Allergy Asthma Immunol Res. 2020 Jan;12(1):164-170
https://doi.org/10.4168/aair.2020.12.1.164
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Brief Communication

Bronchial Response to High and Low Molecular Weight Occupational Inhalant Allergens

Agnieszka Lipińska-Ojrzanowska, Ewa Nowakowska-Świrta,* Marta Wiszniewska, Jolanta Walusiak-Skorupa

Department of Occupational Diseases and Environmental Health, Nofer Institute of Occupational Medicine, Lodz, Poland

Received: Jul 5, 2019
Revised: Jul 31, 2019
Accepted: Aug 11, 2019

Correspondence to
Ewa Nowakowska-Świrta
Department of Occupational Diseases and Environmental Health, Nofer Institute of Occupational Medicine, 8 Teresy St., 91-348 Lodz, Poland.
Tel: +48-42-631-4769
Fax: +48-42-631-4764
E-mail: Ewa.Nowakowska-Swirta@imp.lodz.pl

ORCID iDs
Agnieszka Lipińska-Ojrzanowska
https://orcid.org/0000-0001-8854-1095
Ewa Nowakowska-Świrta
https://orcid.org/0000-0002-8496-8216
Marta Wiszniewska
https://orcid.org/0000-0002-2936-7493
Jolanta Walusiak-Skorupa
https://orcid.org/0000-0003-0836-6800

Disclosure
There are no financial or other issues that might lead to conflict of interest.

ABSTRACT

Purpose: Occupational asthma may be induced by high- or low-molecular weight allergens (HMWA or LMWA, respectively). The study was conducted to compare the pattern of bronchial response in 200 HMWA-induced asthmatics (n = 130) and LMWA-induced asthmatics (n = 70).
Methods: The study participants underwent a single-blind, placebo-controlled specific inhalation challenge (SIC) with workplace allergens, accompanied by evaluation of non-specific bronchial hyperresponsiveness (NSBHR) with methacholine before and after the SIC.
Results: A single early bronchial response more frequently occurred in HMWA-induced asthmatics than in LMWA-induced asthmatics (86.2% vs. 20%). An isolated late bronchial response or atypical patterns were more frequently observed in LMWA-induced asthmatics than in LMWA-induced asthmatics (45.7% vs. 3.8% or 34.3% vs. 10%, respectively). Baseline NSBHR before SIC was more often detected in LMWA-induced asthmatics than in HMWA-induced asthmatics (81.4% vs. 54.6%), and the median value of the provocation concentration of methacholine was relevantly lower in these patients before and after SIC. A significant 3-fold increase in NSBHR after SIC was observed more often in LMWA-induced asthmatics than in HMWA-induced asthmatics (82.8% vs. 66.1%). In addition, compared to LMWA-induced asthmatics, HMWA-induced asthmatics were older, were more frequently active smokers, showed lower level of NSBHR, and more frequently continued their work in harmful occupational exposure.
Conclusions: The results of this study suggest that HMWA-induced asthmatics may have milder clinical courses and that there is a possibility of job continuation despite asthma exacerbation requiring medical surveillance.

Keywords: Occupational asthma; prognosis; bronchial hyperreactivity; allergens; asthma; immunoglobulin E

INTRODUCTION

Allergens are defined as exogenous particles capable of inducing a determined immune response.[1] One of the most common allergen classification takes into consideration their molecular weight identifying low-molecular weight allergens (LMWA) < 5 kDa[2] or < 10 kDa[3,4]

and high-molecular weight allergens (HMWA) > 5 kDa[2] or > 10 kDa.[3,4] The majority of HMWA are proteins or glycopeptides, usually inducing allergic responses via immunoglobulin E (IgE)-mediated mechanism.[5,6] Otherwise, LMWA are considered to be haptens (incomplete or remnant allergens) alone not able to induce IgE synthesis.[7] Specific IgE antibodies have been detected in the sera of LMWA-induced asthmatics, *e.g.* to diisocyanates,[8] quaternary ammonium compounds[9,10] or chloramines.[11] Moreover, LMWA may also play a role as adjuvants in promoting allergic responses to other allergens.[12]

The recognition of occupational respiratory allergy is mainly based on a positive result of specific inhalant challenge (SIC)—a reference diagnostic method in occupational asthma (OA).[3,1345] Different ways of airway inflammation caused by LMWA and HMWA may create various clinical courses of SIC. SIC in OA diagnostics is usually described by changes in spirometry results and bronchial hyperresponsiveness. The peculiarity of active asthma, despite its etiology, is the presence of nonspecific bronchial hyperresponsiveness (NSBHR). This phenomenon is characterized by bronchoconstriction development in response to various agents and non-allergenic agents (*e.g.* chemicals, fragrances, tobacco smoke and cold air). In asthmatic patients, the degree of NSBHR correlates positively with exacerbations. It is worthy to note that NSBHR may decrease in the period of asthma remission and also with the elapsed time after removal from occupational exposure to allergen.[13,16,17]

The degree of NSBHR escalation in methacholine inhalant challenge is categorized according to guidelines elaborated by the European Respiratory Society (ERS) and the American Thoracic Society (ATS).[18,19] At least 3-fold increase in NSBHR 24 hours after SIC compared baseline values is considered a helpful determinant for positive SIC result interpretation in case of equivocal changes in forced expiratory volume in 1 second (FEV1).[13]

The study was conducted to compare the pattern of bronchial response in asthmatics with HMWA- and LMWA-induced asthma, focusing on the phase of bronchial obstruction and changes in NSBHR.

MATERIALS AND METHODS

For the diagnosis of OA in 200 patients, we conducted SIC monitored by spirometry and methacholine challenges. Exclusion criteria with contraindications to SIC is described elsewhere.[13,18-20]

The study protocol is presented in **Figure**. Placebo used on control day was administered: 0.9% sodium chloride for liquid occupational agents or lactose powder for others. If fluctuations in FEV1 on control days did not exceed 10%, the patient underwent SIC with suspected occupational agents. SIC took place in a 6-m^3 challenge chamber and was evaluated according to the previously described protocol and international recommendations.[21,22]

Spirometry and methacholine challenges were carried out using the Jaeger Master Scope Spirometer equipment (VIASYS HealthCare, Höchberg, Germany) in accordance with the ATS and ERS guidelines.[20] Spirometry was conducted at baseline, and 5 and 30 minutes after specific exposure, then hourly for at least 8 and 24 hours post-challenge. Methacholine challenges were performed according to the ATS/ERS protocol.[18,19] The test was carried out at

https://doi.org/10.4168/aair.2020.12.1.164

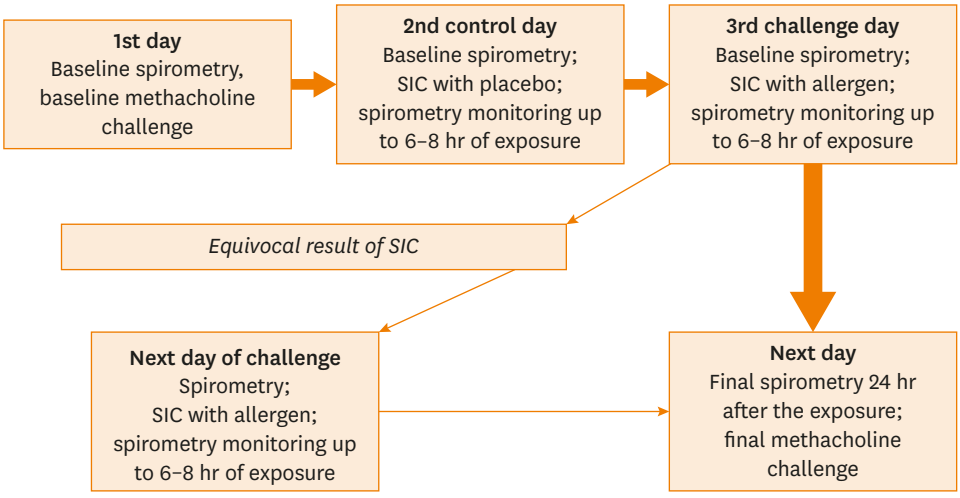

Figure. SIC procedure chart.
SCI, specific inhalant challenge.

least twice, on the day before and 24 hours after SIC. The presence of NSBHR was defined as the provocation concentration (PC_{20}) of methacholine causing a 20% decrease in FEV1 of <16 mg/mL.[20] A positive result of SIC was defined as the occurrence of clinical asthma symptoms and ≥15% fall in FEV1 lasting over 1 hour after SIC, and/or ≥ 3-fold increase in NSBHR 24 hours after SIC compared to baseline PC_{20}.

Statistical analyses were performed by using PQSTAT 1.6.2. Qualitative data were compared using 2×2 contingency tables with Fisher's test. A 2-tailed *P* value of <0.05 was considered significant. Medians and variances, presented with interquartile ranges (IQR 25%-75%), were analyzed by the Kruskal-Wallis modification of analysis of variance test. For a significant increase in NSBHR we estimated an accuracy determining the probability of right diagnosis in case of positive test result ([true positive results + true negative results/ number of the study participants] x 100%). The study protocol was approved by the Regional Bioethical Committee at the Nofer Institute of Occupational Medicine in Lodz (approval No. 20/2011 and 5/2012). Informed consent was obtained from each participant in the diagnostic process.

RESULTS

The study group comprised of 200 patients with OA, the majority were men (68%) and 56.5% (113 persons) had continued their occupational duties in spite of reported work-related respiratory symptoms. Even 40% (80 subjects) were active smokers. In the study group, 130 patients were occupationally exposed to HMWA and 70 to LMWA. HMWA-induced asthmatics were significantly older (about by 11 years) than LMWA-induced asthmatics, showed more frequent active smokers, and continued working in harmful environments (**Table**).

Fall in FEV1 ≥ 15% relative to baseline value before SIC was observed in 126 patients (63%) only at 2 hours after occupational exposure time, and only after the lapse of the 2 hours of SIC in 37 persons (18.5%). Dual phases or atypical responses were observed in 37 other (18.5%) patients (**Table**). A single early bronchial response was significant for HMWA-induced asthmatics and an isolated late bronchial response or atypical patterns were characteristic for LMWA-induced asthmatics (**Table**).

https://doi.org/10.4168/aair.2020.12.1.164

Table. Characteristics of patients, bronchial response pattern after the SIC and the results of NSBHR in patients with OA due to high and low molecular weight agents

Parameter	Total (n = 200)	OA to HMW-A (n = 130)	OA to LMW-A (n = 70)	*P* value*
Age (yr)	44 (33–51)	51 (44–54)	40 (30.5–49)	< 0.01
Sex (male:female)	136:64	90:40	46:24	NS
Current smoking	80 (40.0)	64 (49.2)	16 (22.9)	< 0.01
Period of employment (yr)	21 (13–29)	25 (18–31)	19 (12–28.5)	NS
Current employment in harmful exposure	113 (56.5)	82 (63.1)	31 (44.3)	0.01
NSBHR before SIC	128 (64)	71 (54.6)	57 (81.4)	< 0.01
Median before SIC	-	5.9 (16–1.4.)	3.6 (13.9–1.8)	0.02
NSBHR after SIC	200 (100.0)	130 (100.0)	70 (100.0)	NS
Median after SIC	-	2.3 (6.9–1.2)	1.6 (3.8–0.6)	0.04
Significant increase in NSBHR after SIC	144 (72)	86 (66.1)	58 (82.8)	0.01
ACC of significant increase in NSBHR (%)	-	66.1	82.8	-
Bronchial response type after SIC				
Early-phase response	126 (63)	112 (86.2)	14 (20)	< 0.01
Late-phase response	37 (18.5)	5 (3.8)	32 (45.7)	< 0.01
Dual-phase or atypical response	37 (18.5)	13 (10)	24 (34.3)	< 0.01

Values are presented as median (IQR: 25%–75%) or number of subjects (%) not otherwise specified.
SIC, specific inhalant challenge; NSBHR, non-specific bronchial hyperresponsiveness; OA, occupational asthma; HMW-A, high molecular weight agent; LMW-A, low molecular weight agent; SIC, specific inhalant challenge; NSBHR, non-specific bronchial hyperresponsiveness; NS, not statistically significant; ACC, accuracy; IQR, interquartile range.
*A significant *P* value considered as < 0.05.

Baseline NSBHR was more frequently observed in LMWA-induced asthmatics than in HMWA-induced asthmatics ($P < 0.01$), and the median value of PC_{20} was lower in these patients before and after SIC (**Table**). A significant 3-increase in NSBHR after SIC was observed in the majority of LMWA-induced asthmatics compared to HMWA-induced asthmatics ($P = 0.01$) (**Table**). The accuracy of a significant 3-increase in NSBHR was higher for asthmatic patients due to LMW-A than HMW-A (approximately 82.8% to 66.1%, Table).

DISCUSSION

It has been demonstrated that early recognition of OA, followed by avoiding exposure to offending allergens, is the most important determinant for favorable prognosis.[3,13,23,24] SIC is a standard method for diagnosing OA, however, procedures employed in the diagnosis of bronchial asthma for bakers' asthma may be not useful for recognizing asthma induced by diisocyanates or irritants. Therefore, we found it relevant to carry out investigations confirming observations dedicated for asthma due to LMWA and HMWA.

SIC procedures in our study were preceded by control days with placebos to exclude any false positive results, observed in the early phase of asthmatic reaction as a consequence of inhalant irritation caused by provocative materials.[3,13,25,26] They may also be a consequence of subclinical/early-step airways infection or even smoking during 24 hours after the specific exposure.[13,18]

The FEV1 is a well standardized and repeatable index monitored during SIC.[13,20] Spirometry with FEV1 measurement should be carried out at 10-15 minutes intervals in the first hour after exposure, and then at 30–60 minutes intervals in the next 6-8 hours after specific exposure. In order to reveal a late phase of obstruction bronchial response, FEV1 assessment is also recommended after 24 hours of specific exposure.[13] The positive result of SIC is confirmed by persistent falls in FEV1 ≥ 15% compared to baseline values shown as the percentage of predicted normal values or lower limit of normal (recorded in at least 2

https://doi.org/10.4168/aair.2020.12.1.164

following measurements), on understanding max. 10% of FEV1 variability during 6–8 hours of spirometric monitoring on the control day.[13] In the positive SIC course, 3 typical and 3 atypical patterns of bronchial asthmatic reaction may be. An early, immediate response develops usually within minutes after specific exposure, peaks at about 30 minutes and lasts for up to 2 hours. Late reactions are observed after 2 hours of specific exposure and show the maximum in 6-10 hours and last up to 24-48 hours. The third typical pattern is a dual-phase reaction. The atypical patterns include: persistent immediate reactions up to a few hours after specific exposure, progressive bronchoconstriction and so-called square-waved reaction, similar to dual-phase, but without recovery between early and late phases.[13]

An isolated immediate bronchial response is observed more frequently in patients with IgE-induced inflammation. However, it has also been reported more frequently in women, smokers and patients with a long course of asthma.[14,27,28] In our study, an early-phase bronchoconstriction was also more frequently recorded in HMWA-induced asthmatics (86.2%); however, even 49% of these patients were active smokers compared to 23% of LMWA-induced asthmatics. Furthermore, there was no difference between sex and the type of asthma reaction. An isolated late response and atypical patterns have been reported in non-IgE-asthmatics, often induced by LMWA.[14,27] Our results are in agreement with those of other researchers.[14,29] Meca *et al.*[29] have shown that during SIC, most HMWA-induced asthmatics (82%) presented an early response, while in mainly showed late reactions (73%). Similarly, Vandenplas *et al.*[14] have shown that HMWA-induced asthmatics were associated with early reactions and higher risk of airflow limitation; LMWA-induced asthmatics were associated with late reactions and higher risk of severe exacerbation. Dual-phase reactions have been observed in LMWA- and HMWA-induced asthmatics.[14] We confirmed that late-phase and atypical patterns of bronchial obstruction develop more frequently in LMWA-induced asthmatics than in HMWA-induced asthmatics (45.7% vs. 3.8%, and 34.3% vs. 10%, respectively).

The absence of NSBHR has a high sensitivity of active asthma exclusion, including patients with OA who continue their work in a harmful occupational exposure.[25,30] It is worth to emphasize that even though the majority of HMWA-induced asthmatics have still continued their employment in hazardous workplace (63.1% vs. 44.3% of LMWA-induced asthmatics), the occurrence of baseline NSBHR was observed more frequently in than in HMWA-induced asthmatics (81.4% vs. 54.6%). Moreover, the degree of NSBHR was more severe in these patients before and after SIC. Based on these results, allergic airway responses to LMWA correlate with more severe inflammation; Meca *et al.* [29] have demonstrated that LMWA-induced asthmatics may have more severe symptoms than HMWA-induced asthmatics, and that LMWA-induced asthmatics experienced a greater degree of NSBHR compared with HMWA-induced asthmatics. The differences in the degree of NSBHR after SIC suggest that HMWA and LMWA have different mechanisms of action and are responsible for the severity of asthma. Our results are not in agreement with those of previous studies who have shown that there is no significant difference in the baseline level of NSBHR and the increments in NSBHR after SIC between HMWA-induced asthmatics and LMWA-induced asthmatics.[14]

The limitation of this study is the lack of data related to the level of fractional exhaled nitric oxide (FeNO) during SIC. FeNO Levels are considered a reasonably good indicator of airway inflammation. Some researchers confirmed that the assessment of FeNO after SIC is more helpful in investigating OA caused by HMWA than by LMWA.[14,31] Atopic status, skin prick tests and induced sputum procedure have been introduced on a routine basis; however, such results were not included in the current analysis.

https://doi.org/10.4168/aair.2020.12.1.164

In conclusion, this study showed that compared to LMWA-induced asthmatics, HWMA-induced asthmatics were older, were more frequently active smokers, had lower levels of NSBHR, and more frequently continued their employment in harmful occupational exposure, which suggests milder clinical courses in HWMA-induced asthmatics. There may be a possibility of job continuation despite requiring individual medical surveillance in HMWA-induced asthmatics.

ACKNOWLEDGMENTS

This study is supervised by the Nofer Institute of Occupational Medicine in Lodz (No. 12.27) entitled: "Qualification for respiratory functional testing in occupational medicine practice" and by the National Health Program (No. 6/4/8/NPZ/FRPH/2018/312/495) entitled: "Initiatives taking in the point of prophylaxis occupational and work-related diseases, including military services and supporting health condition of working population."

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