On Health-Related Quality of Life and Diagnostic Improvements in Rhinosinusitis

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A Multi-centre Study on Chronic Rhinosinusitis and Experimental Studies with Doppler Ultrasound as a Diagnostic Tool in Rhinosinusitis

by

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The HRQOL of 207 patients divided into three subgroups, one with recurrent acute rhinosinusitis, and two with chronic rhinosinusitis, with or without nasal polyps, was evaluated with the 22 Sinonasal Outcome Test (SNOT-22), the 36-item short-form questionnaire (SF-36), the Hospital Anxiety and Depression (HAD) scale and a total visual analogue scale (VAS). These patients' HRQOL was significantly decreased compared to normative values. Some significant differences in HRQOL scoring were found between the three subgroups. The study cohort reported 8-14 days of absenteeism per year due to their sinus problems. SNOT-22 and the total VAS appeared to be appropriate outcome measures in cases of rhinosinusitis in the Swedish population.

It is not possible to differentiate serous sinus fluid (with a low viscosity) from mucopurulent sinus secretions (with high viscosity) with computed tomography (CT) or ultrasound. A means of determining the properties of sinus secretions non-invasively would, however, be of value, as bacteria are often found in mucopurulent secretions in rhinosinusitis. In order to improve the diagnosis of these patients, the ultrasound technique was further developed. In this thesis, it was demonstrated that it is possible to induce acoustic streaming in a sinus model, and that the acoustic properties of a fluid can be determined with Doppler ultrasound. The appropriate frequency of the ultrasound was found to be ~5 MHz. The anatomical dimensions of the maxillary and frontal sinuses were studied on computed tomography images in order to be able to develop a clinically useful Doppler instrument. It was shown how serous sinus fluid can be distinguished from mucopurulent sinus secretion with Doppler ultrasound, without exposing the patient to a harmful increase in temperature.

Key words

Rhinosinusitis, nasal polyps, health-related quality of life, absenteeism, Doppler ultrasound, acoustic streaming, attenuation

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To Martin, Thea and Ida

Rather a book on snot, than a snotty book.

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List of publications

I. Sahlstrand-Johnson P, Ohlsson B, Buchwald C, Jannert M, Ahlner-Elmqvist M. A multi-centre study on quality of life and absenteeism in patients with CRS referred for endoscopic surgery. Rhinology:In press. Accepted 18th of May 2011.

II. Jönsson P, Sahlstrand-Johnson P, Holmer N-G, Persson HW, Jannert M, Jansson T. Feasability of measuring acoustic streaming for improved diagnosis of rhinosinusitis. Ultrasound Med. & Biol. 2008;34:228–38.

III. Sahlstrand-Johnson P, Jannert M, Strömbeck A, Abul-Kasim K. Computed tomography measurements of different dimensions of maxillary and frontal sinuses. BMC Medical Imaging 2011;11:8.

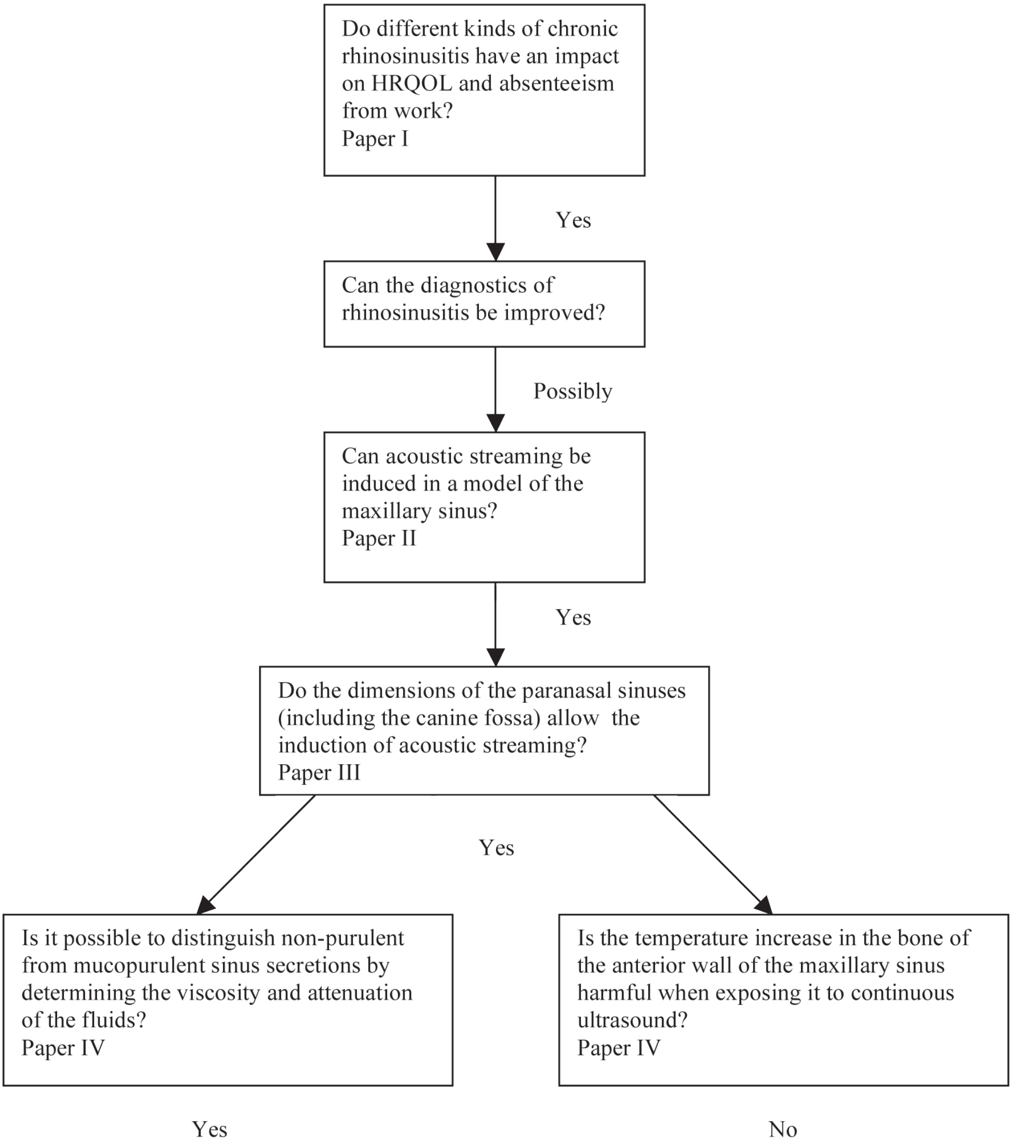
IV. Sahlstrand-Johnson P, Jönsson P, Persson HW, Holmer N-G, Jannert M, Jansson T. In vitro studies and safety assessment of Doppler ultrasound as a diagnostic tool in rhinosinusitis. Ultrasound Med. & Biol. 2010;36:2123-31.

Abbreviations

ARS	Acute rhinosinusitis
CRS	Chronic rhinosinusitis
CSS	Chronic Sinusitis Survey
CT	Computed tomography
EP30S	European Position Paper on Rhinosinusitis and Nasal Polyps
ESR	Erythrocyte sedimentation rate
FESS	Functional endoscopic sinus surgery
HAD	Hospital Anxiety and Depression (scale)
HRQOL	Health-related quality of life
NP	Nasal polyps
RARS	Recurrent acute rhinosinusitis
SNOT-22	22 Sinonasal Outcome Test
SF-36	36-item Short-Form questionnaire
VAS	Visual analogue scale
WFUMB	World Federation for Ultrasound in Medicine and Biology

Thesis at a glance

The following issues were addressed in this thesis:



Introduction

Rhinosinusitis

Rhinosinusitis is an inflammatory process involving the mucosa of the nose and one or more of the paranasal sinuses (Fokkens et al. 2007), and the term is still used to cover this heterogeneous condition. During the past decade, it has become more evident that chronic rhinosinusitis (CRS) is not one disease but rather a range of conditions caused by different underlying diseases or abnormalities, for example: bacterial infection, mucociliary impairment, obstruction caused by anatomical variations of the paranasal sinuses, and allergy (Sturgess et al. 1979; Jones et al. 1997; Slavin 1997; Bhattacharyya 2002; Jones 2002; Zacharek and Krouse 2003).

Rhinosinusitis, in its various forms, is one of the most common reasons for seeking medical advice today. Acute rhinosinusitis (ARS) is the fifth most common diagnosis for which antibiotics are prescribed, according to the US National Ambulatory Medical Care Survey. The prevalence of CRS in Europe appears to be about 9.3% (Tomassen et al. 2010), while the prevalence of nasal polyps (NP) in the total population is 2.7% (Johansson et al. 2003), and seems to increase with age (Larsen and Tos 1997; Rugina et al. 2002; Klossek et al. 2005).

The perception that NP is a subgroup of CRS has evolved over the years, and CRS cohorts are, therefore, often divided into two groups: CRS with NP and those without. Nasal polyps mostly consist of loose connective tissue, oedema, a reduced number of glands and capillaries, and inflammatory cells covered by epithelium (Taylor 1963; Kakoi and Hiraide 1987). Eosinophils are the predominant type of inflammatory cell (Stoop et al. 1993), and interleukin 5 is overexpressed (Bachert et al. 2001). Nasal polyps may significantly decrease health-related quality of life (HRQOL) (Radenne et al. 1999; Alobid et al. 2005; Alobid et al. 2008). There have been reports that patients with NP often differ from other patients with CRS in patient-perceived scoring of the disease (Durr et al. 2001; Hopkins et al. 2006; Ragab et al. 2010; Zheng et al. 2010).

Definitions

According to European Position Paper on Rhinosinusitis and Nasal Polyps (EP3OS) rhinosinusitis (including nasal polyps) is defined as (Fokkens et al. 2007):

- inflammation of the nose and the paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
    - ± facial pain/pressure,
    - ± reduction or loss of sense of smell;

and either

- endoscopic signs of:
    - polyps and/or;
    - mucopurulent discharge primarily from the middle meatus; and/or oedema/mucosal obstruction primarily in middle

      meatus,

and/or

- changes seen in computed tomography (CT) images:
    - mucosal changes within the ostiomeatal complex and/or sinuses.

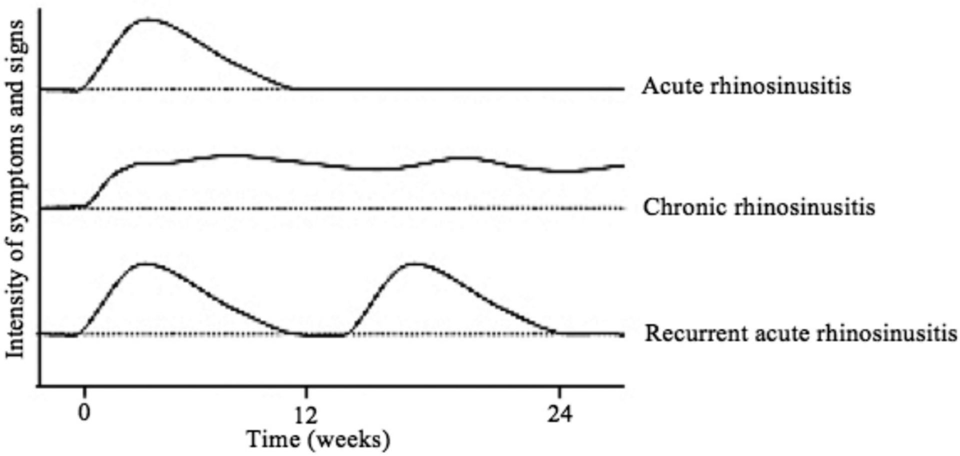


Figure 1. The course of different kinds of rhinosinusitis

Acute disease is defined as that lasting less than 12 weeks, with total resolution of symptoms.

Chronic disease is that lasting more than 12 weeks, without total resolution of symptoms.

Recurrent acute rhinosinusitis (RARS) is defined as: 1) a clinical history of four or more recurrent acute bouts of rhinosinusitis in the previous 12-month period, and 2) a paucity of sinonasal symptoms during intervals between acute episodes (Lanza and Kennedy 1997) (Bhattacharyya and Lee 2005). The courses of the different kinds of rhinosinusitis are illustrated in Figure 1.

Health-related quality of life

Definition

The WHO's definition of health from 1947 states that health is: "*…not only the absence of disease or infirmity, but a state of complete, physical, mental and social well-being*". This has been the basis of the consensus that, in relation to medical care and treatment, quality of life is a multidimensional concept covering all aspects of an individual's well-being, including their physical and mental health, as well as their financial situation (WHO 1958). In clinical research and medicine the multidimensional health-related concept "health-related quality of life" (HRQOL) is often used as a measure of the effects of an illness and its treatment on the patient's perception of their symptoms, functioning and psychological health (Glare and Christakis 2000; Richards and Ramirez 1997).

Different outcome measures

The lack of consensus on the definition of rhinosinusitis has prevented reliable studies on the outcome of different forms of treatment. During the 1990s, there was no standard definition of rhinosinusitis, which made it difficult to diagnose and prescribe adequate treatment of the condition. Subjectively experienced results of various kinds of treatment for rhinosinusitis were common. Gathered evidence-based knowledge on rhinosinusitis became available for the first time with the publication of the first EP3OS document in 2005 (Fokkens et al. 2005). A revision followed in 2007, with criteria for acute and chronic rhinosinusitis (Fokkens et al. 2007). When EP3OS2007 was published, the results of 104 randomized controlled trials on CRS had been published, and the number is increasing steadily.

There are different types of outcome measures for both pharmaceutical treatment and functional endoscopic sinus surgery (FESS). Surgery should be performed only when the most effective pharmaceutical treatment is inadequate, and symptom and HRQOL scores should be the indicators that surgeons focus on. It is stated in EP3OS that CT and endoscopic scores are well correlated (Smith et al. 2005), but the correlation between CT findings, symptoms and HRQOL scores has generally been found to be poor (Holbrook et al. 2005; Browne et al. 2006; Hopkins et al. 2006; Zheng et al. 2010). CT staging of the paranasal sinuses and endoscopic scoring have also been found to be poor predictors of patient satisfaction after FESS (Zheng et al. 2010), whereas preoperative HRQOL scores have proven to be predictive of ultimate patient outcome (Gliklich and Metson 1997).

Another possible outcome measure in the treatment of rhinosinusitis is grading of the sense of smell, as this is regarded as one of the major symptoms in CRS with and without NP and it has been found that olfactory disorders can alter HRQOL (Hummel and Nordin 2005). The butanol olfactory threshold test (Cain et al. 1988) is one method that has been frequently used to measure the effect of FESS on olfaction in patients with NP. In a study by Blomqvist et al. (Blomqvist et al. 2001), the effect of pharmaceutical treatment alone versus combined surgical and pharmaceutical treatment were evaluated, and it was found that pharmaceutical treatment was sufficient to treat most symptoms of NP. In another study by Olsson and Stjarne (2010) it was concluded that FESS improved both sense of smell and olfactory thresholds in the short term in patients with NP.

The importance of assessing HRQOL

Measurements of the HRQOL reflect the effect of symptoms on the patient's daily life, and it has been proved that this is correlated with sinonasal disease severity (Lim et al. 2007). HRQOL scoring has also been proven to correlate with other disease severity. For example, in patients with head and neck cancer, advanced disease is strongly correlated to low HRQOL scores (Hammerlid et al. 2001). It has also been stated that HRQOL scoring can help to predict survival in cases of head and neck cancer (Bjordal et al. 2001). HRQOL scoring is also a way of illustrating the consequences of a disease or the results of treatments, and could thus be used to facilitate communication between doctors and patients. Additionally, measures of the quality of treatments are today required by many actors, e.g. ethics committees, local and regional health authorities and society as a whole.

When initiating the work described in this thesis in 2003, there was a paucity of data in the literature on the subject of HRQOL in patients with rhinosinusitis. At that time, no large study had been published on the effects of chronic sinus problems and subsequent surgery on HRQOL and psychiatric morbidity in Europe. During the past decade, interest in HRQOL assessment in those suffering from rhinosinusitis has increased. At the time of publication of this thesis, 247 articles had been published on HRQOL and rhinosinusitis, according to a search in PubMed. It has thus become evident that rhinosinusitis has a significant impact on HRQOL. In fact, comparisons with other severe chronic diseases have revealed significantly lower HRQOL scores (indicating poorer HRQOL) in measures of bodily pain and social functioning for patients with CRS than in patients with angina pectoris, chronic obstructive pulmonary disease and back pain (Gliklich and Metson 1995a).

HRQOL questionnaires

There are generic HRQOL questionnaires, such as the 36-item Short-Form questionnaire (SF-36)(Ware and Sherbourne 1992; Sullivan et al. 1995; Sullivan et al. 2002), which is one of the most widely used measure for various conditions, including rhinosinusitis. Since sinonasal conditions have a significant adverse effect on HRQOL, questionnaires focused on the symptoms specific to rhinosinusitis and rhinitis have been developed. 22 Sinonasal Outcome Test (SNOT-22) is one of the most frequently used HRQOL instruments in sinonasal research today.

Studies on HRQOL in CRS

During the past ten years prospective studies have been published on the impact of CRS on HRQOL. As the work in this thesis is focused on HRQOL scores of patients with recurrent ARS (RARS) and CRS with and without NP (CRS+/-NP) referred for FESS, some similar studies are briefly described below.

The most extensive outcome study published to date is the National Comparative Audit of Surgery for Chronic Rhinosinusitis and Nasal Polyposis, in which over 3000 patients were included, where SNOT-22 scores were obtained up to 36 months after surgery (Hopkins et al. 2006). Several other studies have also shown significant improvement in HRQOL scoring after FESS (Winstead and Barnett 1998; Ragab et al. 2004; Ragab et al. 2010; Smith et al. 2010). In a Swedish study performed by Olsson and co-workers (2010), it was found that HRQOL in patients with NP and asthma was significantly impaired after FESS, as measured with SF-36. Finally, Durr et al. (2001) compared patients with RARS, CRS+NP and CRS-NP and found differences in the scores on some of the SF-36 subscales, as well as significant differences compared with values of a normal population. However, to the best of the author's knowledge, no European studies have been published on the effect of CRS on HRQOL and absenteeism from work, using the definition of the condition in EP3OS.

Possible improvements of the diagnostics

As rhinosinusitis has a considerable impact on HRQOL and causes a great deal of sick leave, improvement in the diagnosis of this condition would be of value. For example, it may be possible to prevent the development of CRS by improving diagnostic methods. If the content of the paranasal sinus could be determined non-invasively in patients with ARS, it would be possible to provide adequate treatment directly before it develops into a chronic condition. With such a method it would also be possible to prescribe antibiotics only if indicated by the properties of the sinus fluid, and to follow the recovery of a patient. Such a method would increase the efficiency of diagnosing rhinosinusitis, allow watchful waiting, may prevent a decrease in the patient's HRQOL and possibly decrease the prescription of antibiotics. This is also of importance as bacterial resistance poses a considerable threat to health. The development of a Doppler ultrasound method to diagnose and stage sinus infections was therefore undertaken.

Doppler ultrasound

Ultrasound is not new. Bats have used ultrasound to detect food (Figure 2) for more than 50 million years. Ultrasound is also used at sea for detecting icebergs, shoals of fish and submarines (Crowther and Widdington 1947). The technique can also be used to detect cracks in turbines in both aeroplanes and nuclear power stations (Firestone and Frederik 1944). The role of ultrasound in medicine has evolved from detecting gallstones in the 1950s (Ludwig and Struthers 1950), to visualizing cardiac motion (Edler and Hertz 2004) and creating a two-dimensional image of a foetus (Donald et al. 1958; Sunden 1964).

Figure 2. A bat using ultrasound waves to detect food. *Illustration:* Thea Johnson

In otorhinolaryngology, ultrasound can be used to identify lymph nodes, cysts and abscesses. The idea of using ultrasound to distinguish healthy air-filled sinuses from diseased ones was first described by Keidel in 1947 (Keidel). Experiments and development were performed in Germany by Mann, in Finland by Revonta and in Sweden by Jannert and Holmer, in the 1970s and 1980s (Mann et al. 1977; Revonta 1980; Jannert et al. 1982a). Simple, inexpensive ultrasound equipment for use in out-patient clinics was produced in all three countries through fruitful collaboration with industry. The method has now been used, mainly in Europe, in clinical practice for more than 30 years (Figure 3).

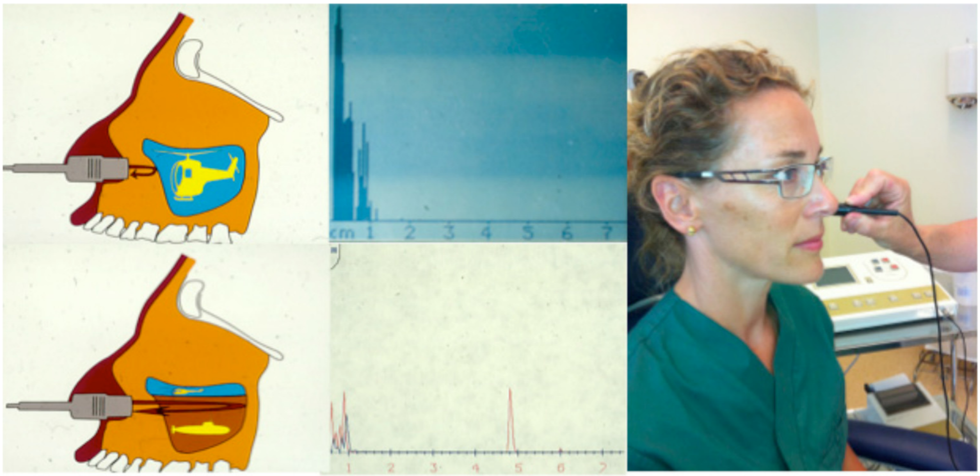


Figure 3. Ultrasound is used to detect fluid in the maxillary and frontal sinuses. When there is fluid in the maxillary sinus there is an echo of the ultrasound, illustrated by the peak at 4-5 cm on the x-axis in the display of the ultrasound equipment.

The Doppler effect

The Doppler effect was first described in 1846 by the Austrian mathematician and physicist, Christian Doppler. If a sound or light wave is reflected by a moving object, the frequency of the reflected wave is changed depending on the speed of the reflecting object (Figure 4). It is thus possible to non-invasively measure the speed of a moving object in the body, for example, the speed of red blood cells. A combination of the ultrasound echo method and Doppler ultrasound technique is used, for example, when examining the carotid arteries or a foetus.

The physics of ultrasound

When an ultrasonic wave meets an interface in human tissue, a fraction of the wave is reflected back towards the transducer, see Figure 5. The transducer, which consists of a piezoelectric material, functions as both an ultrasound transmitter and receiver, and transforms acoustic echoes into electrical signals.

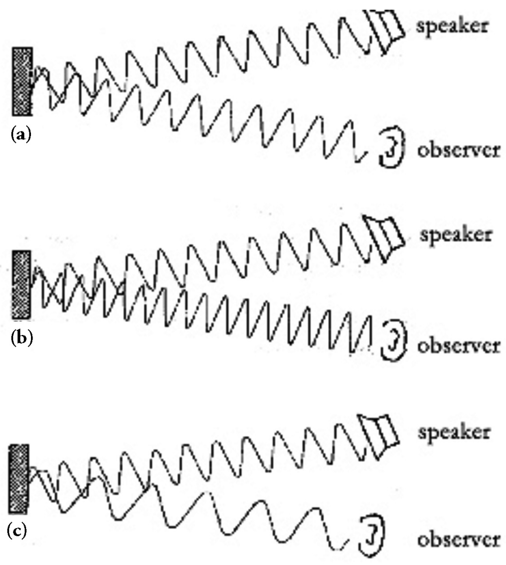


Figure 4. The Doppler effect. If the reflecting object is approaching the observer, (b) there is an increase in the frequency of the sound waves, while the frequency decreases when the reflecting object is receding the observer. (c) Reproduced from Nils-Gunnar Holmer (ed). *Diagnostiskt ultraljud – Grunderna*. Sweden: Bokförlaget Teknikinformation. Lund och Linköping; 1992, with permission.

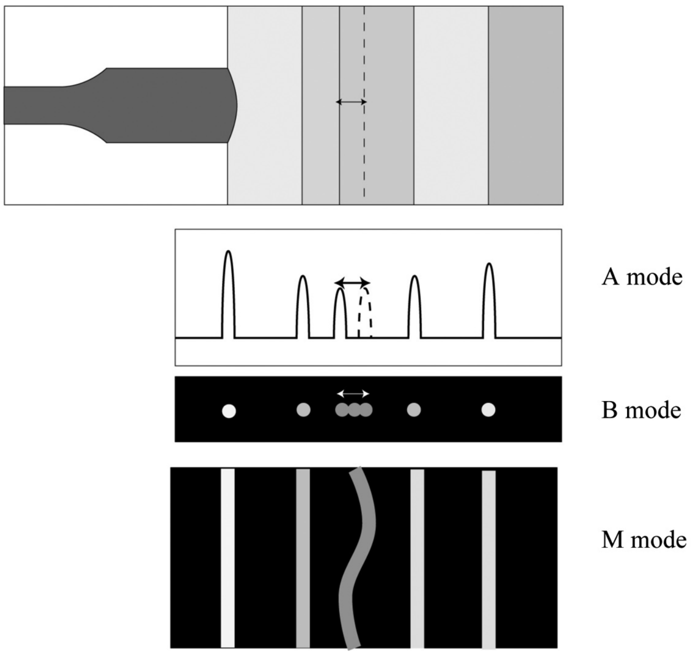


Figure 5. A, B and M mode. The arrow indicates the movement of the reflecting structure. *Illustration*: Monica Almqvist.

Two different ultrasonic methods can be employed for examination of the paranasal sinuses, denoted the A-mode and the B-mode. The A-mode (amplitude mode) is the simpler one, and gives a one-dimensional image of the acoustic echoes (Figure 5). This mode is used today in equipment for the investigation of the maxillary and frontal sinuses. The B-mode (brightness mode) employs the same principle as the A-mode, but the amplitude of the echo is used to control the brightness (Figure 5). Two-dimensional images can be obtained using transducers consisting of many piezoelectric crystal elements in the B-mode. There is a third mode, called the M-mode (motion mode), which registers moving echoes as a curve, the appearance of which is dependent on the movement of the echo-producing object(s) (Figure 5). However, this mode is not used for examining the paranasal sinuses.

Diagnosing acute rhinosinusitis

The use of antibiotics in ARS has been the subject of debate for many years; partly because there previously was no uniform definition of rhinosinusitis, and partly because it has not been possible to determine, easily and quickly, whether the rhinosinusitis in a particular individual is caused by bacteria or not. Generally, ARS has been diagnosed when there has been proof of purulent secretions in the paranasal sinuses, detected with ultrasound, plain radiography or CT. Lindbaek and Hjortdal (2002) have published a review article on the prevalence of clinical signs and symptoms in acute purulent sinusitis in general practice. Purulent secretions, reported by the patient and demonstrated in the nasal cavity by the doctor, were found to be the strongest predictive sign of ARS (van Duijn et al. 1992; Williams et al. 1992; Lindbaek et al. 1996a). Double sickening and an erythrocyte sedimentation rate (ESR) greater than 10 mm/h in males or greater than 20 mm/h in females can also be of diagnostic value (Hansen et al. 1995; Lindbaek et al. 1996a). European diagnostic criteria for ARS were published for the first time in 2005 (Fokkens et al. 2005), which helped clinicians to make more uniform diagnoses. These criteria included nasal discharge and endoscopic signs of mucopurulent discharge from the paranasal sinuses.

In 2005, a study was published comparing the efficacy of a nasal steroid (mometasone furoate) with antibiotics and a placebo in the treatment of ARS (Meltzer et al. 2005). It was found that mometasone furoate was superior to amoxicillin in treating uncomplicated ARS. This finding made it easier to treat ARS and avoid the prescription of antibiotics to patients with putative rhinosinusitis. However, patients who suffer from prolonged disease may still require antibiotic treatment, and possibly sinus irrigation. These patients are often treated at otorhinolaryngology departments at hospitals. It has been reported that one person in four is prescribed at least one course of antibiotics per year in Sweden, and most of these patients are misdiagnosed as suffering from rhinosinusitis (*Dagens Nyheter 24-05-2009*). Uncertainty in the diagnosis of ARS results in the overuse of antibiotics. Since bacterial resistance to antibiotics is a growing problem

worldwide, an improvement in the diagnosis of one of the most common complaints leading to the prescription of antibiotics would be of great benefit.
Studies indicate that ARS with serous sinus fluid (which has a low viscosity) is caused by viruses, whereas mucopurulent sinus secretion (which has a high viscosity) is caused by bacteria (Carenfelt and Lundberg 1977; Carenfelt et al. 1978). Ultrasound and CT merely determine the presence of fluid in the paranasal sinuses; but provide no information on the properties of the fluid. The only way to identify mucopurulent sinus fluid, and thus confirm the need for antibiotics, is by performing a sinus puncture. Sinus puncture and irrigation involve penetrating the maxillary sinus cavity with a needle via the nose through a bony wall, which is an uncomfortable procedure for the patient.

Doppler ultrasound in rhinosinusitis

Acoustic streaming is the term applied to unidirectional flow currents in a fluid, caused by sound waves. It is generated by the absorption of energy from acoustic oscillations of the sound wave (Kamakura et al. 1999). The streaming velocity is inversely proportional to the viscosity of the fluid, as expressed in the equation,(Nyborg 1965):

$$v = C_1 \cdot \frac{\alpha I_{spta}}{c_0 \eta}$$

where v is the streaming velocity in the enclosed fluid; α the sound attenuation, η the fluid viscosity, I_{spta} the spatial peak temporal average sound intensity (referred to below as the intensity), and c_0 the speed of sound in the fluid. The parameter C_1 in the equation depends on the geometry of the container and the sound wave, but for low fluid velocities it is approximately independent of the other parameters in the equation. The higher the attenuation of the fluid, the higher the acoustic streaming velocity and thus the bigger the measurable Doppler-shift. If there are scattering particles in the fluid (as in sinus secretion), their velocity can be measured with Doppler ultrasound.

In the early 1990s, Dymling et al. (1991) observed a difference in acoustic streaming velocity between fresh and sour milk; the latter containing a high concentration of scattering particles. It was more difficult to induce detectable acoustic streaming in sour milk as it has a higher viscosity. Since then, there has also been a growing interest in utilizing acoustic streaming for medical purposes. It has been shown that acoustic streaming can be induced and detected in breast cysts *in vivo* (Nightingale et al. 1999), and can also be used to estimate the viscosity of ovarian cyst content (Clarke et al. 2004). In both these studies acoustic streaming was induced in a fluid volume close to 15 mL, which is typical of the size of a maxillary sinus. However, there is at least one crucial difference between cysts and sinuses; the paranasal sinuses are surrounded by bone. Bone is highly sound attenuating and therefore a large fraction of the sound will be absorbed by the bone and little will reach the sinus cavity. However, the influence of bone attenuation can be minimized in the maxillary sinus by transmitting the incoming ultrasound beam through a region in front of the sinus called the canine fossa, where the bone is thin and compact.

This thesis describes attempts to develop the method of Doppler ultrasound to improve the diagnosis of rhinosinusitis, using the fact that the paranasal sinuses contain secretion when there is infection and inflammation. If the viscosity of the sinus fluid is related to the need for treatment with antibiotics in ARS, Doppler ultrasound could be a valuable diagnostic tool. It was hypothesized that serous sinus fluid with low viscosity (as in virus-induced ARS) would show acoustic streaming, while acoustic streaming would not be detectable in mucopurulent sinus secretion (as in rhinosinusitis caused by bacteria) as it has a much higher viscosity (Figure 6). In other words, a measurable Doppler shift is an indication of serous sinus fluid in rhinosinusitis. Additionally, it would be possible to identify rhinosinusitis caused by dental infection, since the secretion resulting from dental empyaema has a viscosity between that of serous and mucopurulent secretion (clinical experience). Thus, Doppler ultrasound may have the potential to improve the diagnosis of rhinosinusitis, and indicate when the prescription of antibiotics is warranted.

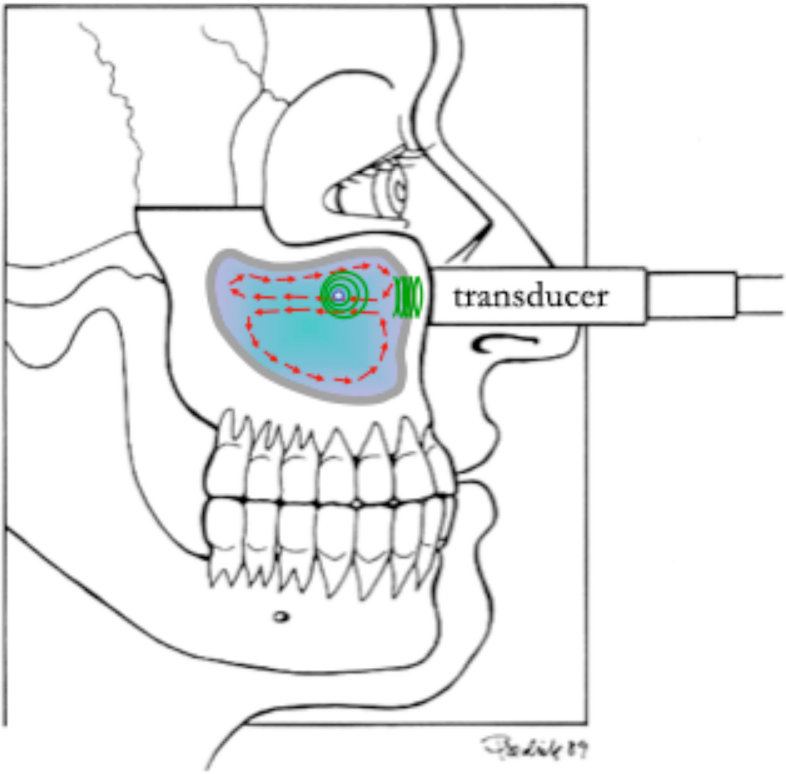


Figure 6. A possible set-up for Doppler ultrasound to distinguish serous from mucopurulent sinus secretions. A detectable acoustic streaming (and consequently a measurable Doppler shift) in the sinus fluid is a sign of non-purulent secretions. *Illustration*: Peter Jönsson.

Aims

The aim of the work presented in this thesis was to study HRQOL, psychiatric morbidity and absenteeism from work in patients with rhinosinusitis, and to investigate a novel application of the Doppler ultrasound technique to improve the diagnosis of rhinosinusitis.

The specific aims and research issues were:

- to assess HRQOL data, psychiatric morbidity and absenteeism from work in patients referred for FESS due to RARS, CRS+NP and CRS-NP, and to evaluate whether there is any difference in HRQOL score between these three subgroups of patients with chronic sinus disease;
- to investigate whether it is possible to induce detectable acoustic streaming in a sinus model, and to identify transducer properties suitable for Doppler ultrasound equipment;
- to determine the dimensions of the paranasal sinuses, especially the thickness of the anterior wall of the maxillary sinus, with regard to gender, side and age, in order to continue the development of clinically applicable Doppler ultrasound equipment; and
- to determine whether it is possible to differentiate between mucopurulent sinus secretions and serous sinus secretions with Doppler ultrasound, and to investigate the increase in temperature of the bone caused by the equipment.

Subjects and Methods

Pilot study

Before performing the first study, a pilot study was performed in 2005-6 on 33 patients admitted for FESS to evaluate the logistics of future studies and the suitability of a number of questionnaires. In that study, the Chronic Sinusitis Survey (CSS) was used as a sinonasal-specific measure, in addition to SF-36 and the Hospital Anxiety and Depression (HAD) scale. CSS is a six-item, duration-based monitor of sinusitis-specific outcomes, which has been demonstrated to have statistical reliability and validity in American studies on patients with rhinosinusitis (Gliklich and Metson 1995b). The questionnaire is divided into a symptom-based section and a medication-based section, and both contain questions about the duration of symptoms during a 2-month period. CSS was translated into Swedish according to international recommendations (Fayers and Machin 2007). However, it was found that the form was difficult to understand and difficult to relate to for Swedish patients. The medication-based section assesses the use of antibiotics, the prescription of nasal sprays, and over-the-counter sinus medications, which are not used to the same extent in Sweden as in the USA. Additionally, the symptom "loss of sense of smell" is not included in the CSS, but should be one of the symptoms evaluated in rhinosinusitis according to EP3OS. A Norwegian study on CSS confirmed the shortcomings of the questionnaire in the Nordic countries, showing a low internal consistency (Stavem et al. 2006). After the pilot study had been completed, SNOT-22 was presented as a suitable HRQOL questionnaire for sinonasal disease. This form includes the cardinal symptoms of rhinosinusitis and has been found the most suitable disease-specific instrument for use in CRS (Morley and Sharp 2006). Thus, SNOT-22 was chosen as the disease-specific HRQOL questionnaire for the study described in Paper I.

Study subjects

Between 2007 and 2009, a total of 283 patients were included in the studies described in this thesis (see Table 1 for patient characteristics). The Regional Ethics Review Board at Lund University approved the studies (LU 413/2005, 100/2009, 403/2009). Informed consent was obtained from all subjects in Studies I and IV. Written consent was not required in Study III as this investigation was performed retrospectively on already existing CT images. (No patients were included in Study II, as this was a technical experimental study.)

Table 1. Patient characteristics of the 283 individuals included in Study I, III and IV.

	Number of subjects	Gender (female/male)	Age range (years)	Diagnose
Study I	207	85/122	18-85	CRS
Study III	60	32/28	18-65	Non-rhinological disorders
Study IV	16	11/5	22-69	ARS

CRS = chronic rhinosinusitis, ARS = acute rhinosinusitis

The following non-compliance was recorded in Paper I: 17 patients did not complete and return the preoperative questionnaires; and 13 patients were excluded because they fulfilled the exclusion criteria or did not have the correct diagnosis; leaving 207 participants. An additional 79 possible patients were not included due to administrative difficulties, e.g. we did not receive information about surgery in time to send out the questionnaires, or it was not possible to contact the patient.

HRQOL and absenteeism among patients with chronic rhinosinusitis

Study overview and design

Two hundred and seven patients with the diagnoses RARS, CRS+NP and CRS-NP were prospectively included in this multi-centre study (**Paper I**). These patients had previously received appropriate medical treatment according to the EP3OS guidelines (Fokkens et al. 2007) without satisfactory response, and were examined and referred for FESS by otorhinolaryngologists at ten Swedish hospitals (five regional and five university hospitals). The definitions of RARS, CRS+NP and CRS-NP, are given in the Introduction. Exclusion criteria were pregnancy, gross immunodeficiency, congenital mucociliary problems, cystic fibrosis, and systemic vasculitis and granulomatous diseases, as these conditions may induce sinus disease and affect HRQOL. The ability to understand the Swedish language was required for inclusion.

Patients who agreed to participate were sent questionnaires (see below) together with appointments for surgery (usually 2-4 weeks prior to surgery). The patients also reported their absenteeism from work due to sinus problems during the past 12 months. The possible alternatives were: 0 days, 1-7 days, 8-14 days, 15-30 days or >30 days. Additionally, they completed a patient characteristics form. At the time of surgery, the surgeon completed a clinician-reported data form.

Questionnaires

22 Sinonasal Outcome Test

SNOT-22 is a patient-reported HRQOL questionnaire developed for use in CRS+/-NP (see Appendix). It contains 22 nose, sinus and general items, and is a modification of SNOT-20 developed by Piccirillo et al. (2002); nasal blockage and loss of sense of taste and smell being added (Browne et al. 2006). It has been validated and is today one of the most frequently used survey instruments in sinonasal research (Hopkins et al. 2009). Lower scores imply a better HRQOL, and the theoretical range of the score is 0 to 110. SNOT-22 was forward-backward translated from English to Swedish and back to Swedish according to international recommendations before being used in this study (Fayers and Machin 2007). A translation check was performed via telephone interviews.

36-item Short-Form Questionnaire

SF-36 is one of the most widely used and tested HRQOL instrument in general health assessment. Eight subscales of general health are measured, ordered according to the degree to which they measure physical vs. mental health. These subscales are physical functioning (PF), role functioning-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role functioning-emotional (RE), and mental health (MH). Furthermore, the subscales can be summarised into two domains, namely physical (PCS) and emotional health (MCS) (Sullivan et al. 1995). As SF-36 is well established and has been translated into numerous languages, there are normative values for different nationalities. In this questionnaire, higher scores imply better HRQOL. The score ranges from 0 to 100.

Hospital Anxiety and Depression Scale

This well-documented HRQOL form contains 14 multiple-choice questions, seven concerning anxiety and seven concerning depression. The HAD scale was designed to screen for psychiatric morbidity and is constructed so that somatic questions are avoided. The cut-offs are > 7 points for possible psychiatric illness and > 10 points for probable psychiatric illness (Zigmond and Snaith 1983).

Visual analogue scale

The VAS is a 100 mm long psychometric response scale, which has been used extensively to score subjective characteristics or attitudes (Priestman and Baum 1976). These kinds of scales have been used in HRQOL assessments for many years, e.g. in patients with cancer (Selby et al. 1984). In this study, it was used to assess combined sinonasal symptoms, and has not previously been validated in this context. The question asked was: “How troublesome have your symptoms of rhinosinusitis been during the last to weeks?”. Lim et al. (2007) considered the relationship between subjective assessment instruments in CRS and found that ‘mild’ equates to a VAS of ≤30, ‘moderate’ to >30-70 and ‘severe’ to >70. The VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end. The patient marks the line at the point they feel represents their perception of their current state.

Endoscopic polyp grading

The surgeons graded the extent of polyps according to an established polyp scoring system (Fokkens et al. 2007): 0 = no visible polyps; 1 = polyps confined to the middle meatus; 2 = polyps below the level of the middle turbinate but not causing total obstruction; 3 = polyps causing total nasal obstruction. In order to analyse whether different combinations of polyp grades were significant in HRQOL scoring, the cohort was further divided based on the polyp scoring system above:

- "NP severity": Group A = polyp extent maximum 1 on both sides; and Group B = polyp extent 2-3 on at least one side
- "NP side": Group I = polyp extent 0 on both sides or at most 1 on one side; Group II = polyp extent 0 on one side and 2 or 3 on the other; Group III = polyp extent 1 on both sides, or polyp extent 1 on one side and 2-3 on the other; Group IV = polyp extent 2 on both sides or polyp extent 2 on one side and 3 on the other; and Group V = polyp extent 3 on both sides.

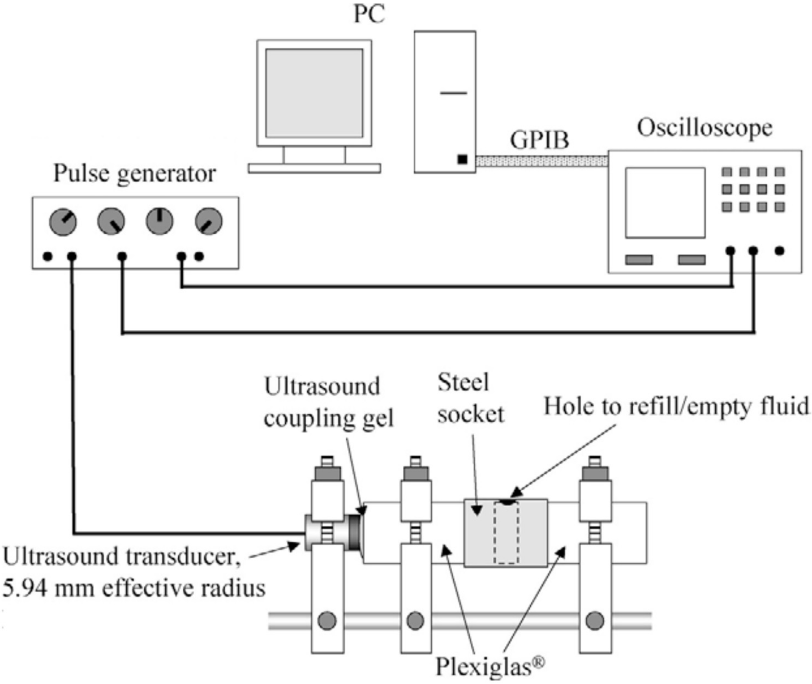
Acoustic streaming in a sinus model

Four different investigations were performed in this study (**Paper II**).

Determination of acoustic properties

Milk (1.5% fat content) was used as model fluid as it contains scattering particles and is of low viscosity, making it a suitable choice for acoustic streaming experiments. The following fluid parameters were evaluated:

- the density (by calculations based on the weight and volume of the sinus sample),
- the viscosity (determined with a falling-ball micro viscometer), and
- the speed and attenuation of sound (measured using the so-called mL method, Figure 7). The measuring container consisted of two 50 mm long rods of Plexiglas® with a diameter of 20 mm, spaced 4.90 mm apart. This gives a total container volume of about 1.5 mL, which permits measurements on mL samples. An ultrasound transducer with an effective radius of 5.94 mm was manufactured in-house.



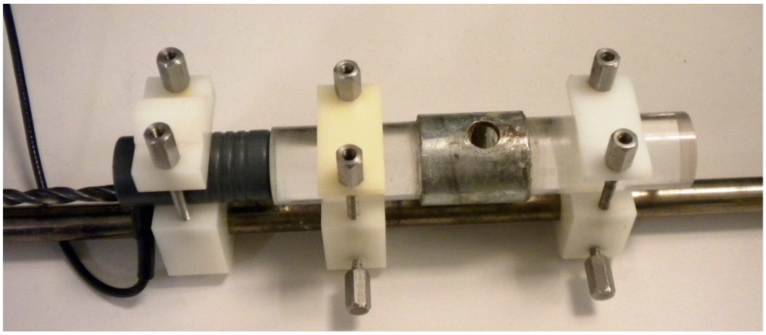


Figure 7. Equipment used to determine the speed and attenuation of sound in a liquid sample. The photo shows the measuring container with trasducer.

Sinus phantom

An anthropomorphic maxillary sinus phantom was constructed using bovine cortical bone (1.08 mm thick), to mimic the bone of the anterior wall of the maxillary sinus. To create the sinus phantom, an impression was taken of a maxillary sinus from a dried human skull and a mould was constructed in agar and graphite powder (Figure 8). This phantom was used for determining if it was possible to induce acoustic streaming in a maxillary sinus.

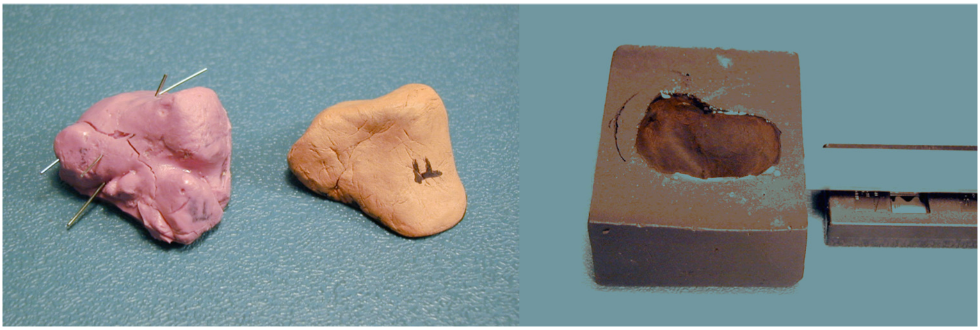


Figure 8. Agar and graphite sinus phantom made from an impression from a human maxillary sinus.

Attenuation of ultrasound by bone

To determine the total attenuation of the ultrasound beam when passing through the bone sample, a model was created in which the bone sample (same bone samples as above) was placed in a water bath (Figure 9).

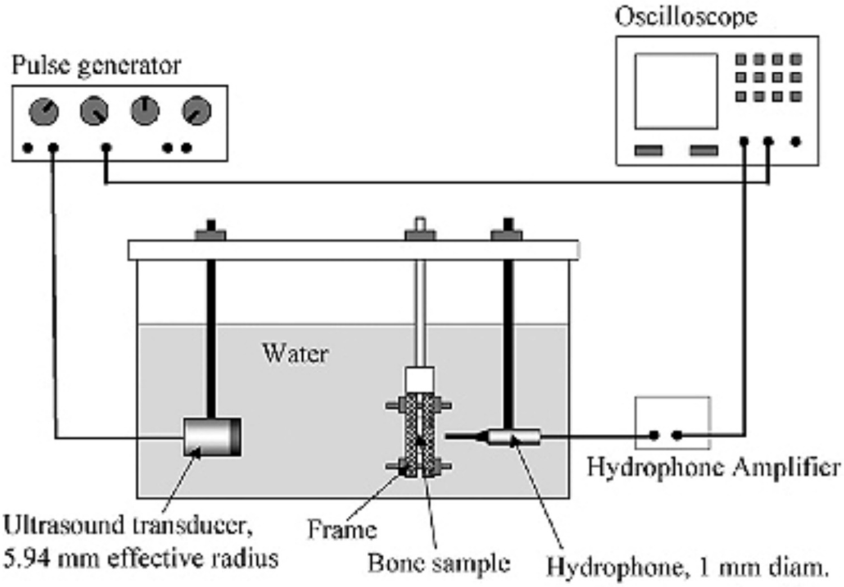


Figure 9. Model used to determine the total attenuation of an ultrasound waves passing through bone.

Properties of the transducer

Computer simulations were performed for five different transducers and a medium with the same acoustic properties as milk, in order to determine the most suitable properties of the transducer with regard to sound frequency, intensity and dimensions (for details, see paper II).

Dimensions of the paranasal sinuses

In this retrospective study (**Paper III**), CT images of 60 consecutive patients (32 females and 28 males) with a median age of 41 years were examined. The cohort was divided into three equally sized groups resulting in age ranges of 18-32, 33-49 and 50-65 years. The indications for CT scan were trauma, headache, neurological deficit and stroke, epilepsy and vertigo, among others. Patients with midfacial injuries were excluded. The images had been obtained with slice collimation of 0.75 mm. The dimensions measured are shown in Figure 10. All the dimensions were measured independently by two neuroradiologists, and the mean values of the measurements obtained by the two readers were used. Incidental findings (mucosal swelling, fluid and retention cysts) were registered. The volume of each maxillary sinus was also calculated using the following equation: (width × anteroposterior diameter × craniocaudal diameter of the sinus) × 0.5. The width used for this calculation was the mean value of the maximal width and the width at the middle of the maxillary sinus on the axial slices (measurements labelled 1 and 2 in Figure 10A). This manually calculated volume was compared with the automatically calculated sinus volume, estimated at the Leonardo work station (Siemens AG, Medical Solutions, Erlangen, Germany) using the volume application.

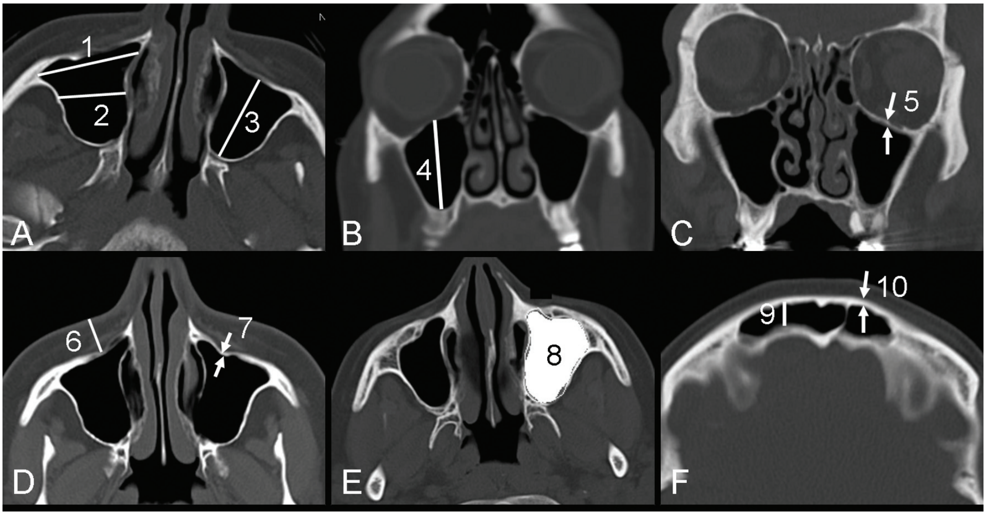


Figure 10. (A, D–F) axial CT images and (B–C) coronal CT image showing the measurement of different dimensions: (1) maximal width of the maxillary sinus, (2) width at the middle of the maxillary sinus, (3) maximal depth (anteroposterior diameter) of the maxillary sinus, (4) maximal height of the maxillary sinus, (5) thickness of the orbital floor, (6) thickness of soft tissue between the anterior wall of the maxillary sinus at the canine fossa and the skin surface, (7) thickness of the anterior wall of the maxillary sinus (canine fossa), and (8) the automatically measured volume estimated at the Leonardo work station. (9) The depth of the frontal sinus, and (10) the thickness of the anterior wall of the frontal sinus were measured at the level of the orbital roof, 1 cm lateral to the midline. All measurements were made on images with skeletal settings.

Acoustic properties of different sinus secretions and safety assessments of Doppler ultrasound

Two different investigations were performed in this study (**Paper IV**).

Acoustic properties of sinus secretions

In this prospectively conducted study the acoustic properties of 18 samples of sinus secretions from 16 patients were investigated; 14 mucopurulent sinus secretions from 13 patients with therapy-resistant ARS, and 4 serous samples from 3 patients with sinus cysts. The samples were aspirated from the maxillary sinus via the nose before sinus irrigation was performed. The density, viscosity, speed of sound and the attenuation by the fluids were determined as described in Paper II.

Temperature measurements

The safety of the Doppler ultrasound method was assessed by determining the increase in temperature when ultrasound is transmitted through a bone sample with the same thickness as the anterior wall of the maxillary sinus. The increase in temperature was measured in two ways:

First, a bovine cortical bone sample of the same thickness as the bony anterior wall of the maxillary sinus (canine fossa) was immersed in water (Figure 11). A continuous-wave transducer manufactured in-house was used to induce the ultrasound waves. Thermocouples were used to measure the increase in temperature in the water due to heating of the bone sample as a result of the absorption of energy from the transducer. The ultrasound intensity was 640 mW/cm^2 and the frequency 4.9 MHz.

Secondly, computer simulations were performed to investigate the temperature increase inside the bone sample. The temperature increase was calculated using the intensity of the ultrasound and the attenuation of the material, which were known in this case (for a detailed description of the computer simulations, see Paper IV).

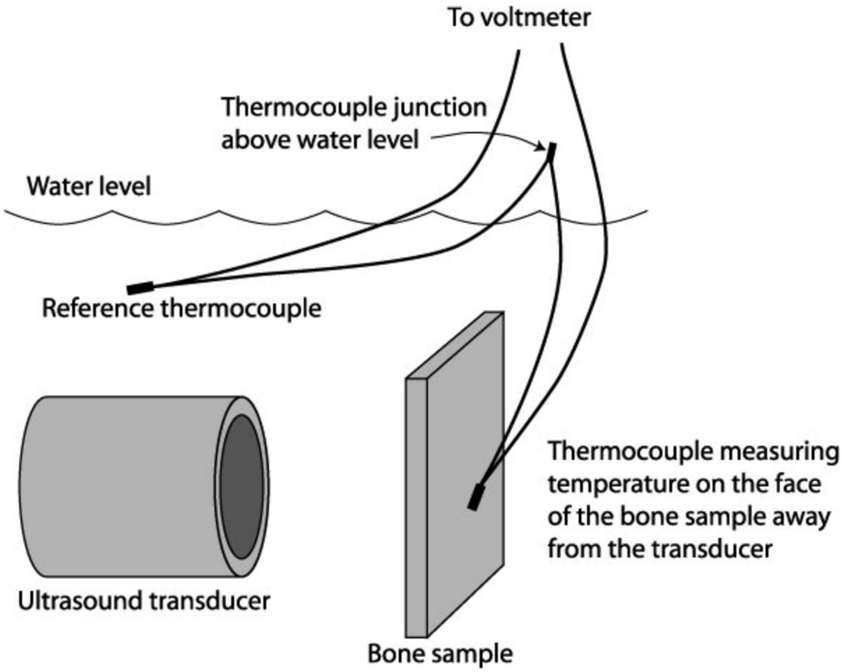


Figure 11. Arrangement used to determine the temperature increase in bone as a result of ultrasound examination.

Statistical analysis

All statistical analysis was performed with SPSS 17-19 (Statistical Package for the Social Sciences). Mean values and standard deviations (SD) of HRQOL scores and polyp scores are presented in Paper I. Mean values ± SD of the measurements made are reported in Papers II, III and IV. Age is given in terms of median values. The 95% confidence interval for the SF-36 scores is given in Paper I.

The required cohort size for Study I was based on a power calculation. According to this calculation a statistical power of 80% would be achieved with a sample size of at least 15 patients in each group regarding the sinonasal-specific HRQOL scores. Spearman's correlation coefficient was used to study correlations in Studies I and III. The Kruskal-Wallis (Paper I) and Mann-Whitney U tests (Papers I, III and IV) were performed to determine differences between groups. To compare the SF-36 scores in the cohort with those of the normal Swedish population (Paper I), the one-sample t-test was used. P values ≤ 0.05 were considered statistically significant.

In Study III, the reliability of the interobserver agreement with regard to the various measurements was analysed by calculating the intraclass correlation coefficient (ICC), and performing a paired-sample t-test to calculate the random errors for the differences. The random error was the SD of the interobserver differences in each measurement.

In Study I, random spot tests were performed on 8% of the material in the database. Only six errors were found, and incorrect data were found in <1% of the cases. Simple mean imputation was used for missing data, when at least 50% of the items had been completed. This method has been proven to be the most appropriate for HRQOL instruments that use unweighted sum scores (Fayers and Machin 2007). For SF-36, it was required that 50% of the items in the same subscale had to be competed for simple mean imputation to be used.

Results

HRQOL and absenteeism in patients with chronic rhinosinusitis

This was a prospective multi-centre study including 207 patients (median age 48 years). The characteristics and scores of the various subgroups (RARS, CRS+NP and CRS-NP) are given in Table 2. Fifty-two patients (25%) had at least one other form of co-morbidity, specified as heart or lung disease, hypertension, diabetes mellitus, rheumatic disease, malignancies or depression. Fifty-one (25%) patients had been referred for FESS previously. Samter's triad (nasal polyps, asthma and hypersensitivity to acetyl salicylic acid) was reported in 10% of the patients with NP.

Table 2. Patient characteristics and scoring.

Variable	All patients	Recurrent acute rhinosinusitis	Chronic rhinosinusitis with NP	Chronic rhinosinusitis without NP
n	207	34	135	38
Age (median)	48	40	54	45
SNOT-22 score[a]	51.8	57.8	49.0	54.5
SF-36 scores				
Physical functioning	80.5	76.8	82.5	76.6
Role physical	62.4	49.2	66.4	59.9
Bodily pain	63.2	48.8	70.6	49.7
General health	60.8	58.8	62.6	56.1
Vitality	51.5	45.1	54.6	45.9
Social functioning	72.8	69.3	74.3	70.4
Role emotional	71.0	65.6	72.6	70.2
Mental health	73.1	69.2	74.7	71.1
Number of patients scoring >7 points on HAD	57 (28%)	11 (32%)	33 (25%)	13 (34%)
HAD score depression	3.9	3.9	3.7	4.6
HAD score anxiety	4.9	6.2	4.4	5.5
VAS score (mm)	67	65	67	70
Nr of pat reporting ≥ 1 day absenteeism due to sinus problems[b]	98 (57%)	20 (77%)	53 (47%)	25 (74%)

[a] missing data = 27
[b] missing data = 34
Scores values are presented as means unless specified otherwise.

There were no statistically significant differences in the total HRQOL score between the three subgroups, but when analysing the separate items in the questionnaires, differences were revealed. Patients with RARS, CRS+NP and CRS-NP scored significantly differently in ten of the SNOT-22 items, and in the BP subscale and MCS domain of SF-36. For example, the scores for patients with RARS and CRS-NP indicated more severe facial pain/pressure in SNOT-22, and more pain on the BP subscale in SF-36 than patients with CRS+NP. Women's scores indicated worse symptoms than men's in SNOT-22, and in all but two of the subscales of SF-36. The patients in all three subgroups scored statistically significantly lower in SF-36 than the normal Swedish population (Figure 12). The value of Cronbach's alpha for the Swedish SNOT-22 was 0.91, implying high internal consistency of the questionnaire.

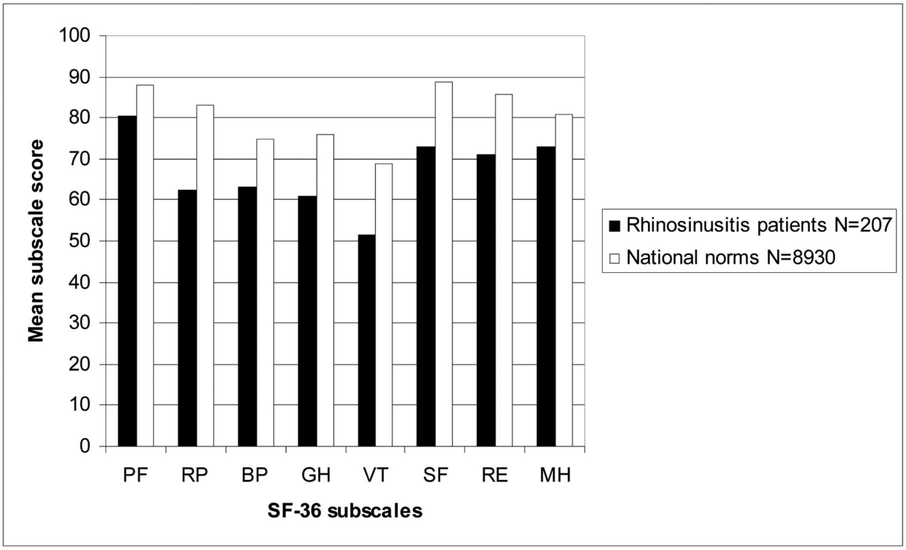


Figure 12. SF-36 health profiles for rhinosinusitis patients and national norms. The higher the score the higher the level of functioning.

According to the HAD scores, 25% of the patients were classified as probable or possible cases of anxiety disorder, and 14% as probable or possible cases of depression disorder. The mean VAS score of combined sinonasal symptoms for all patients was 67. According to the VAS classification, 9.8% of the patients had mild, 37.6% moderate and 52.7% severe disease.

Statistically significant correlations were found between the scoring on all four patient questionnaires. The strongest correlations were found between SNOT-22 and the VT subscale of the SF-36 questionnaire (r=0.7, p<0.000), and between scores on the MH subscale of SF-36 and both anxiety (r=-0.8, p<0.000) and depression scores obtained with the HAD questionnaire (r=-0.7, p<0.000). No significant correlations were found between the total SNOT-22, SF-36, VAS or HAD scores and the three different polyp grades, but when the items of SNOT-22 and the subscales of SF-36 were analysed separately, differences and correlations were revealed (for details, see Paper I). There was no statistically significant difference in scoring of the SNOT-22 questions regarding sleep between patients with unilateral and bilateral nasal obstruction caused by polyps.

Fifty-seven percent of the cohort reported absenteeism from work due to sinus problems. Patients with RARS and CRS-NP reported a statistically significantly higher frequency of sick leave than patients with CRS+NP. Calculating the means of these scores, give rates of absenteeism caused by sinus problems of 8 to 14 days per year.

Acoustic streaming in a sinus model

Determination of acoustic properties

The density of milk was 1026 kg/m^3, the viscosity 1.95 mPas and the sound speed 1511 m/s measured at 19° C. The mean attenuation of ultrasound in milk was 0.21±0.03 dB/(cm·MHz), determined with the mL method in the frequency range 2.75 MHz to 4.5 MHz. Oscillations in the attenuation were caused by interference in the measurement cylinder, but the mean of these oscillations was zero.

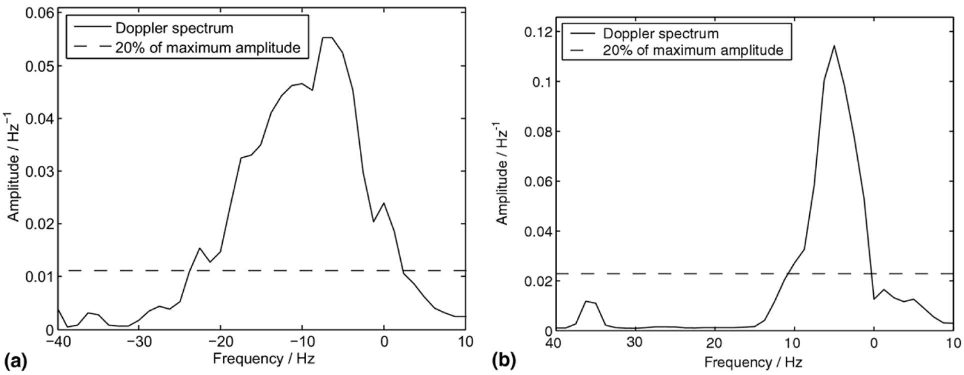


Figure 13. Experimental Doppler spectra from the sinus phantom filled with milk with an ultrasound intensity of 640 mW/cm^2. Measurements are shown (a) without the bone and (b) with the bone placed in front of the transducer. The position for maximum Doppler shift was taken at the frequency where the amplitude of the spectrum dropped to 20% of the top value (indicated with a dashed line).

Sinus phantom and the attenuation of bone

When performing the Doppler experiments in the sinus phantom with the bone placed between the transducer and the sinus phantom, the detected acoustic streaming velocity decreased by 53% (Figure 13). The attenuation by the bone of ultrasound at 4.9 MHz was 7 dB/(cm·MHz), corresponding to an 80% decrease in the intensity, when performing the measurements in a water tank. The discrepancy may be due to the position of the transducer, for example, the transducer may have been positioned closer to the bone sample in the phantom experiment, allowing the ultrasound waves to be reflected between the transducer and the bone.

Properties of the transducer

When analysing the maximum streaming velocity obtained from simulations with five different transducer configurations, it was clear that the most appropriate ultrasound frequency was around 5 MHz, and that the transducer should be flat (unfocused), and the radius of the transducer should correspond to half the radius of the sinus cavity.

Table 3. Female:male distribution of the mean value, SD, median value, range and normal cut-off values of the measurements of different anatomical structures of the maxillary sinuses.

	Whole cohort	Female			Male			p-value
	Mean±SD	Mean±SD (median)	Range	Normal values	Mean±SD (median)	Range	Normal values	
Volume (right)	15.4±5	14±3 (14)	5–19	8–20	18±6 (18)	9–32	6–30	**0.002**
Volume (left)	16±6	15±4 (15)	7–21	7–23	18±7 (18)	7–34	4–32	**0.016**
Craniocaudal diameter (right)	31.3±5	30±3 (31)	20–35	24–36	34±5 (33)	27–43	24–44	**0.004**
Craniocaudal diameter (left)	31.3±5	30±3 (30)	24–34	24–36	33±5 (34)	21–43	23–43	**0.020**
A-P diameter (right)	35±4	35±3 (35)	27–41	29–41	36±3 (36)	31–46	30–42	0.056
A-P diameter (left)	35.6±4	34±4 (34)	27–40	26–42	35±4 (36)	26–43	27–43	0.058
Width (right)	23.4±4	23±3 (22)	12–28	17–29	25±4 (25)	18–34	17–33	**0.018**
Width (left)	23.7±4	23±3 (24)	16–30	17–29	25±5 (25)	14–33	15–35	0.125
Anterior wall thickness at canine fossa (right)	1.1±0.4	1±0.4 (1)	0.6–2.3	0.2–1.8	1.1±0.3 (1.2)	0.6–2.1	0.5–1.7	0.266
Anterior wall thickness at canine fossa (left)	1.1±0.4	1.1±0.4 (1)	0.6–2.5	0.3–1.9	1±0.3 (1)	0.5–1.8	0.4–1.6	0.504

SD indicates standard deviation.
The volume is given in cm^3 whereas other values are given in millimeter.
P-values of statistically significant female:male differences are written in bold style.
Normal values: The lower limit equals mean –2SD whereas the upper limit equals mean +2SD.
A-P diameter indicates anteroposterior diameter (depth).

Dimensions of the paranasal sinuses

The thickness of the canine fossa was determined to be 1.1±0.4 mm, which agrees well with the thickness of the bone sample used in the Doppler ultrasound experiments in Study II. The mean volume of the maxillary sinuses was found to be 15.7±5.3 cm^3. Men had statistically significantly larger maxillary sinuses than women (p = 0.004) (Table 3). No significant differences were found between the right and left sinuses in men or women. There were no significant differences in maxillary sinus volume between age groups (p = 0.299), nor any correlations between different sinus dimensions and the patients' age (r = 0.126, p = 0.172). The degree of agreement between the automated measurement of the volume of maxillary sinuses and the manually calculated volume was almost perfect (ICC 0.90–0.93 and random error of 1.9–2.4 cm^3). In 52 patients the automatically estimated volume was in average 14-17% higher than the calculated volume in the right sided maxillary sinuses. Incidental findings such as minimal mucosal swelling, fluid and retention cysts, were found in 21(35%) of the patients.

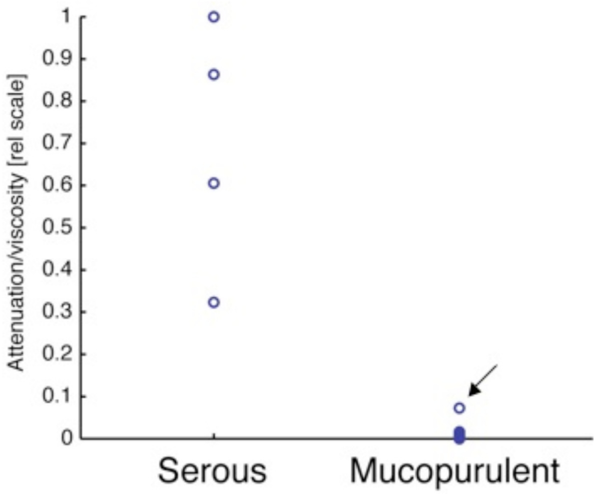


Figure 14. The ratio of attenuation to the viscosity (α/η) for the serous and the mucopurulent sinus fluids. The values are normalized to the maximum value. The ratio is significantly higher in the serous fluid than in the mucopurulent secretions (p<0.001). The arrow indicates the case of the dental empyema.

Acoustic properties of different sinus secretions and safety assessment of Doppler ultrasound

Acoustic properties of sinus secretions

The viscosity of mucopurulent secretion was more than a 1000 times higher than that of serous cyst fluid, and exceeded the upper limit for measurable viscosity of the viscometer. The attenuation of the mucopurulent secretion was 0.32±0.24 dB/(cm·MHz), which is about ten times higher than that of the serous fluid (0.04±0.02 dB/(cm·MHz)). Thus, it would be theoretically possible to detect acoustic streaming in serous fluid but not in mucopurulent secretion (based on the equation given in the Introduction). Purulent secretions from dental empyaema were found to have a lower viscosity than the rest of the purulent samples and thus acoustic streaming velocity would have been possible theoretically, but at very low levels (Figure 14). Bacteria were seen in the majority of the culture swabs from the mucopurulent sinus samples, which strengthens the hypothesis that mucopurulent sinus secretion is caused by bacteria.

Temperature measurements

The experiments in the water bath gave a temperature increase of the bone sample surface of 1.2±0.1°C when the transducer were placed at ≥3.1 mm from the bone sample (Figure 15) (which is the most realistic situation caused by soft tissue in the cheek). In the computer simulations the maximum increase in temperature inside the bone was found to be 1.4°C at an ultrasound intensity of 640 mW/cm^2.

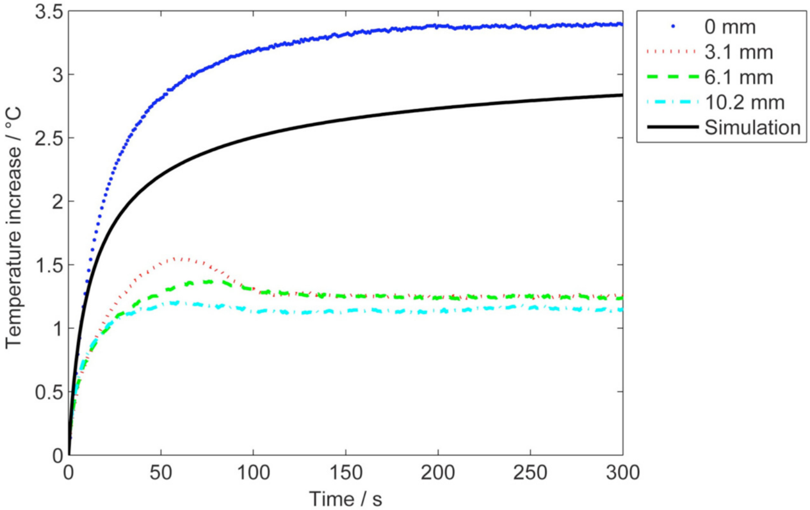


Figure 15. The increase in temperature at the bone surface as a function of time at different distances between the ultrasound transducer and the bone. The results of the computer simulation are given for comparison.

Discussion

General discussion

Chronic rhinosinusitis with and without nasal polyps and recurrent acute rhinosinusitis have a detrimental effect on HRQOL, and led to a considerable degree of absenteeism from work. A VAS using combined sinonasal symptoms seems to offer a simple but effective estimate of the severity of chronic sinus disease. Further, a novel application of the Doppler ultrasound technique can be used to non-invasively stage a sinus infection Non-purulent sinus secretions can be distinguished from mucopurulent sinus secretions with Doppler ultrasound, without causing a harmful increase in temperature of the bone.

HRQOL in rhinosinusitis

During the past decade, there has been a growing awareness of the need to assess sinonasal disease and measure the outcome of rhinological treatment from the patient's perspective. The impact of rhinosinusitis on daily functioning is of greater importance to the patient than, for example, the degree of disease seen on CT scans, showing the relevance of measuring HRQOL in sinonasal disease. HRQOL assessment should not be regarded as a substitute for conventional clinical markers of inflammation of the nose and sinuses, but rather a complement. HRQOL scores may also provide guidance when making choices about treatment and helping patients to identify the problems that are of the greatest concern to them. Measuring HRQOL may also influence clinical decisions and assist the physician in explaining to the patient what can be expected from a certain form of treatment. Furthermore, HRQOL scoring can be used to visualize the effect of treatment in a patient. The predictive value of preoperative HRQOL scoring in FESS is still to be investigated. A VAS using combined sinonasal symptoms could be of assistance when deciding whether surgery is indicated, according to the results in this thesis.

Challenges in measuring HRQOL

Calman defined HRQOL as the gap between our expectations of health and our experience of it (Calman 1984). However, subjective assessments are not always straightforward. As stated by Carr et al. (2001): "*The primary aim of treatment, particularly in* *chronic disease, is to enhance the quality of life by reducing the impact of the disease. Yet, patients with severe disease do not necessarily report having a poor quality of life*". It has been found that some patients with severe disabilities score their HRQOL as good or excellent (Albrecht and Devlieger 1999). However, it can be expected that patients who believe they have a poor HRQOL are those who seek help and care. To be able to draw conclusions from HRQOL scores on the individual level, the pattern at group level must first be analysed.

Patients' perception of their disease will influence their scores. In addition, the patients in a cohort will be at different stages in their disease, although HRQOL might be measured at equal intervals and after the same duration of treatment. Furthermore, people change in their evaluation of HRQOL over time, depending on their degree of acceptance of their disease. It may, therefore, be of importance to record the duration of the disease when measuring HRQOL, to minimize misinterpretation of the data.

Choosing the appropriate HRQOL instrument is a challenge, as the goal should be to measure what is important to the patient. One solution is to combine a generic questionnaire with a disease-specific instrument. The majority of the items in SNOT-22 are not represented in SF-36 (except for SNOT-22 items 12, 17, 18 and 21, see Appendix), so these two instruments complement each other. Another problem is that the importance of items in a HRQOL questionnaire may differ between patients in a cohort. Weighting each of the items in the instrument is one way to solve this problem, however, the questions may become too complicated for the patient to answer. The weighting of the five most important items of SNOT-22 were often misinterpreted by the patients in Study I, and the results were therefore difficult to analyse. Items scored as being "a problem as bad as it can be", were often indicated as being the most important by the patients. Weighting of the SNOT-22 items had not been included in the UK Audit (Hopkins et al. 2006), and the results presented in Paper I support this exclusion.

The choice of HRQOL measures

When choosing the sinonasal HRQOL questionnaire in this work, the demands were that the instrument had been validated, was easy to understand and to score, included items significant for, and specific to, rhinosinusitis and was responsive to changes over time. During this process the EP3OS document was published, defining rhinosinusitis. After concluding that CSS was not appropriate for Swedish conditions, it became evident that SNOT-22 met the demands listed above. Interestingly, SNOT-22 has been one of the most frequently used instruments in outcome studies during the past five years. For example, it was used in the largest study undertaken so far, on surgical outcome in patients with CRS and NP (Hopkins et al. 2006). Hopkins and co-workers have also published a validation study of SNOT-22 and a study on values of a normal population of the questionnaire (Gillett et al. 2009; Hopkins et al. 2009).

It was also deemed valuable to evaluate the correlation between the scores of the sino-nasal questionnaire and a generic HRQOL instrument. The SF-36 was chosen as it is well validated, widely used and is available in many languages. SNOT-22 had not been studied together with SF-36 in rhinosinusitis when starting the study. The HAD scale was chosen to evaluate the prevalence of psychiatric morbidity in CRS and NP.

HRQOL scores in patients with RARS, CRS+NP and CRS-NP

The patients studied in this work had statistically significantly higher preoperative SNOT-22 scores than the patients with CRS and NP in the UK audit (mean 51.8 vs. 42.0 in the UK) indicating a lower HRQOL (Hopkins et al. 2006). This could be because Swedish patients are operated on later in the course of their disease, and/or that other criteria for RARS and CRS+/-NP were used in the present study. The difference in SNOT-22 scores may also be due to differences in the gap between the expectation and perception of health in these two cohorts. The internal consistency of the Swedish SNOT-22 instrument was found to be high (Cronbach's alpha of 0.91), which is of the same level as that found in other languages (Baumann et al. 2007; Lu et al. 2008; Hopkins et al. 2009; Schalek et al. 2010; Lange et al. 2011). This indicates that the items of SNOT-22 are consistent and inter-related. It was also found in the current studies that the comprehension of SNOT-22 was good.

Patients with RARS, CRS+NP and CRS-NP scored statistically significantly lower (indicating lower HRQOL) in all eight SF-36 domains than the normal Swedish population (Figure 12). Compared with Swedish patients with other severe chronic diseases, such as inflammatory bowel disease and asthma, the scores of the patients with rhinosinusitis SF-36 were lower. According to both SNOT-22 and SF-36, patients with NP suffered less pain than patients with RARS and CRS-NP, and this coincides with previous reports (Durr et al. 2001; Hopkins et al. 2006; Ragab et al. 2010; Zheng et al. 2010). The BP subscale of SF-36 was also the only subscale of SF-36 on which the scores differed significantly between the three rhinosinusitis groups. The reason why patients with NP do not experience the same degree of pain as other patients with sinus problems remains unknown, and it would be of interest to investigate this further.

Psychiatric morbidity, measured with the HAD score, does not seem to be overrepresented in patients with RARS or CRS+/-NP awaiting surgery. The rate of depression was 14% and the rate of anxiety 25%, according to the HAD scores. There was no statistically significant difference in total HAD scores between patients with RARS, CRS+NP and CRS-NP.

The VAS has the advantage that it is easy to visualize, and gives patients the opportunity to score exactly according to their perception. It has been claimed that the VAS is more sensitive than ordered categorical scales, such as the Likert scale, although this has been disputed (MacCormack 1988). In the present work, it was found that the higher the VAS score, the worse the patient scored in SNOT-22, in all eight subscales of SF-36 and in HAD. All these correlations were strongly statistically significant, as described above. Consequently, the single question, "How troublesome are your symptoms of rhinosinusitis?" can be used as a simple tool to assess the severity of sinus disease and thus the HRQOL. More than 50% of the cohort suffered from severe disease (>70 mm on the scale), according to the VAS scores.

Absenteeism due to sinus problems

Patients with RARS, CRS+NP and CRS-NP referred for FESS reported a rate of absenteeism from work caused by sinus problems between 8 and 14 days per year. The presence of nasal polyps implied less sick leave in the present study. Hellgren et al. (2010) have reported a mean productivity loss of 5.1 working days per year, as the result of allergic rhinitis and common colds. The findings of their study are not directly comparable to the present results, since the patients were asked to choose one of five intervals of sick leave. The present findings regarding absenteeism due to RARS and CRS+/-NP could be of importance as they give an indication of the cost to society associated with these conditions.

Nasal polyp grading

Several suggestions for different kinds of polyp grading systems have been published. One of the most commonly used endoscopic staging systems was proposed by Lund and Mackay (Lund and MacKay 1994) (0 = no polyps; 1 = polyps confined to the middle meatus; 2 = polyps beyond the middle meatus). Through the years, this scoring system has been slightly modified, to include grade 3 indicating total nasal obstruction. The EP3OS suggests the following grading system for use in research: 0 = no visible polyps; 1 = polyps confined to the middle meatus; 2 = polyps below the level of the middle turbinate but not causing total obstruction; and 3 = polyps causing total nasal obstruction (Fokkens et al. 2007). However, to the best of the author's knowledge, this scoring system has not been thoroughly validated.

Johansson and co-workers (2000) compared the reproducibility of various scoring systems for staging nasal polyps and the inter-individual variations between investigators in 2000. They found that lateral imaging (projecting the extension of the polyps by drawing on a schematic picture of the lateral wall of each nasal cavity) and a scoring system with four steps ad modum Lildholdt et al. (1997) (determining their relationship to fixed anatomical landmarks) were the best scoring methods. The reproducibility of all five systems (including the Lund-Mackay system), tested in that study was found to be acceptable. However, the two grading systems suggested by Johansson and co-workers have not gained ground, and the modified Lund-Mackay system still dominates in published studies. Feeling of nasal obstruction was found not to be correlated with endoscopic grading in the study by Johansson et al. (2000), which agrees with the findings presented in this thesis.

The impact of unilateral vs. bilateral total nasal obstruction on HRQOL has not previously been studied. To evaluate this, the cohort was divided into two subgroups called NP severity and NP side, based on the surgeons' polyp score using the modified Lund-Mackay system. We found differences between these polyp groups in the scores of some of the items of SNOT-22, but surprisingly, in neither feeling of nasal obstruction nor the items on sleep (items 13-15) in SNOT-22. In other words, whether a patient has unilateral or bilateral total obstruction does not have a statistically significant impact on sleep measured by the SNOT-22 score. Thus, endoscopic grading of polyps is not correlated to nasal obstruction measured by SNOT-22. However, there may be clinically significant differences between uni- and bilateral nasal obstruction. These findings could be of relevance when planning the extent of surgery on a patient with NP.

One of the goals of the work presented in this thesis was to identify a suitable outcome measure of the quality of FESS. Assessment of outcome data is a natural way to provide patients with knowledge concerning how much FESS will improve their HRQOL, i.e., the functional effect of the illness on their life. Furthermore, every surgeon should have an interest in proving her/his skills. What is relatively new today, is that society and patients want reassurance that they are being offered treatment of the highest quality. It is thus necessary to present measures of outcome, preferably in open national registers, based on consecutive patients, and not selected surgical outcome, measured by HRQOL scoring.

The only way to assess the actual effect of FESS versus other kinds of treatment is to perform dummy operations, but this presents an ethical problem. An example of how sham surgery can be performed is given by a Swedish study on the effect of pharmaceutical treatment versus combined surgical and pharmaceutical treatment of NP, where the patients were operated on unilaterally (blinded), and evaluated with nasal endoscopy, symptom scores, and olfactory thresholds 12 months postoperatively (Blomqvist et al. 2001).

It should be possible to minimize the impact of chronic rhinosinusitis on patients' HRQOL by helping them to adjust their expectations and adapt to their change in clinical status. Clinicians have the responsibility to explain what can be reasonably expected of a given form of treatment. HRQOL scoring can be helpful when grading sinonasal disease, identifying the problems most important to the patients and choosing appropriate treatment, but assessments of HRQOL cannot replace diagnostic tools. A possible means of improving the diagnosis of rhinosinusitis is discussed below.

Improvement of the diagnostics of rhinosinusitis

Purulent secretion in the nasal cavity has proven to be one of the strongest predictors of ARS (Lindbaek and Hjortdahl 2002). Nasal discharge is also one of the compulsory criteria of ARS according to EP3OS. As described in the introduction, it is usually possible to isolate bacteria from purulent and mucopurulent secretions (which have a high viscosity), whereas bacteria are rarely isolated from serous sinus secretions (which have a low viscosity) (Carenfelt and Lundberg 1977; Carenfelt et al. 1978). Consequently, a diagnostic tool that reveals the purulence of the sinus secretions would be of clinical value. As bacterial resistance is a growing problem, every means of decreasing the prescription of antibiotics should be investigated. In this work, the possibility of improving the staging of a sinus infection using Doppler ultrasound was evaluated. It was shown that acoustic streaming can be induced in a model of the maxillary sinus containing low-viscous fluid, that the dimensions of the maxillary sinuses would allow induction of acoustic streaming, and that it is possible to determine the properties of paranasal sinus fluids safely and non-invasively with Doppler ultrasound.

Acoustic streaming in a model of the maxillary sinus

In Paper II it was shown that acoustic streaming could be generated and detected in an anthropomorphic sinus phantom filled with milk, without exceeding the medical limits for sound intensity. A method based on induced acoustic streaming in the fluid accumulated within a model of the maxillary sinuses was used. Milk was used as the model fluid as it has a low viscosity and contains scattering particles, making it suitable for acoustic streaming experiments. From fluid and bone attenuation measurements, it was determined that an ultrasound frequency of about 5 MHz produced the highest acoustic streaming in the sinus phantom. The equation in the introduction shows that the quotient between attenuation and viscosity plays a vital role in determining the velocity of the acoustic streaming. Other physical properties such as liquid density and the velocity of sound may also affect acoustic streaming, but for biological fluids these differences are expected to be small. By measuring the material parameters, as was done in this work for milk, it would be possible to estimate the velocity of the acoustic streaming for other fluids (such as sinus secretions) from the equation. It was shown to be possible to make such measurements on sinus secretions, although only a small amount of the fluid was available (~1 mL), which may be the case with sinus secretions in ARS.

The choice of ultrasound frequency is very important. In these experiments an ultrasound frequency of 4.9 MHz was used. The attenuation by bone and the properties of the fluid determine the attenuation of the ultrasound waves, and thus the optimal ultrasound frequency. At too high a frequency, the ultrasound will be completely absorbed by the bone, and will not penetrate into the sinus. If, on the other hand, the frequency is too low, the transfer of energy to the sinus fluid will be negligible, and there will be no detectable streaming. In a clinical set-up the frequency should be set, for instance, according to the amplitude of the echo returning from the far wall of the sinus (in the case of a fluid-filled sinus).

The mean attenuation by the bone sample determined in this investigation (7.6 dB/(cm·MHz)) was somewhat higher than that reported previously (Garcia et al. 1978). This could be due to air trapped in the bone sample, increasing the attenuation. Measurements were carried out with and without the bone sample between the transducer and the agar and graphite phantom. The streaming velocity for fluid in the sinus phantom was 53% lower with the bone than without it (Figure 13). As the streaming velocity is approximately proportional to the sound intensity reaching the sinus cavity, this means that the attenuation by the bone was 53%. However, the attenuation of the ultrasound intensity when passing through the bone was 80% at 4.9 MHz (for calculations and details see Paper II). The difference could be partially explained by the difference in position of the ultrasound probe between the experiments. Another reason could be that when the bone is close to the transmitter (as in the sinus phantom experiment), some sound may be reflected back and forth between the bone and the surface of the transducer. This would lead to a higher transmission through the bone, and thus a lower total attenuation.

Simulations of the acoustic streaming in a sealed cavity also showed that the transducer radius should be half the radius of the cavity to optimize the streaming velocity. With a 4.9 MHz continuous-wave transducer operating at I_{spta} of 640 mW/cm^2, an acoustic streaming velocity of 0.19 cm/s was generated and detected in the sinus phantom.

The dimensions of the maxillary sinus would allow use of Doppler ultrasound

In ARS, two or more sets of the paranasal sinuses (maxillary, frontal, ethmoid and sphenoid sinuses) are often affected, and the most common combination has been found to be the maxillary and the ethmoid sinuses (Lindbaek et al. 1996b). The maxillary and frontal sinuses are most accessible for investigation. It has been established in this work, that the choice of radius of the ultrasound beam is dependent on the radius of the sinus cavity (Paper II). Also, the intensity of the ultrasound in the sinus cavity is highly dependent on the thickness of the anterior bony wall of the sinuses, which must therefore be established. The results of Paper III indicate that the Doppler equipment is suitable for investigations of the maxillary and frontal sinuses. For example, the frontal wall of the maxillary sinus (canine fossa) is 1.1 mm thick, which would permit ultrasound waves to pass through it, as shown by the experiments presented here. Furthermore, it is necessary to know the frequency of incidental findings in the Nordic population, since the number of diagnostic CT scans has increased, and subsequently also the number of incidental findings. Both the anatomical dimensions and the incidental findings described in Paper III are of importance for future clinical trials with Doppler ultrasound.

The acoustic properties of sinus secretions

The acoustic properties of different kinds of sinus fluid from patients with sinus cysts and mucopurulent acute rhinosinusitis were determined, and the streaming velocity of different kinds of sinus fluids, which will be clinically relevant when using the equipment *in vivo* in the future, was investigated. In these studies (Paper IV), the acoustic and viscous properties of mucopurulent sinus secretions and cyst fluid were compared with those of milk. It was found that the ratio of the attenuation to the viscosity (α/η) was comparable for milk and serous sinus cyst fluid, but not for mucopurulent secretions. Detectable acoustic streaming, and consequently a measurable Doppler shift, could be generated in the cyst fluid but not in the mucopurulent sinus secretions.

Maxillary cyst fluid was used as a substitute for serous secretions in rhinosinusitis to analyse an uninfected reference serous body fluid that does not require treatment with antibiotics. Maxillary cyst fluid was the most natural choice because of its location and accessibility. Although sinus cysts are common, symptoms are not as common, and sinus aspiration is seldom justified. Consequently, the collection of samples from these patients poses an ethical problem. The value of Doppler shift that distinguishes serous non-bacterial sinus secretions from mucopurulent sinus secretions will be determined in future clinical trials.

Figure 14 shows the ratio of α/η for the two types of sinus fluids. (The viscosity was set to 1000 mPas for cases where the viscosity was outside the range of the instrument.) The α/η ratio was significantly higher in the serous fluids than in the mucopurulent fluids ($p<0.001$). This indicates that it is virtually impossible to induce acoustic streaming at the intensity used here in 11 of the 12 mucopurulent cases, based on the equation in the introduction. On the other hand, a measurable Doppler shift is expected in serous secretions. Acoustic streaming would have been theoretically detectable in one mucopurulent case (a patient with dental empyema), but would have been very low. Thus, according to the results of these experiments, the risk of a false-negative result is small.

Culture swabs were not taken in all patients with ARS, but bacterial growth was seen in all 10 patients from whom swabs were taken (*Streptococcus* and *Staphylococcus*). This supports the hypothesis that the acoustic properties of the sinus fluid are related to the need for treatment with antibiotics in ARS.

Safety of Doppler ultrasound

A safety assessment was performed by determining the temperature increase when ultrasound with an intensity of 640 mW/cm^2 is transmitted through a bone sample with the same thickness as the anterior wall of the maxillary sinus. The maximum increase in temperature inside the bone was 1.14 times higher than at the bone surface, where the temperature increase was measured with a thermocouple. With a stationary temperature increase of 1.2°C at the surface of the bone, this corresponds to a maximum temperature increase of 1.4°C inside the bone. This value is below the limit of 1.5°C, which is the value deemed harmless to the human body according to WFUMB (Barnett and ter Haar 2000). This is relevant considering the close proximity of the eye bulb in this application. However, the ultrasound passes through soft tissue, bone and sinus secretions before reaching the eye, and thus the intensity will be very low, or non-existent when reaching the eye bulb. It can be mentioned that the use of therapeutic ultrasound to relieve symptoms of chronic rhinosinusitis was recently proposed (Young et al. 2010). The intensity in those experiments was up to 1500 mW/cm^2, which is significantly above the level used in the present study. Another advantage of the Doppler ultrasound technique is that it does not expose the patient to any harmful radiation, as does CT, although the radiation dose resulting from a CT scan has been decreased (Abul-Kasim et al. 2009).

Clinical signs and symptoms that correlate with culture-proven ARS

An ESR rate greater than 10 mm/h for males or greater than 20 mm/h for females can be of diagnostic value in ARS (Hansen et al. 1995; Lindbaek et al. 1996a; Hansen et al. 2009). Elevated levels of C-reactive protein (>11 mg/L) and body temperature >38°C have been associated with positive culture from the sinus (presence of *S. pneumoniae* and *H. influenzae*) in patients with symptom of ARS seeking primary health care (Hansen et al. 2009). Others have concluded that elevated values of C-reactive protein (> 40 mg/L) associated with acute maxillary rhinosinusitis should alert the physician to the suspicion of *Streptococcus pyogenes* or *Streptococcus pneumoniae* (Savolainen et al. 1989). Purulent secretion in the nasal cavity, purulent rhinorrhea, double sickening and ESR>10 mm/h have been independently associated with CT findings of ARS, when mucosal thickening of 5 mm or more was considered a significant sign of sinus infection (Lindbaek et al. 1998). If all four of these signs and symptoms occurred simultaneously, the likelihood ratio for ARS according to CT increased immensely (Lindbaek et al. 1996a). When ARS is defined in terms of fluid levels in, or total opacification of, the sinuses according to CT (but not considering bacterial findings), only 63% of patients with clinical symptoms of ARS were correctly diagnosed according to Lindbaek (Lindbaek et al. 1996b).

Another group at Lund University has presented a laser-based method for diagnosing rhinosinusitis (Persson et al. 2007), based on monitoring the gas content in the paranasal sinuses. It is unclear whether this is related to the need of antibiotic treatment. The hypothesis behind their technique is that pathological status of the paranasal sinuses frequently corresponds to blocked sinuses, leading to a change in the gas concentrations in the sinus cavity. Correlations with the purulence of sinus secretions have not been investigated.

Limitations

One shortcoming of the study presented in Paper I is that patients who did not speak Swedish could not participate, as comprehension of the Swedish language was required to be able to answer the questions in the HRQOL forms. Furthermore, it was not possible to include all eligible patients in the study, as some were not reported in time to receive the questionnaires preoperatively. One problem when conducting clinical trials is also the possibility that subjects are deliberately not proposed for inclusion in cases where operative complications are expected, or if the patients are expected not to be fully satisfied with the surgical outcome.

It cannot be ruled out that the data from the patients who chose to participate may be different from those who chose not to participate. Additionally, some non-random selection bias could have occurred. However, we have chosen questionnaires that are well-documented and extensively used. SF-36 and the HAD score have been widely used and translated into different languages, making it possible to compare different populations. As SF-36 is a generic instrument, the impact of different medical conditions can be compared.

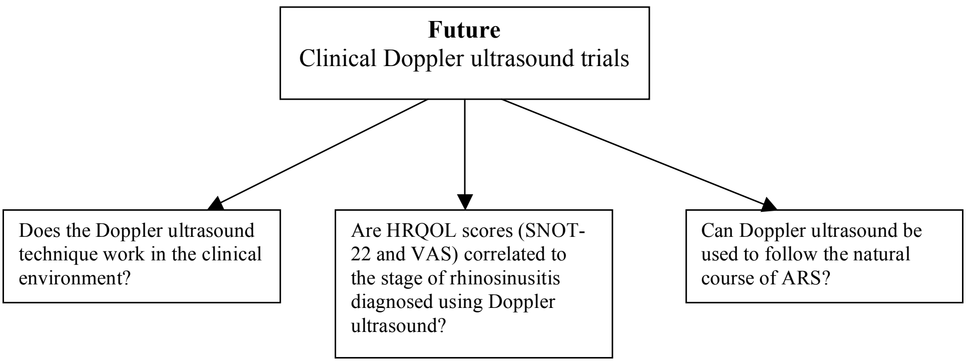
The sensitivity and specificity of ultrasound in ARS has been the subject of debate, as this kind of investigation is dependent on the operator. When the goal is to detect fluid in the maxillary sinus, ultrasound has a sensitivity of up to 0.98 and a specificity of up to 0.97 (Mann et al. 1977; Revonta 1980; Bockmann et al. 1982; Jannert et al. 1982b; Varonen et al. 2003). In the same way as ultrasound examinations are only performed by ultrasound specialists in a radiological or antenatal department, the ultrasound examination of sinuses should only be performed by a clinician in otorhinolaryngology or a GP in primary health care who is very familiar with the procedure and the interpretation of the findings. If the ultrasound examination is performed by specialists, the results will be more precise and predictive of rhinosinusitis. For example, multiple reflections, e.g. when the ultrasound beam is reflected back and forth between the probe and the air in the sinus, can be misinterpreted as back wall echoes. An investigation on the agreement between specialists and GPs has shown moderately good correlations between the interpretation of such ultrasound examinations (Varonen et al. 2003). This could probably be improved with increased training and experience of the technique.

Clinical applications and future research

It was concluded in this work that a total VAS and SNOT-22 are valuable tools when assessing the HRQOL in patients with different kinds of rhinosinusitis. These instruments, especially the VAS, can be used on an everyday basis to evaluate the effects of different kinds of treatment and to demonstrate the effect of the treatment to the patient. The author has already found these tools to be valuable when treating patients with rhinosinusitis in clinical work.

Studies are in progress to evaluate how much HRQOL scores improve after FESS, whether the preoperative HRQOL score has an impact on the perceived outcome of surgery, and whether FESS can decrease absenteeism from work. The findings regarding sick leave due to rhinosinusitis could be of importance as they give an indication of the cost to society associated with this condition. Further studies must be carried out on absenteeism from work resulting from rhinosinusitis, as absentecism is directly associated with national economy. It would be of interest to investigate whether FESS can reduce absenteeism among patients with RARS, CRS+NP and CRS-NP and if this were found to be the case, surgery should perhaps be performed earlier in the course of the disease. It should, however, be pointed out that randomized controlled studies comparing the outcome of different pharmaceuticals and surgical techniques, or combinations, in CRS are still important. It is recommended that validated HRQOL instruments be used when assessing the results of such studies.

Clinical trials are planned in which the Doppler ultrasound technique will be applied to patients with ARS (see Flow chart I). In those trials, measurements made *in vivo* will be compared with measurements performed on the sinus fluid *in vitro* after aspiration of different kinds of sinus secretions. In these trials the natural course of ARS and the effect on HRQOL will also be investigated. If the Doppler ultrasound technique is found to be useful in the clinical setting, this equipment could be used to differentiate between patients with ARS who are in need of antibiotics and those that are not. This would restrict the prescription of antibiotics to those who really need them.



Flow chart I. Future issues to be addressed.

Conclusions

RARS and CRS+/-NP have a significant adverse effect on HRQOL, and cause 8 to 14 days of absenteeism from work per year. Some significant differences were observed in HRQOL scoring and absenteeism between patients with RARS, CRS+NP and CRS-NP. The VAS and the SNOT-22 instruments seem to be useful and appropriate measures of rhinosinusitis in the Swedish population.

Results are also presented in is thesis that demonstrate the potential of a new method of Doppler ultrasound that allows the properties of paranasal sinus fluids to be determined safely and non-invasively. It was found to be possible to induce detectable acoustic streaming in a model of a maxillary sinus. The most appropriate ultrasound frequency for use on the paranasal sinuses is ~5 MHz, and suitable physical properties of a transducer have been identified. According to measurements on head CT scans, the anatomical dimensions of the maxillary sinuses would permit acoustic streaming to be induced by Doppler ultrasound. It has been shown that it is possible to distinguish serous sinus fluid from mucopurulent secretions with Doppler ultrasound in *in vitro* experiments. Finally, it is concluded that the Doppler ultrasound technique does not cause any harmful increase in temperature of a bone sample of the same thickness as the anterior wall of the maxillary sinus. This method could improve the diagnosis of ARS, reduce the suffering of patients with ARS, and potentially restrict the prescription of antibiotics.

Populärvetenskaplig sammanfattning på svenska

Bihåleinflammation (rinosinuit) definieras som inflammation av näsans och bihålornas slemhinna. Akut rinosinuit är den femte vanligaste orsaken till antibiotikaförskrivning. Kronisk rinosinuit verkar vara ett ökande hälsoproblem, som drabbar drygt 9% av Europas befolkning och innebär en stor belastning på hälsoekonomin. Amerikanska studier har visat att rinosinuit påverkar hälsorelaterad livskvalitet (HRQOL) mer än vad andra kroniska tillstånd gör, såsom kärlkramp och kronisk obstruktiv lungsjukdom (KOL).

I denna doktorsavhandling studerades i en multicenterstudie, hur olika typer av kronisk rinosinuit och näspolyper påverkar HRQOL, mental hälsa och sjukskrivning. Dessutom utvecklades en helt ny Doppler-utrustning, med vilken diagnostiken av rinosinuit skulle kunna förbättras.

Tvåhundrasju patienter inkluderades konsekutivt vid tio Öron-, Näs- och Halskliniker i Sverige. Patienterna hade diagnoserna recidiverande rinosinuit och kronisk rinosinuit, med respektive utan näspolyper, och hade anmälts till funktionell endoskopisk bihålekirurgi (FESS). Patienterna fick preoperativt rapportera HRQOL, mental hälsa och sjukfrånvaro p.g.a. sina bihålebesvär. Fyra olika patientenkäter användes i denna analys: 22 Sinonasal Outcome Test (SNOT-22), 36-item short-form questionnaire (SF-36), Hospital Anxiety and Depression Scale (HAD) och Visual analogue scale (VAS) på samtliga bihålebesvär.

Studiepopulationen rapporterade signifikant sämre HRQOL än den svenska normalpopulationen. Det påvisades skillnad i HRQOL-skattning hos de tre olika rinosinuitgrupperna när man analyserade separata frågor i enkäterna. Bl.a. rapporterade patienter med näspolyper lägre grad av smärtproblematik. Patienterna uppgav 8-14 dagars sjukfrånvaro under ett år p.g.a. sina bihålebesvär, och patienter med recidiverade rinosinuit rapporterade högst sjukskrivningstal. En VAS-skala med fråga om hur mycket man totalt besvärades av sin rinosinuit visade sig var ett enkelt sätt att mäta graden av bihålesjukdom.

En möjlig förbättring av diagnostiken av rinosinuit utvärderades. Sedan början av 80-talet har man kunnat ställa diagnosen akut rinosinuit – en av de vanligaste diagnoserna i öppenvården – på ett enkelt och icke-invasivt sätt med hjälp av ett ultraljud. Det finns dock ett behov av ökad diagnostisk säkerhet. Det är idag inte möjligt att med vanligt ultraljud eller skiktröntgen skilja på mukopurulent (trögflytande var) och serös (tunnflytande) bihålevätska. Det har i tidigare studier visats att det växer mer bakterier i mukopurulent bihålevätska än i serös sådan. Det enda sättet att ta reda på om det föreligger mukopurulent vätska i käkhålan, och därmed indikation för antibiotikabehandling, är att spola den, vilket innebär ett obehag för patienten. Om bihålevätskans konsistens kunde mätas med en icke-invasiv metod, så skulle man på det viset kunna avgöra om det är en antibiotikakrävande bihåleinflammation eller inte. I denna avhandling visas att man med Dopplerultraljud kan avgöra bihålesekrets egenskaper.

I experimentella studier visades att akustisk strömning kan induceras i en bihålemodell och att ben med samma tjocklek som käkhålans framvägg tillåter fortledning av ultraljudsvågor. Även lämpliga egenskaper på Dopplerultraljuds-givaren definierades. Genom en röntgenstudie på bihålornas mått konstaterades sedan att anatomin (bentjocklek och bihålevolym) skulle tillåta undersökning av akustisk strömning i bihålevätska med hjälp av Dopplerultraljud. I den sista studien i denna avhandling, konkluderades att det var möjligt att skilja på mukopurulent och serös bihålevätska med hjälp av Dopplerultraljud, utan att inducera en skadlig temperaturökning av käkhålans framvägg.

En ökad kunskap om hur patienter med rinosinuit upplever att deras vardag påverkas av bihålebesvär, kan innebära en ändrad syn på diagnostik och behandling av patienter med rinosinuit. Att beskriva denna livskvalitetssänkning är av betydelse, när resurser ska avsättas till rinosinuitforskning och -vård. I detta avhandlingsarbete har även SNOT-22 och VAS utvärderats, vilka skulle kunna användas som kvalitetsinstrument för behandling av patienter med rinosinuit. Vidare betraktas antibiotikaresistens idag som ett allvarligt hot. Med dessa studier har vi funnit att Dopplerultraljud kan förbättra diagnostiken av rinosinuit, vilket borde kunna minska antibiotikaförskrivningen. Var fjärde person i Sverige tar en kur antibiotika varje år, varav de flesta har fått diagnosen rinosinuit. En förbättring av diagnostiken skulle även innebära en betydande ekonomisk och ekologisk vinst för sjukvård och samhälle.

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Appendix

Date____________ **SINO-NASAL OUTCOME TEST (SNOT-22)**

Personal code number_________________________

Name_____________________________________

Below you will find a list of symptoms and social/emotional consequences of your sinonasal disorder. Please rate your problems, as they have been over the past two weeks. Mark one alternative for each item.

Grading of items
0 = no problem
1 = very mild problem
2 = mild or slight problem
3 = moderate problem
4 = severe problem
5 = problem as bad as it can be

	Grading						The 5 most important items
1. Need to blow nose	0	1	2	3	4	5	☐
2. Sneezing	0	1	2	3	4	5	☐
3. Runny nose	0	1	2	3	4	5	☐
4. Blockage/congestion of nose	0	1	2	3	4	5	☐
5. Sense of taste/smell	0	1	2	3	4	5	☐
6. Cough	0	1	2	3	4	5	☐
7. Post nasal discharge (dripping at the back of your nose)	0	1	2	3	4	5	☐
8. Thick nasal discharge	0	1	2	3	4	5	☐
9. Ear fullness	0	1	2	3	4	5	☐
10. Dizziness	0	1	2	3	4	5	☐
11. Ear pain	0	1	2	3	4	5	☐
12. Facial pain/pressure	0	1	2	3	4	5	☐
13. Difficulty falling asleep	0	1	2	3	4	5	☐
14. Waking up at night	0	1	2	3	4	5	☐
15. Lack of a good night's sleep	0	1	2	3	4	5	☐
16. Waking up tired	0	1	2	3	4	5	☐
17. Fatigue	0	1	2	3	4	5	☐
18. Reduced productivity	0	1	2	3	4	5	☐
19. Reduced concentration	0	1	2	3	4	5	☐
20. Frustrated/restless/irritable	0	1	2	3	4	5	☐
21. Sad	0	1	2	3	4	5	☐
22. Embarrassed	0	1	2	3	4	5	☐

Please mark the most important items affecting your health (maximum of 5 items)

Thank you for your participation.

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