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THIRTY MINUTE-EXPOSURE TO AGED CIGARETTE SMOKE INCREASES NASAL CONGESTION IN NONSMOKERS

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The aim of this study was to assess the effects of short exposures to experimentally aged cigarette smoke on the nose and upper airways. This crossover study compared the effects of 30-min exposures to (1) experimentally aged cigarette smoke at 1 mg/m³ particulate matter (PM)/14 ppm carbon monoxide (CO) and (2) conditioned filtered air on urinary metabolites of nicotine and tobacco-specific nitrosamines. Subjective nasal symptoms were assessed by questionnaire, objective nasal congestion was assessed by anterior rhinomanometry and nasal nitric oxide (NO) concentrations were determined. Experimentally aged cigarette smoke is a validated model for secondhand smoke (SHS). Twenty-six healthy nonsmokers (10 normal, 7 atopic/nonrhinitic, 7 atopic rhinitic, 2 nonatopic/rhinitic) were studied. A 30-min exposure to SHS increased nasal resistance in healthy nonsmokers. The rise in nasal resistance was most pronounced in rhinitic subjects. Significant increases were not noted when atopic subjects were considered independent of rhinitis status. Secondhand smoke exposure also elevated subjective nasal symptoms and urinary concentrations of metabolites of nicotine (cotinine and *trans*-3'-hydroxycotinine) and tobacco-specific nitrosamines [(4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)] in all subgroups of subjects. Exposure-related, subjective nasal symptoms were significantly higher in rhinitic than in normal subjects. Significant changes in nasal NO concentrations were not detected. Data indicate a 30-min exposure to secondhand smoke at 1 mg/m³ PM increases subjective upper respiratory symptoms, increases urinary cotinine and NNAL, and produces objective nasal airflow obstruction in human subjects.

Irritation and congestion of the nose are among the most common complaints in nonsmokers exposed to tobacco smoke, and elevated rates of rhinosinusitis were reported in groups with occupational exposure to secondhand cigarette smoke (SHS) (Samet, 2004; Ebbert et al., 2007). Willes et al. (1998) showed that 2-h exposures to freshly generated

sidestream cigarette smoke, at concentrations of 15 ppm carbon monoxide (CO), produced nasal airflow obstruction as measured by posterior rhinomanometry. By impairing sinus drainage and mucociliary function, any exposure that produces nasal obstruction and inflammation is likely to increase the risk of rhinosinusitis. Rhinosinusitis encompasses

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a spectrum of inflammatory and infectious disease processes that affect the nose and paranasal sinuses. Chronic rhinosinusitis is estimated to affect 16% of the population in the United States and to exert severe effects on health and quality of life (Cherry and Woodwell, 2002; Ly and McCaig, 2002). Occupational exposure to SHS is a known risk factor for upper and lower respiratory symptoms (Eisner, 2010). Atopy and rhinitis are risk factors for rhinosinusitis.

Of note, the paranasal sinuses contain the highest concentration of nitric oxide (NO) in the airways. Measurement of nasal NO has been explored as an indirect indicator of the patency of the osteomeatal complex, the structure whereby the majority of the paranasal sinuses drain into the nasal cavity. A further elaboration of this measurement is documentation of the nasal NO response to humming (acoustic stimulation), a measure that was found to be blunted in patients with chronic rhinosinusitis and polyposis (Lundberg et al., 2003).

Secondhand cigarette smoke is composed of sidestream smoke, released as the cigarette smolders between puffs, and exhaled mainstream smoke. It is a complex mixture that changes chemically and physically with aging. Ventilation rates in homes and businesses are generally quite low, on the order of 0.5–2 air changes/h (Yamamoto et al., 2010). This indicates that SHS emitted indoors lingers for up to 2 h prior to removal by ventilation. During this time, a significant fraction of the semivolatile organic fraction deposits on surfaces and chemical reactions occur that change the particle size and toxicity of the smoke. Schick and Glantz (2006) previously demonstrated that aged sidestream smoke is two- to fourfold more acutely toxic to the respiratory epithelium of laboratory animals than fresh smoke and that the concentration of the tobacco-specific lung carcinogen NNK increases as sidestream smoke ages (Schick and Glantz, 2007). Other investigators have shown that nicotine from SHS that has adsorbed onto surfaces can interact with oxidant gases in the air to form nitrosamines (Sleiman et al., 2010b) and ultrafine particles (Petrick et al., 2010; Sleiman et al., 2010a).

In these studies, a custom-built smoke aging system was used to generate aged cigarette as the best facsimile of real-world SHS exposures (Schick et al., 2012).

The immediate effects of short-term exposures to aged cigarette smoke on nasal airflow and exhaled nasal NO in normal and atopic nonsmokers not normally exposed to SHS (Schick et al., 2012b) were examined to identify early biological responses to SHS that may lead to diseases of the upper airway.

METHODS

Study Population

Healthy (rhinitic or nonrhinitic) nonsmokers between the ages of 18 and 50 yr, who were not routinely exposed to SHS, were recruited from the general population of the San Francisco Bay area through online advertisements. Subjects were screened by phone for the following exclusion criteria: lifetime cigarette consumption >50 packs; smoked tobacco regularly in the past year; smoked any substance within previous 3 mo; use of cocaine, crack, heroin, or methamphetamine; heart disease; family history of mortality from heart disease before age 50 yr; hypertension; diabetes mellitus; pregnancy; nasal polyps or frequent nosebleeds; nasal surgery for sinusitis; perforated eardrums; regular use of any medication with anticholinergic or antihistaminic property; any chronic disease that interfered with airway, mucosal, or neural responses; or exposure to SHS in daily life. The study protocol was approved by the University of California, San Francisco, Committee on Human Research, and all subjects gave written informed consent prior to the study.

Screening

After consent, saliva samples were collected for cotinine testing (cotinine is the major metabolite of nicotine), and subjects were screened for sensitivity to 12 common local aeroallergens, plus saline and histamine controls, by epicutaneous skin prick test.

"Significant" wheal reactions were defined as >3 mm diameter. Subjects with more than one significant wheal reaction were categorized as atopic. A detailed questionnaire was subsequently administered, which included basic demographics, prior allergic/otorhinolaryngologic diagnoses, and self-reported nasal reactivity to allergic and nonallergic triggers. Subjects who reported episodes of sneezing, rhinorrhea, nasal pruritus, or nasal congestion, with or without identified allergic stimuli, occurring either on a persistent or intermittent basis over the course of a typical year were categorized as rhinitic. In the subsequent analysis, atopy and rhinitis status were treated both as independent traits and in combination.

Study Design

This was a randomized crossover design, comparing the effects of a smoke exposure and a clean air exposure. Exposures were separated by a minimum of 20 d to allow full recovery of nasal tissues. Normal and atopic subjects were randomized separately to receive either smoke or clean air exposure first. Six of the 12 nonatopic and 6 of the 14 atopic subjects received smoke first. After each exposure visit, the subject returned the next day for a brief follow-up visit. See Figure 1.

Smoke Exposures

Subjects were exposed to aged cigarette smoke generated in a custom-built system in

the lab (Schick et al., 2012a). Cigarette smoke was generated with a smoking machine (TE10z, Teague Enterprises, Woodland, CA), diluted with conditioned, filtered air, and conducted through a large flow reactor at rates equivalent to the upper ranges of normal residential air exchange rates, creating aged cigarette smoke as a model for SHS. Subjects were exposed to smoke head-only, through a modified, positive-pressure, air-purifying respirator (PPAR) hood (3M Airmate number BE-10-3, 3M, Inc., St. Paul, MN) for 30 min. Particulate matter (PM) concentration was $1106 \mu\text{g}/\text{m}^3 \pm \text{SD } 223 \mu\text{g}/\text{m}^3$ and CO concentration was 14 ± 1.5 ppm. Temperature was $22 \pm 2^\circ\text{C}$ and relative humidity was $50 \pm 5\%$. During exposure, the subject sat in a steel and glass chamber with 0.85 air changes/min of conditioned, filtered air (Aris et al., 1993).

Clean Air Exposures

Subjects were exposed to clean air using the PPAR with a HEPA filter cartridge, while sitting in the same chamber with temperature and relative humidity as already described.

Nasal Symptom Questionnaires

The subjects filled out a 16-item questionnaire with symptoms derived from the Sino-Nasal Outcome Test (SNOT-20) on a visual analog scale from 0 to 5 before, immediately after, and approximately 22 h after each exposure. Scores were quantified manually and rounded to the nearest 0.25.

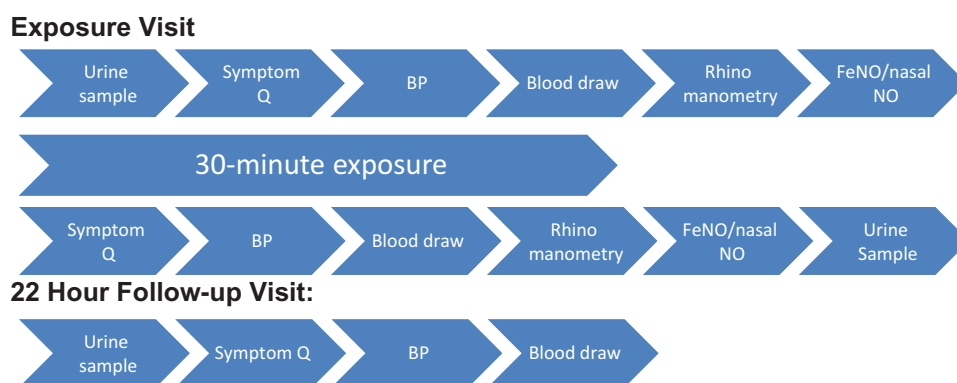


FIGURE 1. Study Protocol (color figure available online).

Nicotine and NNK Metabolite Analyses

Urine samples were collected before the 30-min exposure, approximately 60 min after exposure, and approximately 22 h after exposure. A subset of subjects also collected samples before bed on the day of exposure and with the first void of the following morning. Samples were frozen and taken to the Clinical Pharmacology Laboratory at UCSF for measurement of cotinine, *trans*-3'-hydroxycotinine (3HC), NNAL, and creatinine. NNAL is the major metabolite of NNK, the most carcinogenic tobacco-specific nitrosamine. The analyses were conducted using high-performance liquid chromatography/atmospheric pressure ionization tandem mass spectrometry methods as previously described by Jacob et al. (2008, 2011).

Measurement of Blood Pressure

Blood pressure, pulse, and mean arterial pressure were measured with a Critikon Dinamap vital signs monitor (model 8100, GE Healthcare, Waukesha, WI) before exposure, immediately after exposure, and approximately 22 hr after exposure. Blood pressure was always measured before blood was drawn.

Clinical Blood Tests

Blood samples were collected before, immediately after, and approximately 22 h after exposures and sent to the San Francisco General Hospital Clinical Laboratory for complete blood count, differential cell count, and high-sensitivity C-reactive protein tests.

Nasal Airway Resistance

Anterior rhinomanometry was performed before exposure and 15–20 min after exposure, using a GM Instruments NR6 rhinomanometer (GM Instruments, Kilwinning, Scotland, UK) with a reference pressure of ± 150 Pa. Subjects were trained in the method at the screening visit, 3 wk prior to the first exposure visit. Values represent the mean of three sets of six breaths

each. Anterior rhinomanometry yields four sets of resistance data for each measurement: left inspiration, left expiration, right inspiration, and right expiration.

Resistance for each nostril was calculated as

$$R_{\text{nostril}} = \frac{R_{\text{insp}} + R_{\text{exp}}}{2}$$

Total resistance was calculated as

$$\frac{1}{R_{\text{total}}} = \frac{1}{R_{\text{left}}} + \frac{1}{R_{\text{right}}}$$

Rhinomanometry data were analyzed by using repeated-measures analysis of variance (ANOVA) on two factors: exposure and time point. Paired *t*-tests were used to test the effects of smoke exposure in subgroups.

Exhaled Nasal Nitric Oxide

Exhaled NO was measured with a Sievers 280i (GE Instruments, Boulder, CO), calibrated on a daily basis to filtered air and 45 ppm NO. Subjects performed three oral exhalations, three nasal exhalations, and three nasal exhalations while humming, according to the parallel method of Shusterman et al. (2007). Subjects were trained in the method at the screening visit, 3 wk prior to the first exposure visit. FeNO was calculated on an automated basis by the sampling software (NOAnalysis; GE Analytical Instruments, Boulder, CO). For each nasal NO tracing, the area under the curve for the 10 s immediately following the initial pressure transient was quantified using ImageJ software (National Institutes of Health, Bethesda, MD), average NO was calculated, and humming-to-quiet (H/Q) ratios were constructed, with and without correction for FeNO.

Statistical Analyses

Statistical tests were done using SigmaStat software. Nasal symptom scores from clean air and smoke exposures were compared using repeated-measures ANOVA on two factors: smoke and time point. Pairwise comparisons were done using the Holm–Sidak method.

Using the same methods, the questionnaire data were further tested for effects of atopy, rhinitic status, and gender. Effects of exposure and time point on nicotine and NNK metabolites, blood pressure, blood tests, nasal resistance, and nasal NO were also tested using repeated-measures ANOVA, with pairwise testing using the Holm–Sidak test. Additional tests of subgroups were done using paired *t*-tests. Our original study design compared normal and atopic subjects. For additional post hoc analyses, the subjects into two categories: Normal and rhinitic were separated. The criterion for significance was set at $p < .05$.

RESULTS

Baseline Characteristics of Study Population

Subject characteristics are shown in Table 1. Fourteen subjects were atopic by skin testing, 13 of whom reacted to perennial allergens such as dust mite or animal dander. Seven of the atopic subjects and two of the normal subjects provided a history of symptoms consistent with rhinitis. The average number of positive nasal symptoms was eight for subjects classified as rhinitic and two for subjects classified as nonrhinitic. Racial demographics were representative of the San Francisco Bay Area population.

TABLE 1. Subject Baseline Characteristics

Mean age (yr, range)	30.9 (19–49)
Male	11
Female	15
Mean BMI (SD)	24.3 (4.8)
Caucasian	11
Asian	9
Hispanic	5
African-American	1
Declined to state ethnicity	1
Normal (female)	10 (6)
Atopic, not rhinitic (female)	7 (3)
Atopic, rhinitic (female)	7 (4)
Nonatopic, rhinitic (female)	2 (2)
Preexposure cotinine, ng/ml (SD)	0.38 (0.70)
Preexposure 3-hydroxycotinine, ng/ml (SD)	2.02 (4.29)
Preexposure NNAL, pg/ml (SD)	1.1 (2.26)

TABLE 2. Rhinomanometry Sample Set

Nonatopic/nonrhinitic (female)	6 (4)
Atopic/nonrhinitic (female)	5 (2)
Atopic/rhinitic (female)	7 (4)
Nonatopic/rhinitic (female)	2 (2)

Cotinine, 3-Hydroxycotinine, and NNAL

The mean baseline urinary cotinine was 0.38 ± 0.7 ng/ml. Mean baseline *trans*-3'-hydroxycotinine levels were 2.02 ± 4.29 ng/ml and NNAL levels were 1.1 ± 2.26 pg/ml. Concentrations of all three metabolites increased after SHS exposure (Figure 2). Significant differences were detectable at 1.5 h after initiation of exposure for cotinine and NNAL and with the sample collected before bed (on the day of exposure) for *trans*-3'-hydroxycotinine. Concentrations of cotinine and NNAL began to fall by the next day. Concentrations of *trans*-3'-hydroxycotinine remained elevated through 22 hr after initiation of exposure. The geometric mean of the NNAL:cotinine ratio at 1.5 h after exposure was 3.89×10^{-3} , and the interquartile range was $0.897\text{--}7.87 \times 10^{-3}$.

Nasal Symptoms

Exposure to clean air exerted no significant effects on nasal symptoms (Figures 3A and 3B). Smoke exposure and the time at which the questionnaire was given were associated with statistically significant changes in nine symptoms (supplementary Table S1). These symptom scores could be sorted into two patterns of response:

- Baseline score low, postexposure score high, 22-h score returned to baseline. Odor, nausea, eye irritation, nasal irritation, nasal congestion, and urge to cough followed this pattern (Figure 3A).
- Baseline score low, postexposure score high, 22-h score intermediate between the two. Chest tightness/wheeze, chest irritation, headache, and facial pain followed this pattern (Figure 3B).

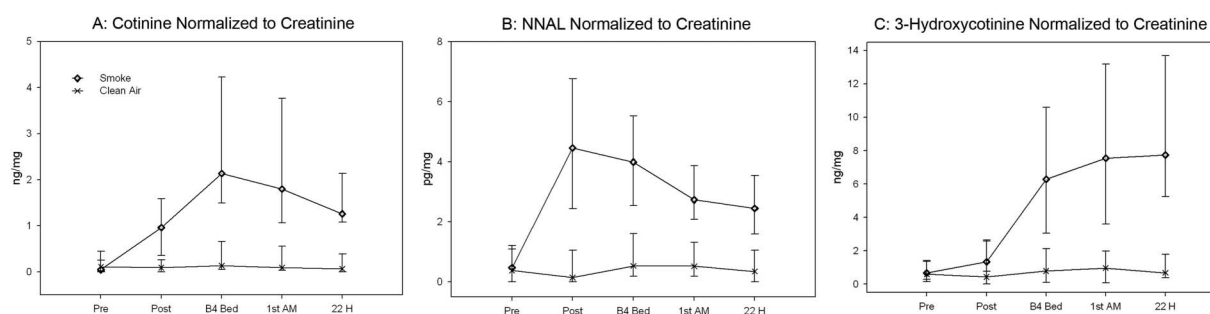


FIGURE 2. (A) Urinary cotinine values rise immediately after exposure, peak at approximately 10 h after exposure, and remain elevated at 22 h after exposure. Points represent median values and error bars represent 25th and 75th percentiles. (B) Urinary NNAL values peak immediately after exposure and remain elevated at 22 h after exposure. Points represent median values and error bars represent 25th and 75th percentiles. (C) Urinary *trans*-3'-hydroxycotinine values rise by approximately 10 h after exposure and continue to increase through 22 h. Points represent median values and error bars represent 25th and 75th percentiles.

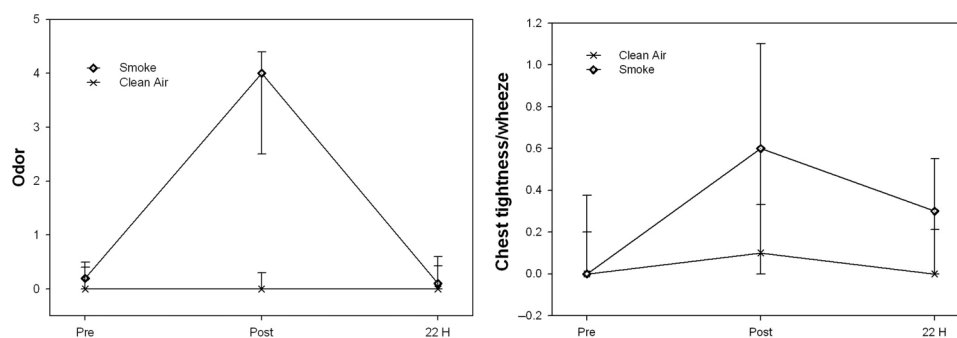


FIGURE 3. (A) Perception of odor: example of pattern A, where the median symptom value is low at baseline, elevated after exposure, and returns to baseline at 22 h. Odor, nausea, eye irritation, nasal irritation, nasal congestion, and urge to cough all showed significant increases after SHS exposure and returned to baseline at 22 h. Error bars represent 25th and 75th percentiles. (B) Perception of chest tightness/wheeze: example of symptom pattern B, where the median symptom value is low at baseline, elevated after exposure, and intermediate between pre and post at 22 h. Chest tightness/wheeze, chest irritation, headache, and facial pain all showed significant increases after SHS exposure and symptom scores were still elevated at 22 h. Error bars represent 25th and 75th percentiles.

All positive symptoms except facial pain and nasal congestion showed a significant interaction between smoke exposure and time point (see supplementary Table S1). Backache and hunger were assessed for validation purposes. Backache scores were not affected by smoke exposure or time point. Hunger scores were not affected by smoke exposure, but increased over time as expected.

Subgroup analyses of rhinitic versus non-rhinitic subjects showed that rhinitics had significantly greater increases in the perception of odor, nasal congestion, and the urge to cough after exposure to SHS. Comparisons of atopic versus nonatopic and male versus female subjects did not show any marked differences (data not shown).

Nasal Patency as Measured by Anterior Rhinomanometry

Four subjects were unable to perform anterior rhinomanometry and there were two subjects for whom data were lost. The final number of subjects with complete data was 20 (Table 2). A significant increase was noted in total nasal resistance in all subjects after 30-min exposure to SHS, but not after exposure to clean air (Figure 4).

In subgroup analyses, significant increases were seen in total nasal resistance in the rhinitic subgroup after exposure to SHS, but not when atopy or gender was considered independently from rhinitis status (data not shown). At baseline, before exposure to SHS or clean air, there were no significant differences between the

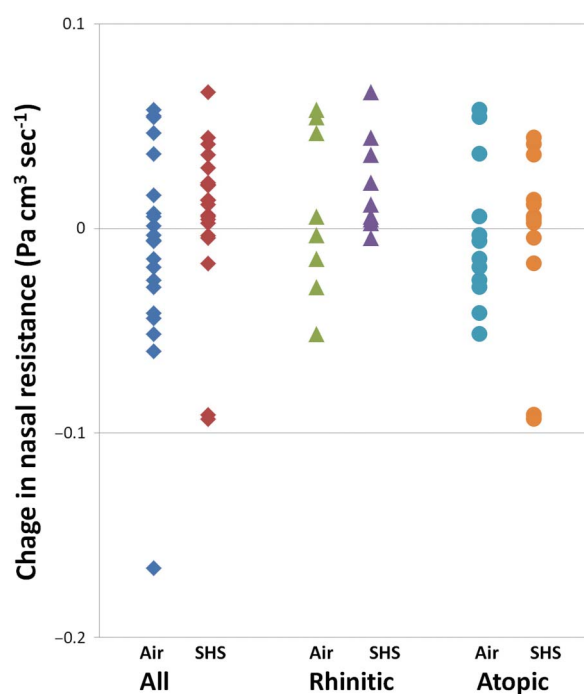


FIGURE 4. Comparison of change in total nasal resistance, measured by anterior rhinomanometry, after 30-min exposure to conditioned, filtered air or SHS. Positive values indicate increase in resistance after exposure. Statistically significant increases in total nasal resistance after SHS exposure were seen in the entire group and in the rhinitic subgroup. There was not a significant increase in nasal resistance in the atopic subgroup (color figure available online).

nasal resistance values of rhinitic and non-rhinitic subjects.

Because anterior rhinomanometry yields data for the left and right nostrils separately, it was also possible to examine changes in unilateral nasal resistance. Due to the nasal cycle, one nostril is usually more congested than the other. In rhinitic subjects, data demonstrated that SHS exposure produced a significant increase in resistance in the least congested nostril. However, significant changes were not found in the most congested nostril in rhinitic subjects. Significant differences were not observed in unilateral resistance when non-rhinitic and rhinitic subjects were combined.

Nasal Exhaled Nitric Oxide

One subject was excluded because of high baseline cotinine levels and there were two data points that were not included in the

analysis because of poor curve quality. There were no significant effects of smoke exposure on FeNO, nasal NO while silent, or nasal NO humming-to-quiet ratio. Subgroup analysis of rhinitic and atopic subjects similarly showed no systematic changes in nasal NO (data not shown).

Blood Sample Analyses, Blood Pressure, Pulse, and Mean Arterial Pressure

No significant effects of smoke exposure were found on complete and differential blood cell counts, C-reactive protein levels, blood pressure, pulse rate, or mean arterial pressure.

DISCUSSION

Secondhand Smoke Exposure System

This study is the first to use a human experimental design to assess the acute effects of a 30-min exposure to SHS on *trans*-3'-hydroxycotinine, NNK, and nasal NO. It is also the first to test a novel aged cigarette smoke aerosol that reproduces the normal chemical changes that occur in homes and public places during SHS exposures, on nasal endpoints (Schick and Glantz, 2006, 2007; Schick et al., 2012b). Our previous studies showed that the respiratory toxicity of sidestream smoke increases as it ages (Schick and Glantz, 2006), and that brief exposures to low concentrations of aged SHS decrease cardiovascular function (Frey et al., 2012). Preliminary studies of our aged SHS aerosol indicated that 50% of the total PM in the SHS is lost to deposition during the 30-min smoke aging process. This reproduces the results seen in studies of tobacco particle emissions and deposition performed in the lab and in real homes and public buildings (Voncken et al., 1994; Ott et al., 2003; Repace et al., 2006) and is an important innovation in the study of acute health effects of SHS exposure. Thirty minutes of aging was selected based upon air exchange rates observed in homes and the target air exchange rates mandated for public buildings (Pandian et al., 1993; Glantz and Schick, 2004; Wilson et al., 2010).

which models an “average” SHS exposure that occur indoors where smoking is permitted. A real indoor exposure can also include fresher smoke, if the smoker is near the nonsmoker, and older smoke, if the ventilation rate is below 2 air changes/h (Matt et al., 2011)

In comparison, the majority of earlier publications on the effects of SHS on nasal congestion and patency used freshly generated cigarette smoke, or smoke that was aged for shorter periods of time. Thus, it is likely that the smoke used in earlier studies contained higher relative concentrations of the particle-phase constituents and lower relative concentrations of the gas-phase constituents of SHS. Exposures that occur in buildings where smoking occurs also include dermal exposure to sorbed smoke chemicals and inhalation of low concentrations of desorbed chemicals. This spectrum of persistent smoke chemicals is now referred to as thirdhand smoke (THS) (Matt et al., 2011). Our SHS exposure system includes the respirable fraction of THS, but not the fraction that may be absorbed dermally.

Biomarkers of SHS Exposure

Cotinine and *trans*-3'-hydroxycotinine (3HC) are metabolites of nicotine. Benowitz et al. (2010a) showed that the sum of cotinine and *trans*-3'-hydroxycotinine may be a more accurate measure of low-level nicotine exposure than cotinine alone. NNAL is a metabolite of the most carcinogenic tobacco-specific nitrosamine known: NNK. The low baseline levels of cotinine, 3HC, and NNAL in our subjects are consistent with levels seen in other studies of nonsmoking populations with low levels of SHS exposure (Aquilina et al., 2010). The probable reason 3HC levels do not rise until the “before bed” sample is that 3HC is a secondary metabolite of cotinine and does not increase until after cotinine is formed (Jacob et al., 2011). The ratio between NNAL and cotinine (a primary metabolite) was reported to be significantly higher in nonsmokers exposed to SHS than in active smokers, possibly because of formation of NNK from nicotine as smoke ages (Schick and Glantz, 2007). Benowitz

et al. (2010b) and Goniewicz et al. (2011) found a ratio of the geometric mean values of NNAL and cotinine in nonsmokers exposed to SHS of 2.85×10^{-3} , while smokers had a ratio of 1.6×10^{-4} . The NNAL:cotinine ratio in our study (3.89×10^{-3} at 1.5 h after start of exposure) is consistent with these findings. These data suggest that there are significantly higher levels of the tobacco-specific nitrosamine NNK in SHS. Previous studies showed that the ratio of NNK:nicotine in the aged smoke aerosol generated in our lab is approximately 4×10^{-4} (Schick et al., 2012a). The ratio of NNK:nicotine in fresh mainstream smoke is approximately 2×10^{-6} and in fresh sidestream smoke it is approximately 1×10^{-4} (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans and World Health Organization, 2004). NNK is a potent lung carcinogen (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans and World Health Organization, 2004).

Nasal Symptoms

The 30-min exposure to SHS, at 1 mg/m³ total PM and 14 ppm CO, increased subjective perceptions of odor, nausea, eye irritation, nasal irritation, nasal congestion, urge to cough, chest tightness/wheeze, chest irritation, headache, and facial pain. Some of the symptoms returned to baseline/clean air levels by the next day. Other symptoms (chest irritation, chest tightness/wheeze, headache, and facial pain) were still significantly higher than baseline or clean air values the next day. Rhinitic subjects reported significantly greater perceptions of odor, nasal congestion, and the urge to cough than nonrhinitic subjects. However, significant differences were not noted between reported symptoms of atopic and nonatopic subjects when atopy was considered independent of rhinitis status.

Increases in Nasal Resistance After SHS Exposure

When Bascom et al. (1996) and Willes et al. (1998) compared effects of 2-h exposures to

fresh sidestream smoke at 1, 5, and 15 ppm CO on nasal resistance, effects were only seen at 15 ppm CO. A comparable CO concentration (14 ppm) was used here, but a shorter exposure period of 30 min. One cannot make accurate comparisons of the concentration of other chemical compounds in the two studies because the smoke age and aerosol handling methods were different. Bascom et al. (1996) used freshly generated sidestream cigarette smoke injected into the air supply of a human exposure chamber that had 8 air changes/h. Thus, the smoke in their studies was aged for an average of 7.5 min (60 min/h $\times$ 1 air change/8 min). Our smoke was aged for 30 min and probably had a lower relative concentration of PM. Based strictly on CO concentration, the time-integrated dose for their 15-ppm exposure was 1800 ppm-min (15 ppm CO $\times$ 120 min). The time-integrated dose in our study was 420 ppm-min (14 ppm CO $\times$ 30 min) (Bascom et al., 1996; Willes et al., 1998). Our study demonstrated an increase in nasal resistance after a shorter period of exposure at a comparable level of CO (a lower time-integrated dose), indicating that the nasal congestive response to SHS might occur at a lower dose than previously demonstrated.

Increases in Nasal Resistance in Rhinitic Subjects

The total (bilateral) nasal resistance among rhinitic subjects after SHS exposure was significantly higher than that of nonrhinitic subjects, but not significantly different between the groups before exposure. As discussed in the following, our current findings are thus consistent with previous observations linking nasal physiologic reactivity to rhinitis and/or atopy status.

Our use of anterior rhinomanometry also gave us the opportunity to examine changes in unilateral nasal airway resistance. The nasal cycle is the pattern of alternating congestion and decongestion of the nasal cavity. At any given time one nostril is usually more congested, with higher resistance to airflow, than the other. This congestion is due to changes

in engorgement of the nasal venous sinusoids (Morris and Shusterman, 2010). In the rhinitic subgroup, exposure to SHS increased resistance in the less congested of the two nostrils. It did not induce significant changes in resistance in the more congested nostril. This suggests that SHS exposure does not exaggerate the normal nasal cycle, and the mechanism of early nasal obstruction due to SHS exposure may involve engorgement of the nasal venous sinusoids of the less congested nostril. No apparent previous reports in the literature of the effects of inhaled irritants that used anterior rhinomanometry were found. However, two groups studying the relationship between nasal resistance and obstructive sleep apnea reported that resistance in the most congested nostril correlated better with measures of apnea severity than bilateral nasal resistance (Li et al., 2005; Tagaya et al., 2010).

Nasal Nitric Oxide

The lack of systematic changes in nasal NO in our study is in accord with recent findings showing that routine exposure to SHS does not increase nasal nNO (Zhou et al., 2011). In a pilot investigation preceding this study it was observed that quiet nasal NO levels correlated with osteomeatal complex area measured by three-dimensional (3D) reconstructions from computed tomography (CT) images and with varied inversely with Lund–Mackay scores. However, data failed to demonstrate a hypothesized correlation between the nasal NO response to acoustic stimulation (humming) and osteomeatal complex area (Shusterman et al., 2012). The negative feNO results suggest that a 30-min exposure to SHS does not produce immediate increases in airway inflammation.

Rhinitis, Atopy, and SHS Sensitivity

Previous studies of the effects of controlled exposures to fresh sidestream cigarette smoke suggested that there may be differences in nasal responses to SHS among a population of historically SHS-sensitive subjects (Bascom,

1991; Bascom et al., 1996; Willes et al., 1998). Bascom et al. (1996) found that a group of historically SHS-sensitive subjects, 70% of whom were atopic, reported greater perceptions of eye irritation, nose–throat irritation, rhinorrhea, chest tightness, and cough than a group of SHS-non-sensitive subjects, 27% of whom were atopic (Bascom 1991). In a later study, Willes et al. (1998) reported no significant difference in nasal responses to SHS among SHS-sensitive subjects, but noted that the largest physiologic and inflammatory responses were experienced by subjects in this category. Our subjects were not classified on the basis of SHS sensitivity. Subjects were specifically recruited with no regular SHS exposure, and many of our subjects reported no history of sustained SHS exposure and no SHS-related symptoms. This is probably because extensive smoke-free regulations had been in place in California for 14 yr before this study was conducted and the smoking prevalence was 13% (California Department of Public Health, 2011).

In our previous investigations, we focused on the differences in response to inhaled irritants between normal subjects and seasonal allergic rhinitic subjects (Shusterman et al., 2003, 2005). In this study, the rhinitic group included both atopic and nonatopic individuals, and (based on skin test reactivity) consisted primarily of perennial allergic rhinitics. Thus, this study is not directly comparable to our previous investigations in which seasonal allergic rhinitics exerted greater physiological responses to irritant provocation. However, studies suggest that nonallergic rhinitis is common. Among allergy clinic patients with rhinitis, 20–46% have perennial, nonallergic rhinitis (Baraniuk and Shusterman, 2007), and roughly 40% of allergic rhinitics share the trait of nonspecific nasal hyperreactivity (to physical and/or chemical stimuli) with nonallergic rhinitics (Dykewicz et al., 1998; Settipane and Lieberman, 2001). Since nonallergic rhinitis is common, our inclusion of subjects with this diagnosis increases the clinical relevance of this study. Our findings suggest that rhinitis, as a symptom complex, may be a more important identifier of populations

that are sensitive to SHS than atopy alone, as defined by skin test reactivity.

SUMMARY

In summary, data showed that 30-min exposure to a chemically accurate and controlled model of SHS produced increases in urinary metabolites of nicotine and NNK, subjective respiratory symptoms, and total nasal resistance. The rise in total nasal resistance was produced by elevation in resistance in the less congested nostril. This exposure did not produce any significant changes in feNO or nasal NO concentrations. This suggests that short exposures to SHS cause rapid changes in the tone of the smooth muscles that control blood flow into the nasal venous sinusoids, but do not produce immediate increases in respiratory inflammation as measured by feNO. This study shows that even brief exposures to experimentally aged cigarette smoke exert negative effects on the upper airways. Any increase in nasal obstruction will likely impair sinus drainage and mucociliary function, which in turn may elevate the risk of rhinosinusitis. Our study shows that even 30-min exposures to SHS increase nasal congestion and that people with rhinitis may be particularly sensitive to the nasal effects of SHS exposure. This provides further proof that a single, short exposure to SHS carries immediate and appreciable adverse health effects, even for healthy people.

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