

ORIGINAL PAPER

Nitric oxide evaluation in upper and lower respiratory tracts in nasal polyposis

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Clinical and
Experimental
Allergy

Summary

Background A decrease in nasal nitric oxide (NO) and an increase in exhaled NO have been demonstrated in patients with nasal polyposis (NP).

Objectives The aims were to evaluate the flux of NO from the three compartments of the respiratory tract, namely, upper nasal, lower conducting and distal airways, and to search for relationships between NO parameters and indexes of upper and lower disease activity (bronchial reactivity and obstruction). The effect of medical treatment of polyposis was also evaluated.

Methods Seventy patients with polyposis were recruited. At baseline, pulmonary function tests (spirometry, plethysmography, bronchomotor response to deep inspiration using forced oscillation measurement of resistance of respiratory system, methacholine challenge, multiple flow rates of exhaled NO and nasal NO measurements) were performed together with an assessment of polyposis [clinical, endoscopic and computed tomography (CT) scores].

Results Statistical relationships were demonstrated between nasal NO flux and severity scores (clinical: $\rho = -0.31$, $P = 0.015$; endoscopic: $\rho = -0.57$, $P < 0.0001$; CT: $\rho = -0.46$, $P = 0.0005$), and between alveolar NO concentration and distal airflow limitation (FEF_{25–75}, $\rho = -0.32$, $P = 0.011$). Thirty-six patients were assessed after 11 [7–13] (median [interquartile]) months of medical treatment, demonstrating an improvement in clinical and endoscopic scores, an increase in nasal NO flux, a decrease in NO flux from conducting airways, an improvement in the mild airflow limitation (forced expiratory volume in 1 s, FEF_{25–75}, even in non-asthmatic patients) and a decrease in the bronchoconstrictor effect of deep inspiration.

Conclusions The medical treatment of NP improves both airway reactivity and obstruction, whatever the presence of asthma, suggesting a functional link between upper and lower airway functions.

Keywords airway hyperresponsiveness, alveolar nitric oxide concentration, deep inspiration, maximum flux of nitric oxide from conducting airway, nasal nitric oxide flux

Submitted 17 October 2007; revised 20 February 2008; accepted 29 February 2008

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Introduction

Nasal nitric oxide (NO) fraction is reduced in nasal polyposis (NP) and may constitute an objective and non-invasive assessment of NP severity [1–3]. In contrast, exhaled NO is increased, even in non-atopic patients with NP [4]. Explanations for such a discrepancy between upper and lower airways, sharing a similar epithelium

(the main source of NO in the gas phase), are lacking. Exhaled NO measurement at a single flow rate does not allow the determination of the respective contribution of alveolar and conducting airway compartments to NO output. In contrast, both theoretical and clinical studies have demonstrated the relevance of exhaled NO measurement at multiple flow rates to determine the alveolar NO concentration and conducting airway NO flux [5, 6]. This

partitioning of anatomical origins of exhaled NO allowed us to describe relationships between flow-independent parameters of exhaled NO and the degree of airway hyperresponsiveness (AHR) [7], and between these exhaled NO parameters and airflow limitation in severe asthmatic children [8]. Inasmuch as a main characteristic of NP is its frequent association with AHR and asthma [9, 10] and because NP could induce *per se* a mild degree of airflow limitation [11], we hypothesized that partitioning of exhaled NO may serve to describe NP phenotypes (AHR, asthma). Consequently, the aims of this study were to evaluate the flux of NO from the three compartments of the respiratory tract, namely, upper nasal, lower conducting and distal airways in patients suffering from NP, and to describe the indexes of upper and lower disease activity. These latter indexes would ideally characterize both airway reactivity and remodelling. Remodelling was assessed by airflow limitation and airway reactivity by methacholine challenge and by the bronchomotor response to deep inhalation. An impairment of the bronchoprotective and bronchodilator responses to deep inhalation is a characteristic of asthma [12] and has not been investigated, to the best of our knowledge, in the context of NP. We hypothesized that the bronchomotor response to deep inhalation would be improved if an improvement in NP occurred upon steroid treatment, constituting another piece of evidence of the functional link between upper and lower airway functions. To this end, in a subgroup of patients, the effects of medical treatment of NP on NO and the disease activity parameters were evaluated.

Methods

Design

During an 18-month period, consecutive patients referred for NP were eligible for this prospective study. In our centre, patients have an initial evaluation (baseline visit) in the absence of any treatment for their NP (except asthma medications) and are reassessed after an ~1-year period of standardized medical treatment (final visit). Consequently, during the study period, the whole group of patients was evaluated at baseline, while a subgroup of patients was seen on two occasions (before and after the medical treatment). According to the new French law (8 August 2004), all tests were performed for clinical purposes using routine techniques; thus, ethical approval was not sought, and all patients were informed of this observational study [13]. Because we established relationships between the decrease in nasal NO and nasal obstruction, an additional group of consecutive patients (not included in the initial group) was evaluated after surgical treatment, a condition where ostia obstruction is eliminated.

Diagnosis and treatment of nasal polyposis

The diagnosis of NP was based on endoscopic examination and on computed tomography (CT), as described previously [14]. All patients received a systematic medical treatment [14]: washing of the nasal cavities, steroid spray (mometasone furoate at a daily dose of 200 µg) and oral steroid administration (prednisolone 1 mg/kg body weight per day for 6 days). During spray administration and the subsequent minute, the patient had oral ventilation. In our experience, this medical treatment allows a control of NP in ~85% of patients [14]. Patients with Wegener's granulomatosis, Churg–Strauss syndrome, primary ciliary dyskinesia (ciliary beat frequency was systematically measured) and cystic fibrosis were not included.

Allergic investigation was realized with specific IgE antibodies measured with the Phadiatop[®] test (Pharmacia Diagnostics AB, Uppsala, Sweden).

Assessment of nasal polyposis severity [9, 10, 14]

Clinical score. It represented the mean score of six symptoms (nasal obstruction, anterior rhinorrhoea, posterior rhinorrhoea, facial pain, sneezing and loss of smell) evaluated on a three-point scale.

Endoscopic score [9, 10]. Polyp size was rated on a five-point scale: 0, normal mucosa; 0.5, absence of polyps but mucosal thickening; 1, mild polyps; 2, moderate polyps; and 3, severe polyps.

Computed tomography scan score. The CT scan of paranasal sinuses was scored according to the Lund–MacKay system. The Lund–MacKay score for each side may range from 0 to 12, and the total score may range from 0 to 24.

Diagnosis and treatment of asthma

The diagnosis of asthma was based on the fact that symptoms of recurrent episodes of airflow obstruction or AHR were present; airflow obstruction has been shown to be at least partially reversible, and alternative diagnoses were excluded, according to the Expert Panel Report of the National Institutes of Health. Classification of asthma severity [intermittent or persistent (mild, moderate, severe)] relied on the same report.

Pulmonary function tests

Nasal nitric oxide and exhaled nitric oxide measurements. Nasal and exhaled NO were measured using a chemiluminescent nitric oxide analyser (ENDONO 8000, Seres, Aix en Provence, France) before performing spirometry.

Nasal NO was measured according to international recommendations [15]: briefly, an occluding foam-rubber olive containing the nosepiece was introduced in one nostril. A transnasal flow rate of 1.3 L/min was used (a stable NO plateau at a flow ranging from 0.9 to 6.2 L/min is observed [16]). Patients were asked to maintain a prolonged breath-hold by mouth closure. Results were expressed as nasal NO output (nL/min), being the product of measured concentration [mean value of the NO plateau minus NO ambient air concentration (< 50 p.p.b.)] and aspiration flow rate, as described previously [17]. The normal value of the nasal NO output is between 200 and 500 nL/min in healthy subjects [1, 18, 19]. It has been demonstrated that intra-individual reproducibility or day-to-day variability can only explain a variation of 20–25% in nasal NO levels [18].

Maximum conducting airway flux of NO (J'_{awNO}) and alveolar NO concentration ($Calv_{NO}$) were calculated after obtaining several exhaled NO measurements at different expiratory flow rates, using the previously described linear approach [5, 6]. Each patient performed at least four expiratory flow rates, in a range of 50–250 mL/s. The criteria used for each exhaled NO measurement were those recommended in the guidelines [15]. We used a validity criterion of this linear approach ($R \geq 0.80$), as described previously [5]. Normal values of the alveolar NO concentration and NO flux from conducting airways have been established previously and are 4.7 ± 0.3 p.p.b. and 33 ± 2 nL/min (mean $\pm$ SEM), respectively [6].

Forced oscillation technique measurement of bronchomotor response to deep inhalation. Respiratory impedance was determined using the standard forced oscillation technique (Oscilink; Datalink-MSR, Rungis, France) according to recommendations [20]. The real component of respiratory impedance [resistance of the respiratory system (R_{rs})] was subjected to linear regression analysis to obtain the intercept (R_0 , resistance extrapolated to 0 Hz). In order to detect modifications of R_{rs} related to deep inhalation, a first sequence of measurement (~ 1 min) was made to standardize tidal breathing, and then a second sequence gave R_{rs} before deep inspiration, which was followed by three consecutive deep inspirations and a subsequent sequence measurement. The effect of deep inspiration was calculated as $100 \times (R_0 \text{ after inspiration} - R_0 \text{ before inspiration}) / R_0 \text{ before inspiration}$ [7]. Consequently, a positive result indicates a bronchoconstrictor effect of deep inhalation, whereas a negative result indicates a bronchodilator effect. In a historical group of healthy non-atopic subjects ($n = 12$), using this method, the coefficients of variation of the three subsequent sequences of R_0 measurement were 5.7%, 4.4% and 5.6%, respectively; the mean effect of deep inhalation at baseline in these healthy subjects was a decrease in R_{rs} of

$0.2 \pm 4.9\%$, which is in agreement with other investigators' results [21].

Spirometry, plethysmography and methacholine inhalation challenge. These tests were conducted according to recent recommendations (MS-PFT and MasterScreen Body, Jaeger, Germany) [22]. Because one of our aims was to evaluate the sole effect of NP treatment on the change in bronchomotor response to deep inhalation and airflow limitation, anti-asthma drugs were not withheld in asthmatic patients. Non-specific airway responsiveness to methacholine was measured using successive doses from 0.05 to 2.4 mg (0.05, 0.20, 0.40, 0.80, 1.6 and 2.4 mg), delivered using a nebulization dosimeter (Aero Doseur Atomisor, Diffusion Technique Française, Saint-Etienne, France). The test was stopped if there was a $\geq 20\%$ decline in forced expiratory volume in 1 s (FEV_1) from the control value or if the maximum cumulative dose had been reached.

Statistical analysis

All values are expressed as median [interquartile range]. We planned to recruit a similar number of patients evaluated on two occasions as in the study of Lamblin et al. [11] ($n = 36$), because these authors demonstrated significant modifications of airflow limitation and airway responsiveness over 1 year. Non-parametric tests were used as appropriate (χ^2 test or Fisher's exact test, Mann-Whitney U -test, Wilcoxon's paired test, Spearman's rank correlation coefficient). Statistical significance was defined as $P < 0.05$. Data were analysed using Statview 5.0 (SAS Institute, Berkeley, CA, USA).

Results

Baseline visit

The characteristics of the 70 patients who were enrolled are summarized in Table 1, according to the presence of AHR. No statistically significant difference in terms of NO measurements was evidenced between patients with and without AHR. No statistical relationship was demonstrated between nasal NO flux and conducting airway NO flux ($P = 0.54$).

Nasal nitric oxide as an index of nasal polyposis severity. Nasal NO flux was statistically associated with all parameters describing NP severity, namely clinical, endoscopic and CT scores (Fig. 1). Among the clinical symptoms, nasal obstruction and loss of smell were responsible for the statistical significance of the relationship between the nasal NO flux and the total clinical score (individual relationships: $\rho = -0.45$, $P = 0.0004$ and $\rho = -0.30$, $P = 0.019$, respectively).

Table 1. Characteristics of the patients with nasal polyposis

Characteristic	Whole population, <i>N</i> = 70	Patients with AHR, <i>N</i> = 32	Patients without AHR, <i>N</i> = 25
Age (years)	49 [40–57]	49 [41–57]	50 [43–57]
Sex ratio, F/M	23/47	14/18	3/22
BMI (kg/m ²)	24.1 [21.7–27.0]	24.8 [21.8–27.8]	24.3 [21.8–27.2]
Current smokers, <i>n</i>	14	4	3
Former smokers, <i>n</i>	25	8	11
Atopy, <i>n</i> (<i>n</i> , tested)	17 (62)	9	4
Asthma, <i>n</i>	13	8	2
Intermittent, <i>n</i>	2	1	0
Persistent, mild, <i>n</i>	6	4	1
Persistent, moderate, <i>n</i>	5	3	1
Asthma treatment			
Short-acting BD	2	1	0
ICS	3	2	0
Combination drugs*	8	5	2
Aspirin intolerance, <i>n</i>	6	2	2
AHR [†] , <i>n</i> (<i>n</i> , tested)	32 (57)	32	0
Nasal polyposis			
Clinical score	6 [4–8]	6 [4–7]	6 [5–8]
Endoscopic score	2 [1–2]	2 [1–3]	2 [1–2]
CT score	16 [11–20]	16 [11–19]	16 [11–20]
Duration (years)	6 [3–12]	5 [2–10]	6 [3–12]
NO parameters			
Nasal NO flux (nL/min)	150 [99–239] (63)	134 [84–235] (29)	150 [117–251] (24)
J'aw _{NO} (nL/min)	93 [44–159] (63)	90 [44–173] (29)	98 [38–139] (24)
Cav _{NO} (p.p.b.)	6.3 [3.8–9.9] (63)	6.1 [3.7–10.3] (29)	5.8 [3.4–9.4] (24)
FE _{NO,0.05} (p.p.b.)	40 [24–59] (63)	37 [22–73] (29)	38 [22–52] (24)
Pulmonary function tests			
PD ₂₀ (µg)	534 [210–908] (32)	534 [210–908] (32)	
FVC (% predicted)	109 [101–119]	107 [99–116]	111 [106–120]
FEV ₁ (% predicted)	103 [94–116]	101 [89–109]	113 [102–120] [#]
FEV ₁ /FVC (%)	80 [74–83]	80 [74–84]	81 [76–84]
FEF _{25–75} (% predicted)	76 [55–101]	70 [54–90]	87 [74–114] [#]
TLC (% predicted)	105 [95–105]	106 [94–114]	106 [99–113]
FRC (% predicted)	108 [93–124]	105 [93–124]	107 [90–124]
RV (predicted)	104 [90–122]	106 [90–124]	101 [90–114]
R _{rs} (cmH ₂ O/L/s)	2.8 [2.2–3.8]	2.9 [2.2–3.7]	2.7 [2.0–3.0]
DI effect (%)	+6 [–2–+14]	+3 [–3–+12]	+8 [–3–+19]

[#]*P* < 0.01 between the two subgroups of patients.

*Denotes association of inhaled corticosteroid and long-acting β_2 -agonist.

[†]Metacholine challenge was not available for 13 patients: 10 for either absolute or relative contraindication, three for technical reasons (AHR, airway hyperresponsiveness). Bronchial responsiveness was evaluated under asthma treatment for the 10 asthmatic patients. Airway hyperresponsiveness was more frequent in women than in men (*P* = 0.02). A more severe endoscopic score was evidenced in asthmatic patients: 3 [1–3] vs. 1 [1–2], *P* = 0.020.

Both nasal and exhaled NO measurements were obtained in 57/70 patients (only one patient was unable to perform both measures). Nasal NO measurement was not obtained in 7/70 patients either due to inability to maintain apnea (*n* = 4) or due to complete nasal obstruction (*n* = 3). Multiple flow analysis of exhaled NO was not obtained in 7/70 patients either due to inability to obtain stable expiratory flow rates (*n* = 2) or due to the absence of linear relationship between expiratory flow rate and NO output (*n* = 5).

BD, bronchodilator; BMI, body mass index; CT, computed tomography; DI, deep inspiration; FCV, forced vital capacity; FEF_{25–75}, maximal midexpiratory flow; FE_{NO,0.05}, exhaled NO fraction measured at 0.05 L/s; FRC, functional residual capacity; ICS, inhaled corticosteroids; PD, provoking dose; R_{rs}, resistance of the respiratory system; RV, residual volume; TLC, total lung capacity; FEV₁, forced expiratory volume in 1 s; NO, nitric oxide.

Additional results obtained in an additional subgroup of patients treated surgically. In 21 patients [six women, mean age 51 (44–55) years], nasal NO was measured 4 [3–7] years after surgery (functional endoscopic sinus surgery, as described previously [23]). A statistical rela-

tionship was still evidenced between nasal NO and CT score (ρ = –0.63, *P* = 0.013).

Parameters associated with airway reactivity and obstruction. Asthmatic patients were characterized by a mild

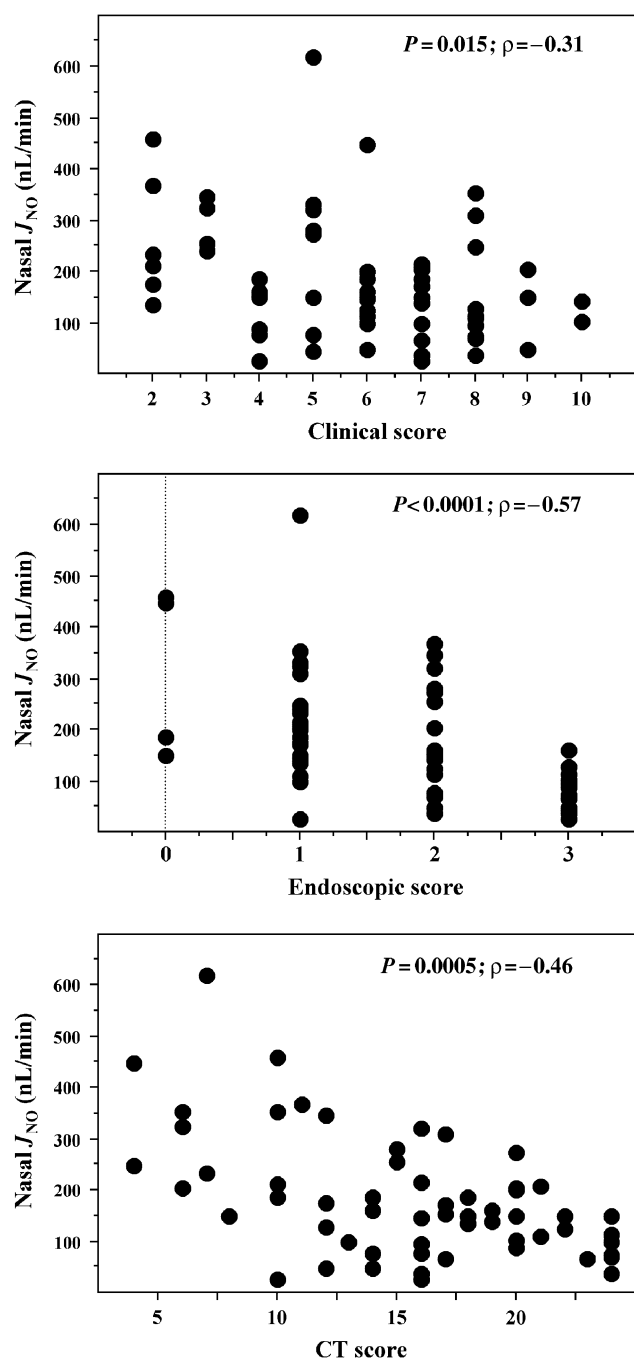


Fig. 1. Relationships between nasal nitric oxide (NO) flux and severity scores of nasal polyposis. Significant relationships were evidenced between nasal NO flux (nasal J_{NO}) and clinical (upper panel), endoscopic (middle panel) and computed tomography (CT) scan (lower panel) scores. The significance of the relationships was still present when only the followed up population was considered (data not shown).

airflow limitation as compared with non-asthmatic patients: FEV₁, 96 [81–106]% vs. 104 [100–117]% predicted, $P=0.034$; FEF_{25–75}, 53 [37–77]% vs. 82 [64–107]% predicted, $P=0.004$; FEV₁/FVC, 73 [68–79]% vs. 81 [76–84]%, $P=0.003$.

Atopic patients as compared with non-atopic subjects were characterized by a higher value of NO flux from conducting airways (114 [82–179] vs. 74 [34–147] nL/min, respectively; $P=0.025$) and by a more constrictive response to deep inspiration (+14 [+6–+26]% vs. +3 [–3–+13]%, respectively; $P=0.008$).

A statistical relationship was evidenced between the degree of airway responsiveness (PD₂₀) and airflow limitation (FEF_{25–75} % predicted: $\rho=0.57$, $P=0.012$; R_{rs} : $\rho=-0.49$, $P=0.034$), which persisted when only non-asthmatic patients were evaluated (data not shown). Alveolar NO concentration and distal airflow limitation (FEF_{25–75} % predicted) were negatively correlated ($\rho=-0.32$, $P=0.011$). A trend towards a significant relationship between PD₂₀ and alveolar NO concentration was also evidenced ($\rho=-0.34$, $P=0.075$), whereas no relationship was evidenced between conducting airway NO flux and PD₂₀.

Final visit

The characteristics of the 36 patients who were followed are summarized in Table 2. The mean lag time between initial and final visits was 11 ± 3 months. Five patients were characterized by an absence of improvement or even a deterioration of their clinical and endoscopic scores, suggesting their steroid unresponsiveness (5/36, ~14%).

Overall, medical treatment was associated with a highly significant improvement in both clinical and endoscopic scores (which were correlated, $\rho=0.55$, $P=0.004$), a significant increase in nasal NO flux, a significant decrease in conducting airway NO flux, a significant decrease in constrictive response to deep inspiration and a significant improvement in distal airflow limitation (Table 2).

Interestingly, the significance of the improvement in airflow limitation also persisted when only non-asthmatic patients were included in the analysis (FEV₁, $P=0.037$; FEF_{25–75}, $P=0.029$).

The sole factor that was significantly influenced by the presence of AHR was the conducting airway NO flux; while it clearly decreased in patients with AHR (decrease of +57 [18–117] nL/min), its progression was more variable in patients without AHR (decrease of +1 [–40–+40] nL/min; $P=0.008$). This effect remained significant in non-asthmatic patients. The presence or absence of atopy did not influence the change of airflow limitation, response to deep inspiration and NO parameters.

Discussion

The main results of this study are that a decrease in nasal NO flux constitutes a marker of severity of NP, and that the medical treatment is associated with an improvement in NP, nasal NO flux, a decrease in NO originating from the bronchial tree, together with a decrease in the

Table 2. Characteristics of the followed-up group

Characteristic	Baseline visit, <i>N</i> = 36	Final visit, <i>N</i> = 36	<i>P</i> -value
Age (years)	52 [40–57]		
Sex ratio, F/M	14/22		
BMI (kg/m ²)	23.4 [21.3–26.2]		
Current smokers, <i>n</i>	6		
Former smokers, <i>n</i>	5		
Atopy, <i>n</i> (<i>n</i> , tested)	11 (34)		
Asthma, <i>n</i>	6		
Intermittent, <i>n</i>	0		
Persistent, mild, <i>n</i>	3		
Persistent, moderate, <i>n</i>	3		
Asthma treatment			
Short-acting BD	0		
ICS	2		
Combination drugs*	4		
Aspirin intolerance, <i>n</i>	3		
AHR [†] , <i>n</i> (<i>n</i> , tested)	17 (30)		
Nasal polyposis			
Clinical score	6 [4–7]	1 [0–3] (31)	< 0.0001
Endoscopic score	2 [1–2]	1 [0–1] (31)	0.0006
CT score	16 [12–20]	Not done	
Duration (years)	5 [2–10]		
NO parameters			
Nasal NO flux (nL/min)	151 [100–206] (32)	223 [139–321] (35)	0.003
J'_{awNO} (nL/min)	117 [67–179] (33)	71 [41–121] (34)	0.008
$C_{avI_{NO}}$ (p.p.b.)	7.8 [4.4–12.0] (33)	4.6 [3.6–7.0] (34)	0.16
$FE_{NO_{0.05}}$ (p.p.b.)	47 [29–73] (33)	31 [18–49] (34)	0.009
Pulmonary function tests			
PD_{20} (µg)	474 [206–994] (17)		
FVC (% predicted)	109 [101–119]	113 [99–120]	0.11
FEV_1 (% predicted)	104 [92–113]	106 [96–119]	0.032
FEV_1/FVC (%)	79 [74–83]	80 [73–84]	0.74
FEF_{25-75} (% predicted)	74 [54–101]	78 [65–108]	0.006
TLC (% predicted)	105 [99–114]		
FRC (% predicted)	110 [96–123]		
RV (predicted)	105 [93–119]		
R_{rs} (cmH ₂ O/L/s)	2.8 [2.0–3.8]	3.0 [2.6–4.0]	0.17
DI effect (%)	+8 [–1–+19]	+2 [–4–+10]	0.040

*Denotes association of inhaled corticosteroid and long-acting β_2 -agonist.

[†]Metacholine challenge was not available for six patients (see Table 1 legend).

On final visit, only spirometry, bronchomotor response to deep inhalation and NO measurements were performed.

No significant difference was demonstrated for any criterion between the whole population and the followed-up subgroup of patients.

All these patients were receiving medical treatment (washing of the nasal cavities, steroid spray) at the time of assessment, and asthmatic patients were evaluated while their treatment was not modified since the initial visit.

BD, bronchodilator; BMI, body mass index; CT, computed tomography; DI, deep inspiration; FCV, forced vital capacity; FEF_{25-75} , maximal midexpiratory flow; $FE_{NO_{0.05}}$, exhaled NO fraction measured at 0.05 L/s; FRC, functional residual capacity; ICS, inhaled corticosteroids; PD, provoking dose; R_{rs} , resistance of the respiratory system; RV, residual volume; TLC, total lung capacity; FEV_1 , forced expiratory volume in 1 s; NO, nitric oxide; AHR, airway hyperresponsiveness.

bronchoconstrictor response to DI and with an improvement in airflow limitation.

When comparing our results with nasal and exhaled NO values obtained in healthy subjects, a frank decrease in nasal NO flux and a moderate increase in exhaled NO in NP are suggested, in agreement with previous authors [1, 2, 24]. The explanations for this decrease in the nasal

NO flux remain to be established. Occlusion of sinus ostia may have participated in this decrease together with a down-regulation of NO synthesis, which seems to characterize inflammatory conditions [25, 26]. The statistical relationships between markers of severity (clinical, radiological and endoscopic scores) and the decrease in the nasal NO flux could have favoured the former hypothesis

[1, 2]. On the other hand, the fact that the statistical relationship between nasal NO and CT score persisted after surgery, a condition where ostia cannot be occluded, favours the latter hypothesis.

The relationship between AHR and pulmonary function has been observed previously [27]. High values of alveolar NO concentrations are evidenced in patients with NP that are correlated with both the degree of airflow limitation (significant) and AHR (trend). Along this line, we demonstrated previously that the increase in distal NO was associated with AHR in patients referred for asthma diagnosis [7], and with distal airflow limitation in another study involving severe asthmatic children [8]. Our study may suggest that distal inflammation occurs in NP, which is associated with airflow limitation.

The main finding of this study is that both airway reactivity (bronchomotor response to deep inspiration) and obstruction are improved by medical treatment of NP, even if these functional characteristics are not clinically significant. Our results further suggest a functional link between upper and lower airway functions, using two new markers (response to deep inspiration and exhaled NO). The efficiency of topical treatment is associated with an increase in nasal NO, and more importantly, a decrease in conducting airway NO flux. One may argue that topical treatment may have been aspirated in lower airways, inducing the decrease in exhaled NO and in the bronchoconstrictor effect of deep inhalation. This hypothesis seems unlikely inasmuch as a specific method was used for topical treatment, which should avoid its inhalation. Furthermore, this global decrease in the conducting airway NO flux was specifically related to patients with AHR. Preferential mouth breathing, which also decreases inhaled NO concentration, secondary to nasal obstruction has been proposed to explain the relationship between chronic nasal diseases and lower respiratory tract disorders [28]. The occurrence of airflow limitation in steroid non-responders has been previously demonstrated [11]; we further extend this finding by demonstrating a significant improvement in airflow limitation after 1 year of medical treatment (~86% of our patients were steroid responders). In the study of Lamblin et al. [11], topical steroid responders did not show an improvement in airflow limitation, which may be related to a more restricted size of their group (18 patients). The degree of improvement in airflow limitation in our study is in accordance with the level of decrease in FEV₁ and FEF₂₅₋₇₅ that was observed in their 28 non-responders to topical steroids over 1 year (~6% and ~9%, respectively). Similar to our results, AHR did not influence the occurrence of airflow limitation in their study.

Our physiological study has potential limitations. The two-compartment model that has been used does not take into account a single-path trumpet model that considers axial diffusion in the conducting airways [29]. Conse-

quently, alveolar NO concentration may represent part of distal NO production by conducting airways. Another limitation is the fact that the clinical relevance of nasal NO measurement is not demonstrated, but our study was not designed for such a demonstration. Further studies are warranted to assess whether its measurement could serve as a screening test to identify non-responders to medical treatment more rapidly. The last limitation was the fact that asthmatic patients were studied while receiving anti-asthma drugs that could have influenced some of the results. But they constituted a small subgroup of our population, and the main result of the improvement in airflow limitation was observed whether or not they were included in the statistical analysis.

In conclusion, steroid responsiveness of NP is associated with an improvement in nasal symptoms, an increase in nasal NO flux and a reduction in both conducting airway NO flux and airflow limitation.

Acknowledgements

The authors wish to thank Mrs Françoise Le Bihan, Mrs Martine Riquelme, Mr Marien Bokouabassa and Mr Xavier Gautier for their expert technical assistance, and Drs Semia Graba, Karin Gillet-Juvin and Mohamed Essalhi for their participation.

Competing interests: The authors declare no financial relationship with any biotechnology and/or pharmaceutical manufacturer that has an interest in the subject matter or materials discussed in the manuscript.

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