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Background: **Specific and nonspecific bronchial responsiveness may decline or disappear after cessation of exposure in the workplace in patients with occupational asthma, leading to false-negative specific inhalation challenge (SIC) results.**
Methods: **Twenty-two patients with suspected diisocyanate-induced asthma were studied. SIC with diisocyanates (toluene diisocyanate [TDI] or hexamethylene diisocyanate [HDI]) was carried out in a 7-m^3 dynamic chamber up to a maximum concentration of 19 parts per billion for 120 min. Methacholine inhalation challenges were performed before and 24 h after SIC with TDI or HDI. Patients who did not show an asthmatic reaction after SIC but had a greater than twofold reduction in provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) after the first isocyanate challenge underwent a second isocyanate SIC 2 days later.**
Results: **The first SIC with isocyanates elicited an asthmatic reaction in 13 patients (59%). In five patients who did not show an asthmatic reaction after the first SIC, PC_{20} exhibited more than a twofold reduction. In three of the five patients, a second SIC with isocyanates elicited an immediate positive asthmatic reaction. Therefore, 3 of 16 patients (19%) were ultimately shown to have bronchial responsiveness to isocyanate; occupational asthma was demonstrated due to post-SIC monitoring of bronchial hyperresponsiveness to methacholine.**
Conclusion: **PC_{20} should be systematically assessed before and after SIC with isocyanates in the absence of significant changes in FEV_1 during SIC to avoid false-negative results.**
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Key words: bronchial hyperresponsiveness; inhalation challenge; isocyanates; occupational asthma

Abbreviations: BHR = bronchial hyperresponsiveness; HDI = hexamethylene diisocyanate; PC_{20} = provocative concentration of methacholine causing a 20% fall in FEV_1; SIC = specific inhalation challenge; TDI = toluene diisocyanate

Specific and nonspecific bronchial hyperresponsiveness (BHR) may decline or disappear after cessation of exposure in the workplace in patients with occupational asthma, leading to false-negative specific inhalation challenge (SIC) results.[1–3] It has been documented that an increase in nonspecific BHR after the SIC, despite the absence of significant changes in airway caliber during SIC, may precede the development of an asthmatic reaction to a second SIC with several occupational agents,[1] but has not been specifically studied in isocyanate-induced asthma. Moreover, Kopferschmitt-Kubler et al[4] described a significant increase in nonspecific BHR after a neg-

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ative isocyanate inhalation challenge result in 7 of 11 patients with a clinical history consistent with isocyanate-induced asthma. However, these authors did not perform a second SIC to confirm bronchial reactivity to isocyanates. The aim of this study was to evaluate prospectively whether the changes in nonspecific BHR in patients with suspected isocyanate-induced asthma before and after SIC could be useful in detecting an initial false-negative isocyanate challenge result.

Materials and Methods

This study included 22 patients with a suspected clinical history of diisocyanate-induced asthma (18 men; age range, 25 to 58 years). Eight patients were atopic, 18 were nonsmokers, and 2 were ex-smokers (Table 1).

Specific IgE to toluene diisocyanate (TDI) and hexamethylene diisocyanate (HDI) was performed by CAP FEIA technique according to the instructions of the manufacturer (Pharmacia; Uppsala, Sweden). A result > 0.35 kU/L was regarded as positive.

All asthma medications were withheld before SIC according to intervals as recommended.[5] Methacholine inhalation test was performed according to Cockcroft et al,[6] with some modifications.[7] The aerosolized particles were generated by a continuous pressurized nebulizer (model 646; DeVilbiss; Somerset, PA) with an output of 0.28 mL/min. The result was expressed as the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}). PC_{20} values < 16 mg/mL were considered to reflect significant BHR.[8]

SIC with TDI were carried out in a 7-m^3 dynamic chamber. A TDI atmosphere was generated in the chamber by passing dry air through TDI contained in a flask and injected into the ultrafiltered air stream in the chamber through a Venturi effect. HDI was nebulized directly into the chamber. Isocyanate concentration was continuously measured with a MDA monitor (model 7100; MDA Scientific; Greenview, IL). On the first day, patients underwent a sham exposure. In the next 2 consecutive days, they were exposed to increasing concentrations of TDI and time intervals of exposure, up to a maximum of 19 parts per billion for 120 min. FEV_1 was measured before exposure, every 10 min during the first hour after SIC, hourly until bedtime, on awakenings, and again the day after. A fall in $FEV_1 \geq 20\%$ from baseline was regarded as a positive asthmatic response. The pattern of asthmatic responses was characterized as immediate, late, dual (immediate followed by a late response), and atypical.

Methacholine inhalation tests were performed before and 24 h after SIC with TDI or HDI. Patients who did not show an asthmatic reaction after SIC but had a greater than twofold reduction in PC_{20} after the first isocyanate challenge underwent a second isocyanate SIC 2 days later.

Results

Nineteen patients were challenged with TDI and three patients received HDI (patients 16, 21, and 22). Patient characteristics and results of challenge tests are summarized in Tables 1, 2, respectively. Four of 22 patients had normal PC_{20} values at baseline. The first SIC with isocyanates elicited an asthmatic reaction in 13 patients (immediate [n = 6], late [n = 1], and dual [n = 6]). Two of these 13 patients had normal PC_{20} values at baseline, but PC_{20} fell within the asthmatic range after SIC with isocyanates. In five patients (patients 1, 2, 16, 17, and

Table 1—*Clinical Characteristics of Patients Included in the Study

Patient No.	Age, yr	Atopy	Smoker	Duration of Exposure, yr	Duration of Symptoms at Work, mo	Last Exposure at Work, mo
1	58	No	No	6	24	1
2	27	No	No	10	8	6
3	25	Yes	No	2.5	7	1
4	57	Yes	No	5	36	0.5
5	55	No	Yes	24	20	6
6	34	No	No	29	40	1
7	35	Yes	No	11	120	1
8	28	No	No	8	72	1
9	40	No	No	14	132	1
10	23	Yes	No	10	12	1
11	36	Yes	No	5	5	1
12	44	No	No	20	60	5
13	30	Yes	No	11	24	1
14	35	No	No	13	110	1
15	26	Yes	No	7	24	12
16	50	No	Yes	35	12	1
17	35	No	No	2	24	1
18	51	No	No	20	60	1
19	39	No	Ex	5	48	1
20	34	No	No	18	72	1
21	46	Yes	No	25	36	1
22	42	No	Ex	20	12	6

*Ex = ex-smoker.

Table 2—*Results of Inhalation Challenges in Patients Included in the Study

Patient No.	Isocyanate Challenge	Baseline PC_{20}, mg/mL	First SIC With Isocyanate, Maximum FEV_1 Fall (%)	Post-SIC PC_{20}, mg/mL	Second SIC With Isocyanate, Maximum FEV_1 Fall (%)	IgE TDI or HDI
1	TDI	> 16	Neg	1.5	I (23)	Neg
2	TDI	3.5	Neg	0.46	I (21)	Neg
3	TDI	1	I (35)	0.36	ND	ND
4	TDI	0.062	L (21)	0.06	ND	Neg
5	TDI	0.7	I (34) L (21)	0.22	ND	ND
6	TDI	0.86	I (21) L (27)	0.25	ND	Neg
7	TDI	0.2	I (29)	0.33	ND	ND
8	TDI	1	I (35) L (20)	0.18	ND	ND
9	TDI	13	I (20)	0.85	ND	ND
10	TDI	ND†	I (42) L (21)	0.62	ND	Neg
11	TDI	> 16	I (30)	10.6	ND	ND
12	TDI	0.3	I (34)	ND	ND	Neg
13	TDI	0.45	I (20)	ND	ND	ND
14	TDI	> 16	I (25) L (27)	13.7	ND	Pos
15	TDI	1.2	Neg	1.2	ND	Neg
16	HDI	2	Neg	0.8	Neg	Neg
17	TDI	10.5	Neg	3.8	Neg	Neg
18	TDI	> 16	Neg	> 16	ND	ND
19	TDI	8	Neg	4	ND	Neg
20	TDI	1.5	Neg	1.8	ND	ND
21	HDI	1	Neg	0.33	I (20)	ND
22	HDI	0.12	I (25) L (33)	0.10	ND	ND

*ND = not done; I = immediate asthmatic reaction; L = late asthmatic reaction; Neg = negative; Pos = positive.
†This patient had a positive bronchodilator test result (> 25% increase of FEV_1 from baseline).

21) who did not show an asthmatic reaction after the first SIC, PC_{20} exhibited a greater than twofold reduction after the isocyanate challenge: 21-fold, sevenfold, 2.5-fold, 2.6-fold, and threefold, respectively. In three patients (patients 1, 2, and 21), a second SIC with isocyanate elicited an immediate asthmatic reaction. In two patients (patients 16 and 17) in whom PC_{20} decreased 2.5-fold and 2.6-fold, respectively, the second isocyanate SIC result was negative. In the 14 patients in whom PC_{20} was monitored after the first isocyanate SIC, it varied from negative to positive in three patients and, in the remaining patients, it showed a reduction that ranged from 0.6-fold to 15.2-fold (mean, fourfold).

Only one of seven patients with SIC-confirmed occupational asthma showed specific IgE to isocyanate. Specific IgE to the incriminated isocyanate was negative in four patients tested with negative SIC results.

Discussion

The proportion of positive SIC results with isocyanates in our series (16 of 22 tests, 73%) is similar to that of previous studies in patients with suspected isocyanate asthma.[9,10] Eight patients (53%) had an immediate asthmatic reaction, including three patients who received a diagnosis after the second SIC, six patients had a dual reaction (40%), and one patient (7%) had a late reaction. In 3 of 16 patients (19%), isocyanate-induced asthma was demonstrated due to post-SIC monitoring of BHR to methacholine. It has been shown that the time interval since the last exposure to the offending agent at work may affect the outcome of specific bronchial responsiveness to occupational agents.[3] The time elapsed since the last exposure at work may have influenced the lack of response to the first SIC in patient 2 (6 months) but was very unlikely in patients 1 and 21 (1 month). These results confirm previous reports that an increase in nonspecific BHR is an early marker of subsequent bronchial response to isocyanates and other agents.[1] The cumulative duration of exposure to isocyanates in our protocol is longer than that used in other studies; therefore, the possibility of underexposure during SIC seems unlikely.

Vandenplas et al[1] reported that one of six patients (16%) with isocyanate-induced asthma required a

second SIC with isocyanates for diagnosis, based on a decrease in the provocative concentration of histamine causing a 20% fall in FEV_1 after the first challenge, a figure similar to our results. However, these authors considered a ≥ 3.1-fold reduction in histamine challenge after SIC to be significant. Lemière et al[11] recommended at least a 1.8-fold decrease in PC_{20} from baseline after exposure to the relevant occupational agent to be clinically significant (sensitivity 73%, specificity 86%). In our series, the patients who received a diagnosis after the second SIC with isocyanates had a greater than threefold reduction in PC_{20}. In two patients (patients 16 and 17), who had 2.5-fold and 2.6-fold reductions in PC_{20}, respectively, the second SIC result was negative. Therefore, the clinical relevance of PC_{20} changes between twofold and threefold after SIC is unclear and may vary from patient to patient. It is also worth mentioning that among the 14 patients with positive SIC results in whom PC_{20} was monitored before and after SIC, it varied from negative to positive in three patients and, in the others, was reduced an average of fourfold.

As observed in this study, specific IgE for isocyanate-protein conjugate antigen is insensitive as a disease marker, since it is found only in a minority of workers with confirmed occupational asthma. However, diisocyanate antigen-specific IgE is rarely demonstrated in workers without occupational asthma.[12,13]

In conclusion, PC_{20} should be systematically assessed before and after isocyanate SIC. This is especially relevant in the absence of significant changes in FEV_1 during SIC. This may help to avoid false-negative SIC results with isocyanates, which in our study represents 19% of the cases. In the evaluation of patients with suspected isocyanate-induced asthma, a threefold or greater decrease in PC_{20} after SIC with isocyanates can be an early and sensitive marker of bronchial reactivity to isocyanates.

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