Spontaneous changes of airway hyperresponsiveness in bronchial asthma

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In patients with bronchial asthma, changes of airway hyperresponsiveness may spontaneously occur with time or may be precipitated by a variety of factors, *e.g.* respiratory tract infections, allergen exposure, occupational hazards or atmospheric pollutants.

Changes of airway responsiveness with time

Changes of airway responsiveness with time can be interpreted according to the period of observation. Changes within one day may reflect a circadian rhythm, changes within several days may be taken in order to estimate reproducibility, and changes within months or years may reflect the prognosis of the disease.

Changes within one day

RACHIELE *et al.* [1] reported on stable asthmatics in whom two histamine inhalation tests were carried out on six different days at 8, 16 and 22 h. In seven out of fifteen asthmatic subjects significant diurnal rhythms with a time range of least excitability between 9.8 and 23.1 h could be demonstrated. Diurnal changes of airway responsiveness may, therefore, be important in some patients with bronchial asthma.

Changes within days or weeks

Several authors have measured airway responsiveness repeatedly within days or weeks in order to estimate reproducibility. COCKROFT [22] reported on 58 subjects in whom the provocative concentration of agonist causing a 20% fall in forced expiratory volume in one second (PC_{20} FEV_1) for histamine had been determined twice within one week. For all subjects PC_{20} FEV_1 was reproducible within ±one doubling-dilution step. The mean percentage difference was 18.7±1.4% with a range from 0–67%. O'BYRNE *et al.* [3] measured PC_{20} FEV_1 for methacholine in 24 asthmatics, on two days within one week, and found a similar degree of reproducibility. JUNIPER *et al.* [4] compared PC_{20} FEV_1, assessed by a histamine and methacholine inhalation test, in 14 normal subjects and 33 asthmatics. They found a correlation coefficient of 0.85, indicating that both bronchoconstrictive agents are equally effective in determining airway responsiveness.

Recently, MAGNUSSEN *et al.* [5] observed that histamine inhalation tests, repeated at hourly intervals in mild asthmatics, produced tachyphylaxis whereas methacholine did not. Alhough these data have suggested different mechanisms being operative in the bronchoconstrictor response following repeated histamine or methacholine (acetylcholine) challenges, the differences are not likely to be important for clinical purposes.

Many patients with bronchial asthma may experience airway obstruction following exercise, hyperventilation or cold air breathing. In almost all patients with *e.g.* exercise-induced asthma, an increased responsiveness of the airways to histamine or methacholine can be demonstrated; however, many patients with hyperresponsiveness to histamine or methacholine do not have exercise-induced asthma. The lack of correlation between the degree of hyperresponsiveness to histamine and exercise can best be demonstrated by assessing the airway response to both stimuli in a dose response fashion. With this experimental approach, we could show that the provocative dose of histamine necessary to increase specific airway resistance by 100% does not correlate with the magnitude of the respiratory heat exchange necessary to provoke the same response. Therefore, data derived from dose-response curves always agree with data using different methods, Since many authors found a close correlation between hyperresponsiveness induced by histamine, methacholine, exercise, and hyperventilation [3].

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Considering that the responsiveness of asthmatic airways to different stimuli may follow different distributions, exercise, hyperventilation and cold air breathing are valid tests to demonstrate hyperresponsiveness in susceptible asthmatics. Recently, TESSIER *et al.* [6] showed that within- and between-day reproducibility of isocapnic cold air challenges was at least as good as comparable data obtained with other stimuli.

Changes within months or years

Little is known about spontaneous changes of bronchial hyperresponsiveness within longer periods of time. SEARS *et al.* [7] showed in a group of 9-year-old children, who had no symptoms but who demonstrated bronchial hyperresponsiveness, that when tested two years later, 50% were no longer hyperresponsive, 25% showed diminshed levels of responsiveness and less than 20% developed symptoms of asthma. No similar data are available for adults having bronchial hyperresponsiveness with or without respiratory symptoms compatible with the diagnosis of asthma. Population-based cross-sectional studies in adult subjects demonstrated that an increased level of bronchial responsiveness is more likely to be associated with respiratory symptoms and reduced levels of pulmonary function [8]. However, it remains to be seen whether long-term spontaneous changes of airways responsiveness determine the risk of the disease.

Some factors that modify airway responsiveness

Bronchial responsiveness to histamine, carbachol and exercise can be altered by exposure to allergens or occupational hazards and by their avoidance.

Recently the role of acute respiratory infection and airway hyperresponsiveness has been extensively studied. In many asthmatic patients acute respiratory infections increase the severity of the disease and the level of bronchial hyperresponsiveness. It has been suggested that an increase in responsiveness by respiratory tract infections is mediated by a worsening of pre-existing epithelial damage [9].

A transient increase in bronchial responsiveness due to atmospheric pollutants has been well documented, both for healthy subjects and patients with asthma. Whereas the importance of ozone on the level of bronchial responsiveness is unequivocal, we could not substantiate the deteriorating effect of low concentrations of nitrogen dioxide on airway responsiveness [10].

Bronchial responsiveness is an important indicator for the integrity of our airways. Several methods have been established which allow determination of the level of responsiveness. The role of hyperresponsiveness to a variety of stimuli on the course, prognosis and therapy of those airway diseases associated with hyperresponsiveness remains to be established.

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