



The current diagnostic role of the specific occupational laboratory challenge test

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Purpose of review

Classically, the specific occupational challenge test has been considered as the reference test in the diagnosis of occupational asthma. The present study assesses the usefulness of this test for diagnosing this disease and compares it with other diagnostic methods.

Recent findings

Occupational asthma is the most frequent work-related respiratory disease in developed countries. Its correct diagnosis is vitally important not only from the medical point of view, but also in view of the disease's major socio-economic repercussions both for the patient and for society as a whole. Diagnosis is based on clinical suspicion of bronchial asthma and of a possible association with the patient's occupation. Various diagnostic strategies have been proposed, including clinical history, immunological test, spirometry, the study of peak flow, the methacholine test and the specific occupational challenge test, as well as studies of bronchial inflammation using noninvasive methods.

Summary

The specific occupational challenge test remains the reference test for the diagnosis of occupational asthma for causal agents of both high and low molecular weight.

Keywords

induced sputum, occupational asthma, peak flow, 'realistic way', specific inhalation challenge

INTRODUCTION

The inhalation of agents in the workplace may be the cause of asthma, or may aggravate an already existing asthma. The former situation, in which the inhalation of an agent in the workplace is directly responsible, is known as occupational asthma, whereas the latter is known as work-exacerbated asthma (WEA). The distinction between the two entities is important, because their treatment, prognosis and medical and social repercussions may differ widely [1^{••}].

Although occupational asthma is the most frequent occupational respiratory disease in industrialized countries, at present there is no international consensus on how the entity should be defined. A general requirement is that the causal agent be specific to the workplace [2^{••}]; another initial condition was that the asthma should have developed through sensitization mechanisms, but in fact evidence of sensitization is only found in a small number of patients and today it is known that different agents can cause asthma without any sensitization at all [3[•]]. In addition, most current guides include the concept of inflammation in the

definition of bronchial asthma, and occupational asthma has recently been defined as a disease characterized by a variable obstruction of the airway and bronchial hyper-responsiveness or inflammation, due to the conditions in a specific working environment [4].

Given the medico-legal and economic repercussions of occupational asthma, correct diagnosis is fundamental [5^{••}–7^{••}]. The origin of occupational asthma may be immunological or nonimmunological, depending on the pathogenic mechanism. Nonimmunological occupational asthma is induced by irritants; the most common form is the reactive airways dysfunction syndrome (RADS), which can be diagnosed relatively straightforwardly on the basis of the clinical history [8]. The diagnosis of

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KEY POINTS

- The diagnosis of work-related asthma, and more specifically of occupational asthma, has serious medical and socio-economic consequences.
- With the exception of the specific occupational challenge test, the performance of the tests used to diagnose occupational asthma is suboptimal.
- The specific occupational laboratory challenge test remains the reference test for the diagnosis of occupational asthma in the case of both high and low-molecular-weight causal agents.
- In spite of the availability of closed-circuit apparatuses in which the exposure to the causal agent is always controlled, the 'realistic way' remains the most commonly used method for the provocation test and is valid for both HMW and LMW agents.

immunological occupational asthma is much more complex, and requires a clear association between the asthma and the patient's occupation. In this situation the clinical history, immunological studies and above all the pulmonary function studies are particularly important [9[¶]].

The review analyses the usefulness of the specific occupational laboratory challenge test (SOLCT) for the diagnosis of occupational asthma. Although the test can also be used to diagnose other diseases such as hypersensitivity pneumonitis, vocal cord dysfunction and eosinophilic bronchitis, here we focus solely on occupational asthma.

CAN OCCUPATIONAL ASTHMA BE CORRECTLY DIAGNOSED WITHOUT USING THE SPECIFIC OCCUPATIONAL LABORATORY CHALLENGE TEST?

The clinical history is essential for the suspicion of occupational asthma but its diagnostic value is low, whether the causal agent is high molecular weight (HMW) or low molecular weight (LMW) [10]. Immunological studies, either *in vivo* (prick tests) or *in vitro* (specific IgE), are only of use when the agent responsible is HMW. HMW agents are believed to act as common airborne allergens through an immunoglobulin IgE-mediated response, whereas LMW agents may induce asthma via a nonspecific immune mechanism [11]. Nevertheless, there are examples of specific IgE with LWM agents (anhydrides, platinum) and nonspecific immune mechanisms have been demonstrated for few LWM agents as isocyanates [11]. Therefore, we stress that a positive result in an immunological test

is not sufficient to establish diagnosis and that, in the case of an HMW agent, a negative result practically rules out this agent as the cause of the disease [9[¶]].

Bronchial challenge tests, both specific and non-specific, and the determination of peak flow (PEF) in periods of exposure and nonexposure are today considered the fundamental tools for establishing the diagnosis of occupational asthma. Some authors claim that, in a patient who is working, a negative methacholine test rules out occupational asthma [12]. However, one study [13] comparing mean sensitivity and specificity in nonspecific bronchial challenge tests and SOLCT established figures of 79.3 and 51.3%, respectively, for the nonspecific tests when the occupational asthma was caused by HMW agents, and figures of 66.7 and 63.9%, respectively, in the case of an LMW agent. When no distinction is made according to molecular weight, mean figures of 83.7% for sensitivity and 48.4% for specificity have been found. In fact, a recent study [14[¶]] showed that patients with occupational asthma were more likely to present normal methacholine PC20 than patients with non-occupational asthma.

The use of PEF in periods of exposure and non-exposure as a diagnostic technique for occupational asthma was proposed around 30 years ago by Burge *et al.* [15,16]. The initial studies [17,18] of PEF found that sensitivity and specificity varied between 81–87 and 74–89%, respectively, when interpreted using visual analysis and taking the SOLCT as reference. However, recent studies based on habitual clinical practice have established values around 70% for sensitivity and 60% for specificity. As other authors have suggested, this discrepancy may be due to the fact that when these studies were performed patients were less likely to take corticosteroids than they are today; hence, the differences in PEF in periods at and off work may have been more marked [19]. Other possible confounding factors in the interpretation of PEF are respiratory tract infections and possible falsification of the recordings [20]. Furthermore, initial studies designed to assess the diagnostic performance of the technique were based on PEF interpretation by a team of observers, with occupational asthma being diagnosed when there was consensus. However, in daily clinical practice, the test is interpreted by a single physician, and in this situation sensitivity and specificity may differ.

The computerized analysis system Oasys was developed to increase the value of the technique. Oasys has a sensitivity of 75% and a specificity of 98% for occupational asthma [21] and a recent study [22] showed that rest–work differences in mean PEF

was the best statistical index for differentiating between workers with occupational asthma and nonoccupational asthmatic individuals or irritant-exposed healthy workers. This system, which plots the maximum, mean, and minimum daily PEF and produces a score comparing periods at work and off work, has been mainly used in the UK. Accurate PEF monitoring depends on the patient's compliance and honesty, and this may contribute to variations in the sensitivity and specificity levels in different countries. In fact in a study performed in Quebec, Girard *et al.* [19] found a sensitivity of 35% and specificity of 65% using this method. But whatever method is used, there is no agreement on the number of daily measurements that should be performed or the minimum time at work and off work needed to obtain the best results. Moore *et al.* [23[■]] demonstrated that longer periods off work in PEF monitoring improve the sensitivity of this test for occupational asthma diagnosis. This may also be a problem, because in some cases employees can only have prolonged periods off work during their annual holidays.

Several studies have tried to assess the diagnostic performance of the combination of two or more tests. One study [13] of the combination of the nonspecific bronchial test and the specific skin prick test in occupational asthma due to HMW agents found a pooled estimate of sensitivity of 61% and a specificity of 82%, and a recent assessment of this combination in bakers reported a sensitivity of 58% and specificity of 89% [24[■]]. There are hardly any studies of the diagnostic performance of the combination of PEF and specific skin prick test, and the studies of PEF and the nonspecific bronchial challenge test do not appear to achieve a significant improvement in diagnosis [19]. Finally, some authors propose combining PEF and the number of eosinophils in induced sputum at work and off work to improve the sensitivity and specificity of occupational asthma diagnosis: Girard *et al.* [19] showed that a 1 or 2% increase in eosinophil count can increase the specificity of the occupational asthma diagnosis by 18 or 27%, respectively.

In this context, many authors consider the SOLCT to be indispensable to correct occupational asthma diagnosis. In fact, as well as being considered the reference test for occupational asthma diagnosis, the SOLCT is also a key technique for identifying new causal agents [25[■]], the agent responsible when a patient is exposed to more than one agent in the workplace [26], the pathogenic mechanisms through which the asthma reaction is produced [27], and when sending a patient back to the original workplace is not feasible.

THE SPECIFIC OCCUPATIONAL LABORATORY CHALLENGE TEST AND THE DIAGNOSIS OF OCCUPATIONAL ASTHMA

Probably the most reliable way to confirm occupational asthma is by exposing the worker to the suspected agent and closely monitoring any functional and inflammatory changes; thus most authors consider the SOLCT as the reference test in occupational asthma diagnosis despite false positives and false negatives [9[■]].

Classically it was thought that false positives might be recorded in patients exposed to doses that may cause irritation, in cases of labile asthma, or in cases of destabilization due to the withdrawal of treatment prior to the test. Similarly, it was thought that false negatives might be due to exposure to insufficient doses of the agent, testing of the wrong agent, or because the patient had not been in contact with the agent for a sufficient period of time prior to the performance of the SOLCT [28]. Currently it is accepted that there are other factors that may affect the result of the test. One is the criterion used to establish its positivity. A test is considered positive when a reduction in the Forced Expiratory Volume in one second (FEV₁) greater than 20% is recorded with respect to the baseline value after inhalation, but the diagnostic performance of different values of FEV₁ reduction has not been assessed. Other parameters of pulmonary function such as the alteration of the small airway, pulmonary resistance or specific conductance, which have been assessed in the nonspecific bronchial test [29], have not been evaluated in the SOLCT.

Another important aspect is the length of time that the test should be performed before a negative result is recorded. For example, in the case of isocyanate testing – the most commonly reported test – there is no agreement regarding the number of hours of exposure before the test is deemed to be negative. Some authors propose a maximum of 2 h, whereas others expose the patient for 4 h. One recent study [30] stressed that periods of exposure below 1 h are not sufficiently sensitive to rule out occupational asthma.

Finally, withdrawing treatment prior to the performance of the test may cause false positives by destabilizing the asthma, whereas maintaining treatment may lead to false negatives. In addition, there is no agreement on the question of exactly how long before the test treatment should be withdrawn; the only exception (as in the nonspecific bronchial test) is short and long-acting β_2 adrenergics, in which the time of withdrawal has been established [31].

It is generally agreed that false positives are easy to control when the test is performed by expert staff,

and that they do not in fact hinder correct diagnosis. In the case of false negatives the situation is quite the opposite. In fact, a recent study [32] showed that around 20% of SOLCT results may be false negatives. Some authors propose the addition of other diagnostic tests such as the methacholine test, eosinophil-induced sputum count or nitric oxide determination before and after inhalation in order to reduce this proportion and to improve the yield of the SOLCT [30,33*].

PERFORMING THE SPECIFIC OCCUPATIONAL LABORATORY CHALLENGE TEST

The specific occupational challenge test can be reproduced in a hospital laboratory or alternatively it can be performed in the workplace [32]. In the laboratory, workplace conditions can be simulated by placing the patient in a challenge chamber – the ‘realistic way’ originally proposed by Pepys and Hutchcroft [34] – or by means of closed-circuit

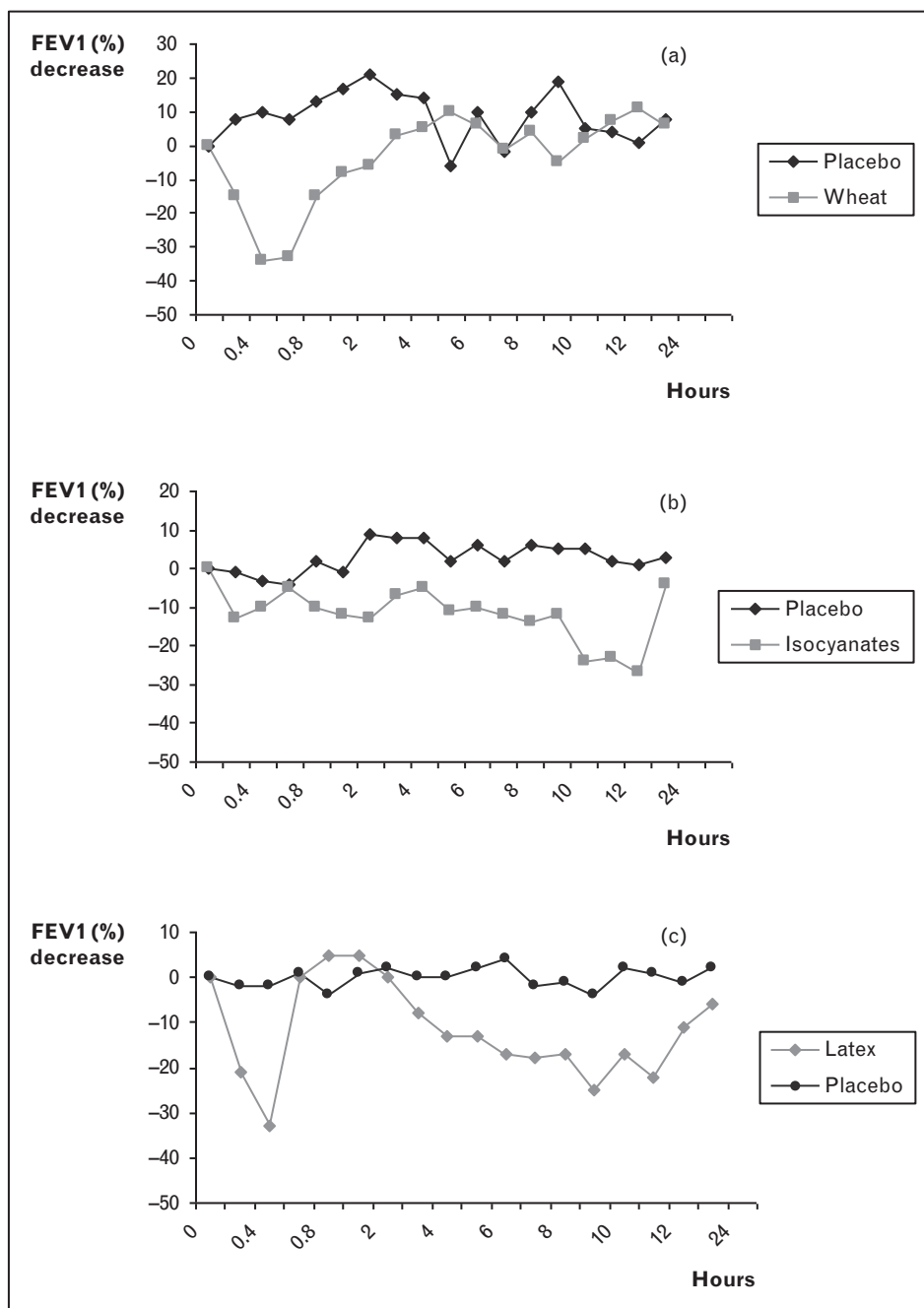


FIGURE 1. SIC results in three different patients. (a) Early response in a patient exposed to wheat. (b) Late response in a patient exposed to isocyanates. (c) Dual response in a patient exposed to latex.

apparatuses in which the exposure to the causal agent is controlled [35]. The 'realistic way' remains the most frequently used method and is valid for both HMW and LMW agents [31]. The test consists of generating an atmosphere inside the cabin with a known concentration of the causal agent. The way in which this atmosphere is created depends on the causal agent. In the case of gases or vapours, the methods for generating a specific concentration can be divided into static or dynamic. In static systems, a known quantity of gas is mixed with a quantity of air to produce a specific concentration, whereas in dynamic systems the airflow and the addition of gas to this airflow are controlled to produce a known level of dilution. These systems provide continuous flow and allow a rapid, predictable change in concentration that favours mixing and minimizes the loss to absorption in the walls of the chamber [36]. If the test involves dust or powder, the patient tips the substance from one tray to another [37], although on occasions the only possible alternative is to reproduce the workplace conditions in the challenge chamber itself [38[■]]. Once the atmosphere is generated the patient enters the booth for a period of time which is adjusted individually depending on

the nature of the asthma. After exposure, the FEV₁ is measured every 10 min and subsequently every hour for 12 h. The test is considered positive if the FEV₁ falls more than 20% from the baseline value. If the result is negative, the exposure time is increased on successive days. The results are expressed on charts recording the percentage of each fall in FEV₁ as a function of time (Fig. 1).

In the case of HMW agents, which are habitually soluble and whose immunological mechanism is mediated by IgE, it is possible to prepare solutions with increasing concentrations of the causal agent which are then administered by aerosol using a nebulizer. The concentration at which the test is initiated is calculated using a formula based on methacholine PC₂₀ and the smallest antigen concentration able to provoke a positive skin response [39].

Some centres have devised closed-circuit apparatuses which allow better control of exposure both to HMW and LMW agents and to increase patient and staff safety. Initially, each agent required a specific apparatus [35,40], but a recently designed closed circuit apparatus (GenaSIC; Fig. 2) [41[■]] is able to aerosolize dust, liquids or vapours while



FIGURE 2. GenaSIC. An example of a close-circuit aerosol generation chamber. This figure is not original; it was previously published in [41[■]] (we have the permission of Dr JL Malo (corresponding author)).

maintaining concentrations stable between 0.001 and 1000 mg/m³. GenaSIC also presents other advantages over earlier equipment [41[■]]: its smaller size facilitates handling and transport and the fact that the generation sequences are automated means that the technical staff need to intervene less. Moreover, GenaSIC is now commercially available. Its main drawback is that it can generate only a limited number of occupational agents; each new agent must be validated before exposure.

CONCLUSION

Occupational asthma has major medico-legal, economic and social repercussions, and so establishing correct diagnosis is vitally important. The diagnostic value of the clinical history is low. Immunological tests may help when the agent responsible is HMW. The serial study of peak flow alternating periods of exposure and nonexposure to the causal agent may be of use, but it may also be influenced by cultural aspects in different countries, making its generalization difficult. With the exception of the analysis of the number of eosinophils in induced sputum, other tests such as FEV₁ measurement, methacholine PC20 or nitric oxide determination in exhaled air do not seem to improve on the diagnostic performance of PEF. We conclude that the specific occupational laboratory challenge test remains the reference test in the diagnosis of occupational asthma and that it should be performed whenever this condition is suspected, whether the causal agent is of high or LMW. However, because of the risk of false positives and negatives, it is important to define standard procedures in terms of its performance, the choice of variables to be analysed, and its interpretation.

Acknowledgements

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Conflicts of interest

The authors declare no conflicts of interest.

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- of special interest
- of outstanding interest

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