

occupational and environmental lung diseases

Inhalation Challenge With Bovine Dander Allergens*

Who Needs It?

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Study objectives: To identify which tests would be useful in selecting patients for a specific inhalation challenge with bovine dander allergens (bSIC).

Design: A prospective study.

Setting: A university hospital.

Patients: Thirty-seven dairy farmers with a clinical suspicion of occupational asthma due to bovine allergens.

Interventions: Each patient (n = 27) underwent histamine challenge, mannitol challenge, exhaled nitric oxide (NO) measurement, bovine-specific serum IgE measurement, and skin-prick test (SPT) with bovine allergens prior to undergoing a bSIC.

Results: Eleven patients responded to the inhalation challenge with bovine allergens. The sensitivity and specificity of the tests, based on this response, were 82% and 65%, respectively, for the histamine challenge; 20% and 94%, respectively, for the mannitol challenge; 27% and 77%, respectively, for the NO measurement; 82% and 100%, respectively, for the bovine-specific serum IgE measurement; and 100% and 50%, respectively, for the SPT. Multiple regression analysis revealed that only IgE-mediated sensitivity to bovine allergens, but neither bronchial hyperreactivity nor exhaled NO concentration, contributed significantly to the response.

Conclusion: Only the SPT with bovine allergens and bovine-specific serum IgE measurements were useful in selecting patients for the bSIC. This challenge should not be performed in SPT-negative subjects. A diagnosis of occupational asthma due to bovine dander allergens could be made without an inhalation challenge test in asthmatic patients with high bovine-specific serum IgE levels. This practice would eliminate the need for the majority of bSICs. (CHEST 2003; 124:383-391)

Key words: agricultural workers' diseases; asthma; bovine; bronchial provocation tests; cow; diagnosis; occupational diseases

Abbreviations: CI = confidence interval; bIgE = bovine-specific IgE; bSIC = specific inhalation challenge with bovine dander allergens; NO = nitric oxide; NPV = negative predictive value; PC = provocative concentration; PC₂₀ = provocative concentration of a substance causing a 20% fall in FEV₁; PD = provocative dose; PEF = peak expiratory flow; PPV = positive predictive value; RDR = response/dose ratio; SIC = specific inhalation challenge; SPT = skin-prick test

Farming increases the risk of asthma more than any other occupation in Finland, and the incidence rate of occupational asthma is high among farmers.^{1,2} Bovine dander allergens are responsible

for most cases of occupational asthma among Finnish farmers, with 60 to 110 new cases being recorded annually.³ Specific inhalation challenge (SIC) with an occupational agent is thought to be the most

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reliable method for establishing a diagnosis of occupational asthma, and a more frequent use of this test has been encouraged.^{4,5}

However, SIC is a time-consuming and expensive method that is often carried out on an inpatient basis. Although it is usually well-tolerated, one has to bear in mind that SIC can provoke severe acute reactions, as well as a late reaction. In addition, it can induce an exacerbation of asthma, with recurrent nocturnal symptoms lasting for several days.⁴ Due to these economic and ethical reasons, the selection of patients to undergo SICs should be done with care.

Occupational asthma can be caused by low-molecular-weight agents or high-molecular-weight agents, and the bovine dander allergens belong to the latter group.^{6,7} In the case of high-molecular-weight allergens, the early response to SIC may be predicted with a knowledge of bronchial responsiveness to either histamine or methacholine, and of the level of allergen sensitization either by skin test or by measuring the serum level of specific IgE.^{8–14} Therefore, the performance of an SIC to a high-molecular-weight allergen may not be mandatory in all cases of occupational asthma, and the main diagnostic indication of SIC may be its use in asthmatic subjects with a low-degree allergy.¹⁵ The problem is how to identify those patients who would benefit most from an SIC.

For several reasons, the selection of patients for SICs may be especially demanding in farmers. First, the suspicion of occupational asthma easily arises in them. One in every three dairy farmers complains of lower airways respiratory symptoms,¹⁶ and as many as 14% of dairy farmers in Finland show a positive skin-prick test (SPT) response for bovine allergens.¹⁷ Second, the demonstration of a temporal relationship between asthmatic symptoms and work exposure is difficult in dairy farmers, as they actually live in their working environment and usually work 7 days a week rather than 5 days. Even if a temporal relationship could be demonstrated, it does not necessarily indicate the presence of occupational asthma since preexisting asthma also can be aggravated in the dusty environment of a farm.¹⁸ This far, even a negative response to an SPT with bovine allergens has not been an exclusion criterion for an SIC with bovine dander allergens (bSIC), since subjects with a negative response to an SPT also have been reported to respond to bovine dander allergens.¹⁹ These facts have led to a high number of referrals for bSICs in our institute. However, the majority of the results of these challenges are negative, and thus there is a need to improve the means of selection of subjects who should undergo a bSIC.

In this study, we examined whether histamine challenge, mannitol challenge, exhaled nitric oxide

(NO) measurement, serum bovine-specific IgE (bIgE) measurement, or SPT with bovine allergens could help in identifying which patients should be subjected to bSIC.

MATERIALS AND METHODS

Subjects

We recruited 38 consecutive dairy farmers who were referred to our laboratory because of a suspicion of occupational asthma due to bovine allergens. All had been referred by a respiratory physician, and the suspicion was based on a temporal relationship between work in a cow shed and asthmatic symptoms and/or ambulatory peak expiratory flow (PEF) variations. Exclusion criteria were unstable asthma, $FEV_1 < 65\%$ of predicted,²⁰ and respiratory tract infection within the last 6 weeks. One patient was excluded because he had responded positively to a sham challenge. The basic characteristics of the remaining 37 subjects are given in Table 1. Before hospital admission, 30 patients had a doctor's diagnosis of asthma. SPTs for common and agricultural allergens (*ie*, cow, storage mites, rye, oat, wheat, and barley) had been performed before the study (Soluprick SQ; ALK Abelló, Hørsholm, Denmark).

The subjects were asked not to work in the cow shed and to measure their PEF (Mini Wright; Clement Clarke International; Harlow, UK) twice daily during the week before hospital admission. They were also asked to withhold therapy with inhaled steroids for 1 week, with leukotriene receptor antagonists for 3 days, with antihistamines for 3 days, with inhaled long-acting β_2 -adrenoreceptor agonists for 48 h, and with anticholinergic agents for 8 h prior to hospital admission. During the study, short-acting β_2 -agonist agents were the only permitted medication, but they were withheld for 6 h before each challenge.

The institutional ethics committee approved this study (approval No. 113/99), and all subjects gave their informed written consent for participation in the study.

Study Design

The patients were hospitalized. From the day of arrival, PEF was monitored every 4 h (Wright peak flowmeter; Aired Ltd; London, UK). On the second and the third day, histamine and mannitol challenges were performed in a random order. On the fourth day, and in the following order, a blood sample was collected for the measurement of bIgE and total IgE concentrations. The exhaled NO concentration was measured, a sham inhalation challenge and further SPTs were performed. On the fifth day, a bSIC was performed. If the result of the bSIC was negative, and if the prestudy SPTs had shown sensitization to some other agricultural allergens, an SIC using the allergen with the greatest skin reaction was performed on the next day. All inhalation challenges were performed at the same time of the day. The patient left the ward on the day after undergoing the last inhalation challenge.

SPTs

SPTs during the study were performed in duplicate, on the volar side of each forearm, by the same nurse. The extracts were bovine dander solution for skin testing (1:100 w/v), bovine dander solution for inhalation challenges (1:100 w/v), histamine (10 mg/mL), an SPT-negative control solution, and 0.9% NaCl. After 15 min, the wheals were measured. The

Table 1—Basic Characteristics of the Subjects and the Results of the Various Tests*

Variable	Responders to bSIC (n = 11)	Nonresponders to bSIC (n = 26)	p Value
Gender, No.			
Female	7	17	
Male	4	9	
Age, yr	40 (35–45)	44 (40–47)	
Current smokers, No.	4	1	
Users of inhaled steroids, No.	9	20	
FEV ₁ , % of predicted	92 (81–102)	92 (86–97)	0.99
Total IgE, † IU/L	213 (148–308)	68 (42–111)	0.005
bIgE, † IU/L	16 (5–50)	0.6 (0.5–0.9)	< 0.0001
Skin response to bovine allergens, mm	4.9 (3.1–6.7)	2.1 (1.4–2.8)	0.0006
RDR to histamine, † % fall in FEV ₁ /mg	26.2 (7.9–86)	7.4 (4.3–13)	0.02
PC ₂₀ for histamine, † ‡ mg/mL	1.8 (0.9–3.6)	4.8 (2.8–8.3)	0.02
RDR to mannitol, † % fall in FEV ₁ /mg (n = 27)	0.007 (0.002–0.025)	0.004 (0.002–0.009)	0.4
Exhaled NO, † ppb	30 (18–49)	23 (17–30)	0.31

*Values given as mean (95% CI) unless otherwise noted. ppb = parts per billion.

†Values given as geometric mean (95% CI).

‡Calculated from those subjects in whom at least a 20% fall in FEV₁ was obtained during the histamine challenge (bSIC responders, 9 subjects; bSIC the nonresponders, 13 subjects).

diameters were calculated with the following formula: maximum diameter + minimum diameter/2. The mean value of the duplicates was used for analysis, and a value of ≥ 3 mm was considered to be positive.²¹

Measurement of Total IgE and bIgE

Commercial tests were used for the determination of total serum IgE levels (Immulate 2000 Total IgE chemiluminescence enzymeimmunoassay; Diagnostic Products Corporation; Los Angeles, CA) and bIgE (UniCAP FEIA fluoroenzymeimmunoassay; Pharmacia & Upjohn Diagnostics AB; Uppsala, Sweden). The antigens in this test were of bovine dander origin. A cutoff value for an abnormal bIgE was defined as 5 IU/L. It was the lower limit of the 95% confidence interval (CI) for bIgE in the responders to bSIC.

Measurement of NO

Exhaled NO was measured using a commercial device (model 280 Nitric Oxide Analyzer; Sievers Instruments, Inc; Boulder, CO), according to the manufacturer's instructions. A cutoff value for an abnormal NO concentration was defined as 46 ppm, which was calculated as the mean + 2 SDs of a healthy population studied in our laboratory using a similar method.²²

Histamine Challenge

Histamine challenge was performed according to the method of Cockcroft et al²³ but using a dosimetric nebulizer (Spira Electro 2; Respiratory Care Center; Hämeenlinna, Finland). The nebulization time was 0.4 s, and was set to start 100 mL after the beginning of inspiration. The peak inspiratory flow did not exceed 0.5 L/s. The nebulization pressure was 200 kPa. These settings gave a calibrated output of 6.5 μ L per inhalation.²⁴ First, spirometry was performed three times. The subject then inhaled normal saline solution 30 times using normal tidal volume respiration, and the spirometry was repeated once at 30 and 90 s following the inhalation. The lower postsaline solution inhalation FEV₁ was used as the reference value. This was followed by a similar inhalation of histamine solutions from 0.03 to 16 mg/mL

in doubling concentrations, with a 5-min interval between each concentration, measured from the beginning of each inhalation. The challenge continued until the FEV₁ had fallen 20%, or until the maximal concentration had been administered.

The provocative concentration of a substance causing a 20% fall in FEV₁ (PC₂₀) was calculated by the linear interpolation of the relationship between the percentage decrease in FEV₁ and the concentration of histamine required to provoke this decrease. A cutoff value for a positive response was defined as a PC₂₀ of 8 mg/mL.²³ The response/dose ratio (RDR) of the histamine challenge was calculated as the percentage fall in FEV₁ after the last dose, divided by the noncumulative dose, in milligrams.

Mannitol Challenge

This challenge was performed according to Anderson et al.²⁵ Due to a delay in obtaining permission from the local authority to perform the mannitol challenge, only 27 patients underwent this challenge. Spray-dried mannitol powder, packed in gelatin capsules containing 5 to 40 mg, was inhaled by the patient using an inhalator (Boehringer Ingelheim Pty LTD; Ingelheim, Germany) until the FEV₁ had fallen 15%, or until the maximal dose of 635 mg had been administered. The provocative dose (PD) of a substance causing a 15% fall in FEV₁ was calculated as described, but the RDR values were calculated using cumulative doses. A cutoff value for a positive response was defined as a fall in FEV₁ of > 15%.

bSIC

The bovine dander allergen solution (Soluprick SQ; ALK Abelló) was delivered via the dosimetric nebulizer. The nebulization time was 0.8 s and was set to start 50 mL after the beginning of inspiration. The peak inspiratory flow did not exceed 0.5 L/s. The nebulization pressure was 200 kPa. These settings were estimated to give an output of 13 μ L per inhalation.²⁴ The subject inhaled each solution 10 times using normal tidal volume respiration and a nose clip.

First, FEV₁ was measured in triplicate, and the greatest value was used as the baseline in the calculations. Then the patient inhaled the allergen solution with doubling concentrations from a

concentration of 0.02 mg/mL until the FEV₁ had fallen 15% or until the maximal concentration of 10 mg/mL had been administered. FEV₁ was measured in duplicate 10 min after each concentration was inhaled. The test was considered to be positive if the FEV₁ fell > 15%. The provocative concentration (PC) of a substance causing a 15% fall in FEV₁ and the RDR-bSIC were calculated as described, using cumulative doses. PEF was measured in triplicate before and immediately after the challenge, then once each hour for 8 h, and subsequently every fourth hour until the next morning to reveal any late reactions. The sham challenge was identical to the bSIC but utilized 0.9% NaCl, with three exposures and 10 inhalations each time.

Statistical Analysis

The results are expressed as the mean and 95% CI. The RDR, PC, and PD values, as well as the IgE and NO concentrations, are geometric means with 95% CIs. These values were log-transformed before all statistical analysis.

The comparison between responders and nonresponders was performed using the Student *t* test. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for each test were calculated based on the response to the bSIC. To create a formula with which to predict the individual sensitivity to a bSIC, simple and multiple regression analyses were used. In this analysis, RDR values were used instead of PD or PC values because RDR values can be calculated for all subjects, not just for responders to the various challenges. A *p* value of < 0.05 was considered to be statistically significant.

RESULTS

Of the 37 patients who completed the study, 11 patients responded to the bSIC, whereas 26 did not. These groups did not differ with respect to age, sex distribution, inhaled steroid usage, and baseline lung function (Table 1). Two subjects who had negative responses to the bSIC responded to other agricultural allergens (*ie*, barley flour and storage mite *Tyrophagus putrescentiae*), but they were analyzed as nonresponders. None of the subjects who did not have a doctor's diagnosis of asthma before the study responded to the bSICs or to any other SICs. As mentioned, only 27 subjects underwent the mannitol challenge. Of them, 10 responded to bSICs. There were no late responders (defined as a > 20% fall in PEF 3 to 8 h after the challenge). The bovine solution for skin testing induced slightly larger skin

wheals than did the bovine solution for inhalation challenges (3.4 mm [95% CI, 2.6 to 4.2 mm] and 2.9 mm [95% CI, 2.1 to 3.7 mm], respectively; *p* = 0.005), but the correlation between the skin responses to the two solutions was close (*r* = 0.92; *p* < 0.0001).

The main results are expressed in Tables 1 and 2. The NPV for an SPT response to a bovine solution for skin testing of < 3 mm was 100%, and the PPV of a bIgE of > 5 IU/L was 100% (Fig 1). In the simple regression analysis, SPT response to bovine solution for inhalation challenges was shown to have the strongest association with RDR-bSIC (*r* = 0.65; *p* < 0.0001; Fig 2). The association between bIgE and RDR-bSIC (*r* = 0.59; *p* = 0.0001; Fig 3) was also clearly stronger than that between the RDR of the histamine challenge and RDR-bSIC (*r* = 0.30; *p* = 0.07; Fig 4). The RDR of the mannitol challenge, NO level, or prechallenge FEV₁ percent of predicted did not show a statistically significant association with RDR-bSIC.

In the multiple regression analysis, the dependent variable was again RDR-bSIC. As mentioned, of the single variables, SPT response to bovine solution for inhalation challenges showed the strongest association with it (*r* = 0.65; *r*² = 0.42). Adding bIgE to the model raised the *r*² to 0.46. However, it did not increase further after adding the RDR of the histamine challenge to the model. The following equation could be created:

$$\log \text{RDR-bSIC} = 0.126 \times \text{SPT} + 0.223 \\ \times \log \text{bIgE} + 0.427 \text{ (} r^2 = 0.46; p < 0.0001 \text{)}$$

DISCUSSION

This study confirmed that clinical history has a poor predictive value for establishing an association between workplace exposures and asthma.^{5,26} Only 13 of the 37 farmers (35%) with a clinical suspicion of occupational asthma actually responded to the SIC with occupational allergens. This figure is less than that reported by Malo et al.²⁶ In that study, of

Table 2—Sensitivity, Specificity, PPV, and NPV for Each Test, Based on the Response to bSIC*

Test	Responders to bSIC, No.	Nonresponders to bSIC, No.	Sensitivity, %	Specificity, %	PPV, %	NPV, %
bIgE > 5 IU/L	9/11	0/26	82	100	100	93
Bovine skin reaction ≥ 3 mm	11/11	13/26	100	50	46	100
Histamine PC ₂₀ ≤ 8 mg/mL	9/11	9/26	82	65	50	89
FEV ₁ fall > 15% in mannitol challenge	2/10	1/17	20	94	67	67
Exhaled NO > 46 ppb	3/11	6/26	27	77	33	71

*See Table 1 for abbreviations not used in the text.

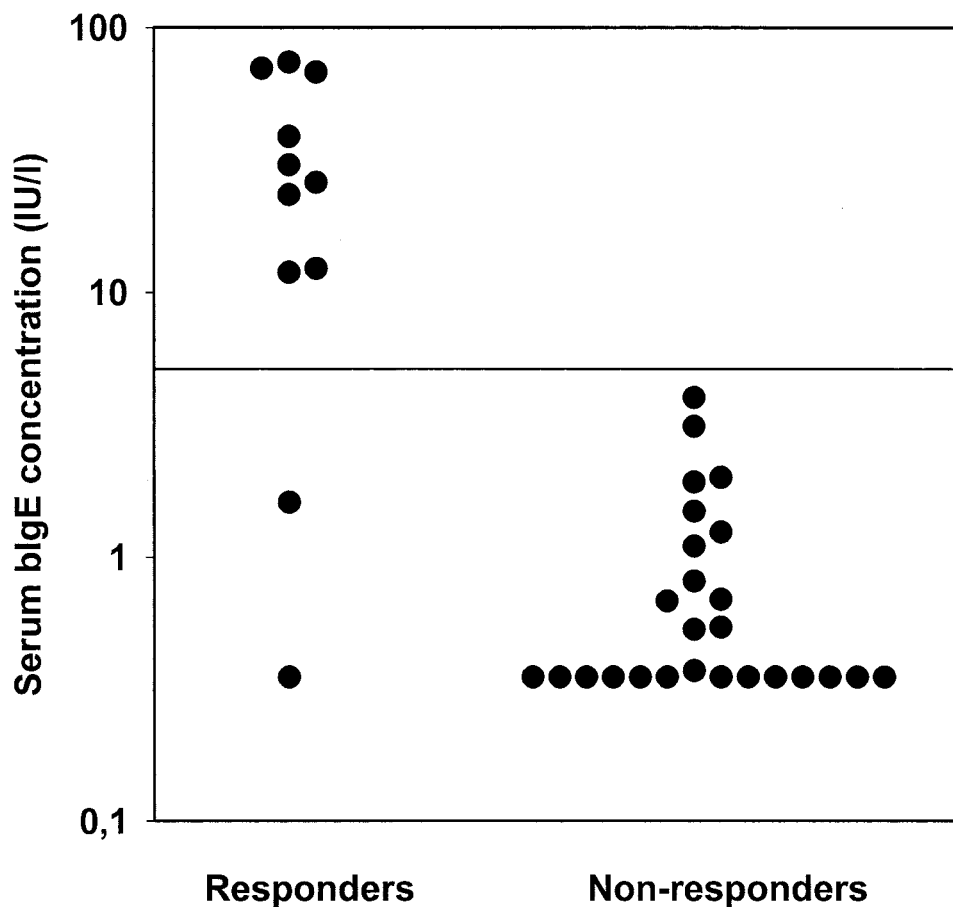


FIGURE 1. Serum bIgE values in farmers who responded to bSICs and in those who did not. In the subjects with no measurable level of bIgE, a value of 0.35 IU/L was given. The horizontal line indicates bIgE value of 5 IU/L, which was the lower limit of the 95% CI for bIgEs in the responders.

the 162 subjects who were referred due to a suspicion of occupational asthma, 75 (46%) were objectively shown to have occupational asthma. These subjects represented a wide variety of occupations. Our finding reflects the special difficulties the clinicians encounter when assessing the probability of occupational asthma among farmers and highlights a need for screening tests. We were able to demonstrate that simple tests, namely, SPTs and bIgE tests, can be used effectively for selecting patients for bSICs. These findings are clinically important, not only from the viewpoint of avoiding a challenge with potential for prolonged effects but also from an economic viewpoint, because challenge requires in-patient care and time lost from work.

The major bovine allergen is Bos d 2, a protein of the lipocalin family.²⁷ Subjects with occupational, cattle-associated asthma respond to an inhalation challenge with purified Bos d 2.²⁸ Bos d 2 is produced in sweat glands and is transported to the skin surface as a carrier of the pheromone ligand.²⁹ Therefore, cow dander preparations

probably include Bos d 2. Indeed, the concentration of Bos d 2 recently has been measured²⁸ from the commercial bovine inhalation challenge solution (ALK) that was used in our study, and it was 5.7 $\mu\text{g/mL}$. In the present study, bovine skin test solutions, bovine inhalation challenge solutions, as well as bovine antigens in the IgE analysis were all of bovine dander origin. Therefore, we think that these tests were valid in the diagnosis of bovine asthma.

Simply by measuring bIgE, 35 of 37 patients (95%) could have been classified correctly without being subjected to bSIC. The PPV of bIgE > 5 IU/L was 100%. Accordingly, in the study of Taivainen et al,³⁰ all 19 patients with a bIgE level of > 3.5 IU/L responded to bSICs. Cow-allergic farmers with asthma have clearly higher bIgE levels than do cow-allergic farmers with rhinitis, which probably is explained by the larger size of the shock organ in asthma (*ie*, lungs vs the nose).³¹ Thus, a bIgE concentration of > 5 IU/L seems to be a reliable indicator for an occupational asthma induced by

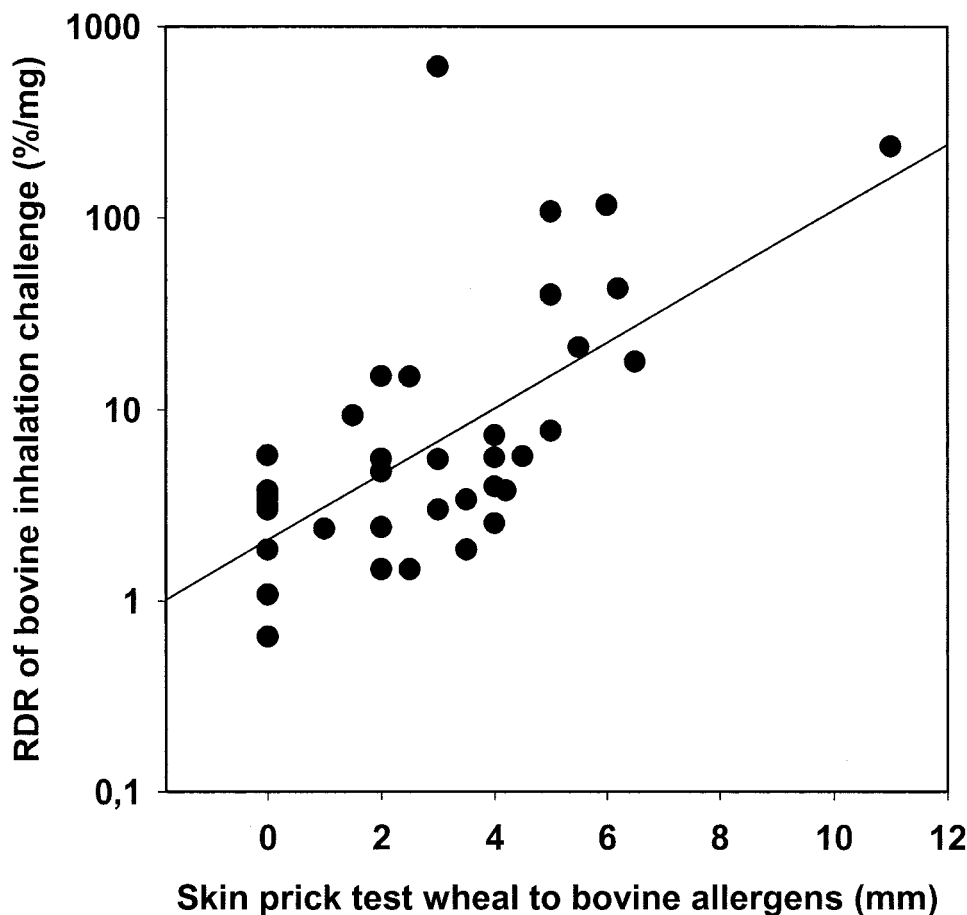


FIGURE 2. The association between the SPT wheal induced by the bovine allergen solution and the response to the inhalation challenge with the same solution, expressed as the RDR ($r = 0.64$; $p < 0.0001$).

bovine allergens, bearing in mind that not all responders to bSICs have bIgE levels above that level.

Although the specificity of a positive SPT result was poor, the sensitivity was high, and the NPV was 100% (*ie*, none of the subjects with an SPT wheal of < 3 mm responded to bSICs). In the study of Taivainen et al,³⁰ the sensitivity of SPT was 94%. Thus, a negative result in SPT virtually excludes bovine asthma. This finding contrasts that of Aas,¹⁹ who reported that even 32% of symptomatic but skin test-negative subjects responded to SICs with various animal danders, including the cow. To our knowledge, there have been no international publications on this issue after that study, which is probably the reason why it has been a common practice in Finland to refer even skin test-negative subjects for bSICs. It is possible that the quality of the allergen extracts was worse in that study, since it is > 30 years old. Our results show that the commonly accepted practice not to perform SICs in skin test-negative individuals⁴ now can be applied to bovine asthma as well.

Our finding that nonspecific bronchial reactivity to histamine lacks specificity in the diagnostics of bovine asthma is in accordance with those of previous studies,⁵ but the finding that histamine was also unhelpful in predicting the responsiveness to bSICs was more surprising. In several previous studies,^{8–12,14} the degree of nonspecific airway reactivity has been shown to be an important determinant of a response to SICs. Our findings are probably due to the very high prevalence of bronchial hyperreactivity in farmers.^{32,33} Iversen et al³² found that as high as 59% of asymptomatic Danish farmers were hyperreactive to histamine. A farming environment subjects the respiratory system to many different substances, not just cow dander. These include a variety of dusts, bacteria, endotoxins, and spores, as well as irritant gases like ammonia, all of which may contribute to the high prevalence of nonspecific bronchial hyperreactivity in farmers.^{18,32} These features of the farming environment probably explain the low specificity of histamine challenge

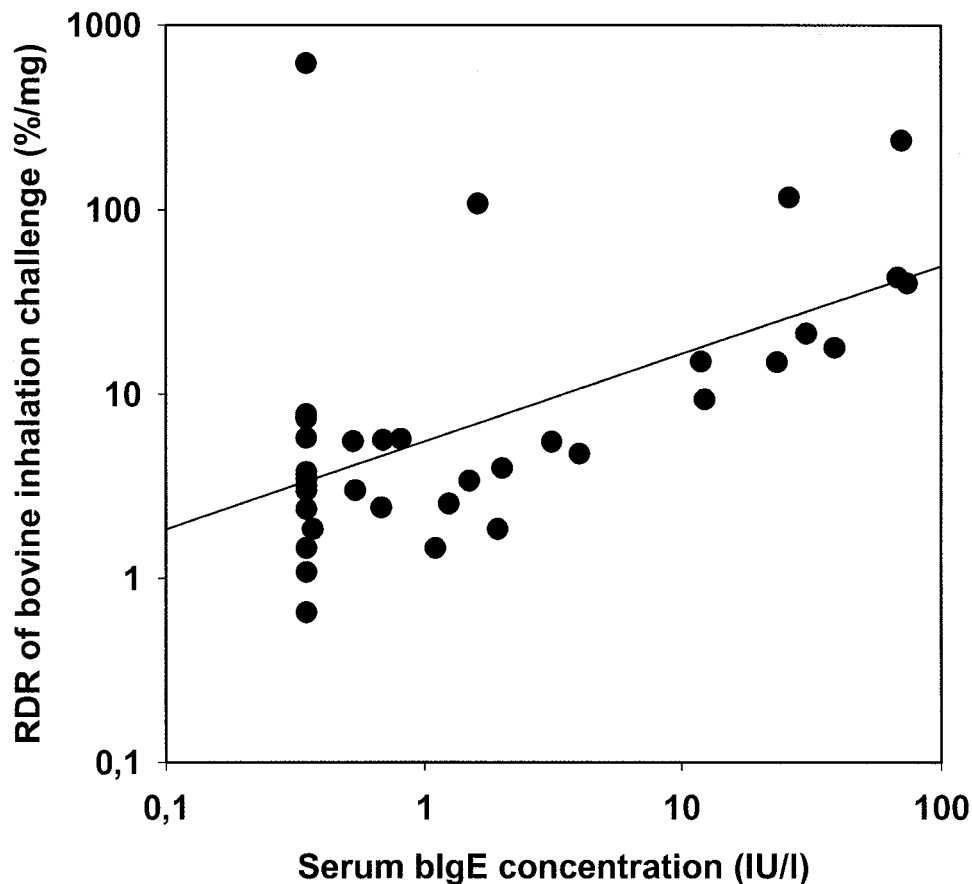


FIGURE 3. The association between serum bIgE concentration and the response to the inhalation challenge with bovine allergens, expressed as the RDR ($r = 0.59$; $p = 0.0001$). In the subjects with no measurable level of bIgE, a value of 0.35 IU/L was given.

in the diagnosis of bovine asthma, and the poor correlation between histamine reactivity and responsiveness to bSICs. It seems clear that bronchial hyperreactivity in a farmer is not an indication to perform an SIC.

It has been suggested that an indirectly acting bronchial stimulus, like mannitol, would better reflect the degree of airway inflammation than a direct-acting stimulus like histamine.³⁴ Therefore, we wanted to study whether the correlation between mannitol challenge and allergen challenge would be stronger than that between histamine challenge and allergen challenge. However, the majority of our patients with bovine asthma did not respond to mannitol, and this response did not correlate significantly with bSIC results, suggesting that mannitol challenge is not useful in selecting patients for bSICs. The main reason for this lack of responsiveness is probably the widespread use of inhaled corticosteroids in our study population since even a treatment of 6 to 8 weeks with inhaled budesonide greatly decreases the airway response to inhaled mannitol.³⁵

Only 9 of our 37 patients had an abnormally high NO concentration in their exhaled air. Again, this probably reflects the common use of inhaled corticosteroids among our patients.³⁶ The exhaled NO concentration did not differ between bSIC responders and nonresponders. Our results corroborate those of Obata et al,³⁷ who could not show any difference in prechallenge NO levels between those who responded to inhaled plicatic acid and those who did not. Furthermore, the exhaled NO level did not correlate with the bSIC results. Thus, NO level proved to be unhelpful both for screening patients for bSICs and for predicting the individual sensitivity to bSICs.

None of the six subjects who did not have a doctor's diagnosis of asthma responded to bSICs. Although the number of these patients was small, this finding suggests that the diagnosis of asthma should be established clearly before referring a subject for an SIC. This recommendation is present, though not emphasized, in international guidelines.^{4,15} An objective confirmation of asthma before considering an SIC may be especially important in

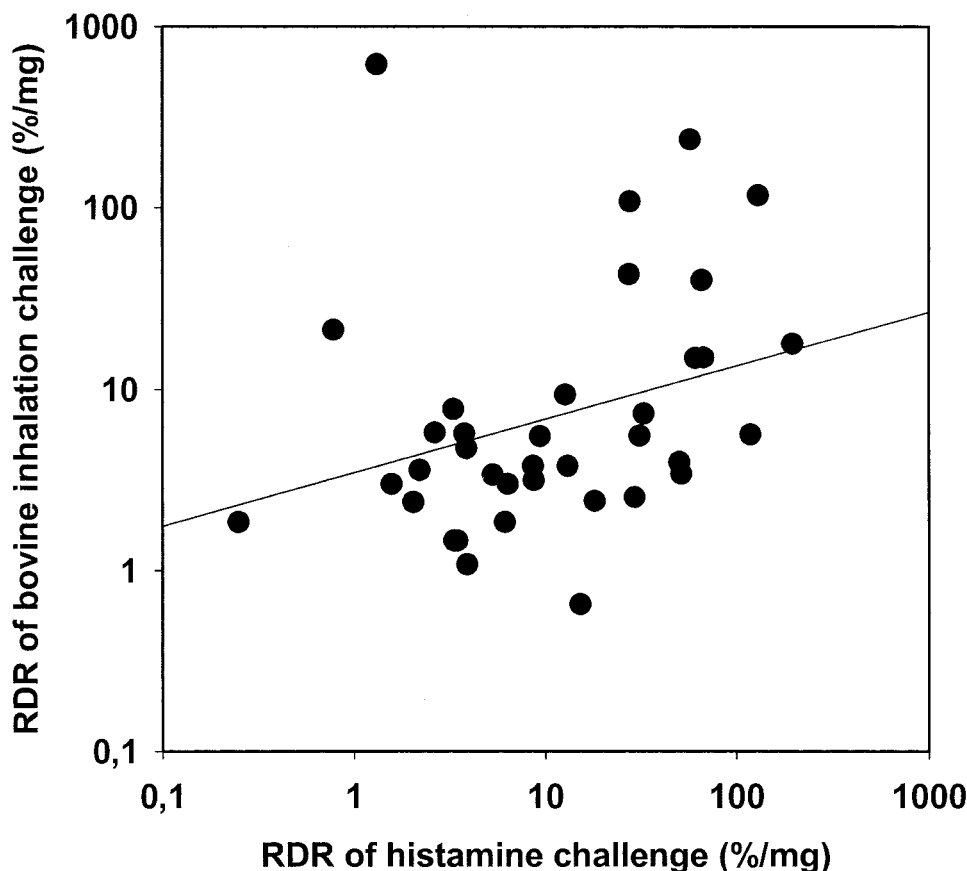


FIGURE 4. The association between bronchial responsiveness to histamine, expressed as the RDR, and the response to the inhalation challenge with bovine allergens, also expressed as the RDR ($r = 0.30$; $p = 0.07$).

farmers, who have a high prevalence of lower airway respiratory symptoms that often are of nonasthmatic origin.¹⁶

Our study can help in reducing the number of bSICs performed, which could lead to remarkable cost savings. We recommend that bSICs should not be performed in SPT-negative patients, given the 100% NPV of this test. Furthermore, a diagnosis of occupational asthma from exposure to bovine allergens could be made without performing a bSIC in asthmatic patients with a bIgE concentration of > 5 IU/L. Thus, only asthmatic patients with SPT reactions to bovine allergens of wheals > 3 mm in size and with < 5 IU/L serum bIgE concentrations should be subjected to bSICs. An analysis of the subjects studied here using these recommendations would have meant that 24 of 37 bSICs (65%) could have been avoided without misclassifying any subject. Assuming that in other laboratories in Finland the proportions of positive and negative responses to bSICs are the same as those in our laboratory, and that the annual incidence of bovine asthma is

about 100 in Finland,³ approximately 340 bSICs must be carried out annually. In our study, 65% of bSICs could have been avoided. Extending our recommendations to the national level would mean about 220 bSICs fewer per year.

In conclusion, although SIC is the “gold standard” for the documentation of occupational asthma,^{4,5} the high prevalence of respiratory symptoms and bronchial hyperreactivity in farmers may lead to a very high demand for access to this expensive test. In the case of asthma due to bovine dander allergens, this study shows that it is possible to reduce the numbers of bSICs without impairing the accuracy of a bovine dander asthma diagnosis. Only asthmatic farmers with an SPT reaction to bovine allergens of a wheal > 3 mm in size and with a < 5 IU/L serum bIgE concentration should be subjected to bSICs. This conclusion supports the view of the European Academy of Allergology and Clinical Immunology,¹⁵ which states that the main diagnostic indication for the performance of an SIC is its use in asthmatic subjects with a low-degree allergy.

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