One Step Forward, Two Steps Back: Bronchial Thermoplasty for Asthma

Increased airway smooth muscle mass and contractility contribute to bronchoconstriction, airflow limitation, and respiratory symptoms in asthma. These observations have led to interest in decreasing airway smooth muscle mass using bronchial thermoplasty as a nonpharmacologic approach to improving asthma control in individuals with severe asthma. Bronchial thermoplasty involves the delivery of thermal energy to the airway wall of medium to large airways through three separate bronchoscopic procedures.

The AIR2 (Asthma Intervention Research) trial, the largest study of bronchial thermoplasty to date, was a sham-controlled clinical trial of nearly 290 adults with severe asthma (1). Participants in both the bronchial and sham thermoplasty groups reported improvements in asthma quality of life over 12 months (the primary outcome), which was assessed by the Asthma Quality of Life Questionnaire (AQLQ). Importantly, both groups reported more than twice the minimum important difference for the AQLQ. However, the difference between groups in the AQLQ was modest and less than the minimum important difference over 12 months. Although some secondary outcomes favored bronchial thermoplasty (asthma exacerbations treated and days lost from school or work) over 12 months, there were no differences between groups in respiratory symptoms, rescue medication use, or lung function. Also, 8% of participants undergoing bronchial thermoplasty (vs. 2% in the sham group) required hospitalizations because of procedure-related complications.

Long-term follow-up in 85% participants in the AIR2 study who received bronchial thermoplasty demonstrated similar rates of asthma exacerbations and lung function over the next 5 years as those demonstrated in the first 12 months (2). The lack of a control group during the long-term follow-up limited the ability to understand the durability of the effects of bronchial thermoplasty. Guidance from experts who developed the 2020 Global Strategy for Asthma Management and Prevention (GINA) report (3) suggests that bronchial thermoplasty is not ready for prime time. The GINA report noted the large placebo effect with bronchial thermoplasty and an increase in asthma exacerbations over the first 3 months after the procedure. Moreover, it is not clear which patients with severe asthma are more likely to benefit from bronchial thermoplasty than be harmed by it. Overall, the GINA expert panel concluded that additional studies comparing long-term outcomes in both the active and sham-treated patients are needed.

It is in this context that the multicenter randomized clinical trial led by Goorsenberg and colleagues and reported in this issue of the *Journal* (pp. 175–184) offers new data (4). The TASMA (Unravelling Targets of Therapy in Bronchial Thermoplasty in Severe Asthma) study sought to quantify the effects at 6 months of bronchial thermoplasty on airway smooth muscle mass (percentage of positive stained desmin and α-smooth muscle actin compared with the total biopsy area) and to identify characteristics associated with improved asthma control and asthma quality of life. Forty participants (mean age, 20 yr) were enrolled in the Netherlands and the United Kingdom and underwent a research bronchoscopy to obtain measurements of baseline airway smooth muscle mass from endobronchial biopsies and then were randomized to immediate or delayed (after 6 mo) bronchial thermoplasty. Unfortunately, this study did not include a sham thermoplasty control group.

Consistent with AIR2 study findings, the authors of the TASMA study reported postprocedure asthma exacerbations, including nine hospitalizations. At 6 months, there was significant improvement in asthma control and asthma quality of life after bronchial thermoplasty compared with delayed treatment. Improvements in these TASMA participant-reported measures are difficult to interpret given the large placebo effect observed in the sham group in the AIR2 study. There were also no significant differences between groups in lung function, airway hyperreactivity, or fraction of expired nitric oxide.

Importantly, Goorsenberg and colleagues report a significant reduction in desmin-positive and α-smooth muscle actin–positive airway smooth muscle mass (primary endpoint) after randomization to bronchial thermoplasty compared with pharmacologic asthma care alone. Unexpectedly, the airway smooth muscle mass (values at baseline, change over 6 mo, or at 6 mo) was *not* associated with Asthma Control Questionnaire or AQLQ improvement. These findings challenge the scientific premise for the use of bronchial thermoplasty in asthma and suggest that patient selection for bronchial thermoplasty based on airway smooth muscle analysis is not likely to be productive. Time to take two steps back! ■

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In Chronic Obstructive Pulmonary Disease Progression, Is It Airway Narrowing or Airway Loss?

First published in *The New England Journal of Medicine* in 1970, Mead's now comprehensively validated hypothesis that the small airways "represent a quiet zone" that offers no resistance to airflow in healthy subjects, but becomes the site of major airflow obstruction in various pulmonary diseases, remains integral to our understanding of airway remodeling in chronic obstructive pulmonary disease (COPD) (1, 2).

Indeed, we now recognize that disease can build up over time in this zone without being detectable by global diagnostic methods such as pulmonary function tests, and therefore it is here that early detection of lung diseases such as COPD must occur (3, 4). This realization has fueled extensive research into new, more sensitive techniques for detecting early signs of disease accumulation in the small airways, leading to the development of numerous nonimaging methods such as forced oscillation (4, 5) and multiple breath washout (6).

Although there is still no clinical imaging technique with high enough resolution to directly visualize the small airways, several sophisticated quantitative imaging methods have produced powerful tools for unmasking small airway disease, such as the parametric response map (PRM), which can indirectly extract regional information about the functional integrity of small airways (7, 8) via the coregistration of computed tomography (CT) images acquired at full expiration and full inspiration.

The low image resolution implies that, like PRM, all CT-based approaches can only evaluate the small airways *indirectly*. In this issue of the *Journal*, however, Bodduluri and colleagues (pp. 185–191) have taken advantage of recent findings (9–11) that, in patients with COPD, more proximal airways display the same features as small airways. These more proximal airways can be visualized directly via CT images obtained at "full inspiration" after bronchodilator administration, and the authors have used such images to evaluate the progression of airway remodeling in patients with COPD (smokers [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 0–4] plus a small group of nonsmokers) to determine whether airway loss or narrowing is more prominent in a given patient by measuring the airway surface–to–volume ratio (SA/V). Airway trees were first segmented, and surface area and volume were then estimated from the three-dimensional segmented airways. The authors then used a simulation to determine the "relative contribution of airway narrowing and airway loss to SA/V" from the change in longitudinal SA/V (ΔSA/V).

On cross-sectional data, baseline SA/V showed an inverse correlation with all-cause mortality and a direct correlation with FEV_1/FVC, FEV_1% predicted, and 6-minute-walk distance. Lower SA/V was also associated with higher subjective life impact measured by St. George's Respiratory Questionnaire. In their longitudinal study, SA/V was inversely correlated with lung function decline measured by FEV_1 loss. Longitudinal analysis also showed that remodeling because of predominant airway loss was associated with significantly higher functional decline (greater FEV_1 loss) and, perhaps most importantly, significantly worse survival rates than airway narrowing–predominant remodeling. Although no breakdown statistics are presented for either 6-minute-walk distance or St. George's Respiratory Questionnaire, the shift within the predominant airway loss cohort, from 52% to 38% current smokers at study's end, is also interesting.

As expected, imaging data showed a significant decrease in total airway count among airway loss subjects, with no change among airway narrowing subjects. Subjects with predominant airway loss also had more emphysema and thicker segmental airway walls at both baseline and follow-up, as well as more air trapping at follow-up than those with predominant airway narrowing. Among those with mild disease, a higher percentage of subjects with predominant airway narrowing remained in the lower GOLD stages at follow-up.

It is clear that Bodduluri and colleagues have produced an important new technique for the structural evaluation of small airways (disease) based on the number of novel insights it provides as well as its potential clinical impact as a diagnostic and prognostic tool, which, if validated, could also be used to identify appropriate treatment

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