DEMANDS OF THE ALLERGIC AND HYPERSENSITIVE POPULATIONS

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Abstract

Bronchial hypperreactivity is the basic defect characteristic for all patients with symptomatic asthma. A review of potential indoor airway irritants and their possible härmfull effects as aggravating factors in asthma are given. At present data on passive smoking and indoor exposure to formaldehyde and NO2 does not allow the setting of standards for the indoor environment. In contrast the most important source of indoor allergens, which is proteins from house-dust mites, are highly dependent on indoor humidity. There is general agreement, that the indoor absolute humidity should not exceed 7.0 g/kg, and in geographic areas, where it is possible to reduce humidity below this level, a standard for minimum ventilation should be established.

Introduction

Asthma is a chronic disease clinically characterized by variable obstruction of the airways, which occurs either spontaneously or as a result of treatment.

Roughly half of asthmatics have an allergic component in their disease manifested by an immunologic IgE-response to environmental allergens such as proteins from house-dust mites, animal dander, pollens etc. and this group af patients associates some of their symptoms to relevant allergen exposure. Furthermore the allergic asthmatics together with the non-allergic asthmatics associates their symptoms to unspecific environmental factors such as physical exercise, inhalation of cold air and damp weather conditions so that in a unselected group of asthmatics, the unspecific factors are the factors most often pointed out as causative of asthma symptoms (table 1).

The underlying basic defect in the airways of asthmatics characteristic for both allergic and non-allergic asthma is bronchial hypperreactivity (7, 29). The airways of asthmatics react with bronchoconstriction to various stimuli of physical or chemical nature.

The indoor environment of modern housing offers a wide range of exposures to the inhabitants of both potential allergenic proteins and airway irritants.

Table 1: The nature and frequency of self-reported symptom aggravating factors in an unselected group of 72 adult asthmatics (Korsgaard et al. 1983, unpublished data).

Aggravating factor	Frequency (%)
Physical exercise	85
Foggy weather	54
All allergens	54
Strong odors	47
Tobacco smoke	45
Dust	36
Cold air	25

In the process of setting standards for the indoor environment meeting the needs of a clean environment for patients with bronchial hypperreactivity we have to understand the basic nature of bronchial hypperreactivity, and the interplay between bronchial hypperreactivity and different indoor exposures in the development and aggravation of airway disease.

Bronchial Hyperreactivity

Determination of the degree of bronchial hypperreactivity has become a valuable diagnostic tool in the diagnosis of bronchial asthma (9). In most laboratories the degree of bronchial hypperreactivity is assessed by inhalation of serial dilutions of either histamine or metacholine (11), with measurements of the degree of bronchoconstriction that follows each dilution.

In case of histamine a patient is said to have a high degree of bronchial hypperreactivity when a fall in lung function (FEV1 or Peak Flow) of more than 20% develops by inhalation of a concentration of histamine of less than 0.125 mg/ml, a medium degree of hyperreactivity with a significant reduction in lung function with inhalation of less than 1.0 mg/ml histamine, a low degree of hyperreactivity with bronchoconstriction with a concentration below 8 mg/ml and lastly if a concentration of more than 8 mg/ml is tolerated the person has no bronchial hyperreactivity.

Pathophysiology of Bronchial Hyperreactivity

The exact pathophysiologic basis for bronchial hyperreactivity is still unknown (29), but several models to understand bronchial hyperreactivity have been proposed (15).

At present the most widely accepted model (15,26) involves a defect autonomic regulation of the airway calibre. In the airway epithelium are located rapidly adapting irritant receptors which, when stimulated, through afferent and efferent pathways in the vagal nerve, induces reflex bronchoconstriction by the release of acethylcholine which again induces constriction of bronchial smooth muscle.

In support of this theory, animal studies (4,34) have demonstrated, that exposure to cigarette smoke disintegrates epithelial tight junctions thereby exposing the inter-epithelial nerve endings, which are thought to be the afferent fibres of the airway irritant receptors. It is thought that there is a close relationship between mucosal permeability and hypersensitivity (18). The mechanisms whereby infection or air pollution causes hyperreactivity is by opening the tight junctions, thereby exposing the underlying irritant receptors so that the threshold concentrations of different irritant causing bronchoconstriction is lowered substantially.

In more general terms, this model of bronchial hyperreactivity depicts that airway inflammation - whatever the cause - exposes airway irritant receptors and this leads to various degrees of bronchial hyperreactivity.

Clinical human studies have demonstrated, that a significant increase in bronchial hyperreactivity is induced by upper airway viral infections (29) leading to infectious airway inflammation just as oxidizing chemicals (9) as ozone can induce a chemical inflammation increasing bronchial hyperreactivity for weeks or months.

In many patients with allergic asthma natural or experimental contact with allergen induces an allergic inflammation, which also change bronchial hyperreactivity. Altonyan (1) have demonstrated, that the response to a standard histamine aerosol challenge is greater in an allergic subject during a period of sustained exposure to allergen such as the pollen season. Correspondingly the effect of allergen prevention has been demonstrated by Platts-Mills et al. (28), who showed, that prolonged allergen avoidance in weeks or months significantly decreases bronchial hyperreactivity.

In studies involving bronchial provocation with relevant allergens it has been demonstrated (12), that the increase in bronchial hyperreactivity is closely correlated to the degree of late phase reaction, which again reflects the degree of allergic inflammation induced by allergen exposure.

Interestingly there is a specific time relationship between allergen provocation, the subsequent development of airway inflammation and the resulting change in bronchial hyperreactivity. The increase in bronchial hyperreactivity is not detectable 2 hours after allergen provocation, is maximal 7 hours after provocation and has disappeared 5 to 7 days after provocation (10).

Frequency of Bronchial Hyperreactivity

In the earliest clinical studies a good relationship between bronchial hyperreactivity and asthma was demonstrated. Townley et al. (37) demonstrated that 100% of current asthmatics showed increased bronchial hyperreactivity. More general it is said (29), that all asthmatic patients have a medium or high degree of bronchial hyperreactivity.

More recent studies (8,14,31) in unselected populations have questionned the value of assessment of bronchial hyperreactvity in the diagnosis of asthma as they find firstly, that the distribution of bronchial reactivity in the population is continuous which indicates that asthmatics only differs quatitatively from the rest of the population, and secondly, that there is a large group of persons in the population with increased bronchial hyperreactivity but no symptoms of airway disease. From a practical point of view it seems reasonable to divide the population in three different groups. Patients with bronchial hyperreactivity and symptoms of asthma constituting about 5% of the population (14,42), a second group of subjects with increased bronchial hyperreactivity but no chest symptoms which constitutes about 5% (9) and a third group of normal subjects without both hyperreactvity and chest symptoms.

In contrast Townley et al. (38) demonstrated, that the distribution of bronchial hyperreactivity in a selected population of normal subjects from atopic families was bimodal with two subpopulations, which indicate a single biochemical or physical defect in bronchial asthma.

Bronchial Hyperreactivity and Indoor Pollution

As mentioned above bronchial hyperreactivity is not only demonstrated by an increased responsiveness to histamine or methacholine, but can be demonstrated to a wide range of physical stimuli just as bronchial hyperreactivity have been demonstrated by challenge with irritant dusts and vapors (26). Furthermore there is a high degree of inter-correlation between the bronchoconstrictor response to different stimuli, just as an increase in bronchial hyperreactivity is associated with increasing severity of asthma (7).

In conclusion 5% of the population have chest symptoms and increased bronchial hyperreactivity, and these patients may suffer from increased symptoms because of indoor air pollution.

In all events this group - or preferable a subgroup with the highest degree of bronchial hyperreactivity - seems to be the group at risk when discussing the health effects of air pollution, and should be selected as the most sensitive group in studies of controlled exposures to indoor air pollutants. As measures of possible deleterious effects of indoor air pollution should be measured not only the acute bronchoconstrictive effect manifested through a reduced lung function, but also the possible effect on bronchial reactivity by appropriate challenges performed several hours after ending of exposure.

Indoor Air Pollutants

With our present knowledge of hypersenstivity and indoor air pollutants it is not possible to evaluate all potential airway irritants occurring indoors. Below are discussed the effects of passive smoking, formaldehyde and nitrogen dioxide with emphasis on the results of controlled exposure studies in patients with asthma.

Passive Smoking

The median concentration of suspended particulate matter in indoor air is strongly correlated to the intensity of tobacco smoking indoors. In dwellings with no tobacco smoking is measured (30) a median concentration of particulates of 91 ug/m3 compared to 169 ug/m3 and 475 ug/m3 in dwellings with 0.5 to 10 and above 10 cigarettes being smoked per day respectively.

In spite of the high indoor concentrations of particulates in smoker's homes, the present evidence of negative health effects of passive smoking in patients with asthma are conflicting.

Epidemiologic studies (review in (32)) have clearly associated passive smoking with a small decrease in lung function and an increase in respiratory symptoms in children of smokers, but the evidence for association of passive smoking with the development of childhood asthma and aggravation of respiratory symptoms in adults are conflicting.

Also the results of experimental studies with adult asthmatic patients exposed to passive smoking are conflicting (table 2). Sheppard et al. (35) and Wiedemann et al. (40) in controlled studies exposed 14 and 9 adult asthmatics to cigarette smoke with an indoor concentration of CO of 24 and 40 to 50 ppm respectively, and both

Table 2: The results of 4 controlled exposure studies on adult patients with bronchial asthma with and without exposure to passive smoking (n.d. = not determined).

Author	(n)	Design	CO-exposure	Lung function	PD-20
(35)	(14)	controlled	24 ppm 120 min.	unchanged	n.d.
(13)	(10)	un-controlled	15-20 ppm 60 min.	20% decreased	n.d.
(23)	(6)	controlled	? 60 min.	11% decreased	increased (x 2.5)*
(40)	(9)	controlled	40-50 ppm 60 min.	unchanged	decreased

*determined 4 hours post-exposure.

were unable to demonstrate negative effects on the pulmonary function. In contrast Dahms et al. (13) in an uncontrolled study found a decrease in FEV1 in 10 asthmatic patients exposed to cigarette smoke corresponding to 15 to 20 ppm CO for 1 hour.

Interestingly Knight & Breslin (23) in a study involving only 6 asthmatic patients exposed to tobacco smoke in one hour was able to demonstrate a 2.5 times increase in bronchial hyperreactivity with histamine challenge test performed 4 hours after the exposure ended. This may reflect the time lag between airway irritation and the subsequent development of inflammation and increase in airway reactivity (10).

From these studies it must be concluded, that although everyday clinical experience convincingly associates passive smoking with aggravation of asthma symptoms (table 1), objective evidence in experimental exposure studies are still lacking.

Formaldehyde

Formaldehyde is highly water soluble and is known to irritate the upper respiratory tract and mucous membranes causing eye and throat irritation, while its effects on the lower respiratory tract are uncertain.

Several epidemiologic studies have associated aggravated asthma symptoms with chronic exposure to formaldehyde in concentrations below 0.7 ppm, and reports of occupational asthma due to hypersensitivity to formaldehyde refer to reactions below 0.4 ppm (5). In comparison typical indoor concentrations in today's dwellings are 0.05 to 0.11 ppm.

In contrast to the epidemiological data mentioned, exposure of asthmatics to formaldehyde in a controlled environment has as yet not demonstrated any effect at all. At present 4 controlled studies have been carried out (table 3) and none of these have demonstrated a reduction in lung function or immediate changes in bronchial reactivity after formaldehyde exposure.

Table 3: The results of 4 controlled exposure studies on adult patients with bronchial asthma with and without exposure to formaldehyde. In no cases was bronchial reactivity assessed hours after exposure (n.d. = not determined).

Author	(n)	Design	Exposure	Lung function	PD-20
(33)	(16)	un-controlled	0.25 ppm 8 hours	unchanged	n.d.
(36)	(7)	controlled	3.00 ppm 10 min.	unchanged	n.d.
(16)	(15)	controlled	0.70 ppm 90 min.	unchanged	unchanged
(41)	(15)	controlled	2.00 ppm 40 min.	unchanged	unchanged

Nitrogen Dioxide

Nitrogen dioxide is in high concentrations a well documented airway irritant causing lung damage.

Indoor sources are different gas-fired appliances, which produces NO2 concentrations with peak values in for example unwented kitchens of up to 1 ppm and 1 hour averages of 0.25 to 0.50 ppm.

The present epidemiological data (review in (32)) on NO2 exposure and health effects have focused on the frequency of chest symptoms and lung function in otherwise healthy children and adults. When populations with and without daily exposure to combustion products from gas stoves are compared consistent evidence of an increased frequency of chest symptoms with a presumed higher NO2 exposure have not been demonstrated. In support of this, large field studies with objective measurements of lung function are inconclusive. At worst the magnitude of effect is extremely small and unlikely to have clinical importance (32).

A total of 9 controlled climate chamber exposure studies on adult asthmatic patients have been performed (table 4), with NO2 concentrations varying from 0.1 ppm to 4.0 ppm.

Table 4: The results of 9 controlled exposure studies on adult patients with bronchial asthma with measures of lung function and bronchial hyperreactivity with and without NO2 exposure (n.d. = not determined).

Author	(n)	Study design	NO2 exposure	Lung function	PD-20	Post PD-20
Kerr et al. (1979)	(13)	controlled	0.5 ppm 120 min.	unchanged	n.d.	n.d.
Hazucha et al. (1983)	(15)	controlled	0.1 ppm 60 min.	unchanged	unchanged	n.d.
Kleinmann et al. (1983)	(31)	controlled + exercise	0.2 ppm 120 min.	unchanged	unchanged	n.d.
Bylin et al. (1985)	(9)	controlled	0.5 ppm 20 min.	unchanged	decreased	n.d.
Koenig et al. (1985)	(10)	controlled	0.12 ppm 60 min.	unchanged	n.d.	n.d.
Linn et al. (1985)	(23)	controlled + exercise	4.0 ppm 75 min.	unchanged	n.d.	n.d.
Bauer et al. (1986)	(15)	controlled + exercise	0.3 ppm 30 min.	decreased	decreased	n.d.
Linn et al. (1986)	(21)	controlled + exercise	3.0 ppm 60 min.	unchanged	unchanged	n.d.
Koenig et al. (1987)	(10)	controlled + exercise	0.18 ppm 40 min.	unchanged	n.d.	n.d.

Overall only one study (3) was able to demonstrate a decrease in lung function with 15 asthmatic patients exposed to 0.3 ppm NO2 for 30 minutes, while other studies (20,21) involving larger groups of patients and substantially higher NO2 exposures of 3.0 and 4.0 ppm were unable to demonstrate a direct bronchoconstrictive effect after NO2 exposure.

In 5 studies NO2 exposure was followed immediately by a determination of the degree of bronchial hyperreactivity, and again the results are inconclusive. Two studies with NO2 exposures of 0.3 ppm (3) and 0.5 ppm (6) demonstrated a significant increased degree of bronchial hyperreactivity within 1 hour after NO2 exposure, while three studies with NO2 exposures of 0.1 to 3.0 ppm were unable to detect changes in the degree of bronchial hypperreactivity.

All studies were performed on patients with mild asthma, and in no cases were the patients tested for possible late effects on bronchial reactivity. In conclusion, definitive statements about the health risk for asthmatics of indoor NO2 exposure cannot be made at present.

Indoor Allergens

Besides occupant exposure to potential irritants in the indoor environment, which is relevant to all asthmatics, the indoor environment in some cases exposes the inhabitants to high concentrations of potential allergens. The relevant allergen can induce an immunological specific IgE-sensitization in an individual, and thereby induce allergic asthma, where any future contact with the allergen in minutes will elicit an attack of asthma.

The quantitative most important indoor allergens are proteins from animal dander (dog, cat etc.) and proteins from house-dust mites. The former hardly possess any diagnostic or therapeutic problems. In this context only allergy to house-dust mites will be discussed in detail.

Since the discovery of house-dust mites in 1964 (39), the association between house-dust mite allergy and asthma have been the subject of intensive investigation. Of special interest has been the possible relation between indoor climate, occurrence of house-dust mites and the subsequent risk of developing mite-asthma or deterioration in already existing disease.

We (2) reviewed the subject in 1982 and concluded then, that the most important indoor factor leading to growth of house-dust mites in dwellings is a high indoor humidity, that the single most important factor for the

development of mite-asthma is a high exposure in bad, humid habitation. Furthermore a threshold limit value of 100 mites per gram house dust was proposed (2) to reduce the incidence of mite-allergy. The reduction in mite growth should be obtained by reduction of the absolute indoor humidity below 7.0 g water vapour per kg dry air in the winter, which again could be achieved by keeping the ventilation rate in average danish dwellings at or above 1.0 air exchange rates per hour.

The problems of mite allergy and indoor climate was reviewed in a recent WHO-meeting (27), where the major conclusions were:
1. The development of mite-asthma is related to actual indoor exposure levels to house-dust mites. It is now possible to recommend standards for sensitization to mites and a level of 100 house-dust mites per gram dust should be regarded as a risk factor of sensitization and the development of asthma.
2. At present, available data suggest that 7.0 g/kg is the level of absolute humidity above which excess mite growth will occur.
3. In some geographic areas it is possible to maintain indoor humidity below 7.0 g/kg and this should be considered.

So our present knowledge about the hypersensitive and allergic patient and the relation to indoor climate conditions suggest possible harmfull effects from exposure of the athmatic to indoor irritants such as formaldehyde, tobacco smoke and NO2, but the present state of documentation does not allow the establishment of hygienic standards.

As concerns allergic asthma with sensitization to house-dust mites, there are general international agreement on a threshold limit value, which, at least in a temperate climate, is best provided by the establishment of minimum ventilation rates, which should be individualized from one geographic area to another in dependence of the outdoor humidity conditions.

In our opinion, the frequency (1 to 2% of the population), severity and the chronic nature of mite-asthma in young individuals justifies that minimum ventilation rates are established in all new buildings thereby providing primary prevention at population level.

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