Aus der Medizinischen Klinik und Poliklinik für Kardiologie und Angiologie Interdisziplinäres Schlafmedizinisches Zentrum der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Outcomes and underlying mechanisms of hypoglossal nerve stimulation in patients with obstructive sleep apnea

Ergebnisse und zugrundeliegende Mechanismen der Hypoglossusnerv-Stimulation bei Patienten mit obstruktiver Schlafapnoe

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

von

Yan Wang

Aus Shandong, China

Datum der Promotion: 30.11.2023

Table of Contents

List of Tables

List of Figures

List of Abbreviations

OSA	Obstructive sleep apnea
HNS	Hypoglossal nerve stimulation
TECSA	Treatment-emergent central sleep apnea
AASM	American Academy of sleep medicine
ICSD-3	International Classification of Diseases, Third Edition
GAD-7	General Anxiety Disorder-7
PHQ-9	Patient Health Questionnaire-9
ESS	Epworth Sleepiness Scale
CCI	Charlson comorbidity index
CHF	Congestive heart failure
HRV	Heart rate variability
Mets	Metabolic syndrome
GERD	Gastroesophageal reflux
LRD	Laryngopharyngeal reflux
BMI	Body mass index
PSG	Polysomnography
HSAT	Home sleep apnea test
CSB	Cheyne-Stokes breathing
OSA	Obstructive sleep apnea
CSA	Central sleep apnea
RERA	Respiratory effort-related arousal
BMI	Body mass index
ODI	Oxygen desaturation index
REM	Rapid eye movement
NREM	Non-rapid eye movement
CPAP	Continuous positive airway pressure
TST	Total sleep time

List of Abbreviations

HI	Hypopnea index
ODI	Oxygen desaturation index
OAI	Obstructive sleep apnea index
CAI	Central sleep apnea index
CMAI	Central and mixed sleep apnea index
WASO	Median wake time after sleep onset
PLMS	Periodic leg movement in sleep
CSR	Cheyne-Stokes respiration
MAD	Median apnea desaturation
PALM	Pcrit, Arousal threshold, Loop Gain, Muscle, Responsiveness
Pcrit	High Passive critical closing pressure
LAT	Low arousal threshold
LG	Loop gain
NHR	Neck circumference/ height ratio
WHR	Waist circumference/ height ratio
dSBQ	Derived STOP-Bang Questionnaire
CPAP	Continuous positive airway pressure
OMT	Orofacial myofunction therapy
UPPP	Uvulopalatopharyngoplasty
MMA	Maxillo-mandibular Advancement
OA	Oral appliance
DISE	Drug-induced Sleep Endoscopy
VOTE	Velum; Oropharynxlayeral wall; Tongue base; Epiglottis
CCC	Complete concentric collapse
PCO2	Pressure of carbon dioxide
AT	Apnea threshold
POSA	Positional obstructive sleep apnea (POSA)
MDA	Mean Disease Alleviation

Abstract

Since 2001, hypoglossal nerve stimulation (HNS) has been used worldwide to treat adult patients with obstructive sleep apnea (OSA). However, the long-term outcomes following HNS and the underlying mechanisms have not been comprehensively investigated, and no studies have reported a persistent development course of a severe complication treatment-emergent central sleep apnea (TECSA) following HNS. Moreover, the prognostic indicators associated with successful HNS therapy to treat OSA and the occurrence of TECSA remain controversial. Therefore, this retrospective study aimed to evaluate the long-term outcomes of HNS and explore the prognostic indicators and underlying mechanisms to improve clinical effectiveness and avoid complications following HNS.

Twenty-seven patients who underwent HNS implantation since 2016 were included in this study. Demographic, pre- and postoperative sleep study characteristics and device settings data were collected to evaluate the effects of HNS during evaluation. We compared the difference between the HNS success (n=13) and failure groups (n=14), and postoperative elevated central sleep apnea (n=3) and non-elevated CSA groups (n=24), respectively, and identified possible factors associated with the successful response to HNS and postoperative elevated CSA. Based on the persistent developmental course and phenotype of TECSA during evaluation, we hypothesized that an appropriate stimulation amplitude would resolve the development of TECSA and performed a titration study to help explore the underlying mechanisms.

During 3 years of evaluation after device activation, HNS reduced OSA events and improved oxygenation with a success rate of 50%. An elevated preoperative Epworth sleepiness scale (ESS) score was associated with treatment failure, while other baseline demographic characteristics and polysomnography data could not predict the effects of HNS. Regarding complications following HNS, three patients had elevated CSA (CAI ≥ 5), which was associated with an increased preoperative ESS and mixed sleep apnea index (MAI). The persistent course of TECSA as well as a strong negative correlation between CSA and OSA revealed that the underlying mechanisms might be multiple combinations of the upper airway effect and high loop gain. In conclusion, HNS is an effective and promising treatment method for patients with OSA who cannot tolerate continuous positive airway pressure therapy (CPAP). Precise patient

selection, individual titration configuration and scheduled follow-ups could help improve the effectiveness and reduce complications following HNS. In addition, a better understanding of the subtypes and endotypes of OSA should be translated into clinical use in the future to identify more predictive factors.

Zusammenfassung

Seit 2001 wird Hypoglossusnerv-Stimulation (HNS) weltweit zur Behandlung erwachsener Patienten mit obstruktiver Schlafapnoe (OSA) eingesetzt. Die Langzeitergebnisse nach HNS und die zugrundeliegenden Mechanismen sind jedoch nicht umfassend untersucht worden, und in keiner Studie wurde über einen anhaltenden Entwicklungsverlauf -Treatment-emergent central sleep apnea (TECSA)-nach HNS berichtet. Darüber hinaus sind die prognostischen Indikatoren für eine erfolgreiche HNS-Therapie zur Behandlung von OSA und das Auftreten von TECSA nach wie vor umstritten. Ziel dieser Studie war es daher, die Langzeitergebnisse der HNS zu prüfen und die prognostischen Indikatoren sowie die zugrunde liegenden Mechanismen zu untersuchen, um die klinische Wirksamkeit zu verbessern und Komplikationen nach der HNS zu vermeiden.

In diese Studie wurden 27 Patienten aufgenommen, die sich seit 2016 einer HNS-Implantation unterzogen. Präoperative demografische Merkmale, Merkmale der Schlafstudie von Polysomnografie /Polygrafie für zu Hause vor und nach der Implantation und Gerätekonfiguration wurden gesammelt, um die Wirkung von HNS während der Auswertung zu bewerten. Aufgrund des anhaltenden Entwicklungsverlaufs und Phänotyps von TECSA während der Auswertung stellten wir die Hypothese auf, dass eine geeignete Stimulationsamplitude die Entwicklung von TECSA auflösen würde, und führten eine Titrationsstudie durch, um die zugrundeliegenden Mechanismen zu erforschen.

Während der dreijährigen Auswertung nach der Aktivierung des Geräts konnte HNS die OSA-Ereignisse reduzieren und die Oxygenierung mit einer Erfolgsrate von 50% verbessern. Ein erhöhter präoperativer Epworth-Sleepiness-Scale (ESS) wert war mit einem Behandlungsversagen assoziiert, während andere Präoperative demografische Merkmale und Merkmale der Polysomnographie die Wirkung von HNS nicht vorhersagen konnten. Was die

Abstract

Komplikationen nach der HNS betrifft, so wiesen drei Patienten einen erhöhten CSA (CAI ≥ 5) auf, der mit einem erhöhten präoperativen ESS wert und einem gemischten Schlafapnoe-Index (MAI) verbunden war. Der anhaltende Verlauf von TECSA und eine starke negative Korrelation zwischen CSA und OSA zeigten, dass die zugrundeliegenden Mechanismen mehrere Kombinationen aus dem Effekt der oberen Atemwege und einer hohen Schleifenverstärkung sein könnten.

Zusammenfassend lässt sich sagen, dass HNS eine wirksame und vielversprechende Behandlungsmethode für Patienten mit OSA ist, die eine kontinuierliche positive Atemwegsdrucktherapie (CPAP) nicht vertragen. Eine genaue Patientenauswahl, eine individuelle Titrationskonfiguration und geplante Nachuntersuchungen könnten dazu beitragen, die Wirksamkeit zu verbessern und Komplikationen nach der HNS zu verringern. Darüber hinaus sollte ein besseres Verständnis der Subtypen und Endtypen der OSA in Zukunft in die klinische Praxis umgesetzt werden, um weitere prädiktive Faktoren zu ermitteln.

1. Introduction

1.1 Obstructive sleep apnea (OSA)

Obstructive sleep apnea (OSA) is a severe health problem that was gradually recognized only in the mid-20th century. It is a common disorder worldwide, affecting 10–17% of men and 3–9% of women;[1] however, although the prevalence of moderate-to-severe OSA is increasing, most cases of OSA are currently not diagnosed and treated. [2]

OSA is characterized by temporary obstruction and cessation of airflow in the upper airway, episodic hypoxemia, and hypercapnia.[2] According to the third edition of the International Classification of Diseases (ICSD-3), the diagnostic criteria for clinically significant OSA are an obstructive apnea-hypopnea index (AHI) ≥ 5 and one of the following symptoms (Table 1): complaints of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms; awakening with breath-holding, gasping or choking; habitual snoring, breathing stops or both during sleep; and diagnosis of systemic hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure (CHF), atrial fibrillation, or type 2 diabetes mellitus.[3]

Table 1 Diagnostic criteria for adult obstructive sleep apnea

(A and B) or C satisfy the criteria
(A) The presence of one or more of the following:
The patient complains of sleepiness, non-restorative sleep, fatigue, or insomnia symptoms
The patient wakes with breath-holding, gasping, or choking
The bed partner or other observer reports habitual snoring, breathing interruptions, or both during the patient's sleep
The patient has been diagnosed with hypertension, a mood disorder, cognitive dysfunction, coronary artery disease, stroke, CHF, atrial fibrillation, or type 2 diabetes mellitus
(B) PSG or OCST demonstrates:
Five or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopneas, or RERAs) per hour of sleep during a PSG or per hour of monitoring (OCST)
Or
(C) PSG or OCST demonstrates:
Fifteen or more predominantly obstructive respiratory events (apneas, hypopneas, or RERAs) per hour of sleep during a PSG or per hour of monitoring (OCST)

Table adapted from AASM, AMERICAN ACADEMY OF SLEEP MEDICINE (AASM). International classification of sleep disorders.[3]

1.2 Comorbidities in patients with OSA

1.2.1 Cardiovascular disease

OSA prevalence is as high as 40-80% in patients with hypertension, heart failure, coronary artery disease, atrial fibrillation, and stroke.[4] The underlying mechanisms include increased sympathetic nervous system activity, endothelial dysfunction, oxidative stress, and systemic inflammation.

1.2.1.1 Hypertension

Epidemiological studies have shown that OSA and hypertension are independently associated, with approximately 1/3 of all hypertensive patients having OSA, and 80% having refractory hypertension (uncontrolled hypertension despite using three or more antihypertensive drugs of different kinds, including a diuretic). The types of hypertension associated with OSA are diastolic, nocturnal and non-dipper hypertension,[5] which are often challenging to detect.[6,7] 24-hour ambulatory blood pressure monitoring is becoming the gold standard for detecting and diagnosing OSA and blood pressure abnormalities.[8]

1.2.1.2 Coronary artery disease and arrhythmias

Previous studies have shown that approximately 50% of patients with coronary artery disease have moderate-severe OSA, and the short- and long-term outcomes in OSA patients with coronary artery disease are poor. Moreover, as many as 50% of patients with OSA have nocturnal arrhythmias. OSA leads to changes in intrathoracic pressure, increased sympathetic nerve activity, changes in heart rate regulation, and ultimately arrhythmias. Patients with OSA almost always exhibit nocturnal cyclic heart rate and rhythm changes, mainly during apnea or hypoventilation. The primary manifestation is bradycardia during apnea, hypoventilation, or even cardiac arrest for a few seconds, while severe hypoxia may cause acute arrhythmias and apnea. Previous studies have demonstrated that CPAP therapy has a positive therapeutic effect on patients with OSA and arrhythmias.[9] Autonomic dysfunction may increase the incidence of arrhythmias by altering heart rate variability (HRV). HRV is considered a reliable and non-invasively detectable measure of autonomic modulation response and adaptation to endogenous and exogenous stimuli.[10] HRV measures may add a new dimension to help understanding of the interplay between cardiac and nervous system involvement in OSA. One study indicated that

HRV during wakefulness could provide additional information about cardiovascular physiology in patients with OSA.[11]

1.2.1.3 Heart failure (HF)

OSA affects more than 50% of patients with heart failure (HF) combined with systolic heart failure and patients with unchanged ejection fraction.[12] Gottlieb et al.[13] found that OSA increased the risk of new-onset HF in men, and that men with severe OSA (AHI > 30) were more likely to develop HF than men without OSA. OSA can induce changes in cardiac structure and function through various mechanisms—for example, an enhanced sympathetic nervous system activity and inflammatory response as well as increased cardiac preload and afterload.

1.2.1.4 Stroke

Stroke is the second leading cause of death worldwide and often has devastating consequences for affected individuals with chronic disabilities. Many studies have indicated that OSA is a risk factor for intracerebral hemorrhage (ICH). The most recent American Heart Association Stroke Guidelines also recommend screening for and treating OSA in this regard.[14,15]

1.2.2 Metabolic syndrome (MetS)

MetS is a group of metabolic abnormalities clustered in a single affected individual. These abnormalities include abdominal obesity, diabetes, impaired glucose metabolism, hyperlipidemia or abnormal lipid metabolism, and hypertension, which in turn is one of the precursors to atherosclerosis, type 2 diabetes, and cardiovascular disease.

MetS is strongly associated with OSA, and 40% of patients with OSA suffer from MetS.[16] A previous study found that the prevalence of lipid metabolism disorders was significantly higher in patients with OSA than in body mass index (BMI)-matched non-OSA patients. However, the relationship between abnormal glucose metabolism and OSA remains controversial. Numerous studies have reported independent positive associations between OSA and insulin resistance, glucose intolerance and diabetes mellitus, whereas some studies have found no such dangerous independent risk.[17]

1.2.3 Cognitive impairment and depression

OSA is an independent risk factor for depression and cognitive impairment/dementia. The possible underlying mechanisms include hypoperfusion, endothelial dysfunction, and neuroinflammation. Intermittent hypoxia of OSA may initiate or amplify the pathological processes that lead to the development or exacerbation of depressive symptoms and cognitive deficits.[18]

1.2.4 Reflux diseases

OSA and reflux diseases are highly prevalent in the population.[19] OSA is known to be highly associated with reflux diseases - both gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR). The primary symptoms of uncomplicated GERD are primarily heartburn (sometimes interpreted as chest pain), regurgitation, and nausea. Many patients with GERD are awakened from sleep due to heartburn. These diseases can also further affect voice and swallowing functions, resulting in an impaired quality of life. The current and most common explanation is that the respiratory drive increases due to airway obstruction during sleep, and the negative thoracic and intraesophageal pressures increase significantly during inspiration, resulting in an increase in the trans-diaphragmatic pressure on the esophageal sphincter and gastric regurgitation of contents into the esophagus and pharynx.[20] However, studies on GERD and LPR are limited, and the reports regarding the effects of treatment methods on patients with OSA remain conflicting.

1.2.5 Quality of life

The most significant subjective feeling reported by patients with OSA is daytime sleepiness, which could increase the risk of road traffic incidents by 2–7 times. In addition, poor concentration, memory loss, morning headache, and other symptoms seriously affect patients' quality of life.[21]

1.3 Diversity of OSA

OSA is a complicated and heterogeneous disease, and the AHI alone is insufficient to represent the wide variety of phenotypes and endotypes. In recent years, several methodologies [22] have been applied to better understand the diversity and inhomogeneity of the OSA patient populations. This could help to guide individual treatment methods, predict treatment outcomes, and identify indicators associated with outcomes following treatment.

1.3.1 Ethnic diversity

The prevalence of OSA differs across ethnic groups. Compared to Caucasians with OSA, Asians with OSA have a lower BMI. Even with the same severity of obesity, Asians are more likely to have a more severe degree of illness than Caucasians, which may be related to the craniofacial structure of Asians.[23] In 2012, a study [24] evaluated the differences in the upper airway, soft tissues and craniofacial structures between Asians from China and Europeans from Iceland with OSA using three-dimensional magnetic resonance imaging (MRI). Chinese patients were found to have a smaller retropalatal airway, more significant soft palate volume (in males), and a differently shaped mandible and maxilla with more bony restrictions.

In addition, studies have shown that the incidence of OSA is higher in Hispanic/Mexican Americans, while OSA prevalence in African Americans is not dissimilar to that in populations of European ancestry.[25] Geographical location and dietary habits also deserve further consideration in this regard.

1.3.2 Gender difference

Now, most studies have shown that the majority of patients with OSA are men (male; female ratio, 2:1). Moreover, the mean AHI was reported to be higher in men than in women. [26] In 2013, a study found that the prevalence of moderate-to-severe OSA among 30–49 year-old men and women was 10% and 3%, and that among 50–70 year-old men and women it was 17% and 9%, respectively.[27] However, a recent study has reported that OSA is highly prevalent in women. The prevalence of OSA remains underdiagnosed in women, partly due to sociocultural factors and differences in presenting symptoms and polysomnographic findings.[28]

1.3.3 Age difference

A number of studies have shown that older male patients are at high risk of developing OSA. In 2017, a large sample study in the United States found the prevalence of OSA in the overall population ranges from 9% to 38%, with a higher prevalence in men. Furthermore, it increased with age, being up to 90% in men and 78% in women in some elderly populations. The prevalence of AHI at ≥15 events/hour ranged from 6% to 17% in the general adult population and increased to 49% in the older age group. The prevalence of OSA is also higher in obese men and women.[29]

Based on a home sleep apnea test (HSAT), the prevalence of OSA (AHI ≥ 30) in those aged ≥ 80 years was found to be as high as 70%, and 19% of them, there were cases of severe OSA (AHI ≥ 30). In summary, old age and sex are risk factors for OSA.

1.3.4 Positional OSA (POSA)

The definition of POSA is an AHI reduction of ≥ 50% from a supine to a non-supine position. The prevalence of POSA in general or sleep clinic populations has been reported to be > 50% in investigated subjects with considerable position dependency. Therefore, POSA constitutes the dominant OSA phenotype in adults, and greater variability in the symptom burden may occur.[30]

1.3.5 Phenotypic subtypes of OSA

The main clinical symptoms of OSA are nocturnal snoring, apnea, recurrent nocturnal awakenings, open-mouth breathing, morning headache, dry mouth, and daytime sleepiness.[31] As Figure 1 shows, using cluster analysis, one study has classified OSA patients into four clinical subgroups by cluster analysis—subtype 1: young, overweight OSA patients with the shortest duration of apnea and the “classic” symptoms (e.g., sleepiness, drowsy driving); subtype 2: older, overweight, predominantly male with minimal to moderate symptom burden, frequent comorbidities and severe OSA with severe hypoxia; subtype 3: middle age, mildly obese, predominantly female, with symptoms of insomnia; subtype 4 was youngest, non-obese, and predominantly male with primarily upper airway symptoms. Clinical feature-based OSA phenotypes with significant prognostic and treatment implications have been identified (e.g., excessive daytime sleepiness OSA), but many current categorizations lack association with meaningful outcomes.

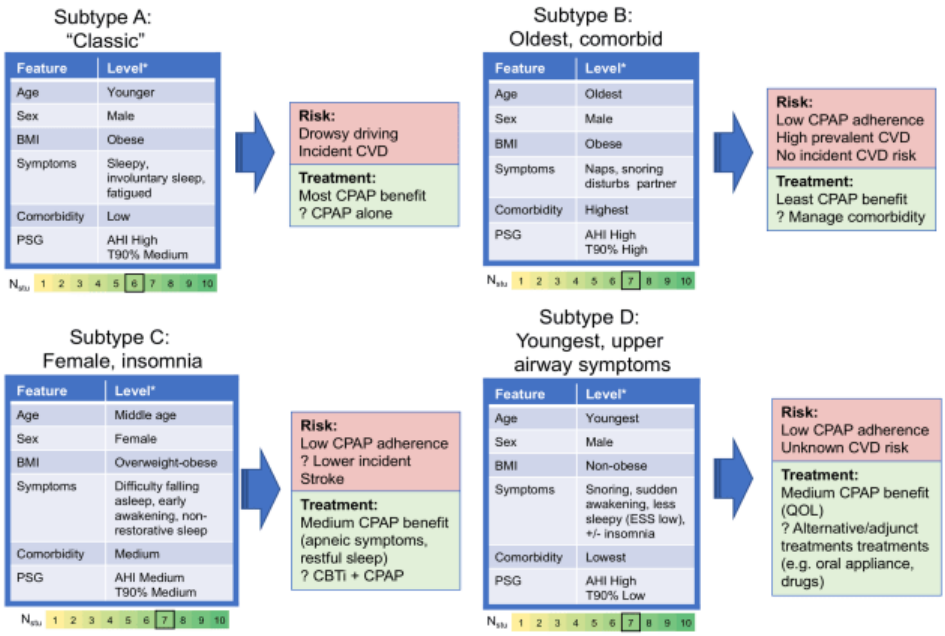


Figure 1: Four subtypes of OSA.

There are four subtypes of OSA based on relative differences between clusters in age, BMI, sex, symptoms and comorbidities followed by OSA physiology as assessed by polysomnography, and their respective risks and treatment method. Figure taken from Zinchuk et al., 2020.[31]

1.4 Mechanisms of OSA

1.4.1 Anatomical factors

Anatomical factors affect the external framework and internal volume of the airways, including the location and three-dimensional size of the craniomaxillofacial skeleton and the volume size of the soft tissue structures. Both craniomaxillofacial skeletal factors and soft tissue factors are genetically related.[32] Bone factors refer to various congenital or acquired craniofacial developmental malformations resulting in a narrow maxillofacial framework structure, manifesting as underdevelopment or recession of the upper and lower jaws. Craniofacial phenotype could be measured by magnetic resonance imaging (MRI), craniofacial cone beam computed tomography (CBCT) and three-dimensional analysis.[33,34] On the other hand, soft tissue factors are related to the tongue, soft palate, and lateral pharyngeal wall tissues (Figure 2). Previous studies have indicated that obesity is one of the independent risk factors for OSA and this is directly related to fat deposition - mainly central abdominal obesity, and pharyngeal- and lingual fat deposition. Abdominal fat deposition can affect respiratory motility and lung volume changes, as well as the regulatory response of the respiratory center, that is, it can inhibit the central control of airway

compliance through loop-gain feedback. Pharyngeal fat deposition can directly alter the volume size of the upper airway, which is most directly measured based on neck circumference. As a fast and invasive imaging examination, tongue fat deposition also can be measured by ultrasound(US).[35]

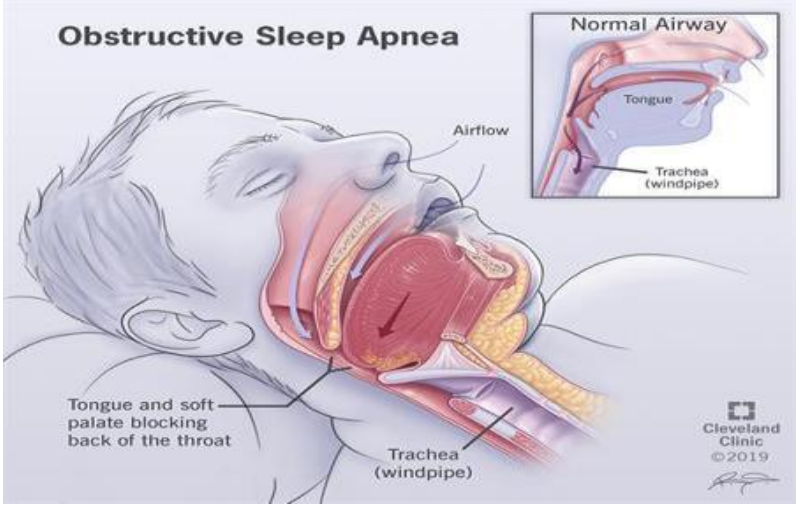


Figure 2: The anatomical soft tissue factors for OSA patients.

The upper airway obstruction improved with the tongue and soft palate blocking the back of the throat while sleeping. Compared with normal airways, the upper airway obstruction improved. Figure reproduced from Cleveland Clinic. (https://my.clevelandclinic.org/health/diseases/8718-sleep-apnea)

1.4.2 OSA endotype (PALM theory)

Clearly, at least four phenotypic mechanisms for OSA are illustrated. 30% of patients predominantly experience anatomical problems, whereas 70% of OSA patients have at least one non-anatomical phenotype as well. A narrow or collapsible upper airway is the primary cause, but not the most critical. Non-anatomical factors, including a high loop gain, a low respiratory arousal threshold, and impairment of pharyngeal dilator muscle control and function during sleep, are crucial determinants of OSA in many people. To categorize OSA patients according to the level of upper airway anatomy impairment, and the non-anatomical phenotypes, the passive critical closing pressure (Pcrit), arousal threshold, loop Gain and muscle responsiveness (PALM) scale were proposd, as shown in Figure 3.[35,36,37]

- *High Pcrit*

Pcrit is the gold standard parameter for assessing upper airway collapsibility during sleep. Clinical studies have found that the Pcrit is higher in individuals with OSA than in those without OSA (Pcrit > +2 cmH_2O (1 cmH_2O = 0.098 kPa): severe anatomical abnormalities, -2 $cmH_2O \leq$ Pcrit $\leq$

+2 cmH_2O: moderate abnormalities; and Pcrit < -2 cmH_2O: mild abnormalities). Although OSA severity increases with increasing Pcrit, the AHI can differ in some patients with the same Pcrit, suggesting the involvement of non-anatomical factors in the development of OSA.

- *Arousal threshold*

Arousal is essential for protecting patients with OSA and was once thought to be the only mechanism for aborting respiratory events in OSA. However, persistent arousals may contribute to the development of OSA by causing sleep fragmentation, perpetuating blood gas disturbances, promoting periodic breathing, and affecting the maintenance of sleep homeostasis. Although there is significant variability in the magnitude of intrathoracic negative pressure in different individuals and sleep periods, the magnitude of negative pressure required for arousal in the same patient is relatively stable. Therefore, the gold standard for determining the arousal threshold is the measured value of epigastric or esophageal pressure when cortical awakening occurs in patients, with -15 cmH2O being the cut-off value of the arousal threshold. Approximately 30–50% of OSA patients have a low arousal threshold (LAT). Possible mechanisms of LAT involvement in OSA include: LAT leading to frequent arousals, sleep fragmentation, and sleep instability, thus preventing patients from entering slow-wave sleep; premature arousal limiting the accumulation of the chemical stimuli required for pharyngeal muscle contraction and thus airway opening to restore airflow; and arousal leading to ventilatory compensation, resulting in significant CO_2 expulsion, which in turn reduces respiratory drive and can cause apnea and central respiratory instability. In 2014, Edwards et al.[38] indicated a clinical predictor of respiratory arousal threshold in OSA patients, i.e. the LAT score + (AHI < 30 events/h)/(SpO_2 nadir > 82.5%) + (F hypopneas > 58.3%)- a score ≥ 2 means Low ArTH, with a sensitivity of 80.4% and specificity of 88.0% (positive predictive value, 87%; negative predictive value: 81%). Thus, it could play an essential role as an easy to use indicator for clinical physicians to assess LAT.

- *Loop gain (LG)*

Loop gain is a cybernetic term used to describe the stability and sensitivity of an individual control system. The loop gain components of respiratory regulation include peripheral and central respiratory chemoreceptors, central respiratory regulation of CO_2 transport in the blood, and the

effector organ (the lungs). Respiratory control instability (high loop gain) can lead to significant fluctuations in ventilation; ventilation disturbances lead to changes in the levels of CO_2, which is the most vital respiratory driver during sleep, and an organism's reactivity to CO_2 level changes is the essence of loop gain. A high loop gain implies instability of the respiratory control system, and affected patients can have significant ventilatory compensation for small changes in circulating CO_2 levels and expel more CO_2 than normal. Eckert et al. showed that approximately 36% of patients had high loop gain. Possible mechanisms of OSA due to high loop gain include: (1) increase in CO_2 due to hypoventilation leads to the development of a rapid and large negative inspiratory pressure, which in turn leads to upper airway collapse; (2) as mentioned earlier, the upper airway muscles are innervated by neuronal fibers from the respiratory center, and high loop gain-induced hyperventilation expels more CO_2, reducing the central ventilatory drive and thus pharyngeal muscle activity; and (3) high loop gain can lead to a decrease in pharyngeal muscle activity in response to small changes in circulating CO_2 levels. (4) A high loop gain can lead to a mismatch between the central respiratory drive to the respiratory muscles and the drive of the upper airway dilator muscles, that is, the activity of the upper airway dilator muscles becomes insufficient to counteract the negative suction generated by the respiratory muscles during inspiration, leading to upper airway narrowing and collapse.

- *Muscle responsiveness*

Upper airway muscle reactivity refers to the influence of respiratory stimuli such as hypoxia, high CO_2, and changes in pharyngeal pressure on pharyngeal muscle activity during sleep. It can be assessed by plotting the relationship between minimum pharyngeal pressure and upper airway muscle electromyography.[36] The chin-lingual muscle is the most important muscle for opening the pharyngeal cavity, and is neurologically driven by pattern generator neurons from the respiratory center of the brainstem. Sleep strongly affects the neural drive of the chin-lingual muscle, but the effect is not a simple inhibition of activity, as initially thought, but varies with increasing respiratory stimuli and changes in sleep phases. The contractility of the chin-lingual muscle decreases rapidly at the onset of sleep, but glossopharyngeal nerve activity increases with CO_2 retention and negative pharyngeal pressure; there is a significant sleep phase-

dependent change in chin-lingual muscle activity, which gradually increases from the REM and N2 phases to the slow-wave sleep phase. Thus, the pathogenesis of OSA involves an interaction between sleep-phase-dependent neural drive and impaired upper airway anatomy.[39]

In conclusion, each phenotype is a potential therapeutic target for OSA patients and could be used to develop targeted non-CPAP therapies.[36] Therefore, more studies should be conducted to explore the relationships between the OSA endotype and the effects of treatment methods, and then translate them into clinical use.

It has been proven that non-CPAP therapies (such as mandibular advancement splints, upper airway surgery, weight loss, positional therapy, and so on) can improve Pcrit in patients with OSA. Patients with a high loop gain or a low respiratory arousal threshold are less likely to respond to mandibular advancement or CPAP therapy.[37] In conclusion, each phenotype is a potential therapeutic target for OSA patients and could be identified to develop targeted non-CPAP therapies for OSA patients, and more studies should be conducted to explore the relationship between OSA endotype and effects of treatment methods, then translate them into clinical use.

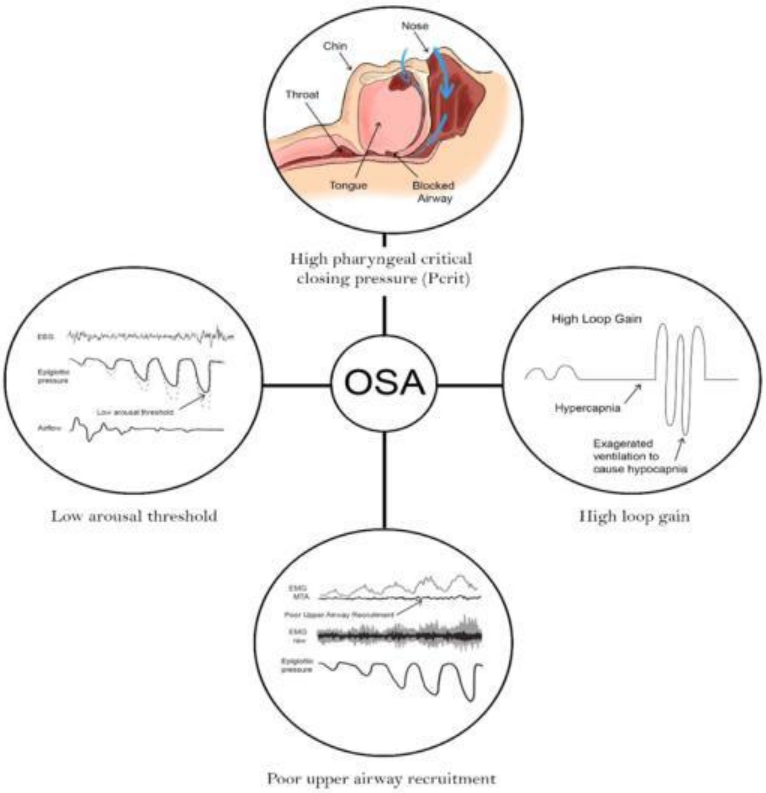


Figure 3: The Pcrit, Arousal threshold, Loop Gain and Muscle responsiveness (PALM) of OSA.

Figure reproduced from Carberry et al., 2019.[37]

1.5 Diagnostic methods for OSA

1.5.1 PSG/HSATs

Full-night in-laboratory PSG is the gold standard method for diagnosing OSA, with data regarding various parameters collected based on electroencephalograms, electrooculograms, submental and anterior tibialis electromyograms, and electrocardiograms. The following are recorded:

- Snoring (detected by a laryngeal microphone placed to the neck)
- Airflow (measured by a nasal pressure transducer and an oral thermistor placed in front of the mouth)
- Arterial oxygen saturation (assessed by a finger pulse oximeter)
- Respiratory movements (detected by thoracic and abdominal sensors)

All variables are recorded using a digital polygraph system. Sleep stages and respiratory events are scored using standard criteria according to the AASM manual.[3]

However, due to the high cost and long waiting times for PSG, the most recent AASM statement indicates that an HSAT that can record at least oxygen saturation (SaO2), airflow, breathing effort, and pulse rate could be an alternative to PSG for OSA diagnosis in adults with symptoms that indicate an increased risk of moderate-to-severe OSA.

1.5.2 Questionnaires

Cheaper and more convenient methods of diagnosing OSA include questionnaires such as the Berlin questionnaire, STOP-Bang questionnaires (snoring, tiredness, observed apnea, blood pressure, BMI, age, neck circumference, and gender), and NoSAS questionnaire (neck circumference, obesity, snoring, age, and sex). A systematic review by Abrishami et al.[40] in 2010 showed that the SBQ was one of the best predictors of moderate-to-severe OSA by displaying the highest sensitivity and methodological validity compared to other questionnaires. It is also a relatively quick procedure and can inform health professionals of OSA severity, which is especially important due to the high frequency of undiagnosed people with OSA. The main issue with the SBQ is that it lacks high specificity, especially for mild OSA diagnoses. Although it has been proposed that efficacy could be improved by combining the SBQ with other diagnostic tools such as the oxygen desaturation index (ODI), this needs further validation.

1.5.3 Other methods

Anthropometric measurements, including height, weight, neck circumference, and waist circumference, could be easy to measure, quick identification tools for large populations. One of the most recent study [41] demonstrated that the neck circumference/height ratio (NHR) is a viable obstructive sleep apnea screening tool, comparable to the derived STOP-Bang Questionnaire (dSBQ) and independent of witnessed apneas and BMI, that can be used for patients with various body types.

Recently, some commercial portable devices have been developed based on electrocardiogram cardiopulmonary coupling and peripheral arterial tone could also prove to be fast and reliable tools for identifying OSA patients.[42,43]

1.6 Treatment methods

1.6.1 Non-surgical treatment methods

1.6.1.1 Life-style modifications

Overweight or obesity are independent risk factors for OSA. However, although weight loss through exercise and dietary interventions results in long-term improvements in OSA parameters, it is insufficient to normalize them completely. Clinical findings have shown that weight loss is more effective in patients with OSA who have underdeveloped craniofacial and narrow structural frames.[44,45] Furthermore, patients with POSA are first treated with postural therapy, and the more significant the difference between lateral AHI and supine AHI, the better the therapy outcomes.[46]

1.6.1.2 Orofacial myofunctional therapy (OMT)

Increased upper airway muscle compliance during sleep is an essential factor in OSA treatment. Theoretically, improving muscle tone through specific movement exercises is a conservative method to reduce the severity of OSA. Myofunctional therapy consists of a combination of oropharyngeal exercises - i.e., mouth and throat exercises. These combinations typically include isotonic and isometric exercises involving several muscles and areas of the mouth, pharynx, and upper respiratory tract to work on speaking, breathing, blowing, sucking, chewing, and swallowing.[47] Camacho et al.[48] summarized nine studies on upper airway muscle exercises in

adults and found that AHI could be reduced from 24.5 to 14.3 times/h, and the patient's subjective symptoms (ESS score) decreased simultaneously.

1.6.1.3 Continuous positive airway pressure (CPAP)

Since 1981, continuous positive airway pressure (CPAP), which inflates the upper airway with air to maintain upper airway patency, has been the standard first-line treatment for patients with OSA, especially for moderate-to-severe OSA. Its clinical suitability and efficacy are well established, and its clinical value has further been confirmed in several recent well-designed clinical trials that have reported improvement of subjective symptoms, such as: sleepiness, quality of life, and neurocognitive function; reduction of cardiovascular diseases such as hypertension; reversal of MetS; and reduced mortality.[49]

However, 30–50% of CPAP users fail to meet the minimum recommended use time and achieve reasonable adherence to long-term treatment, prompting them to search for alternative treatments, including the use of mandibular advancement devices and upper airway surgery. Several improvements have been made in CPAP technology to improve patient adherence and compliance, including diversification of ventilation modes, tubing humidification, and improvements related to the comfort of the mask closure.[50] Therefore, improving compliance with CPAP treatment remains the focus of future research.

1.6.1.4 Oral appliances (OAs)

Oral orthodontic appliances are one of the most common tools used for treating OSA. The mechanism of OAs involves making morphological changes to increase upper airway volume and eliminate obstruction of the upper airway, especially in the oropharynx.[51] OAs can protract the mandible forward and elevate the soft palate. In addition, traction of the soft tongue palate moves forward passively to increase the volume of the palatopharynx and linguopharynx. Doff et al. compared the treatment effects of OA and CPAP use and found that although CPAP is more advantageous in reducing disease severity, the objective efficiency and subjective symptom relief it resulted in were not significantly different from those of OAs. OAs can be effective alternative treatment options for patients with mild-to-moderate OSA and in cases of poor CPAP tolerance by patients with severe OSA. Nevertheless, although OAs can also be associated with poor long-

term compliance in some patients, they can be used for mild-to-moderate OSA because of their non-invasive nature and ease of wear. Therefore, the advantages of non-invasive and easy-to-wear OAs in the treatment of patients with mild-to-moderate OSA are of great value.[52]

1.6.2 Surgical methods

1.6.2.1 Soft palate surgery

Tonsillectomy is the first-choice surgical treatment method for patients with OSA and tonsil hypertrophy, and outcomes following tonsillectomy have proven to be favorable during long-term evaluation.[53] Uvulopalatopharyngoplasty (UPPP) and its modified operations are most commonly used to treat pharyngeal obstructions at present, which consists of trimming and reorienting of the posterior and anterior lateral pharyngeal pillars, excision of the uvula and posterior soft palate, and tonsillectomy- resulting in a small pharyngeal cavity.[54]

1.6.2.2 Tongue base surgery

Tongue base surgery includes genioglossus advancement and hyoid suspension, hyoid suspension, and above all, procedures on the base of the tongue (lingual muscle) or tonsilla lingualis. These are indicated for patients whose upper airway obstruction is in the posterior epiglottis region.[55] The anterior chin-lingual advancement improves muscle tone by changing the attachment point of the chin-lingual muscle in the mandible, whereas hyoid suspension changes the tension of the attached hyoid soft tissues by suspending the hyoid bone; These procedures usually require a combination of UPPP and indicate safe, comparable effects.[56]

1.6.2.3 Maxillo-mandibular advancement (MMA)

MMA expands the airway volume and improves muscle tone by osteotomizing the jaws forward and pulling the soft tissues attached to the jaws.[57] A meta-analysis by Camacho et al.[58] demonstrated that patients with OSA treated with MMA maintained improvements in AHI, sleepiness, and lowest oxygen saturation in the long term. MMA is suitable for patients with severe jaw deformity, CPAP failure, and that have undergone other ineffective procedures. Moreover, it turns out to be capable of alleviating the unfavorable complete concentric collapse (CCC) phenotype under drug-induced sleep endoscopy (DISE).

1.6.2.4 Nasal surgery

This usually refers to septoplasty, wherein, by reducing nasal resistance, the negative intraluminal pressure in the inspiratory phase of the airway is reduced, improving the posterior lingual area narrowing caused by open-mouth breathing and improving the tone of the oropharyngeal muscles. Nasal surgery cannot be recommended as exclusive therapy for OSA treatment, but can be used to treat nasal obstruction and increase adherence to MAD or PAP therapy.[59,60]

1.6.2.5 Tracheotomy

Currently, the use of tracheotomy for OSA treatment is extremely limited, as patient acceptance is low owing to cumbersome postoperative care and undesirable cosmetic effects. Camacho et al.[61] pointed out that this procedure is only appropriate in emergency cases and for patients who refuse or do not tolerate conventional treatments such as CPAP and surgery, and that it should not be used as a routine treatment option.[62]

1.6.2.6 Upper airway stimulation (UAS)

Traditional upper airway surgery modifies the bony and soft tissue surrounding the airway to treat OSA. UAS [63] attempts to treat upper airway obstruction and OSA by rhythmic stimulation of the hypoglossal nerve, and represents a new treatment option for eligible patients to address this neurofeedback loop dysfunction. The sublingual nerve stimulator includes an implantable pacemaker-sized pulse generator that senses chest wall motion during sleep and contracts the genioglossal muscle by stimulating the sublingual nerve. The lingual contraction gently protrudes the tongue, widening the airway at the posterior lingual and posterior palatal levels. Clinical outcomes showed that UAS could effectively improve objective and subjective self-reported sleep and quality of life outcomes.[64]

Moreover, bariatric surgery and multi-level surgery are promising in treating OSA.[65]

1.7 Hypoglossal nerve stimulation (HNS)

1.7.1 HNS techniques

After animal studies in the 1970s, the first human trial on reducing upper airway resistance by transcutaneous electrical stimulation of the genioglossus was reported in 1989. A separate stimulation of the protruding and retracting muscles was realized in 1995 by fine wire electrodes

placed into the tongue transoral.[66] In recent years, several companies have developed hypoglossal stimulation devices for implantation in patients with OSA. Initially, devices that used unilateral stimulation of the hypoglossal nerve were developed. In 2014, a unilateral respiratory frequency-controlled hypoglossal stimulation device finally received U.S. Food and Drug Administration (FDA) approval after a successful phase III trial. Since then, the Apnex Medical Inc. device (no longer on the market), Inspire Medical System (Maple Grove, MN, USA)[67] and LivaNova System (formerly ImThera San Diego, CA, USA)[68] have been induced. As a new development, the Nyxoah Genio System (Mont-Saint-Guibert, Belgium)[69] for bilateral breath rate-independent stimulation of the hypoglossal nerve has been added to these approaches. The difference between device and surgical procedures is shown in Figure 4 and Table 2.

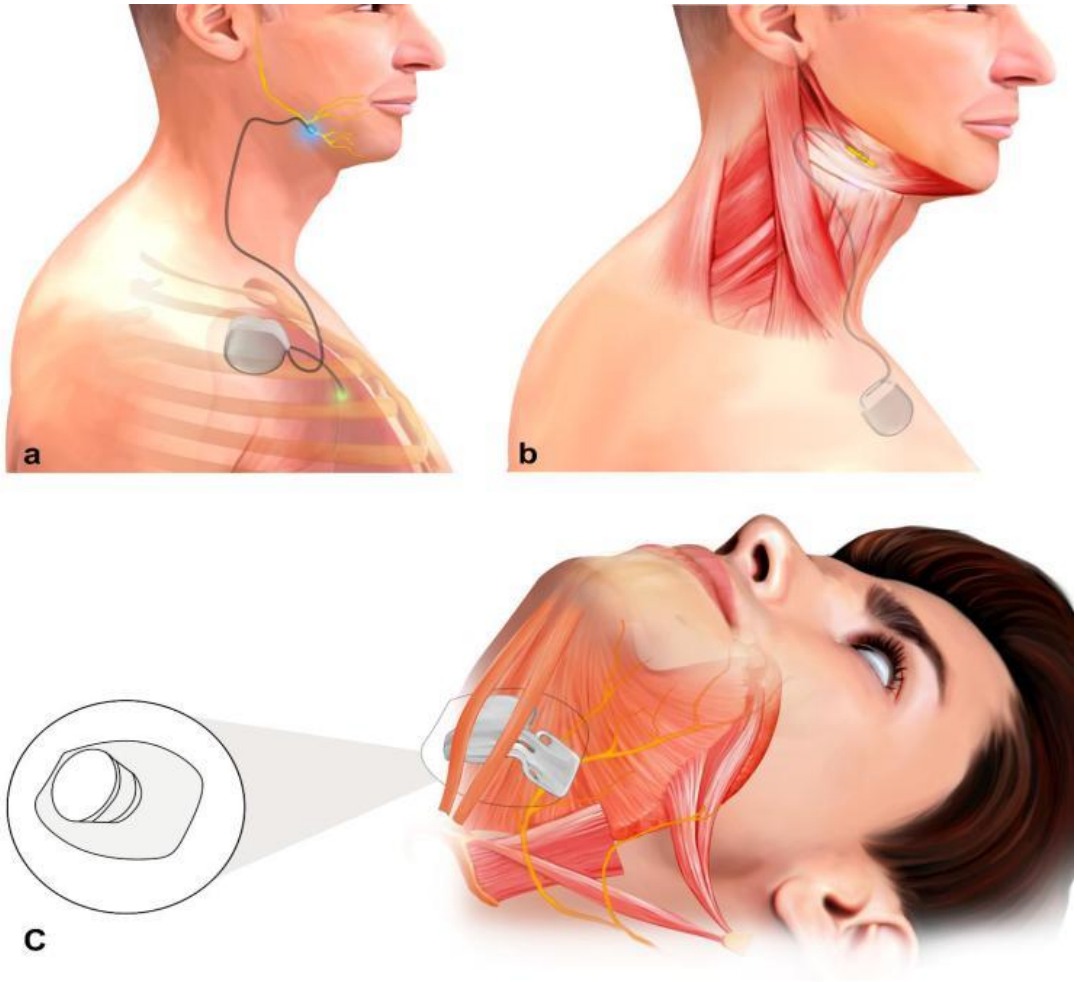


Figure 4: Schematic illustration of different stimulator concepts

a) unilateral distal HNS - breathing cycle controlled (simplified according to Strollo et al. 2015[67] and Kent et al. 2020[70]); b) unilateral proximal HNS – non-breathing cycle controlled (simplified according to Friedmann et al. 2016[68]); c) bilateral distal HNS – non-breathing cycle controlled (simplified according to Eastwood et al. 2020[69]).

Table 2 Comparison of three different HNS stimulators

	Unilateral (Inspire Medical System)	Bilateral (Nyxoah Genio System)	Targeted (LivaNova System)
Placement of stimulation electrode	Distal and medical branches of HN	Distal and medical branches of HN	The main trunk of HN
Implantable device	3 pieces (IPG, stimulation and sensor electrode)	1 piece (stimulation electrode	2 pieces (IPG, stimulation electrode)
MRI	Under certain requirements up to 1.5 Tesla	whole body till 3.0 Tesla	Not compatible
Breathing cycle dependent	Yes	Duty cycle dependent	No
Programming	Telemetry	External programming	Telemetry

1.7.2 Pre-operative patient selection

1.7.2.1 Baseline clinical characteristics

The effect of sublingual nerve stimulation is primarily associated with patient choice. HGS is utilized mainly for individuals with moderate-to-severe OSA who cannot tolerate CPAP treatment. Indicators such as female sex, younger age and low BMI could predict better response rates to HNS. Patel et al.[71] found that younger patients with OSA responded to HNS more effectively than older patients. Thaler et al.[72] found a favorable correlation between female sex and success rate in the ADHERE-Registry cohort. Furthermore, previous studies have reported promising response rates at a BMI ≤ 32 kg/m^2 cut-off, whereas recent data from multicenter studies demonstrated good efficacy even at higher cut-off values of up to 35 kg/m^2.[73,74] Preoperative symptoms assessed by ESS questionnaires and Functional Outcomes of Sleep Questionnaire (FOSQ) were also associated with the success rate of HNS therapy.[75] In addition, concomitant diseases that can affect therapy should be considered when establishing a treatment plan. For example, insomnia disorders and neuromuscular diseases are usually contraindications to stimulation therapy, and the MRI capability of the HNS device should be clarified with the patient in advance.

1.7.2.2 Sleep study (PSG/HSAT)

Initially, patients with OSA are diagnosed by a sleep medicine specialist based on laboratory PSG results. During treatments involving standard PAP therapy or other methods, a sleep study is scheduled at least once a year to monitor the changes and adjust the treatment parameters. If

the treatment fails to treat OSA or is associated with severe complications and low adherence, patients are referred to a head and neck surgeon to be counseled for HNS. Before implantation, diagnostic baseline PSG should be performed again to verify that the patient meets the HNS indication criteria. Reports regarding the association between the HNS success rate and baseline AHI have been contradictory. Evans et al. and others indicated that increased surgical success was associated with a higher preoperative AHI, while Thaler et al.[76] showed that a higher baseline AHI was a negative predictor of success when using other definitions of success, and a lower ODI might predict and distinguish responders for HNS as well.

At present, the value of the specific indicators to predict the treatment outcomes of HNS in sleep studies remains unclear, and there is no study on other factors such as arousal and sleep efficiency. It is an exciting and promising field in the future.

1.7.2.3 Clinical radiographic predictors

Currently, there are few studies on the anatomical and radiological factors that impact HNS treatment. Upper airway collapse can be examined using lateral cephalometry/lateral neck radiography, computed tomography (CT), and ultrasound. Schwab et al.[77] used awake CT to identify anatomical differences between HNS responders and non-responders and indicated that the volume of the soft palate was negatively associated with the success rate of HNS. Similar findings were found by Lee et al.[78], who studied lateral cephalograms of patients with an implanted HNS device. Most recently, ultrasound (US) has been used to identify the morphology of the pharynx, tongue, and base of the tongue, and dynamically detect pharynx obstruction as a quick and non-invasive imaging technique for OSA patients.[79,80,81,81,82]

Further research and clinical investigations are required to establish objective techniques for the anatomical assessment and dynamic assessment of patient morphology with regard to the planned or completed implantation of an HNS device. Ongoing efforts to increase the MRI capabilities of present HNS systems and implement ultrasonic examination techniques will be beneficial in this regard.

1.7.2.4 Drug-Induced sleep endoscopy (DISE)

DISE can be used to simulate upper airway collapse during sleep induced by drugs such as dexmedetomidine, midazolam, or propofol – and then to then determine the location and pattern of upper airway obstruction as well as help predict the effects of HNS. Vanderveken et al. [84] demonstrated that complete concentric collapse (CCC) at the velopharynx is predictive of increased non-responder rate in patients undergoing unilateral distal hypoglossal nerve stimulator implantation, although the study sample size was small. To ensure a therapeutic effect, the velum's complete concentric collapse (CCC) [85] is excluded from HNS implantation. However, the value of CCC in terms of predicting the failure rate of DISE is unclear.[86] In 2021, one patient with CCC who underwent DISE was successfully treated using bilateral HNS.[87] Furthermore, the role of DISE in the counseling of HNS candidates extends beyond solely excluding CCCs related to the velum. A large multicenter cohort study [88] indicated that tongue obstruction during DISE was associated with a better response to HNS. In contrast, patients with oropharyngeal lateral wall collapse and epiglottis-related obstructions had the lowest response rates.

In conclusion, the use of DISE as a patient selection tool for HNS therapy to treat OSA and the predictive value of DISE to assess findings associated with outcomes are both promising, but further studies are still needed.

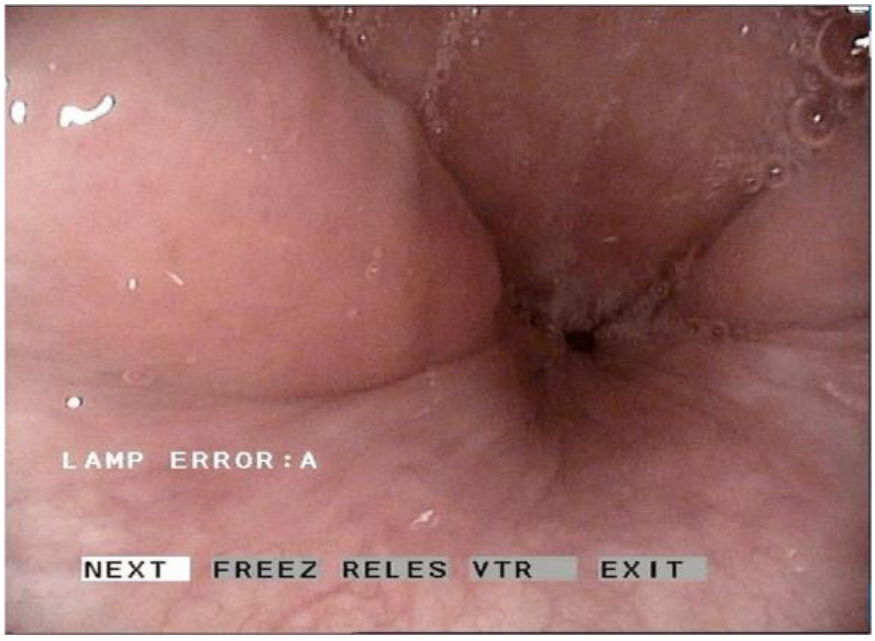


Figure 5: Complete circumferential collapse at velum (CCC) under DISE

1.7.2.5 OSA phenotyping

In addition to anatomical factors, it is now understood that non-anatomical phenotypic mechanisms are crucial determinants in OSA development. The PALM scale was proposed to categorize patients with OSA according to the degree of upper airway anatomy impairment and non-anatomical phenotypes. Eckert et al. pointed out that each phenotype could be a potential therapeutic target for patients with OSA and could be used to select or develop targeted non-CPAP therapies.[89,90]

An analysis of the STAR study cohort data by de Beeck et al.[91] showed no differences between responders and non-responders to HNS therapy in terms of basal PSG measures, except for the arousal index. A more detailed analysis of PSG data revealed that mechanistic PALM factors related to non-anatomical deficits influenced the likelihood of treatment success.[92] A higher arousal threshold was associated with better treatment efficacy, whereas higher loop gain was associated with lower HNS efficacy. They also showed that patients with higher muscle compensation had better HNS therapy outcomes and that treatment efficacy was low for patients with low pharyngeal collapsibility, contradicting the assumption that patients with low muscle responsiveness benefit especially from stimulation therapy. However, the authors pointed out that the cohort included too few patients with severe collapsibility to draw definitive conclusions. Lee et al. demonstrated that patients requiring lower PAP pressures (< 8 cm H_2O) to treat OSA had a better outcome with HNS therapy.

Thus, patient selection by identifying pathophysiological OSA features based on the PALM concept appears to have the potential to add value, but it can neither substitute nor challenge present selection parameters. However, these findings indicate the possibility for future studies to combine routinely obtained sleep study data and clinical data with machine learning-based methodologies based on OSA endotype concepts. The potential of the OSA phenotype to contribute to patient selection for HNS therapy is exciting, and the endotype may help to select therapeutic measures, identify OSA risk factors, and predict treatment response.

1.7.3 Surgical procedures

The upper airway is enlarged by rhythmically stimulating the hypoglossal nerve and causing contraction of the chin-lingual muscle. The main body of the implant is located subcutaneously at the level of the right intercostal space between the second and fourth levels on one side. The receiver electrode, which allows sensory detection of respiratory movements, is positioned at the fourth intercostal level on the right side (as shown in Figure 6). Surgical implantation procedures have been modified over the years, and differ mainly in the different technical and medical approaches used. All systems are implanted under general anesthesia, are initially inactive after surgery, and are activated once the healing process is complete.[93]

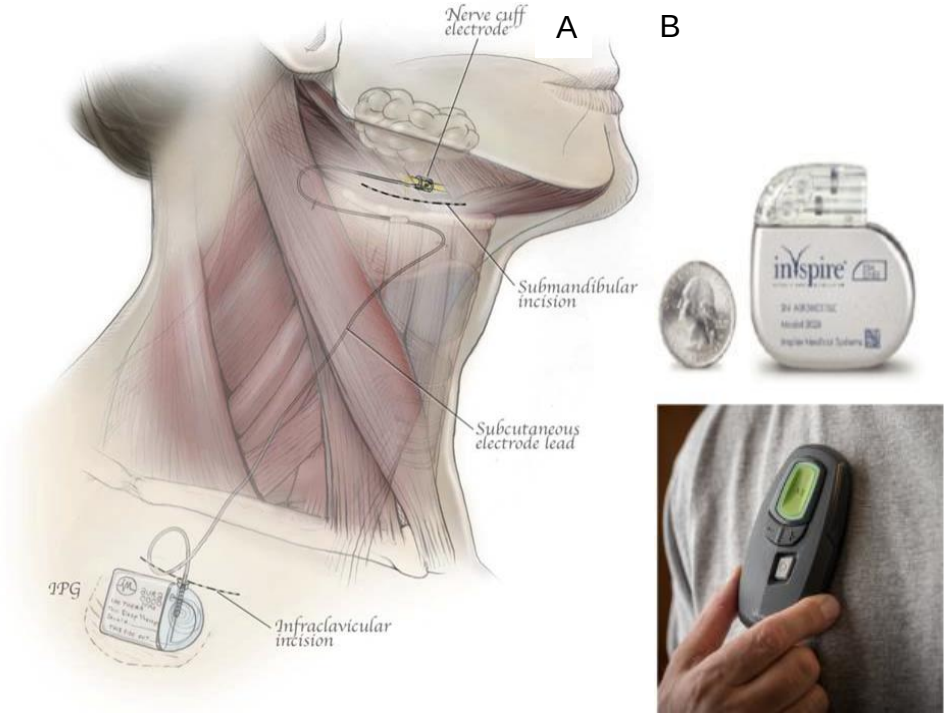


Figure 6: Schematic illustration of the implantation of HNS procedure (Inspire)

A: The treatment works by stimulating the hypoglossal nerve to restore the tone (or stiffen). The stimulating device (and battery) and breathing sensor are implanted in the chest and connected to a stimulation lead that touches the hypoglossal nerve (replaced from Friedman et al., 2016[68]). B: A small HNS stimulator and a hand-held remote control the impulse generator. The device can be turned on when OSA patients go to sleep and off when they wake up by a remote (adopted from Inspire Medical Systems, Inc.).

1.7.4 Postoperative management and care

1.7.4.1 Device titration

Stimulation parameters should be continually titrated to optimize effectiveness and comfort during long-term evaluation following HNS device implantation in a sleep laboratory setting.[94] Studies

show that voltage, electrode configuration, tongue motion patterns, and respiratory sensing quality [95,96,97] can affect HNS therapy outcomes; Pawlak et al.[98] compared the effects of various voltage and electric field combinations under DISE and awake endoscopy and found that different electric configurations could affect patient airway patency. Steffen et al.[99] found that adjusting stimulation parameters could allow for the lowering of amplitude while maintaining functional tongue protrusion and a similar patient control range, eventually contributing to improved adherence and outcomes following HNS device implantation.

Tongue motion phenotype has also been proven to be associated with therapeutic effects. The bilateral protrusion (BP) and ipsilateral protrusion tongue phenotypes are related to a better therapy response, while the response of other tongue patterns such as left protrusion (LP) and mixed activation (MA) is lower.[100,101,102]

1.7.4.2 Patients' adherence and experience

Instead of permanent upper airway modification, patient adherence could be essential for maintaining the long-term effects of HNS. According to previous studies, the mean usage time of HNS devices ranged from 4–7.5 h/night, with patient compliance ranging from 29% to 83%. Good tolerance to HNS and a satisfactory experience is critical to achieving long-term success. These can be achieved by conducting scheduled outpatient visits, home sleep studies, and telephone-linked communication interventions. In 2021, Coca et al.[103] indicated that patients who responded successfully to HNS had significantly better adherence to the recommended therapy duration (> 4 h/night). Meanwhile, Hofauer et al.[104] evaluated the experiences and therapy adherence of 102 patients in Germany and reported that an average objective therapy usage of 5.7 h and subjective usage of 6.8 h/night/week were associated with successful HNS.

Many pre-surgery factors contribute to adherence to HNS, including age and incidence of insomnia, anxiety, depression, and emotional distress. Older patients or those selected based on the general anxiety disorder-7 (GAD-7) and patient health questionnaire-9 (PHQ-9) can have better adherence to stimulation therapy.[105]

In summary, improving patient adherence and experience, which could be achieved by pre-implantation assessment and postoperative monitoring, is essential for improving the long-term effects of HNS.

1.7.4.3 Long-term management

Generally, a titration study is scheduled to monitor the effects of HNS, evaluate patients' adherence, and adjust the HNS device configuration. Soose et al.[106] examined post-implant care routines following five years of clinical HNS implantation and found that personalized post-implant care, involving interventions such as patient education, clinical monitoring, and targeted treatment for complications, is critical for long-term management success. However, follow-up overnight sleep studies in the sleep laboratory during the monitoring process are associated with significant challenges for many reasons, including insufficient sleep laboratory capacity, long waiting lists, busy patient schedules, and recently, the impact of the coronavirus disease (COVID-19).

Owing to their convenience, portability, and low cost, daytime PSG and HSATs have been suggested as alternatives for conventional PSG and have been shown to be practical second-line titration control approaches. In 2021, Bosschieter et al. conducted a prospective single-center observational cohort study of patients with OSA to assess the efficacy of daytime titration and reported it to be a good alternative to nighttime titration. Huyett et al.[107] were the first to demonstrate the successful application of practical home sleep studies and pulse oximetry data to optimize HNS treatment. Furthermore, Steffen et al.[108] assessed the clinical and economic benefits of HSATs for monitoring and optimizing HNS therapy following device activation; this study also underlined the importance of good communication between the otorhinolaryngology clinic where implantation was performed, the local sleep lab, and the patient. Findings regarding the value of commercial portable devices for follow-up and evaluation in routine situations is also promising.[109]

1.7.5 Effects of HNS

HNS has been proven to be a safe alternative to CPAP in treating moderate-to-severe symptoms of OSA. Large multicenter prospective clinical studies have shown that HNS has consistent and long-term effectiveness, as measured by AHI and quality-of-life indicators. HNS may reduce AHI,

and ESS, as well as increase ODI and sleep-related quality of life (e.g., FOSQ (Functional Outcomes of Sleep Questionnaire), SAQLI (Sleep Apnea Quality of Life), and PSQI (Pittsburgh Sleep Quality Index).[110,111, 68] HNS also plays a significant role in the treatment of hypertension and in improving HRV. Long-term effects of HNS on cardiovascular endpoints in patients with OSA are also anticipated.[112,113,114] Moreover, HNS can be used to treat specific OSA populations, including OSA patients with Down syndrome, restless legs syndrome (RLS), and veterans with OSA and comorbid insomnia or post-traumatic stress disorder (PTSD).[115-119]

HNS has been tested as an effective and promising method, with good patient adherence and significant improvements in the objective and subjective severity of OSA. Furthermore, the field is undergoing continuous and impressive development, similar to the field of surgical therapy for OSA.

1.7.6 Complications and adverse events

1.7.6.1 Treatment-emergent central sleep apnea (TECSA)

TECSA, or complex sleep apnea symptoms (CompSAS), has been defined as a CSA that emerges following CPAP therapy despite the resolution of obstructive events. However, with numbers of CSAs being observed with non-PAP therapies such as HNS and MAD, which are being increasingly being used in clinical practice, the definition of TECSA should also include transient and/or persistent CSA after not only PAP treatment, but other kinds of therapy for OSA as well.[120]

Increased CSA following PAP therapy was first described in the 1980s.[121] TECSA is a well-known phenomenon in patients with OSA and was officially recognized in the third edition of the International Classification of Sleep Disorders (ICSD-3) in 2014. TECSA is defined as a central and mixed apnea index (CMAI) of 5 events/h and/or Cheyne-Stokes breathing (CSB) becoming prominent or disruptive on PAP treatment of patients with OSA [baseline central sleep apnea index (CAI) < 5 events/h] when measured during therapeutic device titration 6–8 weeks after device activation. However, owing to insufficient data from case reports and small sample case series, the true prevalence and clinical relevance of TECSA have been challenging to assess and the natural course and underlying pathophysiological mechanisms remain controversial.

Consequently, the possible influence of various factors should be further evaluated to identify predictors of HNS-related TECSA. Future studies should focus on risk assessment, early detection of TECSA (based on comorbid conditions, stimulation parameters, and other factors), clinical management, and most importantly, on patient specific underlying pathophysiology, which could help avoid and resolve TECSA following HNS.

ICSD-3 (AASM, 2014) has defined the following criteria (A-C must be met).[3]

A. More than 5/hour of sleep predominantly obstructive respiratory events detected by PSG.
B. PSG during use of PAP shows significant resolution of obstructive events, while central apnea or hypopnea emerge and persist:
   1. Central AHI > 5 per hour;
   2. Number of central apneas and hypopneas is > 50% of the total number of apneas and hypopneas.
C. The CSA cannot be better explained by another CSA disorder.

1.7.6.2 Cheyne-Stokes breathing (CSB)

In 2019, Sarber et al.[122] reported the appearance of CSB following HNS device implantation in a 60-year-old man with moderate OSA (AHI, 22.6 events/h; obstructive apnea index (OAI), 22.3; CAI, 0.3 events/h) and a history of stage 3 chronic kidney disease, hypertension, hyperlipidemia, type 2 diabetes, bladder and kidney cancer, and depression. As CPAP and auto-PAP could not effectively resolve apnea events (AHI, 31.0 events/h; OAHI, 5.5; CAI, 25.5 events/h), HNS was recommended. The titration study at 3 months after surgery indicated an elevated AHI of 83.8 (OAHI, 4.9; CAI, 78.9 events/h), and CSB was observed throughout the study even with the HNS device turned off; regardless, the obstructive apnea events and subjective daytime sleepiness had improved. Cardiovascular diseases and impaired heart function may contribute to the development of CSB. Thus, close monitoring and repeated titrations are required.

1.7.6.3 Revision surgery

Over the last two decades, HNS devices have become increasingly popular worldwide. However, because most devices have been implanted within the last seven years, data regarding long-term

adverse events are difficult to obtain. Therefore, the safety of revision surgery, including explantation or re-implantation, must be considered. Surgeons must be aware that a patient who has had a stimulator implanted may need to have it updated or removed for various reasons. Based on the reviews of adverse events related to hypoglossal stimulator implantation in the FDA Manufacturer and User Facility Device Experience (MAUDE) database, 42.3% of patients required surgical revision.[123,124] In 2020, Arens et al.[125] reported a series of nine explantations with and without single-staged re-implantation. All procedures were technically challenging, but successful explantation was achieved in each case. The complication rate was much more significant when complete re-implantation was performed or attempted in the same session as explantation alone.

1.7.6.4 Other complications

HNS implantation has been proven to be a safe and effective therapy. Despite this, there are still many technical issues and challenges. There are two types of adverse events: surgery related (including infection, hematoma, localized discomfort, and temporary and mild/transient tongue paresis) and device related (electrical stimulation-related discomfort, tongue abrasion, mouth dryness, implanted device performance difficulties, and mechanical pain associated with the device).[126] After HNS, tongue discomforts due to recurrent stimulation were reported as the most prevalent, which could be resolved by altering the programming parameters and dental adjustment, according to a systematic study of long-term effects. Three case reports reported that pleural effusion, iatrogenic pneumothorax (PTX) following chest sensor lead insertion, and sensor lead penetrating the pleural area were followed by successful re-implantation.[127,128]

2. Aims

2.1 Main aim

To evaluate the long-term outcomes following hypoglossal nerve stimulation implantation for patients with OSA, including intended effects (resolution of OSA and CSA events as well as improved oxygen saturation) and the main severe complication of TECSA.

2.2 Secondary aims

1) To identify the possible factors associated with successful treatment of HNS, including demographical characteristics, specific sleep study data, and patient adherence.

2) To evaluate the possible factors contributing to TECSA following HNS, including demographic characteristics, specific PSG data, sleep stage and stimulation configuration of the HNS device.

3) To explore the underlying mechanism of persistent TECSA based on the development phenotype of TECSA and a trial-titration study.

4) To sum experiences in a standard HNS procedure (precise pre-operative patient selection, individual titration configuration, scheduled postoperative management) and OSA phenotype to improve the subjective and objective effects of HNS and avoid complications.

3. Materials

3.1 Participants

Between 2016 and 2021, 27 patients diagnosed with OSA who underwent implantation of an HNS device (Inspire Medical Systems Inc., Minneapolis, Minnesota, USA) at the otolaryngology department were enrolled restrospectively. Their clinical symptoms were snoring, daytime tiredness and lack of CPAP therapy adherence or OSA symptom relief after 3 months to 1 year of CPAP treatment.

3.2 Inclusion criteria

The study's criteria for implantation and inclusion were participants' age > 18 years, AHI between 15 and 65 with < 25% central events, and failure to accept or adhere to PAP therapy.

3.3 Exclusion criteria

Patients with a body mass index > 35 kg/m2, with a complete concentric collapse (CCC) observed under DISE, or an inability to tolerate surgery, or with anesthesia risk as assessed based on pre-surgery physical examination were excluded from undergoing the surgery.

4. Methods

This retrospective study recruited 27 patients confirmed to have OSA by PSG who underwent implantation of an HNS system at the ENT department. Clinical characteristics, including demographics, sleep study data and HNS device settings, were collected retrospectively from the patients' medical records and HNS programmers. This study was approved by the Ethics Committee of the university (Charité—Universitätsmedizin Berlin approval Number EA2/068/22).

According to the criteria for successful treatment (a postoperative AHI < 20 events/h and a > 50% postoperative reduction in the AHI) following HNS, the 27 patients were divided into the HNS success (n=13) and failure groups (n=14); based on the postoperative CAI (postoperative CAI ≥ 5), the elevated CSA (n=3) and non-elevated CSA groups (n=24) were defined. Differences between the groups were compared to identify possible factors associated with successful response to HNS and postoperative elevated CSA. Furthermore, the underlying mechanism of a persistent TECSA following HNS was explored based on the development phenotype and titration studies.

4.1 Preoperative examination

4.1.1 Clinical characteristics

Patient demographic characteristics (age and gender), anatomical measurements (height and weight), comorbidities, previous treatment methods, possible family history of sleep apnea, and regular medication intake were collected from the electronic medical records and the clinical interviews. Based on the above data, the BMI, ESS and CCI were organized. BMI measures body fat based on height and weight and applies to adult men and women. Daytime sleepiness symptoms were evaluated using the ESS, a self-administered questionnaire comprising eight questions. The Charlson Comorbidity Index (CCI) was used to categorize the comorbidities of the OSA patients based on their corresponding ICD diagnosis code data.

4.1.2 Upper airway evaluation

Before surgery, a physical oropharyngeal examination and DISE were performed to determine the location and structure of the obstruction and to facilitate the development of the surgical

plan. Tonsil and palate size were characterized using the Friedman classification. DISE findings were characterized using the velum, oropharynx, tongue base, and epiglottis (VOTE) classification.

4.1.3 Sleep studies (PSG/HSAT)

All patients with OSA underwent preoperative and postoperative PSG. Electroencephalography was used to detect the voltage between the two electrodes placed in the bilateral frontal region (F3, F4), bilateral central region (C3, C4), and bilateral occipital region, with contralateral bilateral mastoid electrodes (M1, M2) used for reference. Full-night parameters were collected from electroencephalograms, electrooculograms, submental and anterior tibialis electromyograms, and electrocardiograms. Snoring, airflow, arterial oxygen saturation, and respiratory movement were also recorded. All variables were recorded using a digital polysomnography-system. Sleep stages and respiratory events were scored using standard criteria by polysomnographic technologists at the sleep center.

4.1.4 Surgical and anesthesia risk assessment

To avoid surgical and anesthesia risks, age, excessive obesity, cardiopulmonary function, and neurological and endocrine parameters were assessed. In cases of combined hypertension, ischemic heart disease, cardiac arrhythmia, stroke, type II diabetes mellitus, and other related diseases, preoperative medical treatment was used to reduce perioperative complications.

4.2 HNS device implantation

The surgical implantation procedure was performed with two incisions (Figure 7): The first incision is performed anteriorly from the submandibular between the hyoid and mandible. The stimulation electrode was placed on the hypoglossal nerve to stimulate tongue-protrusion function, and the sensing lead is placed between the internal and external intercostal muscles to detect ventilatory effort. Using intramuscular electrodes in the tongue with neural monitoring and visual confirmation during intraoperative stimulation confirms the correct placement. The sensor and stimulation cables were connected to a pulse generator (IPG), which was placed beneath it in the second intercostal space. The system was tested and then turned off at the end of the surgery. Postoperatively, the system's integrity was verified using chest radiography.

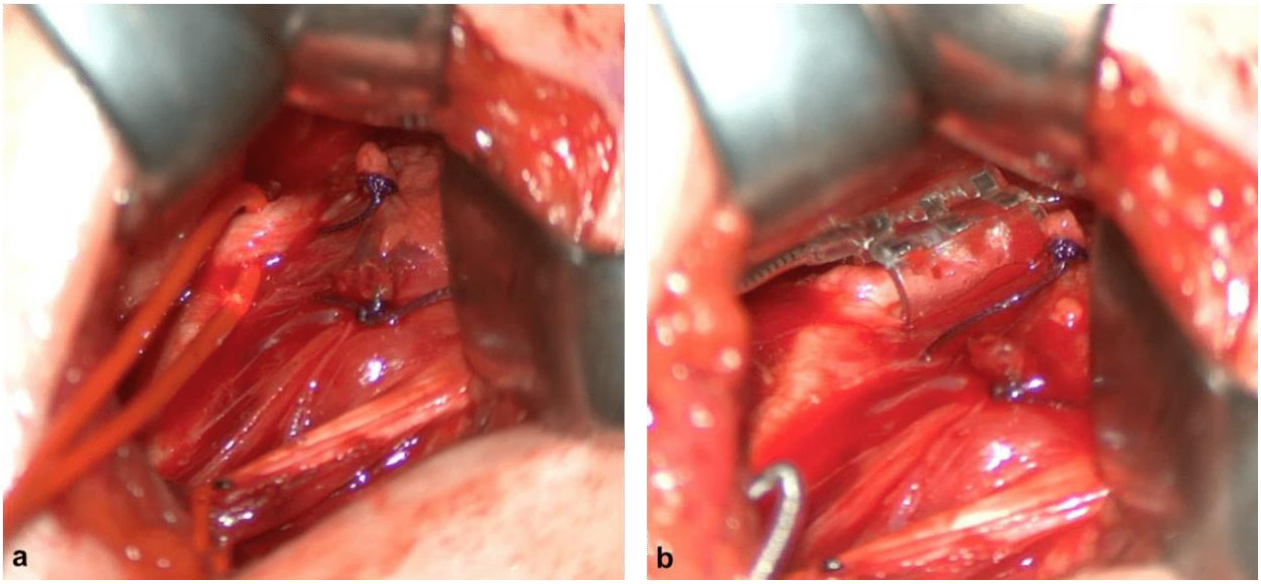


Figure 7: Surgical procedure of HNS.

a: Surgical microscopic image of the medial-distal fibers of the right hypoglossal nerve separated from the others with a loop. b: Surgical microscopic image of the cuff of the stimulating electrode, successfully placed around the medial-distal fibers of the right hypoglossal nerve (Figure reproduced from Arens et al., 2022[129]).

4.3 Postoperative management

4.3.1 HNS activation and titration

Four to eight weeks after implantation, when the healing was complete, the HNS device is generally activated in the daytime with standard settings (bipolar electrode configuration, pulse width 90 µs, frequency 33 Hz), and the stimulation amplitude is titrated on an individual basis (Figure 8). After activation and titration, the patients received guidance on using the device and remote. Before leaving, the patient should be able to demonstrate the functions of the remote, including placing the remote over the generator, turning it on and off, pausing, and adjusting stimulation strength. During follow-up, device configuration, including stimulation amplitude, frequency, pulse width, and electrode configuration, was adjusted to optimal values during office and sleep lab titrations.

Figure 8: Physician programming of HNS device in the German version.

As shown in the physician programmer of HNS, the patients' information, use time/week and settings parameters of HNS, including amplitude, frequency, pulse width, etc., could be collected and changed.

Table 3 Definition of HNS device setting parameters.

Characteristics	Definition
Sensation Threshold	The amplitude level at which the patient first feels the stimulation
Functional Threshold	The amplitude that moves the tongue forward past the lower teeth (Stimulation threshold should be recorded with the patients lying down)
Sub-discomfort Threshold	The amplitude level at which the patient reports discomfort or declines further increases
Therapeutic Amplitude	The lowest amplitude found during the sleep study that effectively reduces OS
Incoming Amplitude	The amplitude that the patient is currently using at home
Pulse width	A measure of the elapsed time between the leading and trailing edges of a single pulse of energy, from 60, 90, 120, 150, 180, and up to 210 μsec
Frequency	The rate of stimulation per second: 20, 25, 30, 33, and up to 40 Hz
Electrode configuration	3 commonly used in clinical practice [+ – +] [o – o] [– – –]

4.3.2 Follow-up management

Regular follow-up sleep studies were performed for each patient to examine the effects of HNS to ensure that they benefited from treatment, and especially for patients with low therapeutic efficiency, insufficient adherence and experience. More active office-based adjustments were performed to help determine the optimal device configuration and improve patients' experience and usage conditions.

4.4 Data collection

Demographic characteristics, pre- and postoperative PSG/HSAT data, and HNS device configurations were collected from the Interdisciplinary Sleep Center and the HNS-Programmers, then stored in a database.

The following variables were evaluated: demographic data (age, sex, BMI, CCI); sleep study data [AHI, ODI, CAI, CMAI, OAI, SpO_2 nadir, SPO_2 average, total sleep time (TST), T90, waking after sleep onset, RERA, sleep latency, REM and NREM sleep); and HNS setting (time of HNS activation, side of implantation, stimulation amplitude, electrode configuration, frequency, and use time).

Table 4 Definition of sleep study characteristics.

Indicators	Definition
Obstructive sleep apnea index (OAI)	The number of obstructive apneas divided by the number of sleep hours.
Central sleep apnea index (CAI)	The number of central apneas divided by the number of sleep hours.
Mixed sleep apnea index (MAI)	The number of mixed apneas divided by the number of sleep hours.
Central and mixed sleep apnea index (CMAI)	The number of central apneas and mixed apneas divided by the number of sleep hours.
Arousal	The physiological and psychological state of being awoken or of sense organs stimulated to a point of perception.
Respiratory effort-related arousal (RERA)	A breathing disorder characterized by OSA airflow reduction associated with increased respiratory effort, which resolves with the appearance of arousals.
Median wake time after sleep onset (WASO), min	A measure of how much time a person spends awake, measured from the moment they first fall asleep until the time they are completely awake and do not try to go back to sleep.
Total sleep time (TST)	The total amount of sleep time scored during the total recording time.
T90,%	The percentage of recording time with SaO2 < 90%
Sleep latency	The length of time that it takes to accomplish the transition from full wakefulness to sleep, normally to the lightest of the non-REM sleep stages
$SPO2_{nadir}$	The lowest peripheral oxygen saturation all night.
Sleep efficacy	The ratio of Total sleep time (TST) to Time in bed (TIB)

4.5 Statistical methods

The SPSS software (IBM SPSS Statistics, version 26.0., Armonk, NY, IBM Corp) was used for the statistical analysis. Overall demographic data are presented in terms of the mean ± standard deviation and range values. The Wilcoxon signed-rank test was used to compare the preoperative and postoperative sleep parameters as they were not normally distributed. The paired t-test was used to compare data with a normal distribution. The Mann–Whitney U test was used for continuous variable data comparison. The Chi-square test or Fisher's exact test were used to compare continuous data. Differences were considered statistically significant at $p < 0.05$.

To evaluate the possible risk factors associated with elevated postoperative CSA (CAI ≥ 5), Fisher's exact test and the $\chi 2$ test were used to compare categorical variables. The independent sample t-test or Mann–Whitney U test were used to compare continuous variable data. Spearman's rank correlation was used to analyze the correlation between OAI and CMAI in patients with TECSA. Differences were considered statistically significant at $p < 0.05$.

5. Results

5.1 Patient characteristics

This study included 27 patients with OSA who underwent HNS implantation (Inspire Medical Systems Inc.) from 2016 to 2021. There were 22 male patients (81.5%), 4 female patients (15%), and one trans-male patient (3.5%), and all patients are Caucasians. The mean age at the time of HNS implantation was 57.04 ± 7.5 years, with a mean preoperative ESS score of 12.17 ± 6.02 and a mean BMI of 29.7 ± 3.15 (range, 20.0–34.5). The mean CCI was 1 ± 1 (range, 0–4), and hypertension was the most common comorbidity among all patients (44.4%).

Before the surgery, 13 of 27 patients underwent PSG, while 14 patients took an HSAT, or the original PSG reports were incomplete. For patients with more than one preoperative sleep study report, we chose the date that was closer to the implantation date. During the evaluation, the median time between surgery and the first postoperative PSG/HSAT was 5 months (range, 0–18 months). Data regarding follow-up visits through the 36 month post-therapy initiation are shown in Figure 9. 23 patients were followed-up during the 0–12 month period, 14 patients between 13 and 24 months, while 6 patients underwent long-term follow-up after 25–36 months, and 4 patients after 3 years.

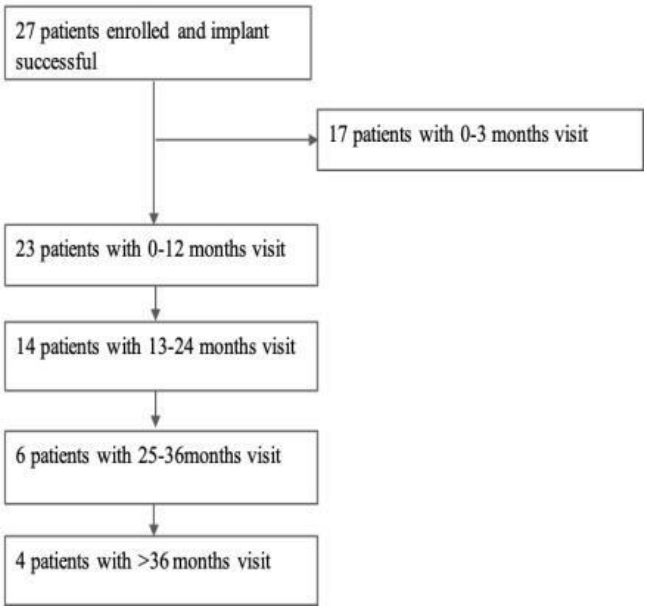


Figure 9: Consort diagram through the 36-month post-therapy initiation visit

23 patients were followed-up during the 0–12 month period, 14 patients between 13–24 months, 6 patients underwent long-term follow-up after 25–36 months, and 4 patients after 3 years.

5.2 Effect of HNS

5.2.1 OSA

5.2.1.1 Overall effect

Table 5 summarizes the overall preoperative and postoperative PSG data for the entire study cohort. All patients had moderate-to-severe OSA prior to surgery (mean AHI, 34.5–12.0 events/h; range, 17.2–59), of which 11 (37%) had moderate OSA and 16 (63%) had severe OSA. AHI for all patients decreased considerably after device activation, from 34.5 ± 12.0 at baseline to 23.5 ± 16.4 after device activation (p=0.001). Additionally, the ODI decreased from 31.3 ± 14.7/h to 22.1 ± 12.2/h (p= 0.02). The mean HI also decreased from 99.6 ± 55.8 to 60.2 ± 51.4 (p= 0.02), and the mean OAI decreased from 16.8 ± 13.0/h to 10.6 ± 10.2/h (p= 0.02). Thus, HNS significantly decreased OSA and hypopnea and improved oxygen desaturation. Moreover, HNS remained consistently effective throughout the evaluation period. Simultaneously, the patient's subjective symptoms (snoring and daytime sleepiness) decreased significantly.

Table 5 Patient sleep study data in overall population and non-TECSA group

	Overall (n=27)			Non-TECSA group (n=25)		
Characteristics	Pre-operative	Post-operative	P value	Pre-operative	Post-operative	P value
AHI, events/h						
Mean ± SD	34.5 ± 12.0	23.5 ± 16.4	*P*=0.01*	34.0 ± 11.6	22.9 ± 12.2	*P*=0.01*
CMAI, events/h						
Mean ± SD	1.7 ± 2.2	2.6 ± 5.0	*P*=0.31	1.56 ± 2.2	1.31 ± 1.5	*P*=0.45
CAI, events/h						
Mean ± SD	0.8 ± 1.3	1.9 ± 4.3	*P*=0.22	.87 ± 1.4	0.82 ±1.1	*P*=0.86
ODI, events/h						
Mean ± SD	31.3 ± 14.7	22.1 ± 12.2	*P*=0.02*	31.1 ±14.5	22.6 ± 13	*P*=0.02*
TST/min						
Mean ± SD	380 ± 81.8	381 ± 54	*P*=0.91	384 ± 83.6	386 ± 52.5	*P*=0.88
OAI, events/h						
Mean ± SD	16.8 ± 13.0	10.6 ± 10.2	*P*=0.02*	16.1 ± 12.9	10.7 ± 10.5	*P*=0.05
SpO2, %						
Mean ± SD	92.3 ± 2.8	92.2 ± 1.9	*P*=0.70	92.5 ± 2.9	92.1 ± 1.9	*P*=0.13

5.2.1.2 Success rate refers to the evaluation period

The success of HNS was defined as a postoperative AHI < 20 events/h along with a > 50% postoperative reduction in AHI. Accordingly, 14 patients (52%) in the overall cohort were successfully treated by HNS after 12 months. Among 4 patients whose baseline AHI was ≤ 20

events/h, only 1 patient responded to HNS when referring to the success criteria: The ratio of preoperative AHI and postoperative AHI ≥ 2. As shown in Table 6, the HNS success rate was effectively maintained throughout 3 years' evaluation, at 47%, 52%, 50%, and 50%, respectively, at 0–3 months, 0–12 months, 2 years, and 3 years, respectively. AHI was decreased continually from 34.5 ± 12.04 event/h at baseline to 26.5 ± 20.5, 25.4 ± 16, 21 ± 10.9 event/h, as well as ODI. The changes during the different evaluation periods, i.e., baseline to 0-3 months, the first year, and the second year following HNS are listed in Table 7.

Table 6 The success treatment rate during post-activation initiation.

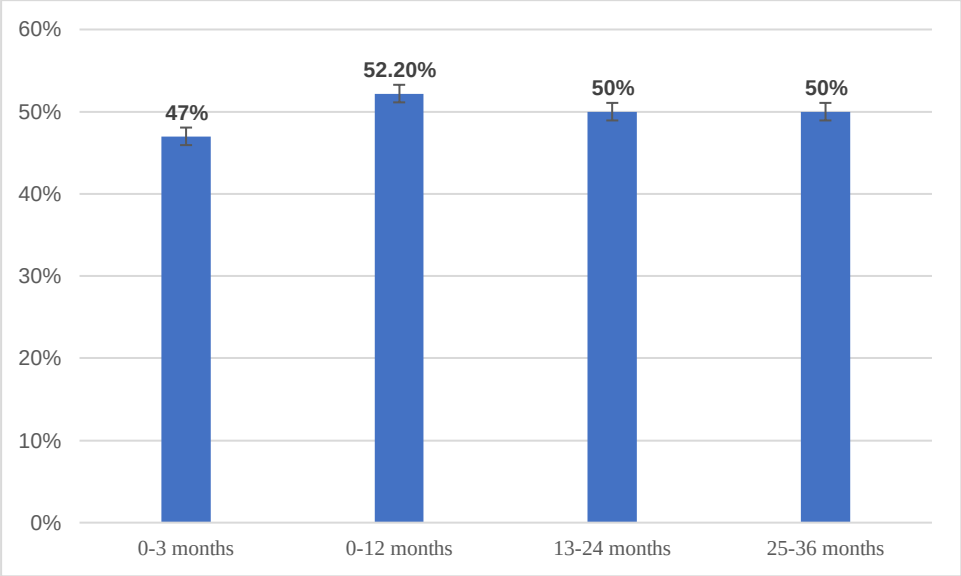


Table 7 Sleep study results by visit (per protocol population)

	Baseline (n=27)	0-3 months (n=17)	0-12 months (n=23)	13-24 months (n=14)	25-36 months (n=6)
AHI, event/h	34.5±12.0	26.5±20.5	25.4±16.9	20.0 ±10.9	29.9±16.1
ODI, event/h	31.3±14.8	25.1±18.6	23.3±16.2	18.9± 11.0	28.2±16.1
CAI, event/h	0.8±1.3	1.7±3.9	2.0±4.8	2.6±7.4	1.4±1.9
CMAI, event/h	1.7±2.3	2.2±4.0	2.5±4.9	5.6±10.6	1.6±2.2
OAI, event/h	16.8±13.0	13.4±15.6	12.8±13.9	7.3±8.6	15.1±12.2

5.2.1.3 Mean disease alleviation (MDA)

The evaluation of HNS treatments for obstructive sleep apnea (OSA) is based primarily on a reduction in respiratory events. In addition, treatment adherence is equally important, particularly for long-term clinical endpoints. At present, the concept of "mean disease alleviation " (MDA) appears to be a new and precise tool for evaluating the true clinical effectiveness of HNS. It is

based on effectiveness (reduction in respiratory events) and compliance percentages and provides an average percentage reduction in disease burden.[130]

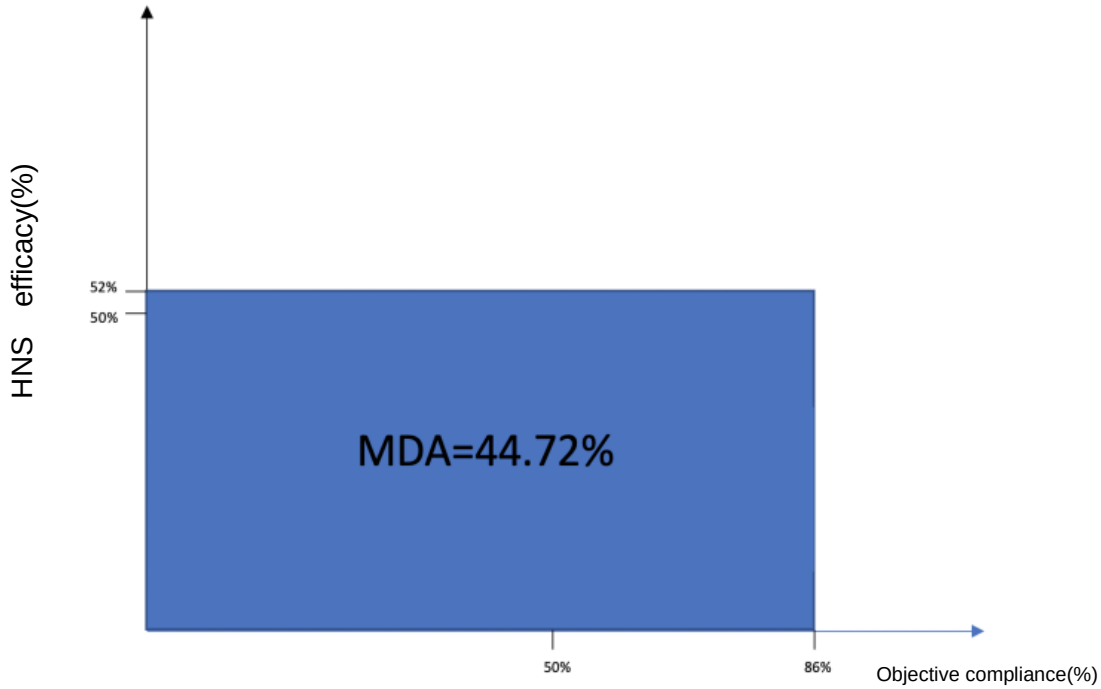


Figure 10: The mean disease alleviation (MDA) of HNS therapy based on the first postoperative sleep study.

Mean disease alleviation (MDA) is equal to the surface area of the rectangle for which the length is given by the adjusted compliance (objective hypoglossal nerve stimulation (HNS) use/total sleep time), and the height is given by the therapeutic efficacy (AHI baseline minus AHI with HNS applied, expressed in percentage). The overall objective compliance of HNS was 86%, with a therapeutic efficiency of 52%, and an MDA (given by compliance with therapeutic OA efficacy, divided by 100) of 44.72%.

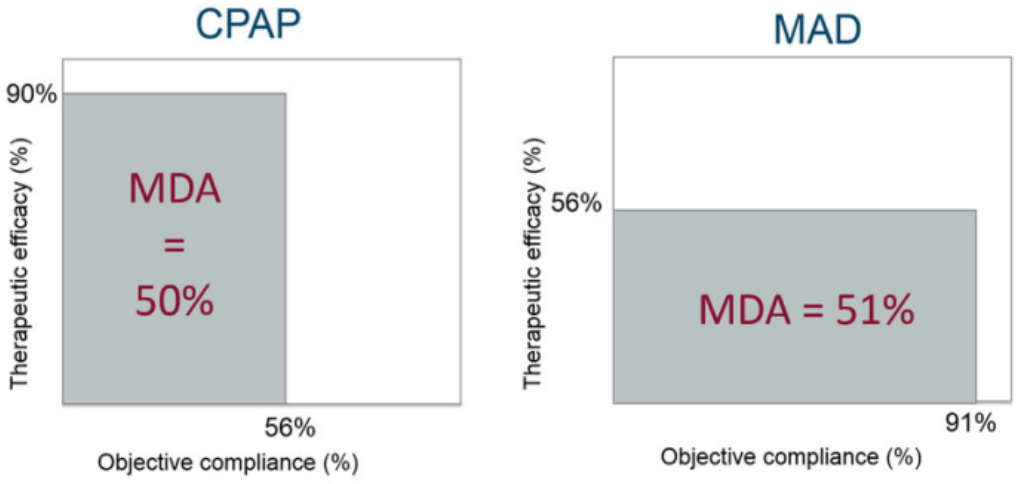


Figure 11: The mean disease alleviation (MDA) of CPAP and MAD therapy.

Refer to the evaluation results in a cohort study, the MDA of the oral appliance was 51% (91% ✕ 56%/100), and CPAP was 50% (56% ✕ 90% /100). Figure reproduced from Dieltjens et al., 2019.[130]

5.2.1.4 Possible factors associated with treatment success of HNS

Based on the results of the first titration sleep study (5 ± 5 months postoperative), this study divided 27 patients into success (n=13) and failure groups (n=14), with a success rate of 48%. The mean baseline ESS scores differed significantly between the two groups (9.5 ± 6 and 14 ± 5, respectively; p=0.03). However, there were no significant differences between the groups in terms of mean BMI (28.9 ± 3.7 and 30.4 ± 2.5 kg/m2, respectively; p = 0.23), AHI (34.6 ± 8.6 and 34.4 ± 14.9 events/h, respectively; p= 0.98), age (59.5 ± 10.7 and 61.3 ± 5.4 years, respectively; p= 0.57), CCI (0.6 ± 0.9 and 1.4 ± 1.3, respectively; p = 0.23) or other factors including CAI, OAI, HI, and ODI. There were no significant differences between the two groups in terms of the traditional or new eligibility criteria (BMI < 32 kg/m^2 or < 35 kg/m^2 and AHI < 65 events/h).

With regard to OSA subtype and endotype, this study evaluated POSA and the apnea threshold by using a clinical predictor of respiratory arousal threshold in OSA patients proposed by Edwards et al. in 2014, that is, the LAT score = (AHI < 30 events/h) + (SpO_2 nadir > 82.5%) + (Hypopneas > 58.3%), score ≥ 2 indicating Low ArTH. Based on the clinical findings, there was no relationship between the outcomes and low apnea threshold (30.7% in the success group and 35.7% in the failure group). In addition, stimulation parameters and device use time could not predict the outcomes following HNS (Table 8).

Results

Table 8 Baseline indicators between HNS success and failure groups

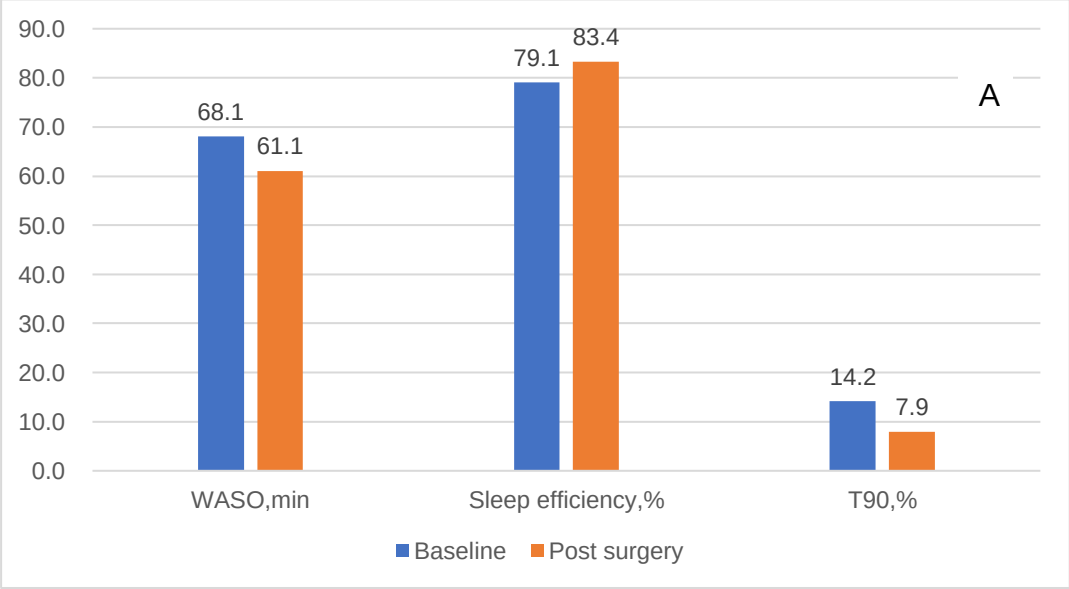
Indicators	Success（N=13）	Failure（N=14）	t/Z/c2	P
Age	59.5 ± 10.7	61.3 ± 5.4	-0.56	0.57
Age at HNS activation	57.1 ± 11.2	58.6 ± 4.7	-0.45	0.65
Baseline ESS	9.5 ± 6.2	14.3 ± 4.8	-2.28	0.03
Baseline CCI	0.6 ± 0.9	1.4 ± 1.3	-1.53	0.13
Baseline BMI	28.9 ± 3.7	30.4 ± 2.5	-1.24	0.23
Baseline AHI	34.6 ± 8.6	34.4 ± 14.9	0.03	0.97
Sex			2.15	0.34
Male	10	12		
Female	3	1		
Trans	0	1		
Baseline BMI≥ 32			/	1.00
Yes	3	4		
No	10	10		
Baseline AHI≥30			/	1.00
Yes	8	8		
No	5	6		
POSA			/	1.00
Yes	8	7		
No	5	4		
Low arousal threshold			/	0.26
Yes	4	5		
No	9	9		
TST, min	349.2 ± 88.7	408.9 ± 65.4	-2.00	0.06
Baseline OAI	14.8 ± 7.9	18.7 ± 16.5	-0.05	0.96
Baseline CAI	0.8 ± 1.4	0.9 ± 1.3	-0.69	0.48
Baseline MAI	0.4 ± 0.7	1.3 ± 2.0	-1.01	0.31
Baseline CMAI	1.1 ± 1.6	2.2 ± 2.7	-0.98	0.33
Baseline ODI	30.7 ± 15.7	31.6 ± 13.2	-0.17	0.86
Baseline HI	18.3 ± 6.7	13.5 ± 9.6	1.48	0.15
Average SPO2	92.8 ± 2.1	91.9 ± 3.3	0.81	0.43
SPO2 nadir	78.1 ± 7.9	75.9 ± 11.5	-0.39	0.69
T90,%	9.2 ± 9.9	19.1 ± 25.7	-0.61	0.54
Snoring percentage,%	15.8 ± 17.9	13.3 ± 14.5	-0.39	0.69
Supine percentage,%	31.6 ± 22.6	33.5 ± 25.7	-0.19	0.85
Supine-AHI	55.2 ± 29.4	50.1 ± 22.9	0.50	0.62
Non-Supine percentage,%	67.9 ± 21.6	66.1 ± 26.6	0.20	0.84
Non-Supine AHI	18.4 ± 12.4	30.9 ± 28.6	-1.55	0.12
Stimulation amplitude, V	1.9 ± 0.9	2.4 ± 0.9	-1.34	0.18
Average use time, h/week	44.6 ± 11.7	35.1 ± 18.9	1.56	0.13

5.2.2 CSA

In addition to assessing the value of HNS for the treatment of OSA, this study also evaluated CSA changes following HNS. CSA was defined as CAI ≥ 1 and classified as severe (CAI ≥ 5) or mild (CAI ≥ 1 and < 5). The prevalence of CSA among the 27 patients with OSA was 33.3% (one case of severe CSA and eight cases of mild CSA). Improvement in CSA was defined as i) preoperative CAI > 5 and postoperative CAI < 5, or ii) preoperative CAI < 5 and postoperative CAI < 1. Based on postoperative PSG, the difference between pre-and postoperative CAI was insignificant. However, the mild baseline CSA of six patients (66.6%) was found to be resolved following HNS, which might indicate the possible ability of HNS to resolve mild CSA events in some patients with OSA.

5.2.3 Sleep architecture

Figure 12 shows comparisons of baseline and post-surgery sleep architecture changes for the 16 patients whose sleep architecture data were obtained. No significant changes in sleep stages, including the REM and NREM (N1, N2, and N3) stages, were observed following HNS. However, improvements in sleep efficacy and reductions in the arousal index, T90, and WASO were observed, although these improvements were not statistically significant.



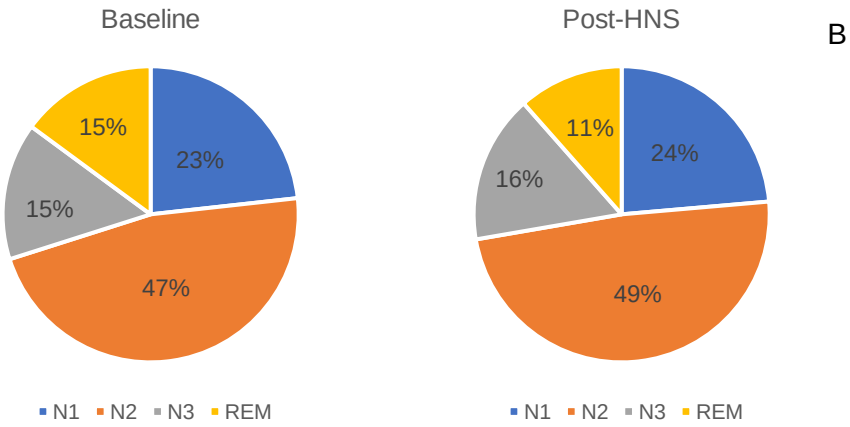


Figure 12 Difference between sleep architecture at baseline and post-surgery

A: The improvement in sleep efficacy, T90, and WASO following HNS; B: There is no significant difference in sleep phase (REM, NREM) before and after the surgery.

5.3 Complications

5.3.1 Elevated CSA

As shown in Figure 13, three patients without preoperative CSA were observed with an elevated CSA (baseline CAI of 0.5, 0 and 1.3 events/h). All 3 patients were moderately obese older males (average age, 60 years) with moderate obesity and severe daytime sleepiness (the mean ESS score of 18.3 ± 2.52). The prevalence of postoperative elevated CSA in the cohort was 11.1%. After HNS implantation, the average CAI increased from 0.6 ± 0.6 at baseline to 12.3 ± 7.1 (p=0.005).

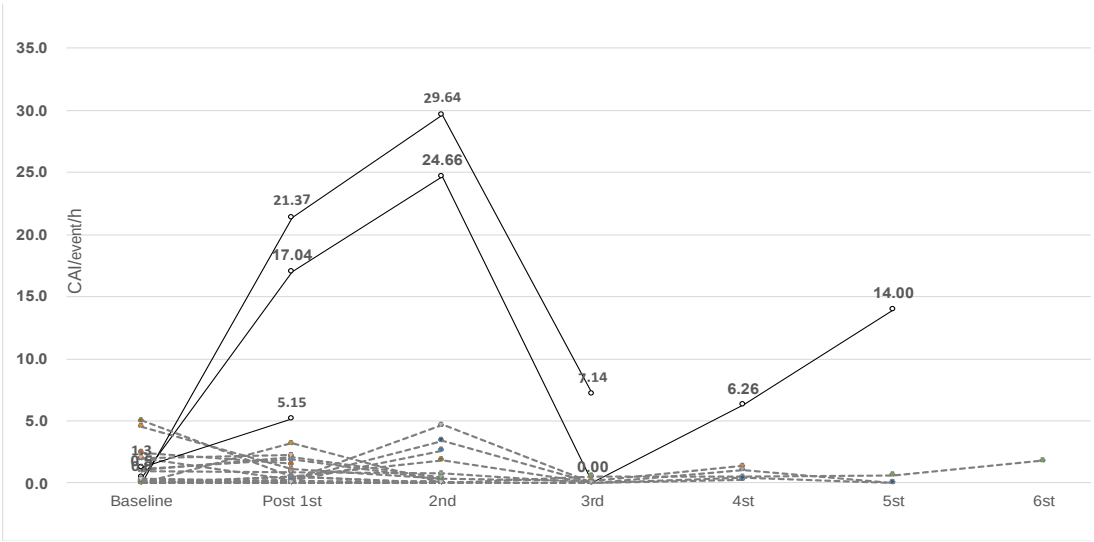


Figure 13: Change in central apnea index (CAI) following HNS.

Both preoperative at baseline and postoperative follow-up of all 27 patients are shown. Patients who had an increased CSA of CAI ≥ 5 following HNS (n = 3) are indicated by a dashed line, whereas patients who had a CAI < 5 following HNS (n = 24) are indicated by a solid line. The postoperative follow-up times used were the 1st, 2nd,3rd and 4-6th. (Note in the diagram, some ordinal numbers are incorrect, they should be “4th” “5th” and “6th””

5.3.1.1 Possible predictor of elevated CSA

Univariate analysis was performed to compare the differences between the postoperative CAI < 5 groups (n= 24) and postoperative CAI ≥ 5 (n= 3) groups. The preoperative factors associated with severe CSA after surgery were an increased ESS score [(11 ± 6) and (18 ± 2.5), respectively;p = 0.004) and an elevated mixed apnea index (MAI) [(0.5 ± 1.1) and (3.4 ± 2.6), respectively;p = 0.014). However, there was no significant difference (p > 0.05) in terms of age (57.7 ± 8.7 and 60 ± 4.6 years, respectively = 0.66), BMI, ODI, AHI, CMAI, or sleep architecture-related parameters. Regarding postoperative characteristics, there were significant differences in AHI, CAI, CMAI, REM-AHI, right-AHI, and implantation location between groups. In contrast, differences in use time, good adherence to HNS (average use time ≥ 28 h), amplitude, and other HNS parameters were not significant (p > 0.05). The results are listed in Table 10, partial results of the presented work have been published in: Comparison of the value of the STOP-BANG questionnaire with oxygen desaturation index in screening obstructive sleep apnea in Germany. Sleep Breath. 2022 Oct 21.

Results

Table 9 Preoperative and postoperative data of CAI <5 and CAI ≥ 5 group

Characteristic	CAI<5（n=24）	CAI≥5（n=3）	t/Z/c2	P
Baseline				
Age (HNS activation),y	58 ± 9	60 ± 5	-0.45	0.66
BMI, kg/m2	29.4 ±3.2	31.9 ±2.3	-1.43	0.15
ESS, points	10.9 ±5.9	18.3 ±2.5	-2.05	0.04*
Gender,%			0.77	0.68
Male	19 (79%)	3 (100%)		
Female	4 (16.7%)	0		
Transsexual	1 (4.3%)	0		
TST, min	380.8 ± 83.8	374.6 ± 77.9	0.12	0.90
AHI, event/h	34.0 ±11.8	38.6 ±15.5	-0.62	0.54
OAI, event/h	15.7 ±13.0	26.3 ±10.8	-1.69	0.09
CAI, event/h	0.8 ± 1.4	0.6 ± 0.7	-0.24	0.81
MAI, event/h	0.5 ± 1.2	3.4 ± 2.6	-2.46	0.01*
CMAI, event/h	1.4 ± 2.1	4.0 ± 3.0	-1.71	0.09
ODI,%	30.2 ±15.1	31.9 ±16.9	-0.18	0.86
Low arousal threshold.	9	0	/	0.53
No-LArt	15	3		
Postoperative sleep characteristic				
TST, min	386.1 ± 53.6	347.6 ± 54.2	-1.23	0.22
AHI, event/h	22.0 ±11.7	41.1 ±5.6	-2.39	0.017*
CAI, event/h	0.6 ± 0.7	12.3 ±7.1	-2.79	0.005*
CMAI, event/h	1.1 ± 1.0	15.1 ±7.4	-2.78	0.005*
ODI	21.7 ±12.5	34.9 ±7.7	-1.85	0.06
Arousal index	17.5 ±13.4	21.4 ±19.0	0.00	1.00
RERA	1.5 ± 3.1	16.1 ±26.8	-1.17	0.24
Sleep efficacy,%	85.2 ±10.2	78.5 ±11.3	1.01	0.32
NREM/TST,%	82.6 ±13.4	86.9 ±5.3	-0.77	0.44
REM/TST,%	10.4 ±6.3	10.9 ±3.1	-0.14	0.89
REM latency, min	152.8 ± 91.5	196.8 ± 44.4	-0.81	0.43
LEFT-AHI, event/h	17.1 ±14.7	33.3 ±5.3	-1.77	0.07
RIGHT-AHI, event/h	13.5 ±11.9	33.1 ±11.6	-2.08	0.04*
Supine-AHI	39.5 ±24.1	41.7 ±30.9	-0.14	0.88
N-supine AHI	15.5 ±12.2	21.4 ±2.9	-0.82	0.42
T90%	8.5 ± 8.7	8.1 ± 7.3	-0.38	0.70
Average SPO2	92.0 ±1.9	93.6 ±1.3	-1.30	0.20
WASO	57.5 ±31.0	66.9 ±37.5	-0.46	0.64
Use time, h/week	38.0 ±14.7	38.4 ±11.7	-0.19	0.84
Amplitude	1.9 ± 0.7	2.5 ± 1.2	-1.37	0.18
Pulse width	95.4 ±13.7	90.0 ±0.0	-1.07	0.28
Frequency	33.5 ±1.6	33.0 ±0.0	-0.51	0.61

*p <0.05 is considered statistically significant.

5.3.2 TECSA

5.3.2.1 The characteristics of 2 patients with TECSA

Of the 3 patients with elevated CSA, two patients were (7.4%) were diagnosed with TECSA (baseline CAI < 5 events/h and with a prominent CMAI of ≥ 5 events/h). This phenomenon was assessed during therapeutic device titration 6–8 weeks after activation. As shown in Table 11, patients 1 and 2 were mildly obese men (BMI of 30 event/h and 34.5 event/h). Patient 1 had an increased ESS score and a medical history of hypertension, and patient 2 had CHD. Following HNS device implantation, both patients reported resolution of OSA symptoms and noticeable improvement in sleep quality. Their bed partners also reported marked changes in snoring and breathing. The OAI of Patient 1 decreased from 37.1 events/h to 11.5 events/h, with CAI increasing from 0.5 to 12.4 events/h. Patient 2 had a baseline AHI of 15.5 events/h, which improved to 6.5 events/h, while the CAI increased from 0 to 19.4 events/h.

Table 10 Pre- and post-implantation characteristics of patients with TECSA

Characteristics	TECSA group (n=2)			
Demographic data	Patient 1		Patient 2	
Age at surgery	61		64	
ESS, points	18		21	
BMI, kg/m2	30.6		34.5	
Gender	Male		Male	
Comorbidity	Hypertension		Hypertension , Coronary heart disease, Diabetes 1	
PSG Characteristics	**Pre-operative**	**Postoperative (average)**	**Pre-operative**	**Postoperative (average)**
AHI, events/h	55.5	44.6	25	34.7
TST, min	349.2	356	312.5	290
OAI, events/h	37.1	11.5	15.5	6.5
CMAI, events/h	6.2	17.2	0.6	21.2
CAI, events/h	0.5	12.4	0	19.4
MAI, events/h	5.7	4.8	0.6	1.8
ODI, events/h	50.5	32.9	17.5	28.3
Sleep architecture				
REM-CAI	0		29	
NREM-CAI	25.3		24.6	
REM-OAI	0		1.2	
NREM-OAI	0		1.3	
Device configuration				
Average use time, h/week	48.5		45	
Implantation location	Left		Right	
Pulse width, μs	33		33	
Frequency, Hz	90		90	
Amplitude, v	2.6		1.5	
Good adherence	Yes		Yes	

5.3.2.2 TECSA phenotype

5.3.2.2.1 Persistent development course of TECSA

In contrast to the spontaneous resolution of TECSA reported by previous studies, this study observed that TECSA did not disappear under continuous therapy and adjustment of device configuration. It persistently occurred and changed during evaluation (the same as is shown in Figure 13).

5.3.2.2.2 Different sleep phases

The PSG investigation found that in the two patients with severe CSA, OSA occurred primarily during the first half of the night and CSA occurred in the second half of the night. The respiratory events were also related to changes in sleep phase. OSA events frequently occurred during REM sleep, whereas CSA occurred during NREM sleep.

5.3.2.2.3 The correlation between OSA and CSA

In addition, Figures 14 and 15 show a consistent developing course of CAI/CMAI and a negative correlation between OSA and CSA. OSA was resolved, but central and mixed sleep apnea increased with varying stimulation amplitudes. Moreover, the OAI increased significantly whereas the CMAI decreased. The Spearman's correlation coefficient between OAI and CMAI was - 0.75 ($p = 0.02$), indicating a substantial and strong negative correlation between CMA and OSA in the two patients with TECSA.

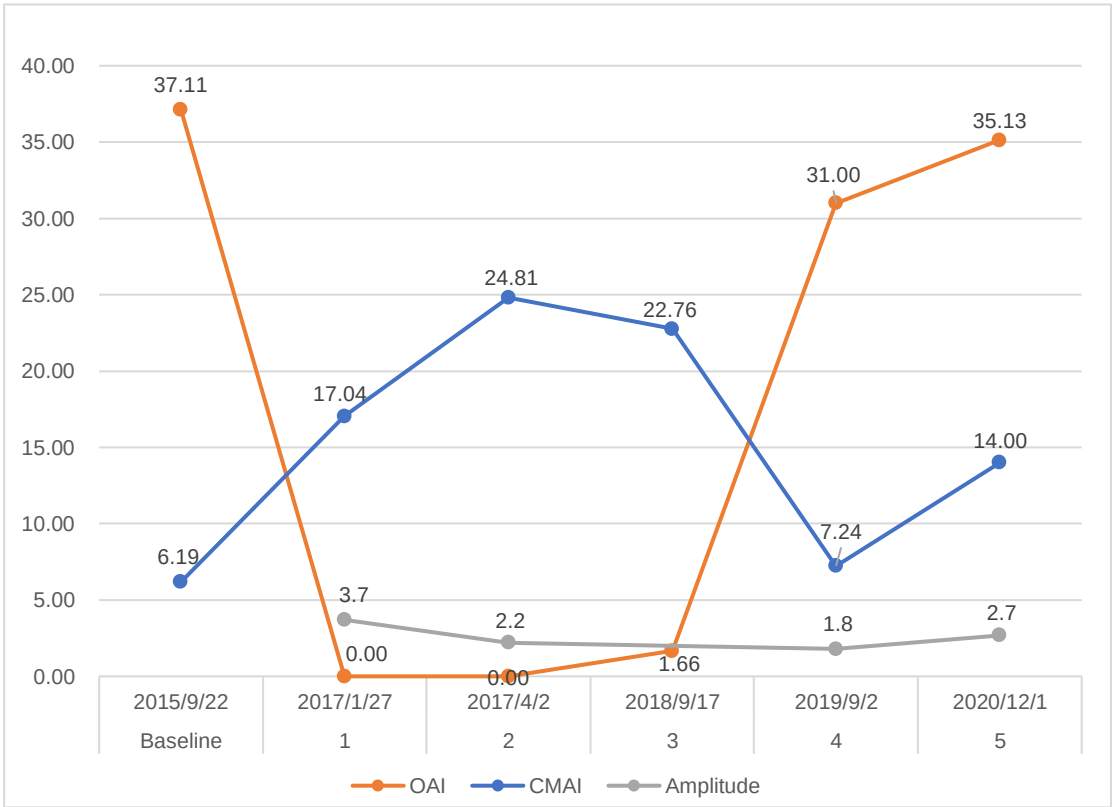


Figure 14: Changes in CMAI, OAI, and stimulation amplitude during follow-up of Patient 1 with TECSA.

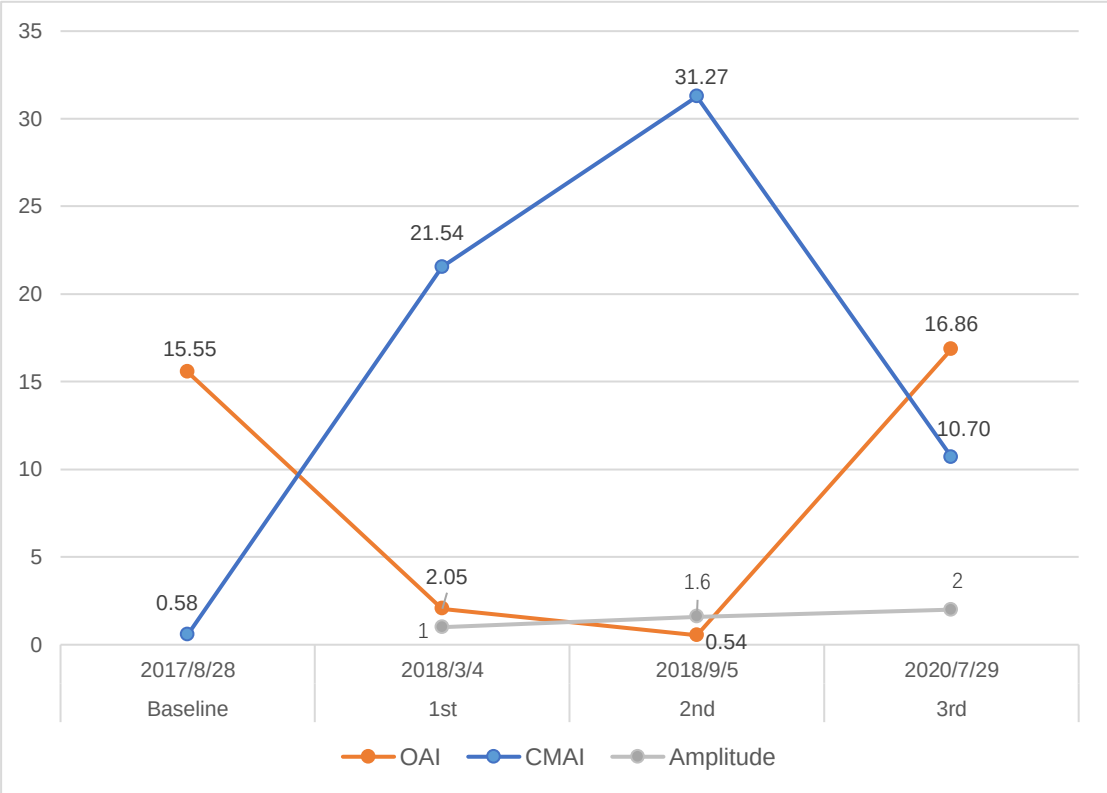


Figure 15: Changes in CMAI, OAI, and stimulation amplitude during follow-up of Patient 2 with TECSA.

5.3.2.3 Titration case study

Based on the development course of CSA, this study hypothesized that stimulation amplitude might be associated with TECSA; therefore, we performed a titration trial to test this hypothesis and explore the underlying mechanism of TECSA. By adjusting the device amplitude at different levels (off, low, standard, and high amplitudes), three conditions (ineffective treatment, appropriate treatment, and overstimulation) were stimulated. The changes in apnea and hypopnea under 3 different conditions were observed.

As shown in Figure 16, patient 1 with TECSA was observed with an all-night evident and severe CSA even with the HNS device off (AHI of 59.6 event/h, CAI of 55.5 event/h and OAI of 1 event/h).

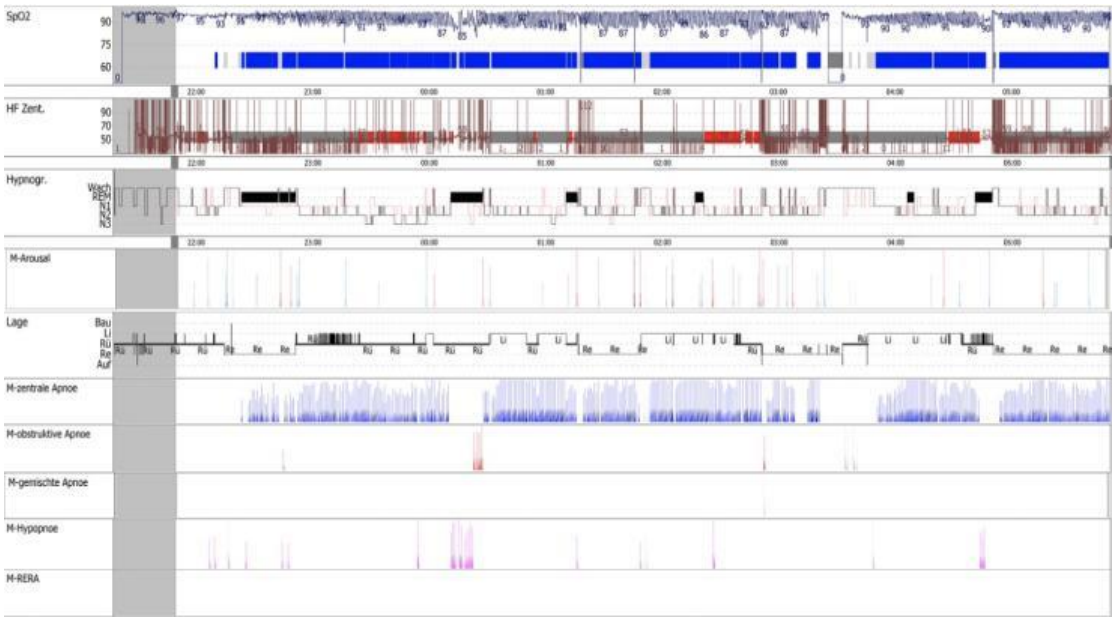


Figure 16: The titration sleep study report of Patient 1 in the TECSA group.

Patient 2 had no central sleep apnea when the device was turned off. After 2 h of steady sleep, the night PSG technologists changed the stimulation amplitude from 1.8 V-1.4 V -2.0 V every 2 h to evaluate the changes in CSA and OSA. The device would be turned off when the patient was awake, turned on at an appropriate stimulation amplitude during REM sleep, and then gradually changed to a new amplitude; thereafter, this cycle was repeated.

The results showed that there was no REM sleep and CSA without HNS; instead, many hypopnea events occurred, and the sleep efficacy (72.2%) was the lowest during all-night sleep (Figure 17). The sleep efficacy was best (94.5%) and the respiratory events were fewer (AHI of 25.1 event/h and ODI of 23.7) when the HNS device was turned on at an amplitude of 1.8 V. Furthermore, while the amplitude was decreased from 1.8 V to 1.2 V, more obstruction apnea and hypopnea occurred (AHI of 41.5, HI of 30.3 event/h). When the HNS device setting was increased from 1.2 V to 2.0 V, more central and obstructive sleep apnea occurred with less hypopnea (AHI of 34, HI of 17.3 event/h). The findings of the titration trial was summarized in Table 13, which support our hypothesis that an appropriate stimulation amplitude can resolve TECSA and result in satisfactory outcomes. However, as patient 2 had a low tolerance for stimulation intensities higher than 2.0 V, observations beyond this amplitude were not possible.

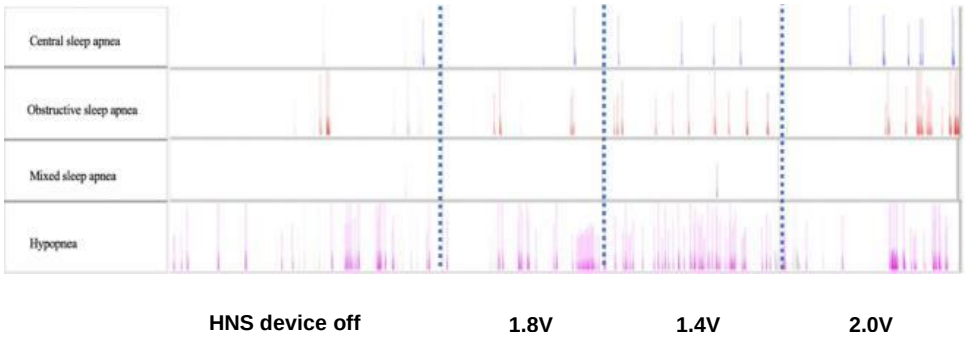


Figure 17: The titration sleep study report at different stimulation amplitudes of Patient 2 in the TECSA group.

The frequency of central apnea, obstructive apnea, mixed apnea, and hypopnea occurring during device off, and at a stimulation amplitude of 1.8V, 1.4V and 2.0V.

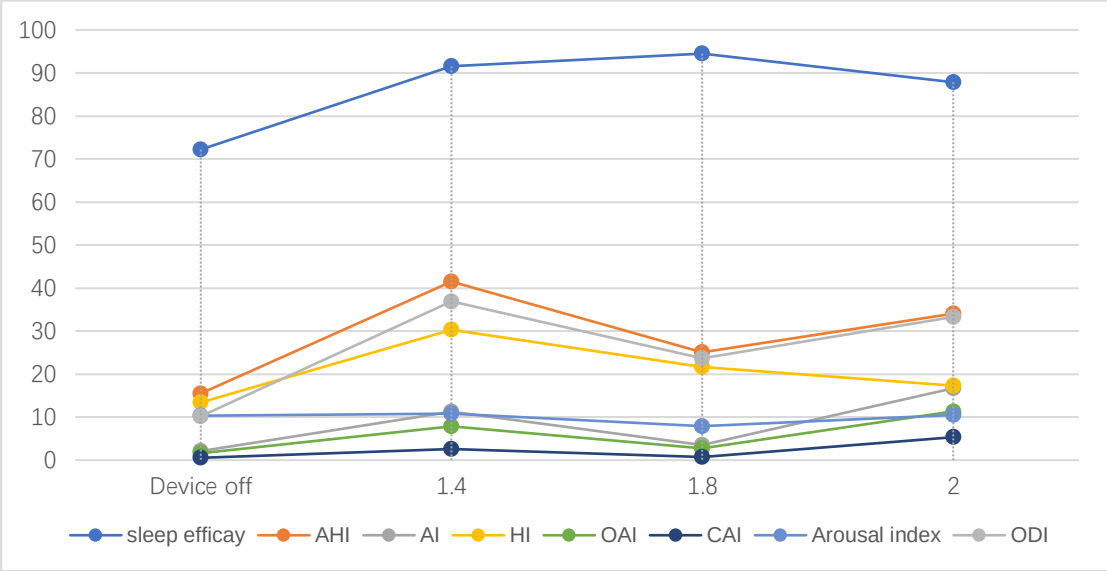


Figure 18: The changes in sleep study characteristics at different stimulation amplitudes.

6. Discussion

Our study showed that HNS could serve as an effective and promising surgical treatment method for OSA. HNS decreased AHI and ODI for OSA patients effectively and consistently, and it reduced the CAI of OSA patients with mild CSA. The preoperative indicator that helped predict the success of HNS was a low baseline ESS score. However, we should not ignore the complications, such as the phenomenon of elevated CSA following HNS, which might be associated with a preoperative increased ESS score and mixed apnea index (MAI) value. Based on the persistent course of the first observed developmental phenotype of TECSA, we identified that an appropriate stimulation amplitude could resolve it, and found that its underlying mechanism following HNS might involve multiple combinations of upper airway effects and high loop gain. In summary, due to the diversity of OSA in phenotypes and endotypes, precise preoperative patient selection, individual device configuration, postoperative management, and further studies on OSA phenotypes are essential to improve and maintain the long-term effect of - and avoid complications after - HNS implantation.

6.1 The outcome of HNS

HNS is a non-anatomy altering surgery for patients with OSA that aims to achieve a good objective and subjective outcome with a minimal complication rate. Furthermore, it is possible to modify medical HNS equipment to improve treatment adherence and long-term results. Therefore, HNS represents one of the most promising technologies in the field of individualized sleep medicine. A meta-analysis of 12 trials reported surgical success rates of 72.4% at 12 months and 75% at 60 months (Inspire Medical Systems, Inc.). The mean AHI difference after 12 months was 17.50 events/h, whereas the mean reduction after 5 years was 18.0 events/h.

Similarly, this study examined the long-term effects of HNS on OSA patients and found that the significant objective metrics of AHI, OAI, and ODI improved more after 3 years of evaluation. The success rate was 52% in the first year and remained stable throughout the assessment period, indicating a significant and long-term benefit in treating OSA. As a new and precise measure for evaluating the true clinical effectiveness of HNS, the MDA of HNS was 44.7% (the objective compliance was 86%, with therapeutic efficiency of 52%), demonstrating a much higher adherence compared with CPAP (the objective compliance was 86%), with a lower actual

therapeutic effect (MAD of 51% and CPAP of 50%). However, our evaluation outcomes were based on the first titration study following HNS (the average duration was 5 months). After HNS device configuration adjustments to improve the adherence and experience of OSA patients, the effectiveness of HNS will be enhanced. Furthermore, because of COVID-19 and the restricted capacity of the sleep center, several sleep investigations were canceled or postponed, particularly for patients with good adherence and apparent symptom improvement, and HSAT was used instead of PSG during follow-up. All of the above may have contributed to the effects during the visit being not as strong as they had been in earlier research.

Many studies have demonstrated that HNS is an effective therapy for obstructive sleep apnea. Nonetheless, the evidence of the HNS effect on dealing with the overlap of OSA and CSA is still limited. Previous studies have shown that obstructive respiratory events can lead to central respiratory events in individuals with vulnerable pharyngeal architecture, and vice versa. The overlap of OSA with CSA has been observed in most sleep apnea patients and can be resolved using various treatment methods. Judd et al. reported that the prevalence of CSA with OSA in children undergoing adenotonsillectomy was 26.8%, and the surgery could lead to the resolution of CSA in the majority of children with OSA (a success rate of 72.9%).[131] Similarly, Patel et al.[132] discovered that following upper airway stimulation, CMAI decreased significantly from 3.6 ± 7.2 to 1.3 ± 5.8 events/h. In our study, the prevalence of CSA with OSA was 33.3%, and 6 of these patients (66.7%) experienced successful treatment of CSA following HNS. However, we did not observe significant reductions in CAI/CAMI following HNS, as the majority of OSA patients (88.9%) in this study had mild CSA at baseline (mean CAI, 0.8 ± 1.3). These results demonstrate the value of HNS for treating patients with CSA overlapping with OSA, possibly owing to the improvement of loop gain and apnea threshold (AT) following HNS.

In addition, Woodson et al. published 3-year STAR trial evidence indicating varying improvement in each stage of sleep at 12-, 18-, and 36-month intervals. Hofauer et al. published similar findings in 2017, but with more specific conclusions– i.e., that N1 stage duration, number of arousals and arousal index, REM rebound, and TST decreased during the study period, while N2 and N3 stage durations remained unchanged. Similarly, Bohorquez et al. found a substantial improvement in N2 and N3 duration among patients who reacted well to HNS, but also reduced N1 sleep percentage, arousal index, and waking after sleep onset (WASO), with no significant changes in

REM sleep duration or sleep latency.[133,135] According to this publication, the difference might be attributed to the fact that non-responders were included in the study. Although this study found the same tendency, mainly due to the lack of complete PSG data, the results were not significant. Further research should be conducted to better understand the long-term consequences of HNS interventions on sleep architecture. These findings may demonstrate further advantages of HNS therapy, identify characteristics that might predict HNS success before surgery, and explain HNS-related adverse effects.

In terms of the prognostic indicators associated with outcomes, including successful treatment and complications after HNS therapy, this study identified the increased baseline ESS score as a predictive indicator associated with the failure of HNS treatment and an elevated CSA (CAI ≥ 5 event/h). However, this study did not find a correlation between treatment outcomes and demographics, comorbid conditions, and sleep study characteristics, or HNS device settings were not associated, especially at a cut-off of BMI at 32 or 35 kg/m^2 and POSA. Previous studies demonstrated that young patients with a higher AHI were more likely to be associated with treatment success and patients with a BMI below 32 kg/m^2 were more likely to respond to HNS. The most recent study by Boroosan et al.[136] found that positive change in the hypopharyngeal cross-sectional area on awake tongue protrusion and severe baseline AHI were positive predictors of successful HNS therapy, while negative predictors were hypopharyngeal cross-sectional area on awake tongue protrusion and BMI > 32. Referring to the elevated CSA, only one study evaluated and reported possible factors associated with it, but it found no relevant factors.[132] As a result, prognostics indicators to predict the success or complication of HNS therapy remain controversial, owing to the small sample of patients who receive HNS device implantation. Further investigation of essential demographic characteristics and sleep study data should be conducted to determine the predicting factors associated with the effects of HNS in order to guide a precise patient selection and an individualized treatment strategies.

In addition to a precise patient selection, individual titration study and adjustments of HNS stimulation parameters are essential in improving the effectiveness and avoiding elevated CSA following HNS.[137] One of the fundamental advantages of the HNS is that the associated devices are adjustable. Stimulation parameters (amplitude, frequency, pulse width, etc.) [98] can be titrated in the clinical- or sleep laboratory setting according to AHI and patient comfort. An advanced

titration of HNS treatment can potentially convert a non-responder into a responder and influence the effects of HNS.[138] Similarly, once TECSA is diagnosed, an immediate change in the HNS configuration should be performed using awake endoscopy or DISE.[139]

Additionally, patient compliance and experience are essential to sustain HNS's long-term benefits.[104] Similarly to CPAP equipment, HNS can be controlled by the patient, who can turn it on and off during sleep, adjust the parameters within a predetermined range for comfort, and regulate delay duration to facilitate sleep onset. As we observed in this study, when the device was briefly turned off, one patient had an apparent elevation in AHI from 40.4 to 76.3 event/h, whereas AHI decreased significantly after restarting the device with a usage time of 50 h/week. As a result, scheduled postoperative management plays an essential role, including follow-up sleep study, good communication between the otorhinolaryngology department and the patient, and cooperation and communication between the interdisciplinary sleep center and ENT department.

6.2 The underlying mechanism of TECSA following HNS

TECSA is a severe complication following HNS and is defined as an increased CSA (CAI ≥ 5) after the complete restoration of airway obstruction, as well as there being more than 50% of central respiratory events rather than obstructive events. Gilmartin et al.[139] were the first to report this phenomenon in 2005, while Morgenthaler et al.[141] proposed the term "complex sleep apnea symptoms." In 2012, Kuźniar et al.[142] evaluated CompSAS with PAP therapy. They found a predominance of obstructive apneas during REM sleep in the supine position, and in contrast, central apneas during non-rapid eye movement (NREM) sleep in the lateral position. In 2014, this syndrome was formally classified as TECSA by the AASM, which is defined as an occurrence following the elimination of upper airway obstruction by PAP treatment and other surgical interventions, such as tracheostomy, maxillomandibular advancement, and UAS.

Chan et al. first noticed a significant elevation in CSA during HNS titration in 2018, but both OSA and CSA disappeared when the patient's device setting was adjusted to unipolar stimulation (- - -). The stimulation amplitude was calibrated between 0.6 and 1.6 V to improve tongue base stimulation during awake endoscopy (AHI, 2.1 events/h). In 2019, Sarber et al.[122] reported the incidence of TECSA (CAI, 78.9 events/h), OAHI of 4.9 events/h, and CSB following HNS device implantation in a patient with mixed sleep apnea (CAI, 12.5 events/h). Moreover, even without

HNS activation, CSA and CSB continued to be persistent throughout follow-up, although subjective OSA adherence and patient experience were satisfactory.

Patel et al.[132] conducted a prospective cohort study with 141 patients who underwent HNS device implantation in 2020, and reported five patients with TECSA(the prevalence of TECSA was 3.3%). Of these, three patients experienced spontaneous remission of TECSA after continuing to use HNS, while the other two patients had the CSA-related symptoms resolved after adjusting the configuration or discontinuing HNS. They hypothesized that the resolution of sleep-related obstruction and restoration of normal lower nighttime partial pressure of carbon dioxide (PCO2) with reduced receptor chemosensitivity might lead to TECSA following the UAS device activation. CSA is reduced with continued therapy and gradual adaptation of chemoreceptors to new levels of nocturnal PCO2. Similarly, after a surgical procedure involving mucotomy with radiofrequency, uvulopalatopharyngoplasty, and partial epiglottectomy, Testani et al.[143] reported a severe, temporary TECSA that resolved spontaneously within 1 month without any particular treatment. In our study, we discovered a persistent course and a significantly negative relationship between CMAI and OAI, in contrast to the spontaneous resolution of TECSA shown by previous investigations.

In this research, the prevalence of TECSA was 7.4%. After activation of HNS, two patients who had no CSA at baseline (preoperative CAI, 0.5 and 0 events/h) developed a new and continuously increasing CSA (postoperative CAI, 12.4 and 19.4 events/h, respectively), with the majority of CSA events occurring during the NREM sleep stage. CSA continued even with the resolution of OSA and vice versa, whereas OSA episodes increased and CSA was reduced when the patient's HNS device amplitude was adjusted to optimize stimulation. Both patients in the TECSA group demonstrated high adherence to HNS, with other configuration defaults being unchangeable during the visit. The pulse width and frequency with bipolar configuration [+–+] were 90s and 33Hz, respectively, indicating that determining an effective range of stimulation amplitude might be associated with TECSA, and both CSA and OSA obtained a satisfactory treatment effect when the stimulation amplitude range was modified to approximately 1.66-2 V. Additionally, the results of the titration sleep study after adjusting the stimulation amplitude with other configurations as unchangeable powerfully support this hypothesis. When compared with the higher and lower

stimulation amplitude, the most significant effect and lowest complication was observed at the appropriate one.

The cyclic absence of effort is often driven by a hypersensitive ventilatory chemoreflex response to opposing changes in airflow, resulting in a high loop gain and overshooting/undershooting of ventilatory oscillations.[144] Based on the development phenotype of TECSA and outcomes of the titration study, we assume that inadequate and overtreatment of upper airway obstruction is related to the specific underlying mechanisms of the phenotype. As a result of long-term nocturnal hypercapnia and sleep apnea, patients with OSA who have severe anatomical problems will have unstable ventilatory regulation (high loop gain/increased chemosensitivity). As demonstrated in Figure 19, an inadequate stimulus amplitude may be ineffective in relieving upper airway obstruction, prompting PCO2 to increase; conversely, over-titration of HNS could relieve ventilatory flow limitations and induce an upper airway effect, and high chemosensitivity might be shown and result in CSA. Figure 20 schematically assumed the relation between prevailing partial pressure of carbon dioxide (PaCO2), apnea threshold (AT, dotted line), ventilation (VE, minute ventilation), CSA, and OSA under different stimulation intensities. The apnea threshold (AT) represents a PaCO2 level below which ventilation ceases. During the device off setting, the prevailing PaCO2 exceeds the AT, OSA persisted with no CSA occurring.[145] While the HNS is set at an optimal stimulation amplitude to treat upper airway obstruction, the prevailing PaCO2 exceeds the AT with normal ventilation, and CSA will not occur while OSA is solved. When HNS overstimulates the upper airway, OSA and inspiratory flow restriction are resolved, and a high loop gain could lead to hyperventilation. CSA develops when PaCO2 is reduced below the AT; an insufficient stimulation of HNS or an accumulation of carbon dioxide (CO2) during apnea can lead to a restoration of the ventilation, then a resolution of CSA and improvement of OSA will be observed.

Furthermore, in this study, we observed that OSA was more likely to occur during REM sleep, whereas CSA occurred during NREM sleep. This is because during REM, the muscles of the whole body as well as the supraglottic airway are relaxed, resulting in increased airway resistance, which - combined with pre-existing airway constriction or anatomical obstruction - promotes more OSA events, especially in the supine position. While respiratory control during NREM sleep

primarily depends on the activity of respiratory center neurons activated by chemoreceptors, the gap between eupneic PCO2 levels and the apneic threshold is highly labile, resulting in CSA events.[146]

In summary, a scalable method for determining physiological endotypes, including loop gain and arousal threshold of sleep apnea from a polysomnographic sleep study, is promising to determine the underlying mechanism by monitoring the levels of arterial PCO2 and determining OSA, which may help to predict and eventually prevent the occurrence of CSA.[147,148]

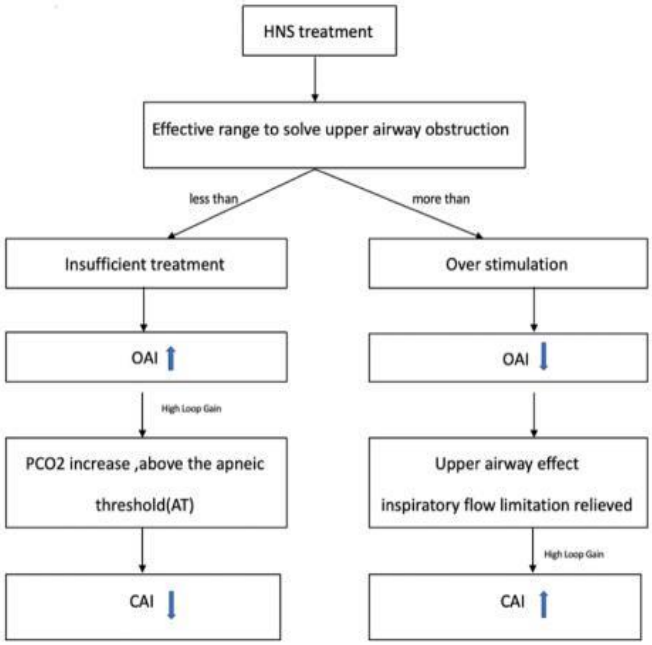


Figure 19: Possible mechanism of a persistent TECSA following HNS

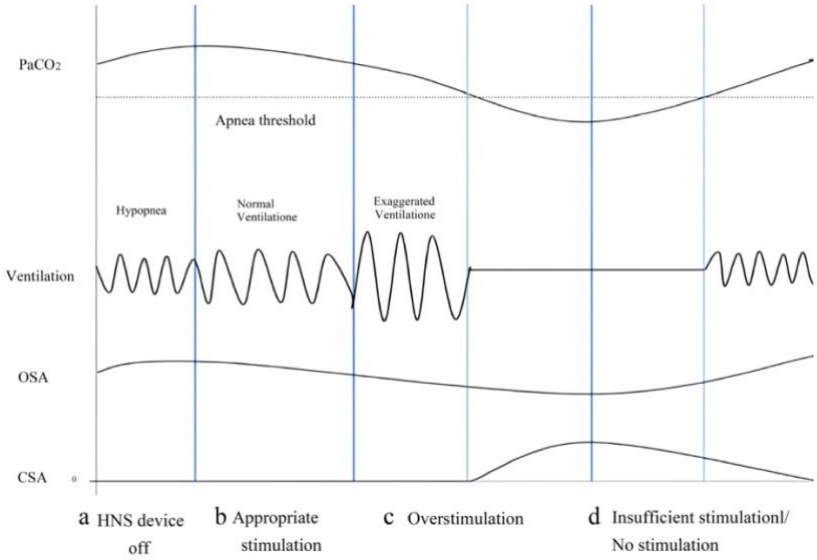


Figure 20: Schematic illustration of the mechanism and pattern of TECSA following HNS

6.3 The value of OSA endotype

As the findings in this study demonstrated, daytime sleepiness symptoms refer to a baseline elevated ESS score that might play an essential role in predicting the failure of HNS therapy as well as TECSA, while in contrast, there is no association between outcomes with the low arousal threshold and POSA, which could reveal the potential value of endotypes and subtypes of OSA in improving its effects and avoiding complications.

However, there are no studies on the relationships between different OSA subtypes and the outcomes following HNS, especially for subtypes 3 and 4 with obvious daytime sleepiness. Furthermore, the PALM model provides a scientific and comprehensive summary of the current understanding of the pathophysiological mechanisms of OSA pathogenesis, which lays the foundation for the precise treatment of OSA. According to a comprehensive phenotypic analysis of baseline PSG data from the STAR trial, mechanistic PALM variables related to non-anatomical impairments were associated with lower HNS treatment efficacy, and a higher arousal threshold was found to be a significant predictor of treatment effectiveness. In 2020, a secondary analysis of the STAR trial data revealed that beneficial values of all these non-anatomical traits were associated with HNS efficacy. A successful response to therapy was independently associated with a higher arousal threshold, lower loop gain (in mild collapsibility), and more effective pharyngeal compensation, which demonstrated the great clinical value of the PALM scale in patient selection and precise and targeted therapy.

In summary, a better understanding of the pathogenesis of OSA will promote the improvement and enhancement of OSA treatment strategies. Further research is required for more accurate therapies based on the PALM model. Furthermore, distinguishing between different PALM subtypes is expected to be the foundation of precision medicine from a clinical application standpoint. Sands et al.[148] developed a composite approach in which all four endotypic traits are estimated by fitting a gain, delay, and time-constant model to the standard PSG airflow signal; however, this is quite complicated for physicians to use in clinics. Most recently, Dutta R et al.[149] developed a novel model for estimating key endotypes using clinical and standard PSG data, including 10 variables for estimating OSA endotype: age, BMI, and eight PSG parameters (total AHI, SpO_2 nadir, arousal index, supine AHI, NREM AHI, fraction hypopneas, and sleep efficiency).

Future research should focus on simple and practical evaluation methodologies and important biological indicators that can be used by physicians and surgeons.

The primary limitations of this study were the limited sample size, the retrospective character and lack of planned follow-up, and missing preoperative sleep data in some cases. As a result, we could not explore the changes related to sleep phases or explore the relationships between HNS-related complications and sleep study indicators such as arousal between effects. Furthermore, during the most recent overnight titration sleep study of patient 1, CSB was detected when the HNS device was turned off. It is difficult to explain why OSA is completely transformed into CSA in patients without cardiovascular disease.

6.4 Implications for future research

On the one hand, the effectiveness and safety of hypoglossal nerve stimulation, which is less invasive than traditional surgical treatment and preserves the body's original tissue structure, have been confirmed in long-term clinical trials, and the use of HNS is gradually expanding, with successful implantation in several children with OSA combined with Down syndrome reported in the literature. Several patients have been implanted with HNS devices as well as pacemakers, cardioverter-defibrillators, and cardiac resynchronization devices, which have proven to be safe and effective. New nerve cuff electrodes with embedded magnets are under further investigation. Currently, HNS is expensive and short-lived and needs to be explored for more precise indications. Despite the preferred treatment for OSA still being CPAP, HNS enriches the treatment of OSA, especially by providing a new treatment option for OSA patients with moderate to severe intolerance to CPAP. HNS technology is currently undergoing rapid forward development; recently, a two-incision technique[70] has been established for the respiratory frequency-controlled unilateral stimulation system (Inspire), and a new simulation technique is available with bilateral medial stimulation of the hypoglossal nerve, and it is currently being further investigated in multicenter studies. In addition to improving existing stimulation techniques, enhancing patient selection, and optimizing postoperative stimulation settings, the topic of identifying new or additional neurostimulation targets appears to be exciting. In the setting of a sleep video endoscopy, Kent et al.[150] found that isolated ansa cervicalis stimulation might improve maximal inspiratory airflow.

On the other hand, due to the diversity of OSA, a precise, individual, and standard application of HNS should be applied in the clinic setting. In terms of prediction indicators, different OSA phenotypes, sleep study characteristics, and general population data can be studied to predict the outcomes of HNS. Concerning the individualized therapy method, OSA phenotype and clinical subtype analyses can be performed using big data analysis techniques, and the best indication population for HNS can be evaluated by combining all aspects of examination results. In terms of patient participation and experience, scheduled follow-up or new technologies such as portable sleep monitoring can be used to collect and track the effects of HNS use and improve patient adherence; this can also be combined with the use of new technologies, such as portable sleep monitoring.

In the future, clinicians need to collect further clinical data and evidence of sleep problems to point the way for further research and make positive and valuable advancements regarding the diagnosis and treatment of OSA using HNS.

7. Conclusions

HNS is an effective, non-invasive, adjustable, promising, and alternative treatment with good adherence to HNS for patients who cannot tolerate CPAP. Due to the diversity of OSA in terms of age, sex, ethnicity, phenotype and endotype, precise preoperative patient selection, individual and standard device configuration, scheduled postoperative management, and follow-up are essential to achieve the best subjective and objective results of HNS, and to avoid or solve the complications after HNS implantation. Low ESS score, young age, low BMI, low neck circumference, and non-supine OSA are indicators of a better likelihood of response to HNS, while patients with high baseline mixed sleep apnea or cardiovascular comorbidities who report severe daytime sleepiness might get TECSA following HNS. In addition, the most optimal therapeutic stimulation configuration with high adherence should be determined by standard titration protocol and scheduled postoperative management. A persistent course and phenotype of TECSA might be associated with the stimulation amplitude, possibly owing to a high loop gain and upper airway effect. To treat existing TECSA, once diagnosed, a titration study should be performed to explore the appropriate stimulation amplitude, and combining the present treatment with other modalities, such as sleep position and oxygen treatment, should also be attempted.

In the future, a better understanding of the subtypes and endotypes of OSA should be translated into clinical use to guide therapeutic interventions, identify risk factors for OSA and predicting OSA treatment response.

Reference list

1. Viana Ada C Jr, Thuler LC, Araújo-Melo MH. Drug-induced sleep endoscopy in the identification of obstruction sites in patients with obstructive sleep apnea: a systematic review. Braz J Otorhinolaryngol. 2015 Jul-Aug;81(4):439-46. doi: 10.1016/j.bjorl.2015.01.007.
2. Amos JM, Durr ML, Nardone HC, Baldassari CM, Duggins A, Ishman SL. Systematic Review of Drug-Induced Sleep Endoscopy Scoring Systems. Otolaryngol Head Neck Surg. 2018 Feb;158(2):240-248. doi: 10.1177/0194599817737966.
3. AASM, AMERICAN ACADEMY OF SLEEP MEDICINE (AASM). International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
4. Yeghiazarians Y, Jneid H, Tietjens JR, Redline S, Brown DL, El-Sherif N, Mehra R, Bozkurt B, Ndumele CE, Somers VK. Obstructive Sleep Apnea and Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation. 2021 Jul 20;144(3):e56-e67. doi: 10.1161/CIR.0000000000000988.
5. Freedman N. Improvements in current treatments and emerging therapies for adult obstructive sleep apnea. F1000Prime Rep. 2014 May 6;6:36. doi: 10.12703/P6-36.
6. Torres G, Sánchez-de-la-Torre M, Barbé F. Relationship Between OSA and Hypertension. Chest. 2015 Sep;148(3):824-832. doi: 10.1378/chest.15-0136.
7. Salman LA, Shulman R, Cohen JB. Obstructive Sleep Apnea, Hypertension, and Cardiovascular Risk: Epidemiology, Pathophysiology, and Management. Curr Cardiol Rep. 2020 Jan 18;22(2):6. doi: 10.1007/s11886-020-1257-y.
8. Pio-Abreu A, Moreno H Jr, Drager LF. Obstructive sleep apnea and ambulatory blood pressure monitoring: current evidence and research gaps. J Hum Hypertens. 2021 Apr;35(4):315-324. doi: 10.1038/s41371-020-00470-8.
9. May AM, Van Wagoner DR, Mehra R. OSA and Cardiac Arrhythmogenesis: Mechanistic Insights. Chest. 2017 Jan;151(1):225-241. doi: 10.1016/j.chest.2016.09.014.
10. Qin H, Steenbergen N, Glos M, Wessel N, Kraemer JF, Vaquerizo-Villar F, Penzel T. The Different Facets of Heart Rate Variability in Obstructive Sleep Apnea. Front Psychiatry. 2021 Jul 22;12:642333. doi: 10.3389/fpsyt.2021.642333.
11. Qin H, Keenan BT, Mazzotti DR, Vaquerizo-Villar F, Kraemer JF, Wessel N, Tufik S, Bittencourt L, Cistulli PA, de Chazal P, Sutherland K, Singh B, Pack AI, Chen NH, Fietze I, Gislason T, Holfinger S, Magalang UJ, Penzel T. Heart rate variability during wakefulness as a marker of obstructive sleep apnea severity. Sleep. 2021 May 14;44(5):zsab018. doi: 10.1093/sleep/zsab018.
12. Sanderson JE, Fang F, Lu M, Ma CY, Wei YX. Obstructive sleep apnoea, intermittent hypoxia and heart failure with a preserved ejection fraction. Heart. 2021 Feb;107(3):190-194. doi: 10.1136/heartjnl-2020-317326.
13. Gottlieb DJ. Sleep Apnea and Cardiovascular Disease. Curr Diab Rep. 2021 Dec 13;21(12):64. doi: 10.1007/s11892-021-01426-z.
14. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; American Heart Association Stroke Council, Council

on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016 Jun;47(6):e98-e169. doi: 10.1161/STR.0000000000000098.

15. Geer JH, Falcone GJ, Vanent KN, Leasure AC, Woo D, Molano JR, Sansing LH, Langefeld CD, Pisani MA, Yaggi HK, Sheth KN. Obstructive Sleep Apnea as a Risk Factor for Intracerebral Hemorrhage. Stroke. 2021 May;52(5):1835-1838. doi: 10.1161/STROKEAHA.120.033342.
16. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol. 2013 Aug 13;62(7):569-76. doi: 10.1016/j.jacc.2013.05.045.
17. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: The road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep Med Rev. 2018 Dec;42:211-219. doi: 10.1016/j.smrv.2018.08.009.
18. Kerner NA, Roose SP. Obstructive Sleep Apnea is Linked to Depression and Cognitive Impairment: Evidence and Potential Mechanisms. Am J Geriatr Psychiatry. 2016 Jun;24(6):496-508. doi: 10.1016/j.jagp.2016.01.134.
19. Lim KG, Morgenthaler TI, Katzka DA. Sleep and Nocturnal Gastroesophageal Reflux: An Update. Chest. 2018 Oct;154(4):963-971. doi: 10.1016/j.chest.2018.05.030.
20. Oh JH. Gastroesophageal reflux disease: recent advances and its association with sleep. Ann N Y Acad Sci. 2016 Sep;1380(1):195-203. doi: 10.1111/nyas.13143.
21. Kuhn E, Schwarz EI, Bratton DJ, Rossi VA, Kohler M. Effects of CPAP and Mandibular Advancement Devices on Health-Related Quality of Life in OSA: A Systematic Review and Meta-analysis. Chest. 2017 Apr;151(4):786-794. doi: 10.1016/j.chest.2017.01.020.
22. Bonsignore MR, Suarez Giron MC, Marrone O, Castrogiovanni A, Montserrat JM. Personalised medicine in sleep respiratory disorders: focus on obstructive sleep apnoea diagnosis and treatment. Eur Respir Rev. 2017 Oct 25;26(146):170069. doi: 10.1183/16000617.0069-2017.
23. Sutherland K, Lee RW, Cistulli PA. Obesity and craniofacial structure as risk factors for obstructive sleep apnoea: impact of ethnicity. Respirology. 2012 Feb;17(2):213-22. doi: 10.1111/j.1440-1843.2011.02082.x.
24. Xu L, Keenan BT, Wiemken AS, Chi L, Staley B, Wang Z, Wang J, Benedikstdottir B, Juliusson S, Pack AI, Gislason T, Schwab RJ. Differences in three-dimensional upper airway anatomy between Asian and European patients with obstructive sleep apnea. Sleep. 2020 May 12;43(5):zsz273. doi: 10.1093/sleep/zsz273.
25. Hnin K, Mukherjee S, Antic NA, Catcheside P, Chai-Coetzer CL, McEvoy D, Vakulin A. The impact of ethnicity on the prevalence and severity of obstructive sleep apnea. Sleep Med Rev. 2018 Oct;41:78-86. doi: 10.1016/j.smrv.2018.01.003.
26. Wahner-Roedler DL, Olson EJ, Narayanan S, Sood R, Hanson AC, Loehrer LL, Sood A. Gender-specific differences in a patient population with obstructive sleep apnea-hypopnea syndrome. Gend Med. 2007
27. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of

sleep-disordered breathing in adults. Am J Epidemiol. 2013 May 1;177(9):1006-14. doi: 10.1093/aje/kws342.

28. Geer JH, Hilbert J. Gender Issues in Obstructive Sleep Apnea. Yale J Biol Med. 2021 Sep 30;94(3):487-496.
29. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS, Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017 Aug;34:70-81. doi: 10.1016/j.smrv.2016.07.002.
30. Zinchuk A, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. Sleep Med Rev. 2017 Oct;35:113-123. doi: 10.1016/j.smrv.2016.10.002.
31. Zinchuk A, Yaggi HK. Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. Chest. 2020 Feb;157(2):403-420. doi: 10.1016/j.chest.2019.09.002.
32. Ersözlü T, Deniz M, Fazlıoglu N, Gultekin E, Altintas N. Understanding potential associations between anatomic and other factors in OSA severity. Sleep Breath. 2021 Nov 29. doi: 10.1007/s11325-021-02539-1.
33. Sutherland K, Schwab RJ, Maislin G, Lee RW, Benedikstdsottir B, Pack AI, Gislason T, Juliusson S, Cistulli PA. Facial phenotyping by quantitative photography reflects craniofacial morphology measured on magnetic resonance imaging in Icelandic sleep apnea patients. Sleep. 2014 May 1;37(5):959-68. doi: 10.5665/sleep.3670.
34. Schwab RJ, Kim C, Bagchi S, Keenan BT, Comyn FL, Wang S, Tapia IE, Huang S, Traylor J, Torigian DA, Bradford RM, Marcus CL. Understanding the anatomic basis for obstructive sleep apnea syndrome in adolescents. Am J Respir Crit Care Med. 2015 Jun 1;191(11):1295-309. doi: 10.1164/rccm.201501-0169OC.
35. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. Sleep Med Rev. 2018 Feb;37:45-59. doi: 10.1016/j.smrv.2016.12.003.
36. Aishah A, Eckert DJ. Phenotypic approach to pharmacotherapy in the management of obstructive sleep apnoea. Curr Opin Pulm Med. 2019 Nov;25(6):594-601. doi: 10.1097/MCP.0000000000000628.
37. Carberry JC, Amatoury J, Eckert DJ. Personalized Management Approach for OSA. Chest. 2018 Mar;153(3):744-755. doi: 10.1016/j.chest.2017.06.011.
38. Edwards BA, Eckert DJ, McSharry DG, Sands SA, Desai A, Kehlmann G, Bakker JP, Genta PR, Owens RL, White DP, Wellman A, Malhotra A. Clinical predictors of the respiratory arousal threshold in patients with obstructive sleep apnea. Am J Respir Crit Care Med. 2014 Dec 1;190(11):1293-300. doi: 10.1164/rccm.201404-0718OC.
39. Carberry JC, Jordan AS, White DP, Wellman A, Eckert DJ. Upper Airway Collapsibility (Pcrit) and Pharyngeal Dilator Muscle Activity are Sleep Stage Dependent. Sleep. 2016 Mar 1;39(3):511-21. doi: 10.5665/sleep.5516. PMID: 26612386; PMCID: PMC4763361.
40. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. Can J Anaesth. 2010 May;57(5):423-38. doi: 10.1007/s12630-010-9280-x.
41. Polesel DN, Nozoe KT, Bittencourt L, Tufik S, Andersen ML, Fernandes MTB, Hachul H. Waist-to-height ratio and waist circumference as the main measures to evaluate obstructive sleep apnea in the woman's reproductive life stages. Women Health. 2021 Mar;61(3):277-288. doi: 10.1080/03630242.2020.1862386.

42. Thomas RJ, Mietus JE, Peng CK, Goldberger AL. An electrocardiogram-based technique to assess cardiopulmonary coupling during sleep. Sleep. 2005 Sep;28(9):1151-61. doi: 10.1093/sleep/28.9.1151.
43. Tondo P, Drigo R, Scioscia G, Ballarin A, Rossi E, Floriani AF, Pauletti A, Foschino Barbaro MP, Lacedonia D. Usefulness of sleep events detection using a wrist worn peripheral arterial tone signal device (WatchPAT™) in a population at low risk of obstructive sleep apnea. J Sleep Res. 2021 Dec;30(6):e13352. doi: 10.1111/jsr.13352.
44. Kuna ST, Reboussin DM, Strotmeyer ES, Millman RP, Zammit G, Walkup MP, Wadden TA, Wing RR, Pi-Sunyer FX, Spira AP, Foster GD; Sleep AHEAD Research Subgroup of the Look AHEAD Research Group. Effects of Weight Loss on Obstructive Sleep Apnea Severity. Ten-Year Results of the Sleep AHEAD Study. Am J Respir Crit Care Med. 2021 Jan 15;203(2):221-229. doi: 10.1164/rccm.201912-2511OC.
45. Sutherland K, Phillips CL, Yee BJ, Grunstein RR, Cistulli PA. Maxillomandibular Volume Influences the Relationship between Weight Loss and Improvement in Obstructive Sleep Apnea. Sleep. 2016 Jan 1;39(1):43-9. doi: 10.5665/sleep.5314.
46. Oksenberg A, Gadoth N, Töyräs J, Leppänen T. Prevalence and characteristics of positional obstructive sleep apnea (POSA) in patients with severe OSA. Sleep Breath. 2020 Jun;24(2):551-559. doi: 10.1007/s11325-019-01897-1.
47. Koka V, De Vito A, Roisman G, Petitjean M, Filograna Pignatelli GR, Padovani D, Randerath W. Orofacial Myofunctional Therapy in Obstructive Sleep Apnea Syndrome: A Pathophysiological Perspective. Medicina (Kaunas). 2021 Apr 1;57(4):323. doi: 10.3390/medicina57040323.
48. Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, Kushida CA. Myofunctional Therapy to Treat Obstructive Sleep Apnea: A Systematic Review and Meta-analysis. Sleep. 2015 May 1;38(5):669-75. doi: 10.5665/sleep.4652.
49. Qaseem A, Holty JE, Owens DK, Dallas P, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013 Oct 1;159(7):471-83. doi: 10.7326/0003-4819-159-7-201310010-00704.
50. Gillespie MB, Reddy RP, White DR, Discolo CM, Overdyk FJ, Nguyen SA. A trial of drug-induced sleep endoscopy in the surgical management of sleep-disordered breathing. Laryngoscope. 2013 Jan;123(1):277-82. doi: 10.1002/lary.23506.
51. Ng JH, Yow M. Oral Appliances in the Management of Obstructive Sleep Apnea. Sleep Med Clin. 2020 Jun;15(2):241-250. doi: 10.1016/j.jsmc.2020.02.010.
52. Wishney M, Darendeliler MA, Dalci O. Myofunctional therapy and prefabricated functional appliances: an overview of the history and evidence. Aust Dent J. 2019 Jun;64(2):135-144. doi: 10.1111/adj.12690.
53. Li HY. Updated Palate Surgery for Obstructive Sleep Apnea. Adv Otorhinolaryngol. 2017;80:74-80. doi: 10.1159/000470869.
54. Friberg D, Sundman J, Browaldh N. Long-term evaluation of satisfaction and side effects after modified uvulopalatopharyngoplasty. Laryngoscope. 2020 Jan;130(1):263-268. doi: 10.1002/lary.27917.
55. De Vito A, Woodson BT, Koka V, Cammaroto G, Iannella G, Bosi M, Pelucchi S, Filograna-Pignatelli GR, El Chater P, Vicini C. OSA Upper Airways Surgery: A Targeted Approach.

Medicina (Kaunas). 2021 Jul 6;57(7):690. doi: 10.3390/medicina57070690.

56. Handler E, Hamans E, Goldberg AN, Mickelson S. Tongue suspension: an evidence-based review and comparison to hypopharyngeal surgery for OSA. Laryngoscope. 2014 Jan;124(1):329-36. doi: 10.1002/lary.24187.
57. Aurora RN, Casey KR, Kristo D, Auerbach S, Bista SR, Chowdhuri S, Karippot A, Lamm C, Ramar K, Zak R, Morgenthaler TI; American Academy of Sleep Medicine. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. Sleep. 2010 Oct;33(10):1408-13. doi: 10.1093/sleep/33.10.1408.
58. Camacho M, Noller MW, Del Do M, Wei JM, Gouveia CJ, Zaghi S, Boyd SB, Guilleminault C. Long-term Results for Maxillomandibular Advancement to Treat Obstructive Sleep Apnea: A Meta-analysis. Otolaryngol Head Neck Surg. 2019 Apr;160(4):580-593. doi: 10.1177/0194599818815158.
59. Camacho M, Malu OO, Kram YA, Nigam G, Riaz M, Song SA, Tolisano AM, Kushida CA. Nasal Dilators (Breathe Right Strips and NoZovent) for Snoring and OSA: A Systematic Review and Meta-Analysis. Pulm Med. 2016;2016:4841310. doi: 10.1155/2016/4841310.
60. Barrera JE. Skeletal Surgery for Obstructive Sleep Apnea. Otolaryngol Clin North Am. 2016 Dec;49(6):1433-1447. doi: 10.1016/j.otc.2016.07.006.
61. Camacho M, Certal V, Brietzke SE, Holty JE, Guilleminault C, Capasso R. Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2014 Mar;124(3):803-11. doi: 10.1002/lary.24433.
62. Barthel SW, Strome M. Snoring, obstructive sleep apnea, and surgery. Med Clin North Am. 1999 Jan;83(1):85-96. doi: 10.1016/s0025-7125(05)70089-4.
63. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, Van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP; STAR Trial Group. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014 Jan 9;370(2):139-49. doi: 10.1056/NEJMoa1308659.
64. Wray CM, Thaler ER. Hypoglossal nerve stimulation for obstructive sleep apnea: A review of the literature. World J Otorhinolaryngol Head Neck Surg. 2016 Dec 22;2(4):230-233. doi: 10.1016/j.wjorl.2016.11.005.
65. de Raaff CAL, de Vries N, van Wagensveld BA. Obstructive sleep apnea and bariatric surgical guidelines: summary and update. Curr Opin Anaesthesiol. 2018 Feb;31(1):104-109. doi: 10.1097/ACO.0000000000000542.
66. Smith PL, Eisele DW, Podszus T, Penzel T, Grote L, Peter JH, Schwartz AR (1996) Electrical stimulation of upper airway musculature. Sleep 19:S284-7
67. Strollo PJ, Gillespie MB, Soose RJ, Maurer JT, de Vries N, Cornelius J, Hanson RD, Padhya TA, Steward DL, Woodson BT, Verbraecken J, Vanderveken OM, Goetting MG, Feldman N, Chabolle F, Badr MS, Randerath W, Strohl KP, Stimulation Therapy for Apnea Reduction (STAR) Trial Group KP, Group for the ST for AR (STAR) T (2015) Upper Airway Stimulation for Obstructive Sleep Apnea: Durability of the Treatment Effect at 18 Months. Sleep 38:1593–8. https://doi.org/10.5665/sleep.5054
68. Friedman M, Jacobowitz O, Hwang MS, Bergler W, Fietze I, Rombaux P, Mwenge GB, Yalamanchali S, Campana J, Maurer JT (2016) Targeted hypoglossal nerve stimulation for the treatment of obstructive sleep apnea: Six-month results. The Laryngoscope 1–6.

https://doi.org/10.1002/lary.25909

69. Eastwood PR, Barnes M, MacKay SG, Wheatley JR, Hillman DR, Nguyên X-L, Lewis R, Campbell MC, Pételle B, Walsh JH, Jones AC, Palme CE, Bizon A, Meslier N, Bertolus C, Maddison KJ, Laccourreye L, Raux G, Denoncin K, Attali V, Gagnadoux F, Launois SH (2019) Bilateral Hypoglossal Nerve Stimulation for Treatment of Adult Obstructive Sleep Apnea. The European respiratory journal. https://doi.org/10.1183/13993003.01320-2019
70. Kent DT, Weiner JS, Chio EG, Weidenbecher M (2020a) Hypoglossal nerve stimulator implantation via a 2-incision technique. Operative Techniques in Otolaryngology-Head and Neck Surgery 31:e35–e42.
71. Patel J, Daniels K, Bogdan L, Huntley C, Boon M. Effect of Gender, Age, and Profound Disease on Upper Airway Stimulation Outcomes. Ann Otol Rhinol Laryngol. 2020 Aug;129(8):772-780. doi: 10.1177/0003489420911656.
72. Lee CH, Seay EG, Walters BK, Scalzitti NJ, Dedhia RC. Therapeutic positive airway pressure level predicts response to hypoglossal nerve stimulation for obstructive sleep apnea. J Clin Sleep Med 2019;15:1165–1172.
73. Steffen A, Sommer JU, Hofauer B, Maurer JT, Hasselbacher K, Heiser C (2018b) Outcome after one year of upper airway stimulation for obstructive sleep apnea in a multicenter German post-market study. The Laryngoscope 128:509–515. https://doi.org/10.1002/lary.26688
74. Heiser C, Steffen A, Boon M, Hofauer B, Doghramji K, Maurer JT, Sommer JU, Soose R, Strollo PJ, Schwab R, Thaler E, Withrow K, Kominsky A, Larsen C, Kezirian EJ, Hsia J, Chia S, Harwick J, Strohl K, Mehra R, ADHERE registry investigators R (2019) Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. The European respiratory journal 53.
75. Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, Padhya TA, Badr MS, Lin H, Vanderveken OM, Mickelson S, Strollo PJ (2018) Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. Otolaryngology–Head and Neck Surgery 159:194–202.
76. Thaler E, Schwab R, Maurer J, Soose R, Larsen C, Stevens S, Stevens D, Boon M, Huntley C, Doghramji K, Waters T, Kominsky A, Steffen A, Kezirian E, Hofauer B, Sommer U, Withrow K, Strohl K, Heiser C. Results of the ADHERE upper airway stimulation registry and predictors of therapy efficacy. Laryngoscope. 2020 May;130(5):1333-1338. doi: 10.1002/lary.28286.
77. Schwab RJ, Wang SH, Verbraecken J, Vanderveken OM, Van de Heyning P, Vos WG, DeBacker JW, Keenan BT, Ni Q, DeBacker W. Anatomic predictors of response and mechanism of action of upper airway stimulation therapy in patients with obstructive sleep apnea. Sleep. 2018 Apr 1;41(4). doi: 10.1093/sleep/zsy021.
78. Lee CH, Seay EG, Reese JW, Wu X, Schwab RJ, Keenan B, Dedhia RC. Clinical Radiographic Predictors of Response to Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea. Otolaryngol Head Neck Surg. 2021 May;164(5):1122-1127. doi: 10.1177/0194599820963141.
79. Arens P, Uecker FC, Fietze I, Penzel T, Olze H, Fischer T, Dommerich S (2019) Evaluation of the base of tongue in obstructive sleep apnea during electric stimulation therapy of the hypoglossal nerve: Current sonographic methods and initial results. Somnologie 23.

https://doi.org/10.1007/s11818-019-0193-9

80. Arens P, Fischer T, Dommerich S, Olze H, Lerchbaumer MH (2021) Ultrasound Shear Wave Elastography of the Tongue during Selective Hypoglossal Nerve Stimulation in Patients with Obstructive Sleep Apnea Syndrome. Ultrasound in Medicine & Biology 47. https://doi.org/10.1016/j.ultrasmedbio.2021.06.009
81. Abuan MRA, Lin WN, Hsin LJ, Lee LA, Fang TJ, Chen NH, Lo YL, Li HY. Tongue imaging during drug-induced sleep ultrasound in obstructive sleep apnea patients. Auris Nasus Larynx 2020;47:828–836.
82. Siegel H, Sonies BC, Graham B, McCutchen C, Hunter K, Vega-Bermudez F, Sato S. Obstructive sleep apnea: A study by simultaneous polysomnography and ultrasonic imaging. Neurology. 2000 May 9;54(9):1872. doi: 10.1212/wnl.54.9.1872.
83. Manlises CO, Chen JW, Huang CC. Dynamic tongue area measurements in ultrasound images for adults with obstructive sleep apnea. J Sleep Res. 2020 Aug;29(4):e13032. doi: 10.1111/jsr.13032.
84. Vanderveken OM, Maurer JT, Hohenhorst W, Hamans E, Lin HS, Vroegop AV, Anders C, de Vries N, Van de Heyning PH. Evaluation of drug-induced sleep endoscopy as a patient selection tool for implanted upper airway stimulation for obstructive sleep apnea. J Clin Sleep Med. 2013 May 15;9(5):433-8. doi: 10.5664/jcsm.2658.
85. Strollo PJ, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, Hanson RD, Padhya TA, Steward DL, Gillespie MB, Woodson BT, van de Heyning PH, Goetting MG, Vanderveken OM, Feldman N, Knaack L, Strohl KP (2014) Upper-airway stimulation for obstructive sleep apnea. The New England journal of medicine 370:139–49. https://doi.org/10.1056/NEJMoa1308659
86. Steffen A, Frenzel H, Wollenberg B, König IR. Patient selection for upper airway stimulation: is concentric collapse in sleep endoscopy predictable? Sleep Breath. 2015 Dec;19(4):1373-6. doi: 10.1007/s11325-015-1277-9.
87. Lewis R, Le J, Czank C, Raux G (2021) Control of OSA in a patient with CCC of soft palate using bilateral hypoglossal nerve stimulation. Clinical Case Reports 9:2222. https://doi.org/10.1002/CCR3.3990
88. Huyett P, Kent DT, D'Agostino MA, Green KK, Soose RJ, Kaffenberger TM, Woodson BT, Huntley C, Boon MS, Heiser C, Birk A, Suurna MV, Lin HS, Waxman JA, Kezirian EJ. Drug-Induced Sleep Endoscopy and Hypoglossal Nerve Stimulation Outcomes: A Multicenter Cohort Study. Laryngoscope. 2021 Jul;131(7):1676-1682. doi: 10.1002/lary.29396.
89. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. Am J Respir Crit Care Med. 2013; 188: 996-1004.
90. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. Nat Sci Sleep. 2018 Jan 23;10:21-34. doi: 10.2147/NSS.S124657.
91. Vanderveken OM, Beyers J, Op de Beeck S, Dieltjens M, Willemen M, Verbraecken JA, De Backer WA, Van de Heyning PH. Development of a Clinical Pathway and Technical Aspects of Upper Airway Stimulation Therapy for Obstructive Sleep Apnea. Front Neurosci. 2017 Sep 21;11:523. doi: 10.3389/fnins.2017.00523.
92. Op de Beeck S, Wellman A, Dieltjens M, Strohl KP, Willemen M, Van de Heyning PH,

Verbraecken JA, Vanderveken OM, Sands SA; STAR Trial Investigators. Endotypic Mechanisms of Successful Hypoglossal Nerve Stimulation for Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2021 Mar 15;203(6):746-755. doi: 10.1164/rccm.202006-2176OC.

93. Heiser C, Thaler E, Boon M, Soose RJ, Woodson BT. Updates of operative techniques for upper airway stimulation. Laryngoscope. 2016 Sep;126 Suppl 7:S12-6. doi: 10.1002/lary.26158.
94. Leung RS, Comondore VR, Ryan CM, Stevens D. Mechanisms of sleep-disordered breathing: causes and consequences. Pflugers Arch. 2012 Jan;463(1):213-30. doi: 10.1007/s00424-011-1055-x.
95. Safiruddin F, Vanderveken OM, de Vries N, Maurer JT, Lee K, Ni Q, Strohl KP (2015) Effect of upper-airway stimulation for obstructive sleep apnoea on airway dimensions. Eur Respir J 45:129–138. https://doi.org/10.1183/09031936.00059414
96. Steffen A, Sommer | J Ulrich, Strohl K, Hasselbacher K, Suurna M v, Benedikt |, Clemens Heiser | (2019) Changes in breath cycle sensing affect outcomes in upper airway stimulation in sleep apnea. https://doi.org/10.1002/lio2.334
97. Meleca J, Kominsky A (2020) Reconfiguration of Upper Airway Stimulation Devices Utilizing Awake Endoscopy. The Laryngoscope 130:2494–2498. https://doi.org/10.1002/LARY.28569
98. Pawlak D, Bohorquez D, König I, Steffen A, Thaler E (2021) Effect of Electrode Configuration and Impulse Strength on Airway Patency in Neurostimulation for Obstructive Sleep Apnea. The Laryngoscope 131:2148–2153. https://doi.org/10.1002/LARY.29530
99. Steffen A, Jeschke S, Soose RJ, Hasselbacher K, König IR (2021b) Neuromodulation: Technology at the Neural Interface Impulse Configuration in Hypoglossal Nerve Stimulation in Obstructive Sleep Apnea: The Effect of Modifying Pulse Width and Frequency. https://doi.org/10.1111/ner.13490
100. Heiser C, Maurer JT, Steffen A (2016a) Functional outcome of tongue motions with selective hypoglossal nerve stimulation in patients with obstructive sleep apnea. Sleep and Breathing 20:553–560. https://doi.org/10.1007/s11325-015-1237-4
101. Heiser C, Edenharter G, Bas M, Wirth M, Hofauer B (2017a) Palatoglossus coupling in selective upper airway stimulation. The Laryngoscope 127:E378–E383. https://doi.org/10.1002/lary.26487
102. Steffen A, Kilic A, König IR, Suurna M v., Hofauer B, Heiser C (2018a) Tongue motion variability with changes of upper airway stimulation electrode configuration and effects on treatment outcomes. The Laryngoscope 128:1970–1976. https://doi.org/10.1002/lary.27064
103. Coca K, Heiser C, Huntley C, Boon M, de Vries N, Mamidala M, Gillespie M (2021) Hypoglossal Nerve Stimulation Usage by Therapy Nonresponders. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery. https://doi.org/10.1177/01945998211036867
104. Hofauer B, Steffen A, Knopf A, Hasselbacher K, Heiser C Patient experience with upper airway stimulation in the treatment of obstructive sleep apnea. https://doi.org/10.1007/s11325-018-1689-4
105. Rosenthal ME, Lyons MM, Schweller J, Yildiz VO, Chio EG, Khan MS (2021) Association

between anxiety, depression, and emotional distress and hypoglossal nerve stimulator adherence. Sleep and Breathing. https://doi.org/10.1007/s11325-021-02366-4

106. Soose RJ, Faber K, Greenberg H, Boon M, Woodson T, Strollo P, author Ryan Soose CJ (2021) Post-implant care pathway: lessons learned and recommendations after 5 years of clinical implementation of hypoglossal nerve stimulation therapy. 4–10. https://doi.org/10.1093/sleep/zsaa279
107. Huyett P, Stagnone R (2020) Use of overnight pulse oximetry and a type 3 sleep study to titrate hypoglossal nerve stimulation therapy. Journal of Clinical Sleep Medicine 16:2109–2111. https://doi.org/10.5664/JCSM.8754
108. Steffen A, König IR, Baptista PM, Abrams N, Jeschke S, Hasselbacher K (2020) Home Sleep Testing to Direct Upper Airway Stimulation Therapy Optimization for Sleep Apnea. https://doi.org/10.1002/lary.29043
109. Steffen A, Heiser C, Galetke W, Herkenrath S-D, Maurer JT, Günther E, Stuck BA, Woehrle H, Löhler J, Randerath W (2021a) Hypoglossal nerve stimulation for obstructive sleep apnea: updated position paper of the German Society of Oto-Rhino-Laryngology, Head and Neck Surgery. European Archives of Oto-Rhino-Laryngology. https://doi.org/10.1007/s00405-021-06902-6
110. Costantino A, Rinaldi V, Moffa A, Luccarelli V, Bressi F, Cassano M, Casale M, Baptista P. Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis. Sleep Breath. 2020 Jun;24(2):399-411. doi: 10.1007/s11325-019-01923-2.
111. Lewis R, Pételle B, Campbell MC, Mackay S, Palme C, Raux G, Sommer ; J Ulrich, Maurer JT (2019) Implantation of the Nyxoah Bilateral Hypoglossal Nerve Stimulator for Obstructive Sleep Apnea. https://doi.org/10.1002/lio2.312
112. Woodson BT, Strohl KP, Soose RJ, Gillespie MB, Maurer JT, de Vries N, Padhya TA, Badr MS, Lin H, Vanderveken OM, Mickelson S, Strollo PJ (2018) Upper Airway Stimulation for Obstructive Sleep Apnea: 5-Year Outcomes. Otolaryngology–Head and Neck Surgery 159:194–202. https://doi.org/10.1177/0194599818762383
113. Dedhia RC, Quyyumi AA, Park J, Shah AJ, Strollo PJ, Bliwise DL (2018) Cardiovascular endpoints for obstructive sleep apnea with twelfth cranial nerve stimulation (CARDIOSA-12): Rationale and methods. The Laryngoscope 128:2635–2643. https://doi.org/10.1002/lary.27284
114. Dedhia RC, Shah AJ, Bliwise DL, Quyyumi AA, Strollo PJ, Li Q, da Poian G, Clifford GD (2019) Hypoglossal Nerve Stimulation and Heart Rate Variability: Analysis of STAR Trial Responders. Otolaryngology-Head and Neck Surgery 160:165–171. https://doi.org/10.1177/0194599818800284
115. Caloway CL, Diercks GR, Keamy D, de Guzman V, Soose R, Raol N, Shott SR, Ishman SL, Hartnick CJ (2019) Update on Hypoglossal Nerve Stimulation in Children With Down Syndrome and Obstructive Sleep Apnea. https://doi.org/10.1002/lary.28138
116. Li C, Boon M, Ishman SL, Suurna M v. (2018) Hypoglossal nerve stimulation in three adults with down syndrome and severe obstructive sleep apnea. The Laryngoscope lary.27723. https://doi.org/10.1002/lary.27723
117. Stenerson ME, Yu PK, Kinane TB, Skotko BG, Hartnick CJ (2021) Long-term stability of hypoglossal nerve stimulation for the treatment of obstructive sleep apnea in children with Down syndrome. International Journal of Pediatric Otorhinolaryngology 149:110868.

https://doi.org/10.1016/J.IJPORL.2021.110868

118. Patil RD, Sarber KM, Epperson M v, Tabangin M, Altaye M, Mesa F, Ishman SL (2020) Hypoglossal Nerve Stimulation: Outcomes in Veterans with Obstructive Sleep Apnea and Common Comorbid Post-traumatic Stress Disorder. https://doi.org/10.1002/lary.29292
119. Myc LA, Churnin IT, Jameson MJ, Davis EM (2018) Treatment of Comorbid Obstructive Sleep Apnea by Upper Airway Stimulation Results in Resolution of Debilitating Symptoms of Restless Legs Syndrome. Journal of Clinical Sleep Medicine 14:1797–1800. https://doi.org/10.5664/jcsm.7400
120. Berger M, Solelhac G, Horvath C, Heinzer R, Brill AK. Treatment-emergent central sleep apnea associated with non-positive airway pressure therapies in obstructive sleep apnea patients: A systematic review. Sleep Med Rev. 2021 Aug;58:101513. doi: 10.1016/j.smrv.2021.101513.
121. Weitzman ED, Kahn E, Pollak CP. Quantitative analysis of sleep and sleep apnea before and after.tracheostomy in patients with the hypersomnia-sleep apnea syndrome. Sleep. 1980;3(3-4):407-23. doi: 10.1093/sleep/3.3-4.407.
122. Sarber KM, Ishman SL, Patil RD. Emergence of Cheyne-Stokes Breathing After Hypoglossal Nerve Stimulator Implant in a Patient With Mixed Sleep Apnea. JAMA Otolaryngol Head Neck Surg. 2019 Apr 1;145(4):389-390. doi: 10.1001/jamaoto.2018.4077.
123. Bestourous DE, Pasick LJ, Benito DA, Zapanta PE (2020) Adverse events associated with the Inspire implantable hypoglossal nerve stimulator: A MAUDE database review. American Journal of Otolaryngology 41:102616. https://doi.org/10.1016/J.AMJOTO.2020.102616
124. Bellamkonda N, Shiba T, Mendelsohn AH (2021) Adverse Events in Hypoglossal Nerve Stimulator Implantation: 5-Year Analysis of the FDA MAUDE Database. Otolaryngology-Head and Neck Surgery 164:443–447. https://doi.org/10.1177/0194599820960069
125. Arens P, Penzel T, Fietze I, Blau A, Weller B, Olze H, Dommerich S. Safety and effectiveness in explantation and re-implantation of hypoglossal nerve stimulation devices. Eur Arch Otorhinolaryngol. 2021 Feb;278(2):477-483. doi: 10.1007/s00405-020-06170-w.
126. Kompelli AR, Ni JS, Nguyen SA, Lentsch EJ, Neskey DM, Meyer TA. The outcomes of hypoglossal nerve stimulation in the management of OSA: A systematic review and meta-analysis. World J Otorhinolaryngol Head Neck Surg. 2018 Sep 25;5(1):41-48. doi: 10.1016/j.wjorl.2018.04.006.
127. Arteaga A, Pitts K, Lewis A (2018) Iatrogenic pneumothorax during hypoglossal nerve stimulator implantation. American journal of otolaryngology 39:636–638. https://doi.org/10.1016/J.AMJOTO.2018.06.014
128. Lou B, Hahn S, Korotun M, Quintero L, Shikowitz M, Greenberg H (2021) Space invader: pleural penetration of a hypoglossal nerve stimulator sensor lead. Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine. https://doi.org/10.5664/JCSM.9492
129. Arens P, Hänsel T, Wang Y. Hypoglossal Nerve Stimulation Therapy. Adv Exp Med Biol. 2022;1384:351-372. doi: 10.1007/978-3-031-06413-5_21.
130. Vanderveken OM, Dieltjens M, Wouters K, De Backer WA, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-

disordered breathing. Thorax. 2013 Jan;68(1):91-6. doi: 10.1136/thoraxjnl-2012-201900.

131. Dieltjens M, Vanderveken O. Oral Appliances in Obstructive Sleep Apnea. Healthcare (Basel). 2019 Nov 8;7(4):141. doi: 10.3390/healthcare7040141.
132. Judd RT, Mokhlesi B, Shogan A, Baroody FM. Improvement in Central Sleep Apnea Following Adenotonsillectomy in Children. Laryngoscope. 2022 Feb;132(2):478-484. doi: 10.1002/lary.29784.
133. Patel J, Daniels K, Bogdan L, Huntley C, Boon M. Elevated Central and Mixed Apnea Index after Upper Airway Stimulation. Otolaryngol Head Neck Surg. 2020 May;162(5):767-772. doi: 10.1177/0194599820912740.
134. Bohorquez D, Mahmoud AF, Yu JL, Thaler ER. Upper airway stimulation therapy and sleep architecture in patients with obstructive sleep apnea. Laryngoscope. 2020 Apr;130(4):1085-1089. doi: 10.1002/lary.28057.
135. Hofauer B, Philip P, Wirth M, Knopf A, Heiser C. Effects of upper-airway stimulation on sleep architecture in patients with obstructive sleep apnea. Sleep Breath. 2017 Dec;21(4):901-908. doi: 10.1007/s11325-017-1519-0.
136. Boroosan A, Salapatas AM, Friedman M. Clinical Predictors of OSA Treatment Success Following Implantation of a Hypoglossal Nerve Stimulation Device. Otolaryngol Head Neck Surg. 2022 Apr 19:1945998221087594. doi: 10.1177/01945998221087594.
137. Dedhia RC, Strollo PJ, Soose RJ. Upper Airway Stimulation for Obstructive Sleep Apnea: Past, Present, and Future. Sleep. 2015;38(6):899-906. Published 2015 Jun 1. doi:10.5665/sleep.4736Wang J, Wang Y, Feng J, Chen BY, Cao J. Complex sleep apnea syndrome. Patient Prefer Adherence. 2013. Jul 3;7:633-41. doi: 10.2147/PPA.S46626.
138. Bender B. Hypoglossusstimulation bei OSAS [Upper Airway Stimulation in OSA]. Laryngorhinootologie. 2016 Nov;95(11):795-807. German. doi: 10.1055/s-0042-116895.
139. Zhang J, Wang L, Guo HJ, Wang Y, Cao J, Chen BY. Treatment-emergent central sleep apnea: a unique sleep-disordered breathing. Chin Med J (Engl). 2020 Nov 20;133(22):2721-2730. doi: 10.1097/CM9.0000000000001125.
140. Gilmartin GS, Daly RW, Thomas RJ. Recognition and management of complex sleep-disordered breathing. Curr Opin Pulm Med. 2005 Nov;11(6):485-93. doi: 10.1097/01.mcp.0000183061.98665.b0.
141. Morgenthaler TI, Kagramanov V, Hanak V, Decker PA. Complex sleep apnea syndrome: is it a unique clinical syndrome? Sleep. 2006 Sep;29(9):1203-9. doi: 10.1093/sleep/29.9.1203.
142. Kuźniar TJ, Morgenthaler TI. Treatment of complex sleep apnea syndrome. Chest. 2012 Oct;142(4):1049-1057. doi: 10.1378/chest.11-3223.
143. Testani E, De Corso E, Losurdo A, Fiorita A, Vollono C, Marca GD, Scarano E. Treatment-emergent central sleep apnoea after surgery for obstructive sleep apnoea. Acta Otorhinolaryngol Ital. 2018 Oct;38(5):476-479. doi: 10.14639/0392-100X-1476.
144. Orr JE, Malhotra A, Sands SA. Pathogenesis of central and complex sleep apnoea. Respirology. 2017.Jan;22(1):43-52. doi: 10.1111/resp.12927.
145. Nigam G, Pathak C, Riaz M. A systematic review on prevalence and risk factors associated with treatment- emergent central sleep apnea. Ann Thorac Med. 2016 Jul-Sep;11(3):202-10. doi: 10.4103/1817-1737.185761.
146. Zhu Z, Hofauer B, Wirth M, Heiser C. Long-term changes of stimulation intensities in

hypoglossal nerve stimulation. J Clin Sleep Med. 2020;16(10):1775-1780. doi:10.5664/jcsm.8320

147. Baptista PM, Costantino A, Moffa A, Rinaldi V, Casale M. Hypoglossal Nerve Stimulation in the Treatment of Obstructive Sleep Apnea: Patient Selection and New Perspectives. Nat Sci Sleep. 2020;12:151-159. Published 2020 Feb 13. doi:10.2147/NSS.S221542
148. Sands SA, Edwards BA, Terrill PI, Taranto-Montemurro L, Azarbarzin A, Marques M, Hess LB, White DP, Wellman A. Phenotyping Pharyngeal Pathophysiology using Polysomnography in Patients with Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2018 May 1;197(9):1187-1197. doi: 10.1164/rccm.201707-1435OC.
149. Dutta R, Delaney G, Toson B, Jordan AS, White DP, Wellman A, Eckert DJ. A Novel Model to Estimate Key Obstructive Sleep Apnea Endotypes from Standard Polysomnography and Clinical Data and Their Contribution to Obstructive Sleep Apnea Severity. Ann Am Thorac Soc. 2021 Apr;18(4):656-667. doi: 10.1513/AnnalsATS.202001-064OC.
150. Kent DT, Zealear D, Schwartz AR (2021) Ansa Cervicalis Stimulation. Chest 159. https://doi.org/10.1016/j.chest.2020.10.010

Statutory Declaration

“I, YanWang, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic, “ Outcomes and underlying mechanisms of hypoglossal nerve stimulation in patients with obstructive sleep apnea / Ergebnisse und zugrundeliegende Mechanismen der Hypoglossusnerv-Stimulation bei Patienten mit obstruktiver Schlafapnoe ” independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts, which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons. I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors (www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Publication list

1. Wang Y, Sun C, Cui X, Guo Y, Wang Q, Liang H. The role of drug-induced sleep endoscopy: predicting and guiding upper airway surgery for adult OSA patients. Sleep Breath. 2018 Dec;22(4):925-931. doi: 10.1007/s11325-018-1730-7.
2. Wang Y, Fietze I, Salanitro M, Penzel T. Comparison of the value of the STOP-BANG questionnaire with oxygen desaturation index in screening obstructive sleep apnea in Germany. Sleep Breath. 2022 Oct 21. doi: 10.1007/s11325-022-02727-7.
3. Wang Y, Penzel T, Salanitro M, Arens P. Persistent Treatment-Emergent Central Sleep Apnea (TECSA) Following Hypoglossal Nerve Stimulation. Nat Sci Sleep. 2022 Dec 22;14:2227-2236. doi: 10.2147/NSS.S382710.

Book chapter

Arens P, Hänsel T, Wang Y. Hypoglossal nerve stimulation. In: Penzel Thomas, Hornero Roberto (eds.). Advances in the Diagnosis and Treatment of Sleep Apnea: Filling the Gap between Physicians and Engineers. Cham: Springer Nature Switzerland.2022,inpress.

Acknowledgments

First and foremost, I would like to express my deepest gratitude to my supervisors and the chair of the interdispline center - Prof. Dr. rer. Physiol Thomas Penzel, for his invaluable patience and continuing support. His immense knowledge and plentiful experience have encouraged me throughout my academic research and daily life. Especially, I want to express my sincere gratitude to the Chinese council scholarship (CSC), which supported for 3-years studentship that allowed me to conduct this thesis.

I would also like to extend my sincere thanks to Dr. Arens Philipp at the otolaryngology department for his valuable guidance and assistance at every research project stage, treasured support which was really influential in shaping my experiment methods and critiquing my results. Many thanks to Dr. Ingo Fietze, Dr. Martin Glos, Dr. Naima Laharnar, Dr. Matthew cilantro, and Mr. Jacob Siegert for their technical support in my study. Also, I want to thank all the colleagues in the sleeping center on Virchow Campus and the outpatient department in Mitte Campus. Their kind help and support have made my study and life in Germany a wonderful time.

Finally, I would like to express my gratitude to my parents, friends and my lovely cat, Schnee. Without their tremendous understanding, encouragement and warm company over the past 3 years, it would be impossible for me to complete my study in Germany.

Confirmation by a statistician

CHARITÉ

CharitéCentrum für Human- und Gesundheitswissenschaften

Charité | Campus Charité Mitte | 10117 Berlin

Name, Vorname: Wang, Yan

Emailadresse: yang.wang@charite.de

Matrikelnummer: 227508

PromotionsbetreuerIn: Prof. Dr. Thomas Penzel

Promotionsinstitution / Klinik: ISMZ – Schlafmedizinische Fachabteilung CVK

Institut für Biometrie und klinische Epidemiologie (iBikE)

Direktor: Prof. Dr. Frank Konietschke

Postanschrift:
Charitéplatz 1 | 10117 Berlin
Besucheranschrift:
Reinhardstraße 58 | 10117 Berlin

Tel. +49 (0)30 450 562171
frank.konietschke@charite.de
https://biometrie.charite.de/

Bescheinigung

Hiermit bescheinige ich, dass Frau Yan Wang innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 20.07.2022

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Zusammenfassung der Patienten – Charakteristika in einer Table 1 unter Angabe von Mittelwert und Standardabweichung für kontinuierliche Variablen und absoluten und relativen Werten für ordinal skalierte Variablen.
- P- Werte dürfen nur deskriptiv interpretiert werden, da es sich um eine explorative Studie handelt und nicht für multiples Testen adjustiert wurde.
- Vergleich prä und post OP mit Vorzeichentests.
- Einflussfaktoren auf Erfolg der OP mit U-Test bzw. Chi-Quadrat-Test sofern die Annahmen erfüllt sind unter Angabe von Effektstärken und Konfidenzintervallen.
- Bei der Subgruppenanalyse mit TECYA Patienten kann auf Grund der kleinen Fallzahl nicht getestet werden.

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 20.07.2022

Name des Beraters/ der Beraterin: Lorena Hafermann

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN
Institut für Biometrie und
Klinische Epidemiologie
Campus Charité Mitte
Charitéplatz 1 | D-10117 Berlin
Sitz: Reinhardtstr. 58

Unterschrift BeraterIn, Institutsstempel