Definition and diagnosis of occupational asthma

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Abstract

Occupational asthma is a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Two types of occupational asthma are distinguished based on their appearance after a latency period or not: the classical occupational asthma requiring a period of sensitization and irritant-induced asthma occurring after acute exposure to high concentrations of irritants. The diagnosis of occupational asthma should be based on objective means and cannot rely only on history (which is, although very sensitive, not sufficiently specific) or even on confirming the presence of asthma with positive skin tests to the relevant allergen/agent found at work. Inquiring about direct or indirect exposure to known sensitizers should be part of the questionnaire of any adult with new onset asthma. Monitoring of peak expiratory flows at and off work is a useful tool but may not be sufficiently sensitive or specific; combining it with monitoring of the provocative concentration of methacoline inducing a 20% fall in FEV_1 and possibly sputum induction may improve the accuracy of the diagnosis. Specific inhalation challenges in the laboratory or in the workplace are the reference standard for confirming the diagnosis of occupational asthma. They are safe when done under the close supervision of an expert physician by trained personnel. Any new case of occupational asthma should be considered as a sentinel event.

Definitions

Work-related asthma refers to asthma symptoms worsened at work. It includes asthma exacerbated at work, discussed in the next chapter, and occupational asthma (OA). Various definitions have been given to OA. The one proposed by Bernstein et al. [1] encompasses most of them: "Occupational asthma is a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace". 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. Relevant agents are airborne dusts, gases, vapors

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or fumes [2]. 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 OA. Two types of OA are distinguished based on their appearance after a latency period or not. The most frequent type, which is usually quoted as OA, appears after a latency period leading to sensitization (either allergic as for most high- and certain low-molecular-weight agents or through unknown mechanisms). The other category does not require a latency period and includes irritant-induced asthma or reactive airways dysfunction syndrome (RADS), which may occur after single or multiple exposures to high concentrations of nonspecific irritants [3, 4] and is discussed in another chapter.

Investigation

As opposed to the traditional pneumoconiosis where the diagnosis is only based on exposure history and chest radiograph abnormalities, OA can be and should be confirmed by objective means. Indeed, the social consequences of making or refuting such a diagnosis are important for both the worker and its employer [5–7]. In order to prevent further deterioration of asthma, it is essential to withdraw the worker from exposure to the offending agent [8, 9]: this imposes a serious stress to the worker and his family and may mean loss of job or benefits or even moving to another town. On the other hand, removing a worker who does not have OA from exposure has the same consequences, whereas adequate environmental control (e.g., reduction of exposure to irritants) and better control of asthma may be sufficient to allow the worker to continue his job without loss of income.

The different steps involved in the investigation of OA are: history, pulmonary function tests, immunological tests, combined monitoring of peak expiratory flows (PEF), non-allergic bronchial responsiveness (NABR) and sputum induction, and specific bronchial challenges. Although specific inhalation challenges are considered the reference standard, all steps involved in the investigation have their own usefulness and they all add up to make the diagnosis, with combination of various elements strengthening its likelihood.

The purpose of this chapter is to review the different steps involved in the investigation of OA with a latency period.

History

The questionnaire is the basic, essential tool used in most epidemiological surveys and all individual assessments.

The classical history of OA is one of a worker whose asthma is worse at work, improving over weekends or holidays. However, this pattern is often absent as

symptoms are also usually present outside the workplace, being triggered by exposure to irritants such as cold air, fumes or upon exercise. Furthermore, the process involved may be in use irregularly or the worker may be unaware that a specific process is involved as he is not involved directly with it. 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. Finally, even workers without work-related asthma regularly report improvement of asthma during weekends and holidays, in 41% and 54% of cases, respectively [10]. A previous history of asthma may also postpone the diagnosis. Symptoms may develop after only a few weeks or after several years, duration of exposure tending to be shorter for low-molecular-weight chemicals [11].

The concomitant occurrence of rhino-conjunctivitis at work, especially in a worker exposed to high-molecular-weight chemicals who develops asthma is surely suggestive of OA [12]. Although rhinitis is as frequent with low- and high-molecular-weight agents, symptoms are usually more severe with the latter [12]. It often precedes or coincides with the development of OA, especially with high-molecular-weight chemicals [12]. Rash (urticaria or contact dermatitis) is sometimes associated with OA, usually on exposed surfaces (droplets) or by direct contact (e.g., latex gloves).

However, a history suggestive of OA, 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 showed in a prospective study of 162 workers referred for OA that the predictive value of a positive questionnaire was only 63%, while the predictive value of a negative questionnaire was 83% [13]. Therefore, in more than one third of cases, objective testing showed that the subjects did not have OA, although the initial questionnaire had been suggestive.

Pulmonary function tests and diagnosis of asthma

To make the diagnosis of OA, one must first confirm the diagnosis of asthma. Although the latter can be confirmed by the presence of reversible airflow obstruction, e.g., increase of FEV_1 greater than 12–15% after a beta-2 agonist, most workers investigated for OA have normal spirometry when seen in the clinic. Furthermore, pre- and post-shift monitoring of FEV_1 has not proven sensitive or specific enough to be a useful tool in the investigation of OA [14–16].

Increased non-allergic bronchial responsiveness (NABR) is the hallmark of asthma, but it is also present in other conditions such as rhinitis and chronic obstructive lung diseases. Therefore, alone, the presence of increased NABR does not make the diagnosis of OA. It may suggest that the subject has OA, common asthma, or one or other of the conditions listed above. There is a need for further

confirmation of work-related asthma. However, the absence of increased NABR as assessed shortly (minutes, hours) after a work shift in a worker who complains of symptoms virtually excludes OA [17], although, in rare instances, specific inhalation challenges have been positive in workers without increased NABR [18, 19]. Even in the presence of OA, NABR may be normal in a worker who has left work for several days (a weekend may be enough [20]) or weeks/months. Return to work or even a specific inhalation test will then increase the bronchial responsiveness in the asthmatic range [21, 22].

Work visit

It is essential to obtain a list of the different agents used at work by the subject but also by colleagues, as the exposure may be indirect, and to find out if other workers have respiratory complaints. This can be done by asking the employer directly or the local health department for the material safety data sheets (MSDS) for the different products used in the plant. Unfortunately, these MSDS are often incomplete, lacking information on sensitizing chemicals found in small amounts that may be enough to trigger asthma [23].

Immunological testing

The presence of immediate skin reactivity or increased specific IgE or IgG antibodies may reflect sensitization and/or exposure to a suspected agent but it 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, 24] and isocyanates [25]. These tests are, however, useful as they can support the diagnosis and may help to identify which agent mat be relevant. The problem is the lack of standardization for most allergens.

With most high-molecular-weight chemicals for which good extracts are available, such as cereals or psyllium, negative skin tests to these allergens cannot entirely exclude the diagnosis of OA but make it very unlikely. Indeed, the worker may still be sensitized to another agent found in the workplace or to another component of the offending agent. Conversely, a positive skin test does not confirm the diagnosis, as its predictive positive value is low. For example, in a study by Bardy et al. [15] the positive and negative predictive values of skin tests/radioallergosorbent test (RAST) to psyllium were 22/16% and 100/100%, respectively. In snow crab-workers' asthma, the odds for the presence of OA in a subject with positive skin tests to snow crab extract or RAST ratio >4.5 were respectively 69% and 79%, whereas the odds for the absence of OA in a subject with negative skin test or RAST ratio <4.5 were 76% and 73%, respectively [24]. With most low-molecular-weight

chemicals, skin tests or specific IgE or IgG are either unavailable or not sufficiently sensitive or specific to refute or to make the diagnosis of OA. Other *in vitro* tests such as basophil histamine release or assay of monocyte chemoattractant protein-1 by peripheral blood mononuclear cells [26] may offer higher sensitivity or specificity but again they do not confirm the diagnosis of OA.

Even if specific inhalation challenges are considered the reference test, they are not always available, and combining various tests may increase the likelihood of a correct diagnosis. In the case of high-molecular-weight agents, combining a history highly suggestive of OA with a positive methacholine challenge and a positive skin test to a high-molecular-weight agent gives a post-test probability of >90% of disease and may be enough. On the other hand, negative combined tests results do not appear to provide clinicians with sufficient certainty to rule out OA [27].

Monitoring of PEF and NABR and sputum cell counts

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 S. Burge and colleagues [28, 29]. Coupling PEF monitoring and changes in NABR for periods at work and away from work has also been proposed [30–32] (Fig. 1). Recently, monitoring of eosinophils in sputum induction has also been proposed [33, 34] as a useful tool. The usefulness of PEF monitoring in diagnosing OA has been reviewed in various consensus reports [7, 35–37].

When compared to specific inhalation challenges as the reference, PEF monitoring has a sensitivity of around 64% and a specificity of 77%. Malo et al. [38] showed that sensitivity and specificity of PEF monitoring was optimal when PEF were measured every 2 hours at work and off-work. Observing the deterioration of asthma while at work is still the best way to evaluate changes in PEF [32, 39]. A computer-based system analysis of PEF has been developed by Gannon and colleagues and validated as a useful tool to assess work-related changes in PEF [40–42]. It is, however, sometimes difficult to distinguish between work-exacerbated asthma and OA, even by experts [43]. The poor sensitivity or specificity of PEF monitoring in certain subjects as compared to specific bronchial challenges can be explained by several means. Indeed, even if performed under close supervision of a technician, PEF may greatly underestimate or overestimate changes in airway caliber as assessed by FEV_1 [44–46]. Furthermore, PEF are effort dependent and thus require collaboration of the worker, which is not always obtained due to fear of loosing his job or malingering in order to get some compensation benefit. When PEF data are stored on a computer chip and subjects are unaware of this, two studies [47, 48] have shown that many workers will falsify their records as around 50% of values are inaccurately reported on diaries either in terms of the recorded value or of the timing of the measurement or as fabricated results.

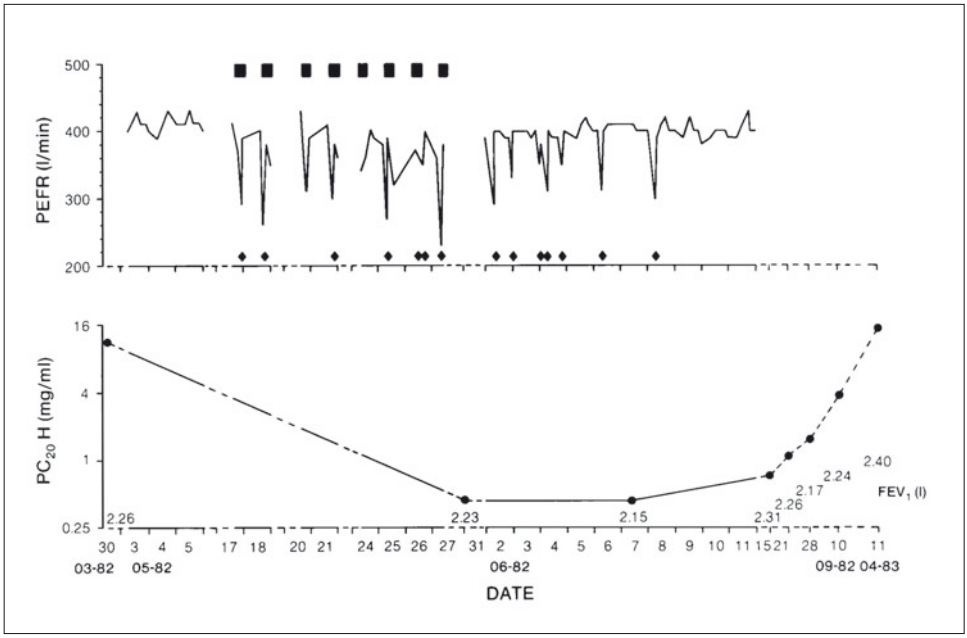


Figure 1.
Monitoring of PEF (PEFR; upper panel) and PC_{20}-histamine (lower panel) in a crab processing worker. Before returning to work, the subject was asymptomatic with borderline PC_{20}. Upon return to work, as illustrated by the black squares, the subject had a recurrence of asthma symptoms requiring rescue salbutamol (illustrated by the losanges) with significant changes in PEF and a significant fall in PC_{20}. Work withdrawal was associated with return to baseline of PEF and gradual, although very slow, recovery of PC_{20} over 1 year. This confirmed the diagnosis of occupational asthma. Reproduced with permission from [59].

The minimum period of monitoring should be at least 2 weeks at work and off-work to be able to draw some conclusions. In certain situations, particularly when asthma is severe or when the nature of the offending agent is unknown and intermittent, the interpretation of the monitoring may be difficult [32]. Subjects should be asked to take their beta-2 agonists on demand only, but should continue their inhaled steroids regularly. Indeed, reduction of inhaled steroids upon return to work may be associated with deterioration of asthma and reduction in PEF, which may be mistaken as diagnostic of OA. We usually avoid long-acting beta-2 agonists and leukotrienes antagonists, but allow the use of theophylline at the same dosage throughout the entire monitoring. In severe asthmatics, it may be necessary to withdraw the subject from work until his asthma is under control and on minimum

treatment before returning him to work; deterioration of asthma may then suggest that asthma is caused by work.

The association of NABR monitoring to PEF monitoring at work and off-work is now frequently used in the investigation of OA [30–32]. NABR can be assessed by several means, but methacholine and histamine inhalation challenges with determination of the provocative concentration inducing a 20% fall in FEV_1 (PC_{20}) are the most reliable and are well standardized. Indeed, whereas exposure to irritants does not induce marked and prolonged changes in NABR, OA may be associated with significant and often long-lasting changes in NABR. However, Côté et al. [31] and Perrin et al. [32] showed that PC_{20} monitoring at and off-work did not improve the sensitivity or specificity of PEF monitoring in diagnosing OA. We recommend that monitoring of PEF is coupled to monitoring of NABR: indeed, when changes in PEF are associated with parallel changes in NABR, the diagnosis of OA is highly probable. If the monitoring of PEF and NABR are discordant, further investigations should be completed, such as specific bronchial challenges in the workplace or in the laboratory. When the monitoring of PEF and NABR shows no evidence of asthma in a symptomatic subject while at work, this is enough to exclude the diagnosis of OA.

As sputum eosinophils may increase following return to work in subjects with OA [33, 34, 49], we are regularly adding this parameter in our evaluation of workers. However, we tend to use a positive result as potentially indicating OA rather than confirming it; when there is a discrepancy between monitoring of PEF, NABR or sputum eosinophils, we tend to complete our investigation with specific inhalation challenges. In the absence of increased NABR and changes in airway caliber, an increased count of sputum eosinophils at work in a worker symptomatic of cough may suggest the diagnosis of eosinophilic occupational bronchitis [50, 51]. Unfortunately, monitoring of sputum induction is available in only a few centers and is of limited value. Finally, there is still no evidence that monitoring of exhaled NO is useful in the investigation of OA but this merits further investigation.

Although monitoring of PEF and NABR are useful tools, they are time consuming, require the subject's collaboration and may be hazardous in workers giving a history of severe asthma at work as exposure may not be titrated as easily as when the challenge is done in the laboratory. They are particularly useful as a screening procedure when the worker is exposed to several sensitizers or when the offending agent is unknown.

Specific inhalation challenges

Specific inhalation challenges (SIC) are still considered the reference test to confirm the diagnosis of OA [52–56]. Originally done in the laboratory and aiming at mimicking work exposure [57], they are now frequently done in the workplace [58, 59].

SIC are safe when performed under the close supervision of an expert physician and with trained personnel and are thus limited to specialized centers. Resuscitative measures should be available. When performed in the laboratory, the exposure chambers should be well ventilated and isolated to minimize exposure to the personnel. The tests can be carried out on an outpatient basis. Most challenges are done in an open fashion, the subject knowing the nature of the exposure. This is inevitable for workplace challenges but when challenges are done in the laboratory, we sometimes blind the exposure if we suspect that the subject is mimicking symptoms (particularly cough).

Although there is no standardized protocol, the methodology is well developed [52, 55, 56].

Drugs should be withheld before specific bronchial challenges according to standard recommendations [55] as with methacholine challenges [60]. Beta-2 agonist (oral and inhaled), inhaled ipratropium bromide and cromoglycate must be withheld for 8 hours. Inhaled long-acting beta-2 agonists, tiotropium and nedocromil, and leukotrienes antagonists should be discontinued for 48 hours. In most subjects, long-acting theophylline should be withheld for 48 hours (or 72 hours for once-a-day tablets), but may have to be continued in subjects who show too much variability in their spirometry throughout the day when they are withheld. If it is used, there should be daily serum monitoring to ensure a uniform effect. Inhaled (and occasionally oral) corticosteroids should be continued at their minimal dosage to keep asthma under control, but taken only in the evening of each challenge day at the same total dose. Although the dose of the agent required to induce a bronchial reaction may indeed be increased by theophylline or corticosteroids, these drugs would not abolish the response if the subject is sensitized.

While FEV_1 is the standard parameter used to assess changes in airway caliber, PEF are not reliable enough particularly in the late bronchial response as they may underestimate or overestimate changes [44]. While some investigators favor the use of airway resistance (R_{aw}), most consider that it is less reliable than FEV_1. In addition, we routinely measure lung volumes on the control day (total lung capacity, residual volume and functional residual capacity) to be able to confirm airways obstruction, as indicated by airway trapping and hyperinflation, during exposure to the offending agents in cases where simple spirometry is dubious (e.g., poor collaboration of the subject).

In all cases, spirometry should be monitored on a control day to ensure stability of airway caliber; in more severe asthmatics, the subject is first observed for at least 8 hours on a non-exposed day, whereas most subjects can be exposed on the first day to a control irritant, e.g., lactose powder, paint diluent, resin, etc., presented in the same way as the suspected agent [52, 55]. FEV_1 is monitored at baseline every 10 minutes for 1 hour, every 30 minutes for 1 hour, and then hourly for at least 8 hours after the end of exposure. If the subject show too much variability of his FEV_1 (>10%) during this control day or if the FEV_1 is too low (we usually require

an FEV_1 >2.0 L or at least >1.5 L and >70% of predicted), the tests should be postponed and asthma controlled by adjusting the medication. At the end of the control day, a methacholine challenge test followed by sputum induction are done to determine the level of NABR as assessed by the PC_{20} dose and the profile of airway inflammation. The PC_{20} may help us determine the starting concentration to the offending agent on the next day, the lower the PC_{20}, the lower the exposure. In cases where allergic alveolitis is also suspected, monitoring of carbon monoxide lung diffusion capacity is measured on control and subsequent days in the morning and late afternoon, as well as monitoring of white blood cell counts.

Challenges preformed in the laboratory

When performed in the laboratory, specific bronchial challenges can be done in several ways, depending on the nature of the agent, i.e., powder, aerosol, liquid or gas. With powders, like flour, psyllium or red cedar, the subject may be exposed to a fine dust, mimicking work exposure by pouring the dust from one tray to another [57] or using a dust generator [61–63], which allows proper monitoring, regulation of exposure, establishment of dose-response curves, and reduces the risk of severe and/or irritant reactions. The agent may be diluted initially with an inert agent such as lactose to avoid severe reactions. Alternatively, the worker may be exposed to an aerosol of a crude extract. Exposure to non-powder agents is usually done by reproducing work environment, e.g., by nebulizing an aerosol of the isocyanates hardener or by having the worker breath over a bottle of methacrylate glue. Isocyanates and other gases can be generated in their gaseous form in a closed circuit generating chamber [64, 65] or a whole-body exposure chamber [66, 67]. Whenever possible, the level of exposure should be monitored to avoid high exposure and therefore irritant reactions.

Baseline spirometry on each exposure day should be reproducible, i.e., <10% of the control day. The exposure should be progressive (1 breath, 10–15 seconds, 1 minute, 2 minutes, 5 minutes, etc.). The total duration of exposure is a function of the type of agent and the history given by the subject. The dose may be conveniently increased sequentially by serial increases of the exposure period, and/or increasing the concentration of the agent. For high-molecular-weight chemicals for which positive skin tests can be elicited, exposure is increased progressively for up to 2 hours with in-between functional assessments, unless the subject gives a history suggestive of an isolated late asthmatic reaction. As on the control day, spirometry is assessed immediately and 10 minutes after each period of exposure. A significant reaction is defined as a 20% fall in FEV_1. At the end of exposure (whether it is after 2 hours or once the FEV_1 has dropped significantly by 20%), spirometry is performed as on the control day for up to 8 hours. With low-molecular-weight chemicals such as isocyanates, which are more often associated with isolated late responses [68], exposure

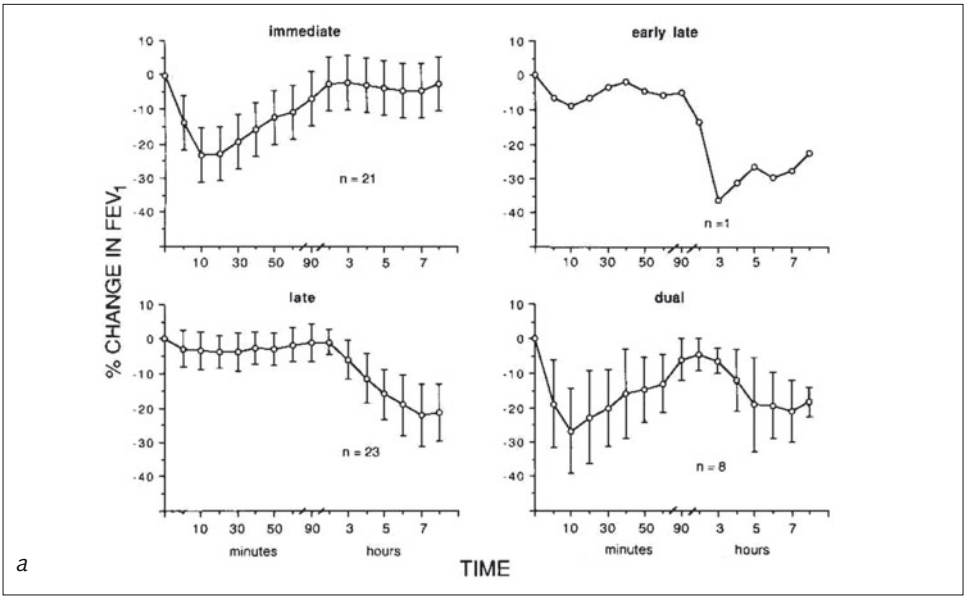
should be more gradual and over a few days: one breath, 15 seconds, 45 seconds and 2 minutes on the first day, 30 minutes on the second day and 2 hours on a third day. However, this pattern of exposure may be modified by reducing the duration of subsequent exposures if there is a suggestion that the subject is starting to react. If there is no significant variation in FEV_1 on the last exposure day, NABR and sputum induction should be reassessed at the end of that day; if there is no significant change from baseline, there is no further exposure, whereas, if PC_{20} is significantly lower or if there is a significant increase in eosinophils, we repeat the exposure on the next day for up to 4 hours as the test may then be positive [69], sometimes even after a shorter exposure.

Tests in the workplace

Tests in the workplace are now done more frequently, especially when the relevant agent at work is unknown or when there are several potential sensitizing agents. They are also done in stepwise manner as the subject may experience a significant fall in FEV_1. Spirometry is performed in the same way throughout the day [58, 59]. Exposure to the offending agent is, however, 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. This may be, however, the only way to confirm the diagnosis of OA especially in cases where the nature of the offending agent is unknown.

Interpretation of the tests

A significant reaction is defined as a 20% fall in FEV_1. Typical patterns of bronchial reactions have been described [57, 68] (Fig. 2a). Immediate reactions are maximal between 10 and 30 minutes after exposure with complete recovery within 1–2 hours; although usually readily reversible by inhaled beta-2 agonists, they are actually the most dangerous as they can be severe and unpredictable, particularly in subjects for whom skin tests with the suspecting agent are not possible, stressing the importance of progressive exposure. Late reactions develop slowly and progressively either 1–2 hours (early late) or 4–8 hours (late) after exposure; they may occasionally be accompanied by fever and general malaise but extrinsic alveolitis should then be considered. Contrary to popular belief, they generally respond well to inhaled beta-2 agonist, although the response may be of shorter duration in some subjects [70]. Dual reactions are a combination of early and late. A recurrent nocturnal asthma pattern has also been described and is likely related to an increase in NABR following exposure [71].



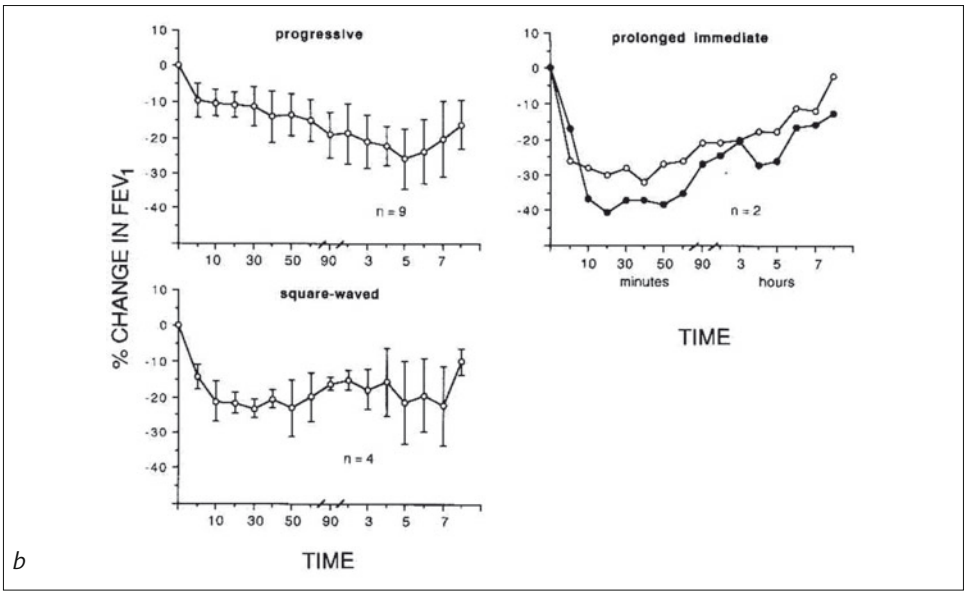


Figure 2.
Patterns of typical (a) and atypical (b) bronchial responses to specific inhalation challenges. Each point represents the mean % change in FEV_1 (n = number of subjects in each group) at several time points following the last inhalation of the responsible agent during a specific inhalation challenge. Reproduced with permission from [68].

Atypical patterns (Fig. 2b) have also been described with isocyanates and other low- or high-molecular-weight chemicals: they include the progressive type (starting within minutes after end of exposure and progressing over the next 7–8 hours), the square-waved reaction (with no recovery between the immediate and late components of the reaction) and finally the prolonged immediate type with slow recovery. Low-molecular-weight chemicals are more often associated with atypical patterns as compared to high-molecular-weight chemicals.

Irritant reactions are not well characterized but falls in FEV_1 that recover rapidly within 10 or 20 minutes are suggestive of an irritant pattern. It may be impossible to interpret results of specific bronchial challenges in subject with too much variability of FEV_1, stressing the importance of an adequate control day.

A positive test confirms the diagnosis of OA, whereas a negative test in the workplace, or in the laboratory, does not absolutely rule out the diagnosis of OA in a worker who has not been exposed to work for several months, as he may have become "desensitized" [22, 59, 69]; this is particularly true if there is a change in PC_{20} following the specific challenges [22, 69]. 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 in the laboratory may also be due to exposure to the wrong agent or administration of a forbidden drug (such as an inhaled beta-2 agonist) before the test. However, if the subject had his/her symptoms during the challenge procedure without any change in spirometry, these tests are conclusive and exclude the diagnosis of OA.

Conclusion

The diagnosis of OA should be based on objective means and cannot rely only on history or even on confirming the presence of asthma and positive skin tests. Monitoring of PEF, PC_{20} and sputum induction are useful tools but may not be sufficiently sensitive or specific. Specific inhalation challenges in the laboratory or in the workplace are the reference standard for confirming the diagnosis of OA, but should be done under the supervision of expert physicians.

Unanswered questions

- What is the role of exhaled NO in the investigation of OA?
- There is a need for a better characterization of the bronchial response to irritants by using indices such as NABR, sputum induction or exhaled NO.
- Duration of exposure to the agent in the laboratory needs to be better standardized. How long should the exposure be before we consider a challenge to be negative, 2, 4 hours?

- Monitoring the exposure is not always possible and this is clearly a limit of specific inhalation challenges as it may be sometimes difficult to exclude an irritant effect. There is thus a need to improve our capacity to do such monitoring.

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