Assessment of the effect of hypoglossal nerve stimulation therapy on the site of collapse during DISE

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List of abbreviations

AHI	Apnea Hypopnea Index
BMI	Body Mass Index
CCC	Complete Concentric Collapse of the palate
CPAP	Continuous Positive Airway Pressure
DISE	Drug-Induced Sleep Endoscopy
HNS	Hypoglossal Nerve Stimulation
MAD	Mandibular Advancement Device
OSA	Obstructive Sleep Apnea
PSG	Polysomnography
SASHB	Sleep Apnea-Specific Hypoxic Burden

SUMMARY

OBJECTIVES
To assess the site, pattern and degree of upper airway collapse before and during hypoglossal nerve stimulation (HNS) treatment using clinical standard drug-induced sleep endoscopy (DISE) and using a novel, non-invasive method predicting site of collapse from raw polysomnography (PSG) data.
Furthermore, outcomes will be compared between responders and non-responders.

HYPOTHESIS
We expect a reduction in collapse severity reflected by a lower degree of obstruction on DISE-scoring and an increased area of the upper airway under HNS treatment. Regarding the site of collapse, we expect an increase in the upper airway area at the tongue base and palatal level due to the mechanical linkage between the retropalatal and retroglossal area through the anterior palatal pillar, as seen in previous studies.

STUDY DESIGN
Prospective interventional study.

STUDY POPULATION
Patients with moderate to severe OSA (AHI>15/h) and scheduled for HNS treatment.

INTERVENTION
Drug-induced sleep endoscopy. Pre-operative as a part of the standard clinical pathway for HNS-eligibility. An additional DISE will be performed after one year of HNS treatment to assess the effect of therapy.

OUTCOME MEASURES
Site, pattern and degree of collapse as assessed during DISE. Diagnostic data as collected in the standard pathway before treatment, with an additional DISE after one year of treatment. Furthermore, raw PSG data will be analyzed to non-invasively determine the site of collapse, using data from baseline PSG and one-year follow-up PSG which are part of the standard clinical pathway.

SETTING AND SAMPLE SIZE
Patients will be recruited at the ENT department at Antwerp University Hospital. Accounting for a patient dropout of 10%, a total of 58 patients will be recruited in order to have an inclusion of 52 patients.
All patients scheduled for HNS-implantation at Antwerp University Hospital will be invited to participate in this study.

TIME SCHEDULE
Patients will be included from April 1st, 2024, until March 31st, 2027.

1 INTRODUCTION AND RATIONALE

Obstructive sleep apnea (OSA) is one of the most prevalent respiratory disorders and the most frequent type of sleep-disordered breathing, characterized by recurrent pharyngeal collapses during sleep. This disturbance results in fragmented, nonrestorative sleep.[1] Furthermore, intermittent hypoxemia might result in both acute and chronic elevation of blood pressure, while also being a risk factor for overall all-cause mortality.[2,3] OSA symptoms include snoring, unrefreshing sleep, fatigue, excessive sleepiness and nocturnal gasping or choking.[4] OSA is diagnosed using polysomnography (PSG), during which several parameters are measured throughout the night, including airflow, electroencephalography, electromyography, oxygen desaturation and heart rate. Using these measures, OSA severity is quantified by the apnea-hypopnea index, capturing the number of apneas and hypopneas per hour of sleep.

As OSA is associated with multiple comorbidities, efficient treatment is mandatory.[5] In clinical practice, the standard treatment for OSA is continuous positive airway pressure (CPAP), which opens the upper airway by creating a pneumatic splint.[6] Alternative treatments include mandibular advancement device (MAD) treatment, which (re)opens the upper airway by protruding the mandible, position treatment to avoid supine position, drug treatments, hypoglossal nerve stimulation treatment (the main focus of this study) and other surgical treatments.[7-9] While CPAP is characterized by an overall greater efficacy, adherence might be limited. Non-CPAP treatments are characterized by a higher adherence, yet their efficacy is patient dependent.

Respiration-synchronized hypoglossal nerve stimulation (HNS) is an innovative technique in which the hypoglossal nerve is stimulated to protrude the tongue during inspiration.[10] A lot of effort has been put in upfront patient selection of this treatment. Especially drug-induced sleep endoscopy (DISE) has shown to be a clinical endotype predictive of HNS treatment outcome. Complete concentric collapse at the level of the palate (CCC) during DISE is even a formal exclusion parameter for HNS treatment.[11] Furthermore, lateral wall collapse was found to be associated with less favorable outcomes.[12,13]

While DISE has been found to be guiding to predict HNS treatment outcome, it is still a time-consuming and invasive diagnostic procedure, requiring the patient to undergo a sedated nasal endoscopy in the operating theatre. Non-invasive techniques for prediction of the site of collapse have been investigated for the past few years. Recently, a novel, innovative tool was developed where the site and pattern of collapse could be associated with airflow shape from baseline polysomnographic data. Several conference proceedings have already been published showing promising prediction of DISE outcomes with the full paper currently under review.[14,15]

While HNS treatment for OSA is applied in multiple centers across the world, the effect of HNS treatment on OSA-specific pathophysiology is still unknown. However, this is highly important for further understanding and future improvement of this therapy. Especially the effect of HNS treatment on lateral wall collapse at the level of the oropharynx could be beneficial for future patient selection, as this is currently not a formal exclusion parameter despite its association with less favorable outcomes. Furthermore, investigating the effect of HNS treatment on each site of collapse would improve our understanding of the mechanism of action of this treatment option. Lastly, assessing the effect of HNS treatment on non-invasive prediction of the site and pattern of collapse could shape a way for quicker and me efficient patient selection. Having all this information could enhance treatment and get us one step closer toward personalized treatment, either using one or multiple treatment options.

2 OBJECTIVES

2.1 Study aims

Primary:

1. To assess the effect of hypoglossal nerve stimulation on the %area-of-collapse at the level of the lateral walls, measured using clinical standard DISE.

Secondary:

2.1 To assess the effect of hypoglossal nerve stimulation on the %area-of-collapse at the level of the palate, tongue base and epiglottis, measured using clinical standard DISE.

2.2 To compare the effect of HNS treatment on the %area-of-collapse (cf. aims 1 and 2.1) between responders and non-responders.

2.3 To assess the effect of hypoglossal nerve stimulation on DISE-scores at each possible site of collapse and to compare these findings.

2.4 To assess the effect of hypoglossal nerve stimulation on non-invasive site of collapse, measured using the newly developed tool.

2.2 Hypotheses

Primary hypothesis: There will be no significant reduction in %area-of-collapse at the level of the lateral walls during one-year follow-up DISE.

Secondary hypotheses:

- There will be a significant reduction in %area-of-collapse at the level of the palate and tongue base during one-year follow-up DISE, but not at the level of the epiglottis.
- Surgical non-responders will have a smaller reduction in %area-of-collapse.
- There will be a reduction in DISE-scores in terms of degree of collapse.
- There will be an effect of hypoglossal nerve stimulation on non-invasive site of collapse.

2.3 Endpoints

Primary endpoints: Δ%area-of-collapse at the level of the lateral walls, between baseline and one year follow-up
Secondary endpoints:

- Δ%area-of-collapse at the level of the palate, tongue base and epiglottis, between baseline and one-year follow-up DISE.
- Δ%area-of-collapse at each possible site of upper airway collapse (palate, lateral walls, tongue base, epiglottis) in responders and non-responders, between baseline and one year follow-up DISE.
- DISE-score (Figure 1) during baseline DISE and during one-year follow-up DISE.
- Non-invasive site and pattern of collapse assessed using the novel developed and validated tool at baseline and 1-year follow-up.

STRUCTURE	DEGREE OF OBSTRUCTION[a]	CONFIGURATION[c]		
		A-P	LATERAL	CONCENTRIC
Velum				
Oropharynx lateral walls[b]				
Tongue Base				
Epiglottis				

Figure 1. VOTE classification system. Taken from Kezirian et al.[16]

3 STUDY DESIGN

3.1 Description study design

Patients who will receive hypoglossal nerve stimulation therapy will be recruited at the pre-operative consultation at the department of ENT. As part of the standard procedure, all patients who are eligible for HNS have already undergone DISE.
To be included in the study, the patient should have undergone or is scheduled to undergo a baseline PSG within two years of HNS implantation.

All patients will undergo HNS-implantation and receive HNS-therapy as part of the standard pathway.
One year after HNS-therapy, patients will undergo another PSG as part of routine practice in these patients. An additional DISE will be performed to assess the effect of HNS on the site, pattern and degree of upper airway collapse.

3.2 Duration

The inclusion of patients will be performed from April 1st, 2024, until March 31st, 2027.

3.3 Time schedule study

- April 2024 - March 2027
    - Pre-operative inclusion of patients who will receive hypoglossal nerve stimulation therapy, at the clinics of the department of ENT at UZA.
    - Implantation of hypoglossal nerve stimulation implant at UZA.
- April 2025 – March 2028
    - Drug-induced sleep endoscopy and polysomnography after one year of hypoglossal nerve stimulation therapy at UZA.

3.4 Setting

UZA, Edegem, Belgium

4 STUDY POPULATION

4.1 Population base

We expect to implant 45 patients per year with HNS treatment, all of which will already have received a DISE before treatment as part of the standard clinical pathway. Therefore, we do not expect an issue to recruit 58 patients over a period of three years.

4.2 Inclusion criteria

Inclusion criteria for this research are:

- 18 years or older.
- Eligible for HNS-therapy:
    - AHI between 15 and 65 events/hour
    - BMI under 32 kg/m^2
    - Absence of complete concentric collapse of palate (CCC) on DISE
    - Intolerance or failure of CPAP-treatment
    - Intolerance or failure of MAD-treatment
    - Combination of central and mixed apneas less than 25% of total apneas on recent PSG (not older than two years)
- Scheduled for HNS-implantation at the Antwerp University Hospital
- Capable of giving informed consent
- Baseline polysomnography planned or performed in the last 2 years at the Antwerp University Hospital

4.3 Exclusion criteria

Exclusion criteria for this research:

- Patients will not receive HNS-therapy at the Antwerp University Hospital

- Known medical history of intellectual disability, memory disorders or current psychiatric disorders (psychotic illness, major depression, or acute anxiety attacks as mentioned by the patient).

4.4 Sample size

Based on previous research,[17] we expect a minimal increase of 10% in upper airway area at the palatal or retrolingual level in the anteroposterior direction with a maximal standard deviation of 18%. Correcting for comparisons at multiple sites (α=0.05/5=0.01) and taking into account a desired power of 90%, at least 52 patients should be included in this protocol. Accounting for a drop-out rate of 10%, a total of 58 patients will be recruited for this study.

5 TREATMENT OF SUBJECTS

After the DISE procedure, patients will follow the standard clinical pathway for HNS-implantation and further treatment. Treatment will be optimized according to standard clinical practice and will not be influenced by participation in this study. Data on treatment outcomes will be collected as part of the study to assess the effect of HNS-therapy on the pathophysiology of OSAS. An additional DISE will be performed at one-year follow-up to assess the effect of HNS-therapy on the site of collapse, without any impact on the treatment.

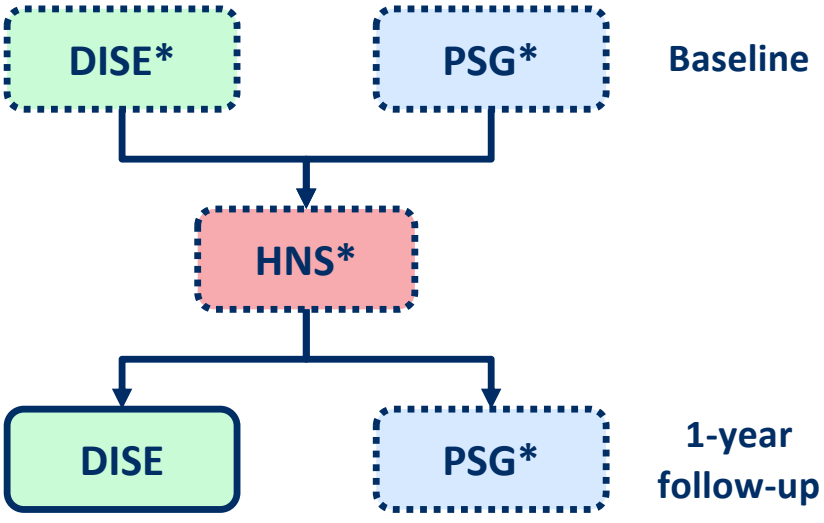
6 METHODS

6.1 Study parameters/endpoints

Site, pattern and degree of collapse as assessed during DISE and diagnostic data as collected in routine clinical practice, both before and after one year of treatment. This will be based on the VOTE classification system (Figure 1).[16]

6.2 Study procedures

Patients who are eligible for HNS-therapy for OSA will be invited to participate in the study. Data from the baseline PSG and baseline DISE as part of the standard pathway for HNS-eligibility will be accessed and collected. All patients will undergo HNS-implantation and receive HNS-therapy as part of the standard pathway.
After one year of treatment, information from the one-year follow-up PSG as part of the standard pathway will be collected. Furthermore, patients will undergo an additional one-year follow-up DISE.
A summary is shown in Figure 2.



**: part of standard pathway for HNS-therapy*

Figure 2. Study procedures

6.2.1 Hypoglossal nerve stimulation (HNS) therapy

The hypoglossal nerve stimulation (HNS) implantation and therapy will be performed according to the standard clinical practice without additional procedures. Information about the surgical procedure will be collected. HNS-implant information and settings will be collected throughout the study until the last study measurement (one-year follow-up PSG and DISE) for that patient. No additional measures or interventions as part of the research project will be performed during implantation or treatment with HNS.

6.2.2 Polysomnography (PSG)

Baseline polysomnography (PSG) is part of the standard clinical pathway for HNS-eligibility in patients with OSA. Furthermore, a PSG at one-year follow-up is part of the standard follow-up pathway in patients receiving HNS-therapy.

In this study, PSG data will be collected from both baseline and one-year follow-up PSGs to assess treatment effect. Additionally, PSG data will be used for non-invasive prediction of the site and pattern of collapse using a novel, validated tool developed at our research group (see 6.2.4).[14,15]

6.2.3 Drug-induced sleep endoscopy (DISE)

Drug-induced sleep endoscopy (DISE) is the clinical standard diagnostic test to assess site, pattern and degree of upper-airway collapse in patients with OSA. Baseline DISE is part of the standard clinical pathway for HNS-eligibility in patients with OSA.

In this study, DISE data will be collected from routine baseline DISE without any additional procedures for the patient. Patients will undergo an additional DISE at one-year follow-up to assess the effect of HNS-therapy on site, pattern and degree of collapse. Both DISEs will be performed according to routine clinical practice. These DISE procedures will be performed in a semi-dark, silent operating theatre. Patients will lay in supine position. During the whole procedure, depth of sleep will be monitored using EEG-derived measurements. Sleep will be induced using 1.5 mg bolus injection midazolam and target-controlled propofol infusion (2.0 – 3.0 µg). A flexible fiberoptic nasopharyngoscope (Olympus END-GP, 3.7 mm diameter, Olympus Europe GmbH, Hamburg, Germany) will be inserted through one of the nostrils into the transnasal cavity. Site, pattern and degree of collapse will be assessed using a standardized scoring system (Figure 1). Other maneuvers, including chin-lift, the use of a simulation bite or lateral position of the head will be performed according to clinical practice.

All DISE procedures will be scored by the same four experts in DISE from our research team, using consensus scoring based on the VOTE-classification (Figure 1) to avoid inter-rater variability.

6.2.4 Non-invasive prediction of site and pattern of collapse

Besides using clinical standard DISE, the site and pattern of collapse can be non-invasively predicted using data novel, validated tool developed in our research group.[14,15] In brief, probability for site of collapse will be calculated based on 6 airflow shape parameters calculated from clinical PSG measurements. Probability of collapse will then be compared at baseline and 1-year follow-up. Patients will not undergo any additional procedures for these analyses.

6.3 Withdrawal of individual subjects

Participants can withdraw at any moment for any reason during the study without any consequences. Treatment of the patient will be continued in the usual matter according to medical standards. The researcher may also decide to withdraw the patient from the study for medical reasons. When new information about the treatment/product becomes available, the researcher will inform the patients. The patient is then allowed to decide whether to stay in the study or withdraw.

6.4 Replacement of individual subjects after withdrawal

No specific replacement of the individual subject will occur after withdrawal during the study, as all subjects undergoing HNS-therapy will be invited to participate in the study. Patient inclusion will continue until 52 patients have a full dataset. With an expected 10% drop-out, we aim to include 58 patients.

6.5 Follow-up of subjects withdrawn from treatment

The reason of withdrawal will be recorded. When a patient withdraws from the study, normal medical treatment will be continued according to the standard clinical pathway.

6.6 Premature termination of the study

Premature termination of the study will take place when a patient experiences severe medical complaints or adverse events take place in which the patient is not able to continue the study (cardiovascular problems, trauma etc.). Before termination, the study coordinator will be consulted.

6.7 End of study

After termination of the study, the patient will receive its optimal treatment according to the standard clinical pathway.

7 SAFETY REPORTING

7.1 Subject information

The investigator will inform the subjects and the ethical committee if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the ethical committee, except when suspension would jeopardize the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.
A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing in patients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life-threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported to the ethical committee, within 15 days after the investigator has first knowledge of the serious adverse reactions.

7.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8 STATISTICAL ANALYSIS

The amount of collapse on palatal, oropharyngeal, tongue base and epiglottic level will be scored in a quantitative way using ImageJ, which will result in %area-of-collapse at baseline and at 1-year follow-up. Patients will be divided in either the "responder" group or the "non-responder" group, based on several definitions as reported in literature, including the Sher15-criteria for Surgical success in which there should be a final AHI of ≤15 and a final AHI reduction of ≥50% at 1-year follow-up.[18,19] Additionally, there should be a mean usage of at least 4 hours a day for surgical response.

Based on these calculations, the following analyses will be performed:

- Descriptive statistics will be performed to visualize an overall change in AHI and overall Δ%area-of-collapse, using the results before HNS-therapy and after one year of HNS-therapy in all patients.
- Normality will be tested for the AHI in all patients. Change in AHI will be analyzed in both responders and non-responders, the results in these two groups will be compared using statistical testing for

significance. Furthermore, change in AHI will also be analyzed for each observed DISE-endotype subgroup based on the site, pattern and degree of upper-airway collapse.
- Δ%area-of-collapse at the different sites of collapse will be analyzed in responders and non-responders, the results of in these two groups will be compared using statistical testing for significance.
- Associations between the change in AHI during PSG and the change in site, pattern and degree of upper-airway collapse during DISE will be analyzed using multiple linear regression.
- Probability of collapse at the four sites will be calculated using the non-invasive tool. Change in probability of collapse at the four sites will be assessed between baseline and 1-year follow-up.

9 ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be conducted according to the law of 07/05/2004.

9.2 Recruitment and consent

The responsible doctor will introduce the study to the patients. When patients meet the inclusion criteria they will be asked to participate in the study. The decision regarding participation in the study, which is made by the patient, is entirely voluntary. Refusal of participation will have no consequences for further treatment of the patient. They will be asked to sign informed consent. (See appendix for patient information and informed consent).

9.3 Objection by minors or incapacitated subjects

Not applicable for this research.

9.4 Benefits and risks assessment, group relatedness

The possible risks for the subjects are the same as for patients undergoing a DISE procedure in current clinical practice. Risks include epistaxis (due to injury from the laryngoscope), laryngospasm and aspiration of saliva.

9.5 Possible advantages and disadvantages of the therapy

Not applicable for this study

9.6 Compensation for injury

All participants are insured through the university hospital (UZA) insurance.

9.7 Incentives

The participants receive no compensation for participating in this study. Patients will receive an additional DISE after one year of HNS-treatment. Patients will have no additional costs by participating in this study.

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