Recalcitrant chronic rhinosinusitis. Difficulties in diagnosis and treatment

Videler, W.J.M.

Citation for published version (APA):
CHAPTER 1

Introduction

W.J.M. Videler and W.J. Fokkens
WHY DO WE HAVE PARANASAL SINUSES?

In a healthy condition, we are not aware of the existence of the paranasal sinuses. However, when inflamed, the sinuses are able to cause extended problems and substantial discomfort. Nowadays otorhinolaryngologists treat rhinosinusitis with different types of medical regimes and if needed they perform sinus surgery in this area inside the head with variable anatomy. “Good progress” one could say, but an obvious question like “why do we have paranasal sinuses?” appears hard to answer. Leonardo Da Vinci once thought that the maxillary sinus contains the humor which nourishes the teeth.1, 2 Although far ahead of his time, this was not a correct conclusion. In the last centuries, more theories trying to answer the same question have been postulated and can be divided in plausible and not plausible.

Not plausible

- **Air-conditioning of the inspired air**
  Till today, it has been suggested that the sinuses play their part in humidifying and warming the inspired air. However, the amount of air that is exchanged during respiration is limited.3-6 According to reports, only one-thousandth of the air volume of the sinuses is exchanged during one respiration cycle, making the contribution to adequate warming and humidification limited.7, 8

- **Increasing the olfactory area**
  Around the 1830’s, Cloquet proposed that the sinuses were covered with olfactory epithelium. A well-developed sinus system would in this way increase the capacity to smell.9 However later it was clearly demonstrated that only a limited area of the human nasal mucosa was reserved for olfaction. Only the upper part of the superior nasal turbinate, the roof of the nasal cavity and a small part of the cranial nasal septum, contain olfactory epithelium.10-12

- **Resonance of the voice**
  In the 17th century it has been suggested that the sinuses play a role in giving the voice a particular quality or timbre. Negus however performed a comparative anatomical study, and found that there was no relation between the presence or absence of the paranasal sinuses and the voice.6 This thought was strengthened by the realization of some authors that the sinuses have poor physical qualities to be a good resonator.3, 13 Important shortcomings are the small sinus ostia covered by turbinates and the lining of the sinus walls with vibration-dampening mucosa.

- **Thermal insulation**
  Proetz proposed the possible role of the sinuses providing thermal insulation to vital parts in the cranium.5 However, Eskimos often possess no frontal sinuses,14 whereas Africans often have large ones.15, 16

- **Absorbing trauma**
  Studying extended air spaces over the cranial vault, into the hollowed horns of ungulates, Negus proposed that the sinuses might absorb trauma and protect sensory
Blaney pointed out the great inter-species variability and noted that most species appearing to suffer high impact trauma to this area had very small sinuses. Lightening of the skull
Several authors suggest that sinuses might have developed to lighten the skull to facilitate balance maintenance of the head. Others calculated that the weight would only increase by 1 per cent if the sinuses were composed of spongy bone. Electromyographic investigations of the neck musculature during loading of the anterior aspect of the head, show that sinuses are not significant as weight reducers.

Flotation device
It has been suggested that monkeys developed the sinuses to easier keep the head including the nasal cavity, out of water. Others noticed that the same group of sinuses occur in all African apes, and they considered it extremely unlikely that an aquatic way of life was the driving force behind this evolutionary process.

Secretion of mucus to moisten the nasal cavity
This theory was proposed by Haller, but it is now known that the sinus mucosa contains a thousand fold less glands than the mucosa of the nasal cavity.

Plausible

Aiding facial growth and skull enlargement
Proetz proposed that the human frontal and maxillary sinuses might be designed to assist forward and downward growth of the face and adjust the enlargement of the cerebral cranium. However, Negus critically noted that individuals with small frontal sinuses do not show deficient facial growth in substantial numbers. Takahashi considered that the sinuses originally developed as an aid to olfaction in ancestral species and that function altered during the evolutionary process of mammals from ancestral primate to human. Key features were the retraction of the maxilla-facial massif and cerebral enlargement and that the sinuses arose as the result of an increase in the angle between the forehead and the frontal cranial base and a decrease angle of the cranial base at the sella turcica.

Evolutionary remnants
The sinuses could just be unwanted residual spaces. It has been stated that their presence does not require additional explanation; we have them because our ancestors had them.

Immune defense and production of Nitric Oxide
The paranasal sinuses seem to be an adjunct in the immune function of the nose, with the production of immunoglobulins and lytic enzymes which destroy peroxidases and peptidoglycans of bacterial cell walls. Nitric oxide has been proven to be produced in the sinuses in substantial volumes and acts as an inhibitor of viral and bacterial growth and up regulates the ciliary beat frequency.
INTRODUCTION

In an attempt to come to a conclusion it is likely to believe that the sinuses arose as an aid for facial growth and architecture, or that they persist as residual remnants of an evolutionary structure with an as yet unknown purpose. In doing so, they have found an additional role as an adjunct to the nasal cavity immune system. Realizing the difficulties in finding an answer to the seemingly easy question "why do we have paranasal sinuses?", puts research in this field in perspective. Although the function of the sinuses is not known, it did become clear that in humans in particular, sinuses can cause significant problems of which the incidence seems to rise in the western world. Recalcitrant chronic rhinosinusitis and its difficulties in diagnosis and treatment is therefore the subject of this thesis.

WHAT IS NORMAL PARANASAL SINUS ANATOMY AND PHYSIOLOGY?

The nose and paranasal sinuses constitute a collection of air filled spaces within the anterior skull. They are named after the bones in which they are located and are called the maxillary, frontal, ethmoid and sphenoid sinus (see Figure 1). The anatomy of the sinuses, the ethmoidal cells in particular, demonstrates a great variability between individuals. This has implications for treatment of sinusitis, especially for sinus surgery. The paranasal sinuses develop as invaginations from the nasal cavity that extend into the facial bones. The maxillary and ethmoid sinus appear during the fetal phase of life and the sphenoid and frontal sinus develop during childhood. Further development of all sinuses takes place from childhood until puberty.

The paranasal sinuses communicate with the nasal cavity through small apertures, which are called ostia in the maxillary and sphenoid sinus. The frontal sinus has a frontonasal recess that drains into the middle meatus of the nasal cavity. The multiple cell complex of the ethmoid has several openings. The sinus ostia play a fundamental role in the normal functioning of the sinuses. Most crucial is the ostiomeatal complex. This is a functional unit comprising the ostium of the maxillary sinus, the ostia of the anterior ethmoidal cells, the infundibulum, the hiatus semilunaris and the middle meatus. A patent ostiomeatal complex allows mucociliary clearance, as well as sufficient ventilation of the sinus, and is vital for the preservation of a healthy sinus-environment.

The nasal cavity and its adjacent paranasal sinuses are lined by pseudostratified columnar ciliated epithelium. This epithelium contains goblet cells and nasal glands, producers of nasal secretions that keep the nose moist and form mucus. Particles and bacteria can be caught in this mucus, rendered harmless by enzymes like lysozyme and lactoferrin, and they are transported towards the nasopharynx, heading for the esophagus. Transport of the mucus in the sinus itself towards the ostia follows distinct patterns. Cilia play an important part in this mucus transport. Their key role becomes clear in pathological situations, for example in patients with ciliary dyskinesia, or patients with abnormal thickened mucus as we find in cystic fibrosis.
WHAT ARE PATHOPHYSIOLOGICAL CHARACTERISTICS OF CHRONIC RHINOSINUSITIS?

The mucosa of the nose and sinuses form a continuum. Inflammation of the nasal mucosa, frequently involves the mucous membranes of the sinuses, hence the term “rhinosinusitis”. Chronic Rhinosinusitis (CRS) has been defined in the European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) as the presence of the following symptoms: nasal blockage or nasal discharge, combined with facial pain and/or loss of smell for more than 12 weeks. The definition is completed by endoscopic signs and/or Computed Tomography (CT) scan changes. An estimated prevalence of 146 per 1000 people has been reported, ranking it as one of the most prevalent chronic diseases. CRS has negative influence on daily life and social functioning and it has severe impact on lower airway disease. It is one of the most common health care problems with consequences like significant medical costs, loss of productivity and absence of work.

CRS covers a spectrum of disease entities with potential different underlying pathophysiological mechanisms, and is considered a multi-factorial disease. Factors contributing can be mucociliary impairment, (bacterial) infection, allergy, swelling of the mucosa for other reasons (for example hormonal driven congestion during pregnancy), but only rarely physical obstruction caused by morphological or anatomical variations in the nasal cavity or paranasal sinus. Problems occur if the ostium patency is not sufficient for...
the amount of mucus, or if ciliary function is impaired. Stasis of secretions follows and bacterial export ceases, causing or exacerbating inflammation of the mucosa. Even more ciliary dysfunction is caused by the further decrease in ventilation. This vicious cycle can be difficult to break, and if conditions persist, it can result in chronic disease. Chronic CRS is treated with intensive nasal rinsing, topical steroids and systemic antibiotics. If symptoms are not reduced by medical treatment, endoscopic sinus surgery is performed in an attempt to create adequate ostia opening providing sufficient ventilation and drainage. Despite these patent postoperative ostia, mucosa persists to be inflamed in some recalcitrant cases, when viewed during nasal endoscopy.

The presence of nasal polyps has substantial interest in literature. On one end of the spectrum we can distinguish CRS without nasal polyps, on the other end there is nasal polyposis seemingly without CRS. As in CRS without polyps facial pain, headache, rhinorrhea, and postnasal drip are frequent symptoms, patients with nasal polyps more often complain about nasal blockage and loss of smell. Clear differentiation between these disease identities seems impossible to date. The question remains as to why the ballooning of mucosa develops in polyposis patients and not in all CRS patients. Nasal polyposis is considered a subgroup of CRS (see Figure 2). Better identification and understanding of these subgroups is one of the greater challenges in the field of CRS research.

Figure 2. Chronic rhinosinusitis and nasal polyposis.

In addition to clinical profiles, pure CRS and nasal polyposis can be differentiated by cytokines, mediators and cellular profiles. Markers for CRS could possibly be derived from inflammatory cells, remodeling processes linked to fibrosis or oedema formation, or from innate or adaptive immunity products like Toll-like receptors or immunoglobulins. The Th1/Th2 polarization could also be a differentiator. Whereas CRS is more a Th1 polarized disease, nasal polyposis reveals more of a Th2 polarization, accompanied by abundant eosinophil and IgE formation. Predominant cells in CRS are neutrophils, but eosinophils, macrophages, lymphocytes, mast cells and basophils are also regularly observed. The mucosal lining in CRS is characterized by basement membrane thickening, goblet cell hyperplasia, and subepithelial oedema. A range of mediators and cytokines has been described to be increased in CRS versus inferior turbinate control tissue. This comprises interleukin-1 (IL-1), IL-3, IL-6, IL-8, tumor necrosis factor α (TNF-α), granulocyte macrophage colony stimulating factor (GM-CSF), intercellular adhesion molecule 1 (ICAM-1), myeloperoxidase (MPO), and eosinophil cationic protein.
Although research in this field is in progress, definite classification awaits further insight into pathomechanisms and exploration of appropriate disease markers.

WHAT IS RECALCITRANT CHRONIC RHINOSINUSITIS?

Patients with recalcitrant CRS are characterized by decreased quality of life caused by ongoing and invalidating symptoms of headache, facial pain, reduction of smell, rhinorrea and postnasal drip. In many cases nasal crusts, nosebleeds and fatigue cause daily problems. Although treated optimally with medication and surgery, these complaints persist for many months, usually years. On nasal endoscopy congestive, inflamed mucosa, with nasal secretions, crusts and sometimes synechiae can be observed, despite sufficient open ostia. Polyps or polypoid mucosal changes can also be present. Patients often have substantial comorbidity such as asthma, allergy, and aspirin intolerance, all of which have been identified as adverse prognostic factors of CRS in the ESS-treated population. CT scans are typically characterized by extensive disease (high Lund-Mackay scores, sometimes combined with additional signs of prolonged disease processes like osteitis of the sinus bone).

In some patients chronic inflammation can be explained by underlying disease. Cystic fibrosis or congenital mucociliary abnormalities can cause problems with the clearance of mucus and cause recalcitrant CRS. Known systemic vasculitis or granulomatous disease like Wegener’s disease surfaces in some patients after more extensive evaluation. Immunodeficiency varying from low immunoglobulin status to HIV-positivity/AIDS, can be the underlying cause of the recalcitrant nature of CRS. To improve the sinonasal situation in these patients, the underlying condition has to be treated as well.

In a majority of patients suffering from recalcitrant CRS, no other underlying etiology is found. However, there are etiological suspects under attention. The apparent and usual suspects are bacteria. However, their role in recalcitrant CRS is not well understood. A number of studies report on the microbiology of middle meatus and sinus cultures, but the contribution of these pathogens to disease remains a matter of debate. Perhaps they are to be seen more as disease modifiers rather than primary etiologic agents. Next suspects are superantigens, which are toxins of microbial or viral origin that target the immune system. They are able to trigger massive polyclonal T-cell proliferation and activation, and cause exacerbation of the ongoing inflammation. It is known that enterotoxins from Staphylococcus aureus can act as superantigens. Recent insights have linked the inflammation in nasal polyposis to an increased prevalence of colonization with Staphylococcus aureus and the release of their cell products. Other research on superantigens and nasal polyps suggest that Staphylococcus aureus indeed secretes superantigen toxins that result in a generalized reaction recruiting eosinophils and causing histopathological changes in patients with nasal polyposis. The role of superantigens in CRS without nasal polyps is not clear. An alternative for the bacterial etiology is the fungal hypothesis, which proposes that patients with CRS mount an eosinophilic response to fungi. The clinical extrapolation of these findings suggests that intranasal fungi in patients with CRS would probably exacerbate the disease process. There were initial promising results, treating CRS with amphotericin an anti-fungal drug. A subsequent randomized, double-blind, placebo-controlled trial by Ebbens et al., using topical
amphotericin, failed to improve the clinical signs and symptoms in CRS patients.\textsuperscript{70} This is in agreement with other reports.\textsuperscript{71,72} Next one in line of possible underlying substrates could be the inflammation of bone. In patients with recalcitrant CRS, CT scans of the paranasal sinuses often demonstrate irregular thickening of the bony lining of the sinuses. Bacteria have not been demonstrated so far in animal or human bone samples. Histological changes identified include periosteal thickening, changes in osteoblast/osteoclast activity, fibrosis of haversian canals and the existence of cellular infiltrates.\textsuperscript{73-76} Biofilm is also a suspect under attention in the etiology of CRS in recent years. The biofilm hypothesis suggests that it continually presents antigen, resulting in chronic inflammation of the mucosa. It might act as an unsurpassable barrier for innate host defense mechanisms as well as preventing antibiotics from reaching the causative micro-organisms.\textsuperscript{77} These characteristics of biofilm could potentially explain important clinical features of recalcitrant CRS. Some studies have reported on the intracellular presence of bacteria in the epithelial cells of the middle meatus mucosa. These intracellular colonies may represent a reservoir for recurrent episodes of CRS that are protected from host defense mechanisms and antibiotic treatment.\textsuperscript{78, 79} The discovery of parts of the puzzle of recalcitrant CRS is ongoing. However, a clear overall pathological explanation, definition, or treatment solution is far from available.

**HOW CAN WE DIAGNOSE CHRONIC RHINOSINUSITIS?**

**Symptoms and definition**

As mentioned earlier, the diagnosis of CRS is based on symptoms, duration of symptoms, clinical examination including nasal endoscopy, and CT scans of the paranasal sinuses. Because the pattern of symptoms and signs is overlapping in all patients with chronic sinus inflammation, differentiation between the subgroups is difficult. One of the problems in this classification process is the definition. As mentioned before, the most recent European definition of CRS is formulated in the latest version of EP\textsuperscript{3}OS.\textsuperscript{34} Close inspection of another leading definition of the American Rhinosinusitis Task Force,\textsuperscript{80} brings minor differences to the light. In that definition symptoms are divided in major and minor criteria. Major criteria included facial pain/pressure, facial congestion/fullness, nasal obstruction/blockage, nasal discharge/purulence, altered sense of smell, purulence in the nasal cavity on examination and fever (acute rhinosinusitis only). Minor factors were headache, (nonacute) fever, halitosis, fatigue, dental pain, cough, and ear pain/pressure/fullness. The existence of at least 2 different definitions underscores the fact that CRS is a variety of disease entities, difficult to grab and comprehend.

**Nasal endoscopy**

Although anterior rhinoscopy is still the first step in the examination of the patient, it is not sufficient to evaluate CRS. Rigid nasal endoscopy is advised in every patient suspected to suffer from CRS for the identification of mucosal congestion, mucopurulent discharge, nasal crust, nasal polyps and scarring. Nasal endoscopy improves diagnostic accuracy and should be emphasized, as an early diagnostic tool.\textsuperscript{81} Main focus of the nasal endoscopy is the middle meatus. It may be performed without or with decongestion. For research purposes, semi-quantitative scores grading oedema, nasal discharge, nasal crusts and polyps have been developed.\textsuperscript{82} Recently, a significant association between symptom-based CRS with positive endoscopic findings has been demonstrated.\textsuperscript{82}
CHAPTER 1

Imaging
Computed Tomography (CT) is the imaging modality of choice to evaluate the extent of pathology within the sinuses, and to study the complex and variable sinonasal bony anatomy pre-operatively. Of several developed CT-staging systems, the Lund-Mackay system is most widely used to assess the severity of mucosal disease. It is an easy to use and validated outcome measure, which relies on a numerical score of 0 to 2 dependent on the opacification of each sinus separately. The patency of the ostiomeatal complex is also taken in account. A maximum score of 12 per side can be derived (see Table 1). CT and endoscopy scores have been shown to correlate well, which is not the case for the correlation between CT and symptoms.

Table 1. CT scoring system according to Lund & Mackay.

<table>
<thead>
<tr>
<th>Sinus System</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxillary (0,1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Ethmoids (0,1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior Ethmoids (0,1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sphenoid (0,1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal (0,1,2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ostiomeatal complex (0 or 2 only)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total points</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Coronal reconstructions of CT scan images of 3 patients with increasing involvement of the sinus mucosa. From nearly no abnormalities to nearly complete opacification of all the sinuses (clockwise).
WHAT ARE TREATMENT OPTIONS IN CHRONIC RHINOSINUSITIS?

Corticosteroids
The use of corticosteroids is an important cornerstone in the treatment of CRS. They are thought to reduce inflammation by decreasing the production of pro-inflammatory cytokines, diminishing the influx of inflammatory cells, and improving nasal blockage. However, the exact mode of action responsible for the anti-inflammatory effect of corticosteroids remains to be fully explained.

Long-term administration of intranasal corticosteroids is safe, produces no mucosal atrophy or other alteration of histological appearance, and does not impair ciliary function or mucociliary clearance. Although the efficacy of intranasal corticosteroids has been well established in patients with nasal polyps, there is insufficient evidence to demonstrate a clear overall benefit in CRS without nasal polyps to date. However, due to its proven efficacy in nasal polyposis, and efficacy has been demonstrated for short courses, intranasal corticosteroids are widely used in the treatment of CRS overall.

Several mostly uncontrolled studies have demonstrated the effects of oral corticosteroids on nasal polyps. A systemic course can be useful in stages of exacerbation of CRS preferably when nasal polyps are present. However, it has been demonstrated recently that the effect lasts only shortly. Polyps and symptoms return to baseline within 3 months.

Antibiotics
Short-term antibiotics (less than 2 weeks) are prescribed frequently in the treatment of patients with CRS. However, data supporting the use of short-course antibiotics are limited. Only one study included a placebo group. Prospective studies available show effects on symptoms in 56% to 95%. No significant difference was found between the different antibiotics compared. It has been demonstrated recently that some antibiotics (doxycycline) are able to reduce polyp size.

Because CRS is considered a mucosal disease, treatment may include long-term low-dose antibiotics to control pathology over a longer period of time. In research most attention, especially in vitro, was drawn to the antibiotics of the macrolide family. Besides their antimicrobial effects, macrolides are thought to have anti-inflammatory capacities based on the blockage of the production of cytokines, such as interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α), combined with effects on neutrophil migration and adhesion, and modulation of synthesis and secretion of mucus. Few studies have examined the efficacy of long-term low-dose antibiotics in CRS. The majority of these uncontrolled investigations report clinical benefit. In the first performed, double-blind, randomized, placebo-controlled trial on the efficacy of 3 months of macrolide treatment in 64 CRS-patients, no significant differences were found. However, a significant benefit of macrolides over placebo was shown in a subpopulation of patients with low IgE. The effect of long-term low-dose antibiotics is not known but seems to work in selected cases even when steroids fail. The mechanism behind this is not well understood, but probably involves down-regulation of the local host immune response as well as a downgrading of the virulence of the colonizing bacteria. However, there is lack of evidence in terms of placebo-controlled, double-blind, randomized trials.
CHAPTER 1

Alternatives in medical therapy
The role of intranasal application of antibiotics is still under discussion. Few studies have explored their therapeutic role in patients with CRS. Several uncontrolled studies indicate that the topical application of antibiotics has a beneficial effect.\textsuperscript{117-121} Others have found that nasal irrigation is useful, but addition of antibiotics represents no supplementary advantage.\textsuperscript{122-124} The use of decongestants, antihistamines for adult CRS has not been evaluated in a randomized controlled trial or no beneficial effect has been found.\textsuperscript{125}

Sinus Surgery
An estimated 50 per cent of patients with CRS will ultimately require Functional Endoscopic Sinus Surgery (FESS) in the treatment of their disease.\textsuperscript{126} In Messenklinger’s original teaching, the primary goal of FESS is reestablishing the ventilation and drainage through natural sinus ostia under direct vision, with the expectation that even extensive pathological mucosa change would reverse itself with the reestablishment of normal drainage.\textsuperscript{127} FESS is not one procedure, but it is tailored to disease extent concentrating on the ostiomeatal complex. In different studies evaluating FESS, favourable outcome has been demonstrated.\textsuperscript{55, 128-136} However a comparison of these studies is difficult due to the heterogeneity of the populations, the varying surgical techniques and differences in follow-up. As in all evaluations of surgical procedures it is hard to fit in a placebo group.

Most patients with CRS have great benefit of conventional medical treatment in combination with FESS. Although success rates of primary FESS are high (around 80-90%),\textsuperscript{56, 128, 129, 132} some patients fail to respond. The majority of these first-time FESS-failures, benefit from revision procedures with success percentages in order of 50%-70%.\textsuperscript{56, 127} Nonetheless, the success rate of these revision procedures decreases with each following intervention. Radical surgery could serve as a last resort in this group of patients. Although we reside in the FESS era, some more radical forms of surgery should be kept in mind as useful tools in selected cases.

AIM AND BRIEF OUTLINE OF THIS THESIS
The main goal of this thesis is to investigate several different aspects of CRS. First we investigated the role of fever in CRS. It is a symptom part of the American CRS definition but not of the European one. Why CRS is recalcitrant in some patients is unclear. To assess one of the factors, suspected to play a role in recalcitrant disease, we put osteitis into the spotlight. We reviewed literature on the role of osteitis in CRS, and our group performed a case-control study to examine the patient and disease factors associated with the presence of osteitis in CRS with the newly developed Global Osteitis Scoring Scale. In chapter 3 we focus on medical treatment options in CRS. We retrospectively analysed a group of patients treated at the outpatient clinic with 2 different long-term low-dose courses of antibiotics. The second part of this chapter reports on the data of the MACS trial, a prospective, double-blind, randomized, placebo-controlled, international, multi-centre trial on the efficacy of azithromycin in patients with recalcitrant CRS. To date, this is only the second RCT on prolonged antibiotic treatment in patients with CRS. In the last part of this chapter we performed a placebo-controlled pilot study in order to determine whether nebulized topical antibiotic therapy improves sinusitis symptoms more than saline-based placebo in patients with recalcitrant CRS. In some unfortunate patients optimal medical
INTRODUCTION

treatment and even repetitive endoscopic sinus surgery procedures fail. In chapter 4 we discuss the possible use of a more radical surgical procedure (Denker's surgery) as a last resort for patients suffering from recalcitrant CRS. We evaluated symptom improvement, as well as quality of life and pain results. Finally, in chapter 5, we discuss the collected results and put them in perspective with literature.
REFERENCE LIST

1 Leonardo da Vinci. 1489.
13 Schaeffer JP. The nose, the paranasal sinuses, nasolachrymal passageways and olfactory organ in man. Philadelphia: Blakiston; 1920.
18 Vessalios A, De Humani Corps Fabrica. 1542; Lib 1, Cap VI-IX. 1542.
19 Highmore N. Corp Human Disquisition Anatom. Hagae; 1651.
INTRODUCTION

INTRODUCTION


CHAPTER 1
