

## Bronchial Challenge: Just Do It!

In this issue of *RESPIRATORY CARE*, Parker and Abu-Hijleh<sup>1</sup> report that, in patients referred for symptoms suggestive of asthma, a positive methacholine challenge cannot be predicted by the commonly used clinical indices. However, when stratified for age, certain symptoms and abnormal spirometry do predict airways hyperresponsiveness (AHR). Parker and Abu-Hijleh also report that the occurrence of AHR in such patients referred for methacholine challenge is low (44%). So what does the study teach us? As we will see, the lessons are many and very important.

Asthma is unique among lung diseases because the diagnosis is made by a combination of clinical history and abnormal pulmonary function test results,<sup>2,3</sup> including air flow obstruction reversible by bronchodilator therapy, variable peak flow, and AHR. At least 2 of these pulmonary function criteria (peak flow variability and AHR) are strongly linked.<sup>3,4</sup> Reversibility of air flow obstruction cannot be used as a criterion with patients who have mild asthma (the most common type of asthma), because these patients often do not have evident air flow obstruction. Peak flow variability, though inexpensive to perform, is known to be insensitive, and the ability of some individuals to perform peak flow at home is suspect.<sup>5</sup> That leaves us with bronchial challenge as the only objective means to establish the diagnosis of asthma.<sup>2,3,6</sup> However, many practitioners question whether a methacholine challenge is needed; they say that the symptoms of asthma should be adequate proof.

---

SEE THE ORIGINAL STUDY ON PAGE 596

---

The study by Parker and Abu-Hijleh<sup>1</sup> shows us that symptoms of asthma are *not* enough to establish a diagnosis of asthma. For the whole study group there were no symptoms that predicted whether a patient would show AHR. This is an incredibly important point. Though we all pride ourselves as well-trained physicians, nurses, or allied health professionals, the truth of the matter is that in order to make a firm diagnosis of asthma, or indeed most diseases, objective data are required.

Years ago I participated in a study (unpublished) of 100 consecutive asthmatics referred for diagnosis and treatment. Detailed questionnaires were given to both patient and physician, and then all the laboratory tests, including pulmonary function tests, were performed. The results were startling.

Neither the patient nor the physician could predict any better than chance (a coin toss) whether a particular patient would show a positive result in a particular pulmonary function test, including the methacholine challenge. The conclusion of that study was that only objective laboratory tests were adequate in establishing the diagnosis of asthma. But sometimes the results of the methacholine challenge do not conform to our expectations. There are several possible reasons for a false positive or a false negative methacholine challenge result, and one needs to be aware of those reasons for the purpose of interpretation.<sup>7</sup>

The study by Parker and Abu-Hijleh also teaches us an important lesson about asthma. Asthma is a very heterogeneous disease; or, in other words, asthma is not asthma. The study shows that the age of the patient is an important determinant of the presentation of asthma. In the Parker and Abu-Hijleh study, when patients were divided into age groups, a considerable number of predictive features of those who were methacholine-positive came to light. Among children nothing seems to predict AHR, and among those > 65 years old there was also a lack of predictive signs or symptoms. These findings suggest that asthma could be a very different disease in the young and the old. For the young the issue is probably a combination of a growing lung and a shorter history of asthma, where not enough time has passed to cause certain features (eg, low forced expiratory volume in the first second [FEV<sub>1</sub>]) and symptoms.<sup>8</sup> Among those > 65 years old the issue of other diseases and an aging lung are probably involved.<sup>9</sup> The teaching point here is that asthma is a very different situation at the 2 extremes of life and the treatment required may be different.<sup>8,9</sup>

Why did so few of the subjects in the Parker and Abu-Hijleh study have positive methacholine challenge results? If they had symptoms of asthma and this is a disease of airway hyperresponsiveness, one would think that more than 44% should have been positive. The answer is complex. In a recent study (unpublished data) we found a similar low incidence (50%) of positive methacholine responsiveness in patients who carried a doctor's diagnosis of asthma and a previous prescription for asthma medication.<sup>10</sup> Accordingly, our first explanation for a negative methacholine challenge result is that the patient did not really have asthma. That may be the case; in the Parker and Abu-Hijleh study the patients were referred because their presentation was unclear and their symptoms were equivocal. There are many conditions that mimic

asthma,<sup>3,7</sup> the most common of which is congestive heart failure.<sup>3,7</sup> Remember too that published studies on asthma are on patients who were carefully screened, not “real-life” and using all comers such as in the Parker and Abu-Hijleh study.

The other likely explanation for the low numbers of positive methacholine challenge result is that the patients had asthma but the AHR had resolved. It is generally not well appreciated that AHR can occur very rapidly, within hours following antigen exposure, and in some patients AHR can resolve just as quickly.<sup>11</sup> This is the reason that the association of AHR to current symptoms is incredibly important in the interpretation of methacholine challenge results.<sup>12</sup> Methacholine challenge therefore should be conducted as quickly as possible in relation to asthma symptoms.

So where does this leave the methacholine challenge test for asthma diagnosis? As is covered in the American Thoracic Society guidelines,<sup>12</sup> the test is best used to rule out, not rule in, an asthma diagnosis. Though the test is very *sensitive* for the presence of asthma, a positive methacholine test is not *specific* for asthma, because various lung diseases (eg, chronic obstructive pulmonary disease, cystic fibrosis, and acute respiratory distress syndrome<sup>1,3,7,12</sup>) can cause AHR. So even a positive methacholine challenge does not necessarily mean the patient has asthma.

So why perform a methacholine challenge at all? Our alternative is to blindly treat the “asthmatic” patient, assuming that he or she is methacholine-positive. The impact of asthma, even mild asthma, on quality of life is substantial,<sup>13</sup> so there is considerable pressure to treat the suspected asthmatic patient because of the debilitating symptoms. Given the cost of modern asthma drugs, and in some cases their adverse effects, treating a patient blindly is inappropriate and, unfortunately, all too common. The impact of taking asthma medication is nontrivial. Accordingly, our patients deserve to really know if they have the disease that we are treating. So in regards to the methacholine challenge test. . . just do it!

**Charles G Irvin PhD**  
Vermont Lung Center  
Department of Medicine  
College of Medicine  
University of Vermont  
Burlington, Vermont

## REFERENCES

1. Parker AL, Abu-Hijleh M. Clinical variables are poor selection criteria for the use of methacholine bronchoprovocation in symptomatic subjects. *Respir Care* 2003;48(6):596–601.
2. Kaminsky DA, Irvin CG. Lung function in asthma. In: Asthma. Barnes PJ, Grunstein MM, Leff A, Woolcock AJ, editors. New York: Lippincott-Raven; 1997;1277–1300.
3. Wagers SS, Irvin CG. The pharmacology of aerosolized airway challenge. *Respir Care Clin N Am* 1999;5(4):633–648.
4. Parameswaran K, Belda J, Sears MR. Use of peak flow variability and methacholine in responsiveness in predicting changes from pretest diagnosis of asthma. *Eur Respir J* 1999;14(6):1358–1362.
5. Irvin CG. Throwing the baby out with the bath water (editorial). *J Asthma* 1996;33(5):275–276.
6. Hunter CJ, Brightling CE, Woltman G, Wardlaw AJ, Pavord ID. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest* 2002;121(4):1051–1057.
7. Irvin CG. Bronchial challenge testing. *Respir Care Clin N Am* 1995; 1(2):265–285.
8. Irvin CG. Interaction between the growing lung and asthma: role of early intervention. *J Allergy Clin Immunol* 2000;105 (2 Pt 2):S540–S546.
9. Enright PL. The diagnosis and measurement of asthma is much tougher in older patients. *Current Opin Allergy Clin Immunol* 2002; 2(3):175–181.
10. The safety of inactivated influenza vaccine in adults and children with asthma. (The American Lung Association Asthma Clinical Research Centers.) *New England J Med* 2001;345(21):1529–1536.
11. Cockcroft DW, Ruffin RE, Dolovich J, Hargreave FE. Allergen induced increase in non-allergic bronchial reactivity. *Clin Allergy* 1977; 7(6):503–513
12. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161(1):309–329.
13. Juniper EF. Health-related quality of life in asthma. *Curr Opin Pulm Med* 1999;5(2):105–110.

---

The author received support from National Heart, Lung, and Blood Institute Grants R01 HL-62746, R01 HL-67273, and P01 HL-67004, and from a Center of Biomedical Research Excellence grant from the National Center for Research Resources, P20 RR-15557.

Correspondence: Charles G Irvin PhD, Vermont Lung Center, Department of Medicine, College of Medicine, University of Vermont, 149 Beaumont Avenue, HSRF 226, Burlington VT 05405. E-mail: charles.irvin@uvm.edu.