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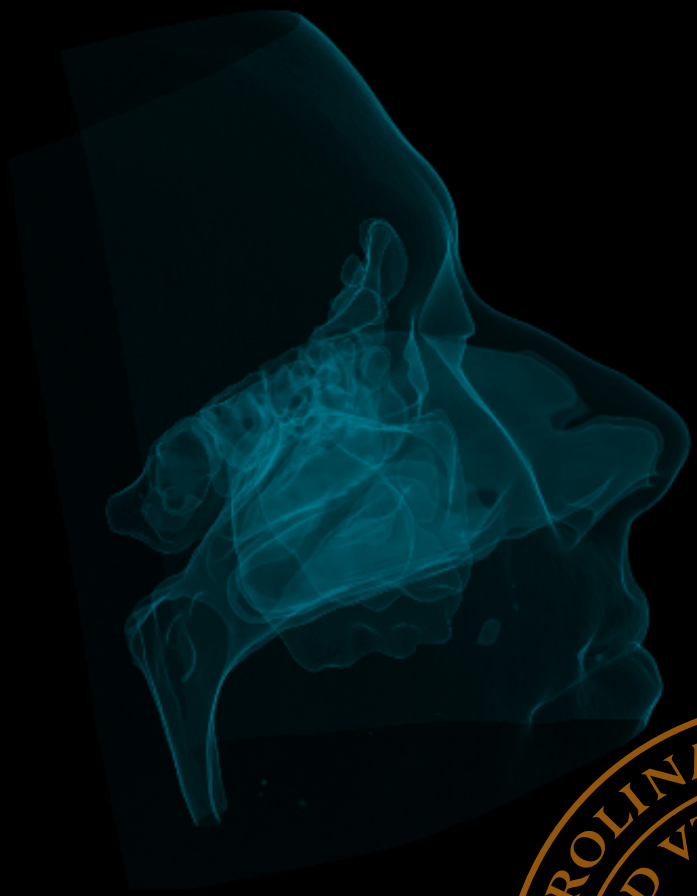

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Background

Obstructive sleep apnea (OSA) is a prevalent disorder and symptoms of nasal obstruction are highly prevalent in OSA. Treatment of nasal obstruction in OSA patients has shown modest and variable outcomes in reducing the apnea hypopnea index (AHI), but significant improvements in other indicators, such as sleep quality and daytime sleepiness as well as reductions in arousals have been observed. We hypothesize that the nose plays a more prominent role in sleep-disordered breathing than previously recorded.

Methods

Three prospective randomized case-control studies of OSA patients diagnosed through a type III sleep study. In study I, patients were examined with 4-phase rhinomanometry (4-PR) and for study II with 4-PR and acoustic rhinometry. The first two studies examined if these common objective methods for measuring nasal patency were associated with respiratory indices in sleep studies. The third study investigated if these differences were associated with a low arousal threshold endotype.

Results

OSA Patients with more hypopneas relative to apneas were more likely to have increased nasal resistance. Acoustic rhinometry measurements were significantly associated with 4-PR but not between the acoustic rhinometry and respiratory variables analyzed in the sleep studies. OSA patients with increased nasal resistance were associated with a low arousal threshold endotype.

Conclusions

OSA patients demonstrating increased nasal resistance are associated with a low arousal endotype and display significant differences in respiratory disturbance during sleep compared to those with normal nasal resistance. This project has demonstrated suitable objective measures to detect these differences which has implications for the future stratification of OSA patients.

Key words: Obstructive Sleep Apnea, Respiratory System Diagnostic Technique, Sleep Hypopnea, nasal obstruction, rhinomanometry	
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This book is dedicated to Theodor, who has had to experience his father's apparent biweekly disappearances with no sensible explanation other than "på jobben". Perhaps one day you will read this book and conclude, that still makes no sense.

Table of Contents

Thesis at a Glance

Aim	Design	Principal finding
Paper I		
To study how increased nasal resistance affects respiratory variables in obstructive sleep apnea (OSA).	Randomized prospective cross-sectional study	OSA Patients with a higher ratio of hypopneas relative to apneas are more than three times more likely to have increased nasal resistance as measured by 4-phase rhinomanometry, regardless of OSA severity.
Paper II		
To examine if OSA patients with an elevated hypopnea apnea ratio are associated with measurable differences in acoustic rhinometry measurements.	Randomized prospective cross-sectional study	No consistent statistically significant associations were found between the acoustic rhinometry variables, and the respiratory variables analyzed in the sleep studies.
Paper III		
To investigate if increased nasal resistance in OSA is associated with a low arousal threshold endotype.	Randomized prospective cross-sectional study	OSA patients with increased nasal resistance are significantly associated with a low arousal threshold endotype.

Populärvetenskaplig sammanfattning

Det naturliga och mest fördelaktiga sättet att andas när man sover är genom näsan. Det ger mindre motstånd än att andas med munnen och det går därför åt minst energi för att hålla den övre luftvägen öppen. Munandning ger större risk for at snarka. Snarkning uppstår av vibrationer i mjukdelarna i de övriga luftvägarna, nämligen mjuka gommen, gomspenen och tungan. Vibrationerna skapas när mjukdelarna möts, såsom i munstycket i en klarinett eller liknande blåsinstrument. Obstruktiv sömnapné, eller OSA, kännetecknas av andningsstörningar under sömn. OSA är ett spektrum från kraftig snarkning med förträngning av de övre luftvägarna till stängning med andningsuppehåll. Detta beror på många faktorer som trånga övre luftvägar, svag uppstramning av muskulaturen i luftvägarna och störda neurologiska kontrollmekanismer av andningen när man sover. Orsaken till trånga övre luftvägar kan vara förträngningar på grund av anatomiska avvikelser. Fetma eller övervikt kan också föra till trånga övre luftvägar.

I denna doktorgradsavhandling har vi sett på vuxna OSA patienter med nästäppa genom tre separata studier. Vi har analyserat om de andas annorlunda när de sover och om de har lättare för att vakna jämfört med patienter med OSA med normalt motstånd i näsan. Vi rekryterade patienter som har fått påvisat OSA genom polygrafi, en sömnundersökning som mäter respiratoriska värden, hjärtrytm och kroppsställning. Vi mätte motståndet i näsan med en apparat som heter 4-fas rhinomanometri. Undersökningen visade att hypopnéer, som innebär periodiskt trånga övre luftvägar, var dominerande andningsstörning hos patienter med OSA med ökat motstånd i näsan. Detta till skillnad från dem som inte var täppta i näsan som hade fler apnéer, dvs fullständiga andningsuppehåll.

I vår andra studie undersökte vi om en annan apparat för mätning av nästäppa, nämligen akustisk rhinometri, kunde avslöja samma fynd. Instrumentet sänder akustiska signaler, såsom ett ekolod, för att mäta geometrisk areal och volym i näsan. Här fann vi att där vi hade mätt ökat motstånd i näsan med 4-fas rhinomanometri också var mindre areal i näsan vid undersökning med akustisk rhinometri. Vi kunde emellertid inte hitta samband mellan de akustiska måtten och de respiratoriska mätresultaten i de polygrafiska sömntesterna.

I studie tre har vi undersökt 315 patienter med OSA med 4-fas rhinomanometri av vilka 197 hade ökat motstånd i näsan. Vi analyserade om de hade lägre tröskel för att vakna. Detta blev gjort via en algoritm med tre värden, nämligen apné-hypopné index (AHI) som anger genomsnittligt antal andningsuppehåll i timmen, hur stor andel av AHI som bestod av hypopnéer och hur djupt syremätningen föll på sitt lägsta. Patienterna med OSA som hade ökat motstånd i näsan hade två gånger högre sannolikhet för å ha en lägre uppvakningströskel.

Original Articles

This thesis draws upon the referenced publications, denoted in the text by Roman numerals.

Paper I

Hoel HC, Kvinnesland K, Berg S. Impact of nasal resistance on the distribution of apneas and hypopneas in obstructive sleep apnea. Sleep Med. 2020 Jul;71:83-88. doi: 10.1016/j.sleep.2020.03.024. Epub 2020 Apr 17. PMID: 32502854.

Paper II

Hoel HC, Kvinnesland K, Berg S. Outcome of nasal measurements in patients with OSA - Mounting evidence of a nasal endotype. Sleep Med. 2023 Mar;103:131-137. doi: 10.1016/j.sleep.2023.01.028. Epub 2023 Feb 3. PMID: 36791622

Paper III

Hoel HC, Berg S. Nasal Obstruction is Associated with a Low Arousal Threshold Endotype

Submitted to *Sleep Medicine*

Acknowledgements

This research was conducted at the Department of Ear, Nose and Throat, Head and Neck Surgery and Sleep Medicine at Lovisenberg Diaconal Hospital and the Faculty of Medicine, Department of Otolaryngology, University of Lund.

I want to convey my gratitude to the participants in these studies, dedicating valuable time for extensive testing in the interest of science. To everyone at Lovisenberg, helping me hone my surgical skills, and for the opportunity to pursue my scientific curiosity.

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To Hanne Berdal, Einar Gran and Lars Vasli, for first employing me at Lovisenberg. To Torunn Forbord, for your patience and enthusiasm in mentoring me on the sinuses. To Karoline Granås, for helping me with the daunting task organizing my study participants, for never denying me a surplus rhinomanometry. To Milada Småstuen for your invaluable help in guiding me in the intricacies of basic statistics. To Pamela Åsten, for translating my text to eloquent Swedish. To Britt Øverland, whose door was always open. To Alexander Grande Hansen, for editing my work, which all too often was excessively verbose for his tastes, his efficient refinements always exquisitely eloquent.

To my advisors Knut Kvinnesland and Søren Berg, please refer to the preface. Rest assured, without you, none of this would be possible. To you I am profoundly grateful.

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To my mother Ellen Elisabeth who put up with me as a child and raised me to be a better person. Who always supported my inquisitive nature, reminding me that my mind was my greatest asset. To my father Kjell who has always supported my interests, defended me, and helped me when I needed. Who helped me build my first and only Hindenburg. For teaching me Ohms law, for this and so many other life lessons, projects, and insights I appreciate, and will forever appreciate.

Finally, to Gry Helen for believing in me and propping me up when I needed it the most, for enduring my endless ramblings, about my own work and unrelated podcasts. For your patience in my pursuit of this seemingly unending task, having to act as a single parent far too often, for far too long. I can only hope to make you efforts feel worth it, you are my shining light, my most sincere gratitude goes to you.

Acronyms and Abbreviations

4-PR	4-phase Rhinomanometry
95% CI	Ninety five percent confidence interval
AASM	American Academy of Sleep Medicine
AHI	Apnea hypopnea index
AI	Apnea index
AR	Acoustic rhinometry
ARAS	Ascending reticular activating system
B	Regression coefficient
BMI	Body mass index
CO_2	Carbon dioxide
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
GABA	Gamma-aminobutyric acid
HAR	Hypopnea to apnea ratio
HI	Hypopnea index
LR_{EFF}	Logarithmic conversion of vertex resistance and effective resistance
MCA	Minimal cross-sectional area in either left or right nasal cavity
NO	Nitric oxide
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnea
PALM	Pcrit, arousal threshold, Loop gain, Muscle responsiveness
Pcrit	Passive critical closing pressure of the pharynx
PG	Standard portable respiratory sleep polygraphy
PROM	Patient recorded output measures
PSG	Polysomnography
REFF	Effective resistance
REM	Rapid eye movement
SDB	Sleep-disordered breathing
SMAS	Superficial musculoaponeurotic system
SpO2	Peripheral oxygen saturation
TMCA	Total minimal cross-sectional area of both nasal cavities
TRPM8	Transient receptor potential melastatin family member 8
TVOL	Total volume of both nasal cavities
VAS	Visual analog scale
VR	Vertex resistance

Preface

As an ENT surgeon struggling with the treatment of my patients with complaints of stuffy noses and falling short, I peered outside the local constraints of my own field.

As luck would have it, I crossed paths with my soon to be surgical mentor, co-advisor, and co-philosopher, Knut Kvinnesland. He opened my eyes to rhinoplasty, a surgical procedure infrequently performed within my own field, nonetheless a well-studied procedure elsewhere. I abruptly appreciated that I was viewing things through a narrow lens but now a broader perspective was on the horizon. Soon lengthy discussions on the Wright brothers and the human condition took hold.

My surgical results improved, and my patients seemed more satisfied. After these surgeries, many, but far from all, stuffy-nosed OSA patients also experienced objective reductions in OSA severity and snoring as well as subjective improvements in their sleep. Many a partner also now slept without earplugs.

In parallel with this development, and in continuation of my good fortune, I met Søren Berg. Søren, a renowned sleep medicine scholar and clinician who in his own words saw potential in me as a researcher, took me under his wing and welcomed me into his home, preparing many a delicious meal accompanied by an equally delicious wine and inspired conversation. By pure happenstance, and during his own doctoral work, Søren had crossed paths with the late Philip Cole, who had already planted a flag asserting the significance of nasal breathing during sleep. Our discourse expanded and the trifecta was complete.

Through our many conversations and in frustration with the conflicting literature regarding nasal breathing and sleep, we set forth to see if we could scientifically support our experiences as well as our intuitions, namely that nasal obstruction has an impact on disturbed breathing during sleep, it depends only on perspective.

Introduction

Obstructive sleep apnea (OSA) is prevalent, particularly in the Western world. Nasal obstruction is a common complaint in the general public and possibly even more common in patients with OSA.

This thesis delves into the possible associations OSA might have with nasal obstruction, measured as increased nasal resistance or narrow nasal passages. In paper I and II we investigated if common methods for measuring nasal patency were associated with any notable differences in the respiratory variables found in a common ambulatory sleep study. In paper III we explored if these measurable differences have an impact on other sleep metrics, specifically if increased nasal resistance in OSA might be associated with a low arousal threshold endotype.

Background

Upper Airway Anatomy

The upper airway refers to the anatomical structures in the head and neck responsible for the passage of air from the outside environment and into the lungs.

Airflow may pass through the nose or the mouth with the epiglottis facilitating closure of the airway for the passage of food and beverage to the esophagus.

Lacking a true delineation between the upper and lower airways, the upper airway is academically demarcated as the anatomical structures located superiorly to the trachea.

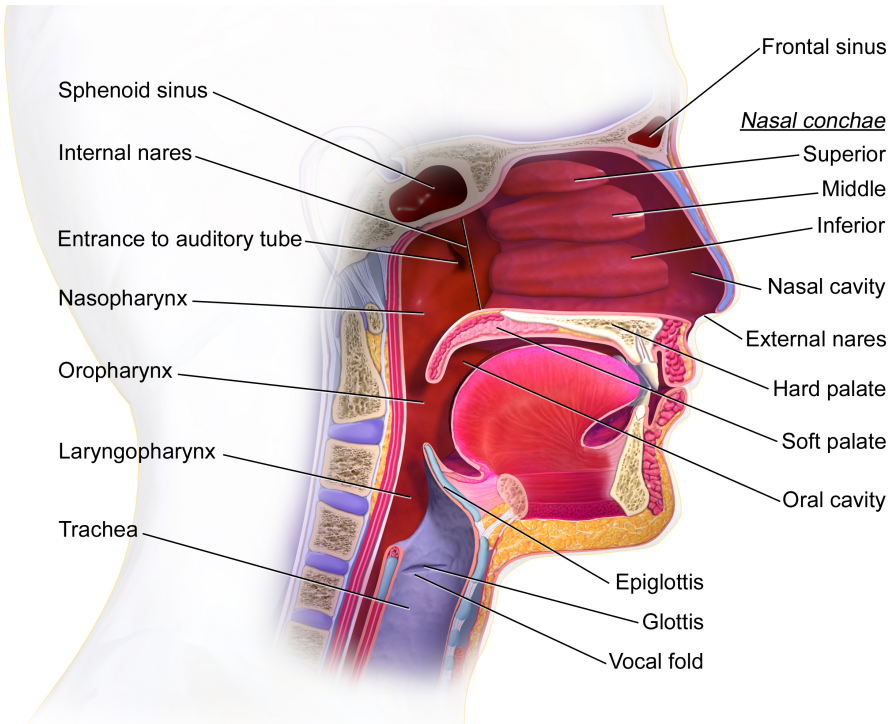

Figure 1. Sagittal view of the upper airway. The upper airway is comprised of the external nose and paired nasal cavities, the pharynx, and the larynx. By the Blausen.com staff 2014, reprinted with permission under the Creative Commons Attribution License.

The Nose and its Anatomy

The nose is divided into the external nose and the internal nasal cavity and extends approximately 7 centimeters from the nasal tip distally to the posterior choana.

External Nose

The external nose is pyramidal in shape and consists of an underlying osseocartilaginous framework supporting a soft tissue envelope made up of periosteum, perichondrium, a neurovascular network, a dense superficial musculoaponeurotic system (SMAS), fatty tissue and skin.

Surface Anatomy

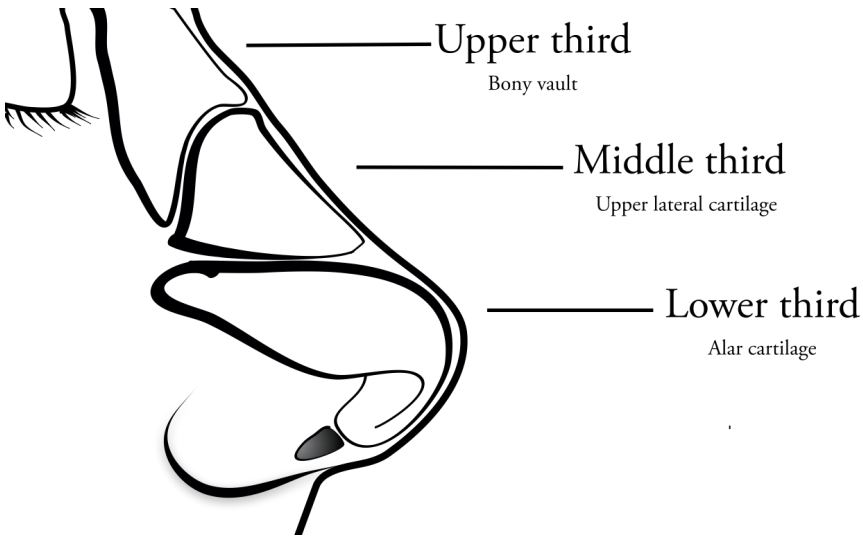

Figure 2. Illustration of nasal thirds. By the author

Clinically, the nose is divided into thirds. The upper third, or nasion, corresponds to of the bony vault of the paired nasal bones. The middle third, or rhinion, describes the area composed of the upper lateral cartilages that encompass the middle vault. The lower third refers to the nasal tip, comprised of the paired lower lateral cartilages and surrounding soft tissue envelope.

While primarily applicable to nasal surgery, these clinical divisions also serve a functional purpose. Given that the lower two-thirds are flexible, while the upper third remains fixed, these divisions have an impact on the airflow characteristics in the nose.

External Nasal Muscles

All facial muscles apart from muscles of mastication are innervated through the VIIth cranial nerve, the facial nerve. Certain of these muscles attach to cartilage, while others connect directly to SMAS. Although there are many facial muscles that relate to the external nose, and most are associated with facial mimicry, the main nasal muscles that affect nasal resistance are:

a) m. Nasalis - consists of two parts: the pars transversa or compressor nasi, and the pars alaris. The pars transversa contributes to compression and elongation of the nose and is responsible contraction and narrowing of the nostrils and nasal vestibule. The pars alaris or alar portion is attached to the lateral portion of lateral crura of the lower lateral cartilage, activation of this muscle aids in dilation of the nostril.

b) m. Levator labii superioris alaeque nasi – contributes to dilation of the nostrils but is mostly responsible for facial mimicry, facilitating the snarl. Incidentally, it has the longest name of any muscle in the human body.

c) m. Depressor septi nasi – depresses the nasal tip and may alter the turbulence of nasal airflow.

Nasal Valve

The distal interior part of the nose, or nasal vestibulum, is traditionally subdivided into the external and internal nasal valve.

The anatomical boundaries to the external nasal valve are defined by the surrounding soft tissue envelope of the nasal skin and underlying cartilage. The interior lining of the external nasal valve consists of skin (keratinized stratified epithelium), sebaceous and sweat glands. Coarse hairs, or vibrissae lacking erectile muscles line the distal 5-7 millimeters of the interior nares.

The internal nasal valve, anatomically bounded laterally by the head of the inferior turbinate, superolaterally by caudal border of the upper lateral cartilage with its fibroadipose attachment to the pyriform aperture and medially by the nasal septum. Whereas the internal lining of the nasal valve initially consists of skin, at the mucocutaneous junction the internal lining transitions into mucosa, consisting of respiratory epithelium, which continues to line the remaining nasal cavity. The narrowest cross-sectional area of the upper airway occurs at the mucocutaneous junction, also referred to as limen nasi, presenting as a ridge, overlying the connection between the upper and lower lateral cartilages, which are connected by the scroll ligaments.

Nasal Cavity

The nasal cavity begins at the external nares and extends to the posterior choanae, extending approximately 7 centimeters. It is initially divided into two bilateral passages which are essentially mirror images of one another. Beginning with the soft tissue columella and continually bounded by the nasal septum until they reach the posterior choanae where the two passages unify in the nasopharynx.

The nasal cavity ends posteriorly in the paired openings called choanae, continuing to the nasopharynx. At the choanae the nasal septum terminates, causing the remaining upper airway to unify into one lumen, continuing so until reaching the lower airway, where it is divided again by the tracheal carina.

Nasal Septum

Consists of the quadrangular plate consisting of hyaline cartilage, transitioning posteriorly into the bony perpendicular plate. Nasal septum size and shape varies across sex, age and ethnicity. Septal thickness also varies as well as within an individual but measures approximately 2 mm in width. Its length, height, and basic geometry has a profound impact on nasal airflow and resistance[(1)].

Nasal Turbinates

Three or four paired structures on the lateral nasal walls consisting of underlying thin bone lined with erectile mucosa make up the nasal turbinates, or nasal conchae. They are classified as the inferior, middle, superior, and supreme turbinates. These bony structures have an irregular surface, are perforated for vascular supply, and lined with mucoperiosteum. A thick submucosal layer consisting of a cavernous plexus with sinusoids that are under autonomic control overlies the mucoperiosteum. Overlying the submucosal layer is a layer of respiratory epithelium densely packed with goblet cells ($8/mm^2$) with decreasing density posteriorly[(2)].

Upper Airway Anatomy Downstream of the Nose

The Pharynx

The pharynx is further divided into three regions, the nasopharynx (located behind the nasal cavity), oropharynx (located behind the mouth), and hypopharynx (located above the larynx).

The nasopharynx, also called the epipharynx is a singular cavity communicating with the nasal cavities through the paired choanae. It extends from the skull base to the upper portion of the soft palate. The posterior wall is lined with lymphoid tissue called the pharyngeal tonsil, or adenoid, and is part of the Waldeyer´s tonsillar ring.

The oropharynx denotes the area inferior to the nasopharynx, located behind the oral cavity, extending inferiorly to the level of the hyoid bone. It is comprised of the soft palate, uvula, and tongue base anteriorly. The palatine tonsils bound the lateral walls of the oropharynx and are situated between the palatoglossal arch anteriorly, and the palatopharyngeal arch posteriorly. Together with the uvula, these arches constitute the soft palate.

The laryngopharynx or hypopharynx is situated inferior to the epiglottis, superiorly bordered by the pharyngoepiglottic fold and its inferior limitation is the upper esophageal sphincter.

The Larynx

Similarly, the larynx is divided into three distinct regions, here based on their relationship to the vocal cords (or glottis): the supraglottis (above the glottis), glottis (the area containing the vocal cords), and subglottis (below the glottis).

Although the larynx is not a major contributor to OSA per se, sensory dysfunction of the endolarynx may play a role in OSA[3, 4].

Upper Airway Physiology

The Nose and its Physiology

The nose facilitates a vast interplay of functionality; with respiration and olfaction being its primary functions. It is both a sensory and autonomic organ where sensory, sympathetic, and parasympathetic functions, as well as central nasopulmonary reflexes often communicate through feedback systems. It serves as a gatekeeper for foreign bodies introduced from the external environment and plays a role in voice modulation.

Respiration

Respiration consists of the inspiration and expiration of air, revealing different functionalities in the nose. First and foremost, adequate airflow is required to enable sufficient gas exchange in the lungs. The physiology behind this is described in further detail in the following section "6.5 Nasal airflow and Nasal Resistance".

Air Conditioning

Airconditioning consists of humidification, heat transfer and filtration. The nose can accommodate wide variations in temperature and humidity in the external environment with air temperature ranging from -50°C to 50°C. Regardless of the air quality in the external environment, when inspired air through the nose reaches the nasopharynx, the approximate temperature is 31°C with 95% relative humidity[5].

Humidification and Heat Transfer

Through the action of serous glands in the nasal mucosa, water is transferred to inspired air. Water and heat transfer occurs mostly from the nasal turbinates, particularly by the inferior nasal turbinates, where the surface area is the largest. Air humidification occurs during inspiration. Dehumidification occurs during expiration, approximately 1/3 of the water expelled during inspiration is recovered. This is due to temperature gradient differences between the air and the nasal cavity surface. Conduction occurs without airflow; convection currents emerge from the temperature gradient. Forced convection occurs during airflow, causing turbulence, increasing the surface area of inspired air.

Filtration

Filtration in the nose can be considered mechanical and chemical. Mechanical filtration facilitates chemical filtration. The nose can filter out particles down to 30 µm, in protection of the lower airway. Vibrissae are the first line of defense, filtering out the largest particles. Air turbulence facilitates particle deposition. Subsequent lines of defense depend on nasal secretions composed of mucus and water. Mucosal cilia transport mucus posteriorly into the nasopharynx at a rate of 3–25 mm/min[6].

Immunity

Outside the scope of this thesis, immunity in the nose consists of the filtration mentioned above, as well as chemical, nonspecific and acquired immunity. Nasal secretions contain glycoproteins, enzymes, circulatory proteins, immunoglobins and immune cells.

Odorant Delivery

Our sense of smell, or olfaction, depends on the delivery of odorant particles to the olfactory epithelium in the roof of the nose. Olfaction is achieved by inhalation through the nose or retronasally, during the mastication and swallowing of food and beverage. Retronasal olfaction combines with sensory input from taste buds in the mouth and oropharynx, enhancing our perception of flavor. Olfactory compounds must have a high level of water and lipid solubility to be perceived. Olfactory receptors are located on the mucosal surface of the cribriform plate and are connected to the olfactory bulb by nonmyelinated nerve fibers. The olfactory area in man is approximately 200-400mm^2 with a density of 5 x 10^4 receptor cells/mm^2.

Nasal Cycle

Although a formal explanation for the phenomenon is lacking, the transient engorgement of erectile mucosal tissue in the anterior nasal septum and inferior turbinates has been identified[7]. Once considered an asymmetric process, further observations have led to the discovery of independent cyclical processes for each nostril, which can last from 2 - 4 hours depending on the awake or sleeping state[8]. This transient swelling of the mucosa leads to changes in nasal resistance as measured by anterior rhinomanometry[9]. This process can be affected by body posture, age, and numerous other physiological mechanisms beyond the realm of this thesis[8, 10, 11].

Nitric oxide

Nitric oxide (NO) is produced in the nasal cavity, and to a lesser degree in the paranasal sinuses, in the presence of oxygen through the action of nitric oxide synthase[12, 13]. NO performs as a chemotransmitter between the nose, pharyngeal muscles, and lungs. Among its many functions, NO maintains pharyngeal muscle tone, functioning as a pulmonary vasodilator, improving oxygenation and ventilation-perfusion ratio[14].

Airflow Sensation in the Nose

The mechanism of airflow sensation in the nose is unclear, however increasingly attributed to the sensation of mucosal cooling through the action of thermoreceptors as opposed to mechanoreceptor stimulation[15-17].

Human thermosensation has been identified to occur in the family of transient receptor potential cation channels. A specific cold receptor in this family, transient receptor potential melastatin family member 8 (TRPM8), has been identified, which responds to cooling below normal skin temperature, and chemicals that produce a cooling sensation, such as menthol[18-20]. In the nose, airflow sensation occurs through the activation of the trigeminal nerve, mediated by TRPM8 temperature activated ion channels and expressed in trigeminal C-fibers or possibly A-δ fibers.

Zhao and colleagues investigated the perception of airflow sensation across different ambient temperature and humidity levels, compared to acoustic rhinometry and anterior rhinomanometry measurements. The study's findings revealed a stronger association between perceived nasal patency and ambient temperature/humidity than to the objective measurements[21].

Previous studies have identified an increased distribution of warm and cold thermoreceptors in the nasal vestibule, compared to the distribution in nearby malar skin or in the nasal cavum[22]. Despite this, provocation studies have identified TRPM8 receptors in the entire nasal cavity. More than 60% of trigeminal afferents in the nasal cavity express TRPM8 receptors[23]. The identification of TRPM8 receptors in abundance around blood vessels in biopsies of human nasal turbinates suggest that these receptors also may mediate neurovascular reflexes, such as vasoconstriction in response to nasal cooling[24].

It is important to note that temperature measurements across the nasal airway vary depending on their location, having an impact on the sensation of cooling and thus the degree of airflow sensation[25, 26]. This idea has been furthered by Zhao and colleagues, where "Regional peak mucosal cooling predicts the perception of nasal patency"[27].

Lindemann et al. demonstrated that subjective measures of nasal patency increased after menthol vapor administration, despite no changes in actual nasal mucosal temperature or changes in anterior rhinomanometry measurements, further indicating that subjective nasal patency has to do with activation of TRPM8 receptors in the nose[28].

Nasal cooling is further coupled to respiratory drive. Animal studies have shown increased afferent trigeminal activity in response to cold air whereas administration of menthol was found to decrease respiratory drive. These effects were abolished after nasal anesthesia[29, 30]. Furthermore, in humans, the ventilatory response to CO_2 was seen to be inhibited by breathing cold air through the nose[31].

Nasal Airflow and Nasal Resistance

Nasal airflow is largely determined by the first point of entry, namely the nares. The narrow most lumen of the nasal valve has the narrowest cross-sectional area in the entire nose, accounting for approximately fifty percent of the entire resistance in the upper airway. Negative pressure produced from forceful contraction of the diaphragm, sucks air into the nose, reaching the alveoli in the lungs to facilitate gas exchange.

The narrowest segment, or valve area, is triangular in the frontal plane and angled slightly diagonally in the sagittal plane. Due to the angulation of the nasal valve, inspired air is directed diagonally upwards and posteriorly. This, in addition to the shape of the nasal cavity, causes the direction of inspired air to alter its course 180° from its entry point in the nostrils to its arrival in the pharynx.

The diameter of the most anterior or distal segment of the valve is larger than the narrowest segment, reminiscent of a cone, or a funnel. When viewed in the axial plane, the anterior one third of the nose from the most distal nares to the inferior turbinate resembles an hourglass in shape.

These characteristics affect the direction, velocity, and pressure of airflow as well as the air dispersion downstream to the valve. Adding to this complexity, the nasal valve is flexible, serving as an airflow regulator. The airway consists of several flexible segments and naturally, these segments must maintain their luminal integrity to oppose the negative pressure forces of respiratory inspiration to avoid complete collapse. Increases in downstream inspiratory forces from the diaphragm in breathing promote collapse of the nasal valve. The various supporting structures oppose these same forces and may affect its shape, thereby affecting the velocity and pressure of inhaled air, thus causing variability in each breath.

The strength or weakness of the nasal valve depends on its inherent shape in each individual nose as well as the qualities of the supporting structures in and around the nasal valve, such as the alar cartilages, the fibrocartilaginous tissue, and the nasal musculature that work to oppose the collapse that inspiratory forces impose. Activation of nasal musculature may decrease mean nasal resistance by 21%[32].

Airflow characteristics in the nose are dynamic, considering that respiration varies in frequency, duration, and intensity, from quiet respiration to heavy breathing during exercise or stress. Airflow may change from mainly laminar, in the resting state, to highly turbulent in the exertional state[33-35]. When air passes through the narrowest segment and into the nasal cavity there is an immediate drop in pressure and corresponding increase in velocity. Vortices are created, affecting the nature of turbulent flow, as well as affecting particle deposition. This has been demonstrated through computational fluid dynamics modelling, a promising technique, due to an exponential increase in computing power[36, 37].

The Nose in Relation to the Remaining Upper Airway

As described in the previous section concerning nasal airflow and nasal resistance, respiratory inspiration is caused mainly from contraction of the diaphragm muscle and secondarily from the skeletal intercostal and accessory musculature. This causes an expansion of the lungs with a corresponding suction force on the upper airway, resulting in the inspiring of air through the nose, the mouth or both.

Respiratory expiration causes the opposite force and positive pressure from the upper airway is transmitted to the alveoli in the lungs. Removal of this resistance by tracheostomy or laryngectomy reduces the dead space but results in a degree of alveolar collapse or reduced lung function[38, 39]. In the same vein, such interventions in the airway may also cause nasal dysfunction through the deprivation of airflow[40-43].

Anatomically and physiologically, the nose is the principal organ where air is distributed to the remaining airway. Nasal breathing in healthy individuals demonstrates less upper airway resistance than the oral route in wakeful breathing and resistance is considerably lower than in oral breathing during sleep[44, 45].

When we breathe through the nose with the mouth closed the tongue is in an extended or protruded position, in close connection with the upper front teeth. The soft palate is engaged, allowing for the maximal flow of air through the nasal cavity, past the choanae and the remaining upper airway.

Increased nasal resistance may affect airflow at several sites, due to flexible segments in the upper airway. In the nares, as previously described, inspiratory suction forces may lead to alar collapse. Further downstream, increased nasal resistance may lead to increased suction forces on the collapsible soft tissues of the pharynx. In the nose, these suction forces are opposed by the action of nasal musculature, particularly the nasalis muscle, and the inherent shape and stability of the underlying cartilaginous framework of the anterior nose[46, 47]. In the pharynx, inspiratory suction forces are opposed by the upper airway dilator muscles responding directly to negative pressure stimuli as well as activation through nasal cold receptors as a response to inspired air, as elucidated in the previous section[48, 49].

If nasal patency fails to meet ventilatory demand, a switch to oral breathing may ensue. The tongue is forced out of the more favorable position which causes retroglossal narrowing. Increased demand is put on the supporting musculature to maintain upper airway patency[50, 51].

Upper Airway Physiology Beyond the Nose

Since the upper airway is partly rigid and partly flexible, suspension of the soft tissue in the upper airway is facilitated by the tension and contraction of the tongue and muscles of the pharynx, concerning approximately twenty muscles. Pharyngeal muscles may be considered dilators or constrictors, depending on their orientation and origin of attachment. It has been hypothesized that the pharyngeal muscles act as a muscular hydrostat, utilizing the incompressible nature of water to maintain morphological integrity and alter pharyngeal shape to facilitate the different actions the pharynx is responsible for. This hypothesis is posed since the pharyngeal lumen is tubular in nature and only a few of surrounding muscles have rigid attachments. Many the pharyngeal muscles are attached to the hyoid bone, a free-floating bone found between the jawbone and the cartilaginous larynx[52].

Electromyographic (EMG) activity suggests that the paired genioglossus muscles are the primary upper airway dilator muscle, which coincidently is the only muscle that protrudes the tongue. The genioglossus muscle responds to negative pressure in the pharynx[48, 53, 54].

Sleep

Although the biological purpose of sleep is not entirely clear, sleep can be distinguished from wakefulness, observed by a loss of consciousness and a lowered cortical response to external stimuli.

Sleep is a complex process with many observed physiological mechanisms affecting the entire human body. The physiological complexity of sleep can be manifested by the hundred-year history of sleep science since human sleep was first recorded in a laboratory by Hans Berger, to this day we still lack a coherent biological hypothesis for why we sleep. However, a vast array of physiological processes have been recorded, increasing our understanding of what occurs when we sleep.

When we sleep, are metabolic rate is lowered, our cortical activity is reduced, and our respiration becomes shallow and more frequent.

Sleep Neurobiology

Excitatory neurons in the ascending reticular arousal system are inhibited by Gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus, affecting arousal in the thalamus and cerebral cortex. This corticothalamic loop, with monoaminergic and cholinergic afferent input to the thalamus, and basal forebrain cholinergic input to the cortex is largely responsible for sleep regulation. The transition from awake / sleep is further balanced by excitatory input from the hypocretin/orexin system found in the hypothalamus.

Sleep Regulation

The two-process model of sleep regulation refers to the interaction between a homeostatic sleep-wake process (process S) and Process C, the circadian pacemaker. Process C is continual, working in a 24-hour cycle, synchronized by light input to the retina and other external stimuli, resulting in increased secretion of melatonin when daylight fades. Process S initiates at the time of awakening, with increasing sleep pressure the longer we are awake.

Sleep Staging

In the laboratory, sleep is observed by the electroencephalogram (EEG), recording brain wave activity. Whereas in the awake state brain waves are observed as desynchronized low voltage and fast frequency, sleep is characterized by high voltage, slow frequency, synchronous brain waves. Sleep is further delineated by the addition of electrooculography (EOG) where rapid eye movement (REM) sleep can be observed.

Sleep is divided into rapid eye movement (REM) and Non-rapid eye movement (NREM) sleep. NREM sleep is divided into three stages of increasing depth, N1, N2 and N3 whereas REM sleep accounts for the fourth stage of sleep. The progression from awake to sleep occurs typically in a patterned cycle of N1 to N3 NREM sleep followed by a period of REM sleep. The threshold for arousal, or awakening from sleep, intensifies throughout the sleep cycle, although infants experience a brief period of lowered arousal threshold following each period of REM sleep.

Sleep Respiration

Ventilation is reduced during sleep and particularly during REM sleep, compared to the awake state. Minute ventilation is significantly lower in all stages of sleep, a particularly acute reduction occurs in REM sleep. This is due to a more shallow and rapid breathing pattern. This occurs in parallel with a reduction in inspiratory drive, measured by the mean inspiratory flow rate, which is similarly markedly decreased during REM sleep. The resulting hypoventilation results in hypoxia and hypercapnia[55]. Reduced chemosensitivity as well as decreased excitatory stimulation of the pharyngeal dilator muscles occurs during sleep[56-58].

Sleep and Physiological Changes in the Nose

Various physiological changes in the nose have been observed during sleep. In recumbency, nasal resistance has been observed to increase in healthy adults, though this increase seemed to be unaffected by sleep[10, 59]. Additional changes in lateral recumbency have been observed, with greater airflow occurring on the unaffected side[8]. The cyclical duration and amplitude of difference in mucosal enlargement is also observed to be increased during sleep, independently of body position[8].

Upper Airway Pathophysiology

Nasal Obstruction

While nasal obstruction is commonly characterized as a subjective descriptor, nasal resistance pertains to a more objective metric. In the context of this dissertation, the terms 'nasal obstruction' and 'increased or elevated nasal resistance' are employed interchangeably, as they fundamentally denote equivalent phenomena, namely a reduction in adequate nasal airflow to meet ventilatory demand.

The etiologies of nasal obstruction are mainly ascribed to anatomical or inflammatory factors, or the combination of both. Physiological factors also affect nasal airway resistance.

Although an equivalent terminology seems to be lacking in the Nordic languages, nasal congestion or nasal stuffiness or fullness describes a type of nasal obstruction that is more often associated with inflammatory factors[60, 61].

Causes of Nasal Obstruction

Anatomical

Nasal obstruction may be due to disproportionate nasal anatomy, decreasing the aerodynamic capabilities of the nose. Specifically, this may have to do with nasoseptal deviations, osseous turbinate hypertrophy, nasal valve dysfunction due to weak or distorted cartilage as well as inadequate development of the nose during childhood, which might be a result of prolonged mouth breathing[62-64].

Inflammatory

There are numerous inflammatory conditions affecting nasal patency, largely leading to swelling of the nasal mucosa, resulting in increased nasal resistance. Some of the conditions identified to have such an impact are: Acute and chronic rhinosinusitis, nasal polyposis, allergic and non-allergic rhinitis, Churg-Strauss syndrome, gastroesophageal reflux disease, granulomatosis with polyangiitis, hormonal changes, pregnancy, thyroid conditions, tobacco smoke, alcohol intake, rhinitis medicamentosa from overuse of nasal decongestants, changes in air humidity and temperature, medications that block sympathetic activity and viral and bacterial infections, among others the common cold.

The deprivation of nasal breathing, as occurs in chronic mouth breathing and more profoundly in tracheostomy and laryngectomy patients has been found to have significant effects on nasal mucosa, mucociliary clearance. increases in venous congestion and reductions in olfactory function[40-43].

Physiological

Nasal vasoconstriction occurs in hypercapnia and is mediated by chemoreceptors, hypoxia has the same effect. Hyperventilation may cause nasal obstruction by the vasodilative effect of metabolic alkalosis resulting from decreased arterial CO_2. Tanaka et al. demonstrated a diminished end tidal PCO_2 which was lower in nasally obstructed subjects both in the awake and sleeping state[65].

The trigeminocardiac or nasiocardiac reflex may lead to severe bradycardia or even cardiac arrest and is a result of direct mechanical stimulation of the nasal mucosa[66].

Posture may affect nasal resistance. When moving from an erect position to a reclined position, nasal resistance is increased, thought to do with increases in hydrostatic pressure. The cyclical changes in the nasal cycle are augmented by recumbency as well as the supine position[10, 59, 67].

The nasal response to axillary pressure or "Crutch reflex" has been documented and is likely an additional mechanism associated with posture during sleep. When pressure is exerted on the axilla, cross-sectional area is reduced and resistance in the ipsilateral nasal passage increases[68-70]. Cold water immersion and isometric exercise of the upper extremity also induce reductions in cross-sectional area in ipsilateral nasal passage[71, 72].

Other physiological mechanisms in the nose occurring during sleep are referred to in "**Sleep and physiological changes in the nose**".

Nasal Obstruction and Disturbed Breathing During Sleep

Numerous studies have demonstrated that temporary nasal blockage such as nasal tamponade in otherwise healthy individuals or OSA patients can induce transient moderate to severe sleep apnea and hypoxia in the former and an exacerbation of their OSA in the latter. Once the blockage is removed, healthy patients return to their habitual eupneic state and OSA patients return to their habitual obstructive state. Experimentally titrated or partial blockage of the nose produces similar effects[73-76].

Pharyngeal Obstruction and Disturbed Breathing During Sleep

As described in the previous section on sleep, when we sleep our respiration is condensed, stimulation of the body diminishes and our response to stimuli decreased. We do however need to keep our airway patent to meet ventilatory demand.

Upper airway collapsibility is associated with passive critical closing pressure of the pharynx (Pcrit), meaning the threshold of atmospheric pressure that causes collapse[77].

Collapse of the upper airway during sleep may be exacerbated by upstream effects from the nose, insufficient action of the pharyngeal musculature or due to fixed narrowing of the pharynx itself[48, 78]. In other words, how crowded it is and how collapsible it is.

Anatomical Causes of Pharyngeal Obstruction

This pharyngeal tonsil or adenoid may hypertrophy during childhood, causing sleep disturbed breathing (SDB) or even OSA, removal can alleviate SDB and OSA, even in children with prominent palatine tonsils[79, 80]. Enlarged palatine tonsils are a common cause of OSA in children, removal facilitates significant improvement in outcome[81].

In a 2011 literature review by an interdisciplinary European Respiratory Society task force concluded that, for patients carefully selected based on tonsillar hypertrophy, tonsillectomy alone should be recommended as a primary surgical treatment[82, 83]. Adults who previously underwent tonsillectomy had a lower risk of developing OSA[84].

Indeed, any pharyngeal narrowing, be it due to craniofacial abnormalities, tumors, or glossopharyngeal fat deposition, may be a causative or aggravating factor in OSA[85-88]. Classification systems have been promoted to describe narrowing in the pharynx with relevance to medical and surgical interventions[89-92]. According to a 2005 Cochrane review, the surgical techniques analyzed failed to show consistent outcomes in favor of surgery. The authors proposed long-term follow-up to verify successful outcomes[93].

Pathophysiological Causes of Pharyngeal Obstruction

Upper airway instability during sleep is a complex topic but may be described generally as the inability for pharyngeal musculature to maintain a patent airway, either due to decreased muscle tone or inadequate feedback mechanisms[48, 94].

Hypotonia, specifically in children, is associated with OSA severity and gives a picture of the mechanism of pharyngeal collapsibility in adults[95]. OSA is linked to the degree of neuromuscular degeneration of the pharyngeal tissue, severity is proposed to be associated with the long-term deleterious effects of vibrations in the pharynx due to snoring or more severe collapsibility of pharyngeal tissue[96, 97].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a prevalent disorder involving an airflow disturbance in the upper airway affecting respiratory inspiration during sleep. Estimates of adult global prevalence vary, due to changing criteria as well as increased sensitivity of measuring equipment. Recent estimates of global prevalence reach close to one billion adults aged 30 – 69 years affected by OSA, of which 425 million are estimated to have moderate to severe OSA[98]. A diagnosis of OSA is generally made through a sleep study with support from patient recorded output measures (PROM).

Obstructive Apnea

Apnea is defined as the cessation of breathing, however in OSA, obstructive apnea more specifically refers to a severe reduction in airflow during inspiration. Although guidelines have changed over the years, the latest American Academy of Sleep Medicine (AASM) guidelines define an obstructive apnea as an airflow reduction from baseline of over 90 percent for ten seconds or greater[99]. As opposed to a central apneas, which arise without respiratory effort, obstructive apneas are due to a mechanical obstruction that occurs somewhere in the flexible areas of the upper airway, despite the respiratory effort to breathe. This mechanical obstruction is often due to a narrowing of the lumen followed by complete collapse of the soft palate, tongue, or other soft tissue in the pharynx.

Obstructive Hypopnea

Whereas obstructive apneas seem clearly defined as the cessation of breathing despite inspiratory effort, some further description is needed to define clinically significant respiratory events where inspiratory airflow is decreased and oxygen desaturation occurs but that do not meet the criteria for scoring an obstructive apnea. Therefore, the concept of hypopneas was established to describe these events[100]. Later, the addition of an associated arousal was applied in the scoring of such events. Several revisions later the 2012 AASM criteria were formed and for this thesis hypopneas were scored according to these, as described in the materials and methods section[99]. These updated criteria also defined differences between central and obstructive hypopneas, where central hypopneas are a result of decreased respiratory effort, whereas obstructive hypopneas describe decreased airflow secondary to increased resistance in the upper airway[99].

Respiratory Associated Arousal During Sleep

The transition from sleep to waking, or the termination of sleep occurs physiologically after a period of REM sleep and after a sufficient duration of sleep has transpired. Arousal from sleep depends on stimulation of the ascending reticular activating system (ARAS) in the brain, leading to an awake state. ARAS denotes a network derived from the brainstem and projecting to the cortex through five neurotransmitter systems, namely norepinephrine, acetylcholine, dopamine, serotonin, and histamine. Stimulation of these neurons heightens cortical activity, resulting in increased alertness.

Arousal, relevant to this thesis, refers to the abrupt discontinuation of sleep that is associated with respiratory stimuli. Respiratory cortical arousals occur when a certain input exceeds a threshold related to ventilatory effort, whether in response to hypoxia, hypercapnia, upper airway resistance or other stimuli associated with respiration.

Beyond the neurological mechanisms of respiratory arousal, such arousals are associated with neuromuscular dilation of the upper airway, largely due to activation of the genioglossus muscle. However, it has been demonstrated that arousals often arise after an obstructed upper airway is opened rather than occurring a priori[101, 102]. This leads to the conclusion that the pharyngeal musculature responds to more than one afferent pathway and that there are both excitatory and inhibitory components to the genioglossus negative-pressure reflex[48, 103].

It has been asserted that respiratory arousal provides a protective function[104]. This is based on evidence that genioglossal EMG activity does not decrease upon resumption of sleep; instead, it is increased[105].

The arousal threshold (ArTH) may be quantified by an epiglottic pressure catheter measuring the lowest esophageal or epiglottic pressure that precedes arousal[106]. A low arousal threshold indicates a propensity for sleep to be prematurely interrupted in reaction to a small rise in ventilatory drive. Chemical compounds that increase the arousal threshold have been studied[107]. Eckert and colleagues associated a low ArTH with an endotype, a term described in the following section "Phenotypes and Endotypes", which was found in approximately 1/3 of OSA patients[108].

An algorithm put forth by Edwards et al. detects a low ArTH without the need for epiglottic pressure monitoring[109]. A 3-tiered score consisting of the following variables, where 1 point is ascribed to each positive value :

AHI < 30, Nadir SpO2 above 82.5%, and a hypopnea fraction of total respiratory events above 58.3%

A total score of 2 or above is consistent with a low arousal threshold endotype. This algorithm yielded an 80.4% sensitivity and an 88.0% specificity for the presence of low ArTH measured by gold-standard epiglottic pressure.

Phenotypes and Endotypes

A phenotype in the context of obstructive sleep apnea may be described as the pathophysiological outcome for a specific individual, whereas an endotype describes the distinct pathophysiological subtype. A comprehensive description of phenotypes and endotypes in OSA is outside the scope of this thesis, nonetheless important to note.

The clinical value of distinguishing endotypes within OSA is to illuminate that OSA severity may be the result of multifactorial pathophysiology, or the sum of its parts, rather than being an isolated disease. Determining these factors in isolation and in combination allows for a personalized medicine approach, tailoring treatment for better outcomes[110, 111].

Various endotypes in OSA have been described, concerning certain anatomical and non-anatomical traits. Eckert and colleagues demonstrated in a rigorous study of 75 OSA patients, that 69% carried one or more nonanatomic pathophysiologic traits[108]. The authors proposed a three-point scale of criteria based on the following traits:

Pcrit	Passive critical closing pressure of the upper airway. An anatomically collapsible upper airway corresponds to a high Pcrit.
Arousal threshold	As previously described, is the level at which arousals occur when a certain input level in relation to ventilatory effort is reached.
Loop gain	Refers to the ventilatory control system. A high loop gain is synonymous with oversensitivity of this system resulting in an overzealous increase in ventilatory drive. Loop gain is quantified as the ventilatory response to a disturbance in ventilation, such as in the abrupt drop in CPAP pressure.
Muscle responsiveness	Describes the amount of EMG activity of the genioglossus muscle in response to negative pharyngeal pressure.

Each of the three categories in this PALM scale embodied several traits combinations where only one of them (2b) demonstrated OSA patients with no non-anatomic traits.

Aims of the study

Purpose

To identify patients with obstructive sleep apnea where nasal obstruction plays a role in their respiratory disturbances during sleep.

General Aims

The overall aim of this project is to gain further insight into nasal respiration during wake and sleep, its anatomy, physiology, and pathophysiology. Based on results from previous studies we hypothesize that the nose plays a more significant role in normal sleep respiration and in that nasal obstruction in particular plays a larger role in sleep-disordered breathing than previously recorded.

To do this we are implementing level III sleep studies, in combination with rhinological investigations and objective measures such as 4-phase rhinomanometry and acoustic rhinometry. These examinations in combination will give us a more detailed view of the factors that influence nasal respiration.

Specific Aims

Paper I

The first study aimed to investigate how increased nasal resistance is associated with the respiratory variables found in an ambulatory type III respiratory sleep study.

Paper II

Based on the findings from the first study we aim to investigate if OSA patients with an elevated hypopnea to apnea ratio or heightened fraction of hypopneas are associated with corresponding differences in acoustic rhinometry measurements.

Paper III

Having found a viable method to identify OSA patients with clinically relevant nasal obstruction in papers I and II we aim to find if these OSA patients are associated with a low arousal threshold endotype as described by Edwards and colleagues[109].

Materials and methods

Study Cohorts

Patient selection for these studies was based on a diagnosis of obstructive sleep apnea. Patients referred to our clinic on the suspicion of OSA were examined with a type III ambulatory respiratory sleep polygraphy. Any Norwegian speaking adult ≥ the age of 18 with an AHI ≥ 5 and no unstable medical condition that would practically prohibit them to complete the clinical examinations were invited to the studies. Participants were not screened for mental or neurological disease.

Methods

Methodology for Measuring Nasal Patency

4-Phase Rhinomanometry

4-phase Rhinomanometry (4-PR) is a high-resolution analysis of pressure and airflow variations across four respiratory phases, providing a temporal depiction of nasal respiratory effort. These four phases encompass the ascending and descending trajectories observed during inspiration and expiration via the nasal route. Increased pressure signifies greater airflow resistance, indicative of nasal obstruction, whereas increased airflow suggests improved nasal patency.

Consensus guidelines from the International and European Rhinologic Societies endorse the use of 4-phase Rhinomanometry as a standardized method for objectively quantifying nasal airflow and patency[112, 113]. The apparatus utilized in this thesis (4-Rhino, RhinoLab GmbH, Rendsburg, Germany) employs a logarithmic transformation model, denoted as Log10R(VR, R_{EFF}), or LR_{EFF}. This incorporates vertex resistance (VR) and effective resistance (R_{EFF}). VR represents the resistance encountered at the point of maximum airflow, while R_{EFF} relates to the mean of flow and differential pressure calculated across 2000 measurements per breath cycle[114]. Nasal obstruction severity is categorized by a five-tier scale based on 20% percentiles of increasing resistance. This classification system was grounded in a meta-analysis encompassing 36,000 individual clinical 4-PR assessments conducted on individuals of Caucasian ethnicity. These measurements were compared with subjective perceptions of obstruction assessed on a Visual Analog Scale (VAS)[115].

Acoustic Rhinometry

Acoustic rhinometry (AR) offers a geometric assessment of nasal cavity dimensions, achieved by emitting an acoustic pulse into the nostrils, which subsequently rebounds off the nasal cavity walls and returns to the instrument. Transmission and reception duration of this acoustic signal allows for the estimation of cross-sectional area at predetermined distances from the probe. Measurements are commonly carried out 0-3 cm from the measurement probe. The acoustic signals are most precise here and where the most resistance occurs in the nose. Volumetric assessments are derived from the integration of the area-distance curve spanning from the probe to a predefined distance. In paper II, a single-impulse acoustic rhinometer (GM Instruments Ltd, Glasgow, UK) was employed.

Acoustic rhinometry (AR) as a means for measuring the geometry of the nasal cavity has been in use for more than three decades. Measuring airway dimensions through acoustic reflections was a technique originally developed by Jackson et al. in 1977[116]. The technique was further developed by Fredberg and colleagues for airway measurements between the mouth and carina[117]. Nasal measurements by AR were developed by Hillberg and colleagues in the mid to late 1980´s[118]. AR as a technique was standardized in 2005 by the Standardization Committee on Objective Assessment of the Nasal Airway of the European Rhinologic Society[112]. The implementation of AR as well as its limitations were described in the European Position Paper on Diagnostic Tools in Rhinology in 2019[113].

Methodology for Measuring Sleep Respiration

Standard portable respiratory sleep polygraphy (NOX Medical T3, ResMed, Reykjavik, Iceland), recorded airflow via nasal pressure cannula, thoracic and abdominal respiratory effort, pulse oximetry, and body position sensor. All respiratory sleep polygraphy recordings were scored manually according to the 2012 American Academy of Sleep Medicine (AASM) guidelines[99]. Apneas were scored when there was a drop in the peak signal excursion by ≥ 90% of pre-event baseline, whereas hypopneas were scored when the peak signal excursions drop by ≥ 30% of pre-event baseline for ≥ 10 seconds using a nasal pressure cannula in association with a ≥ 3% arterial oxygen desaturation. Oxygen desaturation index (ODI) was calculated as the total number of ≥ 3% desaturations divided by analysis time. The apnea hypopnea index was defined as the sum of apneas and hypopneas divided by analysis time (lights off/lights on period during recording session).

The scorer performed these analyses without prior knowledge of inclusion in the study and the scoring was not performed by any of the authors.

Study Variables

Demographic Variables

Sex Females are underrepresented in OSA, partly due to underreporting and underdiagnosis based on "atypical symptoms", attributed to depression, insomnia and fatigue[119]. Increasing focus on women's health is narrowing this divide. After the age of fifty this divide lessens due to the increased prevalence in menopausal women[120].

Age is a well-documented factor influencing OSA severity[121]. Although prevalence seems to increase with age, severity seems to lessen[122]. Theories regarding hormonal, body composition and structural differences regarding age and sex have been advanced, the explanation for this remains unclear[123, 124].

BMI is perhaps the strongest positive factor associated with OSA[125]. Extreme obesity is also associated with an elevated hypopnea to apnea ratio[126].

Nasal Variables

Rhinomanometry

In papers I - III, increased nasal resistance was determined as an elevated 4-PR measurement in one or both nostrils. Unilateral LR_{EFF} values ≥ 1.00 were considered elevated.

Acoustic rhinometry

The dimensions examined at baseline and 15 min after administration of oxymetazoline nasal spray (0.5 mg/ml; two puffs per nostril) were:

1. TMCA cm^2 (total minimal cross-sectional area in square centimeters of both nasal cavities).
2. TVOL cm^3 (the total volume in cubic centimeters of both nasal cavities).
3. MCA cm^2 (minimal cross-sectional area in square centimeters in either left or right nasal cavity)

   All the above three measurements refer to distances 0-3 cm from the device probe.

Respiratory Sleep Polygraphy Variables

AHI	Considered an indicator for OSA severity, apnea hypopnea index is calculated by total number of apneas and hypopneas during sleep by the number of hours of sleep, or total sleep time. In the case of respiratory sleep polygraphy, total recording time is implemented rather than total sleep time.
AI	Apnea index is calculated as the total number of apneas per hour during sleep.
HI	Hypopnea index is calculated as the total numbers of hypopneas per hour during sleep.
HAR	Representing the quotient of the hypopnea index and apnea index, illustrating the relative distribution between the two. In our study, we categorized HAR into low and high groups, with a threshold of 1.00. HAR >1.00 indicates a higher proportion of hypopneas compared to apneas, signifying an elevated HAR.
$F_{hypopneas}$	Fraction of hypopneas, refers to the AHI proportion made up of hypopneas.
ODI	Oxygen desaturation index assesses the severity of oxygen desaturation events during sleep, specifically determining the average number of times per hour of sleep that the blood oxygen level drops by ≥ 3% from baseline.
Avg SpO_2	Desaturation – Average serum pressure oxygen desaturation over the whole sleep recording
Nadir SpO_2	Represents the lowest oxygen desaturation measured during the entire sleep recording.

Other variables

ArTH	A low arousal threshold was detected using the algorithm put forth by Edwards and colleagues[109]. A 3-point score consisting of the following variables: an AHI < 30, Nadir SpO2 above 82.5% and a hypopnea fraction of total respiratory events above 58.3%. The score may have a maximal value of three where one point is given for each of the above variables. A score of 2 or more is consistent with a low ArTH.

Confounding Variables

Due to the multifactorial nature in the pathophysiology of obstructive sleep apnea (OSA), there are several confounding variables that could influence the statistical analysis. Multiple logistic regression and multivariate linear regression models were implemented to address these issues. Confounding variables addressed in the studies were sex, age, body mass index, apnea hypopnea index, oxygen desaturation index and average oxyhemoglobin desaturation as well as nadir or lowest serum pressure oxygen saturation.

Paper I

Multiple logistic regression analysis used the dependent variable hypopnea to apnea ratio (HAR). Independent variables were sex, age, body mass index, apnea hypopnea index, oxygen desaturation index and average oxyhemoglobin desaturation.

In paper I, AHI was dichotomized to AHI 5-30 and AHI > 30. With increasing AHI, the fraction of apneas increases, regardless of other confounding variables. We also aimed to investigate if the median apnea index, hypopnea index, and hypopnea to apnea ratio differed between normal and increased nasal resistance in each group.

Paper II

Multiple logistic regression and multivariate linear regression analysis were used. As in paper I, multiple logistic regression analysis used the dependent variable hypopnea to apnea ratio (HAR). Independent variables were age, BMI, AHI, ODI, Nadir SpO2, TMCA cm2, TVOL cm3, and MCA cm2.

BMI was stratified into a tripartite of BMI < 25, BMI 25 – 30, and BMI > 30. BMI independently influences the hypopnea to apnea ratio. A weak linear relationship exists between BMI and acoustic rhinometry measurements.

Multivariate linear regression analysis was implemented to analyze any linear relationship between the respiratory sleep polygraphy variables, and acoustic rhinometry variables. Dependent variables were HAR, AHI, ODI, Nadir SpO2, AI, HI, as well as BMI. These were all analyzed in separate analyses with the independent variables TMCA cm2, TVOL cm3, and MCA cm2 before **and** after decongestion.

Paper III

Multiple logistic regression was used in this paper to analyze the relationship between arousal threshold (ArTH) and nasal resistance. ArTH was the dependent variable and independent variables were age, sex, BMI and nasal resistance as measured by 4-phase rhinomanometry. Nasal resistance was dichotomized to normal and increased nasal resistance, LR_{EFF} values < 1.0 for the former and > 1.0 for the latter.

Ethical approval

Written informed consent was obtained from all participants prior to inclusion in the studies. The study protocol was approved by the Norwegian Regional Committee for Medical Research Ethics (2016/1493/REK) and was registered in Clinicaltrials.gov (NCT03072173).

Statistics

All statistical analyses were performed using SPSS version 25 for Personal computer and Macintosh (SPSS Inc. Chicago, Illinois).

The p-value

is a statistical measure that gauges the strength of evidence against a null hypothesis. It indicates the probability of obtaining results as extreme as, or more extreme than, the observed data, assuming the null hypothesis is true. A lower p-value suggests stronger evidence against the null hypothesis. In this thesis, p-values <0.05 were considered statistically significant and all tests conducted were two-sided.

The 95% confidence interval (95% CI)

is a range of values around a sample statistic that is likely to contain the true population parameter with 95% certainty. This interval is defined by lower and upper bounds, and it is associated with the standard error, which measures the precision of an estimate and indicates the amount of variability in the sample statistic. Therefore, a smaller interval implies less variability in the sample and greater precision in the estimate.

Statistical methods applied in this thesis:

Students T-test

is a statistical test used to determine if there is a significant difference between the means of two groups, assessing whether the observed differences are likely to be due to chance assuming that the data is normally distributed. This test was used to compare crude differences between groups in papers I-III. In paper III, this test was used to compare the distribution of the demographic variables age and body mass index (BMI) between the normal and increased nasal resistance groups.

Pearson Chi-Squared test ($\chi 2$ test)

examines the association between categorical variables by comparing observed and expected frequencies to determine if there is a significant relationship or pattern in the data. In paper III, the $\chi 2$ test was used to investigate if the distribution of Edwards scores differed between OSA patients with and without increased nasal resistance as measured by 4-phase rhinomanometry.

Mann-Whitney Wilcoxon test

or Mann-Whitney U test is a nonparametric test of the null hypothesis. This test was used to compare differences in non-normally distributed, or skewed, variables between the normal and high nasal resistance groups in papers I - III.

Linear regression

models the relationship between a dependent variable and one or more independent variables, assuming a linear connection. It aims to find the best-fitting line that minimizes the difference between observed and predicted values. Linear regression results are expressed as regression coefficients (B) with 95% confidence intervals. In paper II, multiple linear regression models were used to analyze possible associations between selected acoustic rhinometry covariates and the respiratory and demographic outcomes.

Logistic regression

is a statistical method used for analyzing a dataset in which there are one or more independent variables, or exposures, that can be used to predict the outcome of a categorical dependent variable that is binary, i.e., where there are only two possible outcomes. Multiple logistic regression extends this analysis by allowing the consideration of multiple exposures simultaneously, to understand the influence each independent variable has on the likelihood of a specific outcome. The output of a logistic regression model is usually expressed in odds ratios (OR) and 95% confidence intervals (95% CI). Odds ratios are exponentiated coefficients that represent how much the odds of the outcome variable change for a one-unit increase in the independent variable. It compares the odds of success in one group to the odds in another group. An odds ratio greater than 1 signifies an increase in odds, while a value less than 1 indicates a decrease. An odds ratio of 1.2 indicates that the odds of the event occurring in one group are 1.2 times higher than in the reference group. In other words, there is a 20% increase in the odds of the event happening in the first group compared to the reference group. Univariate and multiple logistic regression were implemented in all three papers.

In paper I and II, the hypopnea to apnea ratio was the dependent variable and was adjusted for age, sex, body mass index, apnea hypopnea index, Oxygen Desaturation index and average SpO_2 desaturation. Although the hypopnea to apnea ratio was the dependent variable, these tests investigated nasal resistance as the independent variable of interest.

For paper III, arousal threshold was the dependent variable and was adjusted for age, sex, and body mass index. This test investigated nasal resistance as the independent variable of interest.

Summary of the Results

Paper I

OSA Patients diagnosed with a type III respiratory sleep polygraphy demonstrating a higher ratio of hypopneas relative to apneas are more than three times more likely (OR = 3.72, 95% CI [1.30 - 10.66], p = 0.015) to have increased nasal resistance as measured by 4-phase rhinomanometry, compared to those who have a lower ratio of hypopneas relative to apneas, regardless of OSA severity.

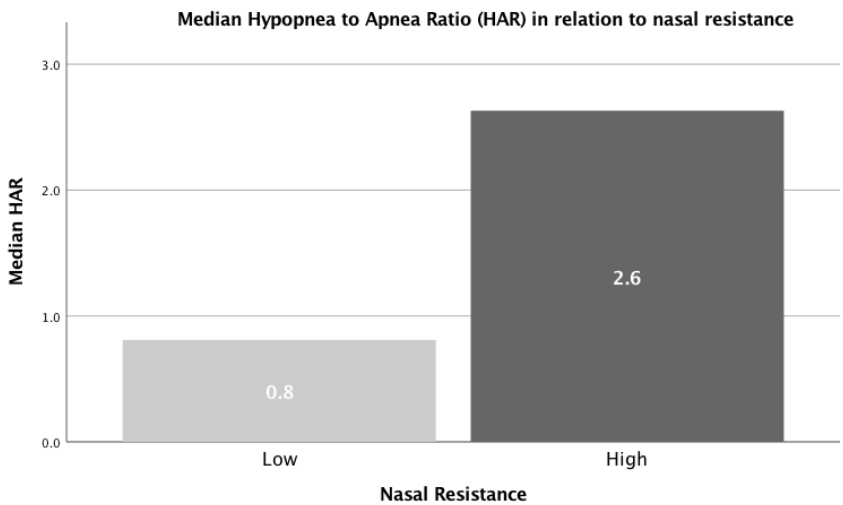

Figure 3. The median Hypopnea to Apnea Ratio (HAR) is significantly higher in OSA patients with increased nasal resistance, compared to those with normal (low in figure) nasal resistance (p = 0.001)

Paper II

Although acoustic rhinometry measurements in OSA patients are associated with 4-phase rhinomanometry measurements, no consistent statistically significant associations were found between the acoustic rhinometry variables, and the respiratory variables analyzed in the respiratory sleep polygraphies.

The main acoustic rhinometry variables minimal cross-sectional area, total area and minimal cross-sectional areas are significantly smaller in patients with increased nasal resistance as measured by 4-phase rhinomanometry ($P < 0.01$).

Male OSA patients with an elevated hypopnea apnea ratio are more than 4 times more likely to present with increased nasal resistance measured by 4-phase rhinomanometry (OR = 4.4, 95% CI [1.5-13.2], $P < 0.01$).

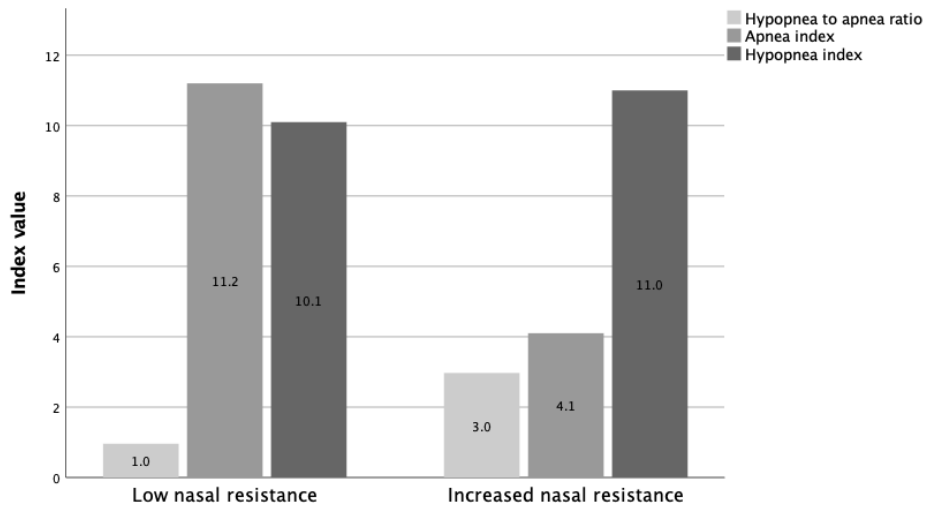

Figure 5. The median hypopnea to apnea ratio is significantly higher in OSA patients with increased nasal resistance (Mann-Whitney rank sum test, $P < 0.01$) This can be explained by a significantly lower apnea index in OSA patients with increased nasal resistance (Mann-Whitney Wilcoxon rank sum test, $P < 0.01$) without a significant difference in the hypopnea index.

Paper III

In accordance with defined criteria for low arousal threshold set forth by Edwards et al[109], OSA patients with increased nasal resistance as measured by 4-phase rhinometry are more than 2 times more likely to be associated with a low arousal threshold.

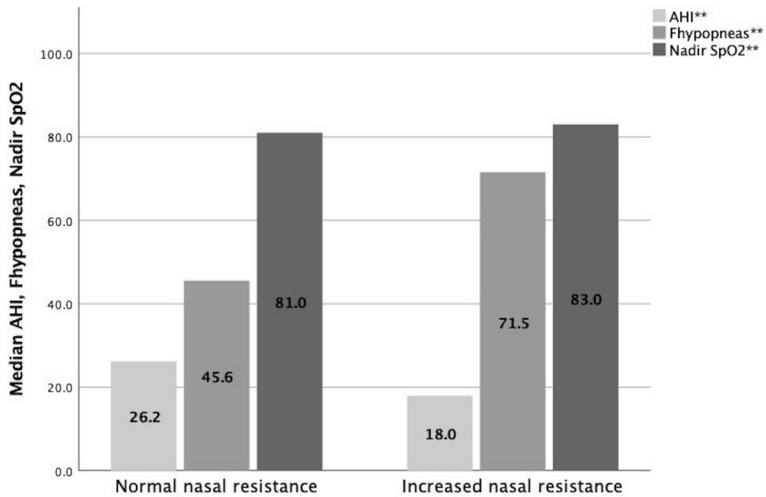

Figure 6. Median AHI, fraction of hypopneas and nadir SpO2 of OSA patients with normal and increased nasal resistance, refer to as 4-phase rhinomanometry LR_{EFF} values below or above 1.0. AHI – Apnea hypopnea index, Fhypopneas - Fraction of events that were hypopneas, SpO2 - Saturation of peripheral oxygen, LREFF – Logarithmic transformation of effective resistance. ** P < 0.05 (Mann-Whitney Wilcoxon rank sum test)

Table 1. Multivariate Logistic regression all patients (N = 315). Arousal threshold (ArTH) is the dependent. Odds ratios > 1.0 refer to higher odds for a low ArTH.

Variable	Odds Ratio	95% CI		P-value
		Lower	Upper	
Age	0.9	0.9	1.0	**< 0.001**
Sex	1.6	0.9	2.8	0.14
BMI	0.9	0.9	1.0	**0.005**
Nasal resistance	2.2	1.3	3.7	**0.002**

ArTH – Arousal threshold, 95% CI – 95% confidence interval, BMI – Body mass index. Nasal resistance refers to 4-phase rhinomanometry.Statistically significant odds highlighted in bold.

Discussion

Obstructive sleep apnea is prevalent in the adult population and current treatment standards may provide either limited adherence, in the case of CPAP, or limited efficacy, in the case of surgery[127-130]. Other common treatments, such as mandibular advancement devices or hypoglossal nerve stimulation and others have their own limitations[131-133]. Accurate detection of the underlying pathophysiology and patient selection seem to be key determinants for success in the treatment of OSA[108, 110, 128].

The results from the papers in this thesis suggest that increased nasal resistance plays a role in disturbed breathing during sleep. Demonstrably these patients present a distinct pattern of breathing disturbance during sleep. Furthermore, this thesis has demonstrated that OSA patients exhibiting increased nasal resistance are readily identifiable, either indirectly through the analysis of a sleep study or directly by way of objective nasal measurements. Additionally, increased nasal resistance in OSA patients seems to be associated with a low arousal threshold endotype.

These findings point to the possibility that a nasal endotype might exist as a subset of pathophysiology within OSA. We argue that this might be the case because with the methodology used in this thesis, similar results have recurred in all three papers. By using uni- and multivariate regression models, nasal resistance has been a reproducible and independent predictor of a different distribution of respiratory disturbance variables in the respiratory sleep polygraphy tests analyzed. This was established despite the randomness of inclusion, no patients underwent the sleep tests because of nasal symptoms, rather they had been referred to our center due to symptoms related to a suspicion of OSA.

Paper II repeated the 4-phase rhinomanometry findings from Paper I but did not find any consistent associations between any of the acoustic rhinometry measurements and the respiratory indices in the sleep studies. We attributed this to the measurement method. Whereas 4-phase rhinomanometry is a flow and pressure measurement, respiratory sleep polygraphy is a flow measurement, acoustic rhinometry is neither. This discrepancy was the most plausible culprit in our inability to find any link between the acoustic rhinometry measurements and the sleep studies.

In paper III we found a possible explanation for the positive findings in papers I and II. OSA patients with increased nasal resistance were more than 2 times more likely to have a low arousal threshold in accordance with the clinical screening tool devised by Edwards and colleagues[109]. Similar to findings by Antonaglia et al.[134] in asthmatic OSA patients, we found 70% of our cohort that had increased nasal resistance scored

an Edward´s score of 2 or higher, as opposed to 44% in the OSA patients with normal nasal resistance.

We propose that the signal effect of inadequate nasal ventilation is at least one of the keys to unlocking the mysteries behind nasal obstruction and OSA. The nose may be considered a respiratory stimulator, and its dysfunction may lead to the opposite[135].

Three primary mechanisms linked to nasal obstruction and associated with respiratory disturbances and arousals in OSA include the nasal-respiratory reflex, chemoreceptor feedback, and the shift to oral breathing preceding pharyngeal collapse.

The nasal-respiratory reflex involves interactions of afferent pathways between the nose, the rest of the airway and to the autonomic nervous system. These pathways are associated with ventilation and arousal during sleep, elucidated through experimental studies. Selective anesthesia of the nasal mucosa and pharynx hinders the arousal response to airway occlusion, while stimulation of these regions may directly provoke arousal[136, 137]. Studies on awake patients suggest that these afferent pathways have more to do with nasal mucosal cooling effects rather than obstruction itself[21, 138-140].

Chemoreceptor feedback occurs directly through the transport of oxygen, CO_2 and NO through the nose to the lungs, affecting ventilatory drive. Oxygen and to a lesser extent CO_2 is transported through the nose, whereas NO is produced in the nose. The nose plays an indirect role in CO_2 homeostasis, when nasal ventilation is inadequate and a swich to oral breathing occurs. In this thesis we have been unable to determine if the OSA patients switch to oral breathing during sleep. Nevertheless, the likely switch to oral breathing inhibits pharyngeal muscular tone, reduces blood oxygenation, increases CO_2 elimination, altering ventilatory timing and drive[65, 135, 141-145].

In Paper I we proposed that OSA patients with increased nasal resistance are more likely to undergo partial collapse of the pharynx, leading to hypopneas rather than complete occlusion (apneas), possibly due to a lower Pcrit.

All these arguments indicate that nasal obstruction disrupts breathing during sleep, either through inappropriate afferent signaling, increased negative inspiratory pressure from the nose to the pharynx, or indirectly through forced partitioning to oral breathing when nasal breathing is insufficient to meet ventilatory demand. Although this thesis cannot establish causative factors directly due to the implemented methodology, the results suggest that OSA patients with nasal obstruction exhibit a distinct pattern of respiratory disturbance, likely leading to more fragmented sleep. Whether this fragmentation results from direct nasal afferent signaling or arousal stimuli during the transition to oral breathing, is perhaps a topic for another dissertation.

Methodological Considerations

Studying nasal obstruction is challenging, studying this topic in relation to respiration during sleep even more so. This difficulty primarily arises from discrepancies between the subjective reporting of nasal obstruction and available methodologies for quantifying said obstruction. Measurement of sleep respiration is also a challenge in the clinical setting due to the resource-intensive nature of the gold standard method, polysomnography, which was outside of the constraints for the funding and scheduling of this thesis.

Apart from this, isolating the complexities of nasal and sleep pathophysiology and analyzing them separately is a formidable task. Our objective was to ascertain whether patients with increased nasal resistance could be identified and if such identification had any clinical implications. Because type III sleep studies like ambulant respiratory sleep polygraphy are mainly a flow analysis, we chose to focus on pressure/flow measurements of the nose. Since rhinomanometry is a more cumbersome method than acoustic rhinometry, we chose to investigate if the latter could also be implemented in identifying respiratory differences in OSA patients.

Study Designs

These studies were designed as cross-sectional, aiming to achieve a high level of real-world representation. Primary limitations inherent in such an approach include challenges in establishing causality, limited variance control, and potential inclusion biases, which, despite randomization, may impact outcomes. Nevertheless, such a design serves as a valuable pathway for observing group differences, analyzing multiple variables, acting as a catalyst for subsequent research endeavors.

The lack of polysomnograms is perhaps the most critical limitation of this thesis, particularly regarding the scoring of hypopneas in paper I-III. The absence of EEG precluded arousal scoring. This is a major weakness in paper III, where the algorithm implemented was originally derived from the analysis of polysomnograms. However, the designers of this algorithm devised it for use in a clinical setting and specified home testing as a potential use case[109]. Moreover, an experienced sleep physiologist performed all PG analyses manually, without prior knowledge of study inclusion.

Nasal measurements in the supine position were not performed in this thesis. In healthy subjects, nasal resistance increases in recumbency, a seemingly physiological phenomenon, however, this mechanism is unclear in OSA patients[59, 146]. We chose therefore to measure habitual nasal resistance in all study participants.

Patient reported outcome measures (PROM) were intentionally excluded from these studies to enable a comparison focused exclusively on objective measurements. The 4-phase rhinomanometer utilized in these studies has previously been validated by meta-analysis comparing subjective perceptions of obstruction assessed by a Visual Analog Scale (VAS) on a large cohort of patients, as previously mentioned in the materials and methods section of this thesis.

Study Subjects

Due to the cross-sectional design of these studies, we consecutively recruited informed participants after they had undergone the ambulatory sleep polygraphies and received a diagnosis of OSA (AHI>5). Therefore, selection was randomized but demographic variability was not controlled for.

Any willing participant ≥ 18 years of age and Norwegian speaking was invited to participate in studies I-III. As stated in paper III, the only exclusion criteria were any unstable medical condition that would disallow participation in the examinations. For the entire thesis, the age of participants ranged from 18-82 years of age. Participants were not screened for mental or neurological disease, which might have inadvertent negative effects on sleep and sleep respiration.

For paper II females were excluded. This was due to recruitment issues in females, a recurring theme in this thesis. An appropriate number of females was necessary to address known differences in acoustic rhinometry measurements between sexes. Lacking any universal reference ranges for acoustic rhinometry for either men or women in the literature we chose to exclude females. We believe the findings are also applicable to females, however a separate study should be done to confirm this.

Over sixty percent (68.3%) of the OSA patients we studied had mild to moderate OSA, or an AHI < 30. Despite random inclusion, one might argue that we have investigated patients with a lower risk for long-term complications because most patients only displayed mild to moderate AHI severity. We would argue that these patients have sought out treatment because of the symptoms they already have.

Study Variables

Hypopnea to apnea ratio (HAR) was implemented in the statistical analysis in papers I and II, whereas HAR as well as fraction of respiratory events that were hypopneas (Fhypopneas) was implemented in study III. Although they tell a similar story, HAR has inherent weaknesses concerning the distribution of apneas and hypopneas. When the ratio between these two variables is skewed, the resulting HAR value may be negligible or immense. In theory, patients when hypopneas are the exclusive respiratory disturbance, HAR is immeasurable. To address this, in paper I-II we dichotomized patients into two categories, those with a HAR > 1, and those with HAR < 1, meaning that they either had an abundance of hypopneas and a paucity of apneas or the reverse. This allowed for a binary logistic regression analysis but did not reflect the continuous nature of the variable. For this we employed nonparametric methods such as the Mann-Whitney Wilcoxon test, however such tests do not account for confounding variables that could affect the results.

For paper III we analyzed the arousal threshold algorithm devised by Edwards and colleagues[109]. As reported earlier, the largest weakness of implementing this algorithm was the lack of polysomnograms, as this algorithm was based on. One might therefor argue that this algorithm is not valid in ambulatory respiratory sleep polygraphy, due to underscoring of hypopneas based on the lack of electroencephalograms. However, as previously mentioned, the authors intended for this algorithm to be used in a clinical setting or in their own words "most home sleep tests"[109]. Although they may have referred to ambulant polysomnography, such testing is currently not widespread.

Study Methods

Acoustic Rhinometry

Conflicting reports exist regarding the correlation between AR measurements and subjective nasal patency. AR cannot discriminate differences in localized cooling effects on the nasal mucosa during inspiration, airflow turbulence, differences in nitric oxide production as well as between differences in other synergistic factors[140, 144]. Retroglossal narrowing exacerbates sleep-disordered breathing in patients with nasal obstruction and may contribute to subjective nocturnal nasal obstruction but retroglossal dimensions are undetected by AR[147]. Nevertheless, a prevailing consensus suggests that smaller AR measurements are associated with diminished nasal patency and subjective perceptions of nasal obstruction within the broader population. Additionally, ample documentation exists affirming sex-based disparities in AR measurements, with women typically exhibiting smaller AR values compared to men[148, 149]. The potential relationships between acoustic rhinometry measurements and the distribution of respiratory variables assessed during a sleep study have received limited scrutiny in OSA patients.

4-Phase Rhinomanometry

Rhinomanometry has inherent technical issues such as patient compliance and unidentified mask leakage, which may lead to erroneous results. Patients with severe nasal resistance may struggle to achieve a valid measurement. In this thesis such patients were excluded, valuable data was therefore lost. Patients were not categorized by the VAS scale but dichotomized into increased nasal resistance and normal nasal resistance, requiring only one nostril with an elevated measurement to qualify. We chose this due to the measurement method; anterior rhinomanometry is a unilateral measurement. A summated reference value is clinically irrelevant, patients might have normal resistance in one nasal passage and severe obstruction in the other, despite summated resistance being within reference values. Posterior rhinomanometry is difficult for patients to perform. Preferably nasal resistance measurements should be carried out during the sleep recording; however, this was technically unfeasible in these studies.

Respiratory Sleep Polygraphy

As previously mentioned, the major weakness in respiratory sleep polygraphy is in scoring hypopneas and arousals, resulting in an underestimation of AHI[150]. This is mainly due to the lack of an electroencephalogram (EEG) signal for the scoring of arousal-based hypopneas, as well as overestimating analysis time versus actual sleep, which may result in underscoring AHI[150]. Nevertheless, we have detected significant differences between nasal resistance groups regarding the distribution of apneas and hypopneas. If underscoring of hypopneas has occurred, we may suspect that these differences would become more profound in polysomnography.

Conclusions

Paper I

Obstructive Sleep Apnea (OSA) patients demonstrating increased nasal resistance as measured by 4-phase rhinomanometry exhibit significantly different patterns of respiratory disturbance during sleep than those with normal nasal resistance. An increased ratio of hypopneas relative to apneas in individuals with OSA may indicate the presence of increased nasal resistance.

Paper II

When comparing two common measurement modalities of nasal patency, namely acoustic rhinometry and 4-phase rhinomanometry, only rhinomanometry is associated with the respiratory indices from the sleep studies we analyzed.

Paper III

OSA patients exhibiting increased nasal resistance as measured by 4-phase rhinomanometry are significantly associated with a low arousal threshold endotype defined by the criteria for low arousal threshold set forth by Edwards and colleagues[109].

Appraisal of the Main Findings

The major findings of this thesis are that OSA patients with clinically relevant increased nasal resistance are identifiable and that they demonstrate a differing pattern of respiratory disturbance during sleep compared to OSA patients without increased nasal resistance.

The findings also allow us to identify from the variables assessed in a standard sleep study to suspect if a patient demonstrates increased nasal resistance and whether they should be referred to further investigations concerning nasal obstruction.

Furthermore, OSA patients with clinically measurable increased nasal resistance are associated with a low arousal threshold endotype, meaning that they may be more likely to suffer from sleep fragmentation due to respiratory disturbance or other stimuli.

This is relevant because the identification of such patients may facilitate a different treatment strategy. First and foremost, we identify that increased nasal resistance may affect their respiratory disturbance during sleep, thus treatment of their underlying nasal pathology may alleviate their obstructive sleep apnea or affect other treatments. Furthermore, identifying that these patients might suffer from fragmented sleep may lead us to conclude that these patients might need more tailored treatment or follow-up, to address their low arousal threshold, which itself is a risk factor for non-compliance to conventional OSA treatment.

Future Studies

This thesis has several implications for future studies. Firstly, a similar study design should be performed using polysomnography as the methodology of sleep recording. Here we could address the shortcomings of paper III to verify a low arousal threshold in OSA patients with increased nasal resistance. Secondly, the additional analysis of patient recorded outcome measures (PROM) could be an additional identifier in OSA patients suffering from nasal obstruction relevant to their sleep quality. Lastly, interventional studies in the treatment of nasal obstruction with the aim to improve patient outcome would be the pinnacle achievement.

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Norsk Medikal A/S provided a 4-phase rhinomanometer (4-Rhino, RhinoLab GmbH, Rendsburg, Germany)

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The role of the nose in snoring and obstructive sleep apnea is unclear. Numerous studies have pointed to the importance of nasal breathing during sleep, many have not found a connection to sleep apnea severity. This thesis has investigated what typifies obstructive sleep apnea patients with nasal obstruction. This was performed through objective nasal measurements and analysis of sleep studies.

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Hoel considers himself a nose nerd and a pulmonaut. This photo is taken during the SARS-CoV-2 pandemic, during testing of a snorkel mask converted to a custom surgical face mask with 3D printed attachments.

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