Allergy 2006: 61: 717–724

© 2006 The Authors
Journal compliation © 2006 Blackwell Munksgaard

DOI: 10.1111/j.1398-9995.2005.01044.x

Original article

Nasal nitric oxide in objective evaluation of chronic rhinosinusitis therapy

Background: The assessment of the response of chronic rhinosinusitis (CRS) to therapy is difficult. Computerized tomographic (CT) scans cannot be repeatedly used so measures such as symptom scores, endoscopic findings, and parallel measures such as saccharin clearance time are employed instead.
Objective: To study the effect of CRS therapy on nasal nitric oxide and to see whether nasal nitric oxide level changes correlate with other assessments.
Methods: The study was a prospective randomized trial of patients with CRS, with or without polyps, who had failed initial medical therapy with douching and nasal corticosteroids and who then had abnormal CT scans. They were treated either medically or surgically, with follow up at 6 and 12 months whilst still taking nasal corticosteroids. Nasal nitric oxide was measured initially and at 6 and 12 months as well as symptom scores, endoscopy, polyp grading, and saccharin clearance time.
Results: Initial absolute nasal nitric oxide levels correlated inversely with CT scan changes, ($P < 0.001$). The percentage rise in nasal nitric oxide seen on both medical and surgical treatment correlated with changes in symptom scores ($P < 0.001$), saccharin clearance time ($P < 0.001$), endoscopic changes ($P < 0.001$), polyp grades ($P < 0.05$ at 6 months, $P < 0.01$ at 12 months) and surgical scores ($P < 0.01$). There was no significant correlation with age, sex, smoking or allergy.
Conclusion: Nasal nitric oxide, which is easily measured, provides a valuable non-invasive objective measure of the response of CRS to therapy. Topical nasal corticosteroids may be needed to reduce the contribution of nasal epithelial nitric oxide and allow that emanating from the sinuses to be measured.

S. M. Ragab[1], V. J. Lund[2], H. A. Saleh[3], G. Scadding[4]

[1]Lecturer of Otolaryngology and Head & Neck Surgery, Tanta University Hospitals, Tanta, Egypt; [2]Professor of Rhinology, Institute of Laryngology and Otology, London, UK; [3]Consultant Rhinologist/Facial Plastic Surgeon, Charing Cross and the Royal Brompton Hospitals, London, UK; [4]Consultant Immunologist, Rhinologist and Allergy Specialist, Royal National Throat Nose and Ear Hospital, London, UK

Key words: chronic rhinosinusitis; computerized tomographic scan; endoscopic sinus surgery; Nasal nitric oxide; nasal polyposis; saccharin clearance time; symptom scores

Dr Glenis Scadding
Rhinology Department
RNTNE Hospital
330 Gray's Inn Road
London WC1X 8DA
UK

Accepted for publication 1 December 2005

Nitric oxide (NO) is a gas formed *in vivo* by three isoforms of the enzyme NO synthase. It is secreted in the respiratory tract with a major contribution from the upper airways especially the paranasal sinuses (1, 2). The biological significance of the airway-derived NO is still uncertain. Nitric oxide has been proposed as a bronchodilator (3), a vasodilator (4, 5) and a major neurotransmitter (6, 7), to have antimicrobial (8, 9), antitumour (10, 11) and mucociliary regulating activities (12–14) and to act as an airborne messenger (15, 16). Nitric oxide may also have proinflammatory actions (17, 18).

Nasal nitric oxide has been reported as decreased in acute rhinosinusitis (19), nasal polyposis (20). primary ciliary dyskinesia (21, 22) and cystic fibrosis (23, 24) and as normal or increased in allergic rhinitis (25–27) and asthma (28–31). In chronic rhinosinusitis (CRS), Lindberg et al. (32) found lower nasal nitric oxide (nNO) levels than healthy controls. Conversely, Arnal et al. (21) found no significant difference in nNO levels between patients with CRS and controls. In the lower airway, exhaled nitric oxide (eNO) measurement excites considerable interest as it provides a simple non-invasive means of measuring airway inflammation in asthma, even in children (33–35). The value of nNO as a measure of the effect of therapy on CRS is still uncertain. Therefore, this study was conducted to study the effect of medical and surgical therapy of CRS upon nNO levels and to investigate the value of nNO as an objective indicator of the effect of therapy on CRS.

Abbreviations: CRS, chronic rhinosinusitis; CT scan, computerized tomographic scan; eNO, exhaled nitric oxide; nNO, nasal nitric oxide; NO, nitric oxide; SCT, saccharin clearance time; VAS, visual analogue scale.

Materials and methods

Ninety patients with CRS who still had troublesome symptoms after initial therapy with dexarhinaspray and nasal douching were recruited into a prospective randomized study of medical *vs* surgical therapy of CRS. The study, which was approved by the Royal Free

Hospital and Medical School Ethics Committee, has been previously reported in detail (36). The study comprised 45 males and 45 females, with a mean age (± SD) of 43 (± 13), 35 CRS with polyposis (19 surgical and 16 medical), 43 asthmatics (23 surgical and 20 medical), three aspirin sensitive (two surgical and one medical) and 49 with positive skin prick test (25 surgical and 24 medical) and 13 smokers (six surgical and seven medical).

The design and flow chart of the study are shown in Figs 1 and 2, respectively.

Subjective assessment

Nasal blockage or congestion, nasal discharge, olfactory disturbance, facial pain or pressure, headache and overall discomfort were used for the scoring criteria, using a visual analogue scale (VAS) (37).

Examination of the nose

Nasal endoscopy was done in all cases. Two endoscopic scoring systems were applied in the study. The first one (38) was used in all cases of the study. The second scoring system was only used in cases of CRS with polyposis (39).

Radiological assessment

A computerized tomographic (CT) scan was ordered if the initial medical treatment failed to control the patient's symptoms. CT scans were assessed and scored in order to define the surgical anatomy and the extent of the disease (38). Only patients with abnormal CT scans were entered into the study.

Nitric oxide

An NO gas analyser (model LR 2000; Logan Research Ltd, Rochester, UK) was used with sampling flow rate adjusted to 250 ml/min. Ambient NO levels were within acceptable limits throughout the study. Sampling from the nostril was done with the patient holding his breath in deep inspiration to close the soft palate and prevent sampling of pulmonary air. This was confirmed by the

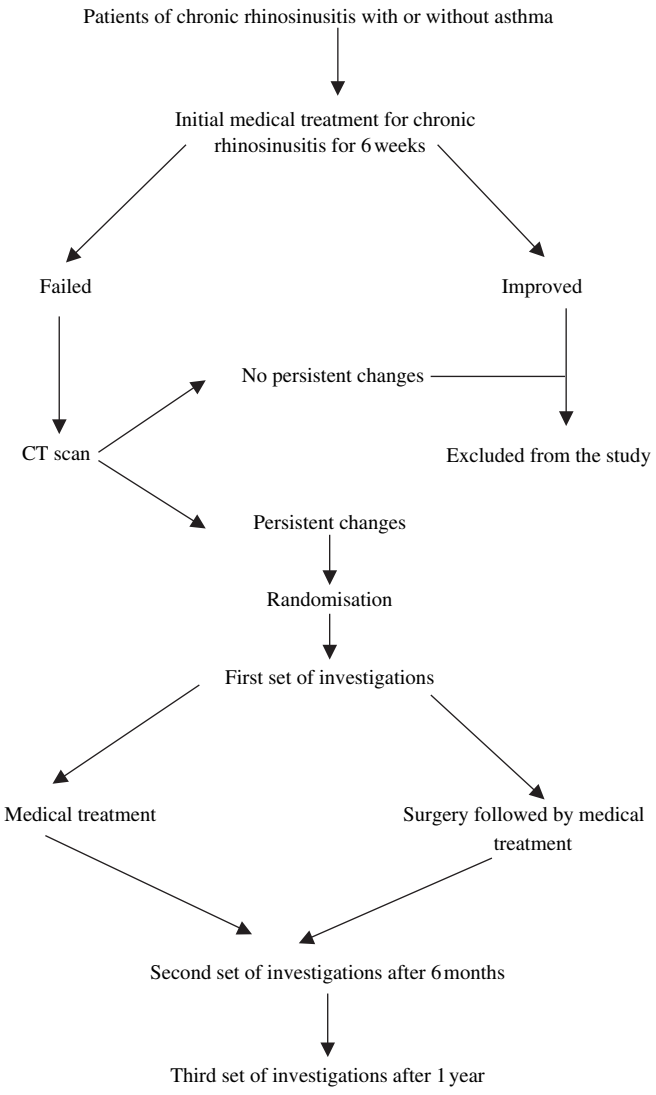

Figure 1. Study design

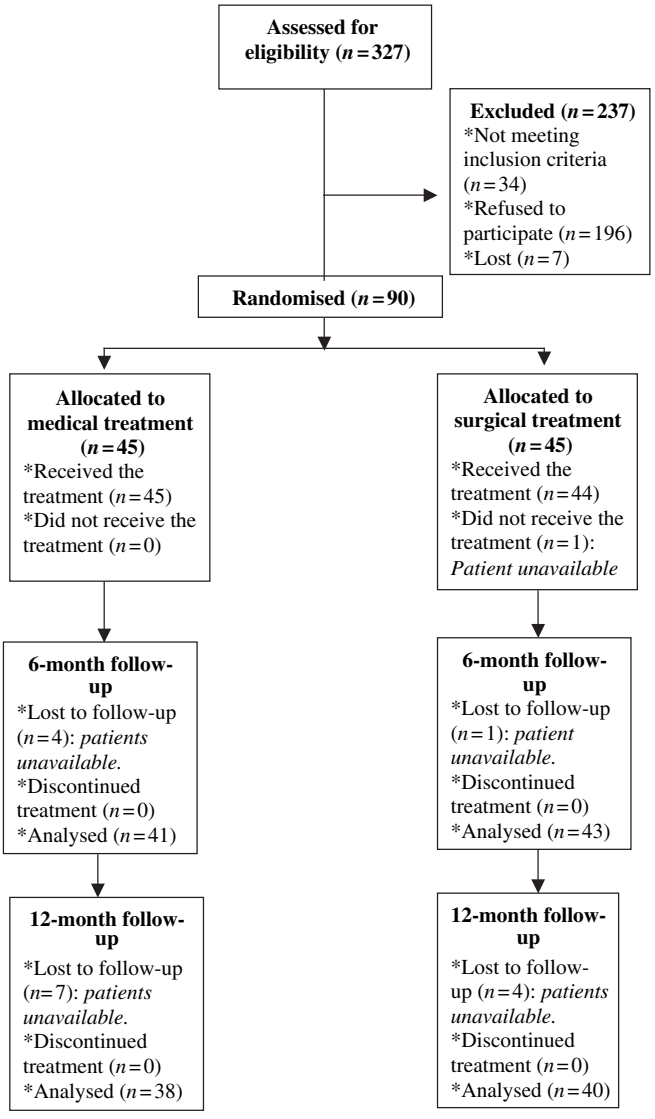

Figure 2. Flow chart of chronic rhinosinusitis trial stages

absence of CO_2 increase during sampling. The value of the last plateau part of the nNO trace taken after > 30 s of breath holding was recorded and the mean of three recordings used.

Saccharine clearance test

A saccharine particle was placed using the endoscope on the lateral nasal wall, 1 cm behind the anterior end of the inferior turbinate after the patient has blown his or her nose to remove secretions. The patient was asked to avoid sniffing or snorting, but was asked to swallow once a minute. The transport time was measured from the placement of the saccharine particle to the first taste perception. If no taste was noticed within 1 h, the test was aborted and a saccharine piece placed on the tip of the tongue to test the subject's taste ability.

Medical treatment

Initial medical treatment. This included a 6-week regimen of dexarhinospray (DRS) and an alkaline nasal douche. DRS was delivered as two puffs into each nostril twice daily, with each metered dose containing 20 μg of dexamethasone-21-isonicotinate and 120 μg of tramazoline hydrochloride. The alkaline nasal douche powder was prepared in a 1 : 1 mixture of sodium chloride and sodium bicarbonate. The douche was also used twice daily. Patients with positive SPT were given allergen avoidance advice.

Medical treatment for the medically randomized group. All patients received a 12-week course of erythromycin, alkaline nasal douche and intranasal corticosteroid preparations. Erythromycin was prescribed orally as 500 mg twice daily for 2 weeks, followed by 250 mg twice daily for 10 weeks. Alkaline nasal douche was prepared and used as instructed above. Intranasal corticosteroid preparations, in patients of CRS without polyposis, were given as DRS, two puffs into each nostril, twice daily, for 2 weeks, followed by a twice daily dose of 100 μg (two sprays) of fluticasone propionate spray into each nostril for 10 weeks. On the contrary, patients suffering CRS with polyposis received a 12-week course of twice daily use of 200 μg (six drops) of fluticasone propionate drops into each nostril. In addition, at 3 months three patients of CRS with polyposis were prescribed a 9-day course of oral prednisolone tablets, 30 mg for 3 days, 20 mg for 3 days and 10 mg for 3 days after failure of the above regimen to control their manifestations. After this, the use of intranasal corticosteroid preparations was tailored to the patient's clinical course, with most patients using them once daily.

Medical treatment after surgery. Following endoscopic sinus surgery, all patients were prescribed a 2-week course of twice-daily use of 500 mg erythromycin, DRS and alkaline nasal douche. This was followed by a 3-month course of twice-daily use of 100 μg (two sprays) of fluticasone propionate intranasal spray (FPANS), into each nostril and alkaline nasal douche. After this, the use of intranasal corticosteroid preparations was tailored to the patient's clinical course with most patients using FPANS daily.

Surgical treatment

Endoscopic sinus surgery was performed following the Messerklinger/Stammberger technique (40) under general anaesthesia. The extent of the procedure was tailored to the extent of sinus disease. A microdebrider was used in some cases of CRS with grade 2 and 3 polyposis. At the end of the procedure, a piece of Telfa was inserted into the ethmoidal cavity and taken out on the following day. Surgical steps were scored according to Lund and Mackay scoring system (38).

Statistical methods

Randomization was performed using random blocks with both patient and investigator unaware of the assignment at the time of randomization. A sample size of 66 patients was calculated to give 80% statistical power in detecting a 30% difference in VAS at the 5% significance level. Ninety individuals were recruited to allow for drop outs. The analysis was done using SPSS for windows version 9 statistics software package. Data were expressed as mean ± SD. P-values < 0.05 were considered significant. Parametric tests such as paired t-test and two-sample t-test were applied for data that followed or were transformed to a normal distribution. Logarithmic transformation was performed to normalize the distribution of NO change data so as to allow the use of parametric tests. Non-parametric tests were applied for ordinal categorized data such as CT scores, polyp grades, surgical and endoscopic scores. Use of individual tests is indicated in the Results section.

Results

Baseline data

No statistical significant difference between the medical and surgical groups was found in the baseline data of any of the following parameters: demographic characteristics, VAS, saccharin clearance time (SCT), NO, nasal volume and endoscopic score. NO readings were obtained in all subjects with a coefficient of variation of < 6%.

NO and CT score

Baseline absolute NO levels correlated significantly with CT scores ($P < 0.001$). The correlation coefficient was −0.483 (Kendall's tau-b). Furthermore, CT scores were categorized into three grades according to severity: grade 1 (0–4), grade 2 (5–8) and grade 3 (9–12). The mean NO levels for the three grades were 537 ± 202, 362 ± 188 and 165 ± 151 ppb, respectively. The differences in baseline NO amongst the groups were statistically significant ($P < 0.001$, Kruskal–Wallis test). The differences between the individual groups were statistically significant as well ($P < 0.001$, Mann–Whitney test).

Treatment effects

Both medical and surgical treatment of CRS significantly improved almost all the subjective and objective parameters of CRS ($P < 0.01$), with no significant differences between the therapies other than total nasal volume, which

Table 1. Changes and significance of absolute values of nasal NO in the medical and surgical groups

Group	Baseline total nasal NO mean (ppb) SD]	6-month total nasal NO [mean (ppb) SD]	Paired *t*-test (*P*-value)	12-month total nasal NO [mean (ppb) SD]	Paired *t*-test (*P*-value)
Surgical group					
CRS	724 ± 486 ($n = 44$)	1137 ± 547 ($n = 42$)	<0.001	1173 ± 524 ($n = 40$)	<0.001
CRS without polyposis	918 ± 477 ($n = 25$)	1277 ± 511 ($n = 23$)	<0.001	1336 ± 437 ($n = 21$)	<0.001
CRS with polyposis	468 ± 373 ($n = 19$)	969 ± 553 ($n = 19$)	<0.001	994 ± 564 ($n = 19$)	<0.001
Medical group					
CRS	773 ± 426 ($n = 45$)	1129 ± 496 ($n = 41$)	<0.001	1240 ± 531 ($n = 38$)	<0.001
CRS without polyposis	976 ± 350 ($n = 29$)	1266 ± 417 ($n = 26$)	<0.001	1334 ± 460 ($n = 25$)	<0.001
CRS with polyposis	405 ± 283 ($n = 16$)	892 ± 545 ($n = 15$)	<0.001	1058 ± 625 ($n = 13$)	<0.001

demonstrated greater increases following surgery ($P < 0.01$) (36).

Change in nasal nitric oxide levels. In the 6 and 12-month settings, NO increased significantly when compared with the baseline levels ($P < 0.01$). The mean improvement percentages from the baseline were consistently higher in the surgical groups. However, the differences between the surgical and medical groups did not reach statistical significance ($P > 0.05$). The differences between the 6 and 12-month absolute levels were statistically insignificant in all groups ($P > 0.05$) except for the medical group of CRS with polyposis ($P < 0.01$) where levels continued to rise. Table 1 illustrates changes and significance of absolute mean nNO in the medical and surgical groups.

NO and SCT. Because of the inability to detect intranasally administered saccharin, 17 and 21 patients were excluded from the 6 and 12-month analysis, respectively. Only one patient showed inability to taste saccharine. Changes in NO when logarithmically transformed correlated significantly with SCT changes ($P < 0.001$). The Correlation coefficients were −0.676 (Kendall's tau-b) in the 6 and −0.693 (Kendall's tau-b) in the 12-month measurements.

Figure 3 demonstrates the negative correlation between the changes in NO and SCT, the equation of simple linear regression and the R^2 values. The equations of simple linear regression were:

$$\text{6-month SCT improvement (expressed in folds of the baseline)} = 0.92 + [-0.94 \times \text{Log 6-month NO improvement (expressed in folds of the baseline)}].$$

$$\text{12-month SCT improvement(expressed in folds of the baseline)} = 0.92 + [-0.96 \times \text{Log 12-month NO improvement (expressed in folds of the baseline)}].$$

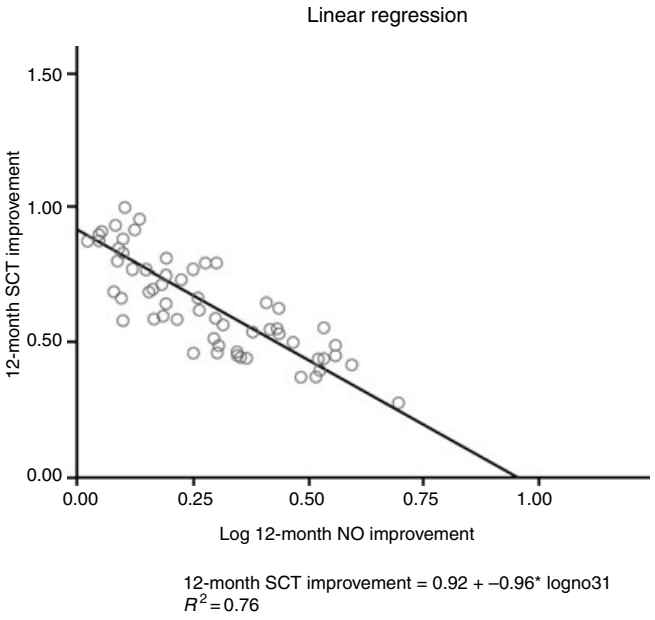

Figure 3. Correlation between 12-month logarithmically transformed NO and SCT changes.

NO and VAS. Percentage changes in NO levels correlated significantly ($P < 0.001$) with percentage changes in VAS. The correlation coefficients were −0.298 (Kendall's tau-b) for the 6-month measurements and −0.362 (Kendall's tau-b) for the 12-month measurements. NO changes also correlated significantly with all individual symptom scores ($P < 0.01$) except pain and headache ($P > 0.05$). The sensitivity of NO measurements to detect any change in VAS was 98.6%, whereas the specificity was 81.8% for the 6-month results. On the contrary, the sensitivity and the specificity in the 12-month setting were 98.6% and 88.9%, respectively.

Nitric oxide and endoscopic score (Fig. 4). NO percentage improvement changes correlated significantly ($P < 0.001$) with endoscopic score changes. The correlation coefficients were −0.368 (Kendall's tau-b) for the 6-month and −0.317 (Kendall's tau-b) for the 12-month measurements. The endoscopic score changes were

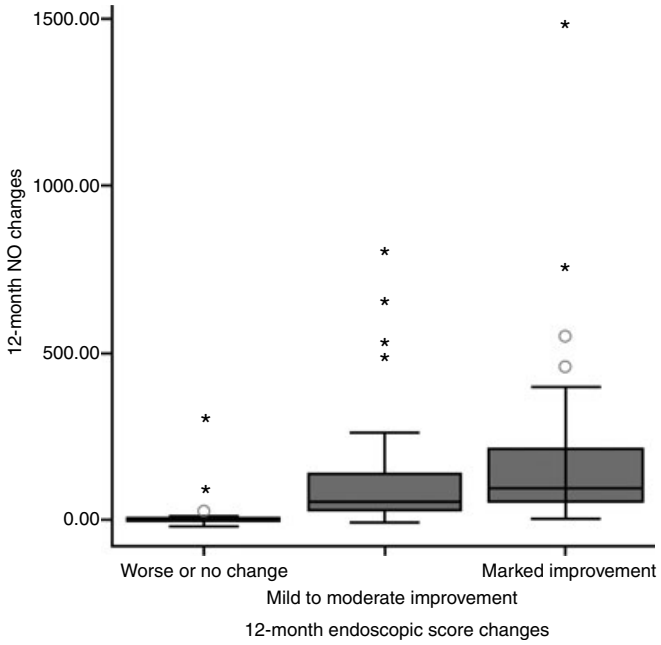

Figure 4. Relationship between the 12-month percentage changes in NO (ppb) and endoscopic score changes.

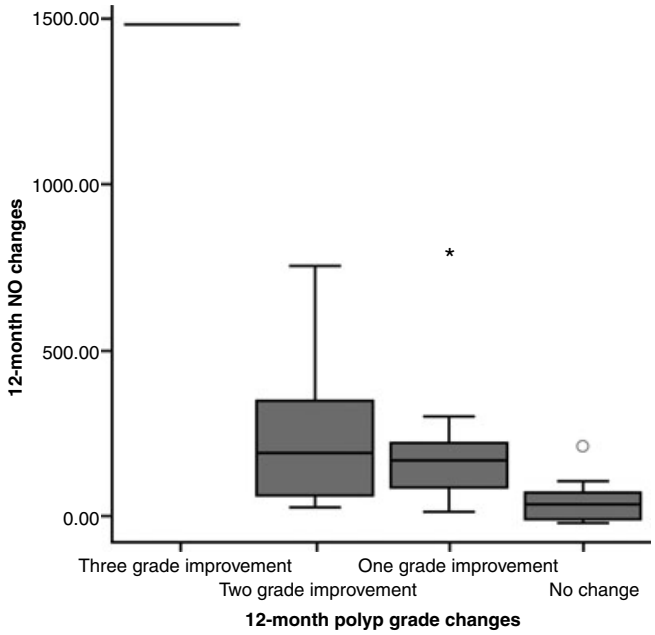

Figure 5. Relationship between the 12-month percentage changes in NO (ppb) and polyp grade changes.

recoded into three categories: worse or no change (0–50%), mild to moderate improvement (−1 to −70%) and marked improvement (−71 to −100%).

The mean percentage NO changes for the three groups were -7 ± 22, 95 ± 123 and 175 ± 225 for the 6-month and 13 ± 16, 107 ± 140 and 168 ± 219 for the 12-month measurements, respectively. The differences in NO changes amongst the groups were statistically significant ($P < 0.01$, Kruskal–Wallis test). The differences in NO changes between each two groups were statistically significant ($P < 0.01$, Mann–Whitney test).

NO and nasal polyposis. Nitric oxide percentage changes correlated significantly with the 6-month ($P < 0.05$) and 12-month ($P < 0.01$) polyp grade changes for the 6-month and for the 12-month changes) (Fig. 5). The correlation coefficients were −0.209 and −0.292 (Kendall's tau-b), respectively. The differences in NO changes amongst the groups were statistically significant ($P < 0.05$, Kruskal–Wallis test). The differences in NO changes between the individual groups did not reach statistical significance ($P > 0.05$, Mann–Whitney test) except when the no change group was included in one side of the equation.

NO and surgical score. Nitric oxide percentage changes correlated significantly with surgical score ($P < 0.01$). The correlation coefficients were 0.291 (Kendall's tau-b) and 0.265 (Kendall's tau-b) for the 6 and 12-month measurements, respectively. According to the surgical score, patients were divided into two groups: group 1 (score 0–4) and group 2 (score 5–7). The difference in NO changes between the two groups was statistically significant ($P < 0.01$, Mann–Whitney test) with the more severely affected patients demonstrating greater percentage improvement.

NO and other factors. No statistical correlation was found between percentage NO changes and age, sex, smoking or atopic status, although there was a tendency for greater NO increases in males, smokers and atopics ($P > 0.05$, Pearson's test).

Discussion

Nitric oxide gas is a mediator widespread in the body. It is continuously secreted in the upper airways, in contrast to the lower airways where NO levels are low unless inflammation occurs. In the upper airways, the human paranasal sinuses are the major source of NO production that floods through sinus ostia and makes a large contribution to the levels of NO found in the nasal cavity (1). There is also a smaller contribution from the nasal mucosa, upregulated via iNOS during inflammation (2).

Patency of sinus ostia is thought to play a pivotal role in maintaining normal sinus physiology with its disruption leading to the development of CRS. Lindberg et al. (32) showed that patients with CRS had lower nNO levels than healthy controls. Colantonio et al. (20) reported that NO levels were reduced corresponding to the grade of nasal polyposis and that they rose on therapy. Therefore,

in this prospective study of treatment of CRS, we investigated the value of nNO as an objective indicator of the effect of therapy.

We found that initial nNO levels were proportional to the degree of sinus involvement with an inverse correlation between nNO levels and the extent of sinus disease as documented by CT scans, endoscopic score and polyp grades in accordance with Arnal et al. (21) who reported that nNO levels were inversely correlated with the extent of sinus pacification on CT scans in patients with CRS with polyposis.

Nasal NO increased significantly with medical and surgical treatment of CRS. Theoretically, nNO levels have been postulated to depend mainly on the amount of NO produced by the ciliated epithelium of the paranasal sinuses and the size of the paranasal sinus ostia (32). The results of this study fit well with this theoretical explanation, as it could be anticipated that treatment of CRS resulted in recovery of the ciliated epithelium of the paranasal sinuses, which regained its normal ability to express iNOS and produce NO that passed through the sinus ostia and increased nNO levels. The higher levels of nNO improvement in the surgical rather than in the medical groups may reflect the role of the paranasal sinus ostial size. However, failure to show any significant difference between the surgical and medical groups demonstrates that the condition of the ciliated epithelium of the paranasal sinuses is probably more relevant than the actual size of the paranasal sinus ostia. Postoperative sinus CT scans are considered unethical due to hazards of radiation, it would seem possible that nNO measurement could serve as an excellent alternative to sinus CT scans.

Attempts at documentation of the impact of therapy in CRS have failed to produce a single objective measurement of choice. Many authors have speculated that nNO might provide such a genuine objective test to quantify the results of different treatments for CRS.

However, this has not been proven. In the present study, percentage nNO changes correlated inversely ($P < 0.001$) with symptom score changes, with excellent sensitivity (98.6%) and specificity (88.9%).

Studies in animals (13) and healthy human sinus mucosa (14, 41) have indicated NO to be a regulator of mucociliary activity in the upper respiratory tract. Arnal et al. (21) reported that patients with Kartagener's syndrome had very low nNO levels, despite the presence of patent paranasal sinuses on CT scans. Lindberg et al. (42) studied a cohort of 12 patients reporting that low levels of nNO correlated with impaired mucociliary activity. In the present study, the correlation between the dynamic changes in nNO and SCT as a result of therapy for CRS were studied in the 73 and 69 patients who detected saccharine in the 6 and 12-month settings, respectively. Nasal NO changes strongly correlated with SCT changes providing support to the previous studies that nNO levels reflect the state of sinonasal mucociliary function. The *in vivo* SCT was preferred to the *in vitro* ciliary beat frequency (CBF), as it would seem more appropriate to study both mucociliary activity and nNO in the same environment and SCT measures the whole mucociliary system, whereas CBF looks only at ciliary activity. The more or less fixed equations of simple linear regression in the 6 and 12-month settings reflect the accuracy of SCT measurements in the present study.

Finally, NO changes bore no relationship to any of the following parameters: age, sex, smoking, skin prick test positivity, grass pollen sensitivity and family history of allergy. Arnal et al. (21) reported that allergic patients with polyposis had a significantly higher nNO levels than non-allergic patients with polyposis. Failure of the present study to show a significant difference between allergic and non-allergic patients may be related to the efficacy of intranasal corticosteroids to control the upregulation of iNOS. Studies in both adults (25) and children (43) showed that topical nasal glucocorticoids significantly lowered the elevated nNO levels in patients with seasonal and perennial allergic rhinitis.

Conclusion

Nasal NO is a valuable objective measurement in monitoring medical and surgical therapy for CRS, when nasal corticosteroids are employed to reduce NO production by nasal mucosa. Nasal NO levels increase with treatment of CRS. The correlation between nNO changes and the patient's own perception of clinical improvement has excellent sensitivity and specificity. However, in the clinical application of nNO measurement in monitoring CRS therapy, it seems more useful if the pretreatment NO level of each patient serves as his own control, as there is a wide variation of nNO values in the normal population, with overlap between normal subjects and CRS patients. The high correlation between nNO changes and SCT changes strongly suggests potential use of NO in diagnosis and even in therapy of diseases affecting sinonasal mucociliary function. Finally, NO measurement is non-invasive, quick and easy, even in children. The chemiluminescence analysers are sensitive, accurate and reproducible. However, they are still expensive and this limits the application of NO in daily clinical practice.

Acknowledgment

This study was part of a doctoral thesis awarded to Sameh M. Ragab at the University of London, 2003.

References

1. Lundberg JO, Rinder J, Weitzberg E, Lundberg JM, Alving K. Nasally exhaled nitric oxide in humans originates mainly in the paranasal sinuses. Acta Physiol Scand 1994;**152**:431–432.
2. Lundberg JO, Farkas-Szallasi T, Weitzberg E, Rinder J, Lidholm J, Anggaard A et al. High nitric oxide production in human paranasal sinuses. Nat Med 1995;**1**:370–373.
3. Gaston B, Reilly J, Drazen JM, Fackler J, Ramdev P, Arnelle D et al. Endogenous nitrogen oxides and bronchodilator *S*-nitrosothiols in human airways. Proc Natl Acad Sci U S A 1993;**90**:10957–10961.
4. Liu SF, Crawley DE, Barnes PJ, Evans TW. Endothelium-derived relaxing factor inhibits hypoxic pulmonary vasoconstriction in rats. Am Rev Respir Dis 1991;**143**:32–37.
5. Martinez C, Cases E, Vila JM, Aldasoro M, Medina P, Marco V et al. Influence of endothelial nitric oxide on neurogenic contraction of human pulmonary arteries. Eur Respir J 1995;**8**:1328–1332.
6. Bai TR, Bramley AM. Effect of an inhibitor of nitric oxide synthase on neural relaxation of human bronchi. Am J Physiol 1993;**264**(5 Pt 1): L425–L430.
7. Belvisi MG, Stretton CD, Miura M, Verleden GM, Tadjkarimi S, Yacoub MH et al. Inhibitory NANC nerves in human tracheal smooth muscle: a quest for the neurotransmitter. J Appl Physiol 1992;**73**:2505–2510.
8. Wei XQ, Charles IG, Smith A, Ure J, Feng GJ, Huang FP et al. Altered immune responses in mice lacking inducible nitric oxide synthase. Nature 1995;**375**:408–411.
9. Laubach VE, Shesely EG, Smithies O, Sherman PA. Mice lacking inducible nitric oxide synthase are not resistant to lipopolysaccharide-induced death. Proc Natl Acad Sci U S A 1995;**92**:10688–10692.
10. Xie K, Fidler IJ. Therapy of cancer metastasis by activation of the inducible nitric oxide synthase. Cancer Metastasis Rev 1998;**17**:55–75.
11. Lala PK. Significance of nitric oxide in carcinogenesis, tumor progression and cancer therapy. Cancer Metastasis Rev 1998;**17**:1–6.
12. Jain B, Rubinstein I, Robbins RA, Leise KL, Sisson JH. Modulation of airway epithelial cell ciliary beat frequency by nitric oxide. Biochem Biophys Res Commun 1993;**191**:83–88.
13. Runer T, Cervin A, Lindberg S, Uddman R. Nitric oxide is a regulator of mucociliary activity in the upper respiratory tract. Otolaryngol Head Neck Surg 1998;**119**:278–287.
14. Runer T, Lindberg S. Effects of nitric oxide on blood flow and mucociliary activity in the human nose. Ann Otol Rhinol Laryngol 1998;**107**:40–46.
15. Gerlach H, Rossaint R, Pappert D, Falke KJ. Time-course and dose-response of nitric oxide inhalation for systemic oxygenation and pulmonary hypertension in patients with adult respiratory distress syndrome. Eur J Clin Invest 1993;**23**:499–502.
16. Puybasset L, Rouby JJ, Mourgeon E, Stewart TE, Cluzel P, Arthaud M et al. Inhaled nitric oxide in acute respiratory failure: dose-response curves. Intensive Care Med 1994;**20**:319–327.
17. Beckman JS, Beckman TW, Chen J, Marshall PA, Freeman BA. Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide. Proc Natl Acad Sci U S A 1990;**87**:1620–1624.
18. Rubbo H, Radi R, Trujillo M, Telleri R, Kalyanaraman B, Barnes S et al. Nitric oxide regulation of superoxide and peroxynitrite-dependent lipid peroxidation. Formation of novel nitrogen-containing oxidized lipid derivatives. J Biol Chem 1994;**269**:26066–26075.
19. Baraldi E, Azzolin NM, Biban P, Zacchello F. Effect of antibiotic therapy on nasal nitric oxide concentration in children with acute sinusitis. Am J Respir Crit Care Med 1997;**155**:1680–1683.
20. Colantonio D, Brouillette L, Parikh A, Scadding GK. Paradoxical low nasal nitric oxide in nasal polyposis. Clin Exp Allergy 2002;**32**:698–701.
21. Arnal JF, Flores P, Rami J, Murris-Espin M, Bremont F, Pasto IA et al. Nasal nitric oxide concentration in paranasal sinus inflammatory diseases. Eur Respir J 1999;**13**:307–312.
22. Lundberg JO, Weitzberg E, Nordvall SL, Kuylenstierna R, Lundberg JM, Alving K. Primarily nasal origin of exhaled nitric oxide and absence in Kartagener's syndrome. Eur Respir J 1994;**7**:1501–1504.
23. Balfour-Lynn IM, Laverty A, Dinwiddie R. Reduced upper airway nitric oxide in cystic fibrosis. Arch Dis Child 1996;**75**:319–322.
24. Dotsch J, Demirakca S, Terbrack HG, Huls G, Rascher W, Kuhl PG. Airway nitric oxide in asthmatic children and patients with cystic fibrosis. Eur Respir J 1996;**9**:2537–2540.
25. Kharitonov SA, Rajakulasingam K, O'Connor B, Durham SR, Barnes PJ. Nasal nitric oxide is increased in patients with asthma and allergic rhinitis and may be modulated by nasal glucocorticoids. J Allergy Clin Immunol 1997;**99**(1 Pt 1): 58–64.
26. Martin U, Bryden K, Devoy M, Howarth P. Increased levels of exhaled nitric oxide during nasal and oral breathing in subjects with seasonal rhinitis. J Allergy Clin Immunol 1996;**97**:768–772.
27. Arnal JF, Didier A, Rami J, M'Rini C, Charlet JP, Serrano E et al. Nasal nitric oxide is increased in allergic rhinitis. Clin Exp Allergy 1997;**27**:358–362.
28. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. Increased nitric oxide in exhaled air of asthmatic patients. Lancet 1994;**343**:133–135.
29. Persson MG, Zetterstrom O, Agrenius V, Ihre E, Gustafsson LE. Single-breath nitric oxide measurements in asthmatic patients and smokers. Lancet 1994;**343**:146–147.
30. Massaro AF, Gaston B, Kita D, Fanta C, Stamler JS, Drazen JM. Expired nitric oxide levels during treatment of acute asthma. Am J Respir Crit Care Med 1995;**152**:800–803.
31. Saleh D, Ernst P, Lim S, Barnes PJ, Giaid A. Increased formation of the potent oxidant peroxynitrite in the airways of asthmatic patients is associated with induction of nitric oxide synthase: effect of inhaled glucocorticoid. FASEB J 1998;**12**:929–937.
32. Lindberg S, Cervin A, Runer T. Nitric oxide (NO) production in the upper airways is decreased in chronic sinusitis. Acta Otolaryngol 1997;**117**:113–117.
33. Warke TJ, Mairs V, Fitch PS, McGovern V, Ennis M, Shields MD. Exhaled nitric oxide in relation to the clinical features of childhood asthma. J Asthma 2004;**41**:751–757.
34. Berkman N, Avital A, Breuer R, Bardach E, Springer C, Godfrey S. Exhaled nitric oxide in the diagnosis of asthma: comparison with bronchial provocation tests. Thorax 2005;**60**:383–388.

35. Warke TJ, Fitch PS, Brown V, Taylor R, Lyons JD, Ennis M et al. Exhaled nitric oxide correlates with airway eosinophils in childhood asthma. Thorax 2002;**57**:383–387.
36. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. Laryngoscope 2004;**114**:923–930.
37. Lund VJ, Kennedy DW. Quantification for staging sinusitis. Ann Otol Rhinol Laryngol Suppl 1995;**167**:17–21.
38. Lund VJ, Mackay IS. Staging in rhinosinusitus. Rhinology 1993;**31**:183–184.
39. Mackay IS, Lund VJ. Imaging and staging. In: Mygind N, Lildholdt T, editors. Nasal Polyposis. An Inflammatory Disease and Its Treatment. Copenhagen: Munksgaard, 1997:137–144.
40. Stammberger H. Surgical technique. In: Stammberger H, editor. Functional Endoscopic Sinus Surgery The Messerklinger Technique. Philadelphia, PA: B.C. Decker, **1991**:283–320.
41. Kim JW, Min YG, Rhee CS, Lee CH, Koh YY, Rhyoo C et al. Regulation of mucociliary motility by nitric oxide and expression of nitric oxide synthase in the human sinus epithelial cells. Laryngoscope 2001;**111**:246–250.
42. Lindberg S, Cervin A, Runer T. Low levels of nasal nitric oxide (NO) correlate to impaired mucociliary function in the upper airways. Acta Otolaryngol 1997;**117**:728–734.
43. Baraldi E, Azzolin NM, Carra S, Dario C, Marchesini L, Zacchello F. Effect of topical steroids on nasal nitric oxide production in children with perennial allergic rhinitis: a pilot study. Respir Med 1998;**92**:558–561.