Title: Occupational rhinitis in workers investigated for occupational asthma
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Abstract

Background. The links between asthma and rhinitis are nowadays referred to as the united airways disease (UAD). Current evidence shows that the UAD model seems to be applicable to occupational rhinitis (OR) and occupational asthma (OA).

Objective. We aimed to objectively assess, in the context of specific inhalation challenge (SIC) testing, the concomitance of bronchial and nasal reaction in the investigation of OR and OA.

Methods. Forty-three subjects with a history of work-related asthma symptoms underwent SIC for confirmation of OA and investigation of OR. Subjects underwent assessment of changes in bronchial calibre by spirometry and assessment of nasal patency and airway inflammation by acoustic rhinometry and nasal lavage.

Results. A positive nasal challenge was observed in 25 SIC whereas a positive bronchial challenge was observed in 17 SIC. A concomitant positive nasal and bronchial challenge was observed in 13 instances. This association was significant (risk ratio= 1.7; 95% CI=1.0 to 2.4; p=0.04) and more frequent in subjects challenged with high molecular weight (n= 11/22) than low-molecular weight agents (n= 2/21). Among subjects with a positive nasal challenge, nasal lavage showed a significant increase in eosinophils at 30 min post-exposure that correlated with changes in nasal patency.

Conclusion. Results provided objective evidence supporting the UAD concept by using OR and OA as a model for demonstrating a concomitant significant physiological reaction of the nose and lungs after challenge. We demonstrated that OR can be assessed by objective means; this condition often coexists with OA but can be present without OA.
Introduction

Occupational asthma (OA) is the most frequent work-related lung disease.[1] As the inflammatory process in the bronchi can also affect the upper airways, the study of occupational rhinitis (OR) in conjunction with OA is of interest. The link between rhinitis and asthma in the general population has led to the proposed ‘united airways disease’ (UAD) model, which also appears to be applicable to OR and OA. Rhinitis symptoms are common among subjects with OA.[2] Epidemiological studies show that subjects with OR have a high risk of asthma.[3] However, current evidence on the link between OR and OA is more supported by occupational epidemiological studies rather than pathophysiological observations.[4,5]

The diagnosis of OA and OR is challenging because it entails the objective demonstration of significant changes in lung and nasal status after exposure to occupational agents in order to confirm the causal association between the occupational exposure and the disease. This diagnosis can be confirmed by performing specific inhalation challenge (SIC) in which the worker is exposed to the suspected agent.[6] This test is considered the “gold standard” for confirming OA. By contrast, there is no standardized procedure to confirm OR; however, assessment of changes in clinical and functional parameters by means of objective and subjective methods during nasal provocation test with suspected aetiological agents is thought to represent an ideal approach for confirming OR.[7-9]

The aim of the present study was to objectively assess, in the context of specific inhalation challenge testing, the concomitance of bronchial and nasal reaction in the diagnosis of asthma and rhinitis following exposure to occupational agents. An ancillary objective was to assess nasal changes in cellular markers of inflammation after SIC

Methods

Study subjects

The study population consisted of 43 subjects with a history suggestive of OA referred to the Hôpital du Sacré-Cœur de Montréal for SIC. Subjects were offered an evaluation of nasal responses during the SIC as an attempt to investigate OR. The evaluation of the nose was not offered if subjects: 1) reported a history compatible with a recent common cold, rhinosinusitis or allergic rhinitis exacerbation; 2) were on regular medications for nasal symptoms; 3) had antecedents of recent nasal surgery; and 4) had significant structural abnormalities in their nasal cavities such as nasal septum perforation or nasal polyposis. Ethical approval for the study was obtained from the Hospital Medical Ethics Committee.

Design

Each SIC involved evaluating a single agent during a control day and at least one active day depending on the time of occurrence of the asthmatic reaction or when the maximum duration of exposure had been achieved in the absence of an asthmatic reaction. In most instances, subjects were assessed within the same week. Two challenge methodologies were used: 1) recreating working conditions in small cubicles or 2) with a closed circuit apparatus that exposes subjects to lower and stable concentrations of the suspected occupational agent.[10] The rationale for selecting one method over the other as the initial procedure was the limited possibility of the closed-circuit equipment to generate the active or control agent.

The investigation of OA by SIC is a common and standardized procedure in our hospital.[11] On the first day the worker is exposed for 30 minutes to a control inert substance
similar in nature to the suspected agent in order to assess non-specific bronchial and nasal responses. The assessment of lung function involves monitoring forced expiratory volume in 1 second (FEV₁) before exposure and then every 10 minutes for one hour, every 30 minutes for two hours and then hourly for a total of 8 hours. In the case of high molecular weight (HMW) agents, exposure is carried out on a single day because these products cause immediate or dual reactions. For low molecular weight (LMW) agents, the exposure is progressively increased from day to day due to the possibility of late reactions that are difficult to predict.[12]

As shown in Figure 1, the assessment of nasal responses during SIC was carried out in parallel to the assessment of lung responses. During each SIC session nasal responses were objectively monitored by acoustic rhinometry (AR) and nasal lavage (NAL). Additional details are provided in the online supplement.

**Acoustic rhinometry**
A trained technician performed AR according to a standardized procedure.[13] An acoustic rhinometer (Hoods Laboratories, Pembroke, MA, USA) was used to measure the nasal volume between 2-5 cm into the nose (Vol₂-₅) and the minimum cross-sectional area (MCA). The Vol₂-₅ was selected as main endpoint to better reflect mucosal changes.[13,14] Three measurements with a coefficient of variation equal to or less than 6% are obtained for each nostril to calculate total Vol₂-₅ and total MCA.

**Nasal lavage**
The NAL protocol was adapted from the procedure described by Naclerio et al.[15] Briefly, the subject is instructed to avoid breathing and swallowing and say “k-k” repeatedly for 10 seconds in order to prevent the fluid being swallowed during the NAL by closing the velopharynx with this action.[16] Then, 5cc of isotonic saline (0.9%) is instilled into one nostril. After 10 seconds the subject expels the fluid into a container; the procedure is performed in the other nostril and the sample is collected and pooled in the same container and immediately placed on ice before processing. (See online supplement)

**Complementary assessments**
Subjects completed a questionnaire that assessed the frequency of nasal symptoms. Atopy was assessed by skin prick test to a set of twenty allergen extracts using standard procedures.[17]

**Definition of outcomes**
Objective changes in nasal patency and bronchial calibre were the main outcomes in this study. A decrease in Vol₂-₅ of ≥ 30% after exposure was considered a positive nasal challenge to confer a diagnosis of OR in the absence of a positive reaction during the control day. The ≥ 30% threshold was selected from the analysis of the variability of Vol₂-₅ of all study subjects during their control sessions(14) and considering findings from published related studies.[18,19] A decrease in FEV₁ of ≥ 20% after exposure was considered a positive bronchial challenge to confer a diagnosis of OA. This is a widely accepted criterion in the literature.[20] NAL results and subjective nasal measurements (symptoms score and VAS) were regarded as supportive to the diagnosis.

**Statistical analysis**
The association between nasal and bronchial parameters was contrasted in a contingency table by Chi-square and Fischer’s exact test analysis. The strength of the association between nasal reaction and bronchial reaction was estimated by computing risk ratio and their 95%
confidence intervals. Pearson and Spearman rank methods were used to perform correlations in parametric data and non-parametric data. The Wilcoxon matched-pairs signed test was used to assess within subject changes in NAL within and between days of investigation. A 5% level of significance was applied to statistical analysis. Statistical analyses were performed by using SPSS 14.0 for Windows (SPSS, Inc., Chicago, IL; USA).

Results

The initial study population consisted in 53 subjects in which 53 control sessions were conducted. Ten subjects were excluded from the study after their control session due to the observed fluctuations in AR measurements. A negative nasal reaction to the control substance was a pre-requisite to continue with the active challenge in the following days. A total of 43 SIC with HMW and LMW agents performed in 43 subjects were analyzed.

Table 1. Baseline anthropometric and clinical characteristics of subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects n</td>
<td>43</td>
</tr>
<tr>
<td>Male: female</td>
<td>30 (70): 13 (30)</td>
</tr>
<tr>
<td>Age yrs</td>
<td>41.4 ± 10.1</td>
</tr>
<tr>
<td>Atopy positive:negative:unknown</td>
<td>32 (66): 7 (16): 4 (9)</td>
</tr>
<tr>
<td>Duration of exposure at work (yrs)</td>
<td>13.6 ± 11.2</td>
</tr>
<tr>
<td>Duration of work-related asthma symptoms (yrs)</td>
<td>4.94 ± 4.6</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>97.8 ± 17.0</td>
</tr>
<tr>
<td>PC20 ≤ 16 mg/ml (n/total, %)</td>
<td>26/43/60.4</td>
</tr>
<tr>
<td>Vol2- 5, cm³</td>
<td>2.78 ± 0.8</td>
</tr>
<tr>
<td>MCA, cm²</td>
<td>0.52 ± 0.1</td>
</tr>
<tr>
<td>Molecular weight of suspected agents HMW:LMW</td>
<td>21 (49): 22 (51)</td>
</tr>
<tr>
<td>History of nasal symptoms *</td>
<td></td>
</tr>
<tr>
<td>all (n=40) : HMW (n=18): LMW (n=22)</td>
<td></td>
</tr>
<tr>
<td>Runny nose</td>
<td>32 (80): 16 (89): 16 (73)</td>
</tr>
<tr>
<td>Sneezing</td>
<td>33 (83): 16 (89): 17 (77)</td>
</tr>
<tr>
<td>Blocked nose</td>
<td>29 (73): 14 (78): 15 (68)</td>
</tr>
<tr>
<td>Itching</td>
<td>29 (73): 14 (78): 15 (68)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean ± SD

S: smoker; ES: ex-smoker; NS: non-smoker;

HMW: high molecular weight; LMW: low molecular weight

PC20: concentration of methacholine that caused a 20% fall in FEV1

* Number of subjects (%) reporting nasal symptoms in all subjects and based on molecular weight of suspected agent. Data from questionnaire was not available for 3 subjects.

Table 1 shows that nasal symptoms were frequent in the study population. The frequency of each nasal symptom in all subjects was above 70%. However, no difference was observed in the frequency of nasal symptoms based on a final positive or negative bronchial challenge (data not shown). The frequency of all nasal symptoms was higher in the group of workers exposed to HMW as compared to LMW agents (Table 1).
Acoustic rhinometry values

The analysis of data from all challenges showed that on the control day of exposure the mean ± SD (range) maximum percentage decreases in AR as compared to baseline were 13.2% ± 8.8% (0% to 28%) for Vol2-5, and 11.9% ± 8.4% (0% to 30%) for MCA. On challenge days of exposure to the active agents, the mean maximum percentage decreases were 31.8% ± 16.5% (0% to 81%) for Vol2-5 and 25.6% ± 16.5% (0% to 77%) for MCA. The correlation between Vol2-5 and MCA measuring these changes during the control day (r = 0.6; p < 0.01) and challenge day (r = 0.9; p < 0.01) was satisfactory and significant.

Results of bronchial and nasal response to the challenge

Table 2 shows the outcome of the 43 SIC included in the analysis. Among those with significant changes in bronchial calibre, most (13/17) also had significant low nasal patency. Among those with no significant low bronchial calibre, about half had significant low nasal patency (12/26). The frequency of reported work-related nasal symptoms in this group was high (runny nose: 100%; itching: 83%; sneezing, 91.7%; nasal blockage: 83.3). Ninety-one percent of subjects in this group also reported the appearance of work-related nasal symptoms before or almost at the same time in relation to the appearance of work-related asthma symptoms. Most of them (9/12) demonstrated clinically significant nasal responses to challenge with the active agent based on nasal symptoms scoring.

Table 2. Outcome of SIC based on nasal and bronchial response and type of suspected agent

<table>
<thead>
<tr>
<th>Group</th>
<th>All SIC</th>
<th>HMW</th>
<th>LMW</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low bronchial calibre*</td>
<td>Low bronchial calibre*</td>
<td>Low bronchial calibre*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>No</td>
<td>4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td>26</td>
<td>43</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>1.7 (1.0, 2.4)</td>
<td>1.3 (0.8, 2.7)</td>
<td>2.4 (0.7, 2.4)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.04</td>
<td>0.6</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*Clinically significant: decrease in FEV1 ≥ 20% from baseline after challenge

§ Clinically significant: decrease in Vol2-5 ≥ 30% from baseline after challenge

RR, risk ratio

p-value by Chi-square and Fischer’s exact when appropriate

A positive nasal challenge was observed in twenty-five of 43 SIC (58.1%) whereas a positive bronchial challenge was observed in 17 of 43 SIC (39.5%). A concomitant positive nasal and bronchial challenge was observed in 13 instances (30.2%). The estimated risk ratio (RR) shown in Table 2 demonstrated a statistically significant positive association of a moderate magnitude between these clinically significant nasal and bronchial responses (RR: 1.7; 95% CI=1.0 to 2.4; p-value= 0.04).

Table 2 also shows that in 11 instances there was a concomitant clinically significant nasal and bronchial reaction in the group challenged with HMW agents. The RR expressing the association in this group was 1.3 (95% CI= 0.8 to 2.7). A joint significant nasal and bronchial reaction was observed in only two instances in the LMW group.

The number and nature of positive and negative SIC is shown in the online supplement along with supplementary description of results on bronchial hyperresponsiveness, atopy and correlation between AR and NAL changes during SIC.
Results of nasal lavages
NAL samples from twenty-five SICs were analysed; NAL was not performed in all SIC due to unavailability of the technique (8 cases); subjects refuse the test (5 cases) or were not able to follow the instructions to collect the sample (5 cases). The analysis of NAL performed in 25 SICs (HMW= 14, LMW=11) showed that the predominant cells at baseline on the control and active day were neutrophils and epithelial cells. There were no statistically significant differences in the percentage of neutrophils, macrophages and epithelial cells comparing the control and active day (data not shown). Lymphocytes were not analyzed because the samples demonstrating these cells were few and the number of cells was too low.

Table 3. Changes in percentage of eosinophils in NAL after exposure to control and active agent in subjects with a final positive or negative nasal challenge.

<table>
<thead>
<tr>
<th>Nasal challenge</th>
<th>Time of NAL during SIC</th>
<th>n</th>
<th>Agent</th>
<th>Before</th>
<th>30 min post</th>
<th>p-value*</th>
<th>6h post</th>
<th>p-value&amp;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td></td>
<td>15</td>
<td>control</td>
<td>0.0 (0.9)</td>
<td>0.0 (0.8)</td>
<td>0.5</td>
<td>0.0 (0.2)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>active</td>
<td>0.0 (0.8)</td>
<td>0.2 (5.2)</td>
<td>0.03</td>
<td>0.2 (2.8)</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-value§</td>
<td>0.2</td>
<td>0.02</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td></td>
<td>8</td>
<td>control</td>
<td>0.7 (1.2)</td>
<td>0.3 (2.2)</td>
<td>0.7</td>
<td>0.3 (0.5)</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>active</td>
<td>0.0 (0.2)</td>
<td>0.3 (1.2)</td>
<td>0.1</td>
<td>0.3 (3.2)</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p-value§</td>
<td>0.07</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Numbers represent median and interquartile range (IQR)
* p-value compares values before and at 30min
& p-value compares values before and at 6h
§ p-value compares values between the control and active day

Table 3 shows that provocation with the control agent did not induce significant changes in the percentage of eosinophils on the control day in subjects with a final positive or negative nasal challenge. By contrast, provocation with the active agent resulted in a significant increase in the percentage of eosinophils in the group of subjects with a final positive nasal challenge at 30 min after total exposure in comparison to baseline values and to values on the control day at the same challenge time. This increase was still apparent 6h later but without reaching statistical significance. There were no significant differences in the early and late eosinophilic response in the group of subjects with a final negative nasal challenge.

Discussion
Results of this study with subjects referred for investigation of possible OA showed that: 1) OR can be assessed by objective means; 2) OR frequently coexists with OA and can be present without OA. Taken together, the results provide further objective evidence in support of the UAD concept by using OA and OR as a model to demonstrate a parallel significant physiological reaction of the nose and lungs after challenge with occupational agents.

In the general population rhinitis may be present in up to 80% of patients with asthma.[21] In our study, the association between OR and OA followed the same pattern, with OR occurring in 76.4% of confirmed cases of OA (Table 2). After carrying out SIC, we found that a confirmed diagnosis of OR was more frequent than a confirmed diagnosis of OA. These
results stress the importance of using objective means in the investigation of OR in order to gain a more accurate perspective of the impact of this disease. They also point out the relevance of using means to also assess upper airways in the context of the assessment of OA.

We observed a positive association of nasal and bronchial responses after challenge with HMW and LMW agents. Our study demonstrated a concomitant significant decline in nasal patency and bronchial calibre in 13 of 43 SIC. The magnitude of the observed association was not marked probably due to our restrictions in sample size. However, the observed changes allowed us to make an objective diagnosis of OR and OA in the same patient, supporting the applicability of the UAD model to rhinitis and asthma of occupational origin. A subanalysis based on the type of agent investigated showed that a clinically significant “united airways” response was more frequent in the case of HMW than LMW agents (Table 2). However, the association of clinically significant nasal and bronchial responses in the HMW group did not reach statistical significance. We consider that these results should be verified by further studies comprising a larger population because though not statistically significant may represent a real effect.

Table 2 also shows that when there is significant lower nasal patency, there is not necessarily any change in lower airways calibre. Accordingly, the results showed that in 12 SIC a diagnosis of OA was not made and therefore OR was the sole diagnosis. This situation is independent of the type of causal agent (HMW or LMW). A ‘stepwise sensitization’ may occur where the nose, as first line of defence becomes sensitized first and then the sensitization process progresses down the respiratory tract until it reaches the bronchi. According to this pattern, we would expect a gradual worsening of lower respiratory tract symptoms among those subjects with OR alone that may ultimately lead to a clear manifested OA if exposure to the offending agent continues. However, although the progression from OR to OA has been documented,[22] it certainly does not occur in all circumstances confronting the hypothesis of the ‘allergic march’ model. Occupational longitudinal epidemiological studies have failed to demonstrate a clear “allergic march”. [23] In the general population it is well established that only a proportion of patients with allergic rhinitis develop asthma.[24] Thus, it is realistic to speculate that more factors are involved in the pathogenesis and natural history of OR. An alternative or complementary hypothesis to explain the isolated expression of OR in some of our study subjects may entail an increased local production of immunoglobulin E (IgE) in the nose. It has been demonstrated that the nasal and bronchial mucosa by themselves have the capability to induce an IgE-mediated immunological response.[25,26] Local production of IgE has been detected in nasal B-cells of patients with allergic rhinitis.[27] A study showed that cultured functional nasal B-cells were able to synthesize IgE.[28] A similar hypothesis may explain isolated cases of OA. Increase in specific IgE in bronchoalveolar lavage has been demonstrated after segmental allergen challenge in atopic asthmatics.[29] In our study we did not observe any significant nasal reaction in 4 of 17 SIC showing a positive bronchial reaction in which, based on the UAD model, we would expect a reaction in both the nose and the bronchi. Two instances may be explained by the induction of an immediate bronchial reaction (at 20 sec and 7 min after the start of the challenge) that precluded extended exposure. Although plausible it seems unlikely; we do not know if the carry-over of the exposure might have induced a significant reaction in the nose because in all cases showing a positive nasal and bronchial reaction, the nose reacted always before than the bronchi. The explanation for these two cases is yet to be determined.
Analogous to induced sputum examination in the investigation of OA,[30] performing NAL may have an additional diagnostic value in the investigation of OR. Our results confirm findings from previous studies that showed that challenges with HMW and LMW agents can induce an influx of eosinophils that can be demonstrated in NAL samples.[31-33] We observed an increase in the percentage of eosinophils $\geq 3\%$ in 8 NAL samples; five of these samples corresponded to cases with positive nasal and bronchial challenges. NAL analysis also showed no changes in the percentage of eosinophils in some subjects that showed a significant decrease in nasal patency after challenge. This finding may suggest an irritant rather than an inflammatory nasal response, however, these subjects tested negative during the control session after exposure to a nonspecific irritant; in addition, seven subjects of this group showed an associated positive bronchial reaction after SIC suggesting an allergic response. No increase in nasal eosinophil count was observed among subjects with an isolated positive bronchial response. We think these observations rather reflect different underlying pathogenic mechanisms that deserve further investigation. In line with other studies,[31] we noticed no significant increase in the proportion of neutrophils after the challenge with either the control or active agent.

Based on our findings the assessment of upper airways inflammation by the NAL technique and the assessment of nasal patency by AR are complementary and therefore can be recommended for the investigation of OR.

Further research efforts in the investigation of OR in the context of the UAD model should focus on determining the pathogenic mechanisms involved in the expression of OR alone or in association with OA for the two categories of causal agent (HMW and LMW). Tests to characterize induced inflammation in the upper and lower airways and their association after exposure to HMW and LMW agents should also be carried out in a larger population.
Acknowledgement of funding: Roberto Castano is a Research Fellow supported by the Center for Asthma in the Workplace, a Canadian Institute of Health Research (CIHR), Centre for Research Development.

Figure 1. The joint SIC protocol: joint assessment of the nose and lungs

Reference List


Figure 1. The joint SIC protocol: joint assessment of the nose and lungs

- **Lung**
  - Prechallenge
  - Challenge
  - Post-challenge
  - Spirometry (FEV1): every 10' for 1h, every 30' for 2h, every hour for 6h

- **Nose**
  - Acoustic rhinometry
  - Nasal lavage
  - Symptoms score
  - VAS
  - Acoustic rhinometry (Vol 2-5 cm, MCA) > at 15', 30' and 60' and then every hour for 6h
  - Symptoms score
  - VAS
  - Nasal Lavage > at 30' and 6h
Online supplementary material

‘Occupational rhinitis in workers investigated for occupational asthma’

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Online supplement 1 (Methods- design). SIC procedures

The suspected offending agent is identified from a detailed occupational history, a review of the material safety data sheets and the results of specific skin prick tests in the case of HMW (proteinaceous) agents. Bronchial responsiveness to methacholine and induced sputum examination are performed following standardized methodologies at the end of the control day and at the end of the day on which a positive reaction is observed or when the total exposure time is reached.[1,2]

The monitoring by AR consisted of a pre-challenge assessment and nine subsequent post-challenge assessments. Upon arrival of the subject (at 7:30 a.m.) a baseline assessment is done after a 20-minute resting period. Then the subject is challenged with the suspected agent and after the total exposure time, measurements are performed at 10, 30 and 60 minutes and then each hour for the subsequent six hours. NAL is performed at baseline and at 30 minutes and six hours after the exposure. Subjective monitoring of nasal responses was performed by scoring nasal congestion and rhinorrhea using a 4 points scale.[3] Clinical symptoms (nasal congestion, rhinorrhea, itching) were also recorded on a 100 mm length VAS (visual analogue scale).[4] These recordings were obtained before each AR measurement.

References:


Online supplement 2 (Methods). Nasal lavage processing

Nasal lavage (NAL) samples are processed within 2 hours. The supernatant was obtained by centrifugation of the sample volume at 3300 rpm for 8 min at 4°C and then frozen at -80°C for future analysis. The pellet was re-suspended in 0.5 mL phosphate-buffered saline (PBS) containing 0.1% wt/vol bovine serum albumin. Cytocentrifuge preparations were made by using 100 microl of the remaining re-suspended cell suspension. The preparation was centrifuged at 450 rpm and slides were stained with Wright-Giemsa to perform differential cell counts. Slides were examined blindly. Leukocyte counts were expressed as a percentage of 300 cells counted and determined by means of light microscopy.

Online supplement 3 (Results) Table. Number and nature of positive and negative SICs

Number of positive and negative specific inhalation challenges (SIC) based on causal agent

<table>
<thead>
<tr>
<th>Agent</th>
<th>Nasal+Bronchial</th>
<th>Nasal alone</th>
<th>Bronchial alone</th>
<th>Negative SIC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-molecular weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flours</td>
<td>9</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Other cereals</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Animal epithelium</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Tea</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>11</strong></td>
<td><strong>4</strong></td>
<td><strong>4</strong></td>
<td><strong>3</strong></td>
</tr>
<tr>
<td><strong>Low-molecular weight</strong></td>
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<tr>
<td>Isocyanates</td>
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<td>-</td>
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</tr>
<tr>
<td>Formaldehyde</td>
<td>-</td>
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<td>-</td>
<td>3</td>
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<tr>
<td>Acrylates</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Resins</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Woods</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Soldering (steel)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
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<td><strong>8</strong></td>
<td><strong>0</strong></td>
<td><strong>11</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13</strong></td>
<td><strong>12</strong></td>
<td><strong>4</strong></td>
<td><strong>14</strong></td>
</tr>
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</table>
Online supplement 4 (Results). Bronchial hyperresponsiveness, atopy
Bronchial hyperresponsiveness at baseline ($PC_{20} \leq 16 \text{ mg/ml}$) was detected in 60.4% of the study subjects (Table 1). Bronchial hyperresponsiveness at baseline was found in 4/4 subjects with a positive bronchial challenge alone. The association between bronchial hyperresponsiveness at baseline and a final positive nasal challenge alone or both positive (nasal and bronchial) was borderline significative ($p=0.06$ and $p=0.08$, respectively). Results showed no association between atopy status and a final positive nasal or bronchial challenge, or both positive (nasal and bronchial) in the same subject (data not shown).

Online supplement 5 (Results). Correlation between acoustic rhinometry and nasal lavage changes during SIC
After SIC, there was a satisfactory and significant correlation between the percentage increase in eosinophils measured in NAL at 30 min post-exposure and the maximum percentage decrease in nasal volume measured by AR ($r=0.52$, $p=0.007$). Figure 2 illustrates this relationship.

![Figure 2. Relationship between changes in nasal patency and eosinophils counts during SIC. The reference line indicates the threshold for a positive diagnosis of OR with acoustic rhinometry.](https://example.com/figure2.png)
Figure 2. Relationship between changes in nasal patency and eosinophils counts during SIC. The reference line indicates the threshold for a positive diagnosis of OR with acoustic rhinometry.
Occupational Rhinitis In Workers Investigated For Occupational Asthma

Roberto Castano, Denyse Gautrin, Gilles Theriault, Carole Trudeau, Heberto Ghezzo and Jean-Luc Malo

Thorax published online October 3, 2008

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