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Use of nasal nitric oxide in the diagnosis of allergic rhinitis and nonallergic rhinitis in patients with and without sinus inflammation

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35 **Abbreviations used**

36 AR - Allergic rhinitis

37 SI – Sinus Inflammation

38 ARwSI - Allergic Rhinitis with Sinus Inflammation

39 ARsSI - Allergic Rhinitis without Sinus Inflammation

40 AUC- Area under the curve

41 CRSsNP - Chronic Rhinosinusitis without Nasal Polyps

42 CRSwNP - Chronic Rhinosinusitis with Nasal Polyps

43 NAR - Nonallergic Rhinitis

44 NARwSI - Nonallergic Rhinitis with Sinus Inflammation

45 NARsSI - Nonallergic Rhinitis without Sinus Inflammation

46 NC - Normal Control

47 nNO - Nasal Nitric Oxide

48 SE-Sensitivity

49 SP-Specificity

50 **What is already known about this topic?**

51 Fractional exhaled nitric oxide (FeNO) has been used in diagnosis and evaluation of
52 therapeutic effects in lower airway inflammation, and nasal NO (nNO) has been used in the
53 evaluation of chronic rhinosinusitis (CRS) with and without nasal polyps. However, nNO has
54 not been evaluated in the differentiation of allergic rhinitis (AR) and nonallergic rhinitis
55 (NAR) with and without sinus inflammation.

56 **What does this article add to our knowledge?**

57 The results of this study suggest that measurement of nNO levels can be used in the
58 differential diagnosis of patients with allergic versus nonallergic rhinitis and associated sinus
59 inflammation.

60 **How does this study impact current management guidelines?**

61 Based on our findings, nNO is a simple tool, which could be used to estimate allergic and
62 nonallergic status in patients with rhinitis, combined with sinus inflammation, and therefore
63 lead to improvement in the management of such patients in the clinic.

64

ABSTRACT

Background: Nasal NO (nNO) has been evaluated in patients with chronic rhinosinusitis with and without nasal polyps. However, nNO levels in patients with allergic rhinitis (AR) and nonallergic rhinitis (NAR) have shown conflicting results in previous studies.

Objective: This study aimed to evaluate the value of nNO in diagnosing AR and NAR and the impact of absence or presence of sinus inflammation.

Methods: A total of 173 consecutive patients scanned with high-resolution CT and 46 normal controls (NCs) were included in our study. Patients were evaluated according to their medical history, nasal symptoms, endoscopic examination and skin prick test. Based on CT scan (Lund-Mackey score >2), all patients were subgrouped as AR with (ARwSI) and without (ARsSI) sinus inflammation, or NAR with (ARwSI) and without (NARsSI) sinus inflammation. nNO levels were measured with NOIX device and eosinophils in nasal smears were evaluated simultaneously. ROC analysis was performed for differential diagnosis of AR, NAR and subgroups.

Results: Ninety-four patients were diagnosed as AR and 79 patients as NAR. The levels of nNO were significantly higher in both patients with AR and NCs compared with patients with NAR (939 ± 335 in AR and 813 ± 272 in NCs vs 670 ± 188 in NAR; $P<0.001$ for both), and significantly higher in patients with AR compared with NCs ($P<0.05$). Based on sinus CT scans, 49% of AR patients (46/94) were defined as ARwSI and 51% of NAR patients (40/79) were defined as NARwSI. ARsSI patients showed highest nNO levels (1180 ± 289) compared with other subgroups ($P<0.001$), and NARwSI patients showed lowest nNO levels (522 ± 120)

86 compared with other subgroups ($P<0.001$). nNO could be used to discriminate AR, NAR and
87 subgroups with acceptable sensitivity and specificity. Moreover, patients with nasal smear
88 eosinophilia had lower nNO levels in patients with NAR only ($P<0.05$).

89 **Conclusions:** nNO levels are different between AR and NAR with/without sinus
90 inflammation, and may be utilized to discriminate these phenotypes.

91 **Key words:** Allergic rhinitis; Nonallergic rhinitis; Sinus inflammation; Diagnosis; Nasal
92 nitric oxide

93 INTRODUCTION

94 Rhinitis is defined as the inflammation of nasal mucosa that affects more than 200 million
95 individuals worldwide.¹ This poses an immense burden for the community by increasing the
96 demands for medical treatment and therapy, and creates indirect expense to society by causing
97 missed work and reduced productivity. Rhinitis can be classified into two distinct groups,
98 concurrent allergy (allergic rhinitis, AR) and without allergy (nonallergic rhinitis, NAR) based
99 on the allergen sensitivity defined by skin prick tests (SPTs) or serum specific IgE. AR and
100 NAR vary in some characteristics² especially when considering rhinitis patients with and
101 without chronic rhinosinusitis (CRS).^{3,4} According to a previous study, clinical and laboratory
102 parameters may help to differentiate the diagnosis of AR and NAR.⁵ However, as SPTs and
103 serum specific IgE tests cannot be performed in all subjects due to economic burden, test
104 reagents may be unavailable for some relevant allergens, such as occupational allergens, and
105 false positive or negative SPTs and/or IgE results may occur, it would be valuable to find and
106 utilize a relatively simple and inexpensive single test for the diagnosis of AR and NAR with
107 and without sinus inflammation.

108 Nitric oxide (NO) is a crucial mediator that is involved in a number of relevant biological
109 mechanisms, and also is a key factor in the regulation of immunity and inflammatory
110 processes.^{6,7} NO has been identified in the upper and lower airways of humans,^{8,9} and several
111 clinical studies have demonstrated that exhaled NO can be used in determining the presence
112 and extent of inflammation in the lower respiratory tract.^{10,11} Similarly, several studies have
113 indicated that nasal NO (nNO) levels could be used in the diagnosis of patients with chronic
114 nasal inflammation, such as chronic rhinosinusitis with and without nasal polyps (CRSSNP

and CRSwNP),¹²⁻¹⁹ even allergic or nonallergic,¹⁹ and in screening patients for sinus opacification.²⁰ Previous studies have also reported that allergic patients with CRS or CRSwNP had higher nNO levels compared to nonallergic patients.¹⁹ Several studies have shown that the sinus CT score (Lund-Mackey) had a negative correlation with nNO levels.^{12,13,15-19} However, the implications of nNO levels have not been fully evaluated in patients with AR and NAR. Some studies have shown increased levels of exhaled nNO in patients with AR,^{21,22} and decreased levels in patients with CRS symptoms,¹⁷ compared with those of normal subjects. A study by Suojalehto et al²³ showed that the nNO levels were lower in allergic patients, and suggested that this might be due to sinus ostium obstruction.

Moreover, patients with AR and NAR may have coexistent CRS. Allergy has been considered to be involved in the pathogenesis and symptom expression of CRS for many years.²⁴ According to a previous study, allergy tests were frequently positive in patients with CRS, and a higher incidence of CRS was noted in AR patients,²⁵ suggesting that chronic sinusitis might be a complication of AR. Some studies have demonstrated that AR is more often associated with sinusitis rather than NAR.²⁶⁻²⁸ However, the existence of CRS did not differ between perennial and seasonal allergen sensitivities.²⁹ Moreover, some studies found that patients with AR and NAR might contribute similarly to the development of CRS.²⁹ Therefore, collectively these studies suggest that CRS status should be considered when evaluating the use of nNO levels in the diagnosis or/and treatment of patients with AR and NAR.

Objective assessments may further improve our understanding regarding the interaction of AR, NAR and sinus inflammation. Therefore, we hypothesized that the nNO level in patients

137 with AR and NAR would be influenced by sinus inflammation, when used as a diagnostic tool.

138 Thus, the objective of this study was to evaluate the value of nNO in diagnosing AR and NAR

139 and the impact of the absence or presence of sinus inflammation.

140

METHODS

Patient population

Patients from the Rhinology Clinics of the Beijing TongRen Hospital, Peking, China were recruited. The protocol of this study and the methods of consent were approved by the Beijing TongRen Hospital Ethics Committee, and all subjects provided written informed consent before enrolment to the study. The process of recruitment took place from Jan 2017 to Dec 2017, during which period a total of 173 consecutive patients diagnosed with rhinitis were evaluated by a physician through a clinical interview. Rhinitis was identified by the presence of episodes of rhinorrhea, nasal congestion and/or attacks of sneezing apart from periods of colds. AR was defined as a history of any of these symptoms with a positive SPT or serum specific IgE,³⁰ whereas NAR was defined by the same set of symptoms but with a negative SPT or serum specific IgE.³¹ All patients were experiencing nasal symptoms. At the same time, 20 patients who were diagnosed with pituitary tumor or lateral skull base mass, and prepared to undergo endoscopic surgery, were recruited as normal controls (NCs). All patients were scanned for sinus CT and examined by nasal endoscopy to exclude patients with nasal polyps and other nasal disorders. In the clinical interview, patients with asthma were ruled out by a respiratory physician.

The exclusion criteria included patients with pregnancy, lactation, psychological problems, obstructive sleep apnea, obviously deviated nasal septum, systemic diseases that affect the nose (e.g., Wegener's granulomatosis, sarcoid, asthma and acute upper or lower respiratory tract infections within 4 weeks before the inclusion visit), occupational rhinitis and infectious rhinitis, use of systemic corticosteroids within 4 weeks before the inclusion visit,

systemic diseases preventing the participation in the study, medical or surgical treatments that influence the study, inability to comply with study protocol and children under 18 years of age.

To evaluate nasal inflammation in all subjects, nNO and nasal smear eosinophils were measured by a laboratory technician and nasal symptoms were evaluated by a doctor who was blinded to the patients' nasal inflammatory status. In the present study, AR and NAR patients with sinus inflammation based on sinus CT scans were labeled as ARwSI and NARwSI, while AR and NAR patients without sinus inflammation were labeled as ARsSI and NARsSI. Thus, the abbreviation of SI specifically represents sinus inflammation without nasal polyps in the present study, particularly as CRS with nasal polyps (CRSwNP) is a completely separate phenotype beyond the scope of present study. Furthermore, the role of nNO in diagnosis of CRSwNP and CRS without nasal polyps (CRSsNP) has been previously evaluated by our group.¹⁹

Nasal symptoms

Blocked nose, rhinorrhea, sneezing, nasal itching, olfactory disturbance, headache and postnasal drip were scored according to a visual analogue scale (VAS) of 0 to 10; where 0 indicates no complaints and 10 indicates unbearable complaints.³² Each symptom was evaluated individually and the total symptoms score (TSS) was calculated as the mean of the individual nasal symptom scores.

Measurement of nNO

nNO measurement was done according to the recommendations of ATS/ERS,³³ using

NIOX® (Aerocrine AB, Sweden). A nasal olive with a central lumen was placed in the naris and air was aspired by a fixed and constant flow rate in the range of 3L/min (transnasal flow rate) by a suction pump with air entrained via the other naris. A side port sampled gas for NO analysis. With the targeted aspiration rate a steady plateau level of NO concentration was obtained within 10–30s. The transnasal flow rate was recorded as the NO concentration is inversely related to the transnasal flow rate. Slow oral exhalation against a resistance of at least 10 cmH₂O was the preferred method to obtain velum closure, velum closure was confirmed to ensure that the measurement of nNO was not influenced by the air from the lower airways.³³ Mean of nNO level was determined after three exhalations performed at >30s intervals. The analyzer was calibrated every 13 days by using certified 2000 ppb calibration gas.

Assessment of atopic status

All subjects were investigated for their clinical history and underwent a careful diagnostic evaluation, including the SPT and serum specific IgE measurements in some patients. SPT was performed as previously described,³⁰ using a panel of standard allergen extracts (Allergopharma, Reinbeck, Germany), including animal dander, trees (mixed tree I, mixed tree II, pine, Locust black), *Humulus*, *Chenopodium*, mugwort, ragweed, Engl Plantain, grass pollen, cereals, dandelion, *Blattellagermanica*, mites (*Dermatophagoides pteronyssinus*, *Der p*, and *Dermatophagoides farina*, *Der f*), and fungi (*Curvularia lunata*, *Candida albicans*, *Penicillium notatum*, *Alternaria alternate*, and *Aspergillus fumigatus*). A positive control (10 mg/mL histamine) and negative control (saline) were also included. Serum samples were collected and serum specific IgE levels of the similar allergens as above SPTs were

determined by CAP System (Pharmacia-Upjohn, Uppsala, Sweden).

Nasal smear eosinophilia

Nasal smears were obtained from the middle portion of the inferior turbinate in both nostrils using a Rhino-Probe device. The secretions were smeared onto microscopic slides and rapidly air dried, before being stained with May-Grünwald-Giemsa.³¹ The stained preparations were examined by a light microscope, under oil immersion at a $\times 1000$ magnification. Eosinophils (EOS) were identified and then counted. Concurrently, the smear backgrounds were evaluated. A percentage of cell type per 100 cells was reported. An experienced cytologist blinded to the clinical status of the patients performed this assay. Nasal eosinophilia was assessed and rated by an experienced cytologist according to the Meltzer semiquantitative scale;³¹ with a score equal to or more than class 2 in a sample from either or both nostrils reflecting positive eosinophilia.³⁴

Nasal endoscopy examination and sinus CT scan

Nasal endoscopy and sinus CT scan were respectively used to assess the deformations in the middle meatus, septal deformation, purulent secretions, polyps, and degree of involvement in sinuses. The sinus CT scans were then reviewed in a blinded fashion by a rhinology specialist. Each scan was scored using the Lund-MacKay (L-M) staging system, with the minimum possible score of 0 and a maximum score of 24.³⁵ The CTs were scored in a random order by a reviewer blinded to the patient data, and the patients were then categorized as having sinus inflammation or no sinus inflammation based on sinus CT scores. Using the previously published L-M cutoff scores of 2 or more, patients were classified based on the

227 radiographic extent of the disease in patients with and without CRS.³⁶

228 **Statistical analysis**

229 Power Analysis and Sample Size Software 11.0 (2017) (NCSS, LLC. Kaysville, Utah.
230 PASS 11.0) was used to determine the sample size based on our previous study.¹⁹ We made α
231 equal to 0.05, $1 - \beta$ equal to 0.9, the Minimum Detectable Difference equal to 100ppb and
232 Standard Deviation equal to 50ppb. We calculated the sample size (N) to be 13 and the power
233 calculation to be 0.9027. All analyses were performed with SPSS ver.13 (SPSS, Inc., Chicago,
234 IL, USA). Noncontinuous data were reported as percentages, normally distributed continuous
235 variables as means $\pm$ standard deviation, and non-normally distributed data as medians (with
236 interquartile ranges in parentheses) or with entire distribution of variables with limited
237 number of categories. Comparisons between the groups were done by χ^2 test, Student's *t* test
238 or Mann-Whitney U test for nominal, continuous normally distributed and continuous
239 non-normally distributed variables, respectively. Crude associations were assessed using
240 ANOVA, and crude differences in continuous variables were compared with Student's *t* test
241 justified by a large sample size. ROC analysis was carried for the differential diagnosis of AR
242 and NAR. The relationships between VAS and nNO level were studied with linear regression
243 models. *P* values of <0.05 were considered to be statistically significant.

RESULTS

Characteristics of the study population

The general characteristics of symptomatic patients and healthy controls are reported in Table 1. The mean age of patients with AR was significantly lower than that of patients with NAR (30.5 ± 8.9 vs 37.7 ± 14.1 years, $P < 0.001$). The frequency of NAR and AR in men was higher than that in women ($P < 0.001$). According to sinus CT scans, 40 of 79 NAR patients were diagnosed with SI, and 46 of 94 AR patients were diagnosed with SI (Table 1). According to the nasal smear for eosinophilia examination, 12 of 79 patients were diagnosed as NAR with eosinophilia, and 44 of 72 patients were diagnosed as AR with eosinophilia (Table 1).

nNO levels in different groups or subgroups based on sinus CT scans and its correlation with other clinical parameters

The mean nNO level was significantly increased in patients with AR (939 ± 335 , $P < 0.05$) and significantly decreased in patients with NAR (670 ± 188 , $P < 0.001$), compared to NCs (850 ± 103). Significant differences of nNO were also found between patients with AR and NAR ($P < 0.001$). As shown in Fig 1, compared with NCs, a significantly increased nNO level was found only in ARsSI (1180 ± 289 , $P < 0.001$), and significantly decreased nNO levels could be found in ARwSI (687 ± 133 , $P < 0.001$) and NARwSI (522 ± 120 , $P < 0.001$) patient groups. However, nNO levels of NARsSI patients showed slight, but not significant difference, compared with nNO levels in NCs (780 ± 84 vs 850 ± 103 , $P > 0.05$). Similarly, significant differences were observed between ARsSI and ARwSI as well as between NARsSI and

NARwSI subgroups (Table 1, Fig 1).

Nasal itching, sneezing, rhinorrhea, postnasal drip, olfactory dysfunction and overall discomfort were significantly higher in patients with AR than NAR and NCs (Table 1). However, the nNO levels showed poor correlations with the nasal symptoms and total IgE, except for nasal itching and overall discomfort in NARwSI, blocked nose in ARsSI and sinus CT score in ARwSI subgroups (Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Predictive properties of nNO levels in the diagnosis of NARsSI, NARwSI, ARsSI and ARwSI

The areas under the curve (AUCs) and cut-off values for nNO levels were used to discriminate between patients with AR, NAR, NARsSI, NARwSI, ARsSI, ARwSI, and NCs as shown in Table 2 and Fig E1 (Fig E1 in this article's Online Repository at www.jaci-inpractice.org). The discriminatory evaluation between most subgroups showed significant differences in AUCs and cut-off values, with acceptable sensitivity and specificity values (Table 2). In particular higher nNO levels and higher sensitivity and specificity values discriminated NCs from ARsSI (SE, 0.833; SP, 0.783; AUC, 0.897), NCs from NARwSI (SE, 0.978; SP, 0.950; AUC, 0.988), as well as ARsSI vs NARsSI (SE, 0.896; SP, 0.974; AUC, 0.968) (Table 2). Similarly, lower nNO levels and lower sensitivity and specificity values were observed for differentiating between NCs and NARsSI (SE=0.652, SP=0.564, AUC=0.675), as well as between NARsSI and ARwSI (SE=0.641, SP=0.652, AUC=0.711) (Table 2).

nNO levels in different groups or subgroups based on nasal eosinophilia and its correlation with other clinical parameters

In our data, 79 patients with NAR and 72 patients with AR had successful nasal smear examination. Nasal EOS was found to be positive in 15% (12/79) of subjects with NAR and 61% (44/72) of subjects with AR, compared to 0% (0/46) of NCs; suggesting a stronger association between AR and nasal EOS than NAR ($P<0.001$). Based on the nasal smear EOS, patients with NAR were divided as NAR with eosinophilia (NAR-EOS(+)) and NAR without nasal eosinophilia (NAR-EOS(-)), as were patients with AR (Table 3). Generally, nNO levels of AR subgroups were significantly higher than those of NAR subgroups (Table 3, Fig 2). Patients with AR-EOS(-) showed lower nasal NO levels when compared with patients with AR-EOS(+), but the differences were not significant (842 ± 294 vs 1003 ± 365 , $P>0.05$). However, significant differences were observed in nNO between (NAR-EOS(+) versus NAR-EOS(-), nasal eosinophilia (541 ± 185 vs 669 ± 156 , $P<0.01$) (Table 3).

As shown in Table 3, patients with NAR-EOS(+) were significantly prone to CRS sinus inflammation ($P<0.001$) compared with patients with NAR-EOS(-). Furthermore, the clinical scores of rhinorrhea and olfactory dysfunction of NAR-EOS(+) subgroup were significantly higher than those of NAR-EOS(-) subgroup ($P<0.05$ and $P<0.001$ respectively). NARwSI patients also had higher prevalence of EOS compared with NARsSI ($P<0.001$) (Table 1).

DISCUSSION

The results of nNO levels are conflicting in AR patients in previous studies, and no prior study has evaluated the nNO levels in NAR patients. It has been reported that patients with AR had higher nNO concentration than NCs,^{21, 37, 38, 39} or similar NO concentrations between AR and NCs.^{40, 41, 42} Bommarito et al found that levels of nNO were significantly lower in patients with CRSwNP compared with patients with CRSsNP, patients without CRS, and controls.¹⁷ However, there were no differences in the nNO levels between patients with AR and healthy subjects in another study.⁴³ Moody et al found that the nNO levels were higher in allergic patients and were not elevated when compared between perennial rhinitis and non-atopic asymptomatic subjects,⁴⁴ and another study reported a similar result.⁴⁵ In our study, we found that patients with AR had higher NO levels and patients with NAR had significantly lower nNO levels when compared with NCs. The possible reasons for discrepancies between studies might be due to the following. Firstly, different techniques for measuring nNO have been used. Secondly, differences in patient selection, e.g. including patients with obstructive sleep apnea and habits of smoking, might have led to higher or lower nNO levels, which may be important sources of variability. Thirdly, the production of NO in the nose and sinuses may not be subject to the same cytokine regulation as that in the lungs of asthmatics and may not be increased in AR. Moreover, patients with NAR and AR have different pathogenetic mechanism. It is generally accepted that afferent sensory nerves play a crucial role in nasal homeostasis and may even cause so called 'neurogenic inflammation' under pathological conditions in NAR patients.⁴⁶ Similarly, inflammatory cells play a crucial role in the nasal mucosa and cause allergic inflammation in AR patients.⁴⁷ Strikingly, one study observed no

epithelial barrier defects in strictly selected NAR patients compared to AR patients.⁴⁸ We speculate that different underlying mechanisms responsible for the induction of neurogenic inflammation in NAR and IgE-mediated inflammation in AR are probably responsible for different nNO levels. Finally, in patients with NAR, NO showed cytotoxic effects and caused inhibition of mitotic activity in the basal cells, leading to epithelial disruption and breakdown of protective functions of the epithelium.⁴⁹

Our study also showed that sinus inflammation had a significant impact on nNO levels, and this has been demonstrated by several previous studies.¹²⁻¹⁹ Sinus CT score was correlated with nNO levels significantly in CRS patients.^{12,13,15,16,17,19} Therefore, we considered that the inconsistent results in the previous studies about nNO levels might be because of the involvement of sinus inflammation. In a study that excluded sinus diseases, AR was associated with higher nNO levels when compared to NCs.⁵⁰ In contrast, Suojalehto et al²³ showed that in patients with allergies, the levels of nNO were lower, attributed to the obstruction of sinus ostium. In the present study, when AR and NAR patients with and without sinus inflammation were compared among subgroups (Fig 1), nNO levels showed significant differences between these subgroups. This demonstrated that not only sinus ostium obstruction but also sinus inflammation can significantly impact the nNO levels in both AR and NAR patients. Indeed, although the nNO levels in AR patients with and without sinus inflammation were similar to those found in a previous study,²³ this was not found to be the case in NAR patients with and without sinus inflammation. In our study, patients with NAR with sinus inflammation had the lowest nNO levels, which was in contrast to the previous study where the NAR patients with higher CT scores had the highest nNO levels in 6

patients.²³ It is possible that this difference might be due to patient selection. However, nNO levels in NAR patients with sinus inflammation in present study was found to be similar to our previous study, where we found lower nNo levels with nonatopic CRSsNP compared with NCs,¹⁹ suggesting that a subset of NAR patients may have similar characteristics to CRSsNP. These results are also similar to other previous studies.¹²⁻¹⁹

Moreover, Segboer et al⁵¹ demonstrated that nasal hyper-reactivity is a common feature in patients with AR or NAR, and it is not possible to differentiate NAR subpopulations based on physical or chemical stimuli. However, our study found that nNO may be a discriminatory factor for the diagnosis of AR/NAR with and without sinus inflammation. Overall, nNO levels in ARsSI or NARwSI were remarkably higher or lower than other three subgroups and could be discriminated qualitatively from the other three subgroups with fine predictive values at cut-off values of 899ppb and 621ppb nNO levels, respectively without the use of SPTs or serum specific IgE and sinus CT scans. Alternatively, under these circumstances, the exact allergic status of subjects could be defined firstly according to SPTs or serum specific IgE combined with clinical history, and then nNO could be used to discriminate between the different AR and NAR subgroups with high specificity and sensitivity values without use of sinus CT scans. In contrast, lower sensitivity and specificity values were observed for comparisons between NCs and NARsSI, and these phenotypes were differentiated easily based on symptom history. Furthermore, low sensitivity and specificity values found among AR, NAR and NC, especially between AR and NC (SE, 0.532; SP, 0.543; AUC, 0.404), and the impact of sinus inflammation may partly explain the contradictory results demonstrated in previous studies.^{21-23,37-42} To our knowledge, this is the first study to evaluate the application

of nNO in the differential diagnosis of AR and NAR with and without sinus inflammation, and suggests that nNO can be used with acceptable sensitivity and specificity in this regard.

Nasal smear eosinophilia was expected to have some impact on the nasal NO levels. However, patients with AR-EOS(+) have high, but not significantly different nNO levels compared with patients with AR-EOS(-), and patients with NAR-EOS(+) have lower nNO levels than NAR-EOS(-) patients, which are in contrast with the findings from previous studies where the patients with eosinophilic CRS showed high nNO levels than non-eosinophilic CRS.^{52,53} In our study, NAR patients with EOS(+) are prone to coexistent sinus inflammation. We speculate that eosinophils may have different impacts on nasal NO levels in patients with NAR versus AR. In NAR patients, EOS(+) may lead to the remodeling of ethmoid mucosa and obstruction of the maxillary sinus,⁵⁴ which may be responsible for the lower NO levels. In AR patients, EOS(+) may lead to allergic edema and congestion of the mucosa in nasal cavity and sinuses, which may be responsible for the higher NO levels. Although, previous studies have suggested that remodeling may be an active primary process that is at least partially independent of inflammation, perhaps commencing in parallel with the inflammatory process,⁵⁵ a recent study has demonstrated that tissue remodeling was not a feature of AR, even in patients with severe persistent allergic rhinitis.⁵⁶ Indeed, our study also showed that lower nNO levels correlated only with sinus inflammation. Therefore, future research should be carried on regarding the influence of remodeling and inflammation on nNO levels in AR and NAR patients.

However, there are some limitations in our study. Firstly, we failed to subgroup NAR patients as vasomotor rhinitis or NARES, and we excluded occupational rhinitis and

infectious rhinitis. Secondly, the use of Rhino-Probe device for obtaining nasal smears, and identification of eosinophils by light microscopy and scoring by the Meltzer semiquantitative scale could possibly lead to small errors in eosinophil counts. Although eosinophil levels can vary in each side of the nose and local allergic rhinitis was not considered in the present study, there is evidence that eosinophil numbers do correlate well with local allergic rhinitis.^{57,58} Thirdly, nNO levels were measured after introducing the local mucosa constrictor in six patients with serious nasal blockage, which might subsequently impact the results.

CONCLUSION

These results have identified several objective and subjective differences between patients with AR and NAR, and highlight the change of nasal inflammatory indicators and its associated changes of nasal airway patency. Measurement of nNO level may be a useful alternative to CT scanning under some circumstances as a diagnostic tool to discriminate AR and NAR patients with and without sinus inflammation, with ARsSI and NARwSI subgroups having the highest and lowest nNO levels, respectively. However, further studies of nasal NO and its relationship to allergic or non-allergic inflammation of nasal and sinus mucosa are warranted.

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563

564 **TABLES**

565 **Table 1.** Demographic and clinical characteristics of subjects with NAR, AR with and without
 566 sinus inflammation and NCs

	NCs N=46	NARsSI N=39	NARwSI N=40	<i>P</i> value NARsSI vs NARwSI	ARsSI N=48	ARwSI N=46	<i>P</i> value ARsSI vs ARwSI	<i>P</i> value For all
Gender (m/f)	36/10	28/11	30/10	0.000	31/17	35/11	0.000	NA
Age	30.7±5.5	37.2±14.0	38.5±14.0	0.601	29.2±7.9	31.9±9.7	0.143	0.001
Nasal NO	850±103	780±84	522±120	0.000	1180±289	687±133	0.000	0.000
Total IgE	51.4±44.4	49.5±96.7	85.9±90.5	0.575	138.3±201.6	247.7±297.6	0.380	0.002
Nasal smear eosinophilia(+/-)	0/46	1/38	11/29	0.000	26/10	18/18	0.500	NA
Blocked nose	NA	5.6±3.1	5.3±3.2	0.643	5.3±3.1	5.3±3.1	0.991	0.943
Nasal itching	NA	1.5±2.6	1.9±2.4	0.556	4.1±3.2	3.1±2.9	0.128	0.000
Sneezing	NA	1.1±2.0	1.9±2.3	0.094	5.5±3.5	5.0±3.7	0.486	0.000
Rhinorrhea	NA	1.6±2.2	3.1±3.2	0.014	5.7±3.6	5.6±3.8	0.927	0.000
Postnasal drip	NA	1.5±2.4	1.6±3.0	0.858	3.0±3.1	2.5±3.4	0.454	0.054
Olfactory dysfunction	NA	1.4±2.6	2.8±3.7	0.055	3.1±3.1	3.1±3.3	0.997	0.045
Headache	NA	3.0±3.1	3.0±3.3	0.938	2.6±3.1	2.5±2.8	0.781	0.804
Overall discomfort (Mean)	NA	2.2±1.5	2.7±1.8	0.238	4.2±2.0	3.9±2.0	0.438	0.000

567 NCs: Normal controls; NARsSI/NARwSI: Nonallergic rhinitis without/with sinus
 568 inflammation; ARsSI/ARwSI: Allergic rhinitis without/with sinus inflammation.

Table 2. Predictive properties of exhaled nasal NO among NCs and patients with NARsCRS, NARwCRS, ARsCRS and ARwCRS

	AUC of ROC	Cut-off value (ppb)	Sensitivity	Specificity	<i>P</i> value
NC vs NAR	0.833	771	0.761	0.722	0.000
NC vs AR	0.543	847	0.532	0.543	0.404
AR vs NAR	0.777	771	0.681	0.722	0.000
NARwSI vs other three subgroups	0.929	621	0.902	0.850	0.000
ARsSI vs other three subgroups	0.985	899	0.896	0.976	0.000
NC vs NARsSI	0.675	792	0.652	0.564	0.006
NC vs NARwSI	0.988	710	0.978	0.950	0.000
NC vs ARsSI	0.897	940	0.833	0.783	0.000
NC vs ARwSI	0.826	750	0.826	0.630	0.000
NARsSI vs NARwSI	0.963	630	0.949	0.850	0.000
NARsSI vs ARsSI	0.968	900	0.896	0.974	0.000
NARsSI vs ARwSI	0.711	757	0.641	0.652	0.001
NARwSI vs ARsSI	1.0	796	1.0	1.0	0.000
NARwSI vs ARwSI	0.824	631	0.761	0.850	0.000
ARsSI vs ARwSI	0.986	810	1.0	0.913	0.000

NO: Nitric oxide; ROC: Receiver operating characteristic; AUC: Area under the curve; NC: Normal control; NARsSI/NARwSI: Nonallergic rhinitis without/with sinus inflammation; ARsSI/ARwSI: Allergic rhinitis without/with sinus inflammation.

575 **Table 3.** Comparison of NAR and AR with and without nasal smear eosinophilia

	NAR-EOS(-) N= 67	NAR-EOS(+) N=12	<i>P</i> value NAR-EOS(-) vs NAR-EOS(+)	AR-EOS(-) N=28	AR-EOS(+) N=44	<i>P</i> value AR-EOS(-) vs AR-EOS(+)	<i>P</i> value for all
SI (+/-)	29/38	11/1	0.000	18/10	18/26	0.500	NA
Gender (m/f)	47/20	11/1	0.000	21/7	29/15	0.000	NA
Age	37.7±14.2	37.8±14.4	0.982	30.5±10.8	30.0±7.6	0.851	0.004
Nasal NO	669±156	541±185	0.009	842±294	1003±365	0.053	0.000
Total IgE	13.5±4.9	15±4.4	0.436	139.7±186.1	275.9±320.2	0.220	0.000
Blocked nose	5.1±3.3	5.7±3.1	0.572	5.6±3.2	5.1±2.9	0.530	0.846
Nasal itching	1.7±2.6	1.4±1.7	0.714	4.0±3.0	3.0±3.2	0.198	0.000
Sneezing	1.4±2.1	2.2±2.5	0.234	5.5±3.4	4.3±3.8	0.173	0.000
Rhinorrhea	2.0±2.8	4.0±2.6	0.021	5.8±3.7	4.4±3.7	0.145	0.000
Postnasal drip	1.6±2.7	1.1±2.9	0.601	2.8±2.9	2.0±3.7	0.826	0.085
Olfactory	1.6±3.0	4.0±3.8	0.006	3.3±3.2	2.5±2.9	0.307	0.007
Headache	3.2±3.3	1.4±1.8	0.066	3.0±3.0	2.5±2.8	0.453	0.237
Overall discomfort (Mean)	2.4±1.7	2.9±1.6	0.318	4.3±1.9	3.5±2.2	0.119	0.000

576 AR: Allergic rhinitis; NAR: Nonallergic rhinitis; EOS: eosinophils.

577

FIGURE LEGENDS

Figure 1. Exhaled nasal NO levels in NAR, AR with and without CRS and NC groups. NO: Nitric oxide; NAR: Nonallergic rhinitis; AR: Allergic rhinitis; NC: Normal control; NARsSI/NARwSI: Nonallergic rhinitis without/with sinus inflammation; ARsSI/ARwSI: Allergic rhinitis without/with sinus inflammation; SI: Sinus Inflammation.

Figure 2. Exhaled nasal nitric oxide (NO) levels in NAR and AR groups with/without eosinophilia EOS(-)/(+). NO: Nitric oxide; NAR: Nonallergic rhinitis; AR: Allergic rhinitis; EOS: Eosinophils.



