CHEST

Original Research

ASTHMA

Incidence of Severe Asthmatic Reactions After Challenge Exposure to Occupational Agents

Olivier Vandenplas, MD, PhD; Vinciane D'Alpaos, MSc; Geneviève Evrard, BSc; and Jacques Jamart, MD

Background: **Specific inhalation challenges (SICs) with occupational agents are used to establish the diagnosis and etiology of occupational asthma. The aim of this study was to assess the frequency and determinants of severe asthmatic reactions induced by various occupational agents during SICs performed using realistic methods of exposure.**

Methods: **The SIC records of 335 consecutive subjects with a positive SIC (ie, ≥ 20% fall in FEV_1) due to various occupational agents were reviewed. Asthmatic reactions were graded as moderate when requiring repeated administration of an inhaled short-acting β_2-agonist (SABA) and severe when requiring repeated SABA and systemic corticosteroids.**

Results: **Overall, 68 of the 335 subjects (20%) required an inhaled SABA during the SICs. The multivariate logistic regression analysis showed that the need for an inhaled SABA increased when the SIC involved a low-molecular-weight agent (LMW) (OR, 2.47; 95% CI, 1.43-4.28) and marginally so when the subjects required regular treatment with an inhaled corticosteroid (OR, 1.62; 95% CI, 0.93-2.80). The severity of asthmatic reactions was graded as moderate in 12% and severe in 3% of the subjects. Of the 10 severe reactions, five developed after exposures ≤ 5 min. Multivariate logistic regression analysis showed that challenging subjects with a LMW agent was the only significant determinant for the development of moderate/severe reactions (OR, 3.05; 95% CI, 1.62-5.73).**

Conclusions: **Challenges with LMW agents are associated with a higher risk of an asthmatic reaction requiring pharmacologic treatment. This study may provide useful guidelines for further improving the safety of SICs.** ***CHEST 2013; 143(5):1261–1268***

Abbreviations: HMW = high molecular weight; LMW = low molecular weight; OA = occupational asthma; PC_{20} = provocative concentration of histamine causing a 20% fall in FEV_1; SABA = short-acting β_2-agonist; SIC = specific inhalation challenge

Timely and accurate diagnosis of immunologically mediated (or sensitizer-induced) occupational asthma (OA) is a crucial step in implementing appropriate interventions and minimizing the adverse health and socioeconomic outcomes of OA.[1-3] There is controversy about the procedures that should be used to investigate the work-relatedness of asthma,[2-5] although specific inhalation challenges (SICs) with the suspected occupational agent is still acknowledged as the gold or reference standard method for diagnosing OA.[2,5] The American College of Chest Physicians (ACCP) guidelines recommend performing a SIC when

For editorial comment see page 1196

Manuscript received August 8, 2012; revision accepted October 1, 2012.

Affiliations: From the Department of Chest Medicine (Dr Vandenplas and Mss D'Alpaos and Evrard), and Scientific Support Unit (Dr Jamart), Centre Hospitalier Universitaire de Mont-Godinne; Université Catholique de Louvain, Yvoir; and Fonds des Maladies Professionnelles (Dr Vandenplas), Brussels, Belgium.

Funding/Support: This work was supported by a grant from the Actions de Recherche Concertées de la Communauté Française de Belgique.

Correspondence to: Olivier Vandenplas, MD, PhD, Department of Chest Medicine, Centre Hospitalier Universitaire de Mont-Godinne; B-5530 Yvoir, Belgium; e-mail: olivier.vandenplas@uclouvain.be

© 2013 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details.

DOI: 10.1378/chest.12-1983

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

the diagnosis or causative agent remains equivocal using other tests.[3]

Nevertheless, surveys revealed that in most countries, SIC is very infrequently completed in subjects evaluated for possible OA.[6-9] Potential issues raised by SICs include the lack of availability of appropriate facilities, the time and expertise required to perform these tests, the cost of the procedure, and concerns about false-positive and false-negative results.[3,7,8] Another important barrier to performing SIC is the fear of placing the patients at a significant risk of severe asthmatic reactions. Life-threatening asthmatic reactions have indeed been occasionally described during SICs,[10] although a questionnaire survey of the current practice of SIC among training programs in pulmonary diseases, allergy and immunology, and occupational medicine in the United States and Canada failed to identify unexpected serious adverse reactions among 259 SIC procedures performed during the year 2000.[7] Malo et al[11] reported that a fall in FEV_1 of $\geq$30% occurred in 44% of the subjects challenged with realistic methods, but the authors commented neither on the clinical impact of these exaggerated responses nor on their determinants. Therefore, the aim of this study was to describe the severity of asthmatic reactions recorded in a large series of positive SICs performed using realistic methods of exposure, as well as to identify the factors that are associated with a higher risk of severe reactions.

Materials and Methods

Study Design and Population

All positive SICs, defined by a $\geq$20% fall in FEV_1, that were documented in subjects investigated for possible OA from January 1992 to December 2011 at Mont-Godinne Hospital were reviewed. SICs with the agent(s) suspected of causing work-related symptoms are routinely performed in our center to diagnose OA provided that the baseline FEV_1 is $\geq$60% of predicted value or 2 L. The procedures used in this study were approved by the Comité d'éthique médicale du Centre Hopitalier Universitaire de Mont-Godinne (approval number 54-2011).

Specific Inhalation Challenges

SICs were carried out according to a previously described standardized protocol[12,13] and international recommendations.[14] The protocol of SICs remained unchanged over the reviewed period. Medications were withdrawn according to their duration of action,[14] and inhaled corticosteroids were halted 72 h prior to the tests. On the first day, the subjects were exposed to a control agent for 30 min to ensure that FEV_1 fluctuations were $\leq$12% of the baseline value. On the following day, the subjects were challenged with the suspected occupational agent(s). The duration of exposure was gradually increased (ie, 1 min, 4 min, 10 min, 15 min, 30 min, and 60 min) until a reproducible $\geq$20% fall in FEV_1 occurred or a cumulative exposure of 2 h was completed. The duration of exposure was increased on the first challenge day in a similar way for both high-molecular-weight (HMW) and low-molecular-weight (LMW) agents, although it has been recommended to increase the duration of exposure to LMW agents on separated days.[12,15] This abbreviated protocol of exposure to LMW agents had to be used because of practical constraints. The subjects were challenged with raw materials; exposure to increasing concentrations of HMW agents diluted in lactose powder or saline were used only in eight SICs involving enzymes and previously unreported plant-derived products.[16,17] Those subjects who did not demonstrate $\geq$20% fall in FEV_1 during the first active test day underwent a repeated challenge for a maximum of 2-3 h on the next day.

Occupational agents were generated in 5 m^3 cubicles using an approach aimed at reproducing as close as possible the conditions of exposure at the workplace in terms of the chemical and physical characteristics of the agent.[12,18] For instance, isocyanates were generated in the following semirealistic way: (1) vapors of toluene diisocyanate were obtained by evaporation of pure toluene diisocyanate at ambient temperature; (2) for hexamethylene diisocyanate, the commercial product used at work (usually paint hardeners containing various prepolymers of hexamethylene diisocyanate) were nebulized; and (3) for diphenylmethane diisocyanate, the commercial preparation was heated to about 80°C.[12,18] The level of exposure during SICs was continuously monitored only for isocyanates with an MDA 7100 monitor (MDA Scientific Inc) and kept below the ceiling value of 20 part per billion. Workplace challenges involving serial supervised measurements of FEV_1 during a work shift were carried out in three subjects because work exposure could not be reproduced in the laboratory.

Spirometry[19,20] was obtained at baseline, immediately after each exposure, then every 15 min for the first hour, every 30 min for the second hour, and hourly thereafter for a total of at least 6 h after the end of exposure to both the control and occupational agents. The pattern of bronchial responses was characterized as immediate, late, dual, or atypical, according to previously described criteria.[18,21,22] Atypical reactions were categorized as "prolonged immediate" (ie, similar to immediate, but with a slower recovery over several hours) and "progressive" (ie, starting within minutes after the end of exposure and progressing over the following hours).

Salbutamol 200-400 μg, an inhaled short-acting β_2-agonist (SABA), was administered before the end of the functional follow-up in the laboratory only when bronchoconstriction was not subjectively tolerated by the subjects or when they showed clinical signs of a severe asthmatic reaction (ie, use of accessory muscles, heart rate $>$120 beats/min, respiratory rate $>$30/min, oxygen saturation $<$92%). At the end of the follow-up period in the laboratory, a SABA was given when FEV_1 was $<$90% of the prechallenge value; since 2006, SABAs have been administered systematically before sputum induction.[13] The subjects were instructed to record their peak expiratory flow rates using a portable instrument after leaving the laboratory and to take an inhaled SABA if they were symptomatic and their peak flow fell by $>$20% from their prechallenge value. Oral or IV corticosteroids were administered when the subjects showed signs of acute respiratory distress or failed to show sustained improvement in FEV_1 after repeated doses of inhaled SABA.[23]

Outcomes

The following information was extracted from SIC records: (1) the maximum percentage fall in FEV_1 as compared with the prechallenge value during both the immediate component of the bronchial response (ie, the first 2 h after the end of challenge exposure) and the nonimmediate component (ie, the period from the second hour postexposure onwards) and (2) the timing and dose of medications that were administered between the end of challenge exposure and the next morning. The severity of

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

asthmatic reactions was graded as: (1) moderate (ie, requiring repeated administration of a SABA over the 24-h postexposure follow-up) and (2) severe (ie, requiring repeated SABA and oral or IV corticosteroids).

Data Analysis

Quantitative data are presented as median with 25th and 75th percentiles. Comparison between subgroups of subjects was made using the χ^2 test for categorical variables and the Wilcoxon rank-sum test for numerical variables. The incidences and 95% CI were estimated using the exact method based on F distribution. Multivariate logistic regression analysis was conducted to evaluate the determinants of moderate or severe reactions and asthmatic reactions requiring an inhaled SABA. The variables meeting a $P \leq .1$ value criterion in univariate comparisons were incorporated into these regressions performed with backward selection by Wald test. All statistical tests are two-tailed. A P value $< .05$ was considered significant. Statistical analysis was performed using the SPSS Statistics 19.0 software (IBM).

Results

The total number of subjects who completed an SIC procedure during the 1992 to 2011 period was 713; 335 subjects (47%) showed a positive response in terms of the changes in FEV_1. A positive SIC was caused by HMW agents in 206 subjects (61%) and LMW agents in 123 subjects (37%); the causal agent remained indeterminate in six cases. Among the HMW substances, latex was the main causative agent (n = 91, 27%), followed by flour and cereals (n = 89, 27%), and various enzymes (n = 14, 4%). The principal LMW causal agents were metals (n = 24, 7%), isocyanates (n = 23, 7%), wood dusts (n = 21, 6%), quaternary ammonium compounds (n = 10, 3%), and persulfate salts (n = 8, 2%).

Asthmatic Reactions

The distribution of the maximum falls in FEV_1 during the SICs is illustrated in Figure 1. The median (25th-75th percentile) maximum decline in FEV_1 at any point during the follow-up period was 29% (25%-39%). One hundred sixty-seven (50%) subjects developed a $\geq 30\%$ fall in FEV_1, including 151 subjects (45%) during the immediate component of the bronchial response and 49 (15%) during the nonimmediate component.

Overall, 68 of the 335 subjects (20%; 95% CI, 16-25%) were administered an inhaled SABA. Fifty-seven (84%) of these subjects required a SABA during the follow-up period in the laboratory; of these, 29 received a SABA during the immediate component of the bronchial response. Ten of the 57 subjects (18%) had to take additional SABA after leaving the laboratory. Of the 11 subjects who took a SABA only after leaving the laboratory, three did so although they had failed to show significant changes in FEV_1 during the postchallenge follow-up in the laboratory. In these three subjects, repeated exposure on the next morning to the suspected agent (ie, latex in two subjects and an epoxy in one subject) resulted in a $\geq 20\%$ fall in FEV_1. Noticeably, only 59 of the 167 subjects (35%) who demonstrated a $\geq 30\%$ fall in FEV_1 required the administration of an inhaled SABA.

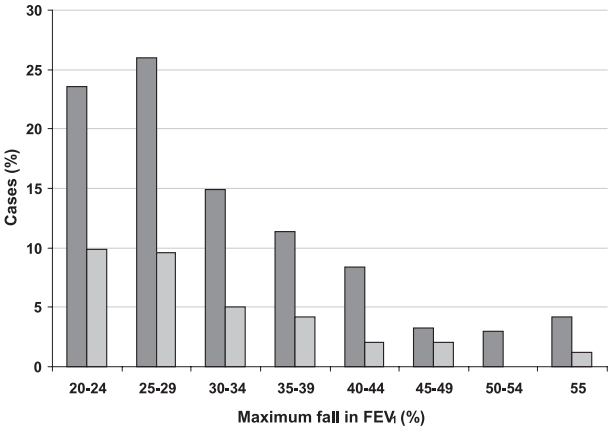

Figure 1. Maximum decreases in FEV_1 during the immediate (dark gray columns) and nonimmediate (light gray columns) components of the bronchial response to occupational agents. The immediate component encompassed the first 2 h after the end of challenge exposures; the nonimmediate component extended from the third hour to the end of the follow-up period in the laboratory (ie, 6 to 8 h after the end of the challenge exposure).

The demographic and clinical characteristics of the subjects who received an inhaled SABA during the functional follow-up are compared with those who did not in Table 1. The subjects who were administered an inhaled SABA had a more pronounced postchallenge decrease in FEV_1, with a median maximum fall of 40% (34%-49%) as compared with those who did not (28%, $P < .001$). There were no significant differences between these two groups in the functional features that reflect the severity of asthma in terms of baseline FEV_1 and provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}), but the subjects who required an inhaled SABA during SICs were treated slightly more frequently with an inhaled corticosteroid (38 of 68, 56%) than those who did not (114 of 267, 43%; $P = .051$). The daily dose of inhaled corticosteroid was in the medium- or high-dose range more frequently in subjects who needed a SABA (28% and 19%, respectively) compared with those who did not (20% and 13%; $P = .036$). Among SICs performed by exposing subjects to LMW agents, 37 of 123 (30%) required a SABA, whereas only 30 of 206 (15%, $P = .003$) subjects challenged with HMW agents needed a SABA. Atypical prolonged reactions more frequently required an inhaled SABA (28 of 61, 46%) compared with the other patterns of reactions (40 of 274, 15%; $P < .001$). The multivariate logistic regression analysis showed that the need for an inhaled SABA increased when the SIC involved a

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

Table 1—*Characteristics of Subjects Who Required an Inhaled SABA During SIC*

Characteristics	Required an Inhaled SABA (n = 68)	Did Not Require an Inhaled SABA (n = 267)	*P* Value
Male patients	35 (51)	169 (63)	.074
Age, y	36 (32-44)	37 (31-47)	.925
Current and ex-smokers	25 (37)	104 (39)	.739
Atopy[a]	40 (59)	164 (61)	.695
Duration of asthma before SIC,[b] mo	34 (12-69)	30 (13-63)	.700
Delay since last work exposure,[b] mo	2 (0.1-15)	3 (0.1-14)	.766
Inhaled corticosteroid[c]	38 (56)	114 (43)	.051
Low dose	6 (9)	25 (9)	.036
Medium dose	19 (28)	54 (20)	…
High dose	13 (19)	35 (13)	…
Severe asthma exacerbation[d]	14 (21)	42 (16)	.338
Baseline FEV_1 % predicted[b]	92 (80-101)	92 (81-101)	.895
Baseline FEV_1 < 80% predicted	16 (24)	56 (21)	.647
Baseline FEV_1/FVC,[b] %	74 (70-80)	75 (69-80)	.380
Baseline FEV_1/FVC < 70%	15 (22)	72 (27)	.410
Baseline PC_{20},[b] mg/mL	1.6 (0.3-3.9)	1.8 (0.4-6.0)	.659
> 16	6 (9)	33 (12)	.503
> 2-16	24 (35)	84 (31)	…
> 0.25-2	22 (32)	101 (38)	…
≤ 0.25	16 (24)	49 (18)	…
Type of occupational agents			
Low molecular weight	37 (54)	86 (32)	.003
High molecular weight	30 (44)	176 (66)	…
Indeterminate	1 (1)	5 (2)	…
Maximum fall in FEV_1 % baseline value[b]	40 (34-49)	28 (24-34)	< .001
Pattern of asthmatic reaction			
Immediate	15 (22)	172 (64)	< .001
Dual	15 (22)	45 (17)	…
Isolated late	3 (4)	16 (6)	…
Atypical prolonged immediate	28 (41)	33 (12)	…
Atypical progressive	7 (10)	1 (0.4)	…

Data are presented as % of available data unless otherwise specified. PC_{20} = provocative concentration of histamine causing a 20% fall in FEV_1; SABA = inhaled short-acting β_2-agonist; SIC = specific inhalation challenge.

[a]Atopy defined by the presence of a positive skin-prick test to at least one common allergen.

[b]Median (25th-75th percentiles).

[c]Daily dose of inhaled corticosteroid expressed as beclomethasone dipropionate equivalent; low dose ≤ 500 μg/d; medium dose > 500 μg but ≤ 1,000 μg/d; and high dose > 1,000 μg/d.

[d]Severe asthma reaction requiring ED visit and/or po/IV corticosteroids when the subject was exposed at work.

LMW agent (OR, 2.47; 95% CI, 1.43-4.28; $P = .001$) and marginally so when the subjects were treated with an inhaled corticosteroid (OR, 1.62; 95% CI, 0.93-2.80; $P = .087$).

The severity of the asthmatic reactions was graded as moderate in 40 subjects (12%; 95% CI, 9-16%) and severe in 10 subjects (3%; 95% CI, 1-5%). The main clinical and functional characteristics of the 10 subjects who experienced a severe asthmatic reaction are presented in Table 2. One-half of the severe reactions occurred after very short exposures, ≤ 5 min. Seven of the 10 severe reactions required repeated administration of SABA and corticosteroids within the first hour after the end of challenge exposure, whatever the final pattern of the bronchial response. One subject (subject number 416 in Table 2) developed a life-threatening asthmatic reaction after a 30-s exposure to methyl diphenylene diisocyanate at a concentration of 5 parts per billion. The subject showed signs of respiratory failure and required subcutaneous administration of epinephrine 0.5 mg in addition to inhaled SABA; he recovered within 1 h.

The demographic and clinical characteristics of the subjects who developed a moderate or severe asthmatic reaction are summarized in Table 3. The proportion of subjects treated with an inhaled corticosteroid was higher (30 of 50, 60%) among those who showed a moderate/severe reaction than among those who did not (122 of 285, 43%; $P = .024$). The proportion of subjects treated with medium or high dose of inhaled corticosteroid was higher in subjects who developed a moderate/severe reaction (34% and 16%, respectively) compared with those who did not (20% and 14%, respectively; $P = .046$). Moderate/severe asthmatic reactions occurred more frequently during SICs with LMW agents (60%) than during SICs with HMW agents (33%; $P = .001$). The occurrence of a severe asthmatic reaction could not be predicted

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

Table 2—*Clinical and Functional Data of Subjects With a Severe Asthmatic Reaction*

Subject	Sex	Age, y	Smoking Habits	Baseline FEV_1, L (% Predicted)	Baseline PC_{20}, mg/mL	Agent	Duration of Challenge Exposure, min	Pattern of Reaction	Maximum Fall in FEV_1, % From Prechallenge	Time to First Administration of SABA, min	Cumulative Dose of SABA, μg
308	F	36	NS	2.54 (90)	0.85	PA[a]	1	I	−60	1	800
312	M	34	ES	3.48 (97)	3.27	Cobalt[a]	30	PI	−63	60	1,200
391	F	55	NS	1.81 (97)	0.75	Cobalt[a]	75	PI	−39	300	800
416	M	46	S	3.25 (89)	1.98	Isocyanates	0.5	I	−56	1	400
512	M	33	NS	3.20 (80)	1.61	Isocyanates	15	D	−32	240	800
591	F	46	NS	2.42 (90)	1.37	Latex[a]	5	PI	−69	1	1,200
623	F	34	S	2.97 (100)	5.30	HBTU[a]	60	PI	−54	15	1,200
709	M	27	ES	4.40 (93)	0.57	Farines[a]	5	PI	−65	1	1,600
727	F	59	NS	2.02 (76)	>32.00	Platinum	1	I	−39	15	400
732	M	55	ES	3.58 (99)	1.51	Wood[a]	120	PI	−38	270	800
Median[b]	…	41	…	3.09	1.56	…	17	…	−55	15	800
	…	(34-55)	…	(2.32-3.58)	(0.83-3.78)	…	(1-86)	…	(39-63)	(1-247)	(700-1,200)

D = dual; ES = ex-smoker; F = female; HBTU = (2-[1H-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate; I = immediate; M = male; NS = nonsmoker; PA = phthalic anhydride; PI = prolonged immediate; S = current smoker. See Table 1 legend for expansion of other abbreviations.

[a]Agents in dry particle form.

[b]Median (25th-75th percentiles).

based on a history of severe asthmatic reaction requiring an ED visit and/or oral/IV corticosteroids when the subject was exposed at work. The rate of moderate/severe reaction was higher (26 of 61, 43%) among atypical, immediate, prolonged reactions compared with the other patterns of reactions (24 of 274, 9%; $P < .001$). The multivariate logistic regression analysis showed that challenge exposure to a LMW agent was the only significant predictor for the development of moderate/severe reactions (OR, 3.05; 95% CI, 1.62-5.73; $P = .001$).

Discussion

This study showed that 20% (95% CI, 16-25%) of the subjects who completed SIC with occupational agents needed the administration of an inhaled bronchodilator during the procedure, but only few (3%; 95% CI, 1-5%) experienced a severe asthmatic reaction requiring repeated administration of a SABA and oral or IV corticosteroids. The majority of these severe reactions occurred during the early postchallenge phase (Table 2), which further indicates that this is the most critical period, requiring close supervision and rapid therapeutic intervention.[12,15]

As far as we are aware, the severity of asthmatic reactions induced by SICs has never been thoroughly described. Malo and coworkers[11] reported that an "exaggerated bronchoconstriction," defined by a fall in FEV_1 of ≥ 30% from baseline value, occurred in 44% of the subjects challenged with realistic methods. In this study, we evaluated the severity of the bronchial response in terms of required treatment rather than the magnitude of airway obstruction, since no threshold value for the fall in FEV_1 has been validated as an indicator of a clinically relevant exaggerated bronchoconstriction. In our series, the incidence of exaggerated bronchoconstriction was similar (ie, 50%) to that reported by Malo et al,[11] but we found that a ≥ 30% fall in FEV_1 was generally well tolerated, requiring administration of an inhaled bronchodilator in only 35% of the subjects who demonstrated such a decline in FEV_1. These findings are consistent with the well-known discordance between the perception and the actual level of airway obstruction.[24]

In addition, we investigated the factors that were predictive for an increased risk of asthmatic reactions requiring a pharmacologic intervention. Challenge exposure to LMW agents appeared as the principal risk factor for the occurrence of asthmatic reactions requiring administration of a SABA with or without oral or IV corticosteroids. This finding could be related to a higher, intrinsic asthmagenic potential of LMW agents. HMW agents are proteins that induce asthma through an IgE-mediated mechanism, whereas the

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

Table 3—*Characteristics of Subjects With Moderate or Severe Asthmatic Reactions*

Characteristic	Moderate/Severe Reactions (n = 50)	Other Reactions (n = 285)	*P* Value
Sex, male	27 (54)	177 (62)	.279
Age, y	36 (32-42)	37 (31-47)	.487
Current and ex-smokers	20 (40)	109 (38)	.815
Atopy[a]	29 (58)	175 (61)	.649
Duration of asthma before SIC,[b] mo	30 (12-73)	31 (13-63)	.926
Delay since last work exposure,[b] mo	2 (0.1-13)	3 (0.1-15)	.934
Inhaled corticosteroid[c]	30 (60)	122 (43)	.024
Low dose	5 (10)	26 (9)	.046
Medium dose	17 (34)	56 (20)	…
High dose	8 (16)	40 (14)	…
Severe asthma exacerbation[d]	14 (21)	42 (16)	.338
Baseline FEV_1 % predicted[b]	93 (80-100)	92 (81-101)	.884
Baseline FEV_1 < 80% predicted	12 (24)	60 (21)	.640
Baseline FEV_1/FVC,[b] %	73 (70-79)	75 (69-80)	.193
Baseline FEV_1/FVC < 70%	11 (22)	76 (27)	.488
Baseline PC_{20},[b] mg/mL	1.5 (0.5-3.5)	1.8 (0.4-6.5)	.268
> 16	1 (2)	38 (13)	.181
> 2-16	19 (38)	89 (31)	…
> 0.25-2	19 (38)	104 (36)	…
≤ 0.25	11 (22)	54 (19)	…
Type of occupational agents			
Low molecular weight	30 (60)	93 (33)	.001
High molecular weight	19 (38)	187 (66)	…
Indeterminate	1 (2)	5 (2)	…
Pattern of asthmatic reaction			
Immediate	7 (14)	180 (63)	<.001
Dual	10 (20)	50 (18)	…
Isolated late	0 (0)	19 (7)	…
Atypical prolonged immediate	26 (52)	35 (12)	…
Atypical progressive	7 (14)	1 (0.4)	…

Data are presented as % of available data unless otherwise specified. See Table 1 legend for expansion of abbreviations.

[a]Atopy defined by the presence of a positive skin-prick test to at least one common allergen.

[b]Median (25th-75th percentiles).

[c]Daily dose of inhaled corticosteroid expressed as beclomethasone dipropionate equivalent; low dose ≤ 500 μg/d; medium dose > 500 μg but ≤ 1,000 μg/d; and high dose > 1,000 μg/d.

[d]Severe asthma reaction requiring ED visit and/or po/IV corticosteroids when the subject was exposed at work.

mechanism of asthmatic reactions remains largely uncertain for most LMW agents that include reactive chemicals, metal salts, and wood dusts,[25] suggesting the possibility that different pathophysiologic mechanisms could account for differences in bronchial reactivity between these two categories of agents.

Our findings are consistent with those reported by Malo et al[26] in a retrospective analysis of 384 subjects who developed an early reaction to various occupational agents. These investigators found that the mean percentage fall in FEV_1 and the proportion of subjects who showed a ≥ 40% fall in FEV_1 during the early component of the bronchial response was greater in subjects challenged with LMW agents (30% and 36%, respectively) compared with HMW agents (25% and 8%, respectively). By contrast, the magnitude of the late component of dual reactions was similar after exposure to HMW and LMW agents. In our study, the risk of reactions requiring pharmacologic treatment was not associated with a specific type of LMW agent. Noticeably only two such reactions were caused by isocyanates (Table 2), possibly because the concentrations were continuously monitored and kept below permissible levels during SICs. It can be also argued that the higher potential of LMW agents for inducing severe reactions could be due to differences in the mode of challenge exposure between LMW and HMW agents. Airway deposition of vapors and liquid aerosols may differ from dry particles. This is unlikely to explain the higher risk associated with challenges with LMW agents since seven of the 10 severe reactions were induced by occupational agents that were generated as dry particles (Table 2). In addition, the duration of exposure to both LMW and HMW agents was gradually increased on the first day according to the same schedule. However, the abbreviated protocol of exposure to LMW agents may have contributed to a higher incidence of atypical prolonged immediate reactions compared with previous reports,[22] and these atypical reactions were more severe than

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

the other patterns of bronchial response. Thus, there is a need for further investigation of the factors that potentially separately affect reactions to HMW and LMW agents.

There was no correlation between the risk of moderate/severe reactions and the baseline level of histamine PC_{20}, a parameter that has been recommended often to guide challenge exposure to occupational agents.[12,14,15] Indeed, studies have documented that the level of specific bronchial reactivity to common allergens, expressed as the concentration of the allergen required to induce a 20% fall in FEV_1, is determined by the baseline level of nonspecific bronchial hyperreactivity to histamine/methacholine and the degree of IgE sensitization to the allergen, usually expressed as the skin end-point concentration.[27,28] However, our findings are consistent with the lack of relationship between the baseline degree of nonspecific bronchial hyperresponsiveness and the level of specific bronchial responsiveness that has been documented in OA due to LMW agents.[29,30] In addition, the level of immunologic sensitization has been identified as the main determinant of specific bronchial responsiveness to HMW agents.[30,31] The need for an inhaled corticosteroid to control asthma, especially with daily doses >500 μg of beclomethasone dipropionate equivalent, had a borderline predictive value for the need to administer an inhaled SABA during the procedure.

Conclusions

The results of this study can assist clinicians in weighing the risk and benefit of performing SIC procedures using a realistic approach in workers evaluated for possible OA. Our results indicate that SICs using such realistic methods of exposure carry only a small risk of inducing severe asthmatic reactions, even when using an abbreviated protocol of exposure for LMW agents. In addition, the results have practical implications supporting previous recommendations[15] that may help further reduce the occurrence of severe reactions: (1) inhalation challenges should be initiated with very short durations of exposure (eg, 5, 10, and 30 s), and (2) the cumulative duration of exposure to LMW agents should be limited to 15 min on the first challenge day.

Acknowledgments

Author contributions: Dr Vandenplas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Dr Vandenplas: contributed to supervision of specific inhalation challenges, the conception of the study, data interpretation, and writing of the manuscript and served as principal author.

Ms D'Alpaos: contributed to the study design; the data collection, interpretation, and analysis; and the writing and reviewing the manuscript.

Ms Evrard: contributed to the performance of specific inhalation challenges, data acquisition, and manuscript review.

Dr Jamart: contributed to data analysis and manuscript review.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or in the preparation of the manuscript.

Other contributions: This work was performed at the Centre Hospitalier Universitaire de Mont-Godinne, Yvoir Belgium. We are grateful to James Hatch for reviewing the final version of the manuscript.

References

1. Vandenplas O, Toren K, Blanc PD. Health and socioeconomic impact of work-related asthma. *Eur Respir J*. 2003;22(4):689-697.
2. Nicholson PJ, Cullinan P, Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. *Occup Environ Med*. 2005;62(5):290-299.
3. Tarlo SM, Balmes J, Balkissoon R, et al. Diagnosis and management of work-related asthma: American College Of Chest Physicians Consensus Statement. *Chest*. 2008;134(suppl 3):1S-41S.
4. Malo JL, Newman Taylor A. Defining occupational asthma and confirming the diagnosis: what do experts suggest? *Occup Environ Med*. 2007;64(6):359-360.
5. Beach J, Russell K, Blitz S, et al. A systematic review of the diagnosis of occupational asthma. *Chest*. 2007;131(2):569-578.
6. Tarlo SM, Leung K, Broder I, Silverman F, Holness DL. Asthmatic subjects symptomatically worse at work: prevalence and characterization among a general asthma clinic population. *Chest*. 2000;118(5):1309-1314.
7. Ortega HG, Weissman DN, Carter DL, Banks D. Use of specific inhalation challenge in the evaluation of workers at risk for occupational asthma: a survey of pulmonary, allergy, and occupational medicine residency training programs in the United States and Canada. *Chest*. 2002;121(4):1323-1328.
8. Barber CM, Naylor S, Bradshaw LM, et al; British Thoracic Society Research Committee. Approaches to the diagnosis and management of occupational asthma amongst UK respiratory physicians. *Respir Med*. 2007;101(9):1903-1908.
9. Santos MS, Jung H, Peyrovi J, Lou W, Liss GM, Tarlo SM. Occupational asthma and work-exacerbated asthma: factors associated with time to diagnostic steps. *Chest*. 2007;131(6):1768-1775.
10. Cartier A, Malo JL, Dolovich J. Occupational asthma in nurses handling psyllium. *Clin Allergy*. 1987;17(1):1-6.
11. Malo JL, Cartier A, Lemière C, et al. Exaggerated bronchoconstriction due to inhalation challenges with occupational agents. *Eur Respir J*. 2004;23(2):300-303.
12. Vandenplas O, Malo JL. Inhalation challenges with agents causing occupational asthma. *Eur Respir J*. 1997;10(11):2612-2629.
13. Vandenplas O, D'Alpaos V, Heymans J, et al. Sputum eosinophilia: an early marker of bronchial response to occupational agents. *Allergy*. 2009;64(5):754-761.
14. Sterk PJ, Fabbri LM, Quanjer PH, et al; Official Statement of the European Respiratory Society. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013

Party Standardization of Lung Function Tests, European Community for Steel and Coal. *Eur Respir J Suppl*. 1993;16:53-83.
15. Vandenplas O, Cartier A, Malo JL. Occupational challenge tests. In: Bernstein IL, Chan-Yeung M, Malo JL, Bernstein D, eds. *Asthma in the Workplace*. New York, NY: Taylor & Francis; 2006:227-252.
16. Vandenplas O, D'Alpaos V, César M, Collet S, Tafforeau M, Thimpont J. Occupational asthma caused by linseed oilcake. *Allergy*. 2008;63(9):1250-1251.
17. Vandenplas O, Sohy C, D'Alpaos V, et al. Tomato-induced occupational asthma in a greenhouse worker. *J Allergy Clin Immunol*. 2008;122(6):1229-1231.
18. Pepys J, Hutchcroft BJ. Bronchial provocation tests in etiologic diagnosis and analysis of asthma. *Am Rev Respir Dis*. 1975;112(6):829-859.
19. Quanjer PH, ed. European Community for Coal and Steel. Standardization of lung function tests. Report working party. *Bull Eur Physiopathol Respir*. 1983;19(suppl. 5):45-51.
20. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med*. 1995;152(3):1107-1136.
21. Perrin B, Cartier A, Ghezzo H, et al. Reassessment of the temporal patterns of bronchial obstruction after exposure to occupational sensitizing agents. *J Allergy Clin Immunol*. 1991;87(3):630-639.
22. Dufour MH, Lemière C, Prince P, Boulet LP. Comparative airway response to high- versus low-molecular weight agents in occupational asthma. *Eur Respir J*. 2009;33(4):734-739.
23. Bateman ED, Hurd SS, Barnes PJ, et al. Global strategy for asthma management and prevention: GINA executive summary. *Eur Respir J*. 2008;31(1):143-178.
24. Banzett RB, Dempsey JA, O'Donnell DE, Wamboldt MZ. Symptom perception and respiratory sensation in asthma. *Am J Respir Crit Care Med*. 2000;162(3 pt 1):1178-1182.
25. Maestrelli P, Boschetto P, Fabbri LM, Mapp CE. Mechanisms of occupational asthma. *J Allergy Clin Immunol*. 2009; 123(3):531-542.
26. Malo JL, Ghezzo H, L'archevêque J. Distinct temporal patterns of immediate asthmatic reactions due to high- and low-molecular-weight agents. *Clin Exp Allergy*. 2012;42(7): 1021-1027.
27. Cockcroft DW, Murdock KY, 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(1):264-267.
28. Cockcroft DW, Davis BE, Boulet LP, et al. The links between allergen skin test sensitivity, airway responsiveness and airway response to allergen. *Allergy*. 2005;60(1):56-59.
29. Merget R, Dierkes A, Rueckmann A, Bergmann EM, 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(2):211-216.
30. Lemière 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(3 pt 1):976-980.
31. Quirce S, Fernández-Nieto M, Escudero C, Cuesta J, de Las Heras M, Sastre J. Bronchial responsiveness to bakery-derived allergens is strongly dependent on specific skin sensitivity. *Allergy*. 2006;61(10):1202-1208.

Downloaded From: http://journal.publications.chestnet.org/ by a Instituto Superiore di Sanit User on 12/12/2013