# Nasal and Exhaled Nitric Oxide in Chronic rhinosinusitis with polyp

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## ABSTRACT

***Background and Objective*** Nitric oxide(NO) is known to be very important mediator and inflammatory marker of human airway. The purpose of this study is to analyze the distribution of nasal NO(nNO) and exhaled NO(eNO) on chronic rhinosinusitis(CRS) with polyp and to predict clinical features of CRS with polyp by NO, which is easy to measure.

***Methods*** We used chemiluminescent analyser to measure nNO and eNO between healthy individuals(32) and CRS with polyp patients(30), CRS with polyp & allergic rhinitis patients(27) and compared it with clinical symptom parameters,laboratory datas and CT scores.

***Results*** Levels of nNO were significantly lower in patients of CRS with polyp(88.5±54.7 ppb) compared to controls(241.0±89.5 ppb). Levels of nNO in patients of CRS with polyp & AR(167.0±47.6 ppb) were significantly higher than CRS with polyp patients and lower than controls. A significant inverse relationship was observed between nNO and Sinus CT scores, severity of nasal obstruction and purulent rhinorrhea in CRS with polyp patients. Low values of nNO separated very well patients with CRS with polyp, and the cutoff value of less than 163 ppb was associated with the best combination of specificity (93%) and sensitivity (81%). Levels of eNO were significantly higher in patients of CRS with polyp(29.8±12.8 ppb) compared to controls(20.5±6.4 ppb) and a significant positive relationship was observed between eNO and CT scores. .

***Conclusion*** The nasal NO would allow for better screening of CRS with polyp which eventually has to be treated with surgery. The upper airway disease could affect the lower airway inflammation and it reflects that “One airway, One disease”.

## CONTACT

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## INTRODUCTION

Exhaled nitric oxide(eNO) is measured NO in the lower respiratory tract through oral cavity. It is being researched as non-invasive marker of asthma and, especially, as marker of eosinophilic airway inflammation. Until recently, measuring eNO was difficult. The patient had to go to the laboratory himself and use multiple complex machines but nowadays portable analyzers like NIOX & MINO have been developed and are used clinically through primary physicians in Korea.

Nasal NO(nNO) is measured NO through the air in the nasal cavity. It is continuously produced in the paranasal sinuses without any inflammatory stimuli. It also has protective effect on upper airway through its toxicity on bacteria, virus, fungus and tumor cells. If there is a inflammatory stimuli, epithelial cell of upper airway increases production of induced NO synthase(iNOS) and therefore NO production increases.

In the field of otorhinolaryngology, primary ciliary diskinesia lacks iNOS in the epithelial cells and therefore shows extremely low level of nNO. In diseases such as nasal polyp, chronic sinusitis, cystic fibrosis show obstruction of osteomeatal unit and consequently, NO produced in the paranasal sinuses can not be secreted to the nasal cavity, causing low level of nNO. In contrast, inflammatory diseases like allergic rhinitis has increased iNOS and thereby shows increased NO production.

This study measured nNO and eNO in patients with chronic rhinosinusitis with polyps and compared with normal control group, analyzed correlation with various clinical symptoms, computerized tomography(CT) imaging, various clinical tests including olfaction, and assessed nNO and eNO measurements as an evaluation tool for chronic rhinosinusitis with polyps

## METHODS AND MATERIALS

**1. Object of study**

89 patients diagnosed as septal deviation or chronic rhinosinusitis with nasal polyp and allergic rhinitis in Hanyang ENT between November 2008 and February 2010 was object of study. Average age was 24.8, male 53(59.6%) and female 36(40.4%).

| | Control group(n=32) | Rhinosinusitis with polyp Allergic rhinitis(-) (n=30) | Rhinosinusitis with polyp Allergic rhinitis(+) (n=27) |
|---|---|---|---|
| Age(years) | 27.39±11.2 | 33.4±17.0 | 33.4±15.0 |
| Sex(M:F) | 16:16 | 16:14 | 21:6 |

- Diagnosis Allergic rhinitis using Skin test or MAST
- R/O Sinusitis using PNS x-ray or OMU CT

Exclusion criteria

- Under 15 years old age.
- Asthma: using PFT
- Previous Nasal surgery
- Medication related nasal symptoms in a week

## METHODS AND MATERIALS

**2. Measurement of NO**

NO concentration was measured through chemical luminsecence analyzer (Sievers ntric oxide analyzer, NOA 280i). After ambient NO was measured, nNO was extracted through 200mL/min air current in the middle of 700ml/min air current collected by suction pump.

Palatopharynx closing was induced by inspiration of air until total lung capacity and then expiration through mouth with sustaining expiratory pressure at 20cm $H_2O$, and then nasal cavity was separted from lower airway.

## RESULTS

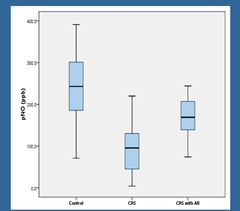
There was no significant difference in age, height, weight, BMI, sex between control and allergic rhinitis group.

**1. pNO & eNO in two groups(pNO = eNO – ambient NO)**

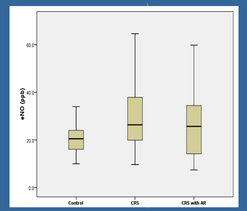
| | pNO | eNO |
|---|---|---|
| Control | 241.0 ± 89.5 ppb | 20.5 ± 6.4 ppb |
| CRS | 88.5 ± 54.7 ppb | 29.8± 12.8 ppb |
| CRS with AR | 167.0 ± 47.6 ppb | 26.2± 15.0 ppb |

**The mean nNO concentrations showed significantly decrease in patients with CRS with polyp compared to controls.**(p<0.0001)
**The mean eNO concentrations showed significantly increase in patients with CRS with polyp compared to controls.**(p<0.009)

pNO




eNO




**2. Age, height, weight and BMI in three groups**

Analysis showed no statistically significant difference in genders, age, height, weight, and BMI in three groups; normal control group, chronic rhinosinusitis with nasal polyp patients group without allergic rhinitis, chronic rhinosinusitis with nasal polyp patients group with allergic rhinitis

**3. Comparison of peripheral blood tests, olfactory function tests and CT scan in three groups**

## RESULTS

**1) Ig E level and eosinophil count in the peripheral blood**

Serum Ig E and eosinophil count in patients group with allergic rhinitis showed statistically significantly higher than normal control group and patients group without allergic rhinitis. ($p$<0.0001, $p$=0.035)

**2) Olfactory function test**

Olfactory threshold in patients groups was statistically significantly lower than normal control group($p$=0.043). Olfactory identification in patients groups was statistically significantly decreased compared with normal control group($p$<0.0001)

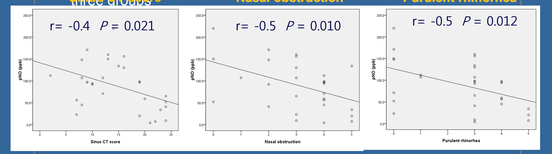
**3) CT scan**

Lund-Mackay score based on CT scan in patients groups showed statistically significantly higher than normal control group($p$<0.0001)

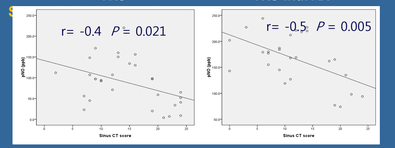
**4) Subjective symptoms**

Purulent rhinorrhea symptom scores in patients groups were statistically significantly higher than normal control group($p$<0.0001). Postnasal drip and headache symptom scores in patients groups were statistically significantly higher than normal control group ($p$=0.021, $p$=0.034). Olfactory disturbance symptom scores in patients groups were statistically significantly higher than normal control group($p$<0.0001). There were no differences in nasal obstruction, facial pain, sputum and cough symptom scores among three groups.

Sinus CT score | Nasal obstruction | Purulent rhinorrhea

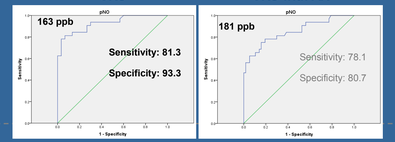



CRS | CRS with AR




**Cutoff value on pNO in the diagnosis of CRS with polyp**

CRS | CRS with AR




## DISCUSSION

- Major part of eNO has been known to be originated from the upper airways, mainly nasal cavities and paranasal sinuses but the origin of nNO measured by aspiration of the air in the nasal cavities has not been determined so far. Lundberg et al. reported in the studies of objects not having clinically chronic rhinosinusitis that NOS-2 distributes in the mucosa of the paranasal sinuses far more than in the mucosa of the nasal cavities through the immunohistochemical staining and most of nNO is produced by NOS-2 in the paranasal sinuses. Scadding et al. reported that nNO is produced continuously by NOS in the normal ciliary mucosal cells of the paranasal sinuses.
- In the acute and chronic rhinosinusits without concomitant nasal polyps, the expression of both nNO and NOS-2 has been reported to be decreased. Especially, Deja et al. demonstrated with a study of patients with chronic rhinosinusitis that reduced expression of NOS-2 in the ciliary epithelial cells of maxillary sinus musosa contributes to reduced NO concentration in the maxillary sinuses. Other study showed increase in nNO with sinusitis treatment. However, it has remained uncertain whether low nNO measurement in acute and chronic sinusitis is caused by the decreased NO production in the maxiallry sinuses or by an obstruction of sinus ostia with the secondary changes of sinusitis; local edema, nasal swelling or mucous retention.
- Several studies, Lundberg et al. and Arnal et al. reported that nNO does not change in chronic rhinosinusitis with nasal polyposis, but most of the studies have proved that nNO decreases in chronic rhinosinusitis with nasal polyposis, which is widely accepted
- Ragab et al. reported that nNO levels correlated inversely with severities of paranasal sinus lesions such as CT scan changes, nasal endoscopic changes and polyp grades and etc, which is similar to Arnal et al.’s study and our study results. They also reported that nNO increases significantly with medications or surgical treatments, as explained by that recovery of paranasal sinus ciliary epithelial cells normalizes the expression of NOS-2 and nNO emanates well through natural ostia resulting in nNO increase.
- Putting these reports together, nNO measurement can be determined by diseases of nasal cavities and paranasal sinuses[8,9,10,11,12] and can be used as an indicator to assess indirectly the extent of sinus mucosa lesions and blockage of ostiomeatal complex.

## CONCLUSIONS

- The nasal NO can be used to predict CRS with polyp when an endoscopic examination or sinus CT scan cannot be performed, especially for doctors who are not ENT specialist.
- The nasal NO would allow for better screening(using cutoff value) of CRS with polyp which eventually have to be treated with ESS.
- An inverse relationship between nasal NO and the extent of sinus disease would help to explain the previous mechanisms like the damage of the ciliated epithelium of the sinuses and the size of the sinus ostia.
- The upper airway disease could affect the lower airway inflammation (the positive relationship between exhaled NO and the extent of sinus disease). It reflects that “One airway, One disease”.
- Standardization of measurement and establishment of more constant cutoff values would increase the usefulness of NO in CRS.