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Trondheim, June 2014

Department of Neuroscience

Norwegian University of Science and Technology

Trondheim, Norway

Department of Otolaryngology, Head and Neck surgery

St Olavs Hospital/Trondheim University Hospital,

Trondheim, Norway

«Å vite når man vet noe og å vite når man ikke vet noe- det er kunnskap»

Konfucius

Norsk Sammendrag

Prevalensen av astma er økende både på verdensbasis og i Norge, og det er anslått at over 8 % av den voksne norske befolkningen lider av denne sykdommen (1). Resultater fra den store Miljø- og barneastmastudien i Oslo, hvor nærmere 1000 barn i Oslo ble fulgt fra fødsel og frem til ti års alder, viste en prevalens av astma på 11.1 % (2). Det er rapporter at over 80 % av astmapasienter har nese- og bihule plager (3, 4). Allergisk rhinitt er en av mange risikofaktorer for utvikling av astma, og epidemiologiske studier har vist at rhinitt kan utvikles flere år før astmasymptomene manifesterer seg (5-10). Derfor bør pasienter med langvarig rhinitt undersøkes i forhold til om de har astma, og astmatikere bør undersøkes om de har rhinitt og nesepolypose. Det er også viktig å ha en kombinert strategi for undersøkelse av de øvre- og nedre luftveier slik at denne pasientgruppen får optimalisert medikamentell behandling av hele luftveissystemet og kirurgisk behandling av de øvre luftveiene når dette er nødvendig (4).

I dette doktorgradsprosjektet ser vi på nese-bihule symptomer, nese-bihule relatert livskvalitet og objektive målinger av romforhold og luftstrøm i nesen hos astmatikere og en ikke astmatisk kontrollgruppe. Ut i fra mitt ståsted som øre-nese-hals lege var det viktig å dokumentere ovennevnte forhold hos astmatikere, og større deler av avhandlingen omfatter de øvre - enn de nedre luftveier hos astmatikere.

Begrepet «The unified airway» (11, 12) beskriver respirasjonssystemet, fra nese og munnhule til den minste alveole, som en enhetlig luftvei og er sentral i denne avhandlingen. Avhandlingen konkluderer med at astmatikere spesielt, og sannsynligvis også andre pasientgrupper med sykdomsprosesser i luftveiene generelt, bør møtes med en tankegang om en enhetlig luftvei.

Artikkel 1: Nittien astmapasienter og 95 ikke astmatiske kontrollpasienter ble undersøkt med spørreskjema angående nese- og bilhulesymptomer ved hjelp av visuelle analoge skalaer (VAS), og nese-bihule relatert livskvalitet, Sino-nasal outcome test 20 (SNOT-20). Maksimal luftstrøms hastighet gjennom nesen ble målt med Peak Nasal Inspiratory Flow (PNIF). Studien viste at astmatikere med og uten allergi hadde økte symptomer fra nese og bihuler, redusert nese-bihule relater livskvalitet og redusert inspiratorisk luftstrøm gjennom nesen sammenlignet med kontrollgruppen.

Artikkel 2: Åttisyv astmapasienter og 91 ikke astmatiske kontroller ble undersøkt med akustisk rhinometri (AR) (volum og tverrsnitts areal) i nesen. Studien viste at astmatikere har lavere minste tverrsnitts areal og volum i nesekaviteten sammenlignet med kontrollgruppen, og at det minste tverrsnitts areal er 2-3 cm inn i nesen hos begge gruppene. Det var ingen forskjell i minste tverrsnitts areal mellom allergiske og ikke-allergiske individer hverken i astma og kontrollgruppen.

Artikkel 3: I denne studien så vi på hvilke faktorer som kan virke inn på PNIF målinger hos 87 astmapasienter sammenlignet med 92 ikke astmatiske kontroller. Studien viste at PNIF påvirkes av astma, forsert ekspiratorisk volum i løpet av 1 sekund (% av forventet) (FEV1 (% predicted)), grad av nesetetthet målt subjektivt med VAS og objektivt med AR, alder og sykdomsstatus. Dette medfører at det må utøves ekstra oppmerksomhet når PNIF verdier hos pasienter med astma eller redusert FEV1 (% predicted) skal vurderes. Astmapasienter hadde 19 ganger større sannsynlighet for å være i en høyere NO-VAS kategori sammenlignet med ikke astmatiske kontroller uavhengig av hvilken PNIF gruppe de tilhørte (lav, middels, høy nasal luftstrøm).

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Content

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List of papers

Paper 1: Sino-nasal characteristics in asthmatic patients.

Thorstensen WM, Bugten V, Sue-Chu M, Fossland NP, Romundstad PR, Steinsvåg SK.

Otolaryngol Head Neck Surg. 2012 Nov;147(5):950-7.

Paper 2: Nasal flow, volumes, and minimal cross sectional areas in asthmatics.

Thorstensen WM, Sue-Chu M, Bugten V, Steinsvåg SK.

Respir Med. 2013 Oct;107(10):1515-20.

Paper 3: The determining factors of peak nasal inspiratory flow and perception of nasal airflow in asthmatics.

Wenche Moe Thorstensen, Malcolm Sue-Chu, Vegard Bugten, Milada Cvancarova, Sverre Karmhus Steinsvåg

Accepted for publication in Rhinology 2nd of March 2014.

Abbreviation list

ACQ = asthma control questionnaire

APC = antigen presenting cells

ARIA = Allergic Rhinitis and its Impact on Asthma

ASL = airway surface layer

AR = acoustic rhinometry

BHR = bronchial hyperresponsiveness

BMI = body mass index

CFD = computational fluid dynamics

CI = confidence interval

CRS = chronic rhinosinusitis

FE_{NO} = fractional exhaled nitric oxide

FESS = functional endoscopic sinus surgery

FEV_1 = forced expiratory volume in one second

GC = glucocorticoids

GERD = gastro esophageal reflux disease

GINA = Global initiative for asthma

ICS = inhaled corticosteroids

IgE/G/A = immunoglobulin E/G/A

INS = intranasal glucocorticosteroids

MCA = minimum cross sectional area

NCI = nasal congestion index

NCV = nasal cavity volume

NO = nitric oxide

NO-VAS = nasal obstruction visual analogue scale

OR = odds ratio

PEF = peak expiratory flow

PNIF = peak nasal inspiratory flow

QoL = quality of life

SNOT-20 = sino-nasal outcome test 20

Th 1 = T-helper 1 cells

Th 2 = T-helper 2 cells

VAS = visual analogue scale

1 Introduction

The concept of the Unified Airway model considers the entire respiratory system from the nose and paranasal sinuses, oropharynx, larynx, trachea, large and small airways as one integrated unit (12). The upper airway is a complicated structure comprising the nasal passages and the mouth placed in parallel, where the nose contains two parallel pathways for airflow. Unlike the lower airway, the nasal mucosa contains venous sinusoids that undergo periodic congestion and decongestion (the nasal cycle) which is essential in filtering, warming and humidifying the inspired air for the best of the lower airway.

It has become increasingly clear that inflammation in the upper respiratory tract affects the lower respiratory tract and vice versa. More than 80 % of adult patients with allergic and non-allergic asthma have symptoms of rhinitis (3, 4, 13), and the co-existence of asthma and allergic rhinitis is associated with more severe asthma symptoms, reduced asthma related quality of life (QoL), and greater challenges in acquiring control over the lower airway symptoms (14). Conversely, 20–50% of patients with rhinitis have asthma (15), and an increase in nonspecific bronchial responsiveness is seen in patients with allergic rhinitis without obvious asthma (16).

Asthma is a global health problem, with increasing prevalence in most countries, and an estimated 300 million sufferers worldwide (17). In Norway, the prevalence of asthma in adults is estimated to 8 % (1). The "Environment and Childhood Asthma (ECA) Study" in Oslo found a prevalence of current asthma of 11.1% (2).

The concept of the unified airway is based on evidence from epidemiological (5-10), pathophysiological (18-20) and treatment outcome studies (21, 22). However, there are few studies that have investigated the upper airway characteristics in asthmatics using subjective and objective tools (23, 24). As en ENT specialist, the purpose of this thesis has been to focus on the structural, functional and subjective characteristics of the noses in asthmatics by

evaluating the association between their subjective sino-nasal complaints, sino-nasal quality of life and nasal airway patency compared with non-asthmatic controls.

1.1 The Unified Airways in health

1.1.1 Anatomy of the Unified Airway

1.1.1.1 Upper airway

External nose and nasal vestibule

The external nose consists of 3 parts; the lobule, the cartilaginous pyramid and the bony pyramid. The lobule (lower 1/3) consists of the medial and lateral crus of the lobular cartilages and soft tissues. The cartilaginous pyramid (middle 1/3) consists of two upper lateral cartilages and septal cartilages. The bony pyramid (superior 1/3) consists of the nasal spine of the frontal bone, the frontal processes of the maxilla and two nasal bones (figure 1).

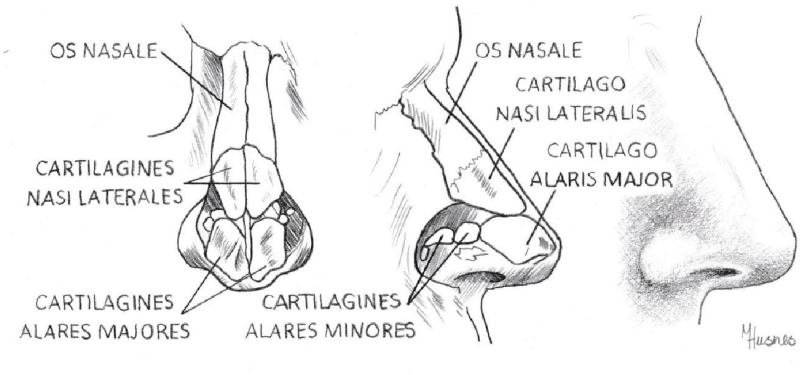

Figure 1. Anatomy of the nose, frontal and lateral view. Illustration Marianne Husnes©

The cartilages counteract collapse and provide rigidity for the nasal vestibule and alae regions during respiration. The nasal vestibule is the anterior segment of the nasal cavity, which is defined by the columella, the membranous septum and the inside of the alae cartilages, and these parts define the external nasal valve, figure 2.

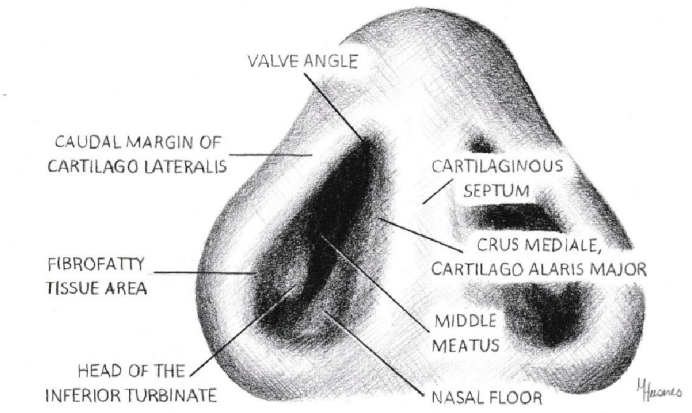

Figure 2. Anatomy of the nasal entrance. Illustration Marianne Husnes©

Nasal valve and internal nose

The internal nasal valve, also referred to as "the internal ostium" or "isthmus nasi", is the relative stenosis forming the transition between the skin-lined nasal vestibule and the mucosa-lined nasal cavity (25).The anatomical boundaries include the septum, the upper lateral cartilages, the piriform aperture and the anterior end of the inferior turbinates and septal body (26, 27), figure 3.

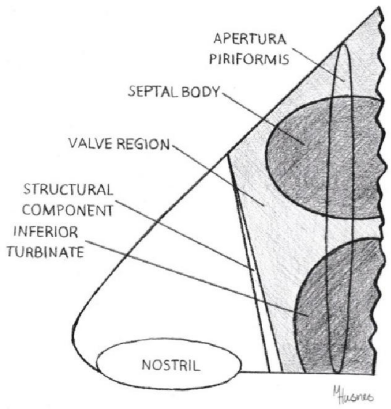

Figure 3. The nasal valve region, sagittal view. Modified from Cole (28) and the thesis of Thomas Kjærgaard. Illustration Marianne Husnes©

The nasal cavity dimensions rapidly increase beyond the nasal valve region. The nasal cavity is divided in two compartments by the nasal septum, which consists of a cartilaginous and a bony part, and it is lined by a respiratory mucosa. The lateral nasal wall consists of 3 to 4 turbinates: the inferior, middle, superior, and in some individuals' also supreme turbinates. The turbinates consist of a bony core coated with respiratory mucosa and a characteristic cavernous tissue embedded in the lamina propria. This cavernous tissue is mostly developed in the inferior turbinates and varies in size. Thus the inferior turbinates contribute significantly to regulation of nasal air flow (29, 30). The sinuses are paired organs which are divided into 4 compartments; maxillary sinuses, ethmoid sinuses, frontal sinuses and sphenoid sinuses, all lined with respiratory epithelium. Patency of the sinus ostia, and intact innate and adaptive immune systems are mandatory to obtain normal sinus function.

Nasal mucosa

The respiratory pseudostratified columnar epithelium lines the entire airway, including the tuba auditiva and middle ear. The sinonasal mucosa is comprised of ciliated columnar

epithelial cells (80%), goblet cells that produce mucus (15%), and progenitor basal cells (5%) (31). The epithelium is covered by an airway surface liquid (ASL) about 10 μm deep. It is in two layers, the sol layer and the gel layer. The watery periciliary sol is surrounding the cilia. Over the sol layer is the gel layer which works as a mucous blanket that traps inhaled particles (32). The low viscosity of the periciliary sol allows the cilia to beat and propel the mucous blanket to the oropharynx, where it is swallowed or expectorated. In the normal "resting" nose, 20-40 ml of mucus are secreted each day from the nasal mucosa (33).

Each epithelial cell has approximately 50 to 200 cilia (31). Ciliary ultra structure is characterized by axonema composed of microtubules with interconnecting dynein arms which enables a biphasic ciliary beat (34). During their active stroke the cilia contact the underside of the mucous gel, and propel the mucus and entrapped particles at ∼3 mm/min (35). In addition, the epithelial cells have hundreds of immotile microvilli which are hairlike projections of actin filaments, 1 to 2 μm in lengths covered by cell membrane. When increasing the total mucosal surface, the microvilli aid in sinonasal sensation, warming and humidifying the inspired air (36, 37).

Arteries and nerves of the nasal cavity

The arterial blood supply to the nasal cavity consists of the anterior and posterior ethmoid arteries, via the ophthalmic artery from the internal carotid artery, and the sphenopalatine artery, via the maxillary artery from the external carotid artery. The ethmoid arteries supply blood to the superior and frontal parts of the nose and septum, and the sphenopalatine artery supplies the posterior parts of the nose and septum. The anterior part of the nose is supplied from alar branches of the facial artery, and septal branches of the superior labial artery, via the facial artery. The arterial blood flow runs anteriorly against inspiration and may warm incoming air (38).

The first cranial nerve, the olfactory tract, ends at the cribriform plate of the ethmoid bone. Olfactory nerves are found on the superior and middle turbinates and on the upper parts of the nasal septum. The trigeminal nerve (cranial nerve V) conducts sensory impulses like temperature, pain and touch from the nose (26). The autonomic innervation of the nasal cavity (Vidian nerve) regulates blood flow to the nasal mucosa (sympathetic system) and nasal secretions (parasympathetic system) (26).

1.1.1.2 Middle airway

The Waldeyer´s ring (39) is located at the opening of the respiratory and digestive tract and is continuously exposed to foreign pathogens and airborne antigens entering the body through the nose and mouth. It consists of the adenoids, the paired tubal tonsils, the lingual tonsils and the paired palatine tonsils. The Waldeyer's ring is most prominent during childhood, when the size of the oro-nasopharyngeal space is not yet fully developed, but decreases spontaneously with age. The larynx consists of the epiglottis, and the thyroid-, arytenoid-, cricoid- and accessory cartilages.
In this thesis the Waldeyer´s ring and the larynx are defined as parts of the middle airway.

1.1.1.3 Lower airway

The trachea is a mucosa covered cartilaginous tube, extending from the lower part of the larynx at the level of the 6^{th} cervical vertebrae to the upper border of the 5^{th} thoracic vertebra where it divides at the carina into the 2 bronchi. The right main bronchus is wider, shorter and more vertical than the left. The right and left main bronchi divide into 3 and 2 lobar bronchi, respectively. The lobar bronchi divide into tertiary bronchi which supply a bronchopulmonary segment. The pulmonary alveoli are the terminal ends of the respiratory tree, which outcrop from either alveolar sacs or alveolar ducts. The alveolar membrane is the

gas-exchange surface. Carbon dioxide rich blood is pumped from the rest of the body into the alveolar blood vessels where carbon dioxide is released and oxygen is absorbed through diffusion.

1.1.2 Physiology of the Unified Airway

The two major functions of the nose are nasal breathing and olfaction, and the major function of the lower airway is transportation of air and gas exchange.

1.1.2.1 Upper airway

The nose is used for inhalation and exhalation of air, and olfaction, and an open nose is essential for human health and normal lung function. During inspiration the air is filtered, tempered, humidified and supplied with nitric oxide (NO) before entering the lower airways. The efficacy of the filter of the nose depends on the size of the inhaled particles. During normal breathing, only a few particles larger than 10 μm (pollen grains) enter the lower airways, while most particles smaller than 2 μm (mould spores) can easily bypass the nose without being trapped in the mucous blanket (40). Conditioning (heating and humidification) of the inspired air is important as cold and dry air are known to cause bronchoconstriction in sensitive asthmatic patients (41-43). By adjusting the mucosal blood flow, the nose can either warm and humidify or extract heat and water from the passing air (44).
The effects of NO are explained later in the text.

The pattern of airflow in the nasal airway is complex, and to be able to understand it, the basic principles of flow of fluids have to be understood. (The equations of the physical laws of fluid mechanics are given in the appendix).

In laminar flow a fluid, i.e. a liquid or gas, proceeds through a tube in a predictable manner, as in a river where the water near the banks is almost still and whereas that in the

center flows more rapidly. Further, Venturi tubes consist of constricted and dilated segments, and are used in industrial and scientific laboratories for measuring the flow of liquids. When gas flows through a Venturi tube and the flow at the two ends is constant, the Bernoulli's principle states that the velocity of the flow within the tube varies. This principle implicates that velocity of flow in constricted areas is increased whereas it is decreased in the dilated areas, as in a river where the flow slows when it enlarges into a basin. The Bernoulli's principle also applies for the nose, where the velocity of the airflow through constricted segments is increased as opposed to decreased through dilated segments (45). In a Venturi tube, the pressure is reduced in areas where the flow is fast, whereas the pressure is increased in areas where the flow is slow. Poiseuille's law (46) is another physical law which is important for airflow. It states that the flow is directly proportional to the difference in pressure times the radius raised to the 4th power. Consequently, minimal increases in the size of the tube or nasal airway cause exponential increases in airflow. Flow is also inversely proportional to the length of the tube, e.g. the longer the nasal cavity, the less the flow.

The cross sectional area varies throughout the nose. It is smallest at the internal nasal valve, larger at the level of the turbinates, and largest at the level of posterior choana. Minimal changes in the cross sectional area of the internal valve may cause profound changes in airflow. Due to the changes in velocity and thus creation of turbulent airflow in different parts of the nose the nasal airflow is complicated to understand. The predominant flow is neither laminar nor turbulent, but a regime of varied disturbances which is termed transitional (47). The highest linear velocities are detected at the minimum cross sectional area (MCA) in the nasal valve region, reaching 12-18 m/s during normal breathing, whereas lowest velocities are in the olfactory region (47, 48).

The nasal airflow is constantly changing due to variations in mucus, cilia, vasoconstriction and vasodilatation, reflexes, and the nasal cycle, figure 4. The latter implies

spontaneous and often reciprocal change in unilateral nasal airflow due to congestion and decongestion of the nasal venous sinuses every 3-7 hours. During a normal cycle, one nasal cavity is assumed to be in a “working phase”, while the opposite cavity is in a “resting phase” which allows restoration of the mucosa. The associated subjective feelings of nasal patency/obstruction as well as the objective assessments of nasal patency are not merely a question of the nasal resistance. The occurrence of turbulences is of importance too.

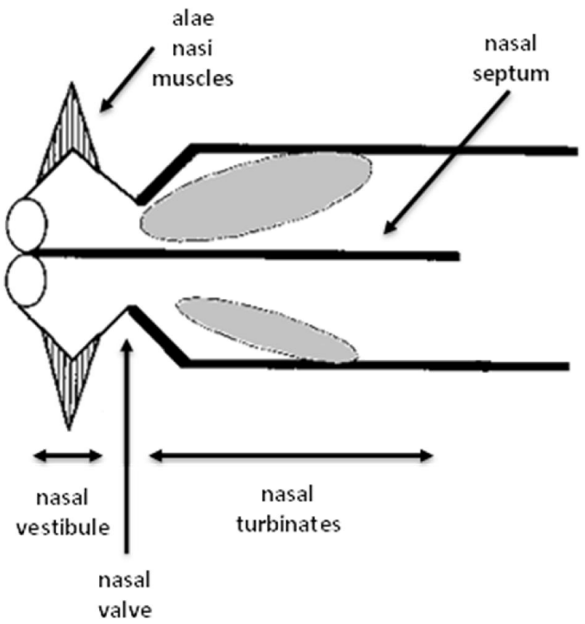

Figure 4. Diagram of the nose. The compliant wall of the nasal vestibule is supported by the alae nasi muscles. The nasal valve is at the level of the anterior tip of the inferior turbinate. The diagram illustrates the normal asymmetry of nasal congestion, with one side of the nose congested due to swelling of the venous sinuses in the nasal turbinates and the other side open and decongested due to constriction of the venous sinuses. The degree of congestion of the tip of the inferior turbinate determines the dynamic cross-sectional area of the nasal valve area and nasal airway resistance. Printed with permission from Eccles (26), slightly modified.

NO is a gas which is continuously produced in the paranasal sinuses. In healthy controls at rest, almost all NO found in exhaled air originates from the upper airways with only a minor contribution from the lower respiratory tract and the lungs (49, 50). The involvement of autogenous NO in regulation of pulmonary function, as an enzymatically produced airborne messenger, is termed "aerocrine" (51). The high local NO concentrations in the nasal airways and the sinuses may help to protect against airborne infectious agents. Thus, the finding of low nasal NO levels in patients with chronic sinus disorders such as Kartagener's syndrome and cystic fibrosis may be used to facilitate early diagnosis of these two respiratory disorders (52).

The olfaction monitors the intake of (noxious and non-noxious) airborne agents into the human respiratory system, and determines to a large degree the flavor and palatability of foods and beverages. It can also protect the lower airways by warning the subjects of several irritants and includes conscious and non-conscious responses of defense (53). The olfactory mucosa consists of pseudostratified columnar epithelium which covers the cribriform plate, the superior septum and sectors of both the superior and middle turbinates in both nasal cavities (54). Humans can detect more than 10000 different odors and discriminate between 5000 odors (38). Patients with nasal polyps and symptoms of nasal blockage experience an impaired sense of smell (55).

1.1.2.2 Middle airway

The adenoids, the paired tubal tonsils, the lingual tonsils and the paired palatine tonsils are all secondary lymphoid organs belonging to the mucosa-associated lymphoid tissue (MALT), and due to the anatomical location, they are continuously exposed to foreign airborne and ingested antigens (56, 57). The larynx is involved in voice production, respiration and protecting the trachea from food aspiration.

1.1.2.3 Lower airway

The cardinal function of the lung is gas exchange. The lung also metabolizes compounds like angiotensin, serotonin and leukotrienes, filters small blood thrombi from the circulation, and acts as a reservoir for blood. The number of conducting airways, i.e. bronchi and bronchioles, is complete at birth and thereafter only increases in size (58). The function of the conducting airways is to lead inspired air to the gas-exchanging regions of the lung. From birth until 3 years of age, lung volume increases mainly due to an increasing number of alveoli, and alveoli may develop until the age of 8 years (59). The functional residual capacity increases from about 80 mL at birth to 3000 mL in the adult (60), and lung weight increases from 60 to 750 g (61). The major portion of this growth affects the respiratory zone, and most alveoli (85%) are added through multiplication after birth. There is an increase in lung parenchyma between the age of 1 month and 7 years by a factor of about 13, whereas the increase slows down until the age of 18 years (62). Later in life, the increase in lung volume is mainly due to expansion of alveoli. When the alveolar number is reduced or the physiological demands are increased, an even greater enlargement of alveoli may take place. Lung size increases at least until growth of the chest wall is complete (58).

During inspiration, the volume of the thoracic cavity increases, and air is drawn into the lung due to the low intra thoracic pressure. The lung is elastic and returns passively to its pre-inspiratory volume during breathing at rest. Gas movement in the alveolar region is chiefly by diffusion. Blood spends about 0.75 second in the capillary at rest. The area of the blood-gas barrier in the lung is enormous (50 to 100 square meters), and the thickness is 0.3μm in many places, so the barrier for diffusion is ideal. CO_2 diffuses about 20 times more rapidly than O_2 through tissue sheets because it has a much higher solubility.

The exhaled volume after a maximal expiration is called the vital capacity. Some gas remains in the lung after a maximal expiration, and this is the residual volume. The volume of gas in the lung after a normal expiration is the functional residual capacity.

The four causes of low oxygen concentration in blood, hypoxemia, are hypoventilation, diffusion limitation, shunt, and ventilation-perfusion inequality. Shunt is the only cause of hypoxemia in which the arterial PO_2 does not rise to the expected level when a patient is given 100% O_2 to breathe. Ventilation-perfusion inequality reduces the gas exchange efficiency of the lung for all gases, which means that the matching of ventilation and blood flow is disturbed.

NO is also produced by the lungs and is present in exhaled breath. Patients with asthma have high levels of NO in their exhaled breath and high levels of inducible nitric oxide synthase (NOS2) enzyme expression in the epithelial cells of their airways, suggesting a role for NO in asthma pathogenesis (63). Thus the concentration of NO in exhaled air increases in airway inflammation, but the interpretation can be difficult because of confounding factors such as height, age, gender, lung function, smoking, and respiratory tract infections, as further described in section 1.4.2 Objective measures of the unified airway.

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1.1.2.4 Mucosa-associated defenses

The airway mucosa has nonspecific defense mechanisms against pathogens that include the normal flora of microbes, the mucociliary system, and a specific immunological-based defense system.

The mucociliary system

The mucociliary system serves as a mechanical, chemical and biological barrier between the respiratory epithelium in the nose and lungs and the pathogens encountering the

airway. Nasal mucus provides a continuous layer in the nasal cavity in which particles in the turbulent airstream can impact and stick. The layer of mucus is moved by the coordinated waves of cilia from the anterior part of the nose to the nasopharynx, where it is swallowed or expectorated. Large particles are filtered out in the nose. Smaller particles that deposit in the conducting airways are removed by a moving staircase of mucus that continually sweeps debris up to the epiglottis, where it is swallowed (64). Mucociliary transport is disturbed in a variety of conditions which affect the activity of the cilia and the composition of the secretions, e.g. viruses, bacteria, cystic fibrosis, primary ciliary dyskinesia, Young's syndrome and Kartagener's syndrome.

The specific, immunological based defense system

The immune system is usually divided in an innate and an adaptive branch, both providing both humoral and cellular based defense mechanisms (figure 5).

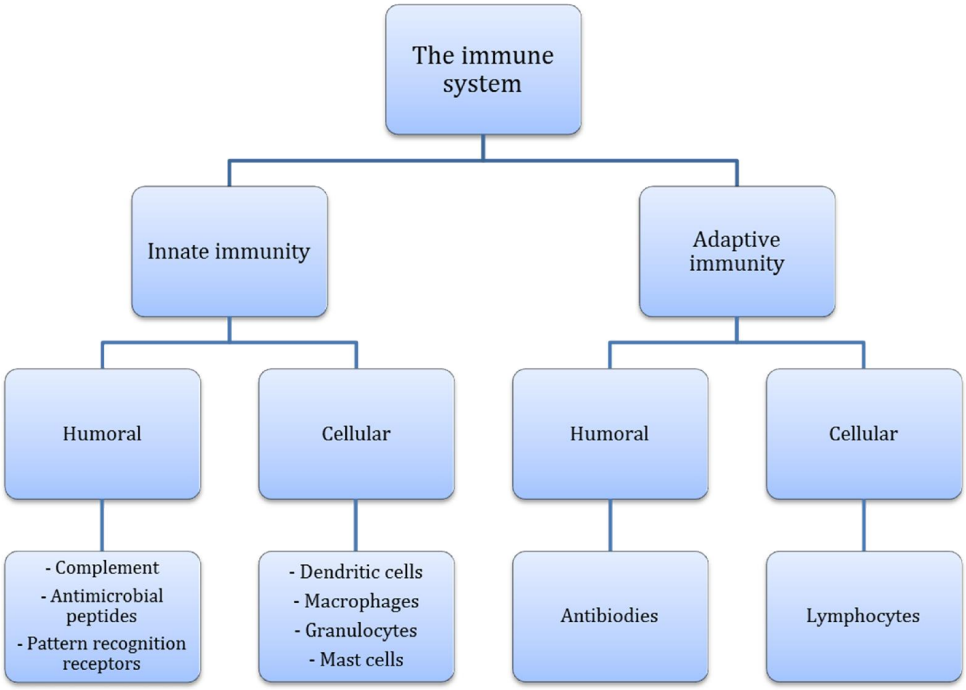

Figure 5. The immune system. Adapted from the thesis of Jesper Bogefors.

The innate immune system is characterized by rapid onset, lack of specificity, limited diversity and no immunological memory. The innate humoral defense is mediated by bioactive molecules, like pattern-recognition receptors, antimicrobial peptides and the complement system. Cellular components of the innate immune system are granulocytes (neutrophils, basophils, and eosinophils), mast cells, dendritic cells and macrophages. These cells are armed with non-specific pattern recognition receptors that trigger the activation of defense mechanisms and stimulate the adaptive immune system (65, 66). Airway secretions contain innate immune defense proteins, including lysozyme, lactoferrin, human β-defensin and secretory leukocyte protease inhibitor, which form an important component of innate immunity against inhaled antigens and micro-organisms (67). The alveoli have no cilia, and particles that deposit there are engulfed by macrophages. The foreign material is then removed from the lung via the lymphatic system or the blood flow (64).

The adaptive part requires some days to develop, is antigen specific, involves lymphocyte interactions, has a long lasting memory, and a marked diversity. It has great abilities of memory and protects the host from reinfections (68, 69). The T- and B lymphocytes constitute the cornerstone of the adaptive immune system, and are responsible for the cell mediated- and the humoral responses. Components of the adaptive immune system are found in nasal secretions and contain immunoglobulins IgA, IgG, IgM, IgE, where secretory IgA is the predominant immunoglobulin in mucosal tissues (70, 71).

1.2 The Unified Airways in disease

1.2.1 Pathophysiological pathways

During the past two decades we have acquired a growing amount of evidence of a pathophysiological link between the upper and lower airways constituting a substantial foundation for the Unified Airway concept (72-74). The upper and lower airways share the same mucosal susceptibility to inhaled substances, and in clinical practice the upper and lower airways should be treated as one entity. Thus, several proposed mechanisms have been offered to explain the Unified Airway model, and so far four main pathophysiological pathways are considered of importance.

The mechanism of primary interest is the one of shared inflammation (19, 20), where inflammatory processes can progress from one portion of the respiratory system to another called inflammatory cross talk. Thus disorders of the respiratory mucosa often present with a similar inflammatory response, which is common to diseases such as rhinitis, rhinosinusitis, and asthma (75). This inflammatory response has been demonstrated by Braunstahl and colleagues (18) who have shown that stimulation of one portion of the airway mucosa with antigen will result in system-wide inflammatory changes within a matter of hours. Thus placement of antigen directly onto the bronchial mucosa using bronchoscopy has been shown to induce nasal inflammation in patients who have allergic rhinitis. In addition, reciprocal induction of bronchial inflammation with nasal antigen stimulation has been demonstrated using a similar model (19). Moreover, experimental studies have shown that stimulation with antigen at one respiratory site can result in expression of inflammatory cytokines at a distant location (18, 19, 76, 77).

A second proposed mechanism is the presence of a nasobronchial reflex where inflammatory conditions, chemical, thermal, and biological irritants in the nasal mucosa might generate nerve impulses which trigger bronchoconstriction. Kaufman and Wright (78)

performed a study where silica particles were applied directly to the nasal mucosa in subjects without asthma. Measurement of pulmonary function in these subjects was reported to demonstrate rapid and significant increases in lower airway resistance, leading to the speculation that a direct reflex was stimulated between the nose and the lungs. Subsequent studies showed that this effect could be blocked through the administration of atropine (78) or with resection of the trigeminal nerve (79). Additional support for this presumed nasobronchial reflex has not been demonstrated, as other studies have failed to replicate the effects of nasal stimulation in causing rapid bronchoconstriction (80-82). In animal models where nasal stimulation has been conducted with thermal, chemical, and mechanical stimuli, no reflex changes in ventilation or oxygenation have been demonstrated (83). Delayed changes can be seen in the lung from 30 minutes to four hours after antigen challenge of the nose (84), but immediate reflex changes in pulmonary function cannot be demonstrated consistently. These findings suggest that mechanisms other than a direct reflex arc may be responsible for the observed relationship between upper and lower airway disease (74).

A third proposed mechanism is oral breathing and consequently a loss of nasal protection of the lower airway. Shturman-Ellstein and colleagues (85) performed in 1978 a study where patients who had exercise-induced asthma were allowed to exercise under three conditions: spontaneous breathing, nasal breathing, and mouth breathing. This study demonstrated that mouth breathing seemed to worsen bronchospasm and nasal breathing appeared to have a protective effect. Thus nasal breathing is suggested to have a beneficial effect on the lower airway through the conditioning of inspired air for delivery to the lungs. It is also shown that asthmatics switch to oral breathing at a significantly lower nasal load compared to healthy controls (86).

A fourth proposed mechanism is aspiration of nasal secretions into the lower airways. Sino nasal infections may disperse to the lower airways in patients with impaired cough reflex

and reduced mucociliary clearance, e.g. progressive neurodegenerative conditions, cystic fibrosis and intensive care unit patients on ventilatory support. Thus, optimization of the nasal function may prevent lower respiratory infections. However, in healthy individuals, seeding of mucopurulent secretions into the lower airways is unlikely to account for coexistent pulmonary disease (87).

1.2.2 Allergy

Allergy is defined as an abnormal adaptive immune response directed against non-infectious environmental substances (allergens), including non-infectious components of certain infectious organisms. In allergic disorders, such as anaphylaxis, allergic rhinitis, some food allergies and allergic asthma, these responses are characterized by the involvement of allergen-specific IgE and T helper 2 (Th2) cells that recognize allergen-derived antigens (88). The diagnosis of allergy is based upon the concordance between a typical history of allergic symptoms and diagnostic tests.

Allergy is a multifactorial disease induced by interaction between host- and environmental factors. Host factors include heredity, sex, race and age. Environmental factors include exposure to allergens, smoking, pollution and infections.

Allergic rhinitis and allergic asthma are characterized by similar inflammatory processes, which is a result of subsequent events which can be divided in to an early phase and a late phase of the allergic response. The early phase starts with an IgE-mediated type I immediate hypersensitivity reaction that can occur within minutes of allergen exposure and is characterized by vasodilation, increased vascular permeability, vascular leakage and oedema. In such reactions, IgE bound to mast cells and basophils is cross linked by allergen, resulting in the release of preformed and newly synthesized mediators (88). Some of the released mediators also promote the local recruitment and activation of leukocytes, contributing to the

development of late-phase reactions. Antigen presenting cells (APC), present in the superficial areas of the skin and mucosa of the airways engulf antigen. The APC migrate to lymph nodes where the antigen stimulates T- and B- lymphocytes. The T-lymphocyte recognizes fragments of antigen bound to the major histocompatibility complex molecules expressed on the surface of the APC. The B-lymphocyte recognizes antigen through their immunoglobulin receptors and develops into plasma cells, which produce specific IgE antibodies that bind to mast cells. Subsequent exposure to allergen results in cross binding of specific IgE on mast cells leading to a degranulation with the release of histamine and proteases. The activation of the T-cell receptor stimulates the naïve T-helper cell which differentiates to either Th1 or Th2 cells, with the following secretion of interferon gamma and interleukins IL-2 (Th1), IL-4, IL-5, IL-9, IL-13 (Th2), IL-3 and Granulocyte-macrophage colony-stimulating factor (both Th1 and Th2) (89). Tissue eosinophilia is a characteristic feature of the late phase reaction, which occurs about four to ten hours (with a maximum after 7-8 hours) after exposure. The eosinophil is a source of leukotrienes, prostaglandins, platelet activating factors, cytokines and cytotoxic proteins, which can be released upon stimulation and are toxic to the airway epithelium. When the allergic stimulus is continuously present, or other noxious stimuli appear in the environment of the patient, the allergic inflammation process may become chronic (88). A common feature of chronic allergic inflammation is tissue remodeling (90).

1.2.3 Upper airway

Nasal blockage can be defined as discomfort due to insufficient airflow through the nose. In the literature many synonyms of nasal obstruction are used like nasal stuffiness, nasal blockage and nasal congestion (91). In this document nasal obstruction also includes the terms nasal blockage and nasal stuffiness, whereas nasal congestion describes the reduced airflow

due to mucosal congestion (92, 93). The prevailing reading in literature of nasal patency is that it characterizes an objective measure of how open the nose is.

The etiology of nasal obstruction may be structural, mucosal or functional/subjective. Structural causes of airflow limitation include abnormalities of the cartilaginous and/or bony constituents of the nose, congenital or acquired, unilateral or bilateral. Septal deviation is common, with a prevalence ranging from 19.4% to 65%, due to different criteria for defining a deviated septum (94, 95), but its clinical significance is questionable because it's a frequent finding in many asymptomatic individuals (96). Septal perforation probably affects 0.9% of a population (97) and often causes symptoms like crusting, bleeding, nasal obstruction, whistling and pain. Almost 40% of septal perforations are completely asymptomatic (98). Enlargement of the inferior turbinate may be caused by osseous thickening of the bone core with cellular hypertrophy- and hyperplasia. Unilateral enlargement is frequently associated with deviation of the septum into the contralateral nasal passage (99). Enlargement of the middle turbinate due to a concha bullosa is a frequently encountered anatomic variant, often associated with septal deviation, and may have the potential to occlude the middle meatus and predispose to inflammation of the paranasal sinuses (100, 101). Other structural causes are adenoidal hypertrophy, anatomical variants in the osteomeatal complex, foreign bodies and choanal atresia (102).

Mucosal causes consist of congestion and inflammation caused by allergic- and non-allergic rhinitis, nasal polyposis, turbinate enlargement, drug reactions, endocrine or metabolic conditions, systemic inflammatory and granulomatous conditions like sarcoidosis and granulomatosis with polyangiitis, and ciliary defects. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Review (102) rhinitis can be classified as: Infectious (viral, bacterial or other), allergic (intermittent or persistent), occupational (intermittent or persistent), drug induced, hormonal, other causes like NARES (non-allergic rhinitis with

eosinophilia syndrome), irritants, food, emotional, atrophic and idiopathic. Turbinate enlargement can be bilateral, caused by nasal inflammations such as allergic and non-allergic rhinitis, environmental triggers e.g. dust, tobacco smoke, medication, and medical causes including pregnancy. Asthmatic patients have more concomitant chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) (7 %) than the general population (4 %) (103). In non-atopic asthma and late-onset asthma, CRSwNP was found even more frequently (104). On the other hand, more than 60 % of CRSwNP patients have lower airway involvement (105). Mechanisms causing inferior turbinate enlargement are mucosal, with dilatation of venous sinuses, tissue oedema, cellular hypertrophy and cellular hyperplasia (99).

Functional causes may be present without any obvious airflow restriction. Such conditions include atrophic rhinitis and empty nose syndrome following radical endonasal surgery or trauma. The lack of obvious pathology in some obstructed noses might be explained by the disruption of normal airflow patterns (106, 107), impaired mucosal sensation (26, 108, 109), and psychological and other non rhinological factors such as individual differences in symptom perception, interpretation and symptom mastering which may influence the subjective outcome (26, 110). Nasal obstruction may be the presenting symptom in a large variety of conditions, some of which is presented in figure 6.

Figure 6. The different etiologies of nasal airway obstruction which may be polyfactorial. Modified from Chandra (106).

1.2.4 Middle airway

In children, enlarged tonsils and/or adenoids may cause Eustachian tube dysfunction/otitis media, rhinosinusitis, obstructive sleep apnea, voice changes, change in facial growth, swallowing problems and can affect overall quality of life.

Enlarged adenoids can obstruct the nasal passageway and it is shown that children with asthma have a larger nasal-adenoid index than controls (111).

Laryngopharyngeal reflux may present with asthma like symptoms. Accumulating evidence suggests a strong association between gastroesophagal reflux disease (GERD) and pulmonary diseases, including adult-onset asthma. The prevalence of GERD in patients with asthma has been reported to range from 30% to 90% (112, 113).

1.2.5 Lower airway

Bronchial responsiveness (BR) may be defined as a tendency of the airways to constrict to a variety of physical or chemical stimuli. Bronchial hyperresponsiveness (BHR) is present when the degree of BR is greater than that observed in normal subjects, but the distinction between normal and heightened BR is not sharp. BHR is linked to both inflammation and repair of the airway and is partially reversible with therapy. Inflammatory changes in the airway wall may lead to excessive narrowing of the airways. Thickening of the airway wall by edema and structural changes amplifies airway narrowing due to contraction of airway smooth muscles for geometric reasons (114). Sensory nerves may be sensitized by inflammation, leading to exaggerated bronchoconstriction in response to sensory stimuli.

The Global initiative for asthma (GINA (17) defines asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early

morning. These episodes are usually associated with widespread, but variable, airflow obstruction within the lung that is often reversible either spontaneously or with treatment (17).

The etiology of asthma is complex, but can be divided into host factors and environmental factors. Host factors include genes, obesity and sex. Multiple genes may be involved in the pathogenesis of asthma (115, 116) and different genes may be involved in different ethnic groups. Asthma is observed more frequently in obese subjects (body mass index (BMI) > 30 kg/m²) and is more difficult to control (117). Male sex is a risk factor for asthma in childhood. Prior to the age of 14, the prevalence of asthma is nearly twice as great in boys as in girls (118). Environmental factors include allergens, infections, occupational sensitizers, tobacco smoke, outdoor/indoor air pollution and diet. Indoor (domestic mites, furred animals, cockroach allergen, fungi, molds, yeasts) and outdoor (pollens, fungi, molds, yeasts) allergens are known to cause exacerbations, but their specific role in the development of asthma is not fully resolved (17). For some allergens, such as those derived from house dust mites and cockroaches, the prevalence of sensitization appears to be directly correlated with exposure (119). Some epidemiologic studies have found that early exposure to dogs and cats may protect a child against allergic sensitization or the development of asthma (120), but others suggest that such exposure may increase the risk of allergic sensitization (121). The "hygiene hypothesis" of asthma suggests that exposure to infections early in life influences the development of a child's immune system along a "non-allergic" pathway, leading to a reduced risk of asthma and other allergic diseases. Although the hygiene hypothesis continues to be investigated, this mechanism may explain observed associations between family size, birth order, day-care attendance, and the risk of asthma (17). Further, over 300 substances have been associated with occupational asthma, which is defined as asthma caused by exposure to an agent encountered in the work environment (17). Tobacco smoke is associated with accelerated decline of lung function in people with asthma (122), increases asthma

severity, may render patients less responsive to treatment with inhaled (123) and systemic (124) glucocorticoids (GC), and reduces the likelihood of asthma being controlled (125). The role of outdoor air pollution causing asthma remains controversial (126). Outbreaks of asthma exacerbations have been shown to occur in relationship to increased levels of air pollution, and this may be related to a general increase in the level of pollutants or to specific allergens to which individuals are sensitized (127). The same has been observed in relation to indoor pollutants, e.g., smoke and fumes from gas and biomass fuels used for heating and cooling, molds, and cockroach infestations. The role of diet, particularly breast feeding, in relation to the development of asthma has been extensively studied. Data reveal that infants fed formulas of infants cow's milk or soy protein have a higher incidence of wheezing illnesses in early childhood compared with those fed breast milk (128).

Several factors contribute to the development of airway narrowing in asthma: airway smooth muscle contraction, airway edema due to increased microvascular leakage in response to inflammatory mediators, airway thickening due to structural changes such as remodeling, and mucus hyper secretion leading to luminal occlusion. The characteristic structural changes in the airways, described as airway remodeling, include the increase in airway smooth muscle, both as hypertrophy and hyperplasia, proliferation of blood vessels, increased numbers of goblet cells and increased size of submucosal glands, and subepithelial fibrosis due to deposition of collagen fibers and proteoglycans under the basement membrane (17).

1.3 Treatment in a Unified Airway perspective

Avoidance of allergens is of uttermost importance in the treatment of upper, middle and lower airway symptoms. Indoor and outdoor allergens should be identified and avoided.

1.3.1 Medical treatment

1.3.1.1 Upper airways

The medical treatment of nasal obstruction involves several therapies. The mechanism of **saline nasal irrigation** depends mainly on washing away allergens and inflammatory mediators induced by allergic reactions (129), remove bacteria, bacterial pus debris (130) in rhinosinusitis, and after nasal surgery. It has been shown that daily nasal saline irrigation improves symptoms and reduces the need for medical therapy in CRS and sinonasal disease (131, 132).

Nasal decongestants are fast acting topical vasoconstrictive drugs acting by stimulating the adrenergic alpha-receptors, effective for the reduction of nasal congestion on a short time basis (133). They can be classified into two major groups: (1) sympathomimetic amines (cocaine, amphetamine, adrenaline, and ephedrine) and (2) imidazolines (oxymetazoline and xylometazoline). Of the imidazolines, oxymetazoline, a selective α-1 and partial α-2 agonist, and xylometazoline, an α-2 agonist, are the most popular and clinically used derivatives. The main side effect of topical decongestants is the development of rhinitis medicamentosa, which may appear in some patients after only 3 days. European guidelines recommend a maximum of 10 days use (134). Oral decongestants usually contain pseudoephedrine, or phenylephrine. Topical- and oral decongestants are not recommended for use in acute and CRSwNP and chronic rhinosinusitis without nasal polyps (CRSsNP) (135).

Oral antihistamines are classified as first, second and third generation. The first generation H1antihistamines such as alimemazin, deschlorpheniramine and prometazin are effective at controlling the rhinorrhea, sneezing and pruritus associated with rhinitis, but unfortunately

these agents cross the blood-brain barrier, thus producing undesirable side effects such as central nervous system depression, sedation leading to impaired performance at home, work and school as well as cardio toxicity. The second-generation antihistamines, such as cetirizin, ebastin, fexofenadin, and loratadin have improved H1 receptor selectivity, faster onset and longer duration of action and fewer adverse effects. Their half-lives are longer (12-24 hours) compared to the first generation (4-12 hours) (136). Both second and third generation, such as desloratadin and levocetirizin, have all anti-allergic and anti-inflammatory properties. Topical antihistamines have been found to be very effective for the overall treatment of allergic rhinitis (137).

Glucocorticosteroids (GC) exert anti-inflammatory effects on the nasal mucosa mediated by inflammatory cells such as eosinophils, T helper type 2 (Th2) cells, mast cells, B cells, dendritic cells and basophils, and also by nasal constitutive cells such as epithelial cells, endothelial cells, fibroblasts and glands/goblet cells. Treatment with GC can also induce regulatory T cells. Further, GC exert regulatory functions by inducing regulatory cytokines and regulatory T cells. Although GC are highly effective in mitigating inflammation, their potent action potentially causes severe adverse effects. To decrease this risk, intranasal glucocorticosteroid formulations (INS) with low systemic availability have been developed for the treatment of allergic rhinitis. INS (drops or spray) are also the primary medical treatment for CRSwNP and CRSsNP. The efficacy of INS in reducing nasal symptoms and reducing polyp size has been demonstrated in many randomized controlled trials (138, 139). Epistaxis, dry nose, nasal burning and nasal irritation are considered to be drug-related events (135). Oral corticosteroids may be administered as rescue therapy only in cases of patients affected by severe symptoms, in particular nasal obstruction, not controlled by other treatments (140).

Antibiotics are not indicated in the treatment of rhinitis and of rhinosinusitis without complications.

Leukotrienes are metabolites of cellular arachadonic acid and contribute to smooth muscle contraction, eosinophilic inflammation and mucus production. **Antileukotrienes** (Singulair®) are viewed as add-on or second-line therapy in current guidelines for the treatment of asthma and rhinitis/rhinosinusitis (141, 142).

Anti-reflux medication could be considered as an option in patients with asthma and CRS, particularly in those where conventional medical and surgical treatment is insufficient (143).

Intranasal chromones (disodium cromoglycate (Lomudal Nasal®)) stabilize mast cells and may improve nasal symptoms by reducing the synthesis and release of mediators such as histamine, leukotrienes and tryptase. They are able to inhibit both early and late phase of the allergic reaction, but they need several applications (three or four times daily) and have a weaker effect on allergic rhinitis symptoms compared with other drugs (144).

Combination therapy with different drugs, with different mechanisms of action, may provide an additional and synergistic beneficial effect. A novel combination therapy with azelastine hydrochloride and fluticasone propionate nasal spray in a single device is now available (Dymista®).

Omalizumab (Xolair®) is a recombinant humanized anti-IgE antibody that blocks the interaction of IgE with mast cells and basophils, which is approved for the treatment of severe persistent allergic asthma. IgE play a central role in the pathogenesis of allergic rhinitis and its efficacy has been evaluated in patients with allergic rhinitis where a clinical benefit was reported (145, 146).

Specific immunotherapy (SIT) like subcutaneous immunotherapy and sublingual immunotherapy are established methods of disease modifying treatments of allergic rhinitis and asthma (147). Future routes for the administration of SIT include intralymphatic

immunotherapy and epicutaneous immunotherapy, which exploit the high density of dendritic cells and the low numbers of mast cells and basophils in lymph nodes and skin, respectively, thus facilitating antigen presentation and minimizing side effects such as anaphylaxis (148, 149).

Histamine H4 receptor antagonists, Phosphodiesterase 4 inhibitors, mast cell activity inhibitors and targeted treatment towards the toll-like receptors may in the future be available for the treatment of allergic rhinitis (150). Cytokines are important in the pathogenesis of allergic inflammation and their inhibition is thus considered a possible pathway for the future treatment of allergic rhinitis (151).

1.3.1.2 Middle airways

Antibiotics are used for the treatment of tonsillitis caused by streptococci or in cases with more severe or prolonged disease.

Acid reflux medication for GERD includes antacids, histamine type 2 receptor antagonists and proton pump inhibitors.

1.3.1.3 Lower airways

Medications to treat asthma can be classified as controllers or relievers. Asthma medication can be administrated by inhalation, orally and by injection.

Controllers

Controllers are medication taken daily on a long term basis to keep asthma under a clinical control mainly through their anti-inflammatory effects. Inhaled GC are the most effective controller currently available. Systemic glucocorticoids, long-acting inhaled β_2 agonists in combination with inhaled GC, leukotriene modifiers, sustained-release theophylline and anti-IgE are alternatives (17).

Relievers

Relievers are medication that acts quickly to reverse bronchoconstriction and relieve symptoms, usually used on an as-needed basis. They include short and long acting inhaled β_2 agonists with rapid to delayed onset, inhaled anticholinergics, sustained release theophylline and oral β_2 agonists (17).

1.3.2 Surgical treatment

Surgery on inferior turbinates is performed when turbinate enlargement is present and conservative treatment fails either solitary or in combination with septal surgery (110). Turbinate reduction can be done by several techniques such as submucosal diathermy, cryosurgery, laser cautery, radiofrequency thermal ablation and coblation (152). The turbinate resection can be partial, total, or submucosal (99).

Septoplasty can be performed when septal deviation and symptoms of nasal obstruction are present (96).

Correction of collapse of the nasal valve is performed when nasal valve dysfunction or collapse is present (153). Several surgical techniques have been described with strengthening and opening maneuvers. This often involves simultaneous surgery on the nasal septum and inferior turbinates.

Surgery of the nasal tip is performed for cosmetic reasons and/or to improve subjective and objective nasal airflow (154).

Functional endoscopic sinus surgery (FESS) is performed to re-establish ventilation and drainage between the sinuses and nasal cavity through the natural ostia of the sinuses. Most surgical procedures start with removal of the uncinate process to facilitate access to the middle meatus, followed by antrostomy to the maxillary sinus, anterior ethmoidectomy, posterior ethmoidectomy, frontal recess surgery, sphenotomy and surgery on concha bullosa.

The surgical procedure depends of the type and extent of disease. Removal of polyps is also essential to re-establish ventilation and drainage of the sinuses.

Tonsillectomy and/or adenoidectomy are among the most common surgical procedures in children. Adenotonsillectomy in patients with asthma can reduce their respiratory symptoms and doses or frequency of medications (155, 156). The effect of adenoidectomy alone on asthma is not yet scientifically documented.

1.3.3 Mechanical dilatators

External dilator Breath Right® is a non-invasive mechanical device aimed to facilitate nasal breathing. It is a spring-loaded plastic strip that by adhesion to the skin overlying the compliant soft tissues of the anterior nose dilates the vestibular lumen. Nozovent is a device made of plastic which is placed in the nostrils and widens them so that nasal airflow is increased.

1.4 Methods to measure symptoms and functions of the Unified Airway

As early as 1895 the rhinologist Kayser described the core challenges in rhinology in a captivating way*: "Although in most cases its seems easy to determine a complete occlusion of the nose during an examination, in many cases it is difficult to translate this objective finding into an assessment as to whether the narrowing of the nasal passages actually impairs the respiratory function of the nose. It is therefore important to be able to perform a functional examination of the nose, i.e. determine whether the flow of air through a particular nose (e.g. that of the patient) is normal. Only the demonstration of a functional insufficiency of the nose can give our therapeutic intervention greater accuracy, and only in this way can we demonstrate any effects of this intervention in an objective manner. After all, we measure the acuity of the eye and the hearing ability of the ear"* (157).

1.4.1 Subjective measures of the unified airway

Symptom assessment of the unified airway is obviously of central importance, thus giving exclusive information about the patient's understanding of the disease and often dictates the need of intervention.

Visual analog scales (VAS) are quantitative measures thoroughly validated in many diseases (158, 159). These scales have been extensively used to assess the severity of rhinitis as well as the efficacy of therapeutic interventions (160).

The Asthma Control Questionnaire (ACQ) is a validated disease-specific test used for evaluation of asthma symptoms (161) where the patients are asked to recall on a 7-point scale (0=no impairment, 6= maximum impairment) how their asthma has been during the last week.

A disease specific quality of life assessment of the unified airways gives a tool to measure the overall effect of specific medical issues on a patient.

The Sino-Nasal Outcome Test-20 (SNOT-20), and the modified versions SNOT 16 and SNOT 22 are validated disease-specific quality-of-life (QoL) questionnaires for rhino-sinusitis (162). The Nasal Obstruction Symptom Evaluation Scale (NOSE) (163) and Rhinitis quality of life questionnaire (164) are similar disease-specific health status instruments for use in patients with nasal obstruction. There are many similar asthma specific health status instruments, e.g. Asthma Quality of Life Questionnaire, Standardized Asthma Quality of Life Questionnaire, Mini Asthma Quality of Life Questionnaire, Asthma Quality of Life Questionnaire for 12 years and older, and Acute Asthma Quality of Life Questionnaire.

1.4.2 Objective measures of the unified airway

Peak nasal inspiratory flow (PNIF) is a noninvasive method used to assess nasal patency. It is a physiological measure obtained during maximal inspiration and indicates the peak nasal airflow in liters per minute. No information is obtained regarding the structure of the nose or the location of nasal obstruction with PNIF, as is the case with acoustic rhinometry.

Acoustic rhinometry (AR) is a sonic echo technique, where the nasal airway is measured noninvasively by cross-sectional area as a function of longitudinal distance along the nasal passage. Nasal passage volumes are calculated from contiguous cross-sectional values. The technique is highly reproducible and exhibits its greatest accuracy in the anterior nose where the nasal valve is located (30, 165, 166). It is a static test conducted during breath-holding. AR is unaffected by airflow pressures on compliant nasal tissues and cannot detect nasal valve collapse that occurs only on inspiration.

Flow volume spirometry is a measure of the speed (flow) and amount (volume) of air that can be inhaled and exhaled. Most spirometers display a flow-volume loop, which graphically depicts the rate of airflow on the Y-axis and the total volume inspired or expired on the X-

axis, and a volume-time curve, showing volume (liters) along the Y-axis and time (seconds) along the X-axis. There are two categories of **bronchial provocation tests**, "direct" and "indirect". The "direct" category includes the pharmacological agents histamine and methacholine. This is a medical test where methacholine and histamine are used to assist the diagnosis of bronchial hyperreactivity and asthma. Both drugs provoke bronchoconstriction, and people with pre-existing airway hyperreactivity, such as asthmatics, will react to lower doses of methacholine and histamine. The "indirect" challenge include the physical stimuli such as exercise, hyperpnoea of dry air, distilled water, hypertonic saline and mannitol, and the pharmacological agent adenosine monophosphate. These stimuli are thought to cause airway narrowing "indirectly" by releasing a wide variety of mediators of bronchoconstriction from inflammatory cells within the airway. These mediators act on specific receptors on bronchial smooth muscle to cause contraction, with airway narrowing as a consequence.

NO can be measured in exhaled air from the lungs as fractional exhaled nitric oxide (FE_{NO}) which is a validated inflammatory marker in the diagnosis and management of patients with asthma, atopy, and allergic rhinitis (167). It is a useful, reproducible, noninvasive, easy to perform, and rapid tool (168). FE_{NO} offers added advantages for patient care including, but not limited to, detection of eosinophilic airway inflammation, determining the likelihood of corticosteroid responsiveness, monitoring of airway inflammation to determine the potential need for corticosteroid, and unmasking of otherwise unsuspected non adherence to corticosteroid therapy (168). The American Thoracic society recommends that FE_{NO} less than 25 ppb (< 20 ppb in children) indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely. FE_{NO} greater than 50 ppb (> 35 ppb in children) indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely, and lastly that FE_{NO} values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context (168).

Rhinomanometry is a method for the objective measurement of nasal airway resistance (NAR) during normal breathing. The measurements of NAR are performed by anterior (anterior nasal cavity), postnasal (posterior nasal cavity) or posterior (in the mouth) rhinomanometry, based on the patient's own respiration (active method) or using flow generated externally (passive method). A newer development is the four phases rhinomanometry and resistometry (169).Rhinostereometry, manometric rhinometry, forced oscillation technique, and nasal spirometry are other methods for measuring nasal cavity dimensions, but the clinical and scientific uses of these are quite limited.

Computational fluid dynamics (CFD) is a technology employed widely in engineering to solve and analyze problems that involve flow of fluids. CFD can be used to demonstrate physiological and pathophysiological airflow conditions in the nose and to do preoperative- and postoperative monitoring of surgical outcome (170).

Digital particle image velocity (DIPV) is an experimental method used to evaluate airflow in an accurately reproduced transparent model of the nasal cavity. DIPV use the same principle as that of movement of dust particles which can be recognized in a sliver of sunlight passing through a window. This method uses optically transparent materials where the flow is seeded with tracer particles and is illuminated with a sheet of laser light, and thus creating models of nasal airflow.

Sniffin' Sticks' is a test of nasal chemosensory performance based on pen-like odor dispensing devices. It comprises three tests of olfactory function; tests for odor threshold, odor discrimination and odor identification (171).

2 Aims of the studies

2.1 General aims:

The overall aim of this thesis is to compare subjective and objective outcomes in noses of asthmatics compared to non-asthmatic controls.

2.2 Specific aims:

1: We aimed to investigate the association between subjective sino-nasal complaints, nasal air flow, and sino-nasal quality of life (QoL) in patients with asthma compared with non-asthmatic subjects.

2: We aimed to investigate nasal airway patency in asthmatics compared to non-asthmatic controls using AR and PNIF.

3: We aimed to investigate the individual effects of a diagnosis of asthma and of lung function on PNIF when adjusted for possible confounders. Further, we investigated the perception of nasal obstruction in asthmatics compared to healthy controls when adjusted for PNIF.

3 Materials and methods

3.1 Study population

This thesis is based on 3 cross-sectional studies with basis in registrations of 103 asthma patients recruited from the Department of Thoracic Medicine, St.Olavs University Hospital, Trondheim, Norway, and 100 non-asthmatic control subjects. The controls were individuals recruited from businesses near by the hospital or patients attending the hospital for other illnesses, which were thought not to affect the upper and lower airways.

The enrollment took place in the period from August 2009 to December 2010. All subjects gave written consent that they were participating in a study concerning the "upper and lower airways in asthmatics", but were not informed further about the specific purposes of the study. Each individual followed the same standard assessment procedure according to study protocols. The research was approved by the Regional Committee for Medical Research and conducted according to the Helsinki Declaration.

3.2 Inclusion and exclusion (figure 7)

The asthma diagnosis was based on the presence of typical asthma symptoms, with either $\geq$ 12% and $\geq$ 200 ml improvement of forced expiratory volume in the first second (FEV_1) from baseline after inhalation of salbutamol or positive methacholine bronchial provocation test (PD20 $FEV_1 \leq 1600$ mg) and in accordance with the British Thoracic Society criteria (172).

In paper 1 exclusion criteria were pregnancy, a history of cancer, presence of acute and chronic rhinosinusitis (CRS), and nasal polyposis on otorhinolaryngological examination, previous nasal surgery, and systemic disease with potential affection of the nose, such as granulomatosis with polyangiitis (Wegener's granulomatosis), cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome, and sarcoidosis. In paper 1 a total of 12 asthmatics and 5

controls were excluded. The asthmatics were excluded due to (number in parenthesis): CRS (9) and septum perforation (3). The controls were excluded due to (number in parenthesis): CRS (2) and questionable pulmonary disease (3).

In paper 2 and 3 the exclusion criteria were the presence of acute and chronic rhinosinusitis and nasal polyposis on oto-rhino-laryngological examination and in accordance to the EPOS 2012 criteria (135), pregnancy, previous nasal surgery, systemic disease with potential affection of the nose, such as granulomatosis with polyangiitis (Wegener's granulomatosis), cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome and sarcoidosis, and a history of cancer. In paper 2 a total of 16 asthmatics and 7 controls were excluded and in paper 3 a total of 16 asthmatics and 8 controls were excluded. The asthmatics in paper 2 and 3 were excluded due to (number in parenthesis): CRS (9), septum perforation (3), missing decongested values (1), patient resistant to accept topical xylometazoline (1) and technical artefact AR (2). The controls in paper 2 were excluded due to (number in parenthesis): CRS (2), questionable pulmonary disease (3), and technical artefact AR (1) and alar insufficiency (1). In paper 3 the controls were excluded due to CRS (2), questionable pulmonary disease (3), technical artefact acoustic rhinometry (1), alar insufficiency (1), and missing value (1).

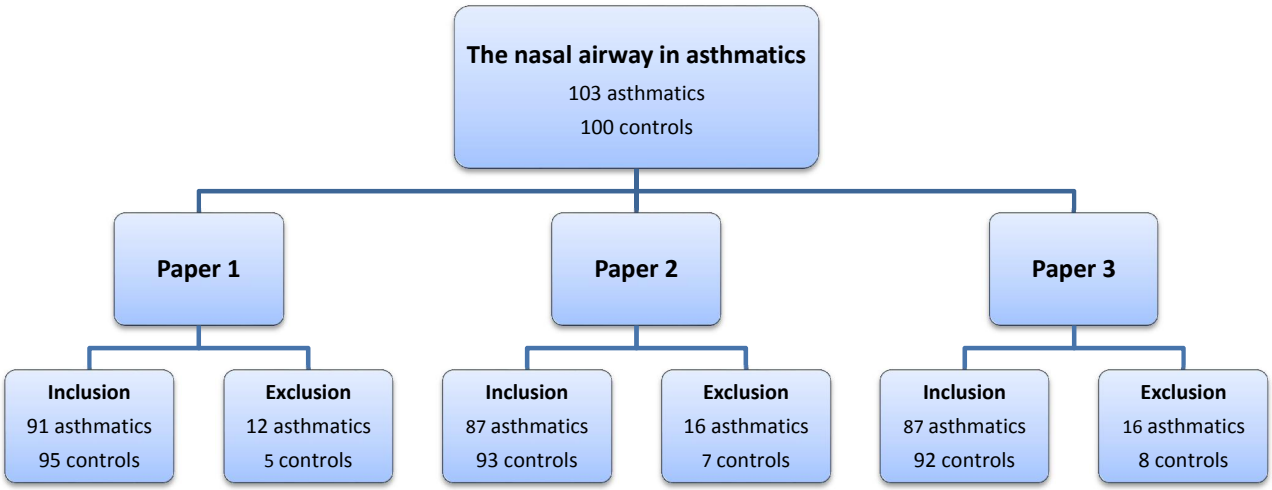

Figure 7. Flow chart over inclusion and exclusion for paper 1, 2 and 3.

3.3 Recordings

All questionnaires used in this thesis are presented in the Appendix.

Visual analogue scale (VAS)

The degree of nasal obstruction, oral breathing, snoring, sleep apnea, nasal discharge/secretions, headache, mid facial pain, rhino-sinusitis, coughing, sneezing, reduced general health, and reduced sense of smell was assessed on a 100 mm Visual Analog Scale (VAS). The endpoints were 0 mm (never) and 100 mm (always).

Quality of life

SNOT-20 was used because it has been translated to Norwegian and validated by Kjærgaard and Steinsvåg. Subjects were asked to grade 20 items on a scale of 0 (no problem) to 5 (problem as severe as can be) on the SNOT-20. The SNOT-20 score for each subject was

defined as the mean value of the response to the 20 items. Furthermore, the SNOT-20 questionnaire was divided into subscales based on the study of Browne et al (173). The first subscale was composed of questions about symptoms related to nose, ear, and face; the second subscale included the questions on psychological issues; and the third subscale addressed sleep function. Questions about cough and waking up tired are separate entities and do not belong to any subscale.

Asthma control questionnaire (ACQ)

Patients were asked to recall how their asthma had been during the previous week and to respond to the symptom (5 questions) and bronchodilator use questions on a 7-point scale (0=no impairment, 6= maximum impairment). In addition the clinic staff scored the FEV_1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions ranging between 0 (totally controlled) and 6 (severely uncontrolled).

Acoustic rhinometry

We used an impulse Acoustic Rhinometer (RhinoMetrics SRE 2100, Rhinoscan Version, Interacoustics, Minneapolis, MN) which was handled by two trained operators throughout the studies in this thesis. Anatomic nose-pieces in two sizes and contact gel between the nose-piece and the nostril were used. The probe was hand held with the subject sitting upright opposite to the investigator holding the breath during the measurements. Recordings were performed according to published protocols (174).

The values obtained by AR represent an average of 3 recordings from the right and left nasal cavity, which were averaged to get an overall mean value due to the variations represented by the nasal cycle. The following measures were recorded; minimal cross sectional area (MCA) in cm^2 from 0 to 3 cm (MCA_{0-3}), 3 to 5.2 cm ($MCA_{3-5.2}$), and 0 to 5.2 cm ($MCA_{0-5.2}$) behind the nostril; nasal cavity volumes (NCV) in cm^3 from 0 to 3 cm (NCV_{0-3}), 3 to 5.2 cm ($NCV_{3-5.2}$), and 0 to 5.2 cm ($NCV_{0-5.2}$) behind the nostril. After the initial

recordings at baseline, the nasal mucosa was decongested with topical xylometazoline (Otrivin 1 mg/ml, Novartis, Basel, Switzerland), two doses given in each nasal cavity, applied in a standardized manner using a hand pump. The mucosa was considered decongested after 10 minutes

Nasal congestion index (NCI)

The effect of topical xylometazoline on MCA, NCV and PNIF was assessed by calculating the nasal congestion index (NCI) (175) for each variable using the following equation: NCI (post xylometazoline value-baseline value)/baseline value. A low NCI indicates minor mucosal congestion as opposed to a high NCI which suggests a high degree of reversible mucosal congestion.

PNIF

Peak nasal inspiratory flow was assessed with a portable PNIF meter (In-check DIAL; Clement Clarke International, Harlow, Essex, UK). The average of three satisfactory maximal nasal inspirations before and after decongestion with topical xylometazoline (Otrivin ® 1 mg/ml) two doses in each nasal cavity was recorded with the patient in the sitting position. Maximum flow registration was limited to 120 l/min. Peak flows exceeding 120 l/min were recorded as 120 l/min.

Skin prick test or specific IgE

Sensitization to house dust mite, cat, dog, horse, timothy grass and birch pollens, mugwort and cladosporium was assessed with either specific IgE measurement (AlaTOP, Diagnostic Products Corporation, Los Angeles, California, USA) or skin prick tests (Soluprick SQ, ALK-Abello, Horsholm, Denmark). Antihistamines were discontinued 4 days prior to skin prick tests. Subjects with typical symptoms of hypersensitivity on exposure to the allergen(s) and positive tests were classified as allergic.

Spirometry

Lung function was assessed by flow volume spirometry (Spirostar USB spirometer, Medikro Oy, Kuopio, Finland) before and 10 minutes after administration of 0.4 mg salbutamol in a spacer (Ventoline, Volumatic, GlaxoSmithKline, Middlesex, UK). The best FEV_1 in liters and percentage of predicted (176) of 3 acceptable attempts before and after salbutamol was recorded, in accordance with international guidelines (177). Predicted normal values were based on reference values of Crapo et al (176).

3.4 Statistics

In study 1 power calculations for inclusion of patients concerning SNOT-20 were done prior to initialization. To obtain 80% power, we needed 100 participants in each group at a significance level of 0.05 (alpha) and given a difference in SNOT-20 of 0.4 between the groups (162). If the difference in SNOT-20 were 0.5 the estimated power was 94%. The data were tested for normal distribution using normal probability plots and continuous variables were presented as mean ± SD. Categorical variables were presented as numbers (%). Differences in mean values were evaluated by independent samples t-test. The correlation between ACQ score and SNOT-20 and between ACQ score and nasal obstruction VAS (NO-VAS) were assessed by linear regression. A p-value of <0.05 was considered to be statistically significant.

In study 2, the data were tested for normal distribution using normal probability plots. The independent samples t-test was used to evaluate differences in mean values in the asthmatic and control groups. Analysis of variance (ANOVA) with the post hoc application of Bonferroni correction was used to assess the effect of allergy status in both asthma and control groups. A p-value of <0.05 was considered to be statistically significant.

In study 3 the level of education was categorized as either basic (≤ 9 years), secondary (10 to 12 years), or tertiary (≥ 13 years), that has been shown to be a good surrogate for socioeconomic status in Norway (178, 179). Subject co-morbidity was defined as the regular use of medication during the last 6 months prior to recruitment for asthma and allergy, pain relief, ischemic heart disease and hypertension, musculoskeletal disease, thyroid disorders, diabetes mellitus, anxiety and depression. Disease status was categorized as cardiovascular disease, other disease and no disease. Smoking status was dichotomized as smoker (current or ever smoked) and nonsmoker, as we did not have precise information about cigarette consumption. NO-VAS was categorized as mild (0-30 mm), moderate (31-70 mm) and severe (71-100 mm) (180). PNIF was used as a continuous variable for linear regression analysis and as an ordinal variable for ordinal logistic regression analysis. For the latter analysis, PNIF was categorized into the following 3 groups: (1) high: ≥ 120 L/min, (2) medium: 90 - 119 L/min and (3) low: 15 - 89 L/min. Of the spirometry variables, FEV_1 is the most robust, and FEV_1 (% predicted) was chosen for linear regression as that is based on height, age, sex and ethnicity of the subject. As there was a strong association between asthma and FEV_1 (% predicted) (t-test, $p<0.001$), we fitted two separate models for PNIF as a continuous variable to avoid multicollinearity. The associations between PNIF and asthma and between PNIF and FEV_1 (% predicted) were modeled with linear regression. Possible confounders such as allergy, other diseases, education, NO-VAS, MCA, weight, height, age, sex and smoking were tested. The model fit was good and assumption of normally distributed residuals was fulfilled. Further, we fitted ordinal logistic regression to assess possible association between VAS (in three categories) and having asthma. PNIF was omitted from the final model as we found the same ratio between having asthma and VAS score when stratified by PNIF group so there was no interaction between PNIF and asthma. The assumption of parallel lines was fulfilled and the model fit was good. The results were expressed as odds ratios (OR) with 95%

confidence intervals (CI). A p-value of <0.01 was considered statistically significant to correct for multiple testing.

All analyses were performed using PASW Statistics, version 18 (paper 1 and 2) and 20 (paper 3) for Windows (SPSS Inc., Chicago, IL, USA).

4 Summary of the results of the papers

4.1 Results paper 1

Both allergic- and non-allergic asthmatics were associated with increased sino-nasal symptoms, reduced sino-nasal QoL, and reduced inspiratory nasal air flow compared to controls

4.2 Results paper 2

We found significantly smaller MCA and NCV in asthmatics than controls and the cross sectional area is at its minimum at 2-3 cm from the nasal orifice in both groups. AR and PNIF measurements are not different in allergic and non-allergic subjects in either group. The effect of xylometazoline is not significantly different between the 2 groups with regard to AR, but there is a significant improvement in PNIF for the asthmatics when assessed by the NCI.

4.3 Results paper 3

We found that PNIF is influenced by an asthma diagnosis and FEV_1 (% predicted), and that asthmatics are more likely to be in a higher NO-VAS category (mild 0-30 mm, moderate 31-70 mm and severe 71-100 mm) which is independent of PNIF group (high, medium and low flow). Other factors associated with PNIF are the degree of nasal obstruction measured both subjectively on a visual analogue scale and objectively with acoustic rhinometry, age and disease status. Thus in patients presenting with nasal obstruction PNIF recordings should be assessed in conjunction with an asthma diagnosis, spirometry and MCA.

5 General discussions

5.1 Methodological considerations

Design

A case-control observational design was used in this study. When all data are collected simultaneously, special caution has to be taken when interpreting the data and especially to establish any relationship between cause and effect. However, case-control studies have made important contributions as instruments for generating hypothesis. If several case-control studies point in the same direction this may have some weight in causality issues as well.

Subjects

To ensure external validity the selection of a representative sample is always important. In this thesis all asthmatics were recruited from the Department of Thoracic Medicine, St. Olavs Hospital, Trondheim University Hospital. This is a tertiary referral hospital for three counties of Møre and Romsdal, Sør-Trøndelag and Nord-Trøndelag with a total of 695,000 inhabitants and a secondary referral hospital for the population of Sør-Trøndelag with 302,000 inhabitants. Although a tertiary hospital, all asthmatics were resident in Trondheim. One might argue that some of the asthmatics recruited were severely affected by their disease. The mean ACQ score of the asthmatics was 1.6 (SD = 1, 95% CI, 1.4-1.8) (181) and according to Juniper et al. (182) an ACQ score of 1.50 or greater indicate that there is an 88% chance that the asthma is not well-controlled. This might represent a self-selection bias where asthmatic patients who experienced more symptoms were most likely to respond to the research invitation.

The non-asthmatics were individuals recruited from businesses near by the hospital or patients attending the hospital for other illnesses, which were thought not to affect the upper and lower airways. Those who chose to participate might have been more interested in their

health than the general population. Ideally, controls should have been asked to participate from a random selection from a national registry (e.g. Norwegian Tax Administration/Folkeregisteret), but this was thought to be difficult in our small clinical study, due to administrative conditions. Still we regard measurements on the controls to be representative for the general population.

Methods

To ensure internal validity the selection of proper instruments for performing the tests is important. In the subjective assessment at least two biases could affect the outcome variables. Firstly, recall biases may influence the pattern of response and cause over- or underestimation of symptoms and questions of QoL. Grading of the VAS symptoms were during the last week, for the SNOT-20 questions during the last two weeks and for the ACQ questions during the last week prior to inclusion, and bias were sought minimalized due to a short period of recall. Secondly, response biases reflect an intentionally incorrect response, and could be relevant in smokers who may intentionally underestimate their smoking. In paper one, 9 % of asthmatics and 13 % of controls were current smokers, in paper two, 10 % of asthmatics and 13 % of controls were current smokers, and in paper three, 13 % of asthmatics and 23 % of controls were current or ever smokers. The % smokers in the 3 studies changed as the number of participants and the dichotomizing for current smoking versus current or ever smokers in these studies differed. Smoking is generally known to be underreported.

Objective assessment of the nasal airway is associated with some uncertainty due to the nasal cycle. AR and PNIF only provide snapshots of nasal geometry and flow and say nothing about dynamics like the resistance. Also, PNIF gives a global characterization of the nasal air flow, but does not give any information about the separate nasal passages or nasal

airflow under resting conditions. Other modalities like rhinomanometry, CFD and PIV could have added extra knowledge to this thesis. CFD and PIV would have been very expensive and time consuming for the nearly 200 patients included in this thesis. Multiple testing by repeated recordings over several hours could allow a more comprehensive assessment of the mucosal changes but would be very time consuming in the clinical setting.

Decongestion with topical xylometazoline was performed in a standardized manner with the administration of two doses of xylometazoline in each nasal cavity (169). Its pharmacological effects on the nose have been examined in previous studies (133, 183). Several factors could affect and decrease the decongestive response, such as inflammatory conditions, differences in sensitivity of the mucosa, differences in delivery of the agent due to anatomical conditions, and stimuli of other triggers, e.g. medications, rhinitis medicamentosa etc. (184).

To exclude the possible confounding of seasonal allergy none of the study participants were included during the pollen season. Antihistamines used for perennial allergy were discontinued 4 days prior to skin prick tests.

Spirometry was performed under standardized conditions (177), and individual spirograms were acceptable if they were free from artefacts such as cough during the first second of exhalation, glottis closure that influenced the measurement, early termination or cut-off, effort that was not maximal throughout, leak and an obstructed mouthpiece. Further they had to show satisfactory exhalation (duration of $\geq$ 6 seconds) and an extrapolated volume $<$ 5% of forced vital capacity or 0.15 liter, whichever is greater.

Statistics

The number of participants included in study 1 was based on power calculations. For the outcome variables in study 2 and 3 we did not perform power calculations.

Although correlation coefficients are frequently applied to estimate the strength of an association between variables (185), it cannot replace regression which provide much more detailed information (186), and thus multiple regression analysis was used in study 3 to assess the association between a diagnosis of asthma and of lung function on PNIF when adjusted for possible confounders.

5.2 Evaluation of results

The main finding of this thesis is that asthmatics have a smaller nasal airway than controls measured by cross-sectional area and volume, and that the sensation of nasal obstruction in asthmatics is different from controls despite being in the same PNIF group. We also found increased nasal symptoms and decreased sino-nasal quality of life in asthmatics compared to controls. Moreover, the nasal airflow measured by PNIF is significantly lower in asthmatics than controls, and we found that asthma, FEV_1 (% pred), degree of nasal obstruction measured both subjectively on a VAS and objectively with AR, age and disease status are other factors which influence nasal airflow. Further, in all three studies, we found no difference in major outcome variables between asthmatics and controls with and without allergy.

The smaller nasal airway of asthmatics

What I consider the most important contributions of this thesis to clinical and scientific medicine are the documentation of a geometrically smaller nasal airway in asthmatics than in controls. The smaller size of the nasal airway in terms of nasal cavity volume and minimal cross sectional areas is previously studied by two research groups (24, 187) where our findings are in accordance with that of Hellgren et al.(24).

One critical issue that needs to be addressed here is to what extent the smaller airways is something that asthmatics are born with, or to what extent it is acquired. To my knowledge, the data necessary to answer this question does not currently exist. However, it has been shown by X-ray that asthmatic children have a reduced epipharyngeal airway compared to controls (111). Another issue is whether the reduction in nasal airway geometry in asthmatics compared to non-asthmatics is caused by the reduced size of the bony and cartilaginous boundaries of the nose or is due to mucosal abnormalities. There are conflicting results concerning structural changes such as basal membrane thickening in the nasal mucosa of patients with asthma (188, 189). In the former study they found no difference, whereas in the latter they found that the thickness of the basal membrane in the corticosteroid-dependent and untreated asthmatics was significantly increased compared with that in control subjects. Further, nasal mucosal inflammation with eosinophilic infiltration has been reported in asthmatic subjects without rhinitis (190). Dhong et al (191) found thickening of the basement membrane, goblet cell hyperplasia and eosinophil infiltration to be more prominent when examining the mucosa of the sinuses in asthmatics compared to non-asthmatics.

Another speculation is whether the asthmatics turn into oral breathers at an earlier stage than non-asthmatics due to the smaller nasal airway geometry. Both the smaller airways and the increased experience of nasal blockage may increase the tendency of mouth breathing that in turn deteriorates the physiological condition of the air that enters the lungs.
Given that asthmatics, due to nasal anatomy or experience of a blocked nose, prematurely turn to oral breathing, the flow in the nasal airways will consequently decrease. There are examples illustrating that the short cut or immobilization of organs lead to changes such as atrophy and functional loss. This is the case in patients who have undergone a total laryngectomy where the nose is excluded from the respiration and thus changes of the physiological functions occur. It is found that the dimensions of the nasal cavity measured by

acoustic rhinometry are found to be significantly and permanently reduced 1 year after total laryngectomy, attributable to the fact that they no longer use their noses (192).

The different perceptions of nasal patency

The second most important finding of this thesis is the documentation of different perceptions of nasal patency between asthmatics and controls. The opportunity to measure nasal patency objectively, and to get a true correlate to the patient's subjective apprehension of nasal obstruction is still one of the core challenges in rhinology. We found that the experience of nasal obstruction was 19-fold greater in asthmatics compared to non-asthmatics despite being in the same PNIF group. One can speculate whether an increased number of sensory sodium channels and sensory- and secretomotor nerve fibers in the nasal mucosa, that has been reported in allergic and non-allergic rhinitis (193, 194), may account for the increased perception of nasal obstruction. The level of perceived breathing difficulty has been reported to be more important than the applied nasal load for the increased propensity of asthmatics to switch to oronasal breathing, compared with non-asthmatic subjects (86). Premature switching to oronasal breathing results in inadequate conditioning and filtering of the inspired air, with drying and cooling of the lower airways, subsequent release of inflammatory cell mediators and development of an asthmatic response (195) and asthma chronicity.

A patient's perception of nasal obstruction may depend on factors beyond the physical caliber of the nose. Patients with objectively measured, longstanding nasal obstruction (e.g., cartilaginous or bony obstruction) may become desensitized to the severity of obstruction over time and rate themselves as having no problem with nasal obstruction, in contrast to patients with no objective nasal obstructions who complains about blocked noses. Studies have shown that the inhalation of menthol, certain volatile oils, camphor, eucalyptus or

vanilla causes a perceived increase in nasal patency without a corresponding reduction in nasal airway resistance (108, 196). Conversely, it has been shown that local anesthesia of the nasal vestibule produced sensations of nasal obstruction without change in the nasal airway resistance (197). Perhaps greater focus upon nasal breathing as a mean for patients with obstructive lung disease to better master their lower airway disease would be beneficial. It has been shown in randomized trials that asthma patients may benefit from a controlled breathing pattern as in yoga (198, 199) although a recent review showed no evidence for effects of yoga compared with sham yoga or breathing exercises (200).

The increased nasal symptoms and decreased sino-nasal quality of life in asthmatics compared to controls is in line with data reported by Hens and coworkers (23). They found that allergic asthmatics, non-allergic asthmatics and patients with chronic obstructive pulmonary disorder reported more nasal symptoms than their respective control subjects, had a higher SNOT-22 score and presented more mucosal abnormalities in the nose.

Allergy and the unified airway

Both allergic and non-allergic asthmatics were associated with increased sinonasal symptoms, reduced sino-nasal QoL, reduced inspiratory nasal air flow, and significantly smaller minimum cross sectional area and nasal cavity volume compared to controls. Allergy was not a significant confounder when we investigated the effect of a diagnosis of asthma and of lung function on PNIF. It is previously reported that both allergic and non-allergic asthma patients had more nasal symptoms and mucosal abnormalities in the nose and had elevated levels of inflammatory markers in nasal secretions (23). Further, the COPSAC study (201) examined a birth cohort of children born to mothers with a history of asthma, and they found that non-allergic rhinitis was twice as common as allergic rhinitis, which is different from studies of adults where the proportion of subjects with non-allergic rhinitis is one third to one

fourth of the rhinitis population (202, 203). Thus nasal inflammation has to be taken in to account in the diagnostic and therapeutic approach of all asthmatic patients, beyond the scope of allergic inflammation (23, 204).

PNIF and pulmonary function

We also found that PNIF is influenced by an asthma diagnosis and FEV_1 (% predicted). Other factors associated with PNIF are the degree of nasal obstruction measured both subjectively on a visual analogue scale, objectively with acoustic rhinometry, and age as well as disease status. Previous studies show a positive correlation between upper airway patency measured by PNIF and lower airway function measured by PEF in adults (205) and in children and adolescents (206). Moreover, an increase in PNIF with a concomitant increase in FEV_1 (% predicted) has been reported in allergic rhinitis after sauna treatment (207).

Thus in patients presenting with nasal obstruction, PNIF and AR should be performed in conjunction with considerations about concomitant asthma and spirometry.

5.3 Limitations

One limitation of this thesis is that the PNIF meter we used has a scale from 15-120 L/min. We should ideally have used the PNIF meter with a scale from 30-370 L/min which gives the full range of nasal inspiratory flow. Nevertheless, the manufacturer, Clement Clarke International confirms that both instruments are calibrated identically, with a performance accuracy of ± 10 % or 10 l/min (whichever is greater) and repeatability of ± 5 l/min. Thus the results in the range 15-120 l/min will be similar for either instrument and the In-Check Dial is used in other studies evaluating nasal obstruction (175, 180, 208-210). A normal value of greater than 120 L/min is commonly used (211) and PNIF values above 120 L/min are only of minor clinical interest because such high peak flows generally exclude nasal obstruction (180,

212). PNIF in excess of 120 L/min was recorded as 120+ L/min, and in paper 3, for the purpose of statistical analysis, set to 120 L/min. Regarding the individuals with PNIF> 120 L/min (5 asthmatics and 21 controls) in paper 3, we performed sensitivity analysis where these individuals were omitted which confirmed our original findings. Also, the purpose of the study in paper 3 was not to give normative data for PNIF in asthmatics, but to show which factors influence the measurement and interpretation of PNIF in patients with asthma. I believe that we have been able to do that despite the limitations of the scale of the PNIF meter.

Another limitation is that SNOT-20 lacks questions about nasal obstruction and loss of smell, which are important aspects in the evaluation of sino-nasal QoL. Further, spirometry and PNIF are highly effort dependent methods. Reliability depends on cooperation, instructions, and standardized techniques, and close attention was paid to these elements for the spirometry, AR and PNIF recordings.

6 Conclusions

Asthmatics need to be met with the understanding of the concept of the unified airway, both in the practice of pulmonary- and otorhinolaryngological medicine. The ability to translate the principles of the unified airway into successful strategies for diagnosis and treatment can lead to improved patient outcomes and quality of life in asthmatics.

In analogy with the proposed specific aims, our main conclusions are as follows:

-Asthmatics have a smaller nasal airway measured by MCA and NCV compared to controls.

-Asthmatics have an increased sensation of nasal obstruction compared to controls.

-Asthmatics have increased sino-nasal symptoms and reduced sino-nasal QoL compared to controls

-Asthmatics have reduced PNIF compared to controls, but special care has to be taken when interpreting PNIF values in patients with asthma or reduced FEV_1 (% pred).

-The above findings are irrespective of allergy in both asthmatics and controls.

7 Future studies

The goal of future studies concerning The Unified Airway would be to answer the essential question: Should the potential of nasal- and sinus disease in asthmatics be investigated and treated more extensively, both medically and surgically with the defined goal of promoting nasal breathing, and does this have any influence on the long-term management of their asthma?

Several investigations have to be carried out to answer this question, and they should include:

-Medical interventions on the nose and how this affects the lungs.

-Surgical interventions on the nose and how this affects the lungs.

-The follow up of a birth cohort with subjective and objective methods of the nose and relate to the development of asthma. Surgical interventions such as adenoidectomy and tonsillectomy in childhood and the impact on asthma could also be addressed.

-The results of paper 2 indicate a need for nasal biopsy studies in asthmatics to further understand the structural changes of the nasal mucosa in asthmatic patients compared to the nasal mucosa of healthy individuals.

-PNIF is a very commonly used measurement tool for nasal airflow, and there is a need to perform similar studies of PNIF and pulmonary function of patients with other pulmonary diseases than asthma.

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9 Appendix

Laminar flow occurs when a fluid, i.e. a liquid or gas, flows in layers, with no disruption between the layers. The motion of the fluid particles is very orderly with no particle exchange between the layers. Turbulent flow is characterized by a random and disordered pattern of flow where the fluid particles exchange momentum between regions of different velocities creating eddies of various scales. Compared to laminar flow over a flat surface, turbulent flow creates a larger drag, i.e. a larger force on the surface dragging in the flow direction.

Flow dynamics can be characterized by the **Reynolds number**, which expresses the ratio of inertial and viscous forces. Laminar flow occurs at low Reynolds numbers whereas turbulent flow occurs at high Reynolds numbers. For flow in a pipe or channel, the Reynolds number, Re, is defined by $Re = \rho V d/\mu$ where ρ = fluid density, V = mean fluid velocity, d = hydraulic diameter of the conduit (4x cross sectional area/wetted perimeter), μ = dynamic fluid viscosity. For a filled circular pipe, d is the pipe diameter.

The physical principles of fluid flow are based on well-known laws of physics, namely the conservation of mass, Newton's second law and the first law of thermodynamics. **Poiseuille's law** states that the volumetric flow rate of a fluid flowing in a circular pipe is directly proportional to the difference in pressure at inlet and outlet times the radius of the pipe raised to the fourth power. The volumetric flow rate is inversely proportional to the length of the pipe. $\Delta P = 8\mu LQ/(\pi r^{4)}$, therefore $Q = \pi r^4 \Delta P/(8\mu L)$

Where ΔP = the pressure loss (P inlet – P outlet), μ = the dynamic viscosity of the fluid, L = the length of the pipe, Q = the volumetric flow rate, r = is the radius of the pipe, π = mathematical constant ≈ 3.14

Bernoulli's principle states that the total pressure in an incompressible inviscid flow is constant along a streamline. The total pressure, which equals the sum of the static pressure and the dynamic pressure, remains constant in the whole flow field, if the incompressible inviscid flow is irrotational.

$p_0 = p + q$

p_0 = total pressure, p = static pressure, q = dynamic pressure

The dynamic pressure can be expressed as $1/2\rho V^2$ where ρ = density and V = modulus of the fluid velocity, hence $p_0 = p + 1/2\rho V^2$

An increase in the velocity of a fluid occurs simultaneously with a decrease in the static pressure and vice versa.

The **Venturi** effect is the reduction in static fluid pressure that results when a fluid is accelerated through a constricted section of a pipe, assuming the flow to be incompressible and inviscid. In the nose, the Venturi effect can be applied in the nasal valve region where the velocity of the inspired air increases, with a resulting drop in static pressure and subsequently inward movement of the compliant lateral nasal wall.

Navn: Diagnose:

Alder:

VAS-skjema for nese-bihule-symptomer

Høyde: Vekt: BMI: Allergi: Astma: Yrke:

Antall sigaretter om dagen: I hvor mange år:

Tett nese	Helt åpen	———	Helt tett
Munnpusting	Aldri	———	Alltid
Snorking	Aldri	———	Alltid
Pustepauser under søvn	Aldri	———	Alltid
Renning fra nesen	Aldri	———	Alltid
Hodepine	Aldri	———	Alltid
Smerter i tenner/midtannsikt	Aldri	———	Alltid
Bihulebetennelse	Aldri	———	Alltid
Hoste	Aldri	———	Alltid
Nysing	Aldri	———	Alltid
Nedsatt allmenntilstand	Aldri	———	Alltid
Nedsatt luktesans	Aldri	———	Alltid

SINO-NASAL OUTCOME TEST

Nedenfor finner du en liste over symptomer og sosiale/følelsesmessige konsekvenser av din neselidelse. Vi vil gjerne vite mer om disse problemene, og vil være takknemlig hvis du vil besvare nedenstående spørsmål etter beste evne. Det er ikke noen riktige eller feile svar, og bare du kan gi oss den rette informasjonen. Vær vennlig å gradere dine problemer med utgangspunkt i situasjonen de **siste to uker**. Takk for at du vil delta.

A. Med utgangspunkt i hvor uttalt problemet er når det oppstår og hvor ofte det opptrer, bes du angi hvor "ille" det er ved at markere med sirkel det tallet som best svarer til det du føler, ut fra denne skala →→→→→→→	Ingen problemer	Meget milde problemer	Milde eller lette problemer	Moderate problemer	Kraftige problemer	Problemene er så kraftige som det er mulig	Viktigste punkter (5)
1. behov for å pusse nese							☐
2. nysing							☐
3. rennende nese							☐
4. hoste							☐
5. renning bak i svelget							☐
6. tykt sekret fra nesen							☐
7. tetthet i ørene							☐
8. svimmelhet							☐
9. øresmerter							☐
10. smerter/trykk i ansiktet							☐
11. vanskelig å falle i søvn							☐
12. våkner om natten							☐
13. mangel av god nattesøvn							☐
14. trøtt når du våkner							☐
15. kraftesløshet							☐
16. nedsatt produktivitet							☐
17. nedsatt konsentrasjon							☐
18. frustrert/rastløs/irritabel							☐
19. trist							☐
20. flau							☐

↑
↑
↑

B.
Vær vennlig å markere de viktigste punktene som påvirker din helsetilstand (maksimum 5 punkter)

KONTROLLSKJEMA FOR ASTMA © PASIENTIDENTIFIKASJON:_____

(NORWEGIAN FOR NORWAY) DATO:_____

Vennligst svar på spørsmålene 1-6.

Sett en ring rundt tallet for det svaret som best beskriver hvordan du har hatt det den siste uken.

1. Hvor ofte har du vanligvis **våknet** om natten **på grunn av astmaen** i den siste uken?
   - 0 Aldri
   - 1 Nesten aldri
   - 2 Noen få ganger
   - 3 Nokså mange ganger
   - 4 Mange ganger
   - 5 Svært mange ganger
   - 6 Umulig å sove på grunn av astmaen

2. Hvor **sterke var astmasymptomene** i den siste uken vanligvis **når du våknet** om morgenen?
   - 0 Ingen symptomer
   - 1 Svært milde symptomer
   - 2 Milde symptomer
   - 3 Moderate symptomer
   - 4 Nokså sterke symptomer
   - 5 Sterke symptomer
   - 6 Meget sterke symptomer

3. Hvor **hemmet var du** generelt sett av astmaen **i dine gjøremål** i den siste uken?
   - 0 Ikke hemmet i det hele tatt
   - 1 Svært lite hemmet
   - 2 Litt hemmet
   - 3 Moderat hemmet
   - 4 Meget hemmet
   - 5 Svært hemmet
   - 6 Totalt hemmet

4. Hvor mye **kortpustethet** opplevde du generelt sett i løpet av den siste uken på grunn av astmaen?
   - 0 Ingen
   - 1 Svært lite
   - 2 Litt
   - 3 Moderat
   - 4 Nokså mye
   - 5 Mye
   - 6 Svært mye

5. Hvor stor del av tiden hadde du **piping i brystet** generelt sett i løpet av den siste uken?

0 Ikke noe av tiden
1 Nesten ikke noe av tiden
2 Litt av tiden
3 En del av tiden
4 En god del av tiden
5 Mesteparten av tiden
6 Hele tiden

6. Hvor mange **sprayer/inhalasjoner med hurtigvirkende astmamedisin** (f.eks. Ventolin/Bricanyl/Berotec) har du vanligvis brukt hver dag den siste uken?

(Vennligst be om hjelp dersom du er usikker på hvorledes du skal svare på dette spørsmålet.)

0 Ingen
1 1 - 2 sprayer/inhalasjoner de fleste dagene
2 3 - 4 sprayer/inhalasjoner de fleste dagene
3 5 - 8 sprayer/inhalasjoner de fleste dagene
4 9 - 12 sprayer/inhalasjoner de fleste dagene
5 13 - 16 sprayer/inhalasjoner de fleste dagene
6 Mer enn 16 sprayer/inhalasjoner de fleste dagene

Fylles ut av en ansatt ved klinikken

7. FEV_1 pre-luftveisdilitator: .....

FEV_1 forventet:.....

FEV_1 % forventet:.....
(Noter reelle verdier på de prikkede linjene og før opp FEV_1 % forventet i neste kolonne)

0 > 95% forventet
1 95 - 90%
2 89 - 80%
3 79 - 70%
4 69 - 60%
5 59 - 50%
6 < 50% forventet

NESE-BIHULE RELATERT LIVSKVALITET HOS ASTMATIKERE

Generelle helseopplysninger

Dato for utfylling: _____ Pasient nr. _____

1: Alder _____ år 2: Høyde _____ cm 3: Vekt: _____ kg

4: Kjønn ☐ Kvinne ☐ Mann

5: Har du pollenallergi? ☐ Ja ☐ Nei

6: Har du dyreallergi? ☐ Ja ☐ Nei

7: Har du middallergi? ☐ Ja ☐ Nei

8: Bruker du medisiner? ☐ Ja ☐ Nei Hvis ja, hvilke:_____
_____

9: Har du andre
sykdommer? ☐ Ja ☐ Nei Hvis ja, hvilke:_____
_____

10: Røyker du? ☐ Ja ☐ Nei Hvis ja, hvor mange pr dag ☐☐ sigaretter
Hvor lenge har du røkt? ☐☐ år

Paper 1

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Paper 2

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Nasal flow, volumes, and minimal cross sectional areas in asthmatics

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KEYWORDS
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Sinusitis;
Acoustic rhinometry;
Peak nasal inspiratory flow

Summary
Background: The Unified Airways hypothesis suggests an involvement of the upper airways in asthma. Critical parameters of the nasal airway can be quantified objectively with acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF).
Objective: We aimed to investigate nasal airway patency in asthmatics compared to non-asthmatic controls. Nasal volume, cross sectional area and flow were measured using acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF) in 87 asthmatics and 93 non-asthmatic controls before and after decongestion with xylometazoline. Nasal congestion index (NCI) was calculated, and allergy status was assessed by skin prick test or specific IgE.
Results: We found significantly smaller minimum cross sectional area and nasal cavity volume in asthmatics than controls, and the cross sectional area is at its minimum at 2–3 cm from the nasal orifice in both groups. AR and PNIF measurements are not different in allergic and non allergic subjects in either group. The effect of xylometazoline is not significantly different between the 2 groups with regard to AR, but there is a significant improvement in PNIF for the asthmatics when assessed by the NCI.

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Conclusion: The present study demonstrates a significantly smaller nasal airway when assessed by minimum cross sectional area and nasal cavity volume in asthmatics than controls, and these findings apply to asthmatics and controls irrespective of allergy status.

Introduction

The Unified Airways hypothesis suggests an involvement of the upper airways in asthma [1—3]. Rhinitis typically precedes the development of asthma and can contribute to unsatisfactory asthma control. Nasal symptoms, airflow, and markers of inflammation directly correlate with lower airway involvement [4]. In both rhinitis and asthma, an inflammatory cell infiltrate with subepithelial oedema is present in the mucosa [5]. Unlike the lower airway, the nasal mucosa contains venous sinusoids that undergo periodic congestion and decongestion (the nasal cycle) that are important for regulation of airflow, humidification and warming of the inspired air. Nasal obstruction may be indicative of structural deformities, infections and inflammatory conditions in the nose, and is frequently reported by asthmatics [6]. Their lack of nasal patency may also be due to factors such as mucosal congestion and changed perception of flow.

Critical parameters of the nasal airway can be quantified objectively with acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF) [7,8]. While the former measures internal nasal volume and minimum cross-sectional areas, the latter measures the maximum nasal inspiratory flow during forced inspiration. The Nasal Congestion Index (NCI) has been suggested as a useful instrument for the evaluation of nasal obstruction by quantifying the effect of topical decongestants applied on the nasal mucosa [9]. There are few studies that have used these tools to investigate the relative contribution of subepithelial oedema and congestion of the venous sinusoids in asthmatics. Hellgren et al. [10] demonstrated increased nasal mucosal swelling in asthmatics compared to healthy controls.

In this study, we measured nasal volume, cross sectional area and flow using AR and PNIF, and assessed the effect of xylometazoline using the NCI in order to further elucidate the role of oedema and congestion in the nasal mucosa of asthmatics.

Methods

Subjects

The study consisted of 87 patients with asthma, and they were recruited from the out-patients' clinic at the Department of Lung Medicine, St Olavs Hospital, University Hospital of Trondheim. The asthma diagnosis was based on the presence of typical asthma symptoms, with either $\geq$12% and $\geq$200 ml improvement of forced expiratory volume in the first second (FEV_1) from baseline after inhalation of salbutamol or positive methacholine bronchial provocation test (PD20 $FEV_1 \leq 1600$ μg) and in accordance with the British Thoracic Society criteria [11].

Ninety-three non-asthmatic controls were mostly recruited from the out-patients' clinic of Department of Otolaryngology, Head and Neck Surgery, St Olavs Hospital, University Hospital of Trondheim, among patients with disorders not affecting the upper airways (e.g. external otitis, and skin diseases in the ENT area). Some controls were also randomly invited from nearby businesses with all types of employments, from manual labour to skilled work. The sample, allergy status, questionnaires and additional recordings were based on a database that has previously been described [6]. Exclusion criteria were the presence of acute and chronic rhinosinusitis and nasal polyposis on oto-rhino-laryngological examination and in accordance to the EPOS 2012 criteria [12], pregnancy, previous nasal surgery, systemic disease with potential affection of the nose, such as Wegener's granulomatosis, cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome and sarcoidosis, and a history of cancer. For the NCI we analyzed 85 patients with asthma and 93 non-asthmatic controls. The missing values were discarded because of one patient with missing decongested values and one patient was resistant to accept topical xylometazoline. The study was approved by the Regional Committee for Medical Research Ethics, and conducted according to the Helsinki Declaration. Written informed consent was obtained.

AR

AR is a sonic echo technique which was used to measure the nasal volumes and minimal cross sectional areas. Nasal passage volumes are calculated from contiguous cross-sectional values.

The measurements were made with an impulse acoustic rhinometer (RhinoMetrics SRE2100, Rhinoscan version 2.5, built 3.2.5.0; Interacoustics, Minneapolis, MN) by two trained operators throughout the study. The probe was hand held with the subject sitting upright and opposite to the investigator. An appropriate anatomic nose adaptor and contact gel between the nose adaptor and the nostril were used, and measurements were made during a breath hold.

Recordings were performed according to published protocols [13]. Briefly, three satisfactory recordings were made from each nasal cavity. The values for each nasal cavity were averaged. Due to the variations represented by the nasal cycle, the sum of the two averages was divided by 2 to obtain the minimal cross sectional area (MCA, cm^2) and nasal cavity volume (NCV, cm^3). The rhinometer was programmed to calculate the MCA_{0-3} and $MCA_{3-5.2}$, and NCV_{0-3} and $NCV_{3-5.2}$, defined as MCA and NCV at 0—3 cm and 3—5.2 cm, respectively from the nasal orifice. $MCA_{0-5.2}$ is the minimum cross sectional area at 0—5.2 cm from the nasal orifice. $NCV_{0-5.2}$ is the sum of NCV_{0-3} and $NCV_{3-5.2}$.

After visual inspection of the rhinometric curves, the rhinometer was reprogrammed to calculate MCA_{0-2} and

MCA_{2-4}, and NCV_{0-2} and NCV_{2-4}, defined as 0–2 and 2–4 cm, respectively from the nasal orifice. MCA_{0-4} is the minimum cross sectional area at 0–4 cm from the nasal orifice. NCV_{0-4} is the sum of NCV_{0-2} and NCV_{2-4}.

PNIF

Peak nasal inspiratory flow was assessed with a portable PNIF meter (In-check DIAL; Clement Clarke International, Harlow, Essex, UK). The average of three satisfactory maximal nasal inspirations with the patient in the sitting position was recorded.

Maximum flow registration was limited to 120 l/min. Peak flows exceeding 120 l/min were recorded as 120 l/min.

Nasal decongestion

After baseline recordings of AR and PNIF, the nasal mucosa was decongested with two sprays of topical xylometazoline (OtrivinVR 1 mg/ml, Novartis, Basel, Switzerland) applied in a standardized manner with a hand pump to each nasal cavity. Recordings of AR and PNIF were repeated after 10 min.

NCI

The effect of topical xylometazoline on MCA, NCV and PNIF was assessed by calculating the Nasal Congestion Index [9] for each variable using the following equation: NCI = (post xylometazoline value − baseline value)/baseline value.

A low NCI indicates minor mucosal congestion as opposed to a high NCI which suggests a high degree of reversible mucosal congestion.

Allergy

Sensitization to house dust mite, cat, dog, horse, timothy grass and birch pollens, mugwort and cladosporium was assessed with either specific IgE measurement (AlaTOP, Diagnostic Products Corporation, Los Angeles, California, USA) or skin prick tests (Soluprick SQ, ALK-Abello, Horsholm, Denmark). Antihistamines were discontinued 4 days prior to skin prick tests. Subjects with typical symptoms of hypersensitivity on exposure to the allergen(s) and positive tests were classified as allergic.

Statistics

The data were tested for normal distribution using normal probability plots and presented as mean, standard deviation (SD) or 95% confidence interval (95% CI). The independent samples *t* test was used to evaluate differences in mean values in the asthmatic and control groups. Analysis of variance (ANOVA) with the post hoc application of Bonferroni correction was used to assess the effect of allergy status in both asthma and control groups. A *P*-value of <0.05 was considered to be statistically significant.

Table 1 Patient demographics.

	Asthmatics, $N = 87$	Controls, $N = 93$
Mean age, years (range)	43.7 (19–64)	44.0 (20–65)
Mean BMI, kg/m^2 (SD)	26.8 (5.0)	25.2 (3.3)
Gender, Male, *n* (%)	36 (41)	41 (44)
Allergy, *n* (%)	52 (60)	20 (22)
Smoking, *n* (%)	9 (10)	12 (13)

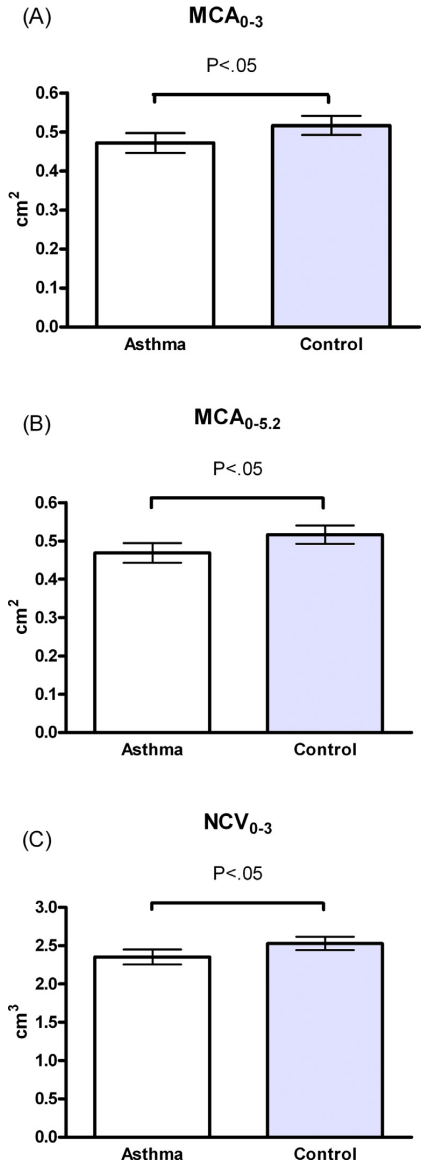

Figure 1 MCA_{0-3} (A), $MCA_{0-5.2}$ (B) and NCV_{0-3} (C) in the asthmatic patients (white bars) and controls (grey bars). Values presented as mean, 95% CI. Abbreviations: MCA = minimum cross sectional area; NCV = nasal cavity volume; $_{0-3}$ = 0–3 cm behind the nasal orifice; $_{0-5.2}$ = 0–5.2 cm behind the nasal orifice.

All statistical analyses were performed using PASW Statistics, version 18 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The demographic data are presented in Table 1. The mean (95% CI) baseline FEV_1 was significantly lower in asthma patients than controls [2.79 (2.61–2.97) vs 3.46 (3.26–3.65) l, $P < 0.001$].

Rhinometry measurements

Data on rhinometric variables at baseline and after topical xylometazoline, calculated as the NCI, are presented in Table 2.

MCA_{0-3}, $MCA_{0-5.2}$ and NCV_{0-3} were significantly lower in asthmatics than in controls (Fig. 1). In the asthma group the MCA for the whole nasal airway ($MCA_{0-5.2}$) was located in the anterior region (MCA_{0-3}) in 95% and more posteriorly ($MCA_{3-5.2}$) in 5% of subjects. In the control group the $MCA_{0-5.2}$ was located in the anterior region (MCA_{0-3}) in 98% and more posteriorly ($MCA_{3-5.2}$) in 2% of the subjects. MCA_{0-2}, MCA_{2-4}, MCA_{0-4} and NCV_{0-2} were significantly lower in asthmatics than in controls (data not shown). The lowest value of the MCA was located at 2–4 cm from the nasal orifice in 59 and 61% of asthmatics and controls, respectively.

NCI was not significantly different between the groups.

Inspiratory flow

The mean (95% CI) PNIF was significantly lower in the asthma group compared to the control group [84 (78–89) vs 102 (98–106) l/min, $P < 0.001$].

The effect of xylometazoline was significantly greater in asthmatics than in controls (Table 2).

Allergy

AR variables and PNIF were not significantly different in asthmatics and controls when analyzed by allergy status (Fig. 2).

Discussion

This study demonstrates that the nasal airway, when assessed by cross sectional area and volume, is significantly smaller in asthmatics than controls, and that the cross sectional area is at its minimum at 2–3 cm from the nasal orifice in both groups. The NCI with regard to AR measurements is not significantly different between the two groups, but there is a significant improvement in NCI for PNIF in the asthmatics. AR and PNIF measurements are not significantly different in allergic and non allergic subjects in either group.

MCA and NCV in asthmatics have been studied previously by two other groups [10,14]. Our finding of a lower MCA at 0–4 cm and NCV at 0–3 cm is in accordance with that of Hellgren et al. They found a decrease in the cross-sectional area at 4 cm and in the volume between 3.3 and 4 cm in the asthma group compared with healthy controls. In contrast, Wålinder et al. did not find any significant difference in minimum cross sectional area and intranasal volume measured between 0 and 5.2 cm in 41 asthmatics and healthy controls.

The location of the MCA in both asthmatics and controls appears to correspond with the location of the internal nasal valve. The latter consists of 4 distinct compartments of airflow resistors: two structural – the cartilaginous termination of the nasal vestibule and the bony entrance to the cavum, and two mucovascular compartments – the inferior turbinate and the septal erectile body, both characterised by numerous venous sinusoids [15]. The magnitude of airflow is determined by the shape and dimensions of these anatomical–physiological narrowings and by airflow velocity [16]. In the present study, it is unlikely that the reduced nasal patency in asthmatics is due to congestion of the venous sinusoids. The decongestive effect of xylometazoline is achieved by vasoconstriction of the nasal venous sinusoids via stimulation of α-2 receptors [17], and there was no significant difference in the NCI for MCA and NCV between the two groups. Thus, the most likely explanation for the differences in nasal patency is the presence of an inflammatory cell substrate, subepithelial oedema and fibrous tissue in those with asthma which is not influenced by decongestive measures. Nasal mucosal inflammation with eosinophilic infiltration has been reported in

Table 2 Acoustic rhinometry and peak nasal inspiratory flow recordings at baseline and nasal congestion index.

Measurement level	Acoustic rhinometry			Nasal congestion index		
	Asthmatics ($N = 87$)	Controls ($N = 93$)	P	Asthmatics ($N = 85$)	Controls ($N = 93$)	P
MCA_{0-3}	0.47 (0.12)	0.52 (0.12)	0.01	0.12 (0.18)	0.09 (0.17)	0.17
$MCA_{3-5.2}$	0.89 (0.35)	0.92 (0.27)	0.57	0.65 (0.47)	0.67 (0.43)	0.77
$MCA_{0-5.2}$	0.47 (0.12)	0.52 (0.12)	<0.01	0.13 (0.19)	0.09 (0.17)	0.10
NCV_{0-3}	2.35 (0.46)	2.53 (0.42)	<0.01	0.09 (0.10)	0.09 (0.10)	0.74
$NCV_{3-5.2}$	2.95 (1.16)	2.97 (0.88)	0.89	0.43 (0.47)	0.43 (0.34)	0.95
$NCV_{0-5.2}$	5.30 (1.45)	5.50 (1.20)	0.32	0.25 (0.24)	0.26 (0.19)	0.65
PNIF	84 (24.4)	102 (18.8)	<0.001	0.14 (0.20)	0.06 (0.11)	<0.01

Data presented as mean (SD). Abbreviations: MCA = minimum cross sectional area; NCV = nasal cavity volume; NCI = nasal congestion index; SD = standard deviation; 0–3 = 0–3 cm behind the nasal orifice; 3–5.2 = 3–5.2 cm behind the nasal orifice; 0–5.2 = 0–5.2 cm behind the nasal orifice; PNIF = peak nasal inspiratory flow.

asthmatic subjects without rhinitis [18]. There are conflicting results concerning structural changes such as basal membrane thickening in the nasal mucosa of patients with asthma [19,20]. Other structural factors that may represent a difference are nasal polyps, CRS, previous nasal surgery and chronic immunological/inflammatory conditions, but subjects with these abnormalities were excluded from the present study.

Nasal airway patency depends on the geometry of the airway, airflow and resistance. According to Poiseuille's law flow is directly proportional to the difference in pressure multiplied by the radius raised to the fourth power. A minimal decrease in the radius of the nasal airway will thus result in a significant reduction in flow [21], illustrated in this study by a reduced MCA and a consequently reduced PNIF in the asthma group. In constricted areas, velocity increases and a relatively negative pressure is generated [21]. These phenomena are seen in the internal nasal valve which represents the flow-limiting region or the bottle-neck area of the nasal cavity. Although the relative changes in NCI MCA in the asthmatic and control groups are equal the MCA in the asthma group is still smaller and this may explain the persistent difference in PNIF after decongestion. In addition to structural and mucosal characteristics, other factors may control nasal airflow. A reduction in forced inspiration may give a reduced stimulation of the sensors for nasal airflow. When the breathing effort is sub maximal or intrapulmonary dynamic resistance is increased, reduced PNIF can give a misleading impression of nasal obstruction. It has also been suggested that asthmatics generally may just have a different subjective perception of nasal obstruction that may explain their oronasal breathing [22].

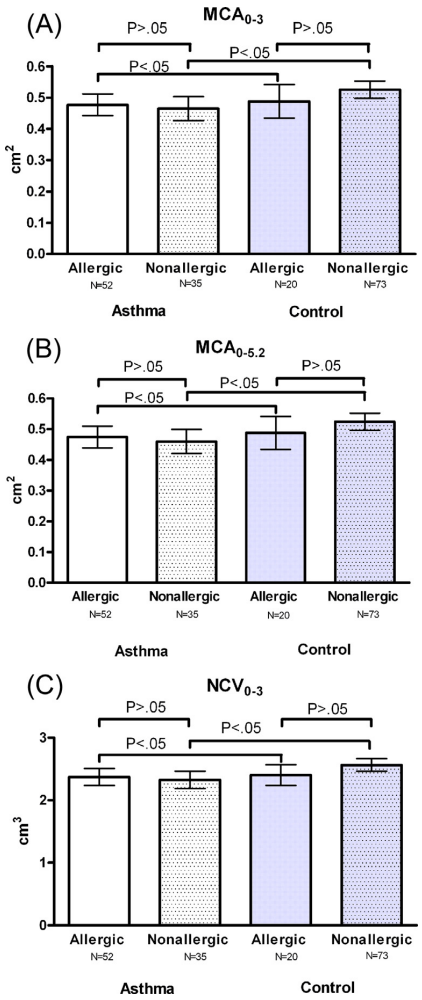

Figure 2 MCA_{0-3} (A), $MCA_{0-5.2}$ (B) and NCV_{0-3} (C) in the allergic asthmatic patients, non-allergic asthmatic patients, allergic controls and non-allergic controls. Values presented as mean, 95% CI. Abbreviations: MCA = minimum cross sectional area; NCV = nasal cavity volume; $_{0-3}$ = 0—3 cm behind the nasal orifice; $_{0-5.2}$ = 0—5.2 cm behind the nasal orifice.

Breathing is a dynamic process, with turbulent and laminar flow occurring simultaneously in different parts of the nasal passage. AR is static in nature and thus has limitations with regard to detecting dynamic changes. On the other hand, PNIF is effort dependent, but the non-rigidity of the ala nasi may induce dynamic collapse in the compliant part of the external nose. Despite a maximum limitation of PNIF recordings to 120 l/min, we demonstrated highly significant differences between asthmatics and controls. In addition, PNIF values above 120 l/min are only of minor clinical interest because such high peak flows generally exclude nasal obstruction [23,24].

We found that both allergic and non-allergic asthmatics have significantly smaller $MCA_{0-5.2}$ and NCV_{0-3} compared to their respective controls. Other studies have reported that both allergic and non-allergic asthma patients had more nasal symptoms and mucosal abnormalities in the nose and had elevated levels of inflammatory markers in nasal secretions, together with a significant impairment of quality of life and reduced inspiratory nasal airflow compared to non-asthmatics [4,6]. This highlights the importance of a thorough oto-rhino-laryngological examination and evaluation in all asthma patients, beyond the scope of allergy.

As alterations in nasal cavity geometry and airflow may compromise lung function, the results of the present investigation indicate a need for nasal biopsy studies in asthmatics to further understand nasal obstruction in these patients. It also indicates a need for considering medical and surgical interventions to open the nose for the benefit of the lungs.

Conflicts of interest

None.

Sponsorships

None.

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Paper 3

The determining factors of peak nasal inspiratory flow and perception of nasal airflow in asthmatics*

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Abstract

Background: The effect of pulmonary pathology on peak nasal inspiratory flow (PNIF) remains largely unknown. We investigated an association between a diagnosis of asthma and of lung function on PNIF when adjusted for possible confounders. Further, we investigated the perception of nasal obstruction in asthmatics compared to healthy controls when adjusted for PNIF.

Methodology: Eighty-seven asthmatics and 92 non-asthmatic controls underwent PNIF (categorized into groups of high, medium and low), acoustic rhinometry (AR) and spirometry, and we assessed symptoms of nasal obstruction on visual analogue scales (VAS) in three categories.

Results: PNIF was significantly associated with asthma and forced expiratory volume in the first second (FEV1) (% predicted). Other factors associated with PNIF were the degree of nasal obstruction measured both subjectively on a VAS and objectively with AR, age and disease status. Asthma patients were 19 times more likely to be in a higher VAS category compared to non-asthmatic controls independent of PNIF group.

Conclusion: Special care has to be taken when interpreting PNIF values in patients with asthma or reduced FEV1 (% predicted). The sensation of nasal obstruction in asthmatics is different from controls despite being in the same PNIF group.

Key words: asthma, rhinitis, Peak Nasal Inspiratory Flow, acoustic rhinometry, spirometry

Introduction

A large body of evidence supports the concept of a unified airway in which signs of disease in one part of the respiratory tract should be considered as a disease of the whole. This concept is sometimes expressed as "one airway, one disease" [1-3]. Clinical studies show that bronchial provocation with grass pollen extract can induce nasal inflammation [4] and nasal allergen challenge in patients with allergic rhinitis can lead to increased airway responsiveness [5].

The incidence of asthma is increasing, and the concomitant presence of rhinitis and chronic rhinosinusitis with asthma is frequently seen [6]. Assessment of the degree of sino-nasal dysfunction in asthmatic patients has significant clinical impact since it is important to diagnose and treat pathology in the upper airways to relieve symptoms from the lower airways [7,8]. It is also known that rhinitis can be the first sign of a lower respiratory tract disorder and the degree of upper airway disease can to some extent determine the severity of lower airway disease [9].

A patient's sensation of nasal patency may be a challenge for the clinician because it can be difficult to relate the subjective feeling to anatomical and physiological variables, such as the internal nasal valve with minimal cross sectional area [10] and airflow. Further, nasal patency assessment with objective measures, such as Peak Nasal Inspiratory Flow (PNIF), has been evaluated in a large number of studies on healthy individuals [11-13], patients complaining of nasal obstruction [14], medical treatment of the nose [15], nasal surgery procedures [16,17] and repeatability [18]. However, despite the well-known association between diseases in the upper and lower airways, very few have studied the use of PNIF on patients with pulmonary disorders [19,20].

The aim of the present study was to investigate the effect of a diagnosis of asthma and of lung function on PNIF when adjusted for possible confounders. Further, we investigated the perception of nasal obstruction in asthmatics compared to healthy controls when adjusted for PNIF.

Materials and methods

Study population

A cross-sectional study was conducted on 179 adult subjects consisting of 87 physician-diagnosed asthma patients and 92 non asthmatic controls. The sample, nasal recordings, questionnaires, and additional recordings were extracted from a database described previously [21].

Asthma was defined as the presence of typical asthma symptoms, variable airflow obstruction and in accordance with the British Thoracic Society criteria [22]. Variable airflow obstruction was defined by at least one of the two following criteria: an increase of ≥12% and ≥ 200 ml in the forced expiratory volume in the first second (FEV1) from baseline and after administration of salbutamol, or a positive bronchial provocation test, defined as the provocative dose of methacholine of ≤ 1600µg that causes a fall in FEV1 of at least 20% from baseline. Exclusion criteria were pregnancy, a history of cancer, previous nasal surgery, systemic disease with potential affection of the nose such as granulomatosis with polyangiitis (Wegener's granulomatosis), cystic fibrosis, primary ciliary dyskinesia, Kartagener's syndrome and sarcoidosis, and the presence of acute and chronic rhinosinusitis and nasal polyposis on oto-rhino-laryngological examination as defined by the EPOS2012 criteria [23]. Control subjects with allergy were not investigated in the pollen season (May-August) and asthmatic subjects were investigated from September 2009 to February 2010.

Written informed consent was obtained from all subjects. The study was approved by the Regional Committees for Medical and Health Research Ethics of Norway and investigations were performed in accordance with the principles of the Declaration of Helsinki.

Peak Nasal Inspiratory Flow (PNIF)

Nasal patency was assessed with a portable PNIF meter (In-check DIAL, Clement Clarke International, Harlow, Essex, UK). A forced maximum inhalation through the nose from residual volume was performed with the subject sitting in an upright position. Three satisfactory maximal nasal inspirations were obtained, and the mean value was calculated.
The scale on the PNIF meter was from 15 to 120 liters/minute (L/min). A flow in excess of 120 L/min was recorded as 120+ L/min , and for the purpose of statistical analysis set to 120 L/min.

Spirometry

Lung function was assessed by flow-volume spirometry measurements (Spirostar USB spirometer, Medikro Oy, Kuopio, Finland) at room temperature. The best FEV1 in liters and percentage of predicted (% predicted)[24] of three acceptable attempts was recorded, in accordance with international guidelines [25]. Predicted normal values were based on reference values of Crapo et al. [24].

Nasal minimal cross sectional area

The cross sectional areas from the nasal orifice to a depth of 5.2 cm into the nasal cavity were assessed with acoustic rhinometry (RhinoMetrics SRE2100, Rhinoscan version 2.5, built 3.2.5.0; Interacoustics, Minneapolis, MN, USA) by two trained operators throughout the study. Recordings were performed according to published protocols [26]. Three recordings were made from each nasal cavity. The mean value for each side was calculated from contiguous cross sectional areas from 0 to 3 cm and from 3 to 5.2 cm. To account for variations between nostrils due to the nasal cycle, the average of the two mean values for each partition was calculated. The lower of the two averages was defined as the nasal minimal cross sectional area (MCA cm^2).

Allergy

Sensitization to pollen (birch, grass and mugwort), cladosporium, house dust mite (*Dermatophagoides pteronyssinus*), and animal epithelia (horse, dog, and cat) was determined by skin prick testing (Soluprick SQ, ALK-Abello, Horsholm, Denmark) or measurement of specific IgE (AlaTOP, Diagnostics Products Corp., Los Angeles, CA, USA). Antihistamines were discontinued 4 days prior to the skin prick test. Allergy was defined as a positive test (reaction with a ≥3-mm-diameter wheal or specific IgE concentration of 0.7 IU/ml or greater) and typical symptoms of hypersensitivity on exposure to the allergen(s).

Nasal obstruction

The subjective degree of nasal obstruction during the previous week was assessed on a 100 mm Visual Analog Scale (NO-VAS) and the endpoints were 0 mm (never) and 100 mm (always).

Table 1. Demographic data on asthmatics and controls.

Variable	Total, n = 179	Asthma, n = 87	Control, n = 92	p
Age, years median, (range)	44 (19-65)	44 (19-64)	44 (20-65)	0.91
BMI, kg/m^2 median, (range)	25.4 (18.0-44.3)	25.7 (18.5-44.3)	25.0 (18.0-35.4)	0.08
Sex, Male/female	76/103	36/51	40/52	0.78
Allergy n (%)	72 (40)	52 (60)	20 (22)	<0.01
Smoking status: Ever/Never	32/147	11/76	21/71	0.08
Level of education in year				<0.01
≤ 9 years n (%)	36 (20)	15 (42)	21 (58)	
10 to 12 years n (%)	75 (42)	47 (63)	28 (37)	
≥ 13 years n (%)	68 (38)	25 (37)	43 (63)	

BMI = body mass index

Statistical analysis

Data were described with median and range for continuous variables and with count and percentages for categorical variables. Crude associations between pairs of categorical variables were assessed with Chi-square tests.

The level of education was categorized as either basic (≤ 9 years), secondary (10 to 12 years), or tertiary (≥ 13 years), that has been shown to be a good surrogate for socioeconomic status in Norway [27,28]. Subject co-morbidity was defined as the regular use of medication during the last 6 months prior to recruitment for asthma and allergy, pain relief, ischemic heart disease and hypertension, musculoskeletal disease, thyroid disorders, diabetes mellitus, anxiety and depression. Disease status was categorized as cardiovascular disease, other disease and no disease. Smoking status was dichotomized as smoker (current or ever smoked) and nonsmoker, as we did not have precise information about cigarette consumption.

NO-VAS was categorized as mild (0-30 mm), moderate (31-70 mm) and severe (71-100 mm)[29]. PNIF was used as a continuous variable for linear regression analysis and as an ordinal variable for ordinal logistic regression analysis. For the latter analysis, PNIF was categorized into the following 3 groups: (1) high: ≥ 120 L/min, (2) medium: 90 - 119 L/min and (3) low: 15 - 89 L/min. Of the spirometry variables, FEV1 is the most robust, and FEV1 (% predicted) was chosen for linear regression as that is based on height, age, sex and ethnicity of the subject. As there was a strong association between asthma and FEV1 (% predicted) (t-test, $p < 0.001$), we fitted two separate models for PNIF as a continuous variable to avoid multicollinearity. The associations between PNIF and asthma and between PNIF and FEV1 (% predicted) were modeled with linear regression. Possible confounders such as allergy, other diseases, education, NO-VAS, MCA, weight, height, age, sex and smoking were tested. The model fit was good and assumption of normally distributed residuals was fulfilled.

Further, we fitted ordinal logistic regression to assess possible association between VAS (in three categories) and having asthma. PNIF was omitted from the final model as we found the same ratio between having asthma and VAS score when stratified by PNIF group so there was no interaction between PNIF and asthma. The assumption of parallel lines was fulfilled and the model fit was good. The results were expressed as odds ratios (OR) with 95% confidence intervals (CI).
All statistical analyses were performed using PASW Statistics, version 20 for Windows (SPSS Inc., Chicago, IL, USA). A p-value of < 0.01 was considered statistically significant to correct for multiple testing.

Results

Subject characteristics are presented in Table 1. Allergy was present in 60 % (n = 52) of asthmatics and 22 % (n = 20) of controls. The association between asthma and PNIF is shown in Model 1 (Table 2A). PNIF was significantly associated with asthma, MCA and age ($p < 0.01$). When all other confounders were kept equal, PNIF was 10 L/min lower in asthmatics than non-asthmatics. Further, PNIF was increased by 4.9 L/min for a 0.1 cm^2 increase in MCA, and was decreased by 0.4 L/min per one year increase in age.

The association between FEV1 (% predicted) and PNIF is shown in Model 2 (Table 2B). PNIF was significantly associated with

Table 2. Multiple linear regression for PNIF as a dependent variable.

A) Model 1: Asthma as an independent variable adjusted for confounders. N=179

Variable	Estimate of β	95% CI	p-value
Asthma [no=ref]	-10.2	-17.8 to -2.7	<0.01
Allergy [no=ref]	-0.1	-6.6 to 6.4	0.98
Disease status [no=ref]	-4.7	-8.6 to -0.7	0.02
Education level [basic=ref]	2.5	-2.1 to 7.0	0.29
NO-VAS [mm]	-0.2	-0.3 to -0.01	0.03
MCA [0.1 cm^2]	4.9	2.2 to 7.6	<0.01
Weight [kg]	0.2	0.0 to 0.5	0.05
Height [cm]	-0.1	-0.6 to 0.4	0.8
Age [years]	-0.4	-0.6 to -0.1	<0.01
Sex [male=ref]	-3.1	-12.6 to 6.4	0.5
Smoking [ever=ref]	0.5	-7.2 to 8.3	0.9

B) Model 2: FEV1 (% predicted) as an independent variable adjusted for confounders. N=179

Variable	Estimate of β	95% CI	p-value
FEV1 (% predicted) [%]	0.3	0.1 to 0.5	<0.01
Allergy [no=ref]	-0.3	-6.4 to 5.9	0.9
Disease status [no=ref]	-6.1	-9.9 to -2.4	<0.01
Education [basic=ref]	4.5	0.4 to 8.6	0.03
NO-VAS [mm]	-0.2	-0.3 to -0.07	<0.01
MCA [0.1 cm2]	5.1	2.5 to 7.6	<0.01
Weight [kg]	0.2	0.1 to 0.4	0.01
Smoking [ever=ref]	2.7	-4.9 to 10.5	0.5

Estimate of beta = the amount of change in the response variable when the explanatory variable is increased by one unit. FEV1 = forced expiratory volume in the first second, MCA = minimal cross sectional area, NO-VAS = nasal obstruction visual analogue scale, PNIF = peak nasal inspiratory flow, ref = reference category for categorical variables.

FEV1 (% predicted), MCA, NO-VAS and other disease ($p < 0.01$). When all other confounders were kept equal, PNIF increased by 0.3 L/min per % increase in FEV1 (% predicted), and increased by 5.1 L/min for every 0.1 cm^2 increase in MCA. There was a decrease of 0.2 L/min in PNIF per mm increase in NO-VAS and a decrease of 6.1 L/min in PNIF in subjects categorized with a disease.

Allergy and smoking status were not significantly associated with PNIF in any of the adjusted analyses.

Asthma patients were 19 times more likely to be in a higher VAS category compared to non-asthmatic controls (OR = 19.4, 95 % CI 7.2-52.5, $p < 0.001$). The odds ratio was independent of the PNIF group (Figure 1).

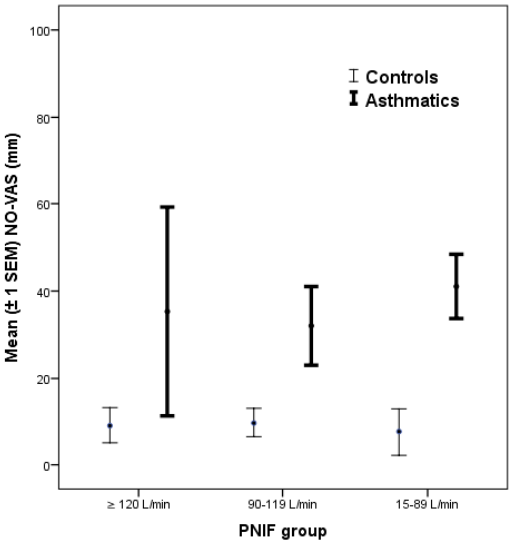

Figure 1. NO-VAS distribution according to PNIF group in asthmatics and controls. NO-VAS= nasal obstruction visual analogue scale, PNIF= peak nasal inspiratory flow.

Discussion

This study demonstrates that PNIF is influenced by an asthma diagnosis and FEV1 (% predicted), and that asthmatics are more likely to be in a higher NO-VAS category which is independent of PNIF group. Other factors associated with PNIF are the degree of nasal obstruction measured both subjectively on a visual analogue scale and objectively with acoustic rhinometry, age and disease status. Thus in patients presenting with nasal obstruction PNIF recordings should be assessed in conjunction with an asthma diagnosis, spirometry and MCA.

In the present study, PNIF is 10 L/min lower in asthmatics than in non-asthmatics and increases by 0.3 L/min for every % increase in FEV1 (% predicted). Thus, when confronted with a patient with nasal obstruction without an obvious rhinological cause, the possibility of asthma should be considered. The clinician should enquire about lower respiratory tract symptoms suggestive of asthma and seek evidence of variable airflow obstruction either with spirometry and reversibility testing or assessing the degree of bronchial hyperresponsiveness. Previous studies show a positive correlation between upper airway patency measured by PNIF and lower airway function measured by PEF in adults [12] and in children and adolescents [30]. Moreover, an increase in PNIF with a concomitant increase in FEV1 (% predicted) has been reported in allergic rhinitis after sauna treatment [31]. PNIF increased by 4.9-5.1 L/min per 0.1 cm^2 increase in MCA when modeled with respect to an asthma diagnosis (Model 1) or by FEV1 (% predicted) as in model 2. The MCA in our sample was located between 0-3 cm from the nasal orifice in almost all of our subjects (95% of asthmatics and 98% of controls) [21]. The internal nasal valve is generally accepted to be located at a distance of 2-3 cm from the nasal orifice [10,32], and surgical procedures performed at the internal nasal valve improve MCA [33-35]. Improvement in MCA should lead to a significant improvement in nasal airflow as Poiseuille's law states that flow is directly proportional to the difference in pressure times the radius raised to the fourth power [36], even though modifications due to the complex flow patterns in the human nose must be taken into consideration [37]. Thus, in asthmatics with obstructed noses, surgical intervention with procedures aimed at the internal nasal valve, could lead to an improvement in nasal air flow which in turn might be beneficial for the lower airways.

We have also shown that asthmatics have a different sensation of nasal obstruction compared to non-asthmatics despite being in the same PNIF group. The likelihood of being in a higher NO-VAS category is 19–fold greater in asthmatics than in non-asthmatic subjects. However, the inter-individual variation is large, as confirmed by the wide confidence interval and it is thus difficult to quantify this association with better precision. Despite this, one can speculate whether an increased number of sensory sodium channels and sensory- and secretomotor nerve fibers in the nasal mucosa, that has been reported in allergic and non-allergic rhinitis [38,39], may account for the increased perception of nasal obstruction. The level of perceived breathing difficulty has been reported to be more important than the applied nasal load for the increased propensity of asthmatics to switch to oronasal breathing, compared with non-asthmatic subjects [40]. Premature switching to oronasal breathing results in inadequate conditioning and filtering of the inspired air, with drying and cooling of the lower airways, subsequent release of inflammatory cell mediators and development of an asthmatic response [41] and asthma chronicity.

The main strengths of our study are the large sample size, possibility to compare asthmatics with non-asthmatics, and the complete information of many possible confounders. However, the study has some limitations. Smoking is known to be under-reported, and we only have information about ever- and never smokers. The information about other diseases was self-reported and might be underestimated. The non-asthmatics were individuals recruited from businesses near by the hospital or patients attending the hospital for other illnesses, which were thought not to affect the upper and lower airways. Those who chose to participate may have been more interested in their health than the general population, but still we regard measurements on these individuals to be representative for the general population.

There are different PNIF meters in clinical use, and our study is based on In-check DIAL which has a scale from 15 to 120 L/min. A normal value of greater than 120 L/min is commonly used [42]. Regarding the individuals with PNIF > 120 L/min (5 asthmatics and 21 controls), we have performed sensitivity analysis where these individuals were omitted which confirms our original findings.

Mainly turbulent airflow prevails at tidal volumes reached during maximum inspiration [43] and thus PNIF does not reflect the nasal resistance during resting respiration. Possible reasons for inaccuracy of the PNIF include random error and operation errors such as measurement with loose face masks or incompletely closed mouth, but these errors were minimalized by two trained operators throughout the study.
The present study emphasizes that special care has to be taken when interpreting PNIF values in patients with asthma or reduced FEV1 (% predicted). The sensation of nasal obstruction in asthmatics is different from controls despite being in the same PNIF group.

Authorship contribution

WMT: Study design, data collection, statistical analysis, paper drafting; MSC: Data collection, paper drafting; VB: Data collection, paper drafting; MC: Statistical analysis; SKS: Study design, paper drafting.

Conflicts of Interest

None declared.

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