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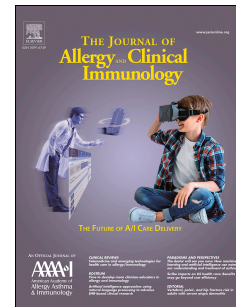
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Bronchial Thermoplasty: The heat that reprograms the airways?

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Conflict of Interest statement:

Jamila Chakir received a grant from Boston Scientific for the histological analysis of bronchial biopsies obtained before and after BT on a local clinical basis (ref 2).

Michel Laviolette participated to the three randomised clinical trials on BT and, recently, to the 10 years follow-up of these subjects (ref 1).

Pierre-Alexandre Gagnon has no conflict of interest.

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Bronchial thermoplasty (BT) is an endoscopic procedure that aims at reducing the hypertrophied asthmatic airway smooth muscle (ASM), and thereby preventing excessive bronchoconstriction, by treating the airways with heat. Three clinical trials showed that BT significantly decreased the numbers of severe asthma exacerbations, hospital emergency visits and admissions to hospital, and improved quality of life. These benefits persisted for 10 years or more¹. Histological examination of the bronchial wall showed that BT not only decreased airway smooth muscle area (ASM)² but also induced substantial changes in the airways inflammatory and remodeling features typical of asthmatic airways (Figure 1). Some of these changes such as the reduction of ASM and the thickening of the basement membrane are long lasting and may be explained by BT effects on specific bronchial structural cells and repair processes². In the current issue, three reports further investigated the effects of BT on airways.

Fang et al previously reported that BT induces a significant reduction of HSP60 level in bronchoalveolar lavage fluid and showed that, *in vitro*, HSP60 upregulates the expression of mitochondria regulator protein arginine methyltransferase-1 (PRMT1)³. In the current issue, they pursued their studies on HSPs and evaluated the effect of heat on epithelial cells derived HSPs⁴. First, they observed an increase in HSP70 and HSP90 levels in endobronchial biopsies one month after BT. Then, they mimicked BT *in vitro* by exposing epithelial and ASM cells to heat gradients. They also treated the cells with recombinant exogenous HSPs. In epithelial cells, these *in vitro* treatments increased their proliferation, decreased their apoptosis and activated both the AKT/mTOR signaling and the C/EBP- β - PRMT1 pathway. In contrast, these *in vitro* treatments were proapoptotic and anti-proliferative in ASM cells, which might explain at least in part the decrease of ASM observed in BT-treated patients. The work by Fang et al. was based on earlier transcriptomic and proteomic data that suggested a role of HSPs regulation as a potential molecular mechanism involved in the structural changes observed post-BT³. As these changes in HSPs were observed 1-month post-BT, whether this mechanism is permanent and sufficient to explain the long-term effects of BT is unknown. Further studies are needed to confirm the lasting effects of these HSPs and their links with pathways involved in ASM ablation and matrix deposition.

Ravi et al.⁵ performed RNA sequencing studies on epithelial cells obtained from BT-treated and -untreated control airways of patients with severe asthma. Six months after BT treatment, transcriptome analysis of epithelial cells obtained from a treated lobe showed an increase in OXPHOS and a reduction in fatty acid metabolism genes compared to cells obtained from the untreated right middle lobe suggesting that BT normalized the metabolic activity of airway epithelium. A previous report evaluating RNA-seq on bronchial brushing samples obtained from severe asthmatic patients treated with a tyrosine kinase inhibitor (Imatinib) showed an increased OXPHOS gene expression and an inhibition of Platelet-Derived Growth Factor (PDGF), a growth factor known to regulate smooth muscle proliferation⁶. Whether BT targets PDGF pathways is also unknown. Ravi et al. used epithelial cells of untreated middle lobe as controls. There is no consensus whether BT can affect the untreated middle lobe. Histological study of Pretolani et al. indicated that BT treatment could diffuse to untreated area⁷, however this observation has not been confirmed by other studies. In the present paper, Ravi et al. observed significant differences in OXPHOS gene expression and lipid profile between BT-treated lobes and the untreated middle lobe, suggesting that BT may not affect the untreated lobe to the same extent.

Ladjemi et al⁸ evaluated 23 subjects with severe asthma presenting a high number of annual severe exacerbations (≥ 10) and a relative blood eosinophilia despite a high daily dose of oral corticosteroids. Their bronchial biopsies demonstrated increased expression of epithelial

expression of MUC5AC, and elevated numbers of eosinophils and cells positive for IL-13, IL-17 and IL-33 in the mucosa, as well as of intramuscular mast cells. After BT, the number of exacerbations decreased dramatically (99%) in fifteen of them (designated as responders) and less (66%) in the other eight (designated as partial responders). At baseline, the responders had higher blood eosinophil count, incidence of atopy and level of total serum IgE than the partial responders. In the responders, BT significantly decreased the blood eosinophil count and the daily dose of oral prednisone, increased the epithelial expression of MUC5AC and the epithelial expression of IFN- α/β , and decreased the numbers of IL-13- and IL-33-positive cells, mucosal eosinophils, and mucosal and intramuscular mast cells. ASM area and SBM thickening were similarly reduced in both groups. This study of subjects presenting a very labile asthma with a persistent bronchial eosinophilic inflammation despite high doses of oral corticosteroids demonstrates the capacity of BT to modulate IL-13-driven airway asthmatic inflammation. The fact that 14 of the 15 responders did not improve with omalizumab suggests that the persistence of eosinophilic inflammation on high doses of oral corticosteroids was not predominantly modulated by allergy but likely by an IL-13 – CCL16 pathway⁹. Moreover, the AIR2 five-year follow-up study including 162 subjects with severe persistent asthma found no difference in the outcome based on the subjects' self-reported allergy status¹⁰. Consequently, beside BT, these subjects with labile and eosinophilic severe asthma are likely good candidates for a monoclonal antibody treatment targeting eosinophil recruitment, as suggested by the authors. In this small group of 15 responders, the observed correlations between clinical and histopathological parameters are possibly due to the concomitant presence of high levels of symptoms and of airway inflammation and remodeling at baseline, together with the high magnitude of improvements brought by BT in both clinical and histological parameters. The previous studies on BT reported many fewer improvements in clinical histological parameters and did not report any correlation between them^{2,7}. Ladjemi et al⁸ suggest that BT could provide benefit to asthmatics presenting different phenotypes and endotypes, although the histological and clinical benefits may be greater in young subjects with severe asthma, atopy and persisting eosinophilic inflammation. However, in such subjects, the intake of oral corticosteroids before and after the inclusion in a BT program must be closely monitored. This monitoring will permit to assure that airway inflammation improvements observed after BT are not due to a better compliance to corticosteroids during the post-BT follow-up notably in the responder patients. Moreover, this is also important to evaluate if the difference in blood eosinophil counts observed between the responder and partial responder patients at the beginning of the study was not due to a better compliance to prednisone in the last group before the inclusion in the study.

In summary, these reports further support that BT, as a one-time treatment, can significantly reverse some asthma-induced airway inflammatory and many remodeling processes, particularly through its effects on epithelial cells. In many ways, it seems to “reprogram” airway homeostasis in a durable fashion, providing sustained and significant clinical benefits. However, links between the histological and the clinical improvements need to be further investigated. Moreover, the proposed changes in airway inflammation parameters and the indication of BT in patients with severe eosinophilic asthma remains to be confirmed.

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Figure 1. Documented Bronchial Thermoplasty effects on asthmatic airways. The black arrows indicate the BT-induced increases and decreases of the measured parameters. The blue arrows indicate the effects of some of the changes observed in epithelial cells on other cells.

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