



Bronchial thermoplasty in asthma: 2-year follow-up using optical coherence tomography

To the Editor:

Bronchial thermoplasty (BT) is a novel, nonpharmacological procedure for treatment of severe asthma. Recently, the Asthma Intervention Research 2 clinical trial demonstrated asthmatics had fewer hospitalisations following BT, which persisted 5 years after therapy [1]. However, it is well recognised that asthma is a heterogeneous disease with distinct asthma phenotypes and, not surprisingly, not all asthmatics in that trial benefited from BT [2].

Although bronchoscopic biopsies, pulmonary function tests, exhaled nitric oxide, sputum eosinophil counts and other biological measures have been proposed as biomarkers for evaluating treatment effects [3], these biomarkers cannot provide regional information to characterise airway remodelling in the targeted airways prior to and longitudinally following treatment. Although imaging approaches, such as computed tomography of the lung [4] and magnetic resonance imaging using inhaled contrast agents [5], do provide regional information, these tests are limited to indirect assessment of the small airways. Optical coherence tomography (OCT) is a minimally invasive imaging technique for visualising airway wall structures with near-histological resolution [6–8]. OCT has been used for the evaluation of airway remodelling [9, 10] and early lung neoplastic changes [8, 11].

Identifying asthma phenotypes with the greatest response to BT is likely to bring the potential for better patient selection and ultimately better patient outcomes, and further research into methods capable of careful patient selection for BT has been strongly recommended [12]. Here, our objective was to provide a pilot study in two asthma patients who underwent BT in order to investigate the role of OCT imaging for evaluating airway remodelling prior to and longitudinally following BT treatment.

Two patients with chronic persistent asthma provided written informed consent. Flexible bronchoscopy was performed under local anaesthesia and conscious sedation [7]; BT was performed according to established protocols (Boston Scientific Corp., Marlborough, MA, USA) [2, 13]. OCT images of the subsegmental branch of the right-lower lobe (RB8a&b and RB9a&b) were acquired prior to and immediately after BT as well as at 3 weeks, 6 weeks, 6 months and 2 years post-BT using a custom-built swept-source OCT system [14] and a C7 Dragonfly Imaging Catheter (St Jude Medical Inc., St Paul, MN, USA). OCT airway segments matched by visual inspection at each time-point were selected for analysis. The lumen area (A_i) and outer wall area (A_o) for three consecutive OCT slices were manually segmented (ImageJ; National Institutes of Health, Bethesda, MD, USA) to generate airway wall (WA) percentage:

$$WA = \frac{A_i}{A_o} \times 100$$

Patient A was a 51-year-old male with no smoking history and an asthma duration of 6 years. Patient B was a 56-year-old female and an ex-smoker at the time of the study (10 pack-years) with an asthma duration of 27 years. Both patients reported similar forced expiratory volume in 1 s (FEV₁) (patient A: 1.63 L (53% pred); patient B: 1.52 L (54% pred)) as well as similar doses of inhaled steroids (4000 µg beclomethasone equivalent per day), salmeterol (100 µg per day) and tiotropium (18 µg per day). However, patient A reported higher doses of prednisone (patient A: 25 mg per day; patient B: 5–10 mg per day) and salbutamol (patient A: 3500–3700 µg per day; patient B: 300–500 µg per day) than patient B prior to BT.

Figure 1a shows OCT images pre-BT, immediately post-BT, and 3 weeks, 6 weeks, 6 months and 2 years post-BT for patients A and B. Patient A showed a remarkably thickened and inflamed epithelium, irregular basement membrane, and prominent smooth muscle pre-BT. Immediately post-BT, copious secretions and sloughing of the epithelium were observed. At 3 and 6 weeks post-BT, the epithelium appeared thinner and the lamina propria appeared thicker from deposition of collagen, and smooth muscle appeared slightly less prominent. At 6 months and 2 years post-BT, OCT showed recurrence of the inflammatory changes in the epithelium. In contrast to patient A, the epithelial layer of patient B was not inflamed pre-BT. Airway wall

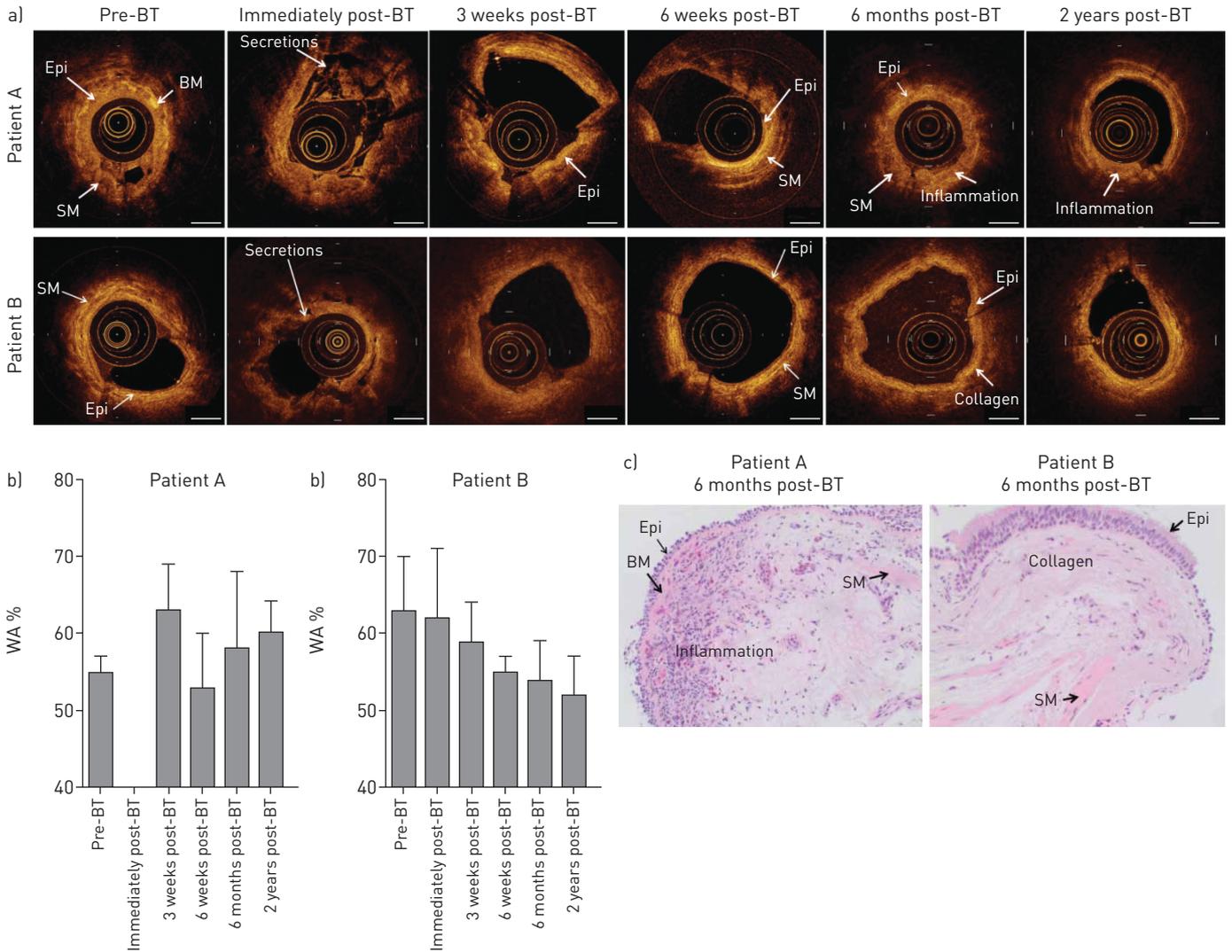


FIGURE 1 a) Optical coherence tomography images (scale bars=1 mm) and b) mean±SD airway measurements prior to and immediately after bronchial thermoplasty (BT), 3 weeks post-BT, 6 weeks post-BT, 6 months post-BT and 2 years post-BT, with c) the corresponding bronchial biopsy at 6 months post-BT. Epi: epithelium; BM: basement membrane; SM: smooth muscle; WA: airway wall.

oedema was visually apparent 3 weeks post-BT but was reduced at week 6. The smooth muscle layer was also less prominent 6 weeks post-BT, and remained the same at 6 months and 2 years. At 6 months and 2 years post-BT, patient B also showed a normal bronchial epithelium with collagen deposition in the submucosa.

Figure 1b shows OCT airway measurements pre-BT, immediately post-BT, and 3 weeks, 6 weeks, 6 months and 2 years post-BT for patients A and B. For Patient A, airway secretions prevented OCT airway measurements immediately post-BT. At week 3, OCT airway measurements showed an increase in WA. Although WA improved slightly at week 6, WA was increased 6 months and 2 years post-BT. In patient A, there was a transient improvement in FEV₁ at 3 and 6 weeks post-BT (pre-BT: 1.63 L; 3 weeks post-BT: 2.14 L; 6 weeks post-BT: 2.27 L). However, symptoms recurred 4 months after treatment and patient A remained on 20–50 mg per day of prednisone due to recurrent exacerbations. FEV₁ was also worse 6 months and 2 years post-BT than pre-BT (6 months post-BT: 1.08 L; 2 years post-BT: 1.11 L).

As shown in figure 1b for patient B, OCT WA was reduced at 3 and 6 weeks compared to baseline. This reduction in WA persisted 6 months and 2 years post-BT. FEV₁ also progressively improved post-BT (pre-BT: 1.52 L; 3 weeks post-BT: 1.68 L; 6 weeks post-BT: 1.78 L; 6 months post-BT: 2.03 L) but dropped slightly 2 years post-BT (2 years post-BT: 1.82 L). Symptoms decreased along with discontinuation of prednisone and less frequent use of rescue medication.

Figure 1c shows histology of RB8 bronchial biopsies 6 months post-BT. For patient A, histology showed a partially denuded epithelium, thickened basement membrane, moderate-to-severe inflammation and

remodelling of the submucosa by collagen deposition. In contrast, for patient B, histology of the same airway showed a normal bronchial epithelium with collagen deposition in the submucosa.

This pilot study illustrates, for the first time, that OCT can be used to evaluate *in vivo* airway remodelling longitudinally following BT in patients with severe asthma. Although the two asthmatics evaluated were similar in age and presented with similar clinical features and spirometry, the asthma patients demonstrated very different responses to BT as well as very distinct OCT airway wall features at baseline.

Following BT in patient A, despite evidence of FEV₁ improvement at weeks 3 and 6, OCT imaging showed no reduction in airway wall thickness and the patient's symptoms returned 4 months post-treatment. In contrast, patient B showed progressive improvements in FEV₁ for at least 6 months and reductions in OCT airway wall thickness, and demonstrated improvements in respiratory symptoms and decreased medication use for 2 years post-BT. Although patient A was a clear BT nonresponder, patient B demonstrated improvements following BT therapy that could not be predicted based on baseline spirometry or clinical features.

Although this study was limited to only two patients, it is certainly hypothesis generating and a number of questions arise from this pilot study. Most important is the question of whether OCT can identify characteristics within the airway wall that predict BT responders. Inflammation is visible on OCT [7, 15] and, notably, in this study, the BT responder showed thickened airway wall without evidence of inflammation in the epithelial layer at baseline compared to the nonresponder.

In summary, we evaluated two severe asthmatics immediately prior to and longitudinally following BT, and demonstrated a reduction in airway wall thickness that persisted 2 years following treatment in the BT responder, as well as differences in airway wall features between the responder and nonresponder prior to treatment. These observations generate hypotheses for a larger study to determine if airway changes defined by OCT imaging can identify asthma patients who will benefit from BT and to determine the long-term effects of the treatment.



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Optical coherence tomography small airway imaging may be used for better patient phenotyping and selection for BT <http://ow.ly/MllnU>

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