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

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To the Editor:

We are writing to call for caution when interpreting the predictions of computational models at the organ-level[1,2] in the context of tissue-scale effects[3]. Having read recent work by Donovan and colleagues[1,2] with great interest, we would like to raise a few points about the use of modelling to understand the mechanisms of therapeutic action of bronchial thermoplasty (BT) in asthma control.

First, the authors postulate a fixed 75% airway smooth muscle (ASM) reduction post-BT, quoting published biopsy data[1,2]. However, relative reductions in ASM mass in reported *in vivo* biopsy studies range from ~ 50-80% as cited and further demonstrated in our study[3], and more recently reported by d'Hooghe *et al*[4]. These reductions are also characterised by strong inter- and intra-patient variability, e.g. in our study the observed relative reduction in ASM mass had an interquartile range of 6 to 90%[3]. Furthermore, acutely, we observed less than 60% reduction in viable ASM cell counts *in vitro* and less than 10% of a large conducting airway was predicted to be heated to therapeutic temperatures *in silico*[3]. Other works also highlight relative resilience of fibroblasts to thermal injury[5], in agreement with more ASM cells (structurally similar to fibroblasts) remaining viable at higher temperatures than bronchial epithelial cells[3]. Even granting 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 in ASM reduction and/or de-activation at the level of individual bronchi that will make a functional impact at the organ level. The future approaches thus lie in integrated tissue- and organ-level models to provide patient-specific spatial heterogeneity of local BT thermal impact.

It is also important to differentiate relative contribution of smaller vs. 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. On the other hand, the reactivity of smaller airways is known to be more prominent in heavily remodelled fatal asthma (e.g. [15] in Donovan, *et al.*[2]), which is confirmed by the results of the study (see Fig. 3(f) in Donovan, *et al.*[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 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 appear less clear[4,7], with no confirmed correlation between clinical outcomes and improvement in functional respiratory tests. However, there is evidence of BT-induced improvement in epithelial integrity[3] that might be associated with long-term altered gene expression profiles in bronchial epithelium[8], potentially contributing to a lower exacerbation incidence rate.

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