Methods of testing nonspecific bronchial hyperresponsiveness

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Many methods of testing nonspecific bronchial responsiveness have been devised, since Curry first demonstrated the heightened bronchial responsiveness of asthmatics to histamine. The preferred route of administration of bronchoconstrictors at the present time is by inhalation, rather than systemically, in order to minimize unacceptable side effects. The agents inhaled have included irritants, cholinergic drugs, numerous mediators and more recently isocapnic hyperventilation of cold air, this latter requiring a rather complicated apparatus. It is not critical which method of inducing bronchoconstriction is used since, in general, they produce comparable responses. For instance, the responses to histamine and methacholine and those to methacholine and isocapnic hyperventilation of cold air correlate well with each other [1, 2]. Nevertheless, the best validated methods, most used in clinical work and epidemiological surveys, involve the inhalation of histamine or methacholine aerosols. Since higher doses of histamine may produce flushing or headaches, methacholine may be preferrable.

Jet nebulizers have mainly been used to generate aerosols for challenge, but ultrasonic nebulizers are now used also. The particle sizes from most commercially available nebulizers are suitable for bronchial provocation [3]. However, the outputs of the jet nebulizers vary considerably, both between nebulizers of the same type and between different types of nebulizer and are critically dependent on the driving pressure or flow rate [3]. The output of the ultrasonic nebulizers is approximately ten times that of the jet nebulizers. Thus, to calculate the dose of bronchoconstrictor inhaled, the output of the nebulizer used must be determined [4]. The depth of inspiration and the breath holding time also influence the site of deposition and the subsequent bronchial response [3], and should therfore, be standardized.

Recently, different delivery systems have been compared. Despite large differences in nebulizer outputs, responses similar in degree and reproducibility have been reported when the method of COCKCROFT *et al.* [5] (two minutes tidal breathing from a continuously running Wright's nebulizer) was compared with the method of CHAI *et al.* [6] (standardized dose of aerosol produced from a DeVilbiss No. 646 nebulizer attached to a breath actuated dosimeter) [7, 8]. Similarly, a rapidly increasing dose regime, given from a hand-operated DeVilbiss No. 40 nebulizer (Yan method), was found to give comparable responses to histamine, in terms of sensitivity and reproducibility, as did the Chai method, the Cockcroft method and another rapid increment dose regime utilizing a Pulmasonic, ultrasonic nebulizer (although, with this latter technique, it was more difficult to standardize the dose of aerosol delivered) [9].

For most clinical and epidemiological purposes peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV_1) measurements are adequate for monitoring changes in airways calibre [4]. They are noninvasive, reproducible measurements which require only simple, inexpensive equipment. Nevertheless, for detailed research work there are advantages to using more sensitive, effort-independent tests, which do not require a big breath to perform and which can distinguish, to some extent, changes in the calibre occurring in larger and smaller airways. Unfortunately, such sensitive tests, including specific airways conductance and flow rates taken from partial expiratory flow-volume curves, are less reproducible and require expensive, nonportable, complicated equipment.

Safe and convenient protocols for performing nonspecific bronchial provocation tests with histamine and methacholine were proposed by the SEPCR Working Group on 'Bronchial Hyperreactivity' [4]. In order to interpret the results, it was recommended that baseline FEV_1 should be within 80% of the predicted normal (when performed for research purposes) and within 80% of best recorded (for clinical puposes) and that no significant bronchoconstriction was produced by the diluent, buffered saline. Responses to doubling concentrations of aerosol should be measured between 1–3 min when the effect has plateaued and the challenges should be performed in a cumulative fashion, since duration of effect of both agents is adequate to allow this [10]. The challenge should be terminated by the time that baseline FEV_1 has fallen by 40%. Furthermore, it was recommended that safe starting doses of histamine and methacholine were 100 μg for normal subjects and 10 μg for possible asthmatics.

Great progress has been made in the past decade as regards standardization of nonspecific bronchial provocation tests. However, the methods used for expressing the results remain controversial. For instance, should dose-response curves be extrapolated beyond the last actual datapoint, in order to calculate a result? Should actual response or percentage change in baseline test be plotted either against actual or log-dose of bronchoconstrictor? Should *in vivo* bronchial challenge results be subjected to the techniques used for *in vitro* muscle experiments, *e.g.* calculation of threshold slope and dose-ratios, or should only two data-points be utilized to give a provocative concentration (PC) or provocative dose of agonist

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causing 20% fall in FEV_1 (PD_{20}) value? Until these issues are resolved it will be difficult to interpret the results of nonspecific bronchial provocation tests with any confidence.

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The relationship between reversibility and hyperreactivity

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Many studies have demonstrated an increased airway reactivity to non-specific stimuli in both patients with asthma (sudden attacks of breathlessness and fully or partly reversible airflow obstruction) and with CAO (chronic dyspnoea of varying intensity and never fully reversible airflow obstruction).

In both patient groups, the initial degree of airflow obstruction is not only related to airway hyperreactivity, but also to the airway response to a bronchodilator. It has, therefore, been suggested that, as a diagnostic test, the response to a constrictor stimulus is the same as, and of no greater value than, the response to a bronchodilator drug.

Airway calibre is determined by autonomic nervous control of smooth muscle cells, inflammation and oedema, mucus production, and loss of elastic recoil. The latter cannot as yet be influenced by therapy. Airway hyperreactivity may be modulated by a decrease in airway calibre (see above), and an increased response of the bronchial smooth muscle (which will not be discussed in this paper). To investigate smooth muscle contraction, investigators generally focus on the parasympathetic bronchoconstricting nervous system and the bronchodilating beta-adrenergic receptor-system. The non-adrenergic non-cholinergic bronchodilating system is still difficult to investigate, as the neurotransmitter remains uncertain. Studies with corticosteroids may elucidate the influence of inflammatory processes on airway calibre. To unravel the relationship between airway hyperreactivity and airway dilatation, an analysis of studies with anticholinergics, beta-mimetics, and inhaled or oral steroids in different patient populations will be useful.

The theory, that airway hyperreactivity and dilatation are interchangeable seems to be supported by the finding that the bronchodilator response to isoprenaline correlates with the constrictive response to histamine in patients with a broad range of airflow obstruction [1]. The numbers of patients with asthma (seven) and CAO (seven) in this study are, however, small. This influences the results considerably as the degree of airflow obstruction does not overlap in the two groups.

There is evidence against the interchangeability of airway hyperreactivity and reversibility, as the response to a bronchoconstrictive and bronchodilating stimulus does not necessarily run parallel. In asthma, sponteneous changes in airway resistance have been observed without changes in airway hyperreactivity, and vice versa. Moreover, the relationship between the baseline airflow obstruction, as measured by forced expiratory volume in one second (FEV_1), and the degree of airway hyperreactivity, as measured by the provocative concentration causing 20% fall in FEV_1 (PC_{20}) of histamine or methacholine, does show a large scatter. Most studies only observe a good correlation with a baseline FEV_1 below 70% of the predicted value, or PC_{20} for histamine below 0.4 $mg \cdot ml^{-1}$ [2]. In the range of 0.4–128 $mg \cdot ml^{-1}$ histamine no significant correlation with FEV_1 % predicted (70–120%) was observed [2].

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