

ORIGINAL ARTICLE

Airway dysfunction in nasal polyposis: a spectrum of asthmatic disease?

P. A. Williamson, S. Vaidyanathan, K. Clearie, M. Barnes and B. J. Lipworth

Asthma & Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK

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Summary

Background Chronic rhinosinusitis with nasal polyposis (CRSwNP) represents an interesting model to investigate the existence of a non-allergic unified airway. The factors associated with airway dysfunction in CRSwNP are not fully understood.

Objective To assess the impact of nasal disease on lower airway dysfunction in CRSwNP.

Methods Fifty-seven patients with CRSwNP underwent spirometry, nasal endoscopy, exhaled nitric oxide, methacholine bronchial challenge, blood sampling for total IgE, eosinophil count and radioallergosorbent testing (NCT00788749). Three phenotypic groups were identified: 'asthma group' (asthma diagnosis); 'inflammatory group' [no asthma diagnosis, but elevated fractionated exhaled nitric oxide (FE_{NO}) and/or bronchial-hyperreactivity (BHR)]; and 'non-inflammatory group' (no asthma diagnosis, no BHR and normal FE_{NO}). Group comparisons, univariate and multivariate analyses were performed to examine associations with airway dysfunction.

Results FEV₁ and FEF_{25–75%} were reduced in asthma, but there was no difference between the non-asthmatic groups. Total IgE and eosinophils were elevated in asthma vs. the non-inflammatory group, but there was no difference for asthma vs. inflammatory groups. BHR was the only significant predictor of FEV₁ ($P < 0.001$). For FEF_{25–75}, BHR and eosinophil count were independent predictors ($P < 0.001$ and $P = 0.04$). Nasal outcomes were not predictors of spirometry.

Conclusion and Clinical Relevance In CRSwNP there is asymptomatic airway dysfunction suggestive of an asthmatic phenotype. Impairment of lung function is significantly associated with BHR and eosinophilia but not parameters of nasal disease suggesting that severity of airway dysfunction relates to the spectrum of asthma rather than rhinosinusitis. Lower airway dysfunction is common in CRSwNP but does not correlate to the severity of nasal disease. Signs and symptoms of asthma should be sought and treated in CRSwNP.

Keywords asthma, nasal polyps, sinusitis

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Correspondence:

Professor Brian J Lipworth, Asthma & Allergy Research Group, Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK.
E-mail: brianlipworth@googlemail.com

Introduction

There is increasing physiological, clinical and epidemiological evidence to support the existence of a 'unified allergic airway' [1]. Allergic rhinitis (AR) may be present in up to 80% of atopic asthma and 34% of patients with AR report lower airway symptoms [2–4]. Experimental models using segmental bronchoscopy have established that the link between nasal and bronchial allergic disease is two-way, bronchial allergen challenge induces a nasal inflammatory response and *vice versa* [5–7]. In a large population-based longitudinal study, the adjusted relative risk for developing asthma was 2.5 for non-AR and 3.71

for AR and there is epidemiological evidence to suggest nasal disease is associated with a more severe asthma phenotype [8–10]. In an observational study of 4335 patients with AR, nasal symptom scores increased with severity of asthma and the prescription of anti-asthma therapy increased with increasing severity of AR. More recently it has also been suggested that the duration of allergic nasal disease may be directly related to the severity of lower airway dysfunction [11].

This growing body of evidence has led researchers to also consider the existence of a 'non-allergic unified airway'. There is an established link between bronchiectasis and

nasal disease [12], and more recently patients with non-allergic asthma and COPD have been shown to have increased nasal symptoms and nasal inflammatory markers compared with controls [8, 13]. Chronic rhinosinusitis with nasal polyposis (CRSwNP) represents another cohort of patients to investigate the unified-airway theory, as it is associated with a high burden of nasal disease and local eosinophilia, including a high proportion of non-atopic individuals [14]. While asthma and CRSwNP often co-exist, the relationship is poorly understood [14]. Compared with AR, there is little data on airway dysfunction in CRSwNP, but it is increasingly recognised that even in the absence of overt asthma, bronchial-hyperreactivity (BHR) and inflammation are often present [15, 16].

In CRSwNP, is not known if asymptomatic asthmatic characteristics (such as BHR and inflammation) have any clinical significance, i.e. whether it is merely a 'milieu' effect secondary to atopy or if there is a direct causal link from upper to lower airways with a risk of subsequent asthma. It is also unknown, which factors predict the likelihood of spirometric abnormality in CRSwNP. The aim of the present study was to investigate the factors influencing lower-airway dysfunction in patients suffering from CRSwNP. We hypothesized that by applying established, non-invasive markers typical of an asthma phenotype, we could better understand the underlying mechanism of airway dysfunction in nasal polyposis.

Methods

Secondary analyses were performed on the screening data of subjects randomized to an RCT of medical therapy for nasal polyposis (NCT00788749). Participants required ≥ 2 of the following symptoms for > 12 weeks – anterior and/or posterior nasal discharge, nasal obstruction, decreased sense of smell and presence of bilateral nasal polyposis of grade 2 or above. Polyp size was graded using the Lildholdt system: polyps not extending beyond upper edge of inferior turbinate, grade 1; polyps extending between the upper and lower edge of the inferior turbinate, grade 2; polyps extending beyond the lower edge of the inferior turbinate, grade 3 [17]. Exclusion criteria were oral prednisolone within the 3 months, sinus surgery within 1 year, recent or concomitant upper respiratory tract infection, mechanical nasal airway obstruction due to septal deviation $> 50\%$, pregnancy or lactation. The study was approved by the Tayside Committee on Medical Research Ethics and participants gave written informed consent. Before the study visits, participants withheld medication as follows: nasal corticosteroids, 1 week; antihistamines and leucotriene receptor antagonists, 4 days; long-acting β -agonists and theophylline, 48 h; short acting β -agonists, 6 h. All participants underwent spirometry, full body plethysmography, nasal endoscopy, exhaled nitric oxide, methacholine bronchial challenge

testing and blood sampling for IgE, eosinophil count, and radioallergosorbent (RAST) testing to common aero-allergens (house dust mite, grass pollen, cat, dog and aspergillus). Atopy was defined as a positive RAST to one or more of these allergens. Three groups were identified from medical history and screening results: asthma, inflammatory and non-inflammatory. These groups were defined as follows: known asthma diagnosed by primary or secondary care physician ('asthma group'); no symptoms or diagnosis of asthma, but evidence of an asthmatic phenotype demonstrated by an elevated fractionated exhaled nitric oxide (FE_{NO}) (> 30 p.p.b.) and/or BHR ('inflammatory group'); and no diagnosis of asthma with no BHR and normal FE_{NO} ('non-inflammatory group').

Study procedures

A SuperSpiro spirometer (Micro Medical Ltd, Chatham, Kent, UK) was used for spirometry and methacholine challenge testing in accordance to guidelines challenge [18, 19]. Full body plethysmography was performed using a (Jaeger Masterscreen (Erich Jaeger, Hoechst, Germany) to derived sRaw [20]. FE_{NO} and nasal nitric oxide (N_{NO}) were measured using an on-line chemiluminescence analyser (Niox[®], Aerocrine AB, Solna, Sweden) in accordance with guidelines [21] with FE_{NO} measurement performed at an exhalation flow rate of 50 mL/s.

Statistical analysis

Data were assessed for normality with the Shapiro–Wilk test and visual inspection of data and Q–Q plots. Non-Gaussian data were logarithmically transformed to achieve normality before analysis. Groups were compared using an overall ANOVA with the Bonferroni correction for multiple pairwise comparisons and a two-tailed significance set at $P < 0.05$. Regression analyses were performed to examine associations between predictors and spirometric indices. A multiple regression model was constructed using predictor variables shown to be significantly associated with spirometry on an initial univariate analysis or deemed of importance *a priori* from the literature or biological plausibility. The resultant model consisted of: age, sex, duration of rhinitis, severity of rhinitis (polyp score), BHR and serum eosinophil count. BHR was coded as a binary variable, with a positive challenge defined as $PC_{20} < 8$ mg/mL. Residuals were tested for normality to ensure assumptions for the models had been met. Statistical analyses were performed using SPSS version 17.0 (Illinois, TX, USA).

Results

Demographic information is shown in Table 1. There was no difference between groups with regards to age, BMI,

Table 1. Demographics and group statistics

Group	Asthma (<i>n</i> = 22)	Inflammatory (<i>n</i> = 17)	Non-inflammatory (<i>n</i> = 18)	Overall significance (<i>P</i>)
Age (years)	50 (44–56)	54 (46–62)	49 (44–55)	0.57
Sex (M : F)	11 : 11	12 : 5	8 : 10	0.23
Body mass index	26.3 (24.5–28.4)	27.0 (25.1–28.9)	27.1 (25.1–29.1)	0.81
Atopy	16/22	12/17	9/18	0.35
Duration of rhinitis (years)	14 (9–19)	11 (3–20)	17 (9–24)	0.50
Rhinitis symptoms (RQLQ)	2.17 (1.57–2.77)	1.65 (0.95–2.36)	2.37 (1.73–2.42)	0.25
Total polyp Score	4.8 (4.4–5.2)	4.8 (4.2–5.3)	4.4 (3.7–5.0)	0.39
N _{NO} (p.p.b.)*	403 (286–569)	372 (268–517)	432 (325–576)	0.81
FE _{NO} (p.p.b.)*	39 (27–56)	45 (32–63)	15 (10–21)	<0.01
Inhaled corticosteroid (µg/day)**	793 (450–1136)	0	0	<0.01
FEV ₁ predicted	84 (77–91.)	101 (94–108)	102 (96–99)	<0.01
FEF _{25–75%} predicted	61 (50–72)	83 (71–95)	90 (79–102)	<0.01
Methacholine PC ₂₀ < 8 mg/mL	16/22	4/17	0/18	<0.01
Serum IgE (kU/L)*	163 (91–290)	96 (43–210)	41 (23–71)	<0.01
Serum Eosinophils (cells/µL)*	0.44 (0.36–0.53)	0.36 (0.26–0.49)	0.25 (0.19–0.34)	<0.01
Specific airway resistance (sRaw)%*	95 (60–149)	84 (68–104)	77 (65–91)	0.66

*Geometric mean [95% confidence interval (CI)]

**Dose equivalent to beclometasone propionate.

Data presented as mean (95% CI) unless stated.

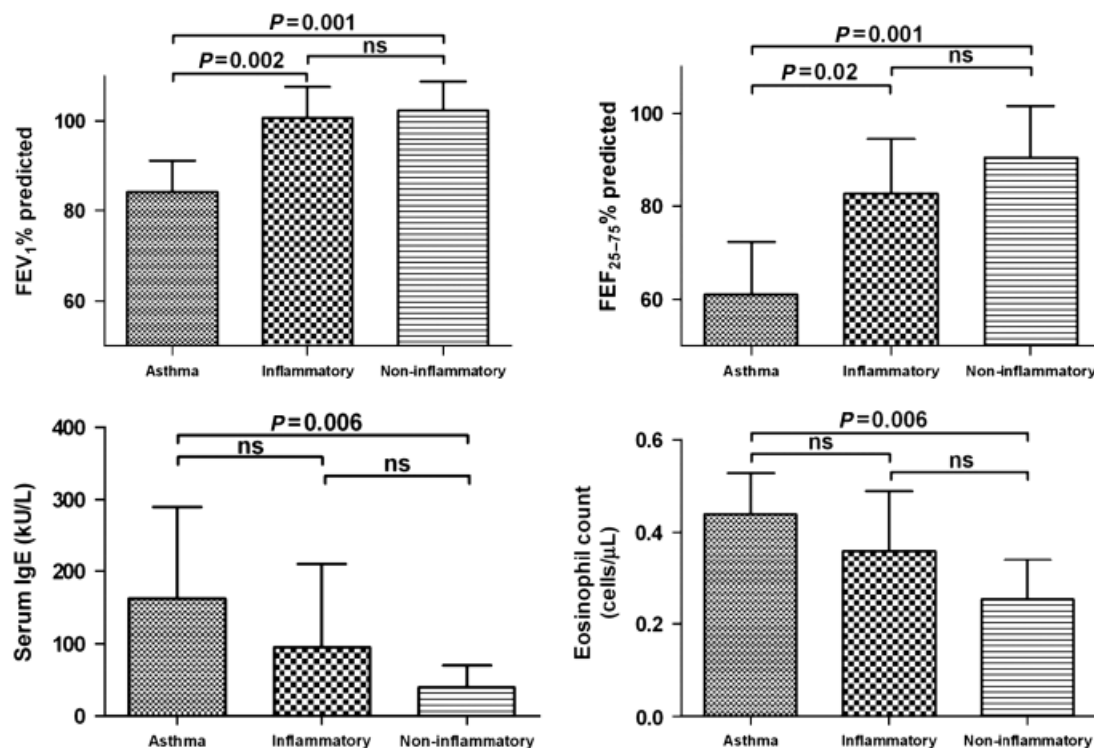


Fig. 1. Histograms showing group comparisons for spirometry as mean [95% confidence interval (CI)] and for serum IgE and eosinophil count as geometric mean (95%CI).

duration of rhinitis, severity of symptoms (RQLQ), total polyp score or N_{NO} (Table 1).

Both FEV₁ and FEF_{25–75%} were reduced in asthmatics compared with inflammatory ($P=0.002$ and $P=0.02$, respectively) and non-inflammatory groups ($P=0.001$ for both), but there was no significant difference between

inflammatory and non-inflammatory groups (see Table 1, Fig. 1). There was a numerical trend for an increase in total airways resistance (sRaw) in asthma compared with inflammatory and non-inflammatory groups.

Serum IgE and serum eosinophils were elevated in the asthma group compared with the non-inflammatory

Table 2. Pearson's correlation coefficients for lung function and test variables

Lung function	Age (<i>r</i>)	Rhinitis duration (<i>r</i>)	Rhinitis symptoms (<i>r</i>)	Polyp score (<i>r</i>)	FE _{NO} * (<i>r</i>)	N _{NO} * (<i>r</i>)	IgE* (<i>r</i>)	Eosinophils* (<i>r</i>)
FEV ₁ % predicted	-0.11	-0.06	0.01	-0.05	-0.02	0.00	-0.14	-0.20
FEF ₂₅₋₇₅ % predicted	-0.16	-0.13	0.12	-0.01	-0.13	0.01	-0.12	-0.27**
Specific airway resistance (sRaw)%	0.09	-0.01	0.01	0.18	0.16	-0.10	0.16	0.16

*Values logarithmically transformed to achieve normality before analysis.

** $P < 0.05$.

Table 3. Model summaries for linear regression

	β	SE of β	β
FEV ₁ % model ($R^2 = 0.47$)			
Constant	112.0	10.8	
Age	-0.2	0.1	-0.13
Sex	-2.7	3.5	-0.10
Eosinophil count	-12.9	6.6	-0.22
BHR	-18.7	3.3	-0.64*
Duration of rhinitis	0.1	0.1	0.06
Polyp score	1.5	1.6	0.10
FEF ₂₅₋₇₅ % model ($R^2 = 0.42$)			
Constant	107.9	19.6	
Age	-0.3	0.2	-0.16
Sex	-0.6	6.3	-0.01
Eosinophil count	-25.3	11.8	-0.25*
BHR	-29.1	6.0	-0.58*
Duration of rhinitis	-0.1	0.2	-0.26
Polyp score	1.9	2.9	0.08

* $P < 0.05$.

group ($P = 0.006$ for both). There was no significant difference between the asthmatic and inflammatory group (see Table 1, Fig. 1).

Univariate analyses demonstrated a moderate association between FEF₂₅₋₇₅% and methacholine PC₂₀ in positive individuals ($r = 0.48$, $P = 0.03$) and serum eosinophils in the whole group ($r = -0.27$, $P < 0.05$, see Table 2). There were no significant associations between FEV₁% and other variables, but a trend for methacholine PC₂₀ in positive individuals ($r = 0.43$, $P = 0.06$).

For the FEV₁% regression model, $R^2 = 0.47$ (see Table 3). After adjusting for other variables, BHR was the only independent variable predicting change in FEV₁% ($P < 0.001$), though there was a trend for eosinophil count ($P = 0.056$).

For the FEF₂₅₋₇₅% regression model $R^2 = 0.42$. BHR and eosinophil count were the only independent predictors ($P < 0.001$ and $P = 0.04$, respectively).

No nasal parameters were predictors of spirometry.

Discussion

We have shown a high prevalence of asymptomatic lower airways dysfunction in patients with CRSwNP. We identified many 'non-asthmatics' (30%) with marked elevation

of FE_{NO} and/or asymptomatic BHR (Table 1). These individuals represent a phenotype suggestive of asthmatic inflammation despite an absence of an asthma diagnosis. Previous papers have also demonstrated a high prevalence of asymptomatic disease, with BHR in non-asthmatics ranging from 42% to 54% [16, 22]. In a paper by Lamblin *et al.* [16] asymptomatic BHR was followed for up to 4 years. BHR was non-progressive over the duration of the study and did not herald development of full-blown clinical asthma. Four years is insufficient to exclude eventual progression to asthma, but it is suggestive that there is a stable spectrum of lower airway dysfunction in CRSwNP that is not fully appreciated with a categorical description of asthma vs. non-asthma.

In the present study, 24% of the non-asthmatic 'inflammatory' group were characterized by BHR to methacholine. BHR is a key feature of the asthma diagnosis and assessment, and is more closely associated with exacerbations than spirometry or symptoms [23]. While this prevalence in our cohort was lower than expected, methacholine is a direct challenge agent and as such could underestimate the total burden of airway inflammation compared with indirect challenges such as AMP or mannitol. To address this we used FE_{NO} as an additional surrogate of inflammation. FE_{NO} correlates closely to eosinophil count in bronchoalveolar lavage and induced sputum [24, 25], and is an independent predictor of exacerbations [26]. We applied a cut-off of 30 p.p.b. based on previously published data [27, 28]. Nitric oxide is also produced in large quantities in the nose (N_{NO}) and inadequate closure of the velum during measurement can lead to contamination of FE_{NO} measurement from the upper airway. N_{NO} was similar between groups indicating that differences in FE_{NO} were driven by lower airway eosinophilic inflammation.

The overall trend of group analyses suggests that lower airway dysfunction is more closely related to an eosinophilic asthma phenotype than to features of nasal disease and this was supported by the multiple linear regression models (Table 1, Fig. 1, Table 3). After taking age, sex, duration of rhinitis and polyp grade into account, the only independent predictor of FEV₁% was BHR. BHR was also a predictor of FEF₂₅₋₇₅% and in combination with serum eosinophil count gave a predictive model where $R^2 = 0.42$. In other words 42% of the change in FEF₂₅₋₇₅% could be

explained by change in BHR and eosinophil count in our cohort. This provides a strong argument that lower airway dysfunction in patients with CRSwNP is most strongly associated with a traditional asthma phenotype and would be against a functional link between severity of rhinitis and lower airway dysfunction *per se*. We are not aware of similar studies in CRSwNP, but our findings contrast to work in AR by Ciprandi et al. [11], which suggested a strong association between duration of nasal disease and spirometry. In addition to differences in diagnosis (CRSwNP vs. AR), there are other differences in population and analysis, which may explain this contrast. As expected in CRSwNP, our cohort demonstrated a spectrum of atopic disease including atopic and non-atopic individuals. A mixed group with regard to atopy is required to assess associations between lung function and atopic disease. In AR, where atopy is by definition more homogeneous, such changes may be less apparent and duration of rhinitis could then play a more significant role.

Age was not included in the regression model by Ciprandi and colleagues, as the authors identified that duration and age had significant colinearity. While the authors concluded that the duration of rhinitis had a significant association to spirometry, an alternative interpretation would be that airway dysfunction is equally well explained by increasing age. This seems plausible given that lung function declines with age and older patients are likely to have had rhinitis for a greater duration. Our model included both age and duration of rhinitis and found no association with either.

Group analyses also demonstrated significant differences between asthmatic and non-asthmatic individuals with a non-inflammatory phenotype. Even though groups were comparable in terms of demographics and nasal disease parameters, there were significant differences in FEV₁, FEF_{25–75%}, serum IgE and serum eosinophils (Table 1, Fig. 1). As Fig. 1 illustrates the inflammatory group was numerically between the asthmatic and non-inflammatory groups, but not statistically different from the non-inflammatory group for FEV₁ or FEF_{25–75%}; or from the asthma group in terms of serum IgE and eosinophils.

FEF_{25–75} has been highlighted as a potentially important marker in rhinitis. In AR it correlates to nasal obstruction and BHR and has been suggested as an early marker of lower airways disease [29–31]. Both FEV₁ and FEF_{25–75} have been seen to fall at 4-year follow-up in treatment-resistant CRSwNP, whereas treatment-responsive patients remained stable [16]. In our study, patients without BHR or elevation of FE_{NO} had well-preserved lung function with a mean FEF_{25–75%} of 90% predicted, despite a similar degree of nasal disease and atopy by RAST test (Table 1). There is intense local eosinophilic disease in nasal polyposis irrespective of atopic status [32]. Our findings suggest that FEF_{25–75} may reflect the systemic burden of eosinophilic disease in patients with CRSwNP.

Full body plethysmography was also used to measure total airways resistance (sRaw). While sRaw is a sensitive test of airway dysfunction it has a wide coefficient of variation and inter-individual variation compared with spirometry [33]. Hence there was no significant difference between groups due to wide, overlapping confidence intervals. For this reason, no further analyses were performed with this variable.

As our group analysis was based upon established asthma or inducible BHR, it is unsurprising that there were progressive differences in spirometry. The importance of these findings is that despite group differences in spirometry there was no difference in nasal disease measured by polyp grade, rhinitis symptoms, N_{NO} or duration of rhinitis. This was supported by univariate and multivariate testing. The disconnect between upper and lower airway disease makes it difficult to conclude that nasal disease severity had any significant effect on lower airway dysfunction. While our cohort were comprehensively assessed, we acknowledge that direct sampling of nasal inflammation with nasal lavage or biopsy would have been desirable and may have demonstrated different characteristics of inflammation, which were associated with lower airway dysfunction. Similarly, inclusion of control groups of healthy individuals or CRS without nasal polyposis would further aid interpretation.

Total serum IgE was elevated in asthmatics compared with the non-inflammatory group in keeping with previous data [34]. Interestingly, the inflammatory group had a similarly elevated level. The group analysis presented a similar trend to serum eosinophilia, however, regression analyses did not show total IgE to be a significant predictor of lung function. This may reflect the wider variation associated with the test compared with the eosinophil count and as such the requirement of greater numbers to demonstrate any association. This is a potential limitation of this study and may explain why other factors such as atopy showed no association. Nonetheless, the group size had sufficient power to detect correlations with BHR and eosinophilia suggesting that their importance outweighs other variables in CRwNP.

Given the common anatomical and pathophysiological root of the upper and lower airway, a non-allergic unified airway is plausible and supported by recent data in COPD and non-atopic asthma [13]. Our understanding may be hampered by over-simplification of disease phenotypes as binary variables such as: 'asthma or non-asthma' and 'atopic or non-atopic'. More accurate phenotyping of individuals by upper and lower airway measurement may provide greater insight into the pathophysiology underlying nasal polyposis and lead to better targeted-therapies. In individuals with CRSwNP but no evidence of an asthmatic phenotype (normal BHR and FE_{NO}), lung function measured by FEV₁ and FEF_{25–75%} was preserved. Asymptomatic individuals with objective evidence of an

asthma phenotype have similar levels of total IgE and serum eosinophilia. This suggests that there is persistent lower airways inflammation and hyper-reactivity in CRSwNP, which is incompletely described by categorizing patients simply as 'asthmatic' and 'non-asthmatic'. Such a simplification may lead researchers to over-interpret lower airways dysfunction in non-allergic, non-asthmatics with CRSwNP, and conclude a functional link between nasal disease and impaired lung function.

Our findings suggest there is a spectrum of systemic, eosinophilic disease in CRSwNP and that this systemic inflammation is expressed in the lungs in features typically associated with asthma. Where this inflammation is more intense, a full-blown asthmatic picture will be clearly evident, but there is likely to be a spectrum of inflammation across a population. While this systemic inflammation is clearly associated with CRSwNP, lower airway dysfunction is best explained in the context of this

traditional asthmatic phenotype than by the severity or duration of nasal pathology.

Conclusions

In CRSwNP, nasal and demographic parameters are equivalent regardless of spirometric findings and nasal parameters do not correlate with spirometry. Impairment of lung function is best explained by the presence of BHR and systemic eosinophilia suggesting that the lower airway dysfunction reflects the full spectrum of atopic asthma rather than a 'non-allergic' unified airway.

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