A Screening Test for Airways Reactivity*
An Abbreviated Methacholine Inhalation Challenge

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A screening test to measure nonspecific airways reactivity was developed and compared to a standard methacholine inhalation challenge in 13 asthmatic patients and ten normal control subjects. The screening challenge consisted of one deep breath, then four breaths of a 5 mg/ml methacholine solution followed by one and four breaths of 25 mg/ml of methacholine. Subjects with a history of wheezing received the 5 mg/ml of methacholine first while those without a history of asthma began the challenge at the 25 mg/ml methacholine concentration. Spirometric tests were employed and the challenge was terminated when FEV₁ fell 20 percent from baseline. The standard methacholine challenge used a dosimeter and all subjects took five breaths of saline solution followed by seven increasing concentrations of methacholine. Dose response curves were constructed and the provocation dose of methacholine that caused a 20 percent fall in FEV₁ was calculated for each protocol. Results of the screening methacholine challenge correlated with those obtained from the more lengthy standard protocol (r=0.94), and correctly identified levels of airways reactivity in asthmatic patients and normal subjects. The abbreviated protocol was rapid (6-12 min), safe, and inexpensive. Since the equipment is readily available and easy to transport, it could be used at sites outside the hospital as a screening test for nonspecific airways reactivity.

The measurement of nonspecific airway reactivity is useful in the study of the pathogenesis of asthma, risk factors for development of chronic obstructive pulmonary disease, as well as investigation of the effects of occupational exposures on airways function. Because of the complexities of standard protocols used to assess airway reactivity, its widespread application in these areas has often been limited. Tests used to measure reactivity include pharmacologic challenge with methacholine or histamine, exercise challenge, and more recently, isocapneic hyperventilation with cold air. Exercise challenge may not be sensitive enough to detect mild increases in reactivity, nor does it lend itself to mass screening protocols. Isocapneic hyperventilation with cold air requires complicated equipment which is expensive, difficult to transport, and not widely available. While the usual pharmacologic challenge procedures with methacholine or histamine are quite sensitive measures of nonspecific airway reactivity, they are tedious and time consuming, often taking more than 60 minutes to complete. Although abbreviated inhalation challenge protocols exist, their results have not been compared to the measurement of airway reactivity using standard inhalation challenge techniques. Thus, the purpose of this study was to design a practical, rapid inhalation challenge protocol to measure nonspecific airways reactivity that would be suitable for screening large population groups, and to compare the results of this abbreviated challenge with a standard inhalation challenge technique.

**METHODS**

The study population consisted of 13 asthmatic patients (eight men and five women, 19 to 30 years of age) with a characteristic clinical history of asthma, and ten normal control subjects (six men and four women, 21 to 37 years of age) who had no history of asthma, atopy, or allergic rhinitis. No asthmatic patients had taken glucocorticoids or sodium cromolyn for at least four weeks prior to our study, while short-acting methylxanthines, sympathomimetics, and antihistamines were withheld for 48 hours prior to study. Methacholine (J.T. Baker, Phillipsburg, N.J.) was diluted in phenol buffered saline solution and was aerosolized through a DeVilbiss no 646 nebulizer (Somerset, Pa.) which was attached to a compressed air source (20 psi). This apparatus delivered a mean droplet diameter of 1.6 ± 3.14 microns (mean ± geometric standard deviation). Using a Stead-Wells spirometer (Warren E. Collins, Braintree, Ma.), three reproducible determinations of FEV₁ and FVC were obtained and the best value was used for subsequent results and calculations.

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The study protocol consisted of two different methacholine challenges. The first was the standard method described by Chai et al.\textsuperscript{1}\textsuperscript{0} Briefly, the subjects were instructed to take five maximal inspirations from FRC. Solutions were nebulized for 0.6 sec by triggering a breath-activated solenoid valve timing circuit (dosimeter). This apparatus delivered an average of 1.026 ± 0.222 ml (mean ± standard error) with every five breaths. After first inhaling control saline solution, all subjects received increasing concentrations of methacholine (0.156, 0.625, 1.25, 2.5, 5.0, 10.0, and 25.0 mg/ml). During the five-minute intervals between inhalations, spirometric tests were performed. When a 20 percent or greater fall in FEV\textsubscript{1} occurred, the challenge was terminated. Then, dose-response curves for methacholine were constructed whereby the dose of agonist required to produce a 20 percent fall in FEV\textsubscript{1} was calculated (PD\textsubscript{20} FEV\textsubscript{1}).

The short methacholine challenge protocol differed from the standard protocol in several ways. No dosimeter was used to administer the methacholine; instead, the subjects were instructed to take slow vital capacity inhalations from a plastic face mask attached to a DeVilbiss nebulizer. This system was manually activated by the technician when the subject signaled he was ready. During inhalations, nose clips were worn and the subjects were asked to keep their eyes closed to avoid possible conjunctival exposure. Successive doses of methacholine consisted of one breath of 5 mg/ml followed by four additional breaths of 5 mg/ml of methacholine, then one breath of 25 mg/ml, and finally four breaths of 25 mg/ml. Those subjects with a history of asthma or wheezing first inhaled one breath of 5 mg/ml of methacholine. In contrast, subjects with no history of asthma, atopy, or wheezing started at a higher concentration of methacholine, one breath of 25 mg/ml, followed by four additional breaths of this concentration. During the five min intervals between methacholine inhalation, spirometry was performed and the endpoint of the challenge was a 20 percent fall from baseline FEV\textsubscript{1}. Dose response curves were constructed in a manner identical to that used in the standard protocol and the PD\textsubscript{20} FEV\textsubscript{1} was calculated.

The data were analyzed by unpaired t-tests, Spearman rank order analysis, and the Pearson products moment coefficient of correlation.\textsuperscript{13,14}

**RESULTS**

Results of baseline pulmonary function tests in both the normal subjects and asthmatic patients were similar on each of the two study days for the standard and the short methacholine challenge ($P > 0.7$). Figure 1 shows the relationship between the PD\textsubscript{20} FEV\textsubscript{1} calculated using the short methacholine challenge test and the PD\textsubscript{20} FEV\textsubscript{1} measured by the standard methacholine protocol. The correlation by rank order analysis was $R = 0.94$ ($P < 0.001$) for all subjects and $R = 0.77$ ($P < 0.01$) for the asthmatic group. The short methacholine test accurately characterized airways hyperreactivity and there was no overlap between asthmatic and normal groups while the standard protocol showed overlap in methacholine sensitivity in four subjects (Fig 2 and 3). During the short challenge, all of the asthmatic patients developed a

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21300/)

**FIGURE 1.** Correlation of PD\textsubscript{20} FEV\textsubscript{1} from the short methacholine protocol and from the standard challenge procedure. PD\textsubscript{20} FEV\textsubscript{1} is the dose of methacholine required to produce a 20 percent fall in FEV\textsubscript{1}.

20 percent fall in FEV\textsubscript{1} at or before reaching a concentration of one breath of 25 mg/ml of methacholine, while even the most sensitive normal subject decreased his FEV\textsubscript{1} by only 7 percent at this dose. For the normal subjects, the upper limit of fall in FEV\textsubscript{1} was 7 percent at one breath of 25 mg/ml, and 23 percent after a total of five breaths of 25 mg/ml.

In the asthmatic group during the short methacholine protocol, FEV\textsubscript{1} fell to 62.4 ± 11 percent

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21300/)

**FIGURE 2.** A comparison of the responses of asthmatic and normal subjects using the short methacholine protocol and the standard challenge procedure.
(mean ± standard deviation) of baseline values (Fig 4). This bronchospasm was rapidly reversed and FEV₁ in the asthmatic group returned to 87.2 ± 9.0 percent of baseline three minutes after two inhalations of isoproterenol (250 μg) (Fig 4).

**Discussion**

This short methacholine challenge protocol accurately assessed airway hyperreactivity in asthmatic subjects and provided results similar to those obtained with a standard, more lengthy, methacholine inhalation challenge technique. Furthermore, it has several advantages for use as a screening test. It is simple to perform, rapid (6-12 minutes), and requires only routine, inexpensive pulmonary laboratory equipment. The training period for both subjects and technicians is negligible. In even the most sensitive of the asthmatic patients that were tested, it proved safe since methacholine-induced bronchospasm was rapidly reversible (Fig 4). Its acceptance was good in all subjects and there were no significant side effects noted, even in the normal subjects who received the higher doses of methacholine.

This protocol has been modified from one originally proposed by Parker and Reed who employed a 25 mg/ml concentration of methacholine for their studies. The major modification was the use of an additional lower concentration of methacholine; the higher 25 mg/ml concentration of methacholine was administered only to individuals who did not have a history of asthma, wheezing, or atopy. Those having a history of wheezing or asthma were treated more cautiously, and first inhaled a lower concentration of methacholine (5 mg/ml). Still, several of the asthmatic subjects who were known to be exquisitely sensitive to methacholine using standard challenge techniques developed large falls in FEV₁. However, all of these asthmatic subjects showed significant improvement in airways function within three minutes after treatment with an aerosol of isoproterenol and none required further drug therapy. An additional modification was the use of a face mask to minimize dispersion of methacholine into the atmosphere.

Both the normal and asthmatic subjects demonstrated wide ranges of methacholine sensitivity.

**Figure 3.** Percentage of fall from baseline FEV₁, observed with the short methacholine challenge for normal subjects and asthmatics.

**Figure 4.** Maximal decrease in FEV₁ as a percentage of baseline FEV₁, after inhaled methacholine and subsequent improvement three minutes after inhaled isoproterenol in asthmatic subjects.
With the standard protocol, two normal subjects had sensitivity which overlapped with the less reactive asthmatic patients. The short challenge showed no overlap in airway sensitivity to methacholine and thus easily distinguished an asthmatic response. Since all subjects had an FEV₁ that was at least 60 percent of predicted, provocational testing in persons with poorer pulmonary function was not investigated and may not be safe. Reactivity in these subjects with severe baseline bronchoconstriction might be better assessed by measuring response to inhaled bronchodilators such as isoproterenol.³

The abbreviated methacholine challenge protocol was comparable to a standard methacholine inhalation challenge test in assessing airways reactivity. This simple, short screening test for airway hyperreactivity may prove useful in the diagnosis and evaluation of subjects with asthma, in patients with dyspnea or cough of unknown etiology, and in other situations such as clinical studies of occupational asthma where the assessment of airway reactivity in large population groups is desirable.

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