Editorial
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Assessment of Bronchodilator Responsiveness after Methacholine–Induced Bronchoconstriction

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Spirometry is the only objective clinical tool available to physicians in the outpatient setting. Patient history is often unreliable and physical examinations are normal when the child doesn't show symptoms. For that reason, spirometry is currently considered essential for asthma diagnosis, severity stratification, and monitoring asthma control in children ≥5 years.[1] Bronchodilator responsiveness (BDR), which is an improvement of forced expiratory volume in 1 second after inhalation of β2-agonists, has traditionally been the definition of asthma[2] and has recently been reported to reflect biomarkers of eosinophilic inflammation,[3,4] bronchial hyperreactivity,[5,6] and airway remodeling.[7] BDR has also been regarded as a good predictor of response to therapy,[8] a marker for long-term prognosis,[5,9] and an important component in defining asthma phenotypes.[10,11]

Since BDR is usually measured by changes in airflow before and after administration of β2-agonists, it is influenced by the baseline airway tone. If the airways at baseline were fully dilated by asthma treatment, airflow would barely increase. Moreover, asthmatic children usually show prebronchodilator spirometry within the normal range, regardless of their symptom-based severity of asthma control.[12] Consequently, impaired β-adrenergic responsiveness, which plays a role in the pathogenesis of asthma, is rarely evident, especially when the children are taking controller medications.

In 1999, Hancox et al.[13] first introduced the 'challenge-rescue' technique to assess BDR. They measured BDR after bronchoconstriction induced by methacholine, because β2-receptor responsiveness was easier to demonstrate under conditions of increased bronchomotor tone. The challenge-rescue model has been widely used[14,15] because it has consistently provided evidence of bronchodilator tolerance, whereas previous studies of stable asthma have not. Moreover, it has obvious clinical relevance; asthmatics usually take β-agonists to relieve symptoms caused by bronchoconstriction.[16]

Despite the usefulness of this approach, some problems exist in terms of data interpretation. BDR to salbutamol is confounded by spontaneous recovery from the bronchoconstricting effects of methacholine. Although spontaneous recovery for 15 minutes after bronchoconstriction is rare,[13] other factors that facilitate recovery from bronchoconstriction may be displayed as an enhanced responsiveness to bronchodilators. On the other hand, geometric factors, such as airway mucus plugging and mucosal edema, might not be discerned from bronchodilator tolerance. Therefore, care must be taken when analyzing BDR data obtained from the challenge-rescue technique.

In the present issue of *Allergy, Asthma, & Immunology Research*, Bauer et al.[17] assessed BDR using the challenge-rescue technique and evaluated the clinical factors that may affect BDR in children with mild to moderate asthma. Though the interpretation of the data is complicated, the results provide interesting information. Asthmatic patients with atopy and/or eosinophilia displayed higher BDR as compared with that of non-atopic and/or non-eosinophilic patients, which provides indirect evidence that BDR may be a marker for inflammation. While admitting that bronchoconstriction induced by methacholine may not exactly reflect clinical exacerbation of asthma, the results raise the possibility that more frequent or severe asthma attacks would occur in non-atopic and/or non-eosinophilic children with asthma. Another interesting finding is that no apparent differences were observed among the medication subgroups. Since inhaled long-acting β2 adrenergic agonists or corticosteroids were discontinued seven days prior to testing in

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this study, it is likely that tolerance to β-agonists would no longer be a concern when medications are withheld for more than seven days.

Assessment of BDR following induced bronchoconstriction may be a useful tool for evaluating impaired β-adrenergic responsiveness, which plays a key role in the pathogenesis of asthma. Further studies are needed to extend the application of BDR assessment to determine management options in asthmatic patients.

REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol 2007;120: S94-138.
2. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-68.
3. Faul JL, Demers EA, Burke CM, Poulter LW. Alterations in airway inflammation and lung function during corticosteroid therapy for atopic asthma. Chest 2002;121:1414-20.
4. Puckett JL, Taylor RW, Leu SY, Guijon OL, Aledia AS, Galant SP, George SC. An elevated bronchodilator response predicts large airway inflammation in mild asthma. Pediatr Pulmonol 2010;45:174-81.
5. Tantisira KG, Fuhlbrigge AL, Tonascia J, Van Natta M, Zeiger RS, Strunk RC, Szefler SJ, Weiss ST. Bronchodilation and bronchoconstriction: predictors of future lung function in childhood asthma. J Allergy Clin Immunol 2006;117:1264-71.
6. Suh DI, Lee JK, Kim CK, Koh YY. Bronchial hyperresponsiveness to methacholine/AMP and the bronchodilator response in asthmatic children. Eur Respir J 2011;37:800-5.
7. Goleva E, Hauk PJ, Boguniewicz J, Martin RJ, Leung DY. Airway remodeling and lack of bronchodilator response in steroid-resistant asthma. J Allergy Clin Immunol 2007;120:1065-72.
8. Martin RJ, Szefler SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, Craig TJ, Dimango EA, Deykin A, Fahy JV, Israel E, Lazarus SC, Lemanske RF Jr, Leone FT, Pesola GR, Peters SP, Sorkness CA, Szwejbka LA, Wechsler ME. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. J Allergy Clin Immunol 2007;119: 73-80.
9. Sharma S, Litonjua AA, Tantisira KG, Fuhlbrigge AL, Szefler SJ, Strunk RC, Zeiger RS, Murphy AJ, Weiss ST. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. J Allergy Clin Immunol 2008;122: 921-8.e4.
10. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med 2008;178:218-24.
11. Galant SP, Morphew T, Newcomb RL, Hioe K, Guijon O, Liao O. The relationship of the bronchodilator response phenotype to poor asthma control in children with normal spirometry. J Pediatr 2011; 158:953-9.e1.
12. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. Am J Respir Crit Care Med 2004;170:426-32.
13. Hancox RJ, Aldridge RE, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Town GI, Taylor DR. Tolerance to beta-agonists during acute bronchoconstriction. Eur Respir J 1999;14:283-7.
14. van der Woude HJ, Winter TH, Aalbers R. Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting beta2 agonists. Thorax 2001;56:529-35.
15. Wraight JM, Hancox RJ, Herbison GP, Cowan JO, Flannery EM, Taylor DR. Bronchodilator tolerance: the impact of increasing bronchoconstriction. Eur Respir J 2003;21:810-5.
16. Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. Clin Rev Allergy Immunol 2006;31:181-96.
17. Bauer S, Park HN, Seo HS, Kim JE, Song DJ, Park SH, Choung JT, Yoo Y, Kim HJ. Assessment of bronchodilator responsiveness following methacholine-induced bronchoconstriction in children with asthma. Allergy Asthma Immunol Res. Forthcoming 2011.