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Influence of personal factors on nasal patency and lavage biomarkers in white-collar workers*

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SUMMARY

Large biological variability between subjects has been shown for both acoustic rhinometry and nasal lavage biomarker concentrations, but relatively little is known about the influence of personal factors on these techniques. The aim was to evaluate if nasal symptoms, acoustic rhinometric measurements and nasal lavage fluid biomarkers are related to age, gender, smoking, atopy or asthma. A standardized nasal investigation was applied in 411 white-collar workers, belonging to three occupational groups: school personnel (n=234), office workers (n=89) and hospital workers (n=88). Lavage fluid analysis included determination of eosinophil cationic protein (ECP), myeloperoxidase (MPO), lysozyme and albumin. Females had smaller nasal dimensions in the anterior part of the nose ($p<0.001$), and lower lavage fluid concentrations of ECP ($p=0.004$), MPO ($p=0.002$), and albumin ($p=0.01$). Rhinometric dimensions or lavage fluid biomarker concentrations were not related to age, smoking, atopy or asthma. Some differences in rhinometric and biomarker measurements were observed between the occupational groups, and adjustment was made for occupation. Rhinometric measures and lavage biomarkers were consistently interrelated, which suggests a combined mucosal swelling and inflammatory reaction. This indicates a potential usefulness of a combined use of acoustic rhinometry and lavage biomarkers to study nasal mucosal reactions.

Key words: acoustic rhinometry, age, albumin, atopy, asthma, eosinophil cationic protein (ECP), gender, lysozyme, myeloperoxidase, nasal lavage, nasal obstruction, rhinitis, smoking

INTRODUCTION

A large biological variability between subjects in acoustic rhinometric and nasal biomarker measurements has been shown in previous studies. Assessments of inter individual variability in acoustic rhinometry have shown coefficients of variation (CV) for the minimal cross-sectional area of 19 to 31% (Corey et al., 1998; Grymer et al., 1997; Roithmann et al., 1994) and for volume of 26 to 39% (Corey et al., 1998; Grymer et al., 1991).

Concerning lavage measurements the inter individual coefficient of variation for cell counts in nasal lavage fluid has been reported to range from 68 to 125%, (Hauser et al., 1994; Koren et al., 1992; Steerenberg et al., 1996) and for eosinophil cationic protein from 38 to 137% (Beppu et al., 1994; Granstrand et al., 1998; Steerenberg et al., 1996).

The anatomical and mucosal structures within the nasal cavity vary considerably between individuals and somewhat contradictory results concerning the influence of personal factors on rhinometric dimensions have been reported in the literature. Among normal adults, the minimal cross-sectional area (MCA) has been found to be both larger (Grymer et al., 1991) and smaller (Millqvist and Bende, 1998) in females. In another study on adults, significant racial differences in MCA were observed (MCA smaller in whites and Asians than in blacks), but there was no significant relation to weight, height, or gender (Corey et al., 1998). In a further study, including children, MCA was positively related to age, weight and height (Millqvist and Bende, 1998).

Concerning the intra-individual variability for acoustic rhinometry, using the same apparatus (Rhin 2000) and the same investigators as in the present study, triplicate measurements showed a relative standard error of variation of 7% for MCA1 and MCA2, 6% for VOL1 and 8% for VOL2 (Wålinder et al., 1997). A similar

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variability (6-9%) of MCA and volume in clinical practice has been found in other studies (Fisher et al., 1995; Millqvist and Bende, 1998). The intra- and interassay coefficients of variation for the determination of lysozyme, ECP, MPO and albumin is less than 11%, according to the laboratory performing the analyses. When the same lavage method and same analytical laboratory were used in an exposure chamber study, a larger day-to-day variability (CV) was found: ECP 69%, lysozyme 42%, MPO 50% and albumin 83% (Wålinder et al., 1999).

Environmental influence on the nasal mucosa has been shown. Nasal mucosal swelling has been demonstrated for exposure to allergens (Nielsen et al., 1996), environmental tobacco smoke (Bascom et al., 1996) and volatile organic compounds (Mölhave et al., 1993). Cellular and biomarker responses in nasal lavage have been observed for bakery work (Brisman et al., 1998), formaldehyde (Pazdrak et al., 1993), mites (Garrelds et al., 1995), ozone (Graham and Koren, 1990), volatile organic compounds (Koren et al., 1992) and wood-dust (Åhman et al., 1995). By measuring biomarker concentrations in nasal lavage, eosinophil cationic protein (ECP) can be considered as an indicator for eosinophil activation (Venge, 1994), myeloperoxidase (MPO) for neutrophil activation (Venge, 1994), lysozyme for secretory activity (Raphael et al., 1989) and albumin for vascular leakage (Raphael et al., 1991).

The main aim of the investigation was to study how nasal symptoms and signs depend on personal factors in white-collar workers. A secondary aim was to determine how nasal symptoms, nasal patency, and lavage biomarkers are interrelated. In order to get a better statistical power with respect to personal factors, data from three studies have been pooled. An evaluation of factors with possible influence on the nasal parameters included: age, gender, tobacco smoking, atopy, asthma and occupation. The protocols of the studies from which data were pooled had been approved by the Ethics Committee of the Medical Faculty of Uppsala University.

MATERIAL AND METHODS

Subjects

Data were pooled from three separate studies on health effects of indoor exposures in primary schools (Wålinder et al., 1998), offices (Wieslander et al., 1999b), and geriatric hospitals (Wieslander et al., 1999a). Medical investigations of nasal patency and biomarkers in nasal lavage were performed with the same methodology (Wålinder et al., 1998). In addition, similar doctor's administered questions on nasal symptoms, and personal factors were used in all studies. Totally, data from 411 subjects was used; 234 school personnel, 89 office workers and 88 hospital workers; from twelve primary schools, three offices and four geriatric hospitals. The participation rates were 84%, 85% and 93% respectively. Out of a total of 411 subjects, data from one lavage and 16 rhinometric measurements were missing. The medical investigations were performed off pollen season (February 1994, October 1994-March 1995, November 1995 and January 1997). Identification of the subjects was made from current lists of employees. Subjects on longer sick leave or off duty for other reasons, and those working less than 20 hours per week, were excluded. Subjects who had an infection or fever the last seven days were asked to come to a new investigation two to four weeks later. All examinations were performed at the working place, and all had been at their workplace at least one hour prior to the examination.

Personal factors and symptoms

Information on personal factors and nasal symptoms the week prior to the medical investigation was gathered by means of a questionnaire. The set of symptoms included four questions on nasal symptoms: nasal obstruction, discharge, itch and sneezing. The prevalence of subjects with at least one nasal symptom was calculated. Atopy was defined as a history of allergic manifestations from exposure to common IgE-mediated allergens in Sweden (tree pollen, grass pollen, or furry animals). Asthmatic disease was defined as doctor's diagnosed asthma. The subjects were considered current smokers if they smoked more than one cigarette per day. The mean age was 46 years (SD=9.4), and other personal factors are given in Table 1.

Acoustic rhinometry

Acoustic rhinometry (Rhin 2000, S.R. Electronics, Denmark; wideband noise; continuously transmitted) was performed in the workplace building, and each individual had been at the working place at least one hour prior to the examination. The measurements were made under standardized forms (sitting), after five minutes rest, and prior to the lavage. By means of acoustic reflection the minimum cross-sectional areas (MCA) on each side of the nose were measured from 0 to 22 mm (MCA1) and from 23 to 54 mm (MCA2), from the nasal opening. Also the volumes of the nasal cavity on the right and left side were measured from 0 to 22 mm (VOL1) and from 23 to 54 mm (VOL2). The mean values were calculated from three subsequent measurements on each side of the nose, and data on nasal dimensions in the present study are presented as the sum of the values from the right and the left side.

Table 1. Relative frequencies (%) of personal factors and mean one week prevalences (%) of nasal symptoms for school personnel, office workers, and hospital workers.

	School personnel (N=234)	Office workers (N=89)	Hospital workers (N=88)	Total material (N=411)
Female	83	82	95	86
Current smoker	15	15	25	17
Atopy	23	31	31	26
Asthma	8	20	8	10
Nasal discharge[a]	19	18	23	20
Sneezing[a]	24	18	31	23
Nasal itching[a]	10	10	20	12
Nasal obstruction[a]	40	33	41	39
At least one nasal symptom[a]	50	45	55	50

[a] The week prior to the investigation

Nasal lavage

Lavage of the nasal mucosa was performed with a 20 ml plastic syringe attached to a nose olive after the rhinometric measurement. The subject was standing, with the head flexed about 30° forward. Room-tempered (20-22°C) sterile 0.9% saline solution was introduced into the nasal cavity. Each nostril was lavaged with 5 ml of solution that was flushed back and forth five times with the syringe, at an interval of a few seconds. The fluid was transferred into 10 ml polypropylene centrifuge tubes that were kept on ice. Within 300 minutes, the solution was centrifuged at 800 g for 5 minutes. The supernatant was recentrifuged at 1400 g for 5 minutes, and immediately frozen to –20°C.

Lysozyme was measured by means of radioimmunoassay. (Venge et al., 1979) The concentrations of ECP and MPO were determined by means of a double antibody radioimmunoassay method (Pharmacia Diagnostics AB, Uppsala, Sweden) (Peterson et al., 1991; Schmekel et al., 1990). Albumin was measured by rate nephelometry on an Array protein system (Beckman Instruments Inc). The detection limits applied by the laboratory for ECP, MPO, lysozyme, and albumin were 1.0 μ/L, 4.0 μ/L, 1.0 μ/L, and 2.0 mg/L respectively. The intra- and inter-assay coefficients of variation for the analyses of lysozyme, ECP, MPO and albumin were less than 11%.

Statistical analysis

The Kendall's rank correlation coefficients were applied to investigate the correlation between two variables which can be expressed in a rank order. For comparisons of the distributions between two groups (i.e. male/female), the Students t test was applied using log transformed data for ECP, MPO and albumin. Multiple linear or logistic regression were used to assess the influence of age, gender, smoking habits, atopy and asthma (SPIDA statistical package, Macquarie University, Australia). Furthermore control was made for type of occupation in the multivariate models. No major violations to the normal distribution of the residuals were present after the values of ECP, MPO and albumin had been logarithmically transformed. No collinearity problems were detected in the models. Adjusted partial regression coefficients or adjusted prevalence odds ratios (OR), with a 95% CI, were calculated in the multivariate models. In all statistical analysis, two-tailed tests and a 5% level of significance were applied.

RESULTS

Nasal symptoms

Nasal symptoms were common in all three occupational groups, 50% of all participants reported at least one nasal symptom during the week prior to the medical investigation. Most common was nasal obstruction (39%). Nasal drop, nasal itching, or sneezing were less common; 20%, 12%, and 23% respectively (Table 1). In the multivariate analysis of the influence of personal factors (Table 2), subjects with atopy had a higher prevalence of discharge, sneezing, and itching. Subjects with asthma had more often sneezing and nasal itching. In addition, the prevalence of sneezing was more common among older subjects (Table 2).

Clinical signs

Females had smaller nasal dimensions in the anterior part of the nose (MCA1 and VOL1) and lower concentration of ECP, MPO and albumin in lavage fluid (Table 3, 4). In order to create crude normal limit values for men and women in white collar professions, lower 95% percentiles for rhinometric data, and upper 95% percentiles for biomarkers in lavage fluid were calculated (Table 5). No significant influence of age, current smoking, atopy or asthma on nasal patency or any type of biomarkers in lavage was observed (Table 3). Median values for rhinometric measures, and concentrations of biomarkers in

Table 3. Multiple linear regression coefficients for rhinometric data and concentration of biomarkers in nasal lavage, in relation to personal factors and occupation.

Nasal parameter	Age (years)	Female gender	Smoking	Atopy	Asthma
MCA1 (cm^2)	-0,001	-0.15***	-0,01	-0,03	0.001
MCA2 (cm^2)	-0,002	-0,08	-0,04	-0,07	-0,03
VOL1 (cm^3)	0.002	-0.57***	0.06	-0,04	0.07
VOL2 (cm^3)	0.01	-0,50	0.30	-0,46	0.01
LogECP (μg/L)	-0,001	-0.11*	-0,06	-0,02	-0,001
Lysozyme (μg/L)	0.003	-0,24	0.03	-0,12	0.06
LogMPO (μg/L)	0.001	-0.18*	0.03	-0,09	-0,07
LogAlbumin (mg/L)	0.002	-0,10	-0,04	0.02	0.02

The multiple linear regression models include one nasal parameter as dependent variable and 5 independent variables: age, gender, smoking, atopy and asthma. Occupation included in the model for adjustment.

Table 2. One week prevalence odds ratios for nasal symptoms in relation to personal factors and occupation.

Symptom	Age OR	(95%CI)	Female gender OR	(95%CI)	Smoking OR	(95%CI)	Atopy OR	(95%CI)	Asthma OR	(95%CI)
Nasal discharge	1,00	(0.98-1.03)	0,78	(0.38-1.58)	0,66	(0.32-1.40)	2,14	(1.22-3.73)**	1,74	(0.81-3.76)
Sneezing	1,04	(1.01-1.06)*	0,65	(0.33-1.26)	1,31	(0.70-2.47)	2,17	(1.26-3.71)**	2,32	(1.10-4.90)*
Nasal itching	1,00	(0.96-1.03)	0,87	(0.35-2.17)	1,06	(0.46-2.41)	2,06	(1.05-4.06)*	2,71	(1.13-6.48)*
Nasal obstruction	1,00	(0.98-1.03)	0,92	(0.51-1.65)	1,19	(0.69-2.06)	1,54	(0.95-2.51)	1,73	(0.84-3.55)
At least one nasal symptom	1,01	(0.99-1.03)	0,85	(0.48-1.53)	1,32	(0.77-2.26)	1,87	(1.15-3.04)*	1,92	(0.90-4.09)

The multiple logistic regression models include one nasal parameter as dependent variable and 5 independent variables: age, gender, smoking, atopy and asthma. Occupation included in the model for adjustment.

Table 4. Rhinometric data and concentration of biomarkers in nasal lavage, among males and females, in the total material (N=411).

	Males (N=59)		Females (N=352)		
Parameter	Median	Interquartile range	Median	Interquartile range	P-value
MCA1 (cm^2)	1.04	0.87 to 1.21	0.91	0.77 to 1.06	<0.001
MCA2 (cm^2)	1.06	0.90 to 1.41	1.10	0.86 to 1.39	NS
VOL1 (cm^3)	3.79	3.37 to 4.48	3.35	3.00 to 3.74	<0.001
VOL2 (cm^3)	7.54	6.11 to 9.54	7.41	6.27 to 8.87	NS
ECP (μg/L)	1.7	1.4 to 2.6	1.4	1.0 to 1.8	0.004
MPO (μg/L)	20.2	9.2 to 46.0	10.3	4.1 to 26.4	0.002
Lysozyme (mg/L)	2.0	0.76 to 4.9	1.7	0.67 to 3.6	NS
Albumin (mg/L)	4.8	<3.0 to 12.3	3.0	<3.0 to 6.6	0.01

Table 5. Limits for lower 95% percentils for rhinometric data, and upper 95% percentils for concentrations of biomarkers in nasal lavage among males and females in the total material (N=411).

Parameter	Males (N=59) 95% percentile limit	Females (N=252) 95% percentile limit
MCA1 (cm^2)	<0.59	<0.58
MCA2 (cm^2)	<0.60	<0.58
VOL1 (cm^3)	<2.72	<2.50
VOL2 (cm^3)	<4.76	<4.71
ECP (μg/L)	>6.3	>4.6
MPO (μg/L)	>119	>103
Lysozyme (mg/L)	>9.6	>7.1
Albumin (mg/L)	>35	>21

lavage, for the three occupational groups are given in Table 6. Both office workers and school personnel had significantly smaller rhinometric parameters (MCA1, MCA2, VOL1 and VOL2) and higher concentrations of ECP and MPO than hospital workers by multiple linear regression analysis.

Relations between symptoms and signs

The anterior nasal volume (VOL1) was significantly decreased ($p<0.05$) among those reporting nasal obstruction (mean=3.38 cm^3; SD=0.56 cm^3), as compared to those without such symptoms (mean=3.50 cm^3; SD=0.63 cm^3). A similar, but non-significant relation (p=0.07), was observed for the anterior minimal cross-sectional area (MCA1). No significant relationships were observed between lavage biomarkers, and any nasal symptoms. The concentration of different biomarkers in lavage fluid were all strongly related to each other (Table 7). There was also a consistent pattern of relations between biomarkers and rhinometric measures, where increased concentrations in lavage fluid of all types of biomarkers were related to decreased nasal patency, irrespectively of the type of rhinometric measure (Table 7).

DISCUSSION

In general, the objective nasal measurements were little influenced by personal factors. Gender differences in the anterior nasal dimensions and lavage biomarker levels were found, but no differences in objective measurements due to age, smoking, atopy or asthma. The consistent pattern of clinical signs, supports a nasal reaction consisting of both a mucosal swelling and an inflammatory response.

The one-week prevalence of nasal symptoms was high; 50% reporting at least one symptom. This is in conformity with the high prevalence rates of nasal symptoms, 42-54%, in office workers observed in other investigations (Burge et al., 1987; Hedge et al., 1989; Jaakkola et al., 1991; Teculescu et al., 1998). Selection bias due to low response rate is less likely since the participation rate was relatively high in all three groups (84-93%) and the buildings were selected to be representative workplaces in the area, irrespectively of the occurrence of symptoms. In addition, the distributions of personal factors were similar in the three occupational groups, justifying pooling of data from the three groups. Recall bias due to awareness of exposure may affect symptom reporting, but is unlikely to affect rhinometric measurements or biomarkers in nasal lavage fluid. Measurement error or intra-individual variability may have introduced some bias in the investigation, especially for lavage measurements. This misclassification is most likely non-differential, and results in a dilution of studied effects, with loss of statistical power. There were some differences of nasal signs between the occupational groups, therefore control was made for occupation to avoid possible confounding. Thus, we do not believe that our conclusions are seriously biased by selection, response or measurement errors.

Age was not related to dimensions or biomarkers. This could be due the exclusion of children and the elderly since the study was performed among employees. Atopy and asthma, well-known risk factors for airway symptoms, were related to an increase in nasal symptoms, but were not associated with clinical nasal signs. This might reflect a non-reactive state of many of the atopics since the investigations were made off pollen season.

There were no evident relations between nasal symptoms and clinical signs in the present study, where only the anterior volume in the nose was correlated to nasal obstruction. This is in agreement with other studies where the feeling of obstruction was not correlated to objective measures of nasal patency (Kim et al., 1998; Roithmann et al., 1994). Other factors than nasal cavity dimensions associated with this symptom are: allergy (Grymer et al., 1997) and sensibility of the mucosa (Eccles and Jones, 1983).

Challenge studies with allergens in sensitized subjects have shown significantly diminished rhinometric dimensions, for example a 50% reduction in area after challenge (Fisher, 1997), and one study without challenge also showed a smaller area at the inferior turbinate in patients with rhinitis compared to nor-

Table 6. Rhinometric data and concentration of biomarkers in nasal lavage, among school personnel, office workers, and hospital workers.

	School personnel (N=234)		Office workers (N=89)		Hospital workers (N=88)		Total (N=411)	
Parameter	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
MCA1 (cm^2)	0.90	0.76 to 1.07	0.94	0.77 to 1.10	1.00	0.85 to 1.15	0.93	0.78 to 1.08
MCA2 (cm^2)	1.06	0.85 to 1.32	1.02	0.78 to 1.38	1.34	1.00 to 1.59	1.10	0.88 to 1.40
VOL1 (cm^3)	3.34	2.99 to 3.66	3.44	3.12 to 4.02	3.61	3.18 to 4.00	3.41	3.03 to 3.81
VOL2 (cm^3)	7.25	6.08 to 8.60	7.19	5.95 to 8.87	8.74	6.82 to 10.44	7.41	6.25 to 9.05
ECP (μg/L)	1.6	1.1 to 2.2	1.5	1.4 to 1.7	<1	<1 to 1.2	1.4	1.0 to 1.9
MPO (μg/L)	21.5	10.0 to 44.9	6.2	2.0 to 14.7	2.0	2.0 to 8.0	11.4	4.4 to 28.9
Lysozyme (mg/L)	3.1	1.8 to 4.8	0.73	0.32 to 1.6	1.0	0.57 to 1.6	1.76	0.70 to 3.64
Albumin (mg/L)	5.6	3.0 to 10.9	<3	<3 to <3	<3	<3 to <3	3.1	1.5 to 7.4

Table 7. Kendall's tau correlation coefficients between rhinometric data and concentration of biomarkers in nasal lavage, in the total material (N=411).

Parameter	ECP	MPO	Lysozyme	Albumin
MCA1 (cm^2)	-0.20***	-0.12***	-0.18***	-0.13***
MCA2 (cm^2)	-0.22***	-0.13***	-0.13***	-0.16***
VOL1 (cm^3)	-0.15***	-0.10**	-0.14***	-0.11**
VOL2 (cm^3)	-0.17***	-0.13***	-0.10**	-0.15***
ECP (μg/L)		0.50***	0.34***	0.45***
MPO (μg/L)			0.38***	0.59***
Lysozyme (mg/L)				0.37***
Albumin (mg/L)				

**p<0.01; ***p<0.001

mal controls (Lenders and Pirsig, 1990). Studies investigating biomarker levels among patients with active allergic rhinitis have shown higher ECP (Beppu et al., 1994; Wilson et al., 1998) and albumin (Wilson et al., 1998) concentrations as compared to non-allergic controls.

In conclusion, gender was the only personal factor of study which was significantly related to nasal measurements. There was a large biological variability between subjects, both concerning nasal dimensions and lavage biomarkers, but it could not be explained by the personal factors in question. However, the consistent pattern between acoustic measurements of nasal patency and biomarker levels, suggests a common mucosal response involving both obstruction and inflammation. This indicates that the combined use of acoustic rhinometry and biomarkers of inflammation in nasal lavage fluid, can be a useful method to study human nasal mucosal reactions.

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