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Thesis for the degree of Philosophiae Doctor

Trondheim, December 2017

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Norsk Sammendrag

Patogenesen til obstruktivt søvnapne syndrom (OSA) ser ut til å være multifaktoriell men de anatomiske og nevroregulatoriske mekanismene som er involvert i sammenfall av de øvre luftveier under søvn er ikke tilstrekkelig definert. Den viktigste passasjen for luft fra omgivelsene til pharynx går via nesekaviteten, og dens rolle i utviklingen av søvnapne syndromet er ikke forstått, selv om dens betydning har vært gjenstand for debatt over flere tiår.

Nesekaviteten er et komplekst anatomisk område med en enda mer kompleks fysiologi. I tillegg til de rent fysiologiske responsene som normal neseventilasjon fører med seg, vil nesens hulrom og dynamiske slimhinne påvirke både hastigheten til luftstrømmen og luftveistrykket før luften når bløtdelene i halsen. I dette området vil det oppstå en gjensidig interaksjon mellom luftstrømmen og veggene i luftveiene som innen strømningsfysikk kalles" Fluid Structure Interaction". Gjennom sannsynligvis multiple reguleringsmekanismer vil denne prosessen etterhvert lede til de sammenfall av luftveiene som karakteriserer OSA.

Når man undersøker og behandler pasienter med OSA opplever man ofte tilbakevendende klager på nesetetthet i pasientgruppen. Kontinuerlig overtrykksbehandling der man benytter et relativt lavt positivt luftveistrykk via en nesemaske eller hel ansiktsmaske (CPAP) er førstevalget ved behandling av sykdommen. Bruk av slik maske krever en funksjonell nesekavitet for å ha adekvat effekt. Når dette ikke er tilfelle, kan OSA pasienter bli tilbudt behandling av nesetettheten, enten medisinsk, kirurgisk eller en kombinasjon av begge.

Nesekirurgi kan være en effektiv måte å behandle nesetetthet på og ved korrekt utførte prosedyrer ser man en reduksjon av resistansen i nesekaviteten. Dette har stor betydning fordi OSA pasientene tolererer maskebruken bedre og behandlingseffekten øker. Hos enkelte pasienter kan man i tillegg se at intranasale endringer etter kirurgi er assosiert med endringer i både de subjektive OSA symptomene og i mindre grad med endringer i de objektive OSA parametrene. Dette leder oss til å anta at hos enkelte kan

nesekirurgi alene endre visse predisponerende faktorer som er nødvendig for sykdomsutviklingen.

I denne Phd tesen undersøkes effekten av å kombinere to spesifikke intranasale kirurgiske prosedyrer hos OSA pasienter, forskjeller i objektive mål av nesekavitetens volum, minste tverrsnittsareal, luftstrøm i nesen samt nese- og bihulerelatert livskvalitet mellom OSA pasienter og friske kontroller. Tesen er del av et samarbeid mellom det medisinske fakultet og fakultet for ingeniørvitenskap ved NTNU samt Sintef industri, og springer ut fra et pågående interdisiplinært samarbeidsprosjekt kalt "Modelling of Obstructive Sleep Apnea by Fluid-Structure Interaction in the Upper Airways". I dette prosjektet undersøkes biomekaniske egenskaper i bløtvevet samt de strømningsfysiske egenskapene i de øvre luftveier hos OSA pasienter. Som et foreløpig resultat av dette samarbeidet inneholder denne tesen også en beskrivelse av en computerbasert matematisk modell (Finite element modell – FE modell) der biomekaniske egenskaper i den bløte gane hos seks OSA pasienter som får utført intranasal kirurgi undersøkes.

Hovedkonklusjonen i denne tesen er at OSA pasienter har mindre tverrsnittsareal og volum især i fremre til midtre del av nesekaviteten og luftstrømmen som når bløtvevet i pharynx vil i det minste til en viss grad påvirkes av endringer i dette området. OSA pasienter har redusert evne til forsert inspirasjon av luftstrømmen gjennom nesekaviteten samt redusert nese- og bihulerelatert livskvalitet. Disse forholdene bør vurderes i utredningen og gjenspeiles i behandlingen av pasientene.

Artikkel 1 er en retrospektiv observasjonsstudie av 59 pasienter med verifisert OSA diagnose og nasalstenose som enten fikk utført septumplastikk alene (n=33) eller septumplastikk kombinert med volumreduserende kirurgi av nedre nesemuslinger (n=26). Vi fant en signifikant reduksjon i AHI i gruppen som fikk kombinert kirurgi hvilket antyder en tilleggseffekt av volumreduserende kirurgi i nesekaviteten hos OSA pasienter.

I artikkel 2 sammenlignes nesekavitetens geometri og funksjon mellom 93 OSA pasienter og 92 friske kontroll individer som ble inkludert over en seks års periode.

Minste tverrsnittsareal og nesekavitetens volum ble målt, i tillegg til høyeste forserte inspiratoriske luftstrøm (PNIF) i begge grupper. Vi fant et lavere tverrsnittsareal, lavere nesevolum og lavere PNIF blant OSA pasienter sammenlignet med kontrollene.

Artikkel 3 bygger på artikkel 2 og her utvides undersøkelsene med pasientrelaterte utfall. Artikkelen beskriver sinonasal livskvalitet, symptomer og inspiratorisk funksjon hos 93 OSA pasienter og 92 kontroll individer ved bruk av en visuell analog skala for nesetetthet (NO-VAS) og en sinonasal utfallstest (SNOT-20) samt PNIF. Den pasient rapporterte nesetettheten var økt i OSA gruppen, og sinonasal livskvalitet var redusert hos OSA pasienter sammenlignet med kontrollene. En positiv korrelasjon mellom endring i PNIF og subjektiv nesetetthet ble observert i kontrollgruppen alene.

Artikkel 4 er et resultat av samarbeidet med institutt for konstruksjonsteknikk ved NTNU og beskriver biomekaniske egenskaper i velopharynx hos seks OSA pasienter med nesetetthet som gjennomgår intranasal kirurgi. Tilgjengelig kommersielt software (Mimics, Abaqus) ble benyttet til å simulere effekten av forskyvning av den bløte gane, lukningstrykket i velopharynx og deformasjonen i bløtvevet. Med denne computerbaserte FE modelleringen kunne vi postulere en korrelasjon mellom anatomien i den bløte gane, OSA parametre og simulert lukningstrykk, samt en lineær korrelasjon mellom deformasjon av den bløte gane og simulert lukningstrykk. Vi fant ingen korrelasjon mellom simulert lukningstrykk og OSA parametre før eller etter intranasal kirurgi. Metoden kan være av betydning i persontilpasset OSA kirurgi, samt i den postoperative evalueringen av resultatene etter luftveiskirurgi i denne pasientgruppen.

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Content

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As always, I must thank my family, my wife, my mother and my sister and my three

stepchildren for their support and encouragement.

List of papers

Paper 1. An observational cohort study of the effects of septoplasty with or without inferior turbinate reduction in patients with obstructive sleep apnea. Moxness MH, Nordgård SN. BMC Ear Nose Throat Disord 2014;14:11.

Paper 2. A comparison of minimal cross-sectional areas, nasal volumes and peak nasal inspiratory flow between patients with obstructive sleep apnea and healthy controls. Moxness MH, Bugten V, Thorstensen WM, Nordgård S, Bruskeland G. Rhinology. 2016 Dec 1;54(4):342-347.

Paper 3. Sinonasal characteristics in patients with obstructive sleep apnea compared to healthy controls. Moxness MHS, Bugten V, Thorstensen WM, Nordgård S. Int J Otolaryngol. 2017;2017:1935284.

Paper 4. Simulation of the upper airways in patients with obstructive sleep apnea and nasal obstruction. A novel finite element method. Published online in Laryngoscope Investigative Otolaryngology 21 February 2018. Moxness MHS, Wülker F, Skallerud B, Nordgård S.

List of abbreviations

AHI = apnea-hypopnea-index
ANOVA = analysis of variance
AR = allergic rhinitis
AR = acoustic rhinometry
ASV = adaptive servoventilation
AVAPS = average volume assured pressure support
biPAP = bilevel positive airway pressure
BMI = body mass index
CFD computational fluid dynamics
COPD = chronic obstructive pulmonary disease
CPAP = continuous positive airway pressure
CRS = chronic rhinosinusitis
CSA = central sleep apnea
CSR = cheyne stokes respiration
CT = computer tomography
DISE = drug induced sleep endoscopy
EMG = electromyogram
ENT = ear, nose and throat
nEPAP = nasal expiratory positive airway pressure
ESS = epworth sleepiness scale
FE = finite element
FSI = fluid-structure interaction
HNS = hypoglossal nerve stimulation
ICSD = International Classification of Sleep Disorders
ISAC = Icelandic Sleep Apnea Cohort study
MAD = mandibular advancement device
MATLAB = matrix laboratory
MCA = minimal cross-sectional area
MLS = multi-level surgery
MMA = maxillomandibular advancement

MOD = mandibular distraction osteogenesis

MRI = magnetic resonance imaging

NAR = non-allergic rhinitis

NCI = nasal congestion index

nCPAP = nasal continuous positive airway pressure

NCV = nasal cavity volume

NOSE = nasal obstruction symptoms evaluation survey

NOTUR = Norwegian Metacenter for Computational Science

NO-VAS = visual analogue scale for nasal obstruction

NTNU = Norges teknisk-naturvitenskapelige universitet

ODI = oxygen desaturation index

OR = odds ratio

OSA = obstructive sleep apnea

PAP = positive airway pressure

PNIF = peak nasal inspiratory flow

PSG = polysomnography

QoL = quality of life

RERA = respiratory effort related arousels

RMSE = root mean squared error

SNOT = sino-nasal outcome test

SPSS = Statistical Package for the Social Sciences

SRBD = sleep related breathing disorders

SSE = sum of squares due to error

2D = two dimensional

3D = three dimensional

TORS = transoral robotic surgery

UAS = upper airway stimulation

UPP = uvulopalatoplasty

UPPP = uvulopalatopharyngeoplasty

VAS = visual analogue scale

WP = work package

1 Introduction

1.1 Motivation

The multifactorial pathogenesis of obstructive sleep apnea (OSA) has led to a multitude of treatment options, and no single therapy exists today that can give relief to all patients suffering from the disease (1). The wide array of treatment schemes is suggestive of a lack of knowledge of the basic mechanisms that leads to the syndrome. And that makes research in this particular field both sensible and interesting. The mainstay of therapy is still a combination of conservative lifestyle changes and use of positive airway pressure devices, for the main part nasal continuous positive airway pressure devices (nCPAP, in the continuation of the text only referred to as CPAP). Nasal expiratory positive airway pressure (nEPAP) has recently been introduced (2) which increases upper airway pressures by way of a mechanical valve placed in the nostrils that allows inspiration to occur, but gives resistance to expiration thus increasing total upper airway pressure. Positive airway pressure devices are known to have difficulties with compliance, which in part reflects the multifactorial pathogenesis of the syndrome. Engelman et al (2003) reported that two-thirds of CPAP users experienced side effects. Morris et al (2006) found that 48 % of CPAP users were intolerant of CPAP defined as self-reported use < 4 hours/night and Rotenberg (2016) did a 20-year review including 82 papers demonstrating a consistently low overall adherence to CPAP of 34,1% (3-5). The review paper by Sawyer et al. (6) describes the dependency of CPAP delivery on the patency of the structures of the upper airways. The CPAP use was strongly influenced by increased nasal resistance due to a decrease in nasal volume and smaller cross-sectional areas in the nasal cavity (4, 7, 8). The subsequent rejection of CPAP therapy is therefore one of the main motivating factors for finding supplementary treatment options.

A meta-analysis by Wu et. al (2017) reports that the apnea-hypopnea index decreased significantly after nasal surgery for OSA (9) and provides at least some evidence supporting isolated treatment of nasal obstruction in OSA patients. Migueis et. al highlights the restoration of sleep in OSA after treatment of nasal obstruction, especially the possibility of reducing sleep fragmentation by decreasing intrathoracic pressure

which ultimately leads to improvement in sleep quality (10). Recently Xiao et. al (2016) demonstrated that nasal obstruction aggravated the psychological symptoms in OSA patients, and that successful nasal surgery significantly improved sleep latency scores, daytime dysfunction scores as well as anxiety and hostility scores (11). Thus, it seems fitting that if positive airway therapy shall be of use over the foreseeable future, the side effects of the treatment must be minimized and the mode of delivery via the upper airways, and the nasal cavity in particular, must be optimized.
Surgical treatment of OSA has been advised against as a primary treatment (12) but has regained some credit as an accessory treatment over the years in light of relatively recent developments, abandoning classical single stage surgeries like uvulopalatoplasties or uvulopharyngeopalatoplasties and moving towards multilevel facial skeleton surgeries of the upper airways and hypoglossal nerve stimulation therapy (13, 14). The surgical treatments are varied and reflect the multifactorial pathogenesis of the disease. This thesis highlights the importance of correcting nasal impairment in sleep apnea treatment from a structural and subjective perspective as well as the importance of working with a multidisciplinary team in order to achieve a sufficient level of knowledge of soft tissue biomechanics.

It seems clear that a normal nasal patency is important in treatment of sleep apnea due to several reasons, the three main reasons being:

1. A functional nasal airway is a prerequisite for positive airway pressure devices to deliver treatment properly. The nasal airway forms the interface between positive airway therapy and the OSA patient. Despite the low compliance to CPAP therapy it remains the gold standard of treatment globally and focus on optimal conditions of the nasal passageways is therefore mandatory.

2. Although treatment of nasal obstruction in most cases will not eradicate obstructive events, it is likely to improve symptoms and reduce the severity of the disease (10, 11, 15, 16).

3. There seem to be subgroups of patients in which surgical treatment of nasal obstruction will be beneficial as an isolated treatment (9, 17-19). This motivates

us to investigate the underlying physiological mechanisms between airflow and the structural pharyngeal wall properties in a selected group of patients, with a relatively easy to do surgical procedure (functional septorhinoplasty) and a relatively short time period between the preoperative and postoperative nasal measurements.

A key to predicting the outcome of treatment of OSA is to fully understand the governing physical mechanisms behind the development of upper airway collapse. However, there is yet to be developed a clinical tool that can predict the response of different therapies on OSA. This is probably due to the fact that we still have not identified the underlying pathophysiological mechanisms that are decisive for maintaining upper airway patency during sleep. A multidisciplinary OSA research group at St Olav Hospital has focused on OSA patients undergoing nasal surgery due to nasal obstruction in an attempt to describe the behaviour of airway dynamics in OSA. The research aims at bridging the gap between physiology, medical research and the available state-of-art technology. To meet the multidisciplinary demands, the research team consists of specialist from St. Olavs Hospital; the Faculty of Health and Medicine (DMF), NTNU; the Faculty of Engineering (IV), NTNU; and SINTEF Industry (former Materials and Chemistry).

2 Sleep Related Breathing Disorders

2.1 Definition

Since Guilleminault in 1976 first introduced the term *obstructive sleep apnea syndrome* including the predominant daytime feature of somnolence (20) and Block described *hyponeas* in 1979 (21) there has been regular revisions of the terminology by the International Classification of Sleep Disorders (ICSD). The Sleep-Related Breathing Disorders (SRBD) are in the latest and third revision of ICSD (ICSD-3) divided into four main sections: OSA disorders, central sleep apnea (CSA) syndromes, sleep-related hypoventilation disorders and sleep-related hypoxemia disorders (22). The most relevant syndromes are OSA and CSA syndromes which can be identified using sleep testing in an out-patient setting. Sleep-related hypoventilation disorders and sleep-

related hypoxemia requires measurements of arterial blood gases and/or transcutaneous CO_2 measures and will not be discussed in detail in this thesis.

2.1.1 OSA Disorders

The criteria for the OSA diagnosis in the adult population requires on of the following two settings:

1. Five or more obstructive events per hour of sleep during polysomnography (PSG) or out-of-center sleep testing, coupled with either symptoms (e.g daytime sleepiness, insomnia, snoring, fatigue, observed apnoea or subjective nocturnal respiratory disturbance) or associated medical disorders (coronary artery disease, hypertension, atrial fibrillation, congestive heart failure, stroke, diabetes, cognitive dysfunction or mood disorder).
2. ≥ 15 obstructive events per hour of sleep, even in the absence of associated symptoms or medical disorders.

ICSD-3 emphasizes that obstructive respiratory events are defined not only as obstructive or mixed apnoeas and hypopneas, but also respiratory effort-related arousals (RERA). An obstructive apnea is defined as a cessation in breathing due to collapse of the upper airway resulting in a reduction in airflow ≥ 90% from baseline lasting ≥ 10 seconds. A hypopnea is a reduction of oronasal flow by > 30% lasting over ten seconds followed by a reduction in oxygen saturation levels of 4% or more (3% is still used as a criterion, but the 4% level of reduction is stated in the last edition of ICSD). The number of oxygen desaturations per hour sleep (ODI) is calculated from this baseline. RERA is defined as a series of respiratory cycles of increasing and decreasing effort lasting ≥ 10 seconds leading to an arousal that does not meet the criteria for apnea or hypopnea.

2.1.2 CSA syndromes

The syndromes are divided into 8 subcategories. There are three primary CSA in which two are coupled to infancy or prematurity. There are two CSA associated with Cheyne

Stokes respiration (CSR) (cyclical episodes of apnea and hyperventilation), the remaining ones are linked to medical disorders, high altitude, use of medications or substances. The last category is the new term "Treatment-emergent central sleep apnea" which defines what we earlier have observed as "complex sleep apnea". This category is defined as an OSA disorder followed by a reduction of obstructive events and emergence of central events during PSG combined with positive airway pressure treatment. The diagnosis of treatment-emergent CSA should be made with caution since there is a number of central episodes that resolve over time when positive airway treatment has been established (23). CSA syndromes must have a presence of five or more central apneas per hour of sleep.

3 Patophysiology of OSA

3.1 The "Balance of forces" model

The upper airways may be seen as a "potentially collapsible tube" (24), or as a "critically stable tube" (25). Normally during both sleep and the wake state, there is a neuromuscular tone that keeps the upper airway open. This neuromuscular drive of the upper airway dilator musculature can be counteracted by the intraluminal negative pressure resulting in partial or complete collapse of the airway, described first by Remmers et. al as the "balance of forces" theory (26).
The muscles of the upper airways that are responsible for controlling a "critically stable" state are:
- the two muscles of the palate (m. tensor palatini and levator palatini),
- the muscles of the tongue (mainly m. genioglossus)
- the muscles that controls the hyoid bone position (m. geniohyoid and m. thyrohyoid) (27) (Figure 1).

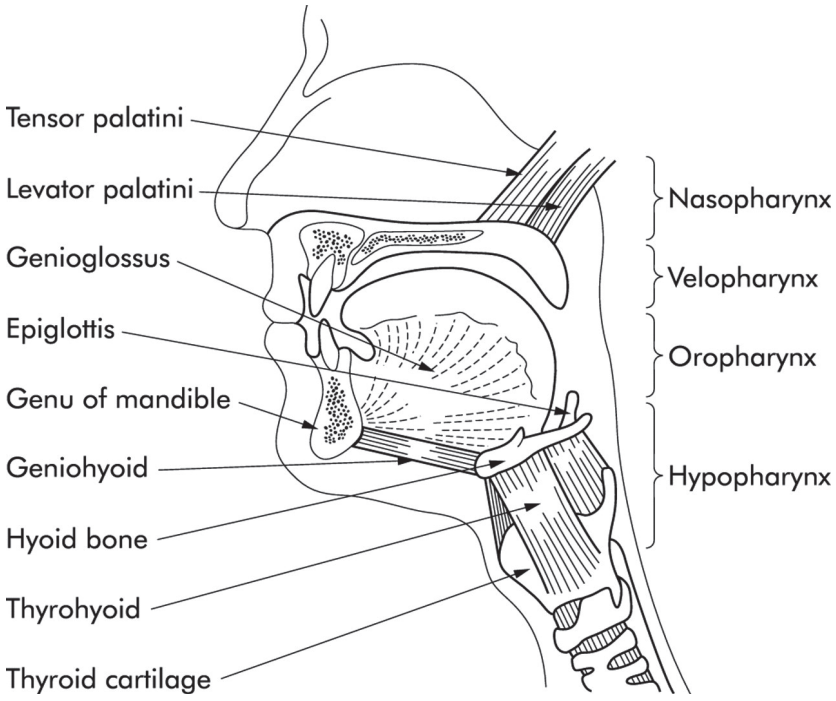
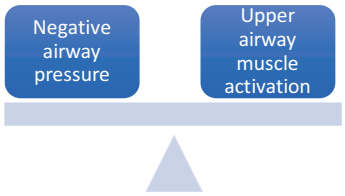


Figure 1. Muscles of the upper airway involved in regulating airway patency. From Fogel 2004 (27). Reprinted with permission.

With increasing negative pressure, there will be an increased activation of these muscles in order to maintain adequate upper airway patency. This is called the "negative pressure reflex" and can be demonstrated by an increased activity in electromyograms (EMG) during wakefulness in the dilator muscles in OSA patients compared to controls (28, 29), and a demonstrable fall in activity during onset of apneas during sleep (26). The increase in activation diminishes to near normal levels in subjects with successful use of CPAP (29). The balance of intraluminal negative pressures and the pressure of increased soft tissue volumes on one side, and the contraction force of the dilator muscles and the effect of the loss of the negative pressure reflex during onset of sleep on the other, will ultimately determine whether the upper airway collapses or not during

sleep (30) (figure 2A, figure 2B). This model allows for theories of mechanoreceptor feedback systems and an influence of chemoreceptor stimuli on the development of OSA. It does not however explain the reason why the "critically stable" tube balances so delicately on the border of collapse, nor does it quantify the magnitude of force exalted by the dilator muscles relative to the magnitude of the intraluminal pressure.

2A



2B

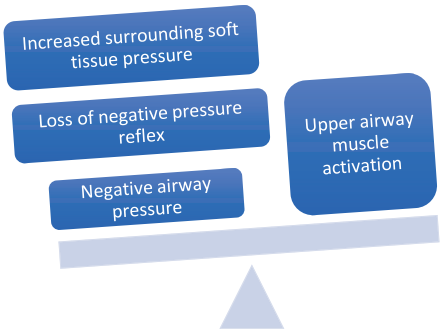


Figure 2. The balance of forces model in OSA. 2A shows the balance of forces during wakefulness under ideal conditions. 2B describes the balance of forces during sleep in OSA

3.2 The Starling resistor analogy

The Starling resistor has demonstrated its usefulness in studies of mechanical properties of collapsible structures such as blood vessels and branches of the lower airways (31-33). In 1996 Gold and Schwartz used the Starling resistor to model the control of the pharyngeal airway (34). This model depicts the upper airways as a rigid tube with a collapsible segment in the middle. The upper end (nasal cavity) and the lower end (larynx, trachea) has a fixed diameter and resistance, and the collapsible segment in the middle (pharynx) is subject to the surrounding pressure (pharyngeal walls, soft tissue) which constitutes the critical closing pressure (Pcrit). The flow through the tube (F) will depend upon the pressure (P) and resistance (R) in the upstream and downstream segment:

$$F = \frac{(Pus - Pds)}{(Rus - Rds)}$$

P_{us} is the pressure in the upstream segment (nasal cavity) and P_{ds} is the pressure in the downstream segment (trachea). R_{us} is the resistance in the upstream segment and R_{ds} defines the resistance in the downstream segment. In figure 3 one can see that the potentially collapsible segment (pharynx) will be completely obstructed when $P_{crit} > P_{us}$ and P_{ds} (3B) and it will partially close if $P_{us} > P_{crit} > P_{ds}$ (3C) and it remains open if P_{us} and $P_{ds} > P_{crit}$ (3C). In a fully hypotonic airway there is strong evidence that it behaves like a Starling resistor (35). A decrease in P_{ds} will induce inspiratory airflow limitation up to a certain point where P_{crit} replaces P_{ds} as the effective downstream pressure to insure further inspiratory airflow giving rise to high frequency oscillations in flow (snoring) as well as hypopneas and episodes of RERAs. In order for the upper airway to fully occlude, the P_{us} must also fall below P_{crit}. At this point, there will be a clinically state of obstructive apneas with ensuing recurrent oxygen desaturations, micro-arousals and metabolic oxidative stress (34, 36, 37). The Starling resistor analogy is an enticing model in the way it easily explains the governing forces that results in possible collapsibility in a hollow and hypotonic tube. However, the upper airway can scarcely be described as a passive and axisymmetric tube. It is a complex geometric structure with both rigid bony and cartilaginous parts (nasal cavity, hard palate, laryngeal framework and trachea) and compressible and flexible parts that exhibits characteristic

soft tissue mechanical properties. Consideration of alternative models to explain pharyngeal collapse has therefore been suggested (24).

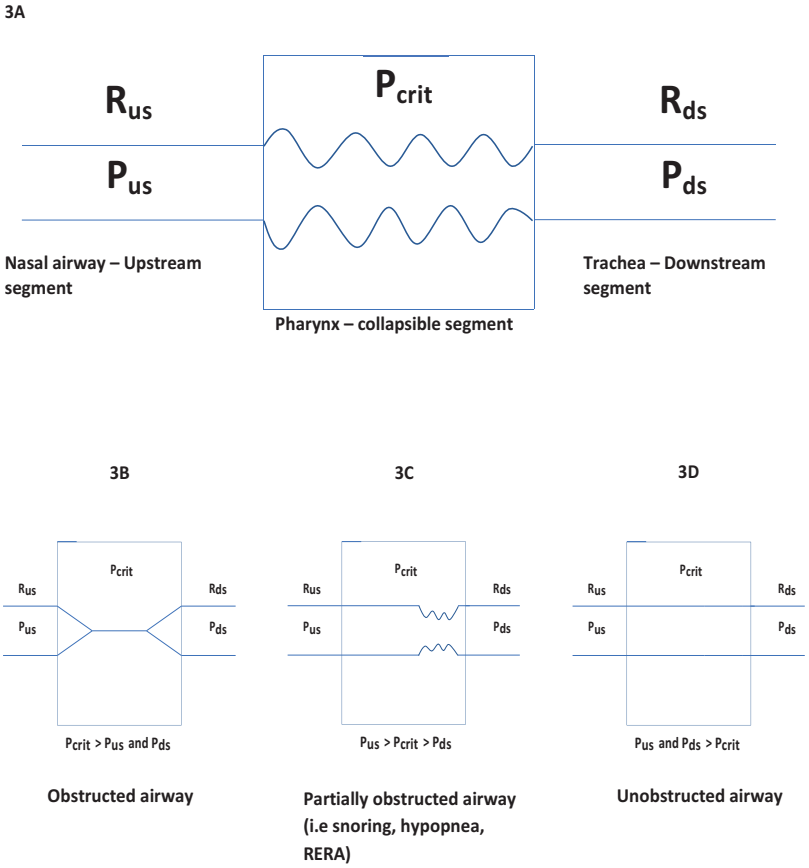


Figure 3. The Starling resistor analogy in OSA. 3A shows the three segments representing the nasal airway, the pharynx and the trachea. 3B shows a completly obstructed airway, 3B a partially obstructed airway and 3C a normal, unobstructed airway. R_{us} = Resistance upstream, P_{us} = Pressure upstream, R_{ds} = Resistance downstream, P_{ds} = Pressure downstream, P_{crit} = Critical closing pressure. Modified from Schwartz and Smith (35).

3.3 Computational Models

The two above mentioned models represent the classical way of describing the characteristics of the upper airway during inspiratory flow. However, both have shortcomings and cannot be relied upon to describe the nature of OSA development accurately, hence the need to bridge the two models into personalized models that can be relied upon to explain the phenomenon of upper airway collapse during sleep. The theories of solid and fluid structure mechanics are well known within the scientific fields of structural engineering and theoretical physics, and there is an emerging notion within the medical community to apply these principles to formulate a simplified but more correct physical model of OSA development. There are obvious reasons to do so. A prerequisite for establishing a simplified and verifiable model is to understand the basic mechanisms leading to upper airway collapse. Some studies show the interaction between laminar and turbulent airflow in simplified human airway models (38) but in order to convey the complex interaction between the airflow and the pharyngeal wall there is a need for anatomically accurate airway models using high resolution CT images in a strictly controlled and standardized setting (39). Numerical mathematics is the basis for developing models that can describe the interaction between changes in airflow through the upper airway tract and the pharyngeal walls by way of fluid-structure interaction, and the use of Computational Fluid Dynamic (CFD) simulations to visualise and potentially predict where collapse of the airway occurs. Van Hirtum describes a suggested theoretical transition from simplified mathematical models like the Lumped-segments model (40) and Flexibel beam models (41) towards a more accurate experimental physiological model in which apneas and hypopneas can be reproduced, and where different parameters can be imposed and measured (24).

4. Non-surgical treatment

OSA is increasingly being recognized as a diverse disease with several phenotypes based on sex, age and ethnicity (42) and on clinical presentation with or without daytime sleepiness and with or without night time insomnia (43). One of the most common variants of sleep apnea is related to posture, the so called supine position-

related OSA and constitutes a dominant phenotype with a prevalence of 20 – 60% (42). Obesity is also considered a major risk factor for progression of OSA, with a prevalence of the disease in severe obese patients nearly twice that of persons with normal weight in an adult population (44). Non-surgical treatment of OSA is considered the first line of treatment, but it consists of a wide range of measures, including conservative positional therapies and weight loss, pharmacotherapy, positive airway pressure devices and mandibular advancement devices. The conservative treatment of OSA has shown its usefulness particularly in patients suffering from this specific type of OSA.

4.1 Conservative treatment

Supine position-related OSA is defined as a doubling of the apnea-hypopnea-index (AHI) in the supine position regardless of the number of events in the non-supine position. If the non-supine position is < 5 events/hour the condition is named supine-isolated OSA, otherwise it is named supine-predominant OSA (42, 45). The treatment consists of getting the patient to sleep in a non-supine position for the majority of the number of hours of sleep. Positional therapy is usually divided into two categories: advice on sleep hygiene, which still dominates the treatment options offered in general practice (46) and more recently the use of sleep position devices, like the electronic sleep position trainer (47) which has shown promising results in reduction of AHI and functional sleep outcomes in moderat OSA patients (48).
Weight loss as a treatment of OSA has been investigated in a randomized clinical trial by Kajaste et al. (49) using a behavioural weight reduction programme over two years. The average weight loss was 13,5% from the weight at baseline, resulting in a reduction of the ODI by over 50% at 6 and 12 months. However, weight loss achieved by conservative measures alone is limited, and more dramatic ways of reducing weight such as bariatric surgery has been promoted as one more treatment option in OSA (50).

4.2 Pharmacotherapy

There are two suggested pharmacological pathways in the theoretical medical treatment of OSA (51). One could try to enhance the airway volume and/or increase activation in

the pharyngeal dilator musculature, but the possible pharmacological substances or receptor targets still remain obscure. The second pathway is to raise the arousal threshold and/or reduce the sensitivity of ventilatory control mechanisms, an idea that has gained some interest due to available on-market drugs that can assert the pharmacological effects in question. Eszopiclone, a non-benzodiazepine sedative, is shown to increase arousal thresholds without impairing dilator muscle responsiveness in OSA patients with low arousal thresholds (between 0 and -15 cm H_2O) giving hope for treatment in a subgroup of OSA patients (52). Acetazolamide, a carbonic anhydrase inhibitor commonly known in the treatment of glaucoma, intracranial hypertension, altitude sickness and heart failure, will lower the post-apnea hyperventilation thus creating a more stable ventilatory control (reducing the so called "loop gain") resulting in less arousals in OSA patients (53). There is reason to believe that effective medication to treat OSA can be an alternative to using positive airway devices or undergoing surgery, but the lack of large-scale and stringently conducted randomized trials and adverse side-effects of the drugs has put this line of treatment on hold (54, 55).

4.3 Positive airway pressure (PAP)

The different types of PAP devices include continuous PAP (CPAP), auto-adjusting CPAP, bilevel PAP (biPAP), auto-adjusting biPAP, adaptive servoventilation (ASV) and average volume-assured pressure support (AVAPS) (56). All positive airway pressure devices involve three main components: a motor generating pressure, a mask that covers either the nose or both the nose and mouth, and a connecting tube between the motor and the mask. The aforementioned nEPAP is an exception to the rule, but large clinical data is scarce, and this form of PAP device will not be discussed further in this thesis.

4.3.1 CPAP

The mainstay of treatment is CPAP. Colin Sullivan, a respiratory physician at the Royal Prince Alfred Hospital, made the ground-breaking discovery of using positive

airway pressure applied through the nasal airways in a patient with severe apnea in June 1980. The patient was initially recommended a tracheotomy but was reluctant to the surgery. Instead he volunteered to try a pressure experiment. During the following night, Dr Sullivan and co-workers watched as they could "turn off" an "turn on" the patients apneas solely by adjusting the air pressure in the circuit (57).

Today the CPAP devices on market are delivering pressures in the range of 4 cm H_2O up to 20 cm H_2O. They are increasingly being made as auto-adjusting CPAPs that have the ability to decrease the pressure range once the breathing stabilizes after obstructive events (56), although a fixed pressure CPAP can be the treatment of choice if the patient experiences several positional changes that creates sudden increases in the degree of obstructions making the auto-adjusting CPAP unable to adjust in time (58).

4.3.2 BiPAP

When a patient requires a high inspiratory pressure, typically over 20 cm H_2O, a bilevel PAP can be applied. It will give a higher inspiratory pressure of up to 30 cm H_2O and lower the pressure during expiration, often improving the tolerance of the nasal mask during the night (56). The pressures of inspiration and expiration are independently adjusted and results in lower expiratory positive airway pressures compared to the CPAP treatment (59). Usually the BiPAP is of clinical importance in patients that is intolerant to CPAP treatment due to requirement of high inspiratory pressure as well as barotrauma complications, but the adherence of the BiPAP treatment is not considered improved compared to CPAP treatment, and the equipment is more expensive (60). Like the CPAP the BiPAP can be fitted with automatic adjustment of the pressure in response to respiratory events (Auto-adjusting BiPAP).

4.3.3 Adaptive servoventilation (ASV)

Like the CPAP and the BiPAP treatment, an ASV will increase the expiratory airway pressure preventing undue collapse of the airway during sleep. In contrast to the two former PAP devices, an ASV will also provide a dynamic adjustment of inspiratory

pressure support breath-by-breath and has been increasingly used in treatment of CSA (61) and some studies have shown favourable outcomes with ASV treatment on CSA secondary to heartfailure and CSR (62, 63). Recently the use of ASV in the treatment of chronic heart failure associated CSA with a left ventricular ejection fraction ≤ 45% and moderate or severe CSA has been advised against, due to a demonstration of increased risk of cardiac mortality in this subgroup. However, the treatment is still optional in chronic heart failure associated CSA with a left ventricular ejection fraction > 45% or mild chronic heart failure associated CSA (64).

4.3.4 Average volume-assured pressure support (AVAPS)

AVAPS is essentially a biPAP with an added feature of providing a more precise control of tidal volume in respiratory unstable patients (56). Patients with sleep-related hypoventilation disorders are expected to benefit from AVAPS treatment, in particular patients with obesity hypoventilation syndrome and patients with chronic respiratory insufficiency. In patients with a combination of chronic obstructive pulmonary disease (COPD) and OSA, the so-called "overlap syndrome" (65), studies show that patients experience an increased rate of sleep disturbances and have more profound nocturnal oxygen desaturation compared to patients who suffer from either disease alone (66, 67). In addition to supplementing the theory of "the unified airway" (68) in regard to COPD and upper airway SRBD, it raises the question of AVAPS as a possible biPAP treatment in patients with concomitant COPD and OSA (65).

4.4 Mandibular advancement devices (MAD)

MAD are dental splints that move the mandibula, the base of the tounge and the hyoid bone to a more anterior and inferior position, thereby increasing the pharyngeal airspace. In large scale meta-analysis MAD has shown to improve AHI by -9.3 events/hour, although CPAP had a larger treatment effect (AHI improvement by -25.4 events/hour) (69). MAD holds its position as the main non-PAP treatment available (70). Cephalometric data suggests that the mandibular plane angle and the distance from

the hyoid bone and the mandibular plane have a predictive value for treatment effect of MAD in OSA patients (71). Level A recommendations states that treatment with MAD for OSA is beneficial in patients with mild to moderate disease, and those that are non-tolerate of CPAP treatment (69,70).

5 Surgical treatment

In line of the problematic adherence rate of CPAP treatment over time, the question arises if the first-line treatment of today should be revised. Rotenberg (5) highlights this question in a review of 82 controlled clinical trials for CPAP treatment and 69 controlled and non-controlled surgery trials, one of the main findings being a large subset of patients not using the CPAP device at all or fail to use it enough hours during the night, as well as a larger mortality in CPAP users (7,1%) compared to patients undergoing uvulopalatopharyngoplasty (3,4%) (72).

The number of surgical therapies that are applied to treat OSA reflect the multifactorial pathways leading to the disease. Most physicians will advocate that surgical treatment will be secondary to failure of conservative treatment, or as a complimentary procedure to less invasive treatment options (61, 73). The aim of any surgical treatment is to address the anatomical site of collapse and alter the functional anatomy in a manner that reduces the respiratory upper airway collapse. It can do so by either stiffening the soft tissues, bypassing the airway obstruction or by increasing the upper airway dimensions (74).

5.1 Tracheotomy

Tracheotomy as treatment for OSA is the ultimate bypass procedure, creating a ventilation system that is independent on the function of the upper airways. In a recent meta-analysis, it was shown that tracheotomy significantly reduced the apnea index and oxygen desaturation index as well as subjective sleepiness and mortality in adult OSA patients (75). Both tubed and permanent (tubeless) tracheostomies are being performed, the latter being of importance due to its reversibility should the condition at some point

change (76). Complications to such treatment are common, consisting of a reduction in psychological or social functioning, as well as physical complications like skin infections, formation of granulation tissue, fistula formation and lower airway infections with plugging of the tracheostoma with crusts or mucus (77). Due to the relatively high complication rates, tracheotomy is considered to be an option in patients refractory to other forms of treatment.

5.2 Palatopharyngeal surgery

Uvulopalatopharyngoplasty (UPPP) and the less invasive variant, uvulopalatoplasty (UPP), is still among the most frequently performed SRBD surgeries (78, 79) and is often misperceived by many as equivalent with the term "upper airway surgery" (80). There are a multitude of variations in technique and use of surgical instruments, but all have a common goal of modifying the upper pharyngeal airspace and soft palate.
The variations in technique includes the Fujita technique, the Fairbanks technique, the lateral pharyngoplasty technique and the expansive pharyngoplasty technique. The main difference between the first two and the latter two is that Fujita and Fairbanks includes a resection of the uvula in the original surgery, while the pharyngoplasty techniques preserves the uvula and maximises the lateralization of the posterior pharyngeal pillars (81). Since then a number of modifications have been applied such as uvulopalatal flap surgery (82), expansion sphincter pharyngoplasty (83), palatal implants (84-86) and relocation pharyngoplasty (87). The variations in use of instruments varies from cold techniques using retractors and steel dissectors to hot techniques using laser, radiofrequency or ultrasound to perform the procedures.

UPPP was originally described by Ikematsu (88) and made popular globally through the description of the technique by Fujita et. al in 1981(89). The surgical success rate, defined as a 50% reduction in AHI, of single-level surgery with UPPP has been relatively low, just under 50% (90) and Friedman developed a three-stage clinical scoring system based on palate position, tonsil size and body mass index (BMI) in order to select patients to surgery (Table 1)(91). Palate position 1 – 4 describes how much of the palate is visible, 1 = entire uvula and tonsils, 2 = uvula but not tonsils, 3 = soft

palate, 4 = hard palate. Tonsil size describes the location of tonsils in relation to the tonsillar pillars and midline, 0 = no tonsils seen, 1 = tonsils seen in fossa, 2 = tonsils visible beyond anterior pillars, 3 = tonsils extended ¾ of way to midline, 4 = tonsils extended to midline.

Stage	Palate position	Tonsil size	BMI
I	1,2	3,4	< 40
II	1,2,3,4	3,4	< 40
III	3,4	0,1,2	< 40
IV	1,2,3,4	0,1,2,3,4	> 40

Table 1. The modified Friedman classification for OSA patients. Stage IV includes any patient with significant craniofacial or other anatomic deformities.

According to this selection, only stage I patients would benefit from UPPP alone with an increasing reduction in success with increasing clinical stage. Stage 1 patients had a success rate of 80.6%, stage 2 patients 37.9% and stage 3 patients 8.1% (91). Single-level surgical procedures have become less frequent and multi-level surgery has become more frequent over the past two decades (92), reflecting the current view that pharyngeal obstruction occurs at several levels of the upper airways.

5.3 Multi-level surgery (MLS)

The low level of success rate in single-level surgery in OSA has led to the proposal of MLS as an option for treatment (93). There are no exact definitions of MLS, but some authors refer to the concept if at least one surgical intervention to the tongue base or hypopharynx is combined with one or more surgical interventions to the soft palate or tonsils (93, 94). In a systematic review in 2008, Lin included articles only if they involved surgical intervention to at least two of the three following upper airway sites: nasal cavity, oropharynx, and hypopharynx.

The development of nasopharyngoscopy under sedation, so-called drug-induced sleep endoscopy (DISE), has enabled a 3D examination of the upper airway dynamics under

conditions that resembles natural sleep. The major advantages of this diagnostic tool are a more accurate description of the anatomical surgical landmarks and the possibility to plan treatment plans for individual patients (95). The introduction of DISE has also led to a reduction in unnecessary MLS procedures through identification of individual apnea sites in the upper airway, and an increased surgical success rate due to better treatment selection (96). Lin et al showed a surgical success rate of 66,4 % in 1,978 patients undergoing MLS, an improvement over single-level UPPP of 17%. On the other hand, the overall complication rate was found to be 14,6% (97). In recent years there are reports of using transoral robotic surgery (TORS) in performing MLS in OSA (98). The surgical success rate in a nonrandomized trial by Thaler et al. performing TORS with posterior glossectomy and lateral pharyngectomy in combination with UPPP was reported to 56% in patients with no prior OSA surgery, and the total sleep time spent at below 90% O_2 saturation was improved from 14% to 3.6% (99), and Garas et. al found an effectiveness over 75% in non-obese patients, and over 50% in patients with BMI 30-35 kgm $^{-2}$ (100). Although precision and visualization are far superior in TORS, the complication rates have been reported in the range of 20,5% - 24,4% and in addition the procedure is still costly compared to traditional treatments (98).

5.4 Skeletal surgery

Surgery of the airway skeletal framework includes genioglossus advancement, hyoid bone myotomy/suspension, maxillomandibular advancement (MMA) or mandibular distraction osteogenesis (MOD). The goal of this "box" treatment is to reposition the soft tissues by altering their suspension to the skeleton. While genioglossus advancement and hyoid bone myotome/suspension usually is not performed as single-level procedures but are often part of multi-level procedures including UPPP and tongue base surgery (101, 102), MMA is considered to be the most effective single surgery approach next to tracheotomy (103). Mean reductions in AHI are reported to be in excess of 80% and the rates of surgical success in excess of 85% (104) as well as marked improvement in lowest oxygen saturation levels (105), which makes the effect of MMA comparable to CPAP treatment. Complications to the surgery have been reportedly low, with a major complication rate of 1% (106). However, the procedure is

invasive, it alters the aesthetic appearance of the face and it requires longer hospital recovery time, and is still often regarded as a treatment for patients that are refractory to CPAP treatment or patients with established craniofacial deformities (103, 107)

5.5 Upper airway stimulation (UAS)

Stimulation of the lingual muscles can alter the airflow in the upper airways, demonstrated on humans during sleep by Schwartz et al. in 1996 by placing fine wire electrodes intramuscularly through the mouth. If the retractor musculature was stimulated the airflow decreased, and if the protrusor musculature was stimulated the airflow increased and was shown to decrease the frequency of obstructive events (108). An alternative, and less bothersome, approach emerged as hypoglossal nerve stimulation (HNS) or Upper Airway Stimulation (UAS) as described by Strollo et. al and Strohl et.al (109, 110) (Figure 4). The XII cranial nerve controls all intrinsic and extrinsic muscles of the tongue, and electric stimulation will counteract the inadequate neural drive, rather than the passive mechanical deficiencies treated by PAP therapy, surgery or MAD (110). In a randomized sham-controlled trial using transcutaneous electrical stimulation 47 % of the patients improved the oxygen desaturation index (ODI) compared with sham, with a total reduction of ODI by 10.0/hour and AHI by 9.1/hour (111). The UAS has been demonstrated to be safe and efficacious in moderate to severe OSA in patients with a BMI < 32 and AHI ≤ 50 and that did not have a complete palatal collapse, with an improvement in AHI from baseline of 75% and significant improvements in patient reported outcomes (112). The procedure requires DISE to be performed preoperatively in order to verify the site of collapse, and the development of a clinical pathway that can provide standardization of both procedure and patient selection is needed (113).

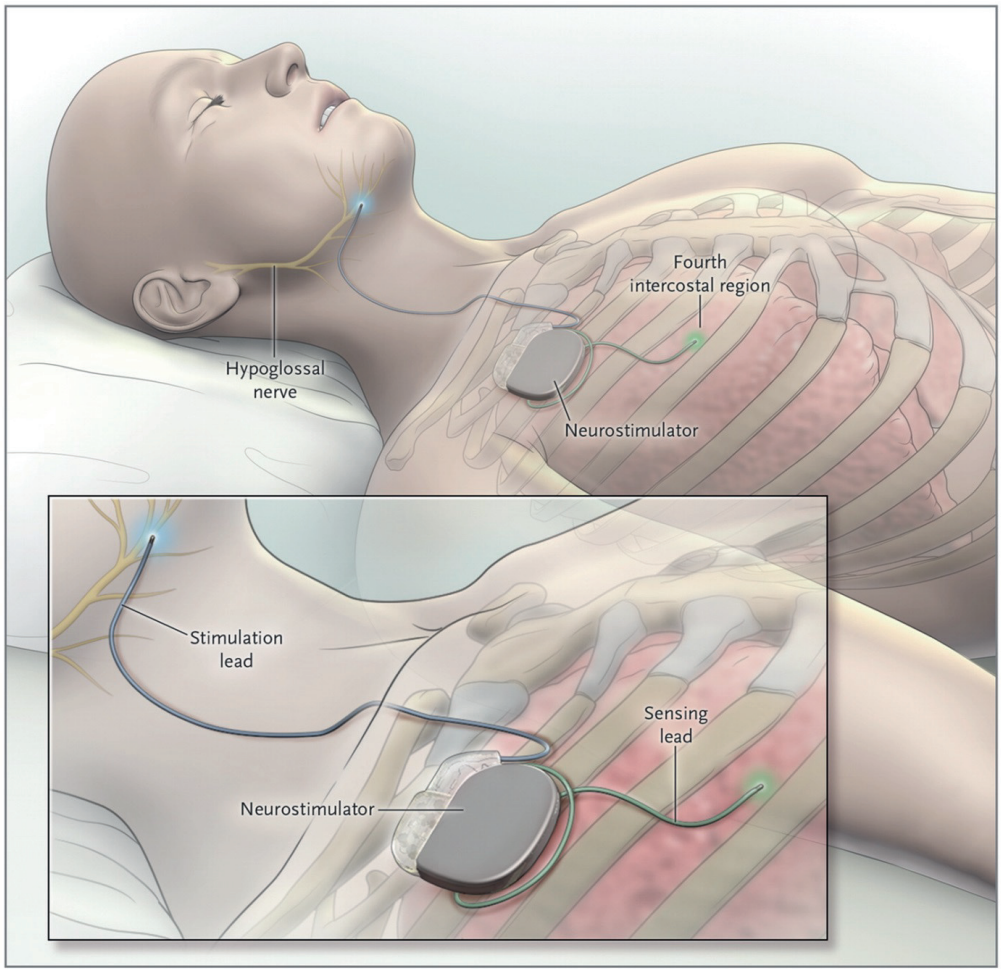


Figure 4. The sensing lead is placed in the intercostal muscles between the fourth and fifth rib to detect ventilator effort, the neurostimulator is placed in a pocket infraclavicularly and the stimulating lead is placed distally on the hypoglossal nerve to ensure a protrusion effect of the genioglossus muscle. From Strollo et al. (2014) (109), Copyright © Massachusetts Medical Society. Reprinted with permission.

5.6 Bariatric surgery

The prevalence of OSA in obese patients is reported to be approximately 70% (114). Romero-Corral displayed 19 studies assessing weight loss after bariatric surgery that showed an average reduction in AHI of 36, and an average reduction in BMI of 15, suggesting a reduction of 2,3 AHI pr unit reduction in BMI (50). On the other hand, bariatric surgery is major surgery with possible side effects, and only a few patients will have their OSA resolved completely (115).

6 Nasal involvement in OSA

In order to understand the possible influence that changes in the nasal airway can assert on upper airway patency, a thorough knowledge of nasal anatomy, causes of nasal obstruction and nasal airflow aerodynamics will be necessary.

6.1 Nasal anatomy

The nasal vestibule represents the skin-coated enlarged atrium in the most anterior part of the nose, it borders to the medial crus and the lateral crus of the lower lateral cartilage and the nasal floor (116). The most anterior area of the vestibule will often be described as the "external nasal valve" (117).

In addition to an "external nasal valve" there is also a substantial interest in the "internal nasal valve" even though there has been controversy as to the anatomy and terminology of this functional area of the nose (118, 119). Most authors agree upon a definition that includes the upper lateral cartilages, the piriform aperture, the anterior parts of the inferior turbinates and the septal wall (117, 120, 121).

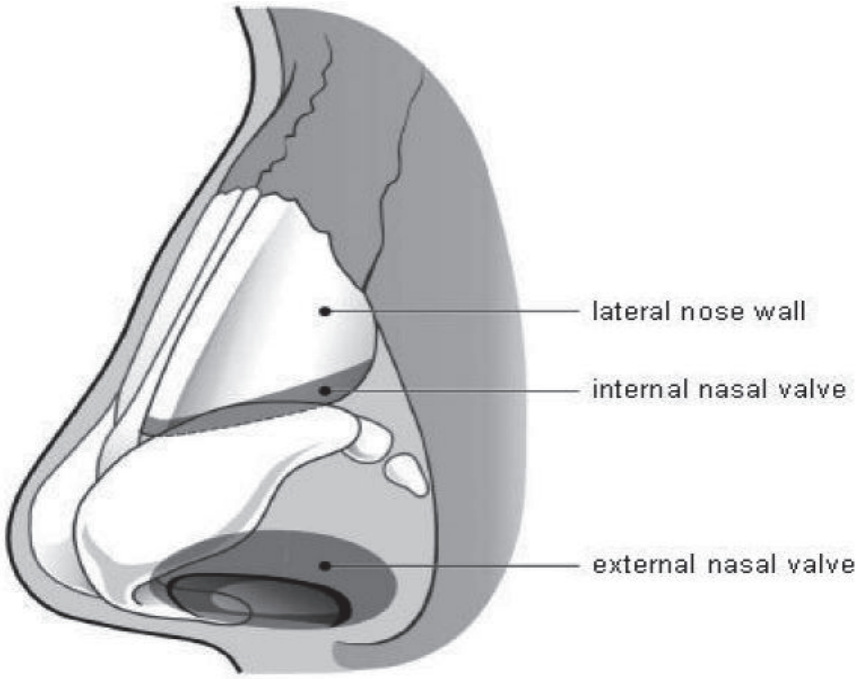


Figure 5. Illustration of the external and internal nasal valve area. From Bloching 2007 (117). Reprinted with permission according to the Creative Commons Attribution License.

The angel between the septal cartilage and upper lateral cartilages that define the roof of this area is reported to be 10 - 15° (121, 122), and the location is allegedly in the vicinity of 1.3 cm from the nares (119). The nasal respiratory section includes the larger part of the nasal cavity and includes the inferior, middle and superior turbinates (Figure 6). In contrast to the vestibule the mucosal lining of this part of the nose consist of pseudostratified respiratory epthelium that includes both ciliated, non-ciliated, mucous and basal cells (123). The turbinates demarcate the spheno-ethmoidal recess, superior, middle and inferior meatuses which allows airflow at resting conditions to be mainly laminar, with air flowing mostly through the middle and superior meatus when inhaling air and mostly along the middle and inferior meatus during expiration (124). The roof of the nasal cavity contains the olfactory region and it occupies approximately the upper third of the nasal respiratory section and is lined with olfactory epithelium including ciliated olfactory receptor neurons.

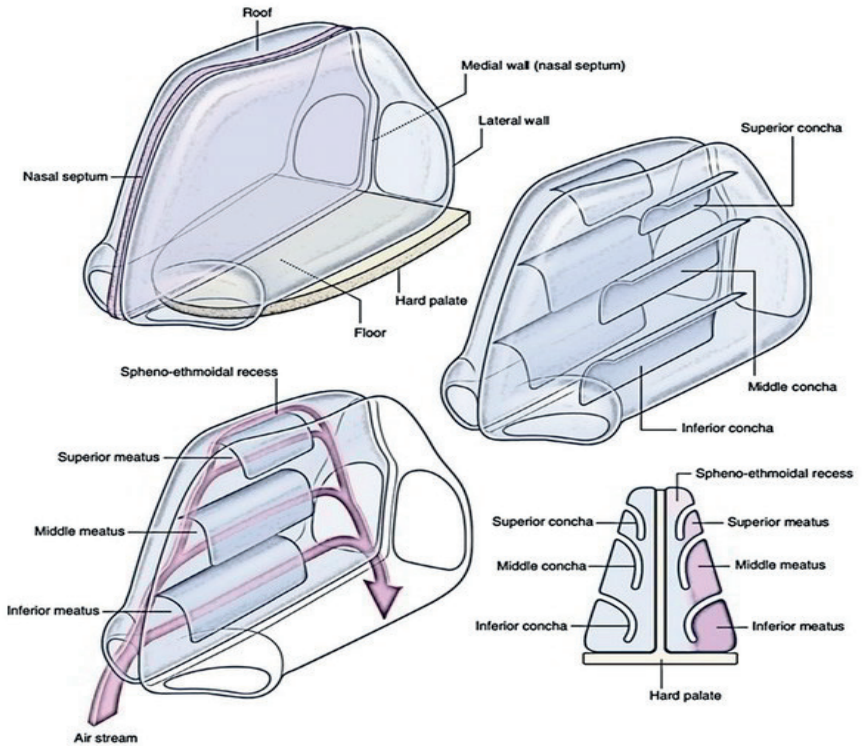


Figure 6. Schematic drawing of the nasal cavity, superior, middle and inferior turbinates (concha) and their corresponding meatus, and the nasal roof containing the olfactory region. "Nasal cavity" Earth´s Lab, July 24th, 2017. Web. 31st, Jan 2018. https://www.earthslab.com/anatomy/nasal-cavity/.

6.2 Causes of nasal obstruction

Nasal obstruction might be congenital or acquired at some point during a lifetime. It may be a result of a structural change in the nasal cavity or it may arise due to nasal congestion of the mucosal lining. An overview of possible causes of nasal obstruction has been suggested by Chandra (125) and a modified version is listed in table 2.

Structural	Inflammatory	Other
Choanal atresia	Rhinosinusitis/Rhinitis	Nasal foreign body
Adenoid hypertrophy	Nasal polyposis	Pregnancy
Concha bullosa	Samter`s Triad	Obesity
Cystic fibrosis	Inferior turbinate hyperplasia	Medical treatment
Ciliary Dysmotility	Infectious disease	Idiopathic
Neoplasms	Systemic disease	
Facial Trauma		
Surgical Trauma		
Rhinoseptal deviation		
Septal perforation		
Loss of nasal gateway competence		
Inferior turbinate hyperplasia		

Table 2. Causes of nasal obstruction. Modified from Chandra, Patadia and Raviv (125).

6.3 Experimental evidence

The arguably most compelling study that demonstrates a link between nasal function and development of upper airway collapse is the study by Suratt where upper airway collapse was induced by packing the nasal cavity with gauze in eight non-obese normal male volunteers without any prior nasal complaints (126). However, inducing apnea by blocking the nasal passageway completely is not a probable or accurate description of nasal obstruction in OSA patients. There is seldom a complete obstruction of the nasal cavity, but rather different degrees of obstruction in different levels of the nose, and even in cases with pan-sinusitis and grade IV polyposis there will be a gradual onset of fluctuating symptoms. Another study investigated both partial and complete obstruction of the nasal cavities in ten normal adults without any abnormalities of the upper airways and documented a significant increase in the number of apneas, as well as in the number of microarousals and alterations of sleep pattern (127). Lofaso et al. measured nasal resistance by posterior rhinomanometry in 528 unselected persons with snoring and found a higher nasal resistance in persons with verified OSA than in persons without OSA (128). EMG of the genioglossus muscle during nasal breathing has been shown to be significantly reduced after topical nasal anesthesia, and the mean phasic inspiratory EMG of both the genioglossus muscle and the alae nasi musculature was significantly greater during nasal breathing than during oral breathing suggestive of an influence on upper airway dilator muscles of nasal airflow (129). A compelling experiment demonstrating the nasal ventilatory reflex mechanism was performed by McNicholas where he induced increased upper airway obstruction after applying topical local anaesthesia in the upper airways in healthy subjects (130).

6.4 Clinical evidence

6.4.1 Allergic rhinitis (AR)

Allergic rhinitis is a highly prevalent disease (131) and is associated with nasal congestion and sleep disordered breathing (131, 132). Although the different mediators of AR such as histamine, prostaglandins, cytokines and leukotrienes may be directly

involved in sleep regulation (134), nasal obstruction associated with AR is in itself a cause of reduced sleep quality (135). The length of obstructive events in patients with AR are longer, and the frequency of the events higher, in periods when symptomatic nasal obstruction is dominant compared to asymptomatic periods (136). Treatment of nasal congestion with intranasal corticosteroids has shown a correlation with improved sleep and reduced daytime sleepiness (137). The use of leukotriene receptor antagonists in OSA patients with AR has demonstrated favourable results on OSA parameters in adults, but the effect of topical nasal decongestion is limited and might even aggravate sleep disturbances and is only recommended used as short-term treatment (138, 139).

6.4.2 Non-allergic rhinitis (NAR)

The role of NAR as a risk for OSA is still unclear, but some studies suggest NAR to be at least as high a risk factor, or higher, as AR. In an observational study of 48 adults OSA was diagnosed in 83% of those with NAR, compared to 36% of those with AR (140). More recently, Zheng et. al (141) demonstrated the prevalence of AR and NAR in 240 OSA patients to be 27.1 % and 28,7%, respectively. Despite the relatively high prevalence of AR and NAR in OSA, the presence of allergic disease did not seem to be associated with OSA severity. In a controlled prospective study, nasal cytology was performed in 19 OSA patients at baseline and after eight weeks with CPAP treatment, and compared to 13 controls non-compliant with CPAP (142). Rhinopathy was present in all OSA patients and the use of CPAP induced a significant reduction of infiltration of inflammatory cells (eosinophils, neutrophils, lymphocytes and muciparous cells) in the treatment group alone. Chronic rhinosinusitis (CRS) is associated with reduced sleep quality and reduced overall QoL (143, 144) and a recent cohort study concludes with a higher risk of CRS in OSA regardless of gender (145), but there is still no known causal relationship between development of CRS and OSA.

6.4.3 Structural nasal changes

Nasal endoscopy enhances the clinical evaluation of intranasal characteristics to a large extent compared to simple anterior rhinoscopy examination alone. A retrospective study on 274 OSA patients examined with flexible video fiberoptic examination revealed a total of 26.6% intranasal structural changes that required further treatment (146), septal deviations accounting for 20%. Nasal polyposis was found in 4% of the patients. When examining the frequency of pathological ear, nose and throat findings in OSA patients, Mayer-Brix established that 31% had one or more pathological findings and that 19% had obstructions of the nasal cavity (147). Dahlqvist et. al did a study of 766 patients with mild to moderate OSA and found nasal pathologies in 41% among men and 21% among women, where moderate to severe septal deviation amounted to 36% of the obstruction in the male noses and 20% in the female noses (148). Thus, based on these findings the prevalence of nasal septal deviation in an adult population with OSA lies in the range of 25 – 30 % or above, whereas a reported clinical diagnosis of septal deviation in 687 school children aged 6-15 years is found to be 9.5% (149), increasing with age as a confounding variable. On the other hand, septal deviation prevalence in normal adults is substantial, up to 90% in selected patients in selected ENT hospitals, with 34% lacking symptoms on nasal obstruction (150).
The effect of treatment of intranasal deformities on OSA has been a matter of discussion for decades. Studies on the effect of single surgery on inferior turbinates in OSA patients is scarce and there are no measures on definite objective OSA endpoints, only on patient comfort and morbidity (151).

6.4.4 Epidemiological evidence

There is probably no reason to doubt that inducing partial or complete obstruction of the nose will result in an increased upper airway collapse during sleep and that nasal congestion can give rise to subjective complaints of daytime sleepiness, as shown in the experimental studies by Surat (126) and Lavie (127).

Healthy subjects will almost exclusively breathe through the nasal cavity during sleep, as demonstrated by Fitzpatrick et. al in 2003 (152). The prevalence of nasal obstruction in a normal population is reported to be 15% (154) and the prevalence of nasal obstruction in untreated OSA patients is recently investigated in the Icelandic Sleep Apnea Cohort (ISAC) study, and was found to be 35% (154).

In addition, data from the Wisconsin Sleep Cohort study, an ongoing largescale longitudinal study of causes and consequences of sleep disorders, has showed a positive correlation between self-reported nasal congestion and daytime sleepiness and incidence of snoring (155). In another study on the same cohort material, nasal congestion was associated with AHI > 5, but was strongly related to habitual snoring regardless of the level of AHI. The odds ratio (OR) for habitual snoring and severe nasal congestion at night was 3.3 (132). Snoring and obesity seem to be useful markers for OSA progression over time (156). The strong association of nasal congestion with habitual snoring will therefore raise the question of a causal link between altered nasal ventilation and OSA development. It also points towards a possible mechanism for early intervention to decrease nasal congestion as an approach to reduce OSA prevalence.

6.5 Effects of nasal treatment in OSA

6.5.1 Conservative treatment

The treatment of nasal congestion secondary to chronic rhinitis will usually consist of applying nasal decongestants and/or topical corticosteroids to reduce oedema and inflammation. More recently the use of antileukotrienes has shown effect on AR (157) but there are no trials showing the effect of the latter on OSA. The effects of nasal decongestants like topical oxymetazoline has been investigated in two cross-sectional and blinded studies. Kerr et al. found a mild improvement in arousel index, but no alterations in AHI or oxygen saturation or daytime sleepiness in a small study of ten moderate to severe OSA patients given topical oxymetazoline versus placebo (158). McLean et al. did a sham-controlled crossover study (topical decongestants and external

nasal dilator strip) in ten patients with moderate to severe OSA and found a significant reduction in AHI, improvement in sleep architecture and reduced oral breathing, but no effect on daytime sleepiness. The design of the study does not differentiate between the effect of the decongestant given, or the use of the external dilator strip (159). Kiely et al. did a double blinded trial in 10 snorers (normal AHI) and 13 OSA patients (mean AHI 26.5) that were randomized to treatment with either topical Fluticasone or placebo and found a significant reduction in AHI and subjective nasal resistance, but no difference in sleep architecture, snoring or oxygen saturation (160). These studies are small, and the conclusions that are drawn should be interpreted with caution.

6.5.2 Surgical treatment

Adenotonsillectomy in children is known to improve the objective OSA parameters dramatically in children, with one relatively large study on 79 children aged 3 – 14 years, showing a reduction in AHI of 87% (preoperative value 27,5 – postoperative value 3,5) (161) and in a meta-analysis Friedman demonstrated an overall treatment success rate in 1,079 patients of 66.3% (162). Adenoidectomy alone, accounting solely for the relief of posterior nasal obstruction in children, was shown to be comparable to adenotonsillectomy in 121 non-obese children with tonsil size < Friedman stage 3 and lower AHI < 10 (163).

The surgical treatment of nasal obstruction in OSA patients have included a variety of different procedures pooled together and are often performed with a set of different techniques, including septal deviation surgery, surgery of the inferior turbinates, functional and esthetic rhinoplasty, external and internal nasal valve surgery, functional endoscopic sinus surgery and polypectomy (164). To date, there are no randomized controlled trials that has demonstrated an effect of nasal surgery on AHI (165). There are, however, some meta-analysis published over the last decade that demonstrates an effect of nasal surgery on OSA as a primary endpoint. Wu et al. showed a small, but significant effect on pooled nasal surgery on AHI and ESS scores in a meta-analysis published in 2017 (9), and the meta-analysis by Li et. al. in 2011 demonstrated an overall effect of nasal surgery on OSA of 16,7% (166) whereas Ishii et al. in 2015 found an effect on daytime sleepiness alone (16). In addition, Värendh et. al demonstrated

that surgical treatment of chronic rhinosinusitis with nasal polyposis reduced the risk of OSA in a subgroup of patients (154). The inclusion of a multitude of surgical procedures that affects several intranasal anatomical sites, and the tendency to use questionnaires or other qualitative tools to measure endpoints rather than objective measurements has been standard practice (164), reflecting the insufficiency of pre- and postoperative objective measures of nasal airflow.

7 Nasal aerodynamics

7.1 Fluid mechanics

In order to characterize the effect of nasal surgery, one has to perform tests on the basic variables; the nasal airflow and the solid structures of the nasal cavity, much in the same way an engineer would do tests on a model dam prior to building it, or tests on steel alloys and the effect of wind-turbulence before constructing a bridge. The Bernoulli equation combines Newton's laws of motion - which states that an acceleration of air within a tube (the nose) must come from an unbalance in static pressure at two different locations within the tube – with the energy conserving statement saying that the total energy of the airstream inside the tube is unchanged. As the total energy must be unchanged, an increase in kinetic energy (velocity) will be accompanied by a reduction in potential energy (static pressure – p). Using the "dynamic pressure" equation which states that the kinetic energy of a volume of air is equal to the half of the density (ρ) times the squared velocity (V) of this volume of air, and the total amount of pressure (H) is given by the sum of both the potential and the kinetic energy, we have the following equation:

$$H = p + \frac{1}{2}\rho V^2$$

This Bernoulli equation states that the sum of static pressure and dynamic pressure in the flow tube remains the same. It follows from the equation that if the velocity increases, the static pressure (p) will be decreased in order for the total amount of pressure (H) to be unchanged. If the area of the tube decreases, the kinetic energy must increase since the same volume must pass through a smaller space, and again the static pressure must decrease in order to maintain the laws of energy conservation.

If we transfer this to the nasal cavity, in order for the total energy of the airstream to be constant when an obstacle in the nasal cavity makes the volume smaller and the velocity across the obstruction increases, the static pressure in that area decreases. Conversely, when we alter the nasal cavity during surgery, making the nasal cavity area larger, the velocity drops and the static pressure increases. When static pressure increases, the negative pressure required to drive the flow of air through the nasal cavity will be reduced. Under normal circumstances the Bernoulli effect will accelerate the air from an area with high static pressure (the nasal orifice) to an area with low static pressure (the "internal nasal valve" area).

The Bernoulli equation is regarded as the simplest model for flow of a fluid through a pipe, it concerns itself only with applying the law of conservation of mechanical energy to the moving fluid. For low velocities, the flow will be laminar (typically 12 – 18 m/s in the "internal nasal valve" area, slowing to 2-3 m/s in the posterior part of the nose at resting conditions) (167). The laminar flow through a pipe is described by the Hagen-Poiseuilles law, introducing the length of the pipe and the viscosity of the fluid as a measure of friction. It states that the flow rate (F) is proportional to the pressure difference between the proximal and distal end (nasal orifice to the nasopharynx) and the fourth power of the radius of the pipe:

$$F = \frac{\pi p r^4}{8\eta l}$$

Here p is pressure, r the radius and l the length of the pipe and η equals the viscosity of the fluid. π remains the mathematical constant of 3.14 (the ratio of a circles circumference to its diameter). Even a small increase or decrease of the radius will alter the flow significantly, modified by the viscosity of the fluid or gas flowing through the pipe.

The Hagen-Poiseuilles law states that flow is directly proportionate with pressure, and we find the resemblance to Ohm`s law describing that the current through a conductor is directly proportional to voltage, and it is convenient to write the equation as Ohm`s law, introducing the concept of flow resistance (R):

$$F = \frac{p}{R} \quad \rightarrow \quad R = \frac{p}{F} \text{ (Ohm`s law)}$$

From the Hagen-Poiseuilles law we get that:

$$p = \frac{8\eta l F}{\pi r^4}$$

Thus,

$$R = \frac{8\eta l}{\pi r^4}$$

The concept of flow resistance can be described as the opposition to flow caused by the forces of friction. As the above equation tells us, the resistance is inversely proportional to the airway radius to the fourth power. A small airway will have a much greater resistance than a large airway. The nasal cavity represents the narrowest part of the total upper airway, and nasal resistance accounts for at least 50% of the total airway resistance. Within the nasal airway, the area near the internal nasal valve contributes the maximal resistance (168).

The above mentioned physical equations are the foundation of the basic understanding of how flow through a tube occurs, the nasal cavity being no exception. However, Bernoullis law applies to a cylindrical shaped tube, and Hagen-Pouiseuilles law applies to only laminar flows, relatively high viscosity and relatively long or narrow tubes. They fail to explain fluid dynamic changes due to wall stress and vortical flow. The nasal cavity is not cylindrical, and the airflow is often a mixture of both laminar and turbulent flow, depending on the airflow velocity and on changes in intranasal anatomy. Low viscosity and a wide pipe may give rise to turbulent flows and influence of the friction factor, which makes it necessary to use more complex models to understand the fluid dynamics. The Darcy-Weisbach equation introduces the Reynolds number, a dimensionless quantity used in fluid dynamics to help predict flow patterns. At

Reynolds number below 2000 laminar flow usually occurs, and turbulent flow occurs usually when the Reynolds number is above 2000. The Reynolds number is defined as:

$$Re = \frac{\nu D}{\mu}$$

ν = fluid velocity, D = tube diameter and μ is the fluid dynamic viscosity.

The Navier-Stokes equations are regarded as the most influential equations in the study of viscous fluids, taking into account both viscosity of the fluid and thermal conductivity. The equations are a set of coupled differential equations that in theory could be solved for any given flow problem by calculus, but they require major approximations (like the simpler Euler equations) in order to be solved analytically. However, computer codes can employ Navier-Stokes equations in numerical solutions of highly complex fluid flow problems, by different techniques such as finite-element methods (as demonstrated in paper 4), finite-volume methods and finite-difference methods. This branch of fluid dynamics is referred to as Computational Fluid Dynamics (CFD) and is currently being used in most engineering fields and in industrial products and systems, including aerodynamics, hydrodynamics, meteorology, architectural design, and recently in biomedical research and diagnostic, including upper airway disease (168-170)

7.2 Measures of nasal airflow and patency

The measurement of nasal airflow can be recorded during forced inspiration showing the maximal inspiratory flow, or with simultaneous pressure recordings (171).
Nasal patency can be evaluated using diagnostic imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) and volumetry, but the portable acoustic rhinometry (AR) is the preferred diagnostic tools due to reduced costs, its simplicity and reproducible technique (172).

7.2.1 Peak Nasal Inspiratory Flow (PNIF)

PNIF consists of a nasal mask which the patient holds over the nose without distorting the alar sidewalls or the upper lateral cartilages. The patient will be asked to inhale as hard as possible through the nose starting at full expiration. Usually three sets of satisfactory conducted inspirations will be obtained and the mean or the highest value (173) is taken as the true value of PNIF. It is a relatively cheap and fast technique, it does not depend on computers for analysing the data, and it has a good reproducibility with a reported correlation coefficient of 92% (174).

7.2.2 Rhinomanometry

Rhinomanometry will provide a measure of nasal resistance by obtaining the airflow in the nasal cavity and the pressure gradient between the nasal orifice and the pressure in the choana that drives the airflow (the narionchoanal pressure difference). In chapter 7.1 we stated the resemblance of Hagen-Poiseuilles law to Ohm`s law stating that the resistance is a derivative of the pressure (P) and the airflow (F):

$$R = \frac{P}{F}$$

Active anterior rhinomanometry is the most common method of rhinomanometry (175). It measures the airflow in one nasal cavity while the narionchoanal pressure gradient is obtained from the contralateral side. It will measure the nasal resistance in $Pa/cm^3/s$ at a differential pressure of 150 Pa, and the normal nasal airflow resistance under congested nasal mucosal conditions are reported to be 0.25 $Pa/cm^3/s$ (176).
Patients with preoperative higher nasal resistance are more likely to benefit from surgery, reporting higher subjective satisfaction outcomes than patients with lower preoperative nasal resistance (177). Rhinomanometry provides an overall assessment of the relation between pressure drop and flow but does not consider the influence of anatomical or physiological obstructions in the nasal cavity.

7.2.3 Acoustic rhinometry (AR)

AR generates an acoustic wave transmitted into the nostril through a tube. It uses the reflected sound signals to create a plot of the minimal-cross sectional areas (MCA) as a function of the distance from the nasal orifice. These data can in turn be used to analyse nasal cavity volumes (178). It will produce an area-distance curve which usually shows at least three deflections. The two most anterior deflections will represent the nasal vault and the head of the inferior turbinate, while the third notch in the posterior part of the nasal cavity will often be more variable, demonstrating the reduced accuracy of AR in this section of the nose (179). One of the two most anterior notches in the area-distance curve will almost invariably represent the absolute MCA, though this will vary according to the state of congestion (173). AR provides an objective, static view of the anterior section of the nasal cavity, in contrast to the dynamic physiological assessment provided by rhinomanometry.

7.2.4 Nasal congestion index (NCI)

NCI is a measure of nasal obstruction due to mucosal odema. It quantifies the reversible mucosal congestion and is believed to be of use for evaluating subjective complaints of nasal obstruction (180). It is defined by the formula:

$$\frac{Decongested\ value - baseline\ value}{baseline\ value}$$

7.3 Subjective nasal symptoms and Quality of life

7.3.1. Nasal Obstruction Symptoms Evaluation survey (NOSE)

The NOSE survey consists of five items, and each scored using a 5-point Likert scale to make a total score range of 0 through 100. The five items are nasal congestion or stuffiness, nasal blockage or obstruction, trouble breathing through my nose, trouble sleeping and inability to get enough air through the nose during exercise or exertion. It

is found to be a valid, responsive and reliable instrument that is easy to complete, and that has a possible role in measuring outcomes in adults with nasal obstruction (181).

7.3.2 Sino-Nasal Outcome Test (SNOT)

Presently the Sino-Nasal Outcome Test consists of several nasal, sinus and general items to determine the disease specific health related QoL measure in patients with rhinosinusitis (182). The test is a modification of the 31-item Rhinosinusitis Outcome Measure (183) and comes in three major versions, the SNOT-16, SNOT-20 and SNOT-22. In addition, there is a proposed SNOT-23 in which the aesthetic appearance of the nose after surgery is made an item (184). These QoL instruments have all been validated and found to be reliable, easy to conduct and responsive to meaningful clinical change of condition (185).

7.3.3 Visual Analogue Scale (VAS)

There is a strong correlation between subjective VAS for nasal obstruction (NO-VAS) and nasal resistance (186) and VAS has proven to be significantly correlated to validated instruments like the rhinoconjunctivitis quality of life questionnaire (187)intr. Both normative and symptomatic values of subjective nasal obstruction can be established for meaningful clinical use (188).

8 Aims of the studies

8.1 Overall aim

The primary aim of this thesis is to evaluate the subjective and objective outcomes in nasal airflow and patency between OSA patients and healthy controls. The secondary aim is to introduce a multidisciplinary approach involving adjacent fields of structural and fluid mechanical engineering in order to update our description of nasal airflow and patency, and its influence on velopharyngeal insufficiency in OSA patients.

8.2 Multidisiplinary research team

Prior to the start of the research in 2010 it was obvious that the key to predicting any outcome of OSA treatment was to fully comprehend the physical mechanisms underlying OSA development. We needed to improve our understanding of the airflow in the upper airways, the upper airway features and characteristics responsible for the syndrome to occur. In order to achieve this, mathematical models were needed. The multidisciplinary research group that was formed consisted of specialist within each of the following different disiplines; ENT surgery, computational fluid dynamics and structural engineering, with the overall aim to try to form a basis for a novel understanding of OSA and ultimately create a better diagnostic and treatment tool for the disease. It is clear that it is in the interface between these specific scientific areas that the challenges arise; for instance, to calculate the effect that changes in airflow will exert on the different soft tissues in the pharynx, how the elasticity or stiffness of the soft tissue will affect the airflow in turn, or how to interpret how changes in airflow can give rise to subjective, qualitative sensations of nasal obstruction, or lack thereof, in patients with SRBD. The research group formed 4 different work-packages (WP 1 - 4) in order to bridge the gaps between the different scientific fields, and this phd thesis is based on parts of WP 1.

Although the focus of the multidisciplinary research group is of a magnitude that is beyond the scope of this thesis, the different work-packages form a backdrop for the current clinical research and it is essential that it is described briefly in this section.

8.2.1 Work-Package 1 (WP 1): Clinical research

The clinical assumption of an improved subjective effect on sleep when performing reductive surgery of the inferior turbinates in addition to septoplasty prompted the investigation of effects on OSA parameters in patients having either septoplasty alone or with concomitant inferior turbinate reduction (paper 1). A comparative study of nasal airflow and patency between OSA patients and a normal control group was performed as well as a comparison on validated QoL measures between the groups

(paper 2 and 3). Data was further collected on 30 patients with OSA and intranasal deformities, consisting of CT and MRI imaging of the nasal cavity and upper airways, AR, PNIF and rhinomanometry and VAS and SNOT questionnaires on nasal obstruction. Excised animal soft tissue (animal laboratory, NTNU) was obtained for studies of structural properties and elasticity in WP 2. The patient specific data obtained on geometry (paper 4), flow and pressure were provided for WP 4.

8.2.2 Work-Package 2 (WP 2): Soft tissue modelling

Realistic material models for the upper airway soft tissue is required in order to carry out fluid-structure interaction simulations. Test data of mechanical response of biological soft tissue is very scarce, but recently the Department of Structural Engineering at NTNU has manufactured a biaxial test rig that can test small pieces of soft tissue in different ambient conditions such as air, solvent and at different temperatures. WP 1 would provide WP 2 with excised biological soft tissue from the upper airway. Commercial software such as Abaqus (189) is to be used in order to make finite element programs in 2D or 3D dimensions. WP 2 would provide WP 3 and WP 4 with material properties required to make tine interaction between soft tissue and fluid in the upper airways.

8.2.3 Work-Package 3 (WP 3): Mathematical modelling of fluid-structure interactions (FSI)

The mathematical modelling will be based on a simplified 2D model. A multi-block approach will be used to represent the geometry in the upper airways, which allows using structured grids for complex geometries. The deformation of the soft tissues will be modelled in collaboration with WP 2. A high order time integration scheme will be used for accuracy and powerful parallel computers provided by NTNU and the Norwegian Metacenter for Computational Science (NOTUR) will be employed for very large simulations on fine grids. The WP 3 fluid-structure interaction model (FSI) will be used as a standard calibration for the CFD modelling developed in WP 4.

8.2.4 Work-Package 4 (WP 4): Patient Specific Modelling

Patient specific modelling consists of two parts. The first part consists of establishing a 3D CFD model of the upper airways based on geometry obtained in CT/MRI data from WP 1. By performing CFD simulations of specific patients, correlations of key flow parameters to treatment (in this case intranasal surgery) can be evaluated. The second part consists of implementing the FSI model to be able to assess the impact of the interaction between fluid and the deformable fluid-tissue interface. WP 4 will aim at fulfilling three main tasks: 1) geometry modelling, 2) fluid dynamics and 3) validation of the model. It relies on the results from WP 2 for structural properties of the soft tissues and on WP 3 for developing a sub-grid model required to obtain a converged solution. Relevant software, such as Mimics (190), will be used to process data from WP 1 before and after nasal surgery in order to form a basis for CFD analysis of the qualitative results of surgery and quantitative effect on flow parameters.

8.3 Specific aims

8.3.1 Paper 1

The aim of paper one was to evaluate OSA parameters and subjective measures of nasal obstruction and sleep quality in patients that had two types of nasal surgery performed. In one group septoplasty was performed as a single procedure, in the other group both septoplasty and surgery of the inferior turbinates was performed.

8.3.2 Paper 2

The aim of paper two was to investigate the nasal patency and nasal airflow in OSA patients compared to a healthy control group using AR and PNIF.

8.3.3 Paper 3

The aim of paper three was to establish an association between subjective sino-nasal complaints, nasal airflow and sino-nasal QoL in patients with OSA compared to a healthy control group using PNIF, VAS scores and SNOT-20.

8.3.4 Paper 4

The aim of paper 4 was to investigate simulated/experimental biomechanical properties of the velopharynx in OSA patients undergoing intranasal surgery for nasal obstruction using a computational finite element method (FEM) based on CT images and soft tissue composition.

9 Materials and methods Paper 1 – 4

The thesis consists of four papers that differ to some extent in design and methods. The first paper is an observational retrospective cohort study, paper two and three has a cross-sectional design with cases and normal controls that have been enlisted prospectively over a five-year period, and the last paper is an experimental computational simulation based on clinical data in six patients with OSA and nasal obstruction that requires nasal surgery. The trials were approved by the national regional ethics committee and registered in Clinicaltrials.gov. In paper 1, 2 and 3, SPSS (SPSS inc., Chicago, IL, USA) was used for the statistical analysis. Version 19.0 was used in paper 1 and version 23.0 was used in paper 2 and 3. Due to the mathematical calculations in paper 4, MATLAB (MathWorks®, version R2015b, The MathWorks, Inc., Natick, Massachusetts) was used.

In the following sections, there will be a consecutive description of the methodology, inclusion and exclusion criteria, data collection and statistics in paper 1, paper 2 and 3 and paper 4.

9.1 Paper 1

9.1.1 Method

The first paper is a descriptive retrospective cohort study in which all OSA patients who underwent either septoplasty alone or septoplasty with turbinectomy in the period august 2008 until December 2010 was eligible for participating in the study (figure 7). All patients signed an informed written consent prior to collecting the data. A simple dichotomous questionnaire was constructed to evaluate the subjective evaluation of nasal surgery on nasal obstruction and quality of sleep. Portable sleep polygraphy was performed at baseline and three months after nasal surgery. The patients were referred to the sleep clinic by general practitioners or otolaryngologist due to suspicion of SRBD. Since this trial was purely descriptive and retrospective in its design, there was no loss to follow up, and the response to the questionnaire was 76% in the septoplasty group and 77% in the combined surgery group.

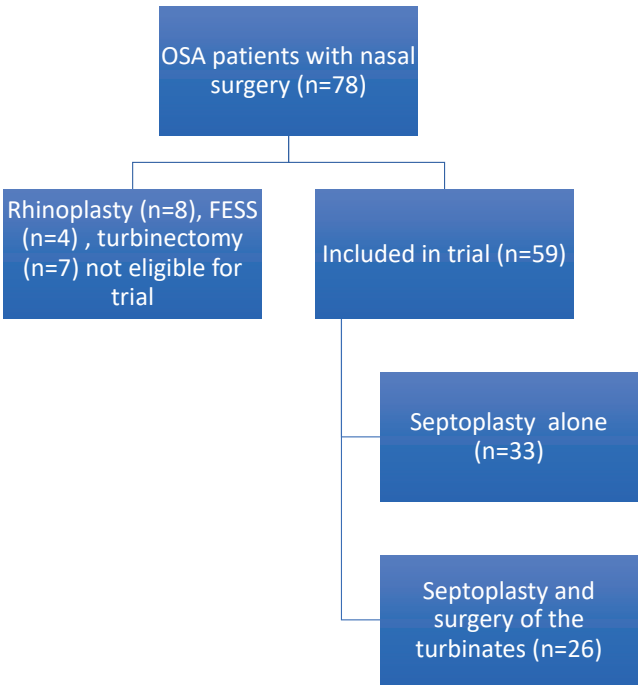


Figure 7. Flow chart of the patient selection in paper 1.

9.1.2 Inclusion and exclusion

All patients underwent a nocturnal sleep polygraph to ensure the OSA diagnosis. Patients with confirmed OSA and clinically significant nasal obstruction due to a septal deviation with or without hypertrophy of the inferior turbinates were offered intranasal surgery. They were included in the trial if the AHI was > 5 and the body mass index (BMI) was < 35. Exclusion criteria were evidence of chronic rhinosinusitis or enlarged adenoids and prior nasal surgery or prolonged use of nasal steroids over the last three months.

9.1.3 Data collection

All patients underwent a nocturnal sleep polygraph using Embletta™ Portable Diagnostic System (RESMed, San Diega, California, USA) or Reggie polygraph (Camtech, Oslo, Norway) at the point of diagnosis and three months postoperatively. At the trial start they were asked to evaluate the effect of the surgery on nasal obstruction and sleep quality. The alternatives in the dichotomous questionnaire were: 1. Did you experience an effect on nasal obstruction after surgery? Yes or No. 2. Did you experience an effect on your sleep quality after surgery? Yes or No. The answers were graded in a visual analogue scale ranging for 0-100 (divided into equal tenths 0-10) with 0 = no agreement and 10 = full agreement. The primary outcomes consisted of the alterations in AHI, ODI, BMI and the Epworth sleepiness scale (ESS) between the groups. The secondary outcomes were assessments of subjective evaluations in nasal obstruction and sleep quality between the groups.

9.1.4 Statistics

In paper 1 the Wilcoxon matched-pairs test was applied to measure the difference in mean of paired observations before and after surgery in variables without normal distribution, while variables with normal distribution were evaluated using the paired t-test. An independent t-test was used for comparison of means between groups. To obtain a power of 0.80 we needed 31 patients in each group with the significance level at 0.05 and a clinical meaningful difference in AHI of 10 between the groups. A p-

value < 0.05 was considered statistically significant. The values of AHI were skewed and log transformation using natural logarithm was used to transform data to normality.

9.2 Paper 2 and 3

The collection of data from OSA patients and controls from 2010 – 2015 constitutes a common database for both papers. The following description of method, inclusion and exclusion criteria and data collection is thus common to both.

9.2.1 Method

The data collected in the assessment of nasal patency, nasal airflow and validated sino-nasal QoL between cases of OSA patients and a cohort of healthy controls was matched for gender and there was no statistical difference in age, level of education, self-reported heart disease or allergy. 109 patients with verified OSA were considered for inclusion in the study, sixteen patients were excluded due to inability to perform PNIF or inadequate results when performing AR, resulting in 93 patients included in the trial (figure 8). All patients were referred to the sleep clinic by general practioners, ENT specialist, specialist in pulmonary or internal medicine to confirm a suspected SRBD. 103 controls were selected from outpatient clinics at Aleris Hospital and the ENT department, St. Olavs Hospital, and among hospital workers and workers outside of the hospitals as part of their annual health check-up. The OSA population is predominantly male and our patient group was no exception with a male proportion of 73 %. The control group was deliberately matched for gender so that confounding due to gender specific differences could be reduced. One of the controls were excluded due to inability to perform PNIF and ten were excluded due to heavy snoring, daytime drowsiness or suspicion of SRBD bringing the total number of controls that were part of the trial to 92 (figure 8). The request to join as controls was performed by registered nurses prior to nasal examination in order to be blinded to the clinical outcome. All study subjects signed a written consent prior to inclusion in the study. Nasal patency was measured using AR, nasal airflow was measured using PNIF. The subjective evaluation was conducted using SNOT-20 and VAS for nasal obstruction. The primary outcomes in paper 2 were

differences in minimal cross-sectional areas in two specific areas in the nasal cavity, as well as differences in nasal cavity volume and nasal airflow between the groups. The primary outcomes in paper 3 were differences in subjective measures of nasal obstruction and QoL between OSA patients and healthy controls, and the relationship between subjective measures of nasal obstruction and nasal airflow.

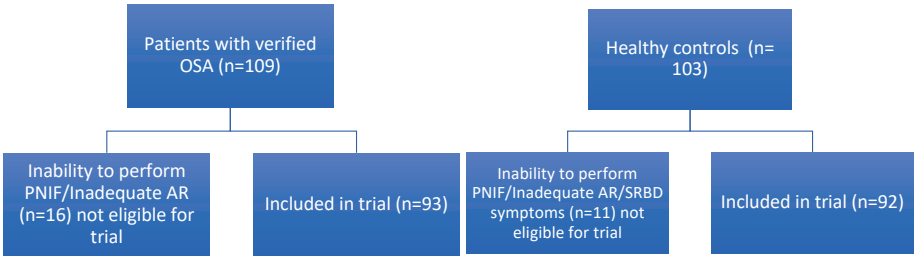


Figure 8. Flow chart of the patient selection in paper 2 and 3.

9.2.2 Inclusion and exclusion

We included patients and controls between the age of 18 – 75. The patient group had verified the OSA diagnosis with a portable sleep polygraph. The exclusion criteria in both groups were previous nasal surgery, the use of nasal steroids or decongestants the last three months prior to inclusion as well as clinical evidence of chronic rhinosinusitis. In the control group, complaints of daytime drowsiness, excessive snoring or observed apneas by others were regarded as additional exclusion criteria.

9.2.3 Data collection

As in paper 1, all patients included in paper 2 and 3 had their OSA diagnosis verified with a portable sleep polygraph. In the period 2010-2013 we used the Embletta system (Embletta™ Portable Diagnostic System, Resmed, San Diego, California, USA). From 2014 we used the Nox Medical T3 system (Nox Medical T3™, Resmed, Reykjavik, Iceland). Apnea was defined as a drop in peak signal ≥ 90% of pre-event baseline

lasting for ≥ 10 seconds. Hypopnea was scored if the peak signal dropped by ≥ 30% of pre-event baseline using nasal pressure for ≥ 10 seconds in association with ≥ 3% arterial oxygen desaturation. AHI > 5 was considered abnormal. All sleep test results were checked manually by a sleep physiologist experienced in interpreting sleep recordings. The measurements of nasal patency were made using an acoustic rhinometer (Rhiometrics SRE2100™, Rhinoscan version 2.5, built 3.2.5.0; Interacoustics, Minneapolis, MN, USA). Three trained investigators performed the measurements with the test person sitting directly in front of them, and the mean of three approved measurements from each nasal cavity was defined as the true value. The rhinometer was set to calculate the minimal cross-sectional area (MCA) and nasal cavity volume (NCV) in two areas of the nasal cavity. The most anterior part was defined as 0 – 30 mm measured from the nasal orifice, and the posterior part was defined as 30 – 52 mm from the nostril, thus defining the $MCA_{0\text{-}3}/NCV_{0\text{-}3}$ and $MCA_{3\text{-}5.2}/NCV_{3\text{-}5.2}$ respectively. The measurements were obtained at baseline and 15 minutes after decongestion of the nasal mucosal lining with topical xylometazoline (Otrivin™ 1 mg/ml, Novartis, Basel, Switzerland). PNIF was measured before AR was performed, again both at baseline and 15 minutes after decongestion. The same operators performed the test using a portable PNIF meter (in-check DIAL™; Clement Clarke International, Harlow, Essex, UK). The mean of three approved PNIF measurements was recorded with the subjects in a sitting position directly opposite the operator and the head held in a level position. NCI was calculated for both MCA and NCV, following the formula described in section 7.2.4. The Sino-Nasal Outcome Test-20 (SNOT-20) was used as the preferred instrument of measuring health related QoL in paper 3. The latest modified version, SNOT-22, includes the additional items of experienced nasal congestion and reduced sense of smell and taste, but this version was not validated in Norwegian at the onset of the trial and could not be used. The patients were asked to grade the 20 items on the SNOT questionnaire on a Likert-type scale from 0 (no complaint) to 5 (severe complaint). The scores were calculated in two separate manners. The mean value of the response to the 20 items was defined as the total SNOT score. The twenty items were further divided into four subsets as described by Browne (191) reflecting the rhinological complaints, ear and facial complaints, sleep function and psychological issues. The mean value of each subset was calculated and is believed to a more precise way of reporting SNOT

values, compared to reporting mean total scores alone (192). The visual analogue scale for nasal obstruction (NO-VAS) consists of eleven specific symptoms that patients and controls reported on a 100-mm scale. Nasal obstruction, headache, facial pain, facial pressure, reduced sense of smell, nasal discharge, sneezing, coughing, snoring, oral breathing and reduced general condition were graded from 0 (no symptoms) to 100 mm (as troublesome as can be).

9.2.4 Statistics

In paper 2 and 3 all data showed a normal distribution and an independent t-test was used to compare the mean values between the groups. The sample size calculations in paper 2 was performed before the trial started and showed that we needed 91 patients in each group in order to obtain a power of 0.80 with the significance level set to 0.05 and with a clinical significant difference in MCA of 0.05 cm^2. In paper 3, in order to detect a difference in SNOT-20 of 0.2 between the groups, we needed 100 subjects in each group with the power set to 0.80 and the chosen significance level at 0.05. Taking into account a probable dropout rate of ten percent, we needed 101 persons in each group at baseline. The data were matched for gender variance, and there were no significant differences in age, educational level or self-reported heart disease or allergy. However, there was a significant difference between the groups regarding weight and BMI, reflecting the strong association between bodyweight and OSA. Multivariate linear regression analysis was applied to adjust for the possible confounding of bodyweight. In the subgroup analysis in paper 3 we also applied one-way analysis of variance (ANOVA) with Bonferroni for multiple comparisons, and the Pearson correlation coefficient was used to evaluate the correlation between NO-VAS and PNIF.

9.3 Paper 4

Paper 4 is the result of the collaboration with the multidisciplinary research team, and the design reflects the effort of trying to bridge the basic science of structural soft tissue biomechanics with clinical medical research and differs somewhat from a classic

clinical research design in being an experimental study with the power to create new hypothesis of sleep apnea development.

9.3.1 Method

Paper 4 is an experimental computational study based on six OSA patients with nasal obstruction that required intranasal surgery. Data was collected from a total of 30 patients with OSA and concomitant nasal obstruction in need of surgery as described in the multidisciplinary collaboration in section 8.2.1. A biomedical engineering program, Mimics (Materialise Mimics Innovation Suite®, Mimics research 19.0, Leuven, Belgium) was used to process and reconstruct 3-D geometry of patient specific CT scans, which were needed to create a finite element mesh of the anatomy. The FE method is a computational mathematical technique solving complex partial differential equations in physics (figure 9). Two different finite element models were constructed for each patient, one based on geometric properties of the soft palate (homogeneous model) and one on the soft tissue composition of the soft palate (layered model) using the computer-aided engineering software Abaqus (Abaqus/CAE® version 6.14-1, Dassault Systèmes Simulia Corp, Providence, RI, USA).
FE simulations were carried out using the Neo-Hookean model, which is the simplest hyperelastic material model and is an appropriate approximation of the behaviour of soft tissues of the upper airways at small strains (193). We conducted the simulations with a soft, medium and a stiff Neo-Hookean material model. The parameters used in the homogeneous model are found in the works of Birch and Srodon, Pirnar et. al and Yu et. al (194-196). The model parameters for the adipose, glandular, muscular, tendinous and mucosal tissues in the layered model is obtained in the works of Kuehn and Kahane, Ettema and Kuehn, Kuehn and Moon and Cho et. al (197-200). The primary outcomes in paper 4 was the influence of the difference in soft palate geometry on displacement due to gravitational loads and on closing pressure and the secondary outcome was to evaluate possible correlations between computed critical closing pressure and objective measures of OSA in patients undergoing nasal surgery.

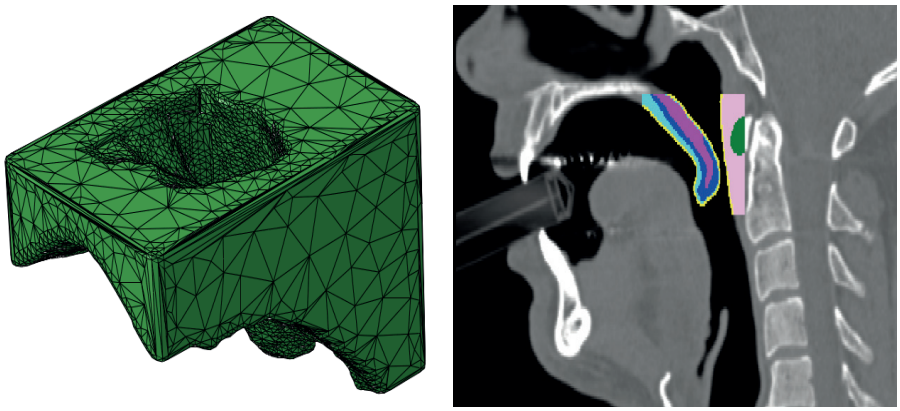


Figure 9. 3-D mesh of the velopharynx used in the FE model (left) and CT image with colour plot of the anatomical boundaries (right).

9.3.2 Inclusion and exclusion

Inclusion criterias were verified OSA with a portable sleep polygraph, age 18 – 75 and clinical structural intranasal anomalies requiring nasal surgery. Exclusion criterias were previous nasal surgery, use of nasal steroids or topical decongestants three months prior to inclusion and evidence of chronic rhinosinusitis. Out of 30 potential candidates, there were five that were excluded due to missing or inaccurate CT images, one did not show for the postoperative sleep polygraphy, one was excluded due to surgical treatment of a thyroid tumor that compressed the airway and one patient withdrew from the trial, bringing the total number of possible candidates to 22. Six patients displaying large variations in soft palate anatomy were then selected to participate in the study (figure 10).

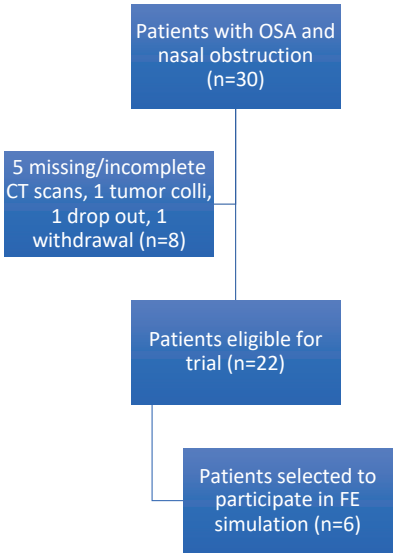


Figure 10. Flow chart of patient selection in paper 4.

9.3.3 Data collection

Due to high computational costs, there is a limitation on the number of patients that can be included in the study. Previous studies of soft tissue biomechanics of the upper airway are usually based on single cases. We managed to include six patients mainly because we had access to master thesis students performing the computational simulations. We selected six patients that displayed a wide array of variations in the anatomy of the soft palate based on preoperative CT images. CT scans with a resolution of 0.46 mm in the x and y-direction and 0.7 mm in the z-direction were processed in Mimics and formed the basis for the homogeneous model. The layered model was based on histology studies in literature since no experimental data was available. The homogeneous model was used to evaluate the influence of macro-anatomy on gravitational loads and pressure. The layered model was utilized to investigate the impact of the different soft tissues that constitutes the soft palate.

9.3.4 Statistics

In paper 4 the objective was to establish possible correlations between geometrical anatomical measures and stipulated outcomes of closing pressure, thus clinical sample size calculations were of little interest. The linear least-squares method is an approach where a mathematical model can fit to data where the ideal values are expressed linearly. This method was used to calculate a suitable fit measure. The sum of squares due to error (SSE), the R-square and the root mean squared error (RMSE) was obtained to express the goodness of fit. A small value for SSE and RMSE and a R-square close to 1 would indicate a good fit when validating the model with the anatomical measures in the patient samples. In addition to measuring goodness of fit tests for single anatomical measures, we also constructed combined anatomic measures creating "shape factors". When anatomic features were combined we increase the accuracy of the test by including more influencing factors, which may otherwise have been neglected.

10 Results

10.1 Results of paper 1

When comparing the results before and after surgery in group 1 (septoplasty alone) and group 2 (combined septoplasty and reductive surgery of the inferior turbinates), there was a significant reduction in AHI in group 2 from 17,4 to 11,7 ($p < 0.01$). All the other objective parameters remained unchanged, but the subjective evaluation in ESS was highly significant before and after surgery in both groups. In group 1 ESS was reduced from 11,54 to 10.00 ($p < 0.01$) and in group 2 from 9,74 to 7,59 ($p < 0,01$). When comparing the mean differences between the groups, AHI was significantly lower in group 2 (mean AHI difference 5,7) compared to group 1 (mean AHI difference 1,7), $p = 0,029$. There were no significant differences of mean ODI, ESS or BMI between the groups. In group 1, 96% reported that the procedure was effective in regard to nasal obstruction, and 68% that it improved the quality of sleep. In group 2, the corresponding proportions were 85% and 80%. The results of the questionnaire did not

show a statistical difference between the groups, but a significantly larger proportion in group 2 reported a good improvement in sleep quality postoperatively.

10.2 Results of paper 2

In paper two we investigated the differences in nasal geometry and function between OSA patients and healthy controls using AR and PNIF. The mean MCA_{0-3} in the OSA group was 0,49 cm^2 compared to 0,55 cm^2 in the healthy group ($p < 0,01$) and the mean NCV_{0-3} was 2,51 cm^3 in OSA patients compared to 2,73 cm^3 in controls ($p < 0,01$). PNIF measurements were significantly lower in the OSA group compared to the healthy control group (105 litres/minute versus 117 litres/minute, $p < 0,01$). NCI for volume was lower in the OSA group both in the anterior part of the nose (0,054 versus 0,09, $p = 0,03$) and in the anterior and posterior part combined (0,29 versus 0,37, $p = 0,03$). The difference between the means was statistically significant at a chosen level of significance of 0.05.

10.3 Results of paper 3

In paper three we added measurements of subjective nasal obstruction and function to the growing database of information on differences in nasal characteristics between OSA patients and controls. The mean SNOT-20 score was 1,69 in the OSA group and 0,55 in the control group ($p < 0,001$). Correspondingly, the NO-VAS score of 41,3 in the OSA group was significantly higher compared to the score of 14,7 in the control group ($p < 0,001$). There were similar differences in the SNOT-20 subsets: In the rhinologic subset the OSA score was 1,28 and in the controls 0,46 ($p < 0,001$), in the ear/facial subset the OSA score was 0,83 compared to 0,39 in controls ($p < 0,001$), in the sleep subset the corresponding scores were 2,52 versus 0,79 ($p < 0,001$) and in the psychological subset the scores were 1,88 compared to 0,49 ($p < 0,001$).

Within the OSA group we stratified the patients into levels of AHI severity: mild (0 – 14,9), moderate (15,0 – 29,9) and severe (≥ 30). We found a positive correlation with the severity of OSA and total SNOT score and NO-VAS score, however the differences

between the stratas were not statistically significant. Within the four subsets of SNOT-20, there was a statistical difference only in the sleep subset and the different levels of OSA severity: Mild and moderate levels of AHI had a mean difference of 0,89 ($p < 0,05$), and mild and severe levels of AHI had a mean difference of 0,88 ($p < 0,05$), but there was no statistical difference between moderate to severe levels of AHI, with a mean difference of 0,02 ($p = 1,0$).

We found that the change in PNIF after decongestion was positively correlated to NO-VAS score only in the healthy control group. The higher the NO-VAS score (i.e. the more obstructed the patient believed him/herself to be) the higher the degree of inspiratory flow after decongestion.

The influence of other disease such as asthma and allergy seemed to play a part only in the OSA group. The asthma and allergy proportion of the OSA group scored significantly higher in the VAS symptom "general health" than both patients with reported heart disease and patients claiming not to have any accompanying disease.

10.4 Results of paper 4

In the computational FE simulation, we looked at the influence of soft palate anatomy on tissue deformation due to gravitational loads, and on closing pressure.

Influence of anatomy on tissue deformation due to gravitational loads:
A "shape-factor" of the soft palate was constructed in the homogeneous model. It is determined by the product of the soft palate length (l) and mean width (w), divided by its mean thickness (t):

$$\text{Shape factor} = \frac{lw}{t}$$

The shape-factor demonstrated a good correlation with the maximal displacement of the soft palate due to gravitational loads, i.e. a long, wide and thin soft palate will be more prone to displacement. Even though the mean thickness, direct length and mean width

separately were good fits to the FE model, the shape-factor yielded an even better fit to the model.

In the layered model the displacement of the soft tissue was extremely small due to the stiffness of the oral mucosa used in the material model (gingiva). Adipose soft tissue, muscle tissue and glandular tissue are comparable in stiffness to the medium homogeneous model in our Neo-Hookean material model, but the parameters for oral mucosa is more than one order of magnitude stiffer. The layered soft palate model does therefore not describe the material parameters of the soft palate appropriately.

Influence of anatomy on closing pressure:
In the homogeneous model the displacement of the soft palate at the critical closing pressure can be visualised in the FE simulation. We found that the maximal displacement can be seen at the tip of the uvula, but the location of the airway collapse was at the level of the lateral attachments of the soft palate to the pharyngeal wall in five out of six patients. The soft palate width was the sole anatomical feature that correlated best with the simulated closing pressure. The wider the soft palate, the less negative the closing pressure, and hence the more prone to velopharyngeal collapse. However, one interesting feature in the simulations was that the maximal displacement of the soft palate seemed to have a relationship to closing pressure that was of a higher order, possibly exponential.
In the layered model, we could replace the values for the unsatisfactory material parameters of the oral mucosa with the values for the homogeneous model, letting the other soft tissue parameters remain unchanged, thus creating a new mixed layered model. We found a more profound difference between the different material models in patients with more negative closing pressure. The higher the closing pressure (and thus the more compliant the soft palate is and more prone to collapse) the less the composition of the different soft tissues seems to matter.

Influence of strain on closing pressure:
Strain is a description of resistance to deformation in the soft tissue, i.e. deformation is the change of the shape of an object when forces are acting upon it, strain is a force

created when bonds within the object are resisting the deformation. The total transverse strain of the soft palate showed a strong correlation to closing pressure. A less negative closing pressure corresponds to small strain in the transverse direction.

Influence of nasal surgery on the soft palate:

The closing pressure of the velopharynx in our FE models did not show a linear relationship to preoperative AHI levels, nor to change in AHI after nasal surgery. The FE model of the soft palate does not seem to be a suitable tool to predict the outcome of nasal surgery on OSA parameters.

11 Discussion

11.1 Design

This thesis is based on four papers with different type of designs. The idea that different surgical treatment regimens of nasal obstruction in OSA patients might lead to a difference in outcome of OSA parameters emerged from clinical observations in the treatment of these patients over several years. We designed paper one as a retrospective cohort study due to the relatively large pool of patients that had already been exposed to the treatment. The retrospective design allowed us to make use of the available data on OSA parameters before and after surgery, what type of nasal obstruction was present in each case and what type of surgical treatment that was performed. The use of a historical setting is effective when studying relatively rare or unusual exposures. Since most OSA patients do not complain about nasal obstruction, and even fewer have a nasal condition that requires nasal surgery, the retrospective design seemed to be an appropriate choice. In spite of being less costly and less time consuming than a prospective study, the obvious disadvantage is that the design does not allow for control of selection of patients prior to study start and that the data collected was not intended for a scientific study from the start. The retrospective design is more likely to have poor control of possible confounders as well as bias in both selection of patients, in detection of the exposure, in performance of the surgery and in measuring and analysing the outcomes on OSA parameters.

In paper two and three there is an observational case and control design where patients and controls are included prospectively over a five-year time period. However, the collection of data for the AR, PNIF as well as SNOT-20 and NO-VAS scores are done at one point in time for each single subject participating in the trial. The use of cross-sectional collection of data comparing the exposed group of OSA cases with matched non-exposed controls have the advantage of testing to see if the disease (OSA) is related to the outcome of interest (i.e. difference in MCA, NCV, PNIF, SNOT-20 scores and NO-VAS scores), but it will not give any evidence of causality between the exposure and the outcome. Using a case-control design on the other hand can control the selection into cases and controls and thus identify a possible risk factors in both groups separately. Even though any evidence of causality in a case and control setting also is suggestive at best, the level of evidence is stronger and repeated measurements that points in the same direction will solidify an opinion of causality in many cases. In theory, one could construct a prospective cohort study in order to establish a causal link, but it would be time consuming and costly and dependent on large longitudinal population databases most likely conducted on a national scale. A controlled randomisation of treatment of nasal obstruction in a selected group of patients with similar nasal anomalies could be feasible and could demonstrate a causative link between nasal obstruction and OSA by proving a reduction of disease in the active treatment group compared to a placebo group. Such a design could, however, raise some ethical issues in particular with randomising patients to less effective treatments or no treatment at all.

Paper 4 differs in design due to the experimental computational methods used. It is a theoretical study using empirical data/observations from CT images of the upper airways and results from portable sleep polygraphs in six OSA patients undergoing nasal surgery. These empirical anatomical and physiological data are then used to construct theoretical correlations between anatomy, gravitational loads and soft tissue strain to simulated closing pressures of the upper airway, and OSA parameters before and after nasal surgery. This design is not apt to determine any causal mechanisms between exposures and outcomes. The FE models created are nothing but approximations of the real world, in this case patient specific anatomy and soft tissue

properties of the velopharynx. Instead, they can create new hypothesis that can be applied in future clinical trials, or used for validation purposes in comparison to established models that represent the real system.

11.2 External validity

The idea of making the results of one study applicable to other situations, with other study participants at another time and place is usually referred to as external validation or generalisation of the study. The information of study participant recruitment and implementation of the procedures that are performed are crucial to the external validity of the study. The patients selected in our study were all recruited from Aleris Hospital Solsiden, Trondheim which is a tertiary referral hospital for the middle part of Norway. All OSA patients were recruited from this specific geographical area after referral to the sleep laboratory from general practitioners or specialists in the fields of otolaryngology-head and neck surgery, pulmonary medicine or internal medicine. In paper one the study participants were asked to join the trial by sending them an invitation in writing by the registered nurse in charge of the sleep laboratory. These patients had already been through the necessary surgical treatment, and there is an obvious risk of selection bias either by patients that wanted to participate because of poor treatment effect or a feeling of obligation because they recently had been receiving treatment. The same applies for the results of the questionnaire, in which patients with very favourable results might be overrepresented in the fraction that completed and returned the forms. However, the selection bias would in this case be distributed evenly among the two particular groups that we wanted to compare. The data were collected in retrospect and numerous possible interfering events might have occurred, of which the investigators have no means of controlling, and that could influence the outcome of the study in a profound way. The same surgeon performed all surgeries but one and all patients were treated within the same hospital with the same standard surgical procedures and in approximately the same timeframe.

The healthy control group used in paper two and paper three were recruited among hospital workers and persons attending annual health check-ups required by their

employers in various businesses located within the Trondheim area. The controls were included in a database intended for prior trials involving the study of nasal involvement in asthmatics (201), but due to the high proportion of males in the OSA group we had to adjust for the gender differences. 29 women were randomly removed from the controls and 28 men were added as new controls, thus making the gender distribution equal in both groups. The selection of controls is somewhat problematic. Ideally, they should be representative of the same population as the cases with the exception of not having the disease in question themselves. One may argue that the controls in our trial does not fulfil this requirement, since the control group never had a sleep polygraph test performed to verify that they did not have OSA. However, if we had certain knowledge that all controls were without the disease, the outcome in the two groups would have been even more pronounced than what we were able to demonstrate. In addition, clinical symptoms of OSA among the control group were grounds for exclusion from the study. Hence, the controls were matched with the OSA group for all matters except the disease in a manner that was foreseeable and manageable within the limits of the project.

In paper four we selected six patients out of thirty solely on basis of having large variations in the soft palate geometry, measured on patient specific CT images. All the CT images were performed at the department of radiology, St Olavs Hospital, Trondheim. We used a CT protocol that determined a fixed position of the head compared to the surroundings and all patients were fitted with a 20-mm mouthpiece to ensure the same position of the mandibula relative to the maxilla when performing the image diagnostic procedure.

11.3 Internal validity

Internal validity refers to our ability to trust the cause and effect relationship in the study, in other words how we can reduce the possible confounders or random variables that influences our results. The investigations of nasal patency were all performed at the rhinological laboratory shared by the ENT dep St Olav and NTNU, by a total of three experienced members of the ENT department/NTNU. The procedures were performed

in an ordered, preplanned manner to reduce the performance bias. The sleep polygraph was performed as an overnight procedure at the sleep laboratory, Aleris Hospital, Trondheim attended at night by fifth or sixth year medical students. All sleep reports were examined manually by a sleep physiologist to reduce the possible misdiagnosis of the automatic scoring. The same surgeon performed all procedures except one, ensuring that the variations in surgical technique were kept at a minimum.

Several types of cognitive biases can influence any of the participants in such a way that the true response of the subjective evaluation of nasal obstruction is prevented. There are three particular types of bias that may be of influence in our trial: recall bias, response bias and acquiescence bias.

The SNOT-20 questionnaire and NO-VAS were graded by all participants prior to the nasal examinations and recall bias is a plausible pitfall. To reduce the risk of recall bias, the participants were asked to consider the items of the SNOT scores going back only the last two weeks prior to completing the questionnaire, and only one week in regard to the symptom score of the NO-VAS.
Response bias is prevalent in surveys and questionnaires where self-reporting is involved. It can be related to any part of the process where the patients receive information and later is asked to produce a response. One specific type of response bias is acquiescence bias, where the subjects will tend to agree or endorse statements that they think is correct, that the investigator would like to hear or will be beneficial to the study or themselves. If the patients believe that there might be a link between the ailment they are afflicted with (OSA) and the degree of nasal obstruction, they are inclined to answer the questionnaires accordingly.

A complete eradication of response biases is impossible. In trying to remedy the possible bias problems, we used a questionnaire and a VAS scale that has been validated in the native language spoken by the study participants, and the questionnaire was kept short in order to reduce survey fatigue. We also conducted the survey so that the answers were anonymous. Another way of reducing response bias would be to

conduct the survey online, diminishing the possible cognitive bias pressure and increasing the chance of the participants to answer truthfully.

11.4 Discussion of the results

The main result of this thesis is the demonstration of a smaller nasal airway in OSA patients compared to healthy controls, and that the geometrical differences seem to be located in the anterior to the middle part of the nose. This finding is supported by the larger effect on OSA parameters in patients undergoing both septoplasty and surgery of the inferior turbinates, the latter being of importance due to their anatomical placement starting in the "internal valve" area, situated in the anterior section of the nasal cavity, and stretching on into the choanal area in the posterior part of the nose. Shuaib and Stupak demonstrated a significant reduction in AHI of 35% in 26 patients who underwent functional rhinoplasty to repair their nasal inlet area. Excluding patients with a BMI > 30 resulted in further improvement in AHI with a reduction of 57% from the baseline (18). The difference in nasal geometry between OSA and healthy subjects is supported by the profound difference in the degree of nasal obstruction measured by subjective Qol instruments such as the SNOT-20 and the NO-VAS, and the reduction in airflow in OSA compared to controls measured by PNIF described in paper 3. A possible method of investigating the biomechanical soft tissue changes that occur in OSA is suggested in the fourth and last study. Although it does not explain why nasal surgery may change OSA parameters, it represents a novel approach to investigation of closing pressure and the influence of anatomy and soft tissue strain in OSA development. It may be regarded as a way of making alternative hypothesis of OSA development and as a starting point for new clinical trials.

11.4.1 The nasal gateway

The most important feature of this thesis is the reduced cross-sectional area and volume found in the anterior to middle part of the nasal cavity in OSA patients compared to

controls described in paper two. MCA and NCV in the anterior part in OSA were not correlated to BMI, suggesting that weight is not the dominating cause. The increased effect on OSA parameters when performing septoplasty combined with reductive surgery of the inferior turbinates as shown in paper one might be a result of changes made in the anterior section of the nasal cavity as described by Shuaib (18), or by a more complete resolution of nasal obstruction due to more extensive surgery as suggested by Stupak where he advocates selecting OSA patients for maximal nasal obstruction and performing extensive nasal surgery as the key to nasal surgical success in these patients (202). The combination of correcting an anterior septal deviation, as well as reducing the volume along the entire length of the inferior turbinate is in accordance with the theory of Stupak. The second important feature is the reduced ventilator function in OSA patients compared to controls demonstrated by PNIF in both paper two and three.

Previous studies on this topic include Liu (203) comparing nasal obstruction in subgroups of OSA, showing that severe OSA tended to have smaller MCA compared to mild and moderat OSA and the study by Hellgren in 2009 (204) demonstrating that MCA was unaffected by postural change (from a sitting position to supine positon) in OSA patients, while being reduced in normal subjects. Our results are in accordance with the study by Liu, showing smaller MCA in OSA patients compared to controls, even though measures of MCA or NCV at different sections within the nasal cavity were not obtained in their study. The study by Hellgren also bear a resemblance to our study in the description of regulatory mechanisms. He concluded that OSA patients lack the regulatory mechanisms that control the supine nasal patency. We found that OSA patients are lacking the response to decongestion measured by PNIF, suggesting a loss of regulatory mechanism in the nasal mucosa otherwise present in healthy subjects. This thesis adds on to this knowledge by introducing the anterior part of the nasal cavity as the area of interest in OSA, showing not only that there is a correlation between anterior nasal cavity dimensions and OSA, but also that OSA patients seem to be suffering from nasal obstruction to a higher degree than controls. Paper four demonstrates that computational FE models may represent a tool for investigating the biomechanical alterations that occur in the upper airway in OSA.

Paper one suggests an added effect on OSA by combining septal surgery with reduction of the nasal turbines. It also demonstrates the high degree of patient satisfaction on nasal obstruction after septoplasty, and perhaps more interestingly the relative high impact on subjective sleep improvement. 80% in the combined surgery group vs 68% in the single septoplasty group stated improvement in sleep after surgery, coinciding with the significantly higher scores on the SNOT subdomain of sleep in OSA patients demonstrated in paper three. The combined surgery was performed when there was a clinical indication present for both procedures. We can therefore not conclude that surgery of the inferior turbinates will be beneficial in all septoplasty surgeries in OSA patients, but we point to the importance of also including such surgery when there are clinical reasons to do so. The surgery is usually performed by reducing the mucosal thickness along the entire length of the inferior turbinates, or by fracturing the posterior part of the turbinate towards the lateral side. There is no certain way of determining how much or how little the inferior turbinates should be reduced. Too much resection will increase the chance of developing an empty nose syndrome (205) and too little will not relieve the obstruction. Another unanswered question is the influence of the different methods used in treating inferior turbinate hyperplasia. The different methods could in theory give different outcomes, i.e. if nasal mucosa was damaged more than necessary by one specific method thus giving reduced viscosity of the mucus layer and a larger friction component to airflow.

The main target area for surgical mucosal reduction is the anterior 1/3-1/2 of the turbinate, which constitutes part of what we call the internal valve area. This area remains poorly defined, with a narrative assertion that it begins 1.3 cm from the nares (119). The reference to a "valve" is also imprecise. A valve is usually an organ that regulates flow by either stopping the flow or regulating the flow in one or two directions, and there exists no such nasal intrinsic mechanism that can be detected by nasal endoscopy or imaging modalities. However, computational fluid dynamics can demonstrate the development of a vortical flow in the vicinity of the "valve" area during inspiration (206), and this feature might represent a possible confounder when investigating nasal resistance in this area of the nose. Along the same lines there is a concept of an optimal angle of 10-15° between the septum and the upper border of the upper lateral cartilage which is thought to be of key importance within the "internal

valve" area. This angle is inconsistent at best when measured using endoscopy or imaging, and the results after surgical treatment with spreader grafts or flaring sutures is not predictable (121). Attempts to alter this angle as an isolated treatment of nasal obstruction is therefore not sufficient.

Some authors have therefore argued that science should replace the old "myths" of the "external and internal nasal valve", and that the nomenclature should be changed accordingly (207). An "inlet area" is a well-defined term in fluid mechanics and can replace the "external valve" terminology. Beyond this inlet area there is vertical narrowing that can expand or contract, and the term "nasal gateway" is suggested as an appropriate descriptor of this area, replacing the notion of an "internal valve". The "nasal gateway" should be defined by computational 3D modelling, starting at approximately 2 cm from the nares, extending at least 1 cm beyond the pyriform aperture (119, 207) reaching into the middle section of the nasal cavity. Our colleagues in fluid and mechanical engineering are familiar with such modelling and there should exist a common ground for upper airway research that crosses the traditional boundaries between medicine and engineering science to achieve more accurate pathophysiological OSA models, as discussed in chapter 3.3, as well as a more accurate model of the pathophysiology of nasal obstruction in general. The multidisplinary team involved in our four work-packages is an attempt to achieve such a common platform, and to contribute to the change from non-scientific to scientific description of the complex physiology in the nasal airway.

We did not find any linearity between closing pressure in the velopharynx and AHI in patients with nasal obstruction. Hence, it should be natural to look for other possible sites of collapse in the upper airway, such as the oropharyngeal space, and to control confounding variables, such as obesity. Much like patients with an overcrowded oropharynx being staged in the Friedman classification, there may therefore be grounds to stage OSA patients with nasal obstruction in a similar manner, taking into account the scale of both oropharyngeal and nasal obstruction and BMI. The combined degree of anterior nasal obstruction and oropharyngeal obstruction can determine which subgroup will benefit the most from nasal cavity surgery or medical treatment. A cut off value of BMI of 30 might be useful in order to investigate the potential role of

overweight in such a classification, and this cut off value is also used in a relatively large and recent OSA cohort study (ISAC) (208) as well as the study by Shuaib reflecting on the role of functional rhinoplasty in OSA (18).

11.4.2 Inflammatory pathway

The anterior part of the nasal cavity might play a key role in OSA development in specific patient groups. In paper two we could demonstrate a smaller MCA and NCV in the anterior part in OSA patients compared to controls, which represents another link to the importance of change in the nasal gateway in these patients. There is no proven causal link between the lower MCA and NCV in the OSA patients and development of the disease, but one might assume that OSA predisposes the reduction in MCA and NCV either by way of inflammation of the nasal mucosa or by worsening of a congenital malformation in the nasal gateway or an acquired nasal deformity developed over years. The hypothesis of OSA as a symptom of an inflammatory systemic disease is backed by the controlled study showing increased levels and activity of inflammatory cells in nasal mucosa in OSA patients by Gelardi and Shadan (142, 209), and our demonstration of the inability in OSA patients to increase PNIF even after decongestion with xylometazoline as well as a reduced NCI for volume in the anterior part of the nose. The lack of response in PNIF after decongestion in OSA patiens might be due to inflammation of the mucosa not affected by vasoconstriction, or a dysfunction of the neuropeptides responsible for mucosal oedema, like the calcitonin gene related peptide (210-212). This suggest that decongestants will not be as effective in OSA patients with nasal obstruction compared to non-OSA patients with the same condition. PNIF is demonstrated to be reduced in asthmatics (198), so care should be taken when interpreting PNIF measurements in asthmatic OSA patients.
Studies that propose a link between OSA and development of asthma (213, 214) support the theory of OSA as an inflammatory disease. So does the higher incidence of CRS in OSA patients (145) and in vitro examinations of intermittent hypoxia resulting in significant oxidative stress (215). Oxidative stress yields increased sympathetic activity and endothelial dysfunction, representing the mechanisms leading to the clinical manifestations in OSA (figure 11).

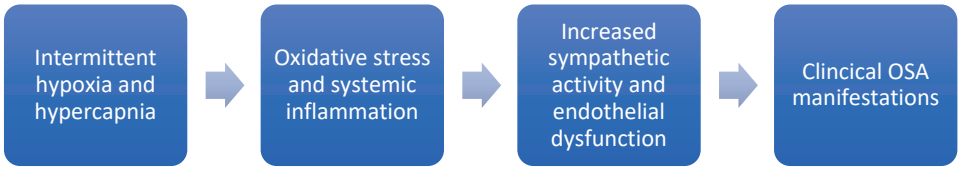


Figure 11. Schematic diagram showing the inflammatory pathway in OSA

11.4.3 Subjective nasal obstruction

The effect on PAP treatment and subjective sinonasal QoL and daytime sleepiness in OSA patients is well documented (216, 217) despite the elusive effect of restoring normal nasal function on objective OSA measures. Our results in paper three are in accordance with these studies, demonstrating a highly significant reduction in QoL not only for the rhinological subset, but for all subsets in SNOT-20 as well as the NO-VAS. The use of the newer version of SNOT-22 that includes the sense of nasal congestion and smell, as well as the proposed SNOT-23 that includes a question on aesthetic outcome regarding the shape of the nose after septorhinoplasties (184), will probably help reinforce the differences between patient related outcomes in OSA compared to controls. In the Icelandic Sleep Apnea Cohort study the prevalence of nasal obstruction in OSA patients was reported to be a substantial 35% (154). Even without the prospects of reducing the objective OSA parameters, nasal obstruction is a health reported outcome that should be of concern and should bring about measures of alleviation. This is also reflected in paper one, where we could find that 68% of the patients that had septoplasty performed, and 80% of the patients that had combined surgery performed, reported an improved quality of sleep.

11.4.4 Interdisciplinary modelling

In the fourth paper, we attempt to construct a 3D model of the soft tissues of the velopharynx in six OSA patients undergoing nasal surgery. Previous modelling of the upper airways includes two-dimensional models investigating the mid-sagittal plane of the pharynx, and the available three-dimensional models demonstrates that material

modelling influences the response of the soft tissues when loads are applied, but they do not consider the influence of the lateral pharyngeal walls and are frequently based on single patient CT/MRI scans. In contrast to former studies, our models take into account the hyperelastic properties of the soft palate, the non-linearity of the deformation when forces are applied, and the forces of the lateral pharyngeal wall.

We did not find any correlation between AHI before or after surgery to simulated closing pressure of the velopharynx, thus the FE model of the soft palate is unable to explain the changes in OSA seen in certain patients after surgical treatment for nasal obstruction. The possible treatment effect after intranasal surgery may arise due to an effect in other sites of the upper airways, i.e. the base of tongue, the pharyngeal lateral walls or the hypopharynx, or by inducing the switch from oral to nasal flow enhancing neuroregulatory mechanisms that facilitates normal breathing.

However, we demonstrated a correlation between the anatomical width of the soft palate and simulated closing pressure in the velopharynx, and this was reflected in the measures of transverse strain that showed a strong linear correlation to simulated closing pressure. The length of the soft palate seems to be of inferior importance in regard to simulated closing pressure. One possible explanation is that the longitudinal direction of the soft palate is free at the distal end and membrane strain does not develop. In the transverse direction on the other hand, the palate is fixed at each lateral side and membrane strain will develop together with bending strain. Since the distal end of the soft palate, including the uvula, does not seem to be the most important site of collapse, surgical treatment of this area will not affect the patency of the soft palate and this seems to be reflected in clinical practice.

11.5 Limitations

A limitation in paper one is the retrospective design. It is not possible to draw any firm conclusions in a historic material due to the possible confounders and bias that are associated with this design. Still, it is of value when studying a distinct exposure within the OSA population and it stimulates the motives of doing a prospective cohort with a

larger patient population. The questionnaire used in paper one is not validated, and may also be prone to recall bias, but it was kept short and dichotomous in order to reduce reader misinterpretation. The controls in paper two and three did not have a sleep polygraph performed, so it is quite possible that some individuals in the control group might have an AHI value of 5 or above. However, symptoms of daytime drowsiness, excessive snoring or observed apneas by others were exclusion criterias. Still, if there were OSA sufferers in the control group, a removal of these would probably strengthen the differences, making the results even more polarized between the groups. Paper four is an experimental study and is not a reflection of real values for closing pressure or soft tissue deformation. The FE models are approximations of the anatomy and function, and validation of the models in larger cohorts are needed in order to draw firm conclusions especially on the relation between anatomical features and soft tissue strain.

12 Conclusion

Nasal obstruction is of importance in OSA in several ways: It is necessary in order for established treatment to work sufficiently; there is a demonstrated smaller nasal gateway area in OSA patients compared to healthy individuals; the patients regard normal nasal function as an important health related outcome and treatment of nasal obstruction can help reveal the mechanisms that ultimately leads to upper airway collapse during sleep. Our studies indicate an inadequate PNIF response after decongestion in OSA patients, suggestive of a loss of regulatory mucosal function or a larger bone to mucosa ratio within the OSA population compared to the healthy population. In light of this, diagnostic measures of nasal obstruction and a more radical treatment of obstruction in the anterior to middle section of the nasal cavity, other than decongestants, should be made a priority along with other specific OSA treatment. Correct diagnosis and predictability of treatment requires a fundamental knowledge of airflow and soft tissue mechanics, and FE modelling represents a new tool that might be put to use also in clinical otolaryngological settings. So far, our FE models do not support the hypothesis that the velopharynx is the site of collapse in OSA patients with an impaired nasal airway. However, we did find linear correlations between the soft palate width as well as the transverse strain of the soft palate and simulated closing

pressure. Efforts should therefore be made to encourage trials that combine clinical research, soft tissue biomechanics and fluid dynamics as a benchmark in the research of upper airway dysfunctions.

13 Future studies

A clinical trial exploring the effect of septorhinoplasty including surgery of the nasal gateway in OSA patients with anterior nasal obstruction compared to septoplasty alone is a natural consequence of our studies. Data could be stratified into subgroups similar to the Friedman classification for OSA patients, as mentioned in chapter 11.4.1. Introducing pharmacological treatment in a third arm is an option. A strengthened cooperation with colleagues within the engineering sciences is a fundamental part of developing more exact diagnostic and treatment strategies of nasal obstruction and OSA in the future. As a consequence of our collaboration with experts within the field of soft tissue biomechanics and structural engineering, a trial that explores FE models of larger sections of the upper airways before and after intranasal surgery using CT imaging with higher resolution (cone beam CT) to construct CFD models would be feasible. In the planning of larger prospective cohort studies, one could define nasal obstruction as an exposure, either as an inflammatory condition or as an acquired condition, to try to establish a causal link between nasal obstruction and OSA.

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15 Appendix

Forsøk å svare på begge spørsmål og sett kryss etter beste evne på linjen:

1. **Hadde du effekt av neseoperasjonen i forhold til å bli mer åpen i nesen? (sett ring) JA NEI**

Hvis JA: Hvor mye bedre ble du etter operasjonen? Sett et kryss på streken

Ingen bedring I----------I Mest tenkelige bedring

Hvis NEI: Hvor mye verre ble du etter operasjonen? Sett et kryss på streken

Ingen forverring I----------I Mest tenkelige forverring

2. **Hadde du effekt av neseoperasjonen i forhold din følelse av å sove bedre? (sett ring) JA NEI**

Hvis JA: Hvor stor effekt mener du at operasjonen hadde på din følelse av å sove bedre?

Ingen bedring I----------I Mest tenkelige bedring

Hvis NEI: Hvor mye verre ble du etter operasjonen med hensyn til søvn?

Ingen forverring I----------I Mest tenkelige forverring

Eksempel:

I----------X----------I

Kjærgård/Steinsvåg -06

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)

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

16 Paper 1-4

Paper

Moxness and Nordgård *BMC Ear, Nose and Throat Disorders* 2014, **14**:11
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BMC
Ear, Nose & Throat Disorders

RESEARCH ARTICLE Open Access

An observational cohort study of the effects of septoplasty with or without inferior turbinate reduction in patients with obstructive sleep apnea

Mads Henrik Strand Moxness[1] and Ståle Nordgård[2,3,4*]

Abstract

Background: The objective of this observational study was to evaluate the outcomes of intranasal surgery in patients with obstructive sleep apnea (OSA) in a single institution in Norway.

Methods: Fifty-nine patients with OSA and clinically significant nasal obstruction underwent either septoplasty alone or septoplasty with concomitant volume reduction of the turbinates from August 2008 until the end of December 2010. Subjects were scheduled for sleep polygraphy before and 3 months after treatment.
In this observational single-centre cohort study we evaluated and compared the effect of these two specific surgical procedures on sleep related parameters.

Results: There was a significant reduction in the apnea-hypopnea index (AHI) only in the group that had septoplasty with turbinate reduction (17.4, (SD 14.4) – 11.7, (SD 8.2), p <0.01), and this effect was significantly better than in the group treated with septoplasty alone. Other objective parameters remained unchanged. Subjective assessments obtained with a postoperative questionnaire showed an equally positive effect on diurnal sleepiness and nasal obstruction in both groups, and a better effect on sleep quality in the combined treatment group.

Conclusion: The effect of nasal surgery on obstructive sleep apnea seemed to be greater when there were indications for combined surgery of the inferior turbinates and the nasal septum, compared to when there were indications for septoplasty alone.

Keywords: Apnea, Nose, Surgery, Septum, Concha, Turbinate

Background

There is growing interest in the field of sleep-related disorders (SRD) and in obstructive sleep apnea (OSA) particularly. This is due to the impact of SRD on global health, and a result of more profound insight into the effects of sleep deprivation, and the biomechanical and physiological changes that occur during the development of upper airway collapse during sleep [1]. The traditional way of understanding the collapsing airway includes both theories of neuromuscular regulation [2] and theories of fluid structure interaction [3]. Surgical treatments for OSA have been performed in several forms over the last 3 decades [4]. To date, tracheotomy is the only surgical procedure with definite and lasting success, but it is regarded as a method with unwanted side effects. Multiple level surgery has gained support, as well as maxillomandibular surgery, but these are also major procedures and the same concerns regarding morbidity apply for these. The effect of limited and less extensive surgery of the upper airways still needs evaluation regarding selection of procedure and results. Nasal surgery has been performed extensively in these patients, often with good effect on quality of life (QOL) measures [5,6]. Still, there is no conclusive evidence of clinical effect, and the different nasal procedures performed are often quite randomly chosen. To our

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knowledge, there are no other clinical studies that compare the results of different nasal procedures for nasal obstruction in patients with OSA. We have evaluated and compared the results of two specific surgical procedures in the nasal cavity, septoplasty alone and septoplasty with simultaneous turbinate volume reduction.

Methods

This study was an observational single-centre cohort study. It was approved by the national regional ethics committee and was registered in Clincaltrials.gov. (NCT01282125). Between August 2008 and December 2010, 78 patients with OSA were treated surgically for nasal obstruction in Aleris Hospital in Trondheim, Norway. Fifty-nine of these had been treated with septoplasty alone or septoplasty combined with volume reductive surgery of the turbinates. Group 1 (n = 33) consisted of patients who had undergone septoplasty alone, and group 2 (n = 26) of patients treated with combined septoplasty and volume reductive surgery. The remaining patients underwent rhinoseptoplasties (n = 8), functional endoscopic sinus surgery (n = 4) and turbinate resection (n = 7) as single procedures, but the groups were too small to be subanalyzed. All patients in the two analyzed groups underwent traditional cartilage preserving septoplasty under general anesthesia. The volume reductive surgery comprised radiofrequency tissue ablation (n = 10) (BM 780-II, Sutter Medizintechnik Gmbh), lateral fracture of the lower turbinate (n = 15), and surgical reduction of concha bullosa (n = 1).

The patients were referred to the sleep clinic for suspected OSA from either primary care physicians or ENT specialists within a specific geographical area. All patients underwent a nocturnal sleep evaluation with an Embletta™ Portable Diagnostic System (ResMed, San Diego, California, USA) or a Reggie polygraph (Camtech, Oslo, Norway) and a clinical examination. There were no prior history of nasal surgery or prolonged use of nasal steroids. None of the patients were diagnosed with chronic rhinosinusitis or enlarged adenoids. Patients with confirmed OSA and clinically significant nasal obstruction due to a septal deviation with or without hypertrophy of turbinates were offered intranasal surgery as a first line of treatment. The decision to supplement septoplasty with volume reductive surgery in selected patients was based on the clinical evaluation, and not supported by objective measurements. If there were a coherence between the patients complaints of nasal blockage on both sides, and there was obvious swelling of the inferior turbinates that was relieved after decongestion with tetracain/adrenalin over 5-10 minutes in the office, one would recommend that turbinate reduction should be performed at the time of the septal surgery. Only patients with apnea-hypopnea index (AHI) >5 and BMI <35 were included. All patients used saline irrigation 6-8 times a day for two weeks postoperatively. No intranasal steroids were administered. Optional pain relief was 50 mg of diclofenac sodium three times a day and 30-60 mg of codein phosphate in combination with 500 mg of paracetamol. The same surgeon (MM) treated all but one patient. The patients were informed of the possibility of crusting in the nose for a period up to three weeks after surgery, but there were no postoperative infections and no necrosis or loss of nasal function at the follow up three months later.

The effects of intranasal surgery on OSA were evaluated routinely after 3 months with a repeated polygraph. Subjective assessment of daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) preoperatively and 3 months postoperatively. In a dichotomous questionnaire, the patients were asked to evaluate the effects of surgery on nasal obstruction and the subjective quality of sleep. At the same time a written informed consent was obtained from all the participants. The alternatives in the questionnaire were: 1. Did you experience an effect on your nasal obstruction after surgery? Yes or No. 2. Did you experience an effect on your sleep quality after surgery? Yes or No. If patients reported a positive outcome, they were asked to supplement the answer with a visual analog scale (VAS) in which their agreement of surgical effect was graded in a continuous scale ranging from 0 = no agreement to 10 = full agreement. Scores between 0-3 were defined as "mild", scores >3-7 were defined as "moderate", and scores >7-10 were considered "good" [7]. The primary outcome was alterations in the AHI, oxygen desaturation index (ODI), body mass index (BMI) and Epworth Sleepiness Scale (ESS) in the two groups. The secondary outcome was to evaluate the effect of surgery on sleep quality and nasal obstruction reported in the questionnaire. SPSS 19.0 was used for the statistical evaluations. Preoperative and postoperative values were evaluated using the Wilcoxon matched-pairs test in continuous variables without normal distribution (ODI, ESS). Variables with normal distribution (BMI, AHI) were evaluated using the paired t-test. The values for AHI were transformed using natural logarithm in order to create a normal distribution. An independent t-test was used to compare the changes of the objective measures and VAS after surgery between group 1 and 2. Differences with $p < 0.05$ were considered significant.

Results

In both groups, there was a predominance of males (97% in group 1 and 85% in group 2), and the mean age was 47.5 (30 – 68) in group 1 and 45.3 (23 - 68) in group 2. The groups did not differ significantly regarding preoperative AHI, ODI, ESS, Mallampati score, age,

gender or BMI. We looked at changes in the objective parameters before and after surgery in three ways: the overall changes in both groups pooled together, changes within each group, and the changes in the mean difference between the groups (Table 1). Overall, in both groups together, there was no significant reduction in mean AHI after surgery: 18.1 (±13.7) - 16.6 (±12.9), (95% CI -1.84, 4.83), p = 0.365, mean ODI: 14.2 (±12.3) – 12.4 (±10.7), (95% CI -1.16, 4.75), p = 0.229 or mean BMI: 28.1 (±3.2) – 28.3 (±3.0), (95% CI – 0.673, 0.285), p = 0.422. The reduction in mean ESS, however, was highly statistically significant: 10.7 (±3.7) – 8.9 (±3.8), (CI 1.00, 2.61), p <0.001. In comparison, when we looked at each group separately, we found a significant reduction in group 2 in mean AHI: 17.4 (±14.4) – 11.7 (±8.2), (95% CI 0.004, 0.006), p = 0.007 and mean ESS: 9.7 (±3.4) – 7.6 (±2.2), (95% CI 0.004, 0.006), p = 0.006. In group 1 there was no significant reduction in mean AHI, ODI or BMI after surgery, but there was a significant reduction in the mean ESS score: 11.5 (±3.7) – 10.0 (±4.5), (95% CI 0.53, 2.54), p = 0.004. The changes in mean ODI levels did not fall below the 0.05 level of significance in either category, although there were near significant values in group 2. The reduction in the difference of mean AHI after surgery was significant between the groups: 1,7 (±8,8) – 5,7 (±16,1), (95% CI 0.8, 14.0), p = 0.029, but the effects on ESS, ODI and BMI were not significant between the two groups . Success criteria defined as a postoperative drop in AHI <20 and/or 50% reduction in AHI [8] were met by 15.2% (5/33) in group 1, and by 27% (7/26) in group 2, but the difference in surgical success was not statistically significant. There were 76% questionnaire responders in group 1 and 77% in group 2. In group 1, 96% answered that the procedure was effective with regard to nasal obstruction, and 68% that it improved their quality of sleep. In group 2 the corresponding percentages were 85% and 80%. The difference between the groups was not statistically significant. A significantly larger proportion in group 2 reported a good improvement in sleep quality: mean 0.08 (±0.27) – mean 0.35 (±0.49), (95% CI 0.037, 0.503), p = 0.024 (Figure 1).

Table 1 Baseline values and postoperative values

	Surgery					
	Septoplasty		Septoplasty and volume reduction		Overall results	
Preoperative values	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
AHI	18.75	13.36	17.39	14.38	18.15	13.71
ODI	14.29	12.00	14.12	12.73	14.21	12.22
ESS	11.54	3.72	9.74	3.42	10.74	3.67
BMI	28.33	3.40	27.80	3.05	28.10	3.23
Postoperative values	Mean	SD	Mean	SD	Mean	SD
AHI	20.46	14.64	11.70	8.19	16.60	12.90
ODI	14.87	12.25	9.30	7.36	12.42	10.67
ESS	10.00	4.51	7.59	2.18	8.94	3.84
BMI	28.69	3.12	27.77	2.70	28.28	2.95
P-values of the difference						
AHI	0.273		0.007		0.365	
ODI	0.671		0.064		0.229	
ESS	0.004		0.006		<0.001	
BMI	0.202		0.716		0.422	
P-values of the difference between treatment groups						
AHI			0.029			
ODI			0.069			
ESS			0.454			
BMI			0.429			

There are no significant differences at baseline between the groups. There is a significant reduction of AHI between the two surgery groups.

Discussion

Intranasal surgery is currently regarded as important in order to improve compliance with treatment using nasal continuous positive airway pressure (CPAP)/bilevel positive airway pressure (BiPAP) devices in patients with OSA. The impact of intranasal surgery on objective measurements in OSA patients is unclear, but is regarded as limited, as shown by Verse et al in 2002 [9]. In a rare blinded randomized controlled study with sham surgery (septal resection +/- turbinectomies) in 2008, Koutserelakis et al [10] found responders only in the real surgery group. They concluded that nasal surgery rarely treats OSA effectively. In a meta-analysis of 13 studies that dealt with nasal surgery alone in OSA patients [11], the reviewers concluded that nasal surgery for obstruction alone does not reduce AHI significantly but ameliorates daytime sleepiness and clinical symptoms of snoring. Only one of these studies described a statistically significant reduction in AHI [12]. However, the observation period in this study was only 1 month as opposed to 3 months in ours, and the study group was mixed and underwent either septal resection alone or combined with turbinate surgery. One study by Li et al [13] described a homogenous patient group comparable to ours with septal deviation and hypertrophic inferior turbinates (n = 44). They found no significant effect of surgery on AHI, and a lower success rate of 16%. The procedure differed somewhat from ours in that only septal resections were performed under local anesthesia. It may indicate that the impact of the septal deviation on nasal obstruction preoperatively or postoperatively differs from that in our study. In surgical practice different nasal procedures are often performed simultaneously, and previous clinical

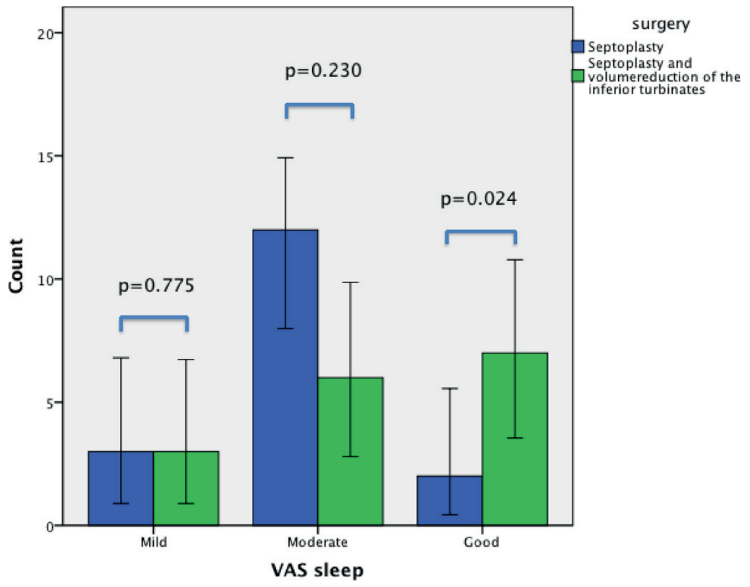

Figure 1 The self-reported improvement of sleep quality after surgery. The improvement (VAS sleep) described as mild, moderate or good. The values for septoplasty in blue (left) and the values for septoplasty and volumereduction of the inferior turbinates in green (right).

studies represent no exception [9,10,12,14,15]. If we had presented the results pooled as a single study group, without a comparison of the two different surgical approaches, we would have missed the statistically significant improvement in patients with combined surgical treatment. Assessments of the overall effect of nasal surgery on OSA predict that 16.7% will have a reduction in AHI [10] that meets the criteria by Sher [8,9]. In this observational study, we singled out two different intranasal surgical procedures for comparison and found that there were statistical differences in the outcome of AHI between septoplasty alone and septoplasty combined with volume reductive surgery in OSA patients. Using the same Sher criteria, we found a near twofold increase in treatment success in the combined surgery group compared with the septoplasty group. This difference did not reach statistical significance but it is possible that it would do so in a larger study group as the difference in AHI reduction was significant. One might anticipate that the better effect on OSA might be due to a larger effect on nasal obstruction in patients in need of combined surgery. It is also possible that the additional inferior turbinate hypertrophy affected the laminar airflow and pharyngeal walls negatively to a higher degree, and hence this group achieved a better result after surgery. Li et al [13] found that patients with a low Friedman tongue position had better results from nasal surgery and Morinaga et al reported less effect in patients with a narrow retroglossal space and high Mallampati score. It may indicate that the increased contribution of pharyngeal structures to OSA will worsen the final results as the percentage of the nasal obstruction is diminished. On the other hand, it may also indicate that the effect of surgery was better for patients with concomitant increased volume of the turbinates and septal deviation because the total contribution of the nasal obstruction to OSA development may have been greater than in patients with septal deviation alone.

In this observational study, there are some limitations that should be taken into consideration. The number of patients in group 2 is low and could represent a statistical uncertainty. There is a higher night-to-night sleep polygraph variation regarding AHI in mild or moderate sleep apnea than in severe apnea that may influence the results on an individual basis [16]. This might suggest that a follow-up study should be performed in patients for whom there is a discrepancy between subjective and objective results. Furthermore, there is a lack of objective measuring of nasal obstruction in an outpatient setting that would otherwise help the surgeon in deciding which type of surgery to perform. Our study is an observational cohort study, and the patients were therefore not randomized to specific treatment groups. As a result, we cannot conclude that combined

surgery is better than septoplasty alone in all patients with clinical indications for septal surgery. There may also be possible side effects of supplementing volume reductive surgery in all OSA patients with septal deformities, and this approach should be avoided. However, the results for OSA in our material seemed to be better when both turbinate hypertrophy and septal deviation were treated. Even though combined surgery does not imply a cure for the majority of the patients, there was a reduction of symptoms, verified by the questionnaire, which indicates that 80% perceived an improvement in their quality of sleep after the combined surgery. This study then supports the view that an effect on daytime sleepiness is observed more often than on obstructive apnea and hence that nasal surgery alone is best suited for patients with mild or moderate obstructive sleep apnea. As long as we do not have any single treatment that provides a cure for OSA and not all patients with mild and moderate OSA will accept or tolerate CPAP or oral devices, there will be a place for targeted surgical treatments that improve QOL in these patients.

Conclusion

In this observational cohort study, the effect on AHI was significantly better when indication for septoplasty combined with surgery of the inferior turbinates was present, compared to septoplasty alone. The overall effect in both groups pooled together showed no significant effect on reduction of the objective parameters but a significant reduction in the subjective ESS score. This implies that intranasal surgery has a good effect on the subjective quality of sleep in OSA patients, and that there might be an added effect on AHI in selected patients with both septal deviation and hypertrophy of the inferior turbinates. Future randomized and prospective studies that can identify responders to nasal surgery as well as what type of intranasal surgery needed.

Competing interests

The authors declare that they have no competing interests, neither financially nor non-financially.

Authors' contributions

MM performed the surgery, collected the sleep related perameters, analysed data and contributed in writing the manuscript. SN contributed to design, analysed and interpreted data, contributed in writing the manuscript, and reviewed the final version. Both authors read and approved the final manuscript.

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A comparison of minimal cross sectional areas, nasal volumes and peak nasal inspiratory flow between patients with obstructive sleep apnea and healthy controls*

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Abstract

Background: The differences in nasal geometry and function between OSA patients and healthy individuals are not known. Our aim was to evaluate the differences in nasal geometry and function using acoustic rhinometry (AR) and peak nasal inspiratory flow (PNIF) between an OSA population and healthy controls.

Methodology: The study was designed as a prospective case-control study. Ninety-three OSA patients and 92 controls were enrolled from 2010 – 2015. The minimal cross-sectional area (MCA) and the nasal cavity volume (NCV) in two parts of the nose (MCA_{0-3}/NCV_{0-3} and $MCA_{3-5.2}$/$NCV_{3-5.2}$) and PNIF were measured at baseline and after decongestion.

Results: The mean MCA_{0-3} in the OSA group was 0.49 cm^2 compared to 0.55 cm^2 in controls ($p < 0.01$, 95% CI [-0.10, -0.02]). The mean NCV_{0-3} correspondingly was 2.51 cm^3 compared to 2.73 cm^3 in controls ($p < 0.01$, 95% CI [-0.37, -0.08]). PNIF measured 105 litres/minute in the OSA group and 117 litres/minute in the controls ($p < 0.01$, 95% CI [-21.8, -3.71]).

Conclusions: OSA patients have a lower minimum cross-sectional area, nasal cavity volume and peak inspiratory flow compared to controls. Our study supports the view that changes in the nasal cavity may contribute to development of OSA.

Key words: nasal cavity, sleep apnea syndromes, nasal surgical procedures, rhinometry, and continuous positive airway pressure

Introduction

In obstructive sleep apnea (OSA) nasal continuous positive airway pressure devices (nCPAP) remains the preferred treatment, despite various surgical procedures evolving during the last three decades [1]. The use of nCPAP treatment requires a functional nasal cavity in order to work adequately, and nasal surgery may be needed to reduce nasal resistance [2]. When applying the Sher criteria for surgical success of OSA [3, 4], 15 – 17% of patients with nasal obstruction will benefit from nasal surgery as a primary treatment. In some cases nasal surgery is reported to increase the number of apnea and hypopneas [3] and to induce central apnoea [4]. There are studies that suggest a connection between nasal patency and OSA [5], and a study by Lofaso [6] has shown increased nasal resistance in patients with OSA compared to controls. Still, little is known about potential differences in nasal geometry and function between OSA patients and healthy individuals. The primary aim of this study was to compare objective measures of minimal cross-sectional area (MCA), nasal cavity volume (NCV) and peak nasal inspiratory flow (PNIF) between patients with OSA and a group of healthy individuals. The secondary aim was to evaluate possible differences in the nasal congestion index (NCI).

Materials and methods

The study was designed as a prospective case-control trial and was approved by the Norwegian Regional Committee for Medi-

cal Research Ethics (REK) and was registered in Clinicaltrials.gov (NCT01282125). Ninety-three patients with verified OSA and 92 normal controls aged > 18 years and < 75 years were included in the period 2010 to 2015 from two tertiary medical centres in central Norway. The patients were selected from Aleris Hospital in Trondheim, Norway and the controls were selected randomly both from the outpatient clinics at Aleris Hospital and the ENT department, St. Olavs University Hospital. The controls were hospital workers or workers outside of the hospital included from annual controls as part of their mandatory occupational health service check ups. Registered nurses were in charge of the selection and were blinded in regards to information on upper airway examinations. Written informed consent was obtained from all patients and controls prior to inclusion in the trial. Inclusion criteria in the patient group were OSA, verified with a portable sleep polygraph, no prior nasal surgery and no use of nasal steroids or nasal decongestion the last three months prior to inclusion, and no clinical evidence of nasal polyposis. The OSA group was referred to the hospital from general practitioners, ENT specialist or pulmonary specialist in central Norway. Inclusion criteria in the control group were no prior nasal surgery, no use of nasal steroids or nasal decongestion the last three months prior to inclusion, no clinical evidence of nasal polyposis and no complaints of daytime drowsiness, excessive snoring or observed apneas by others.

Method

All patients underwent a portable sleep polygraph to verify the OSA diagnosis (Embletta Diagnostic System, ResMed, San Diego, CA, USA, and Nox Medical T3, ResMed, Reykjavík, Iceland). Apnea was scored when there was a drop in the peak signal by ≥ 90% of pre-event baseline using an oronasal sensor for ≥ 10 seconds. Hypopnea was scored when the peak signal dropped by ≥ 30% of pre-event baseline using nasal pressure for ≥ 10 seconds in association with ≥ 3% arterial oxygen desaturation. An apnea-hypopnea-index (AHI) > 5 per hour was considered abnormal. An experienced sleep physiologist examined the results manually to ensure the diagnosis. Both patients and controls were then subjected to an outpatient examination using acoustic rhinometry (AR) to obtain geometrical data in the nose, and peak nasal inspiratory flow (PNIF) to measure the maximum forced inspiration. None of the OSA patients were subject to CPAP treatment prior to the tests, although some had their initial adjustment and fitting of the masks in advance.

Acoustic rhinometry (AR)

AR was performed measuring the minimal cross-sectional area (MCA) and nasal cavity volume (NCV) in two areas of the nasal cavity. AR utilizes a sonographic technique and all measurements were made with an acoustic rhinometer (Rhinometrics SRE2100, Rhinoscan version 2.5, built 3.2.5.0; Interacoustics, Minneapolis, MN, USA). Three trained operators made the measurements with the subjects sitting opposite to the investigator using a handheld probe and a nose adaptor. Sufficient contact between the adaptor and the nose was secured using contact gel, and the average of three satisfactory recordings was obtained. The rhinometer calculated the cross sectional area and volume in two parts of the nose. The most anterior part was defined as 0 – 30 mm measured from the nostrils, and the posterior part 30 – 52 mm from the nostrils, defining the MCA0-3/ NCV0-3 and MCA3-5.2/ NCV3-5.2 areas respectively, a classification previously described by Kjærgaard and Steinsvåg in 2009 [7]. Measurements were obtained at baseline and 15 minutes after decongestion of the nasal mucosa with topical xylometazoline (Otrivin® 1 mg/ml, Novartis, Basel, Switzerland). The total nasal cavity volume ($NCV_{0\text{-}5.2}$) was calculated from the combined values of $NCV_{0\text{-}3}$ and $NCV_{3\text{-}5.2}$. Sixteen patients were excluded due to inadequate AR measurements.

Peak nasal inspiratory flow (PNIF)

The maximal nasal inspiratory flow was measured using a portable PNIF meter (in-check DIAL; Clement Clarke International, Harlow, Essex, UK). The mean of three approved PNIF measurements was recorded with the subjects in a sitting position and the head held in a level position. PNIF was obtained before AR was performed, and both procedures were repeated after decongestion. One control was unable to perform PNIF.

Nasal congestion index (NCI)

The nasal congestion index was obtained to evaluate the swelling of nasal mucosa. We used the following formula: [decongested value – baseline value]/ baseline value. NCI was calculated for the following values: $MCA_{0\text{-}3}$, $MCA_{3\text{-}5.2}$, $NCV_{0\text{-}3}$, $NCV_{3\text{-}5.2}$ and $NCV_{0\text{-}5.2}$.

Statistics

All data showed a normal distribution and are reported as mean values with standard deviation (SD) and 95% confidence intervals (95% CI). An independent sample t-test was used to compare the mean values. The p-value was considered significant if $p < 0.05$. We considered a difference of 0.05 cm^2 in $MCA_{0\text{-}3}$ as a clinically significant difference between the groups, which is slightly lower than the mean difference in MCA in this study (0.06 cm^2) and equal to the mean difference in MCA in similar studies [8]. In order to prove this difference with a level of significance set at 0.05 and strength of 0.80, we needed 91 subjects in each group. A multivariate linear regression analysis was used to adjust for the possible confounding of bodyweight and BMI. We did not conclude with a strong dependency on age upon the outcome of AHI and we did not include age in the multivariate analysis. SPSS, version 23 for Mac, was used for the statistical analysis (SPSS Inc., Chicago, IL, USA).

Table 1. Patient demographics.

	OSA (N=93)	Controls (N=92)	P
Gender			
Female (%)	25 (26,9)	23 (25,0)	0.77
Male (%)	68 (73,1)	69 (75)	
Mean age, years (range)	49.3 (27-72)	46.0 (20-69)	0.06
Mean height , m (SD)	1.77 (0.10)	1.78 (.09)	0.40
Mean weight, kg (SD)	95.4 (16.7)	82.4 (14.6)	<0.01
Education, years (%)			
<9	12 (12.9)	12 (13.0)	0.72
10-12	28 (30.1)	24 (26.1)	
>13	53 (57.0)	56 (60.9)	
Disease, n (%)			
Heart disease	9 (9.7)	8 (8.7)	0.80
Allergy	17 (18.3)	10 (10.9)	0.15
Mean BMI, kg/m² (SD)	30.3 (4.3)	25.8 (3.5)	<0.01

Results

Table 1 shows the baseline data in both groups. The mean AHI in the OSA group was 31.22 (9.0 - 93.3). The distance from the nasal orifice to the lowest value of MCA was in both cases coinciding with MCA_{0-3}, and was not statistically different in the groups (1.90 cm in the OSA group and 1.86 cm in the control group, p > 0.10).

MCA and NCV

MCA_{0-3}, $MCA_{3-5.2}$ and NCV_{0-3} were significantly lower in the OSA group at baseline. In addition, $NCV_{3-5.2}$ and $NCV_{0-5.2}$ differed significantly from the control group after decongestion (Table 2). When analysing the covariates of weight and BMI, we found that these variables did not significantly predict MCA_{0-3} in the OSA group (F (2,90) = 1,10, p= 0.34, R2 = .024) nor NCV_{0-3} (F (2,90) = 3,00, p =0.06 R2 = .062).

PNIF

PNIF was significantly lower in the OSA group compared to the controls both at baseline and after decongestion (Table 2). The change in PNIF (delta PNIF = PNIF after decongestion – PNIF before decongestion) was also lower in the OSA group compared to the controls (Figure 1).

NCI

NCI was significantly lower in the patient group for volume in the anterior part and for the total nasal volume, but not for MCA_{0-3}, nor for $MCA_{3-5.2}$ or $NCV_{3-5.2}$ (Table 3).

Subgroup analysis

OSA was classified as mild (AHI < 15, n = 16), moderate (AHI 15 – 29.9, n = 36) and severe (AHI > 30, n = 41). In the subgroup analysis MCA_{0-3} and NCV_{0-3} were significantly smaller ($p < 0.05$) in patients with mild and severe OSA both at baseline and after decongestion compared to the controls. The moderate OSA group showed significantly smaller MCA_{0-3} and NCV_{0-3} only after decongestion compared to the controls ($p<0.05$).

Discussion

This study demonstrates a significantly smaller cross sectional area and smaller nasal cavity volume in OSA patients than in controls. The difference between the groups is greater in the anterior part of the nose, from 0–3 cm and is enhanced after decongestion. This can support the idea of a more profound anatomical deviation in OSA patients in the area of the nasal vestibulum, anterior part of the nasal septum and inferior turbinates, commonly referred to as the nasal valve area. Another explanation for the smaller nasal cavity in OSA patients could theoretically be hypoplasia of the nasal cavity due to lack of function over time, with a predominant oral breathing instead of nasal breathing. A parallel to this development can be seen in asthmatics where lung function is decreased when nasal

Table 2. Minimum cross sectional area, nasal cavity volume and peak nasal inspiratory flow at baseline and after decongestion.

	Before decongestion				After decongestion			
	OSA (N=93)	Controls (N=92)	P	95% CI	OSA (N=93)	Controls (N=92)	P	95%CI
MCA_{0-3}	0.49 (0.14)	0.55 (0.13)	<0.01	(-.10, -.02)	0.54 (0.13)	0.60 (0.14)	<0.01	(-.10, -.02)
$MCA_{3-5.2}$	0.95 (0.40)	1.08 (0.41)	0.03	(-.25, -.01)	1.29 (0.48)	1.60 (0.53)	<0.01	(-.45, -.16)
NCV_{0-3}	2.51 (0.47)	2.73 (0.53)	<0.01	(-.37, -.08)	2.62 (0.49)	2.95 (0.54)	<0.01	(-.48, -.18)
$NCV_{3-5.2}$	3.41 (1.25)	3.57 (1.34)	0.43	(-.52, .22)	4.83 (1.31)	5.49 (1.64)	<0.01	(-1.09, -.23)
$NCV_{0-5.2}$	5.91 (1.54)	6.30 (1.75)	0.12	(-.85, .10)	7.46 (1.64)	8.45 (2.04)	<0.01	(-1.53, -.46)
PNIF	105 (25)	117 (36) (N=91)	<0.01	(-21.8, -3.71)	113 (20)	129 (46) (N=91)	<0.01	(-26.3, -5.68)

MCA = minimum cross sectional area; NCV = nasal cavity volume, PNIF = peak nasal inspiratory flow. Data presented as mean (SD) and 95% confidence interval (95% CI).

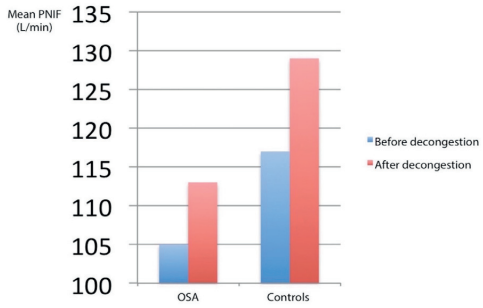

Figure 1. Peak nasal inspiratory flow (PNIF) at baseline and after decongestion in obstructive sleep apnea patients (OSA) and controls. There is a significant difference in PNIF between the groups both at baseline (blue column, $p < 0.01$) and after decongestion (red column, $p < 0.01$).

Table 3. Nasal congestion index for minimum cross sectional area and nasal cavity volume.

	OSA (N=93)	Controls (N=92)	P	95%CI
NCI-MCA_{0-3}	0.13 (0.22)	0.09 (0.17)	0.19	(-.02, .09)
NCI-$MCA_{3-5.2}$	0.48 (0.78)	0.56 (0.43)	0.36	(-.27, .10)
NCI-NCV_{0-3}	0.054 (0.10)	0.09 (0.11)	0.03	(-.07, -.004)
NCI-$NCV_{3-5.2}$	0.53 (0.57)	0.62 (0.39)	0.17	(-.24, .04)
NCI-$NCV_{0-5.2}$	0.29 (0.26)	0.37 (0.23)	0.03	(-.15, -.006)

NCI = nasal congestion index, MCA = minimum cross sectional area, NCV = nasal cavity volume. Data presented as mean (SD) and 95% confidence interval (95% CI).

breathing is obstructed [8,9] and in laryngectomy patients up to two years after surgery [10]. In both studies MCA and NCV were found to be smaller in the diseased group compared to controls. Further, the PNIF values were significantly lower in the OSA group. The most likely reason for this is the smaller MCA_{0-3} in the patient group. The difference in MCA and NCV between the groups is confined mostly in the nasal valve area, which is the site of most resistance in the upper airway [11]. The nasal valve is made up of the upper crest of the nasal septum and the upper lateral cartilage, the bony entrance to the nasal cavity, the inferior turbinate and the length of the erectile septal body [12]. A slight decrease in the radius in this area will have a large negative impact on the flow rate according to Poiseuilles law which states that the volume flow rate is dependent upon the radius raised to the fourth power [13]. It is therefore likely that even small changes in nasal architecture in the nasal valve will be a limiting factor for the airflow downstream. Even though we demonstrated that BMI did not contribute significantly to the prediction of PNIF, a reduction in lung function is correlated to a lower forced inspiratory flow as demonstrated in patients with obstructive pulmonary disease [8]. There is also the possibility that the reduced PNIF values in OSA patients is due to a second obstructive site downstream in the oro-or hypopharynx or an inadequate contraction of the pharyngeal dilator muscles as explained by the nasal ventilatory reflex mechanism [14]. A relative obstruction during inspiration could be caused by enlarged pharyngeal tissue, an enlarged tongue base with posterior displacement of the epiglottis, or enlarged tonsils. Senchak et al. demonstrated the latter where adult tonsillectomy in young, overweight males with a median Friedman stage of 3 was clearly beneficial in OSA treatment [15]. The lack of proper nasal ventilatory reflex mechanisms was demonstrated by McNicholas et al. in a study where anaesthesia of the nasal mucosa induced an increased upper airway obstruction [14]. Others have demonstrated that concentration of nasal nitric oxide (NO), a potent vasodilator in the lungs, is dependent on airflow [16] and that reduction of inhaled NO can alter the ventilation-perfusion ratio in the lungs and thus might influence the inspiratory flow [17]. In addition to significantly lower PNIF value in the OSA group, the present study also demonstrates a lower increase in PNIF after decongestion in the OSA group compared to controls. Although the difference in increase of PNIF is not statistically significant, it does reflect the reduced capacity of forced inhalation in OSA patients even after decongestion of the nose. This may either be viewed as a fundamental characteristic of OSA, or as a fundamental trait of decongestion itself in OSA patients. NCI values for both NCV_{0-3} and $NCV_{0-5.2}$ showed a significant lower value in the OSA group reflecting a lower mucosal congestion compared to the higher reversible congestion in controls (Table 3). We did not find any significant reduction of NCI values for MCA, only for NCV in the anterior part. Since the use of topical xylometazoline will reduce mucosa by vasoconstriction alone [18], this is an indication of additional factors causing narrowing or mucosal oedema in OSA patients. We can suggest three possible explanations. There might be inflammatory responses in OSA [19] that are not subject to nasal decongestion in the same way as non-OSA subjects. As a continuation of this idea, there might be a dysfunction in the relatively newly described mucosal regulation by particular classes of neuropeptides [20]. A rise in expired CO_2, as seen in periods with prolonged apnea, can possibly interact with mucosal sensory neurons, some of which contain calcitonin gene related peptide (CGRP) which regulates arterial and arteriovenous vessels beneath the epithelial basement membrane [21, 22] and are not involved in the regulation of the venous sinusoids. A third explanation could be that the bony anatomy of the inferior turbinate in OSA patients differs from the controls.

A smaller distance between the inferior turbinate and nasal septum will thus explain less decongestion of the mucosa in the OSA patients. This explanation can be supported of an earlier trial where we demonstrated that OSA patients improved after septoplasty when inferior turbinate reduction was incorporated in the procedure [23].

However, a larger nasal cavity in which the airflow is restored in a more laminar fashion, for instance after septal or volume-reductive surgery, does not mean that OSA patients will be relieved of apneas. In the literature there are examples of intranasal surgeries that lead to an increase in apneas in some patients [3, 4]. We can hypothesize that some of the negative effect can be mechanical, due to a larger input of flow downstream, and hence a larger suction force in the collapsible segment in the hypopharynx. In a starling resistor model there would be a collapsible segment in the pharynx and collapse occurs when the critical pressure in the pharynx is greater than the pressure in the rigid inlet area (the nose). If the inlet pressure drops after surgery, it might become lower than the pressure in the pharynx leading to a collapse [24]. Recent publications by Owens et.al have demonstrated that the Starling resistor model is insufficient in predicting nasal airflow alone [25]. It might be possible that intranasal surgery interferes with the neuroregulatory mechanisms in such a way that it inhibits the proper response in the dilator muscles of the throat. The central apnea that sometimes can be observed after successful intranasal surgery [4] is most likely due to the same mechanisms that causes the complex OSA seen when introducing CPAP therapy in selected cases; a ventilatory decrease in CO2 and a loss of the central respiratory drive [26].

Limitations of the study

One cannot rule out the possibility that some subjects in the control group might have OSA, since they did not undergo a sleep polygraph. However, exclusion of these controls would strengthen the differences rather than weaken them. There is also a possibility that the OSA group to some extent could be biased in the sense that ENT specialists, who might be more focused on nasal obstruction than general practitioners or pulmonary specialists, referred a larger proportion of this group to sleep polygraphy. This is, however, not different from usual clinical practice where patients are referred mainly from ENT specialists to sleep polygraphy. We have not performed any analysis of variations due to seasonal changes, but the inclusion period spanned several years, which would minimize possible bias due to pollen season or wintertime.

Conclusion

Compared to a healthy population the nasal cavity is smaller in OSA patients, and the difference is greatest at the site of the nasal valve area. A reduced response to decongestion in the OSA group indicates a larger bone to mucosa ratio of the anterior part of the inferior turbinate or an inflammatory cause of mucosal oedema. The resulting smaller inlet area of the nose is a probable cause of the reduction in peak nasal inspiratory flow in OSA patients compared to controls. This study supports the view that a narrow nose may contribute to development of OSA but it is still unclear how a smaller nasal cavity contributes to changes in airway collapse.

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Authorship contribution

MHSM has written the main text and collected the data in both groups and been in charge of the statistical analysis, tables and figures. VB has been a co-author and helped in the design and text work, tables and figures. WMT has been a co-author and helped in text work and in collection of parts of the control group. SN has been in charge of the supervision of collection of data, helped in the design and the text work. GB has helped in the text work related to the analysis of sleep recordings.

Conflict of interest

To our knowledge, there is no conflict of interest.

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Research Article

Sinonasal Characteristics in Patients with Obstructive Sleep Apnea Compared to Healthy Controls

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Background. The difference in nasal obstruction between OSA patients and healthy individuals is not adequately documented. Our aim was to describe the sinonasal quality of life and nasal function in OSA patients and healthy controls using the sinonasal outcome test-20 (SNOT-20), nasal obstruction visual analog scale (NO-VAS), and peak nasal inspiratory flow (PNIF). *Methodology and Principal*. Ninety-three OSA patients and 92 controls were included in a case-control study from 2010 to 2015. *Results*. Mean SNOT-20 score in the OSA group was 1.69 (SD 0.84) compared to 0.55 (SD 0.69) in controls ($p < 0.001$, 95% CI [0.9, 1.4]). The mean NO-VAS score was 41.3 (SD 12.8) and 14.7 (SD 14.4) in the OSA group and controls, respectively, ($p < 0.001$, 95% CI [22.7, 30.6]). PNIF measured 105 litres/minute in the OSA group and 117 litres/minute in controls ($p < 0.01$, 95% CI [−21.8, −3.71]). There was a positive correlation between subjective nasal obstruction and change in PNIF after decongestion in the control group alone. *Conclusions*. OSA patients have a reduced sinonasal QoL and lower peak nasal inspiratory flow compared to controls. Treatment of nasal obstruction in OSA patients should be made a priority along with treatment of the ailment itself.

1. Introduction

Sinonasal complaints are associated with obstructive sleep apnea (OSA) [1], and the relief of sinonasal obstruction has been shown to reduce subjective complaints of daytime sleepiness [2]. Excessive daytime sleepiness is one of the main symptoms in obstructive sleep apnea syndrome and a major concern due to the strong association with a reduction in motor skills such as handling vehicles and machines [3]. Even though sinonasal complaints have been described within an OSA cohort, there is still little information on the extent of complaints compared to the normal population. The primary goal of this study was to compare sinonasal quality of life (QoL) in OSA patients with a group of healthy controls. The secondary aim was to compare symptoms and nasal airflow in the two groups.

2. Materials and Methods

The study was designed as a prospective case-control trial and was approved by the Norwegian Regional Committee for Medical Research Ethics (REK) and registered in Clinicaltrials.gov. Ninety-three persons were included in the patient group and 92 in the control group. The patients were selected from two tertiary medical centers in central Norway in the period 2010 to 2015. General practitioners or specialists in otorhinolaryngology, pulmonary medicine, and internal medicine referred the patients to confirm their suspicions of sleep related disorders. They all underwent a sleep polygraph to verify the diagnosis. The controls were randomly chosen among hospital workers and workers outside of the hospital as part of their annual health check-up. All patients and controls signed a written consent before inclusion in the

trial. Because of the skewness in gender distribution in OSA patients, we adjusted the gender in the control group to match the distribution in the patient group. The request to join the study as controls was done by registered nurses prior to clinical examination so they were blinded in regard to information on clinical examination of the nasal cavity. The inclusion criterion in the patient group was a verified diagnosis of OSA by a portable sleep polygraph test. We included patients and controls between the age of 18 and 75. In both groups the exclusion criteria were prior nasal surgery, use of decongestants or nasal steroids over the last 3 months, and evidence of chronic rhinosinusitis with or without nasal polyposis. Complaints of daytime sleepiness, excessive snoring, or observed respiratory distress by others were also considered exclusion criteria in the control group.

2.1. Sleep Polygraph Test. A portable sleep polygraph test (Embletta Diagnostic System, ResMed, San Diego, California, USA, and Nox Medical T3, ResMed, Reykjavík, Iceland) was performed on all patients to verify the OSA diagnosis. A drop in the peak signal by ≥90% of preevent baseline for ≥10 seconds using an oronasal sensor was the determining factor for apneas. Correspondingly, hypopnea was scored when the peak signal dropped by ≥30% of preevent baseline using nasal pressure for ≥10 seconds in association with ≥3% arterial oxygen desaturation. An apnea-hypopnea-index (AHI) > 5 per hour was considered abnormal. An experienced sleep physiologist examined all sleep reports manually prior to the diagnosis. The respiratory disturbance index and oxygen desaturation index were evaluated but did not form the basis for the OSA diagnosis in this study.

2.2. Sinonasal Outcome Test. Sinonasal Outcome Test-20 (SNOT-20) is a validated patient reported measure of health related QoL in sinonasal disease [4, 5]. The later modified version, SNOT-22, was still not validated in Norwegian at the onset of the trial. The patients were asked to grade 20 items on a scale from 0 (no complaints) to 5 (problem as severe as can be). The SNOT-20 score for each subject was defined as the mean value of the response to the 20 items. SNOT-20 is divided into four different subsets as described by Browne et al. [6]: rhinologic problems, ear and facial problems, sleep function, and psychological issues. These subdomains have been found to be methodologically sound and are believed to improve the precision of the questionnaire compared to reporting single SNOT-20 scores alone [5].

2.3. Visual Analog Scale. The patients and controls reported symptoms as nasal obstruction, headache, facial pain, facial pressure, reduced sense of smell, nasal discharge, sneezing, coughing, snoring, oral breathing, and reduced general condition on a 100 mm visual analog scale (VAS). 0 mm on the scale equals "no symptoms" and 100 mm represents "as troublesome symptoms as possible." The use of VAS in assessment of nasal obstruction (NO-VAS) has been validated and there is a strong correlation between the subjective VAS for nasal obstruction and nasal resistance [7].

2.4. Peak Nasal Inspiratory Flow (PNIF). PNIF is an established clinical tool for evaluating nasal function [8]. It has been validated as a simple and reliable procedure that corresponds strongly with reports of subjective nasal obstruction. A portable PNIF meter (in-check DIAL; Clement Clarke International, Harlow, Essex, UK) was used. The mean of three approved PNIF measurements was recorded before and after decongestion with topical xylometazoline (Otrivin® 1 mg/ml, Novartis, Basel, Switzerland) with the subjects in a sitting position and the head held in a level position. A mean value after three approved measurements of 120 L/min was considered normal. One control was unable to perform PNIF.

2.5. Statistical Analysis. All data in the tables are presented as mean, standard deviation (SD), and 95 percent confidence interval (95% CI). The mean values between the patient group and the control group were analysed using an independent samples t-test. We used linear regression analysis and one-way analysis of variance (ANOVA) with Bonferroni for multiple comparisons tests in the subgroup analysis and to evaluate the significance of demographic variables. In addition we used the Pearson correlation coefficient to evaluate the correlation between NO-VAS and PNIF. If we wanted to detect a difference in SNOT-20 of 0.2 between the patient group and the control group, with a power of 80% and a level of significance set at 0.05, we needed 100 patients in each group. The complete set of data was analysed using IBM SPSS version 23.0 (SPSS Inc., Chicago, Illinois, USA).

3. Results

The groups were matched in age, gender distribution, and educational level but there was a significant difference between the groups regarding weight and BMI as expected since weight is strongly associated with development of OSA [9]. However, BMI did not contribute in a significant way to the total SNOT score ($p = 0.82$) or VAS-NO score ($p = 0.45$) in the patient group. There was a relatively even distribution of heart disease and asthma/allergy in both groups (Table 1).

3.1. SNOT-20. The OSA patients had an impairment in sinonasal QoL compared to the control group, with mean SNOT-20 scores of 1.69 (SD 0.84) and 0.55 (SD 0.69), respectively, $p < 0.001$. Similarly, there were highly significant differences between the groups for all items except for ear pain ($p = 0.11$). The difference between the groups in the four subsets of SNOT-20 was also highly significant, with better outcomes in the control group (Table 2).

3.2. VAS. The total VAS score was 41,3 (SD 12,8) in the patient group and 15,6 (SD 13) in the control group ($p < 0{,}001$). In addition, the differences in the subsets of the VAS scores were highly significant with the exception of headache and pain (Table 3).

3.3. PNIF. There was a difference in PNIF scores between the OSA group and control group both at baseline (105 versus 117 l/min, $p < 0{,}010$) and after decongestion (113 versus

Table 1: Patient demographics.

	OSA (N = 93)	Controls (N = 92)	p value
Gender			
Female (%)	25 (26,9)	23 (25,0)	0.77
Male (%)	68 (73,1)	69 (75)	
Mean age, years (range)	49.3 (27–72)	46.0 (20–69)	0.06
Mean height, m (SD)	1.77 (0.10)	1.78 (.09)	0.40
Mean weight, kg (SD)	95.4 (16.7)	82.4 (14.6)	<0.01
Education, years (%)			
<9	12 (12.9)	12 (13.0)	0.72
10–12	28 (30.1)	24 (26.1)	
>13	53 (57.0)	56 (60.9)	
Disease, n (%)			
Heart disease	9 (9.7)	8 (8.7)	0.80
Allergy	17 (18.3)	10 (10.9)	0.15
Mean BMI, kg/m^2 (SD)	30.3 (4.3)	25.8 (3.5)	<0.01

Table 2: Scores for the Sinonasal Outcome Test (SNOT-20) in the OSA group and controls. Data presented as mean (SD) and 95% CI.

Question	OSA group (n = 93)	Control group (n = 92)	p value	95% CI
Need to blow nose[a]	1.58 (1.32)	0.63 (0.91)	<0.001	(0.6, 1.3)
Sneezing[a]	1.39 (1.26)	0.61 (0.81)	<0.001	(0.5, 1.1)
Runny nose[a]	1.20 (1.19)	0.40 (0.68)	<0.001	(0.5, 1.1)
Cough	1.41 (1.36)	0.40 (0.76)	<0.001	(0.7, 1.3)
Postnasal discharge[a]	1.00 (1.34)	0.23 (0.58)	<0.001	(0.5, 1.1)
Thick nasal discharge[a]	1.20 (1.35)	0.42 (0.83)	<0.001	(0.5, 1.1)
Ear fullness[b]	1.26 (1.29)	0.58 (1.06)	<0.001	(0.3, 1.0)
Dizziness[b]	0.96 (1.38)	0.46 (0.93)	0.004	(0.2, 0.8)
Ear pain[b]	0.51 (0.95)	0.29 (0.82)	0.106	(−0.1, 0.5)
Facial pain/pressure[b]	0.63 (1.12)	0.25 (0.72)	0.006	(0.1, 0.7)
Difficulty falling to sleep[c]	1.32 (1.55)	0.49 (1.05)	<0.001	(0.5, 1.2)
Wake up at night[c]	2.72 (1.39)	0.91 (1.35)	<0.001	(1.4, 2.2)
Lack of good night's sleep[c]	3.53 (1.26)	0.99 (1.51)	<0.001	(2.1, 2.9)
Wake up tired	3.32 (1.24)	1.46 (2.00)	<0.001	(1.4, 2.4)
Fatigue[d]	2.44 (1.56)	0.60 (1.15)	<0.001	(1.5, 2.2)
Reduced productivity[d]	2.44 (1.56)	0.61 (1.15)	<0.001	(1.4, 2.2)
Reduced concentration[d]	2.52 (1.54)	0.69 (1.16)	<0.001	(1.4, 2.2)
Frustrated/restless/irritable[d]	2.12 (1.54)	0.59 (1.10)	<0.001	(1.1, 1.9)
Sad[d]	1.16 (1.33)	0.27 (0.61)	<0.001	(0.6, 1.2)
Embarrassed[d]	0.65 (1.15)	0.10 (0.39)	<0.001	(0.3, 0.8)
Subset				
Rhinologic[a]	1.28 (0.96)	0.46 (0.58)	<0.001	(0.6, 1.1)
Ear/facial[b]	0.83 (0.88)	0.39 (0.73)	<0.001	(0.2, 0.7)
Sleep function[c]	2.52 (1.07)	0.79 (1.18)	<0.001	(1.4, 2.1)
Psychological function[d]	1.88 (1.19)	0.49 (0.83)	<0.001	(1.1, 1.7)
Mean SNOT-20	1.69 (0.84)	0.55 (0.69)	<0.001	(0.9, 1.4)

[a]Questions = rhinologic subset, [b]Questions = ear/facial subset, [c]Questions = sleep functions subset, and [d]Questions = psychological subset.

129 l/min, $p < 0{,}010$), respectively. There was a significant positive correlation between the absolute difference in PNIF before and after decongestion (delta PNIF) and NO-VAS scores in the control group ($p = 0.026$, $r = 0.232$) but not in the patient group ($p = 0.891$, $r = 0.014$) (Figure 1).

3.4. Subgroup Analysis

3.4.1. AHI Severity. When stratifying the OSA group by AHI levels into mild (0–14,9), moderate (15–29,9), and severe (>30) we could see a positive correlation with total SNOT

Table 3: Visual Analog Scale (VAS) scores for sinonasal symptoms in OSA patients and controls. Data presented as mean (SD) and 95% CI.

Symptoms	OSA group (n = 93)	Control group (n = 92)	p value	95% CI
Nasal blockage	46.2 (25,5)	14.1 (17.1)	<0.001	(25.7, 38.3)
Oral breathing	55.5 (26.2)	19.0 (23.1)	<0.001	(29.4, 43.7)
Snoring	84.2 (17.5)	36.1 (31.7)	<0.001	(40.6, 55.5)
Sleep apnea	77.5 (21.0)	14.2 (22.0)	<0.001	(57.1, 69.6)
Nasal discharge	28.8 (24.0)	12.9 (17.0)	<0.001	(9.9, 22.0)
Headache	32.5 (27.1)	20.8 (24.2)	0.002	(4.3, 19.2)
Midfacial pain	16.0 (20.5)	9.8 (15.9)	0.024	(0.8, 11.5)
Rhinosinusitis	16.6 (20.1)	4.8 (8.0)	<0.001	(7.3, 16.2)
Coughing	32.1 (25.3)	11.6 (14.0)	<0.001	(14.6, 26.4)
Sneezing	43.8 (59.0)	19.4 (19.8)	<0.001	(11.6, 37.2)
Reduced general health	29.5 (24.3)	11.6 (19.6)	<0.001	(11.5, 24.3)
Total VAS score	41.3 (12.8)	14.7 (14.4)	<0.001	(22.7, 30.6)

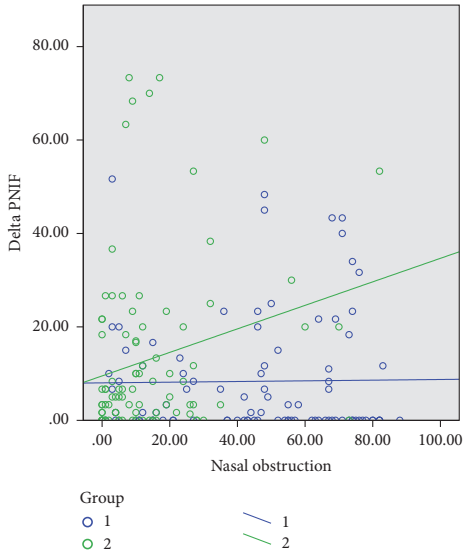

Figure 1: The change in PNIF before and after decongestion with xylometazoline compared to level of subjective nasal obstruction. Blue dots and line = OSA group. Green dots and line = controls. Delta PNIF = the absolute difference in PNIF at baseline and after decongestion (l/min). There is a significant positive correlation between VAS nasal obstruction and delta PNIF only in the control group.

score, total VAS score, and NO-VAS score, although not statistically significant. When we looked at the four subdomains of SNOT-20, there was a significant difference only in the sleep subdomain (F (2,90) = 4.95, $p < 0.01$) between mild (mean 1.79), moderate (mean 2.69), and severe levels of AHI (mean 2.67). The multiple comparison test showed a significant difference between mild and moderate AHI (mean difference 0.89, $p < 0.05$, 95% CI [−1.64, −0.14]) and mild and severe AHI (mean difference 0.88, $p < 0.05$, 95% CI [0.14, 1.61]) but not between the moderate and severe levels of AHI (mean difference 0.02, $p = 1.0$, 95% CI [−0.55, 0.59]). When looking into the individual scores of the SNOT-20 questionnaire we could find a significant score in the subscore of "waking up at night" between mild (mean 1.88) and severe (mean 2.98) levels of AHI (mean difference 1.1, $p < 0.05$, 95% CI [−2.07, −0.13]). Regarding symptoms on VAS, there were significant differences in "snoring" between mild (mean 73.4) and severe (mean 88.4) levels of AHI (mean difference 15.0, $p < 0.05$, 95% CI [−27.1, −2.9]) and in "apnea" between both mild (mean 62.8) and severe (mean 86.3) levels of AHI (mean difference 23.5, $p < 0.001$, 95% CI [−37.3, −9.6]) and between moderate (mean 74.1) and severe (mean 86.3) levels of AHI (mean difference 12.2, $p < 0.05$, 95% CI [−22.9, −1.4]). Regarding the symptom of "headache" there was a significant level of difference only between moderate (mean 25.7) and severe (mean 40.5) levels of AHI (mean difference 14.7, $p < 0.05$, 95% CI [−29,4, −0.03]).

3.5. Age. We stratified the groups in age under 45, between 45 to 60, and over 60 but there were no differences between the age groups or between the patient group and controls regarding the subdomains of SNOT-20, total VAS score, or NO-VAS score.

3.6. Self-Reported Asthma/Allergy and Heart Disease. OSA patients with self-reported asthma/allergy had a significantly higher NO-VAS score (mean 57.2) compared to patients with self-reported heart disease (mean 21.7, mean difference 35.6, $p < 0.01$, 95% CI [11.7, 59.5]) but not compared to patients reporting no disease (mean 47.3, mean difference 9.9, $p > 0.05$, 95% CI [−5.9, 25.7]). In the "general health" symptom the asthma/allergy fraction in the OSA group scored significantly higher (mean 44.1) than the heart disease fraction (mean 16.2, mean difference 27.9, $p < 0.05$, 95% CI [4.47, 51.3]) and they also scored significantly higher compared to those who claimed not to have any disease (mean 27.9, mean difference 16.3, $p < 0.05$, 95% CI [0.80, 31.7]). In the control group there were no significant differences in VAS scores between the disease groups.

4. Discussion

We could demonstrate a marked reduction in sinonasal QoL in OSA patients compared to controls and an association between the degree of subjective nasal obstruction on VAS and the change in inspiratory flow in controls alone (Figure 1). The importance of normal nasal function in OSA patients has been noted in several publications in the past [10–15]. These studies generally tend to describe two important features regarding nasal patency and OSA. Firstly, they describe the facilitation of nasal continuous positive airway pressure devices or bilevel positive airway pressure devices (nCPAP/biPap) due to lower nasal resistance after medical and/or surgical treatment of nasal obstruction. Secondly, they describe the self-reported reduction in daytime sleepiness following a successful treatment of nasal obstruction in OSA patients. Despite the obvious effect of restoring nasal function on positive airway pressure treatment and subjective daytime sleepiness in patients, the effect on objective measures of obstructive sleep apnea keeps eluding us. These conflicting results raise more questions: Should we believe in QoL measures and postulate that the diagnostic tools we use today does not quite give a good enough measure of the daytime sleepiness associated with OSA? This view is supported by the increasing tendency to see obstructive sleep apnea as a result of a combination of not only the number of apneas and hypopneas, but also the nocturnal hypoxemia and respiratory disturbance index [16]. This has also led to the emerging notion of using OSA phenotyping to decide on specific treatment options [17]. The other question will be to see whether sinonasal characteristics differ not only in regard to OSA severity but also when compared to a supposedly healthy cohort.

In our study we could observe that, within the OSA group, the total SNOT scores and VAS scores were positively correlated to the severity of AHI. Although the differences did not reach the chosen level of significance it indicates a clear association between nasal complaints and severity of disease. This verifies the results in the study by Kuan et al. where sinonasal complaints evaluated by the SNOT-22 score seemed to be correlated to OSA severity [1].

When we expand our view and compare the OSA group to a healthy cohort, we find significant differences between groups for all symptoms given on VAS and all items in SNOT-20 except ear pain. All the four SNOT-20 subdomains showed a highly statistical difference between the OSA group and the controls, and the subanalysis showed a positive correlation in the subdomain of sleep with severity of AHI. This is consistent with earlier studies showing the association between cognitive impairment and OSA severity [18]. The level of difference in both SNOT-20 and VAS is stronger between the patient group and the controls than between the different levels of AHI severity in the patient group. We believe that this points to a strong association between obstructive sleep apnea and nasal obstruction regardless of severity measured by AHI. This does not, however, yield any information as to whether it is a causative association or merely a concurrent phenomenon, but it falls in line with earlier studies that demonstrate that lower nasal cavity volumes and impairment of nasal function are associated with development of OSA [19]. Treatment of septal deviations in OSA patients has also been shown to lead to better QoL and relief of nasal symptoms compared to healthy individuals which gives more strength to this observed association [20]. The differences in total SNOT score and total VAS score were more pronounced between patients with a mild and moderate AHI level than between patients with a moderate and severe AHI level. This might suggest that nasal involvement has a greater impact on milder forms of OSA and that expectations of possible curative treatments of nasal obstruction in OSA should be limited to this group.

Self-reported asthma and allergy in the OSA group seemed to be correlated to higher VAS-NO scores compared to patients with heart disease and are coherent with studies indicating a synergistic effect between asthma and OSA [21] in much the same way as seen with chronic obstructive pulmonary disease [22]. This synergistic effect is also reflected in the subgroup analysis where there were significant differences in the VAS symptom "general health" in OSA patients with asthma/allergy compared to nonallergy/nonasthmatic OSA patients. In the control group a higher VAS nasal obstruction score was positively correlated to the absolute difference in PNIF before and after decongestion, reflecting their ability to increase nasal function as the nasal mucosal swelling was reduced. The higher the NO-VAS score, the higher the change in PNIF after decongestion. This correlation was not seen in the OSA group (Figure 1). The inability to increase PNIF in the patient group after decongestion, as well as the reported higher nasal obstruction scores in asthma and allergic patients, can be supportive of the idea of an inflammatory component in the nasal mucosa that is not affected by decongestion by xylometazoline or that there is a higher bone to mucosa ratio in the nasal valve area of the nose in OSA patients. Reports on proinflammatory cytokines like interleukin-6 (IL 6) are also suggestive of an association between OSA with objective excessive daytime sleepiness and low grade inflammation [23]. Asthmatics are known to have a reduced PNIF compared to nonasthmatics [24] and asthma in OSA patients might be considered a mediator in the reduction of PNIF in OSA patients.

4.1. Strengths and Limitations. The major strength of this study is the pragmatic study design based on prospective data in an everyday clinical setting and the relatively large study population. A limitation of SNOT-20 compared to SNOT-22 is that the latest version of the questionnaire has two additional questions on nasal congestion and decreased sense of smell/taste. Even though our study showed a marked difference in all twenty subsets, information on differences in problems with olfactory function and nasal blockage would have given additional value to the study. Our control group was recruited at random from occupational check-ups and from coworkers at the hospital. Although they made the inclusion criteria, they did not undergo a sleep polygraph to exclude the OSA diagnosis. But the elimination of a potential OSA fraction among controls would only give strength to the differences between the groups rather than weaken them.

The self-reported asthma/allergy and heart disease might be prone to misclassification bias and the results may be underestimated.

5. Conclusion

Sinonasal QoL is significantly reduced in OSA patients compared to a normal cohort measured by SNOT-20, subdomains of SNOT-20, and nasal obstruction VAS score. The subanalysis showed a positive, but not statistically significant, correlation between AHI levels and QoL measures. Subanalysis also showed that the ability to increase nasal inspiratory flow in OSA patients was unaffected by xylometazoline compared to controls, suggesting that additional factors other than AHI sublevels might increase sinonasal complaints in OSA patients. A possible mechanism could be that OSA patients have a smaller inlet area of the nose caused by nasal inflammatory pathways or a reduction of the skeletal framework that constitutes the nasal valve area. Due to its large impact on QoL, relief of nasal obstruction should be a concern in treatment of OSA patients.

Conflicts of Interest

To our knowledge, there are no conflicts of interest.

Authors' Contributions

Mads H. S. Moxness has written the main text and collected the data in both groups and been in charge of the statistical analysis, tables, and figures. Vegard Bugten has been a coauthor and helped in the design and text work. Wenche Moe Thorstensen has been a coauthor and helped in text work and in collection of parts of the control group. Ståle Nordgård has been in charge of the supervision of collection of data and helped in the design and the text work.

Acknowledgments

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Laryngoscope Investigative Otolaryngology

Simulation of the Upper Airways in Patients with Obstructive Sleep Apnea and Nasal Obstruction: A Novel Finite Element Method

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Objective: To evaluate the biomechanical properties of the soft palate and velopharynx in patients with obstructive sleep apnea (OSA) and nasal obstruction.

Study design: Prospective experimental study.

Materials and methods: Two finite element (FE) models of the soft palate were created in six patients undergoing nasal surgery, one homogeneous model based on CT images, and one layered model based on soft tissue composition. The influence of anatomy on displacement caused by a gravitational load and closing pressure were evaluated in both models. The strains in the transverse and longitudinal direction were obtained for each patient.

Results: The individual anatomy influences both its structural stiffness and its gravitational displacement. The soft palate width was the sole anatomical parameter correlated to the critical closing pressure, but the maximal displacement due to gravity may have a relationship to closing pressure of possibly an exponential order. The airway occlusion occurred mainly at the lateral attachments of the soft palate. The total transverse strain showed a strong correlation with maximal closing pressure. There was no relationship between the critical closing pressure and the preoperative AHI levels, or the change in AHI after surgery.

Conclusion: Hyperelastic FE models both in the homogeneous and layered model represent a novel method of evaluating soft tissue biomechanics of the upper airway. The obstruction occurs mainly at the level of the lateral attachments to the pharyngeal wall, and the width of the soft palate is an indicator of the degree of critical closing pressure. A less negative closing pressure corresponds to small total transverse strain. The effect of nasal surgery on OSA is most likely not explained by change in soft palate biomechanics.

Key Words: sleep apnea, nasal obstruction, nasal surgery, upper airways.

Level of Evidence: N/A.

INTRODUCTION

The upper airways may be described as a "critically stable tube" in terms of biomechanics.[1] The balance between the neural drive that enables the dilator muscles to keep the airways open and the counteraction of the intraluminal forces is complex and may be disrupted if the inward stress of the soft tissues exceeds the airway pressure as demonstrated by hypopneas (airway narrowing) and apnoeas (complete obstruction) in patients suffering from obstructive sleep apnea (OSA). Treatment of OSA ranges from conservative lifestyle restrictions, changes in posture during sleep, positive airway pressure devices and mandibular splints, to extensive surgeries of the upper airways. Surgical treatment of the nasal cavity and velopharynx has frequently been performed because it lowers the intraluminal resistance and facilitates airflow, and results in alterations in soft tissue biomechanical behavior in some patients.[1–3] Successful OSA surgeries are reported,[2,3] but long-term positive outcomes are relatively low[4,5] and most surgeons would emphasize that careful preoperative selection of patients is of key importance.[6] This reflects the lack of standardized treatment and the inability to fully understand the underlying mechanisms that govern the airflow and structural changes in the upper airway during sleep. Our primary aim was to investigate the biomechanical response of the soft palate in OSA using computational finite element (FE) simulations. The secondary aim was to use FE models to evaluate correlations between computational critical closing pressures of the velopharynx and objective OSA measures in patients that underwent nasal surgery. Unlike previous biomechanical studies of the upper airway, we created

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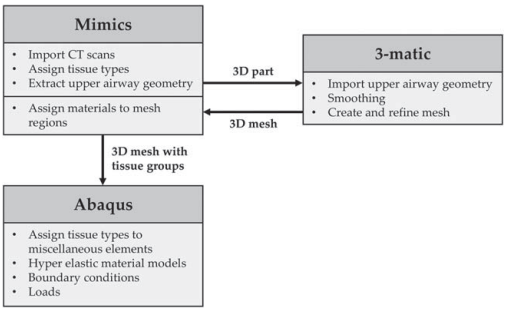

Fig. 1. Workflow of the FE modelling.
FE = finite element

hyperelastic and histology-based 3D models of the soft palate and velopharynx in order to describe the closing pressure and the soft tissue deformation due to gravity.

MATERIALS AND METHODS

This prospective controlled study was approved by the Norwegian Ethical Committee and registered in clinicaltrials.gov (NCT01282125). A total of 30 patients with verified OSA by portable polysomnography (Embletta Diagnostic System, ResMed, San Diego, California, U.S.A., and Nox Medical T3, ResMed, Reykjavík, Iceland) and nasal obstruction underwent nasal surgery. We selected six patients with large variations in the anatomy of the soft palate from this cohort to participate in the computational FE simulations. The biomedical engineering program Mimics (Materialise Mimics Innovation Suite, Mimics Research 19.0, Leuven, Belgium) was used to process sagittal, coronal, and axial CT scans and to reconstruct them in 3D geometry. Two different FE models were constructed for each patient, one based on geometric properties of the soft palate (homogeneous model) and one on the soft tissue composition of the soft palate (layered model). A Neo-Hookean material model was employed to account for the soft tissue elasticity. FE simulations were conducted with Abaqus (Abaqus/CAE version 6.14-1, Dassault Systèmes Simulia Corp., Providence, Rhode Island, U.S.A.) in order to compute the maximal displacement of the soft palate as well as the critical closing pressure (P_{crit}) at the time of airway occlusion. The workflow of the model generation is displayed in Figure 1. The relation of anatomic measures of the soft palate to its displacement caused by the gravitational and pressure load was investigated to identify anatomical risk factors. In order to predict the effect more accurately we constructed a "shape factor" in which the dependence of the deformation caused by gravitation in more than one anatomic feature is taken into account. As a description of deformation, we calculated three sets of strains in Abaqus: The transverse strain (from one lateral side to the other, the x-axis, LE11), and the longitudinal strain (from the hard palate to uvula, the y-axis, LE22) and the strain orthogonal to these (z-axis, LE33). All strain components can represent a mix of membrane strain and bending strain, depending on the magnitude of soft palate displacements. The logarithmic (true) strain was used. The following descriptions of computational simulations and material models reflects the emerging new research field of clinical otorhinolaryngology and structural engineering.

MATLAB (MathWorks, version R2015b, The MathWorks, Inc., Natick, Massachusetts, U.S.A.) was used in the statistical analysis to calculate a suitable fit measure (eg, linear) for the anatomic measures using the linear least-squares method. The sum of squares due to error (SSE), the R-square and the root mean squared error (RMSE) was calculated to estimate the goodness of fit. Typically, a small value for SSE and RMSE, and an R-square closer to 1 would indicate a good fit in validating the model with the anatomical measures.

FE Models

FE models are computational models that provide approximations of partial differential equations (PDE) which are used to describe problems of time or space in physics.[7] FE models of the soft palate and the velopharyngeal airway were created to investigate the influence of anatomical features on the displacement of the soft palate. CT scans with a resolution of 0.46 mm in the x and y direction and 0.7 mm in the z direction were processed in Mimics. Mimics enabled the automatic distinction between bone and soft tissue, while groups of different types of soft tissues had to be selected manually based on literature on histology.[8–11] The modelling domain includes the soft palate from its base at the hard palate to the tip of the uvula and the posterior and lateral walls. The geometry resulting from the tissue segmentation was smoothed using the Materialise module 3-matic (Materialise 3-matic, Research 11.0, Leuven, Belgium). Subsequently, the geometry was meshed with 10-noded tetrahedral elements with a maximum edge length of 1 mm that is a suitable compromise between anatomical accuracy and computational cost caused by the number of elements. The number of elements depends on the shape and size of the soft palate and upper airway and our models consisted of approximately 250,000 elements and one million degrees of freedom.

The homogeneous soft tissue model was utilized to investigate the influence of the macro-anatomy on gravitational loads and pressure. The layered model was used to examine the impact of the different soft tissues that constitutes the soft palate. As no experimental data was available for the soft tissues of the soft palate, material parameters were taken from the literature. For the homogeneous soft tissue model (Table I), parameters describing the overall properties of the soft palate were found in the studies by Birch and Srodon, Pirnar et al., and Yu et al.[12–14] For the layered material model parameters of the soft palate, the material parameters for adipose, glandular, muscular, tendinous, and

TABLE I.
The Elastic Properties of the Human Soft Palate.

Paper	Material Model	Young's modulus (E [Pa])	Poisson ratio (v [-])
Birch and Srodon (2009)	Soft	9.8×10^2	0.45
Pirnar et al. (2015)	Medium stiff	7.54×10^3	0.49
Yu et al. (2014)	Stiff	2.5×10^4	0.42

The Youngs modulus is the stiffness of the material. The Poisson ratio explains the contraction of the soft tissue material when an external pulling force is being exerted.

TABLE II.
The Elastic Properties of Different Soft Tissues Used in FE Simulations of the Velopharynx.

Model	Paper used	Young's modulus (E [Pa])	Poisson ratio (v [-])
Adipose soft	Carter et al. (2012)	5.73×10^2	0.45
	Ramiao et al. (2016)		
Adipose medium stiff	Alkhouli et al. (2013)	2.74×10^3	0.45
	Omidi et al. (2014)		
	Ramiao et al. (2016)		
Adipose stiff	Carter et al. (2012)	2.25×10^4	0.45
	Ramiao et al. (2016)		
Bone	Carrigy et al. (2015)	1.58×10^{10}	0.35
	Huang et al. (2013)		
	Pelteret and Reddy (2012)		
	Rho et al. (1993)		
Glandular soft	Carter et al. (2012)	2.59×10^3	0.45
	Ramiao et al. (2016)		
Glandular stiff	Carter et al. (2012)	3.39×10^4	0.45
	Ramiao et al. (2016)		
Muscle soft	Chen et al. (1996)	4.16×10^3	0.45
	Gennison et al. (2010)		
	Huang et al. (2007)		
Muscle medium stiff	Kajee et al. (2013)	2.44×10^4	0.45
	Mathur et al. (2001)		
	Morrow et al. (2010)		
Muscle stiff	Gennison et al. (2010)	5.34×10^5	0.45
	Morrow et al. (2010)		
	Yu et al. (2014)		
Mucosa soft	Sawada et al. (2011)	2.3×10^5	0.45
Mucosa stiff	Chen et al. (2015)	2.75×10^6	0.45
	Yuko et al. (2015)		
Tendon	Carrigy et al. (2015)	3.9×10^7	0.45

The Young's modulus is the stiffness of the material. The Poisson ratio explains the contraction of the soft tissue material when an external pulling force is being exerted.
FE = finite element.

mucosal tissue were obtained from the works of Kuehn and Kahane, Etterna and Kuehn, Kuehn and Moon, and Cho et al.[8–11] All papers used to describe the parameters are stated in Table II. Soft tissues were modelled as hyperelastic whereas bone was modelled as linear elastic. The material parameters reported in the literature vary considerably. This is in accordance with the fact that the modulus of elasticity of one tissue type can vary significantly between individuals and even within one individual.[15] As a consequence, more than one set of material parameters was applied for each tissue type.

Previous modelling of the upper airways varies in complexity of geometry and material modelling. Two-dimensional models investigate the pharyngeal mechanisms in the mid-sagittal plane, however, they do not consider the influence of the lateral walls[27] (Berry et al. 1999, Huang et al. 2007). Three-dimensional models demonstrated that material modelling influences the response of the soft tissues when loads were applied (Pelteret et al. 2014, Zhao et al. 2013) but they are costly and are frequently based on single-patient CT or MRI data.

MATERIAL MODEL

The mechanical behavior of soft tissue is governed by the protein macromolecules elastin and collagen,

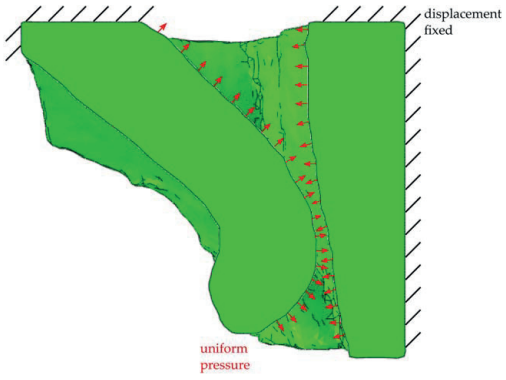

Fig. 2. Sketch of the boundary conditions. The boundaries of the model were chosen to match surfaces where soft tissue adheres to bone to ensure physically valid boundary conditions. A minimum of 4 mm soft tissue was included between the lateral airway walls and the lateral boundaries of the models.

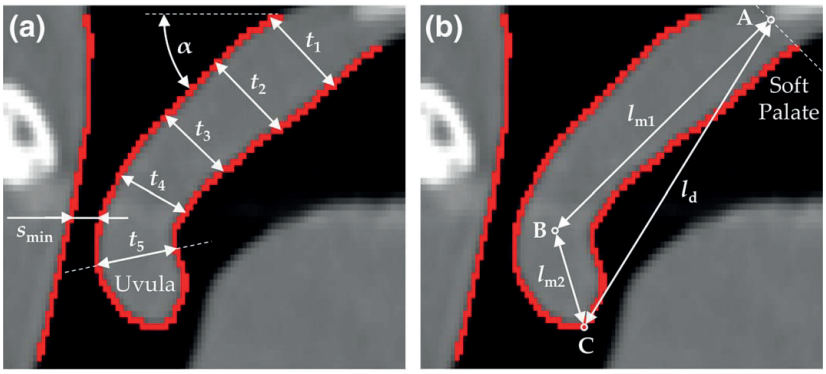

Fig. 3. A. Thickness and angle of the soft palate and the minimum airway space. The mean thickness (t_{mean}) and the mean airway width (w_{mean}) were calculated from five evenly distributed locations from the base of the hard palate to the base of the uvula. B. Measures of length of the soft palate.

which are present in the extracellular matrix. Elastin is the most linear elastic biosolid material. When subjected to loads, the stretching mechanism initially depends on elastin and there is no load on the collagen fibers yet. This leads to a quasilinear behavior at low strains where the loading curve is almost a straight line. Collagen is the main load-carrying element in soft tissues. As long as there is no load on the collagen fibers, they are at least partly in an amorphous configuration. With increasing loads, the collagen fibers start to bear loads and to straighten in the load direction. The material behavior is nonlinear during this process and the soft tissue stiffens significantly. When the collagen fibres are aligned, the stress strain relation becomes linear and the tissue is stiff compared to its stiffness under small loads.[16–19] For the physiological displacement levels of the soft palate the materials mainly operate in the linear regime, and for this the Neo-Hookean model is an acceptable first approach.[17] It is the simplest hyperelastic material model and the strain energy density function Ψ requires only two material parameters c_{10} and D_1 that quantify the stiffness and the compressibility of the soft tissue, respectively.

$$\Psi = \frac{1}{2}c_{10}(I_1 - 3) + \frac{1}{D_1}(J_{el} - 1)^2$$

I_1 is the parameter that characterises the deformation and J_{el} is the elastic volume change.[20,21]

FE Modelling and Posture/Gravity Loads

The displacement of the anterior, lateral, posterior, and proximal side of the FE model was set to zero to model the restriction of the hard palate, the cervical spine, and other tissues on the deformation of the soft tissues of the upper airway (Fig. 2). C3D10H elements (used in stress analysis to simulate incompressible materials) were applied to prevent unnatural stiffening and to grant optimal simulation results. A gravitational load was used to model the difference between the upright and the supine position as most apnea events occur in the supine position.[22,23] The displacements of the soft palate due to a change from the upright to the supine position reported in the literature vary from 1.4 mm[24] to 2.36 mm,[25] the average displacement being 2.02 mm. The computed displacements resulting from supine to

TABLE III.
Maximum Airway Widening Due to Gravity for Different Neo-Hookean Material Models in the Homogeneous and Layered Model and Mixed Model.

	Material model	Patient 1 (mm)	Patient 2 (mm)	Patient 3 (mm)	Patient 4 (mm)	Patient 5 (mm)	Patient 6 (mm)
Homogeneous model	Soft	7.80	15.25	15.83	2.35	5.60	9.16
	Medium	1.31	2.79	3.81	0.27	0.71	1.34
	Stiff	0.53	0.88	1.21	0.09	0.23	0.42
Layered model	Soft	0.45	0.56	1.1	0.42	0.43	0.68
	Medium	0.041	0.048	0.11	0.031	0.16	0.066
	Stiff	0.026	0.033	0.055	0.018	0.067	0.033
Mixed model	Soft	1.65	3.35	4.54	0.38	0.98	1.66
	Medium	1.07	2.43	3.28	0.21	0.59	1.09

Reported average airway widening in the literature is 2.0 mm.

TABLE IV.
Patient Demographics.

P	G	BMI	Thickness (mm)	Width (mm)	s_{min} (mm)	Area ($mm^{2)}$	Volume ($mm^{3)}$	AHI pre	AHI post	P_{crit} (cm H_2O)
1	m	33.1	9.1 ± 1.0	21.8 ± 1.5	1.1	968 ± 86	8812 ± 1262	41	30.7	−1.2
2	m	25.9	6.5 ± 0.5	24.2 ± 4.1	1.0	1060 ± 182	6890 ± 1275	19.1	15.2	−0.4
3	m	25.2	6.5 ± 0.5	29.8 ± 4.2	0.3	1475 ± 209	9589 ± 1543	50.1	53.4	−0.1
4	f	27.0	8.5 ± 1.2	13.3 ± 6.0	0.5	573 ± 260	4851 ± 2306	18.1	19.2	−4.1
5	m	24.3	9.4 ± 0.8	23.0 ± 6.1	0.8	1014 ± 275	9514 ± 2709	18.0	5.6	−1.9
6	m	26.9	9.1 ± 0.9	22.7 ± 3.6	0.4	891 ± 153	8110 ± 1603	11.1	3.1	−0.7

Geometry of the soft palate, minimal airway space (s_{min}), baseline and postoperative values of the apnea-hypopnea-index (AHI) and critical closing pressure (P_{crit}).
BMI = body mass index; G= gender; P = Patient number.

upright position presented in Table III are compared to this value in order to have a guide on what material parameter set is most representative. Negative intraluminal pressure during inspiration narrows the airway and might lead to airway collapse.[26–28] As the displacement of the soft palate is governed by air pressure with minimal influence of shear forces,[29] the load on the soft palate during inspiration was modelled as a uniformly distributed negative pressure. The distance from the soft palate to the pharyngeal wall was monitored during the Abaqus simulations. The closing pressure was identified as the pressure when the distance between the soft palate and the wall was below a very small value, ie, a simplification avoiding performing contact analysis.

RESULTS

The patient demographics and geometric values of the soft palate, the apnea-hypopnea-index (AHI) and minimal airway space are listed in Table IV. The table also provides the computed critical closing pressures.

The Homogenous Soft Palate Model

Finite element simulations were conducted with a soft, medium, and a stiff Neo-Hookean material model (Tables (I–III), II, and III). The medium stiff homogeneous model is the most accurate choice of model to evaluate gravitational deformation, compared to literature.[25] The displacement due to gravity may be used to measure the effect of individual anatomy on soft palate

TABLE V.
Goodness-of-Fit Measures for the Soft Palate.

	Measure	SSE	R-square	RMSE	$\dot{y}$
Influence of anatomy on tissue deformation due to gravity	t_{mean}	2.32	0.74	0.76	8.2 mm
	l_d	19.31	0.81	2.20	41.9 mm
	l_{mid}	32.27	0.41	2.84	44.1 mm
	w_{mean}	40.32	0.72	3.18	22.5 mm
	u_{mean}	5.19	0.18	1.14	6.4 mm
	V	1.40×10^7	0.16	1.87×10^3	7.96×10^3 mm^3
	Shape factor l_{mid}	993.62	0.94	15.28	128.38 mm
	Shape factor l_d	718.52	0.96	13.40	123.90 mm
Influence of anatomy on closing pressure	t_{mean}	7.06	0.20	1.33	8.2 mm
	l_d	59.24	0.43	3.85	41.9 mm
	l_{mid}	51.06	0.06	3.57	44.1 mm
	w_{mean}	22.61	0.84	2.38	22.5 mm
	$U2_{max\ linear\ fit}$	3.21	0.64	0.90	1.7 mm
	$U2_{max\ exp.fit}$	0.87	0.90	0.54	1.7 mm
	b_{min}	0.55	$8.3x10^{-4}$	0.37	0.7 mm
	A	1.43×10^5	0.66	189.15	997.2 mm^2
	Shape factor l_{mid}	7.43×10^3	0.55	43.11	128.3 mm
	Shape factor l_d	7.89×10^3	0.57	44.41	123.8 mm

FE simulations of the influence of anatomical measures on tissue deformation and closing pressure. $\dot{y}$ reflects the mathematical expectations of the anatomical features.
A = area; b_{min} = minimal airway space; FE = finite element; l_d = length direct. l_{mid} = length midline; t = thickness; u = uvula length; U2 = maximal deformation; V = volume; w = width

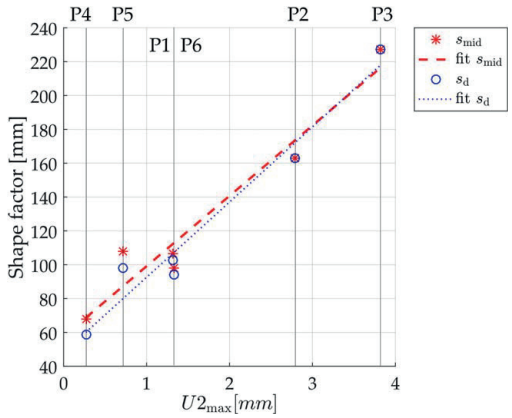

Fig. 4. The shape factor of the soft palate and maximal displacement ($U2_{max}$) due to gravity. Red asterix and line = shape factor using the midline length (s_{mid}). Blue circle and line = shape factor using the direct length (s_d).

stiffness and tissue deformation. The mean thickness, direct length, and mean width of the soft palate were separately good fits to the FE model (Table IV). In order to predict the effect more accurately we constructed a "shape factor." A shape factor of the soft palate is determined by the product of its length and width divided by its thickness: $s = l \cdot w_{mean}/t_{mean}$. Since the sagittal shape of the soft palate is angled at the base of the uvula we determined to types of soft palate lengths, the midline length (l_{mid}) and the direct length (l_d) (Figs. 3A and 3B). Compared to using the volume of the soft palate, the shape factor yielded a good correlation with the maximal displacement of the soft palate due to gravitational loads with the l_d giving a marginally better fit than l_{mid} (Table V, Fig. 4). The length of the uvula and the volume of the

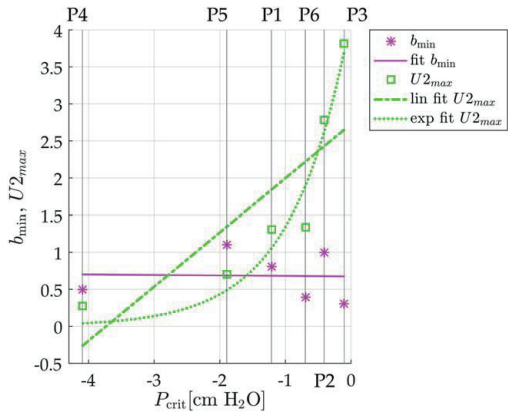

Fig. 5. Minimum airway space (b_{min}), maximal displacement due to gravity ($U2_{max}$) and closing pressure. The maximal displacement has a relationship to closing pressure of a higher order, possibly exponential.

soft palate had a poor goodness of fit measure, indicating a weak relationship between uvula length and soft palate volume and tissue displacement (Table V). One interesting feature in our simulations was that the maximal displacement of the soft palate might be an indicator for soft palatal compliance and seemed to have a relationship to closing pressure that was of a higher order (Fig. 5), but with only six simulations the results are still uncertain.

In the FE model, the displacement of the soft palate at the critical closing pressure (P_{crit}) could be visualized. The maximal displacement can be seen at the tip of the uvula, but the location of the airway obstruction was at the level of the lateral attachment to the pharyngeal wall rather than at the distal end of the soft palate in five of six patients (Figs. 6 and 7). The influence of the soft palate anatomy on closing pressure was considered in the same manner as with gravitational loads. The single most reliable fit of the anatomic measures on the closing pressure was the width of the soft palate (Fig. 8).

The Layered Soft Palate Model

The displacement of the soft tissue due to gravity in the layered model was extremely small due to the stiffness of oral mucosa used in the model. Adipose soft tissue, musculature, and glandular soft tissue are comparable in stiffness to the medium homogeneous model, while the oral mucosa is at least one order of magnitude stiffer than the medium homogeneous model. The material parameters for oral palatal mucosa in the literature are from the masticatory mucosa lining the dorsum of the tongue, hard palate, and gingiva, and unsuitably stiff for modelling the soft palate. We replaced the material parameters of the oral mucosa with the values for the medium homogeneous model and let the other soft tissue parameters remain, thus creating a new mixed layered model (Table II). The layered soft palate model is therefore not able to describe the material properties of the soft palate appropriately and reflects the lack of sufficient experimental data for soft palate mucosa. The effect of the different compositions of soft tissue on the closing pressure is illustrated in Figure 9. It reveals a more profound difference between the material models in patients with a more negative closing pressure. The higher the closing pressure, and thus the more compliant the soft palate becomes, the less the composition of the soft tissue seems to matter. Similar to the homogeneous model, the airway occlusion is primarily at the level of the lateral attachment of the soft palate to the pharyngeal wall.

Strain

The total transverse strain of the soft palate, defined as the posterior mid-sagittal point with the highest strain (LE11), correlates strongly with the closing pressure (Figs. 10 and 11) with an R-square of 0.92. A less negative closing pressure corresponds to small strain in the transverse direction. The strains in the LE22 and LE33 direction did not show the same degree of linearity as LE11, with an R-square of 0.88 and 0.68,

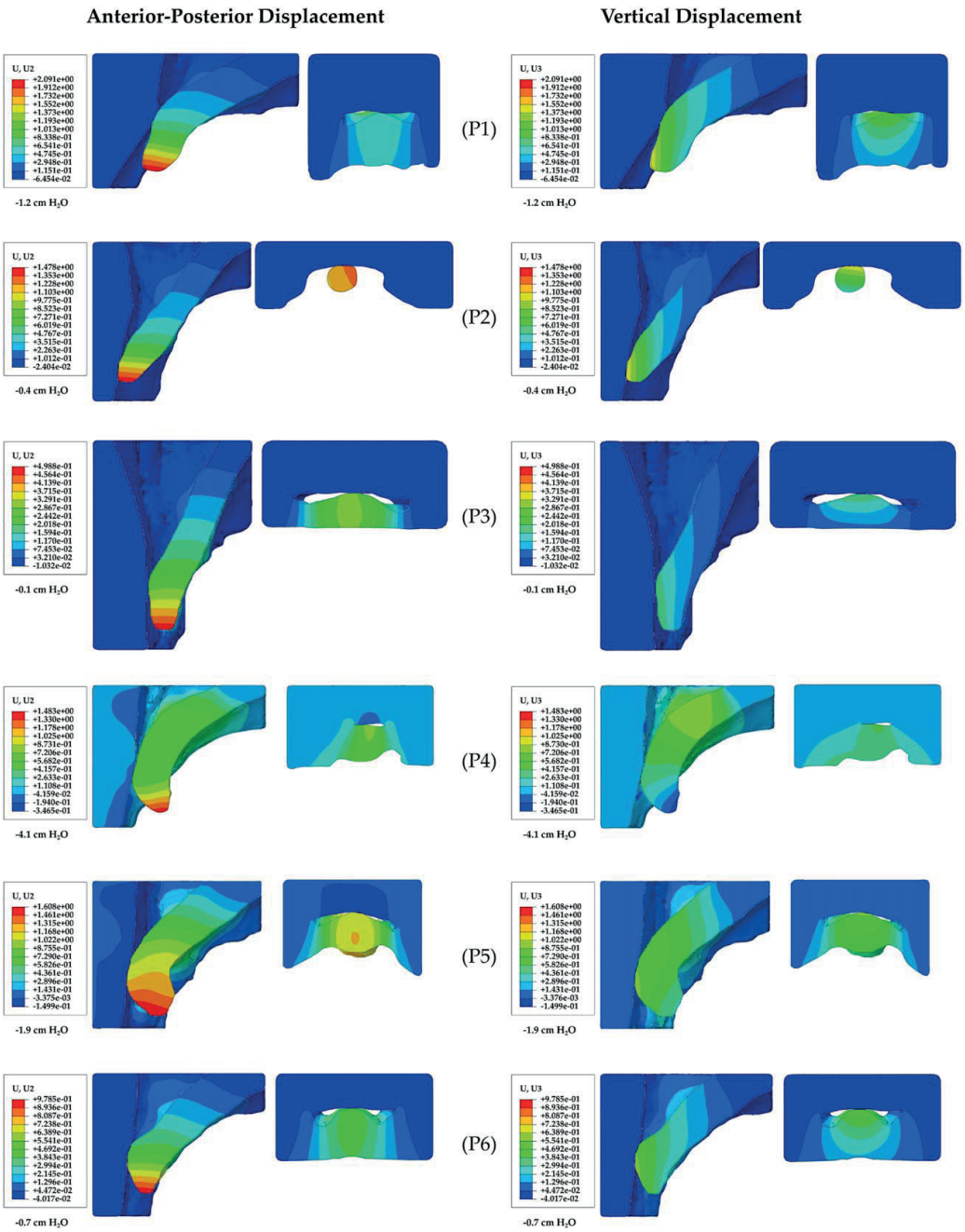

Fig. 6. Displacement of the soft palate in the anterior-posterior direction (figures on the left), and in the vertical direction (figures on the right). Patient numbers 1–6 from top to bottom (P1–P6).

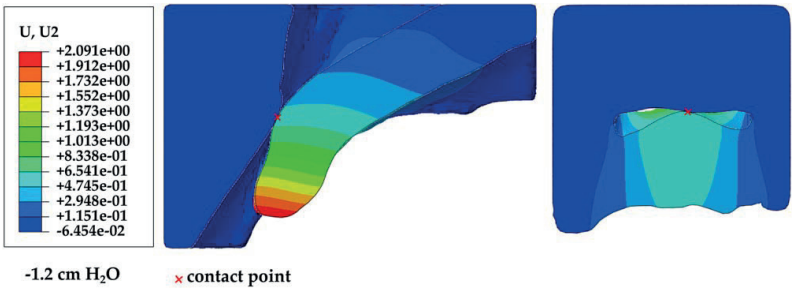

Fig. 7. Point of contact between the velopharynx and the posterior pharyngeal wall in the sagittal and axial plane, defining the simulated closing pressure in the FE models.
FE = finite element

respectively. For LE22 maximum strain values were situated at the anterior (oral) part of the soft palate for most of the patients and were generally smaller than the maximum transverse strain. Based on the histology study by Ettema and Kuhn, the palate has a layered structure with a dominating collagen and muscle fiber orientation in the transverse direction.[8] For low tensile strains the collagen fibers are curved (wavy) and do not carry any significant stress. Almost all biological soft tissues with collagen fibers embedded in an extracellular matrix show a "knee point" in the stress versus strain curve, eg, Gasser et al., 2006 and Skallerud et al., 2011.[30,31] Prior to this point, elastin provides some resistance to strain. After this point, the collagen fibers straighten out and provide a significant increase in resistance to straining. Although our simulations are based on a simplified hyperelastic material model that does not account for the collagen, the strain levels computed in the palates are in the low range where stiffness is governed by elastin. Hence, our material model is representative. Figure 10 demonstrates that the maximal transverse strain is mainly located at the area of obstruction, and not at the area of maximal displacement.

The Minimal Airway Space

The minimum airway space was defined from the CT scans in each patient as the minimum length from the dorsal side of the soft palate to the posterior pharyngeal wall. The subsequent minimal airway space (b_{min}) in the FE models was also determined for each patient. In contrast to assumption there was no obvious relation between b_{min} and $P_{crit,}$ with an extremely small R-square (Table V) indicating that airway diameter alone is not sufficient to predict airway collapse.

Effect of Nasal Surgery on the Soft Palate

The overall reduction of AHI in the group was 19.2%. Surgical success defined as a decrease in AHI of 50% or more was achieved in two out of six patients. Four patients achieved a decrease in AHI by 20% or

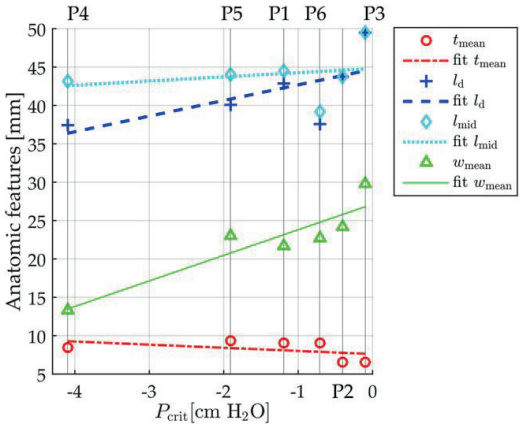

Fig. 8. Individual anatomic measures of the soft palate and closing pressure. Patients sorted by ascending closing pressure. The mean width (green triangle and line) is the only anatomic measure that yields a reasonable goodness of fit.

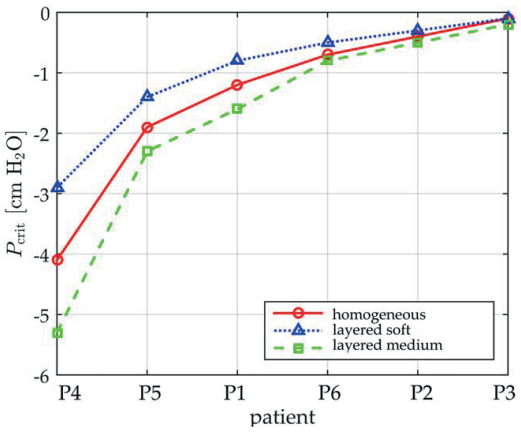

Fig. 9. Closing pressure in the supine position for different material models. Increasing closing pressure corresponds to increasing compliance of the soft palate.

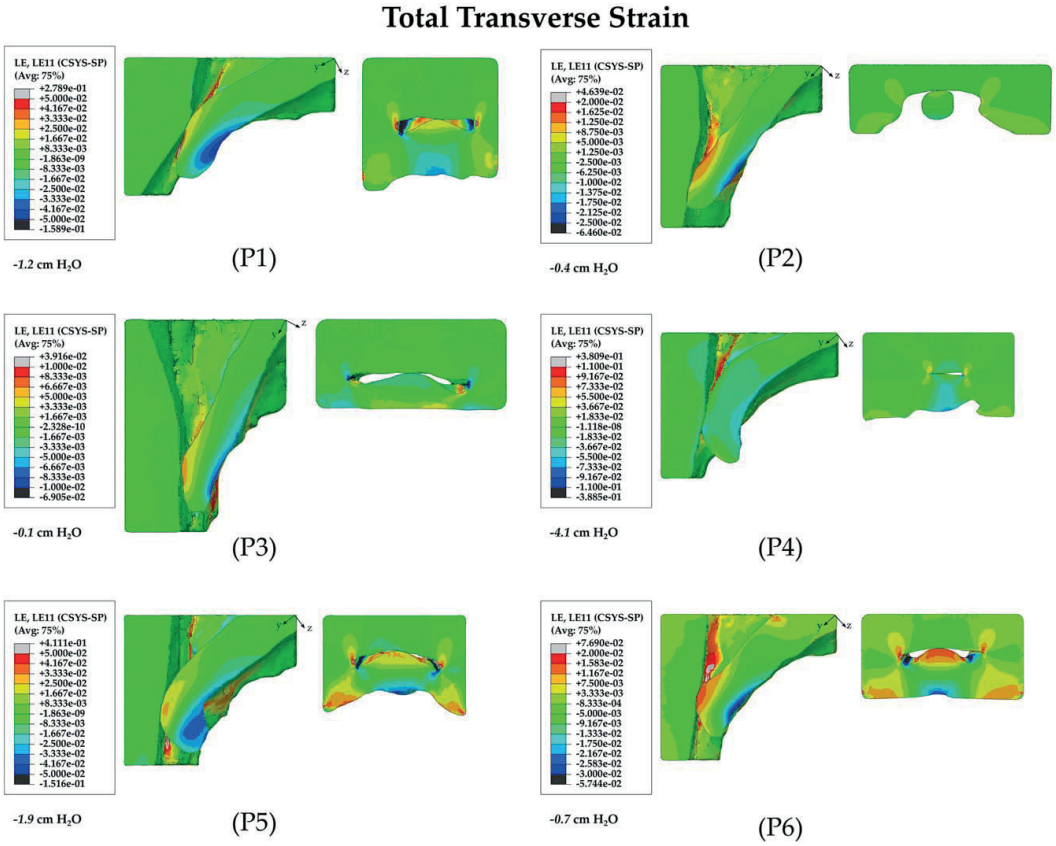

Fig. 10. Total strain in the lateral to lateral direction. Sagittal plane to the left, axial plane to the right. Patient number 1–6 from top to bottom (P1–P6).

more, and two patients experienced a worsening of the condition defined as an increase in AHI by 6%. The P_{crit} and the medical data of preoperative AHI level showed no linear relationship. Similarly, the P_{crit} did not show a linear relationship to change in AHI after nasal surgery. A high AHI does not necessarily translate into a high (less negative) simulated P_{crit} and as a consequence the FE-model of the soft palate and velopharynx does not seem to be a suitable tool to predict the severity of OSA or the outcome on OSA after nasal surgery.

DISCUSSION

Our FE models indicate that the individual shape of the soft palate influences the closing pressure and the stiffness of the soft tissue in the velopharynx. The evaluation of passive mechanical behaviour of the soft tissues in the upper airway is challenging because there will be a neural driving mechanism in the airway musculature. Pelteret and Reddy demonstrated in 2013 a considerable difference in the displacement of the tongue due to gravity in their FE model depending on whether active muscle control was applied or not.[30,32] Studies of paralyzed human airways, however, demonstrate that the upper airways in OSA patients are more compliant than in healthy subjects suggesting that geometric characteristics alone can influence the biomechanical response of the airway.[33,34] The shape factor of the soft palate influences the tissue gravitational displacement in a positive linear fashion and may be used as a way of determining the level of tissue deformation due to posture in OSA patients. Even though the mean thickness, length, and width clearly shows a positive correlation to tissue displacement, the combined value of the shape factor seems to be more accurate (Fig. 4). The notion of a shape factor based on combined geometric values may be applied to other defined anatomical sites in the airway, ie, the tongue or even the total pharyngeal soft tissue compartment. The length of the uvula and the volume of the soft palate both have an inappropriate fit and are unable to explain the degree of displacement of the soft palate.

The concept of the critical closing pressure (P_{crit}) is widely used as a means to describe the collapsibility of the airway.[1,35] However, the upper airways cannot

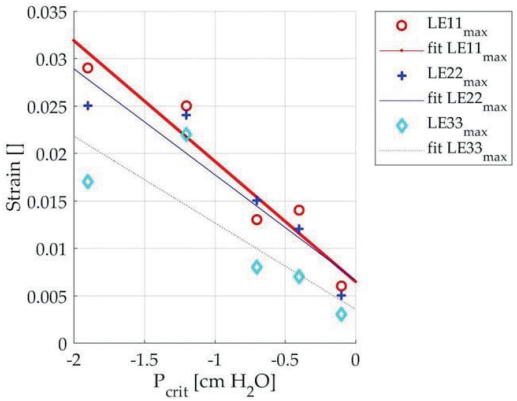

Fig. 11. Strains and closing pressure. LE11 (red circles and line) shows a better linear fit that LE22 and LE33. One should note that although a linear correlation between strain and pressure is obtained, the linear curve does not go through the origin. Hence, one should be careful in using this result for closing pressures near zero. The palatal load for patient 4 is mainly dominated by shear stresses and bending stresses and is therefore not included in the plot.

automatically be explained by a Starling resistor mechanism, because it does not take into account the muscle activity and biomechanical qualities of the velopharynx.[36] The minimum airway space is insufficient to predict the collapse of the upper airway and may be caused by the fact that the displacement of the soft palate is not merely in the anterior-posterior direction but has a vertical component as well. Even though the maximal displacement is at the distal end of the soft palate, the FE models show that the airway occlusion is at the level of the lateral attachment of the soft palate to the pharyngeal wall in all but one case. Consequently, surgical procedures involving the soft tissue in the distal part of the soft palate are likely to have a limited impact on closing pressure and the development of apneas, which is consistent with the repetitively low success scores of soft palate surgery on OSA outcome.[37,38] Similar to the effect of gravity on tissue deformation, the length of the uvula and the volume of the soft palate do not show a linear relationship to the closing pressure. Of all the anatomical landmarks, it seems that the mean width of the soft palate is the most likely anatomical landmark that can be correlated to the critical closing pressure. The shape factor is not a predictor of closing pressure. However, the maximal displacement of the soft palate may have a relationship to the closing pressure that is not linear, but of a higher order, possibly exponential (Fig. 5 and Table V). A bigger sample size is necessary to identify the maximal displacement as an indicator of soft palate compliance and critical closing pressure (Fig. 4). The macro anatomy seemed to have a more substantial influence in patients with a less negative closing pressure, while the effect of the difference in soft tissue composition was more pronounced in patients with a stiffer soft palate and a more negative closing pressure (Fig. 6). Difference in soft tissue composition may therefore have a larger clinical impact in social snoring or patients with mild to moderate OSA than in patients with more severe upper airway collapse. It does not, however, mean that the layered model is inferior to the homogeneous model in severe OSA. Rather it points to other areas of the upper airway that may contribute to the disease in severe cases of OSA.

There seems to be a strong correlation between total transverse strain and closing pressure in our models (Fig. 11). In our model, the soft palate resembles a plate that is fixed at three sides (hard palate anteriorly, bony attachments to each lateral side) and free at the fourth distal end in the direction of the uvula. In the mid-sagittal plane, the boundary conditions resembles a cantilever type, and the strain is dominated by bending strain due to the curvature along the longitudinal y-axis (LE22). In the transverse plane, due to the boundary conditions, the strain will be a combination of bending (due to the curvature along the transverse x-axis) and membrane tension (LE11). In this transverse plane, membrane strain in the longitudinal y-axis (LE22) does not develop as the distal uvula end is free. Thus, the strain along the transverse axis (LE11) was of largest interest and was used to check for correlation against closing pressure. This also has a link to the anatomical measure of soft palate width, that showed a correlation to closing pressure.

The strain along mid thickness in the lateral to lateral direction describes mainly membrane strain. In some patients, we saw a tensile membrane strain on the posterior side of the soft palate, but a compressive strain on the anterior side. This can probably be explained by an additional large bending contribution as well, meaning that there is a curvature in both the x and y direction giving bending strains in both directions. The membrane strain at mid thickness is superposed to this (on the posterior side the curvature in the y-direction gives a tensile bending strain in addition to tensile membrane strain. On the anterior side the curvature gives a compressive bending strain that is superposed to the membrane strain). The total transverse strain is the dominant strain components except in patients 2 and 4. In patient 2, bending strain and membrane strain have approximately the same order of magnitude (therefore maximum principal strain seems to be compression at both sides of the soft palate), but the total strain value fits the linearity when plotted versus closing pressure. In patient 4, the closing of the airway occurs very close to the attachment of the soft palate to the lateral airway walls. One can also note that the soft palate width in this patient is about half the size of the others (Table III). This leads to the upper airway negative pressure being carried to a much larger extent by shear stresses and bending stresses, ie, the transverse membrane stress and strain are less compared to the other patients. Since the strain cannot be regarded as a measure of total transverse strain this case is not included in Figure 11. It should be mentioned that we neglect any neuromuscular activation. The striated muscle fibers in the palate provides a contraction reflex when the palate

approach closure. Studies show that this reflex and corresponding activation level is significantly reduced compared to healthy persons, as reported previously.[39,40] Not accounting for the reduced muscle activation in sleep apnea patients may be considered as a conservative approach to predict the closing pressure. Further studies should be carried out in order to resolve this issue.

Surgery of the distal part of the soft palate as an isolated procedure is no longer advised[41] due to unsatisfactory results with failure in 40–60%[42] and long-term side effects such as dysphagia, globulus sensation, velopharyngeal insufficiency, and xerostomia in a mean of 58% of the patients.[43,44] This is consistent with our results in that the distal part of the soft palate does not seem to be the most prominent site of obstruction when it comes to high obstructions.

We found no correlation between minimum airway space and the critical closing pressure (Table V). The exact positioning of the lower jaw during medical imaging can influence the minimal airway space of the upper airways and no standard method has been introduced to minimize bias in this regard. The impact of observed airway space should therefore not be relied upon to give solid information on the degree of obstruction in the velopharyngeal area. In order to reduce such systematic error, we had all patients fitted with a 20-mm mouthpiece during the imaging procedures.

Nasal surgery relieves symptoms in most OSA patients[45,46] and is known to reduce the number of apneas to some degree.[47] However, no guidelines exist as to what type of nasal surgery to perform and no method is available to predict the surgical outcome. In addition to increasing the compliance for pressure devices, the surgical alterations in the nasal cavity are reported to reduce the AHI by 50% in 15% of the patients.[47,48] We found an average reduction in AHI of 19.2% and a surgical success in 33% three months after nasal surgery. All patients had septoplasty and turbinectomy performed. There was no correlation between simulated P_{crit} and preoperative AHI in our study. The patient with the highest AHI preoperatively also had the least negative simulated P_{crit}, which could have been an indication of a relationship between the preoperative AHI values and the FE model. However, none of the other patient data gave support to this view. This suggests that the effect on OSA outcome in nasal surgery is more likely dependent on the structural intranasal alterations induced by the surgery itself or on changes in other parts of the upper airway secondary to the restoration of nasal patency, possibly by inducing a switch from oral to nasal breathing which enables normal muscular neuroregulation in the pharynx as well as creating a larger anteroposterior diameter in the retroglottic area.[48,49] It is worth mentioning that our patients had surgery done in the anterior part of the nasal cavity which includes the posterior part of the nasal vault, which may be an area of importance in OSA patients.[50] Since nasal surgery does create change in the upper airway compliance, it may be used as a tool to investigate the changes in upper airway biomechanics using FE simulations. A FE model that comprises solely one anatomic feature seems to be insufficient to comprehend all relevant effects of OSA. A more extensive model including the nasal cavity, the soft palate, the tongue, the epiglottis and the hypopharynx might increase modelling accuracy.

Even though the soft palate is the most important site of airway collapse in patients with oropharyngeal obstructions,[35] its biomechanical properties are less researched and it is usually modelled as linear-elastic and homogeneous, instead of hyperelastic, nonlinear and heterogeneous. The available full 3D models are usually expensive to conduct and in most cases the data is derived from a single patient. A larger study population will therefore be necessary to obtain clinically valid data.

Strengths and Limitations

The hyperelastic and nonlinear model of the velopharynx and soft palate represents a new approach to evaluate the biomechanics of the upper airways. Former research on the topic is scarce, and 3-D simulations are mostly confined to single patient studies due to high computational costs. The inclusion of six patients enhances the chances of creating a more reliable model, and an even larger study population would be preferable. However, the FE models are only an approximation of the actual anatomic site and velopharyngeal function. Larger study populations that include the hypopharynx and larynx are needed in order to verify the relationship between upper airway anatomic landmarks, maximum deformity of the soft tissue, total transverse strain and P_{crit}. In particular the relation between anatomical features versus membrane strain and bending strain needs further studies with larger cohorts. The resolution of the CT scans restricts the FE models, and particularly the study of histologic structures. The relationship between the solid soft tissues and the fluid within the airways have not been investigated, hence the influence of fluid–structure interaction is not accounted for.

CONCLUSION

Our FE simulations indicate a correlation between anatomic measures, displacement of the soft palate, and OSA, as well as a correlation between total transverse strain of the soft palate and closing pressure. Previous modelling of the soft palate does not take into account the hyperelastic properties of the soft palate, or the possible effects of the different soft tissues that constitute the palate or the forces caused by its lateral attachment to the pharyngeal wall. FE simulations applying hyperelastic, nonlinear, and heterogeneous material models show that the primary site of obstruction of the soft palate in OSA is at the level of the lateral attachments rather than at the distal part of the soft palate, and this observation may explain the relatively low success rate observed in single soft palate surgery in OSA patients. The closing pressure is correlated to total transverse strain and FE simulations may represent a possible way to predict closing pressure in the velopharynx, but the possible interaction of neuromuscular activation on strain should be accounted for in future studies. The FE

simulations indicate that the soft palate may not represent the primary site of critical closing pressure in OSA after nasal surgery. FE models of larger sections of the upper airway are needed to predict P_{crit} and OSA severity more accurately. Soft tissue biomechanics and fluid structure interaction will be of increasing importance in the planning of surgical interventions in obstructive sleep apnea and upper airway disorders.

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