

Nasal nitric oxide as a long-term monitoring and prognostic biomarker of mucosal health in chronic rhinosinusitis

Daniel J. Lee, MD , Jonathan Yip, MD, FRCSC and John M. Lee, MD, MSc, FRCSC 

Background: Nasal nitric oxide (nNO) is a potential biomarker of chronic rhinosinusitis (CRS), and correlates well with endoscopic and radiologic severity of disease. However, the long-term profile of nNO as a biomarker is not established in the literature. The objectives of our study were to examine whether nNO can maintain this correlation in a 5-year follow-up after endoscopic sinus surgery (ESS) and to investigate whether nNO value can be used to prognosticate revision rates in patients with CRS.

Methods: We enrolled CRS patients 5 years after initial ESS at our institution. Patients underwent initial ESS at our institution between January 2013 and January 2015. Patients prospectively had the following measurements at baseline, 1 month, 6 months, and 5 years post-ESS: nNO levels, Lund-Kennedy Endoscopy Score (LKES), and 22-item Sino-Nasal Outcome Test-22 (SNOT-22) score. We also compared the nNO levels between patients who underwent revision ESS and those who did not.

Results: There were 32 patients included in the study with 8 patients undergoing revision ESS during the 5-year

follow-up. nNO levels were elevated at 1 month, 6 months, and 5 years post-ESS compared to baseline. A significant negative correlation between nNO and LKES was found at 5 years post-ESS. nNO levels were significantly reduced at baseline and 6 months post-ESS in the revision cohort compared to the nonrevision cohort despite having comparable radiologic severity.

Conclusion: nNO may serve as a noninvasive long-term biomarker to monitor sinus disease severity and to prognosticate results in patients with CRS. This has implications for potential integration into clinical practice. © 2020 ARS-AAOA, LLC.

Key Words:

sinusitis; paranasal sinuses; nitric oxide; biomarker

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Nitric oxide (NO) is an endogenously produced gas within the respiratory tract and regulates numerous physiological processes including blood flow, neurotransmission, and host defense.¹⁻⁶ In the lower airway, exhaled

NO from the lungs is elevated in eosinophilic asthma and is used as a diagnostic and monitoring tool for airway inflammation at the time of diagnosis and during therapy.^{7,8} In the upper airway, nasal NO (nNO) has been shown to be produced constitutively by the mucosa of the paranasal sinuses via the actions of inducible NO synthase.^{9,10} Physiologically, the purpose of high levels of nNO within the paranasal sinuses is hypothesized to maintain its health and sterility, via mucociliary regulation, antimicrobial activity, airborne messaging, and modifications to the inflammatory cascade.⁹⁻¹²

Previous studies have shown a reduced level of nNO in patients with chronic rhinosinusitis (CRS), which correlated with endoscopic and radiological markers of disease severity.^{10,13-18} For this reason, many have raised a possibility of nNO as a diagnostic tool for CRS. In addition, a previous study from our group demonstrated the utility of nNO to monitor sinus mucosal health after endoscopic sinus surgery (ESS) for those who failed appropriate medical therapy.¹⁹ In specific, nNO was found to be reduced

Division of Rhinology, Department of Otolaryngology-Head & Neck Surgery, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

Correspondence to: John M. Lee MD, MSc, FRCSC, St. Michael's Hospital, 30 Bond Street, 8 Cardinal Carter Wing, Toronto, ON, M5B 1W8; e-mail: john.lee@unityhealth.to

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at baseline but increased significantly following ESS at 1-month and 6-month postoperative periods. This correlated well with endoscopy findings. Overall, nNO can be used as a valuable objective measurement of CRS to monitor sinus disease severity and response to therapy. However, the long-term profile of nNO as a biomarker for CRS has not been well established. In specific, it remains uncertain whether nNO can sustain this correlation on a long-term basis beyond the initial 1-year postoperative period. In addition, it is unclear whether nNO can potentially be used as a biomarker to predict whether patients would require revision surgery in the future.

Therefore, our primary objective was to determine whether nNO level can be used to monitor sinonasal mucosal health on a long-term basis after endoscopic sinus surgery (ESS). We also sought to identify whether nNO levels in the postoperative period could prognosticate the probability of revision surgery in a 5-year follow-up period.

Patients and methods

Study design and patient population

Approval of this study was granted by the Research Ethics Board at St. Michael's Hospital, Toronto, ON, Canada. We enrolled the patients from our previous prospective study,¹⁹ which consisted of a cohort of patients between January 2013 and January 2015 with a diagnosis of CRS with and without nasal polyposis (CRSwNP/CRSsNP). The diagnosis was made according to the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) Guidelines. The patients had previously failed appropriate medical therapy and underwent ESS by the senior author (J.M.L.) during the initial study timeline. Patients were contacted and reevaluated in the senior author's clinic between December 2018 and July 2019 for a 5-year follow-up. Patients were excluded if they had unilateral disease, or a concomitant diagnosis of cystic fibrosis, primary ciliary dyskinesia, or immune deficiency. Informed consent was obtained for all included patients.

ESS and postoperative protocol

The extent of initial and revision surgery was largely based on the extent of disease, but generally followed “full-house ESS” principles (bilateral maxillary antrostomy, total ethmoidectomy, sphenoidotomy and frontal sinusotomy—Draf IIa/b). Postoperatively, all patients were started on large-volume saline irrigations, 2 weeks of oral antibiotics, and a short course of oral steroids (the latter was only for CRSwNP). Thereafter, all patients were maintained on saline irrigations and nasal steroids. Adjuvant medical treatment during regularly scheduled follow-up visits was dictated by patient symptoms and endoscopy findings. Patients were consented for revision ESS if they developed increased frequency of exacerbations or significant worsening of symptoms (nasal congestion/obstruction, facial

pain/pressure, discharge, and hyposmia/anosmia) and objective findings on endoscopy or computed tomography (CT) despite maintaining on appropriate medical therapy, defined as 3 weeks of oral antibiotics, 12 days of oral steroids (for CRSwNP), and at least 3 months of large-volume saline irrigations and intranasal corticosteroids.

Outcome measures and data collection

Baseline characteristics were collected and included: age, gender, revision status, and the presence of asthma, environmental allergies, and aspirin-exacerbated respiratory disease (AERD). Revision status since the initial ESS at St. Michael's Hospital was also recorded. Primary outcome measure was nNO levels measured preoperatively and 1 month, 6 months, and 5 years postoperatively. nNO measurement was performed with a nasal NO analyzer (Eco Medics CLD 88sp NO Analyzer; Eco Physics Inc., Ann Arbor, MI) in accordance with the American Thoracic Society guidelines.⁸ Each nostril was measured independently at a fixed flow rate of 300 mL/minute while velum closure was achieved by forced exhalation against a high-expiratory resistor. nNO values were recorded after a steady-state plateau was achieved and the mean nNO was recorded as an average of both nares. nNO values are reported as parts per billion (ppb). Secondary clinical outcomes included the 22-item Sino-Nasal Outcome Test (SNOT-22) scores and the clinician-derived Lund-Kennedy Endoscopy Score (LKES) at each aforementioned time point. The surgeon performing the endoscopic examination was blinded to nNO measurements at each visit. Baseline CT scans were reviewed and scored with Lund-Mackay (LM) score.

Statistical analysis

Demographic and clinical characteristics were summarized descriptively by reporting the median and range or interquartile range (IQR) for continuous variables and the frequency and proportion for categorical variables. Differences in characteristics between 2 comparison groups were compared using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variables. The Friedman test and Dunn's multiple comparisons test were used for comparison of means at each time point. Pearson and Spearman correlations were used to examine potential relationships between nNO and the clinical parameters of LM score, SNOT-22, and LKES. For comparison of revision cohort vs nonrevision cohort, we elected to only include CRSwNP patients because no CRSsNP patients underwent revision surgery and do represent a distinct subtype of CRS compared to CRSwNP. Sensitivity analyses were performed with respect to comorbid asthma and AERD. All analyses were done using SPSS Statistics (IBM SPSS Statistics Version 20; IBM Corp., Armonk, NY) and statistical significance was set at an alpha level of 0.05.

TABLE 1. Baseline patient demographics

Characteristic	Total cohort (n = 32)	CRSwNP only		<i>p</i> ^a
		Revision (n = 8)	Nonrevision (n = 20)	
Age (years), mean (range)	55.8 (31–80)	54.1 (33–80)	57.2 (31–79)	0.62
Male, n (%)	17 (53.1)	4 (50.0)	12 (60.0)	0.63
CRSwNP, n (%)	28 (87.5)	Not applicable		
Asthma, n (%)	20 (62.5)	8 (100)	11 (55.0)	0.021
Environmental allergies, n (%)	18 (56.3)	5 (62.5)	11 (55.0)	0.72
AERD, n (%)	5 (15.6)	4 (50.0)	1 (5.0)	0.005
LM score, median (IQR)	18.0 (13.5–21.75)	19.5 (16.25–23.5)	18.5 (15.25–21.75)	0.63
Revision surgery, n (%)	25 (78.1)	Not applicable		
Revision since last study, n (%)	8 (25.0)			

^a Values of *p* are for comparison between revision and nonrevision groups. Statistically significant values of *p* are in bold.

CRSwNP = chronic rhinosinusitis with nasal polyposis; AERD = aspirin-exacerbated respiratory disease; IQR = interquartile range; LM = Lund-Mackay.

Results

Study population and baseline characteristics

Out of the original 39 patients, 32 patients (82.1%) completed the 5-year follow-up visits and measurements. Baseline characteristics are shown in Table 1. The mean age was 55.8 years (range, 31 to 80 years). Twenty-eight patients (87.5%) patients had CRSwNP; there were 20 patients with asthma (62.5%) and 5 patients with AERD (15.6%). Twenty-five patients (78.1%) had previously undergone sinus surgery prior to the initial consultation with the senior author (J.M.L.). These 25 patients had comparable baseline sinonasal characteristics compared to the 7 patients who did not have previous sinus surgery in terms of baseline nNO levels (362.25 [IQR, 85.55–638.68] vs 273.10 [IQR, 23.13–430.60], *p* = 0.73), SNOT-22 score (52.0 [IQR, 37.5–63.0] vs 49.0 [IQR, 25.0–80.0], *p* = 0.96), LKES (8.0 [IQR, 6.0–10.0] vs 8.0 [IQR, 5.0–10.0], *p* = 0.61), and LMS (18.0 [IQR, 13.0–22.0] vs 20.0 [IQR, 16.0–21.0], *p* = 0.70) at the time of initial consultation with the senior author (J.M.L.). Eight patients (25.0%) had undergone a revision sinus surgery within the 5-year follow-up period since the initial study.

Long-term nNO measurement in the total cohort

In the current cohort, there remained the previously observed significant improvement from baseline (343.93 ppb [IQR, 83.63–604.61]) to 1 month post-ESS (612.1 ppb [IQR, 389.49–904.65]) and 6 months post-ESS (563.25 ppb [IQR, 244.58–1077.98] (*p* < 0.001 for both). In addition, nNO remained elevated at the 5-year mark (656.925 ppb [IQR, 339.71–802.65]) compared to the baseline (*p* < 0.001). However, there was no difference in nNO levels among the 1-month, 6-month, and 5-year postoperative periods. The trend is depicted in Figure 1 and Table 2.

Similar to our previous study, CRSwNP had lower baseline nNO levels than CRSsNP (269.23 ppb [IQR, 57.55–448.77] vs 732.75 ppb [IQR, 576.54–955.19], *p* < 0.001). Although patients with CRSwNP had significant improvement from baseline to 1 month, 6 months, and 5 years post-operation, patients with CRSsNP demonstrated no change from baseline to any postoperative periods. The trend is depicted in Supporting Table 1. We also performed a sensitivity analysis with respect to comorbid asthma and AERD for patients with CRSwNP. There was no statistical difference among CRSwNP without asthma or AERD, CRSwNP with asthma, and AERD patients (Supporting Table 2).

Long-term clinical outcomes (SNOT-22 and LKES) and relationships among measurements in the total cohort

All patients showed significant improvement in SNOT-22 from baseline (52 [IQR, 34.5–64.5]) to 1 month post-ESS (19.5 [IQR, 9.5–33.0]) and 6 months post-ESS (23.0 [IQR, 11.5–34.5]). However, there was no difference between

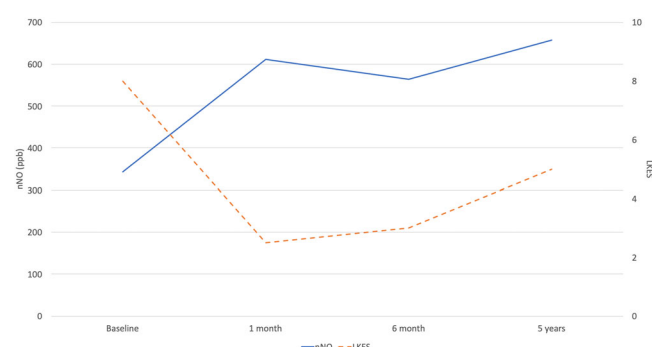


FIGURE 1. Line graph of nNO level and LKES scores following ESS in the total cohort. ESS = endoscopic sinus surgery; LKES = Lund-Kennedy Endoscopy Score; nNO = nasal nitric oxide; ppb = parts per billion.

TABLE 2. nNO levels, SNOT-22, and LKES in the total cohort (n = 32)

Parameter	Baseline	1 month	6 months	5 years
nNO levels (ppb)	343.93 (83.63–604.61)	612.10 (389.49–904.65)	563.25 (244.58–1077.98)	656.93 (339.71–802.65)
SNOT-22	52.0 (34.5–64.5)	19.5 (9.5–33.0)	23.0 (11.5–34.5)	36.0 (14.0–49.5)
LKES	8.0 (6.0–10.0)	2.5 (1.0–6.0)	3.0 (1.0–6.0)	5.0 (2.0–8.0)

*All values are median (IQR).

IQR = interquartile range; LKES = Lund-Kennedy Endoscopy Score; nNO = nasal nitric oxide; SNOT-22 = 22-item Sino-Nasal Outcome Test.

baseline and 5 years post-ESS (36.0 [IQR, 14.0–49.5], $p = 0.060$). The LKES improved from baseline (8 [IQR, 6.0–10.0]) to 1 month post-ESS (2.5 [IQR, 1.0–6.0]), 6 months post-ESS (3.0 [IQR, 1.0–6.0]), and 5 years post-ESS (5.0 [IQR, 2.0–8.0]). There were no differences among all the post-ESS SNOT-22 and LKES values.

Our previous study showed a negative correlation between nNO and LKES in the CRSwNP group at 1 month and 6 months post-ESS but no correlation between nNO and SNOT-22. Similarly, there was a negative correlation between nNO and LKES at 5 years post-ESS ($r = -0.775$, $p < 0.001$) follow-up (Fig. 2) but no correlation between nNO and SNOT-22 at 5 years post ESS ($r = -0.301$, $p = 0.13$).

Revision cohort vs nonrevision cohort

In total, there were 8 patients who underwent revision ESS during the 5-year duration. Mean time to revision surgery was 3.3 years (range, 1.59–4.96 years). Mean time from the revision surgery to data collection at the 5-year mark was 1.7 years (range, 0.57–3.1 years). All 8 patients had CRSwNP and therefore we compared this group against those with CRSwNP who did not undergo revision surgery. Baseline characteristics are shown in Table 1. In the revision group, there were higher proportions of asthma and AERD patients ($p = 0.021$, $p = 0.005$, respectively). Baseline LM score was not different between the groups.

The trend of nNO levels in the revision group compared to the nonrevision group is depicted in Table 3 and Figure 3. The revision group had significantly lower nNO

level at baseline compared to the nonrevision group (52.42 ppb [IQR, 1.73–103.58] vs 379.00 ppb [IQR, 199.33–466.66], $p = 0.009$). Although there was no difference between the 2 groups at 1 month post-ESS (409.83 ppb [IQR, 217.99–582.63] vs 658.2 ppb [IQR, 334.63–944.14], $p = 0.067$), there was a significantly lower nNO level in the revision group at 6 months post-ESS (135.9 ppb [IQR, 61.70–712.80] vs 721.2 ppb [IQR, 312.62–1199.30], $p = 0.016$). There was no difference between the groups at 5 years post-ESS (273.93 ppb [IQR, 91.21–767.41] vs 656.93 ppb [IQR, 419.29–764.5], $p = 0.067$). In the nonrevision cohort, nNO levels showed significant improvement from baseline to 1 month, 6 months, and 5 years post-ESS ($p < 0.05$ for all). However, in the revision cohort, although there was improvement from baseline to 1 month post-ESS there was no difference between baseline and 6 months post-ESS or baseline and 5 years post-ESS.

Due to a higher proportion of AERD patients in the revision cohort, we elected to perform a subgroup analysis within the revision cohort to assess the nNO levels in AERD patients compared to non-AERD subjects (Table 4). At baseline, there was no difference in LM score (21 [IQR, 16.5–24] in AERD vs 19 [IQR, 12–21.75] in non-AERD, $p = 0.38$). There was no difference in nNO levels between AERD and non-AERD patients in the revision cohort at baseline, 1 month, 6 months, and 5 years post-ESS. However, it is important to note that there were only 4 patients in each group, likely limiting our statistical power in this subgroup analysis.

Discussion

To our knowledge, this is the first study to investigate nNO levels in patients with CRS on a long-term basis beyond the initial postoperative period of 1 year. In the current study, we showed that the improvement of nNO levels from baseline to 1 month and 6 months post-ESS was sustained at 5-year follow-up. There remains a significant negative correlation between nNO and endoscopy scores at 5-year follow-up visits. Similar to our previous study, there was no correlation between nNO levels and SNOT-22 scores. In addition, with the limits of small sample size, SNOT-22 scores were no different between the revision and no revision cohort at various time points. This is not surprising because multiple studies have demonstrated conflicting evidence with regard to correlation between patient-reported

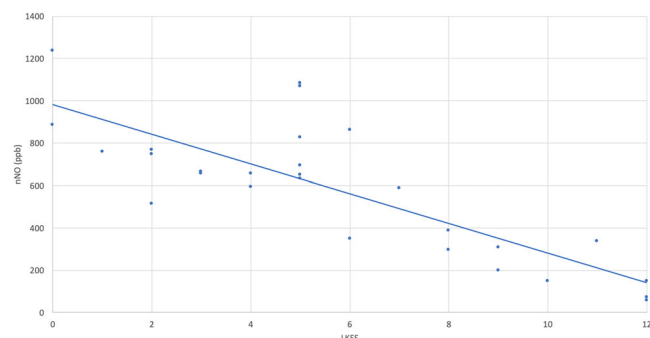


FIGURE 2. Plot of nNO vs LKES at 5 years post-ESS. ESS = endoscopic sinus surgery; LKES = Lund-Kennedy Endoscopy Score; nNO = nasal nitric oxide.

TABLE 3. Revision vs no revision cohort among CRSwNP patients (n = 28)*

Parameter	Baseline	1 month	6 months	5 years
nNO levels (ppb)				
Revision, median (IQR) (n = 8)	52.42 (1.73–103.58)	409.83 (217.99–582.63)	135.90 (61.70–712.8)	273.93 (91.21–767.41)
No revision, median (IQR) (n = 20)	378.98 (199.33–466.66)	658.20 (334.63–944.14)	721.20 (312.62–1199.30)	656.93 (419.29–764.50)
<i>p</i>	0.009	0.067	0.016	0.067
LKES				
Revision, median (IQR) (n = 8)	10.0 (8.5–11.5)	6.0 (4.25–6.0)	6.0 (2.0–8.0)	8.0 (6.0–11.5)
No revision, median (IQR) (n = 20)	8.0 (6.25–8.0)	2.0 (1.0–5.75)	3.0 (1.0–6.0)	4.5 (2.0–7.25)
<i>p</i>	0.028	0.034	0.135	0.008
SNOT-22				
Revision, median (IQR) (n = 8)	44.0 (28.25–55.25)	20.0 (14.0–28.5)	25.0 (13.0–31.0)	36.0 (18.0–43.0)
No revision, median (IQR) (n = 20)	57.5 (41.0–77.5)	10.5 (5.0–43.0)	37.0 (11.0–44.0)	43.0 (8.25–63.75)
<i>p</i>	0.067	0.415	0.583	0.690

*Statistically significant *p* values are in bold.

CRSwNP = chronic rhinosinusitis with nasal polyposis; IQR = interquartile range; LKES = Lund-Kennedy Endoscopy Score; nNO = nasal nitric oxide; ppb = parts per billion; SNOT-22 = 22-item Sino-Nasal Outcome Test.

symptoms and objective measures.^{20–23} Overall, this indicates that nNO can be a good long-term objective marker of sinonasal mucosal health in CRS patients who had failed appropriate medical therapy and undergone ESS.

Another distinctive finding in our study is the significantly reduced nNO levels at baseline and 6 months in those who required revision ESS compared to those who did not, despite having similar baseline CT scores. Thus, nNO levels may reflect the level of disordered mucosa and inflammation, which may not be completely captured by the CT scans. In other words, those who underwent revision likely had a higher initial inflammatory load, leading to recalcitrant disease and subsequent revision procedures in this group.²⁴ A recent study demonstrated decreased nNO levels in eosinophilic CRS compared to non-eosinophilic CRS.²⁵ Considering that the entire revision surgery group had concomitant asthma, with 50% having AERD, it can

be postulated that this patient population had a significantly higher load of eosinophilic inflammation in the nasal mucosa, leading to lower nNO levels with a T helper 2 (Th2)-polarized inflammatory environment. Therefore, significantly low nNO levels at baseline and at 6 months post-ESS may have a prognostic value by indicating high inflammatory load with a higher likelihood of needing revision surgery.

Although the exact pathophysiology of nNO in CRS remains unclear, studies have shown that a reduction of tissue plasminogen (t-PA) in the setting of Th2 inflammation, which in turn would promote abnormal fibrin deposition with nasal polyposis and reduce nNO production through t-PA/low-density-lipoprotein receptor-related protein-1 pathway.^{26,27} Another hypothesis is that the decreased level of nNO may contribute to the pathogenesis of CRS, because nNO regulates local host defense and ciliary motility.^{4,11} Whether a mediator or a marker of sinonasal inflammation, nNO is an attractive candidate as a noninvasive physiological biomarker for CRS, because an ideal biomarker would be easy to obtain with reasonable expense and minimal patient discomfort and should be reliable in discriminating pathological from normal disease. The implication would be that nNO could potentially be used to monitor disease progression in CRSwNP, helping the surgeon prognosticate long-term sinus health. In our study, the lower levels of nNO at 6 months post-sinus surgery could serve as a keystone biomarker to determine the trajectory of patient outcomes following ESS. This may be invaluable for both managing patient expectations and also potentially for initiating new adjuvant treatments (ie, biologics) following surgery. With respect to CRSsNP, although there was only a small number of CRSsNP

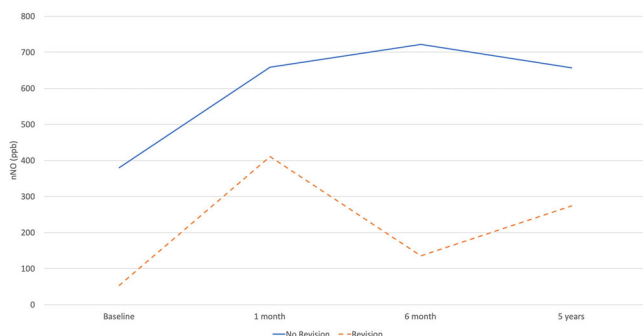


FIGURE 3. Line graph of nNO levels between revision and non-revision group among CRSwNP patients. CRSwNP = chronic rhinosinusitis with nasal polyposis; nNO = nasal nitric oxide; ppb = parts per billion.

TABLE 4. Comparison of AERD with non-AERD patients within the revision cohort

Parameter	nNO levels (ppb)			
	Baseline	1 month	6 month	5 years
AERD, median (IQR) (n = 4)	11.79 (0.11–67.06)	291.98 (80.65–443.93)	61.70 (49.85–61.70)	110.58 (60.56–477.68)
No AERD, median (IQR) (n = 4)	98.85 (26.51–650.70)	511.925 (389.48–793.44)	474.15 (119.32–953.66)	587.68 (236.96–852.48)
<i>p</i> ^a	0.083	0.25	0.077	0.083

^aStatistically significant *p* values are in bold.

AERD = aspirin-exacerbated respiratory disease; IQR = interquartile range; nNO = nasal nitric oxide; ppb = parts per billion.

patients in our study, the results show that nNO does not change in the postoperative period up to 5 years compared to baseline values in CRSsNP. This observation again shows that there is no evidence suggesting that ESS leads to liberation of nNO. Overall, our study shows a promising potential of nNO as a noninvasive biomarker that may aid in clinical decision making with respect to managing patient expectations, determining prognosis, and deciding on new adjuvant treatments. However, further work is needed to establish baseline nNO levels with standardized protocol, cost effectiveness, and potentially explore its role in investigating and managing the different endotypes of CRS.

There are limitations in the current study. First, the cohort is skewed toward CRSwNP and has a high proportion of patients with concomitant asthma. This is a function of our tertiary care practice. With advancement in medical knowledge over the 5 years, we recognize that there may have been a change in asthma management and this may contribute to confounding results. However, it is important to note that there was no difference in nNO levels for CRSwNP patients with asthma and those without. In addition, in our subgroup analyses, we are limited by the sample size and may be underpowered. Although there was a trend toward lower nNO values in AERD patients, we were unable to detect a significant difference in nNO between AERD and non-AERD patients. Also, this may have contributed to detecting nonsignificant changes in SNOT-22 from baseline to 5 years. Furthermore, we recognize the postoperative regimen was not standardized because these were modified

based on clinical parameters during the follow-up visit. We acknowledge that this may have confounded the study results. Last, because of the nature of the senior author's practice, a large number of patients had ESS at outside institutions. Although this may have affected the results of the study, we report in the results section that there was no difference between those who had previous surgery at an outside institution and those who did not in terms of baseline nNO levels, LKES, LMS, or SNOT-22 scores.

Conclusion

nNO may serve as a noninvasive long-term biomarker that may aid in monitoring and prognostication of CRSwNP. nNO correlated well with sinus mucosal health at 5 years post-ESS. In addition to correlating well with sinus mucosal health, nNO levels were significantly lower at baseline and also at 6 months postsurgery in patients who ultimately required revision ESS. Further work is needed to establish whether there is a threshold nNO level that can help prognosticate disease status. 

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Supplementary information for:

Nasal Nitric Oxide as a Long-term Prognostic Biomarker of Mucosal Health in Chronic Rhinosinusitis

Supplementary Table 1. nNO levels in CRSwNP vs. CRSsNP

	Baseline	1 month	6 month	5 years
CRSwNP (n=28)	269.23 (57.55-448.765)	581.10 (300.53 – 882.33)	590.13 (230.96 – 1055.96)	641.18 (316.15 – 764.50)
CRSsNP (n=4)	732.75 (576.54 – 955.19)	767.60 (606.18 – 948.95)	563.25 (449.30 – 565.25)	772.28(707.46 – 1123.96)
p-value	0.010	0.23	0.39	0.077

*nNO= nasal nitric oxide, CRSwNP = Chronic rhinosinusitis with nasal polyposis, CRSsNP = Chronic rhinosinusitis without nasal polyposis

**Statistically significant p-values are bolded.

Supplementary Table 2. Sensitivity analysis with nNO levels for co-morbid asthma and AERD among CRSwNP patients

	Baseline	1 month	6 month	5 years
Group 1: CRSwNP (n=9) No Asthma or AERD	425.75 (225.90 – 453.10)	833.4 (234.05 – 1098.80)	1033.63 (419.40 – 1212.61)	648.8 (490.95 – 775.83)
Group 2: CRSwNP Asthma (n=14)	255.52 (77.65 – 504.665)	581.1 (394.76 – 863.93)	447.55 (288.19 – 764.09)	676.025 (330.05 – 838.83)
Group 3: CRSwNP AERD (n=5)	23.13 (0.23 – 417.20)	422.25 (107.67 – 572.75)	98.80 (52.81 – 1004.10)	149.3 (64.33 – 676.83)
p-value (Group 1 vs. Group 2)	0.26	0.75	0.076	0.95
p-value (Group 1 vs. Group 3)	0.072	0.13	0.13	0.072
p-value (Group 2 vs. Group 3)	0.096	0.096	0.17	0.096

*nNO= nasal nitric oxide, CRSwNP = Chronic rhinosinusitis with nasal polyposis, AERD = Aspirin-exacerbated respiratory disease