temperatures (3). Even granting a possible long-term decrease in ASM content of the treated airways, we still expect a significant degree of heterogeneity. It therefore appears important to identify the threshold percentage of ASM reduction and/or deactivation at the level of individual bronchi that will make a functional impact at the organ level. Future approaches will thus rely on integrated tissue- and organ-level models to assess the patient-specific spatial heterogeneity of local BT thermal impacts.

It is also important to differentiate the relative contribution of smaller versus larger bronchi to the clinical impact of BT (either direct or indirect). The organ-level model (1) suggests the largest airways as a key pathway to improved ventilation. However, the reactivity of smaller airways is known to be more prominent in heavily remodeled fatal asthma (e.g., Reference 15 in Donovan and colleagues [2]), which is confirmed by the results of the study (*see* Figure 3F in Donovan and colleagues [1] in agreement with tissue biomechanical models [6]). An integrated tissue model (3) also indicates that the potential impact of BT is strongest at the distal end of accessible bronchi and thus could affect highly reactive ASM-rich airways in patients with severe near-fatal asthma.

Finally, although the clinical effect of BT on reducing the frequency of exacerbation episodes is better established, the impact of BT mechanisms on lung function appears to be less clear (4, 7), with no confirmed correlation between clinical outcomes and improvement in functional respiratory tests. However, there is evidence of a BT-induced improvement in epithelial integrity (3) that might be associated with long-term altered gene expression profiles in bronchial epithelium (8), which may contribute to a lower exacerbation incidence rate. ■

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Reply to: Comment on "Unraveling a Clinical Paradox: Why Does Bronchial Thermoplasty Work in Asthma?"

From the Authors:

Bronchial thermoplasty (BT) has garnered much recent interest with regard to its underlying mechanism of action and the potential for patient-specific, targeted therapies that rely upon an understanding of those mechanisms. Brook and colleagues have written with several specific comments regarding recent work, including our recent study of BT that demonstrated the potential for functional improvements arising from airway smooth muscle (ASM) ablation in the treated central airways alone, with treatment effects propagating toward the periphery in the form of reduced ventilation heterogeneity (1). We are happy to respond to the comments of Brook and colleagues regarding the assumptions inherent in our recent study, and to provide new data to examine the queries raised.

Regarding the Assumed Level of ASM Ablation Resulting From BT

Brook and colleagues suggest that our assumed figure of 75% ASM ablation in the treated airways may be too high. This value, as they point out, is within the published range from biopsy studies (2–5), albeit at the upper limit. However, concerns about a threshold effect are unfounded. To establish how the degree of ASM ablation affects lung function, here we present original data obtained using our published methods. As shown in Figure 1, the degree of functional improvement is close to linearly proportional to the assumed ASM ablation, meaning that a more conservative estimate of 50% ASM ablation would still result in more than 80% of the originally reported improvement. In short, our central finding that functional improvements after BT are driven by structural changes to the treated large airways is robust to the assumed level of ASM ablation.

On the individual level, however, the idea of a threshold effect is relevant (6), and indeed this lies at the heart of efforts to create patient-specific, targeted versions of BT (7). Intersubject or interoperator variability is of course likely, given evidence that the number of BT activations predicts the

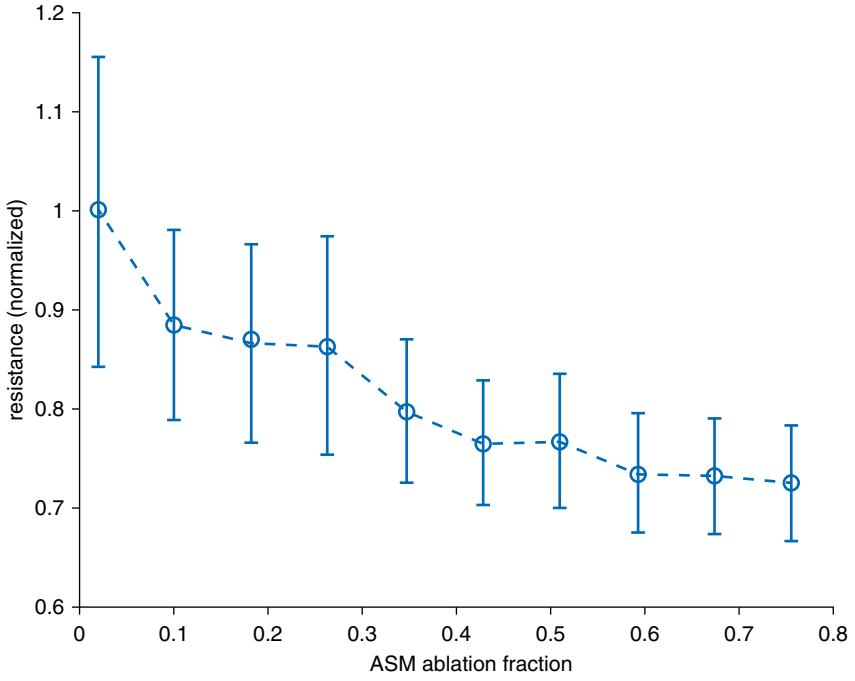

Figure 1. Functional improvement after bronchial thermoplasty as a function of the assumed airway smooth muscle (ASM) ablation fraction, calculated using the same methodology as described in Reference 1 for a population with fatal asthma at ~77% of maximal *in vivo* activation. Resistance is normalized to the baseline (zero ablation) case, and error bars give the SD ($n = 25$).

resulting response (8). Ultimately, the question of the exact nature of the ASM reduction may be answered with the use of bronchoscopic optical coherence tomography, which allows direct access to treated airways (9), coupled with the potential for polarization-sensitive optical coherence tomography to resolve the ASM layer (10).

On the Importance of Small Airways Relative to Large Airways

Brook and colleagues point out that the airways distal to those treatable by BT have a significant impact in severe asthma. We completely agree. The central finding of our study—that treatment of the central airways alone does have an impact on function—does not preclude a prominent role for the small airways. Indeed, our model results suggest that BT-treated patients with fatal asthma remain at a functional deficit relative to subjects with untreated nonfatal asthma, and similarly that BT-treated patients with nonfatal asthma do not improve to the level of the population without asthma. It seems likely that much of this remaining deficit lies with the airways distal to the treatment, and indeed that this is a promising opportunity for future treatment, as suggested by our hypothetical "extended" BT, which treated one additional distal generation relative to current practice, resulting in commensurately greater improvement (1).

Non-ASM Ablation Effects

Brook and colleagues point out that there is also evidence to suggest that BT induces other effects beyond ASM ablation in directly treated airways. Given the uncertainty surrounding the mechanism of BT, it was natural that the respiratory field would seek alternative explanations, which we freely acknowledged in our publication. In addition to their results regarding epithelial integrity (11), others have demonstrated or proposed changes in inflammatory mediators (12), nerve fibers (13), gene networks (14), and heat transfer to the small airways (15) after BT. Some or all of these pathways may be important.

Our central hypothesis, however, was that ASM ablation in the treated large airways alone was sufficient to generate functional improvement after BT. That this hypothesis was supported in no way precludes any of the other effects described above. The results of our study are nonetheless compatible with findings from clinical trials. Functional improvements are minimal at baseline but increase with both asthma severity and ASM tone. Such functional changes will be difficult to detect in a clinical setting due to safety concerns that (rightly) place a limit on ASM contraction, e.g., during a bronchial challenge. Outside the clinical laboratory, there is no such limit on ASM contraction, and it is reasonable to postulate that an ASM contraction could exceed the level that would otherwise be deemed safe, or at the very least could occur in an uncontrolled manner. It is therefore intuitive that the benefits of BT would manifest in indirect measures of health status outside the clinic, including asthma control, exacerbations, and hospitalizations.

Finally, a note regarding the call for caution in the interpretation of results. A scientific program without restrictions would facilitate mechanistic studies on living, breathing humans *in vivo*. Reality is of course much more limited, born out of ethical considerations regarding the

welfare of study participants and technical challenges. A pragmatic compromise to overcome such obstacles is to model biological behavior. Investigators regularly use animal models, wherein the internal or external environment of the organism is first modified to simulate human disease, which subsequently provides an opportunity to study underlying mechanisms and reveal new disease targets. The inherent assumption of all studies that use animal models is that the clear differences between the animal and human forms do not impact the hypothesis in question. Alternatively, mathematical models of human function may be used, informed by the core disciplines of physics and chemistry and known physiological data in the literature, carrying different but no more or less assumptions than biological models. An immediate strength of mathematical simulations is that the modeling processes specifically govern human behavior, and thus are intuitively more relevant. On the other hand, mathematical models will never recapitulate the full complexity of biology, but indeed this is one of their advantages: they reduce the system to its essential elements. As George Box famously wrote, "All models are wrong, but some are useful"—and this note of caution should be applied equally to all models, whether animal, *in vitro*, cell line, or otherwise. ■

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