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Comparative analysis of nasal and lung function in non-asthmatic children and adolescents with chronic rhinitis

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ABSTRACT

Introduction. Nasal obstruction (NO) is a cardinal chronic rhinitis (CR) symptom. There is a relationship between the degree of NO and bronchial obstruction in patients with rhinitis and asthma, an event not studied in individuals with rhinitis and without asthma.

Objectives. To investigate the correlation between nasal and pulmonary function in children and adolescents with chronic allergic rhinitis (AR) and non-allergic rhinitis (NAR) without asthma and the correspondence between eosinophils in nasal secretion (NSEos) and nasal and pulmonary function in AR.

Population and methods. Patients with AR and NAR, without asthma, were included. Nasal function was assessed peak nasal inspiratory flow (PNIF z-score) and pulmonary function by spirometry (z-score). NSEos counts were performed in patients with AR. Pearson's and Spearman's tests were used to evaluate the correlation between variables. A p <0.05 was considered significant.

Results. Seventy-seven patients (females n = 37) between 7 and 16 years of age were included. A positive correlation was found between PNIF with $FEF_{25-75\%}$ and FEV_1 in the total sample of patients (r = 0.304; p = 0.007) (r = 0.293; p = 0.009) and the subgroup with AR (r = 0.351; p = 0.005) (r = 0.294; p = 0.020), respectively. In 40 patients with AR, no correlation was found between NSEos (%) and PNIF (r = -0.120; p = 0.462) nor with $FEF_{25-75\%}$ (r = -0.157; p = 0.340) or FEV_1 (r = 0.107; p= 0.511).

Conclusion. In children and adolescents with CR without asthma, PNIF correlated with $FEF_{25-75\%}$ and FEV_1, with greater strength in the AR subgroup. Still, no correlation was obtained between NSEos and nasal and pulmonary function.

Keywords: *spirometry; nasal obstruction; rhinitis; peak expiratory flow; maximal midexpiratory flow rate.*

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INTRODUCTION

The concept of "one airway, one disease" implies an anatomical-physiological unity between the upper airway (UA) and the lower airway (LA), which has consequent implications.[1] Previous studies have shown that 22% to 25% of children and adolescents with rhinitis manifest subclinical spirometric alterations without symptomatic expression of asthma,[2] and 50% of patients with allergic rhinitis (AR) exhibit an elevated exhaled nitric oxide fraction (FeNO) as a marker of eosinophilic inflammation in bronchi.[3]

The main functions of the nose are olfaction, filtration, and conditioning of inspired air.[4] Nasal obstruction (NO), produced by inflammation of the nasal mucosa, mediated by eosinophils in AR, with vasodilatation and rhinorrhea, is one of the most frequent cardinal symptoms of chronic rhinitis (CR) of any etiology, and its presence may condition or aggravate the pathophysiology and respiratory symptoms beyond the nose.[5]

While peak nasal inspiratory flow (PNIF) is a less sensitive measurement than determining nasal resistance by active anterior rhinomanometry (AARM), it is a simple, quick, and practical method to assess the magnitude of NO in the office.

Volume-flow curve spirometry is commonly used to assess lung function and mainly applies to asthma and other respiratory diseases of childhood.[7]

Traditionally, the forced expiratory volume in the first second (FEV_1) of forced vital capacity (FVC) and FEV_1 are the parameters of choice for determining bronchial obstruction, while the forced expiratory mid-flow between 25% and 75% of FVC ($FEF_{25-75\%}$) represents the flow in the most peripheral airway and, due to its high sensitivity, may be altered even with normal FEV_1.[8,9]

Previous studies have shown that the degree of NO measured by AARM could influence pulmonary function in patients with rhinitis and asthma.[10-13] The correlation between nasal function measured by PNIF and pulmonary function evaluated by spirometry in children and adolescents with CR in the absence of asthma is unknown.

The main objective of this study was to estimate the correlation between nasal function measured by PNIF and lung function evaluated by spirometry in children and adolescents with AR and non-allergic rhinitis (NAR) without asthma. Secondarily, the association between eosinophils in nasal secretion and PNIF and lung function parameters in patients with AR.

POPULATION AND METHODS

A prospective, observational, and analytical design included children and adolescents of both sexes who consulted the Allergy and Immunology Service of the Clínica Universitaria Reina Fabiola in the city of Córdoba, Argentina, from March 1, 2021 to May 1, 2022, with an exclusive diagnosis of AR and NAR, without asthma, defined by the presence of rhinorrhea, sneezing, blockage and nasal pruritus, and the result of skin tests with aeroallergens.

Patients with the following clinical situations were excluded:

- History of asthma or equivalent symptoms (cough, dyspnea, and/or wheezing).
- Acute or chronic UA infection.
- Anatomical nasal alterations, septal deviation, adenoid hypertrophy, and nasal polyposis.
- Previous or current use of allergen-specific immunotherapy.
- Medication with intranasal or systemic steroids, antihistamines, leukotriene antagonists, and alpha-adrenergic antagonists in the last four weeks.
- Active or passive exposure to cigarette smoke in the family environment.

The presence of sensitization was tested using skin tests (prick test) with a standardized panel with the following allergens from the Q-Pharma Argentina laboratory: mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Blomia tropicalis*), environmental fungi (*Alternaria* sp, *Aspergillus* sp, *Cladosporium*, *Mucor*, *Rhizopus*, *Penicillum*), dog and cat epithelium, a mix of trees, grasses and compositae pollens, phenolate saline solution (negative control) and histamine 1 mg/ml (positive control). The tests were performed on the anterior aspect of the forearm, using a Pricker type lancet (Diater Laboratories™) with reading at fifteen minutes with a millimetric ruler. A papule of 3 or more millimeters was considered positive as an average reading of the orthogonal diameters.[14] Rhinitis with one or more positive allergen skin tests was considered allergic; its absence was NAR compatible.

The nasal flow measurement was carried out with a PNIF device model In-Check Nasal™ of Clement Clark International Limited (Scotland, UK). The measurement comprised a range between 30 and 370 liters/minute, as marked on the device's cylinder. The best of three successive measurements, not differing by more than 10%, in a seated position, with an interval of one minute, was chosen.[6] The results obtained were

transformed into z-score, considering the normal values as a reference according to Papachristou et al.[15]

Spirometry by flow-volume curve was performed with a Vitalograph spirometer™ model 2120 UK to the international standards of the American Thoracic Society/European Respiratory Society (ATS/ERS).[7] The following parameters were considered: FVC, FEV1, FEV_1/FVC index, and $FEF_{25-75\%}$ deduced from the best of three baseline determinations that met acceptability and repeatability criteria according to ATS/ERS.[7]

Spirometric parameters were expressed in absolute values (liters or liters per second) and transformed to z-scores concerning normal theoretical values according to the Global Lung Function Initiative (GLI-2012)[16,17] using the ERS-GLI tool provided at https://gli-calculator.ersnet.org/index.html.

The nasal cytology study was performed in 40 out of 62 patients with AR, based on samples of secretions extracted from the mucosal surface of the inferior turbinate with hematoxylin-eosin stain. Samples from 22 patients were excluded because they were not suitable for analysis. With optical microscopy, we read the samples in twenty fields of 40 × and the differential eosinophil count in absolute and percentages of total cells observed.[18]

In all cases, allergen skin tests, PNIF determinations, volume flow curve spirometry, and nasal cytology were performed by different operators on the same day, between 09:00 and 12:00 a.m., to avoid circadian influences.

Statistical analysis

Using InfoStat™[19] and R-Medic™[20] statistical software, descriptive statistics were performed, and the difference of proportions, two independent samples t-test or Mann-Whitney test, and Pearson's correlation test were used to evaluate the association between PNIF variables and spirometry in the total sample of patients included and in the subgroups with AR and NAR separately. Spearman's correlation test was applied to establish the correlation between the percentage of NSEos and nasal and pulmonary function in patients with AR. A significance level of 5% was used.

Ethical aspects

The project was approved by the Institutional Health Research Ethics Committee (CIEIS) of the Clínica Universitaria Reina Fabiola (registry # 17/2013). It was performed in compliance with the regulations of the Helsinki Declaration and good clinical practice. Informed consent, signed by the parents, was requested for the performance of all the studies and the use of the data, and confidentiality was guaranteed by Law 25326 about the Protection of Personal Data.

RESULTS

The study included 77 patients of both sexes (women n = 37) aged between 7 and 16 years (mean = 11.86 ± 2.51 years), with AR (n = 62) and NAR (n = 15) (*Table 1*). We found a positive correlation between PNIF (z score) and $FEF_{25-75\%}$ (z score) in the total sample of patients (r = 0.304; $p = 0.007$) and the subgroup with AR (r = 0.351; $p = 0.005$) (*Figure 1*) and with FEV_1 (r = 0. 293; $p = 0.009$ and r = 0.294; $p = 0.020$, respectively, for total patients and AR only) (*Figure 2*). No correlation was obtained between PNIF and FVC and FEV_1/FVC values in rhinitis phenotypes (*Table 2*). In 40 patients with AR, no correlation was found between NSEos (%) and PNIF (r = -0.120; $p = 0.462$) or with $FEF_{25-75\%}$ (r = -0.157; $p = 0.340$) or with FEV_1 (r = 0.107; $p = 0.511$).

DISCUSSION

Considering the upper and lower airways as a "single airway, single disease" summarizes a new paradigm that authors and clinical guidelines have disseminated in the last two decades.[21,22]

NO is the most bothersome symptom for patients suffering from CR.[5] The subjective sensation may differ from its objective assessment.[23]

Although AARM and acoustic rhinometry (ARh) are the methods of choice for the study of NO due to their high sensitivity and specificity, routine use is limited by their complexity.[6,24]

The PNIF is a simple, faster, safer and more accessible method for measuring nasal airflow and can be administered in an outpatient setting.[24] It has been shown that rhinitis can be accompanied by spirometric changes, bronchial hyperreactivity and inflammation of the lower airways.[2] It is intriguing to know whether the objective study of NO magnitude correlates with what happens in the intrathoracic airway as determined by spirometry when analyzing the interrelationship between UA and LA.

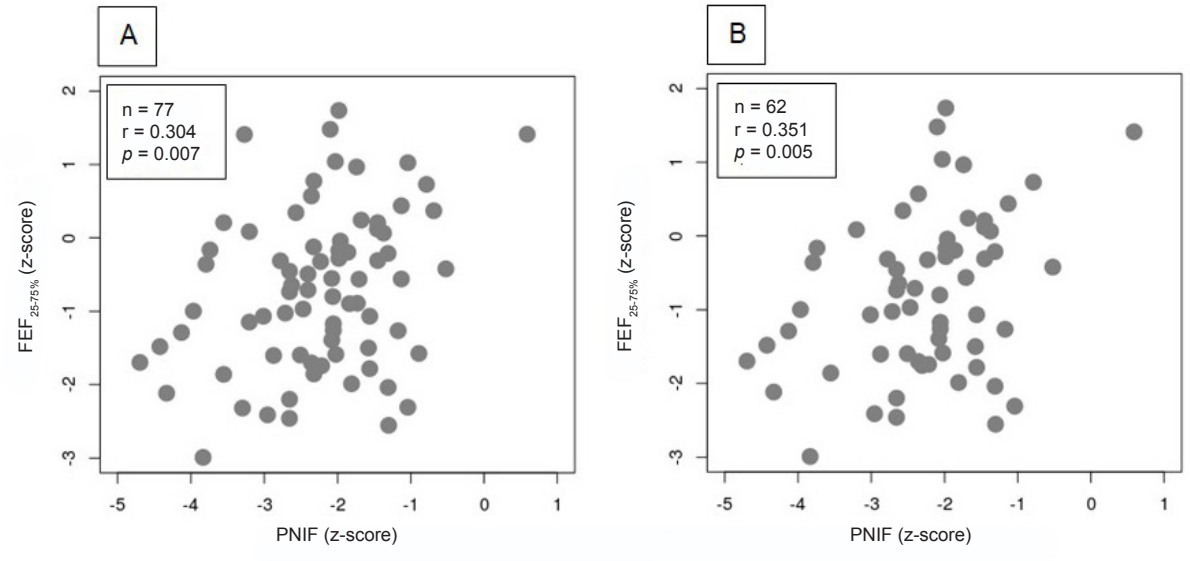
Some evidence suggests a correlation between nasal and bronchial resistance in adults[10] and children[11-13,25] with CR who simultaneously have asthma. We are not aware of such an

Table 1. Characteristics of patients with chronic rhinitis included in the study

Variable	Allergic rhinitis (n = 62)	Non-allergic rhinitis (n = 15)	*p-value*
Women n (%)	28 (45.2)	9 (60)	0.456
Age (years)*	11.85 ± 2.58 (7.5-16.08)	11.91 ± 2.25 (8.58-15.91)	0.862
Body mass index (kg/m^2)*	19.09 ± 3.80 (12.57-30.97)	20.19 ± 3.12 (17.10-28.63)	0.198
Duration of rhinitis (months)*	58.04 ± 38.19 (6-149)	53.19 ± 38.19 (9-167)	0.419
Baseline PNIF (z-score)*	-2.28 ± 0.99 (-4.7-0.59)	-2.14 ± 0.93 (-3.55-0.69)	0.629
FVC (liters)*	2.6 ± 0.83 (1.53-5.43)	2.48 ± 0.64 (1.61-3.61)	0.839
FVC (z-score)*	-1 ± 1 (-2.89-1.02)	-1.12 ± 1 (-2.45-0.10)	0.740
FEV_1 (liters)*	2.22 ± 0.64 (1.35-4.13)	2.23 ± 0.62 (1.43-3.51)	0.834
FEV_1 (z-score)*	-1 ± 1 (-2.91-1.21)	-1 ± 1 (-2.45-0.09)	0.499
FEV_1/FVC (z-score)*	-1 ± 1 (-2.88-1.02)	-1 ± 1 (-2.45-0.09)	0.741
$FEF_{-75\,\%}$ (liters/sec)*	2.48 ± 0.76 (1.08-4.15)	2.76 ± 1.10 (1.58-5.58)	0.537
$FEF_{-75\,\%}$ (z-score)*	-1 ± 1 (-2.99-1.74)	0 ± 1 (-2.32-1.41)	0.267

PNIF: peak nasal inspiratory flow;. FVC: forced vital capacity.
FEV_1: forced expiratory volume in the first second of FVC.
$FEF_{25-75\%}$: forced expiratory flow between 25-75% of FVC.
**Data are expressed as mean, standard deviation, and range (in parentheses).*

Figure 1. Correlation between peak nasal inspiratory flow (PNIF); and forced expiratory flow between 25-75% of the FVC ($FEF_{25-75\%}$) in the total patients with rhinitis (n = 77) (A) and in the subgroup of patients with allergic rhinitis (n = 62) (B)



analysis being performed in patients with rhinitis without clinically evident asthma.

Previous studies showed partially coincident results, depending on which spirometric

Figure 2. Correlation between peak nasal inspiratory flow (PNIF) and forced expiratory volume in the first second of FVC (FEV_1) in the total patients with rhinitis (n = 77) (A) and the subgroup of patients with allergic rhinitis (n = 62) (B)

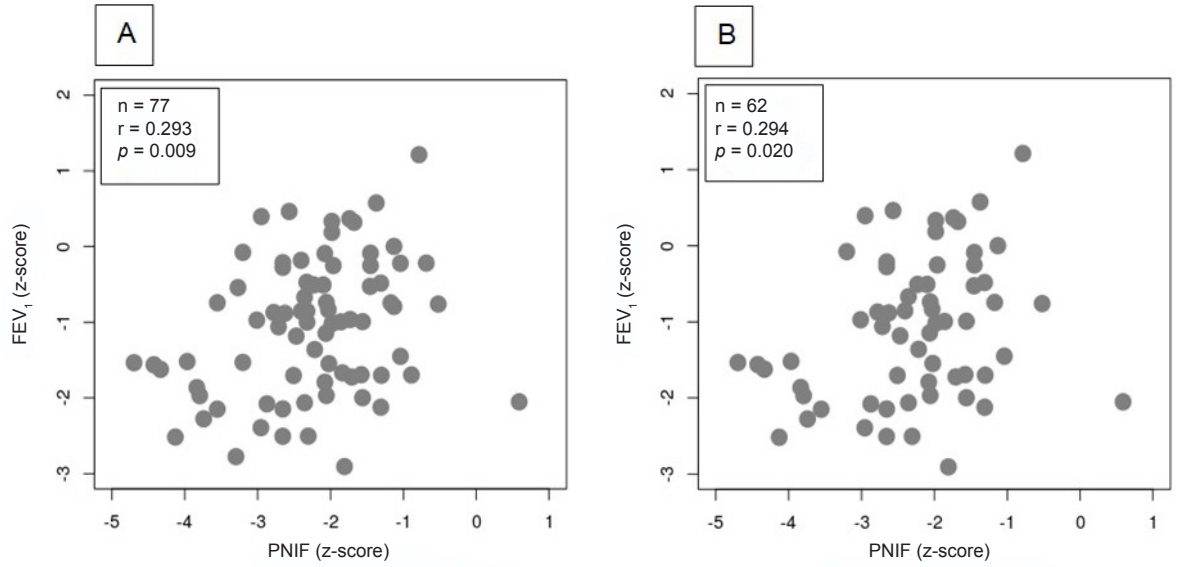


Table 2. Correlation between nasal function parameters (*PNIF*) and lung function parameters derived from volume flow curve in total rhinitis patients and the subgroups with allergic and non-allergic rhinitis

	FVC	FEV_1/FVC	FEV_1	$FEF_{25-75\%}$
PNIF in total patients with rhinitis (n = 77)	r = 0.155 IC (-0.071 - 0.366) *p* = 0.179	r = 0.212 IC (-0.013 - 0,416) *p* = 0.064	r = 0.293 IC (0.075 - 0.486) ***p* = 0.009**	r = 0.304 IC (0.084 - 0.495) ***p* = 0.007**
PNIF in patients with allergic rhinitis (n = 62)	r = -0.144 IC (-0.110 - 0.380) *p* = 0.264	r = 0.239 IC (-0.011 - 0.461) *p* = 0.062	r = 0.294 IC (0.048 - 0.507) ***p* = 0.020**	r = 0.351 IC (0.110 - 0.554) ***p* = 0.005**
PNIF in patients with non-allergic rhinitis (n = 15)	r = 0.236 IC (-0,315 - 0.667) *p* = 0.397	r = 0.069 IC (-0.460 - 0.561) *p* = 0.806	r = 0.271 IC (-0.0280 - 0.688) *p* = 0.328	r = 0.059 IC (-0.467 - 0.555) *p* = 0.832

PNIF: peak nasal inspiratory flow;. FVC: forced vital capacity.
FEV_1: forced expiratory volume in the first second of FVC.
$FEF_{25-75\%}$: forced expiratory flow between 25-75% of FVC.
PNIF values and spirometry parameters are expressed as z-scores.
r: Pearson's correlation coefficient.
CI: 95% confidence interval.
p: statistical significance value.

parameters were correlated with nasal function. Chawes et al.,[11] in children with rhinitis and asthma evaluated at 6 years of age, included in the birth cohort Copenhagen Prospective Study on Asthma in Childhood, observed a significant correlation between nasal resistance measured by acoustic rhinomanometry and FEV_1, both at baseline and post-decongestion and post-bronchodilation values. These findings could objectively reflect clinically manifest comorbidity.

Yukselen et al.[25] detected a significant positive correlation between FEV_1 (% predictive) and absolute PNIF values (liters) in children with mite-sensitive rhinitis and asthma. In our study, we obtained a significant correlation with FEV_1 and, in addition, with $FEF_{25-75\%}$, with greater methodological precision when considering the transformation to the z-score of all the variables compared.

Motomura et al.[12], in children with rhinitis and allergic asthma, showed that pale nasal mucosa was associated with increased eosinophilic inflammation and a proportional limitation of nasal and bronchial flows, as represented by FVC and FEV_1.

This association was not observed with $FEF_{25-75\%}$. On the contrary, Iyer et al.[26] detected, in adults with AR, that the increased nasal resistance determined by AARM implied an increased risk of latent small airway disease and bronchial hyperreactivity to histamine. Recently, Krasilnikova et al.[13] corrected the total nasal resistance values derived from the AARM to a percentage concerning reference values by the spirometric values in children with rhinitis and allergic asthma; they observed a weak but significant correlation between this nasal function parameter and the MEF_{75} ($r = 0.24$; $p = 0.04$), a result influenced by the sex of the patients (males: $r = 0.28$; $p = 0.03$ vs. females: $r = 0.07$; $p = 0.71$). Our results, using a less rigorous measurement of nasal flow (not nasal resistance by AARM), showed a similar correlation with $FEF_{25-75\%,}$ an indirect indicator, like MEF_{25}, of the resistance of the more peripheral bronchial airway. The difference concerning the study above is that we used PNIF instead of AARM, and our patients included only those with rhinitis (without asthma), which makes the finding more interesting. Like the last author, we did not observe a correlation between nasal function and the FEV_1/FVC ratio.

Several local mechanisms could explain the interaction as a unit between the nose, the paranasal sinuses, and the lung.[27] The theories suggested are the NO's loss of protective function, the stimulation of a nasal-sinus-bronchial reflex, and the spread of inflammatory content from the nose by aspiration into the bronchial tract secondary to post-nasal discharge.

These mechanisms could apply to rhinitis regardless of its origin, yet, on their own, they would fail to explain the nose-lung connection.[1,27] Therefore, the loss of air conditioning due to the obstruction generated by rhinitis could only partially justify our findings. A bidirectional eosinophilic inflammatory mechanism through the systemic bloodstream with simultaneous impact on the nose and bronchi is the most accepted but only applicable to the allergic phenotype of respiratory disease.[28] This could contribute simultaneously to nasal and small airway obstruction and explain why the correlation we observed occurred only in patients with AR. However, our results did not establish a significant correlation between NSEos and nasal and pulmonary flows, suggesting that other factors not investigated by us could contribute simultaneously to the NO and of the bronchi in patients with RA.

Haccuria et al.[29] described that nitric oxide in patients with RA without asthma is produced, mainly in the small airway, similar to individuals with allergic asthma.

This similarity in eosinophilic inflammation in the more peripheral airway would explain the more robust involvement of the $FEF_{25-75\%}$ observed in our patients with AR. However, we also admit that the small number of patients could be another reason for the absence of correlation between nasal and bronchial flow in the group with NAR beyond any pathophysiological justification.

Our study demonstrates a significant correlation between nasal flow, a quantitative expression of nasal obstruction, and bronchial airflows using methods easily applicable to clinical practice, such as PNIF and conventional spirometry. Unlike other authors, we verified this in patients with rhinitis without clinically manifesting asthma.

However, some weaknesses should be mentioned. Due to the successive inclusion of our patients, the group with NAR was very small compared to the allergic group, probably due to the bias of being patients referred to an Allergy and Immunology service. This could explain the absence of correlation between PNIF and the various lung function parameters in the group with AR. Furthermore, our measurement was performed by PNIF, a less sensitive method than AARM. Its correlation was evident with FEV_1 and $FEF_{25-75\%}$ but not with the FEV_1/FVC index classically considered for diagnosing bronchial obstruction.

In conclusion, in children and adolescents with chronic rhinitis without asthma, a positive correlation was found between nasal and pulmonary function, with greater strength in the subgroup with AR. Nasal function assessed by PNIF correlated with $FEF_{25-75\%}$ and FEV_1 from spirometry. NSEos did not correlate with nasal and pulmonary function.

Prospective studies with follow-up of these patients will allow us to elucidate the definitive clinical significance of our findings.

Research background

The study is part of the project "Evaluation of respiratory allergic disease: the concept of airway

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