Editorial

Knowledge gaps in the field of bronchial thermoplasty

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In the article, "*Recent advances in bronchial thermoplasty for severe asthma*: *a narrative review*", the authors provide an overview of recent literature about bronchial thermoplasty (BT) (1). BT has been shown to decrease the number of exacerbations, hospital emergency visits, hospital admissions and to improve asthma control and quality of life in large randomized control trials (RCTs) (1,2). Furthermore, long-term extension studies and real world registries have mirrored these favourable outcomes with follow-up up to 10 years (3). Next to these clinical outcomes, Wu *et al.* describe important aspects about the safety, adverse effects, complications and working mechanism of BT. The aim of this editorial is to provide complementary views and to elaborate on remaining knowledge gaps.

BT has been designed to target the airway smooth muscle (ASM), considering its role in the pathophysiology of asthma (4). Indeed, an increased ASM mass has shown to be related with asthma severity and a decrease in lung function (5). The significant reduction in the ASM mass after BT has been demonstrated in multiple studies (6-10). However, conflicting data exist on the association between the reduction of ASM mass after BT and clinical response. In the recent TASMA RCT, improvements in clinical parameters such as asthma control questionnaire (ACQ), asthma quality of life questionnaire (AQLQ) and exacerbation rate were found, however no association between reduction in ASM and improvement in ACQ or AQLQ at 6 months was detected (10). Ladjemi and colleagues describe similar reductions in ASM mass in both responders and partial responders, and a correlation between the ASM measured at 3 months and clinical parameters at 12 months after BT was shown (8). Taken together, as mentioned in the review of Wu *et al.*, it seems that the mechanism of action of BT cannot be explained by the reduction of the ASM alone.

Airway remodeling is the collective term given to the structural changes that occur within the asthmatic airway. Among increased ASM mass as a hallmark of asthma related airway remodeling, extra cellular matrix (ECM), including the reticular basement membrane (RBM), contributes to airway remodelling as well (11). Research has shown BT impacts on the gene expression related to this airway remodeling (12). In addition, histopathological studies have reported a reduction in thickness of the RBM after BT (6,7) which correlated with the asthma control score (7,8). Conversely, Papakonstantinou *et al.*, did not describe changes in RBM thickness (13). Unanswered questions remain on histopathological changes of ECM components induced by BT and their potential associations with clinical response (14). Additional research is needed to unravel the exact effect of BT on the ECM, which can contribute to further comprehend the mechanism of action.

Another important compartment of the airway wall relevant to explore, is the bronchial epithelium. As mentioned by Wu *et al.*, a reduction in epithelial neuroendocrine cells and nerve fibres have been described in small mechanistic studies and have showed to be associated with clinical response after BT (7,15). BT may enhance host immune responses and therefore attenuate exacerbations and symptoms by increasing epithelial MUC5AC and anti-viral IFN-α/β expression (8). The changes in the epithelium together with airway remodeling observed after BT are potentially regulated by heat shock proteins (HSP). In *in vitro* studies, Fang *et al.* reported a reduction

of HSP60 by airway epithelial cells after BT, and thereby reduce remodeling and inflammation of airway fibroblasts. Furthermore, they reported an increase in HSP70 and HSP90 in endobronchial biopsies resulting in an improved epithelial cell regeneration and an anti-proliferative effect in ASM cells (16). This suggests BT supports the regeneration of the epithelium, but limits ASM remodeling. Next to this, Ravi *et al.* showed that the metabolic gene expression profile of BT treated airways shift towards a healthier state after BT (17). In summary, next to the effect of BT on structural airway remodelling including ASM and ECM, the impact on the epithelium might be a contributing factor to the favourable outcomes after the treatment as well. Future research might be directed to the effect of BT on the epithelium and the interaction with airway remodeling features.

A relative new imaging technique which could contribute to understand the role of airway remodeling in asthma related to treatment, including BT, is (polarization sensitive)-optical coherence tomography [(PS)-OCT)]. Standard OCT is a high-resolution infrared light based imaging technique that can be applied during standard bronchoscopy and can detect airway structures and dimensions in complete airway segments in a minimally invasive manner (18). PS-OCT adds the detection and quantification of birefringent airway wall components including ASM and potentially ECM (19,20). Therefore (PS)-OCT has been investigated in the evaluation of acute and late stage airway wall changes after BT (21,22). More studies are needed to further establish the added value of (PS)-OCT in detecting features of airway remodeling, including ASM content over full airway segments and how this relates to lung function and clinical outcome.

Ultimately, the mechanism of action of BT is most likely a combination of treatment effects on multiple airway wall compartments as summarized above. But how does this relate to the responder profile? In guidelines and practice recommendations, BT is mainly recommended for patients with T2-low asthma or failure on biologics (1,23,24). Interestingly, it has been suggested BT provides optimal clinical outcomes after normalizing sputum inflammatory cell counts first (25). It can be hypothesized that BT is most effective in severe asthma patients who remain uncontrolled despite optimized anti-inflammatory therapy. Furthermore, it is striking that within recent studies focused on delineating responders profiles, BT response was actually associated with atopy, mild to moderate eosinophil counts and IgE at baseline (8,10,26). In line with these data, since the large BT RCTs that showed effectiveness of BT were executed before the introduction of biologics (with the exception for anti-IgE), it is most likely that a large proportion of patients is these trials were T2-high asthma patients (1-3). Taken together, it might be that the combination of inflammatory control and airway remodeling modification is the key for optimal asthma treatment. Future registries implicating these current understanding of BT responder profiles along with extensive asthma phenotyping including precision medicine, multi-omics strategies and cost-effectiveness analysis compared to biologicals, would be of great value to the more exact positioning of BT in the treatment guidelines for severe asthma.

The review of Wu *et al.* provides us with an overview of the existing data about BT. In this short editorial we aimed to present additional insights in BT and identifying knowledge gaps about the mechanism of action and responder profile. Despite these knowledge gaps, there is accumulating evidence demonstrating the efficacy of BT. In our opinion, BT treatment is underutilized and should be offered more frequently, preferably in registries with extensive asthma phenotyping and responder analysis. Considering the data available, including long term extension studies, recent RCT trial results and real-world registries, it is prime time to reconsider the positioning of BT in guidelines, with the aim to provide severe asthma patients the best and most-cost-effective treatment options.

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