

Occupational asthma: What have we learned?

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Occupational asthma is one of the most frequent work-related diseases and may represent between 2% and 6% of all cases of asthma. It is defined as asthma causally and specifically related to exposure to airborne dusts, gases, vapors, or fumes in the working environment. Because it may cause long-lasting disability, it is important to properly identify affected workers and to withdraw them from exposure to the sensitizing agent as soon as possible. Although the history is the clue to the diagnosis, it is not sensitive or specific. The diagnosis should be confirmed by objective means, essentially by monitoring of peak expiratory flow and nonallergic bronchial responsiveness or by specific inhalation challenges. In this article the author reviews the investigation of occupational asthma. (*J Allergy Clin Immunol* 1998;102:S90-5.)

Asthma is one of the most frequent occupational lung diseases.¹ As proposed by Newman-Taylor,² occupational asthma can be defined as "variable airways narrowing causally related to exposure in the working environment to airborne dusts, gases, vapours or fumes." Two elements in this definition are important. The agent (identified or not) should be specific to the workplace and be causally related to the disease. This definition thus excludes asthma triggered by irritant mechanisms such as cold air or exercise. A previous history of asthma does not exclude the diagnosis of occupational asthma. The aim of this article is to review the latest information available on occupational asthma, particularly on its investigation.

PREVALENCE AND ETIOLOGIES

The true prevalence of occupational asthma among subjects with asthma has been estimated to be between 2% and 6%.³ Several individual and industrial factors have been identified. Among individual factors, atopy is the most important for high molecular weight agents. Smoking is generally not a risk factor, although it has been associated with occupational asthma to crab allergens.⁴ The role of nonallergic bronchial responsiveness (NABR) as a predisposing factor is unknown, although it is usually considered to be an acquired phenomenon rather than a predisposing factor. Among industrial factors the type of agent surely comes first; isocyanates are among the most frequent agents responsible for occupa-

Abbreviations used

NABR: Nonallergic bronchial responsiveness
PEF: Peak expiratory flow

tional asthma in most industrial countries³ followed by animals, flour, and grains. Several lists of known occupational agents have been published⁵ and will need to be upgraded on a regular basis. Finally, spills and high exposure are thought to be relevant risk factors, at least in some industries (red cedar⁶ and isocyanates⁷).

INVESTIGATION

As opposed to the traditional pneumoconioses, in which the diagnosis is only based on exposure history and chest radiograph abnormalities, occupational asthma needs to be confirmed by objective means. As reviewed elsewhere,⁸ the different steps involved in the investigation of occupational asthma are history, pulmonary function tests, immunologic tests, combined monitoring of peak expiratory flow (PEF) and NABR, and specific bronchial challenges.

History

The questionnaire is the basic, essential tool used in most epidemiologic surveys and all individual assessments. The classical history of occupational asthma is one of a worker whose asthma is worse at work, with improvement over weekends or holidays. However, this pattern is often absent because symptoms are also usually present outside the workplace, being triggered by exposure to irritants such as cold air, fumes, or exercise. In many cases symptoms are even more severe at home, awaking the subject at night, and weekends may not be long enough to allow recuperation. A previous history of asthma may postpone the diagnosis.

The concomitant occurrence of rhinoconjunctivitis at work and occasionally of urticaria in a worker in whom asthma develops, especially when exposed to high molecular weight allergens, is surely suggestive of occupational asthma. Chan-Yeung and Desjardins⁶ recently showed that rhinitis occurring in workers exposed to red cedar may be a predisposing factor for the development of occupational asthma. Rhinitis often precedes or coincides with the development of occupational asthma, especially with high molecular weight agents.⁹ Symptoms may develop after only a few weeks or after several years, with the duration of exposure tending to be shorter for low molecular weight chemicals.¹⁰

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However, a history suggestive of occupational asthma, even in a worker exposed to a known sensitizer, is not sufficient to make the diagnosis; questionnaires are sensitive but not specific tools. Indeed, even in the hands of expert physicians, we recently showed in a prospective study of 162 workers referred for occupational asthma that the predictive value of a positive questionnaire was only 63%, whereas the predictive value of a negative questionnaire was better (ie, 83%).¹¹ Therefore in more than one third of cases, objective testing showed that the subjects did not have occupational asthma, although the initial questionnaire had been suggestive. It is also our experience that closed questionnaires administered for epidemiologic surveys are unsatisfactory because they are too sensitive.

Pulmonary function tests: Making the diagnosis of asthma

Although the diagnosis of asthma can be confirmed by the presence of reversible airways obstruction (eg, increase in FEV₁ of greater than 15% after administration of a β_2 -agonist), most workers investigated for occupational asthma have normal spirometry when seen in the clinic. Pre- and post-shift monitoring of FEV₁ has not proved sensitive or specific enough to be a useful tool in the investigation of occupational asthma.¹²

Increased NABR is the hallmark of asthma but is also present in persons without chest symptoms who have rhinitis and patients with chronic obstructive lung disease. Therefore on the one hand, the presence of increased NABR does not make the diagnosis of occupational asthma. It may suggest that the subject has occupational asthma, common asthma, or one of the conditions listed above. There is a need for further confirmation of work-related asthma. On the other hand, the absence of increased NABR in a subject currently at work (such as the end of a working week) and complaining of symptoms virtually excludes occupational asthma. However, even in the presence of occupational asthma, bronchial responsiveness may be normal in a worker who has left work for several days (a weekend may be enough¹³), weeks, or months. Return to work or even a specific inhalation test will then increase NABR into the asthmatic range.¹⁴

Immunologic testing

The presence of immediate skin reactivity or increased specific IgE or IgG antibodies may reflect exposure or sensitization, but does not imply that the target organ (the bronchi in this instance) is involved. This has been shown for common allergens and occupational sensitizers, such as snow crab,¹⁵ psyllium,¹² and isocyanates.¹⁶ With high molecular weight agents, such as cereals or psyllium, negative skin test responses to these allergens cannot entirely exclude the diagnosis of occupational asthma, but they do make it unlikely. The worker may still be sensitized to another agent found in the workplace or to another component of the offending agent. For example, in snow-crab workers with asthma, the likelihood of the

presence of occupational asthma in a subject with a positive skin test response to snow-crab extract or a RAST ratio greater than 4.5 was found to be 69% and 79%, respectively, whereas the likelihood of the absence of occupational asthma in a subject with a negative skin test response or RAST ratio less than 4.5 was 76% and 73%, respectively.¹⁵ With low molecular weight agents, such as isocyanates and red cedar, negative skin test responses or specific IgE or IgG neither refute nor make the diagnosis of occupational asthma^{16,17}; furthermore, skin tests are usually not available.

Monitoring of PEF and NABR

The availability of portable, inexpensive devices has allowed physicians to monitor PEF at work and off work. This approach was first used in the investigation of work-related asthma by Burge et al.¹⁸ Coupling PEF monitoring and changes in NABR for periods at work and away from work has also been proposed (Fig 1).¹⁹⁻²¹ The usefulness of PEF monitoring in diagnosing occupational asthma has been recently reviewed.²²

The sensitivity and specificity of PEF monitoring in confirming occupational asthma were assessed prospectively in 2 studies using specific inhalation challenges, which are considered the gold standard for comparison.^{20,21} Sensitivity and specificity were 81% to 89% and 74% to 89%, respectively. Similar findings have been shown by others,²³ although Burge et al¹⁸ found a greater sensitivity of 100% and specificity of 77%. In a recent study²⁴ we showed that sensitivity and specificity of PEF monitoring was optimal when PEF were measured every 2 hours at work and off work. Eyeballing the deterioration of asthma while at work is still the best way to evaluate changes in PEF.^{21,25} The poor sensitivity or specificity of PEF monitoring in certain subjects compared with specific bronchial challenges can be explained in several ways. PEF is effort dependent and thus requires the collaboration of the worker. This is not always obtained due to fear of losing the job or to malingering to get compensation benefit. When PEF data are stored on a computer chip and subjects are unaware of this, 2 recent studies^{26,27} have shown that many workers falsify their records; around 50% of values were inaccurately reported on diaries either in terms of the recorded value or of the timing of the measurement or of fabricated results. Even if performed under the close supervision of a technician, PEF may greatly underestimate or overestimate changes in airway caliber as assessed by FEV₁.²⁸⁻³⁰ Although FEV₁ is more reliable than PEF in assessing airway caliber, when performed under the close supervision of a technician, monitoring of FEV₁ at and off work has not proven to be superior to simple PEF monitoring.^{31,32}

The minimum period of monitoring should be at least 2 weeks at work and off work to be able to draw conclusions. In certain situations, particularly when asthma is severe or when exposure to the offending agent is unknown and intermittent, the interpretation of the monitoring may be difficult.²¹ Subjects should be asked to

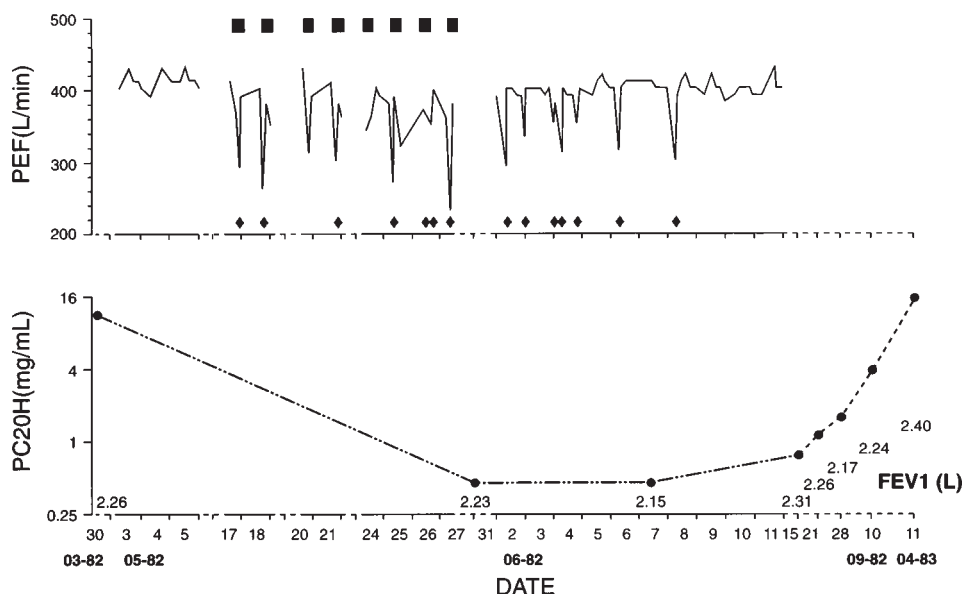


FIG 1. Combined monitoring of PEF (*upper panel*) and PC₂₀ (*lower panel*) in the same subject before and after return to work. *Squares* represent the time spent at work, whereas *diamonds* illustrate the use of inhaled salbutamol (albuterol). Baseline FEV₁ values before each histamine inhalation test are shown; they vary by no more than 6% from one test to another. (From Cartier A et al. *J Allergy Clin Immunol* 1984;74:261-9).

take their short-acting β_2 -agonists only on demand but should continue their inhaled steroids and, if needed, their theophylline or long-acting β_2 -agonists at the same dosage throughout the period of monitoring. A reduction of inhaled steroids on return to work may be associated with deterioration of asthma and reduction in PEF; this may be mistaken erroneously as diagnostic of occupational asthma. In patients with severe asthma, it may be necessary to withdraw the patient from work until the asthma is under control and the minimum treatment has been established. Then on return to work, a deterioration of asthma will suggest that it is caused by the work.

The association of NABR monitoring to PEF monitoring at work and off work is now frequently used in the investigation of occupational asthma.¹⁹⁻²¹ NABR can be assessed in several ways, but methacholine and histamine inhalation challenges with determination of the PC₂₀ are the most reliable and are well standardized. Indeed, although exposure to irritants does not usually change NABR, occupational asthma may be associated with significant and often long-lasting changes.³³ However, Côté et al²⁰ and Perrin et al²¹ showed that PC₂₀ monitoring at and off work did not improve the sensitivity or specificity of PEF monitoring in diagnosing occupational asthma. When changes in PEF are associated with parallel changes in NABR, the diagnosis of occupational asthma is highly probable. If the monitoring of PEF and NABR are discordant, further investigations should be performed such as specific bronchial challenges in the workplace or the laboratory.

Although monitoring of PEF and NABR are useful tools, they are time consuming, require subject's col-

laboration, and may be hazardous in workers giving a history of severe asthma at work. Also, their exposure may not be titrated as easily as when the challenge is done in the laboratory. Monitoring at work is particularly useful to confirm the diagnosis of occupational asthma when the worker is exposed to several sensitizers, when the offending agent is unknown, or when there is a good history of occupational asthma with increased NABR and positive skin test responses to a relevant agent found in the workplace.

SPECIFIC BRONCHIAL CHALLENGES

These tests are still considered the gold standard to confirm the diagnosis of occupational asthma.³⁴ Originally done in the laboratory and aiming to mimic work exposure,³⁵ they can also be done in the workplace.⁴ The tests should be limited to specialized centers with trained personnel and where resuscitative measures are available. They should always be carried out under the close supervision of an expert physician. The exposure chambers should be well ventilated and isolated to minimize exposure to laboratory personnel. In most patients the tests can be carried out on an outpatient basis.

Performing the tests

Drugs should be withheld before specific bronchial challenges according to standard recommendations.³⁴ In all cases spirometry (FEV₁ and forced vital capacity) should be monitored on a control day for at least 8 hours to ensure stability of airway caliber. At the end of the control day, we usually perform a methacholine challenge test to determine the level of NABR as assessed by

the PC₂₀. This value will help to determine the starting concentration of the offending agent on the next day because the lower the PC₂₀, the lower the exposure. FEV₁ is the standard parameter used to assess airway caliber; PEF is not reliable enough because it may underestimate or overestimate changes,²⁶ and specific conductance or airway resistance are also less useful and less specific than FEV₁. In cases where allergic alveolitis is also suspected, monitoring of carbon monoxide lung diffusion capacity is done on control and subsequent days in the morning and late afternoon, as well as monitoring of white blood cell counts.

Specific bronchial challenges in the laboratory

When performed in the laboratory, specific bronchial challenges can be done in several ways, depending on the nature of the agent (ie powder, aerosol, liquid, or gas). With powders (eg, flour, psyllium, or red cedar), the subject may be exposed to a fine dust mimicking work exposure³⁵ either by pouring the dust from one tray to another or by using a dust generator.³⁶⁻³⁸ The latter allows proper monitoring and regulation of exposure and establishment of dose-response curves, and it also reduces the risk of severe or irritant reactions. Alternatively, the worker may be exposed to an aerosol of a crude extract. Exposure to nonpowder agents is usually done by reproducing the work environment (eg, by nebulizing an aerosol of hexamethylene diisocyanate or by having the worker breathe over a bottle of methacrylate glue). Isocyanates and other gases can be generated in their gaseous form in a small chamber to improve safety of exposure.³⁶⁻³⁸ Whenever possible, the level of exposure should be monitored to avoid high exposure and therefore irritant reactions. In most cases exposure is done in an open fashion, with the subject knowing the nature of the exposure.

Baseline spirometry on each exposure day should be reproducible (ie, $\pm 10\%$ of the control day). Exposure should always be progressive (eg, 1 breath, 10 to 15 seconds, 1 minute, 2 minutes, 5 minutes, and so on up to 2 hours).³⁴ The total duration of exposure is dependent on the type of agent and the history given by the subject. A significant reaction is defined as a 20% fall in FEV₁, which is also greater than on the control day. If there is no significant variation in FEV₁ on the last exposure day, the NABR should be reassessed at the end of that day. If there is no significant change from baseline, there is no further exposure, whereas if PC₂₀ is significantly lower, we repeat the exposure on the next day for up to 4 hours because the test response may then be positive.³⁹

Specific bronchial challenges in the workplace

Exposure to the offending agent in the workplace is less well controlled and monitored than in the laboratory, and it may be difficult to ensure that the subject is really exposed to the relevant agent at work because the involved process may not be in use. Exposure at work, however, may be the only way to confirm the diagnosis of occupational asthma, especially when the nature of the offending agent is unknown. The work exposures are also done stepwise to prevent severe asthma. Spirometry

is followed in the same way to laboratory challenges throughout the day.⁴

Interpretation of the tests

As mentioned previously, a significant reaction is defined as a 20% fall in FEV₁. Typical patterns of bronchial responses have been described.^{35,40} Immediate reactions are maximal between 10 and 30 minutes after exposure, with complete recovery within 1 to 2 hours. Although usually readily reversible by inhaled β_2 -agonists, they are the most dangerous because they can be severe and unpredictable, particularly in subjects for whom skin tests with the suspecting agent are not possible. This stresses the importance of beginning with a low dose and of progressive exposure. Late responses develop slowly and progressively after either 1 to 2 hours (*early late*) or 4 to 8 hours (*late*). They can occasionally be accompanied by fever and general malaise, and extrinsic alveolitis should then be considered. Contrary to popular belief, late responses generally respond well to inhaled β_2 -agonist, although the effect of this may be short in some subjects.⁴¹ Dual responses are a combination of early and late. A recurrent nocturnal asthma pattern has also been described and is likely related to increase in NABR after exposure.⁴² The pattern of recurrent nocturnal asthma after exposure is usually associated with a heightening of NABR.

Atypical patterns have also been described with isocyanates and other low or high molecular weight chemicals. These include the progressive type (starting within minutes after end of exposure and progressing over the next 7 to 8 hours), the square-waved reaction (with no recovery between the immediate and late components of the reaction), and the prolonged immediate type with slow recovery. Low molecular weight chemicals are more often associated with atypical patterns compared with high molecular weight chemicals.

Irritant responses have not been well defined yet, but a fall in FEV₁ that recovers rapidly within 10 or 20 minutes is suggestive of an irritant pattern. It may be impossible to interpret results of specific bronchial challenges in subjects with too much variability of FEV₁, stressing the importance of an adequate control day.

A positive test response confirms the diagnosis of occupational asthma. A negative test response in the workplace or in the laboratory does not absolutely rule out the diagnosis of occupational asthma in the worker who has not been exposed at work for several months because he may have become desensitized.^{4,39,43} The worker should be returned to work with monitoring of PEF and bronchial responsiveness for at least a few weeks before excluding the diagnosis. False-negative challenges may also be due to exposure to the wrong agent or administration of a forbidden drug (such as an inhaled β_2 -agonist) before the test.

Justification of investigation

The diagnosis of occupational asthma needs to be made objectively because the medical and social conse-

quences of making or refuting the diagnosis are important for both the worker and the employer. When occupational asthma is present from the medical point of view, it is important to withdraw the worker from exposure to the offending agent to prevent further deterioration of asthma.⁴⁴ This imposes serious stress to the worker and his family and may mean the loss of a job or benefits or even moving to another town. On the other hand, removing the worker from exposure who does not have occupational asthma has the same consequences, whereas adequate environmental control (reduction of exposure to irritants for example) and better control of asthma may be sufficient to allow the worker to continue his job without loss of income. The cost of indemnity for occupational asthma will obviously vary from country to country, but it is important.⁴⁵

CONCLUSION

Reliance on history or skin test responses is not sufficient to confirm the diagnosis. There is a need for objective confirmation of worsening asthma at work. In some cases, particularly when there is a known sensitizer in the workplace, monitoring of PEF and PC₂₀ may be enough but may not be conclusive. In subjects who are still exposed, specific challenges in the laboratory or in the workplace can confirm or exclude the diagnosis more rapidly in most cases. They may be the only way to confirm the diagnosis when the work environment has changed. The cost of specific challenges is low compared with the cost of misdiagnosing a worker with occupational asthma.

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