
Persistence of bronchial reactivity to occupational agents after removal from exposure and identification of associated factors

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Objectives: To examine the outcome of specific bronchial reactivity to occupational agents in patients with occupational asthma who have been removed from exposure to the offending agents and to identify risk factors for the persistence of specific bronchial reactivity.

Data Sources: A PubMed (National Library of Medicine) search of articles published from January 1, 1985, through December 31, 2001, with the keywords *occupational asthma* and *bronchial reactivity* was performed.

Study Selection: This article represents a synthesis of these PubMed sources and the opinion of the author.

Results: Specific bronchial reactivity persists in most cases even a long time after removal from exposure to the offending agents. This condition does not seem to be correlated with the persistence of bronchial reactivity to methacholine but seems to be related to the persisting level of specific IgE to the occupational agents in the case of high-molecular-weight agents and platinum salts.

Conclusions: Patients who have been diagnosed as having occupational asthma are at risk of developing an asthmatic reaction in the minutes following re-exposure to the offending agent, even if they no longer experience asthma symptoms, have normalized their bronchial reactivity, and have not been exposed to the offending agent for years. It is, therefore, crucial that these patients remain unexposed to the agent that caused their occupational asthma.

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INTRODUCTION

The course of occupational asthma (OA) after removal from exposure is variable. Approximately 25% of workers with OA experience a significant improvement of their asthmatic symptoms and normalize their pulmonary function and bronchial reactivity to methacholine after removal from exposure, whereas most workers with OA continue to have active disease even after removal from exposure.^{1,2} This condition may persist for several years, although the outcome is more favorable in patients who have been unexposed for 5 years or more.³ The main prognosis factors identified so far are the duration of exposure before and after the onset of asthmatic symptoms, the severity of asthma at the time of the diagnosis, and the type of asthmatic reaction induced by specific inhalation challenges. The presence of specific IgE to isocyanates seems to be a good prognosis factor, probably because the diagnosis is made earlier in the patients who show high levels of specific IgE to isocyanates.⁴ The presence of airway inflammation at the time of the diagnosis may also be a prognostic factor.⁵ However, the prognosis factors identified for OA relate more to the persistence of asthmatic symptoms or

persistence of bronchial reactivity to methacholine or histamine than to the persistence of specific bronchial reactivity (SBR) to occupational agents. Recent evidence shows that the outcome of SBR may be different from the outcome of bronchial reactivity to methacholine.⁶

This study was performed to examine the outcome of SBR to occupational agents in patients with OA who have been removed from exposure to the offending agents and to identify risk factors for the persistence of SBR. A PubMed (National Library of Medicine) search of articles published from January 1, 1985, through December 31, 2001, with the keywords *occupational asthma* and *bronchial reactivity* was performed. This article represents a synthesis of these PubMed sources and the opinion of the author.

OUTCOME OF SBR

The outcome of SBR and the factors that affect it are less well known. Some investigators have described a decrease or loss of SBR to the offending agents after removal from exposure in selected case reports. This phenomenon has been described primarily with reference to low-molecular-weight agents.

However, the cessation of asthmatic symptoms does not ensure that the workers will not experience additional asthmatic reactions on reexposure to the offending agents. The SBR to isocyanates,^{7–9} platinum salts,¹⁰ and high-molecular-

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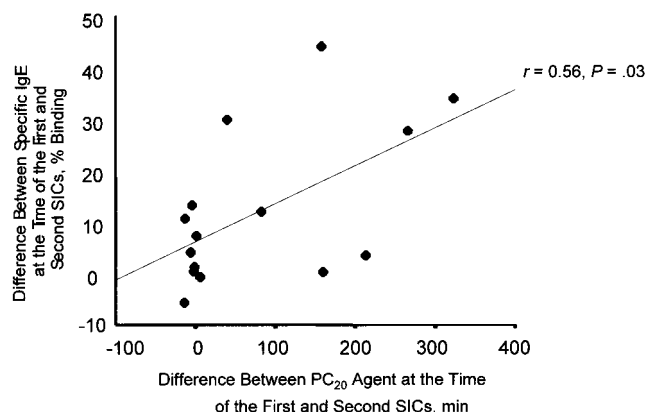


Figure 1. Positive correlation between the difference in the concentration of methacholine inducing a 20% decrease in forced expiratory volume in 1 second (PC_{20} agent) at the time of the first and second specific inhalation challenges (SICs) and the difference in specific IgE level at the time of the first and second SICs.

weight agents⁷ has been assessed several years after removal of patients from exposure. In those studies, 20 to 40% of patients did not have asthmatic reactions on re-exposure to isocyanates, whereas 12% did not have asthmatic reactions on reexposure to high-molecular-weight agents.

In a study by Mapp et al,⁹ 35 patients with OA due to toluene diisocyanate (TDI) previously diagnosed by specific inhalation challenges (SICs) were exposed to TDI 10 months after the first challenge.⁹ Eight (23%) of the 35 patients with OA due to TDI previously diagnosed by SIC did not experience an asthmatic reaction on reexposure to isocyanates 10 months later. The dose of methacholine inducing a 20% decrease in forced expiratory volume in 1 second (FEV_1) was higher in these patients than in those who experienced an asthmatic reaction on reexposure. Paggiaro et al⁸ re-exposed 16 patients with OA due to TDI 48 months after the first SIC to this agent in the same manner. Nine of these patients did not experience any change in FEV_1 after re-exposure to isocyanates. There was an improvement in bronchial reactivity to methacholine only in those patients who had a negative SIC result at the time of the second challenge. Merget et al¹⁰ re-exposed 24 patients with OA due to platinum salts to the same agent 19 months after removal from their workplace. These patients had the same SBR to platinum salts as at the time of diagnosis.

We studied 15 patients with OA (8 to a high- and 7 to a low-molecular-weight agent, isocyanates in all instances) proved by SICs performed at least 2 years after the diagnosis.⁷ Patients were re-exposed at least 2 years after the diagnosis in the same way as during the initial SIC. There was a significant improvement in bronchial reactivity to methacholine in 7 of the 15 patients. Nine (60%) of the 15 patients had a decrease in their SBR, whereas 4 patients kept the same

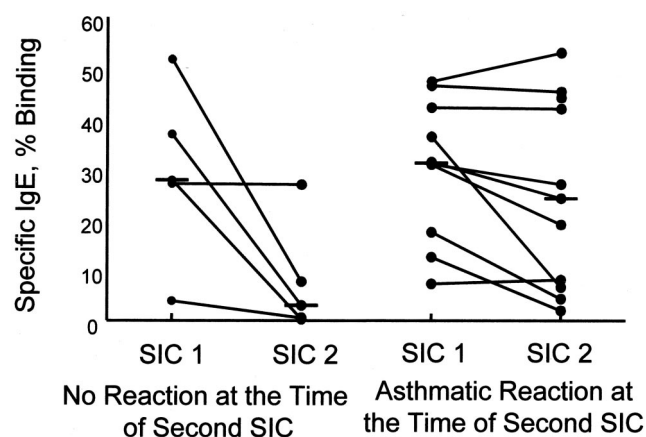


Figure 2. Changes in levels of specific IgE in patients who did and did not experience an asthmatic reaction after the second specific inhalation challenge (SIC). Medians are represented by horizontal lines.

SBR after removal from exposure. Among the patients who had a decrease of their SBR, only 1 had a complete loss of SBR. The decrease in SBR could not be explained by changes in bronchial reactivity to methacholine, molecular weight of the offending agent, decrease of antibody level against offending agents, or duration of exposure at work. After removal from exposure to the offending agent, most patients (60%) showed decreased but persistent SBR to high- and low-molecular-weight agents.

CORRELATION OF SBR WITH BRONCHIAL REACTIVITY TO METHACHOLINE OR HISTAMINE

In the late 1950s, Tiffeneau¹¹ hypothesized that SBR to common inhalants was related to both non-SBR and specific immunological reactivity; later, others confirmed this hypothesis.¹²⁻¹⁴ Some authors set an equation to predict the concentration of allergen needed to induce an asthmatic reaction based on the concentration of methacholine inducing a 20% decrease in FEV_1 and the wheal diameter of the skin prick test.¹² Those studies were performed in asthmatic patients with mild-to-moderate bronchial hyperreactivity. However, the relationship between bronchial reactivity to methacholine or histamine and SBR may not be as good for occupational agents as it is for common inhalants.

In 1996, Merget et al¹³ found no correlation between methacholine reactivity and SBR to platinum salts in 57 patients with OA due to platinum salts. The SBR was not correlated with bronchial reactivity to methacholine. On the contrary, there was a correlation between skin reactivity and SBR to platinum salts.

More recently, we investigated 16 patients with previously diagnosed OA caused by high-molecular-weight agents in our center to determine whether they retained a measurable SBR

to these agents despite normalization of bronchial reactivity to methacholine at the time of the study.⁶ Two patients exposed to guar gum were also part of our previous study.⁷ The patients had been exposed to flour in 7 instances, psyllium in 5, and guar gum in 4. They had been removed from exposure to these agents for a mean $\pm$ SD of 5.7 ± 4.0 years, no longer showed evidence of persisting asthma, and had a normal lung function. The workers were re-exposed to the same sensitizing agent by SICs, in the same way as at the time of the diagnosis, to assess their current SBR to the sensitizer. Eleven of the 16 patients had an asthmatic reaction at the time of the study; the duration of exposure necessary to induce the asthmatic reaction was the same as that needed at the time of diagnosis. In this study, the patients who experienced an asthmatic reaction had not improved their SBR, despite improvement and normalization of their bronchial reactivity to methacholine. Bronchial hyperreactivity might modulate the severity of SBR, but it does not appear to be a prerequisite for the occurrence of an asthmatic reaction after exposure to a sensitizer.

SBR AND SPECIFIC IMMUNIZATION

The SBR seems to be more correlated with specific immunization than with bronchial reactivity to methacholine. Indeed, Merget et al¹³ found a correlation between skin reactivity and SBR to platinum salts, whereas there was no correlation between SBR and bronchial reactivity to methacholine. We found a positive correlation between the decrease of the level of specific IgE to occupational agents and the decrease of SBR to occupational agents after removal from exposure in patients who became asymptomatic after removal from exposure to the offending agent (Figure 1).⁶ The decrease in specific IgE levels between the diagnosis and the re-exposure to the offending agent was much greater in the patients who did not react to the second SIC than in those who reacted on both occasions (Figure 2).⁶

The SBR to high-molecular-weight agents persists in most cases despite a normalization of bronchial reactivity to methacholine, and this persistence is associated with a persistence of specific immunization to the agent. It seems that a certain amount of specific IgE is mandatory for demonstrating SBR. Bryant et al¹⁴ clearly demonstrated the strong correlation between SBR to common inhalants and the concentration of specific IgE to the same allergens in asthmatic patients. An association between the severity of asthmatic reaction after allergen challenge and the level of sensitization to the allergen has also been shown with common allergens.¹⁵ A high amount of specific IgE might indicate a high risk of developing an asthmatic reaction in case of re-exposure to the allergen that previously caused the OA, even in patients who no longer complain of asthmatic symptoms and have normalized their non-SBR. Indeed, despite a complete disappearance of asthmatic symptoms, absence of treatment, and a normal bronchial reactivity to methacholine, patients with a high amount of specific IgE reacted to the offending agent within a few minutes of exposure.

CONCLUSION

It is crucial that patients with OA stay away from work, even if they no longer complain of asthmatic symptoms and have normalized their non-SBR. Indeed, these patients could develop a severe asthmatic reaction within a few minutes of re-exposure, even a long time after removal from exposure to the agent.

REFERENCES

1. Chan-Yeung M, MacLean L, Paggiaro P. Follow-up study of 232 patients with occupational asthma caused by western red cedar (*Thyja plicata*). *J Allergy Clin Immunol*. 1987;79:792-796.
2. Park HS, Nahm DH. Prognostic factors for toluene diisocyanate-induced occupational asthma after removal from exposure. *Clin Exp Allergy*. 1997; 27:1145-1150.
3. Perfetti L, Cartier A, Ghezzi H, Gautrin D, Malo JL. Follow-up of occupational asthma after removal from or diminution of exposure to the responsible agent: relevance of the length of the interval from cessation of exposure. *Chest*. 1998;114:398-403.
4. Piirila PL, Nordman H, Keskinen HM, Luukkonen R, Salo SP, et al. Long-term follow-up of hexamethylene diisocyanate-, diphenylmethane diisocyanate-, and toluene diisocyanate-induced asthma. *Am J Respir Crit Care Med*. 2000;162:516-522.
5. Paggiaro P, Bacci E, Paoletti P, Bernard P, Dente F, et al. Bronchoalveolar lavage and morphology of the airways after cessation of exposure in asthmatic subjects sensitized to toluene diisocyanate. *Chest*. 1990;98:536-542.
6. Lemiere C, Cartier A, Malo JL, Lehrer SB. Persistent specific bronchial reactivity to occupational agents in workers with normal nonspecific bronchial reactivity. *Am J Respir Crit Care Med*. 2000;162:976-980.
7. Lemiere C, Cartier A, Dolovich J, Chan-Yeung M, Grammer L, et al. Outcome of specific bronchial responsiveness to occupational agents after removal from exposure. *Am J Respir Crit Care Med*. 1996;154:329-333.
8. Paggiaro PL, Vagaggini B, Dente FL, Bacci E, Bancalari L, et al. Bronchial hyperresponsiveness and toluene diisocyanate: long-term change in sensitized asthmatic subjects. *Chest*. 1993; 103:1123-1128.
9. Mapp C, Corona P, Marzo ND, Fabbri L. Persistent asthma due to isocyanates: a follow-up study of subjects with occupational asthma due to toluene diisocyanate. *Am Rev Respir Dis*. 1988; 137:1326-1329.
10. Merget R, Reineke M, Rueckmann A, Bergmann E, Schultze-Werninghaus G. Nonspecific and specific bronchial responsiveness in occupational asthma caused by platinum salts after allergen avoidance. *Am J Respir Crit Care Med*. 1994;150:1146-1149.
11. Tiffeneau R. Hypersensibilité cholinergo-histaminique pulmonaire de l'asthmatique: relation avec l'hypersensibilité allergénique pulmonaire. *Acta Allergol*. 1958;Suppl:187-221.
12. Cockcroft D, Murdock K, Kirby J, Hargreave F. Prediction of airway responsiveness to allergen from skin sensitivity to allergen and airway responsiveness to histamine. *Am Rev Respir Dis*. 1987;135:264-267.

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13. Merget R, Dierkes A, Rueckmann A, Bergmann E, Schultze-Werninghaus G. Absence of relationship between degree of nonspecific and specific bronchial responsiveness in occupational asthma due to platinum salts. *Eur Respir J*. 1996;9: 211–216.
 14. Bryant D, Burns M, Lazarus L. The correlation between skin tests, bronchial provocation tests and the serum level of IgE specific for common allergens in patients with asthma. *Clin Allergy*. 1975;5:145–157.
 15. Witteman AM, Mulder M, Aalberse RC, Jansen HM, van der Zee JS. Bronchial allergen challenge in subjects with low levels

of allergic sensitization to indoor allergens. *Allergy*. 1999;54: 366–374.

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