VILNIUS UNIVERSITY
MEDICAL FACULTY

The Final thesis

Phenotypes in Obstructive Sleep Apnea

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2024

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List of abbreviations:

1. **OSA - Obstructive sleep apnea**
2. **EDS- Excessive-Daytime-Sleepiness**
3. **PSG – Polysomnography**
4. **CPAP - Continuous positive airway pressure**
5. **UPPP - Uvulo-palato-pharyngoplasty**
6. **MMA - Maxillomandibular advancement**
7. **LG – Loop Gain**

1. Summary

Obstructive sleep apnea is a burden affecting millions worldwide. It is a common chronic disorder, classified as heterogeneous, linked to airway obstruction, leading to oxygen deprivation and sleep-associated disorders(1).

It is classified as heterogeneous, as there is a specific variability in severity (from light to severe), symptoms (from broad multi-symptomatic cases to asymptomatic patients), etiologies, and treatment responses. Etiological causes for this condition include genetic factors, environmental factors, and lifestyle choices(2). Those repeated episodes of airway collapse during the night can significantly impact the affected individuals' quality of life, decreasing life quality and causing various health problems(3).
Discussing OSA while focusing on different phenotypes and their appropriate treatment options is the primary goal of this thesis.

2. Keywords.

Airway obstruction, CPAP, Obesity, Excessive Daytime Sleepiness, Phenotype treatment, Phenotyping, Sleep apnea, Sleep disorder, Stertor.

3. Introduction

Obstructive sleep apnea is an underdiagnosed disease in our society, even with our society's obesity crisis (4). It is becoming increasingly important to diagnose and treat it appropriately. It is the most prevalent sleep disorder, and understanding and classifying it into different phenotypes can help recognize other patient clusters and optimize their treatment. Phenotyping gives patients optimum care and a treatment plan aligned with their needs(1).

In this thesis, the importance of phenotypes will be discussed critically, highlighting the advantages and shortcomings of different studies. It aims to give a whole picture of OSA, its etiology, epidemiology, diagnostic criteria, and available treatment options with scientific grounding. It is not only anatomy-related, but OSA has multiple causes, multiple faces (Phenotypes), and the possibility of each face treatment modification.

4. Definition

There are different sleep apnea-related disorders; thus, OSA is the most common. This obstruction can be complete or partial, with or without oxygen deprivation – it does lead, in most cases, to sleep and circadian rhythm disturbances and fatigue, leading to possible cognitive impairment. Common symptoms of OSA include loud snoring (stertor), excessive sleepiness during the day (hypersomnia), and restless nights of sleep (insomnia)(5).

It needs a multidisciplinary approach, as it sometimes requires a team of various healthcare professionals: somnologists (sleep specialists), pulmonologists, neurologists, otolaryngologists (ear, nose, and throat specialists), and trained dentists to find the source and treatment plan(6).

5. Epidemiology

The prevalence of OSA worldwide is estimated to be between 3% and 7%, and specific population subgroups are at a greater risk(7).

OSA is affecting men and women. Especially women after menopause have an increased risk, which is equal to the male risk. Pre-menopausal women have a lower risk than men (9). Regarding age, there is a correlation that shows that OSA is more common in the middle-aged and elderly population(8).

Increased BMI, especially an increased fat deposition (9) around the neck, resulting in airway narrowing, is crucial to developing OSA. As Section 6 indicates, co-morbidities increase the risk. Therefore, this patient group is more likely to be a patient suffering from OSA. Genetics also plays an important role. More research is conducted to find possible polymorphisms and variables (10) that help with screening, treatment, and avoiding health consequences of the disease.

As well as ethnic background, there are studies suggesting a higher likelihood of African-Americans, Hispanics, and Asians suffering from OSA linked to anatomical traits (craniofacial features, for example)(11).

6. Risk factors:

The most common risk factors are male gender(12), smoking, alcohol consumption(13), advanced age(14), large neck circumference, and obesity, and those are crucial for treatment strategies, as some are modifiable. Obesity is the most critical risk factor and is part of the obesity crisis, one that is increasing its prevalence in our population. Obesity rates have tripled since 1975(15).
Patients with a medical history of hypertension, diabetes, metabolic syndrome, past myocardial infarction, arrhythmia, heart failure, asthma, and stroke, are typical. Those comorbidities have to be taken into account for treatment options as well(7).

7. Etiology

The etiology of OSA is an intricate subject. Multiple factors play into the pathogenesis, affecting pharyngeal narrowing and collapse during sleep.
Significant impacts leading to obstruction are linked to sleep-related reduced ventilatory muscle contraction and mixed risk factors, including neuromuscular and anatomic risk factors. Talking anatomy, large neck circumference, soft tissue accumulation, and bone or vessel enlargement promote pharyngeal narrowing and additional pressure on the upper airway.
This pressure increases the risk of pharyngeal collapsibility and insufficient space for the airway at resting intervals. Furthermore, decreased upper airway muscle tone correlates with airway collapsibility. As mentioned in section 6, the most common risk factors are obesity, male, and advancing age. An interesting fact is that the severity decreases with age when there is a decline in BMI. Summing up, incidence increases with age, and severity decreases (16).

As stated in the study of Jennifer M. Slowik; Abdulghani Sankari; Jacob F. Collen, “Obstructive sleep apnea”; (16)
Anatomical risk factors for OSA are Micrognathia (formerly known as mandibular hypoplasia), retrognathia (formerly known as mandibular retrognathia), facial elongation, mandibular hypoplasia, adenoid and tonsillar hypertrophy, and inferior displacement of the hyoid.

Central fat distribution, obesity, advanced age, male gender, supine sleeping position, and pregnancy are non-anatomical risk factors for OSA.

Associated Medical Disorders range from endocrine disorders (e.g., diabetes mellitus, metabolic syndrome, acromegaly, and hypothyroidism), neurological disorders (e.g., stroke, spinal cord injury, and myasthenia gravis), cardiovascular disorders (congestive heart failure, atrial fibrillation) to syndromes like Down-, Prader Willi-, obesity hypoventilation-syndrome(16).

8. Pathophysiology

The pathophysiology of OSA is complex and multifactorial, and individual variations exist. It can be challenging as the elderly population is more often affected, and therefore, more comorbidities play a role that must be considered. Not to forget compliance, as there is also a higher chance of having a patient with OSA and dementia(17).

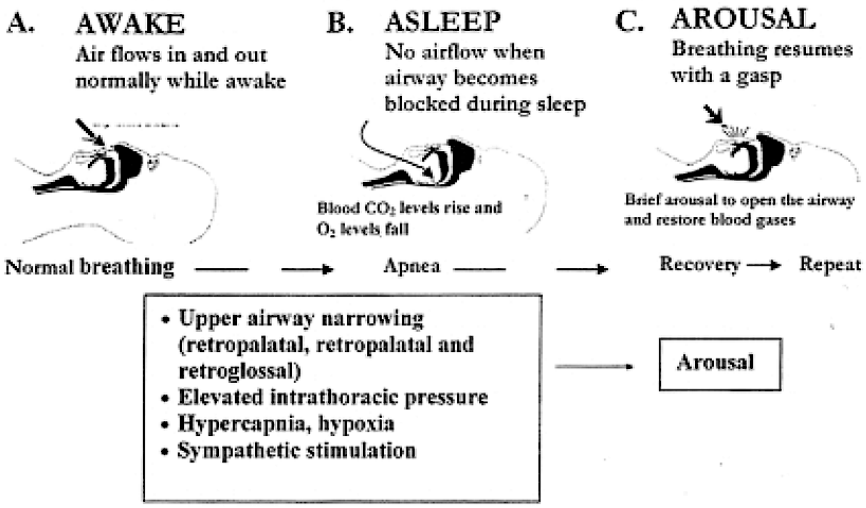


Figure 1: OSA mechanism(18)

The primary cause of OSA, the obstruction of the airflow, is the result of a collapsing upper airway during sleep. It can be caused by anatomical abnormalities, reduced muscle tone, or impaired neuromuscular control. During the night, the muscle tone is already decreased, so the reduced muscle tone increases the chance of OSA. The obstruction of the airways can result in a reduced or complete cessation of airflow, which can result in hypoxemia and hypercapnia. The reduced oxygen level activates the brain's response to increasing carbon dioxide levels, resulting in arousal and sleep disruptions. Those sleep disruptions are the body's mechanism to increase oxygen supply. Usually, those disruptions tend to occur multiple times a night, impacting sleep quality and, therefore, a tremendous impact on life quality.

In consequence, patients complain about excessive daytime sleepiness. Besides the EDS, intermittent oxygen insufficiency and reoxygenation cycles with increased intrathoracic pressure benefit systemic inflammation, oxidative stress, and endothelial dysfunction. Therefore, treatment is essential; poorly treated or undiagnosed OSA can lead to the development of several comorbidities, ranging from hypertension to cardiovascular diseases, metabolic disorders, and neurocognitive impairment(19).

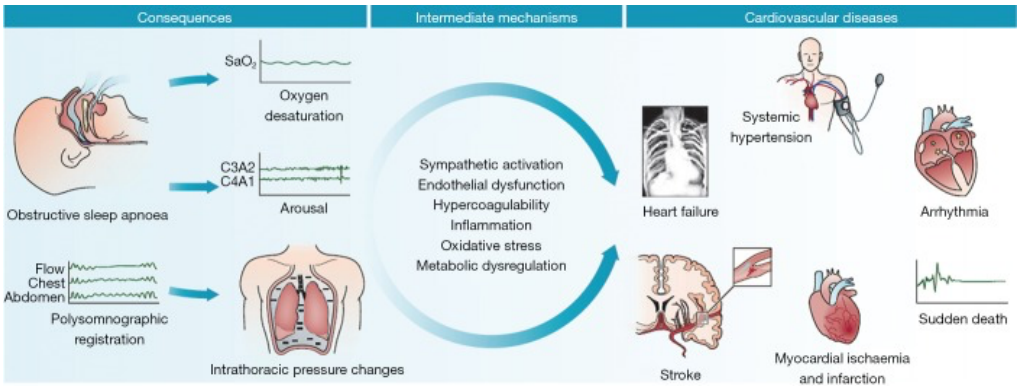


Figure 2: Impact of OSA(2)

9. Clinical presentation of OSA

Obstructive sleep apnea (OSA) is a sleep disorder, and the clinical presentation of OSA can vary among individuals. A hallmark of OSA symptoms is EDS, even after a night's sleep. As a consequence, fatigue, difficulty concentrating, and decreased productivity. The patient or the partner mentions loud snoring every night, and OSA is associated with loud and persistent snoring. Abrupt pauses because of breathing, gasping for air, or waking up are usual, sometimes accompanied by choking sounds. The patient often complains about lousy sleep quality, as their sleep is so-called "fragmented sleep"; the recurrent awakening leads to EDS and is often accompanied by increased irritability and restlessness. Mood swings and memory problems significantly impact the patient's quality of life. Some patients suffer from morning headaches linked to changes in oxygen levels and increased carbon dioxide levels at night. Dry mouth mucosa and sore throat suggest OSA, resulting from active mouth breathing at night. Nocturia due to disrupted sleep patterns and increased thoracic pressure can favor fluid shifts in the body, resulting in increased urine production(20).

10. Diagnostic criteria and tests

The diagnostic criteria for OSA are based on anamnesis, clinical assessment, and sleep study results. The diagnostic latter can look as such: Clinical Symptoms: Loud snoring, breathing pauses during sleep (reported by relatives), EDS, morning headaches, mood swings, and difficulty concentrating. If the patient suffers from those symptoms, further steps can be taken if he is in the risk groups (section 6).

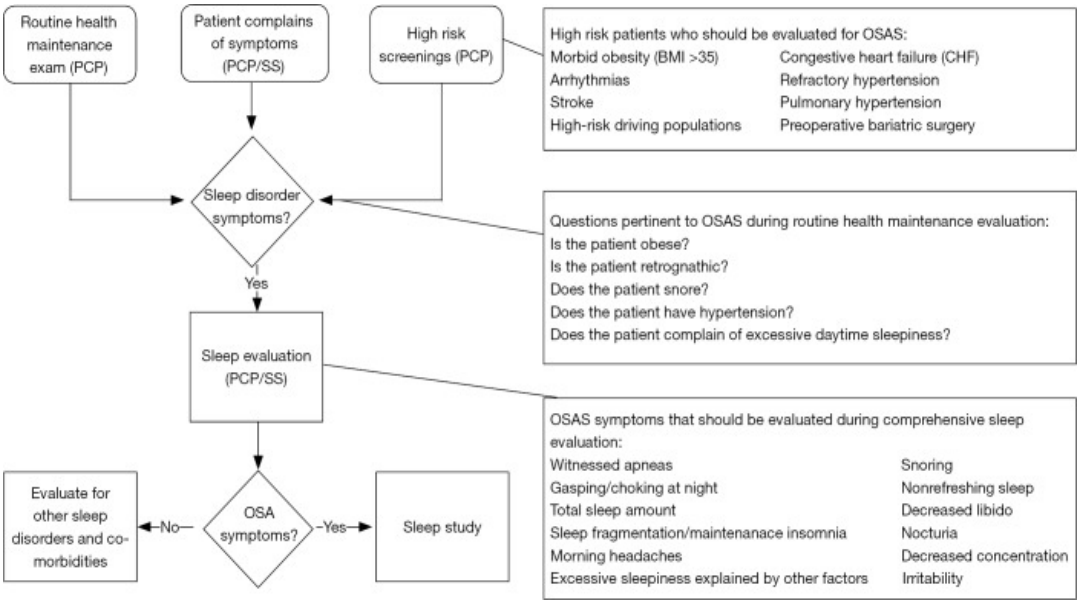


Figure 3: Diagnostic algorithm of OSA(20)

Sleep Study: The gold standard for OSA diagnostics is polysomnography. It monitors various physiological parameters during sleep, including airflow, respiratory effort, oxygen saturation levels, heart rate, and brain activity. Polysomnography (PSG) is a comprehensive test that examines sleep and is a diagnostic tool in sleep medicine. It involves the collection of seven or more data channels, including electroencephalogram and electrooculogram, for sleep staging. Similar to electromyogram, electrocardiogram, and respiratory channels. (21)

When OSA is suspected, sleep specialist assessment and polysomnography are crucial to avoid the risk of untreated central sleep apnea or hypoventilation. Conditions associated with central sleep and hypoventilation are congestive heart failure, obesity with a serum bicarbonate level of more than 27 mmol/L, severe lung disease, neurologic disease, neuromuscular disease, and opioid use. PSG is indicated for evaluation for suspected sleep disorders and the assessment after nondiagnostic home sleep apnea testing among patients with a high pretest probability of OSA(21).

Apnea-Hypopnea Index (AHI): (22) The apnea-hypopnea index (AHI) is the combined average number of apneas and hypopneas per hour of sleep. According to the American Academy of Sleep Medicine (AASM), it is categorized into mild (5-15 events/hour), moderate (15-30 events/hr), and severe (> 30 events/hr)(23).

The AHI has been used for decades – but not without criticism. Due to its high sensitivity and low specificity, there is probably a high rate of false-positive results, even in the "high severity" range.

“Thus, this single test result should never be a proxy for a disease state.” - **On the rise and fall of the apnea−hypopnea index: A historical review and critical appraisal** by Dirk A. Pevernagie, Barbara Gnidovec-Strazisar, Ludger Grote, Raphael Heinzer, Walter T. McNicholas, Thomas Penzel, Winfried Randerath, Sophia Schiza, Johan Verbraecken, Erna S. Arnardottir.

Drug-induced sleep endoscopy (DISE) is a diagnostic tool to evaluate the upper airway of individuals experiencing snoring and obstructive sleep apnea, mimicking the natural sleep setting. Through DISE, various classifications, such as the VOTE Classification, have been developed, classifying findings according to the structures leading to airway obstruction. OSA manifesting in multiple segments of the upper airway, including naso-, oro-, and hypopharynx, is a result of the DISE study. It proves to be a valuable method for assessing the dynamics and functionality of the upper airway. (24)

11. General treatment recommendations

Obesity, the number one risk factor, is often modifiable. The patient should be informed about possibilities for weight loss, nutritional adjustments, and lifestyle changes from which his OSA would benefit. Important pillars in treatment are: Weight reduction can help to reduce the severity of the symptoms; Quitting alcohol can help on the weight loss journey as well as for the relaxation of the upper airway muscles; Quitting smoking reduces airway inflammation, therefore less obstruction. A balanced approach from nutritional change, more daily exercise, and behavioral changes are important for the success of the treatment. One should remember to highlight sleep hygiene. A patient taking care of his sleep schedule and environment can improve his condition by enhancing his overall sleep quality. An improved sleep quality leads to more energy throughout the day and less severe symptoms of fatigue during the day((9)

12. Continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea

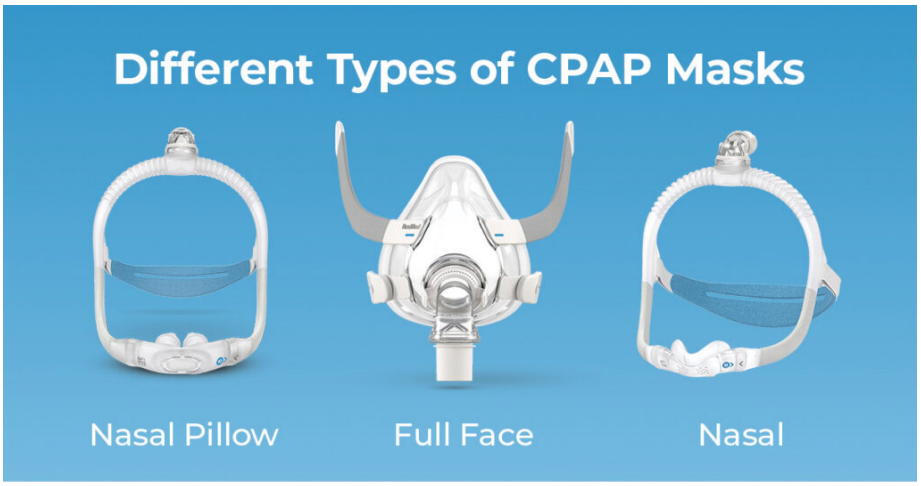


Figure 4: Types of CPAP masks (25)

CPAP – Continuous Positive Airway Pressure – is a non-invasive therapy option for patients suffering from OSA. The patient is instructed to use a CPAP machine that delivers a constant flow of pressurized air – the rate and mask can be individualized. Available options are nose, mouth, or both. The positive steady pressure helps keep the airways open during sleep, preventing obstruction and reducing episodes of apnea and hypopnea. Hence, there is less oxygen deprivation at night. It is considered the best treatment option for OSA, as it is non-invasive, meaning no surgery is needed, and it shows promising results. It reduces EDS and the risk of associated health complications (26).

Advantages

The advantages of CPAP are evident, and the therapy is considered the gold standard of treatment for OSA. It has been proven that it alleviates symptoms and improves sleep and life quality simultaneously (17); this improvement can be immediate, as the oxygen inflow improves, improves breathing, resulting in better sleep quality and less EDS (17). Besides increasing the quality of life, it positively impacts health by reducing the overall associated health risks (diabetes, cardiovascular, high blood pressure) of OSA (27). It is essential to mention that it can be adapted to the patient – different masks, pressure rates, and adjustments throughout the disease; it can be adapted to a certain degree (25).

Disadvantages

The most important complaint about CPAP is the mask discomfort while falling asleep, sleeping, or both. For some, it makes falling asleep impossible; others state that it needs time to get used to. With this steady oxygen pressure, others suffer from congestion and dry mucous membranes in the nose, which irritate them and reduce their sleep quality.

In any case, getting used to the CPAP takes time – some succeed and benefit immensely. Others see no benefit due to the lack of compliance(27).
One major disadvantage is transportability; CPAPs require a power source, and some must be in travel-friendly sizes. Even though progress has been made, and lighter, compacter ones are on the market, the dependency on electricity remains(28).

Challenges of CPAP

Compliance with CPAP therapy is necessary for OSA symptom management and relief. They (27)improve the individual's quality of life while decreasing multiple OSA-associated health risks. Before starting CPAP, healthcare professionals must inform the patient about the proper technique and possible challenges (e.g., getting used to sleeping while wearing a mask) and ensure long-term compliance. Using it continuously will bring results. Meanwhile, non-adherence rates are around 46% to 83% in different groups, stating less than 4-hour usage of CPAP. Studies prove clinical impact from 6 hours onwards – reducing EDS and enhancing daily functionality. It ensures a steady, continuous pressure – one rate - during inhalation and exhalation (27). That is one of the critical differences to APAP, which aligns pressure-wise with the patient's inhalation (29). Some patients using CPAP complain of breathing discomfort because of the continuous pressure. So, the physicians are trying to adjust the pressure force or are inclined to use APAPs for this patient. It is essential to highlight that CPAP is the most commonly used and extensively studied device for OSA(27).

13. Surgical treatment options for obstructive sleep apnea

If there is treatment failure with CPAP therapy, other options include oral appliances and surgical interventions. What surgical procedure is required for individual factors, anatomical considerations, comorbidities, and the severity of OSA (30). Standard surgical procedures for OSA include Uvulopalatopharyngoplasty (UPPP), tonsillectomy and adenoidectomy, septoplasty, maxillomandibular advancement (MMA), hyoid suspension, palatal implants,

lingual tonsillectomy, and tracheostomy. For all of them, it needs pre-surgical evaluation. PSG and home sleep testing are unsuitable for determining the obstruction's location in the OSA patient. A thorough patient anamnesis, including main complaints, symptoms, and surgical history, is critical. If the patient has been treated with CPAP, oral appliances or weight loss has been evaluated (30).

Assessing the nasal airway for deformities, collapse, septal position, turbinate size, and polyps is crucial for surgical treatment options. The oral cavity, oropharynx and tongue size and position, dental health, and palate position also provide insight into potential upper airway surgery. The entire upper airways can be examined via trans-nasal flexible laryngoscopy. (30)

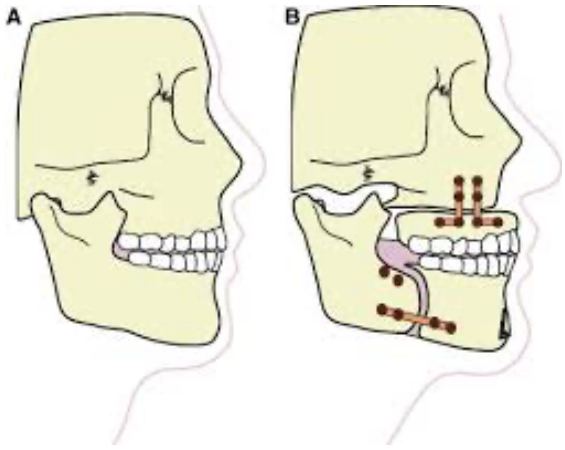
About MMA, it is an invasive surgical option for OSA patients. The surgery aims to enlarge the upper airway by physically expanding the facial skeletal framework. It widens the nasopharyngeal, retropalatal, and hypo-pharyngeal airway. As mentioned, – it is an invasive procedure with multiple risks, which range from expected consequences of the condition, including discomfort, inflammation, misalignment of the jaw, unsatisfactory cosmetic outcome, loss of sensation in the face, tingling sensations, limited mobility in the jaw, and regression of the surgical correction over time; And minor hemorrhage, local infection, and extrusion of hardware. It is a highly effective treatment, but there are risks. Thus, transparency is essential, and this procedure should be offered primarily to more severe OSA cases (31).

UPPP is the most common surgical procedure used to treat obstructive sleep apnea. It is considered a standard procedure. It is indicated for patients who are not able to comply with other treatment options (e.g., CPAP) or report treatment failure. It is an invasive treatment that involves resecting the uvula, distal margin of the soft palate, palatine tonsil, and excessive lateral pharyngeal tissues. Ideal candidates for the procedure are individuals whose upper airway exhibits anatomical narrowing and collapse limited to the velopharyngeal or retropalatal region.

If they are eligible for this procedure, Fiberoptic pharyngoscopy, cephalometric roentgenography, computed tomography, and some fluoroscopy are used to select the patients. Proper selection is vital to make the procedure safer. Unfortunately, it is not for everyone's success, and even if there is an improvement, relapses happen. Possible complications are associated with loss of airway function, exacerbation of apnea, and cardiopulmonary sequelae. It occurs in up to 13-25% of the patients. Post-surgery follow-ups

are mandatory, as studies show that the efficacy of the UPPP decreases over time, and the treatment has to be adapted(32).

Overview of MMA and UPP:



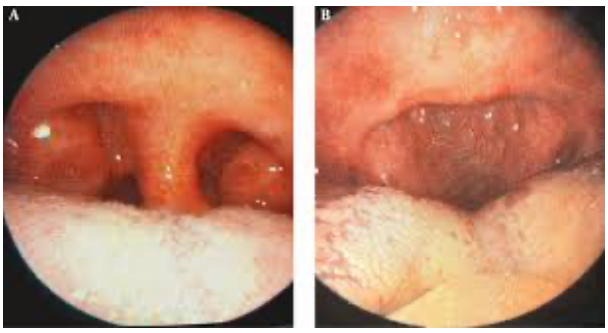


Figure 5: Before and after MMA (33) **Figure 6: UPPP - Before and After** (34)

Bariatric surgery—also known as gastric sleeve gastrectomy—can play a role in OSA treatment. Reducing weight decreases abdominal fat. (35) Not only will OSA symptoms diminish, but other cardiovascular co-morbidities will benefit from the weight loss. It is a surgical intervention worth considering, for example, in morbidly obese patients (BMI>40) who would not qualify for the previously described procedures.

Alternatives:

About tongue retaining spints: They are customizable monobloc orals used for OSA treatment. It displaces the tongue anteriorly with suction force while the patient sleeps. It offers a non-surgical treatment option (36).

About mandibular advancement: It is used for mild to moderate cases of OSA. These devices advance the mandible and tongue anteriorly, thus enlarging the upper airway and decreasing its collapsibility during sleep. There are different designs and fabrications; they can be custom-made or prefabricated(37).

14. Phenotypes

Phenotypes are: "The observable characteristics in an individual resulting from the expression of genes; the clinical presentation of an individual with a particular genotype." – **National Cancer Institute**(38).

They can help comprehend the disease's complexity and the population it affects. In the best case, phenotypes express the endotype. An endotype is a distinct disease subgroup with specific biological mechanisms, a.k.a. pathways underlying the disease(39).
By phenotyping diseases, meaning phenotype identification, the aim is to add progress to diagnostics, treatment, and prognosis. Hence why, it should be done carefully. It can be grouped by features (molecular vs clinical) and experimental approaches (supervised vs unsupervised). Clinical phenotyping is oriented by characteristics and measurements like clinical symptoms, demographics, comorbidities, physiological and anatomical measurements, and treatment responsiveness. Molecular phenotyping orientates itself on the molecular level: on DNA, RA, mRNA, MiRNA, proteins, and others. It ranges from mono to polymorphisms. Individuals experiencing different OSA symptoms have been used for phenotyping for decades. Up to 60% reported EDS and high rates of impaired concentration, mood lability, and other neurocognitive difficulties. Efficient treatment of the patient group with EDS in OSA has shown a reduction in high blood pressure, vascular risk coefficient, and an overall improvement in life quality. Therefore, OSA with EDS has been suggested to become a distinct phenotype.

Due to various factors contributing to EDS, it is unlikely to be established as a phenotype. On the other hand, there is an increase in recognition of age, gender, and race(40).

Obesity-related phenotype

It is the most common one, as it is also the most prevalent risk factor. Patients from this phenotype tend to have moderate to severe sleep apnea. Sex-wise, men are at higher risk than women. Not only is the high BMI a problem here, but the fat distribution around the neck and waist is, too. The fat deposition in the para-pharyngeal area promotes OSA. The abdominal fat distribution reduces lung volume, causing caudal traction on the pharynx, harming pharyngeal

stability. On the bright side, obesity is a modifiable risk factor. Weight loss measures (lifestyle modifications, bariatric surgeries) effectively treat OSA(41).
Additional information about lifestyle modification can be found in section 11 (general treatment recommendations).

Gender-related phenotype:

Men are 2-3 more likely to have OSA than women. Their periods of apnea are more extended, and their oxygen desaturation is more significant.; Even if their BMI is lower.
The male prevalence correlates with anatomic features linked to increased fat deposition in the parapharyngeal area and waist. Furthermore, their pharyngeal airway is longer and more vulnerable. Treatment-wise, there are many options, ranging from CPAP to surgeries and lifestyle modifications(41).

Age-related phenotype

It is a significant phenotype, and its frequency grows until age 65, when it reaches a plateau stage. As in the obesity and gender-related phenotype, it is linked to reduced airway space due to fat deposition. Another factor is the genioglossal responsiveness to negative intra-pharyngeal pressure. This pressure and responsiveness can deteriorate with age. An increase in spontaneous arousal has been suggested to lower the arousal threshold. In addition to that, aging impacts the ventilatory control system and reduces the LG. Compared to younger patient groups, airway anatomy/stability is more important in the elderly/older adults.
Treatment-wise, nasal CPAP devices have been proven effective in improving OSA and sleep quality. (41)

Menopausal women

In menopausal women, the risk triples. Especially the severity of the OSA in the NREM phase increases, whereas younger women typically suffer more from the REM-associated OSA. One of the reasons for the tripled risk is the longer pharyngeal airway in postmenopausal women. The decline of sex hormones such as estrogen and progesterone hurts the upper airway patency and ventilatory drive(41). Hand in hand with the endocrine system changes, often, women gain weight during or after menopause. Thus, a higher BMI, larger neck

circumference, and a higher waist-hip ratio. All the factors that priorly made men more susceptible to developing OSA.(42)
The risk can be reduced by hormone replacement therapy. The study situation needs to be more extensive, and the studies are old. There is no clear evidence that the hormonal decline is the reason for the increase in OSA in postmenopausal women.

“Women had smaller airway volume, reduced upper airway cross-sectional area and longer airway length in perimenopausal years, and a significantly lower hyoid position in postmenopausal years. These changes may be related to menopause itself and independent of the changes associated with aging.” – these are the results of the study “A Cone Beam CT Study of Upper Airway Morphology in Perimenopausal and Postmenopausal Women. “
by Wanxin Zhang[1] and Xuemei Gao[1] .

PCOS

In adults suffering from PCOS, a 9.74x higher risk of developing OSA has been observed. There are no clear answers to the pathophysiological mechanisms for the increased risk. It is suggested that central obesity, hyperandrogenemia, and insulin resistance – either one or several factors together- favor the development of OSA in women with PCOS(43).
Treatment-wise, CPAP is advised. But most importantly, this patient group also remains often underdiagnosed, and it is vital to pay attention to women with PCOS(44).

Pregnancy

There are two groups of pregnant women with OSA: women with pre-existing OSA (chronic) and gestational OSA. The gestational type usually starts with snoring, and then the first obstructive events happen, linked to physiological and hormonal changes of pregnancy. Physiological changes include upper airway edema and more significant negative upper airway pressure due to estrogen and progesterone changes. Some evidence suggests that gestational OSA is temporary and might resolve itself. The term gestational OSA needs to be formally defined. It requires studies and research.
Treatment-wise, CPAP is advised and close monitoring of mother and child. (45)

Ethnicity related phenotype

Most importantly, the Asian population seems to feature craniofacial restrictions that are beneficial for developing OSA despite a lower average BMI(41). The severity of OSA is increased in the Chinese population compared to the European population. (11)
African Americans are more prone to obesity and enlarged upper airway soft tissues. Caucasians tend to have both soft tissue and bone abnormalities(41). Treatment-wise, OSA patients with this type of OSA benefit more from surgeries than from CPAP(41).

Positional phenotype

It is a dominant phenotype of OSA, with a 20% to 60% prevalence in the general population. The supine position is unfavorable for upper airway anatomy, reducing lung volume and inhibiting the dilator muscles' ability to compensate for the airway collapse. Patients from this group report more sleepiness than other groups, leading to the assumption that the supine position has an increased impact on EDS: There are two sub-categories: supine-predominant and supine-isolated. The isolated type has a doubling of AHI in a supine position and a non-supine AHI of<5—the predominant. The predominant type also has a doubling of AHI, although the non-supine is above 5 events/hour. The isolated type is more common in younger males. The predominant one's patient group has a higher BMI.

Treatment-wise recognition is valuable, as these patients respond well to oral appliances. Furthermore, the positional device improves the AHI. They are great alternatives for CPAP, especially if these patients have been non-compliant with CPAP.

Low Arousal or high arousal threshold – phenotype

Respiratory arousal threshold can be explained as the likelihood of waking up from the sleep stage. It is defined as 3 seconds of high-frequency activity on the electroencephalogram. In sleep studies, those measurements are taken by the PSG and scored as the respiratory arousal index. They were then measured as average hourly sleep arousal due to respiratory events/changes.

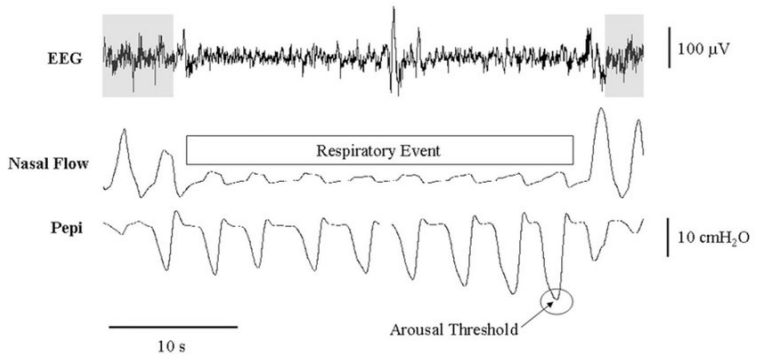


Figure 7: Arousal threshold (46)

Circa one-third of OSA patients are affected by **low** arousal threshold. Those sleep interruptions make the inflow of oxygen possible. They might be associated with rapid activation of upper airway motor neurons, accelerating pharyngeal dilator muscle activity resulting from the opening of the upper airway, and a hyper-ventilatory response. This response can lead to carbon dioxide levels below the chemical apnea threshold, which can lead to apnea. This hypocapnia can be crucial, impacting the activity of the upper airway dilators, decreasing the neural output, and therefore resulting in airway collapse. This can lead to ventilatory control de-stabilization, persisting apnea, and side effects.

How do we identify this phenotype? Clinical tests reveal specific clinical variables like AHI, nadir Spo2 (the lowest oxygen saturation value of the patient), and the frequency of hypopneas. Typical for this phenotype is an AHI < 30 events/hours, nadir Sp02 > 82.5%, and hypopneas> 58% frequency.

What is characteristic of these patients is that they wake up before the oxygen saturation gets too low. They tend to have a mild or moderate OSA. The frequency of hypopneas is higher than apnea. This phenotype can be targeted pharmacologically, ranging from sedatives to improve sleep quality and reduce OSA and its impacts on those patients' quality of life. Arousal threshold can be increased by up to 48% (range from 23%) with drugs like eszopiclone (Z-drug, non-benzo-diazepane) and trazodone (SSRI). This approach needs more studies and needs more backup (41).

Patients with **high** arousal do not wake up quickly, leading to a particular risk of acquiring arousal failure due to a neuro-malfunction caused by repetitive exposures to hypoxemia over an extended period. The threshold is high in patients with severe OSA, some even with CPAP

treatment. The correlation between chronic sleep fragmentation and intermittent hypoxemia is discussed. Thus, the etiology is not clear. This patient group is at an elevated risk of respiratory events when opioids are used – hence why diagnosis of those patients is essential. Neural output decrease resulting in upper airway collapsibility can be caused by opioid usage. If a patient has been diagnosed with OSA or is suspected, this has to be considered during the perioperative periods. On the other hand, sedatives and narcotics can prevent respiratory arrest and sudden unexpected deaths in this patient group, as they are in the state of "arousal-dependent survival."

No clear hallmarks are established – neither for low – for this patient group identification. Continuous postoperative monitoring with high-resolution pulse oximetry helps detect early desaturation impacted treatment and end-tidal carbon dioxide (via capnography)((41).

Capnography is the continuous analysis and recording of the CO2 concentration in respiratory gas (47).

Low Arousal Threshold	**High Arousal Threshold**
Higher propensity to wake up from sleep	Lower propensity to wake up from sleep
More likely to have mild-to-moderate OSA	Predominantly associated with severe OSA
Sedatives may be beneficial	Sedatives may evoke a respiratory arrest
Associated with less hypoxia due to reduced apnea duration	More prone to hypoxia due to prolonged apneas

Figure 7 Table: Comparison of low vs high threshold OSA

High loop gain

This patient group's phenotype is characterized by instability in ventilatory control, which promotes apnea. The cyclical breathing pattern causes this unstable ventilatory control due to sleep fragmentation (sleep/wakefulness cycles) (41).

Loop gain can be understood as the stability or instability in a system controlled by a feedback loop, which modulates the system's output. This control system is there to act on ventilatory disturbances. Loop gain (OSA specific) is the ratio of the ventilatory response to a ventilatory disturbance. For better understanding, if the magnitude of the reaction (hyperventilation) is greater or equal to the magnitude of the disturbance (apnea), the ratio will be ≥1, and the system will be classified with a high loop gain and instability. If the LG is <1, it is considered stable, with slight breathing fluctuation (41).

Systems with high LG tend to have an oversensitive ventilatory control system, which results in states of hypoxia and hypercapnia. How the high LG impacts the OSA severity is still unclear, but there are 2 potential mechanisms worth mentioning. Elevated LG could cause increased oscillations from the central ventilatory control in the brainstem, which controls the activity of upper airway dilator muscles. On the other hand, periods of low central respiratory drive have been associated with lower upper airway dilator muscle activity, thus high airway resistance and increased tendency to airway collapse(41).

Another possible mechanism is elevated LG, which can lead to an increase in the ventilatory response to arousal. The resulting hyperventilation with hypocapnia and decreased respiratory drive can result in central apnea, leading to a cycle of periodic breathing (unstable patterns) (41).

Treatment-wise, treatments that effectively reduce LG should be evaluated. Stabilization of the ventilation with oxygen has proven to be effective. It also reduces hypoxia and hypercapnia. Acetazolamide (carbonic anhydrase inhibitor) is an option, which causes metabolic acidosis and increases baseline ventilation.

One obstacle in those patients -likewise to high/low threshold patients – is the identification. It is challenging to measure loop gain, as the methods are not routine in current sleep laboratories and are challenging and experimental in clinical practice (41).

Poor muscle response to nerve stimuli

The decreased muscle tonus of the upper airway dilator muscles determines the OSA pathogenesis of this phenotype. It is essential to know that the genioglossus is one of the biggest extrinsic muscles of the tongue and the primary upper airway dilator muscle. The tongue is pulled forward due to the contraction of the genioglossus, and the upper airway dilates directly. It is sensitive to chemical input, like hypoxia or hypercapnia, increasing negative intra-pharyngeal pressure. In OSA patients, the electromyographic activity of the genioglossus is greater but, on the other hand, reduced during sleep onset. The hypothesis is that this is linked to an inadequate increase in neural drive to upper airway dilator muscles due to negative pharyngeal collapsing pressure caused by tidal breathing.

This muscle's muscle activity is reduced in both phasic (with eye movement) and tonic (without), rapid eye movement (REM) sleep compared if one compares it to nonrapid eye movement (NREM) in this patient group. Obstruction can increase in frequency and duration and is correlated with more severe hypoxemia during REM vs. NREM phases((41).

The genioglossal can be measured via an electromyogram. It is not part of the routine clinical tests for OSA patients but can be included in the PSG. The myogram result can show a progressive increase in the genioglossus muscle activity during an obstruction. During an obstruction where airflow is not sufficiently restored, there is a peak in arousal, and the patient tends to wake up (41).

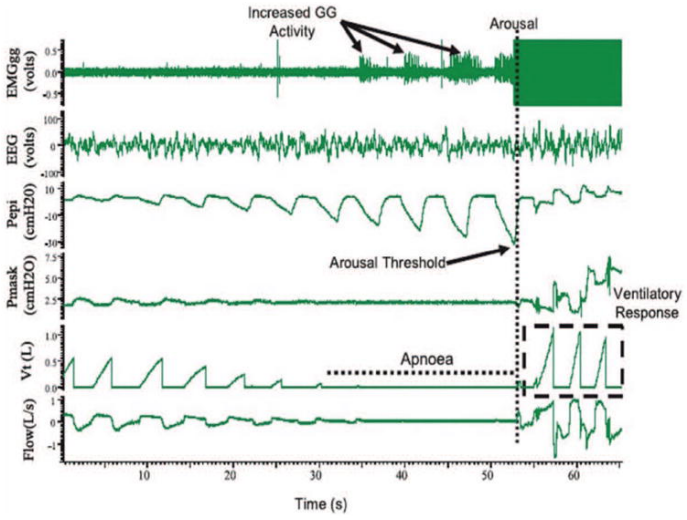


Figure 8: EMG spike during obstruction

Treatment-wise, this hyperactivity of the upper airway muscles has multiple options. One is with direct electrical stimulation of the hypoglossal nerve or the genioglossus muscle. This stimulation has effectively improved airway patency and reduced pharyngeal narrowing pressure (48).

Pharmacological treatment options include paroxetine (an SSRI) and mirtazapine (a tetracyclic antidepressant). These drugs can promote the dilatation of the upper airway muscles, but they have a limited impact on the consistent treatment of AHI (41).

Anatomy related

The anatomy-related phenotype linked to upper airway collapsibility is correlated to the presence or absence of this OSA type and its severity grade. In two-thirds of this subgroup, obesity, and craniofacial abnormalities have been measured.

The combination of structurally narrower and more fragile pharyngeal airways is often linked to severe OSA. Those patients also have a high critical closing pressure (PCrit).

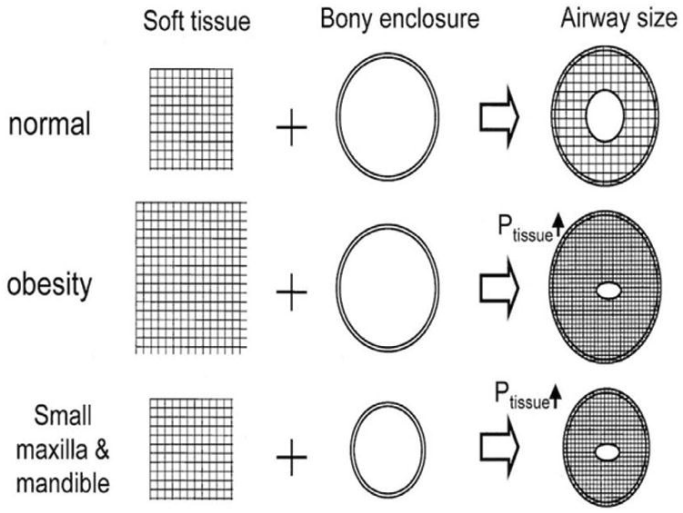


Figure 9: The role of obesity and upper airway enclosure and its impact on airway size(41)

Explanation: "Critical closing pressure (Pcrit) is the gold standard measure for the degree of pharyngeal airway collapsibility. Various physiological factors and treatments affect upper airway collapsibility. Recently, it has been shown that the baseline value of Pcrit is helpful in the upfront selection of therapy options." – **Critical to Know Pcrit: A Review on Pharyngeal Critical Closing Pressure in Obstructive Sleep Apnea((49)**

As mentioned, obesity is crucial in this phenotype, most notably in patients with high closing pressure at the retropalatal airway. Small maxilla and mandible are linked to high closing pressure in retropalatal and retroglossal areas. Those craniofacial abnormalities and a broader neck circumference strongly predict sleep-disordered breathing, and physicians should consider these features.

With a broader neck circumference, fat deposition in the para-pharyngeal area is crucial for developing sleep apnea, especially positional sleep apnea. Among men, the android pattern of fat deposition in the abdomen reduces lung volume and caudal traction of the pharynx, augmenting pharyngeal collapsibility. Symptoms can be relieved through lifestyle modifications or bariatric surgery.

Craniofacial morphology requires a multidisciplinary physician team to give the patient the corresponding treatment based on the phenotype (50). Craniofacial morphology includes inferior positioning of the hyoid bone, retro-positioning of the mandible, a smaller cranial base, increased craniocervical extension angle, and abnormal upper airway soft tissue morphology. These features increase the likelihood of developing OSA, as they are part of the pathogenesis.

Oral appliances like mandibular advancement or tongue retaining splints can be used to obtain symptom relief. For some, these are great alternatives to CPAP. More invasive procedures include uvulo-palato-pharyngoplasty (UPPP) and maxillomandibular advancement surgery(31).

15. Conclusion

Researching phenotypes and their appropriate treatment highlights how diverse OSA is. Ranging from obesity, anatomy-related, postmenopausal women, and PCOS – affecting all different groups of society. Thus, the treatment approach is still "One size fits all."

More research is required to simplify the patient identification process and provide cost-efficient and better-personalized treatment. The examination of the patient should start where risk factors end. Diagnosing the patient ensures the individual's safety and health journey. Practitioners need to triage these patients more efficiently to execute better care. Nevertheless, CPAP is, for a reason, the gold standard, as it does serve most phenotypes to a certain extent.

Investing in OSA awareness and research is essential, as many lifestyle modifications will make us a healthier society with a higher quality of life. More attention will make more significant financial resources accessible to improve treatment modalities and diagnostic possibilities.

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