Characterizing Mechanisms of Upper Airway Obstruction During Drug-Induced Sleep Endoscopy (DISE)

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Study Summary

Title	**Characterizing Mechanisms of Upper Airway Obstruction During Drug-Induced Sleep Endoscopy (DISE)**
Short Title	DISE-CAD
IRB Number	833511
Methodology	Prospective, single cohort
Study Duration	5 years
Number of Subjects	Study A: 100; Study B: 100
Study Center	University of Pennsylvania
Objectives	The study will contain two distinct pathways, **Study A** and **Study B**, in order to efficiently execute the protocol. Study A will focus primarily on measurements obtained as part of routine clinical care. Study B will focus on enhanced imaging and physiology techniques in patients using lingual muscle stimulation (Inspire). *As of 6/11/2021, the target recruitment for Study A was completed* **Study A:** • To determine the contribution of defects in upper airway function to the pathogenesis of airway obstruction at specific sites of pharyngeal collapse by characterizing upper airway pressure-flow/area relationships during DISE. • To determine the impact of jaw thrust and mouth closure maneuvers to functional determinants of upper airway obstruction at specific sites of pharyngeal collapse. • To examine effects of maxillo-mandibular restriction and tongue size on upper airway functional properties during DISE. **Study B** (In addition to the objectives for Study A)**:** • To assess effects of stimulating specific lingual muscles on upper airway patency during natural sleep and drug-induced sleep • To assess whether craniofacial morphology predicts improvements in pharyngeal patency during sleep with stimulation.

Main Inclusion and Exclusion Criteria	**Inclusion Criteria:** • Adults (≥ 22yrs) willing and capable of providing informed consent • Implanted with the MRI-conditional Inspire hypoglossal nerve stimulator (Model 3028 or later)* • Compliant with Inspire therapy (> 20 hours/week over 2+ weeks) as a standalone treatment for sleep-disordered breathing • Inspire remote model 2500 or later. **Exclusion Criteria:** • MRI contraindications (claustrophobia, ferromagnetic implants/foreign bodies, etc.)* • Inspire Implant Model 3024 • Inspire Remote Model 3032 • Patients who have fallen asleep while during resulting in an accident or "near miss" accident within 1 year prior to device implantation. • Inability to sleep in the supine position (by self-report) • History of severe difficulty initiating or maintaining sleep in the laboratory. • Pregnant women** *The Inspire implant model 3028 is not considered an MRI contraindication. **Women of child bearing potential must undergo a urine pregnancy test (UPT) prior to enrollment. A second UPT is performed prior to DISE as part of routine clinical workup. This study involves temporarily stopping treatment of obstructive sleep apnea, which may harm the fetus.
Statistical Methodology	ANOVA to compare responses in physiologic measures of upper airway patency to (1) positional maneuvers while accounting for potential covariates of these responses, and (2) hypoglossal nerve stimulation via Inspire.
Data and Safety Monitoring Plan	Principal Investigator will monitor study data and subject safety.

1. Abstract

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstruction due to inadequate muscle tone during sleep leading to nocturnal hypercapnia, repeated oxyhemoglobin desaturations and arousals. CPAP is the therapeutic mainstay for OSA, but adherence remains poor. The loss of motor input to the tongue during sleep has been implicated as a cause for upper airway collapse. Activation of tongue muscles with implanted hypoglossal nerve stimulators is an effective therapy for some OSA patients. Nevertheless, approximately 1/3 of OSA patients did not respond to hypoglossal nerve stimulation despite rigorous selection criteria, leaving large segments of CPAP intolerant patients at risk for OSA-related morbidity. Thus, there is a critical knowledge gap in the role of lingual muscle activity in the maintenance of airway patency. We can probe the impact of muscle tone on pharyngeal function during drug-induced sleep endoscopy (DISE), which has been used in recent years to simulate natural sleep and implicate specific neuroanatomic structures in the pathogenesis of airway collapse. Nevertheless, DISE clinical exams do not routinely determine the functional impact of anatomic and neuromuscular factors on airflow obstruction.

The current protocol consists of two studies. In **Study A**, we will enhance our DISE measurements by characterizing the determinants of upper airway obstruction. This study will build on a standard of care evaluation of (1) sleep disordered breathing via polysomnography, (2) upper airway imaging via computerized

tomography (CT), and (3) drug-induced sleep endoscopy (DISE). In **Study B**, we will electrically stimulate tongue muscles with Inspire therapy (HGNS) to determine their effect on pharyngeal patency.

Study A:

Upper airway pressure-flow and pressure-area relationships will be characterized during a standard-of-care DISE by stepping through a range of nasal pressure (CPAP) levels to derive functional determinants of upper airway obstruction during sleep. **Our overall hypothesis is that specific defects in upper airway function can be discerned from upper airway pressure-flow and pressure-area relationships that mouth closure and jaw thrust mitigate disturbances in pharyngeal compliance and tissue pressure, respectively.** We will address this hypothesis by characterizing upper airway pressure-flow and pressure-area relationships while elucidating the impact of jaw and neck position on these relationships. Our findings will allow us to streamline the upper airway exam during DISE, and will further the goal of developing personalized solutions that address specific pathogenic mechanisms of pharyngeal collapse and airflow obstruction during sleep.

Study B:

This study is designed to examine underlying mechanisms of action of lingual muscles in the maintenance of airway patency during sleep. Specifically, the protocol will improve our understanding of the anatomic and physiologic determinants of response to hypoglossal nerve stimulation with Inspire therapy. **Our major hypothesis is that specific tongue muscles are responsible for relieving upper airway obstruction during sleep.** To address this hypothesis, we will (1) selectively stimulate the hypoglossal nerve and measure effects on airway patency during natural sleep and Drug Induced Sleep Endoscopy (DISE). We will also 2) examine the impact of anatomic factors (e.g., the size of the maxillo-mandibular enclosure) on airway responses to stimulation.

To address these objectives, we will characterize the mechanism(s) of airflow obstruction during sleep, which can result from elevations in (1) pharyngeal collapsibility and in (2) resistance (narrowing) of airway segments upstream to the site of pharyngeal collapse. Elevations in airway collapsibility can result in turn from (3) increases in pharyngeal compliance, and from compression by (4) surrounding tissue, and/or (5) bony structures including the upper and lower jaws, and/or (6) a loss of neuromotor activity in tongue muscles. These pharyngeal properties can be determined by (1) characterizing pressure-flow and pressure-area relationships during natural sleep and DISE, and by (2) stimulating tongue muscles during DISE and natural sleep.

2. Objectives

a) **Study A:** Characterizing the determinants of upper airway obstruction

1) To determine the contribution of defects in upper airway function to the pathogenesis of airway obstruction at specific sites of pharyngeal collapse by characterizing upper airway pressure-flow/area relationships during DISE.
   We hypothesize that increases in tissue compression and pharyngeal compliance will be associated with primary sites of airway obstruction at the base of tongue and nasopharynx, respectively.

2) To determine the impact of jaw thrust and mouth closure on functional determinants of upper airway obstruction at specific sites of pharyngeal collapse.

We hypothesize that jaw thrust and mouth closure will preferentially mitigate tissue compression and restore airway patency at the tongue base.

3) To examine effects of maxillo-mandibular restriction and tongue morphology on pharyngeal function during DISE.
We hypothesize that maxillo-mandibular restriction and that tongue size and fat content will predict the degree of pharyngeal compression and elevations in airway collapsibility.

b) ***Study B:** Electrical Stimulation of Tongue Muscles
1) To assess effects of stimulating the hypoglossal nerve on upper airway patency during DISE and on tongue morphology.
We hypothesize that hypoglossal nerve stimulation will lead to improvements in upper airway patency during DISE.

2) To assess whether craniofacial morphology predicts improvements in pharyngeal patency during DISE with stimulation.
We hypothesize that maxillo-mandibular restriction will be associated with diminished responses in airway patency to stimulation during DISE.

***Objectives #1-3 from Study A also apply to Study B.**

3. Background

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstructions due to inadequate muscle tone during sleep[1], leading to nocturnal hypercapnia, repeated oxyhemoglobin desaturations, and arousals. The prevalence of OSA is 24-27% in middle-aged men, 40-45% in older men, 9% in middle-aged women, and 25-30% in older women[2,3]. OSA is a major cause of morbidity and mortality in Western society and contributes significantly to the development and progression of neurocognitive, metabolic, cardiovascular, and oncologic diseases[4–12]. Nasal continuous positive airway pressure (CPAP) remains the mainstay of treatment for this disorder, despite high rates of non-adherence among patients[13–15]. Multiple surgical approaches have been developed to relieve upper airway obstruction, although the precise indications for each procedure remain unclear[16–31]. This protocol addresses a critical unmet need to develop personalized therapeutic alternatives to CPAP by identifying underlying mechanisms of upper airway obstruction during sleep.

In prior studies, pharyngeal obstruction has been attributed to increases in airway compliance (i.e., a loss of pharyngeal stiffness) and/or excess compression by surrounding soft tissue and bony structures including the tongue and maxillo-mandibular frame, respectively[32–34]. Fatty infiltration of the tongue and peripharyngeal tissues along can compress the pharynx when tongue and pharyngeal muscle tone declines during sleep[35–40]. The primary goal of the current protocol is to characterize underlying mechanisms of upper airway obstruction by elucidating disturbances in airway compliance and tissue pressures. We further postulate that these mechanisms exert differential control on the collapsibility of specific pharyngeal segments (oro- vs. velopharynx).

To define the functional impact of pharyngeal compliance and surrounding tissue pressures on the overall collapsibility of the pharynx, we will characterize upper airway pressure-flow and area relationships during drug-induced sleep endoscopy (DISE). We hypothesize that specific mechanical properties determine the severity of airflow obstruction. This procedure is routinely deployed in OSA patients who are contemplating

surgical alternatives to CPAP therapy. We will derive mechanical parameters of upper airway function from pharyngeal pressure-flow/area relationships to determine their net effect on pharyngeal compliance and tissue pressure. Our experimental approach requires us to step through several CPAP pressure levels briefly while measuring tidal airflow and pharyngeal luminal cross-sectional area in the oro- and velopharynx. We will then implicate disturbances in pharyngeal compliance and/or tissue pressure in the pathogenesis of upper airway obstruction by examining the impact of positional maneuvers designed to mitigate these disturbances (viz., mouth closure and jaw thrust, respectively). Subject will also undergo an MRI scan of the head and neck to determine the extent to which maxillo-mandibular size and tongue size and fat content compress pharyngeal structures[41].

One of the major determinants of upper airway patency is the tone of muscles in the tongue. **Our hypothesis is that activating specific lingual muscles are required to best restore pharyngeal patency during sleep (Study B).** To address this hypothesis, we will stimulate patients previously implanted with the Inspire hypoglossal nerve stimulation (HGNS) device as part of routine clinical care (Inspire Medical Systems, Minneapolis, MN). We will determine the effects on stimulating the hypoglossal nerve on upper airway patency during sleep, and determine anatomic correlates of these responses.

It is well recognized that lingual muscle neuromuscular activity plays a major role in the maintenance of pharyngeal patency during sleep. Several lines of evidence suggest that a fundamental defect in neuromuscular control is required for the pathogenesis of upper airway obstruction in OSA[10,43]. The genioglossus can prevent the tongue from prolapsing into the pharynx and occluding the airway. Additional studies in rodents, however, suggested that other lingual muscles work in concert with the genioglossus to stabilize airway patency. Specifically, Fuller et al. demonstrated marked increases in tongue protrudor (genioglossus) and retractor (stylo- and hyoglossus) muscles during hypercapneic stimulation of the airway musculature, suggesting that both muscle groups play a role in stabilizing tongue structures when ventilatory drive is high[44]. In humans, Dotan et al. documented markedly different activation patterns between sleep and wakefulness[45] with concomitant increases in both protrudor and retractor activity during wakefulness, but only isolated protrudor activity with, and a loss of retractor activity during sleep[45]. Combined electrical stimulation of protrudors and retractors during sleep led to greater reductions in pharyngeal collapsibility than did stimulating the protrudors alone[32]. The findings suggest that synergistic effects of lingual protrudors and retractors can restore airway patency during sleep.

OSA is associated with distinct craniofacial characteristics which can compromise pharyngeal patency during sleep[41]. Nonetheless, the impact of these craniofacial features on responses to tongue muscle stimulation has not been examined. Another aim of this research is to characterize the effects of lingual muscles required to overcome specific defects in upper airway anatomic and neuromotor control of pharyngeal patency in apneic patients.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

Patients with implanted hypoglossal nerve stimulation (Inspire®) devices will be recruited for this protocol from the University of Pennsylvania or Thomas Jefferson University. All study procedures will be conducted by the clinical research team at the Hospital of the University of Pennsylvania campus (including HUP main, HUP Pavilion and PCAM). Medical records of these referrals will be assessed preemptively or at the time of the clinic or procedure visit for eligibility for this protocol. The patients will be asked whether they are interested in participating in the protocol, at which point informed consent will be obtained for those willing and eligible to enroll. Participants will also

complete a standard MRI screening form to assess eligibility for MRI, including potential claustrophobia.

Design *(see Study Flow below)*

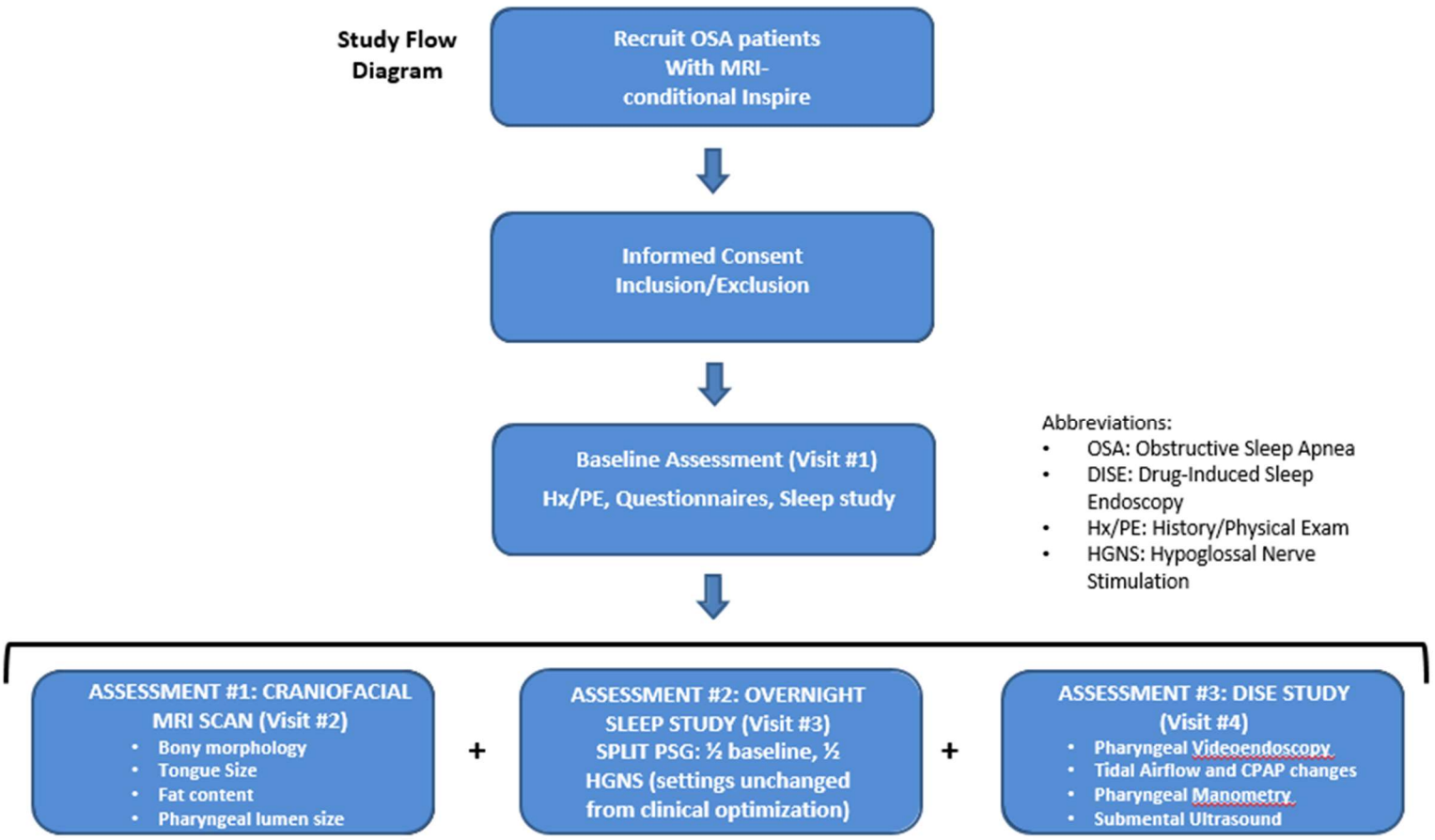
Participants will initially be consented and screened for this study with a brief medical history and physical exam (Visit #1). The diagnosis of obstructive sleep apnea may be confirmed from prior sleep study reports. This visit may occur during routine clinical follow-up, if applicable, and may have already been completed prior to study enrollment (primary exception: Thomas Jefferson University patients). Once all inclusion criteria have been met, participants will continue with 3 additional assessments/visits (total 4 visits) per research protocol. In order to facilitate scheduling, these visits may occur in any order:

Eligible participants will undergo upper airway imaging (Visit #2), where craniofacial morphology will be assessed with MRI measurements and digital morphometric measurements (Study B only).
Participants will then attend an in-lab overnight sleep study (Visit #3). This will be a full standard polysomnography study where brain activity, body movements, modified EKG, respiratory parameters, and oxygenation will be monitored according to gold standard AASM guidelines. The sleep study will be performed in a split-night fashion including (1) a baseline sleep assessment to measure apnea severity, and (2) hypoglossal nerve stimulation with Inspire to measure response to therapy.

Prior to sleep, patients will undergo facial measurements. A digital camera with laser pointers will be used to capture a series of craniofacial photographs (frontal, profile and neck extended) and intra-oral photographs (junction of the hard and soft palate, airway, or base of tongue). The participant will then perform serial tongue force exercises using a bulb behind their front teeth to assess tongue force.
Thereafter, responses to stimulation will be assessed during DISE with ultrasound measurements of tongue morphology and with measurements of pharyngeal patency during DISE (Visit #4). Responses in pharyngeal patency will be assessed with video endoscopy, pharyngeal manometry, and tidal airflow monitoring (Studies A+B) while briefly stimulating tongue muscles during DISE (Study B only).

COVID-testing for each of the visits/assessments listed above will be required per departmental guidelines/regulations.

Each of the specific study procedures shown in the Study Design are described immediately below.



	Visit 1: Screening/ Consent*	Visit 2: MRI	Visit 3: Sleep Study*	Visit 4: DISE
Informed Consent	X			
History and Physical	X			
Questionnaires	X			
Study A (Baseline Protocol)				
DISE				X
Pharyngeal Manometry				X
Tidal Airflow Monitoring				X
Airflow Manipulation				X
Ultrasound				X
Study B (Stimulation Protocol)				
MRI		X		
Digital Morphometrics			X	
Tongue Force			X	
In-Lab Sleep Study			X	
DISE				X

Pharyngeal Manometry				X
Tidal Airflow Monitoring				X
Airflow Manipulation				X
Ultrasound				X
Nerve Stimulation			X	X

*The screening/consent visit may occur during the first scheduled assessment (MRI, PSG, or DISE) to facilitate scheduling and reduce patient burden.

Visit #1: Clinical Evaluation

1. Baseline Questionnaires: Standard screening questionnaires will be administered initially at the time subjects are screened and consented. These questionnaires will assess several demographic, anthropometric, and physical health domains (see attached questionnaires). We will administer the standard Sleep Surgery clinical questionnaire which includes ESS, ISI, FOSQ-10, NOSE, sleep quality, snoring, etc. We will perform an Inspire device download to evaluate study eligibility (therapy compliance), and record their treatment settings. Patients without the most recent Inspire remote will be provided with one.

Visit #2: Overnight Sleep Study, Digital Morphometrics, Tongue Force Assessment

1. Sleep study monitoring (polysomnography): Standard monitoring of sleep will occur during Visit #2. For patients opting for Study A only, the sleep study may have already been performed as part of routine clinical care. For Study B, overnight nocturnal recordings will be performed in our sleep laboratory and will follow the same procedures (#1-5) outlined in Visits #3-4 below. The study will include monitoring of EEG, submental EMG, EOG, S_pO_2, tidal airflow, thoraco-abdominal efforts, and body position. Recordings will be archived on an institutionally secured and managed network drive and accessible only to study personnel. Recordings will be accessed via a HIPAA secured web portal. Patients will be required to wash out from therapy between 5-7 days prior to PSG, i.e. they cannot use HGNS or other therapies during this time. A split night study will be performed (partially with HGNS, partially without). HGNS will not be titrated, i.e. we will use the settings optimized by clinical care prior to study participation. Patients must have a minimum of one hour of supine non-REM stage 2 sleep during both the baseline and treatment (with HGNS) assessments. If patients are unable to meet these criteria, they will not proceed with DISE.

2. Digital Morphometrics of the Airway: Several photographs of the face and the inside of the mouth will be taken using a digital camera (Powershot SX120 IS, Canon Inc., Japan). The digital camera and a device with two parallel-oriented laser pointers will be secured to a monopod (Manfrotto 682B) to help with capturing accurate measurements. The monopod will be positioned approximately 40cm from the patient. The research team will ensure the laser pointers do not shine into the patient's eyes. Key surface markers will be identified by palpation and marked using a skin-safe marking pen: (1) gonion profile by identifying the most posterior and lateral point on the external angle of the mandible, (2) condylion by identifying the area of skin anterior to the ear canal, and (3) gonion neck extended by identifying the most posterior and inferior angle of the mandible while the patient's neck is maximally extended. The patient will be seated upright against a wall with a neutral head position and mouth/lips closed, and the research team will capture (1) frontal, (2) profile, and (3) neck extended photographs.

Intraoral photographs will be taken with the subject positioned in the same fashion using the same equipment setup. The subject will be asked to "show your teeth and smile" to provide maximal visualization of the oral cavity without obstruction by the lips. The subject will be instructed to open his/her mouth until it reaches maximal range of vertical motion and to breathe rhythmically through his/her mouth. The research team will capture (1) Open Mouth, No Phonation, (2) Open Mouth, Tongue Extended Maximally, Frontal, (3) Open Mouth, Tongue Extended Maximally, Profile, and (4) Open Mouth, With Tongue Depressor, No Phonation. The tongue depressor will be used to ensure visualization of the uvula.

3. Tongue Force Measurements: The patient will be asked to place a small bulb behind the front teeth. The research team will instruct the subject to press their tongue against the bulb as hard as possible for two seconds. This exercise will be repeated four times, with 30 seconds of rest in between each attempt. The patient will then be instructed to press and hold their tongue against the bulb as hard as possible for 35 seconds. This exercise will be repeated three times, with 2 minutes of rest in between each attempt.

Visit #3: MRI

1. Craniofacial Morphology with Magnetic Resonance Imaging: MRI will be performed to quantify tongue and maxillo-mandibular enclosure volumes. High-resolution 3D images will be acquired at high magnetic field strength (3T Siemens Verio, Ehrlangen, Germany). Our imaging protocol consists of T1 Spin echo, 3D CISS, 3D STIR SPACE and 3D VIBE sequences with parameters optimized for high-resolution 3D imaging. Our approach has several advantages over standard neck imaging techniques as follows. (1) Acquisition of high spatial resolution isotropic data within an acceptable time frame will allow us to evaluate the pharynx in its entirety. (2) Isotropic voxel dimensions will facilitate reconstruction of the axially acquired images in all planes without loss of image quality, thus supporting highly accurate linear measurement resistant to asymmetric positioning and/or poorly visualized oblique structures in a single orthogonal plane. (3) 3D images provide for linear mandibular, maxillary, and airway measurements with the highest degree of accuracy. In addition, we will perform Dixon imaging to measure tongue fat and cine (MRI - fast gradient echo) to measure dynamic upper airway images.

Visits #4: Drug Induced Sleep Endoscopy (DISE)

During DISE, patients will be moderately sedated with Propofol (2.5mg/kg load followed by continuous drip of 6 – 12 mg/kg/hr). The patient will be fitted with a nasal CPAP mask. A fiberoptic scope will be passed through an airtight seal in the mask, through the nose into the pharynx to visualize upper airway obstruction. The previously mentioned steps are part of the standard-of-care DISE protocol.

The following procedures are performed during DISE:

1. Tidal Airflow Monitoring: Subjects will be fitted with a nasal mask through which tidal airflow will be monitored to assess dynamic changes in airway patency with stimulation. The nasal mask will be connected to a variable pressure source. The nasal pressure will be manipulated to measure pharyngeal cross-sectional area at various levels of upper airway patency, as previously described[46–68].

2. CPAP Level Manipulation: The nasal pressure will be manipulated to measure pharyngeal cross-sectional area and tidal airflow at various levels of upper airway patency, as previously described[46–68]. Nasal pressure will be maintained at an elevated holding pressure at which airflow obstruction is abolished, and then dropped step-wise for several breaths to pressures that induce inspiratory flow limitation and complete obstruction.

3. Pharyngeal Manometry: In addition to standard sleep monitoring, up to two 7 French Millar catheters (Houston, TX) will be passed perinasally to monitor pharyngeal pressure swings and will be used subsequently as an internal calibration marker for measurements of pharyngeal cross-sectional area on videoendoscopy images during sleep studies[32,33]. To facilitate this process, we will administer 2% Viscous Lidocaine perinasally before passing the catheter(s).

4. Ultrasound procedures: Ultrasound will be performed in each study participant after propofol-induced sleep has been initiated. Measurements during DISE will take about 10 minutes. Images will be acquired with and without stimulation of tongue protrudors.

5. Lingual Muscle Stimulation (Study B only):

   Patients will have already undergone HGNS implantation and device setting optimization as part of clinical standard-of-care. The Inspire programmer will be used to turn on and off stimulation during DISE and PSG procedures.

b. Study duration and number of study visits required of research participants.

Each participant will be asked to participate for the duration of Visit 1 (1-2 hour clinic visit), Visit 2 (up to one half day for imaging procedures), Visit 3 (baseline overnight sleep study), and Visit 4 (1 half day for DISE procedure). We anticipate that approximately 20% of participants will not be able to complete all of these visits. Participants' participation in these assessments will remain completely voluntary.

We estimate that it will take us about 5 years to collect, process, and fully analyze the ultrasound and DISE study data. Each subject's active participation is anticipated to last for about 1 month.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

There is no blinding of subjects. Investigators will be blinded before measurement of acquired images to avoid observer confirmation bias.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

Participants will temporarily stop all therapy for OSA (particularly Inspire) for 5-7 nights prior to their sleep study. Each participant's medical therapy will continue unaffected by this study with the addition of submental ultrasound examination, MRI, and of one unscheduled polysomnography.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Adult patients (≥ 22 yrs) willing and capable of providing informed consent
- Implanted with the MRI-conditional Inspire hypoglossal nerve stimulator (Model 3028)*
- Compliant with Inspire therapy (> 20 hours/week over 2+ weeks) as a standalone treatment for sleep-disordered breathing
- Inspire Remote Model 2500 or later

Exclusion Criteria:

- MRI contraindications (claustrophobia, ferromagnetic implants/foreign bodies, etc.)*
- Inspire Model 3024
- Inspire Remote Model 3032
- Patients who have fallen asleep while during resulting in an accident or "near miss" accident within 1 year prior to device implantation.
- Inability to sleep in the supine position (by self report)
- History of severe difficulty initiating or maintaining sleep in the laboratory.
- Pregnant women**

* The Inspire model 3028 is not considered an MRI contraindication.

**Women of child bearing potential must undergo a urine pregnancy test (UPT) prior to enrollment. A second UPT is performed prior to DISE as part of routine clinical workup. This study involves temporarily stopping treatment of obstructive sleep apnea, which may harm the fetus.

6. Drugs/Substances/Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

We will administer propofol, which is routinely given for DISE procedures. The rationale for choosing this drug is based on its reliability, well-established tolerability, safety, and low muscle-relaxant profile.

Lidocaine jelly (~2 mL) will be squirted into each nostril prior to passing the pharyngeal catheter and endoscope.

The protocol will involve recruiting patients already implanted with the Inspire HGNS system. We have selected this device in place of stimulating with custom fine-wire electrodes to reduce patient burden. The Inspire device is safe, well-tolerated, and FDA-approved for treatment for OSA.

Overnight sleep study will be used to characterize patients' sleep apnea. This test consists of a standardized array of non-invasive sensors applied to the head (EEG), chin and legs (EMGs), upper lip (airflow) the finger (oximetry), and chest/abdomen (respiratory effort, ECG). It records physiologic signals non-invasively that detect apneic episodes and characterize sleep/wake state.

b. Drug and device management

Propofol and equipment for conducting drug-induced sleep endoscopy will be procured and administered by trained endoscopy/operating room staff. The Inspire stimulator will have already been implanted as part of routine clinical care and will be operated by trained staff using the Inspire Programmer.

7. Study Statistics

Our primary independent variable is stimulation status (on versus off). Additional predictors of responses to stimulation will include measurements of tongue and craniofacial morphology.

a. The impact of these independent variables will be examined on the following primary outcome variables:

- Tidal airflow and related flow-surrogates for upper airway collapsibility
- Pharyngeal cross-sectional area in the velo- and oropharynx

b. Secondary outcome variables:

N/A

c. Statistical plan including sample size justification and interim data analysis:

Using an ANOVA framework for estimating sample size for a 1x3 factorial design (Specific Aim A: complete responder, partial responder, and non-responder), we calculate the sample required to detect within-subject changes in upper airway function (e.g., the severity of upper airway obstruction during DISE as reflected by measurements of pharyngeal collapsibility, P_{CRIT}), based on published data demonstrating decreases in pharyngeal collapsibility (P_{CRIT}) of ~3.5±2.0 cmH_2O during stimulation [34]. This response accounts for ~24% of the total variance (η2), which yields an effect size (f) of ~0.40. Our data also demonstrate within-subject correlations of at least 0.5 for repeated P_{CRIT} measurements [69,70]. Using these parameters, we calculated that 15 subjects would be required to detect significant differences in each of 3 responder categories with an alpha of 0.05 and a power of 90%. To account for measurements in both sexes, subject attrition, and incomplete measurements, we propose an 'n' of 45 subjects to complete the protocol. We also plan to examine the effects of sex and BMI on this outcome, which will require an additional 30-60 subjects (total n = 100) for the entire protocol. This sample size will allow us sufficient power to detect substantial effects of stimulation on tongue morphology (Specific Aim B) and effects of craniofacial structures on tidal airflow and markers of airway collapsibility (Specific Aim C).

d. Early stopping rules.

- This is a low-risk study designed to examine underlying mechanisms of action of lingual and hypoglossal nerve stimulation treatment in patients with obstructive sleep apnea. Since the protocol will involve temporarily stopping HGNS treatment for 5 days, one risk includes excessive daytime sleepiness. We have attempted to minimize subject risk with the strict exclusion criterion, "Patients who have fallen asleep while during resulting in an accident or 'near miss' accident within 1 year prior to device implantation." In addition, we will advise patients against driving and operating heavy machinery during this 5-7 night washout period and we will perform a check-in call after the first 2 nights without therapy. We will specifically ask patients if they have fallen asleep while driving, and will withdraw any patients answering yes. We also recognize and inform each subject of his/her right to withdraw from the clinical study at any time.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Baseline Questionnaires: These surveys acquire information that is routinely collected in the process of enrolling participants in clinical studies. There are not any significant physical risks with these procedures. As with all medical information, there is always the risk of psychological distress if personal health information is not held confidential. In order to minimize this risk, electronic PHI will be stored in a password-protected database (REDCap), and written information will be stored in locked files or file-rooms when not attended by study personnel.

Therapy Washout: Patients participating in Part B will undergo a 5-7-night therapy washout, i.e. they will not use Inspire for treatment of obstructive sleep apnea during this period. Untreated OSA increases the risk for excessive daytime sleepiness and consequently, motor-vehicle accidents. We have attempted to minimize subject risk with the strict exclusion criterion, "Patients who have fallen asleep while during resulting in an accident or 'near miss' accident within 1 year prior to device implantation." In addition, during the patient consent (Visit 1), we will advise the patient against driving while sleepy. We will also perform a check-in call after 2 nights off therapy.

Ultrasound procedure for tongue imaging: Ultrasound is a non-invasive, inexpensive, and easy way to examine the morphology of the tongue and its response to stimulation. There is minimal discomfort associated with examination.

Craniofacial Morphology with Magnetic Resonance Imaging: The primary risk of MRI involves scanning patients implanted with the Inspire HGNS system. The specific MRI protocol (e.g. magnet strength, scan location, etc) outlined within the Inspire manual (see supplementary documentation) will need to be followed in order to conduct the scans safely and effectively. The only other risks posed by MRI relate to claustrophobia which is occasionally experienced by subjects when they lie in the scanner, metal objects or implantable devices that might interfere with the scanning procedure, and metal objects flying into the magnet. Participants with claustrophobia or implanted metallic devices incompatible with MRI (other than Inspire) will be excluded from study. These risks will be mitigated by screening subjects for these potential risks, and through the use of personnel specifically trained to work safely with patients in the MRI environment. All personnel involved in the MRI protocol will be certified through compliance training to work in the MRI scanner. We will obtain device implant ID cards and contact Inspire Medical Systems in order to verify the patient has a MRI-conditional device.

Digital Morphometrics & Tongue Force Measurements: There are minimal risks associated with capturing these measurements. The measurements may be slightly uncomfortable, and the subject may experience mild tongue soreness after the tongue force assessment. The research team will use the monopod to mount the camera/laser in a fixed position to ensure the laser pointers do not shine into the patient's eyes while capturing digital morphometric photographs.

Sleep study monitoring (polysomnography): The risks during sleep studies are minimal and confined to minor skin irritation from the placement of adhesive electrodes. It is known that participants with sleep disordered breathing and/or severe nocturnal oxygen desaturation are at increased risk for sudden death during sleep from their underlying breathing disorder. Participants' oxygenation will be assessed in these nocturnal recordings and they will be notified if sustained periods of marked hypoxemia ($SaO_2 < 90\%$) develop. Those with severe nocturnal oxyhemoglobin desaturations and/or recurrent sleep disordered breathing events will be notified of these abnormalities, and their treating Inspire physician will be made aware for an AHI $\geq$ 30 episodes/hr or if the cumulative time spent with an $SaO_2<90\%$ is $\geq$10% of total recording time. Additionally, emergency resuscitative equipment is immediately available in the laboratory. Full-night sleep studies will be conducted by technicians

who are trained not only in basic cardiopulmonary resuscitation but in the analysis of the EEG and ECG which are being continuously monitored throughout the study.

Propofol administration: Propofol will be given intravenously during the sedated sleep procedure under the care of a skilled airway team (anesthesiologist and head & neck surgeon) in a fully-enabled endoscopy suite.

Risks of Propofol (Diprivan®):

- Common: fast or slow heart rate, low blood pressure, burning/stinging or infection at injection site, apnea, rash, and itching.
- Serious, yet rare: seizure.

Pharyngeal manometry and videoendoscopy: This procedure is a minimally invasive outpatient procedure and can be associated with mild discomfort. Two thin nasal catheters and the nasopharyngoscope are passed through one nostril into the pharynx. Passing the scope through the nostril may result in mild nasal irritation or epistaxis as well as minor gagging. Patients usually acclimatize to the sensation within 5 minutes.

Any incidental finding on videoendoscopy will be evaluated, and an official report will be generated and included in the patient's medical record. The subject will be notified of the incidental finding. Depending on the type of incidental finding, referral may be suggested for evaluation by an appropriate physician (e.g., ENT). We will also discuss the incidental finding with the participant so as to alleviate any anxiety that might ensue and inform the participant about clinical resources available to address any clinical concerns about the finding.

Tidal airflow monitoring and nasal pressure alterations: The risks of monitoring tidal airflow with a nasal mask are minimal and consist of claustrophobia. Exposure to alterations nasal pressure applied to the mask are also of minimal risk.

Topical Lidocaine and Oxymetazoline: The risks are minimal since we will inquire beforehand about sensitivity to these agents during surgical time-out as part of standard of care. Subjects may feel an initial slight burning sensation in their nostrils and an urge to swallow.

Lingual Muscle Stimulation: The Inspire device will be tested during wakefulness to determine the tongue protrusion pattern, stimulation level (voltage), electrode configuration, and the respiratory sensing synchrony.

Recruitment and Informed Consent: There is risk that recruitment and consent practices will not comply with standard regulations and may, as a result, compromise the rights and privacy of potential study participants.

The study team will work diligently to ensure study recruitment will be handled with sensitivity and in compliance with all regulations.

Men and women will be recruited from existing or referred clinic patients. All study recruits will be informed of: 1) why the research is being conducted, 2) why they are being contacted, 3) the protocol, and 4) the voluntary nature of their participation. If they are interested in participation in the current protocol, they will be scheduled for a face-to-face encounter in which they will be able

to ask questions about participation in the trial from the research coordinator and/or study doctor.

It will be made clear that all participation in the study is completely voluntary. Informed consent will be obtained in person, after an interview with each participant by the investigators and/or study coordinators responsible for this specific protocol who will fully explain the research protocol, risks and possible benefits. The signed consent form will also contain specific explanations of the possible risks in layman's terms. Patients will have the opportunity to ask questions prior to signing the consent form and will be told that they are under no obligation and may withdraw without compromising their care.

b. Steps taken to minimize the risks:

To minimize risk of confidentiality all data will be stored in a REDCap database and/or on an institutionally secured and managed network drive. Subjects will be assigned a study ID and their data will be attached to that ID.

c. Data Safety and Monitoring Plan:

The plan for collection, description, monitoring, and analysis of adverse events is presented in accordance with guidelines for adverse event reporting to the IRB.

We will use the following definitions and grading scales for monitoring purposes:

Definition of adverse event (AE)/adverse device effect (ADE): any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure.

Definition of serious adverse event (SAE): any event that is fatal or life-threatening, that is permanently disabling, requires or extends hospitalization of the subject, represents a significant overdose or breach of protocol, suggests that a drug, device, or procedure used in a research protocol has produced a congenital anomaly or cancer, or in the opinion of the investigator, represents other significant hazards or potentially serious harm to the research subject or others.

Definition of unanticipated adverse device effect (UADE): A UADE is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Adverse events will be graded as (a) mild (adverse event of little clinical significance), (b) moderate (adverse event between mild and severe – causing some limitation of usual activities), or (c) severe (an event that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, represents a significant overdose or breach of protocol, results in congenital anomalies/birth defects or produces cancer, or in the opinion of the investigator, represents other significant hazards or potentially serious harm to the research subject or others), and their attribution will be classified as (a) not related (clearly not related), (b) possible (may be related), (c) probable (likely related), (d) definite (clearly related), or (e) unable to assess.

The Data Safety and Monitoring Plan for this project is designed in accordance with NIH guidelines published in http://grants.nih.gov/grants/guide/notice-files/not98-084.html. Adverse events and

deviations will be reported to the regulatory sponsor, and to IRB as applicable. Serious adverse events will be reported to the regulatory sponsor and to IRB in accordance with institutional reporting requirements. It is our intention to make any serious adverse event known to these entities within 24 hours with follow-up information as it is acquired. Additional safeguards for research subjects will ultimately accrue from our approach to data sharing. Our first approach is the traditional one of publishing results in peer-reviewed scientific journals. The growing use of computerized data repositories in association with scientific publications permits the storage and public access of much more detailed and extensive information than has previously been available, and we plan to make use of such venues. Final versions of these manuscripts will be furnished to the public through the NIH repository for manuscripts in accordance with current policy. (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-045.html) We also will provide data tables of de-identified data (limited dataset) to other scientists for their independent analyses with completion of a data-use agreement that is compliant with HIPAA guidelines. We will make data from this study public after publication of primary results.

Procedures to Access and Store Research Data: Urgent results and/or incidental findings will be communicated to the patient and sent to the participant's physician. All the data being used for research will be entered into a database by study identification number only. Research charts will be kept in locked cabinets. Access to research information including personal health information will only be provided to study team members.

Data Confidentiality: Data which include identifiable personal health information (PHI) will be collected during patient encounters using REDCap (Research Electronic Data Capture) or managed on the department's institutionally-managed access-restricted shared drive. The REDCap system contains robust data integrity features and as well as nightly backups. It has excellent security and privacy features, with extensive audit logging. REDCap will also be used to store electronically generated data from overnight polysomnography (PSG) and calculated measurements from magnetic resonance imagining (MRI) analysis. Images from the digital morphometrics will be stored on the department's institutionally-managed access-restricted shared drive. The digital images will be deleted one year after participant consent is obtained. Electronic medical records are kept in a secure, password-protected database, and written information is stored in locked file cabinets or file rooms when not attended by study personnel.

PHI will be stored in accordance with HIPAA regulations and local policies and practices. This includes the storage of PHI in locked cabinets or rooms, limited access to secure data areas by certified participating study personnel, password protection for electronic medical records, and explanation of HIPAA regulations on the study consent form. Data such as laboratory studies that are collected as part of this study may be transmitted to the participants' treating physicians with the consent of the participant. Participants are informed in the consent that PHI may also be disclosed for auditing purposes by the FDA or other regulatory bodies and is subject to subpoena. PHI is not transmitted to the coordinating center or central laboratory in that all data is identified only by an anonymous study ID, and other identifying information such as birthdate is not entered into the central study database. Source records that are transmitted to the coordinating center for data quality audits have identifying information redacted.

d. Legal risks such as the risks that would be associated with breach of confidentiality:

Breach of confidentiality would result in unauthorized individuals having access to information about the participant's medical history. Therefore, all research staff selected to participate in this study

are highly qualified and board certified, when applicable. They are all fully aware of HIPAA regulations regarding patient confidentiality. To prevent unauthorized access:

(1) Data collected will be kept strictly confidential; this information will be used only for completing the study objectives and in an anonymous form for statistical analyses

(2) All digital files will be stored on a password secured REDCap database and/or on an institutionally secured and managed network drive and restricted to study investigators and associated staff, on a need-to-know basis

(3) Subject data will be stored with unique identifiers and will be password protected. All computers will require log-on passwords.

9. Benefits

Participant Benefits: No direct benefit to participants is anticipated.

Societal Benefits: This study promises to develop personalized approaches for selecting patients for hypoglossal nerve stimulation therapy for sleep apnea. In characterizing factors linked to enhanced responses in upper airway patency with stimulation, we hope to elucidate impact of lingual stimulation on airway biomechanical properties that mediate improvements in airway patency. The proposed research should help determine the subgroup of patients for whom hypoglossal stimulation is indicated in the future.

Overall Risk-Benefit Analysis: It is possible that patients receiving Inspire therapy are suboptimally treated. This protocol has the potential to identify these patients and may prompt them to consider further evaluation with their Inspire physician.

10. Payment and Remuneration

Volunteers will receive $150 for completing baseline polysomnography (Assessment #3), $100 for completing MRI (Assessment #2), and $150 for completing the DISE (Assessment #4). If they are asked to repeat Assessment # 3, they will be paid an additional $150.
These volunteers will be compensated $25 to cover travel expenses. Payment will be issued at the completion of the study, via check or ClinCard, and will be prorated if applicable.

11. Costs

There are no costs to subjects for participation in this study.

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