

Clinical Assessment of Bronchial Hyperresponsiveness due to Nonspecific and Specific Agents*

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FEV₁ = forced expiratory volume in 1 s; PGF_{2α} = prostaglandin F_{2α}

NONSPECIFIC BRONCHIAL HYPERRESPONSIVENESS

It has been recognized for many years that patients with asthma have increased levels of bronchial responsiveness to pharmacologic, physical, and chemical stimuli. The level of responsiveness correlates reasonably with the severity of asthma.¹ The association between bronchial hyperresponsiveness and bronchial asthma is not absolute. Occupational asthma may occur in the absence of hyperresponsiveness.² In community surveys, hyperresponsiveness has been detected in up to 14% of random samples of the population.³ In those studies, the most important determinants of responsiveness were positive skin test responses to common allergens in the young and smoking habits in the older subjects. There is evidence that bronchial hyperresponsiveness is also increased after upper respiratory tract infections in subjects not considered to be asthmatic;⁴ however, this would not appear to influence outcome significantly in community studies.³

The epidemiologic measurement of bronchial hyperresponsiveness in an occupational setting is in its infancy.^{5,6} Already different methods and protocols are being used in field studies, which will make comparison between studies potentially difficult.

The value of such studies also must be prospectively evaluated. It is possible that hyperreactivity in an asymptomatic individual may prove to be a predisposing factor in the development of occupational asthma or bronchitis. A small number of cross-sectional studies have measured airways reactivity in the evaluation of work forces exposed to flour⁷ or grain^{8,9} dusts. In these studies, bronchial hyperreactivity was associated with the presence of respiratory symptoms^{7,8} and with current or past exposure to dust.^{7,9} The measurement of hyperresponsiveness has also proved valuable in following the recovery of individuals with occupational asthma.¹⁰

Finally, the measurement of hyperreactivity has been used as a research tool to evaluate the mechanisms underlying the airway responses in occupational asthma. The role of the late asthmatic reaction rather than the immediate reaction in altering bronchial hyperreactivity has been well established.¹¹ More recently this change in airway reactivity has been shown to follow the immediate asthmatic response but precede the onset of the late asthmatic response.¹² This finding has important implications with regard to the

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mechanisms and treatment of asthma.

Methods

Bronchial hyperresponsiveness may be demonstrated with a variety of constrictor stimuli, including histamine, methacholine, cold air, fog, exercise, sulfur dioxide, and PGF_{2α}. Of these various stimuli, the most widely used and best evaluated are histamine and methacholine. Three protocols have been devised for measuring hyperresponsiveness using either of these stimuli.

CHAI METHOD. The dosimeter method of Chai² uses incremental, cumulative doubling doses of methacholine or histamine, originally delivered via a De Vilbiss no 42 nebulizer and more recently via a De Vilbiss no 646 nebulizer. The dilutional increments for methacholine range from 0.075 mg/ml to 25.0 mg/ml, and for histamine, from 0.03 mg/ml to 10 mg/ml. Five breaths of each dilution are administered at 5-minute intervals, and a positive response is designated as a greater than 20% reduction in FEV₁ sustained for three minutes following the challenge.

COCKCROFT METHOD. This method utilizes the same doubling dosage regimen of histamine and methacholine.¹⁴ The aerosol is generated using a Wright's nebulizer primed with 5 ml of test solution and an oxygen flow rate of 7 L/min. It is delivered directly into a face mask and inhaled through the mouth (the nose is closed by a clip) by quiet tidal breathing for 2 minutes. Challenges are conducted at 5-minute intervals.

YAN METHOD. This is a rapid, simple method for measuring bronchial responsiveness.¹⁵ A hand-held De Vilbiss no 40 nebulizer is used to generate the aerosol. The nebulizers are standardized to produce an output of 0.003 ml per puff (0.0018 to 0.0042 ml). Each nebulizer is primed with 1 ml of saline or histamine in concentrations of 0.3, 0.6, 2.5, or 5.0 g/100 ml. Histamine is administered in a regimen that achieves cumulative doubling doses of 0.03 to 7.8 μmol. Inhalations are administered by expressing 1 or more puffs from the nebulizer directly in front of the subject's open mouth, at the beginning of a near maximal inspiration from functional residual capacity. The inspiration is held for 3 s.

Comparisons of Methods and Results

A number of studies have been carried out comparing responsiveness to histamine and to methacholine, intrasubject day-to-day variability, and techniques of aerosol generation. In practically all studies using similar aerosol generation methods, responsiveness to histamine correlates closely with methacholine.^{16,17} Under carefully controlled conditions, responses to histamine and methacholine are highly

reproducible.^{16,18,19} The 95% confidence intervals of PC₂₀ histamine is a ± 1.6 -fold difference in PC₂₀ from 1 visit to another.^{18,19}

The various methods of aerosol generation and inhalation have been compared: the Chai method with the Cockcroft method,²⁰ the Yan method with the Cockcroft and Chai methods.²¹ These studies indicate that bronchial responsiveness can be measured reliably with any of the 3 methods. There are significant differences in the time required to conduct these various methods of measuring airway responsiveness: the Cockcroft and Chai methods take up to 45 minutes to complete, whereas the Yan method may be completed in less than 15 minutes. A modified protocol for methacholine challenge (Chai method) has been evaluated that reduces the test time to approximately 35 minutes without compromising safety or sensitivity.²² The modification involves the omission of low doses in individuals whose history suggests they never had asthma. A similar shortened protocol for histamine challenge produced significant distortion of PD₂₀, suggesting that histamine is less suitable than methacholine for use in such protocols.²³ The incidence of side effects is slightly lower with methacholine than with histamine, particularly at higher concentrations.^{24,25}

The method of calculating PC₂₀ from the dose-response curve is another aspect of the determination of bronchial hyperresponsiveness that requires standardization. It is customary to use the last 2 points of the dose-response curve, that is, the 2 points on either side of the 20% fall in FEV₁, to calculate the PC₂₀. The PC₂₀ is then determined by logarithmic or linear interpolation between these 2 points. The interpolation may be performed using an algebraic formula or by manually graphing the log dose or dose versus response. These various methods of calculating PC₂₀ have been compared.²⁶ The differences between PC₂₀ calculated logarithmically or linearly were small (0% to 6%; mean: $3.7\% \pm 2.1\%$ [SD]), much smaller than the observed difference on repeated PC₂₀ testing. Manual graphing for interpolating PC₂₀ produced greater error than the use of algebraic formulas. The authors of the study suggested that for simplicity and accuracy, formulas should be used for either linear or logarithmic interpolation.

The measurement of nonspecific bronchial hyperresponsiveness is of potential importance in the epidemiologic investigation of populations exposed to dust and fumes as well as to known pulmonary sensitizers. It is important that the techniques of measurement be standardized and be rapid and simple to administer, avoiding bulky or expensive equipment. Of the 3 methods discussed, the Yan method, although not at present widely adopted in clinical and research work, appears to fulfill all of the scientific and practical requirements demanded.

SPECIFIC BRONCHIAL HYPERRESPONSIVENESS

Bronchial provocation studies are increasingly performed to establish specific causes of occupational asthma. Unlike the measurement of nonspecific hyperresponsiveness with histamine or methacholine, which is an exceptionally safe procedure, the measurement of specific bronchial responsiveness is potentially dangerous. There are 3 reasons for conducting such an investigation: to document a previously unrecognized cause of occupational asthma, to establish a

specific etiologic diagnosis when this is in doubt, and finally, in circumstances when an individual is exposed to more than one potential pulmonary sensitizer.

The tests themselves are time-consuming and must be conducted with great care, in a hospital. It is advisable for the individual to be an in-patient during testing. A physician must directly supervise the provocation test itself, with full cardiopulmonary resuscitation facilities and adrenaline drawn up in a syringe available for immediate use. As other patients and staff personnel should not be exposed to the allergen being tested, the studies should be conducted in an exhaust-ventilated exposure chamber.

Methods

A variety of different methods for bronchial provocation testing have been described.²⁷ Those allergens suitable for testing in solution may be nebulized according to standardized procedures so that reproducible amounts of allergen are delivered to the subject. Two different methods^{13,27} have been widely used; both give acceptable results in terms of safety and reproducibility.

DOSIMETER METHOD. The allergen is delivered via a dosimeter to deliver known amounts of allergen during each inspiratory maneuver. The number of inspirations is recorded.

TIDAL BREATHING METHOD. The allergen is expressed from a continuous-output nebulizer primed with a fixed volume of allergen solution and delivered via a 500-ml rebreathing bag linked to an oronasal mask for fixed time periods.

In both methods, the same nebulizer should be used throughout the study period for each subject. An initial control day is mandatory, during which the diluent solution is used and lung function is monitored before and for 7 to 8 hours after challenge. This protocol will identify possible nonspecific irritant responses to diluent and also measure diurnal variation in airway caliber, which, when present, may make the interpretation of late asthmatic responses difficult.

The starting dose of allergen may be calculated either from the skin reactivity of the allergen solution (the starting concentration being that which produces less than a 3-mm wheal on prick skin testing of the subject) or by taking 3 to 4 doubling concentrations below the predicted immediate asthmatic response.²⁸ The allergen is inhaled in increasing concentrations at 10- to 15-minute intervals. In the dosimeter method, these are usually doubling concentrations, with 5 inhalations at each concentration.

In the tidal breathing method, 10 fold concentration increases are used. The challenge period at each concentration is 5 minutes. This 5-minute period is further divided into 1-, 2- and 2-minute challenges, with 10 minutes between each challenge. The FEV₁ is measured at the end of each 10-minute rest period before a further challenge is administered by either method. In general, a 20% fall in FEV₁ is regarded as a positive response, and when this is achieved, the challenge is stopped. Lung function is measured at 10- to 15-minute intervals for the first hour and then hourly for an additional 7 hours (or longer, if a late asthmatic response is developing).

The dosimeter method and tidal breathing methods of allergen provocation have been compared. Despite the more accurate dose delivery of the dosimeter, the bronchial response with either method is highly comparable.²⁹

OCCUPATIONAL METHOD. For many causes of occupational asthma, challenge with a nebulized solution of the agent is either technically not possible or unsafe. In such cases, an occupational type challenge is performed.^{27,28} The individual's work situation is simulated as closely as possible within the challenge chamber. This may involve painting, soldering, sanding, or a variety of other activities. It is most important when devising these types of challenge to have a clear idea of how the individual is exposed at work. For instance, it would be inappropriate to challenge a nurse with a drug (in powder form) to which she is exposed at work while measuring small quantities into beakers, by asking her to tip large quantities of the material from 1 container to another. The severity of the response that the subject describes occurring at work also needs to be taken into account when devising the challenge.

Initially, short challenge periods are used, perhaps only 1 minute with a 10-minute interval, and lung function is measured before the challenge is repeated for slowly increasing periods of time. Although these forms of challenge are not as well controlled as nebulization, tests that are performed in the same way and for the same duration give reasonably reproducible results. In addition to measuring spirometry, nonspecific bronchial hyperresponsiveness monitored before the challenge and for 7 to 8 hours after the challenge may provide additional useful information; the late asthmatic reaction is associated with temporary increase in bronchial responsiveness that may last for a number of days.

A control day is again necessary, and as far as is practicable the control test should be carried out in a single-blind fashion. The control day for a car spray painter would entail using the spray paint without the isocyanate hardener added. Chemical dusts may be suspended in well-dried lactose, thus disguising their presence.²⁷ The chemical constituents of solder flux may be manipulated to exclude the chemical being tested on the control day.

Recently, a new method for conducting specific inhalation challenges with occupational allergens in particulate form has been described.³⁰ The particle size of the allergen is first reduced in a cyclone sample mill. The allergen is then placed in a vibrating reservoir, which feeds the allergen onto a rotating disk. The speed with which the allergen is delivered and the speed of the rotating disk control the amount of allergen released into the delivery system. Compressed air creating a Venturi effect leads to aerosol delivery from the disk to the subject via a horizontal cylinder. A hole in the side of the cylinder connected to a face mask enables the subject to breathe the aerosol. The concentration and particle size of the allergen are continuously measured using a photometer and a cascade impactor connected to the cylinder. The system allows the delivery of allergen to the subject in well-controlled concentrations. This method appears to be an important development in particulate inhalation challenge testing: it is safer, the pulmonary responses are more reproducible, and the technique avoids excessive exposures that might cause irritant responses in

individuals with hyperreactive airways.

A further important factor influencing the outcome of allergen inhalation testing is medication taken by the subject. As far as is possible, all respiratory drugs should be withdrawn during the period of testing, since these may inhibit both immediate and late bronchial responses.

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