

mannitol), which is probably a better asthma marker than methacholine responsiveness. Integration of additional inflammatory markers, especially sputum eosinophil counts, might also prove valuable.

The lack of association of greater AHR with higher levels of many blood-related biomarkers is initially somewhat surprising. In asthmatic patients increases in both blood and sputum eosinophils have been positively associated with AHR, although correlations with fraction of exhaled nitric oxide have been inconsistent.^{9,10} Furthermore, in asthmatic patients it has been shown (although never replicated) that dosing patients with inhaled corticosteroids on the basis of their AHR led to improved outcomes¹¹ and higher inhaled corticosteroid doses. Thus inflammation and inflammatory markers appear to have some relationship with AHR in asthmatic patients. In asthmatic patients these relationships appear to be related to both direct and indirect measures of AHR. Although a direct comparison of the biomarkers measured in the COPD trials with the traditional asthma biomarkers is not possible, T_H2/type 2 biomarkers, including eotaxin, similarly did not positively associate with AHR. However, it is conceivable that levels of type 1 biomarkers (interferons and interferon-inducible protein 10) might also be inversely related to AHR in asthmatic patients. Thus the relationship of AHR to inflammation is likely to be complex, biomarker dependent, and perhaps disease specific.

Finally, it is critical to address the effect of all these measures on clinical approaches to patient care. Despite the fact that treatment based on AHR can lead to better outcomes in asthmatic patients, this approach has never been implemented or even promoted in various asthma guidelines. This is likely because of the difficulty in performing the test or tests, the inherent variability of the test, and perhaps the higher doses of inhaled corticosteroids required to lead to the improved outcomes. In patients with COPD, although there is a suggestion that decrease in lung function and even death is linked to AHR, the treatment choices to improve this AHR might be more limited. In fact, the most likely treatment approach would be one targeted at improving the degree of airway obstruction (as opposed to indirectly through effects on inflammation).

The study by Tkakova et al¹ appears to have performed the methacholine challenges on minimal background medication, with subsequent treatment limited to corticosteroids, short-acting bronchodilators, or both. Given the marginal effect of

both long-acting β -agonists and long-acting muscarinic agents on survival in patients with COPD, it is conceivable that specifically targeting patients with high AHR with bronchodilator approaches could affect outcomes, including death.^{12,13} Prospective studies of indirect AHR and inflammatory biomarkers are needed before clinically meaningful, guideline-affecting recommendations can be made.

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