Abbreviated Methacholine Challenge
How Safe Are Short Procedures?

To the Editor:

Increased nonspecific bronchial hyperresponsiveness to pharmacologic agents such as methacholine is a hallmark of asthma. The measurement of airway reactivity is quite sensitive, but testing is tedious and time consuming. It is not surprising to find in the literature many attempts aimed to design the shortest possible yet safe inhalation challenge protocol. While there is an abundance of such rapid protocols set for epidemiologic studies of randomized, largely healthy populations, there are only a few recommendations for short protocols that may be applicable in the population seen in a lung function referral center. The work of Juniper et al4 should be mentioned in particular, as it was adopted by the Canadian Thoracic Association and seemed to have gained some popularity worldwide. However, those of us who test patients in referral centers know that this issue is far from being settled, and that many centers run their own abbreviated procedures. In fact, the American Thoracic Society published an official guideline for methacholine challenge testing, but could not come up with an agreed-on protocol, and I am quoting: “Many different protocols have been used . . . and the committee was unable to come to a single recommendation.”

Three articles have been published recently on this issue, two appeared in the European Respiratory Journal, and one appeared in this journal.10 The study of Cockcroft et al10 is essentially a retrospective inspection of 1,000 tests that were performed according to the protocol recommended by Juniper et al.4 According to this study, the initial inhalation concentration can be > 0.03 mg/mL, and a fourfold rather than doubling concentration steps may be taken in most cases. The results seem very encouraging in that the probability of a severe response (ie, \(\Delta FEV_1 \geq 40\%\)) was kept to a reasonable level of 1.3% of the tested population (4.1% of all responders). We feel that the recent publication of Cockcroft et al10 warrants further discussion on four particular aspects:

1. The practice of choosing a more conservative strategy when dealing with patients rather than a randomized, largely healthy population stems from our a priori knowledge that a much larger proportion of subjects will respond to the challenge test. The clinical distribution of patients studied by us and by Troyanov et al10 yielded indeed 60% positive responders. The study of Cockcroft et al,10 however, yielded a disappointingly low number of positive responders (32%), close to results obtained from epidemiologic studies.

2. The algorithm suggested by Cockcroft et al10 differs from ours in that it critically relies on obtaining a medical history of the patient and knowing his or her medication needs. These criteria require a greater need for the attending physician and/or better technician training. They are also subjective and are prone to large variability between practicing centers. We feel that our algorithm overcomes these shortcomings by relying solely on an objective criterion (ie, baseline value of \(FEV_1/FVC \geq 80\%\)). Furthermore, this is more practical to implement in a busy clinical center, as it simplifies laboratory routines.

3. Juniper et al4 and Cockcroft et al10 suggested that in asthmatic subjects with normal baseline lung function, the initial concentration could be as high as 1 mg/mL if they are maintained on intermittent bronchodilators, and 2 mg/mL if they receive no medications. The American Thoracic Society official statement7 adopted a slightly more cautious view in recommending that only subjects “not known to have asthma and taking no asthma medications” could be started at a dose of 1 mg/mL. In our experience, 62 of 280 subjects (22.1%) with baseline \(FEV_1/FVC \geq 80\%\) had a positive response (ie, \(\Delta FEV_1 \geq 20\%\)) at an inhalation concentration of 0.5 mg/mL, 22 of them having a provocative concentration of methacholine causing a 20% fall in \(FEV_1 \leq 0.25\) mg/mL. While some of our patients were receiving antiasthmatic medications, it is very probable that many of these 62 patients would have had a very severe response had they been started at an initial concentration of 1 mg/mL as suggested here. Thus, we do not feel that these recommendations are safe enough. Our algorithm suggesting the use of 0.21 mg/mL as the initial concentration was found to be safe.

4. Juniper et al4 and Cockcroft et al10 further suggested a fourfold increase as compared to our tripling concentration steps. It is intuitively obvious that our algorithm is more conservative and hence safer. Cockcroft et al10 cut this risk by falling back to the doubling concentration protocol when a response of \(\Delta FEV_1 \geq 5\%\) was observed. We feel that such a small change in \(FEV_1\) falls within test variability and will impose unnecessary spurious recordings. Instead, our algorithm calls for falling back when a \(\Delta FEV_1 \geq 10\%\) is observed.

In summary, both algorithms9,10 are successful in shortening the test to an average of about 30 min while keeping it as safe as the standard test (ie, 3 to 4% occurrence rate of severe responses). Our algorithm appears to be safer in our group of patients, and it is quite possible that outcome depends on patient composition. As was correctly pointed out in the editorial adjoining this publication,11 the use of methacholine challenge testing is highly recommended and abbreviated algorithms will bring about the needed wider use of it. However, a more careful look at suggested protocols is needed before the final verdict is reached.

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