



The use of specific inhalation challenge in hypersensitivity pneumonitis

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Purpose of review

The diagnosis of hypersensitivity pneumonitis remains a dilemma because of the absence of any characteristic features able to distinguish it from other interstitial lung diseases. We analyze the current role of the specific inhalation challenge (SIC) in the diagnosis of this entity.

Recent findings

Few descriptions of the use of SIC for the diagnosis of hypersensitivity pneumonitis have been published in recent years. In fact, hypersensitivity pneumonitis is still diagnosed on the basis of clinical criteria, as there is no agreement on the diagnostic utility of SIC. Two major reviews carried out in the past year have concluded that this test is not standardized and is usually unnecessary; however, a third study found that the test can indeed recreate the symptoms and functional abnormalities in the laboratory, and may therefore be of considerable use in the diagnosis of hypersensitivity pneumonitis.

Summary

Hypersensitivity pneumonitis remains a diagnostic challenge. Given that the main cause of the disease is sensitization and hyper-responsiveness to specific antigens in susceptible individuals, SIC is an obvious candidate as the gold standard for diagnosis of this entity. The present review analyzes the reasons for the test's limited use, assesses its diagnostic utility, and proposes a basis for its standardization.

Keywords

BAL lymphocytosis, bird fancier's lung, extrinsic allergic alveolitis, immune response, pulmonary function test

INTRODUCTION

Hypersensitivity pneumonitis, also known as extrinsic allergic alveolitis, is a syndrome caused by an exaggerated immune response to the inhalation of a variety of antigen particles found in the environment. Data from European countries indicate that hypersensitivity pneumonitis represents 4–15% of all interstitial diseases [1] with an incidence rate of 0.9 cases per 100 000 person-years [2]. The most common forms of hypersensitivity pneumonitis are farmer's lung and pigeon breeder's lung, but the proportion of individuals who are exposed to these antigens and will develop hypersensitivity pneumonitis is unknown. Some studies estimate the prevalence of hypersensitivity pneumonitis to range from 1% to 19% in exposed farmers [3] and from 6% to 20% in exposed pigeon breeders [4]. Although other causes like 'Chacinero's lung' [5], 'steam iron lung' [6,7] and 'saxophone player lung' [8] have recently been described, the interest today is focused on 'hot tub lung' [9] and 'metal working fluid hypersensitivity pneumonitis' [10]. Antigens responsible for all these types of hypersensitivity

pneumonitis originate mainly in bacteria, molds, yeast, or fowl. Exposure to chemicals, such as isocyanates, methacrylate, zinc, inks, dyes, spores from fungi [11], and exposure to certain woods [12], or to other recently described antigens like colistin [13] and catechin [14] can also induce hypersensitivity pneumonitis.

The finding of specific-IgG antibodies in most cases of hypersensitivity pneumonitis has suggested that a type III hypersensitivity mechanism may be responsible for this pathology. Although a type III hypersensitivity physiopathological mechanism has been proposed since Pepys *et al.* [15] first described

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KEY POINTS

- Hypersensitivity pneumonitis represent a large percentage of diffuse interstitial pneumopathies.
- Hypersensitivity pneumonitis is diagnosed on the basis of clinical criteria. The lack of a specific diagnostic test leads to underdiagnosis; in undiagnosed cases, the steps necessary to control the disease are not taken.
- Although it is not standardized, the SIC has proved to be well tolerated and to have high sensitivity and specificity and therefore a high diagnostic yield.
- Given the pathogenesis of the disease, SIC is probably the 'gold standard' diagnostic test. Efforts should be made to standardize the test's performance and interpretation.

the condition, it is currently known that a type IV hypersensitivity mechanism mediated by T cells may also be involved [16²²]. In fact, several authors have implicated a Th1 mechanism in cases of acute or subacute clinical symptoms and a Th2 mechanism in cases which evolve towards pulmonary fibrosis, and state that the finding of IgG-specific antibodies indicates exposure but not necessarily pathology [17,18]. Recent studies suggest that Th17 cells are also involved in hypersensitivity pneumonitis [19]. Th1 and Th17 cells promote lung inflammation, whereas regulatory T cells help downregulate the disease by suppressing the proliferative response of activated T cells. It may be because of these cells that many individuals exposed to hypersensitivity pneumonitis antigens do not develop the disease [20²²]. Finally, some authors suggest that the inflammatory responses seen in hypersensitivity pneumonitis are initiated by causative agents via toll-like receptors, receptors that are expressed in immune cells and recognize most antigens. In hypersensitivity pneumonitis, when specific toll-like receptors are activated, they react through an intracellular pathway known as the MyD88 pathway to release large numbers of pro-inflammatory cytokines and mediators [21²²].

Because of the involvement of multiple antigens in the genesis of hypersensitivity pneumonitis, the absence of a conclusive identification of the physiopathological mechanisms, and the variability in the forms of clinical presentation and the pathology results, the entity currently lacks a clear definition and its diagnostic criteria are not well established. This study analyzes the possible utility of the SIC both in the diagnosis of hypersensitivity pneumonitis and also in the evaluation of new causative

antigens. We discuss how the test should be performed, and what parameters should be assessed to ensure correct interpretation.

DEFINITION AND DIAGNOSIS OF HYPERSENSITIVITY PNEUMONITIS

The two major groups of international experts have failed to arrive at a consensual definition of hypersensitivity pneumonitis [21²²]. According to the National Heart, Lung and Blood Institute/Office of Rare Diseases workshop, 'hypersensitivity pneumonitis is a complex health syndrome of varying intensity, clinical presentation, and natural history. Hypersensitivity pneumonitis is the result of an immunologically induced inflammation of the lung parenchyma in response to inhalation exposure to a large variety of antigens' [22], although the Hypersensitivity Pneumonitis Study Group defined the condition as 'a pulmonary disease with symptoms of dyspnea and cough resulting from the inhalation of an antigen to which the patient has been previously sensitized' [23]. The two definitions agree that hypersensitivity pneumonitis is caused by the inhalation of an antigen to which the patient is sensitized and hyper-responsive, and that sensitization and exposure alone in the absence of symptoms do not define the disease, regardless of the presence of specific-IgG antibodies. In this context, and establishing a parallel with occupational asthma, it is surprising that the SIC is not considered as the fundamental tool in the diagnosis of this entity [16²²,21²²], especially bearing in mind the wide variations in the clinical presentation of these conditions and in their immunological and histopathological responses [24²²].

The clinical presentation of hypersensitivity pneumonitis has been conventionally classified into acute, subacute and chronic. However, this classification is not widely accepted because it is sometimes difficult to distinguish between these forms; little is known about the latency between exposure and symptom onset, and it is not clear that they represent different stages of the disease. Using data from the patient cohort of the Hypersensitivity Pneumonitis Study Group and applying cluster analysis, Lacasse *et al.* [25] established two populations: cluster 1, comprising patients with recurrent systemic symptoms and normal chest radiographs, and cluster 2, who showed significantly more clubbing, hypoxemia, restrictive patterns on the pulmonary function test, and fibrosis on the HRCT scan. Interestingly, there was considerable disagreement between the current classification of hypersensitivity pneumonitis and the results of Lacasse *et al.* [25] analysis, particularly with regard to the

definition of subacute hypersensitivity pneumonitis.

The immune response is certainly the basis of the disease. The presence of specific-IgG antibodies to the inducing antigen demonstrates sensitization but, as we noted above, it is not necessarily diagnostic. According to Costabel *et al.* [16[■]], for example, between 30% and 60% of healthy farmers produce precipitating antibodies to the antigens to which they are exposed, but between 10% and 15% of patients do not develop serum precipitins; therefore, a negative finding does not rule out the presence of disease. In relation to the inflammatory response, bronchoalveolar lavage (BAL) is a highly sensitive method. It is generally accepted that the disease is characterized by an increase in the total cell counts with a large increase in the percentage of T-lymphocytes. However, in patients who are smokers or have chronic fibrotic parenchymal abnormalities, the BAL lymphocytosis may be lower. Moreover, an increase in BAL lymphocytosis may be found in asymptomatic-exposed individuals without clinical consequences [26]. Finally, the histopathology varies in relation to the stage of the disease. The acute response is a nonspecific diffuse pneumonitis with infiltration of mononuclear cells and neutrophils in the bronchioles, alveoli, and the interstitium; subacute hypersensitivity pneumonitis is characterized by a granulomatous bronchiolocentric interstitial pneumonitis, while chronic forms present with fibrotic changes and architectural distortion superimposed on the subacute changes. In these cases, the pathological patterns may mimic usual interstitial pneumonia-like patterns, nonspecific interstitial pneumonia, organizing pneumonia, or airway-centered interstitial fibrosis [24[■]].

Given this uncertainty regarding the various diagnostic tests and the misgivings that many authors express concerning the SIC, it is no surprise that today the diagnosis of hypersensitivity pneumonitis is made on the basis of several criteria.

Classically, three criteria have been used: antigen exposure associated with exposure-related symptoms; proof of sensitization; and demonstration of a characteristic pattern on chest radiography and/or a pulmonary function test with lymphocytosis in the BAL fluid. Since 2003, the results of the Hypersensitivity Pneumonitis Study Group [23] have often been presented as new diagnostic criteria for hypersensitivity pneumonitis, even though this was not the authors' objective [21[■]]; rather, as they say, they aimed to develop a clinical prediction rule for the diagnosis of active hypersensitivity pneumonitis. They identified six significant predictors for hypersensitivity pneumonitis (exposure to a known offending antigen, positive precipitating antibodies, recurrent episodes of symptoms, inspiratory crackles, symptoms 4–8 h after exposure and weight loss). The probability of hypersensitivity pneumonitis ranged from 98% when all six predictors were present to 0% when none of the predictors was identified. Given these considerations, probably the most widely used criteria for the diagnosis of hypersensitivity pneumonitis are those proposed roughly a decade ago by Schuyler and Cormier [27], which are listed in Table 1. In general, the diagnosis is made when at least four major and two minor criteria are present and if other conditions with similar characteristics are ruled out.

SPECIFIC PROVOCATION TEST AND DIAGNOSIS OF HYPERSENSITIVITY PNEUMONITIS

In the early 1960s, when the diagnosis of hypersensitivity pneumonitis was uncertain, many specialized centers proceeded to SIC. From then until now, only four studies have investigated the utility of this test in hypersensitivity pneumonitis diagnosis (Table 2) [28–31].

The first of these studies was performed in 1980 by Hendrick *et al.* [28]. These authors studied

Table 1. Major and minor criteria for the diagnosis of hypersensitivity pneumonitis

Major criteria	Minor criteria
Symptoms consistent with hypersensitivity pneumonitis	Bilateral basal crackles
Evidence of appropriate antigen exposure in medical history and/or detection of specific precipitins in serum and/or BAL	Decrease in DLCO
Findings consistent with hypersensitivity pneumonitis on chest plain films or chest computed tomography	Arterial hypoxemia, at least following exercise
Lymphocytosis in BAL (when performed)	
Histological changes consistent with hypersensitivity pneumonitis	
Positive SIC (reproduction of symptoms and laboratory abnormalities following exposure to the suspected antigen)	

BAL, bronchoalveolar lavage; SIC, specific inhalation challenge; DLCO, lung diffusion capacity.

Table 2. Utility of Specific inhalation challenge in the diagnosis of hypersensitivity pneumonitis

	Patients	Antigen	Result of the SIC
Hendrick <i>et al.</i> [28]	29 hypersensitivity pneumonitis suspicion 2 controls	Avian antigens	15/144 equivocal results Specificity: 95% Sensitivity*: 85–48%
Ramirez-Venegas <i>et al.</i> [29]	17 chronic hypersensitivity pneumonitis 17 other interstitial lung disease 5 controls	Avian antigens	3/39 equivocal results Specificity*: 82–86% Sensitivity*: 100–76%
Ohtani <i>et al.</i> [30]	11 chronic hypersensitivity pneumonitis	Avian antigens	0/11 equivocal results
Morell <i>et al.</i> [31]	59 hypersensitivity pneumonitis 30 healthy pigeon keepers 20 other diffuse interstitial lung disease	Avian antigens	5/59 equivocal results Specificity: 100% Sensitivity: 92%

*According to different responses elicited in the test.

31 patients – 29 with suspected hypersensitivity pneumonitis, and two controls. After performing 144 SIC, the authors observed a definitive pattern of positive late response and concluded that the test could actually be useful for the diagnosis of hypersensitivity pneumonitis. The second study was conducted by Ramirez-Venegas *et al.* [29] in 1998. After studying 17 patients with chronic hypersensitivity pneumonitis induced by avian antigens, 17 with other interstitial lung diseases and five healthy controls, these authors vouched for the utility of SIC as a diagnostic tool for hypersensitivity pneumonitis. The third study, by Ohtani *et al.* [30] in 2000, examined 11 patients with chronic bird fancier's lung; its results also supported the use of this test for diagnosis. Finally, the fourth study was conducted by Morell *et al.* [31] in 2008. These authors administered the SIC to 59 patients with bird fancier's lung, and to a control group comprising 20 healthy pigeon keepers and 20 patients with

diffuse interstitial lung disease other than hypersensitivity pneumonitis. The test was positive in 54 of the 59 patients with bird fancier's lung and negative in all controls; the authors concluded that the test had a sensitivity of 92% and a specificity of 100%.

In the last 2 years, most of the articles published on the use of SIC in hypersensitivity pneumonitis have sought to diagnose different types of hypersensitivity pneumonitis or identify new agents (Table 3). Nevertheless, Uzun *et al.* [34[■]] used the SIC to determine the prevalence of pigeon breeder's disease among pigeon breeders in Samsun province in Turkey. A natural provocation test applied on eight patients made one diagnosis with hypersensitivity pneumonitis in a patient with a positive test, and another patient with a negative test was diagnosed with hypersensitivity pneumonitis using clinical criteria. Takemura *et al.* [35[■]] diagnosed different types of chronic hypersensitivity

Table 3. Specific inhalation challenge to diagnose hypersensitivity pneumonitis or to identify new agents (studies performed in the last 2 years)

Author (reference)	Indication	Type of hypersensitivity pneumonitis	Agent	Type of SIC
Morell <i>et al.</i> [5 [■]]	Diagnosis of hypersensitivity pneumonitis	Chacinero's lung	Different types of fungi	Aerosolized SIC
Toribio <i>et al.</i> [12 [■]]	New agent	Medium-density fibreboard hypersensitivity pneumonitis	Pinewood fibre	Realistic in challenge room
Otera <i>et al.</i> [14 [■]]	New agent	Green tea hypersensitivity pneumonitis	Catechins	Aerosolized SIC
Mitsui <i>et al.</i> [32]	Diagnosis of hypersensitivity pneumonitis	Leaky walls hypersensitivity pneumonitis	<i>Aspergillus fumigatus</i>	Aerosolized SIC
Kupeli <i>et al.</i> [33]	Diagnosis of hypersensitivity pneumonitis and new agent	Hard cash	Freshly minted banknotes	Natural SIC

SIC, specific inhalation challenge.

pneumonitis using SIC and other criteria in order to study pathological differences between chronic hypersensitivity pneumonitis and idiopathic pulmonary fibrosis/usual interstitial pneumonia. These authors concluded that centrilobular fibrosis, bridging fibrosis and organizing pneumonia, in addition to bronchiolitis, granulomas and giant cells, are characteristic features of chronic hypersensitivity pneumonitis presenting a usual interstitial pneumonia-like pattern.

The SIC may be indicated if there is a suspicion of hypersensitivity pneumonitis. Like other challenge tests, it is contraindicated in cases of cardiac infarction or cerebral vascular accident in the last 3 months, severe arrhythmias or uncontrolled epilepsy or in general when the performance of spirometry is contraindicated [36]. As for the significance of the pulmonary function test scores, it is generally accepted that the SIC is contraindicated when both the forced vital capacity (FVC) and the diffusing capacity of the lung for carbon monoxide (DLCO) are below 60% of their theoretical value; however, based on the experience we have accumulated, we perform SIC with FVC and DLCO values above 50% and 40% of the reference values respectively, and we have found no severe reactions in positive cases (see below). Of course, the SIC is contraindicated in cases of respiratory insufficiency ($\text{PaO}_2 < 60$ mmHg).

Interestingly, some authors think that SIC should not be performed in any circumstances on the grounds that the test itself may sensitize the patient and cause illness [37]. However, this possibility has not been demonstrated to date.

HOW TO PERFORM THE SPECIFIC PROVOCATION TEST

Three methods have been proposed to perform the SIC. Some authors hold that natural workplace or home exposure is a reasonable way to provoke symptoms or deterioration of functional parameters in unclear cases of hypersensitivity pneumonitis [16²²,34²³]. Nevertheless, this form of the test is probably the least standardized, the least safe and the hardest to perform, and fails to conclusively establish the causative agent because it does not discriminate between possible different exposures. There is no agreement on how, and for how long, the patient should be re-exposed. Probably the exposure should be performed in increasing periods of time on successive days, as in the case of occupational asthma [38]. It is also unclear whether a physician or other health professional must be present during the re-exposure. When possible, it may be advisable to try to reproduce the working or environmental

conditions in a challenge chamber. This method has not been widely used [7,39] and although it does not conclusively identify the causative agent, its advantages are that it may be easier to standardize and may also be safer, as it is supervised at all times by health staff and the exposure conditions can be controlled.

The third method consists of using an aerosolized extract material of the suspected causative agent. This method is probably the most commonly used and one of the first descriptions of this was published by Williams in 1963 [40] and since then large series have been performed following these indications, with minimal changes [28–31]. Briefly, antigenic extracts are prepared from different kinds of materials (pigeon sera, hay, wood, and so on). Soluble proteins are extracted from fresh material with ammonium bicarbonate buffer 0.2 ml/l (pH 7.9) overnight at 4°C. The solution is centrifuged and the supernatant dialysed at 4°C against distilled water using a 3500-d pore-size membrane. The material obtained from the dialysate is lyophilized and the protein concentration determined by the bicinchoninic acid method. When fungi are the suspected cause of hypersensitivity pneumonitis, commercialized extracts can be used. Aerosols are made from solutions of the extract using different kinds of nebulizer (Wright, De Vilbiss 646, Hudson, and so on). The duration of the nebulization and the concentrations of extract used are not standardized, and both parameters vary according to the study.

We perform the SIC in the hospital setting after obtaining the patient's written consent. Using a De Vilbiss 646 nebulizer (De Vilbiss, Somerset, Pennsylvania, USA) or, in the last 10 years, a Mefar MB3 dosimeter (Mefar, Ele H₂O, Medicali, Brescia, Italy), which releases the solution during the first second of each inspiration, the patient is requested to inhale 2 ml of the suspected antigen at a dilution of 1/100 (0.01 mg protein/ml). When the test proves negative, a new antigen dilution of 1/10 (0.1 mg protein/ml) is inhaled on the next day. The day prior to the SIC is scheduled as a control day on which the patient inhales 2 ml of physiological saline solution. The inhalation normally lasts between 20 and 30 min. Our comparative analysis of the performance of the De Vilbiss 646 and Mefar MB3 nebulizers using an APS-3320 (Aerodynamic Particle Sizer; TSI, St Paul, Minnesota, USA) showed that the Mefar MB3 obtains a higher output (98.5 µl vs. 64.0 µl) ($P < 0.0001$) and a higher percentage of particles between 1 and 5 µm (25.5 vs. 23.0) ($P = 0.003$) (data not published).

Once the exposure has been performed, the patient must be observed for at least 24 h. There is no consensus on the parameters that should be

monitored over this time. It is generally agreed that the monitoring should include clinical aspects (body temperature, appearance of respiratory symptoms, appearance of systemic symptoms, such as flu-like symptoms, changes in the physical examination as crackles occurrence or increase), pulmonary function (basically FVC and DLCO) and measurement of SaO₂. Some authors also perform an exercise test [28], chest radiographs, high-resolution computed tomography, and fibre optic bronchoscopy with bronchoalveolar lavage [30] or blood analysis with leukocyte counts [29,30]. At our centre FVC, FEV₁, DLCO and body temperature are recorded at baseline, 20 min after the inhalation, and every hour thereafter for the next 8 hours. Blood cell count, chest radiograph and O₂ saturation measurement are also recorded before and 8 hours after the inhalation [31,41].

Our centre's experience using this protocol is positive, as shown by the studies [5*,12*,31,41–43]

published in different types of hypersensitivity pneumonitis. Nor have any important adverse effects been observed, and even though the administration of nonsteroid anti-inflammatory drugs has been necessary in a few patients to control systemic symptoms, such as fever and arthromyalgias, no corticosteroid or supplemental oxygen administration has been required. It should also be noted that SIC is performed on an outpatient basis without the need for hospitalization.

HOW TO EVALUATE THE SPECIFIC PROVOCATION TEST

Again, a variety of criteria have been proposed for establishing the positivity of the test (Table 4) [28–31]. The diagnostic criteria used by our group (Table 4) [31] are similar to the ones described by other authors, although we assign more value to pulmonary function studies. In addition, the level of

Table 4. Criteria for specific inhalation challenge positivity	
	The test is considered positive when any one of the following responses is elicited:
Hendrick <i>et al.</i> [28]	1) Symptoms and signs appropriate to an influenza-like illness
	2) At least one of the following criteria with respect to clinical status and baseline analytical values:
	Increase of exercise minute ventilation > 15%
	Rise in body temperature > 37.2°C
	Increase in circulating neutrophils >2500 µl
	Increase in exercise respiratory frequency >25%
	Decrease in circulating lymphocytes >500 µl
Ramirez-Venegas <i>et al.</i> [29]	Decrease in FVC >15%
	1) At least one of the following criteria with respect to clinical status and baseline analytical values:
	Decrease in FVC >16%
	Decrease in PaO ₂ >3 mmHg
	Decrease in SaO ₂ > 3%
Othani <i>et al.</i> [30]	Rise in body temperature > 0.5°C
	1) At least one of the following criteria with respect to clinical status and baseline analytical values:
	Peripheral leukocytosis
	Increase in alveolar-arterial oxygen pressure difference
	Rise in body temperature
Morell <i>et al.</i> [31]	Development of respiratory symptoms (cough and dyspnea)
	1) FVC decrease >15% or DLCO decrease >20% compared with baseline values
	2) 10–15% FVC decrease and at least one of the following criteria with respect to clinical status and baseline analytical values:
	White blood cell increase ≥20%
	O ₂ saturation decrease ≥3%
	Significant radiological changes
	Rise in body temperature >0.5°C
	Clinical symptoms (e.g., cough, dyspnea)
	3) FVC decrease <10% but with evidence of three or more of the abovementioned clinical or analytical criteria

DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity.

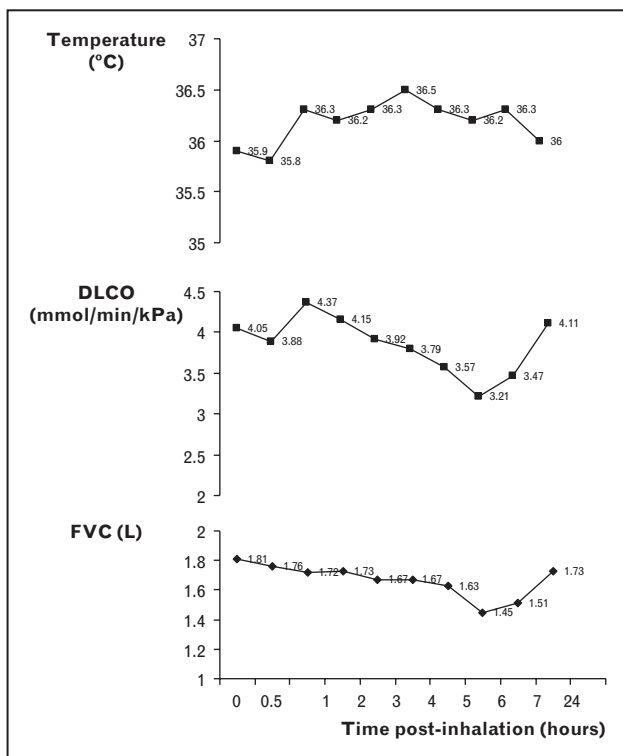


FIGURE 1. Positive result of a specific inhalation challenge with *Aspergillus fumigatus* in a patient exposed to home dampness: changes in temperature and decreases of 21% and 20% in DLCO and FVC, respectively, are observed.

antigen exposure in our case is probably lower. In this sense, the maximum exposure in the studies of Otani *et al.* [30] was 680 µg protein, whereas in our group, the maximum dose is 200 µg protein. This may mean that fewer respiratory and systemic symptoms are produced and that the possible alterations of the pulmonary function are rapidly reversible. In this regard, monitoring patients' pulmonary function every hour for 8 h after the inhalation may identify changes which will probably be missed if the monitoring is performed after 24 h, as other studies have done. As we noted above, applying these criteria in the specific case of bird fancier's lung, the sensitivity of the test was 92% and the specificity 100% [31]. Figure 1 shows a positive result of a SIC with *Aspergillus fumigatus*.

CONCLUSION

Even bearing in mind that hypersensitivity pneumonitis is relatively common among interstitial pulmonary diseases, our understanding of the condition is far from complete. Its incidence and prevalence are unknown and the physiopathology of the illness is not well defined; there are doubts surrounding the natural history of the disease and, above all, about how diagnosis should be performed.

As a result of this, possible hypersensitivity pneumonitis may sometimes be considered to be other diffuse interstitial diseases. Currently the SIC is not considered necessary for the diagnosis of hypersensitivity pneumonitis, basically due to the lack of standardization of the test. Nonetheless, several studies have demonstrated the test's safety and its high diagnostic yield. Efforts should be made to standardize both the way in which the SIC is performed and its interpretation as, in view of the pathogenesis of the disease, it is probably the diagnostic test of choice.

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Conflicts of interest

There are no conflicts of interest. Group projects related to the SIC in hypersensitivity pneumonitis are partially supported by FIS PI1001577 (Instituto de Salud Carlos III), SEPAR.

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