

"Hot Stuff"

Bronchial Thermoplasty for Asthma

Although the combined use of antiinflammatory and bronchodilating medications is generally successful at controlling asthma symptoms, there remains a small but significant number of patients with persistent symptoms and frequent exacerbations (1). These patients often require oral corticosteroids to control the disease, a medical regimen that can be associated with significant side effects (2). As a result, researchers are continuously trying to develop more specifically targeted treatments that are not only effective but also reduce the need for pharmacotherapy (3). One such possible treatment is bronchial thermoplasty, which is addressed in this issue of the *Journal* (pp. 965–969) by Cox and colleagues (4).

Bronchial thermoplasty is a newly developed procedure in which controlled thermal energy is applied directly to airways in the lungs through a bronchoscope. It was originally designed to reinforce the membranous part of the bronchi in patients with collapsible airways, but turned out in animals (5) and in humans (6) to reduce the contractility of the airway smooth muscle. The technique involves the delivery of radio frequency energy to the airway wall, which heats the tissue up to about 65°C, high enough to reduce smooth muscle mass, but low enough to avoid tissue destruction and scarring (5). Under general or local anesthesia, the catheter containing an expandable basket is passed through the working channel of a standard bronchoscope and is positioned in small- to medium-sized airways. Several airways are treated under direct vision in a half-hour procedure. Usually, three separate treatment episodes are required to treat all the accessible airways of both lungs.

In this uncontrolled, open-label, safety design study, Cox and colleagues studied 16 patients with mild to moderate asthma who underwent bronchial thermoplasty and who were assessed at 12 weeks, 12 months, and 2 years post-treatment. They found that the procedure was well tolerated, and that there were no severe reactions to treatment. All subjects showed a reduction in airway hyperresponsiveness, associated with improvements in daily symptoms and peak expiratory flow. These beneficial effects were sustained over the whole period of 2 years.

This study by Cox and colleagues is important both from pathophysiologic and clinical points of view. First, it provides a unique insight into the mechanisms of airway hyperresponsiveness in asthma. The ability of asthmatic airways to constrict more promptly and excessively to inhaled stimuli than is the case for normal airways is considered a key feature of the disease, and may be fundamental to its pathogenesis (7). Over the last decades, several mechanisms of airway hyperresponsiveness have been proposed, ranging from mucosal inflammation and alterations in airway geometry (8), to peribronchial inflammation with airway–parenchymal uncoupling (9), to intrinsic abnormalities of the airway smooth muscle itself (10).

The study by Cox and colleagues, as simple as it is, is uniquely hypothesis-testing and shows that modifying structural elements

of the airway wall can profoundly influence airway hyperresponsiveness. Does it indicate that the airway smooth muscle is the sole contributor to this characteristic feature of asthma? No, unfortunately, it doesn't. Although it is intuitively obvious that airways with reduced muscle mass are likely to contract less in response to stimulation, there are other possibilities, including damage to nerves or vessels, changes in mucus gland structure and function, alterations in the type of inflammation, and changes in airway compliance that may modulate this effect. Thus, the debate on the relative importance of muscular and nonmuscular elements in bronchial hyperresponsiveness in asthma has not been resolved by this study (11). Further *in vivo* structure-function studies specifically eliminating potential contributors to bronchial hyperresponsiveness are certainly the proper way to proceed.

From a clinical point of view, the study by Cox and colleagues is even more fascinating, because it suggests that bronchial thermoplasty has the potential to become a realistic therapeutic option in chronic asthma not satisfactorily controlled with pharmacotherapy. There are, however, several important issues to be considered. First, the long-term consequences of the procedure are not yet determined. The good news is that over a period of 2 years, none of the serious concerns speculated about, such as development of fixed obstruction, bronchial instability, or chronic progressive tissue damage, have developed (12). However, one could still envisage adverse effects in the long term. No one knows exactly what is the role of smooth muscle in the airway wall. It might be vestigial tissue without any essential physiologic function (13). However, this is teleologically unlikely and it cannot be excluded that certain disorders might appear, including permanent widening of the large airways, chronic infections with ensuing bronchiectasis, or increased collapsibility of the airway wall. Therefore, long-term observation of subjects undergoing this procedure is mandatory.

A second point of concern is whether the procedure targets the appropriate airways. There is now abundant evidence that the distal airways are involved in asthma, particularly in severe disease (14). Inadequate treatment of the peripheral airways might be the primary reason why patients with refractory asthma do not respond satisfactorily to inhaled therapy, and are at risk of severe asthma exacerbations (15). Bronchial thermoplasty does not access the peripheral airways, which may not only be a drawback of the technique but also may impose risks. If patients refrain from pharmacotherapy after bronchial thermoplasty because of symptomatic improvement, the distal airways might become more inflamed and obstructed than before. This might lead to increased airway closure, excessive airway narrowing, and severe asthma exacerbations (16). Pilot studies using bronchial thermoplasty in patients with severe asthma, probably the most relevant group for this technique, are underway, and we have to await the long-term outcomes of these before we can utilize this treatment to patients with severe asthma. In any case, bronchial thermoplasty should never be applied without proper anti-inflammatory pharmacotherapy in these patients.

Whether bronchial thermoplasty will earn a place in the treatment of asthma remains to be determined. However, this study

shows the potential for a completely new approach of treating asthma and stimulates the development of new hypotheses. For patients with refractory asthma, bronchial thermoplasty might become a real breakthrough, particularly for those with severe airway hyperresponsiveness. It is now the task of the investigators involved in further studies, the manufacturer of the device, and the medical community to understand more fully the role of this development that might become a real opportunity for a selected, and often difficult to treat, group of patients with asthma.

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Assessing Tuberculosis Transmission and Virulence The Vanishing Tuberculin Skin Test

With the introduction of IFN- γ release assays (IGRAs), a new era in testing for latent tuberculosis infection (LTBI) has begun (1, 2). These assays test for latent tuberculosis by mimicking in a test tube at least some of the phenomena associated with a type IV delayed-type hypersensitivity reaction. Peripheral blood mononuclear cells (PBMCs) contained in whole blood samples are exposed to mycobacterial proteins, and IFN- γ release, primarily by sensitized T cells, is measured. The recent refinement of these assays to stimulate PBMCs with proteins that are released by *Mycobacterium tuberculosis*, but not the vaccine strain of *M. bovis*, offers the advantage of a test that can distinguish between true infection with *M. tuberculosis* and prior vaccination with bacille Calmette-Guérin (BCG) (3). To guide physicians in the United States, the Centers for Disease Control and Prevention (CDC) recently issued guidelines for the use of the one IGRA currently licensed in this country (4). These guidelines state that IGRAs can be used in place of tuberculin skin testing (TST) in all circumstances, although caveats are offered that point out the dearth of data regarding the use of these tests in certain populations, such as those with HIV infection and persons at extremes of age. The CDC guidelines reflect evidence that suggests that, in comparison with TST, currently available IGRAs are more specific (primarily because of fewer false-positive results in persons who have received BCG) and of roughly equal or perhaps slightly lower sensitivity (5, 6). The guidelines also point out the pressing need for further research to evaluate unresolved questions, particularly concerning the performance characteristics of IGRAs in various populations.

In this context, how should the study by Anderson and co-workers in this issue of the *AJRCCM* (pp. 1038–1042) be viewed

(7)? These investigators conducted a contact investigation of schoolchildren exposed to an index case with advanced cavitary tuberculosis. They found that only 2 of 75 exposed children (2.7%) had positive results on skin testing (using the Heaf test), whereas 16 of 75 (22%) were positive when evaluated with an IGRA of the authors' own development.

There are several limitations in Anderson and colleagues' study. The sample size was relatively small, and only 62.5% of potential contacts agreed to participate. The cut-off for determining a positive IGRA was derived from a relatively small group of control subjects, and results in the control subjects demonstrated considerable splay in the results. The authors could detect no relationship between duration and proximity of contact to the index case and IGRA results, although they did not rigorously assess these factors. Skin testing in this study was done using the Heaf test, which is believed to be a less reliable method of assessing LTBI than Mantoux testing (8). For evaluating contacts, if Mantoux testing had been used (for which the American Thoracic Society and CDC recommend a cut-off of 5 mm of induration as defining a positive result in close contacts), it is likely that substantially more children, perhaps as many as 11 of 75 (15%), would have been classified as having LTBI, according to the data presented in Table 1. Such findings would have reduced the discrepancy between TST and IGRA results substantially.

The current report points out the difficulty of evaluating any new test in the absence of a true gold standard for LTBI. A natural history study of untreated exposed persons who are tested both with the standard TST and a new assay and then monitored to see which method most accurately predicts the