Subjects with seasonal allergic rhinitis and nonrhinitic subjects react differentially to nasal provocation with chlorine gas

Dennis J. Shusterman, MD, MPH,[a] Mary Alice Murphy, MD, MPH,[b] and John R. Balmes, MD[a] *San Francisco, Calif.*

Background: Nasal irritation and associated symptoms (nasal congestion, rhinorrhea, and sinus headache) are important elements of the response to indoor and outdoor air pollution. Marked interindividual variability in such symptoms has been suggested clinically and epidemiologically, but little experimental data exist on this issue.

Objective: We sought to test the hypothesis that subjects with seasonal allergic rhinitis (SAR) exhibit a more marked physiologic response (congestion) after nasal irritant provocation than do nonrhinitic subjects.

Methods: We studied eight subjects with SAR and eight nonrhinitc subjects; subjects with SAR were studied out of season. In a single-blind crossover study, subjects had their nasal airway resistance (NAR) measured in triplicate before, immediately after, and 15 minutes after a 15-minute exposure to either filtered air or 0.5 ppm chlorine in filtered air, administered through a nasal mask in a climate-controlled chamber. Log-transformed NAR values were analyzed in a repeated-measures analysis of variance model, with confirmatory testing using paired t tests.

Results: The net (chlorine minus air day) percent change in NAR from baseline (before exposure) to immediately after exposure was +24% in the SAR group and +3% in the nonrhinitic group ($p < 0.05$). The corresponding net changes from baseline to 15 minutes after exposure were +21% in the SAR group and –1% in the nonrhinitic group ($p < 0.05$).

Conclusions: The observed augmented nasal congestive response of subjects with SAR versus nonrhinitic subjects to a controlled low-level chemical irritant provocation is consistent with epidemiologic surveys showing a higher prevalence of nasal symptoms among subjects with SAR than nonrhinitic subjects in environments involving irritant air pollutants. (J Allergy Clin Immunol 1998;101:732-40.)

Key words: *Seasonal allergic rhinitis, nasal irritation, rhinomanometry*

Epidemiologically, eye, nose, and throat irritation (trigeminally mediated sensations) are among the acute symptoms most frequently reported by individuals exposed to environmental tobacco smoke,[1, 2] workers in problem buildings,[3-6] and residents living near selected industrial emission sources.[7, 8] In addition, irritant-associated symptoms of the upper respiratory tract (e.g., nasal congestion, rhinorrhea, and sinus headache) may mimic an allergic response, posing a potential problem of differential diagnosis for the clinician.[9] In light of these facts, any systematic differences in nasal-irritant sensitivity within the population would be of interest to clinicians, public health practitioners, and chemical risk assessors.

Abbreviations used

ETS:	Environmental tobacco smoke
NAR:	Nasal airway resistance
RANOVA:	Repeated-measures analysis of variance
SAR:	Seasonal allergic rhinitis

Several observers have linked nasal reactivity to environmental irritants (including environmental tobacco smoke and volatile organic compounds) with preexisting allergic rhinitis. This link has appeared in epidemiologic surveys,[2, 4] as well as in limited experimental studies.[9, 10] If this link is real, it could have important implications because up to 20% of the United States population has allergic rhinitis and could therefore constitute a susceptible subgroup with respect to the effects of irritant air pollutants.[11] The current experiment seeks to examine this issue directly, comparing the physiologic reactivity to irritant provocation of two groups: subjects with seasonal allergic rhinitis (SAR) and nonrhinitic subjects.

METHODS

The study consisted of a randomized cross-over experiment in which each subject, serving as his or her own control, breathed either an irritant atmosphere (chlorine gas at 0.5 ppm) or clean air during 15-minute exposure periods 1 week apart (Fig. 1). The physiologic endpoint of interest was nasal airway resistance (NAR), as documented by active posterior rhinomanometry performed before, immediately after, and 15 minutes after the exposure sessions. Equal numbers of subjects with SAR and nonrhinitic subjects were tested, and subjects with SAR were tested out of season. The study design was counterbalanced with respect to subject gender and order of exposure (i.e., chlorine or air first). The aim of the experiment was to test the hypothesis that subjects with SAR will exhibit a more marked physiologic response (congestion) to a given nasal irritant provocation than will nonrhinitic subjects.

From [a]the Division of Occupational and Environmental Medicine and [b]the Department of Pediatrics, University of California, San Francisco.

Supported by National Institute on Deafness and Other Communication Disorders (NIDCD) grant no. K08 DC00121.

Received for publication Nov. 20, 1997; revised Jan. 22, 1998; accepted for publication Feb. 17, 1998.

Reprint requests: Dennis Shusterman, MD, MPH, Upper Airway Biology Laboratory, University of California, Berkeley/Richmond Field Station, 1301 So. 46th St., Bldg. 112, Richmond, CA 94804.

0091-6749/98 $5.00 + 0 **1/1/89690**

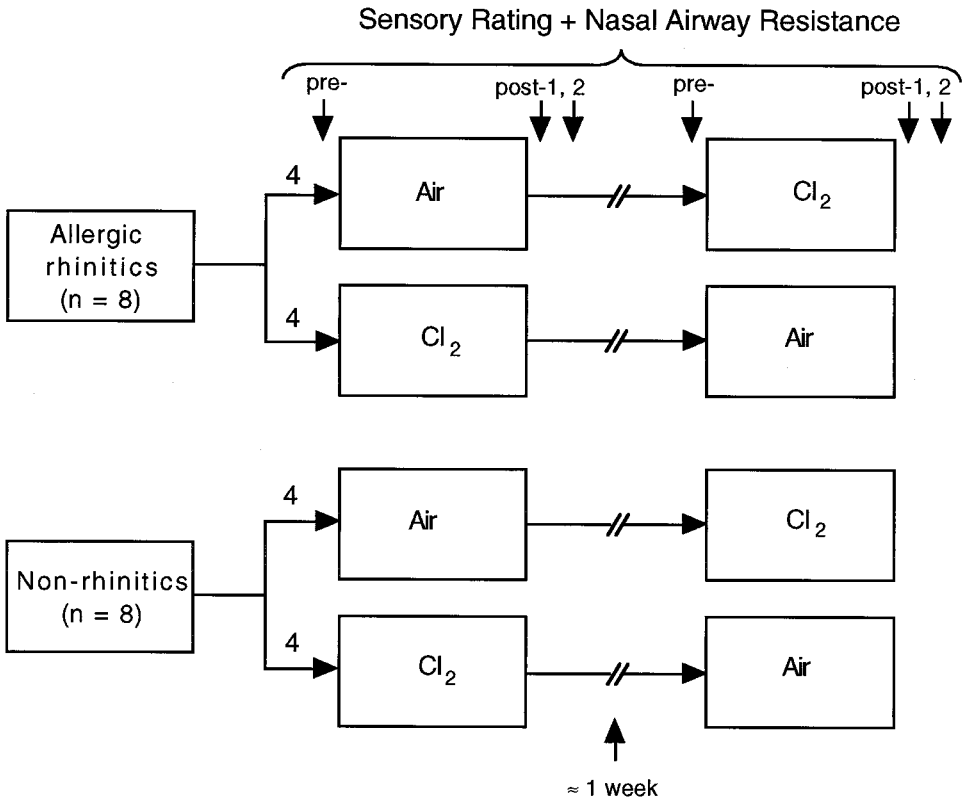

FIG. 1. Overall study design for chlorine provocation. Study was counterbalanced with respect to both gender and order of exposure (i.e., equal numbers of male and female rhinitic and nonrhinitic subjects were exposed to air or chlorine first).

Chlorine was chosen as the provocation agent of choice because (1) it is highly water soluble and hence likely to produce predominantly upper respiratory tract symptoms when administered nasally at an appropriate concentration; (2) it is considered neither a carcinogen or teratogen by the US Environmental Protection Agency; (3) as a gas its concentration is relatively easily controlled; and (4) it is environmentally relevant in terms of its role in accidental releases and household chemical mishaps.[12, 13] In keeping with the goal of achieving a predominant upper airway effect, the concentration and duration of exposure was chosen on the basis of a review of prior controlled human exposure studies with this agent.[14-16] Finally, as a further safeguard against potential adverse testing events, subjects who were identified as having asthma were excluded (see below).

Subjects were recruited by using an advertisement in a student newspaper and postings at a college campus and university medical center. The single inclusion criterion was age between 18 and 40 years. Exclusion criteria included current cigarette smoking (or within the previous 6 months), a previous diagnosis of asthma, pregnancy (current or contemplated within 6 months), active lactation, a history of severe allergic reactions (anaphylaxis or angioedema), and continuous therapy with medications having antihistaminic side effects (e.g., tricyclic antidepressants). After completion of a screening questionnaire, subjects read and signed an informed consent document approved by both the Committee on Human Research of the University of California, San Francisco and the Committee for the Protection of Human Subjects of the University of California, Berkeley. A detailed questionnaire was then administered that solicited information on prior smoking history, prior otolaryngologic diagnoses, symptoms consistent with upper respiratory tract allergies, prior allergy testing, prior allergen desensitization therapy, current medications, potential workplace exposures to irritants, and self-reported upper respiratory tract reactivity to physical and chemical agents. These latter measures included an *environmental tobacco smoke (ETS) Score* of 0 to 15 (upper respiratory tract symptoms related to ETS exposure) and a *vasomotor rhinitis score* of 0 to 5 (rhinorrhea or congestion in response to changes in temperature or humidity, exposure to household cleaning products, bright lights, perfumes or colognes, and consumption of hot or spicy foods).[17]

After questionnaire administration, potential subjects underwent skin prick testing. This involved a standardized panel consisting of 13 regionally common aeroallergens (or mixes) plus histamine and saline controls. For purposes of this study, subjects with SAR were defined as subjects with (1) a history of seasonally occurring sneezing, nasal pruritis, rhinorrhea, postnasal drip, and/or nasal congestion, with or without known precipitants; and (2) skin test reactivity to at least one seasonally occurring agent from the panel that corroborated the history. Skin test reactivity is defined as a wheal reaction to skin prick testing with a diameter greater than or equal to the histamine control. Subjects with SAR who also had skin test reactivity to perennial allergens were retained in the study if allergen control measures in their home, place of work, or both rendered them essentially symptom-free outside of their pollen season. Nonrhinitic subjects were defined as subjects who

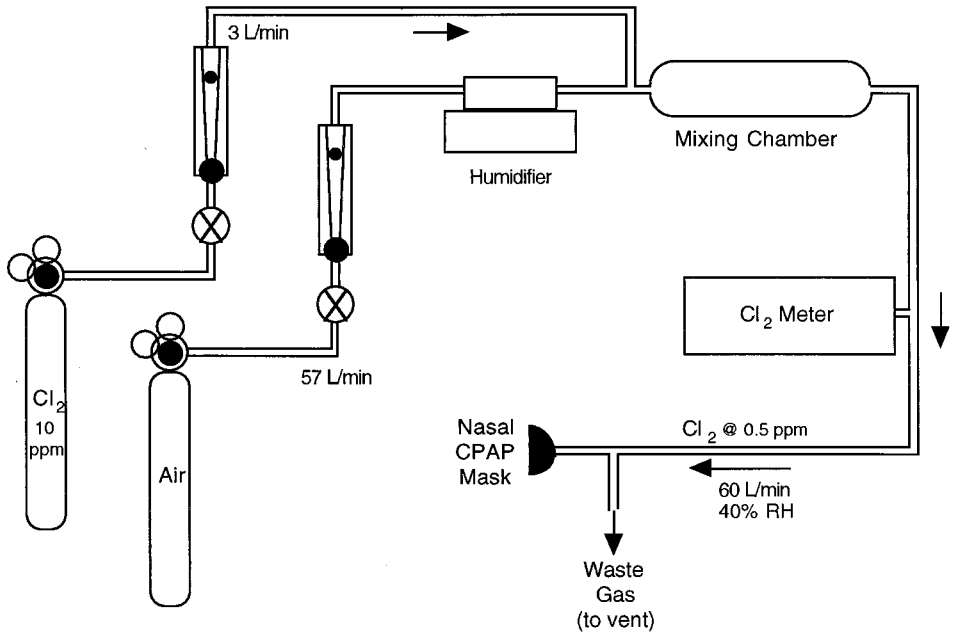

FIG 2. Schematic of chlorine dilution apparatus. Note that exposure was by nasal mask with scavenger hose attached to T-piece, allowing subject to transition from exposure to physiologic testing without leaving climate-controlled chamber. *CPAP,* Continuous positive airway pressure.

report, at most, infrequent nasal symptoms without identified seasonal variation or precipitants and with significant skin test reactivity to no more than one agent in the panel of 13 aeroallergens. Before skin testing, subjects were asked to refrain from taking antihistamines for 72 hours (terfenadine or hydroxyzine for 3 weeks, astemizole for 12 weeks).

Once subsequent testing was scheduled, subjects were asked to contact study personnel and reschedule testing if they experienced symptoms consistent with an acute respiratory tract infection or an acute exacerbation of their allergic rhinitis. Testing was delayed until subjects were asymptomatic for a period of at least 7 days (presumed allergies) or 3 weeks (suspected infection) if such symptoms were reported. Subjects were asked to refrain from wearing perfumes, colognes, or aftershaves on days in which provocation testing was scheduled. In addition, the following medication preclusions applied: no antihistamines for at least 72 hours (terfenadine and hydroxyzine, 2 weeks; astemizole, 12 weeks), no nasal or oral steroids for at least 2 weeks, no nasal cromolyn sodium for at least 48 hours, no oral or nasal decongestants for at least 48 hours, and no miscellaneous nasal sprays (e.g., saline) for at least 24 hours.

A week before provocation testing, subjects visited the laboratory to learn the technique of active posterior rhinomanometry.[18] The rhinomanometer used for this purpose was a model NR6-2 (GM Instruments, Kilwinnig, U.K.) modified to allow the use of a microbiologic filter (Model MQ306; Vacumetrics, Inc., Ventura, Calif.) between the mask and pneumotachometer. On the occasion of this visit, a variety of coaching techniques were used as needed during rhinomanometry; however, consistent with the experience of other investigators, two subjects were unable to produce meaningful pressure-volume tracings and were subsequently discontinued from the study (see below).

Provocation testing took place in a 950 cubic foot custom-built climate-controlled chamber with a charcoal- and HEPA-filtered air supply regulated at 22° ± 1° C and 40% ± 3% relative humidity. On provocation testing days, subjects entered the climate-controlled chamber and rested quietly for 15 minutes before any provocation testing occurred. During this time, the day's procedures were explained, and pulmonary peak flow was measured in triplicate with a peak flowmeter (Wright Peak Flow Mini-Meter; Clement Clarke International, Ltd.). After the acclimation period, subjects rated any preexisting nasal irritation (burning, stinging, or tingling on the inside of the nose) by adjusting the dial of a rotary potentiometer calibrated with the descriptors *none*, *slight*, *moderate*, *strong*, *very strong*, and *overpowering*.[19] The output of the potentiometer (ranging from 0.00 to 5.00 units) was recorded by the one of the investigators from the display of a digital voltmeter. A paper-and-pencil checklist labeled with the same descriptors noted above was given to the subject to rate the following additional symptoms/sensations: nasal congestion, runny nose, postnasal drip, headache, and odor. Symptom rating was followed by a triplicate measure of NAR by using the rhinomanometry technique outlined above. Each of the three NAR measurements consisted of the average, over 2 to 4 consecutive breaths, of the inspiratory and expiratory resistance calculated by using the pressure-cutoff method (75 Pa).[20] If a given recording contained a hysteresis loop that crossed the 75 Pa cutoff line, or if the automatic triggering of the rhinomanometer's software recorded fewer than two full breaths, the recording was repeated. The rhinomanometer was calibrated on a daily basis; the pressure channel to a tolerance of ±3% by using a Model 405 incline manometer (Airflow Developments, Inc., High Wycombe, G.B.) and flow to a tolerance of ±5% with a Model 235 flowmeter (Cole-Parmer/Gilmont Instruments, Vernon Hills, Ill.).

After eliciting baseline symptoms and NAR, the investigator stepped behind a translucent screen and adjusted the breathing

mixture for the nasal mask assembly. The chlorine dilution apparatus (Fig. 2) blended compressed medical-grade air (Nellcor Puritan-Bennett, San Ramon, Calif.) and compressed chlorine (diluted to 10 ppm in medical-grade air; AGA Gas, Inc., Maumee, Ohio) in a stainless steel mixing chamber (Model FMX7311; Omega Engineering, Stamford, Conn.). Diluent air, which comprised either 95% or 100% of the total flow depending on the exposure condition, was preconditioned to 22° C and 40% RH by using a Model 009700 humidifier-heater (Intertech Corporation, Bannockburn, Ill.). Immediately downstream from the mixing chamber was the sampling port for an electrochemical chlorine monitor (Model 1340; Interscan Corp., Chatsworth, Calif.), which continuously sampled the gas mixture and fed its output to a strip-chart recorder (Model 1200; Linear Instruments, Inc., Irvine, Calif.). The gas mixture was conveyed to the subject with 2.5 cm diameter corrugated respiratory tubing connected by T-piece to a nasal continuous positive airway pressure mask (Series 3121; Respironics, Inc., Murraysville, Pa.), which was sized according to the individual subject. The second limb of the T-piece connected to a low-pressure scavenger system, which led to an exhaust outside of the chamber and building. The combination of a high flow rate (60 L/min) and the scavenger system allowed subjects to breathe with negligible superimposed pressure or resistance. The chlorine meter was recalibrated on a daily basis by using the certified contents of the chlorine cylinder as the standard.

The 15-minute exposure period through a nasal mask took place on a single-blind basis, and the order of presentation was subject to limited randomization (within the constraints of the counterbalanced study design). Immediately after cessation of exposure (and then again 15 minutes later) the investigator asked subjects to rerate any sensation of nasal irritation by using the sensory potentiometer, as well as to score additional symptoms/sensations by using the paper-and-pencil checklist. The second odor rating referred to the subject's impression at the end of exposure, immediately before removing the nasal mask. NAR was remeasured times three after each symptom-rating session, and finally, pulmonary peak flow was reassessed times three. At the conclusion of the last testing session, the investigator asked each subject, "Between last week and this week, were you aware of your exposure condition?"

The statistical hypothesis tested was that subjects with SAR would show a significantly greater increase in NAR (comparing chlorine- vs air-exposure days), as well as significantly greater symptom rating increases, than would nonrhinitic subjects. For each metric, the Shapiro-Wilk test was applied for normality. Given the skewed distribution of both crude NAR and pre- to postexposure changes in NAR (as well as the wide range of baseline NAR values) proportional changes in NAR were studied throughout.[16] This metric took the form of percent change in NAR (from daily baseline) for purposes of analysis of variance (ANOVA) and graphical representation, and log-transformed NAR for repeated-measures ANOVA (RANOVA). The latter consisted of a 5-factor RANOVA model with three grouping variables (rhinitis status, gender, and order of exposure) and two trial variables (exposure condition and time). For symptom rating, the pre- to postexposure difference was examined. For each statistical hypothesis, the above RANOVA model was applied, and, if significant for the main or interactive effect of interest, confirmatory testing was performed using a subject-matched two-tailed t test comparing outcomes for the risk/exposure stratum in question. Finally, net percent change in NAR (chlorine minus air) was compared for rhinitic subjects versus nonrhinitic subjects by using an unmatched t test. It was also examined in linear regressions against vasomotor score, ETS score, and against the change in subjective congestion rating (before exposure to 15 minutes after exposure).

TABLE I. Pooled NAR data: Mean crude values (Pa/L/sec [SEM])

		Before exposure (baseline)	End of exposure	15 minutes after exposure
Rhinitic subjects	Cl_2	274 (29)	347 (59)	331 (56)
	Air	248 (18)	246 (31)	239 (26)
Nonrhinitic subjects	Cl_2	264 (19)	275 (19)	278 (15)
	Air	240 (27)	243 (27)	258 (26)

RESULTS

Subject recruitment and screening

A total of 68 subjects responded to various postings and advertisements and were provided with a screening questionnaire. Of 51 initial respondents, three were eliminated because of the presence of a contraindicating condition (asthma, pregnancy, or lactation), and 11 were held in reserve because of an excess of nonrhinitic respondents. Informed consent forms were conveyed to the remaining 37 prospective subjects, 25 of whom returned them. Detailed questionnaires were then distributed, and all were returned completed. Two subjects withdrew from the study at this stage because of time limitations, and an additional two nonrhinitic subjects were placed on reserve. Twenty-one subjects were referred for allergy skin tests. Of these, three were eliminated because of discrepancies between their questionnaire responses and skin test results. Of the 18 qualified subjects, two were unable to reproducibly perform the rhinomanometry technique. The sixteen remaining study participants were evenly divided by gender, with mean ages of 25.8 years for the SAR group and 29.4 years for the nonrhinitic group.

NAR

Table I presents the mean of crude (untransformed) NAR values for rhinitic and nonrhinitic subjects before, immediately after, and 15 minutes after air and chlorine exposures. Table II presents the corresponding values for mean percent changes in NAR from baseline for chlorine, air, and chlorine minus air (net percent change in NAR). Fig. 3 shows the mean (± SEM) net percent change in NAR from baseline for postexposure conditions 1 and 2. The mean net percent change in NAR from baseline to immediately after exposure was +24% in the SAR group and +3% in the nonrhinitic group. The corresponding net changes from baseline to 15 minutes after exposure were +21% in the SAR group and –1% in the nonrhinitic group. In the RANOVA model the interaction term for rhinitis*time*condition was significant ($p < 0.05$). In a paired t tests among rhinitic subjects (two-tailed), the distribution of NAR values (percent change from baseline) was significantly different when comparing chlorine and air days ($p < 0.05$

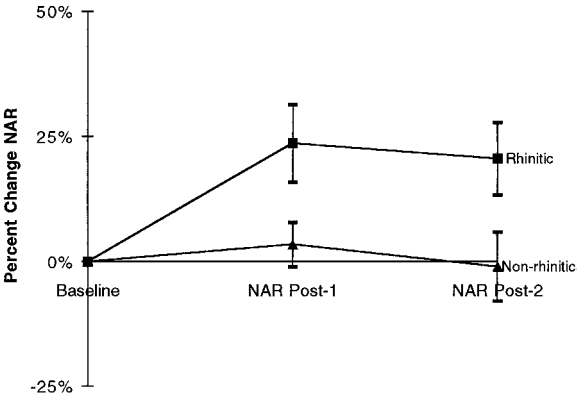

FIG. 3. Net percent change in nasal airway resistance (from baseline) ± SEM (chlorine minus air condition) for postexposure times 1 and 2 by rhinitis status ($p < 0.05$ by ANOVA at both testing times).

TABLE II. Individual NAR data: Mean percent change from baseline

	Mean % Change in NAR (SEM)	
	End of exposure	15 minutes after exposure
Rhinitic subjects		
Cl_2	+22.3% (9.4)	+16.8% (9.4)
Air	−1.4% (7.0)	−3.9% (6.2)
Net difference (Cl_2 − Air)	+23.7%	+20.7%
Nonrhinitic subjects		
Cl_2	+4.7% (4.6)	+7.4% (6.5)
Air	+1.3% (2.4)	+8.4% (4.2)
Net difference (Cl_2 − Air)	+3.4%	−1.0%
Rhinitis Effect (Cl_2 − Air, Rhinitic subjects − Nonrhinitic subjects)	+20.3%*	+21.7%*

*$p < 0.05$ for (rhinitis*time*condition) effect in repeated-measures model (chlorine vs air; post- vs preexposure; rhinitic subjects vs nonrhinitic subjects).

for both postexposure times 1 and 2); no such differences were apparent for nonrhinitic subjects (Fig. 4). Finally, examining net percent change in NAR from baseline (chlorine minus air values) in separate one-way ANOVAs (for postexposure times 1 and 2), the distribution of values for subjects with SAR and nonrhinitic subjects was significantly different ($p < 0.05$). In sum, subjects with SAR experienced congestion to a significantly greater degree than did nonrhinitic subjects when chlorine and air exposure conditions were compared immediately after, as well as 15 minutes after, provocation exposure.

In terms of self-reported nasal reactivity to irritants and physical stimuli, vasomotor scores ranged from 0 to 3, with a mean of 1.25, and ETS scores ranged from 0 to 3, with a mean of 0.31. Separate linear regressions were performed for net percent change in NAR versus each of these scores at postexposure times 1 and 2. For both testing times, the vasomotor score yielded small positive regression coefficients (+3% per score unit); however, neither was significantly different from zero. The regression coefficients for ETS score were somewhat more substantial (+13% to 14% per score unit), and for postexposure time 1, the slope was significantly different from zero. However, given the fact that only three of 16 subjects had nonzero ETS scores, and that the highest ETS score reported here was only one-fifth of the maximum possible (15), the generalizability of these findings is probably limited.

Symptoms

In general, symptom intensities were modest, with odor ratings averaging 1.25 (and irritation ratings averaging 0.61) at the end of chlorine exposure (1.00 being slight and 2.00 being moderate). Some subjects did not detect the odor of chlorine at 0.5 ppm, and a quarter of the subjects were unable to distinguish between the exposure conditions on the two testing days. On a pooled basis (subjects with SAR plus nonrhinitic subjects), significant chlorine-related increases were apparent for mean ratings of odor (end of exposure; $p < 0.001$), nasal irritation (immediately after exposure; $p < 0.01$), and nasal congestion (15 minutes after exposure; $p < 0.05$). Odor, nasal irritation, and nasal congestion were subsequently analyzed separately by rhinitis status. As noted in Fig. 5, subjects with SAR showed greater time-related increases in these three symptoms as a group than did nonrhinitic subjects. No significant exposure-related changes were observed for rhinorrhea, postnasal drip, or headache, either on a pooled or stratified basis.

Finally, the relationship between subjective and objective nasal congestion was examined. In a pooled (subjects with SAR plus nonrhinitic subjects) analysis, a one-point change in subjective nasal congestion rating was associated, on the average, with an 8% change in net percent change in NAR. However, this effect was not statistically significant ($r^2 = 0.03$, $p \cong 0.50$), and the regression line became horizontal when rhinitis status was controlled for. Thus, within either the SAR or nonrhinitic subgroup, there was essentially no relationship between subjective and objective congestion after chlorine exposure.

Pulmonary peak flow

Pulmonary peak flow was obtained before and after exposure as a safeguard to detect potential acute lower airway effects of low-level chlorine inhalation. None of the subjects exhibited clinically significant changes in peak flow (i.e., decreases ≥10% of baseline), nor did they complain of cough, wheezing, or chest tightness on chlorine exposure days.

DISCUSSION

Our study demonstrated differential upper respiratory tract physiologic reactivity to a nasal irritant challenge comparing subjects with SAR and nonrhinitic subjects,

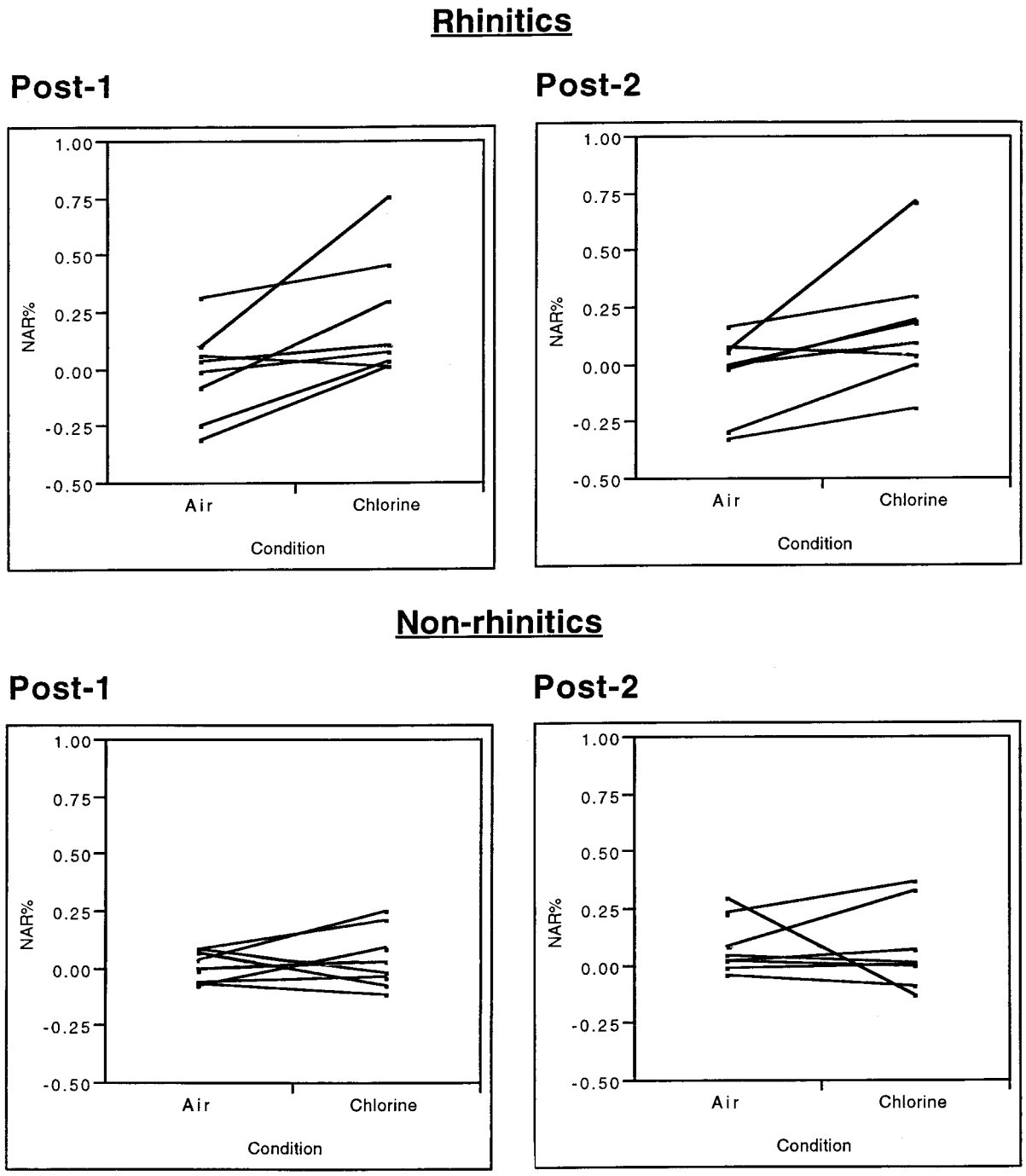

FIG. 4. Paired analyses of percent change in nasal airway resistance (from baseline) stratified by rhinitis status and time ($p < 0.05$ by paired t test for rhinitic subjects only at both testing times).

as evidenced by a greater proportional increase in NAR from baseline to after exposure when comparing the chlorine and air exposure conditions. Rhinitic subjects also reported greater exposure-related increases in perceived odor intensity, nasal irritation, and nasal congestion than did nonrhinitic subjects. The relationship between subjective and objective nasal congestion, on the other hand, was extremely weak and disappeared entirely when analyses were confined to either the rhinitic or nonrhinitic subgroup.

The results reported here are unlikely to be due to confounding because a stratified sample of rhinitic and nonrhinitic subjects was used, and the study design was counter-balanced with respect to subject gender and order of exposure. Our results agree with those of Bascom et al.[9] and Kjaergaard et al.[10] both of whom

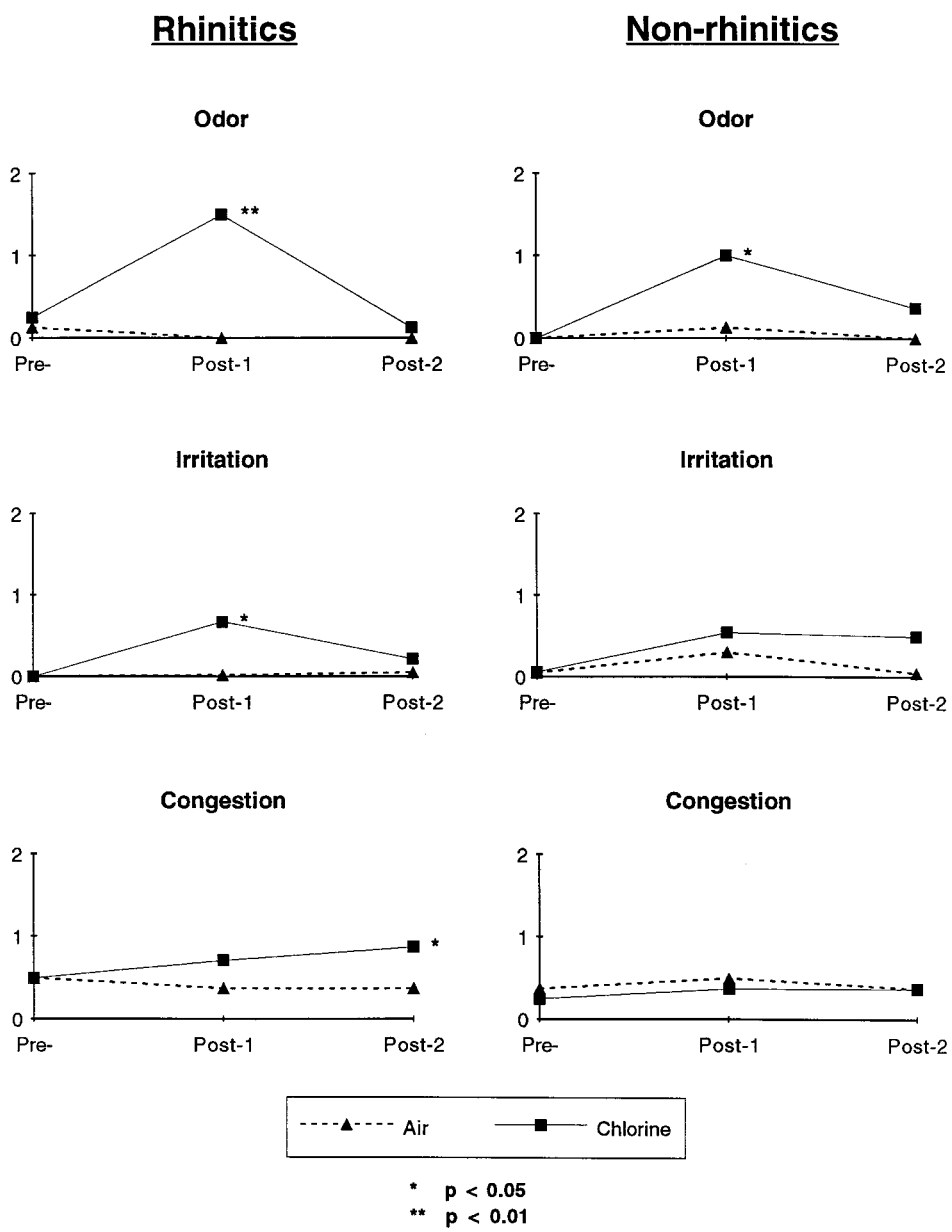

FIG. 5. Symptom ratings by time stratified by rhinitis status (1 = slight and 2 = moderate). Significant elevations were apparent, comparing chlorine and air exposures, for odor intensity ($p < 0.01$ at end of exposure for rhinitic subjects and $p < 0.05$ for nonrhinitic subjects), nasal irritation ($p < 0.05$ at end of exposure for rhinitic subjects only), and nasal congestion ($p < 0.05$ at 15 minutes after exposure for rhinitic subjects only).

showed differential nasal irritant sensitivity by allergic rhinitis status among subgroups selected either explicitly (Kjaergaard) or incidentally (Bascom) to contrast response on this trait (see below). Our failure to find a significant correlation between subjective and objective nasal congestion is also consistent with the published literature.[21]

The issue of interindividual variability in upper airway susceptibility to irritant chemicals is one of considerable clinical interest. Experimentally, the only published study directly examining atopy as a risk factor for upper respiratory tract irritant reactivity is that of Kjaergaard et al.,[10] who exposed 18 of each group of subjects (subjects with SAR and normal subjects) to either a mixture of 22 volatile organic compounds at 20 mg/m^3 or to clean air times 4 hours. In this experiment, the subjects with SAR reported greater eye, nose, and throat irritation and showed greater evidence of an inflammatory response in tear fluid than did the normal subjects. Although both

groups showed a decrease of nasal volume by acoustic rhinometry, no differential response (between rhinitic and nonrhinitic subjects) was evident in this regard. Bascom et al.[9, 22] found that subjects who are historically reactive to ETS manifest greater changes in nasal airway resistance after ETS provocation than do self-reported nonreactors. Because 60% to 70% of their historically sensitive subjects (but only 30% of their nonsensitive subjects) had positive skin test results, their studies may have indirectly addressed the issue of atopy as a risk factor. Significantly, despite the similarity of ETS-induced symptoms to those of allergic rhinitis, the usual markers of IgE-mediated allergic response (histamine, TAME-esterase, albumin, and kinins) were not elevated in nasal lavage fluid after ETS provocation.[9]

Epidemiologically, an association between preexisting atopy and nasal symptoms has been noted in investigations of so-called "problem buildings" in which no bioaerosol problem has been identified.[4] Furthermore, reports of nasal symptoms in response to ETS exposure are more common among individuals with a prior history of atopy than in nonatopic subjects.[2] Despite this empirical association with atopy, only a small proportion of ETS-sensitive subjects have positive skin test reactivity to tobacco-leaf extract or tobacco-smoke condensates.[23] The implication to be drawn from this work is that although a prior history of respiratory allergies appears to be a risk factor for upper respiratory tract reactivity to airborne irritants, the mechanism of response is probably not classical allergy. The most credible candidate for a nonallergic nasal response mechanism involves the irritant (nociceptor) receptor system of the trigeminal nerve.[24] Within this system, irritant-sensitive C and Aδ fibers innervate the nasal and oral cavities and give rise to both local (neuropeptide-mediated) and central (parasympathetic and sympathetic) reflexes.[25-32]

In the explanatory model proposed by ourselves and others, preexisting allergic inflammation primes some portion of the neurogenic reflex loop for response to chemical irritants.[33] Of note, subjects with SAR in our study were studied within 1 to 2 months of the end of their respective allergy seasons to preserve any priming effect and simultaneously avoid extraneous allergic triggering of symptoms. Depending on the actual reflex (or reflexes) involved, priming could take the form of a lowered sensory threshold and/or an augmented store of neuropeptides in afferent (trigeminal) nerve branches, a facilitated brainstem reflex, augmented acetylcholine release from the efferent (facial) nerve, or augmented responsiveness of the end organ (in this case, nasal mucosal capacitance vessels) to neuroimmune mediators. Our current data do not permit us to localize the site of modulation of irritant-induced reflexes. However, as a step to understanding this problem, future work will center on defining the relative contributions of autonomic and axon reflexes in the vasodilation/airway congestion response to irritant provocation.

We thank Peter Bachetti, PhD, and Mark Huddes, PhD, for their assistance with the statistical analysis; James Baraniuk, MD, Paul Blanc, MD, William Cain, PhD, and Kelvin Lee, MD, for their assistance with the study design; and Mr. Berkeley Choate for his technical assistance with the climate-controlled chamber.

REFERENCES

1. Centers for Disease Control and Prevention. Discomfort from environmental tobacco smoke among employees at worksites with minimal smoking restrictions—United States, 1988. MMWR 1992;41:351-4.
2. Cummings KM, Zaki A, Markello S. Variation in sensitivity to environmental tobacco smoke among adult non-smokers. Int J Epidemiol 1991;20:121-5.
3. Fisk WJ, Mendell MJ, Daisey JM, Faulkner D, Hodgson AT, Nematollahi M, et al. Phase 1 of the California healthy building study: a summary. Indoor Air 1993;3:246-54.
4. Hall HI, Leaderer BP, Cain WS, Fidler AT. Personal risk factors associated with mucosal symptom prevalence in office workers. Indoor Air 1993;3:206-9.
5. Kreiss K. The epidemiology of building-related complaints and illness. Occup Med 1989;4:575-92.
6. Wallace LA, Nelson CJ, Highsmith R, Dunteman G. Association of personal and workplace characteristics with health, comfort and odor: a survey of 3948 office workers in three buildings. Indoor Air 1993;3:193-205.
7. Kharrazi M, Smith DF, Blake E, Vance WA, Goldman LR. Real-time surveillance of symptoms and odor complaints during the trial excavation of a toxic waste site. In: Andrews JS, Frumkin H, Johnson BL, Mehlman MA, Xintaras C, Bucsela JA, editors. Hazardous waste and public health: International Congress on the Health Effects of Hazardous Waste. Princeton (NJ): Princeton Scientific Publishers; 1994. p. 806-14.
8. Shusterman D, Lipscomb J, Neutra R, Satin K. Symptom prevalence and odor-worry interaction near hazardous waste sites. Environ Health Perspect 1991;94:25-30.
9. Bascom R, Kulle T, Kagey-Sobotka A, Proud D. Upper respiratory tract environmental tobacco smoke sensitivity. Am Rev Respir Dis 1991;143:1304-11.
10. Kjeergaard SK, Rasmussen TR, Moelhave L, Pedersen OF. An experimental comparison of indoor air VOC effects on hayfever and healthy subjects. In: Maroni M, editor. Proceedings of healthy buildings '95. Vol. 1. Milan: Healthy Buildings '95; 1995. p. 567-72.
11. Settipane GA. Rhinitis: introduction. In: Settipane GA, editor. Rhinitis. 2nd ed. Providence (RI): OceanSide Publications; 1991. p. 1-11.
12. United States Environmental Protection Agency. 1992 toxics release inventory: public data release. Washington (DC): US Environmental Protection Agency; April 1994.
13. Centers for Disease Control and Prevention. Chlorine gas toxicity from mixture of bleach with other cleaning products—California. MMWR 1991;40:619-29.
14. Anglen DM. Sensory response of human subjects to chlorine in air (dissertation). Ann Arbor (MI): UMI Dissertation Services; 1981.
15. D'Alessandro A, Kuschner W, Wong H, Boushey HA, Blanc PD. Exaggerated response to chlorine inhalation among persons with nonspecific airway hyperreactivity. Chest 1996;109:331-7.
16. Rotman HH, Fliegelman MJ, Moore T, Smith RG, Anglen DM, Kowalski CJ, et al. Effects of low concentrations of chlorine on pulmonary function in humans. J Appl Physiol 1983;54:1120-4.
17. Shusterman D, Balmes J. Measurement of nasal irritant sensitivity to pulsed carbon dioxide: a pilot study. Arch Environ Med 1997;52:334-40.
18. Solomon WR. Nasal provocative testing. In: Spector SL, editor. Provocation testing in clinical practice. New York: Marcel Dekker; 1995. p. 647-92.
19. Cain WS, See LC, Tosun T. Irritation and odor from formaldehyde: chamber studies. Proceedings of the ASHRAE Conference IAQ'86: Managing Indoor Air for Health and Energy Conservation; Atlanta,

Ga.; Apr. 20-23, 1986. Atlanta: American Society of Heating, Refrigerating and Air-Conditioning Engineers; 1986. p. 126-37.
20. Clement PAR. Committee report on standardization of rhinomanometry. Rhinology 1984;22:151-5.
21. Tomkinson A, Eccles R. Comparison of the relative abilities of acoustic rhinometry, rhinomanometry, and the visual analog scale in detecting change in the nasal cavity in a healthy adult population. Am J Rhinol 1996;10:161-5.
22. Willes SR, Fitzgerald TK, Bascom R. Nasal inhalation challenge studies with sidestream tobacco smoke. Arch Environ Health 1992;47:223-30.
23. Stankus RP, Sastre J, Salvaggio JE. Asthma induced by exposure to low molecular weight compounds and cigarette smoke. In: Simmons DH, editor. Current pulmonology. Vol. 9. Chicago: Year Book Medical Publishers; 1988. p. 369-94.
24. Cometto-Muniz JE, Cain WS. Sensory irritation: relation to indoor air pollution. Ann NY Acad Sci 1992;641:137-51.
25. Baraniuk JN, Kaliner MA. Neuropeptides and nasal secretion. J Allergy Clin Immunol 1990;86(Suppl):620-7.
26. Baraniuk JN. Sensory, parasympathetic, and sympathetic neural influences in the nasal mucosa. J Allergy Clin Immunol 1992; 6(Suppl):1045-50.
27. Baraniuk JN. Neural control of the upper respiratory tract. In: Kaliner MA, Barnes PJ, Kunkel GHH, Baraniuk JN, editors. Neuropeptides in respiratory medicine. New York: Marcel Dekker; 1994. p. 79-123.
28. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract (Part 1). Am Rev Respir Dis 1991;144:1187-98.
29. Barnes PJ, Baraniuk JN, Belvisi MG. Neuropeptides in the respiratory tract (Part 2). Am Rev Respir Dis 1991;144:1391-9.
30. Raphael GD, Heney EV, Baraniuk JN, Kim I, Meredith SD, Kaliner MA. The pathophysiology of rhinitis: lactoferrin and lysozyme in nasal secretions. J Clin Invest 1989;84:1528-35.
31. Silver WL. Neural and pharmacological basis for nasal irritation. Ann NY Acad Sci 1992;641:152-63.
32. Widdicombe JG. Nasal pathophysiology. Respir Med 1990;84(Suppl A):3-9.
33. Bascom R. Differential responsiveness to irritant mixtures: Possible mechanisms. Ann NY Acad Sci. 1992;641:225-47.