The role of allergic rhinitis in nasal responses to sudden temperature changes

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Background: Air conditioning–induced rhinitis in allergic individuals is a common epidemiologic finding, but its physiopathology is still controversial. The aim of this study was to describe and compare the effects of experimental air conditioning temperature changes on the nasal mucosa of individuals with persistent allergic rhinitis compared with a control group.

Methods: A case-control challenge study was performed in a laboratory of thermal comfort with experimental twin challenge chambers set at a 12°C difference in temperature. A group of 32 patients with persistent allergic rhinitis and a group of 16 control subjects were exposed for 30 minutes, 3 times alternately in each chamber. Nasal symptom scores were recorded and nasal samples collected before, immediately after, and 24 and 48 hours after the challenge.

Results: The rhinitis group showed a higher symptom score, epithelial shedding, percentage of eosinophils, total inflammatory cells, leukotriene C_4, eosinophil cationic protein, albumin, and tryptase levels compared with controls. There was also a significant increase in symptom score, total cells recovered, percentage of eosinophils, epithelial shedding, albumin, myeloperoxidase, and soluble intercellular adhesion molecule 1 in both groups compared with baseline levels.

Conclusion: Sudden temperature changes led to a more pronounced inflammatory nasal response in the rhinitis group with the recruitment and activation of eosinophils.

Clinical implications: Persistent allergic rhinitis is a risk factor for developing sudden temperature change–related rhinitis even in the absence of allergen exposure. (J Allergy Clin Immunol 2006;118:1126-32.)

Key words: *Indoor air quality, environmental illness, air conditioning, inflammatory mediators*

Abbreviations used

ECP: Eosinophil cationic protein
IAQ: Indoor air quality
LT: Leukotriene
PAR: Persistent allergic rhinitis
sICAM-1: Soluble intercellular adhesion molecule 1

Indoor air quality (IAQ) is rapidly gaining importance as a public health issue worldwide, as urban society spends progressively more time indoors. IAQ-related problems are reported in various climatic conditions including tropical climates,[1] and are considered the most common environmental health issue faced by clinicians.[2] The factors associated with IAQ have a complex interaction and include temperature, humidity, air exchange rates, exposure to organic and inorganic indoor air pollution, odors, air movement, and work and psychosocial factors. The changes in the work pattern of the new office environment are characterized as dynamic, with interactive project teams and different or shared workplaces.[3] This increased movement can lead to increased exposure to different indoor and outdoor conditions with wide range and sudden temperature changes. The presence of air conditioning systems[1,4,5] and atopic phenotype[6-8] are risk factors consistently associated with mucosal symptoms in IAQ epidemiologic studies. Interestingly enough, most studies do not find causal allergen exposure in nonresidential and nonindustrial settings.[9-11]

Allergic rhinitis is clinically defined as a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose. Symptoms of rhinitis include rhinorrhea, nasal obstruction, nasal itching, and sneezing, which are reversible spontaneously or with treatment. Allergic rhinitis is a global problem affecting 10% to 25% of the population and can be subdivided into intermittent or persistent disease according to the frequency of the symptoms.[12] Allergen exposure is the most potent trigger of nasal symptoms, but the nasal mucosa of the allergic population has a lower threshold to various stimuli.[13] Considering that cold and dry air can induce mast cell degranulation in individuals with allergy,[14] the role of air conditioning–related sudden temperature changes per se in the atopic population remains to be elucidated. The aim of the current study was to induce experimental sudden temperature

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changes to describe possible symptoms and inflammatory changes in the nasal mucosa of individuals with allergy compared with controls.

METHODS

Selection of individuals

After the authorization of the ethics committee of the State University of Sao Paulo (Protocol 930/02), 48 individuals who signed a consent form were selected out of patients with allergy and healthy individuals. The participants in the study ranged in age from 20 to 45 years and were not undergoing treatment for endocrine, infectious, or rheumatologic diseases. They underwent a medical history, physical examination, and skin prick testing with standardized allergens. The tests were performed in duplicate with epicutaneous puncture and evaluated after 20 minutes according to a standard procedure. Tests were considered positive for allergen sensitization with mean arithmetic papules larger than 4 mm for allergens. Individuals with positive reactions to saline or negative reactions to histamine were excluded. The case group consisted of 32 individuals, 22 men and 10 women who had allergic rhinitis (nasal pruritus, aqueous nasal discharge, sneezing, and nasal blockage) and positive cutaneous tests for at least 1 allergen (*Dermatophagoides pteronyssinus*, *Blomia tropicalis*, *Aspergillus fumigatus*, *Alternaria alternata*, dog and cat epithelium, 10 mg/mL histamine and saline (ASAC PHARMA, International Pharmaceutical Immunology, Alicante, Spain). All patients from the rhinitis group were classified as persistent allergic rhinitis (PAR) according to the Allergic Rhinitis and its Impact on Asthma study criteria.[12] The control group was composed of 8 men and 8 women without history or symptoms of allergic diseases and who had negative tests for allergic diseases, age-matched with the case group. Another group of 6 individuals with PAR not exposed to temperature changes was used to address the variance in the results because of nasal sampling and natural variation in nasal epithelium in allergic rhinitis. Individuals with evidence of viral illnesses, immunologic impairment, or use of any antihistamine or anti-inflammatory medication 14 days before temperature tests were excluded.

Temperature tests

The selected population dressed in standardized thermal protection of 1.0 clothing units (CLO).[15] Temperature tests were conducted in twin isolated chambers controlled for temperature, humidity, sound, light, and ventilation. The chambers had exclusive air supply from a fan coil with a nominal output of 340 m^3/h and a chiller with a capacity of 5 tons of refrigeration. The experimental system supplied air exchange rates of more than 27 m^3/h/person, which assured carbon dioxide levels in the chambers of less than 700 parts per million. Individuals were introduced into separate chambers for temperature challenges. The 2 chambers had a temperature difference of 12°C or 26.6°F, where the warm chamber was 26°C (78.8°F) and the cold chamber 14°C (57.2°F), both with the relative humidity of the indoor air set at 60% ± 2%. After 30 minutes of acclimatization, individuals were asked to move from one chamber to the other. All participants completed arbitrarily chosen 3 rounds of temperature changes totaling 3 hours of challenge and after final acclimatization were re-examined and submitted to nasal sampling before, immediately after, and 24 and 48 hours after challenge.

Clinical evaluation

All participants had a medical history taken and were given a physical examination to complete the Meltzer Modified Rhinitis Score.[16,17] In brief, symptoms of nasal pruritus, nasal drip, nasal blockage/sneezing, and post nasal drip and physical findings of rhinorrhea, inferior turbinate edema, inferior turbinate appearance, and oropharyngeal alterations were quantified on a scale of 0 to 3 for each item, with a maximum total score of 24 points.

Nasal samples were obtained before, immediately after (4 hours), and 24 and 48 hours after beginning the challenge. Nasal samples were obtained by using nasal brushes with gentle rotational movement on the superior part of both inferior turbinates for 30 seconds according to a previously described technique.[18] Samples were diluted in 5 mL PBS. Afterward, samples were centrifuged in a refrigerated centrifuge at 170*g* for 10 minutes. Aliquots of the supernatants were frozen at –80°C. The cell pellet was resuspended in 1 mL PBS. One volume of a solution containing 0.5% crystal violet dissolved in 30% acetic acid was added to 9 volumes of the cell suspension. The total cell number was determined by counting in a hemocytometer. Differential cell counts were performed after cytocentrifugation and staining with hematoxylin/eosin (Hema 3, Fisher Scientific Company, Swedesboro, NJ).

Inflammatory mediators

The levels of the following mediators were measured in cell-free supernatants of nasal samples:

- Leukotriene (LT) C_4 and histamine were assayed by using commercially available ELISA kits (Cayman Chemical Co, Ann Arbor, Mich). Detection limits were 10 pg/mL and 0.5 nmol/L, respectively.
- Soluble intercellular adhesion molecule 1 (sICAM-1) levels were determined by using an ELISA kit (R&D Systems, Abingdon, United Kingdom) with a detection limit of 0.35 ng/mL.
- Tryptase and eosinophilic cationic protein (ECP) were determined with commercially available assays (Pharmacia CAP System, Uppsala, Sweden) according to the manufacturer's instructions. Detection limits were 2 μg/L for the ECP and 1 μg/L for the tryptase.
- Albumin was measured by means of nephelometry (N Antiserum anti-Albumin, Dade Behring, Deerfield, Ill), with a detection limit of 1.4 mg/L.

Myeloperoxidase activity in cell lysates was quantified by changes in absorbance (OD 460 nm) resulting from decomposition of H_2O_2 in the presence of orthodianisidine.[19]

Levels of indoor pollution

Indoor air was monitored for the following:

- Viable fungal spores. Samples were collected with a 6-stage Andersen sampler (Andersen Samplers Inc, Atlanta, Ga), and Sabouraud dextrose agar (Acomedia, Baltimore, Md) Petri dishes with 10 μg/mL of agar sabouraud dextrose with chloramphenicol were used for the culture, identification, counting, and measurement of airborne fungal spores.
- Particulate matter, using the manual gravimetric method (Handi-Vol, Rio de Janeiro, Brazil) and laser particle counter (Hand-Held 3016, Lighthouse, Tulsa, Okla).
- Carbon dioxide levels in parts per million (CO_2 monitor 535, Testo, Hamburg, Germany).

Statistical analysis

Cell count for each cell type was expressed as percentage of total cells. Differences among groups and time were examined by ANOVA repeated measures to compare group differences (group effect) and to compare variations in time after the challenge (time effect) in both groups. These results were investigated in depth using post hoc comparisons (Newman-Keuls test). Previous results from a study of 17 cases and 16 controls showed a minimum difference between groups of 9.23% among all variables studied. A 2-tailed *t* test was used for power calculation, indicating that 32 individuals with

rhinitis and 16 controls would be required to have more than 80% power to detect group differences in most inflammatory mediators, using traditional α levels set at 0.05. To evaluate the intrinsic variance of nasal mucosa components and the effects of the sampling technique of the nonexposed individuals, changes in values were compared by using the Friedman ANOVA. For a possible relationship between eosinophils and ECP, and neutrophils and myeloperoxidase changes, the Spearman rank correlation coefficient was determined. *P* values less than .05 were considered significant. Logarithmic transformation was used for variables that did not show a normal distribution.

Role of the funding source

The sponsor of the study was a government organization that supports research and had no role in the study design, data collection, data interpretation, and writing of the report. The principal investigators had full access to all data of the study and the final responsibility for the decision to submit the report for publication.

RESULTS

There was a high rate of compliance in the procedures, totaling 98.5% of the scheduled nasal samples and clinical evaluations. Indoor pollution level of viable fungal spores was 131 ± 108 (mean ± SD) colony-forming units per square meter, mean carbon dioxide level was 408 ± 108 ppm, and particulate matter was 5.78 ± 3.87 μg/m^3. The effects of the challenge were considered concerning differences from baseline levels (time effect) and differences between the rhinitis and control groups (group effect).

Symptom scores and nasal cytology

Symptom scores were higher in the rhinitis than in control group during all of the experiments ($P < .001$) and were significantly elevated in both groups 4, 24, and 48 hours after beginning the challenge compared with baseline ($P < .001$; Fig 1, *A*). Total cell count was significantly elevated in both groups immediately after the challenge compared with prechallenge levels (time effect $P < .001$), but no difference between groups was observed ($P = .923$; Fig 1, *B*). The percentage of epithelial cells recovered was lower in the rhinitis group compared with controls (group effect $P = .049$), but in both groups, it was significantly reduced 24 hours after challenge compared with baseline levels (time effect $P < .001$; Fig 1, *C*). The percentage of inflammatory cells recovered was higher in the rhinitis group compared with controls (group effect $P < .001$). The rhinitis group demonstrated an increase in the percentage of inflammatory cells 24 hours after challenge compared with baseline (time effect $P = .017$; Fig 1, *D*). The eosinophil percentage of the inflammatory cells recovered was also higher in the rhinitis group compared with controls (group effect $P < .001$), but the percentage of eosinophils was statistically increased in both groups after challenge compared with baseline levels (time effect $P < .001$). In the rhinitis group, the eosinophil percentage was higher at 24 hours compared with baseline ($P = .018$) and to 4 hours ($P = .011$) after challenge. In the control group, baseline levels were lower than that at 24 hours ($P = .007$) and 48 hours ($P = .003$) after challenge (Fig 1, *E*). The other cellular elements such as neutrophils and macrophages did not show differences between groups or from baseline levels.

Inflammatory mediators

Histamine levels did not demonstrate differences between the rhinitis and control groups (group effect $P = .408$), and no differences from baseline were found in either group after challenge (time effect $P = .146$; Fig 2, *A*). LTC_4 levels were higher in the rhinitis group (group effect $P = .003$). In the rhinitis group, there was a significant increase 24 hours after challenge compared with baseline levels (time effect $P = .016$; Fig 2, *B*). Albumin levels were higher in the rhinitis group compared with controls ($P = .004$). Compared with baseline, albumin levels were significantly elevated 4 hours and 24 hours after challenge in both groups (time effect $P < .001$), but it remained elevated after 48 hours in the rhinitis group ($P < .001$; Fig 2, *C*). Myeloperoxidase levels did not show differences between groups (group effect $P = .620$), but baseline levels were significantly increased 4 hours, 24 hours, and 48 hours after challenge in both groups (time effect $P < .001$; Fig 2, *D*). The rhinitis group had a weak positive correlation between neutrophils and myeloperoxidase levels (Spearman $\rho = 0.178$; $P = .046$), whereas the controls had no correlation (Spearman $\rho = 0.132$; $P = .307$). sICAM showed no differences between groups (group effect $P = .977$), but in the rhinitis group, there was a significant increase at 4, 24, and 48 hours in sICAM-1 levels compared with baseline (time effect $P < .001$; Fig 2, *E*). ECP levels showed marked differences comparing individuals with rhinitis with controls (group effect $P < .001$). The rhinitis group demonstrated a significant increase from ECP baseline levels at 4, 24, and 48 hours after challenge (time effect $P < .001$; Fig 2, *F*). The rhinitis group showed a positive correlation between eosinophils and ECP levels (Spearman $\rho = 0.417$; $P < .001$), whereas the controls showed no correlation (Spearman $\rho = 0.207$; $P = .107$).Tryptase levels were higher in the rhinitis group ($P < .001$). In the rhinitis group, levels 4 and 24 hours after exposure were higher than baseline (time effect $P < .001$; Fig 2, *G*).

Nonexposed individuals

A significant increase in albumin samples 24 hours after baseline levels was observed ($P = .011$). The other measurements did not demonstrate significant variation (data not shown).

DISCUSSION

These results indicate that air conditioning–induced temperature changes can cause an immediate nasal response consisting of significant desquamation of mucosal epithelial cells in both groups, but more pronounced in the rhinitis group. The rhinitis group showed an amplified reaction suggestive of a dual inflammatory process with a late-phase response characterized by an inflammatory

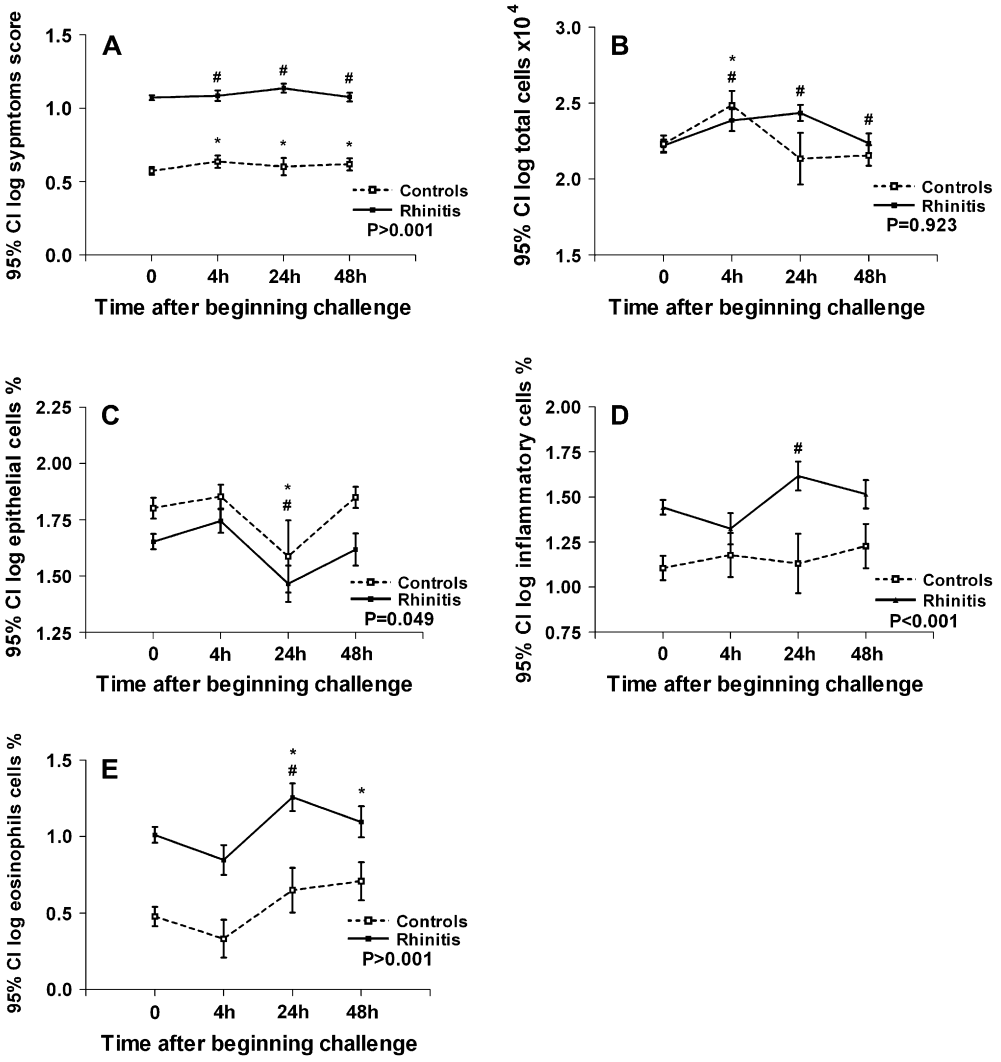

FIG 1. Ninety-five percent CI for baseline levels (0), immediately after (4 hours), 24 hours after, and 48 hours after of the following. **A,** Symptom score (*controls: 0 < 4 hours, 24 hours, and 48 hours; #rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **B,** Total cell count (*controls: 0 < 4 hours; #rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **C,** Epithelial cells (*controls: 0 > 24 hours; #rhinitis: 0 > 24 hours). **D,** Inflammatory cells (#rhinitis: 0 < 24 hours). **E,** Eosinophils (*controls: 0 < 24 hours and 48 hours; #rhinitis: 0 < 24 hours). *P* levels for repeated measures ANOVA comparing rhinitis and controls.

response with significant leukocyte and eosinophilic infiltration and eosinophil and neutrophil activation with a peak 24 hours after challenge. In addition, all individuals showed increased levels of myeloperoxidase and sICAM-1 after challenge, suggestive of an active inflammatory process with participation of β2 integrins and common inflammatory mediators. To the best of our knowledge, this is the first time that the mechanism of sudden temperature change intolerance induced by air conditioning has been described in an atopic population.

Subjective perceptions are prone to be influenced by various personal factors including mood, personal confidence, and other characteristics related to personality and circumstances. This could influence self-reported symptoms such as nasal itching, sneezing, and other subjective perceptions, but should not interfere with a blind examiner evaluation. On the other hand, simulated conditions can eliminate job-related stress and dissatisfaction, which consistently influence IAQ perception.[20] Indoor pollution levels were much lower than those recommended for acceptable indoor air quality[21] during the whole experiment and were considered consistently low. Apart from the experimental temperature changes, the indoor specifications described are not related to measurable respiratory alterations.[22,23] Because allergic exposure at home was not addressed, additional allergen exposure cannot be ruled out, in spite of no evidence of increased exposure compared with baseline throughout the experiment. Redundant increase in most inflammatory mediators 24 hours after challenge including controls also does not favor other sources of stimulation for the results presented. Nasal brushing has gained increasing interest because

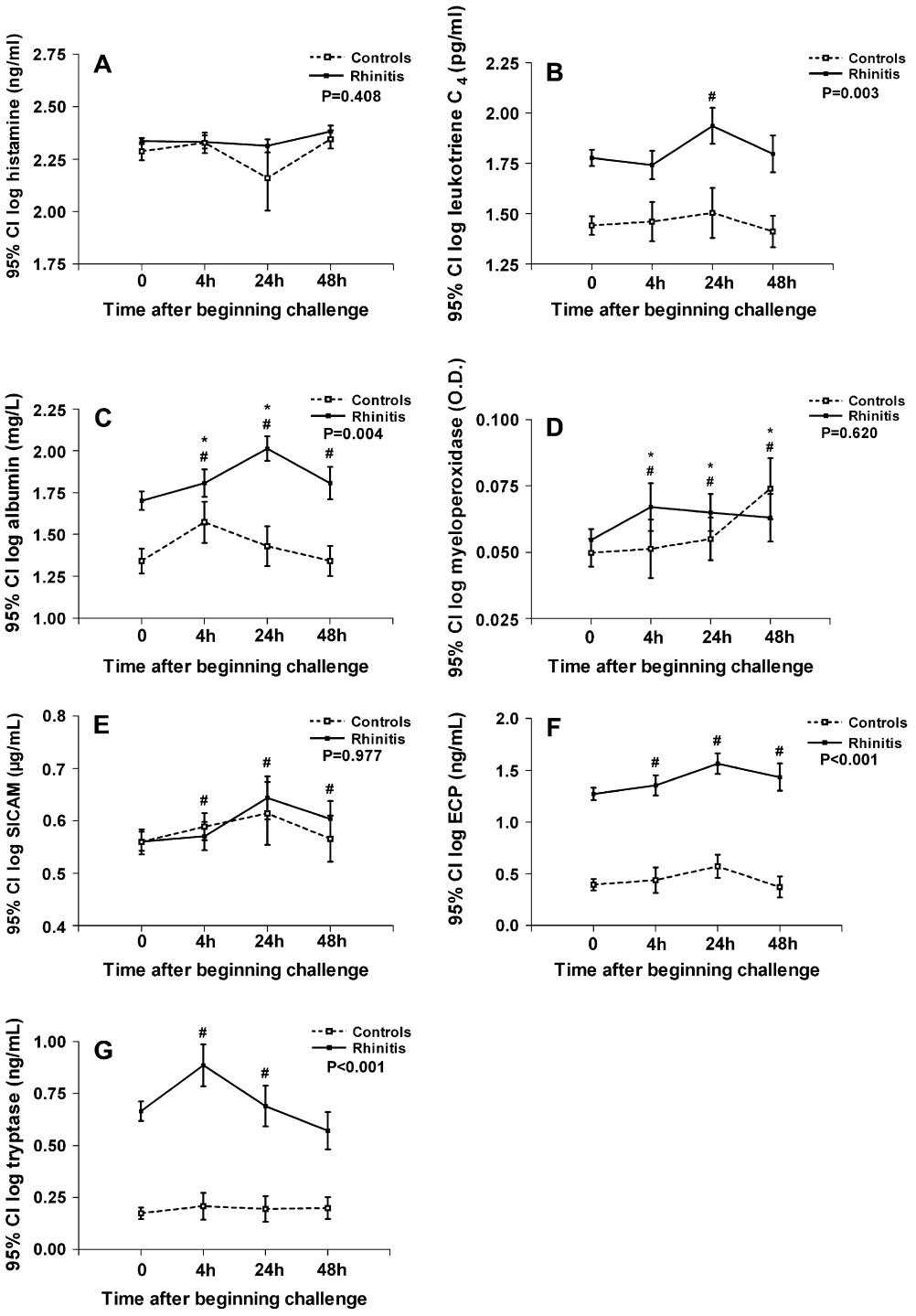

FIG 2. Ninety-five percent CI for baseline levels (0), immediately after (4 hours), 24 hours after, and 48 hours after of the following. **A,** Histamine levels. **B,** LTC_4 levels (#rhinitis: 0 < 24 hours). **C,** Albumin levels (*controls: 0 < 4 hours, 24 hours; #rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **D,** Myeloperoxidase levels (*controls: 0 < 4 hours, 24 hours, and 48 hours; #rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **E,** sICAM-1 levels (#rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **F,** ECP levels (#rhinitis: 0 < 4 hours, 24 hours, and 48 hours). **G,** Tryptase levels (#rhinitis: 0 < 4 hours and 24 hours). *P* levels for repeated measures ANOVA comparing rhinitis and controls.

of its better reproducibility, better correlation with symptoms, ease of repetition, and minimal trauma.[24] Inadvertent vigorous brushing technique could lead to a repetitive predominance of red blood cells, neutrophils, and macrophage cells as a result of a traumatic rhinitis. To rule out traumatic rhinitis, a method control group with 6 individuals with PAR adopting the same nasal sampling technique and the same time intervals was performed. The results showed only a significant albumin variation. The source of albumin can be either vascular leakage or glandular origin because of its low molecular weight (66,000 d) and could be considered nonspecific variability in nasal sampling in individuals with PAR. The outcomes measures of allergic rhinitis have been recently reviewed in the Journal.[25]

Cell subsets were evaluated in terms of percentage of total cells. This approach is best for evaluating the cell profile of the mucosa, but it is limited in that total cell numbers present in samples cannot be estimated. The decreasing percentage of epithelial cells obtained during consecutive samplings is suggestive of a common epithelial shedding in both groups during temperature challenges. The high degree of epithelial shedding in the anterior nasal turbinate and eosinophil recruitment is similar to that observed in individuals with allergy during natural allergenic exposure.[26] Eosinophils are considered the most prominent effector cells in the late-phase response, and their role in the pathogenesis of allergic diseases is believed to be critical. Eosinophils are in fact able to produce a wide array of proinflammatory cytokines and to release cytotoxic proteins, including major basic protein, eosinophil-derived neurotoxin, eosinophil peroxidase, and ECP, all potentially harmful for the integrity of the nasal and bronchial mucosa.[27] Accordingly, a full comprehension of the mechanisms capable of modulating the recruitment and inflammatory activities of this important cell appears to be crucial. Although late-phase nasal response is difficult to establish, the increasing leukocyte recovery from the nasal mucosa, with a significant rise in percentage of eosinophils that were positively correlated with the ECP, is suggestive of a progressive inflammatory response occurring more intensely 24 hours after challenge in the rhinitis group.

Although we found significant increases in the eosinophil counts in nasal mucosa, there was no evidence of alteration of baseline histamine levels after challenge (Fig 2, *A*). Histamine is a major contributor to disease expression through its action on neural and vascular receptors within the nose, inducing nasal itch, sneeze, rhinorrhea, and nasal blockage. These effects are predominantly mediated via H_1 receptors. Unchanged levels of histamine in samples probably reflect the brief availability of free histamine in nasal fluids.[28] The LTC_4 is generated by the arachidonic acid pathway via 5-lipoxygenase. Its levels classically rise on IgE-dependent stimulation, but also during upper respiratory tract viral infections.[29] A late increase in nasal LTC_4 levels but not in LTB_4 has been described with antigen stimulation,[30] but not with nonspecific nasal stimulation to our best knowledge.

Albumin is a useful marker of acute plasma protein exudation that occurs in response to a wide range of stimuli such as histamine, allergens, kinins, and substance P. We observed an increase in albumin levels in both groups compared with baseline levels, but higher and more persistent levels in the rhinitis groups (Fig 2, *C*). Albumin leakage has already been demonstrated with irritant stimulus in individuals with allergic rhinitis in the absence of allergen exposure.[31]

Myeloperoxidase is present in neutrophil granules and has been used as a marker of cell activation in acute sinusitis with no distinction between atopics and nonatopics.[32] The marked elevation observed in myeloperoxidase levels compared with baseline levels (Fig 2, *D*) indicates neutrophil activation in both groups that persisted for 48 hours after temperature changes.

Eosinophil cationic protein is present in eosinophil granules and is released during eosinophil activation and in late-phase reaction after allergen challenge.[12] Interestingly enough, the association of elevated ECP levels associated with urban living environments is suggestive of the activation of nasal mediators and amplification of the inflammatory response because of nonallergenic stimuli, which has gained recent attention.[33,34] Mast cell involvement is also critical in the immediate and late-phase allergic nasal inflammatory reaction, and β-tryptase levels are markers of mast cell involvement. Our results showed increased tryptase levels in the rhinitis group with an earlier elevation compared with the other mediators evaluated. A possible early mast cell involvement after cold air exposure in allergic individuals has already been described.[14] It appears that longer-lasting sudden temperature changes in the lower range could have the same effect as much colder temperatures (–3°C to –10°C) and lower relative humidity (<10%) for short periods used by Togias et al.[14]

Adhesion molecules may act as important inflammatory molecules by causing the adherence and accumulation of inflammatory cells such as eosinophils at the foci of inflammation. Intercellular adhesion molecule 1 on endothelium plays an important role in the migration of activated leukocytes to sites of inflammation. Intercellular adhesion molecule 1 is shed by the cell and detected in plasma as sICAM-1. The regulation and significance of sICAM-1 is yet unclear, but sICAM-1 is increased in many pathological conditions, including allergic reactions and viral diseases induced by rhinovirus.

Challenges with nonallergenic stimuli on target organs of allergic diseases (eg, the nose, lung, eye, and skin) have shown that the degree of nonspecific tissue reactivity contributes significantly to the clinical picture of allergic diseases, and the heterogeneity of allergic phenotypes is best approached taking into account a wider variety of symptom triggers.[35] Considering that none of the tested individuals had nasal eosinophilic syndromes, this study contributes to the understanding of the mechanism of physical stimuli leading to inflammatory responses in the allergic population. This is in contrast with the nonallergic noneosinophilic rhinitis that, in spite of nasal hyperresponsiveness to nonallergenic stimuli, showed no demonstrable

inflammation, and it has been considered a misnomer because of the absence of inflammatory alterations.[13]

Taken together, these findings do not exactly reproduce an immediate IgE-mediated nasal response but have some features in common. They suggest the occurrence of hyperreactivity of the nasal mucosa in the rhinitis group with immediate epithelial shedding followed by an inflammatory response with the recruitment and activation of eosinophils, resulting in higher symptom scores in response to artificially induced sudden temperature changes.

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