Facteurs pronostics dans le traitement chirurgical de la rhinosinusite chronique

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ABBREVIATIONS

CRS	Chronic rhinosinusitis
NPs	Nasal polyps
OMC	Ostiomeatal complex
CT	Computed tomography
ATD	Aspirin triad disease
GERD	Gastroesophageal reflux disease
MCT	Mucociliary transport
AFRS	Allergic fungal rhinosinusitis
OSNs	Olfactory sensory neurons
UPSIT	University of Pennsylvania smell identification test
nNO	Nasal nitric oxide
NOS	Nitric oxide synthase
ppb	Part per billion
nCO	Nasal carbon monoxide
ppm	Part per million
HO	Heme oxygenase
ESS	Endoscopic sinus surgery
MRI	Magnetic resonance imaging
VAS	Visual analogue scale
ANOVA	Analysis of variance
MMA	Middle meatal antrostomy
tNAR	Total nasal airway resistance
ISA	Intracellular Staphylococcus aureus

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Prof. Sayed El Sherif

“If I have seen further it is by standing on the shoulders of giants”

-Isaac Newton-

RESUME

Le but de cette étude a été d'identifier certains facteurs pronostiques qui pourraient influencer le résultat à long terme de la chirurgie endoscopique rhino sinusienne chez 42 patients souffrant de rhinosinusite chronique resistant aux traitement médical. Nous avons évalué l'intensité des symptômes, les performances olfactives, la production nasale de monoxyde d'azote (NO) et de monoxyde de carbone (CO) et l'importance de l'infiltat inflammatoire des muqueuses rhinosinusienne avant l'opération et pendant une durée de 6 à 29 mois (moyenne de 16 mois) post opératoire. Une amélioration significative des symptômes a été observée chez 85,7% des patients. Aucune augmentation significative de la production nasale de NO n'a été observée. Par contre, la production de CO a été diminuée de façon significative. Les facteurs associés à un mauvais pronostic sont l'âge, la présence d'un syndrome de Widal, une importante éosinophilie tissulaire et la présence de staphylococcus intracellulaire.

INTRODUCTION

La rhinosinusite chronique (RSC) est une des maladies les plus fréquentes, affectant jusqu'à 19% de la population selon des études épidémiologiques effectuées aux USA. Les coûts socio-économiques de cette pathologie sont préoccupants. La RSC a une influence importante sur le fonctionnement de l'ensemble des voies respiratoires, en particulier l'asthme bronchique. La rhinosinusite chronique a un impact significatif sur la qualité de vie des patients affectés. Un certain nombre d'études épidémiologiques ont mis en évidence une augmentation des maladies cardiovasculaires en présence d'une RSC. Les mécanismes physiopathologiques de la rhinosinusite chronique sont probablement multifactoriels. La prise en charge thérapeutique consiste en général à proposer tout d'abord un traitement médical. Le traitement médical de la RSC comprend l'application endonasale de corticostéroïdes topiques et des lavages des fosses nasales au sérum physiologique. Plusieurs méta-analyses ont confirmé l'efficacité des corticostéroïdes topiques et/ou systémiques dans la RSC. Par contre l'indication à l'antibiothérapie reste sujet à controverse. En cas d'échec des traitements conservateurs, une prise en charge chirurgicale peut être proposée. Le développement des fibres optiques a fortement contribué à l'essor de la Rhinologie et de la chirurgie rhinosinusienne sous contrôle endoscopique. L'étiologie de la RSC étant probablement multifactorielle, les facteurs pronostiques ayant une influence sur les résultats à long terme du traitement chirurgical restent difficiles à identifier. Selon plusieurs articles de revues récents, l'asthme bronchique est probablement la comorbidité la plus fréquemment identifiée comme ayant une influence négative sur les résultats à long terme de la chirurgie rhinosinusienne. Lors

d'une étude clinique précédente, nous avions mis en évidence une corrélation significative entre l'importance de l'infiltration de la muqueuse du cornet moyen par des éosinophiles et les taux de récidive post opératoire. De multiples paramètres restent encore à évaluer. Il s'agit, entre autre, des performances olfactives, de la production de nasale de monoxyde de carbone (CO) et de monoxyde d'azote (NO). La présence de staphylococcus aureus intracellulaires a également été évoquée parmi les facteurs de mauvais pronostics.

Le but de cette étude a été d'identifier certains paramètres qui pourraient influencer le résultat à long terme de la chirurgie endoscopique rhinosinusienne. Nous avons évalué l'influence de la chirurgie endoscopique endosinusienne sur les performances olfactives, la production nasale de monoxyde d'azote (NO) et de monoxyde de carbone (CO). Quarante deux patients souffrant de rhinosinusite chronique ont été suivis pendant une durée de 6 à 29 mois (moyenne de 16 mois). Nous avons également mesuré un certain nombre de paramètres chez 20 sujets sains qui constituaient le groupe contrôle. En pré-opératoire, une anamnèse détaillée et un examen endoscopique des voies respiratoires supérieures avec quantification des anomalies anatomiques et de l'inflammation ont été réalisés. L'influence des symptômes de la rhinosinusite chronique sur la qualité de vie des patients a été évaluée avant et après l'intervention chirurgicale. Tous les patients ont bénéficié d'un CT-scan du massif facial. Les anomalies radiologiques ont été quantifiées selon l'échelle de Lund-Mackay. Les performances olfactives de chaque patient ont été évaluées en utilisant les Sniffin' Sticks. La production nasale de NO et de CO ainsi que la résistance respiratoire nasale ont été mesurées. Tous les patients ont bénéficié d'une chirurgie endoscopique rhinosinusienne sous anesthésie générale. Les différentes

procédures chirurgicales effectuées ont été évaluées selon le score de Lund. Tous les tissus réséqués lors de l'intervention chirurgicale ont été analysés par le même histo-pathologiste et la sévérité de l'inflammation chronique et la densité d'infiltration des muqueuses rhinosinusiennes par des éosinophiles ont été chiffrées. Une analyse immuno-histologique a été effectuée par microscopie confocale afin de mettre en évidence la présence de staphylococcus aureus intracellulaires.

1. INTRODUCTION

1.1. Definitions:

1.1.1. Chronic rhinosinusitis:

Chronic rhinosinusitis (CRS) with or without nasal polyps (NPs) is defined as an inflammation of the nose and the paranasal sinuses mucosa, characterized by at least two or more of the following symptoms: nasal obstruction, nasal discharge (anterior or posterior nasal drip), facial pain or pressure, and a reduction or loss of smell. Endoscopic examination may include edema and erythema of the middle meatus mucosa, mucopurulent discharge from the middle meatus, or polyps. Computed tomography (CT) of the head should confirm the presence of mucosal changes within the ostiomeatal complex (OMC) and/or the sinuses **[1, 2]**.

Rhinosinusitis can be classified according to the duration of symptoms into:

- Acute/intermittent: in which the symptoms last less than 12 weeks with complete resolution of symptoms.
- Chronic/persistent: in which the symptoms last more than 12 weeks without complete resolution of symptoms **[1]**.

1.1.2. Nasal polyps and CRS:

Nasal polyps and CRS are often considered together as one disease entity because it seems impossible to differentiate between them. Nasal polyposis is therefore considered the ultimate stage of CRS. Chronic rhinosinusitis has been recently classified into: CRS without NPs and CRS with NPs **[1, 2]**.

1.1.3. Widal syndrome:

Aspirin triad disease (ATD), first reported by Widal in 1922, is a well-known syndrome associating NPs, bronchial asthma, and non-steroidal anti inflammatory drugs (NSAIDs) intolerance **[3]**. Samter and Beers subsequently suggested that the disorder is a nonimmunologic systemic disease **[4]**. The pathophysiology of the disease remains elusive but may be related to a disorder of eicosanoids biosynthesis. Eicosanoids are hormones, but unlike most hormones, are not stored by cells. In response to extracellular stimuli, they are synthesized and released within 5 to 60 seconds. They are products of arachidonic acid metabolism, which is acted upon by cyclooxygenase and lipoxygenase. The cyclooxygenase pathway involves the creation of prostaglandins and thromboxanes, whereas the lipoxygenase pathway serves to create leukotrienes and hydroxy eicosatetranoic acid. Cyclooxygenase is irreversibly inhibited by aspirin and NSAIDs resulting in a shift to the lipoxygenase pathway. These lipoxygenase products promote bronchoconstriction and vasodilatation resulting in the increased airway edema and secretions associated with the inflammatory process in ATD **[5, 6]**.

1.2. Epidemiology:

Chronic rhinosinusitis is one of the most common health problems, with significant direct medical costs and severe impact on lower airway disease and general health outcomes [**7, 8]**. When reviewing the current literature on CRS, it becomes clear that giving an accurate estimate of the prevalence of CRS remains speculative, because of the heterogeneity of the disorder **[1]**. It was estimated that CRS, defined as having “sinus trouble” for more than 3 months, affects 15.5% of the total population in the United

States **[9]**. By screening a population in Belgium without sinonasal complaints, it was estimated that 6% of subjects suffered from chronic nasal discharge and 40% had signs of mucosal swelling of more than 3 mm on MRI **[10]**. Patients with certain diseases develop CRS more often, for example, 25-30% of allergic patients **[11]**, 43% of asthmatic patients, 37% of patients with transplants, and 54-68% of patients with AIDS **[12]**.

1.3. Histopathology:

1.3.1. Histopathology of CRS without NPs:

In CRS without NPs, the mucosal lining is characterized by goblet cells hyperplasia, thickening of the basement membrane, limited subepithelial edema, and prominent fibrosis. The main infiltrating cells of the mucosa are neutrophils. Eosinophils and mast cells can also be found, though their percentage share is much lower than in CRS with NPs. A range of inflammatory mediators such as interleukins (ILs) and cytokines have been shown to be increased. These include IL-1, IL-3, IL-5, IL-6, IL-8, tumour necrosis factor-α (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF), intracellular adhesion molecule-1 (ICAM-1), myeloperoxidase, eosinophil cationic protein (ECP), and major basic protein (MBP). Chronic rhinosinusitis without NPs is characterized by a predominantly neutrophilic inflammation with a lesser contribution to eosinophilia. These cytokines and inflammatory mediators profile is similar to that one found in acute viral rhinosinusitis. These findings therefore suggest that the underlying pathological process might involve yet unknown inflammation, after both acute and chronic infection, or an immune response to chronic infection **[2, 13]**.

1.3.2. Histopathology of CRS with NPs:

In CRS with NPs, changes referred to as polypoid degeneration of the nasal and paranasal mucosa develop. Epithelial cells become flattened and colloidal fluid, composed of albumins and other plasma proteins, accumulates in the subepithelial layer. High accumulation of the fluid in the subepithelial layer leads to development of pseudocysts which can bulge the epithelium producing polyps. Between pseudocysts, there is a network built from fibronectine fibers surrounded by fibroblasts and eosinophils. However, the largest eosinophil infiltration develops at the top of the bulge, which forms the polyp, just under the epithelial layer. High accumulation of both mature eosinophils and progenitor cells for eosinophils and mast cells is found in the tissue of NPs. Simultaneously, other elements of the subepithelial layer of mucosa such as capillaries, mucous glands, and nerve fibers tend to be reduced. The nasal polyp tissue shows an increased concentration of the following cytokines and chemokines: IL-1β, IL-3, IL-5, IL-8, IL-13, TNF-α, GM-CSF, RANTES (regulated upon activation normal T-cells expressed and secreted), eotaxins as well as increased expression of adhesion molecules ICAM-1, vascular cell adhesion molecule-1(VCAM-1) and selectins. Taking into account the participation of T lymphocytes, the cytokine profile in NPs is described as mixed Th1/Th2, irrespective of the coexisting allergy. Nasal polyps manifest also a high concentration of the following mediators: histamine, tryptase and ECP, also irrespective of the coexistent allergy **[2, 13, 14]**.

A small percent of CRS with NPs does not have its source in the eosinophilic inflammation of the mucosa of the nose and paranasal sinuses, but the inflammation is dominated by neutrophils. Nasal polyps, in which neutrophils predominate, develop

primarily in the course of CRS which accompanies disturbances in the paranasal sinuses ventilation as well as congenital and acquired disturbances of the local and general immunity. Classic examples of CRS with neutrophil-dominated NPs include cystic fibrosis and primary ciliary dyskinesia. In all these diseases, chronic bacterial infection plays an essential role in the development of CRS and hence the domination of the neutrophil cells in the polyp tissue. The cytokine profile of the neutrophil-dominated NPs resembles the profile encountered in acute rhinosinusitis **[2, 15]**.

1.4. Pathophysiology:

The pathophysiology of CRS remains unclear for the scientific community. Three factors, however, appear crucial for the normal physiologic functioning of the sinuses: patency of the OMC, normal mucociliary transport, and normal quantity and quality of secretions. Disruption of one or more of these factors can predispose to endonasal and paranasal sinuses infection and chronic inflammation **[16]**. The factors which should be mentioned as playing a role in the complex pathogenesis of CRS include:

a. Environmental factors:
    - Infection (bacteria, fungi, and viruses).
    - Medications, irritants, toxic substances, pollutants.
    - Trauma, surgery.
b. Systemic host factors:
    - Specific hyperreactivity (allergic inflammation).
    - Non-specific hyperreactivity.
    - Hormonal rhinitis.

- Gastroesophageal reflux disease (GERD).
- Immunodeficiency.
- Congenital mucociliary dysfunction.
- Dysfunction of the autonomic nervous system.

c. Local host factors:

- Anatomical conditions.
- Acquired mucociliary dysfunction.
- Tumors **[2, 13]**.

1.4.1. Role of anatomic obstruction of sinus ostia in CRS:

When sinus ostium obstruction occurs, a pathologic accumulation of mucosal secretions develops, that may serve as a medium for bacterial overgrowth. The sinus cavity develops an acidic pH, and anaerobic conditions evolve. Eventually, the mucosal surface, including the cilia, is damaged, and ineffective mucociliary clearance further promotes CRS. Moreover, obstruction of the sinus ostium leads to the development of negative intrasinus pressure due to resorption of air within the sinus cavity. Therefore, the obstruction triggers the development of a vicious cycle of ciliary dysfunction, retention of secretions, obstruction of lymph drainage, edema, as well as mucosal hyperplasia, which may lead to chronic disease **[17, 18]**.

Clearly a number of anatomical variations in the anatomy of the nasal cavity in the region of the OMC may predispose patients to transient or persistent sinus ostial obstruction. The most common variations include severe nasal septal deviations, hypertrophic and pneumatized middle turbinate (concha bullosa), and atypical migration of ethmoid air cells during sinus development (agger nasi cells, Haller's cells). Although the presence of

any of the previously described anatomical variants does not correlate by itself with the development of CRS, their compromise of the nasal cavity self cleaning mechanisms and OMC specifically is the main determinant of resultant sinus pathology **[19]**.

1.4.2. Role of altered mucociliary transport in CRS:

Mucociliary transport (MCT) system represents the self cleaning mechanism of the airway and the first barrier of the nasal cavity and nasal sinuses against various biological and physical insults. The MCT time is significantly delayed in patients with CRS. This may be due to an increase in the viscoelasticity of the mucus following the acute release of mediators of inflammation, together with a reduction in the periciliary stratum, which slows down the metachronus wave of the MCT **[20]**. In addition, the increase in the viscosity of mucus may be related to an increase in goblet cell number and secretory activity. A decreased ciliary beating frequency correlates well with an increase in the number of goblet cells **[21]**. However, evidence is gathering that in the majority of patients with CRS, ciliary dyskinesias are primarily the consequence rather than the cause of CRS. Secondary ciliary dyskinesia found in patients with CRS is probably reversible although restoration takes some time **[22]**.

Three hereditary disorders, primary ciliary dyskinesia (immotile cilia syndrome or Kartegner's syndrome), cystic fibrosis, and Young syndrome, have been shown to be always associated with MCT failure, leading to infertility and chronic sinopulmonary infections **[19]**.

1.4.3. Role of bacteria in CRS:

Although it is often hypothesized that CRS evolves from acute rhinosinusitis, the role of bacteria in CRS is far from clear. Three categories of bacteria have been reported in

patients with CRS. The first category includes microorganisms similar to that found in acute rhinosinusitis (S. pneumoniae, H. influenzae, and Moraxella catarrhalis). The second category includes microorganisms particular to CRS, and includes Staphylococcus aureus and Pseudomonas aeruginosa. These organisms have frequently been identified in patients whose condition has not improved after both antibiotic treatment regimens and endoscopic sinus surgery (ESS). The third category includes Staphylococcus epidermidis, other coagulase-negative staphylococci, Corynebacterium species, and anaerobes **[19]**.

Some authors suggest that as chronicity develops, the aerobic and facultative species are replaced by anaerobes. This change may result from the selective pressure of antimicrobial agents that enable resistant organisms to survive, and from the development of conditions appropriate for anaerobic growth, which include the reduction of oxygen tension and the increase of acidity within the sinus. However, the contribution of the different pathogens to the disease remains unclear **[23, 24]**.

Recently, the role of bacterial biofilm in CRS has been studied by several authors. Bacteria in nature exist in two states, free-floating planktonic bacteria and matrix-enclosed bacteria, which are attached to a surface (biofilm) **[25]**. Biofilms are defined as organized community of bacteria adherent to a surface and contained in an extracellular polymeric substance made of exopolysaccharides, nucleic acids, and proteins **[26, 27]**. The biofilm forming capacity of S. aureus and P. aeruginosa is associated with poor medical treatment results and plays an important role in the chronicity of the disorder **[28]**. Another mechanism that may contribute to long-term endonasal persistence of S. aureus in some patients is the intracellular reservoir, which was documented recently and

was found to be associated with recurrent attacks of rhinosinusitis with persistence of monoclonal S. aureus infection and poor antibiotic treatment results **[29, 30]**.

1.4.4. Role of fungi in CRS:

The spectrum of fungal involvement in CRS runs from benign colonization to potentially life threatening invasive disease. Fungal colonization of the nose and paranasal sinuses appears to be a common finding in both normal and diseased states, although there is considerable debate over the prevalence of colonization.

Allergic fungal rhinosinusitis (AFRS) is a distinct subset of CRS in which patients will have positive evidence of fungal allergy to the fungus colonizing their allergic mucin in the majority of cases. These patients with AFRS typically demonstrate the following characteristics: gross production of eosinophilic mucin containing non invasive fungal hyphae, NPs, characteristic radiographic findings, immunocompetence, and allergy to cultured fungi **[2]**. Recent studies suggest that fungi can play an alternate role in the development of CRS, whereby patients become sensitized by colonizing fungi through a non-IgE mediated mechanism. This sensitization is hypothesized to lead to local eosinophilic chemotaxis, inflammation, and tissue injury **[2]**. This concept of fungal rhinosinusitis encompasses most patients with CRS. This assertion was based on finding positive fungal culture by using a new culture technique in 96% of patients with CRS. However, the same percentage was found in controls. No increase in type I mediated hypersensitivity was found in patients as compared with controls. The term “eosinophilic chronic rhinosinusitis” was proposed to replace the previously used nomenclature **[31]**.

1.4.5. Role of allergy in CRS:

The contribution of allergic responses in CRS has long been controversial. It has been postulated that swelling of the nasal mucosa in allergic rhinitis at the site of sinus ostia may compromise ventilation and even obstruct the sinus ostia, leading to mucus retention and infection **[32]**. However, other epidemiological studies showed no increase in the incidence of CRS in the pollen season in sensitized individuals **[33]**. In a small prospective study, no difference in prevalence of purulent rhinosinusitis was found between patient with and without allergic rhinitis **[34]**.

Although an allergic cause of NPs had been presumed since the early 1930s **[35]**, this suggestion was challenged in the 1970s, when a retrospective study demonstrated that more NPs were found in the nonatopic group than in the atopic group **[36]**, and subsequent studies demonstrated that multiple positive skin test responses were less common in patients with NPs compared with responses in the general population **[37]**. However, tissue IgE concentrations have been found to be increased irrespective of skin test results, suggesting a possible local IgE production **[37, 38]**. Recent studies showed that specific IgE in NPs is unrelated to skin prick test positivity, and that total IgE correlates to markers of eosinophilic inflammation, although not to mast cell activation markers. Specific IgE to S. aureus enterotoxins A and B were found in 50% of eosinophilic NPs suggesting a possible role of superantigens as disease modifiers **[39]**.

1.4.6. Role of osteitis in CRS:

Mucosal changes has been well described in CRS, yet little is known about the underlying bone, despite clinical and experimental evidence suggesting that bone may be involved in CRS. Recent work has demonstrated that patients undergoing surgery for

CRS were found to have evidence of marked acceleration in bone physiology with histological changes including new bone formation, fibrosis, and presence of inflammatory cells. These findings are consistent with osteomyelitis. However, the term "osteitis" was used to describe the condition of the sinus bone because of the lack of a marrow space in the flat bones of the sinus cavity. This suggests that underlying bone may serve as a catalyst for CRS. However, to date bacterial organisms have not been identified in the bone in either humans or animal models of CRS **[1, 40]**.

1.4.7. Role of gastroesophageal reflux in CRS:

Recently, attention has been directed toward the role of gastroesophageal or esophagonasopharyngeal reflux in the pathogenesis of CRS. The mechanism by which reflux may affect the sinonasal cavity remains unclear, but three mechanisms have been proposed. The first mechanism suggests that direct reflux of gastric juice into the nasopharynx may cause mucosal edema and inflammation, leading to secondary obstruction of sinus ostia **[41, 42]**. The second theory revolves around a sensory mediated neurogenic inflammation, stating that chronic stimulation of the afferent nerve fibers may result in sinonasal edema and secondary ostial obstruction **[43 - 45]**. The final possible mechanism involves the possible role of Helicobacter pylori in CRS. It was possible to detect H. pylori in the sinus mucosa of some patients with CRS using polymerase chain reaction (PCR). However, whether H. pylori is one of the causative agents of CRS or is a result of CRS is not yet known **[46, 47]**.

1.4.8. Role of genetic factors in CRS:

Although chronic sinus disease has been observed in family members, no genetic abnormality has been identified linked to CRS. However, the role of genetic factors in

CRS has been implicated in patients with cystic fibrosis and primary ciliary dyskinesias as Kartegner's syndrome **[1]**.

Genetic etiology is suspected in the background of the formation of NPs as well, on the basis of familial aggregation **[48]**. According to several authors, HLA-DR antigens are expressed on the surfaces of the paranasal inflammatory cells in the paranasal mucosa and NPs **[49, 50]**. Nasal polyposis represents therefore a multifactorial polygenic disease **[51, 52]**. In NPs as compared with normal tissue, a number of genes with altered expression were identified. Moreover, IL-17 may play an important role in occurrence of NPs by overexpression **[53]**.

1.4.9. Role of immunodeficiency in CRS:

Deficiencies in the immune system, both local and systemic, can contribute to CRS. The similarities of CRS symptoms in immunodeficient patients and in normal individuals make it difficult to predict, if a patient's immune system is compromised. Many immunodeficient patients, particularly those with a humoral defect, have a history of repeated antibiotics treatment and sinus surgery before their immune disease is recognized. However, a recurrent or persistent CRS despite appropriate antimicrobials may raise suspicion that immunodeficiency is a factor contributing to the disease. The common immunodeficiencies associated with increased incidence of nose and sinus infections include selective IgA deficiency (SIAD), common variable immunodeficiency (CVID), IgG subclass deficiencies, selective antibody deficiency, X-linked agammaglobulinemia (XLA), and human immunodeficiency virus (HIV) **[16]**. Identification of immune defects is beneficial in several ways e.g. prophylactic antibiotic therapy can reduce or resolve symptoms in patients with mild immune deficits, and

intravenous immunoglobulin (IVIG) can be added in more refractory disease with beneficial results **[54]**. The immunological testing should be an integral part of the evaluation of patients with refractory CRS **[55]**.

1.5. CRS and olfactory dysfunction:

Chronic rhinosinusitis is a common cause of olfactory dysfunction accounting for at least 25% of smell loss cases. Olfactory dysfunction can result in problems including safety concerns, hygienic matters, appetite disorders, and change in emotional and sexual behavior **[56, 57, 58]**.

1.5.1. Mechanism of olfactory dysfunction in CRS:

The mechanism of olfactory dysfunction in CRS remains controversial. Traditionally, olfactory deficit in CRS patients have been attributed to nasal obstruction, respiratory mucosa edema, and decreased airflow to the olfactory cleft, making them conductive disorders **[59]**. However, more recently it was speculated that rather than being only an obstructive phenomenon from NPs, olfactory deficit may result from the direct effect of inflammatory processes on the olfactory epithelium, the surface of the olfactory receptors, or the olfactory mucus bathing the receptors. This speculation resulted from the observation that in anosmic CRS patients with NPs undergoing sinus surgery alone, 50% had a persistent postoperative olfactory deficit. This olfactory deficit was treated successfully by oral steroids **[60, 61]**. Later, this was documented by Kern who studied the pathology of the olfactory epithelium biopsies obtained from patients undergoing sinus surgery. He reported that the pathological process in the respiratory region of the nose could involve the olfactory mucosa resulting in hyposmia and anosmia **[62]**.

Theoretically, inflammation within the olfactory neuroepithelium could contribute to smell loss by various mechanisms. Mediators released by lymphocytes and macrophages triggers hypersecretion in respiratory and Bowman's gland **[63]**. Hypersecretion alters the ion concentration of olfactory mucus, affecting the microenvironment of olfactory neurons and possibly the transduction process **[64]**. In addition, these mediators may be toxic to neurons. In particular, inflammatory mediators released by lymphocytes, macrophages, and eosinophils most likely trigger caspase-3 activation in olfactory sensory neurons (OSNs). OSNs death by caspase-3 activation is a significant component of olfactory dysfunction in CRS **[65]**.

1.5.2. Methods for evaluation of olfaction:

Modern tests of olfactory function fall into three general classes: psychophysical, electrophysiological, and psychophysiological. Psychophysical tests are those in which the stimuli are presented and the subject is required to report some element of his or her perception (e.g., detection threshold, discrimination, identification). Electrophysiological tests are those in which a stimulus influence on the body is measured by electrical changes in the olfactory pathway in the CNS. Examples include the odor evoked potential, measured from electrodes placed on the scalp, and the electro-olfactogram, measured from electrodes placed near or upon the olfactory neuroepithelium. Psychophysiological tests rely on stimulus-related changes in measures typically controlled by the autonomic nervous system. Included are tests that measure changes in heart rate, blood pressure, respiration rate, and various indices of inhalation after odorant stimulation **[66, 67, 68]**. Because electrophysiological testing techniques have not proven

practical in most centers, psychophysical techniques have remained the mainstay in olfactory testing **[69]**.

Recently, several screening tests were developed and standardized **[70, 71, 72]**. A well known example is the University of Pennsylvania smell identification test (UPSIT)®. In this test, the odorants are liberated by scratching microencapsulated odor labels mounted on paper **[73]**. Another well established method of odor application is used in the sniffin' sticks test®. Here, the odorants are liberated through the tip of a pen **[74, 75]**. Because each test has its own merits in terms of facility of administration, cost, and reproducibility of results, no globally accepted gold standard smell test exists **[69]**.

1.5.3. Management of olfactory dysfunction with CRS:

Although improvement in olfaction is often possible, it is frequently transient and incomplete. In addition to surgery and antibiotics, systemic and topical steroids are helpful in alleviating olfactory dysfunction in this setting. Although systemic steroids are usually more effective than topically administered steroids, prescription of systemic steroids over a long period is not possible due to the side effects. Topical steroids with short courses of systemic steroids with long intervals between the courses may be an effective approach **[76]**.

1.6. CRS and nasal obstruction:

Nasal obstruction is a common symptom associated with acute and CRS. The sense of nasal obstruction in CRS is usually caused by nasal mucosal edema and congestion. The edema of the nasal mucosa is secondary to the extravasation of plasma proteins from veins. This phenomenon occurs in both cases of acute or chronic inflammatory diseases.

Nasal congestion is caused by swelling of nasal blood vessels, mainly erectile venous sinusoids that expand to restrict, and sometimes completely obstruct, the airflow through one or both nasal passages. Nasal obstruction associated with nasal congestion can be distinguished from anatomical obstruction by the application of a topical nasal decongestant (sympathicomimetic vasoconstrictor) spray. Any remaining restriction in the nasal airflow after treatment with topical decongestant is supposed to be due to anatomical obstruction such as deviated nasal septum, polyps or any type of tumors **[77]**.

1.6.1. Subjective and objective nasal obstruction:

The overall feeling of nasal obstruction, however, is thought to be due to a combination of factors, including nasal resistance to airflow and more subjective changes including psychological factors, Eustachian tube function, and cold air thermoreceptors in the nasal mucosa **[78]**. The objective nasal resistance to airflow, as measured by rhinomanometry, and subjective nasal sensation of airflow are two separate, indirectly related, modalities **[79 - 82]**. Inhalation of aromatics, especially L-menthol, has been shown to improve the sensation of nasal airflow without decreasing the objective nasal airway resistance. This effect is due to the stimulation of the cold receptors in the nasal vestibule and nasal cavity mucosa supplied by the trigeminal nerve. The same effect is achieved by sucking L-menthol lozenges which stimulate the palatal mucosa sensory nerves which belong to the trigeminal nerve **[83 – 88]**.

1.6.2. The nasal cycle:

The nasal cycle has been recognized for more than a century **[89]**, as a physiologic phenomenon that may cause a periodic change of the nasal airway patency. The nasal cycle is defined as the spontaneous change in nasal airflow due to the congestion and

decongestion of the nasal erectile venous sinusoids **[90]**. Despite this, the regulative mechanism of nasal cycle is unclear, and the manifestations of nasal cycle (e.g. pattern, frequency, duration, and amplitude) in both normal and pathologic conditions are not well understood **[91]**. The function of the nasal cycle is not clear, but it appears to be involved in various functions of the nose, including humidification and mucociliary clearance **[92]**. The origin of the nasal cycle is most likely located in the hypothalamus **[93]**. The duration of the nasal cycle, as shown in previous studies, varies from 30 minutes to 6 hours and was demonstrated in 13% to 80% of adults **[94]**. The nasal cycle has been reported in laryngectomized patients, which suggests that it is independent on afferent input from nasal airflow for its generation **[95]**.

1.6.3. Mechanism of nasal congestion:

Nasal congestion is caused by swelling of specialized erectile vessels named capacitance veins in the nasal mucosa. These are sometimes referred to as venous sinusoids, venous sinuses, or venous erectile tissue **[96]**. They are innervated by a dense network of sympathetic nerves, supplied via the cervical sympathetic nerves, which are distributed to the nose via branches of the maxillary and ophthalmic divisions of the trigeminal nerve **[90]**. The sympathetic nerves release neurotransmitters as noradrenaline and neuropeptide Y that cause an intense vasoconstriction. Stimulation of the nasal parasympathetic nerves induces vasodilatation, glandular secretion, and increased blood flow through nasal glands **[97 – 100]**.

Nasal congestion, associated with nasal infection, can be explained by the effects of local vasodilator mediators on nasal blood vessels and nerves. These mediators include histamine, prostaglandins, cytokines and interleukins (IL, MBP, ECP, RANTES, etc…)

which are synthesized locally in the nasal mucosa **[97, 100]**. Both histamine and prostaglandin E2 have been shown to inhibit the release of noradrenaline from the sympathetic nerve endings. This effect of inflammatory mediators on sympathetic nerve endings may be a further cause of nasal congestion **[101]**. In contrast, most of the inflammatory mediators stimulate the sensory nerve endings, which are very abundant in the nasal mucosa, leading to a neurogenic inflammation.

1.6.4. Objective assessment of nasal obstruction:

a. Rhinohygrometry:

In this simple test a cold mirror or shiny metal surface is placed beneath the nose and the size of the resultant condensation spot is measured. This was first described by Zwaardemaker in 1894 **[102]**. This test has stood the test of time as a qualitative clinical test of the nasal airway. However in studies of nasal physiology, the semi-quantitative nature of the technique renders it flawed for scientific studies **[103]**.

b. Nasal peak flow:

It may be measured as either inspiratory or expiratory maximal air flow. These methods have the disadvantages of alar collapse on forced inspiration and expulsion of secretions on expiration. Both methods are effort dependent and assume normal function of the lower airways **[104]**.

c. Rhinostereometry:

This is a method for measurement of the distance between the medial and lateral wall of the nasal cavity. The distance is determined using an inbuilt scale in a microscope, and the head position has to be fixed to assure measurements at the same position during repeated measurements. This gives only limited information of isolated structures and not

of the larger part of the nasal airway **[105, 106]**. Changes of 0.18 mm can be detected but this technique remains principally an experimental tool **[104]**.

d. Acoustic rhinometry:

This is a useful method to estimate the nasal anatomy and vascular volume changes associated with congestion. In this method, sound is presented to the nose via a nosepiece and the reflected sound is recorded by means of a microphone. The amplitude and delay in the reflected sound is then calculated by computer analysis. The minimum cross-sectional area of the nose and hence the anatomy, can then be estimated. However, this method does not offer any information about the dynamics of nasal airflow **[107]**.

e. Rhinomanometry:

It is the measurement of the pressure encountered by air passing through the nasal cavity **[108]**. Active anterior rhinomanometry (the patient is actively breathing through one nasal cavity while the narinochoanal pressure difference is assessed in the contralateral nasal cavity) is the most commonly used method of rhinomanometry. However, it can not be used in case of septal perforation, or in subjects with total nasal obstruction. Passive anterior rhinomanometry (the pressure is measured for each nasal cavity separately at a given airflow of 250 cm^3/sec) is fast but less accurate than both other types of rhinomanometry and is mainly used for nasal provocation tests. Active posterior rhinomanometry (the choanal pressure is measured via a tube placed in the back of the mouth while the airflow is measured for both nasal cavities simultaneously) is frequently hampered by gag and suction reflexes and is therefore limited to physiological studies or assessment of the nasal patency in the presence of septal perforations or if one nasal cavity is completely obstructed **[109]**.

f. Spirometry:

This is a portable device which is easy to use and has shown a good correlation with rhinomanometry in investigating airflow. However, nasal spirometry does not give a measurement of nasal airflow resistance but provides a measure of nasal airflow partitioning **[100]**.

1.7. Nasal nitric oxide (nNO):

Nitric oxide (NO) is a potent biological mediator that plays an important role in a variety of physiologic and pathophysiologic processes in the body. It has been proposed as a bronchodilator **[110]**, a vasodilator **[111, 112]**, and a major neurotransmitter **[113, 114]**. It was also proposed to have antimicrobial **[115, 116]**, antiviral **[117]**, and antitumor properties **[118, 119]**. In addition, it may act as an airborne messenger **[120, 121]**.

1.7.1. Nitric oxide synthesis:

Nitric oxide is synthesized from the semiessential amino acid L-arginine by the action of one of the three forms of nitric oxide synthase (NOS) with the production of L-citrulline (Fig. 1). For this chemical reaction there are several cofactors, among which are oxygen and nicotinamide dinucleotide phosphate (NADPH) **[122]**.

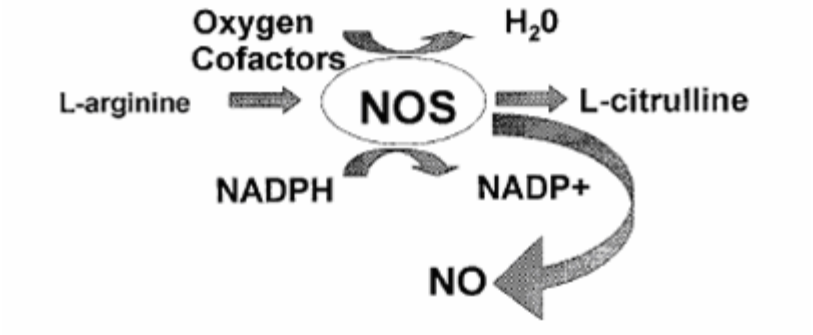

Fig. 1. Synthesis of nitric oxide.

The NOS exists in at least 2 isotypes: the constitutive NOS (cNOS) and inducible NOS (iNOS). cNOS may be named according to its location as endothelial NOS (eNOS) and neuronal NOS (nNOS) **[123]**. The NO produced is oxidized to nitrite (NO_2-), which can be used to monitor NO formation, nitrate (NO_3-), and peroxynitrite (ONOO-) ions **[124]**.

1.7.2. Nasal nitric oxide production:

It is not known with certainty whether the majority of NO released from the adult nose is derived from the epithelium lining of the nasal cavity or whether it comes also from the paranasal sinuses. Nitric oxide levels in the paranasal sinuses have been demonstrated to be several times higher than those in the nose and it was suggested that the majority of nNO originate in the sinuses **[125, 126]**. However, other studies suggested that 90% of nNO is derived from the nose itself **[127]**. Nitric oxide acts as a regulator of mucociliary function in the nasal airway. Animal studies have shown a dose-dependant increase in maxillary sinus ciliary beat frequency with the addition of L-arginine **[128]**. Very low, or absent, levels of nNO have been found in children with primary ciliary dyskinesia and cystic fibrosis **[129, 130]**. It has probably also an important role in host defense within the paranasal sinuses since NO is bactericidal and antiviral **[131]**. The nNO was found to be normal or increased in allergic rhinitis **[132, 133]** and asthma **[134]**. However, it was found to be decreased in acute rhinosinusitis, CRS, and NPs **[135 – 137]**.

The value of nNO as a measure of the effect of therapy on CRS is still uncertain. Recent studies have reported that nNO production was inversely correlated with the extent of sinus disease as documented by CT scans score, endoscopic score, and polyp stage **[137, 138]**. The nNO levels were found to increase significantly with medical and surgical treatment of CRS. This may be explained by the recovery of the ciliated epithelium of the

nasal cavities and the paranasal sinuses, which regains its normal ability to produce NO that passes through potent ostia **[138]**. Ragab *et al* demonstrated a high correlation between the nNO changes and the saccharine clearance test changes which strongly suggest the potential use of NO in diagnosis and even therapy of diseases affecting sinonasal mucociliary function **[138]**.

1.7.3. Measurement of nNO:

Nitric oxide can be measured directly or indirectly. Indirect methods have been used to measure NO level in the fluid phase where it has a very short half life. These include the measurement of nitrate and nitrite which are the stable end products of NO metabolism, or the use of immunohistochemical techniques to localize NOS. Direct measurement of exhaled NO is by means of chemiluminescence. In the analyzer sampled air containing NO is reacting with excess ozone, producing the radical NO_2. This returns to the resting NO_2 with the release of a proton. The NO concentration in the sample is proportional to the amount of electromagnetic energy emitted. Measurement is recorded in parts per billion (ppb) **[131, 139, 140]**. There is no standardized technique for measuring nNO and several methods have been used. The commonest method in use is that of direct nasal aspiration using the NO analyzer pump **[141]**. One difficulty in determining nNO concentration is ensuring that only air from the nasal airway is sampled without being diluted by air from the oropharynx and the lower respiratory tract **[131]**. The European Respiratory Society Force on measurement of NO in exhaled air and the American Thoracic Society have proposed sampling directly from the nose whilst the patient holds breath in full respiration. This leads to the closure of the soft palate and the absence of contamination with NO from the lower airway **[139, 142, 143]**.

1.8. Nasal carbon monoxide (nCO):

Carbon monoxide (CO) has recently emerged as an endogenously produced gaseous mediator that, like NO, appears to be involved in both upper and lower airway inflammation **[144]**. A role for CO as a peripheral transmitter involved in nonadrenergic, noncholinergic relaxation of the gut smooth muscles has been proposed **[145]**, and recent in vivo results indicated that exogenous CO can induce broncho-dilatation by an NO independent, cyclic GMP-related mechanism **[146]**.

1.8.1. Carbon monoxide synthesis:

There are many sources for CO production, but the degradation of heme to biliverdin and CO appears to be the dominating one in most species (Fig.2) **[147]**. The enzyme heme oxygenase (HO), with two isoforms (HO-1 and HO-2), seems to be the rate limiting factor. HO-1 is reported to be inducible, while HO-2 is constitutively expressed **[148]**. HO-2-like immunoreactivity is seen in nerve cell bodies, in intrinsic parasympathetic ganglia of guinea pig airways, and in local parasympathetic ganglia of human trachea and bronchi.

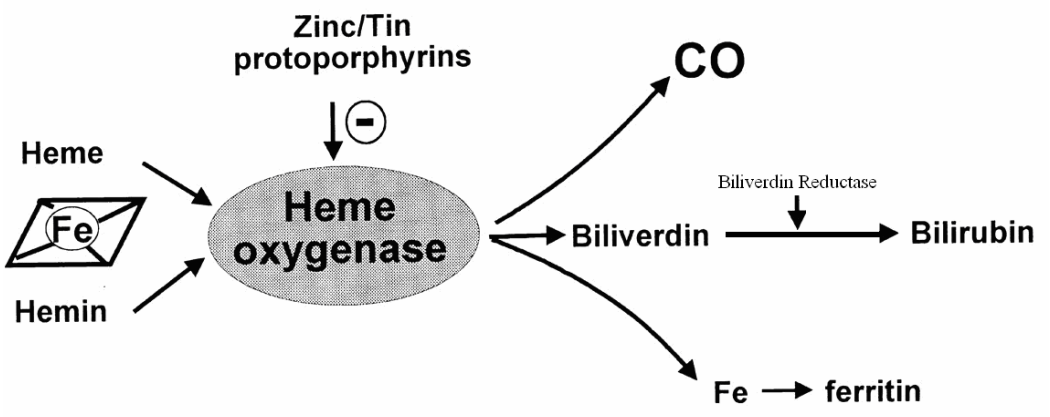

Fig. 2. Synthesis of carbon monoxide.

These findings suggest that CO serves as a modulator of synaptic neurotransmission in the lung **[149]**. Both HO-l- and HO-2-like immunoreactivities are also found in the airway smooth muscle and in the respiratory epithelium of guinea pigs, indicating a direct role for CO in airway regulation **[150]**.

The amount of CO in exhaled air was found to be increased among patients with asthma during periods of non-steroid treatment, during asthma exacerbation, and after allergen challenge **[151 – 153]**.

1.8.2. Nasal carbon monoxide production:

Yamaya *et al* indicated that CO, in analogy with NO, also can be produced in the upper respiratory airways, thus contributing to the total CO content of exhaled air **[154]**. A recent work by Andersson *et al* demonstrated that CO can be reproducibly measured in the nose and paranasal sinuses and the enzymes responsible for local CO production are present in the nasal airway. They found equal concentration of CO in the nose and paranasal sinuses, indicating a uniform production in both locations **[144]**.

The nCO levels were found to be higher in patients with allergic rhinitis than in normal patients with no increase in the lower airway CO production. This observation suggests that the nasal airways are the primary focus of inflammation as well as CO production during specific hyperreactivity. The nCO production was found to be increased also in patients with upper respiratory tract infections when compared to normal patients, with an increase in the lower airway CO production as well. These findings strongly suggest a role for CO as a marker or mediator of nasal inflammation **[155]**.

1.8.3. Measurement of nCO:

Carbon monoxide can be quantified by several different techniques. Most of the measurements in humans have been made using electrochemical CO sensors. Exhaled CO can also be measured by adjustable laser spectrophotometer, or by a near-infrared CO analyzer **[156]**. Near-infrared instruments, are used for continuous monitoring of atmospheric CO, and are fairly sensitive and stable. However, they are larger than electrochemical CO sensors and sensitive to water and CO_2 concentrations **[147]**.

1.9. Radiographic diagnosis of CRS:

The role of radiographic modalities is to provide an accurate display of the regional morphology and show the nature and location of ostiomeatal obstruction. Since an increasing number of patients undergo ESS as a therapeutic regimen for their disease, appropriate use of radiographic modalities is critical in providing a "roadmap" for the surgeon to delimit the surgical procedure as well as ensure its safety and accuracy **[157]**.

1.9.1. Standard plain X-ray films:

Although plain film technology might be less costly than other diagnostic measures with a lower dose of radiation exposure, it falls short of providing adequate diagnostic information. Plain films fail to provide the required information on patient's anatomical variations, the paranasal sinus perimeter, and the extent of inflammatory disease. Thus, because of its low sensitivity and specificity plain films are inadequate for diagnosis or to guide surgery **[2]**. This technique has no place nowadays in the management of CRS.

1.9.2. Computed tomography (CT scan):

This is the imaging modality of choice confirming the extent of pathology and the anatomy. Given its resolution of the regional bony anatomy and mucosa, it has proved to be the optimal modality in providing the anatomic roadmap for the surgeon performing ESS. Information afforded by the coronal plane has proven to correlate with the endoscopic information and has been the favored plane to study the patient's anatomy and plan a surgical procedure. However, the axial CT sections provide more adequate assessment of the posterior ethmoid and sphenoid sinuses, as well as, the exact location of the optic nerve and internal carotid artery **[32, 158, 159]**.

CT staging of CRS:

Several authors have attempted to use the CT information, specifically the volume of inflammatory disease within the paranasal sinuses, in an attempt to stage patients with rhinosinusitis. The various staging systems are primarily focused on the presence of and the quantity of the inflammatory disease within the paranasal sinus. The most accepted staging system is the one proposed by Lund-Mackay **[2, 160]**.

Low dose CT scan:

One concern regarding the performance of routine CT scans of the paranasal sinuses is that of radiation exposure, particularly to the lens of the eye. Conventional CT scanning is performed at 225 to 390 Milli-amperes (mAs), a level exposing the patient to a moderate radiation dose. However, it was possible to reduce the dose during scanning to levels between 80 to 160 mAs without compromising the diagnostic value of the scan or precluding its utility in preoperative planning. Soft tissue contrast is slightly decreased when a lower radiation dose is used. However, this decrease does not affect the

sensitivity and specificity of the scan. For the evaluation of CRS, the use of low-dose CT is highly recommended **[161]**.

1.9.3. Magnetic resonance imaging (MRI):

Although MRI is superior to CT in the delineation of mucosal disease, it is not routinely used in evaluating patients for ESS. Poor delineation of the bone-air interface results in poor visualization of the ostiomeatal complex **[162]**. The MRI may be useful in combination with the CT in cases of suspected neoplasia, encephalocele, meningocele or intracranial complications. However, it is not the primary imaging modality in CRS **[163]**. Three-dimensional reconstruction software that allows the fusion of CT and MR images, has aided substantially in preoperative planning of complex cases involving tumors or lesions in close proximity to major vascular and neurological structures **[164]**.

1.10. Medical treatment of CRS:

Medical treatment has a prominent role in the treatment of CRS and can be valuable in reducing the risk of recurrent NPs especially in patients who previously underwent one or multiple surgical interventions. In CRS, patients may show an improvement in subjective symptoms to an extent of approximately 25% in the so-called “stable episodes” over a 4-week period, whereas objective clinical parameters vary insignificantly **[165]**. Steroids, used topically or systemically or both, generally have a strong anti-inflammatory effect and can reduce eosinophilia, as they directly interact with several chemokines and cytokines involved in the inflammatory process. The suppressive effect on the T-cell production of IL-5 is an especially important aspect in this regard **[166, 167]**. Several prospective studies, involving objective measurement of nasal function, have established

the role of topical steroids in CRS **[168–170]**. Systemic corticosteroids have been evaluated in nasal polyposis and seem to result in temporary symptomatic relief, as well as helping to delay or facilitate surgical interventions **[171, 172]**. In order to avoid the side effects, a standardized administration protocol for oral steroids was suggested for NPs. It includes a daily dosage of 1 mg/kg body weight as a single dose during the breakfast for 5 days, maximum 4 times per year **[173]**. All patients diagnosed with aspirin intolerance have a considerable chance of improvement or decreased risk of recurrence, if adaptive desensitization therapy is performed **[165]**. Antibiotics have not been established as an effective treatment in patients with CRS since the role of bacteria in its pathogenesis is still doubtful **[174, 175]**. A number of clinical reports have stated that long-term, low-dose macrolide antibiotics are effective in treating CRS with improvement of symptoms between 60% and 80% in different studies **[176, 177]**. In a prospective randomized controlled trial, low dose erythromycin for 3 months and endoscopic sinus surgery showed the same subjective and objective improvement, except for the nasal volume which was better in the surgery group, after one year follow up **[178]**. The mechanism of the macrolides action probably involves down regulation of the local host immune response as well as downgrading of the virulence of colonizing bacteria. No evidence of beneficial effect of antihistamines in the treatment for CRS is found, except if allergic rhinitis is an underlying condition **[1, 179]**. Mucolytics have been suggested, by a cohort study, to decrease the duration of treatment **[180]**. Local antifungal preparations have been used following the introduction of the fungal hypothesis. Amphotericin B as nasal/sinus lavage showed 75% subjective improvement in one study **[181]**; whereas, in another study, its effect was equal to saline lavage **[182]**.

In CRS with NPs, combined topical corticosteroids with amphotericin B lavage for 4 weeks have led to disappearance of the polyps in 48% of previously operated patients **[183]**. Nasal and antral irrigations with saline or hypertonic saline have been shown to be effective treatment in terms of alleviation of symptoms and improvement of endoscopic signs. Hypertonic saline is preferred to isotonic treatment as it improves the mucociliary clearance **[1, 184]**.

1.11. Endoscopic Sinus Surgery (ESS):

Endoscopy was first applied to the nose and paranasal sinuses in the 1970s by Messerklinger **[185, 186]**. Since its introduction, ESS has become the standard surgical option for the treatment of CRS. Endoscopic Sinus Surgery is based on two main principles. The first principle is that obstruction of the narrow clefts of the anterior ethmoid (the ethmoidal infundibulum and frontal recess) leads to obstruction of the maxillary, frontal and anterior ethmoid sinuses. Stated another way, persistent disease in one of these sinuses is most likely due to undiagnosed, untreated anterior ethmoid disease **[187]**. The second principle is that the relief of obstruction in the anterior ethmoids may allow the other sinuses to drain and return to normal. It is implied in this concept that the mucosal disease is reversible with adequate drainage **[188]**. The operation can be performed under local or general anesthesia depending on the preference of the surgeon and the patient **[189, 190]**. Septal correction during ESS is typically best achieved with an endoscopic approach. Endoscopic septoplasty allows the deviated nasal septum to be addressed under excellent visualization, without the necessity either to change to a head light or to change instrumentation **[189–191]**.

2. AIM OF THE WORK

The main objective of this study is to evaluate:

1. The impact of some of the prognostic factors mentioned in the literature (old age, anatomic variants, associated co-morbidities, extent of the disease, previous sinus surgery, tissue eosinophilia, and intracellular residency of S. aureus) on the subjective and objective long-term outcome of ESS in CRS patients;
2. The difference in the olfactory functions and nNO between healthy individuals and CRS patients;
3. The effect of ESS on the olfactory functions, nasal airway resistance, nNO, and nCO in the different groups of patients;
4. The level of nNO nCO in the different groups of patients before and after surgery, to find out if they can be used to monitor treatment of CRS;
5. The correlation between the different diagnostic tools and the studied variables.

3. PATIENTS AND METHODS

3.1. Study design:

This is a retrospective study with a prospective follow up of a case series of patients who underwent ESS for the management of CRS during the period between January 2004 and September 2006 in the Rhinology-Olfactology Unit of the clinic of Otorhinolaryngology Head and Neck Surgery, Geneva University Hospitals. The follow up period ranged between 6 and 29 months with a mean of 16.29 ± 1 month.

3.1.1. Inclusion criteria:

- Inflammation of the nose and paranasal sinuses for more than 12 months, despite adequate medical treatment, characterized by two or more of the following symptoms:
  - Blockage/congestion;
  - Discharge: anterior/post nasal drip;
  - Facial pain/pressure;
  - Reduction or loss of the sense of smell.

and either

- Endoscopic signs:
  - Polyps;
  - Mucopurulent discharge from middle meatus;
  - Oedema/mucosal obstruction primarily in the middle meatus;
  - Anatomical deformities of the septum and/or the turbinates.

and/or

- CT changes: mucosal changes within ostiomeatal complex and/or sinuses.

Only patients who attended all the follow up visits and underwent all the pre- and post-operative investigations were included in the study.

3.1.2. Exclusion Criteria:

1- Immune deficiency or suppression.

2- Ciliary motility disorders.

3- Wegner's granulomatosis and other granulomatosis diseases.

4- Sino-nasal malignancy.

5- Systemic disease (e.g. cancer, severe cardiovascular disease).

6- Age below 18 years.

3.1.3. Control group:

Twenty healthy adults without any nasal complaints were also recruited as a control group. For them we measured only the olfactory threshold and nNO level.

3.2. Pre-operative evaluation:

3.2.1. History:

a) Personal history: Name, age, sex, occupation, and environment (smoking, exposure to irritants).

b) Complaint and present history: Analysis of the patient's chief complaints with special emphasis on CRS symptoms.

c) Medical history: Previous medical treatment for CRS (antibiotics, topical and systemic corticosteroids, etc...) or for any other disease (allergy, hypertension, asthma, GERD, etc...) including questions about the dose and duration of treatment and the achieved results. It included also past history of surgery.

d) Family history: History of allergy, asthma, polyposis, migraine, genetic diseases, etc….

3.2.2. Endoscopic examination:

Technique:

Diagnostic nasal endoscopy was done for all patients at the time of initial evaluation in the outpatient clinic and the findings were recorded. Diagnostic nasal endoscopy is done while the patient is seated in the upright position and the examiner is standing on his right side. Examination is performed with the 0 degree wide angle 4mm telescope. The first endoscopical examination is done before vasoconstrictor application to differentiate between mucosal disease and anatomical disease. Then the nose is sprayed with Cocaine HCl 5% or Xylocaine-adrenaline 1% for local anesthesia and vasoconstriction. First the telescope is introduced along the floor of the nose to the nasopharynx. This allows inspecting the septum, the inferior turbinate, the inferior meatus, the nasolacrimal duct, and the Eustachian tube orifice. In the second step the telescope is advanced between the inferior and middle turbinate to the sphenoethmoidal recess. This allows visualizing the middle, superior, and supreme turbinate with their corresponding meati. The third step includes visualizing the middle meatus. The uncinate process, bulla ethmoidalis, accessory maxillary sinus ostia, and frontal recess can be seen according to the degree of

pathology present. Finally the telescope is directed superiorly to have a look on the olfactory cleft.

Endoscopic score:

We used the endoscopic appearance score from Lund for quantifying the pre-operative state of the nasal cavities **[192]**. The scoring was done before applying the local anesthetic-vasoconstrictor spray to avoid changes of the mucous membrane and alteration of the appearance of discharge and edema. The presence of polyps, discharge, edema, scarring or adhesions and crusting were determined endoscopically and scored as 0, 1, or 2 points. (Table 1). Absence of polyps = 0; presence of polyps confined to the middle meatus = 1; presence of polyps beyond the middle meatus = 2. No edema = 0; mild edema = 1; severe edema = 2. No discharge = 0; clear and thin discharge = 1; thick and purulent discharge = 2. By adding the left and right scores, a pre-operative score of 0-12 was given to each patient.

For post-operative assessment, scarring and crusting are added to the score where 0 = absent; 1 = mild; and 2 = severe. A post-operative score of 0-20 was given to each patient during the final evaluation.

Characteristic	Right	Left
Polyp (0,1,2)		
Edema (0,1,2)		
Discharge (0,1,2)		
For post-operative assessment:		
Scarring (0,1,2)		
Crusting (0,1,2)		
Total Score:		

Table 1. Endoscopic appearance score [192].

3.2.3. Questionnaire:

The patients were asked to rate their symptoms on a visual analogue scale (VAS) of 1- 5, where "1" means no symptom present, "2" means mild symptom, "3" means moderate symptom, "4" means severe symptom, and "5" means the most severe symptom. The symptoms evaluated were nasal obstruction (right and left), anterior nasal discharge and post-nasal drip (right and left), headache, and facial pain. A total symptoms score (6 - 30) was obtained for each patient. The same questionnaire was used after 3 months and during the final evaluation. Success was defined as 5 points or more decrease in total symptoms score. Failure was defined as 5 points or more increase in total symptoms score. No change was defined as 1-4 points increase or decrease in total symptoms score.

3.2.4. Investigations:

a) CT scan:

CT scans were done for all patients preoperatively to determine the extent of pathology and to detail the anatomy with identifying the anatomical variations that may have implications on surgery. CT scans were strictly done after adequate medical treatment. CT scans were never done during acute attacks of rhinosinusitis or upper respiratory tract infections. CT scans were obtained in coronal, axial, and sagittal planes for all patients.

For purpose of staging of CT scan findings, we used the Lund-Mackay staging system (Table 2), being simple and reliable **[160]**. Each sinus (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal) is graded between 0 and 2 (0 = no abnormality, 1 = partial opacification, and 2 = total opacification). The ostiomeatal complex is scored

as “0” when non-obstructed and “2” when obstructed. A total score of 0-12 is considered for each side separately, and then a total score of 0-24 is obtained for each patient.

Sinus System	Right	Left
Maxillary (0,1,2)		
Anterior Ethmoids (0,1,2)		
Posterior Ethmoids (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Ostiomeatal Complex (0 or 2 only)		
Total Points		

Table 2. The Lund-Mackay CT staging system [160].

b) CO measurement:

CO in exhaled and sampled air was measured with the use of an infrared analyzer (Fisher Rosemount NGA 2000, provided by FLS Airloq AB, Stockholm, Sweden). According to the manufacturer, the minimum detectable concentration of CO was 0.2 ppm. The analyzer was calibrated with known concentrations of CO for measurements in the range of 0 to 10 ppm. Gaseous nitrogen (Air Liquide Gas AB, Malmo, Sweden) was used between every set of measurements for baseline verification and 0 calibration. All measurements were made at room temperature (22°C - 24°C). Ambient levels of CO were continuously recorded and were subtracted from measured CO values to compensate for alternating background levels. All subjects were seated in an upright position and all measurements were repeated 3 times with a resting period of 2 to 3 minutes between measurements. Measurement of nasal CO levels was done before surgery, after 3 months, and during the final evaluation.

A nasal olive of suitable size was gently introduced into the nasal vestibule and nasal air was drawn into the CO analyzer by a vacuum pump (0.4 L/mm). The contralateral nostril was left open, allowing a stream of room air to enter the nose while the subject was constantly breathing through the mouth. This allows for a small risk of contamination of nasal air with air from the lower airways. This was the basic sampling technique for CO sampling used throughout the study, when not stated otherwise.

c) NO measurement:

Nasal NO measurements were performed with a NO chemiluminescence analyzer (Exhalizer CLD 77 AM; Ecophysics, Dürnten, Switzerland) and the recommended breath-holding technique **[139, 142, 143]**. The analyzer was calibrated weekly with a known amount of NO (84.6 ± 2% ppb NO in nitrogen, 200 bar, 7.2 ppb NO_2; AGA gas AB, Sundbyberg, Sweden). Ambient levels of NO were recorded and were subtracted from measured NO values to compensate for alternating background levels. All subjects were seated in an upright position and all measurements were repeated 2 times with a resting period of 2 to 3 minutes between measurements.

A nasal olive of suitable size was gently introduced into the nasal vestibule and was connected directly to the sampling tube (teflon) of the NO analyzer (sampling rate 0.38 L min^{-1}). Patients were asked to breath through the mouth, without speaking or swallowing. The contralateral nostril was left open. Before starting the NO measurements, each subject was asked to perform the same above-mentioned procedure while nasal CO_2 was measured to test the subjects capability to perform a correct velopalatinal closure. Only persons, capable to perform a correct velopalatinal closure were included in the study.

NO analyzer signal output was fed to a computer data acquisition program (NO Analysis Software WBreath MFC Application, Version 3.0, Medizintechnik AG, Zurich, Switzerland) with a real time display of NO versus time written directly to the computer's hard disc as a data file. This program plotted NO concentrations against time and produced a graphic output. After 30 seconds of breath-holding, a plateau in the NO level was observed on the screen. Software extrapolation of the mean from this plateau was accepted as the on-line measurement value.

d) Testing of Olfactory Performance:

- Orthonasal Testing:

Psychophysical testing of olfactory function was performed with the validated Sniffin' Sticks test® **[193]**. Odors are presented to the patients in felt tip pens. The pens had a length of 14 cm, with an inner diameter of 1.3 cm. Instead of liquid dye the tampon was filled with liquid odorants or odorants dissolved in propylene glycol, to a total volume of 4 ml. For odor presentation the cap was removed by the experimenter for 3 seconds and the pen's tip was placed approximately 2 cm in front of both nostrils. This test encompasses three different approaches.

First, odor thresholds are assessed for n-butanol with stepwise dilutions in a series of 16 dilutions. Thresholds are determined using the single staircase technique based on a three-alternative forced-choice task. Second, patients are asked to discriminate between different odors. For each discrimination task, three pens are presented, two containing the same odor and the third containing the target odorant which, again, comprises a three-alternative forced-choice task. The target odors should be recognized in a series of 16

trials. To prevent visual detection of the target sticks, subjects were blindfolded with a sleeping mask. Third, a series of 16 odors was presented to the patients together with a list of four verbal descriptors for identification. Subjects were asked to identify the odors using this multiple forced-choice approach.

- Retronasal Testing:

We performed retronasal olfactory testing by using odorized powders as described and previously standardized presented to the oral cavity, so that orthonasal and gustatory stimuli were avoided **[194]**. Twenty odors were chosen for the retronasal testing: coffee, vanilla, cinnamon, cacao, raspberry, orange, garlic, strawberry, cloves, nutmeg, onion, cheese, curry, milk, banana, mushroom, coconut, lemon, paprika, and celery. Odorous powders were applied to the midline of the tongue on a fenestrated plastic stick for 3 seconds. Like with orthonasal testing, participants were asked to identify the odor from a list of four items. After administration of each powder, participants rinsed their mouth with water.

e) Rhinomanometry:

Active anterior rhinomanometry was done for all patients pre-operatively. Measurement was done for both nasal cavities separately using the Rhinometer 200 (ATMOS, Lenzkirch, Germany). Resistance values were obtained after 10 breaths at 150 Pa and values are given in $Pa/cm^3/sec$. Measurements were taken under controlled conditions and repeated 10 minutes after topical vasoconstriction with 100 µL of 1% phenylephrine/dimentinden solution (Vibrocil; Novartis Consumer Health, Basel, Switzerland).

f) Allergy and immunology testing:

Every patient underwent an allergic testing (prick test) and an immunologic work-up, including the evaluation of a possible immunoglobulin deficiency including IgG subclass deficiencies. Patients who had any immunological deficiency were excluded from the study.

3.3. Operative procedures:

All operations were done under general anesthesia in the Rhinology-Olfactology Unit of the Otorhinolaryngology Head and Neck Department, Geneva University Hospitals. All the operations were performed by the same surgeon. All operations were done endoscopically with an endoscopic camera and monitor display.

3.3.1. Operative technique:

Both nasal cavities are packed with small Merocel pledgets having a ligature tail soaked in adrenaline 1:1000 for vasoconstriction. The excess solution is well squeezed out before applying the pledgets. The pledgets are left in situ for 10 minutes and then removed. A mixture of 1% lidocaine with adrenaline (1:100,000) is used for injection under the mucosa at the anterior attachment of the middle turbinate for vasoconstriction and prevention of neurogenic inflammation that may result from surgical trauma. Turbinate scissors are then used to resect approximately the anterior inferior one third of the middle turbinate. Then anterior ethmoidectomy, posterior ethmoidectomy, and sphenoidotomy are performed according to the extent of the pathology in the pre-operative CT scan. Middle meatus antrostomy of a suitable size (1-2 cm) is done if indicated with preservation of the uncinate process when possible as we appreciate its protective role for

the mucosa of the maxillary sinus. Any accessory ostia are included into the middle meatus antrostomy to avoid circulation of secretions. The middle meatus antrostomy is dilated superiorly, inferiorly and posteriorly. No dilatation is done anteriorly to preserve the uncinate process and to avoid injury to the lacrimal apparatus. Inferior meatus antrostomy is done in some case with extensive pathology in the maxillary sinus to allow better visualization of the sinus and elimination of the pathology present. The frontal recess is then cleaned if necessary with exploration and widening of the frontal sinus ostium with preservation of the mucosa as much as possible to avoid post-operative scar formation and stenosis. Septoplasty and inferior turbinoplasty are done under endoscopic control if indicated. The endoscopic intervention is done in the wider side, and then the septum is corrected from this side, followed by the endoscopic intervention in the previously narrower side.

At the end of the operation an oval haemostatic tampon with a ligature tail (STIP, Audio Technologies, Piacenza, Italy) is inserted into the ethmoidal cavity. If septoplasty is also done another merocel laminated nasal dressing with drawstring and ventilation tube (Medtronic, XOMED, FL, USA) soaked with an ointment of betamethasone dipropionate and gentamicin (Diprogenta; Essex Chemie, Luzern, Switzerland) is inserted in each side.

3.3.2. Surgery Score:

We used a modification of the surgical score proposed by Lund for staging the surgical procedures **[192]**. We added septoplasty and inferior turbinoplasty to the original score. A total score of 0 – 18 was given for each patient. (table 3).

3.3.3. Bacteriological examination:

Nasal swabs were taken from the nasal vestibule, middle meatus, and posterior part of the nasal cavity near the choana for bacteriological examination.

Detection of intracellular S. aureus was done according to the technique previously described by Clement *et al* **[29]**.

	Right	Left
Uncinectomy (0,1)		
Middle meatal antrostomy (0,1)		
Anterior ethmoidectomy (0,1)		
Posterior ethmoidectomy (0,1)		
Sphenoidotomy (0,1)		
Frontal recess surgery (0,1)		
Reduction of the middle turbinate (0, 1)		
Inferior turbinoplasty (0,1)		
Septoplasty (0,2)		
Total Score		

Table 3. The modified surgery score [192].

3.3.4. Histopathological examination:

Mucosal samples from the middle turbinate and from the polyps were collected separately for each side. They are dehydrated and embedded in paraffin and stained in hematoxylin and eosin. Then they are examined under a Zeiss microscope at 40x magnification. Histological analysis included evaluation of the integrity of the pseudostratified columnar epithelium, the presence or absence of edema, and the density of inflammatory cells. We used a scale graded from 0 to 3, where "0" means no inflammatory cells and "3" represents abundant inflammatory cells. The degree of tissue eosinophilia was also graded in the same way.

3.4. Post-operative follow-up:

The nasal pack is removed after 48 hours, the nose is examined endoscopically and any secretions or blood clots are aspirated from the nasal cavity and sinuses. The patient is then allowed to go home. Post-operative treatment included regular saline nasal lavage

and topical corticosteroids. Antibiotics were restricted to cases with evidence of bacterial infection. Patients were followed up weekly for 4 weeks, then monthly for six months, then every six months. Post-operative care included removal of crusts, irrigation of the sinus cavity with normal saline or hypertonic saline solutions, and limited application of ointment with betamethasone dipropionate and gentamicin (Diprogenta, Essex Chemie, Luzern, Switzerland).

After three months the following parameters were recorded: intensity of the symptoms using the same preoperative questionnaire, tNAR, nNO and nCO measurement, and tests of olfactory performance.

At the final evaluation, which was done 16 ± 1 month, the following parameters were recorded: intensity of symptoms, post-operative endoscopic score, tNAR, nNO and nCO measurements.

3.5. Statistical Analysis:

All data were computerized for statistical analysis using the InStat3 package (GraphPad Software, Inc., San Diego, CA) for scientific statistical analysis. We used multiple analysis of variance (ANOVA) test for comparison of the measurements at different intervals with the Tukey-Kramer multiple comparison test. We used paired Student t test for comparison of the olfactory performance before and after surgery, and unpaired Student t test for comparisons between CRS patients and control groups. A linear regression analysis was used to identify the relation between the different variables. The level of significance was chosen at $p < 0.05$. The level significance was presented in the figures and tables in stars, where * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$.

4. RESULTS

4.1. Patients characteristics:

The study included 42 patients, 26 males (62%) and 16 females (38%). The age of the patients ranged between 21 and 75 years with a mean of 47.9 ± 1.85 years. The disease was unilateral in 4 patients (9.5%) and bilateral in 38 patients (90.5%). The following anatomical variants were detected: 36 patients (88%) had septal deviation, 7 patients (16.6%) had pneumatized middle turbinate (concha bullosa), 5 patients (11.9%) had paradoxically bent middle turbinate, and 3 patients (7.1%) had infra-orbital ethmoidal cells (Haller's cells) (Fig. 3).

The main pre-operative symptoms were nasal discharge (anterior and posterior) (90.5%), followed by nasal obstruction (88%), headache (66.6%) and facial pain (57.1%) (Fig. 4).

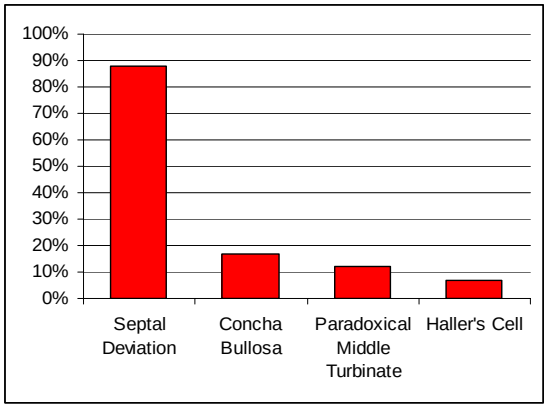

Fig. 3. Percentage of anatomic variants

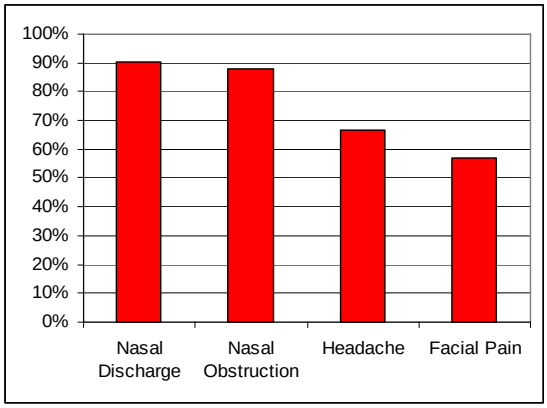

Fig. 4. Pre-operative symptoms

Lund-Mackay CT score ranged between 2 and 24 with a mean of 13.5 ± 0.92. The pre-operative endoscopic score ranged between 2 and 12 with a mean of 7.21 ± 0.44. Twenty one patients (50%) had NPs, 17 patients (40.4%) were documented to have allergy, 9 patients (21.4%) had bronchial asthma, 5 patients (11.9%) had aspirin intolerance triad (Widal syndrome), 8 patients (19%) had previous sinus surgery, 9 patients (21.4%) were

shown to have intracellular monoclonal S. aureus strains, and 10 patients (23.8%) were smokers.

4.2. Operative Procedure:

Operation	No. of patients	%
Septoplasty + Ethmoidectomy ± MMA*.	24	57.1
Ethmoidectomy ± MMA.	8	19.1
Septoplasty + Ethmoidectomy + Sphenoidotomy ± MMA.	7	16.7
Ethmoidectomy + Sphenoidotomy ± MMA.	3	7.1

* MMA = Middle Meatal Antrostomy.

Table 4. Type of the operations performed

The surgery score ranged between 4 and 14 with a mean of 8.85 ± 0.35. No major complications were reported in the series of patients. Minor complications encountered were septal abscess in one patient (1.7%) and post-operative bleeding in one patient (1.7%). During the follow up period, 3 patients (7.1%) required revision surgery which was done under local anesthesia. One patient required a revision sphenoidotomy and two patients required resection of synechiae between the middle turbinate and lateral nasal wall.

4.3. Subjective Evaluation:

Improvement of Symptoms:

The total symptoms score was significantly reduced from a preoperative mean of 21.69 ± 0.85 to 9.94 ± 0.61 after 3 months which represents a 54% reduction ($p < 0.001$), then it was 10.64 ± 0.61 during the final evaluation after 16 months ($p < 0.001$) (Fig. 5).

The nasal obstruction was significantly reduced from a pre-operative mean of 3.51 ± 0.19 to 1.35 ± 0.12 after 3 months which represents a 64% reduction ($p < 0.001$), then it was 1.75 ± 0.11 after 16 months ($p < 0.001$) (Fig. 6).

The nasal discharge was significantly reduced from a pre-operative mean of 4.4 ± 0.19 to 2.18 ± 0.24 after 3 months which represents a 50% reduction ($p < 0.001$), then it was 2.13 ± 0.18 after 16 months ($p < 0.001$) (Fig. 6).

The headache was significantly reduced from a pre-operative mean of 2.97 ± 0.25 to 1.54 ± 0.2 after 3 months which represents a 48 % reduction ($p < 0.001$), then it was 1.54 ± 0.15 after 16 months ($p < 0.001$) (Fig. 6).

The facial pain was significantly reduced from a pre-operative mean of 2.88 ± 0.28 to 1.51 ± 0.14 after 3 months which represents a 47.5 % reduction ($p < 0.001$), then it was 1.3 ± 0.12 after 16 months ($p < 0.001$) (Fig. 6).

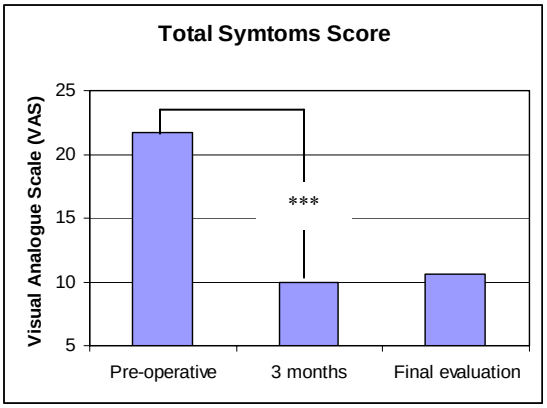

Fig. 5. Total Symptoms Score

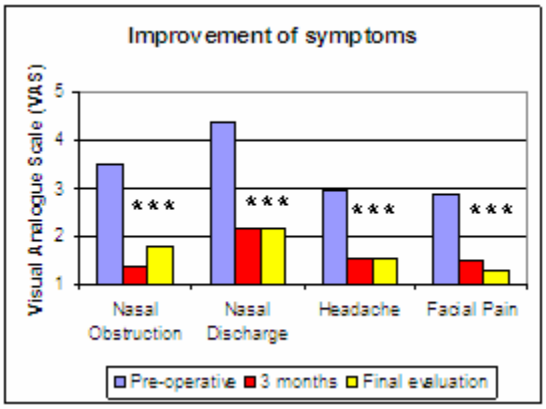

Fig. 6. Differential Symptoms Scores

The final evaluation showed that 36 patients (85.7%) had success, while 6 patients (14.3%) did not express significant improvement of their total symptoms score.

4.4. Objective Evaluation:

The nasal NO production was increased from a pre-operative mean of 503 ± 40.19 ppb to 527.73 ± 32.46 ppb after 3 months, then to 562.19 ± 27.08 ppb after 16 months; however, this increase was non significant. The nasal NO production in the control group was 685.91 ± 54.6 ppb, which is significantly higher than in the CRS group pre-operatively ($p < 0.001$), after 3 months ($p < 0.01$), and after 16 months ($p < 0.05$) (Fig. 7).

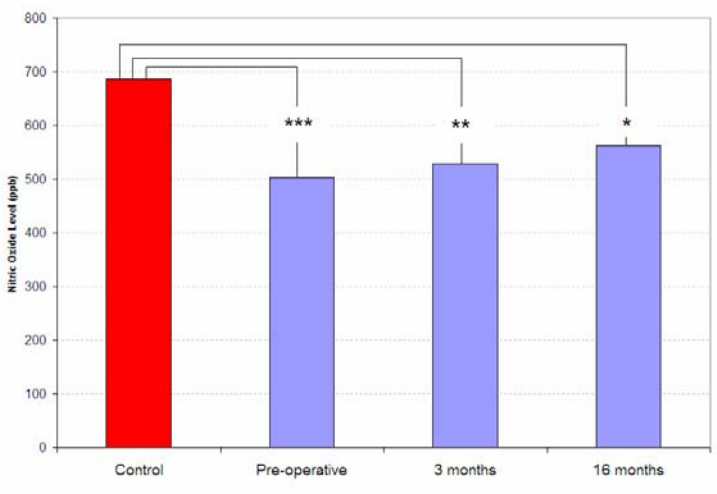

Fig. 7. Nasal nitric oxide production in CRS group and control group

The nasal CO level was slightly decreased from a pre-operative mean of 2.8 ± 0.43 ppm to 2.7 ± 0.43 ppm after 3 months, then it was significantly reduced after 16 months to a mean of 1.56 ± 0.26 ppm ($p < 0.05$) (Fig. 8).

Total nasal airway resistance (tNAR) was significantly reduced from a pre-operative mean of 1.26 ± 0.1 Pa/cm^3/sec to 0.93 ± 0.07 Pa/cm^3/sec after 3 months ($p < 0.05$), then it was 0.92 ± 0.06 Pa/cm^3/sec after 16 months (Fig. 9). The change of tNAR after topical vasoconstrictor was decreased from a pre-operative mean value of 0.67 ± 0.14 Pa/cm^3/sec to 0.54 ± 0.13 Pa/cm^3/sec after 3 months then to 0.38 ± 0.1 Pa/cm^3/sec after 16 months.

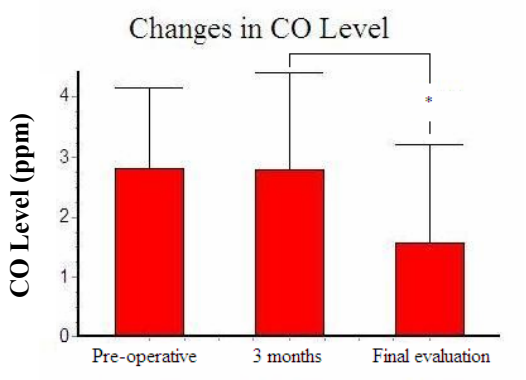

Fig. 8. Changes in CO level

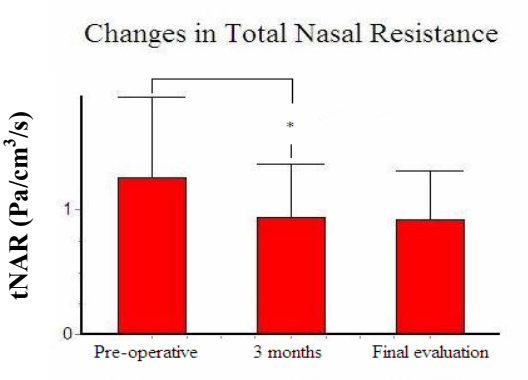

Fig. 9. Changes in tNAR

The orthonasal olfaction was slightly increased from a pre-operative mean of 6.73 ± 0.38 to 7.13 ± 0.35 after 3 months. The retronasal olfaction was 6.9 ± 0.38 pre-operatively and 7.03 ± 0.28 after 3 months. The olfactory threshold was 6.81 ± 0.59 pre-operatively and 6.83 ± 0.56 after 3 months. The olfactory threshold in the control group was 10.21 ± 0.35. This was significantly higher than the CRS group both pre-operatively ($p < 0.001$), and after 3 months ($p < 0.01$) (Fig. 10).

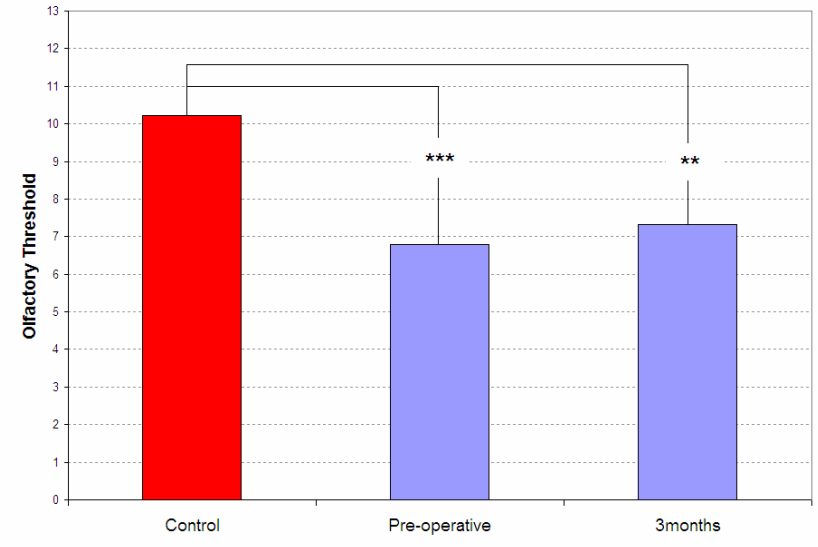

Fig. 10. The olfactory threshold in CRS group and control group

4.5. Study of the Prognostic Factors (Table 5):

- **Age:** A negative correlation was found between the age of the patients and the improvement of symptoms (r = -0.489, $p < 0.001$) and the olfactory threshold (r = -0.3423, $p < 0.05$).
- **Symptoms score:** A negative correlation was found between the intensity of symptoms and nNO level pre-operatively (r = -0.803, $p < 0.0001$).
- **Pre-operative endoscopic score:** A positive correlation was found between the pre-operative endoscopic score and the CT score ($r = 0.678$, $p < 0.0001$), the surgery score ($r = 0.312$, $p < 0.05$), and the degree of tissue eosinophilia ($r = 0.489$, $p = 0.001$).
- **Nasal NO level:** A negative correlation was found between the nNO level pre-operatively and the degree of eosinophilia (r = -0.411, $p < 0.05$). A positive correlation was found between the nNO level and the olfactory threshold pre-operatively (r = 0.6487, $p < 0.0001$) and after 3 months ($r = 0.4884$, $p <0.001$) (Fig. 11). In the control group the nNO level did not correlate with the olfactory threshold ($r = 0.12$, $p > 0.05$) (Fig. 12).

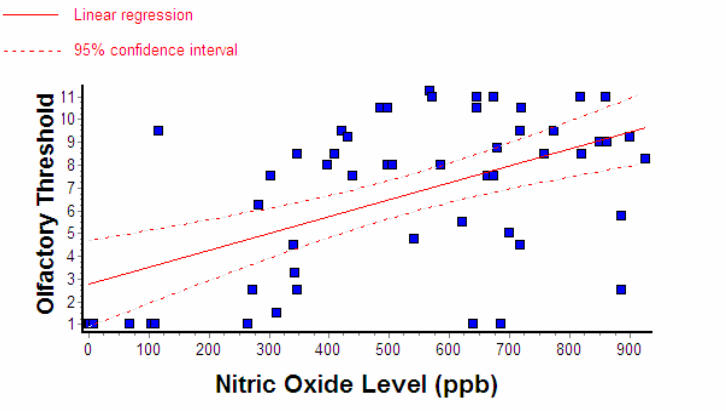

Fig.11. The correlation between olfactory threshold and nNO production in CRS group pre-operatively, (r = 0.648, $p < 0.0001$)

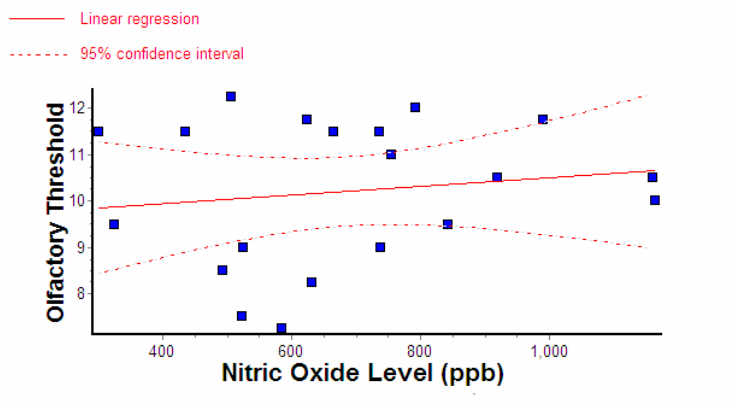

Fig.12. The correlation between nNO production and olfactory threshold in the control group (NS)

- **Nasal CO level:** A negative correlation was found between nCO level pre-operatively and the degree of tissue eosinophilia (r = -0.406, $p < 0.05$). A positive correlation was found between the nCO level and the olfactory threshold pre-operatively ($r = 0.452$, $p < 0.01$) but not after 3 months.
- **tNAR:** A positive correlation was found between the tNAR and the nasal obstruction score on VAS preoperatively ($r = 0.331$, $p < 0.05$), after 3 months ($r = 0.626$, $p < 0.0001$), and after 16 months ($r = 0.369$, $p < 0.05$).
- **Surgery Score:** A positive correlation was found between the surgery score and the CT score ($r = 0.517$, $p < 0.001$).
- **The degree of inflammation and eosinophilia:** A positive correlation was found between the degree of inflammation and the CT score ($r = 0.320$, $p < 0.05$). A positive correlation was also observed between the degree of eosinophilia and the CT score ($r = 0.507$, $p < 0.001$). A positive correlation was found between the degree of eosinophilia and the degree of change in tNAR after topical vasoconstrictor pre-operatively ($r = 0.351$, $p < 0.05$). However, this correlation was not found after 3 months or after 16

months. A negative correlation was found between the degree of eosinophilia and the olfactory functions pre-operatively ($r = -0.444$, $p < 0.01$).

- **CT score:** No correlation was found between the CT score and the olfactory functions or the improvement of symptoms.
- **Olfactory functions:** No correlation was found between the olfactory functions and the improvement of symptoms.
- **Anatomic variants:** No correlation was found between the anatomic variants and the improvement of symptoms.
- **Post-operative endoscopic score:**
-
-
- A positive correlation was found between the post-operative endoscopic score and the post-operative total symptoms score on VAS ($r = 0.314$, $p < 0.05$).

	Age	Total Symptoms Score	Pre-operative Endoscopic Score	Anatomic Variants	Lund-Mackay CT Score	nNO Level	nCO Level	tNAR	Olfaction	Surgery Score	Tissue Eosinophilia	Post-operative Endoscopic Score	Improvement of Symptoms
Age		NS	NS	NS	NS	NS	NS	NS	-	NS	NS	NS	-
Total Symptoms Score	NS		NS	NS	NS	-	NS	NS	NS	NS	NS	NS	NS
Pre-operative Endoscopic Score	NS	NS		NS	+	NS	NS	NS	NS	+	+	NS	NS
Anatomic Variants	NS	NS	NS		NS	NS	NS	NS	NS	NS	NS	NS	NS
Lund-Mackay CT Score	NS	NS	+	NS		NS	NS	NS	NS	+	+	NS	NS
nNO Level	NS	-	NS	NS	NS		NS	NS	+	NS	-	NS	NS
nCO Level	NS	NS	NS	NS	NS	NS		NS	+	NS	-	NS	NS
tNAR	NS	NS	NS	NS	NS	NS	NS		NS	NS	NS	NS	NS
Olfaction	-	NS	NS	NS	NS	+	+	NS		NS	-	NS	NS
Surgery Score	NS	NS	+	NS	+	NS	NS	NS	NS		NS	NS	NS
Tissue Eosinophilia	NS	NS	+	NS	+	-	-	NS	-	NS		NS	NS
Post-op. Endoscopic Score	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Improvement of Symptoms	-	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	

Table 5. The correlations between the different variables

4.6. Relevant characteristics (parameters) among the different groups of patients studied:

For studying the effect of the different factors, we divided the patients into different groups and compared each two groups separately as follows:

4.6.1. CRS with NPs vs. CRS without NPs:

The nNO production pre-operatively was found to be significantly higher in CRS without NPs with a mean of 615.68 ± 37.92 ppb vs. 442.66 ± 56.63 ppb in CRS with NPs ($p < 0.05$) (Fig. 13). After 3 and 16 months, nNO level was elevated in both groups without significant difference between them.

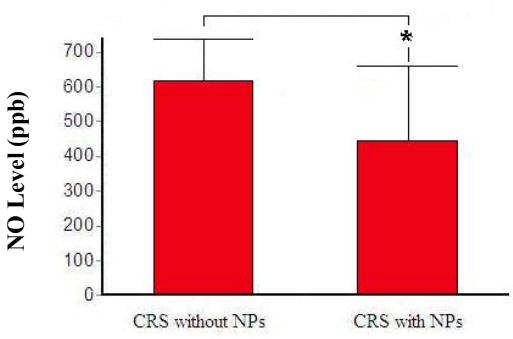

Fig. 13. The NO level pre-operatively in CRS with and without NPs

The olfactory threshold was significantly higher in CRS without NPs pre-operatively and after 3 months (Table 6).

	CRS without NPs (N = 21)	**CRS with NPs** (N = 21)	**t**	***p***
Pre-operative	7.72 ± 0.74	5.59 ± 0.72	2.046	*
3 months	8.08 ± 0.55	5.95 ± 0.87	2.048	*

Table 6. The olfactory threshold in CRS with and without NPs

The pre-operative endoscopic score and the surgery score were significantly higher in CRS with NPs. The post-operative endoscopic score was also higher in the polyposis group but the difference was not significant (Table 7).

	CRS without NPs (N = 21)	**CRS with NPs** (N = 21)	**t**	***p***
Pre-operative endoscopic score	4.90 ± 0.38	9.52 ± 0.37	8.604	***
Surgery score	8.14 ± 0.47	9.57 ± 0.47	2.126	**
Post-operative endoscopic score	1.04 ± 0.31	1.42 ± 0.41	0.7246	**NS**

Table 7. Pre-operative endoscopic score, surgery score and post-operative endoscopic score in CRS with and without NPs

Both the CT score and the degree of eosinophilia were significantly higher in CRS with NPs (Table 8).

	CRS without NPs (N = 21)	**CRS with NPs** (N = 21)	**t**	***p***
CT score	9.57 ± 1.02	17.47 ± 0.92	5.712	****
Eosinophilia	0.61 ± 0.18	1.76 ± 0.25	3.582	***

Table 8. Degree of eosinophilia and CT score in CRS with and without NPs

4.6.2. CRS with Widal syndrome vs. CRS without the syndrome:

The CT scores in patients with and without Widal syndrome were 20.4 ± 1.5 and 9.57 ± 1.02 respectively and the difference was statistically significant ($p < 0.0001$) (Fig.14).The degree of tissue eosinophilia in patients with and without Widal syndrome were 1.8 ±

0.58 and 0.61 ± 0.18 respectively and the difference was statistically significant ($p < 0.05$) (Fig. 15).

The post-operative endoscopic score was 3 ± 0.27, 1.23 ± 0.21 in patients with and without Widal syndrome respectively, and the difference was statistically significant ($p < 0.0001$).

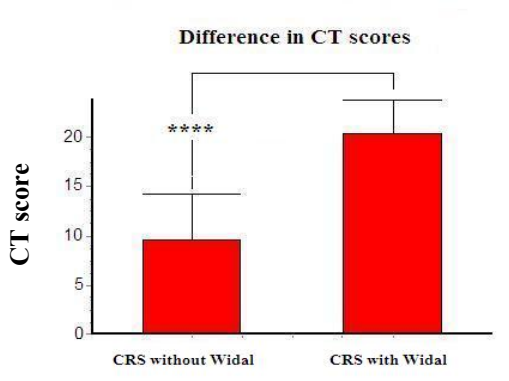

Fig. 14. Difference in CT scores between patients with and without Widal syndrome

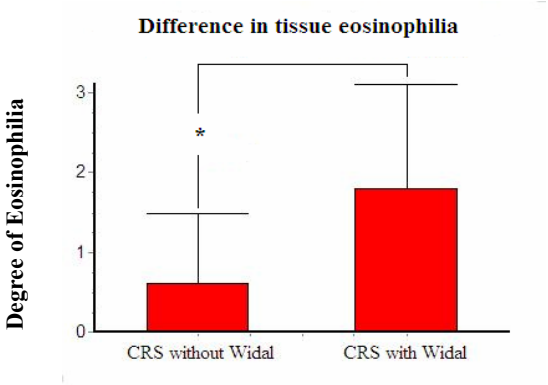

Fig. 15. Difference in tissue eosinophilia between patients with and without Widal Syndrome

4.6.3. CRS with allergy vs. CRS without allergy:

Both nNO level and nCO level were significantly lower in allergic patients than non-allergic patients pre-operatively (Table 9).

	CRS without allergy (N = 25)	**CRS with allergy** (N = 17)	**t**	***p***
nNO level	587.44 ± 42.36	395.32 ± 66.31	2.257	**
nCO level	3.599 ± 0.69	1.822 ± 0.23	2.213	**

Table 9. The nNO and nCO level in CRS with and without allergy

The olfactory threshold was significantly lower in allergic patients pre-operatively, while after 3 months it was lower but not significant (Table 10).

	CRS without allergy (N = 25)	CRS with allergy (N = 17)	t	*p*
Pre-operative	7.78 ± 0.72	5.63 ± 0.75	2.055	**
3 months	8.14 ± 0.62	6.07 ± 0.82	1.917	**NS**

Table 10. The olfactory threshold in CRS with and without allergy

The total olfactory functions in allergic and non-allergic patients pre-operatively was 15.5 ± 1.48 and 20.12 ± 1.66 respectively and the difference was statistically significant ($p < 0.05$) (Fig. 16). After 3 months the total olfactory functions in allergic and non-allergic patients was 21.75 ± 1.42 and 17.39 ± 1.36 respectively and the difference was again statistically significant ($p < 0.05$) (Fig. 17).

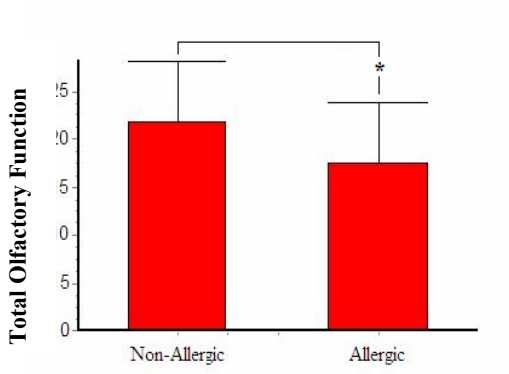

Fig. 16. Difference in olfactory functions between allergics and non-allergics pre-operatively

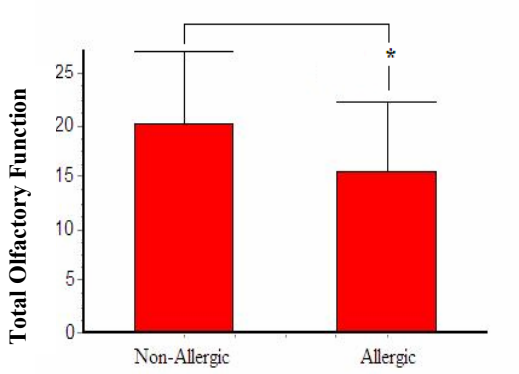

Fig. 17. Difference in olfactory functions between allergics and non-allergics after 3 months

4.6.4. CRS with bronchial asthma vs. CRS without bronchial asthma:

No significant difference could be found between both groups.

4.6.5. CRS in smokers vs. CRS in non-smokers:

The nCO level was significantly higher in smokers, pre-operatively, after 3 months and at the final evaluation (Table 11). None of them had quit smoking during the study.

	Non-smokers (N = 32)	Smokers (N = 10)	t	*p*
Pre-operative	1.93 ± 0.15	5.69 ± 1.34	5.012	****
3 months	2.13 ± 0.13	5.13 ± 1.37	4.393	***
Final evaluation	1.41 ± 0.26	3.75 ± 1.76	2.182	**

Table 11. The nCO level in smokers and non smokers

4.6.6. CRS with previous sinus surgery vs. CRS without previous surgery:

Pre-operative endoscopic score was significantly higher in patients with previous sinus surgery. However, no significant difference was found in the surgery score or the post-operative endoscopic score (Table 12).

	First surgery (N = 34)	Revision surgery (N = 8)	t	*p*
Pre-operative endoscopic score	6.75 ± 0.46	9.13 ± 1.12	2.161	**
Surgery score	9.02 ± 0.39	8.13 ± 0.76	1.015	**NS**
Post-operative endoscopic score	1.323 ± 0.30	0.875 ± 0.44	0.669	**NS**

Table 12. Pre-operative endoscopic score, surgery score and post-operative endoscopic score in CRS with and without previous surgery

Eosinophilia was significantly higher in patients with previous sinus surgery (Table 13).

	First surgery (N = 34)	Revision surgery (N = 8)	t	*p*
Eosinophilia	1 ± 0.19	2 ± 0.37	2.276	**

Table 13. Eosinophilia in patients with and without previous surgery

4.6.7. CRS with eosinophilia vs. CRS without eosinophilia:

The nNO level pre-operatively in patients with and without eosinophilia was 459.08 ± 62.69 ppb and 658.82 ± 35.35 ppb respectively and the difference was statistically significant ($p < 0.05$) (Fig. 18).

The nCO level pre-operatively in patients with and without eosinophilia was 2.04 ± 0.2 ppm and 4.63 ± 1.1 ppm respectively and the difference was statistically significant ($p < 0.01$) (Fig. 19).

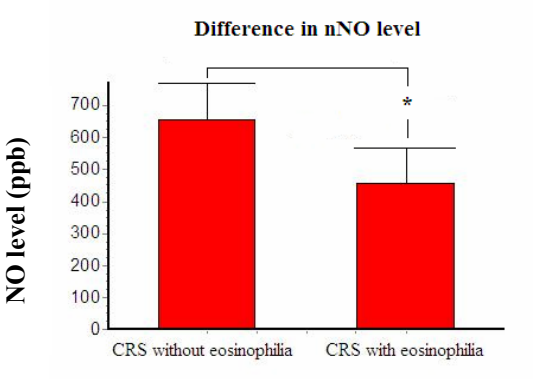

Fig. 18. Difference in nNO level between patients with and without eosinophilia

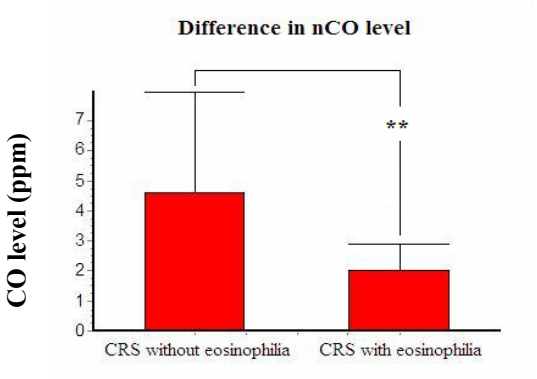

Fig. 19. Difference in nCO level between patients with and without eosinophilia

The olfactory threshold pre-operatively was significantly higher in CRS without eosinophilia, however, after 3 months the difference was not statistically significant (Table 14).

	CRS without eosinophilia (N = 17)	**CRS with eosinophilia** (N = 25)	**t**	***p***
Pre-operative	7.89 ± 0.62	5.59 ± 0.75	2.108	**
3 months	7.65 ± 0.98	6.69 ± 0.65	1.398	**NS**

Table 14. Olfactory threshold in CRS with and without eosinophilia

Both the pre-operative endoscopic score and the surgery score were significantly higher in patients with eosinophilia. However, no significant difference was found in the post-operative endoscopic score (Table 15).

	CRS without eosinophilia (N = 17)	**CRS with eosinophilia** (N = 25)	**t**	***p***
Pre-operative endoscopic score	5.64 ± 0.71	8.28 ± 0.47	3.195	***
Surgery score	7.82 ± 0.55	9.56 ± 0.40	2.599	**
Post-operative endoscopic score	1.58 ± 0.47	1 ± 0.30	1.108	**NS**

Table 15. Pre-operative endoscopic score, surgery score and post-operative endoscopic score in CRS with and without eosinophilia

The CT score in patients with and without eosinophilia was 15.76 ± 0.93 and 10.23 ± 1.52 respectively and the difference was statistically significant ($p < 0.01$) (Fig.20).

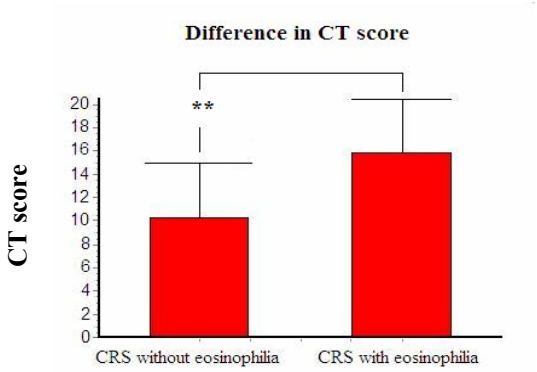

Fig 20. Difference in CT score in CRS with and without eosinophilia

The improvement of symptoms was significantly lower in patients with eosinophilia (Table 16).

	CRS without eosinophilia (N = 17)	**CRS with eosinophilia** (N = 25)	**t**	***p***
Improvement of symptoms	- 13.16 ± 1.15	- 8.7 ± 1.66	2.279	**

Table 16. Improvement of symptoms in CRS with and without eosinophilia

4.6.8. CRS with intracellular S. aureus (ISA) vs. CRS without:

The post-operative endoscopic score in patients with and without intracellular S.aureus was 2.55 ± 0.70 and 1.12 ± 0.70 respectively, the difference was statistically significant ($p < 0.05$) (Fig. 21).

The improvement of symptoms in patients with and without intracellular S.aureus was -7 ± 2.58 and -11.9 ± 1.01 respectively, the difference was statistically significant ($p < 0.05$) (Fig. 22).

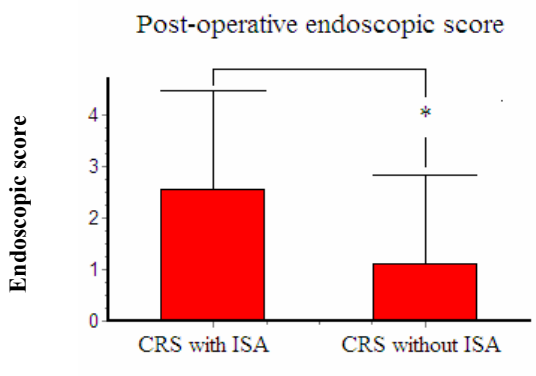

Fig. 21. Post-operative endoscopic score in patients with and without ISA

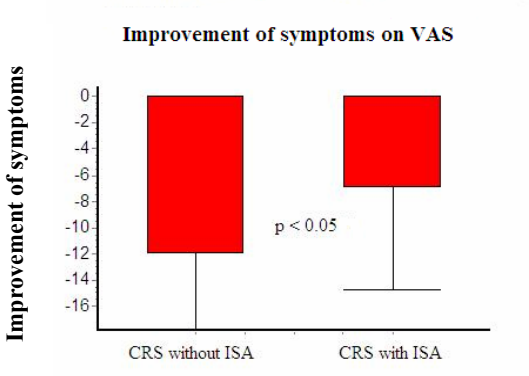

Fig. 22. Improvement of symptoms in patients with and without ISA

5. DISCUSSION

The main findings of this study are: 1) The surgical treatment of CRS is associated with an increase in nNO and a decrease in nCO production post-operatively. 2) The level of nNO correlates positively with the olfactory threshold in CRS patients, but not in healthy individuals. 3) The nNO correlates negatively with the degree of tissue eosinophilia. 4) The olfactory deficit in patients with NPs is most likely due to mucosal inflammation rather than airway obstruction. 4) The relevant prognostic factors for poor long-term outcome after ESS are old age, tissue eosinophilia, Widal syndrome, and the presence of monoclonal intracellular S. aureus.

5.1. Epidemiology:

The age of the patients studied was according to our selection criteria with a mean of about 48 years which is in agreement with previous studies of adult population **[195-197]**. Although there is no sex predominance in CRS without NPs, the literature reports a male to female ratio of 2.2:1 for NPs **[198, 199]** and this is in accordance with our series. The incidence of NPs in CRS is shown in previous publications to be between 30 and 55% **[196, 197, 200-203]**. According to the previous data, we suggest that a representative population has been studied.

5.2. Subjective evaluation:

In our case series which included CRS patients with and without NPs, the nasal discharge (anterior and posterior) was the main presenting symptom (90.5%), followed by nasal

obstruction (88%), headache (66.6%), and facial pain (57.1%). There is no agreement in the literature about the frequency of the presenting symptoms in patients with CRS. It depends mainly on the ratio of patients with NPs to patients without NPs in the studied group. Many authors emphasize that nasal obstruction, loss of smell and anterior nasal discharge are more severe in CRS patients with NPs, whereas headache and facial pain occur much less frequently **[204, 205]**. Damm *et al* in a similar group, showed that the main presenting symptom was nasal obstruction (92.4%) followed by post-nasal drip (87.4%), dry upper respiratory tract syndrome (68.3%), headache (63.6%), and asthmatic complaints (34.1%) **[206]**. Freidman *et al*, in a similar group, stated that the presenting symptoms in a descending order were nasal obstruction (93%), headache (75%), post-nasal drip (48%), and nasal discharge (28%) **[207]**. Giger *et al* studied a group of 60 CRS patients without NPs. They reported that the most common symptom was nasal obstruction (98%) followed by headache or facial pressure (67%) and anterior and/or posterior rhinorrhea (67%) **[208]**.

We used the visual analogue scale for quantifying the symptoms of the patients. It is a well validated tool for measuring a characteristic or attitude that is believed to range across a continuum of values and cannot be easily measured **[209, 210]**. There was a significant reduction of all symptoms at 3 months which was maintained till the time of final evaluation. The best improvement was in the nasal obstruction, followed by the nasal discharge, headache, and facial pain. The above results find their confirmation in previous clinical studies discussing the subjective results of ESS. Mehanna *et al* discovered that the patients who had nasal obstruction as their main symptom reported the greatest benefit, followed by headache and facial pain; while, patients with rhinorrhea

as their main symptom reported the least benefit **[211]**. Friedman *et al* found that the best results are obtained in nasal obstruction and headache; while, symptoms of nasal discharge and anosmia improves less significantly **[207]**.

In the present study, the success rate was comparable to those published previously. An overall 80% to 98% success rate for ESS is given in all fields of application in the literature **[32, 195, 212-218]**. However, a small percentage of patients (5% to 20%) do not improve or have recurrences, even in the hands of very experienced surgeons. Many authors attribute this to multiple factors including local and/or systemic host factors as well as environmental circumstances such as pollution, dust, pollens, cigarette smoke, and psychological factors **[213]**.

5.3. Objective evaluation:

5.3.1. Nasal NO (nNO):

The nNO level was found to be significantly lower in polyposis, allergy, and eosinophilia groups. There was a tendency for lower nNO levels in Widal syndrome, intracellular S. aureus carriers, previous surgery, and smoking groups, and higher nNO levels in patients with asthma but these trends didn't reach statistical significance.

Lindberg *et al* showed that patients with CRS had lower nNO levels than normal controls **[136]**. This is explained by the diminished number of ciliated cells which express iNOS, or the blockage of the sinus ostia **[136]**. The nNO level has been shown to be decreased in patients with NPs. Colantonio *et al* reported that nNO levels were reduced corresponding to the stage of NPs and that they rose on therapy. They also found a significant correlation between the visual reduction in polyp size and the increase in nNO

levels **[219]**. Nicoucar *et al* reported a significant increase in nNO level 3 months after ESS and attributed that to the patency of the sinus ostia and the improvement of inflammation post-operatively **[220]**. Ragab *et al* compared the surgical and medical treatment of CRS. They found that nNO level increased significantly in both groups after treatment, however, the surgical group showed more improvement and they attributed that to the role of the patency of paranasal sinus ostia. They found the nNO level to be significantly lower in CRS with NPs than CRS without NPs **[138]**. The nNO level was also shown to be increased in patients with bronchial asthma in many studies **[134, 221-223]**. Nasal NO level was shown to be lower in cigarette smokers **[224]**. This is explained by either the metaplasia of ciliated epithelium into cuboidal and squamous epithelium seen in smokers, which results in a decreased NO production **[136]**, or the inhibition of NO synthase (NOS) by the NO produced from tobacco smoke **[225]**. The nNO level seems to be elevated in allergic rhinitis in some studies **[132, 137, 226-234]**, but is similar in others in comparison with healthy controls and seems to be modified by corticosteroids **[138, 235-237]**. One might speculate that iNOS is upregulated in the nose during rhinitis **[238]**, which may explain the higher levels of nNO reported in some studies. On the other hand, the swelling of the nasal mucosa present during rhinitis might also lead to partial blockage of the sinus ostia, which would result in reduced passage of sinus NO to the nasal cavity where it is measured **[239]**. Hence, there is no unambiguous answer to the question whether nNO reflects allergic rhinitis or not. The low level of nNO level in allergic patients in our series could be attributed to two factors. Firstly, the effect of NPs, which were present in 66% of the allergic patients. It was shown before that the nNO levels are significantly lower in the allergic patients with NPs than the non-symptomatic

allergic patients, it maybe the same level or even lower than the healthy controls **[219, 240]**. Secondly, the use of intranasal and systemic corticosteroids, which have been shown to decrease the nNO production in patients with allergic rhinitis **[234, 241]**. Decreased nNO level in CRS with eosinophilia can be explained by the fact that eosinophils express the highest NADPH oxidase activities among phagocytic cells, and thus generate the highest amounts of superoxide anion **[242]**. As superoxide anion is recognized as one of the major inactivators of NO, it can be speculated that eosinophilia could contribute to the decreased NO levels **[243]**.

The nNO level correlated positively with the olfactory threshold before and after surgery. Moreover, the nNO level correlated negatively with the degree of tissue eosinophilia and also with the pre-operative symptoms on VAS. Ragab *et al* found a correlation between the VAS, the endoscopic score, the surgical score and the nNO level **[138]**. However, Vural *et al* could not find a correlation between nNO level and the patients' symptoms **[244]**. Ekroos *et al* showed that the nNO level does not correlate with the age or the gender of the patients **[245]**. For the first time the relation between the nNO level, the olfactory threshold, and the degree of tissue eosinophilia is demonstrated. A correlation was found previously between the degree of eosinophilia and the severity of the CT scan scores **[246]**. The degree of opacity of the ethmoidal sinuses showed a significant correlation with the olfactory threshold **[247]**. Patients with severe peripheral and tissue eosinophilia were found to have less olfactory functions than patients with mild eosinophilia in one study. However, the authors did not analyze the significance of this observation **[248]**. This relation could be explained by the fact that significantly lower nNO levels are found in patients with NPs, and they correlate with the stage of polyps

[219]. Those patients have significantly lower olfactory threshold and significantly higher eosinophilia than patients without NPs as already shown **[138, 200]**.

Nitric oxide seems to be important for olfaction. It is one of the neurotransmitters which play an important role in olfactory information processing both in vertebrates and invertebrates **[249, 250]**. Previous observations suggested that NO-mediated signalling in olfactory systems operates in parallel with conventional synaptic transmission to synchronize neural activity **[251]**. The role of NO in central olfactory processing is suggested by dense staining in the olfactory bulb with an antibody directed at neuronal nitric oxide synthase (nNOS) and dense staining for nicotinamide adenine dinucleotide phosphate (NADPH), an electron donor that serves as a co-substrate for NOS **[252]**. Nitric oxide is also suggested to be very important for fine olfactory discrimination. It has been demonstrated in honeybees that the local L-NAME injection to the antennal lobes, which is the primary olfactory centre in the insect brain, impaired the olfactory discrimination **[253]**. It has been shown that NO increases the frequency of the spontaneous oscillation in the PC lobe, the olfactory processing centre of Limax brain, by increasing the burst frequency of the bursting cells in the PC lobe, whereas NO depletion slows or stops the oscillation **[254]**. This implies that NO can affect olfactory discrimination **[251]**. Nitric oxide might also play a role in developmental or regenerative processes occurring in the olfactory epithelium **[255]**. This was further confirmed by the use of nNOS antibodies, which showed that NOS is expressed transiently by newly developing olfactory receptor neurons **[256]**. It can also mediate those plasticity changes in the brain that underlie memory formation through cGMP-dependant potentiation of glutamate release **[257]**. However, the source of NO employed in the olfactory processing

is not exactly known. It has been shown to be produced in olfactory neurons **[256]**. The olfactory epithelium is highly vascularized, and NO produced in the blood vessels could also provide a source of NO that diffuses to the sensory neurons. Moreover, normal respiration produces high concentration of NO in the nasal lumen **[258]**.

Failure to demonstrate the correlation between nNO and olfactory threshold in healthy individuals in the control group may suggest that the airborne nNO does not directly influence olfactory function. The significant correlation between olfaction and nNO in CRS patients is rather a consequence of the chronic inflammatory processes on both parameters than a direct mechanism between olfactory function and nNO level. As seen above, CRS has a lowering influence on olfaction as well as on nNO. At first glance, this seems to suggest that both parameters (nNO and olfaction) are related. However, if this assumption would exist, this correlation should also be found in healthy subjects, which was obviously not the case. Having said this, we conclude that, olfactory function as measured in the present study and nNO do not influence each other significantly. Both, olfactory function and nNO have in common that chronic inflammation lowers them.

5.3.2. Nasal CO (nCO):

The nCO level was found to be significantly higher in smokers group. The nCO level was significantly lower in allergy and eosinophilia groups. No significant difference in nCO production was found in polyposis, Widal syndrome or bronchial asthma. The level of nCO in smokers was previously shown to be above the normal physiological range, although this can depend on the amount and duration of smoking **[259]**. Exhaled CO is increased in patients with inflammatory pulmonary disease such as bronchial asthma,

bronchiectasis, upper respiratory tract infections, and seasonal allergic rhinitis. In such cases nCO increases in parallel **[151, 156, 260]**. Nevertheless, and according to one study, exhaled CO in asthmatic patients is not higher than in control individuals **[261]**. The level of nCO was said to be higher in patients with allergic rhinitis and patients with URTI. The ability of the nasal airways to increase CO production during allergic rhinitis and URTI strongly suggests a role of CO as a marker or a mediator of nasal inflammation **[155, 262]**.

Nicoucar *et al* demonstrated that nCO production did not change post-operatively **[220]**; however, they had a follow up period of 3 months only. In our study the change was also not significant after 3 months, but became significant at the final evaluation. The underlying mechanism may be a slow decrease of the airway inflammation as observed previously in bronchial asthma after treatment **[151, 152, 260]**.

5.3.3. Total nasal airway resistance:

The total nasal airway resistance (tNAR) was significantly reduced post-operatively. The tNAR correlated positively with the subjective nasal obstruction measured on the VAS both pre and post-operatively. The reduction in tNAR after topical vasoconstrictor was gradually decreased post-operatively. The degree of change in tNAR after the topical vasoconstrictor correlated positively with the degree of inflammation and tissue eosinophilia pre-operatively, but not post-operatively. These findings confirm the results obtained by Giger *et al*, who found a significant decrease in tNAR at 4 months and 2 years after surgery. They have also demonstrated a good correlation between the subjective and objective evaluation of nasal obstruction. The change in tNAR with

phenylephrine in their study was significant before surgery and non significant after 4 months and 2 years **[208]**. The marked decrease in the topical vasoconstrictor induced decongestion of the nasal mucosa post-operatively is most likely secondary to the reduction of the chronic inflammatory state of the nasal mucosa. This finding was confirmed in our study by the positive correlation found between the degree of inflammation, tissue eosinophilia, and the degree of reduction of tNAR after vasoconstrictor application. Application of vasoconstrictor is associated with an increase in the nasal volume and subsequently, a decrease in nasal airway resistance **[207, 263]**; however, a recent study denies its effect and attributes that to the abnormal behavior of the mucosa in CRS **[264]**. Sipila *et al* found a correlation between subjective sensation of nasal obstruction and anterior rhinomanometry findings **[81]**. However, other authors indicated that sensation of nasal obstruction does not correlate with rhinomanometry recordings **[79, 80, 83, 265]**. The tNAR was expected to be significantly higher in polyposis group, but this was not statistically proven. We attribute this to the long course of topical corticosteroids therapy that the patients received before surgery. Patients received at least 6 months of topical corticosteroids pre-operatively, this course is able to decrease the size of the polyps and decrease the tNAR in most of the patients. As the active anterior rhinomanometry measurements correlated well with the subjective nasal obstruction pre and post-operatively, we suggest that it is a reliable method of assessing the functional status of the nasal cavities in different clinical situations **[81, 266]**.

5.3.4. Olfaction:

We have observed a minimal non significant improvement in olfactory functions post-operatively. This increase was more obvious in orthonasal than retronasal olfaction, which showed almost no change. The olfactory threshold correlated negatively with the age of the patients and the degree of tissue eosinophilia. Our results are in accordance with those obtained by Lund and colleagues, who reported that olfaction showed no overall improvement in the objective test despite a significant subjective improvement **[267]**. Most of the patients in our series reported that their olfaction has been improved post-operatively. We believe that this is strongly influenced by the subjective sensation of nasal airflow as was shown before by Landis *et al* **[268]**. This observation was not analyzed in our study. Delnak *et al* found that the subjective improvement was much more pronounced than the objective improvement and they concluded that the rate of improvement is lower than generally assumed **[269-271]**. Lack of improvement of olfaction post-operatively can be attributed to persistent mucosal inflammation/edema in the region of the olfactory epithelium, post-operative edema, local polyp recurrence, scar tissue, or granulations **[272, 273]**. On the opposite, several authors reported significant objective improvement of olfaction following surgery **[272, 274-276]**.

The olfactory dysfunction in polyposis is most likely due to the obstruction of the olfactory cleft by polypoid mucosa and secretions passing through the superior meatus. In addition, the inflammatory substances such as, major basic protein (MBP) and eosinophilic cationic protein (ECP) released from activated eosinophils, induce edema of the olfactory epithelium and olfactory dysfunction **[248]**. Landis and colleagues have shown better retronasal than orthonasal olfaction in patients with NPs and concluded that

the olfactory loss in NPs is caused by regional mechanical or inflammatory factors rather than a sensorineural deficit **[277]**. Orthonasal olfaction is supposed to improve with the relief of nasal obstruction; while, retronasal olfaction is not affected by nasal obstruction and will not benefit from its relief, since orthonasal and retronasal olfactory stimuli have been shown to be processed differently **[277]**. Blomqvist *et al* compared medical and surgical treatment of NPs. They concluded that when hyposmia is the primary symptom, no additional benefit seems to be gained from surgical treatment. The sense of smell was improved by the combination of oral and local steroids and surgery had no additional effect **[205]**.

Poor olfactory function has been observed in patients with severe eosinophilia **[248]**. The degree of olfactory dysfunction is more severe in CRS patients with bronchial asthma, which is a representative disease of eosinophilic infiltration. The olfactory dysfunction in these patients is less likely to be improved after surgery **[278]**. Olfactory function decreases with age with more than half of the persons between 65 and 80 years of age and more than three quarters of those 80 years of age and older having significant olfactory loss **[279, 280]**. A negative correlation was observed between olfactory threshold and age. A significantly better olfaction was found in women compared with men. However, no difference was found in olfactory threshold between smokers and non-smokers **[281]**.

5.3.5. CT scan score:

We used the staging system of Lund and Mackay **[160]**. This is the most accepted and recommended CT staging system **[1, 2]**. It achieves the highest level of intra and inter-

observer agreement without being time consuming when compared with the other scoring systems **[282]**.

The CT score was significantly higher in polyposis, Widal syndrome, and eosinophilia groups. The CT scan score correlated positively with the pre-operative endoscopic score, the surgery score, and the degree of tissue eosinophilia. Smith *et al* found a significantly higher CT score in NPs, ASA intolerance, and asthma groups, but the difference was not significant in allergy, previous surgery or smoking groups **[197]**. Deal *et al* also showed a significantly higher CT score in polyp patients **[196]**. This could be attributed to the nature of the polypoid mucosa that makes the appearance of the sinus CT scans worse with a corresponding higher score assigned **[160, 283]**. Our observations oppose the findings of Kennedy, who found that his CT staging system correlated with the surgical outcome more than the pathological process **[215]**, and Wang *et al* who stated that the Lund-Mackay CT score predicted the amount of bleeding and the occurrence of complications as well as the response to surgery **[284]**. Watlet *et al* found a correlation between the CT score and the VAS at baseline and 6 months after surgery as well as the surgery score; but it was not a predictor of the post-operative healing **[202]**. In contrast, several other authors stated that the CT score doesn't correlate with the symptoms or the surgical outcome **[285-292]**. CT has also been shown not to correlate with surgical findings **[293-295]**. The few studies examining the association between CT findings and histopathology have failed to find any correlation with the extent of the inflammatory cellular infiltrate **[296, 297]**. In our case series we could find a positive correlation between the degree of tissue eosinophilia and the CT score. Interestingly, the CT scan has

been shown previously to be correlated directly with peripheral eosinophilia **[298, 299]** and the eosinophil percentage in bronchial sputum in asthmatics **[300]**.

On evaluating the CT scans, we demonstrated the following anatomic variants: septal deviation (88%), concha bullosa (16.6%), paradoxically bent middle turbinate (11.9%), and Haller's cells (7%). However, the anatomic variants did not correlate with the patients' symptom intensity or their improvement after surgery. There are marked discrepancies in the prevalence of ethmoid bone anatomical variations among various authors. A review of literature shows that there is no consistent difference in the prevalence of anatomical variations between a symptomatic group and a control group. Jones *et al*, in 100 patients and 100 control, showed that the incidence of concha bullosa in controls and patients was 23% and 18% respectively, paradoxical middle turbinate 16% and 7%, Haller's cells 12% and 6%, and septal deviation 24% and 24% **[301]**. Bolger *et al* showed the incidence of concha bullosa in controls and patients to be 50% and 53.3% respectively, paradoxical middle turbinate 22.3% and 27.1%, and Haller's cells 41.6% and 45.9% **[302]**. Lloyd *et al* showed the following incidence: concha bullosa 14% and 24% in controls and patients respectively and paradoxical middle turbinate 17% and 15% respectively **[303, 304]**. While some authors showed more prevalence of septal deviation and concha bullosa in CRS patients **[305, 306]**, others have not **[301, 307]**. Among a cohort of 2112 adults, Gray reported a septal deviation rate of 79% **[308]**. The incidence of concha bullosa was shown in the literature to be between 8-53%, paradoxically bent middle turbinate between 7-30%, and Haller's cells between 4-45% **[301-307]**. According to some authors, the anatomic variants were not predictive for the surgical outcome in the long-term follow-up **[201, 218]**. These variations may contribute

to OMC disorder. Surgical correction of them appears to be adequate to eradicate the local dysfunction, and these patients are expected to do well in the long term in the absence of other systemic factors. Stammberger reported similar conclusions, stating that the best results after ESS were obtained in cases with anatomic variants **[32]**.

5.3.6. Endoscopic score:

We used the endoscopic score proposed by Lund **[192]**. The preoperative endoscopic score was significantly higher in polyposis, Widal syndrome, eosinophilia, and previous surgery groups. The pre-operative endoscopic score correlated positively with the surgery score and the degree of tissue eosinophilia. The post-operative endoscopic score was significantly higher in patients with intracellular S.aureus and in patients with Widal syndrome. It correlated positively with the symptoms of the patients on VAS during the final evaluation. Deal *et al* showed that the endoscopic score was significantly higher preoperatively, after 6 months and 12 months in polyposis group than CRS without NPs **[196]**. In the study of Smith *et al* polyposis, ASA intolerance, asthma, and previous surgery groups had worse endoscopic score both pre and post-operatively, while the difference was not significant in the allergy and smoking groups. The higher score observed in the previous surgery group could be due to the "scarring" component of the scoring system **[197]**. In agreement with previous studies, we observed that post-operative endoscopic score correlated quite well with the subjective evaluation of symptoms **[202, 309]**. However, other authors stated that the postoperative objective endoscopic score doesn't always correlate with the subjective symptoms improvement especially in NPs patients **[310-312]**.

5.4. Operative procedures:

5.4.1. Partial middle turbinate resection:

In our case series, we have resected the antero-inferior part of the middle turbinate in order to improve visualization, prevent post-operative adhesions, and facilitate both post-operative follow up and accessibility of the topical corticosteroids. This technique was first advocated by Wigand *et al* in 1978 **[313]**. Considerable controversy exists as to whether the middle turbinate should be preserved during endoscopic sinus surgery. Several investigators have expressed their concerns regarding middle turbinate resections and the potential risk of crusting, bleeding, anosmia, and frontal duct stenosis **[314-316]**. Others have published data showing increased antrostomy patency rates, increased air flow, and decreased revision rates when they partially resected the middle turbinate **[317-319]**. In our study, the technique had no complications during or after surgery. Toffel has used this technique for 16 years and reported a very low rate (2.5%) of synechiae **[320]**. When compared with the middle turbinate preservation technique, it was associated with better ventilation and maintenance of the OMC patency, especially when an anatomic anomaly or concha bullosa is present **[321]**.

5.4.2. Small versus large antrostomies:

We have made small middle meatal antrostomies in our patients, as we were more concerned with including the natural ostium in the created opening rather than creating a large antrostomy. Small-sized antrostomies were found to be associated with better functional results than the large ones **[322, 323]**. The attempt to create a too large antrostomy may lead to excessive stripping of mucosa and creation of raw bony areas

[323]. The attempt to fashion a large antrostomy may also interfere with the common mucus and lymphatic pathway of drainage. Moreover, the frontal and ethmoid drainage may lead to dripping of mucus into the maxillary sinus through the large antrostomy **[324]**. In addition, no significant difference in maxillary sinus ventilation was found when comparing large antrostomies with small ones **[325]**.

5.4.3. Preservation of the uncinate process:

In our technique, by preserving the uncinate process, we expect to protect the mucosa of the maxillary sinus from the cold airflow irritation which may lead to mucociliary clearance reduction and squamous metaplasia with subsequent retention of secretions and recurrent infections. The uncinate process has probably a protective role in preventing deposition of bacteriae and allergens in the sinus during the inspiratory phase **[326]**. Moreover, the uncinate process preserving technique has shown better results than the conventional technique, especially with respect to recurrent postnasal discharge and residual disease **[327]**. It is clear that excessive patency of the maxillary sinuses that are not traditionally directly exposed to nasal airflow may in fact increase bacterial infection rates after ESS **[328]**. Retaining of the uncinate doesn't lead to recirculation of mucus or obstruction of the ostium. Furthermore, it reduces scarring at the root of the turbinate which may lead to frontal recess scarring **[195]**.

5.4.4. Septoplasty:

Septoplasty and turbinoplasty were included in the ESS operation in order to provide maximal relief of symptoms at the first attempt of surgery. Since relief of nasal

obstruction, as a quality of life main component, is a goal of the surgery, septoplasty is a viable proposition **[329]**. Septoplasty and turbinoplasty have been shown to augment the results of ESS and increase the patients' satisfaction after surgery **[330-333]**.

5.4.5. Surgery score:

We have modified the surgery score proposed by Lund **[192]** by adding scores for septoplasty and inferior turbinoplasty. The surgery score correlated positively with the CT scan score and the pre-operative endoscopic score. Watlet *et al* have shown similar surgery score in CRS with and without NPs, and stated that it is not predictive for the outcome. They have also demonstrated a positive correlation with the CT score but not with the pre-operative endoscopic score **[202]**.

5.4.6. Complications and revision surgery:

Our study confirms the low complications profile of ESS reported in several previous studies **[334-336]**.

5.4.7. Degree of inflammation and eosinophilia:

The degree of inflammation and tissue eosinophilia was found to be significantly higher in polyposis, Widal syndrome, and revision surgery groups. It was also higher in allergy and bronchial asthma groups, but didn't reach a statistical significance. This is in accordance with the previous publications showing that the tissue eosinophilia is more marked in CRS patients with NPs **[200]**. Other reports have shown that tissue eosinophilia in NPs of aspirin sensitive patients is more frequent than in aspirin tolerant

patients **[337]**. It was also previously demonstrated that tissue eosinophilia is greater when CRS is accompanied by asthma or allergic rhinitis **[338]**. The mechanism of eosinophils recruitment in tissue has been suggested on the basis of identification of specific eosinophil chemotactic factors or specific eosinophil adhesion to cytokine-activated endothelial cells **[339-342]**. Another factor which may be responsible for the persistence of eosinophils is the inhibition of eosinophil apoptosis mediated by IL5 **[343]**. However, it was also hypothesized that eosinophils are triggered by the extramucosal fungi after the detection of fungi in 96% of CRS patients which gave the rise to the term "Eosinophilic Fungal Rhinosinusitis" **[31, 344]**.

5.5. Prognostic Factors:

Old age and severe tissue eosinophilia were associated with poor subjective outcome. Widal syndrome had a poor objective, but good subjective outcome. The age correlated negatively with the subjective improvement in our study which implies that elderly patients experienced less favorable outcome. There are many factors which may lead to less satisfactory results in the elderly population. Firstly, the nasal and paranasal mucosal changes, including mucosal atrophy, decreased mucus production, and decreased mucociliary clearance, resulting in excess crusting. Secondly, the atrophy of the supporting fibro-fatty tissues of the nose, with potential loss of support of nasal structures and associated nasal obstruction **[345]**. Thirdly, evidence suggests that antibody-mediated immune function against common upper-respiratory infectious agents is impaired in the geriatric population **[346]**. There is also an increased incidence of epistaxis and olfactory impairment in the elderly **[347, 348]**. However, the studies which compared the results of

ESS for CRS between geriatric and adult population showed that the results of ESS were similar in both groups and concluded that ESS is a safe and effective treatment modality for older persons with CRS **[201, 347, 348]**.

Patients who demonstrated chronic intracellular S.aureus carriage in our study had a significantly less subjective and objective improvement. Most of these patients experienced recurrent attacks of rhinosinusitis which required several systemic antibiotic treatments. Intracellular residency of S.aureus in epithelial cells of the nasal mucosa has been shown to be a significant risk factor for recurrent episodes of rhinosinusitis due to persistent patient-specific bacterial clonotypes, which appear to be refractory to antimicrobial and surgical therapy **[30]**. Management of recurrent CRS episodes in patients yielding intracellular S. aureus reservoirs is difficult and problematic. The intracellular location combined with the lack of efficient bactericidal mechanisms in non-professional phagocytes are assumed to protect intracellular bacteria from professional phagocytes and from antimicrobial agents whose action is mainly extracellular **[349]**. This really represents a future challenge for rhinologist, pathologists and infectious disease specialists. In the mean time the only treatment that we could offer to those patients is frequent nasal lavage with sodium hypochlorite (NaOCl). A recent study showed that 0.05% NaOCl may be used on nasal epithelium and found to be effective in treating persistent CRS as an alternative to antibiotic therapy **[350]**.

The tissue eosinophilia in our study correlated negatively with the post-operative subjective improvement. We speculated that tissue eosinophilia is a negative prognostic factor in CRS patients undergoing ESS. It is well known that eosinophils perpetuate tissue inflammation by secreting granule proteins, chemical mediators and cytokines and

participate in pathological changes such as epithelial injury and desquamation, subepithelial fibrosis and hyperresponsiveness **[351]**. A negative correlation was shown between eosinophilia and the symptomatic improvement rate after a course of macrolide therapy **[352]**. Our findings do not go well with the finding of Baudoin *et al*, who stated that tissue eosinophilia was not a valuable predictive factor. However, it can predict less improvement in nasal secretion after surgery **[353]**. Moran *et al* stated that neither total magnitude of inflammation nor the presence of specific inflammatory cell types correlated with surgical outcome **[354]**. An increased number of cells expressing IL-5 mRNA in the ethmoid sinuses at the time of surgery was considered to be predictive of poor surgical outcome **[355]**. However, this was beyond the scope of our study. It was also mentioned that hyperostosis may predict a bad prognosis and a more prolonged course of postoperative antibiotic treatment **[356]** since it might obliterate the haversian system of the bone making antibiotic penetration more difficult **[357]**.

Patients with NPs had the same subjective and objective improvement experienced by patients without NPs. However, patients with Widal syndrome had significantly less objective outcome. This finding correlates well with previous publications which pointed out Widal syndrome as a negative predictor for the surgical outcome **[197, 211, 215]**. Polyposis in ASA tolerant patients was not predictive of poor outcome which contradicts a wide range of publications mentioning NPs per se as a negative prognostic factor **[196, 215]**. Vlemig and de Vries found that patients with NPs have a better subjective outcome than those without NPs. However, when the objective results were examined; 52% of patients with NPs were found to have subjective improvement, but had an objectively poor result. Patients with persistent mucosal disease were often asymptomatic for the

duration of the follow up **[311]**. Danielsen and Olofsson used both subjective and endoscopic assessment with 90% and 71% improvement rates, respectively, with a mean follow up of 41 months. The difference was attributed to the patients with primary NPs, who had fewer symptoms than expected from the clinical endoscopic examination **[310]**. Gender was not a prognostic factor, since both sexes experienced the same results **[201, 358]**. Patients with allergic rhinitis who kept on receiving their anti-allergic treatment had the same results as non-allergic patients. This was seen before in previous studies **[195, 202, 309]**. Although many authors recognized allergy as a negative prognostic factor **[201, 215, 359, 360]** and a risk factor for revision surgery **[13, 361, 362]**. On the other hand, Friedman *et al* reported better response in patients with diagnosed and medically treated allergies **[207]**.

Asthma had no effect on the satisfactory outcome of the patients. This is the same conclusion given by some previous investigators **[195, 202, 334, 360]**. Although improvement in asthma and bronchitis symptoms with a reduction of the systemic steroid use after surgery has been demonstrated **[363, 364]**, asthma is correlated to poor outcomes after ESS in some studies **[215, 309, 365, 366]**. Kountakis and Bradley found an increased incidence of revision surgery in asthmatic patients compared with non asthmatics **[367]**.

Previous sinus surgery was not associated with poor results as previously mentioned **[201, 215, 284, 334, 368]**. However, other investigators reported the same percent of success in primary and revision surgery **[363]**. It has been thought that patients undergoing revision ESS have poorer outcome than those undergoing primary ESS because the recurrence of the disease was a negative prognostic factor. Recent data from

Bhattacharyya, however, suggest that the symptomatic relief provided by revision ESS is similar to relief provided for patients undergoing primary ESS **[369]**. The same conclusion was achieved by McMains and Kountakis **[370]**. Kuhl and Schultz-Coulon investigated 2 groups of patients undergoing either primary or revision ESS. They found that the success of ESS was not correlated with the medical history, preoperative CT findings, or the surgical techniques used. They reported that 15% to 20% of the patients will develop recurrence after ESS, and despite all diagnostic and therapeutic tools available at present, it is not possible to predict who will experience recurrence and when **[371]**.

Smoking was not a negative prognostic factor in our study. This was previously shown in other publications **[195, 202, 309]**. Smoking or exposure to smoke has been reported to be a negative predictor of success for the ESS in both adults **[334, 372-374]** and children **[375, 376]**. Tobacco smoking involves several factors that may affect the nasal mucosa. Tobacco smoke heat as well as toxic elements may directly be involved in the destruction of the ciliary cells. Also, continuous irritation of the nasal mucosa by tobacco fumes may induce an inflammatory reaction. It was reported that the up-regulation and production of proinflammatory cytokines from the tobacco smoke itself, may be the factor responsible for inflammation of the sinuses **[374, 377]**.

The anatomic variants and extent of the disease in the preoperative CT were not predictors of the outcome of surgery as mentioned before. Wang *et al* mentioned that preoperative total symptoms score predicted post-operative symptoms score **[284]**. However, this was not the case in our study.

There are other possible prognostic factors which have been mentioned before in the literature, but they were not investigated in the current study. Chambers *et al* stated that the only factor that had negative impact on the result was GERD **[195]**. Smith *et al* concluded that psychological depression predicts poor outcome in ESS **[197]**. Diminished immunity, genetic factors were mentioned also as negative prognostic factors **[378, 379]**. However, these two factors were among the exclusion criteria of the present study.

6. SUMMARY

The aim of this study was to identify prognostic factors that may affect the outcome of endoscopic sinus surgery (ESS) in chronic rhinosinusitis (CRS). Therefore, we have evaluated the effect of ESS on olfaction, nasal nitric oxide (nNO), and nasal carbon monoxide (nCO). Forty two CRS patients were included in the study and 20 healthy individuals were included as a control group. Patients were followed up for a period of 16.29 ± 1.08 months. Preoperatively, history was taken and endoscopic examination and scoring were recorded. The patients filled the same questionnaire pre-operatively, 3 months, and at least 6 months after surgery. All patients had CT scans which were graded according to Lund-Mackay system. Olfactory performance was evaluated using the Sniffin' Sticks pre-operatively and 3 months post-operatively. The nNO, nCO production and total nasal airway resistance (tNAR) were measured pre-operatively, 3 months, and at least 6 months after surgery. All patients underwent ESS under general anesthesia. The surgical procedures were graded with a modified Lund score. The specimens were graded histopathologically, according to the degree of chronic inflammation and tissue eosinophilia. Bacteriological examination was done with confocal microscopy for detection of intracellular S.aureus (ISA). No major complications were encountered. The overall subjective success rate was 85.7%. Post-operatively, patients reported marked reduction in all CRS symptoms. There was a non significant increase in nNO with time. The nCO production decreased significantly. The tNAR was reduced after surgery. No change was encountered in the olfactory performance. The nNO production and olfactory threshold were higher in the control group than the CRS group, both pre-operatively and

post-operatively. The age of the patients correlated negatively with the improvement of symptoms and the olfactory threshold. The CT score correlated positively with the endoscopic score, the surgery score, and the degree of tissue eosinophilia. The nNO level correlated positively with the olfactory threshold pre and post-operatively in CRS patients, but not in the control group. It correlated negatively with the intensity of symptoms and the degree of tissue eosinophilia. The presence of anatomic variants did not correlate with the improvement of symptoms. Patients with polyposis showed less nNO level and olfactory threshold, but higher CT and endoscopic scores. Patients with Widal syndrome had higher CT score and tissue eosinophilia. Both nNO and nCO levels were lower in allergic patients, who demonstrated also lower olfactory functions than non-allergic patients. Higher levels of nCO were recorded in smokers pre and post-operatively. Patients with previous sinus surgery had higher endoscopic score and tissue eosinophilia. Patients with tissue eosinophilia had lower nNO and nCO levels and less olfactory function, but they had higher CT and endoscopic scores, with less improvement of symptoms. Patients with ISA had higher post-operative endoscopic score and less subjective improvement of symptoms. The factors associated with a bad prognosis in ESS were old age, Widal syndrome, tissue eosinophilia, and the carrier state of ISA.

7. CONCLUSION

When medical treatment does not improve the patients' symptoms, ESS seems to be an effective and safe treatment for CRS on a long-term evaluation. It is associated with an increase in nNO and a decrease in nCO levels postoperatively. Intracellular S. aureus, aging, tissue eosinophilia, and Widal syndrome were found to be associated with a less favorable long-term outcome. In contrast, anatomic variants, allergy, bronchial asthma, and smoking do not seem to affect the prognosis of ESS in patients with CRS. Further basic science and clinical studies are strongly needed to improve our understanding of the multifactorial pathophysiologic mechanisms underlying this disease.

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