

Original article

Nasal provocation test in the diagnosis of natural rubber latex allergy

Background: Natural rubber latex (NRL) allergy in workers using rubber gloves has been an occupational health problem for the last 10 years. In the case of the occupational agents, clinical history may be far from conclusive; hence, appropriate provocation should be carried out. The objective was to evaluate the usefulness of the nasal challenge test in the diagnosis of allergic rhinitis in subjects occupationally exposed to NRL.

Methods: A single-blind, placebo-controlled study was conducted in 16 nurses with respiratory symptoms (bronchial asthma and/or rhinitis) related to NRL exposure as well as positive skin prick test (SPT) response to NRL. The controls were nine nurses with asthma and/or perennial rhinitis unrelated to NRL exposure; six atopic patients not occupationally exposed to NRL, with asthma and/or perennial rhinitis; and six healthy subjects. All the controls had negative results of SPT with NRL. Patients with a history of anaphylaxis or positive results of RAST to NRL were not considered in the study. The “nasal pool” technique was used to evaluate the cellular response and changes in protein level and ECP concentration in nasal washings after topical provocation with allergen or placebo.

Results: A significant increase was noted in eosinophil and basophil number, albumin/total protein ratio, and ECP level only in NRL SPT-positive patients subjected to nasal challenge with NRL. Neither bronchial nor systemic reactions were found after the nasal provocation with NRL.

Conclusions: The nasal challenge test appears to be useful for diagnosing occupational rhinitis in NRL-sensitized patients.

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The tests used in the diagnosis of natural rubber latex (NRL) allergy include both *in vivo* and *in vitro* methods. None of these tests can be said to have 100% diagnostic accuracy, mainly because of the variety of NRL allergens (1). The provocation tests which ensure a whole allergenic spectrum of NRL have been considered to be decisive for the diagnosis of NRL allergy (1, 2). The “use” test with rubber gloves is relatively safe and conclusive in patients with allergic diseases of the skin (1). However, in patients suffering from respiratory symptoms, it may yield negative results. The bronchial inhalation challenge is specific and highly sensitive and can identify health-care workers with NRL-induced occupational asthma, but it may sometimes be troublesome and even dangerous in subjects with systemic manifestations of allergy (3–5). Moreover, bronchial provocation may not indicate only patients with allergic rhinitis. In most cases, the nasal challenge can be an alternative. The dose of the allergen is much lower, meaning more safety for the patient. Furthermore, the sampling of biological material (nasal secretion or nasal

lavage fluid) is less complicated (6). The purpose of the present study was to assess the applicability of the “nasal pool” technique in the diagnosis of NRL allergy, as well as to evaluate the cellular response and the changes in protein level and eosinophil cationic protein (ECP) concentration in nasal lavage fluid.

Material and methods

Subjects

Four groups of nonsmoking subjects were enrolled in the study. The selection criteria for the study groups are presented in Table 1.

Group A comprised 16 nurses (mean age: 41.9 ± 7.6 years) with respiratory symptoms (eight with rhinitis and eight with bronchial asthma and rhinitis) related to NRL exposure who had positive skin prick test (SPT) responses to both standardized commercial and non-standardized in-house NRL extracts. Nine group A subjects reported local urticaria to latex gloves and were

Table 1. Selection criteria for study groups

Group	History of NRL airway allergy	Atopy	Occupational exposure to NRL	Positive results of SPT to NRL	Positive RAST to latex
A	+	Not considered	+	+	-
B	-	+	+	-	-
C	-	+	-	-	-
D	-	-	-	-	-

positive in the "use test" with NRL glove. Eight nurses showed atopy defined as a positive result of SPT with common aeroallergens.

Group B comprised nine nurses (mean age 43.1 ± 8.8 years) with perennial respiratory symptoms (five with rhinitis and four with bronchial asthma and rhinitis) not related to NRL exposure and positive SPT results with common aeroallergens. Three of them were sensitized to chloramine T and suffered from local urticaria to chloramine T. Diagnosis of sensitisation to chloramine T has been confirmed by positive results of RAST (Pharmacia Diagnostics AB, Uppsala, Sweden). One nurse had a positive history of acute urticaria induced by peanut, and in another one, this disorder was caused by tomato ingestion. Allergy to tomato was confirmed by prick to prick testing with fresh fruit (7).

Group C comprised 6 atopic patients (mean age 35 ± 9.6 years) with perennial respiratory symptoms (three with rhinitis; three with asthma and rhinitis). One of them had a positive history of local urticaria to house dust and another one of acute urticaria after strawberry ingestion.

Group D comprised 6 healthy individuals (mean age 47.3 ± 5.5 years). All the controls (groups B, C, and D) had negative results of SPT with NRL. Only the nurses were occupationally exposed to NRL. The patients with a history of anaphylaxis or positive results of RAST to NRL were excluded from the study. The study participants did not receive any systemic or local medication, except inhaled short-acting β_2 -agonists, for 14 days before the study. The nurses were not exposed to NRL and chloramine T for at least 14 days before the project started. All the patients were hospitalized in a latex-free environment during the course of the study.

Study protocol

The study was designed as a biphasic, crossover, single-blind trial. At phase 1, the subjects were challenged with placebo. At least 7 days later, the allergen challenge was performed. The study was approved by the Regional Medical Ethics Committee, and all the participants gave their written consent prior to the study.

Preparation of an in-house NRL extract

The NRL solution was prepared by washing pieces of NRL gloves of six different brands, as well as catheters

and drains, with phosphate-buffered saline (PBS) (Dulbecco, Sigma, USA) at 37°C for 2.5 h. The solution was then decanted, filtered, and lyophilized. The protein content was estimated at 1000 $\mu\text{g}/\text{ml}$, pH 7.4.

Skin prick tests

SPTs to commercial NRL at 1:100 w/v (Stallergènes, Fresnes, France) and to in-house NRL solution with a protein content of 1000 $\mu\text{g}/\text{ml}$ were performed. The negative control was an allergen diluent, and the positive control, a histamine solution. All the tested sites were examined after 20 min. A wheal 3 mm greater than the negative control and a flare 5 mm greater than the negative control were considered positive. All the procedures were conducted by standard methods (8). The biologic standardization of the in-house NRL preparation was based on a study of a group of 31 patients with clinical histories indicative of NRL allergy, and a positive response to SPT with a standardized commercial NRL allergen (Stallergènes, SA, Fresnes, France). Fourteen of the subjects also had positive results in a commercial NRL RAST. Thirty-one healthy individuals comprised the control group. Twenty-seven of the NRL-allergic patients had a positive response to the SPT. Thus, the sensitivity of the SPT was 87%. None of the control subjects presented a positive response to the SPT. The specificity of the SPT was found to be 100%.

The "use" (or "wear") test

A "use" test was done with the finger pieces cut off from the examined NRL gloves and applied to a dampened finger of the patient. The appearance of one or more hives after a 20-min period was considered a positive response. In some cases, when the results of a finger piece test were read, an entire glove was also applied for 20 min. A vinyl glove served as a negative control (9).

NRL radioallergosorbent test (RAST)

A commercial *in vitro* NRL RAST was performed with allergen disks (Phadezym k82, Pharmacia Diagnostics AB, Uppsala, Sweden). The results were expressed quantitatively in kilo units per liter and considered positive at values greater than 0.35 kU/l.

Nasal lavage and challenge procedure

All the procedures were performed by the "nasal pool" method (10). Before the provocation, each nostril was washed 10 times with 6 ml of saline solution with the "nasal pool" device, a 5-ml syringe closely fitting the nostril. Nasal washings were collected immediately before the provocation and 30 min, and 4 and 24 h afterward. The in-house NRL extract was suspended in 6 ml of PBS solution without Ca^{2+} and Mg^{2+} (1000 $\mu\text{g}/\text{ml}$ NRL protein solution). PBS was used as placebo. A volume of 6 ml of saline was injected into

the nasal cavity for 5 min and then recovered. Then the allergen was applied to the nasal mucosa by the same procedure. This technique permitted the application of the agents at predetermined concentrations over a large and well-defined area of the nasal mucosa for extended periods of time. All washings were always performed on the same side of the nasal cavity.

Symptom score

The number of sneezes and the degree of mucosal edema, rhinorrhea, and itching were evaluated. Total symptom scores (SS) ranged from 0 to 8 and represented the sum of the scores for sneezing (0 sneezes: 0 points; 1–4 sneezes: 1 point; >4 sneezes: 2 points), rhinorrhea (none: 0 points; mild: 1 point; abundant: 2 points), mucosal edema (none: 0 points; mild: 1 point; nasal block: 2 points), and itching (none: 0 points; itching of the nose or throat: 1 point; itching of the nose and throat: 2 points). Positive clinical challenge was defined as the total score of more than 3 points (11).

Nasal washing processing

Nasal washings were centrifuged (10 min at 1000 rpm) to isolate the cell pellet and the supernatant. The obtained sediment was washed with sterile PBS (Dulbecco, Sigma, USA) and 0.1% human serum albumin (HSA) (Behringwerke AG, Germany) and then suspended in 1 ml buffer with HSA. The cells were stained as follows:

- 1) by the Turk method for leukocytes
- 2) by the Dunger method for eosinophils
- 3) with 0.06% toluidine blue in 30% ethanol for basophils (metachromatic cells).

The cells were counted in a Fuchs-Rosenthal chamber. The number of cells in 1 ml of the recovered fluid was determined.

The samples were further centrifuged at 2000 rpm for 5 min, transferred onto a slide, and air-dried. The slides were stained by the Giemsa method. On each slide, the first 200 cells were classified into epithelial cells, eosinophils, neutrophils, basophils, and mononuclear cells (a category including lymphocytes and monocytes).

The supernatant total protein content was evaluated according to Lowry et al. (12). The albumin concentration was measured by the “rocket” Laurell method (the assay ranged between 20 and 200 µg/ml) (13). The permeability index, i.e., albumin to total protein ratio, was calculated.

Mediator levels

The nasal ECP concentration was measured by radioimmunoassay (RIA kits, Pharmacia, Sweden), according to the manufacturer’s protocol. The samples for

these assays were collected before and 30 min and 4 and 24 h after the provocation test.

Pulmonary function

Bronchial response was measured by serial monitoring of forced expiratory volume in 1 s (FEV_{1s}) and peak expiratory flow rate (PEFR) by a spirometer (Vicat 2A, Mijnhardt, The Netherlands) before and 5 min, and 5 and 24 h after the provocation. All the subjects were instructed beforehand how to use the peak flow meter for hourly PEFR measurements.

Statistics

The data were analyzed by a parametric two-way ANOVA and Tukey’s test for multiple comparisons. The differences were regarded as significant at $P < 0.05$.

Results

Symptom score

The allergen challenge induced the symptoms of rhinitis in all subjects. The symptoms were most severe in group A (score 8.0 ± 0.0) followed by groups B, C, and D (scores 7.6 ± 1.3 , 7.6 ± 0.9 , and 7.3 ± 1.2 , respectively). Statistical analysis revealed significant differences between groups A and D ($F_{3,33} = 8.04$, $P = 0.001$). The symptom score was also higher in groups A and B than in group D at 4 h after the provocation ($F_{3,165} = 11.18$, $P < 0.001$), and in group A than in the other three groups at 24 h after the challenge ($F_{3,165} = 10.38$, $P < 0.001$) (Fig. 1).

No subject developed a clinical response to placebo. Only in three subjects from group A and two subjects from group B did slight itching appear during the provocation, and it lasted for several minutes after the challenge.

Cellular findings

The provocation with NRL resulted in an increase in the total number of leukocytes in nasal washings from all the groups at all time points. At 24 h after the provocation, the differences between the groups were statistically significant ($F_{3,124} = 14.12$, $P < 0.001$) – the total leukocyte count in group A was higher than in the other groups. Significant differences were observed in the total leukocyte count in group A ($F_{3,93} = 21.18$, $P < 0.001$) between 0 min and 4 h, and between 24 h and 0 min, 30 min, and 4 h after the provocation. The increase induced by NRL, as compared to placebo, was significantly higher at 4 h ($F_{1,120} = 5.47$, $P < 0.02$) and 24 h ($F_{1,120} = 49.26$, $P < 0.001$). The neutrophil proportion changed significantly in this group ($F_{3,93} = 11.06$, $P < 0.001$) – at 4 h, it was higher than at 0 h, and at 24 h than at 0 and 30 min. Significant differences were also noted in group B ($F_{3,93} = 7.58$, $P < 0.01$) – at 4 and 24 h

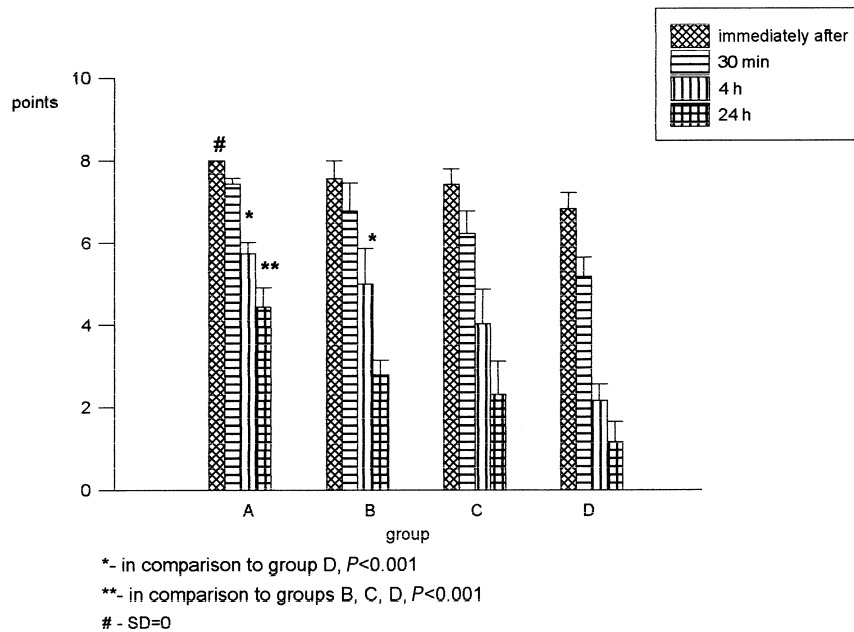


Figure 1. Evaluation of clinical score after nasal challenge test with NRL.

after NRL provocation, the percentage of neutrophils was higher than before the testing.

An analysis of the total eosinophil count revealed significant differences only in group A ($F_{3,99} = 14.59$, $P < 0.001$). The values were higher after 4 h than at 0 and after 24 h than at 0, 30 min, and 4 h. Moreover, the groups differed significantly after 24 h ($F_{3,132} = 12.22$, $P < 0.001$). In group A, the eosinophil count was higher than in the other groups. Also in group A, significant differences between the results of NRL and placebo provocation tests were observed ($F_{1,30} = 16.15$, $P < 0.001$) – the eosinophil count after NRL provocation was higher after 4 h ($F_{1,120} = 7.52$, $P < 0.01$) and 24 h ($F_{1,120} = 30.62$, $P < 0.001$) (Fig. 2).

An analysis of the proportion of eosinophils revealed significant differences between the groups ($F_{3,33} = 9.76$, $P < 0.001$) – in group A, the percentage was higher than in groups B, C, and D. The eosinophil percentage in group A was higher after 30 min ($F_{3,132} = 5.98$, $P < 0.001$) than in groups C and D, and after 4 h ($F_{3,132} = 10.08$, $P < 0.001$) and 24 h ($F_{3,132} = 14.22$, $P < 0.001$) than in groups B, C, and D. In group A, a significant increase in the proportion of eosinophils after 30 min, and 4 h and 24 h ($F_{3,99} = 29.04$, $P < 0.001$) was found. A stronger effect of the provocation with NRL than placebo was also noted in this group ($F_{1,30} = 17.69$, $P < 0.001$) (Fig. 3).

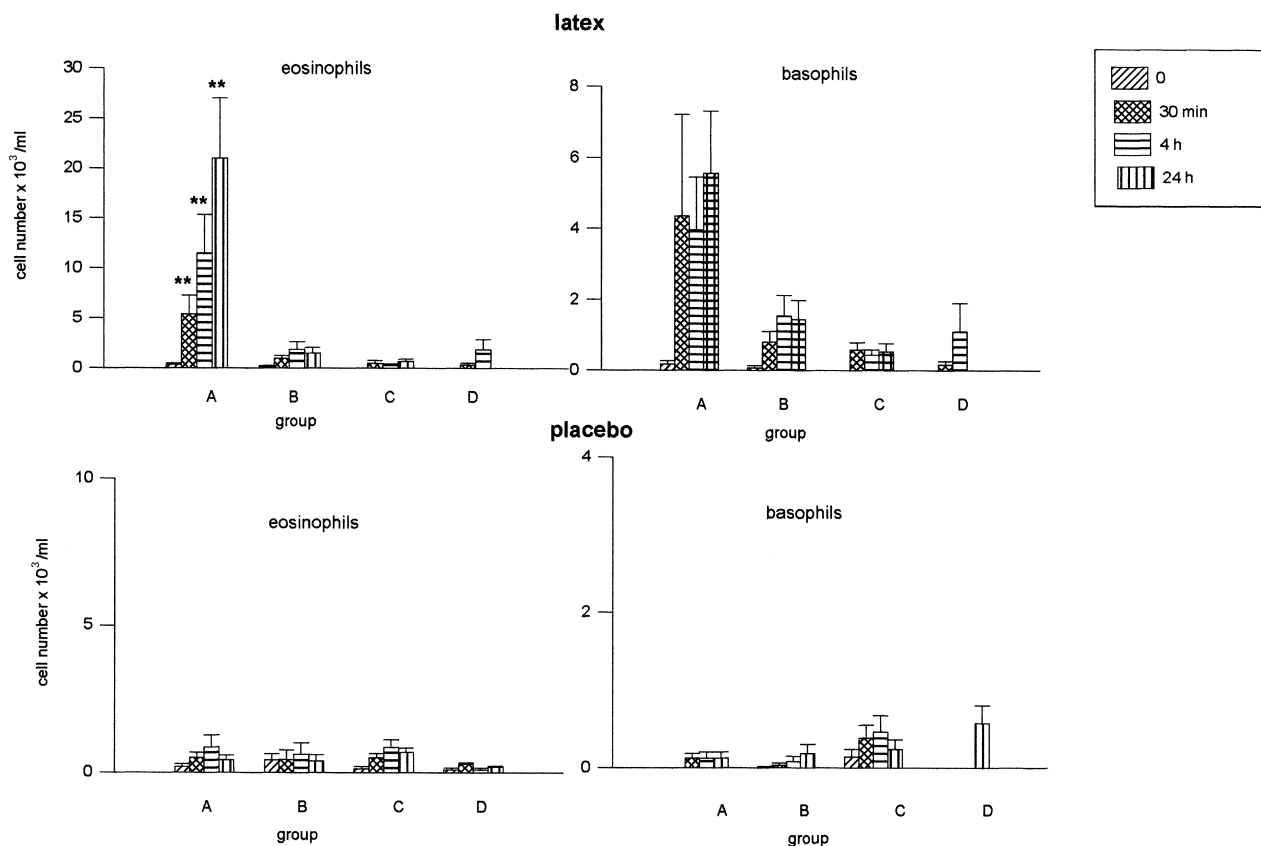
An analysis of the changes in the total basophil count did not reveal significant differences between groups, but the comparison of the effects of NRL and placebo provocation showed significantly higher values in group A after allergen provocation ($F_{1,30} = 9.37$, $P < 0.001$) (Fig. 2).

The basophil proportion was higher in group A than in groups C and D ($F_{3,33} = 7.39$, $P < 0.01$). Significant differences were found in group A ($F_{3,99} = 36.75$, $P < 0.001$) – the percentage was higher after 30 min, 4 h, and 24 h than before the challenge – and in group B ($F_{3,99} = 5.86$, $P < 0.02$) – the basophil proportion after 4 and 24 h was higher than the initial value. In group A, the effect of NRL provocation was significantly stronger than the response to placebo ($F_{1,30} = 32.46$, $P < 0.001$) (Fig. 3).

The provocation with placebo did not produce statistically significant changes in the cytograms of the nasal washings. Only the total leukocyte count and the proportion of neutrophils showed an increasing tendency at successive time points, but this finding had no statistical significance.

Biochemical findings

An effect of the group factor on the permeability index in NRL provocation was found ($F_{3,31} = 8.01$, $P < 0.01$). Significant differences between the groups were observed at 30 min ($F_{3,124} = 6.96$, $P < 0.001$) – in group A, the permeability index was higher than in groups B and C – and at 4 h ($F_{3,124} = 10.80$, $P < 0.001$) and 24 h ($F_{3,124} = 12.61$, $P < 0.001$) – after the provocation, the permeability index in group A was higher than in all other groups. Moreover, in group A, significant differences could be observed between permeability indices at successive time points ($F_{3,93} = 15.56$, $P < 0.001$) – at 30 min, 4 h, and 24 h, the values were higher than before the challenge. The effect of NRL provocation in this group was also stronger ($F_{1,30} = 16.55$, $P < 0.001$) (Fig. 4).



** - in comparison to 0, $P < 0.001$

Figure 2. Changes in total eosinophil and basophil number induced by nasal challenge test with NRL and placebo.

Protein analysis of the nasal washings (including the mucosal/vascular permeability index) did not show the influence of placebo provocation in any of the groups (Fig. 4).

An increase in ECP concentration was found both after NRL and placebo provocation in all the groups at all time points, but the differences were statistically significant only in group A (ECP: $F_{3,90} = 23.48$, $P < 0.001$) – at 24 h as compared to 0, 30 min, and 4 h after allergen challenge. The groups differed significantly at 24 h after challenge (ECP: $F_{3,120} = 13.19$, $P < 0.001$) – the concentrations in group A were significantly higher than in all the other groups (Fig. 5).

The influence of nasal challenge on FEV_{1s} and PEF

Neither NRL nor placebo provocation induced significant changes in FEV_1 and PEF in any subject.

Discussion

In the case of exposure to occupational allergens, the clinical history may be far from conclusive; hence, appropriate provocation testing should be carried out (6). The specific challenge test is used to confirm the

relationship between the occupational agent and the symptoms and to reproduce the temporal relationship between exposure and the onset of symptoms. Since the bronchial challenge may sometimes be complicated to perform, or even dangerous, we adopted the “nasal pool” provocation as a useful and safer method (14, 15).

Skin testing performed with natural latex has been demonstrated to be the best method of screening and diagnosing NRL allergy, and we consider this technique a suitable reference method (1, 16, 17). The patients with positive results of RAST to natural latex have not been included in the study. NRL RAST seems to detect highly allergic patients accurately, and we presume that no challenge tests are needed in these patients (1, 18).

Nasal provocation with the NRL glove extract has for the first time been performed by Jaeger et al., but its results were assessed only by rhinomanometry (19). The nasal challenge method, along with an estimation of the cell number and the biochemical examination of the lavage fluid or secretion, allows one to distinguish between the allergic and irritant effects of various substances on the respiratory system. In the present study, all the groups, including controls, demonstrated rises in their nasal symptoms immediately after NRL challenge, but not after placebo challenge, suggesting

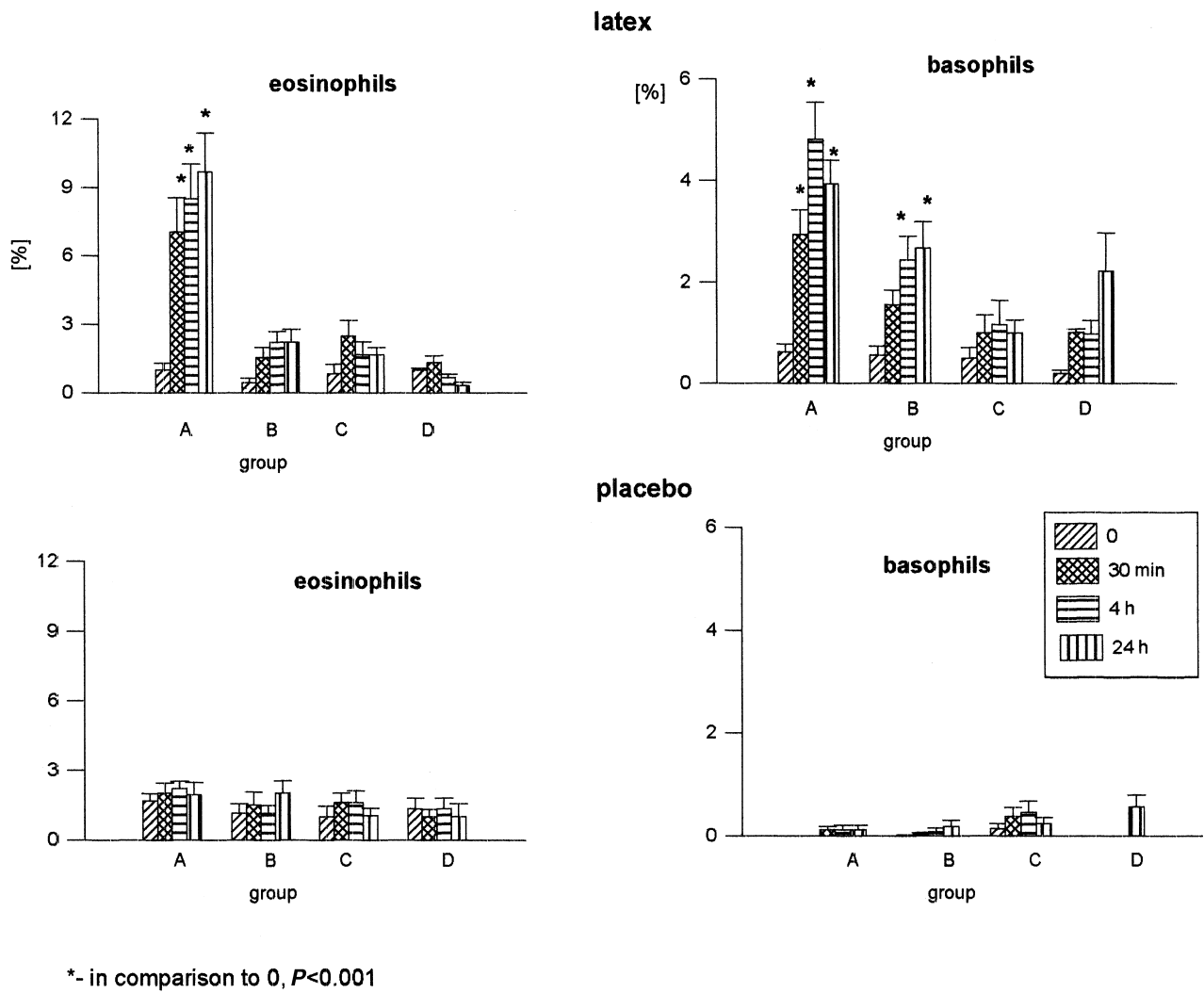


Figure 3. Changes in eosinophil and basophil percentage induced by nasal challenge with NRL and placebo.

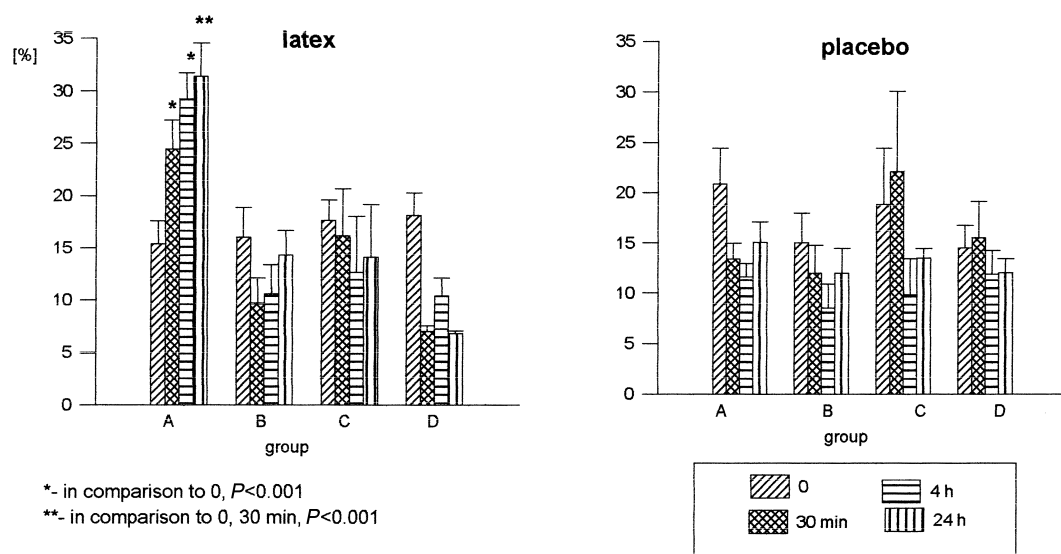


Figure 4. Changes in permeability index induced by nasal challenge test with NRL and placebo.

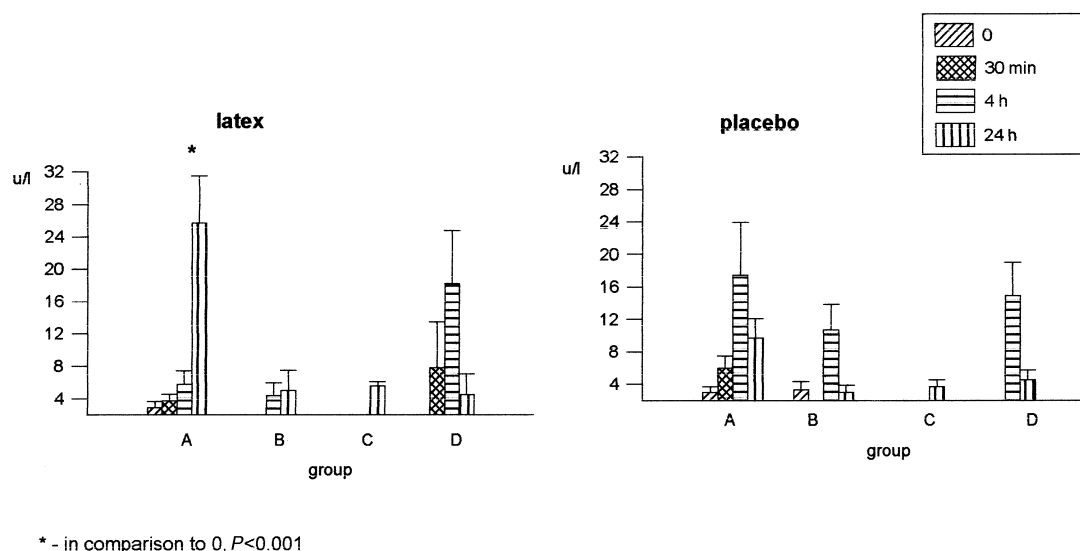


Figure 5. Changes in concentration of ECP in nasal lavage induced by NRL and placebo.

that the NRL solution used for provocation might contain impurities that provoke nonspecific irritation. The most common side-effects with the use of different rubber products are of toxic nature (20). This makes the nasal symptoms a useless parameter in the separation of responders from nonresponders, immediately after the challenge.

An increase in the number of granulocytes and total protein level in the nasal lavage fluid has been observed in the irritant-type reaction. It was, however, brief and did not affect the relative number of eosinophils and basophils or the relative concentration of albumin (14). In some healthy subjects and in patients treated with placebo, an increase in the eosinophil number occurred, but only by 1–3 cells. In the present study, we observed the typical allergic reaction of a prolonged increase in the total cell count and eosinophil number, a less pronounced but very specific increase in metachromatic cell number, and an increase in albumin/protein ratio for up to 24 h, as well as in the symptom score value after allergen challenge, in almost all the patients with positive results of SPT with NRL. Another event found after allergen challenge in this group was a prolonged increase in ECP level. An increase in ECP concentration was at first observed 4 h after nasal challenge, along with a significant increase in the eosinophil count and permeability index. Wang et al. noted that a combined measurement of the percentage of eosinophils and the ECP concentration in nasal secretion seems to be useful for monitoring and assessing the condition of chronic nasal inflammation in patients with allergic rhinitis (21). Raulf-Heimsoth et al. also observed a significantly higher ECP level in nasal fluid and in the eosinophil number and percentage in nasal brush 24 h after NRL challenge with powdered NRL gloves in NRL-allergic patients with respiratory symptoms (22). We also regarded the nasal challenge test as positive when the

increase in eosinophil number and in permeability index persisted for up to 24 h after the challenge.

A statistically significant difference in basophil proportion was also noted between group B and other control groups. Group B comprised atopic patients with occupational exposure to NRL, thus being a high-risk group for NRL sensitization. One cannot exclude the possibility that among the patients from this group there might have been a patient with low antilatel IgE level who would respond to the mucosal provocation by cytologic abnormalities in the nasal lavage fluid or with cross-reactivity between tomato and NRL (23, 24). Positive challenge indicates only a patient's sensitivity to the allergen and may be unrelated to the disease. In such a patient, further exposure to the allergen may lead to a clinical state of the disease and respiratory impairment. Inhalant allergens can also produce only respiratory symptoms without positive skin reaction to their extracts (6).

The results of the study indicated the clinical relevance of nasal allergen challenge and SPT. Nasal provocation allows one to identify patients with positive results of the SPT to NRL and the rhinitis symptoms related to NRL exposure in the workplace.

According to recent studies, rhinitis is nearly a universal phenomenon in patients with allergic asthma, occurring in 99% of adults; thus, the nasal provocation test can indicate patients with NRL-related asthma in almost all cases (25). The results of our studies demonstrated no bronchoconstriction after nasal provocation with the allergen in patients with asthma and rhinitis – the nasal challenge is definitely a safer diagnostic alternative than bronchial challenge for such patients. Nasal challenge also seems to be useful in patients with natural latex allergy of the airways. However, the common application of the method is limited by a possibly nonspecific irritation induced by

NRL solution, as not every clinician is capable of counting eosinophils and estimating levels of ECP and markers of vascular permeability in nasal secretions. It is possible to reduce the nonspecific reactivity regarding the symptoms observed in the present study by improving the purity of the NRL solution. These symptoms would be very helpful in identifying the

patients who develop only the early phase of allergic reaction.

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