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Review

Nitric Oxide in Chronic Rhinosinusitis: Compartment-Specific Biology and Use as a Biomarker

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Abstract

Background: Nitric oxide (NO) is a gaseous signaling molecule involved in host defense and inflammation in chronic rhinosinusitis (CRS). Because previous studies report contradictory changes in nasal NO (nNO), fractional exhaled NO (FeNO), and NO synthase (NOS) expression, this review evaluates their compartment-specific mechanisms and clinical utility as CRS biomarkers. Methods: PubMed was searched for human studies published between May 1994 and June 2026. Following sequential screening of 487 initial records, 28 eligible articles (14 mechanistic and 14 clinical) were included. Results: In type 2/eosinophilic CRS, elevated nNO and FeNO are primarily driven by inducible NOS (iNOS). Conversely, severe acute infection reduces iNOS expression and nNO levels. Furthermore, the arginase–NOS axis regulates NO bioavailability via L-arginine competition, particularly in non-atopic CRS phenotypes. Clinically, directly measured nNO is generally reduced in CRS—especially CRS with nasal polyps (CRSwNP)—reflecting sinus ostial obstruction and epithelial dysfunction, and recovers following ventilation restoration. In contrast, FeNO and tissue NOS are elevated in eosinophilic/type 2-dominant CRS. Conclusions: NO is neither uniformly protective nor pathogenic in CRS. Instead, nNO primarily reflects local sinus ostial patency and epithelial function, whereas FeNO reflects lower airway type 2 inflammatory burden and comorbid asthma.

Keywords: nitric oxide; chronic rhinosinusitis; nasal polyps; nasal nitric oxide; fractional exhaled nitric oxide; nitric oxide synthase; arginase; biomarkers

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Academic Editor: Alexandros Georgakilas

Received: 15 October 2026
Revised: 20 November 2026
Accepted: 24 November 2026
Published: 26 November 2026

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1. Introduction

1.1. Chronic Rhinosinusitis: Definition, Classification, and Disease Burden

Chronic rhinosinusitis (CRS) is an inflammatory disorder of the nasal and paranasal sinus mucosa that lasts for 12 weeks or longer. In adults, CRS manifests as nasal obstruc-

tion and/or nasal discharge with an additional symptom of facial pain/pressure and/or decreased/loss of smell [1]. Confirmation requires the presence of nasal polyps, or mucopurulent discharge, or mucosal edema of the middle meatus based on nasal endoscopy, or mucosal changes based on computed tomography (CT) of the paranasal sinuses [1]. CRS imposes a substantial disease burden and is associated with high utilization of healthcare resources, high costs for surgical and medical treatment, decreased productivity, and impaired health-related quality of life [2].

Clinical practice guidelines classify CRS as CRS with nasal polyps (CRSwNP) or CRS without nasal polyps (CRSsNP) [1]. This distinction is related to the underlying endotype, histological features, and treatment response. Recent studies have classified CRS as type 2 or non-type 2 based on the endotype because phenotype alone, such as the presence or absence of nasal polyps, does not adequately explain the heterogeneous pathobiology of this disease [1]. CRS also frequently coexists with allergic rhinitis and asthma, diseases that affect the upper and lower airways and have similar inflammatory mechanisms and immune responses. CRS may therefore be interpreted from the perspective of the 'one airway, one disease' hypothesis, which considers the upper and lower airways as a single unit. This perspective has implications for the clinical role of nitric oxide (NO) and the utility of NO-based biomarkers [3].

1.2. Nitric Oxide and Nitric Oxide Synthases: Basic Biochemistry

NO is a diffusible free-radical gaseous signaling molecule that is generated from L-arginine via nitric oxide synthase (NOS), and its synthesis requires molecular oxygen and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) [4]. The three major NOS isoforms are neuronal NOS (nNOS or NOS1), endothelial NOS (eNOS or NOS3), and inducible NOS (iNOS or NOS2). nNOS and eNOS generally have constitutive expression, produce small amounts of NO for short periods, and depend on calcium/calmodulin (CaM). In contrast, exposure to stimuli such as proinflammatory cytokines or bacterial lipopolysaccharide (LPS) can induce the transcription of *iNOS*, which can generate large amounts of NO over relatively prolonged periods [5,6]. Because the induction of iNOS is closely linked to activation of the innate immune response, its expression can be used as an indicator of local inflammatory activity in the sinonasal mucosa and other mucosal tissues.

L-arginine metabolism regulates the production of NO (Figure 1). In particular, arginase (ARG) and iNOS both use L-arginine as a substrate, and the ARG-mediated conversion of L-arginine into ornithine and urea decreases the production of NO. The ARG-iNOS axis plays an important role in regulating the production and bioavailability of NO in inflamed sinonasal tissue [7].

1.3. Nasal Nitric Oxide (nNO) and Fractional Exhaled Nitric Oxide (FeNO) as Airway Biomarkers

The physiological roles of NO in the respiratory tract depend on the specific anatomical compartment. Nasal nitric oxide (nNO) is primarily derived from NO produced in the nasal cavity and paranasal sinuses, particularly by the sinus epithelium; under normal conditions, the nNO concentration is markedly higher than that in the lower airways [8]. The paranasal sinuses produce and store high concentrations of NO, which subsequently diffuses into the nasal cavity through the natural ostia.

Patients with primary ciliary dyskinesia (PCD) typically exhibit very low levels of nNO. In particular, Kartagener syndrome, a PCD phenotype accompanied by situs inversus, is associated with decreased nNO levels resulting from ciliary dysfunction and impaired NO production in the sinonasal mucosa. Accordingly, nNO measurement serves as a useful screening tool for PCD in appropriate clinical settings [8].

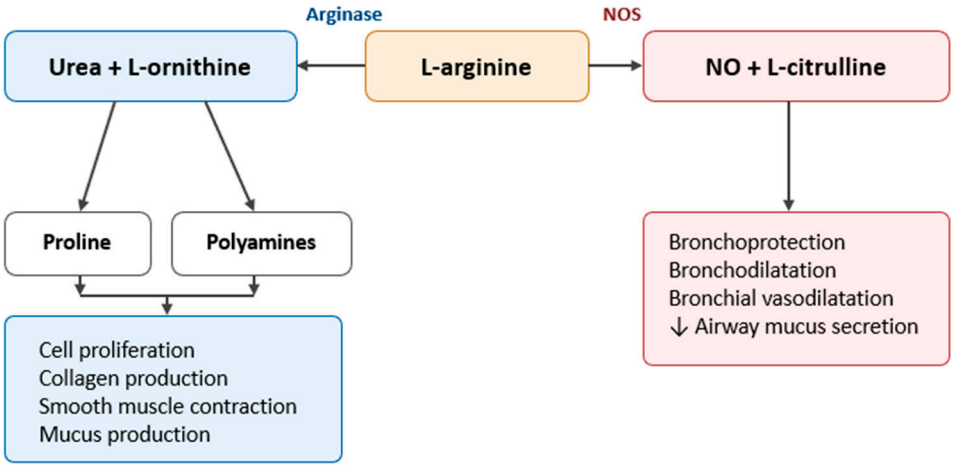

Figure 1. Substrate competition in the ARG-NOS axis. Redrawn from Vlad and Albu [7].

NO measurements are significantly influenced by the sampling site, exhalation flow rate, breathing maneuver, and velum closure. The European Respiratory Society (ERS) technical standard for exhaled biomarkers updated the recommendations for measuring FeNO and nNO [9]. Furthermore, for sinonasal diseases, the European position paper on diagnostic tools details the nNO measurement techniques and their diagnostic applications [10].

FeNO is a widely recognized, noninvasive biomarker used to identify type 2 or eosinophilic airway inflammation in asthma; an elevated level in patients with CRS can indicate comorbid lower airway type 2 inflammation and asthma. Conversely, nNO holds potential value as a biomarker reflecting physiological and pathophysiological changes within the local sinonasal environment. Because nNO and FeNO reflect distinct anatomical compartments and different inflammatory conditions, they should not be interpreted as equivalent markers of the same pathological condition.

1.4. Aim of This Review

Despite the many previous physiological and methodological studies of the role of NO in CRS, there have been many seemingly contradictory results. Some studies reported a decreased level of nNO in patients with CRS, particularly CRSwNP, because of sinus ostial obstruction and sinonasal epithelial dysfunction. Other studies suggested that tissue expression of NOS, NO metabolites, and FeNO was increased in patients with eosinophilic or type 2-dominant CRS.

This suggests that NO is not a simple biomarker. Instead, NO mediates several processes and interpretation of the NO level depends on the measurement compartment, sinus ventilation and ostial patency, epithelial function, inflammatory endotype, and the state of the ARG-iNOS axis. In this narrative review, we first examined the enzymatic and molecular mechanisms by which NO is produced in the sinonasal mucosa. We then synthesized studies that examined the diagnostic, phenotypic, and prognostic utility of nNO and FeNO in rhinosinusitis. Our general purpose was to clarify the mechanistic basis and clinical significance of the different changes in NO-related indices in different anatomical compartments and the clinical phenotypes of patients with CRS.

2. Methods

2.1. Literature Search and Selection

The PubMed database was searched for articles published from May 1994 to June 2026 using the search terms “nitric oxide” AND “sinusitis”. The inclusion criteria were: (i) original article on human subjects; (ii) study whose main topic was NO production,

NOS expression, ARG activity, NO metabolites, nNO, or FeNO in relation to sinusitis or CRS; and (iii) publication in the English language. Articles not published in English, non-human studies, studies in which sinusitis or NO was not the central topic, review articles, case reports, conference abstracts, and duplicate publications were excluded. A total of 487 records were initially identified. During the initial title-screening stage, 280 records were excluded because their titles clearly indicated non-human or in vitro subjects, non-sinonasal diseases (e.g., isolated lower airway disease, cardiovascular or neurological disorders), or irrelevant article types (e.g., review articles, case reports, editorials, or non-English publications), leaving 207 potentially relevant records for abstract screening. Review of the abstracts of these 207 records indicated that 39 studies potentially met the inclusion criteria and were selected for full-text review. Full-text review led to the exclusion of 1 article for which the full text could not be obtained and 10 articles that did not primarily address NO production or function in the sinonasal mucosa. Finally, 28 studies were included in the literature review (Figure 2).

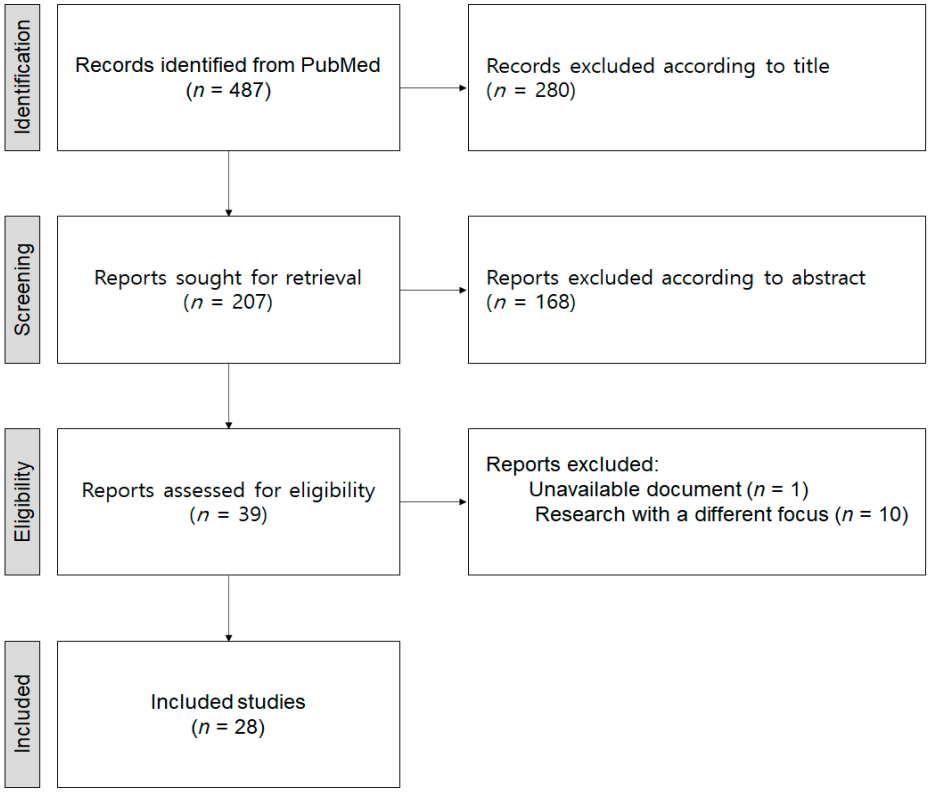

Figure 2. Protocol used to identify eligible publications.

2.2. Data Extraction and Analysis

The 28 selected studies were classified into two categories according to their objectives. The first category (14 studies) examined the enzymatic and molecular mechanisms of NO production in the sinonasal mucosa. These studies focused on the expression and regulation of NOS isoforms (iNOS, eNOS, and nNOS) and substrate competition for L-arginine in the ARG-iNOS axis. The second category (14 studies) evaluated the clinical utility of nNO or FeNO measurements in rhinosinusitis. These studies examined the diagnostic, phenotypic, and prognostic value of nNO and FeNO.

For each of the 28 studies, the study design, characteristics and number of subjects, clinical phenotype or inflammatory endotype of the target disease, NO-related indices (NO, NOS isoforms, ARG, or NO metabolites), measurement and detection methods, and main

results and conclusions presented by the original authors were analyzed. The extracted data were synthesized and a narrative analysis was used to describe the mechanisms of NO production in the sinonasal mucosa and the clinical significance of nNO and FeNO in CRS.

3. Discussion

3.1. Mechanisms of NO Production: Nos and Arg Expression in Rhinosinusitis

The 14 studies in this category are discussed in Sections 3.1.1–3.1.4: three studies of iNOS expression (Section 3.1.1), two of eNOS expression and activation (Section 3.1.2), and two of ARG expression (Section 3.1.3), for a total of seven mechanistic studies, followed by seven clinical and interventional studies that directly quantified nNO, FeNO, or NO metabolites together with NOS expression (Section 3.1.4).

3.1.1. iNOS Expression in the Pathogenesis of Nasal Polyps and Sinusitis

Three studies directly evaluated the expression of iNOS in sinonasal tissue. One study examined the role of iNOS in the pathogenesis of nasal polyps in patients with CRS. These researchers used immunohistochemistry to compare the mucosa from the maxillary sinus, ethmoid sinus, and nasal cavity of 24 CRS patients who had nasal polyps with the inferior turbinate mucosa of 9 CRS controls who did not have polyps. They calculated an iNOS positivity index (PI) and determined the distribution of inflammatory cells in 8 compartments, in which the epithelial, subepithelial, and deep layers were subdivided into perivascular, glandular, and endothelial compartments. The proportion of polymorphonuclear leukocytes was significantly higher in the ethmoid and maxillary sinus mucosa of the polyp group ($p = 0.005$ and $p = 0.006$, respectively) and the total cellular iNOS-PI in the ethmoid sinus mucosa was also significantly higher in the polyp group ($p = 0.010$). They attributed this result mainly to the fibroblastic expression of iNOS. iNOS positivity was consistently lower in the edematous, cell-poor subepithelial and deep layers of the polyps than in areas of high cell density. Correlation analysis showed that iNOS expression in the deep layer was negatively associated with the duration of polyposis and a history of heavier smoking. The authors proposed that iNOS-derived NO may contribute to polyp formation by increasing vascular permeability, stromal edema, migration of inflammatory cells into the mucosal stroma, and secretion from mucosal glands [11].

The second study was a cross-sectional investigation of FeNO and the production and metabolism of NO in 33 patients with untreated eosinophilic CRS (ECRS), 16 patients with non-ECRS, and 38 healthy controls. The results showed that orally exhaled FeNO and nNO were significantly higher in the ECRS group [12]. Quantitative real-time polymerase chain reaction (PCR) of ethmoid sinus mucosa and nasal polyp tissue showed that patients with ECRS had increased expression of iNOS and interleukin-5 (IL-5). Immunohistochemistry also demonstrated a high level of nitrotyrosine (NT) in the ECRS group, and that this NT colocalized with eosinophils. Because NT is a marker of NO-dependent damage, these findings suggest that the increases in oral/nasal FeNO and NT in ECRS were related to NO production and metabolism driven by eosinophil infiltration and the increased expression of iNOS. These results suggest that iNOS-mediated production of NO and nitrative stress may occur during eosinophilic inflammation [12].

The third study measured NO by fenestration of the maxillary sinus in 11 patients who had sepsis with radiologic maxillary sinusitis and 11 controls who had no airway obstruction. They found that the NO level was markedly lower in the patients than the controls (31 ± 10 ppb vs. 2554 ± 385 ppb, $p < 0.001$). iNOS was expressed mainly in the cilia and microvilli of maxillary sinus epithelial cells of the controls, and this apparently contributed to the enhanced ciliary function and nonspecific immune responses. Immunohistochemistry and in situ hybridization experiments showed a markedly decreased expression of iNOS in

the maxillary sinus epithelium. The authors interpreted these findings as indicating that iNOS-mediated NO production may be impaired by severe systemic infection, and this may weaken local mucosal defense and increase susceptibility to a secondary infection [13].

The results of these 3 studies suggest that iNOS-mediated NO production varies according to the type of inflammation and the clinical context. Patients with chronic type 2 sinusitis or eosinophilic sinusitis have increased iNOS expression and increased NO-related indices; patients with sepsis accompanied by radiologic acute maxillary sinusitis have decreased expression of iNOS and a marked NO deficiency. NO and iNOS therefore seem to have different roles in different sinonasal diseases, possibly because of the different modes of regulation in different types of immunological inflammation and the presence of a systemic condition.

3.1.2. eNOS Expression and Activation-Related Signaling in CRSwNP

Two studies evaluated the expression of eNOS and the mechanisms regulating its activity in the pathophysiology of nasal polyps [14,15]. eNOS is activated by phosphorylation at Ser 1177 and inhibited by phosphorylation at Thr 495 [16]. A retrospective study examined 84 patients with non-eosinophilic CRSwNP, 55 patients with eosinophilic CRSwNP (Eos CRSwNP), and 37 healthy controls. The results indicated a higher level of nNO in the eosinophilic CRSwNP group than in the non-eosinophilic CRSwNP group, leading these researchers to suggest using nNO for the diagnosis of eosinophilic CRSwNP [14]. The levels of iNOS, eNOS, and phosphorylated eNOS (p-eNOS) were also greater in CRSwNP tissues than in control tissues, and the level of p-eNOS was particularly high in eosinophilic CRSwNP. Studies of the underlying mechanisms using primary cultured human nasal epithelial cells indicated that interleukin-13 (IL-13) decreased the expression of tight junction (TJ)-related proteins. However, dexamethasone increased the phosphorylation of Akt and eNOS, the production of NO, and the expression of TJ proteins, and these effects were attenuated by the use of Akt or eNOS inhibitors. These findings suggest that dexamethasone regulates NO production through the Akt/eNOS pathway and protects against IL-13-induced damage to TJs [14].

The other study used microarray analysis, immunofluorescence, and western blotting to measure the expression of eNOS and other genes. The expression of eNOS mRNA was 1.4-fold greater in nasal polyp tissue than in normal inferior turbinate mucosa, whereas the expression of NOS trafficking inducer (NOSTRIN) and caspase-8 (CASP8), which function in the intracellular trafficking and regulation of eNOS, was decreased by 0.53-fold and 0.44-fold, respectively. In ex vivo polyp tissues, 1,8-cineole reduced eNOS phosphorylation in a phospho-kinase array (0.48-fold, $n = 3$); however, the reduction observed via western blot analysis (0.71-fold, $n = 10$) was not statistically significant, and neither eNOS activity nor NO production was directly measured. Therefore, these data suggest, but do not firmly establish, the hypothesis that eNOS phosphorylation contributes to vascular permeability and tissue edema in nasal polyps [15].

These two studies suggest that eNOS expression and phosphorylation are increased in CRSwNP, and that the level of p-eNOS is especially elevated in eosinophilic CRSwNP. There is also evidence that the Akt/eNOS pathway may regulate the production of NO and epithelial barrier function, and that increased eNOS phosphorylation in nasal polyps may contribute to increased vascular permeability, tissue edema, and inflammatory responses.

3.1.3. Competitive Regulation of NO Production by ARG

ARG metabolizes L-arginine into ornithine and urea, and this decreases the amount of L-arginine available to NOS, thereby suppressing the production of NO. Two studies

suggested that changes in the expression and activity of ARG can regulate the bioavailability of NO in CRS.

A real-time PCR study compared 36 samples of CRS lesional tissue with 29 samples of normal sinus mucosa. They found that ARG1 expression was low in all samples but that ARG2 expression was significantly higher in CRS tissue than in controls (2.22 ± 0.42 vs. 1.31 ± 0.21, $p = 0.016$). This increase was particularly pronounced in tissues of CRSsNP patients ($p = 0.0175$), without allergy ($p = 0.005$), and without asthma ($p = 0.028$). These results raised the possibility that the increased expression of ARG decreased the production of NO through substrate competition, and that iNOS is related to the subtype-specific pathogenesis of CRS [7].

The other study compared 18 patients with CRSsNP and 27 patients with CRSwNP. The results showed that oral and nasal FeNO levels were significantly higher and NOS2 expression was significantly increased in the CRSwNP group. The CRSsNP group had increased expression of ARG, and immunohistological staining showed significant ARG reactivity in epithelial and glandular cells. These authors proposed that NO, whose level is determined by a balance between ARG and NOS activity, could be a useful marker for differentiating CRS phenotypes [17].

3.1.4. Clinical and Interventional Studies of NO Measurement and NOS Expression

Seven studies performed direct quantification of nNO or NO metabolites, and some of them also evaluated the concurrent expression of different NOS isoforms, clinical characteristics of patients, and changes following surgical intervention.

The first study used chemiluminescence to measure nNO in healthy volunteers ($n = 66$), patients with the common cold ($n = 6$), and patients with chronic sinusitis ($n = 12$). The mean nNO concentration in healthy volunteers was 233.2 ± 66.8 ppb, similar to the level in patients with the common cold. However, patients with chronic sinusitis had a significantly decreased level of nNO (96.4 ± 72.8 ppb). Because NO functions in the regulation of mucociliary clearance and in antibacterial and antiviral defense, the authors proposed that the decreased level of nNO may contribute to the pathophysiology of chronic sinusitis. Consistently, the two patients with the lowest nNO levels had clinical findings suggestive of acquired mucociliary dysfunction [18].

The second study analyzed NO metabolites in maxillary sinus lavage fluid from normal controls ($n = 12$), patients with CRSwNP ($n = 14$), and patients with CRSsNP ($n = 11$). The results indicated that NO metabolite concentrations were significantly higher in the chronic sinusitis groups than the normal group, but this difference was unrelated to the presence of nasal polyps (CRSwNP, 18.04 ± 3.51 μmol/L; CRSsNP, 16.78 ± 2.91 μmol/L; healthy controls, 8.085 ± 1.43 μmol/L). The increased level of NO metabolites in the maxillary sinus contrasted with the decreased nNO in patients with sinusitis in several studies. These authors suggested that inflammatory cells increased the levels of NO, but that NO could not diffuse into other cells because of the excessive secretions and thick aqueous epithelial lining in sinusitis, and the rapid metabolism of NO in the maxillary sinus [19].

The third study measured nasal NO in 7 patients who had allergic rhinitis with nasal polyposis, 20 patients who had non-allergic rhinitis with nasal polyposis, 10 patients who had non-allergic rhinitis with CRS, 6 patients who had Kartagener syndrome, and 42 controls. The nNO level in patients who had non-allergic rhinitis with nasal polyposis was 150 ± 20 ppb, significantly lower than the controls (223 ± 6 ppb, $p = 0.01$) and patients who had allergic rhinitis with nasal polyps (272 ± 28 ppb; $p < 0.0001$). Except for the Kartagener group (which had the lowest nNO level despite open sinuses), the nNO level was inversely correlated with the degree of sinus obstruction determined by sinus CT. The authors considered these results in light of previous studies, and suggested that nNO could

be used as an index that reflects the allergic status and certain anatomical features, such as the patency of the sinus ostia [20].

The fourth study was an interventional study that evaluated the effect of sinus obstruction after an intervention. In particular, these researchers measured NO and NO metabolites in the maxillary sinus and nasal cavity of 9 patients with nosocomial maxillary sinusitis associated with severe sepsis who underwent sinus drainage and lavage and antibiotic therapy, followed by removal of the nasogastric tube [21]. Four days after the start of treatment, the NO concentration in the maxillary sinus increased significantly from a median of 70 ppb to 2050 ppb ($p < 0.0001$), and the nNO increased significantly from 100 ppb to 180 ppb ($p < 0.001$). These results showed that maxillary sinus NO and nNO concentrations increased after treatment of maxillary sinusitis with antibiotics and daily lavage. The authors concluded that treatment of the sinusitis decreased the number of inflammatory cells and bacteria, thereby decreasing the metabolism of NO and increasing the sinus level of NO [21].

The fifth study was a prospective study that examined 36 patients with ECRS who received surgical treatment ($n = 24$) or medical treatment ($n = 12$). The results demonstrated that oral FeNO was 50.9 ppb before endoscopic sinus surgery (ESS) and 36.8 ppb at 6 months after surgery. However, the nasal FeNO increased from postsurgical month 1 (62.3 ppb) to postsurgical month 6 (93.6 ppb). The authors attributed the increased nasal FeNO to the increased NO from the healed sinus mucosa and the decreased oral FeNO to the cessation of the underlying lower airway inflammation that characterizes ECRS [22].

The sixth study compared the preoperative levels of nNO, iNOS, and eNOS in maxillary and ethmoid sinus mucosa of patients with CRSwNP ($n = 10$) or non-CRSwNP controls ($n = 10$). The results showed that the CRSwNP group had increased levels of iNOS and eNOS, but a decreased level of nNO. This shows that increased *NOS* expression in tissue does not necessarily translate into a higher NO concentration in the nasal cavity. The authors' interpretation was that although increased iNOS and eNOS expression increased the potential for greater NO production, nNO may nevertheless be low because of metabolism in the inflammatory environment [23].

The seventh study was a retrospective analysis of 85 patients with CRSwNP and 28 controls undergoing septoplasty; the patients with CRSwNP were subdivided into groups with epithelial hyperplasia, goblet cell hyperplasia, or squamous metaplasia. The nNO level was significantly lower in all patient groups than in the control group ($p \leq 0.02$). The nNO level was also inversely correlated with the Lund–Mackay score in all remodeling subtypes. Notably, the nNO level showed moderate ability in distinguishing each of the histological subtypes, and areas under the curves (AUCs) of the receiver operating characteristic (ROC) curves ranged from 0.720 to 0.898. These results suggest that a decreased level of nNO may be associated with the presence of nasal polyps, radiological severity of disease, and specific patterns of epithelial remodeling [24].

These 7 studies of the role of NO in CRS showed different patterns depending on the measurement site and the nature of the disease. Sinus obstruction and mucus accumulation may decrease NO in the nasal cavity or sinuses, but maxillary sinus lavage fluid may have increased levels of NO metabolites. Moreover, the increased tissue expression of iNOS and eNOS does not necessarily lead to increased nNO because the nNO level is affected by NO production, diffusion, oxidation/metabolism, and elimination. After treatment, nNO may increase with the recovery of sinus ventilation and mucosal function, and oral FeNO may decrease when lower airway inflammation decreases.

To clarify the different NO measurement units reported across these studies, it is important to distinguish their physical and biochemical meanings: (1) parts per billion (ppb) represents the fractional gas-phase concentration of NO sampled directly from the

nasal cavity, sinus cavity, or exhaled breath; (2) nanoliters per minute (nL/min) represents the calculated NO output rate (the product of gas-phase NO concentration and sampling flow rate); and (3) micromoles per liter (μmol/L) represents the liquid-phase concentration of stable oxidative NO metabolites (nitrite and nitrate, NOx) quantified via the Griess reaction in sinus lavage fluid or mucosal secretions.

3.1.5. Summary of NO Production Mechanisms

The 14 studies examining the mechanisms of NO production and the expression of NOS and ARG in rhinosinusitis suggest that NO production and NO concentration in the sinonasal mucosa are influenced by the expression and activity of different NOS isoforms, substrate competition for L-arginine, patency of the sinus ostia, epithelial function, and the local inflammatory endotype. Many studies performing direct measurements of nNO have reported that this level is lower in patients with CRS or CRSwNP than in controls. This decrease may be related to sinus ostial obstruction, decreased sinus ventilation, and epithelial dysfunction. Furthermore, increases in nNO following drainage, infection control, or ESS support the interpretation that nNO reflects the state of sinus ventilation and ostial patency. Therefore, the nNO level should not be interpreted simply as the absolute amount of NO produced in the tissue; rather, it reflects the combined outcome of NO synthesized in the sinuses, NO delivered to the nasal cavity, and the functional integrity of the epithelium. These studies also indicated that the tissue expression of NOS, the level of NO metabolites, and oral FeNO values tend to be greater in patients with eosinophilic or type 2-dominant CRS. In particular, increased expression of iNOS and eNOS, eNOS phosphorylation, nitrotyrosine expression, and elevated levels of NO metabolites suggest that these changes are associated with eosinophilic inflammation, oxidative/nitrative stress, and tissue remodeling.

An important consideration is that the levels of nNO and FeNO, as well as the tissue expression of NOS, can change in opposite directions in patients with CRS. The nNO level appears to primarily reflect sinus ostial patency, sinus ventilation, and epithelial function, whereas FeNO reflects the lower airway type 2 inflammatory burden and comorbid asthma. Consequently, nNO and FeNO should not be interpreted as interchangeable indicators of an overall 'NO status' in CRS; instead, the measurement compartment and pathophysiological significance of each index must be clearly distinguished. Accordingly, when interpreting NO-related indices in CRS, the inflammatory endotype and other clinical findings should be considered in an integrated manner, rather than relying on a single isolated index (Table 1).

Table 1. Studies of the production of NO and NOS in the sinonasal mucosa in patients with CRS (Section 3.1, $n = 14$).

Author, Year [Reference]	Population (n, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Muluk et al., 2013 [11]	24 adults with polyps (mean 46.5 y) vs. 9 controls	Polyps	Tissue iNOS immunohistochemistry, positivity index (PI)	PMNC% ↑ (ethmoid 25, maxillary 55 vs. 5); ethmoid all-cell iNOS PI ↑ (2.0 vs. 1.0, $p = 0.010$); no layer-wise PI difference ($p > 0.05$)
Takeno et al., 2013 [12]	ECRS 33, non-ECRS 16, normal 38	Japanese ECRS criteria	NObreath, oral 50 mL/s for 16 s, nasal adaptor; tissue RT-PCR	Oral FeNO ↑ in ECRS 47.6 vs. 13.5 / 15.3 ppb; nasal FeNO ↓ in non-ECRS 30.5 vs. ECRS 53.9 / normal 45.5; iNOS and IL-5 mRNA ↑; nitrotyrosine ↑

Table 1. *Cont.*

Author, Year [Reference]	Population (*n*, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Deja et al., 2003 [13]	Maxillary sinusitis with sepsis	Radiologic maxillary sinusitis	Sinus gas NO, iNOS	Sinus NO ↓, epithelial iNOS ↓
Tang et al., 2023 [14]	CRSwNP 139 (Eos 55, non-Eos 84), controls 37 (adults)	Tissue eosinophils >10/HPF	Sunvou, 5 mL/s, nasal olive, ppb; tissue western blot, HNEC experiments	nNO ↓ in CRSwNP 205.6 vs. 517.8 ppb; Eos 254.4 > non-Eos 174.0 ($p < 0.001$); iNOS, eNOS, p-eNOS ↑; tight junctions ↓
Koennecke et al., 2018 [15]	42 (CRSwNP 34, controls 8; mean 47.5 y), tissue	Histologic eosinophilic CRSwNP	Microarray, western blot, phospho-array	Polyp eNOS mRNA 1.40-fold, p-eNOS 19.7-fold ↑ ($p \leq 0.05$); 1,8-cineol ↓ p-eNOS (0.48-fold)
Vlad & Albu, 2019 [7]	CRS 36 vs. controls 29 (adults, mean 45.8 / 42.7 y)	Polyps, allergy, asthma subgroups	Ethmoid mucosa RT-PCR	ARG2 ↑ in CRS 2.22 vs. 1.31 ($p = 0.016$), CRSsNP 3.14 ($p = 0.0175$); ARG1 low
Taruya et al., 2015 [17]	CRSsNP 18, CRSwNP 27 (61–62 y)	Polyps; tissue eosinophils	NObreath 50 mL/s; RT-PCR, IHC	CRSwNP: NOS2 mRNA ↑, oral and nasal FeNO ↑ (52 vs. 32.4 ppb); CRSsNP: ARG2 ↑, nasal FeNO ↓
Lindberg et al., 1997 [18]	Healthy 66 (3–68 y), common cold 6, chronic sinusitis 12 (46.8 ± 14.9 y)	Chronic sinusitis by CT	Chemiluminescence (CLD 700), 0.66 L/min, nasal olive, oral breathing, ppb	nNO ↓: 96.4 ± 72.8 vs. 233.2 ± 66.8 ppb ($p < 0.001$); common cold unchanged; two lowest cases had acquired ciliary dysfunction
Naraghi et al., 2007 [19]	37 (controls 12, CRSwNP 14, CRSsNP 11; mean age 30–36 y)	History, endoscopy, CT	Maxillary lavage NO metabolites (nitrate + nitrite, Griess), µmol/L	NOx ↑: 18.04 / 16.78 vs. 8.09 µmol/L ($p = 0.006$ / 0.008); no difference by polyps
Arnal et al., 1999 [20]	Controls 42, non-allergic polyposis 20, allergic polyposis 7, sinusitis 10, Kartagener 6	Endoscopy, CT score	Chemiluminescence (Cosma), 0.7 L/min, nasal olive, ppb	Non-allergic polyposis nNO ↓ 146 ± 13 vs. control 223 ± 6 ($p = 0.01$); allergic polyposis 272 ± 28 (↑ vs. non-allergic); inverse with CT; Kartagener very low
Degano et al., 2005 [21]	9 adults, nosocomial maxillary sinusitis in ICU	CT maxillary opacification	Sinus gas (Tedlar, 0.1 L/min) and nasal NO (Cosma 0.7 L/min); lavage NOx (µmol/L)	After 4 days of treatment, sinus NO ↑ 70→2050 ppb, nNO ↑ 100→180 ppb ($p < 0.001$); NOx unchanged
Noda et al., 2012 [22]	ECRS 36 (medical 12, surgical 24) vs. normal 32	Japanese ECRS criteria	Handheld electrochemical (NObreath), oral 50 mL/s for 16 s, nasal adaptor, ppb	Surgical group at 6 months: nasal FeNO ↑ 50.6→93.6 ppb, oral FeNO ↓ 50.9→36.8 ppb; medical group unchanged; iNOS and IL-5 mRNA ↑

Table 1. *Cont.*

Author, Year [Reference]	Population (*n*, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Wu et al., 2024 [23]	20 adults (CRSwNP 10, controls 10; mean 57.0 ± 8.9 y, 65% male), prospective cohort, tissue mRNA	CRSwNP undergoing surgery vs. non-polyp patients undergoing endoscopic surgery	NIOX MINO Nasal (day of surgery, ppb); maxillary/ethmoid tissue Nanostring nCounter (iNOS, eNOS mRNA)	nNO ↓ 136.6 ± 106.2 vs. 260.7 ± 100.7 ppb ($p < 0.05$); iNOS and eNOS mRNA ↑ (unadjusted, $p < 0.05$), not correlated with nNO ($p > 0.05$); nNO inversely correlated with endoscopy ($r^2 = 0.33$) and CT score ($r^2 = 0.20$)
Liang et al., 2026 [24]	Adults, CRSwNP 85 (epithelial hyperplasia 25, goblet cell hyperplasia 47, squamous metaplasia 13), controls 28	Three epithelial remodeling types (H&E)	Sunvou-CA2122, 10 mL/s, one nostril occluded, whistle, ppb	nNO control 428.7 > squamous metaplasia 331.4 > hyperplasia 214.5 and goblet cell hyperplasia 222.0 ppb; inversely correlated with Lund-Mackay score

Abbreviations: ARG, arginase; AUC, area under the curve; CASP8, caspase-8; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; eNOS, endothelial nitric oxide synthase; ESS, endoscopic sinus surgery; FeNO, fractional exhaled nitric oxide; IL, interleukin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; NOS, nitric oxide synthase; NOSTRIN, nitric oxide synthase trafficking inducer; nNO, nasal nitric oxide; PCR, polymerase chain reaction; PMN, polymorphonuclear leukocyte; p-eNOS, phosphorylated eNOS; ROC, receiver operating characteristic; TJ, tight junction.

3.2. Diagnostic and Prognostic Value of nNO and FeNO in Rhinosinusitis

3.2.1. nNO and FeNO for the Diagnosis and Phenotyping of CRS

Seven studies evaluated the utility of nNO or FeNO for diagnosing CRS or differentiating the major clinical phenotypes of CRS.

The first study was a cohort study of 88 patients with CRS and 20 healthy volunteers. The result showed that nNO was significantly higher in a CRSsNP subgroup than in a CRSwNP subgroup (591 ± 153 vs. 360 ± 181 ppb, $p < 0.001$) and was significantly lower in all CRS patients than in the healthy control group (449 ± 204 vs. 881 ± 161 ppb, $p < 0.001$). In addition, a positive skin prick test was associated with higher nNO in both CRS subgroups. ROC analysis indicated that nNO had a sensitivity that ranged from 70 to 90% for distinguishing different pairs of these three groups [25].

The second study compared nNO in 70 patients with CRSwNP (24 eosinophilic and 46 non-eosinophilic) and 30 healthy controls and found that the level of nNO was significantly higher in the eosinophilic CRSwNP group than in the non-eosinophilic CRSwNP group ($p < 0.0001$). ROC analysis indicated that nNO could discriminate eosinophilic from non-eosinophilic CRSwNP with an AUC of 0.803. At the optimal cutoff (329 ppb), the sensitivity was 83.3% and the specificity was 71.7%, suggesting reliable discrimination of these CRSwNP subtypes [26].

The third study measured nNO in 73 patients who had persistent symptoms (e.g., nasal obstruction, nasal discharge, facial pain, and reduced sense of smell) for 12 weeks or longer (30 with CRSwNP, 14 with CRSsNP, and 29 without CRS) and healthy controls. The median level of nNO was significantly lower in the CRSwNP group (340 ppb) than in the CRSsNP group (762 ppb), the symptomatic non-CRS group (917 ppb), and the healthy

controls (843 ppb) (all $p < 0.001$) [27]. ROC analysis with an nNO cutoff of 442 ppb showed that the sensitivity was 87% and the specificity was 91% for the diagnosis of CRSwNP [27].

The fourth study compared patients with ECRS, non-ECRS, and normal controls. The results showed that nNO was significantly lower in the ECRS group than in the non-ECRS group and healthy controls. nNO also had a negative correlation with the blood eosinophil count and sinus CT score, but no significant correlation with the nasal polyp score. During postoperative follow-up, nNO tended to increase after ESS but this was not statistically significant. The authors suggested that mucosal damage decreased the level of nNO, particularly when there was eosinophilic inflammation, and that NO may increase due to the post-surgical recovery of the sinus mucosa [28].

The fifth study was a case–control study which compared patients with CRS and chronic rhinitis. The results demonstrated that FeNO (cutoff, 329.00 ppb) reliably distinguished CRS from chronic rhinitis (AUC: 0.808; sensitivity: 81.30%; specificity: 69.20%) [29].

The sixth study measured nNO and exhaled NO (FeNO) in normal subjects, patients with CRSwNP, and patients with CRSwNP and allergic rhinitis. The results showed that the nNO level was 88.5 ± 54.7 ppb in the CRSwNP group, 241.0 ± 89.5 ppb in healthy controls, and 167.0 ± 47 ppb in the CRSwNP with allergic rhinitis group, and that all pairwise differences were significant [30]. For an nNO cutoff of 163 ppb, the sensitivity was 81% and the specificity was 93% for the diagnosis of CRSwNP. However, the FeNO level was significantly greater in the CRSwNP group than the normal group, and there were no significant pairwise differences among the other groups. The authors suggested that nNO may be useful for screening of the CRSwNP phenotype [29].

The seventh study was a regression analysis of 93 patients with CRS. The results showed that the presence of nasal polyps ($p = 0.01$), comorbid asthma ($p < 0.001$), and respiratory symptoms without bronchial hyper-responsiveness ($p = 0.01$) were independent predictors of an elevated FeNO. Based on these results, the authors proposed that the presence of nasal polyps in patients with CRS was associated with asthma and an elevated FeNO. Their analysis of patients with respiratory symptoms but without bronchial hyper-responsiveness showed that eosinophilic airway inflammation and increased FeNO were only present in those with nasal polyps. These authors therefore proposed that the two types of CRS (with and without nasal polyps) have significant clinical and biological differences [31].

3.2.2. nNO and FeNO as Indicators of Disease Severity, Prognosis, and Treatment Response

Four studies evaluated the association of changes in nNO or FeNO with treatment response, disease severity, and prognosis.

One study measured the nNO level for 5 years after ESS in 32 patients with CRS, and showed that this level was greater than the preoperative level at 1 month, 6 months, and 5 years after surgery. Measurements of changes in the level of nNO in patients with CRSwNP who underwent revision surgery within 5 years ($n = 8$) and those who did not ($n = 20$) indicated that this level was significantly higher in the non-surgical group at 1 month, 6 months, and 5 years. In the surgery group, the nNO level was significantly greater at 1 month after surgery than before surgery, and was similar at 1 month, 5 months, and 5 years after surgery. The authors proposed nNO had potential use as a noninvasive and simple biomarker for tracking disease progression in CRSwNP [32].

The second study examined 90 patients with CRS who were unresponsive to initial medical treatment, and randomized them to a medical treatment ($n = 45$) or surgical treatment ($n = 45$). In both groups, the nNO level was significantly higher at 6 months and 1 year than at baseline. Also in both groups, the change in nNO was associated with a decreased symptom score ($p < 0.001$), decreased saccharin clearance time ($p < 0.001$), normalization of endoscopic findings ($p < 0.001$), decreased polyp grade ($p < 0.05$ at

6 months and $p < 0.01$ at 12 months), and a lower surgical score ($p < 0.01$). The authors suggested that nNO measurements are useful for objective monitoring of the response to medical or surgical treatment in patients with CRS. Because topical nasal corticosteroids modulate NO derived from the nasal mucosa, they also proposed that this treatment may help nNO to reflect sinus-derived NO relatively better [33].

The third study examined patients who had CRSwNP with ECRS ($n = 23$) and without ECRS ($n = 22$), and measured FeNO before and 2 months after ESS. The results showed that the preoperative FeNO level was significantly higher in the ECRS group. The ECRS group (but not the non-ECRS group) had significant decreases in FeNO and the blood eosinophil count at 2 months after surgery. The FeNO level also had significant positive correlations with the blood eosinophil count and the eosinophil count in nasal polyps. These findings suggest that FeNO may have potential as a noninvasive indicator of changes in the degree of comorbid lower airway type 2 inflammation and systemic eosinophilic inflammation in patients with ECRS [34].

The fourth study was a longitudinal pilot study that examined 12 patients in each of three groups: CRSsNP, symptoms of CRS but radiologically normal sinuses, and healthy controls. These three groups had no significant differences in nNO measured using the aspiration method and the humming maneuver. There were also no significant changes of nNO in the CRSsNP group and the healthy controls after medical treatment. The authors concluded that the level of nNO does not reliably indicate sinus patency in patients with CRSsNP [35].

3.2.3. Association Between Upper and Lower Airway Inflammation and NO in CRS

Three studies evaluated the relationship between NO and upper airway disease, lower airway inflammation, and comorbid asthma in CRS.

One study examined 94 patients with CRSwNP who underwent ESS and were classified histologically as type 2 CRSwNP ($n = 40$) or non-type 2 CRSwNP ($n = 54$). The results showed that the FeNO level and percentage of eosinophils were significantly greater in the type 2 CRSwNP group. In patients with CRSwNP, FeNO also correlated significantly with blood eosinophils and the ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC). An FeNO of 27 ppb reliably discriminated asthmatic type 2 CRSwNP from non-type-2 CRSwNP (AUC: 0.848). For an FeNO of 68 ppb and a blood eosinophil percentage of 5.6% (optimal cutoff values), the AUC was 0.931, the sensitivity was 95.5%, and the specificity was 86.1%. These authors concluded that FeNO is a useful index for screening of type 2 CRSwNP with asthma, and may help in selecting appropriate treatments [36].

The second study compared patients with CRSsNP ($n = 19$), CRSwNP ($n = 93$), and controls with allergic rhinitis ($n = 9$). The FeNO level was significantly greater in patients with CRS ($n = 112$) than the controls. However, when the CRS group was subdivided according to asthma status, there was no significant difference between the CRSsNP and CRSwNP subgroups. Furthermore, comparison of patients with CRS who received a biologic treatment (dupilumab) or a standard treatment (nasal irrigation and intranasal corticosteroid spray) demonstrated that only the group which received the biologic treatment had a significant post-treatment decrease in FeNO, and clinical improvements in the 22-item Sino-Nasal Outcome Test (SNOT-22) and Lund–Kennedy score. These results suggest that FeNO is not determined solely by the presence or absence of asthma, but is related to CRS-associated sinonasal mucosal inflammation, symptom severity, and objective sinonasal pathology. The FeNO level therefore may have potential as a marker for multiple variables, including treatment response [37].

Similarly, other studies have demonstrated that dupilumab improved NO indices, including FeNO and nNO, within 15 days, and maintained these improvements for up to

30 days [38]. In patients with comorbid asthma, the FeNO level decreased from 50 to 27 ppb over a minimum of 6 months [39]. However, results regarding mepolizumab have been inconsistent; while one real-world cohort demonstrated a significant reduction in FeNO from 50 to 23 ppb after 6 months [40], another study reported no significant decrease [41]. Therefore, at present, it appears more appropriate to use FeNO as a biomarker for identifying type 2 inflammation and comorbid asthma rather than for guiding the selection of specific biologic therapies.

The third study compared FeNO and nNO in 57 patients with CRSwNP in a primary care setting and 30 healthy controls. The results showed that the FeNO was significantly greater in the CRSwNP group regardless of asthma status. Within the CRSwNP group, the FeNO level was significantly higher in patients with asthma than those without asthma, and there was no significant difference between CRSwNP patients without asthma and healthy controls. The nNO level was significantly lower in the CRSwNP group than in healthy controls, but did not differ significantly according to asthma status within the CRSwNP group. These authors suggested that subclinical lower airway inflammation is common in patients with CRSwNP in a primary care setting, even in the absence of asthma. The results also showed that nNO (which reflects the local upper airway environment) and FeNO (which reflects lower airway inflammation) can change in opposite directions, apparently inconsistent with the 'one airway, one disease' hypothesis [42].

We also highlight the current evidence gap regarding anti-IL-5Rα (benralizumab) and anti-IgE (omalizumab) therapies in CRS, concluding that FeNO and nNO are currently best utilized to identify baseline type 2 inflammation, comorbid asthma, and early pharmacodynamic responses to IL-4/IL-13 blockade rather than as standalone criteria for biologic selection.

3.2.4. Summary of Clinical Utility

The 14 studies reviewed in this section suggest that nNO and FeNO have potential as tools for the diagnosis of CRS and the discrimination of clinical phenotypes and inflammatory endotypes of CRS, assessing disease severity, monitoring treatment response, and evaluating comorbid lower airway inflammation. In particular, nNO tends to be lower in patients with CRSwNP and in some patients with eosinophilic or type 2 inflammatory CRS, whereas the FeNO tends to be greater in patients with CRSwNP, eosinophilic inflammation, and comorbid lower airway inflammation. However, because of differences in the methods of measurement, clinical characteristics of patient groups, presence of comorbid allergy and asthma, use of medications, and disease definitions, there were inconsistencies in the direction and magnitude of these associations. Therefore, the general statement that nNO tends to be lower in patients with CRSwNP primarily reflects the overall comparison between CRSwNP patients as a broad phenotype and healthy controls, whereas intra-group variations are heavily influenced by the underlying inflammatory endotype. Specifically, nNO levels can vary significantly according to the eosinophilic endotype within CRSwNP cohorts.

Some studies showed that it was useful to measure nNO for the diagnosis of CRSwNP and discrimination of the eosinophilic phenotype, and that there is evidence of a postoperative increase in nNO and changes in nNO associated with the disease course. However, other studies of CRSsNP found no significant between-group differences or post-treatment changes in nNO, indicating the clinical utility of nNO measurements may vary among CRS phenotypes. In addition, the nNO cutoff values proposed for diagnosing CRSwNP and discrimination of eCRSwNP from neCRSwNP differed among studies (163, 329, and 442 ppb). These differences may be explained by differences in the measurement devices and methods, anatomical state of the nasal cavity and sinuses, patency of the sinus ostia, presence of nasal polyps, presence of allergic rhinitis, and comorbid lower airway inflammation.

A high FeNO level tended to be associated with CRSwNP and with eosinophilic or type 2 inflammation, and some studies also reported significant positive associations of FeNO with the blood eosinophil count, tissue eosinophil infiltration, asthma, and post-treatment clinical improvement. However, because FeNO can be influenced by comorbid asthma and by CRS, nasal polyps, and allergic disease, the FeNO level alone should not be used to diagnose or exclude lower airway disease in patients with CRS. The criteria used for the clinical interpretation of FeNO should also be distinguished from the exploratory cutoff values proposed in several CRS studies.

We suggest that nNO and FeNO should not be used as indices that have uniform thresholds applicable to all patients with CRS. Instead, we believe these measurements should be used as complementary biomarkers that are interpreted by considering the measurement compartment and method, phenotype, endotype, presence of comorbid asthma, and treatment status. The nNO level is an upper airway index that is affected by sinus ventilation, ostial patency, NO-producing capacity of the nasal mucosa, and the measurement conditions. By contrast, the FeNO level is an index of the lower airway that is related to type 2 inflammation, but is also influenced by CRS and allergic upper airway disease. Rather than regarding these two measurements as interchangeable indices of a single "NO status", it is preferable to use them as tools for the complementary assessment of the different compartments of the upper and lower airways. However, standardization of measurement protocols and establishment of validated phenotype-specific cutoff values are needed before there is widespread clinical application (Tables 2 and 3).

Table 2. Studies of the diagnostic and prognostic value of nNO and FeNO in patients with CRS (Section 3.2, $n = 14$).

Author, Year [Reference]	Population (n, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Liu et al., 2017 [25]	CRS 88 (CRSwNP 54, CRSsNP 34), controls 20	EPOS 2007; atopy by skin prick	NIOX, nasal olive, ppb	Control 881 > CRSsNP 591 > CRSwNP 360; atopic ↑; CRSsNP vs. CRSwNP cutoff 456 ppb, AUC 0.83
Lv et al., 2020 [26]	CRSwNP 70 (eCRSwNP 24, non-e 46), controls 30	Tissue eosinophils	nNO, ppb	eCRSwNP nNO ↑ vs. non-e ($p < 0.0001$); cutoff >329 ppb, sensitivity 83.3%, specificity 71.7%, AUC 0.803
Bommarito et al., 2008 [27]	Patients with suspected CRS, controls	CT-defined CRS; CRSwNP/CRSsNP by endoscopy	nNO, ppb	CRSwNP 340 vs. CRSsNP 762 vs. controls 843; cutoff <442 ppb, sensitivity 87%, specificity 91%
Yoshida et al., 2019 [28]	ECRS, non-ECRS, normal	Japanese ECRS criteria	nNO	nNO ↓ in ECRS vs. other groups; inversely correlated with eosinophils and CT score; no rise right after surgery

Table 2. *Cont.*

Author, Year [Reference]	Population (*n*, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Zhang et al., 2019 [29]	Inflammation 35 vs. healthy 30 (adults)	CRS vs. chronic rhinitis	nNO, ppb (labeled FeNO)	Patients ↓; patients vs. healthy 412.73 ppb, AUC 0.760; CRS vs. chronic rhinitis 329.00 ppb, sensitivity 81.3%, specificity 69.2%, AUC 0.808
Jeong et al., 2014 [30]	Controls 32, CRSwNP 30, CRSwNP+AR 27 (adults)	Bilateral polyps, with or without AR	Chemiluminescence, nNO and eNO, ppb	nNO 88.5 vs. control 241.0 (↓), with AR 167.0; cutoff 163 ppb, sensitivity 81%, specificity 93%; eNO positively correlated with CT
Guida et al., 2010 [31]	CRS 93	Polyps yes/no	Exhaled NO (eNO)	Polyps and asthma independently associated with higher eNO; differing phenotypes by polyps
Lee et al., 2020 [32]	CRS 32 (CRSwNP 28; mean 55.8 y), 5-year follow-up after ESS	CRS by AAO-HNS criteria; revision vs. no revision (CRSwNP 28)	CLD 88sp, 300 mL/min, each nostril, forced exhalation against resistance; baseline, 1 month, 6 months, 5 years; ppb	nNO ↑ 343.9 → 612.1 (1 month) → 656.9 ppb (5 years), inversely correlated with LKES; revision group baseline nNO ↓ 52.4 vs. 379.0 ppb ($p = 0.009$), still lower at 6 months
Ragab et al., 2006 [33]	CRS 90 (with or without polyps), 6- and 12-month follow-up	CT abnormality; medical vs. surgical, randomized	Baseline nNO, tracked at 6 and 12 months	Baseline nNO inversely correlated with CT changes ($p < 0.001$); nNO rise correlated with symptom, saccharin and endoscopy improvement
Kambara et al., 2017 [34]	CRSwNP 45 (ECRS 23, non-ECRS 22)	JESREC	FeNO	FeNO ↑ in ECRS; ↓ after surgery in ECRS only; correlated with blood eosinophils
Alexandersson et al., 2021 [35]	CRSsNP 12, symptoms-only 12, healthy 12	Symptoms plus CT	nNO by aspiration and humming, SNOT-22, before and after treatment	No nNO difference between groups (trend ↓); no change after treatment
Park et al., 2023 [36]	CRSwNP 94 (FESS)	T2-CRSwNP, histologic and clinical definitions	FeNO, ppb	FeNO 27 ppb, AUC 0.848 (sensitivity 90.9%, specificity 63.9%); FeNO 68 ppb + eosinophils 5.6% AUC 0.931

Table 2. *Cont.*

Author, Year [Reference]	Population (*n*, Adult/Pediatric, Age)	Phenotype Definition	Measurement (Device, Flow, Site/Assay)	Key Result (↑↓ vs. Comparator)
Olonisakin et al., 2022 [37]	CRS 112 (CRSsNP 19, CRSwNP 93; AR 7)	Polyps yes/no	FeNO (NIOX VERO), nasal mucus cytokines	FeNO 47.12 (asthma) vs. 43.24 ppb; correlated with CCL26, TNFα, SNOT-22, endoscopy
Frendø et al., 2018 [42]	CRSwNP 57 (primary care), controls 30	EPOS	nNO and FeNO	nNO ↓ vs. controls; FeNO elevated in 29% without asthma (59% with asthma)

Abbreviations: AUC, area under the curve; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; eNO, exhaled nitric oxide; ESS, endoscopic sinus surgery; FeNO, fractional exhaled nitric oxide; nNO, nasal nitric oxide; NO, nitric oxide; ROC, receiver operating characteristic.

Table 3. The nNO and FeNO measurements in the studies differed in device, flow rate, and sampling site.

Author, Year [Reference]	Type	Device	Flow	Site/Maneuver	Velum Closure
Lindberg et al., 1997 [18]	nNO	Chemiluminescence CLD 700	0.66 L/min	One nostril olive, oral breathing	Not closed
Arnal et al., 1999 [20]	nNO	Chemiluminescence (Cosma)	0.7 L/min	One nostril olive, oral breathing	Not closed
Deja et al., 2003 [13]	Sinus gas NO	Chemiluminescence CLD 700	0.1 L/min aspiration (Tedlar bag)	Needle/cannula in maxillary sinus	NA
Degano et al., 2005 [21]	Sinus gas + nNO	Chemiluminescence (Cosma)	0.1 L/min (sinus), 0.7 L/min (nose)	Albertini drain; nasal olive	NR
Noda et al., 2012 [22]	Oral + nasal FeNO	NObreath (electrochemical)	50 mL/s, 16 s	Mouth closed, exhale via nasal adaptor	Exhalation itself
Taruya et al., 2015 [17]	Oral + nasal FeNO	NObreath (electrochemical)	50 mL/s, 16 s	Mouth closed, exhale via nasal adaptor	Exhalation itself
Liu et al., 2017 [25]	nNO	NIOX (handheld)	0.25–3 L/min	Nasal olive; slow exhalation against resistance	Resistance (≥10 cmH_2O)
Lee et al., 2020 [32]	nNO	Eco Medics CLD 88sp	300 mL/min	Each nostril; forced exhalation	High-resistance exhalation
Alexandersson et al., 2021 [35]	nNO	Aspiration + humming	NR	NR	Humming
Olonisakin et al., 2022 [37]	FeNO	NIOX VERO	NR (standard 50 mL/s)	Oral	Resistance
Tang et al., 2023 [14]	nNO	Sunvou (nanocoulomb)	5 mL/s	Nasal olive, tidal breathing	NR
Wu et al., 2024 [23]	nNO	NIOX MINO Nasal	NR	Nasal, on day of surgery	NR
Liang et al., 2026 [24]	nNO	Sunvou-CA2122	10 mL/s	One nostril occluded	Whistling

Abbreviations: FeNO, fractional exhaled nitric oxide; NA, not applicable; nNO, nasal nitric oxide; NO, nitric oxide; NR, not reported.

3.3. Pathophysiological Role and Clinical Significance of Nitric Oxide in Chronic Rhinosinusitis

Taken together, the mechanistic and clinical studies analyzed here indicate that NO is not a simple indicator of CRS severity or inflammatory status. Instead, the direction of NO change depends on the measurement compartment, inflammatory phenotype and endotype, sinus ostial patency, epithelial function, and the balance of the ARG-NOS axis.

NO functions in host defense, mucociliary clearance, vascular responses, and the regulation of epithelial function in the normal sinonasal mucosa. NO is produced in the paranasal sinuses of the upper airway and is subsequently delivered through the natural ostia to the nasal cavity, where it can be measured. Patients with chronic type 2 or eosinophilic inflammation exhibit increased iNOS expression and an accumulation of NO metabolites. In this context, NO likely contributes to mucosal defense and the maintenance of epithelial function, while also being implicated in tissue damage and remodeling within the setting of chronic inflammation. NO-related findings differ depending on the type and duration of inflammation. For example, increased NO levels and NOS expression can occur in chronic type 2 inflammation, whereas decreased local NO levels and reduced iNOS expression can manifest in acute sinusitis accompanied by sepsis. This suggests that the biological role of NO varies according to the type, duration, and severity of inflammation, as well as the immune status of the patient.

Reports indicating that iNOS-related NO production in nasal polyp tissue may be associated with increased vascular permeability, mucosal edema, inflammatory cell migration, and glandular activity suggest that NO actively participates in the formation of nasal polyps and tissue remodeling. In addition, experimental findings demonstrating that corticosteroid-induced activation of the Akt/eNOS signaling pathway maintains the expression of epithelial tight junction (TJ) proteins and epithelial barrier integrity by increasing NO production support the interpretation that NO is not merely a byproduct of the inflammatory response, but actively functions in sinonasal epithelial defense. However, further prospective and interventional studies are necessary to establish the causality of these relationships and their subsequent effects on the clinical course of the disease and treatment outcomes.

The ARG-NOS regulatory axis is of particular importance. By competing for L-arginine, ARG limits the production and local bioavailability of NO. The ARG-NOS regulatory axis may play a critical role in the pathophysiology of specific non-atopic CRS phenotypes. Furthermore, NO-related phenotypes are likely governed by the dynamic balance between ARG and NOS activity, rather than merely by the expression of a single enzyme. The ARG-NOS axis should therefore be recognized as a key regulatory pathway determining NO bioavailability in the sinonasal mucosa. This raises the possibility that modulating ARG activity or manipulating L-arginine anabolism and catabolism holds potential as a novel therapeutic strategy for CRS. In particular, future studies should investigate whether interventions targeting the ARG-NOS axis can confer clinical benefits in patients with CRS who exhibit a limited response to existing type 2-targeted biologic therapies.

A clinically important finding among the studies analyzed here is the apparent discrepancy between the levels of nNO and FeNO relative to the tissue expression of NOS. Many studies utilizing direct nNO measurements have reported that nNO levels in patients with CRS and CRSwNP are lower than those in healthy controls. This reduction is likely attributable to sinus ostial obstruction, decreased sinus ventilation, and epithelial or ciliary dysfunction, suggesting that nNO primarily reflects the ostial patency and local epithelial function of the sinuses. Observations that the nNO level remains low despite increased tissue expression of iNOS or eNOS underscore that the nNO concentration is not dictated solely by the tissue level of NOS.

In contrast, FeNO and tissue NOS expression tend to be elevated in patients with eosinophilic or type 2-dominant CRS. Previous evidence suggests that FeNO reflects the systemic or lower airway type 2 inflammatory burden more accurately than the structural state of local sinonasal lesions. However, because FeNO is influenced by a multitude of factors—including asthma control status, the use of inhaled or intranasal corticosteroids, allergic rhinitis, smoking, and specific measurement conditions—these confounding variables must be carefully considered when interpreting FeNO as an independent biomarker for CRS.

This discrepancy between nNO and FeNO levels provides a physiological rationale for distinguishing their potential clinical applications. nNO can be utilized to assess sinus ostial patency, sinus ventilation, and local sinonasal epithelial function, as well as to monitor the recovery of the local microenvironment following medical or surgical interventions. Conversely, FeNO may be more valuable for identifying eosinophilic or type 2-dominant CRS phenotypes and for detecting comorbid asthma or subclinical lower airway inflammation. Consequently, these measurements should be interpreted as complementary biomarkers: nNO reflects the structural and functional integrity of the local upper airway compartment, whereas FeNO serves as an indicator of the type 2 inflammatory burden within the lower airway or systemic compartment.

3.4. Limitations

Several methodological and interpretative limitations should be considered when evaluating the findings of this review. First, with respect to the review methodology itself, this work was conducted as a narrative review rather than a formal systematic review with quantitative meta-analysis. The literature search was restricted to a single database (PubMed) and English-language original articles, and title, abstract, and full-text screening was performed by a single author, which may introduce selection or publication bias and omit relevant non-English or grey literature. Furthermore, because the included studies varied substantially in study design, biomarker assays, and outcome reporting, formal statistical pooling or standardized risk-of-bias assessment was not feasible.

Second, several limitations of the current literature directly constrain clinical interpretation. The studies included in this review were predominantly cross-sectional with relatively small sample sizes, limiting causal inference, and they exhibited substantial heterogeneity regarding clinical phenotypes, inflammatory endotype definitions, allergic status, comorbid asthma, the presence of nasal polyps, smoking history, and therapeutic histories (including intranasal or inhaled corticosteroids and targeted biologics). Furthermore, measurement devices, anatomical sampling sites, exhalation flow rates, and methods of velum closure varied considerably across studies (Table 3), contributing to a wide and inconsistent range of reported nNO cutoff values (163–442 ppb) and precluding universal clinical thresholds. Therefore, future multicenter longitudinal studies employing standardized measurement protocols, rigorous phenotypic and endotypic stratification, and the systematic tracking of clinical outcomes—such as disease recurrence, revision surgery, and responsiveness to biologic therapies—are needed to validate the clinical utility of NO biomarkers in CRS.

4. Conclusions

The evidence reviewed herein demonstrates that the absolute NO level is unsuitable as a simple indicator of either protective or pathogenic processes in the pathophysiology of CRS. Instead, the biological effects of NO are highly complex, varying significantly depending on the specific anatomical compartment, inflammatory phenotype, and broader clinical context of the disease. NO production in the sinonasal mucosa is tightly regulated by the interplay between the expression and activity of NOS isoforms (iNOS and eNOS) and substrate com-

petition for L-arginine by ARG. Patients with chronic type 2 or eosinophilic inflammation typically exhibit upregulated iNOS and eNOS expression, increased NO production, and elevated FeNO levels. Conversely, in patients with severe acute sinus infection accompanied by sepsis, local iNOS expression and nNO levels are markedly diminished. Furthermore, the ARG-NOS regulatory axis dictates NO bioavailability and phenotypic FeNO patterns in specific CRS subsets. Consequently, the pharmacological modulation of ARG activity and L-arginine metabolism holds promise as a novel therapeutic strategy, though rigorous validation of its safety and efficacy is required prior to clinical implementation.

Clinically, nNO and FeNO serve as valuable noninvasive biomarkers; however, they reflect distinct physiological domains and must not be interpreted interchangeably. The clinical application and interpretation of these NO measurements must be highly individualized, carefully factoring in the anatomical compartment, CRS phenotype, inflammatory endotype, presence of nasal polyps, allergic status, and comorbid asthma. To definitively establish the clinical utility of nNO and FeNO, large-scale, multicenter, prospective cohort and longitudinal follow-up studies are essential. Such studies are necessary to standardize measurement devices and protocols, and to validate optimal diagnostic cutoff values stratified by specific phenotypes and endotypes.

Ultimately, a comprehensive understanding of the compartment-specific and phenotype-dependent functions of NO is crucial for maximizing the diagnostic and prognostic value of these biomarkers. Rather than viewing nNO and FeNO simply as isolated diagnostic markers, this review proposes that they be interpreted within an integrated pathophysiological framework that connects local sinonasal NO production, sinus ostial patency, and epithelial barrier function with the broader systemic burden of type 2 airway inflammation.

Author Contributions: Conceptualization, J.G.D., D.C.P. and S.G.Y.; data curation, S.H.L., H.O.K., J.M.L., Y.J.C. and M.K.S.; formal analysis, H.O.K. and J.M.L.; funding acquisition, S.S.K. and S.G.Y.; methodology, S.H.L., J.G.D., H.O.K., J.M.L., Y.J.C., M.K.S. and S.S.K.; project administration, S.G.Y.; visualization, S.H.L., D.C.P. and S.G.Y.; writing—original draft, S.H.L., J.G.D. and S.G.Y.; writing—review and editing, S.H.L., J.G.D. and S.G.Y. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea (NRF) grant funded by the Korean government (NRF-2025S1A5C3A03022311) (NRF-2018R1A6A1A03025124) (NRF-2022R1A2C1091779). This research was supported by a grant of the National Bio Bigdata Project, funded by four ministries (Ministry of Health and Welfare, Ministry of Science and ICT, Ministry of Trade, Industry and Resources, and Korea Disease Control and Prevention Agency) of Korea (RS-2024-00509118). This research was supported by a grant from the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (RS-2026-25542789). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ARG, arginase; AUC, area under the curve; CaM, calcium/calmodulin; CASP8, caspase-8; CRS, chronic rhinosinusitis; CRSsNP, CRS without nasal polyps; CRSwNP, CRS with nasal polyps; CT, computed tomography; ECRS, eosinophilic CRS; eNOS, endothelial NOS; ESS, endoscopic sinus surgery; FeNO, fractional exhaled NO; FEV_1/FVC, forced expiratory volume in 1 s/forced vital

capacity; IL, interleukin; iNOS, inducible NOS; LPS, lipopolysaccharide; NADPH, nicotinamide adenine dinucleotide phosphate; nNO, nasal NO; nNOS, neuronal NOS; NO, nitric oxide; NOS, nitric oxide synthase; NOSTRIN, NOS trafficking inducer; NT, nitrotyrosine; PCD, primary ciliary dyskinesia; PCR, polymerase chain reaction; PI, positivity index; PMN, polymorphonuclear leukocyte; p-eNOS, phosphorylated eNOS; ROC, receiver operating characteristic; SNOT-22, 22-item Sino-Nasal Outcome Test; TJ, tight junction.

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