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Review

Inhalation Challenge Tests in Occupational Asthma: Why Are Multiple Tests Needed?

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Abstract

Occupational and environmental lung diseases are on the rise because of the widespread use of various toxic agents in industry. Asthma etiopathogenesis is unclear because of exposure to high and low molecular agents in workplaces. Approximately 15–25% of asthma in adults is reported to be related to occupational exposure. The prevalence of occupational asthma (OA) is predicted to be high. The difficulties in diagnosing OA results in inadequate treatment, permanent airway damage, and medicolegal and social problems. As with other occupational diseases, it is necessary to demonstrate a direct causal relationship between the suspected agent and OA. Spirometry, peak expiratory flow rate, and/or non-specific bronchial hyperresponsiveness are frequently used to show airway hyperresponsiveness at the workplace and away from work. However, there are some controversies about the specificity and sensitivity of these test methods. Furthermore, these tests do not identify the exposure agent, which could be the causative agent. Specific inhalation challenge (SIC) tests that demonstrate the direct causal relationship are currently the gold standard. However, their positive and negative predictive values have not yet been established; therefore, many low molecular weight agents could cause late or atypical reactions. Therefore, a negative SIC test cannot exclude the disease. This review describes the procedures for the SIC test and discusses the importance of using the combined test methods with the SIC test.

KEYWORDS: Control day, exposure day, occupational asthma, specific inhalation challenge TEST

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INTRODUCTION

Work-related asthma can be classified into 2 general groups: occupational asthma (OA) and work-aggravated asthma. OA is defined as asthma that occurs as a result of direct exposure at the workplace or after a certain period of exposure to a sensitizing or irritant agent in the workplace. Work-aggravated asthma is defined as exacerbation of symptoms in workers with pre-existing or coincident asthma [1]. This review will focus on OA.

OA has become the second-most common occupational lung disease after pneumoconiosis in developing countries [1]. The incidence of OA ranges from 50 per million to 250 per million workers [2]. Approximately 10–25% of the cases of adult-onset asthma are caused by occupational exposure [3]. More than 200 specific agents encountered at work can cause asthma [4]. It is recommended that OA should be suspected in every newly diagnosed case of adult asthma [5].

OA can be divided into 2 groups: allergic OA, which has 2 subtypes–immunoglobulin (Ig)-E dependent and IgE independent–and non-allergic OA, known as irritant-induced OA. Irritant-induced OA is further divided into 2 groups [6]; if only 1 exposure agent is responsible for the disease, it is called reactive airways dysfunction syndrome; after multiple exposures, it is called irritant-induced OA [7, 8]. The exposure agents are classified into low molecular weight (LMW) and high molecular weight (HMW) agents. HMW agents usually induce IgE-dependent OA.

OA should be confirmed by an objective method instead of the conventional diagnosis of pneumoconiosis, which is done based on the history of exposure and chest radiograph abnormalities. The most important step in diagnosing OA is conducting a detailed occupational exposure history. It is followed by tests that will determine the relationship between the agent and the disease. It is difficult to detect the exposure agent that causes asthma and/or establish a direct causal relationship between the suspected occupational exposure agent and asthma.

Specific inhalation challenge (SIC) tests are currently recognized as the gold standard to diagnose OA. However, negative SIC tests do not exclude OA. As with other occupational diseases, accurately diagnosing OA constitutes the basis of cura-

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tive treatment by protecting the patient from further exposure to the agent. Owing to medicolegal obligations, workers' disabilities, and compensation rights, it is vital to use the most accurate methods to diagnose OA [9, 10]. The diagnosis of OA should follow evidence-based guidelines. It should be remembered that negative test results do not exclude OA [11]. This study assesses how the SIC tests are used within a certain algorithm and evaluates the significance of the airway bronchial hyperresponsiveness tests and inflammation markers in the diagnosis of OA.

Traditional Methods for Diagnosing Occupational Asthma

The first step to diagnosing OA is to record a detailed occupational history. An occupational questionnaire helps identify the possible responsible agent; however, it is not sufficient for diagnosis. The positive predictive value and the negative predictive value of questionnaires for diagnosing OA are 63% and 83%, respectively [12].

To diagnose OA, the diagnosis of asthma must first be confirmed. This verification is usually done with the non-specific bronchial provocation test [5]. However, studies have indicated that the presence of baseline non-specific bronchial hyperresponsiveness (NSBH) has a low specificity (48–64%) and low positive predictive value (55–62%) for diagnosing OA [13, 14, 15]. Furthermore, the presence of NSBH demonstrated logical sensitivity (84%) and a negative predictive value of 75% for predicting OA. Therefore, the fairly high negative predictive value of NSBH suggests that the absence of NSBH can be used to rule out active OA [16].

Immunologic sensitization does not mean that the person has OA. Specific antibodies are usually significantly involved in Ig-E dependent phenomena. The presence of specific IgG antibodies in response to polyisocyanate exposure or the presence of IgE antibodies in diisocyanate-induced asthma is not sufficiently sensitive or specific for a diagnosis of OA [21]. Furthermore, a positive skin test against an allergen does not mean that the allergen is linked to OA. The studies exposing individuals to specific agents reported that significant airflow limitations were not induced despite the presence of guar gum or psyllium-associated skin reactivity and bronchial hyperresponsiveness [12, 17]. Therefore, the use of immunological tests alone to confirm a diagnosis of OA is not recommended.

MAIN POINTS

- Occupational asthma should be kept in mind in adult patients with OA and detailed occupational exposure history should be taken.
- There are many industrial agents that cause OA. Often there are multiple exposures and it is difficult to detect causative agents. It causes difficulty to make a definitive diagnosis.
- Although PEFR monitoring is the most common method for diagnosing OA, this method is insufficient to determine the causative agent. PEFR monitoring which is recorded by the employee has some handicaps.
- The specific BPT is based on mimicking workplace environments at laboratory and it is the most objective method to diagnose OA and to determine the responsible agent.

The most comprehensive method for diagnosing OA is peak expiratory flow rate (PEFR) monitoring [18]. The specificity and sensitivity of PEFR monitoring is lower than those of the SIC test [19, 20]. Changes in PEFR at work and away from work had a high specificity (91%) but low sensitivity (50–60%) [21, 22]. Changes at and away from work may show the presence of airflow limitation because of workplace exposures. However, this method has some limitations. PEFR is affected by respiratory effort and the results are independent of a technician, requiring the collaboration of the worker. Therefore, monitoring PEFR may allow for differentiating any overestimated or underestimated results; however, it can be misused in regards to issues associated with job loss or compensation [8].

The SIC test is carried out effectively and reliably in a limited number of centers around the world [23]. usually OA is usually diagnosed with a SIC test in Quebec, Canada; Leuven, Belgium; Barcelona, Spain and several other centers in Europe [24].

Brief History of the Specific Inhalation Challenge

Blackley was the first researcher to perform inhalation challenges using common allergens [25]. In 1952, Herxheimer documented the occurrence of late reactions associated with bronchial inflammation and the eosinophilic bronchitis characteristic of asthma [26]. The occurrence of these late reactions after exposure to common allergens was later confirmed by other investigators [27]. In 1970, Pepys suggested the use of specific inhalation tests in the diagnosis of OA after he observed severe asthmatic reactions in workers who built boats for the Oxford and Cambridge boat race using a mixture of 2-part polyurethane/toluene diisocyanate marine varnish. He proposed observing the effects of these 2 varnishing materials separately. On the first day of the experiment, a worker painted wood with polyurethane alone, but no emergent effects were observed; the next day, a mixture of the 2 materials was used to paint the wood, resulting in asthmatic reactions. This test demonstrated that the occupational agent could be used as a provocation test, eliciting analyzable and reproducible results [28].

To diagnose OA today, functional assessments are carried out on a patient by exposing them to the responsible agents in a laboratory at limited centers [29]. Mimicking the workplace environment in laboratory conditions is the basis of the SIC test. Monitoring PEFR rates and NSBH at and away from work can be used together with the SIC test [21, 33].

Safety Precautions and Preparatory Arrangements for Inhalation Challenge Tests

SIC tests are potentially dangerous because they can cause severe and life-threatening asthmatic reactions. Therefore, they should be performed in specialized centers by well-trained technicians complying with challenge protocols. A well-trained technician should be have full knowledged of the inhalation challenge protocol, when to stop further exposure [24], and on emergency procedures. During these procedures, close supervision by an experienced physician

should be provided [30]. Occupational challenge tests can be performed in a laboratory in exposure chambers, mimicking work exposure. The exposure chambers should be well ventilated and well-isolated to minimize the exposure of personnel. The tests can be performed in outpatient clinics.

SIC tests take nearly 8 hours. Patients come to a laboratory early in the morning and may leave in the late afternoon. The procedures and potential adverse effects that may occur during or after the tests should be explained to patients in detail before starting the tests. The challenge tests should be performed after collecting informed consent forms from the patients following the explanations. At the end of the day, if any induced airway obstruction still exists, the physician should start an inhaled β_2-adrenergic agent and observe patient response; the patient should have an improved response before discharge. If the response is insufficient, the patient should be hospitalized and treatment should be started if needed. Patients should be informed about the potential late-phase asthmatic reactions prior to discharge.

SIC is contraindicated in patients with severe airflow limitation. The European Academy of Allergy and Clinical Immunology Subcommittee recommends that the baseline forced expiratory volume (FEV_1) should be ≥ 70% of the predicted value to perform provocation tests using allergens [31]. In addition, SICs should only be performed if asthma is stable. Relative contraindications for SIC include any recent or unstable cardiovascular disease, uncontrolled epilepsy, pregnancy, recent (< 4 weeks) respiratory tract infections, and a patient's inability to understand the procedures [32, 33].

Procedures to Manage Medication Before the Tests

In ideal conditions, the use of all bronchodilator and anti-inflammatory medications should be stopped before the challenge test although it is often not possible in patients with moderate or severe asthma owing to the potential risk of spontaneously developing large fluctuations in FEV_1 values. Patients should stop inhaled $beta_2$-adrenergic agents at least 8 h before the test. Sustained-release theophylline preparations should be stopped at least 48 h before the challenge. If the subject receives once-a-day theophylline preparations, these medications should be stopped 72 h before the test. If the patient has unstable asthma, they should continue to receive their theophylline and cromolyn sodium preparations [34]. Treatment with inhaled corticosteroids can be continued [35]. In patients who take medications to control unstable asthma, the total dose should be administrated at the end of each challenge day but no sooner than 8 h before the next challenge. Challenge tests have been reported to elicit positive reactions in patients on antiasthma medication when the tests are performed in this way [36].

Inhalation Challenge Test Procedures

Control Day

The aim of the control day is to determine whether the asthma is stable. This is achieved by monitoring the caliber of the airway on the control day when no exposure is performed. The control substance is usually selected with reference to the agents suspected of causing OA. The challenging agents are also required to have the same physical appearance as the suspected occupational agents [37]. The substances generally used as control substances are presented in Table 1.

Spirometer parameters including FEV_1, forced vital capacity (FVC), and FEV_1/FVC; PEFR, oral temperature, and complete blood count (CBC) should be measured at the beginning of the day and recorded as baseline values. Patients are exposed to a control substance for 30 min. FEV_1 fluctuations should be less than 10% throughout an observation period of 8 h. At the end of the control day, the patient CBC should be examined, as should other spirometer parameters and PEFR.

Day of Exposure

The basic principle of the SIC test is to mimic the exposure at the workplace to the suspected causative agent of asthma. Challenge tests can be performed by examining individuals in a closed-circuit chamber in the laboratory, mimicking the exposure at the workplace, but they can also be performed in the workplace. Exposure chambers should be well-ventilated and isolated to minimize the exposure of staff to the challenging agents.

Baseline spirometer values, PEFR, and temperature should be examined at the beginning of the exposure day. Baseline FEV_1 values on the day of exposure should be compared with the value elicited on the control day to ensure patient safety and stability. If the difference between these two values is < 10%, FEV_1 should be repeated every 15 min for 1 h until the FEV_1 level becomes comparable to the level obtained on the control day. If the FEV_1 level does not improve, the challenge test can be postponed to the next day. If alveolitis is suspected, the patient should be evaluated using a carbon monoxide lung diffusion test, CBC, and radiological examination.

After ensuring functional stability, the patient is exposed to the suspected challenging agents. Monitoring with spirometer should be conducted over a period of at least 8 h; every 10 min for the first hour, every 30 min for the second hour, and hourly after that. Exposure should be terminated when FEV_1 drops by ≥ 20%.

If the Challenge is Positive

If an immediate reaction occurs, FEV_1, symptoms, and clinical findings on the patient should be monitored. When the fall in FEV_1 is < 10% or exceeds the control day value, a methacholine challenge and sputum induction tests are performed. When a semi-retarded or double reaction develops, FEV_1 drops by > 10%, or values comparable to those on the control day cannot be achieved, a methacholine challenge is performed the next day. The sputum induction test can be performed at the end of the exposure day.

If the challenge is negative

A methacholine challenge test and sputum induction test should be done, at the end of the day or investigation period, when the test is negative. If there is a more than more than 3.2-fold reduction in the provocative concentration 20% fall in FEV_1 (PC_{20}) value after exposure, re-exposure should be performed the next day [38, 39].

Duration of Exposure

It has not yet been clarified how long a patient should be exposed to the causative substance before the test can be

Table 1. Control substances [57].

High molecular weight agents	
EXPOSURE AGENTS	**CONTROL AGENTS**
Flours: wheat, rye, oats, barley, soy, buckwheat	Lactose
Grains and animal feed	Lactose or saline
Enzymes: amylases, lipases, proteases, cellulases, xylanases, enzyme mixtures	Lactose
Natural rubber latex: gloves	PVC or nitrile gloves
Wood dusts: Obeche, Teak, Iroko, Western Red Cedar, Ebony; Ash, Beech, Pine	
Medium density fiberboard (MDF)	Pine or spruce wood
Formaldehyde painted on to cardboard for MDF	
Animal-derived protein	Lactose powder used for animal bedding (flakes + powder)
	Lactose powder in unused animal bedding (dusting or tipping)
	Unused bedding for live animals
	Negative IgE for fish
Decorative plants and vegetables	Saline control solution, cutting lettuce
Foodstuffs and spices	Lactose or saline
Low molecular weight agents	
Methylene diphenyl diisocyanate	Solvent
Hexamethylene diisocyanate (usually in a paint or glue hardener or a related product)	Butyl-acetate or saline
Toluene diisocyanate	Solvent or saline
Other plastic chemicals: epoxy resins, acrylic resins, powder paints, acid anhydrides, etc.	Butyl-acetate or saline
Acrylic resins: acrylates, methyl-acrylates and products based on them	Solvent Latex gloves, cleaning agents for methyl-methacrylate
Cyanoacrylate: instant glues and related products	Solvent
Phthalic acid anhydrides	Lactose
Welding fumes	Mild steel
Nickel	Solvent or saline
Cobalt	Lactose
Chromium	Solvent or saline
Platinum salts	
Palladium	
Iridium	Lactose
Soldering materials	
Colophony	Non-colophony wire or heated ethanol
Per sulfates	Lactose
Formaldehyde	
Glutaraldehyde	Water, saline

considered negative. The threshold duration of exposure to a challenging agent is reported to be > 2 h in 25% of patients before an asthmatic reaction is induced [40]. It has also been reported that 4 h of exposure may be required for hexamethylene diisocyanate [41]. A longer duration of exposure is required when the challenge test is performed with the LMW agents or when the baseline NSBH severity is relatively mild. The duration of exposure should be increased if the duration of work-related asthma symptoms are short [40].

The duration of a positive reaction is determined by the physical and chemical features of exposure agents and individual factors [29]. Atypical reactions have been described with exposure to isocyanates and other LMW agents [42]. The definitions of the reaction types are presented in Table 2.

Challenge Tests at the Workplace

When the challenge test is performed at the workplace, a control day test should be performed as previously described. It should be ensured that the patient has discontinued any medications before this.

Table 2. Types of reactions

TYPICAL REACTIONS	
Immediate reaction	Maximal 10–30 min after exposure, with complete recovery within 1–2 h; although usually readily reversible by inhaled β2-agonists, these 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. This stresses the importance of progressive exposure.
Late reaction	Develop slowly and progressively, either 1–2 h ("early late") or 4–8 h (late) after exposure; may occasionally be accompanied by fever and general malaise; if so, extrinsic alveolitis should then be considered. Contrary to popular belief, they generally respond well to inhaled β2-agonists [53], although the response may be shorter in some subjects.
Dual reaction	A combination of early and late. A recurrent nocturnal asthma pattern has also been described and is probably related to an increase in NSBH following exposure.
ATYPICAL REACTIONS	
Progressive	Starting within minutes of end of exposure and progressing over the next 7–8 h.
Squared-waved reaction	No recovery between the immediate and late components of the reaction.
Prolonged immediate type	Slow recovery.

NSBH: non-specific bronchial hyperresponsiveness

The testing device should be placed in a room where the suspected causative agent is not present. The patient should not take the stairs at the workplace on the day of the test. Baseline spirometer values, PEFR, and temperature should be measured at the beginning of the day. The FEV_1 level should be comparable to the baseline. A technician should record whether the patient has taken a short-acting β-agonist for bronchoconstriction or used a closed-circuit paper bag for hyperventilation. Spirometer parameters, PEFR, and temperature should be monitored in the same way as previously described for the laboratory procedures.

The SIC tests require many phases and a relatively long follow-up. Monitoring the spirometry parameters and PEFR at frequent intervals may lead to a decrease in the respiratory effort of the patient. The technician should exercise vigilance to identify such conditions. If a decrease in respiratory effort is observed, the patient should rest. The hemodynamic stabilization of the patient should be ensured; if not, the patient may need to be admitted to the hospital.

What Do the Functional and Inflammation Tests Indicate?

FEV_1 and Peak Expiratory Flow

FEV_1 has been accepted as the gold standard parameter for assessing the bronchial responsiveness. It is used with SIC test as it has been proven to be standardized and reproducible. [43]. It is easy for the technician to perform and the patient to undergo and requires portable and relatively inexpensive instrumentation. Functional tests are well-defined parameters to demonstrate airway hyperresponsiveness and obstruction. However, they depend on subject effort and require collaboration [28].

In OA, it has been demonstrated that the decline in FEV_1 is approximately 100 mL/year if a worker continues to be exposed to a causative agent at the workplace. If exposure is prevented, an increase in FEV_1 levels of approximately 12 mL in the first year is expected [44]. The change in FEV_1 levels after the removal of the causative agent is an independent reliable value for monitoring patient improvement [45].

PEFR is monitored with FEV_1 during the control and exposure days. Patients should continue measuring PEFRs during the evening and night after discharge from the hospital to identify any late reactions.

PEFR can be easily monitored using a cheap device. The reproducibility of PEFR is slightly lower than FEV_1; however, this test requires more muscular effort compared with FEV_1 and it has recently been shown to be less sensitive [46]. Body plethysmography and measurements of respiratory resistance by forced oscillation techniques are not effort-dependent; however, they are more expensive and less reproducible [37].

PEF monitoring is recommended to be performed every 2 h daily at and away from work for a minimum of 2 weeks to allow for optimal evaluation. If asthma is severe, the patient is exposed to unidentified agents at work and at home, or exposure is intermittent, the results of the PEF monitoring will be difficult to evaluate. Changes in the patient's treatment regimen, such as reductions in the steroid dose, may cause a deterioration of asthma and lead to a decrease in PEF at the workplace. This may lead to a false diagnosis of OA. In patients with severe asthma, the recommendation is to remove the patient from the workplace until the asthma is controlled with minimal treatment [35]. Nevertheless, PEF monitoring during the SIC is an easy method to monitor the emergence of late reactions after the patient leaves the hospital.

Non-specific Bronchial Hyperresponsiveness

As a negative SIC test cannot exclude OA, monitoring bronchial responsiveness and/or the airway inflammation is important. A recent study has demonstrated that a negative methacholine challenge at and away from work (using PC_{20} > 16 mg/mL as the cut-off point for normality) may rule out OA. The negative predictive value of using the methacholine challenge test at work was reported to be 95.2%. The sensitivity and specificity of the methacholine challenge test were reported to be 80.2% and 47.1%, respectively [15].

Monitoring and evaluating NSBH and PEF together has been shown to be produce more sensitive and specific results than

Table 3. Overview of changes in PC20 and sputum eosinophil after the SIC in OA

Authors and Publication Year	Number of cases	Type of exposure agents	Before the SIC		After the SIC	
			PC20 (mg/mL)	Eosinophil (%)	PC20 (mg/mL)	Eosinophil (%)
Cote JL et al., 1990 [20]	14	Cedar dust	1.8	Undefined	0.9	Undefined
Malo JL et al., 1994 [58]	1	Polypropylene	3.1	Undefined	2.2	Undefined
Lemiere C et al., 2000 [51]	16	HMW agents	23.2	Undefined	9.3	Undefined
Lemiere C et al., 2001 [59]	17	8 cases of LMW agent exposure, 9 cases of HMW agent exposure	6.0	0.5	1.9	9.0
El-Zein M et al., 2003 [60]	6	Welding fumes	20.3	Undefined	5.66	Undefined
Prince P et al., 2012 [61]	82	41 cases of LMW agent exposure, 41 cases of HMW agent exposure	LMW = 4.8 HMW = 3.4	1.8	LMW = 1.27 HMW = 0.62	7.9
Vandenplas O et al., 2013[62]	17	Cleaning agents	1.4	1.8	0.5	10.0
Lemiere C et al., 2014[55]	98	Mainly HMW agents	2.5	1.5	1.12	7.5
Wittczak T, 2012[63]	9	Metals	5.01	1.1	2.27	4.3
Racine G et al., 2017[64]	71	35 cases of LMW agent exposure, 35 cases of HMW agent exposure	4.6	1.0	1.9	8.0

SIC: specific inhalation challenge; OA: occupational asthma; HMW: high molecular weight; LMW: low molecular weight; PC: provocation concentration

if they were used separately [42]. A concomitant change in both PEF and NSBH makes a diagnosis of OA highly probable. The American College of Chest Physicians (ACCP) consensus report suggests that there must be at least 2 weeks between the period at the workplace and the period away to repeat the methacholine challenge test [16]. If an SIC test is scheduled, the NSBH should be measured before the SIC test and at least once after obtaining a negative SIC result.

Provocative Concentrations Causing a 20% Decline in FEV1 Levels

Assessing PC_{20} before the SIC helps predict a potential response to a specific agent. Low PC_{20} levels indicate an immediate response ($PC_{20} \leq 0.25$ mg/mL) whereas high levels (maximum 128 mg/mL) may indicate a late response [15]. The duration of exposure for an optimally performed SIC test has not been clearly defined. Unfortunately, early termination of exposure may be misleading for confirming a diagnosis. It has been demonstrated that changes in PC_{20} can be taken into account when no significant changes are observed in the spirometer [47].

It is typical for non-allergic bronchial hyperresponsiveness to increase after the emergence of late reactions but not after immediate asthmatic reactions (p=0.002; odds for the presence of significant changes in PC_{20} in a late reaction = 59%; odds for the absence of significant changes in PC_{20} in an immediate reaction = 83%) [47]. A ≥ 3.2-fold decrease in PC_{20} after exposure to a suspected causative agent has been demonstrated to be associated with a 20% fall in FEV_1 levels compared to baseline values. These findings indicate that some changes develop in the airways. In patients for whom this is the case, a physician should continue the investigation by increasing the duration of exposure to the suspected agent [28, 47]. Changes in PC_{20} levels after the SIC, as reported in selected studies, have been presented in Table 3.

Oral Temperature and Complete Blood Count

Oral temperature is recorded hourly to document any possible hypersensitive pneumonitis. Blood eosinophilia or leukocytosis are examined at the beginning of the control day and end of the first day. They are repeated at the same intervals the following morning if the challenge test results are positive. The serum can be stored for further immunologic testing [28].

The eosinophil count in the peripheral blood may increase after some patients spend a period of time at work. The median percentage increase in the eosinophil count in sputum being higher than the blood eosinophil count by 92% and 43%, respectively, [48] combined with a low diagnostic value of blood eosinophilia can confirm a diagnosis of OA. However, CBC can be beneficial in making a differential diagnosis of alveolitis or infectious lung diseases.

Eosinophil Count in Sputum

Diagnosing OA can be highly challenging. Therefore, new innovative tests and a combination of multiple tests are required to improve its diagnostic accuracy. After the occupational exposure, an increase in the induced sputum eosinophil count is an early marker of specific bronchial reactivity. This parameter may help identify subjects who will develop an asthmatic reaction after repeated exposure [49]. It has been shown that the eosinophil count in induced sputum increases after 7 h of exposure to occupational agents and it has been found to persist over 24 h after the exposure. Hence, the sputum induction test can be a predictor for OA with or without

the SIC tests [50] (Table 3). An increase in induced sputum eosinophil count of > 3% after the first day of exposure during the SIC appears to be one of the most accurate parameters to predict asthmatic reactions following repeated exposures with a sensitivity of 67% and a specificity of 97% [49]. Lemiere et al. [51]. determined that an increase in induced sputum eosinophil count on the day of exposure preceded a 20% decrease in $FEV_{1,}$ although there were no changes in other functional parameters. Thus, even without any changes in respiratory functions, an increase in induced sputum eosinophil count should lead practitioners to conduct exposure challenge tests to the suspected causative agents in the laboratory to determine whether an asthmatic reaction will occur [51]. In some centers in Europe and in the Department of Chest Medicine, Sacré-Coeur Hospital, Montreal, Quebec, Canada, induced sputum eosinophilia has been used as an important component of the SIC test.

Some studies have reported that subjects who were diagnosed with OA and exposed to toluene diisocyanate had an increased neutrophil count in induced sputum. The reason for this non-eosinophilic airway inflammation is unknown. The predictive value of the changes in the neutrophil count to make a diagnosis of OA has also not been established yet.

Changes in induced sputum eosinophil count can provide an objective measure as PEF and/or PC_{20} are open to misinterpretation when they are not performed by competent staff [52]. Induced sputum can also provide benefits in determining the presence of sensitization when the suspected causative agent at the workplace cannot be identified. A combination of induced sputum eosinophilia with changes in PEF and PC_{20} levels with the methacholine challenge at or away from work results in 84% sensitivity and 64% specificity [53].

However, the test is not free of the potential to produce a misleading diagnosis as it is not performed routinely in many centers, thereby limiting the number of laboratories qualified to conduct it. Even if the test is performed by experienced and well-qualified staff, the results can only be predictive as it has not been clarified whether patients with occupational eosinophilic bronchitis will develop OA given continuous exposure to the causative agent [51]. However, the sputum induction test is also a useful method for diagnosing occupational eosinophilic bronchitis and making a differential diagnosis.

Exhaled Nitric Oxide

Some investigators have proposed that the fraction of exhaled nitric oxide (FeNO) be evaluated along with the results of the SIC test for a more accurate diagnosis of OA. Florentin et al. [54] have found that a threshold of 8.5 ppb FeNO demonstrated a 78.9% sensitivity and 42.8% specificity in identifying OA. Lemiere et al. [55]. have reported that there was a robust association between an increase in FeNO and asthmatic reactions induced by HMW agents. However, the results of the multivariate logistic regression analysis demonstrated that a threshold duration of exposure for a 20% decline in FEV_1 levels during the SIC test and the maximum fall in FEV_1 did not significantly affect the FeNO [55]. An increase in the FeNO following an exposure to a causative agent is not specific, nor does it result in a high positive predictive value. Changes in FeNO are less sensitive than the elicited changes in induced sputum eosinophilia [56]. Furthermore, FeNO can be affected by various factors and is not specific to the type of airway inflammation [56]; however, [57-64] it could be an option for patients who fail to provide sputum samples in appropriate amounts [13].

CONCLUSION

It has been determined that it is insufficient to use a single test to confirm a diagnosis of OA. The advantages and disadvantages of individual tests have been demonstrated. Referring to ACCP guidelines can be useful when facilities to perform a SIC test is not available. More work is needed to ensure easy accessibility to SIC tests. It is necessary to use a combination of tests, if the SIC test result is negative, to accurately diagnose OA. Evaluating changes in PC_{20} levels and sputum eosinophil counts after the SIC test appears useful to diagnosing OA.

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