

ORIGINAL RESEARCH—ALLERGY

# Relationship between rhinitis duration and worsening of nasal function

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**BACKGROUND:** While it is well known that asthma is characterized by airway remodeling, few studies instead have investigated this issue in patients with allergic rhinitis (AR).

**OBJECTIVE:** The aim of the study was to evaluate nasal function, ie, nasal airflow, in a cohort of patients with persistent AR (PER).

**METHODS:** One hundred patients, 50 with short-term and 50 with long-term PER, were prospectively and consecutively evaluated, clinically evaluated by visit, skin prick test, and rhinomanometry.

**RESULTS:** Nasal airflow values were significantly lower (median flow: 348 mL/sec) in patients with long-term rhinitis (median duration nine years) as compared to patients with short-term (median duration one year) rhinitis (median flow: 466 mL/sec) ( $P < 0.0001$ ).

**CONCLUSION:** This study provides the first evidence that patients with PER may show a progressive worsening of nasal airflow depending on the duration of the disorder.

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Allergic rhinitis (AR) is characterized by typical symptoms, the most important being nasal obstruction, which is dependent on allergic inflammation. Nasal obstruction may be roughly evaluated subjectively, by the perception of air passage throughout the nose, and objectively, by measuring nasal airflow by rhinomanometry.<sup>1</sup> It has been evidenced that allergic inflammation markers, such as Th2-type cytokines and nasal eosinophils, correlate well with limited nasal airflow. AR has been recently reclassified by the ARIA (Allergic Rhinitis and its Impact on Asthma) workshop.<sup>2</sup> The new classification of “intermittent” (ITR) and “persistent” (PER) considers the duration of symptoms (days/week and consecutive weeks), the symptom severity (mild or moderate-severe), and the impact on quality of life.

AR is a common chronic disorder and is frequently associated with asthma, as underlined by the same ARIA document.<sup>2</sup> It is well accepted that several structural changes, including epithelial disruption, goblet cell hyperplasia, mucus gland hypertrophy, enhanced airway collagen deposition, airway myofibroblast transformation, increased matrix protein deposition, and smooth muscle hypertrophy

and hyperplasia, marked asthma are encompassed within the term airway remodeling.<sup>3</sup> However, two recent reviews pointed out the paucity of studies concerning the evaluation of structural changes in patients with AR.<sup>4,5</sup> The main aspects thus far considered have been: epithelium, reticular basement membrane, and matrix proteins.

Regarding epithelial impairment, an electron microscopic study revealed epithelial damage and torn tight junctions of the epithelial cells in the nasal mucosa of allergic patients.<sup>6</sup> Moreover, patients with seasonal AR had a thicker epithelium than normal subjects outside of the pollen season.<sup>7</sup> During pollen season, marked goblet cell hyperplasia was present in AR patients, whereas metaplasia and ciliated cell dysplasia were present throughout the year.<sup>8</sup> However, another study provided negative findings in the same setting.<sup>9</sup> Whereas in patients with perennial AR, epithelial cell metaplasia was observed in nasal biopsy specimens,<sup>10</sup> in addition, reticular basement membrane impairment, such as pseudothickening, caused by collagen and fibrous protein deposition, even though to a lesser extent than in asthma, has been reported in AR.<sup>11</sup> Finally, matrix metalloproteinase 9 was increased after positive nasal allergen challenge.<sup>12</sup>

In contrast with these findings, a recent study did not reveal any structural changes in the nasal mucosa of allergic patients despite the presence of inflammatory cells.<sup>13</sup> Instead, other studies have looked more at chronic rhinosinusitis (CRS). One study evidenced that the histopathologic findings of asthma, namely heterogeneous eosinophilic inflammation and features of airway remodeling, are also present in CRS.<sup>14</sup> These findings, coupled with the coexistence of common clinical features for both diseases, suggest that the same pathologic disease process is manifest, presenting as CRS in the sinonasal tissue and as asthma in the lower airway. Sobol et al demonstrated that the sinus mucosal inflammatory profile was similar in adults and children with chronic sinusitis.<sup>15</sup> However, the degree of tissue eosinophilia and remodeling was significantly greater in adult sinus specimens when compared with those of children with chronic sinusitis.

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These studies focused only on morphologic changes and did not investigate functional changes as a consequence of nasal remodeling. Therefore, the purpose of this cross-sectional study was to evaluate nasal function, ie, the nasal airflow, in a cohort of patients with PER.

## MATERIALS AND METHODS

### Study Design

One hundred patients with PER were prospectively and consecutively evaluated. The mean age was 22.8 years (SD, 5.0) with a minimum age of 18 and a maximum of 40 years. The mean rhinitis duration was 5.9 years (SD, 5.5). All subjects were naval seamen who were referred to the Naval Medical Service, La Spezia, Italy for a mandatory periodic visit. The Navy Medical Service Institutional Review Board approved the study and written informed consent was obtained from each subject. A detailed clinical history was taken and complete physical examination, nasal endoscopy, and rhinomanometry were performed on all patients.

For enrollment in the study, patients were required to have: 1) a diagnosis of PER, 2) moderate or severe nasal obstruction, as described below, and 3) duration of symptoms less than two years or greater than six years. Patients reporting concomitant or one or more past asthma symptoms (including persistent cough, wheezing, dyspnea, and shortness of breath, either diurnal or nocturnal) were excluded to obtain a homogeneous cohort. Subjects with acute upper respiratory infections, anatomic nasal disorders (ie, significant septum deviation), or nasal polyps, and patients using nasal or oral corticosteroids or decongestants, antileukotrienes, and antihistamines within the previous four weeks were also excluded.

The diagnosis of PER was made on the basis of a history of nasal symptoms and positive skin prick test according to validated criteria.<sup>2</sup>

### Subjects

Patients were recruited on the basis of the disease duration: the first group included patients with short-term rhinitis (with a disease duration shorter than or equal to two years) ( $n = 50$ ) and the second group included patients with long-term rhinitis (with a disease duration longer than or equal to six years) ( $n = 50$ ). We theoretically hypothesized that a short duration would not determine relevant structural alterations, whereas a longer duration could cause them.

### Symptoms

Nasal obstruction symptom was assessed through a medical questionnaire and evaluated on the following scale: 0 = absent, 1 = mild (symptom was present but was not annoying or troublesome), 2 = moderate (symptom was frequently troublesome but did not interfere with either normal daily activity or sleep), and 3 = severe (symptom was sufficiently troublesome to have interfered with normal daily activity or sleep).

### Skin Prick Tests

The test was performed as stated by the European Academy of Allergy and Clinical Immunology.<sup>16</sup> The panel consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grasses mix, *Compositae* mix, *Parietaria officinalis* and *judaica*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, and *Aspergilli* mix (Stallergenes, Milan, Italy).

### Rhinomanometry

Nasal airflow was measured by active anterior electronic rhinomanometry (ZAN 100 Rhino Flow Handy II, ZAN, Messgeraete GmbH, Germany) according to validated criteria.<sup>17</sup> Nasal airflow was considered as the sum of recorded airflow through the right and left nostrils, measured in milliliters per second at a pressure difference of 150 Pa across the nasal passage.

### Statistical Analysis and Data Definitions

Descriptive statistics were first performed; qualitative parameters were reported as percentages with exact binomial 95% confidence intervals (95% CI) and quantitative parameters were reported as medians with first and third quartiles; 95% confidence intervals of group differences have been calculated and reported either for qualitative variables or for quantitative parameters. Comparison between qualitative parameters was performed by the  $\chi^2$  test. A comparison of quantitative variables between the two groups of subjects (patients with short-term vs long-term rhinitis) was made by means of the nonparametric Mann-Whitney  $U$  test since the parameters were not normally distributed. Correlations between nasal airflow and rhinitis duration were made by means of the nonparametric Spearman's correlation coefficient ( $r_s$ ). All tests were two-sided and a  $P$  value less than 0.05 was considered statistically significant. The package "Statistica release 6" (StatSoft Corp., Tulsa, OK) was used for all analyses.

## RESULTS

One hundred patients, 50 with short-term and 50 with long-term rhinitis, were included in the study. A complete description of the two groups of patients is reported in Table 1. The two groups were homogeneous for gender, sensitization (all patients were sensitized to *Dermatophagoides*, and 76% of the first group (95% CI: 62%-87%) and 70% of the second (95% CI: 55% to 82%) were also positive for pollens;  $P = 0.50$ ; difference between the groups: 6% and 95% CI of the 2 groups difference: from  $-11.4\%$  to  $23.4\%$ ), and overall age.

The median rhinitis duration was one year in the short-term group. In contrast, it was nine years in the long-term group, with a significant difference between the two groups ( $P < 0.0001$ ). The percentage of patients with a severe obstruction score (score = 3) was significantly higher (72%) in the long-term rhinitis group as compared to the

**Table 1**  
Demographic and clinical parameters of the study patients

	Short-term rhinitis (n = 50)	Long-term rhinitis (n = 50)	P
Gender: males, n (%)	35 (70%)	37 (74%)	0.66
Difference in percentages of males and 95% CI of the group difference	4% (-13.6%–21.6%)		
Age (yrs): median	22 [20–24]	21 [20–22]	0.72
Mean difference and 95% CI of the group difference	0.5 (-2.5–1.5)		
Rhinitis duration (y): median	1 [1–2]	9 [8–12]	<0.0001
Mean difference and 95% CI of the group difference	8.9 (7.7–10.2)		
Obstruction score: moderate, n (%)	28 (56%)	14 (28%)	0.0046
Obstruction score: severe, n (%)	22 (44%)	36 (72%)	
Difference in percentages of patients with moderate obstruction and 95% CI of the group difference	28% (9.4%–46.6%)		
Nasal airflow (mL/sec): median	466 [398–494]	348 [302–419]	<0.0001
Mean difference and 95% CI of the group difference	77.9 (44.0–111.8)		

Figures in round parentheses are percentages calculated over the total number of subjects reported at the top of the column. Figures in squared parentheses represent first and third quartiles.

short-term group (44%) ( $P = 0.0046$ ), as reported in Table 1. Consequently, the percentage of patients with a moderate obstruction score (score = 2) was significantly higher (56%) in the short-term rhinitis group as compared to the long-term group (28%) ( $P = 0.0046$ ). This statistically significant difference has also been demonstrated by the 95% CI of the group difference that does not include the value of zero (95% CI of the group difference: 9.6% to 46.6%).

As shown in Table 1 and Figure 1, nasal airflow values were significantly lower (median flow: 348 mL/sec) in patients with long-term rhinitis as compared to patients with short-term rhinitis (median flow: 466 mL/sec) ( $P < 0.0001$ ).

There was a slight inverse correlation between rhinitis duration and nasal airflow ( $r_s = -0.37$ ;  $P < 0.001$ ). Nasal airflow was significantly lower (median, 327 mL/sec; first to third quartiles: 301 to 405 mL/sec) in patients with severe obstruction with respect to patients with moderate obstruction (median, 485 mL/sec; first to third quartiles: 461 to 516 mL/sec) (Mann-Whitney  $U$  test;  $P < 0.0001$ ). Disease duration was significantly lower (median, two years; first to third quartiles: one to six years) in patients with moderate obstruction with respect to patients with severe obstruction (median, eight years; first to third quartiles: two to 10 years) (Mann-Whitney  $U$  test;  $P = 0.0009$ ).

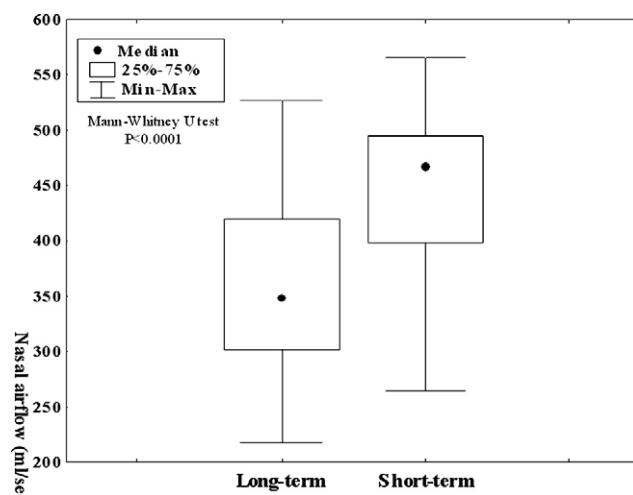
## DISCUSSION

Allergic rhinitis is characterized by an inflammatory response that increases the frequency of symptom occurrence. In particular, nasal obstruction constitutes the most common symptom resulting from allergic inflammation, and may be considered the key symptom in patients with AR.<sup>18</sup> Nasal obstruction may be evaluated both subjectively by scoring

symptoms and objectively by assessing airflow with rhinomanometry.<sup>2</sup> The limitation of the nasal airflow may be reversible to decongesting and the degree of recovery is associated with inflammatory grade; consequently, severe inflammation is characterized by a poor response to this test.<sup>18</sup>

Allergic inflammation is dependent on allergen exposure even though symptoms may not appear; this phenomenon is referred to as minimal persistent inflammation.<sup>19</sup> The cascade of chronic inflammatory events determines the occurrence of structural changes, and is more evident in the lower airways.

Some recent reviews have analyzed the features of airway remodeling in AR.<sup>4,5</sup> Epithelial disruption and desquamation are infrequently observed in the nasal epithelium of patients with AR. Moreover, it seems that there is some



**Figure 1** Nasal airflow values in long-term and in short-term groups.

pseudo-thickening of the reticular basement membrane caused by collagen and fibrous protein deposition, but to a lesser extent than in asthma.<sup>6</sup> Regarding blood vessels, two recent studies have provided evidence of increased expression of angiogenic markers in patients with pollen AR.<sup>20,21</sup> In addition, it has been recently reported that, in AR patients, matrix metalloproteinases (MMPs) MMP-2 and MMP-9 are the major proteolytic enzymes that induce nasal airway remodeling.<sup>22</sup> These enzymes are also important in the migration of inflammatory cells through basement membrane components. Furthermore, models of chronic inflammation also reveal the participation of platelets in tissue remodeling events, whereas platelet depletion was found to be more effective in suppressing airway remodeling processes than the administration of glucocorticosteroids.<sup>23</sup> This process of destruction and repair of airway tissue architecture is perhaps enhanced by platelet activation. Regardless, the most recent review concludes that airway remodeling exists in rhinitis, but it seems to be far less extensive than in asthma.<sup>4,5</sup> On the other hand, unlike the asthma model, no study has investigated the possible functional consequences of nasal remodeling in AR and therefore no relationship between nasal airflow and airway remodeling has previously been demonstrated.

Considering the evidence provided by a recent study that the duration of AR is a relevant risk factor for FEV1 worsening as well as house dust mite sensitization,<sup>24</sup> this study aimed to evaluate the effect of AR duration on nasal function, ie, nasal airflow, in two cohorts of patients (ie, short-term and long-term) with PER alone. Indeed, the purpose of the study was to evaluate whether the well-known features of airway remodeling seen in patients with asthma could also determine impairment of nasal airflow in AR.

The first finding shows that the duration of PER may involve a more consistent and significant percentage of patients with severe obstruction. Consequently, a significant diminution in nasal airflow is observed in patients with long-term PER. This issue represents the most relevant finding of the study. It appears evident that PER duration may determine a worsening of nasal function involving the air passages throughout the nasal cavities.

In addition, this finding was reinforced by evidence that there was a slight inverse correlation between rhinitis duration and nasal airflow, and disease duration was significantly lower in patients with moderate obstruction with respect to patients with severe obstruction. Nasal airflow was, furthermore, significantly lower in patients with severe obstruction with respect to patients with moderate obstruction.

A possible explanation for this phenomenon might be the persistence of allergic inflammation, typical of PER.<sup>19</sup> Chronic inflammation may cause a characteristic anatomic feature: the hypertrophy of turbinates. Hypertrophic turbinates are very frequently observable in AR patients.<sup>24,25</sup> The obvious consequence of turbinate enlargement is the reduction of nasal cavities, which in turn causes a limitation

in airflow. Therefore, this study underscores the relevance of progressive nasal airflow worsening that might depend on chronic inflammation, which in turn may determine structural alterations.

As in asthma, poor response to bronchodilators may indicate airway remodeling; a reduced response to decongestants could also have the same significance in AR. Preliminary findings of another study conducted in AR patients would seem to support this idea, as a progressive reduction of nasal airflow reversibility significantly depends on duration of the disorder (manuscript in preparation).

In conclusion, this study provides the first evidence that patients with PER may show a progressive worsening of nasal airflow depending on the duration of the disorder. Further studies should be addressed to correlate this functional issue with morphostructural changes.

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## AUTHOR CONTRIBUTIONS

**Giorgio Ciprandi**, study design and writing; **Ignazio Cirillo**, conduction; **Angela Pistorio**, statistical analysis; **Stefania LaGrutta**, revision.

## FINANCIAL DISCLOSURE

None.

## REFERENCES

1. Kern EB. Committee report on standardization of rhinomanometry. *Rhinology* 1981;19:231–6.
2. Bousquet J, van Cauwenberge P, Khaltaev N, and the WHO Panel. Allergic rhinitis and its impact on asthma. ARIA. In collaboration with the World Health Organization. *J Allergy Clin Immunol* 2001;108:S1–315.
3. Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002;418:426–30.
4. Salib RJ, Howarth PH. Remodelling of the upper airways in allergic rhinitis: is it a feature of the disease? *Clin Exp Allergy* 2003;33:1629–33.
5. Bousquet J, Jacquot W, Vignola M, et al. Allergic rhinitis: a disease remodelling the upper airways? *J Allergy Clin Immunol* 2004;113:43–9.

6. Ishii J, Naito K, Miyata S, et al. An electron microscopic study of the relation between epithelial cell damage and eosinophils in the nasal mucosa of patients with nasal allergy. *Alerugi* 2000;49:1156–62.
7. Lim MC, Taylor RM, Naclerio RM. The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage. *Am J Respir Crit Care Med* 1995;151:136–44.
8. Gluck U, Gebbers J. Epithelial changes in seasonal allergic rhinitis throughout the year. *ORL J Otorhinolaryngol Relat Spec* 2000;62:68–75.
9. Karlsson G, Pipkorn U. Natural allergen exposure does not influence the density of goblet cells in the nasal mucosa of patients with seasonal allergic rhinitis. *ORL J Otorhinolaryngol Relat Spec* 1989;51:171–4.
10. Laliberte F, Laliberte MF, Lecart S, et al. Clinical and pathologic methods to assess the long-term safety of nasal corticosteroids. French Triamcinolone Study Group. *Allergy* 2000;55:718–22.
11. Sanai A, Nagata H, Konno A. Extensive interstitial collagen deposition on the basement membrane zone in allergic nasal mucosa. *Acta Otolaryngol* 1999;119:473–8.
12. van Toorenbergen AW, Gerth van Wijk R, Vermeulen AM. Allergen-induced matrix metalloproteinase-9 in nasal lavage fluid. *Allergy* 1999;54:293–4.
13. Braunstahl GJ, Fokkens WJ, Overbeek SE, et al. Mucosal and systemic inflammatory changes in allergic rhinitis and asthma: a comparison between upper and lower airways. *Clin Exp Allergy* 2003;33:579–87.
14. Ponikau JU, Sheris DA, Kephart GM, et al. Features of airway remodeling and eosinophilic inflammation in chronic rhinosinusitis: is the histopathology similar to asthma? *J Allergy Clin Immunol* 2003;112:877–82.
15. Sobol SE, Fukakusa M, Christodouopoulos P, et al. Inflammation and remodeling of the sinus mucosa in children and adults with chronic sinusitis. *Laryngoscope* 2003;113:410–4.
16. Dreborg S, editor. EAACI Subcommittee on Skin Tests. Skin tests used in type I allergy testing. Position paper. *Allergy* 1989;44(Suppl 10):22–31.
17. Ciprandi G, Cirillo I, Klersy C, et al. The response to decongestion test is associated with sensitizations and allergic inflammation. *Ann Allergy Asthma Immunol* 2006;96:431–6.
18. Ciprandi G, Cirillo I, Klersy C, et al. Nasal obstruction is the key symptom in hay fever patients. *Otolaryngol Head Neck Surg* 2005;133:429–35.
19. Ciprandi G, Buscaglia S, Pesce GP, et al. Minimal persistent inflammation is present at mucosal level in asymptomatic rhinitic patients with allergy due to mites. *J Allergy Clin Immunol* 1995;96:971–9.
20. Kirmaz C, Ozbilgin K, Yuksel H, et al. Increased expression of angiogenic markers in patients with seasonal allergic rhinitis. *Eur Cytokine Netw* 2004;15:317–22.
21. Yuksel H, Kose C, Yilmaz O, et al. Increased expression of tissue vascular endothelial growth factor and foetal liver kinase-1 receptor in seasonal allergic rhinitis and relevance to asthma component. *Clin Exp Allergy* 2007;37:1183–8.
22. Asano K, Kanai KI, Suzuki H. Suppressive activity of fexofenadine hydrochloride on metalloproteinase production from nasal fibroblasts in vitro. *Clin Exp Allergy* 2004;34:1890–8.
23. Pitchford SC. Defining a role for platelets in allergic inflammation. *Biochem Soc Trans* 2007;35:1104–8.
24. Ciprandi G, Cirillo I, Pistorio A. Impact of allergic rhinitis on asthma: effects on spirometric parameters. *Allergy* 2008;63:255–60.
25. Berger G, Goldberg A, Ophir D. The inferior turbinate mast cell population of patients with perennial allergic and nonallergic rhinitis. *Am J Rhinol* 1997;11:63–6.