

Increased nasal mucosal swelling in subjects with asthma

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Summary

Objective The objective of this study was to evaluate nasal mucosal swelling with acoustic rhinometry in subjects with asthma and in healthy controls.

Methods We examined 184 individuals with asthma and compared with 156 randomly selected controls outside the pollen season, where 144 subjects in the asthma group and 80 controls had a previous history of non-infectious rhinitis (NIR). Nasal mucosal swelling was assessed with acoustic rhinometry before and after nasal decongestion with oxymetazoline and was analysed for the cross-sectional area (4 cm from the nostril) and the volume between 3.3 and 4 cm from the nostril. Symptom scores for nasal blockage, secretion, itching and sneezing were assessed on a 0–10 visual analogue scale as well as peak nasal inspiratory flow and spirometry.

Results Before decongestion there was a decrease in the cross-sectional area at 4 cm (1.32 cm^2 vs. 1.59 cm^2 , mean left + right $P=0.04$) and in the volume (1.70 vs. 1.91 cm^3 $P=0.03$) in the asthma group compared with healthy controls. After decongestion there were no significant differences in cross-sectional area at 4 cm (1.66 vs. 1.73 cm^2 $P=0.32$) or volume (2.12 vs. 2.24 cm^3 $P=0.32$). Combined nasal symptom scores were higher in the asthma group (1.8 vs. 0.8 , $P=0.0001$) and peak nasal inspiratory flow was lower (119 vs. 124 L/min , $P=0.38$) than the healthy controls. FEV_1 (% predicted) was also lower in asthma group (84 vs. 93% $P<0.0001$).

Conclusion We have been able to demonstrate an increased nasal mucosal swelling in a population sample of persons with asthma compared to healthy controls. These data support previous reports of a generalized airway inflammation in patients with asthma and suggest that acoustic rhinometry can be used to monitor the nasal mucosal swelling in these patients.

Keywords asthma, non-infectious rhinitis, acoustic rhinometry

Submitted 6 March 2001; revised 11 June 2001; accepted 16 July 2001

Introduction

Epidemiological studies have indicated that rhinitis is common in patients with bronchial asthma, affecting 74–99% of the asthma population [1,2]. We have previously assessed self-reported non-infectious rhinitis (NIR) in a population sample of subjects with asthma and a random sample of controls using a validated rhinitis question [3]. As previously described, NIR is defined as problems with nasal blockage, secretion or sneezing, since the age of 15 years that was not common cold, and thus includes both allergic and non-allergic rhinitis [4]. We found 82% NIR among both men and women in the asthma group ($n=315$) compared with 47% ($n=699$) of the women and 45% of the men in the control group ($n=689$) ($P=0.001$), Hellgren, unpublished data.

One of the main symptoms of rhinitis is nasal blockage. Intranasal steroids have been found to reduce symptoms of nasal blockage and increase peak nasal inspiratory flow

(PNIF) in patients with asthma and rhinitis, indicating an effect on nasal inflammation and on nasal patency [5–7]. It is thus likely that rhinitis in asthma is accompanied by an increased swelling of the nasal mucosa. To our knowledge this has not been verified before in direct studies of the nasal mucosa. One study including 41 persons with asthma using acoustic rhinometry found no significant differences in minimum cross-sectional area or intranasal volume compared with healthy controls [8].

Since it has been suggested that rhinitis in asthma is part of a generalized airway inflammation, an increased swelling of the nasal mucosa would be expected.

To investigate this further, we have assessed nasal mucosal swelling outside the pollen season, using acoustic rhinometry, in a population sample of subjects with asthma compared with a random selection of non-asthmatic controls.

Materials and methods

Subjects

The asthma group in this study is part of a prospective asthma study that was started in 1986 at the Allergy Department,

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Sahlgrenska University Hospital, Göteborg, and originally included 420 asthma patients between 18 and 60 years of age [9].

The diagnosis of asthma was defined as a recent onset of typical asthma symptoms (attacks of dyspnoea, wheezing, dyspnoea or cough induced by asthma triggers, symptom relief by bronchodilators) and at least one of the following criteria.

- Three amplitude differences in peak expiratory flow, (PEF) variations of at least 20% during two weeks of registration.
- FEV₁ increased by $\geq 15\%$ from the initial value after the inhalation of β_2 bronchodilators.
- FEV₁ increased by $\geq 15\%$ after two weeks of treatment with oral steroids.
- PC₂₀ ≤ 4 mg/L at methacholine challenge test.

In 1996, a questionnaire on asthma and rhinitis was mailed to the asthma group and a random sample of 1904 controls from the same area [9]. The prevalence of NIR was assessed (see below) and was later used to stratify the subjects in the clinical study.

In 1998, we invited the remaining subjects in the asthma population, who participated in the questionnaire study ($n = 315$) to participate in a clinical study of rhinitis together with a random subsample from the control group. From the controls, 200 who answered yes to the rhinitis question (NIR controls), and 200 who answered no (non-NIR controls), were randomly selected (Table 1).

Subjects who had moved more than 40 km from Göteborg and were expected to have difficulty attending the clinical examination and those who had died were excluded. We thus invited 302 asthma patients, 166 controls in the NIR group and 155 in the non-NIR group. Due to failure to respond, refusal to participate and sickness, we finally examined 184 asthma patients (61%), 80 NIR controls (48%) and 76 non-NIR controls (49%).

Definition of non-infectious rhinitis

The prevalence of NIR was assessed with a slightly modified question from the 'International study of asthma and allergies in childhood' (ISAAC): 'Have you ever had a problem with sneezing, or a runny, or a blocked nose when you DID NOT have a cold or the flu?' [3,10]. The wording of the question has been adapted to assess adult onset rhinitis, by excluding symptoms before the age of 15. As previously described, persons who answered 'yes' to this question were considered to have NIR [4]. This definition of rhinitis was chosen because both allergic and non-allergic rhinitis have been reported as risk factors for developing asthma [11]. The NIR question does not stratify rhinitis according to known allergic status. We have also

increased the sensitivity for NIR, by disregarding the duration of symptoms, since rhinitis and asthma are known to vary in intensity and recurrence over time.

Medications

Nasal steroids were discontinued 4 weeks and antihistamines 5 days before examination. Inhaled pulmonary steroids or oral steroids were not discontinued. Short-acting β_2 agonists were not taken for 4 h before examination and long-acting β_2 agonists for 3 days before. Ipratropiumbromide was not taken for 12 h before examination.

Study design

The clinical examination was conducted outside the pollen season at the Allergy Department, Sahlgrenska University Hospital. Each subject was asked to fill out a questionnaire addressing asthma, rhinitis and smoking habits. The presence of hayfever was assessed with the following question: 'Have you currently or previously had hayfever, that is nasal blockage, runny nose and/or sneezing attacks, during the spring and/or summer that was not due to a common cold?' [3].

Skin prick test and atopy

Skin prick test has previously been performed in 157 subjects in the asthma group within the longitudinal asthma study [9]. Self-reported atopy was assessed with the question: 'As a child, did you have any form of allergy, such as eczema, asthma or hayfever?' [3]. The clinical examination was made after 30 min of adaptation to the ambient air conditions.

Spirometry

A trained nurse assessed spirometry, using a dry spirometer, (Vitalograph, Buckingham, UK) according to the American Thoracic Society [12], expressed as a percentage of the predicted [13].

Symptom score

Current symptoms of nasal blockage, secretion, itching and sneezing were rated on a 0–10 visual analogue scale (VAS, 0 = no symptoms, 10 = worst possible symptoms). A mean of the four symptom scores was calculated (mean score).

Nasal blockage was additionally rated after decongestion. The difference in blockage score before and after decongestion was calculated (Δ blockage).

Anterior rhinoscopy

All subjects were examined with anterior rhinoscopy, using a speculum and a headlamp. All examinations were performed by the same ear, nose and throat (ENT) specialist (J. H.). Presence of NIR was blinded to the investigator. Nasal mucosal colour was recorded as pale or red. Nasal polyps were recorded. Septal deviations and hypertrophy of the inferior turbinate were also recorded as the side that was most obstructed.

Decongestion

Acoustic rhinometry and peak nasal inspiratory flow, (PNIF) were performed before and after decongestion of the nasal mucosa. Commercially available oxymetazoline 0.5 mg/mL (Nezeril[®], Draco, Sweden) was sprayed twice into each nasal cavity. The mucosa was considered decongested after 10 min.

Table 1. The development of the study population in chronological order. The underlying population aged 18–60 in 1986 was 370 000. The percentage of the invited subjects who were examined in 1998 is presented within brackets

	Asthma (n)		Controls (n)
Included 1986	420		
Remaining 1996	407	Included 1996	1.904
<i>Present study population</i>			
Remaining 1998	315	Subsample 1998	200 NIR 200 non-NIR
Invited	302		166 155
Examined	184(60%)		80(48%) 76(49%)

PNIF

The PNIF was monitored with a PNIF meter (In-check™, Clement Clarke International Limited, Essex, UK). The maximum value out of three consecutive measurements was recorded [14].

Acoustic rhinometry

Intranasal geometry was assessed with acoustic rhinometry (Rhin 2100, Rhinometrics, Copenhagen, Denmark) [15]. We used anatomic nose-pieces in two sizes and Vaseline contact gel between the nose-piece and the nostril. The probe was hand-held with the subject sitting opposite the investigator in an upright position, holding his/her breath during the measurements. Three similar recordings were made on each side to produce a mean [16]. The same reviewer manually reviewed all the acoustic rhinometry data, and 11 unilateral recordings were discarded because of obstructive anterior septal deviations with subsequent invalid readings beyond the obstruction. These were evenly distributed between the three main groups. The cross-sectional area 4 cm from the nostril (CA 4), the volume between 3.3 and 4 cm from the nostril (volume) and the minimum cross-sectional area (MCA) were calculated.

The study was approved by the local ethics committee.

Statistical analyses

Comparisons between groups of FEV₁, mean score before decongestion and PNIF, MCA, CA, volume, and Δ blockage before and after decongestion were made using a non-parametric Kruskal–Wallis test and the *P*-values have generally been given. A *P*-value of <0.05 was considered statistically significant. The association between acoustic rhinometry data as the dependent variables and different explanatory variables was tested using multiple linear regression and the significance of the slope in the multivariate regression model was based on the *t*-distribution. For the linear regression models, PROC REG from the SAS statistical package was used. The nasal mucosal swelling was expressed as logarithm transformed volume 3.3–4 cm from the nostril.

Results

Subjects

Baseline data for the examined subjects (attendees) and the unexamined subjects (non-attendees) are presented in Table 2.

Among the attendees in the asthma group, one fifth were no longer using any medication for their asthma and another 20% used only β_2 agonists indicating a remission or a very mild disease in some subjects.

Skin prick test and atopy

The result of the skin prick test, previously performed in the asthma group, showed that 88/157 (56%) were skin prick-positive for perennial allergens such as house dust mite or cat. Self reported atopy was present in 19% of the non-NIR controls, 22% of the NIR controls, 19% of the non-NIR asthma subjects and 41% of the NIR asthma subjects.

Table 2. Baseline data for attendees (A) and non-attendees (NA)

	N	Age (years)	Sex females (%)	Smokers (%)
Asthma A	184	48	62	54
Asthma NA	118	41	63	36
NIR Controls A	80	48	63	55
NIR Controls NA	86	43	42	31
Non-NIR Controls A	76	49	49	65
Non-NIR Controls NA	79	45	52	28

Spirometry

Spirometry data are presented in Table 3.

Anterior rhinoscopy

Anterior rhinoscopy revealed reddening of the nasal mucosa in 34% of the non-NIR controls, 23% of the NIR controls, 29% of the non-NIR asthma subjects and 29% of the NIR asthma subjects. In the asthma group 50% had an asymmetry between the left and right side with regard to septal deviation and/or turbinate hypertrophy. Non-NIR controls had an asymmetry in 57% and NIR controls in 53%. Nasal polyps were present in 13 cases on the left side and 19 cases on the right side of the subjects with asthma (*n* = 20). In the NIR controls, polyps were present in one case on the left side and two cases on the right side (*n* = 2). No polyps were observed in the non-NIR controls.

Symptom score

Prior to decongestion, both the asthma group and the rhinitis group had a higher mean score than the non-NIR controls (*P* = 0.0001), Table 3. The main symptom was nasal blockage in all three groups ranging from 1.1–2.3, followed by sneezing 1.0–2.4, and secretion 0.9–2.0. After decongestion, the change in subjective nasal blockage, Δ blockage, was more pronounced in the asthma group and NIR control group compared with the non-NIR control group (*P* = 0.002–0.004).

PNIF

Before decongestion the PNIF was lower in the asthma group (119 vs. 124 L/min, *P* = 0.38) and in NIR controls (109 vs. 124 L/min, *P* = 0.01) than in the non-NIR control group. The PNIF increased by 14% in the asthma group, 12% in the NIR control group and 10% in the non-NIR control group after decongestion.

Acoustic rhinometry

The acoustic rhinometry data are presented in Table 3. Before decongestion, subjects with asthma had a significantly lower mean CA 4, mean left + right side (1.32 vs. 1.59 cm², *P* = 0.04) and volume (1.70 vs. 1.90 cm³, *P* = 0.03) than non-NIR controls. In the multivariate linear regression model, adjusting for smoking, sex, FEV₁, and atopy, the asthma group showed significantly (*P* = 0.029) more nasal mucosal swelling.

The MCA was also calculated and it was lower in the asthma group than in the non-NIR control group (0.61 vs. 0.64 cm²) but not significant. The increase in MCA after decongestion,

Table 3. Comparison between asthma, NIR asthma, non-NIR asthma, NIR controls and non-NIR controls

Method	Asthma	NIR asthma	Non-NIR asthma	NIR controls	Non-NIR controls
N	184	144	40	80	76
FEV ₁ (% predicted)	84	85	77	90	93
Mean score (VAS 0–10)	1.8 (<i>P</i> = 0.0001)	1.9 (<i>P</i> = 0.0001)	1.4 (<i>P</i> = 0.04)	1.7 (<i>P</i> = 0.0001)	0.8
Δ blockage (VAS 0–10)	1.1 (0.004)	1.0 (<i>P</i> = 0.01)	1.2	1.1 (<i>P</i> = 0.002)	0.6
PNIF before (L/min)	119	118	124	109 (<i>P</i> = 0.01)	124
PNIF after (L/min)	136	136	136	122 (<i>P</i> = 0.02)	136
CA 4 before (cm ²)	1.32 (<i>P</i> = 0.04)	1.31 (<i>P</i> = 0.03)	1.34	1.34	1.59
CA 4 after (cm ²)	1.66	1.66	1.60	1.51	1.73
Volume before (cm ³)	1.70 (<i>P</i> = 0.03)	1.68 (<i>P</i> = 0.02)	1.74	1.75	1.90
Volume after (cm ³)	2.12	2.11	2.13	2.05	2.24

P = significance level compared with controls. NIR = non-infectious rhinitis. VAS = visual analogue scale.

ΔMCA, increased significantly in the asthma group (0.05 vs. 0.01 cm², *P* = 0.05).

When controlling the asthma group for NIR (Table 3), the increase in CA 4 after decongestion was less in the non-NIR asthma group compared with the NIR asthma group.

When controlling for asthma symptoms during the past two years, there was a significant reduction in FEV₁% predicted (81 vs. 87, *P* = 0.02) and an increase in mean score (2 vs. 1.5, *P* = 0.05) compared with those who reported no asthma symptoms during that period (*n* = 84), but there were no significant differences in the acoustic rhinometry data.

Discussion

In the present study, we found an increased, reversible swelling of the nasal mucosa in persons with asthma compared with healthy controls. A previous history of NIR tended to strengthen this relationship.

In the design of this study, we made a clinical evaluation of subjects who had participated in a population-based questionnaire study two years before. The main reason for choosing a population-based sampling frame for the subjects is that this increases the external validity of the results. Secondly, the asthma group was well-defined with regard to their asthma and the group comprised a substantial number of subjects who could easily be addressed. Finally, the pre-existing questionnaire data would help us to characterize those subjects who did not participate in the clinical examination.

One problem with this design, however, was the relatively high percentage of 'drop outs', especially in the control group, which naturally reduces the external validity. Some subjects had moved from the geographical area, but most non-attendees never answered the invitation despite three reminders and two phone calls. We believe that there could have been a lack of motivation in some subjects after having participated in the original questionnaire study, especially as the present study included a clinical visit to the hospital.

Self-reported NIR did not differ between attendees and non-attendees with asthma. In fact, the single most important difference between attendees and non-attendees was the predominance of smokers (present and past) among the attendees. This selection was most obvious in the non-NIR controls, which was supported by a decrease in lung function. We have previously found that smoking is a risk factor for NIR (incidence rate

1.6, 95% confidence interval (CI) 1.4–2.0) (Hellgren, submitted). Due to the relative predominance of smokers among the non-NIR controls, any difference in mucosal swelling seen between the asthmatic subjects and the non-NIR controls could thus be expected to be decreased rather than increased.

Another possible bias in the selection of subjects was the predominance of women in the asthma group compared with the non-NIR controls. A multiple regression adjusted for sex, age and smoking habits however, did not change the results. (Table 4).

Because of the recurrent nature of airway inflammation and the fact that both allergic and non-allergic rhinitis may be present in asthma we have used a wide definition of rhinitis termed NIR. The disadvantage with this definition is that nasal symptoms due to normal nasal physiology may be classified as NIR. The retrospective character of the question may also contribute to a loss of information due to recall bias. The prevalence of NIR in the asthma group was however, similar to previous prevalence reports of allergic rhinitis in asthma.

The high prevalence of NIR in the asthma group was supported in the present study by a significant increase in pre-decongested total mean symptom score (*P* = 0.0001), where nasal blockage was the most common symptom (Table 3). The symptom scores were generally low in all three groups, reflecting the fact that subjects were classified according to a history of rhinitis and not current symptoms.

Anterior rhinoscopy was performed mainly to be able to exclude anatomical obstructions such as severe septal deviations, major polyps or tumours. Since we were looking at

Table 4. Variables included in a multiple linear regression model with volume between 3.3 and 4 cm from the nostril (cm³) as the dependent variable

Variable	Coefficient	SE	<i>P</i> -value
Intercept	1.94	0.21	–
Age (year)	0.0019	0.0035	0.58
Never-smokers ¹	–0.16	0.12	0.18
Ex-smokers ²	–0.03	0.12	0.80
Sex ³	–0.14	0.086	0.12
Asthma vs. controls ⁴	–0.21	0.09	0.029

¹Never-smokers = 1, others = 0; ²Ex-smokers = 1, others = 0; ³0 = females, 1 = males; ⁴1 = asthma group, 0 = controls.

cumulative episodes of rhinitis, and symptom scores were low, many subjects could be expected to have little or no visible reaction in the nasal mucosa. Reddening of the nasal mucosa was in fact more common in the non-NIR controls than in subjects with asthma indicating that the colour of the nasal mucosa is of little use in the study of non-acute rhinitis in asthma.

In the assessment of nasal airflow with PNIF, the subjects with asthma scored lower prior to decongestion than the non-NIR controls but the difference was not significant.

The NIR controls maintained a lower PNIF after decongestion, which could indicate more structural nasal problems in this group.

Our acoustic rhinometry measurements on the other hand showed a significant decrease in cross-sectional area and volume in the asthma group compared with non-NIR controls. In accordance with Grymer et al. we analysed the cross-sectional area at 4 cm from the nostril [17]. In addition, we analysed the volume between the anterior part of the inferior turbinate at 3.3 cm and CA 4, which was also significantly lower in the asthma group [17]. One possible source of bias could be the presence of nasal polyps. Anterior rhinoscopy, revealed more nasal polyps in the asthma group as expected. The 2.5 times larger decongestant effect at CA 4, seen in the asthma group, however, supports the presence of an increased mucosal swelling as nasal decongestants have been found to have no effect on nasal polyps when monitored with CT scanning [18].

In order to evaluate the importance of previous NIR for the nasal mucosal swelling, the asthma group was stratified for NIR as well. The results showed that the pre-decongested CA 4 and volume remained virtually unchanged in the NIR asthma group, while the difference decreased in the non-NIR asthma group compared with non-NIR controls.

Our findings are supported by a recently published report from Gaga et al. where an increased number of eosinophils was found in nasal biopsies from subjects with asthma compared to healthy controls, regardless of if they had nasal symptoms or not [19]. The reason that not all the subjects in the asthma group report NIR could be several. The non-NIR asthma group had a significantly lower FEV₁ (% predicted) than the NIR asthma group (77 vs. 85 $P = 0.002$), indicating more severe asthma in this group. It has previously been demonstrated that the quality of life correlates with FEV₁ and it is thus possible that nasal problems are perceived differently in this group compared to the group with milder asthma [20]. It has also been demonstrated that the perception of nasal obstruction is not always related to changes in airway resistance, and that sensory function and differences in respiratory demand may be of importance [21,22].

Hayfever is known to be common in asthma, but since this study was performed outside the pollen season, hayfever is not likely to be the cause. Hayfever patients without asthma do not report increased nasal symptoms outside the pollen season, nor do they exhibit increased nasal mucosal swelling when monitored with acoustic rhinometry [14]. Perennial allergic rhinitis could be a possible mechanism, considering that almost 60% of the asthma patients were skin prick-positive to perennial allergens. Non-allergic rhinitis may however, also be of importance since only 40% of the asthma subjects reported atopy.

Acoustic rhinometry is a comparatively new, objective and highly reproducible method to assess intranasal geometry. We believe that the present result opens new possibilities to monitor nasal mucosal swelling in asthma, addressing treatment and prevention.

In conclusion, we have been able to demonstrate an increased nasal mucosal swelling in a population sample of persons with asthma compared to healthy controls. These data support previous reports of a generalized airway inflammation in patients with asthma and suggest that acoustic rhinometry can be used to monitor the nasal mucosal swelling in these patients.

Acknowledgements

This paper was supported by the following organisations: The Herman Krefting Fund for Medical Research, The Medical Society Göteborg, GlaxoWellcome, Sweden, The Torsten and Ragnar Söderberg Foundation for Scientific Research and The Swedish Council for Work-life Research.

References

- Greisner WA, Settipane RJ, Settipane GA. Co-existence of asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Asthma Proc* 1998; 19 (4):185–8.
- Kapsali T, Horowitz E, Diemer F, Togias A. Rhinitis is ubiquitous in allergic asthmatics (abstract). *J Allergy Clin Immunol* 1997; 99:S138.
- Charpin D, Sibbald B, Weeke E, Wuthrich B. Epidemiologic identification of allergic rhinitis. *Allergy* 1996; 51 (5):293–8.
- Hellgren J, Eriksson C, Karlsson G, Hagberg S, Olin AC, Toren K. Nasal symptoms among workers exposed to soft paper dust. *Int Arch Occup Environ Health* 2001; 74 (2):129–32.
- Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992; 90 (2):250–6.
- Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993; 91 (1 Part 1):97–101.
- Mastalerz L, Milewski M, Duplaga M, Nizankowska E, Szczeklik A. Intranasal fluticasone propionate for chronic eosinophilic rhinitis in patients with aspirin-induced asthma. *Allergy* 1997; 52 (9):895–900.
- Walinder R, Wieslander G, Norback D, Erwall C, Venge P. Influence of personal factors on nasal patency and lavage biomarkers in white-collar workers. *Rhinology* 2000; 38 (3):130–5.
- Balder B, Lindholm NB, Lowhagen O et al. Predictors of self-assessed work ability among subjects with recent-onset asthma. *Respir Med* 1998; 92 (5):729–34.
- Asher MI, Keil U, Anderson HR et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; 8 (3):483–91.
- Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: An independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 104 (2 Part 1):301–4.
- ATS statement – Snowbird workshop on standardization of spirometry. *Am Rev Respir Dis* 1979; 119 (5):831–8.

- 13 Knudson RJ, Slatin RC, Lebowitz MD, Burrows B. The maximal expiratory flow-Volume curve. Normal standards, variability, and effects of age. *Am Rev Respir Dis* 1976; 113 (5):587–600.
- 14 Hellgren J, Jarlstedt J, Dimberg L, Toren K, Karlsson G. A study of some current methods for assessment of nasal histamine reactivity. *Clin Otolaryngol* 1997; 22 (6):536–41.
- 15 Hilberg O, Jackson AC, Swift DL, Pedersen OF. Acoustic rhinometry: evaluation of nasal cavity geometry by acoustic reflection. *J Appl Physiol* 1989; 66 (1):295–303.
- 16 Hilberg O, Pedersen OF. Acoustic rhinometry: recommendations for technical specifications and standard operating procedures. *Rhinol Suppl* 2000; 16:3–17.
- 17 Grymer LF, Hilberg O, Pedersen OF, Rasmussen TR. Acoustic rhinometry: values from adults with subjective normal nasal patency. *Rhinology* 1991; 29 (1):35–47.
- 18 Elbez M, De Pressigny M, Halimi P, Aidan D, Bonfils P, Trotoux J. Does the use of nasal vasoconstrictor agents change tomodesitometric images of nasosinus polypoidosis? *Ann Otolaryngol Chir Cervicofac* 1993; 110 (5):277–80.
- 19 Gaga M, Lambrou P, Papageorgiou N et al. Eosinophils are a feature of upper and lower airway pathology in non-atopic asthma, irrespective of the presence of rhinitis. *Clin Exp Allergy* 2000; 30 (5):663–9.
- 20 Bousquet J, Knani J, Dhivert H et al. Quality of life in asthma. I. Internal consistency and validity of the SF-36 questionnaire. *Am J Respir Crit Care Med* 1994; 149 (2 Part 1):371–5.
- 21 Eccles R, Lancashire B, Tolley NS. Experimental studies on nasal sensation of airflow. *Acta Otolaryngol* 1987; 103 (3–4):303–6.
- 22 Naito K, Cole P, Fraschetti J, Humphrey D. Nasal patency: subjective and objective. *Am J Rhinol* 1989; 2:93–7.