symptom-free days, symptom scores, rescue medication use, mean rate of exacerbations, and morning peak expiratory flow, but it showed no differences in the key functional measures: airway responsiveness (provocative concentration causing a 20% fall in FEV_1 [PC20]) and FEV_1. The RISA (Research in Severe Asthma) trial (40) in severe asthma similarly showed improvements in quality-of-life questionnaire scores and rescue medication use, and also prebronchodilator FEV_1 was significantly improved. Because of the potential for a large placebo effect, the sham-controlled AIR2 trial (41) is arguably the most authoritative; significant improvements were found in quality-of-life questionnaire scores, severe exacerbations, emergency visits, and missed days of school/work, but without any significant improvement in FEV_1 or morning peak expiratory flow.

We argue that the nature of our predicted functional improvements is in fact consistent with the description above, albeit that the findings are mixed, and indeed helps to explain their apparent inconsistency. The key aspect is that we predict that functional improvements are almost nonexistent at baseline but increase with both asthma severity and degree of stimulus. Such changes will be difficult to detect in a clinical setting because it is only

in severe situations, where function tests are not well tolerated by patients, that these functional differences become large. For example, in the AIR trial (39), long-acting β-adrenoceptor agonists and short-acting β_2-agonists were withdrawn before spirometry only if tolerated. It is perhaps not surprising, then, that the clinical trials have failed to show consistent functional improvements. However, such changes would still be expected to manifest in indirect measures such as quality-of-life questionnaire scores, severe exacerbations, emergency visits, and missed days of school/work—exactly as shown by AIR2. Evidence for BT-induced impairment of airway closure (42), demonstration of mixed contraction–dilation patterns *in vivo* (35), and the inability, so far, to find consistent nonlocal structural changes resulting from BT also lend support to this global flow redistribution mechanism.

Our methods account for both heterogeneity of lung structure as well as intrinsic instability on the scale of a full human lung; this crucially allows propagation of effects elicited by reduction of ASM in BT-treated airways out to the periphery. Thus, it is possible for changes in central airway structure after BT to trigger global redistribution of clustered flow patterns in the lung, reducing spatial heterogeneity, and furthermore that these changes account for significant improvements in lung function during bronchial provocation, in line with observed clinical response to BT. Importantly, this BT-induced improvement is an emergent phenomenon in a complex system; that is, feedback mechanisms (e.g., redirection of airflow) at the level of individual elements (airways) give rise to ordered behavior on a larger scale (lung-wide flow patterns). It arises from the structural alteration of a small number of BT-treated central airways only—no other mechanisms are required, and this effect would be difficult to predict *a priori* from the structural data alone.

Closer examination of the data suggests an explanation for the aforementioned changes, namely the way in which structural changes in the large airways induce functional changes in the small airways. It appears that the BT-induced global flow redistribution arises because, although the changes in the BT-treated large airways can be relatively small, even small improvements "upstream" are sufficient to allow reopening, at the margin, of some subtended regions. Any such reopening allows partial reversal of some hyperinflation regions otherwise developed in compensation for poor ventilation in other locations. Thus, the overall effect is toward less heterogeneous (and more functionally efficient) flow patterns.

On the basis of this central finding, we also examined two other questions of interest. We considered variations of the existing BT treatment protocol in terms of both single-lobe treatment (LL only) and a hypothetical extended BT (treating one additional airway generation). The extended BT proposal shows increased treatment effectiveness and may be promising, especially for more severe cases (41). The results from the LL-only case provide a plausible set of testable hypotheses, given that current treatment practice involves sequential lobar treatments (13). In depth examination of *in vivo* lobar treatment effects could be assessed between treatments, provided that sufficient time is allowed for acute inflammation to resolve. Similarly, the extended BT protocol is a natural extension requiring only an incremental decrease in catheter size and somewhat increased procedural complexity.

We also propose a more ambitious therapeutic advancement, namely patient-specific approaches to both patient selection and treatment design. The prospect that there are asthma subpopulations that are intrinsically less susceptible to BT raises two tantalizing prospects. One is that it might be possible to classify BT response phenotypes on the basis of pretreatment airway structure. The current data set is consistent with the hypothesis that the patients who go on to show a BT response are those with greater (pretreatment) ASM in the airways targeted by BT; however, we do not have the statistical power required to draw that inference with any significance. A second option would be to take a more direct precision medicine approach: use patient-specific structural airway data from central airways, perhaps in combination with CT and polarization-sensitive optical coherence tomography (43), to design an optimal BT treatment package for that patient, which optimally reduces ventilation heterogeneity and improves functional response.

There are several methodological assumptions and limitations of this study that merit discussion. It is important to note that we considered only the long-term effects of BT which arise from reduction of ASM in the treated airways, and we did not consider any short-term effects, such as inflammation or exacerbation either during or shortly after the treatment. This is especially pertinent in considering extended BT for severe cases, in which the consequences of acute responses and complications would require careful assessment. In considering the effects of BT on the FA group near the plateau (e.g., at maximal agonist dose), it is worth noting that a significant portion of simulations in the control FA group at maximal activation were discarded for exceeding preset intrapleural pressure limits, so the statistical power for this point is reduced. It is thus likely that the results actually understate the effect of BT for patients with FA at or near the maximal dose. For additional details, *see* the data supplement. Finally, the proposed mechanism of BT in the present study is theoretical and requires experimental validation. Imaging technology has advanced to the point where it should be possible to detect changes in ventilation of the magnitude observed in the present study. BT has already been shown, via ^{3}He magnetic resonance imaging and CT, to exhibit mixed ventilation responses on a regional basis (38), and more recent advances (44) suggest that capabilities now exist to demonstrate this effect with greater spatial resolution.

Taken together, the results of the present study suggest that the primary method of action for BT in asthma is nonlocal alteration of flow patterns toward decreased spatial ventilation heterogeneity, caused by local thermal ablation of ASM in the treated central airways. This is an emergent phenomenon in a complex system that cannot be easily predicted from changes in airway structure alone. Nonlocal structural effects may still contribute, but they are likely to be secondary phenomena. By providing a more basic understanding of both the underlying pathophysiology of asthma and the central method of action of BT, this interdisciplinary solution to a clinical puzzle provides possible routes to both short-term improvements of existing therapies and longer-term development of novel therapies. Both possibilities hinge on a key insight: that significant functional improvements can arise from reductions in spatial flow heterogeneity, and that this can be achieved by the direct targeting of large airways alone. This central idea has potential implications beyond BT; for example, the

effectiveness of aerosolized pharmacological treatments depends on particle deposition patterns, which are in turn strongly influenced by aerosol particle size (45–47). Although much effort has been dedicated to reducing particle size to increase deposition in the smaller airways, our present results suggest that a more subtle approach may be warranted. Given the effectiveness of large airway–only treatment in BT via global flow pattern alteration, optimizing particle deposition patterns to target the smaller airways may not be the best approach if this compromises effective treatment of the larger airways. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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