

Diagnosing of bakers' respiratory allergy: Is specific inhalation challenge test essential?

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ABSTRACT

The diagnosis of occupational asthma (OA) and/or rhinitis needs to be confirmed by means of objective methods, because it is followed by important social and financial consequences. The aim of the study was to evaluate sensitivity and specificity of diagnostic methods as skin-prick tests (SPTs) to occupational allergens, evaluation of allergen-specific serum IgE, and nonspecific bronchial hyperreactivity with reference to a specific inhalation challenge test in diagnosing bakers' respiratory allergy due to wheat flour. The study group included 358 bakers suspected of having OA due to wheat flour. They underwent physical examination, SPTs to common and occupational allergens, allergen-specific IgE determination, spirometry, nonspecific bronchial challenge, and specific inhalation test. The sensitivity of SPTs to occupational allergens in recognition of baker's rhinitis was low (47.9%) unlike the estimation of allergen-specific IgE (76.4%), with relatively high specificity (77.4 and 68.3%, respectively). Bronchial hyperreactivity ($PC_{20} < 8$ mg/mL) was the most sensitive method, whereas high degree of bronchial hyperreactivity ($PC_{20} < 1$ mg/m³) alone or bronchial hyperreactivity ($PC_{20} < 8$ mg/m³) combined with the skin reactivity to wheat flour was the most specific method of recognizing OA. Neither SPTs to occupational allergens nor evaluation of serum allergen-specific IgE alone or combined with nonspecific bronchial hyperreactivity are characterized by sufficient diagnostic accuracy to replace the specific inhalation challenge test. For the establishment of a definite diagnosis of baker's asthma, specific challenge testing with occupational allergens should be performed.

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The prevalence of occupational asthma (OA) is estimated for 9% of the asthmatic population (range, 5–19%),¹ whereas the incidence of bakers' asthma ranges from 0.334 to 2.46 cases/1000 person-years.² In Poland flour dust is the most frequent cause of OA (51.2% of all cases).³ The prevalence of occupational rhinitis among bakers varies from 18 to 29%.^{4,5} The diagnosis of occupational allergy needs to be confirmed by means of objective methods, because it is followed by important social and financial consequences. The diagnosis of OA requires both the diagnosis of asthma and the establishment of work relatedness by objective means. The aim of the study was to evaluate sensitivity and specificity of diagnostic methods as skin-prick tests (SPTs) to occupational allergens, evaluation of allergen-specific serum IgE, and nonspecific bronchial hyperreactivity with reference to a specific inhalation challenge test in diagnosing bakers' respiratory allergy due to wheat flour.

METHODS

Subjects and Study Scheme

The study group comprised 358 bakers suspected of having occupational allergy due to wheat flour diagnosed at our Department of Occupational Diseases between 1999 and 2009. At that period of time 402 subjects reporting work-related respiratory symptoms with suspected OA or/and allergic rhinitis due to wheat flour were hospitalized. However, subjects in whom the specific inhalation challenge test (SICT) had not been performed ($n = 34$) or with occupational allergy caused by other occupational allergens (α -amylase, $n = 3$; other flours, $n = 6$) and one patient with recognized carcinoid were not enrolled for the study. For the purpose of further analysis, 358 bakers were divided into groups depending on the result of examination and SICT.

The first group comprised 287 patients with rhinitis symptoms who underwent SICT with evaluation of nasal lavage fluid (NLF). In that group, diagnostic relevance analysis was conducted for 123 subjects with occupational allergic rhinitis in comparison with 164 bakers with rhinitis symptoms but negative challenge test. Distinct analysis was performed for subjects with isolated occupational rhinitis (without asthma; $n = 44$).

The second group consisted of 314 patients reporting work-related lower airway symptoms who underwent specific challenge with spirometry and histamine chal-

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lenge test. Diagnostic relevance analysis was conducted for 151 subjects with recognized OA referring to 163 bakers with asthmatic symptoms but with negative SICT, *i.e.*, without recognized occupational allergy. Subjects with isolated occupational rhinitis ($n = 44$) were excluded from this analysis.

The Regional Bioethical Committee approved the study protocol. All of the participants gave their informed consent before the study.

QUESTIONNAIRE

The subjects were administered a questionnaire that was an adaptation of the instrument developed by the International Union against Tuberculosis and Lung Disease.⁶ It included a history of respiratory and skin symptoms, personal and family history of atopy, exposure to pet allergens at home, medication use, and smoking habits.

SKIN-PRICK TESTS

SPTs were performed on the volar part of the forearm with a standard battery of common allergens and bakery series, including tree and grass pollens, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, molds, feathers, α -amylase, oatmeal, wheat, corn, barley, and rye flour (Allergopharma, Reinbek, Germany). Negative control was allergen diluent and the positive control was 1 mg/mL of histamine dihydrochloride solution. The largest wheal diameter was assessed after 15 minutes. A wheal diameter of 3 mm or more and equal to or greater than one-half of that formed by histamine was defined as positive, hence indicating sensitization.

TOTAL AND SPECIFIC IgE

Total serum IgE was evaluated using ImmunoCap (Phadia AB, Uppsala, Sweden). Total IgE level >100 KU/L was considered as elevated. Specific antibodies against wheat flour and α -amylase were measured using the ImmunoCap (f4, k87; Phadia AB, Uppsala, Sweden). IgE levels of >0.35 kU/L were regarded as positive.

INHALATION CHALLENGE TESTS

Specific inhalation challenge tests with wheat flour were performed in a worksite simulation setting (room space, 6 m² with temperature 22–25°C) with the patient's own samples. The patient was sifting ~500 g of wheat flour for 30 minutes or until asthmatic reaction symptoms appeared. Potato flour was used as placebo; the test was performed on the previous day before specific challenge. Measurements of dust concentration in the provocation chamber showed a mean concentration of 33.6 ± 12.3 mg/m³.

The bakers who did not show a significant ($\geq 20\%$) fall in forced expiratory volume in 1 second (FEV₁) during the challenge test underwent a repeated challenge test for 2 hours on the next day. In patients with changes in FEV₁ ranging between 10 and 20% after that challenge, the exposure was prolonged up to 3 hours.

The study participants did not receive any systemic or local medication. Inhaled short-acting β_2 -agonists were stopped at least 6 hours before the study, inhaled long-acting β_2 -agonists were stopped at least 48 hours before the study, inhaled steroids were stopped at least 5 days before the study, and systemic steroids were stopped at least 14 days before the study. Antihistamine medications 7–42 days before challenge test depends on the time of the acting. The patient informed the physician about medication use and about the day when the treatment was stopped.

SYMPTOM SCORE

The number of sneezes and the degree of mucosal edema, rhinorrhea, and itching were evaluated. Total symptom score ranged from 0 to 8 and represented the sum of the scores for sneezing (0 sneezes, 0 points; 1–4 sneezes, 1 point; >4 sneezes, 2 points), rhinorrhea (none, 0 points; mild, 1 point; abundant, 2 points), mucosal edema (none, 0 points; mild, 1 point; nasal block, 2 points), and itching (none, 0 points; itching of the nose or throat, 1 point; itching of the nose and throat, 2 points).⁷

PULMONARY FUNCTION

Resting spirometry (Vicat 2A; Mijnhardt, Odijk, The Netherlands) was performed in all subjects reporting chest symptoms. Bronchial response was measured by serial monitoring of FEV₁ and peak expiratory flow rate before and 5 and 30 minutes and 1, 2, 4, 6, and 24 hours after the provocation.

Histamine challenge was performed according to Cockcroft.⁸ Bronchial response was measured by FEV₁ monitoring. The nonspecific bronchial hyperreactivity was evaluated on the day before the SICT and 24 hours after the test.

NASAL LAVAGE AND CHALLENGE PROCEDURE

All of the procedures were performed as in the “nasal pool” method.⁹ Nasal washings were collected immediately before the provocation and 30 minutes and 4 and 24 hours afterward; the washings processing has been described in detail elsewhere.¹⁰

DIAGNOSTIC CRITERIA

Occupational allergic rhinitis was recognized in subjects reporting work-related nasal symptoms with positive nasal response to provocation test, *i.e.*, total score

Table 1 Characteristic of patients with isolated occupational rhinitis ($n = 44$), occupational rhinitis ($n = 123$), occupational asthma ($n = 151$), and in subjects without occupational respiratory allergy ($n = 163$) participating in the study

	Patients with Recognized		Without Occupational Allergy $n = 163$
	Occupational Rhinitis	Occupational Asthma $n = 151$	
	All $n = 123$	Isolated Occupational Rhinitis $n = 44$	
Age (mean $\pm$ SD) (yr)	35.6 $\pm$ 10.9	37.0 $\pm$ 11.1	41.3 $\pm$ 11.9
Sex: male/female	107:16 (87%:13%)	33:11 (75%:25%)	124:39 (76.1%:23.9%)
Duration of exposure before the incidence of symptoms (mean $\pm$ SD) (yr)	10.8 $\pm$ 7.6	11.6 $\pm$ 8.6	13.2 $\pm$ 9.6
Duration of respiratory symptoms (mean $\pm$ SD) (yr)	5.9 $\pm$ 5.5	5.8 $\pm$ 5.2	7.4 $\pm$ 7.1
Reported symptoms			
Cough	91 (73.9%)	29 (65.9%)	126 (77.3%)
Dyspnea	115 (93.5%)	36 (81.8%)	143 (87.7%)
Rhinitis	123 (100%)	44 (100%)	114 (69.9%)
Skin symptoms	26 (21.1%)	13 (29.5%)	34 (20.9%)
Family history of atopy	35 (28.5%)	14 (31.8%)	35 (21.5%)

of >3 points and significant increase in total count and proportion of eosinophils (twofold increase and eosinophilia at least 5% after challenge) in NLF. OA was recognized in subjects reporting work-related chest symptoms, for whom an SICT induced significant bronchial response (at least a 20% decrease in FEV_1)—early or dual asthmatic reaction or a threefold increase in nonspecific bronchial hyperreactivity accompanied by increase sputum eosinophilia.

STATISTICAL ANALYSIS

The sensitivity, specificity, and predictive values of the applied tests were calculated according to the following formulas¹¹: sensitivity, ($rp/(rp + fn)$); specificity, ($rn/(fp + rn)$); positive predictive value (PPV), ($rp/(rp + fp)$); and negative predictive value (NPV), ($rn/(fn + rn)$) using challenge test results as gold standard. The aforementioned abbreviations are defined as follows: right positive (rp) results (bakers with positive SICT and positive specific IgE/positive SPT/result of histamine PC_{20}); false positive (fp) results (bakers with negative SICT and positive specific IgE/positive SPT/result of histamine PC_{20}); false negative (fn) results (bakers with positive SICT and negative specific IgE/negative SPT/result of histamine PC_{20}); and right negative (rn) results (bak-

ers with negative SICT and negative specific IgE/negative SPT/result of histamine PC_{20}).

RESULTS

The study group consisted of 291 male and 67 female subjects. The rates of symptoms reported are presented in Table 1. In patients with OA, the latency period, *i.e.*, duration of exposure before the occurrence of symptoms, was 10.9 ± 7.9 years and the duration of those symptoms was 6.7 ± 6.6 years. Among patients with occupational allergy, the longest latency period was observed in patients with isolated occupational rhinitis (11.6 ± 8.6 years), but, equally, the duration of those symptoms was the shortest one. It should be also noted that most patients with isolated rhinitis, in whom asthma was not recognized, reported such symptoms as cough and dyspnea. In 79 patients suffering from OA occupational rhinitis was also recognized.

The results of SPT to common and occupational allergens are presented in Tables 2 and 3. In bakers with both occupational rhinitis and OA the most frequent allergens yielding positive results were *D. pteronyssinus*, *D. farinae*, and grass pollens. Among occupational allergens the most frequent positive results were wheat and rye flour. Twenty-five subjects with OA had positive SPT to another kind of flour and did not show sensitization in SPT to wheat and rye flour.

Table 2 The results of skin-prick tests (SPT) to common and occupational allergens in patients with suspected occupational rhinitis

SPT ⁺ to	Patients with Work-Related Rhinitis			
	All <i>n</i> = 287	Result of Specific Challenge Test (nasal lavage)		
		Positive		Negative <i>n</i> = 164
		Isolated Rhinitis <i>n</i> = 44	Rhinitis and Asthma <i>n</i> = 123	
At least one common allergen	152 (52.9%)	25 (56.8%)	81 (65.9%)	71 (43.3%)
At least one occupational allergen	162 (56.4%)	28 (63.6%)	93 (75.6%)	69 (42.1%)
α -Amylase	20 (6.9%)	2 (4.5%)	14 (11.4%)	6 (3.7%)
Wheat flour	96 (33.4%)	16 (36.4%)	59 (47.9%)	37 (22.6%)
Rye flour	95 (33.1%)	16 (36.4%)	65 (52.8%)	30 (18.3%)
Corn flour	37 (12.9%)	4 (9.1%)	29 (23.6%)	8 (4.9%)
Oatmeal flour	36 (12.5%)	3 (6.8%)	25 (20.3%)	11 (6.7%)
Barley flour	56 (19.5%)	5 (11.4%)	39 (31.7%)	17 (10.4%)

Table 3 The results of skin-prick test (SPT) to common and occupational allergens in patients with suspected occupational asthma

SPT ⁺ to:	Patients with Work-Related Chest Symptoms		
	All <i>n</i> = 314	Results of Specific Challenge Test	
		Positive <i>n</i> = 151	Negative <i>n</i> = 163
At least one common allergen	158 (50.3%)	89 (58.9%)	69 (42.3%)
At least one occupational allergen	147 (46.8%)	100 (72.8%)	47 (28.8%)
α -Amylase	18 (5.7%)	12 (7.9%)	6 (3.7%)
Wheat flour	86 (27.4%)	63 (41.7%)	23 (14.1%)
Rye flour	86 (27.4%)	69 (45.7%)	17 (10.4%)
Corn flour	37 (11.8%)	30 (19.9%)	7 (4.3%)
Oatmeal flour	36 (11.5%)	32 (21.2%)	4 (2.4%)
Barley flour	57 (18.2%)	48 (31.8%)	9 (5.5%)

The results of evaluation of total and allergen-specific IgE are presented in Table 4. Total IgE level was elevated in all groups and a significant percentage of subjects with >100 kU/L of IgE were found. Allergen-specific IgE to wheat flour was found in 76.4% of patients with occupational rhinitis and in 61.6% with OA.

SICT did not cause spirometric changes or bronchial hyperreactivity (average PC₂₀, 11.2 ± 5.4 mg/mL before provocation, 9.9 ± 5.9 mg/mL after provocation) in patients with isolated rhinitis. Among patients with isolated rhinitis two subjects (4.5%) in histamine test revealed significant bronchial hyperreactivity (PC₂₀ < 1 mg/mL), results from 1 to 8 mg/mL were obtained in five subjects. On the other hand, seven subjects (4.6%) with OA did not reveal bronchial hyperreactivity before SICT. It was induced in the result of specific aller-

gen exposure. Twenty-three bakers (14.1%) revealed significant bronchial hyperreactivity (PC₂₀ < 1 mg/mL) despite the fact that they had negative results of SICT (data not presented in Tables).

The sensitivity, specificity, and predictive value of diagnostic methods in recognition of baker's rhinitis are presented in Table 5. The sensitivity of SPT to occupational allergens was low (47.9%) unlike the estimation of allergen-specific IgE (76.4%), with relatively high specificity (77.4 and 68.3%, respectively).

The sensitivity, specificity, and predictive value of diagnostic methods in recognition of baker's asthma are presented in Table 6. Bronchial hyperreactivity (PC₂₀ < 8 mg/mL) was the most sensitive method, whereas high degree of bronchial hyperreactivity (PC₂₀ < 1 mg/m³) alone or bronchial hyperreactivity (PC₂₀ < 8 mg/m³) combined with the skin reactivity to

Table 4 The results of evaluation of total and specific IgE level among patients with occupational rhinitis, occupational asthma, and in subjects without occupational respiratory allergy

	Patients with Recognized				
	Negative <i>n</i> = 164	Rhinitis		Occupational Asthma <i>n</i> = 151	Without Occupational Allergy <i>n</i> = 163
		Occupational Rhinitis			
		Isolated <i>n</i> = 44	All <i>n</i> = 123		
Total IgE, level kU/L (mean ± SD)	208.9 ± 172.6	275 ± 275.3	311.6 ± 355.2	283.7 ± 318.5	221.6 ± 180.3
Range of concentration, kU/L (minimum, maximum)	2–1000	6–1150	6–2260	29–2260	5–1000
Total IgE, >100 kU/L	59 (35.9%)	19 (43.2%)	61 (49.6%)	76 (50.3%)	60 (36.8%)
asIgE to occupational allergens:	58 (35.4%)	33 (75%)	100 (81.3%)	102 (67.5%)	43 (26.4%)
asIgE to wheat flour	52 (31.7%)	32 (72.7%)	94 (76.4%)	93 (61.6%)	37 (22.7%)
asIgE to α-amylase	16 (9.8%)	6 (13.6%)	23 (18.7%)	25 (16.6%)	12 (7.4%)

Table 5 Sensitivity, specificity, and predictive value of diagnostic methods in recognition of occupational rhinitis

Test	Sensitivity	Specificity	PPV	NPV
Isolated rhinitis (<i>n</i> = 44)				
SPT to wheat flour	36.4%	77.4%	30.2%	81.9%
Serum asIgE to wheat flour	72.7%	68.3%	46.4%	90.3%
Rhinitis with or without asthma (<i>n</i> = 123)				
SPT to wheat flour	47.9%	77.4%	61.5%	66.5%
Serum asIgE to wheat flour	76.4%	68.3%	64.4%	79.4%

NPV = negative predictive value; PPV = positive predictive value.

Table 6 Sensitivity, specificity, and predictive value of diagnostic methods in recognition of baker's asthma

Test	Sensitivity	Specificity	PPV	NPV
SPT to wheat flour	41.7%	85.9%	73.3%	61.4%
Serum asIgE to wheat flour	61.6%	77.3%	71.5%	68.5%
Bronchial hyperreactivity, PC ₂₀ < 1 mg/m ³	42.4%	85.9%	73.6%	61.7%
Bronchial hyperreactivity, PC ₂₀ < 8 mg/m ³	67.6%	73.6%	70.3%	71%
SPT to wheat flour and bronchial hyperreactivity, PC ₂₀ < 8 mg/m ³	58.3%	89.1%	79.8%	69.2%
Serum asIgE to wheat flour and hyperreactivity, PC ₂₀ < 8 mg/m ³	47.7%	87.7%	78.3%	64.4%
SPT and/or asIgE to wheat flour and hyperreactivity, PC ₂₀ < 8 mg/m ³	49.7%	86.5%	77.3%	65%

NPV = negative predictive value; PPV = positive predictive value; SPT = skin-prick test.

wheat flour was the most specific method of recognizing OA.

DISCUSSION

Diagnostic process of OA must answer two main questions. The first one is if the patient suffers from asthma and, if yes, the next question is if this is asthma induced by workplace allergens. It is also important to distinguish OA and work-aggravated asthma with symptoms due to irritant substances or exercise.¹²

The consequences of such diagnosis are important. In many countries, where recognition of OA is not associated with financial compensation, the patient is not interested in obtaining this diagnosis or leaving his/her work. However, there are some countries, *e.g.*, Poland or Germany, where diagnosis of occupational respiratory allergy lead to significant compensation for employees. In these cases, both the clinical history and the peak expiratory flow measurements in the workplace may not be a sufficient diagnostic tool. Baur *et al.*¹³ showed that 41% of German bakers reporting breathing difficulties in the workplace do not show any signs of bronchial hyperresponsiveness. It seems that claiming compensation plays a very important role in such cases. Therefore, diagnosis of occupational respiratory allergy must be conducted very accurately with the most objective methods to prove the occupational origin of reported symptoms.¹⁴

The clinical history, conducted mostly as a questionnaire, is the first important part of the allergic disease diagnostic process also in OA. Malo *et al.*¹⁵ establish that questions about improvement of symptoms on weekends and vacations had the highest sensitivity of 77 and 88% and specificity of 44 and 24%, respectively. Authors also indicated that the PPV of the questionnaire is 63% and NPV is 83%. The questionnaire being a considerably sensitive method, but with a low specificity¹⁶ is not usually an efficient tool in detecting new cases of OA.¹⁷ There is a lack of generally accepted questionnaires for epidemiological or clinical studies in OA.^{16,18}

Assessment of sensitization is the next diagnostic stage in occupational allergy and includes skin tests and/or specific IgE measurement. Particularly, SPTs are easily available and often used as the first diagnostic step in cases when occupational respiratory allergy is suspected. In our study SPTs to wheat flour was characterized by sensitivities of 47.9 and 41.7% in recognizing occupational rhinitis and asthma, respectively. Specificity of SPTs was much higher (~80%). Also, Sander *et al.*¹⁹ revealed the low sensitivity SPTs to wheat flour, which appropriately amounted to 50 and 40% for ALK (Copenhagen, Denmark) and Bencard (Neuss, Germany) extracts and to rye flour (67 and 45%). Similarly, van Kampen *et al.*²⁰ showed that pro-

ducers' dependent discrepancies in sensitivity of SPT extracts for wheat flour ranged from 38 to 88%, and specificity was between 84 and 95%. Moreover, authors showed that the tests sensitivity with individual flour extracts depends on the protein content. It is higher if more proteins at different molecular weight are contained in SPT extract.^{19,20} The highest sensitivity (68% for wheat flour SPT) solution was described by van Kampen *et al.*²¹; simultaneously, specificity was 74%, PPV was 74%, and NPV was 68%. On the other hand, comparison of specific SPTs to SICT for patients exposed to high molecular weight agents revealed sensitivity and specificity to be 80.6 and 59.6%, respectively.²²

In comparison with SPT, estimation of serum-specific IgE was a more sensitive method in diagnostics of occupational rhinitis and OA (76.4 and 61.6%, respectively), but with lower specificity (68.3 and 77.3%, respectively). In the diagnosis of bakers' asthma van Kampen *et al.* showed specificity of 68%, sensitivity of 87%, PPV of 74%, and NPV of 82% for wheat flour-specific IgE.²¹ There is general agreement that allergen-specific IgE estimation *in vitro* is more sensitive but less specific test than SPTs¹⁶ and positive results are found also among patients non-sensitized to this allergen.²³

SICT is a gold standard for the diagnosis of OA and bakers' allergy.¹⁶ Therefore, reference point for evaluation of diagnostic accuracy of each method was the result of SICT, evaluated by spirometric changes and bronchial hyperreactivity in case of asthma and evaluation of changes in NLF when diagnosing rhinitis. In most studies SICT has been used as the main standard for the diagnosis of OA²² (reference point to determine final diagnosis), but there are opinions that SICT should be considered as a "reference standard" rather than the "gold standard"²⁴ as it is mainly painted. The control group comprised bakers reporting respiratory symptoms but without occupational allergy. Therefore, even subjects with isolated occupational rhinitis were excluded from the asthma control group, because of the possibility of the presence of inflammation of the bronchial mucosae in some rhinitic patients.²⁵

The fp and fn results of provocation challenge tests may be a problem. The fp results can result from discontinuing antiasthmatic treatment among patients with severe asthma. This case should be detected in placebo challenge tests. Therefore, placebo challenge tests preceded specific inhalation tests, moreover monitoring measurement of airborne dust/allergen concentration during challenge usually allowed to avoid irritating effects. The high levels of wheat flour concentrations (high dust levels) during specific challenge tests may cause an irritant effect, especially in patients with asthmatic bronchial hyperreactivity. De Zotti *et al.*²⁶ showed that the risk of such effect can be only ruled out among patients not sensitized to flour

and without nonspecific bronchial hyperreactivity. Nevertheless, there are patients with atopic asthma caused by common aeroallergens and without sensitization to occupational factors in whom SICT can induce obturation and rhinitic symptoms. Such cases require objective diagnostic methods.

Even a greater problem are the fn results. It is easy to identify a group of patients who did not stop bronchodilator or steroid treatment—this situation may be related to fn results. However, there are subjects with normalization of their nonspecific bronchial reactivity after removal from workplace exposure. In some cases, it is necessary to reexpose the patient to the occupational agent in the workplace for a few days, to determine significant decrease in FEV₁ or increase in nonspecific bronchial hyperreactivity.²⁷ Lemiere *et al.*²⁸ conclude that specific bronchial reactivity to high-molecular-weight agents persists in most cases despite a normalization of nonspecific bronchial reactivity, and this is associated with a persistence of specific immunization.

SICT performed according to a previously described protocol allowed us to exclude patients without OA. It is highly improbable that the bakers who did not show any changes in FEV₁ or in PC₂₀ in specific challenge during 2 days time could develop an asthmatic reaction later.²⁹ In the present study, such prolongation of duration of SICT was needed in 14 cases to reveal a positive result of the test. Some patients with normal baseline bronchial reactivity showed an increase in nonspecific bronchial hyperreactivity induced by a specific challenge.²⁷ In our study, seven bakers without signs of bronchial hyperreactivity before specific challenge developed hyperreactivity afterward. Moreover, the increase in nonspecific bronchial hyperreactivity was found in many patients with OA. Changes in bronchial hyperreactivity are an early, very sensitive marker of bronchial response to allergen inhalation. Recurrent and significant (at least threefold increase) increase in bronchial hyperreactivity, even without spirometric changes during the challenge, are sufficient to recognizing OA.²⁹

On the other hand, neither fn results nor “ignored” asthma cases are found among currently exposed employees without bronchial hyperreactivity.¹⁶ In our study, histamine challenge test (PC₂₀ < 8 mg/mL) was characterized by sensitivity of 67.6% and specificity of 73.6%. Especially high specificity (nearly 90%) was found for the combination of positive result of histamine test and sensitization to occupational allergens. For comparison, in a study by Beach *et al.*,²² the sensitivity of 79.3% and specificity of 51.3% of a single nonspecific bronchial provocation test to SICT for high molecular weight agents were described. Furthermore, a single nonspecific bronchial provocation test and specific SPT in combination among subjects exposed to

high molecular weight agents showed a sensitivity of 60.6% and specificity of 82.5%.²² In a case of asthma due to latex, Vandenplas *et al.*³⁰ showed that the SPT to latex had the highest—100% sensitivity and predictive value—and histamine challenge sensitivity yielded 90%, specificity was 7%, PPV was 68%, and NPV was 25%.

Contrary to our results, van Kampen *et al.*²¹ concluded that a high concentration of flour-specific IgE in the sera or clearly positive SPT results with flour extracts in symptomatic bakers are a good indicator for a positive inhalation challenge test with flours. Thus, in such cases, specific challenges may be dispensable. Authors suggested that challenge tests with flours should be considered preferably in subjects with low-grade or without specific sensitization.²¹

CONCLUSIONS

Results of our study indicate that neither SPTs to occupational allergens nor evaluation of serum allergen-specific IgE alone or combined with nonspecific bronchial hyperreactivity are characterized by sufficient diagnostic accuracy to replace the specific inhalation challenge test. For the establishment of a definite diagnosis of baker's asthma, specific challenge testing with occupational allergens should be performed.

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