



Bronchial thermoplasty: what we know, what we don't know, and what we need to know

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Bronchial thermoplasty leads to sustained improvements in airway remodelling and clinical outcomes in severe asthma, but questions remain about how it works, who should be treated, and where it fits in current treatment guidelines <https://bit.ly/3xl1qZC>

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Bronchial thermoplasty is a non-pharmacological treatment for severe asthma, which aims to reverse the remodelling changes typically seen in the airways of asthma patients. Radiofrequency energy is applied to the airway walls using a bronchoscope-delivered thermoplasty catheter comprising a basket of four conducting wires which expand to contact the airway wall. The thermoplasty catheter is designed to heat the airway wall to approximately 65°C for 10 s. Over three procedures approximately 3 weeks apart, the majority of the bronchial tree (airways of calibre 3–10 mm) is treated; typically the right lower lobe in procedure one, the left lower lobe in procedure two, and both upper lobes in procedure three. The right middle lobe is not usually treated due to the risk of airway wall oedema leading to obstruction and right middle lobe collapse (termed “right middle lobe syndrome”) [1].

The safety and efficacy of thermoplasty was demonstrated in randomised clinical trials in the late 2000s [2, 3], including the pivotal AIR2 trial [4], which randomised 288 patients to thermoplasty or sham procedure in a 2:1 ratio. This showed improvements in Asthma Quality of Life Questionnaire (AQLQ) scores in those treated with thermoplasty compared to sham procedure, although a large sham procedure effect was also seen. Thermoplasty-treated patients had fewer asthma exacerbations, emergency department visits, and days missed from school or work in the 12 months after treatment, compared to those undergoing sham procedure.

CHAUDHURI *et al.* [5] recently published follow-up data for approximately half of the patients included in these first efficacy trials, examining safety and clinical outcomes 10–15 years after thermoplasty treatment. This showed that thermoplasty was safe in the long term, and that the clinical benefits were sustained beyond 10 years, with exacerbation rates, AQLQ score and Asthma Control Questionnaire (ACQ) score all remaining improved compared to pre-thermoplasty values.

The mechanisms underlying the clinical benefits of thermoplasty are still not fully understood. Pre-clinical trials in dogs identified a reduction in airway smooth muscle mass accompanied by an improvement in airway hyper-responsiveness following thermoplasty [6], and therefore this has been assumed to be the mechanism by which thermoplasty leads to clinical benefit. A number of small uncontrolled observational studies have investigated the remodelling effects of thermoplasty in humans by comparing pre- and post-thermoplasty bronchial biopsies. A reduction in airway smooth muscle mass has consistently been shown (relative reduction approximately 50–80%) [7–13], although there has been no consistent signal to show an accompanying change in airway hyper-responsiveness or lung function. Other remodelling changes have also been demonstrated in response to thermoplasty, including reductions in reticular basement membrane thickness [9–11], submucosal and airway smooth muscle-associated nerve fibres [11], and epithelial neuroendocrine cells [11], and improvements in epithelial integrity [12].

Despite studies consistently demonstrating clinical benefits and remodelling improvements, a robust relationship between these elements has not been seen. One small study demonstrated a correlation between airway smooth muscle mass reduction and improvements in asthma questionnaire scores and exacerbation rate [11], but other studies have not been able to replicate this. The mechanisms involved, therefore, remain uncertain.

It is also unclear which patients should be considered for thermoplasty treatment, and what factors may predict response to treatment. This lack of clarity is particularly stark when contrasted with the well-evidenced biomarker-guided approach to biologic treatments for severe asthma. Guidelines, such as those produced by the Global Initiative for Asthma [14] and the British Thoracic Society/Scottish Intercollegiate Guidelines Network [15], currently place thermoplasty at the bottom of the list as the final consideration for severe asthma patients ineligible for T2 biologics, or those with inadequate response to biologics. There is no evidence to support this being the correct positioning for thermoplasty in asthma treatment algorithms. Indeed, the TASMA trial recently showed that high blood eosinophil count and/or high IgE level were associated with greater improvement in AQLQ and ACQ scores in response to thermoplasty [13], suggesting that there may be more of a role for thermoplasty in T2-high patients than current guideline positioning suggests.

In this issue of the *European Respiratory Journal*, JENDZJOWSKY *et al.* [16] present results of a three-faceted mechanistic study investigating remodelling changes following thermoplasty, using an animal (porcine) model, *in vitro* and *in vivo* methods. In their animal model, the heat distribution in the airway wall was recorded using a thermal camera throughout the 10-s thermoplasty activation, and for 8 s after. This showed a peak temperature of 82.9°C at the four points which the thermoplasty catheter contacts the airway wall, with an average temperature over the 18 s of 64°C. Importantly, a large proportion of the airway wall located between the catheter contact points did not reach 65°C, as also shown using computer modelling by our own group [12].

In vitro, JENDZJOWSKY *et al.* [16] use growth media heated to different temperatures to closely replicate the temperature profiles of the airway wall at both the catheter contact points, and between the contact points. The temperatures reached at the catheter contact points caused disruption of airway smooth muscle cell morphology and viability, which occurred with 30 min and was sustained at 24 h. However, temperatures reached between the catheter contact points did not lead to changes in airway smooth muscle cell morphology; the comparatively modest effect on cell viability at 30 min was temporary, and fully recovered by 3 h. This is consistent with our own data obtained using similar methods, which also shows an important temperature threshold of approximately 65°C at peak (mean 59°C over 10 s) to achieve a sustained effect on airway smooth muscle cell viability up to 14 days after heat exposure [12]. Interestingly, JENDZJOWSKY *et al.* [16] did not see an effect on bronchial epithelial cells on exposure to either temperature profile, in contrast to our own study which showed reduced epithelial cell viability at 65°C, with evidence of recovery by day 10 (in contrast to 70°C which saw no subsequent recovery) [12].

JENDZJOWSKY *et al.* [16] also report remodelling effects *in vivo*, using pre- and post-thermoplasty bronchial biopsies from nine patients. They demonstrate reductions in airway smooth muscle mass and submucosal nerve bundles at 6 weeks and 12 months post-thermoplasty, in keeping with existing literature. At 6 weeks, submucosal collagen deposition reduced and vascularity increased, but these effects returned to baseline at 12 months, and may represent acute repair responses. No effects were seen on basement membrane thickness (in contrast to other studies), goblet cells or submucosal gland area.

With this study, JENDZJOWSKY *et al.* [16] add further evidence to our mechanistic understanding of thermoplasty, and provide reassurance regarding the longevity of remodelling benefits to at least 12 months post-treatment. However, there remain a number of unanswered questions.

First, through different modelling approaches and *in vitro* work, both JENDZJOWSKY *et al.* [16] and our group [12] have shown that substantial proportions of the airway wall are not heated to the temperatures needed to impact cell viability. It seems implausible that biopsy samples obtained from patients after thermoplasty are from the precise point on the airway wall which was in contact with the thermoplasty catheter and therefore reached the required temperature. And yet, biopsies consistently show improvements in remodelling features, suggesting other mechanisms are involved aside from the direct effect of heat on the tissues. There may be several concurrent mechanisms at play, and we remain some distance away from fully understanding these.

Secondly, it is unclear which patients will gain most benefit from thermoplasty, and where thermoplasty should fit within severe asthma treatment pathways. All of the published remodelling studies are limited by

small population size, including the present study (n=9) by JENDZJOWSKY *et al.* [16]. Larger trials, including mechanistic studies, are needed to attempt to link remodelling changes with clinical outcomes, and establish a responder phenotype. This should hopefully shed light on patient selection criteria, and clarify the positioning of thermoplasty within treatment guidelines.

Relatedly, we need a clear understanding of the way that thermoplasty is being used in clinical practice today. With a lack of evidence guiding patient selection decisions, there is undoubtedly significant variability between asthma centres regarding patient selection and timing of thermoplasty.

Finally, we need to understand the role of thermoplasty in the era of biologics for severe asthma. Thermoplasty pre-dates all current asthma biologics except anti-IgE. The playing field of severe asthma management has dramatically changed, with newer biologics targeting IL-5 (or its receptor) and IL-4/13, with others on the horizon. No thermoplasty studies have been undertaken to understand where it fits amongst these agents. Thermoplasty should perhaps not be dismissed in favour of biologics. Reassuring safety and efficacy data beyond 10 years, and remodelling data beyond 1 year, combined with a significant cost saving for a one-off treatment compared to long term biologic therapy, should make thermoplasty an attractive option.

The findings from JENDZJOWSKY *et al.* [16] add to the consistent body of evidence supporting the use of thermoplasty; so why is thermoplasty considered relatively infrequently? Unanswered questions about mechanisms, patient selection and guideline positioning may be the reasons. But these questions will never be answered unless we trust the data we already have, and commit to discovering more.

Conflict of interest: The authors declare no conflicts of interest.

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