

Responses in Tongue Morphology and Pharyngeal Patency to Lingual Muscle Stimulation

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Study Summary

Title	Responses in Tongue Morphology and Pharyngeal Patency to Lingual Muscle Stimulation
Short Title	Tongue Stimulation on Upper Airway Patency
IRB Number	833511
Methodology	Prospective, single cohort
Study Duration	3 years
Study Center	University of Pennsylvania
Objectives	<ul style="list-style-type: none"> • To assess effects of stimulating specific lingual muscles on upper airway patency during sleep and on tongue morphology during wakefulness • To correlate improvements in upper airway patency during sleep with stimulation to alterations in tongue shape and position when stimulating during wakefulness. • To assess whether craniofacial morphology predicts improvements in pharyngeal patency during sleep with stimulation.
Number of Subjects	50
Main Inclusion and Exclusion Criteria	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Adults (≥ 22 yrs) • Moderate to severe obstructive sleep apnea (AHI ≥ 20) • No underlying cardiac disease <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Significant cardiac disease, unstable or recent cardiac events • Active pulmonary, liver, or renal disease • Uncontrolled hypertension (BP > 160/100) • Neuromuscular disease • Major psychiatric disease • Lifestyle considerations by the use of excessive alcohol, tobacco, or drugs and involvement in shift work occupations that preclude study in the laboratory • Pregnancy • Anticoagulation therapy (e.g. Coumadin, Dabigatran) • MRI contraindications (claustrophobia, ferromagnetic implants/foreign bodies, etc.)
Statistical Methodology	ANOVA to compare responses in physiologic measures of upper airway patency to separate and combined lingual protruder and retractor stimulation.
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.

The current study is designed to examine underlying mechanisms of action of lingual muscles in the maintenance of airway patency during sleep. **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 specific lingual muscle groups (viz., protrudors and retractors) and measure effects on airway patency during Drug Induced Sleep Endoscopy (DISE). We will also (2) correlate responses in patency to alterations in tongue morphology (as assessed with ultrasound imaging). A final goal is to (3) examine the impact of anatomic factors (e.g., the size of the maxillo-mandibular enclosure) on airway responses to stimulation.

2. Objectives (include all primary and secondary objectives)

- a) To assess effects of stimulating specific lingual muscles on upper airway patency during DISE and on tongue morphology.
We hypothesize that stimulation will lead to improvements in upper airway patency during DISE when tongue protrudors are stimulated, and that concomitant stimulation of retractors will augment this response.
- b) To correlate improvements in upper airway patency during sleep with stimulation to alterations in tongue shape and position when stimulating during DISE.
We hypothesize that the restoration of airway patency during sleep will be associated with anterior tongue movement and preservation of tongue shape when stimulated during DISE.
- c) 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.

3. Background

Obstructive sleep apnea (OSA) is characterized by recurrent upper airway obstructions due to inadequate muscle tone during sleep, 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. 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. One of the major determinants of upper airway patency is the tone of muscles in the tongue. **Our central hypothesis is that activating specific lingual muscles – both the protrudors and retractors**

– **are required to best restore pharyngeal patency during sleep.** To address this hypothesis, we will stimulate specific lingual muscles in participants with moderate to severe OSA. Apneic patients will undergo selective transoral fine wire stimulation, as previously described^{1,2}. We will determine the effects on stimulating lingual protrudors with and without retractors 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^{3,4}. 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 protruder (genioglossus) and retractor (stylo- and hyoglossus) muscles during hypercapnic stimulation of the airway musculature, suggesting that both muscle groups play a role in stabilizing tongue structures when ventilatory drive is high⁵. In humans, Dotan et al. documented markedly different activation patterns between sleep and wakefulness⁶ with concomitant increases in both protruder and retractor activity during wakefulness, but only isolated protruder activity with, and a loss of retractor activity during sleep⁶. Combined electrical stimulation of protrudors and retractors during sleep led to greater reductions in pharyngeal collapsibility than did stimulating the protrudors alone⁷. 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 sleep⁸. 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 moderate to severe obstructive sleep apnea will be recruited from social media, flyers, and/or from existing clinic patients. Research participants who have already consented to be contacted for research and/or already have a professional relationship with the study team physicians will also be recruited. Any recruitment flyers or social media advertisements will be submitted for IRB review prior to use.

Patients with obstructive sleep apnea who are referred to the PI for clinical evaluation with DISE will be recruited for this protocol. 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)

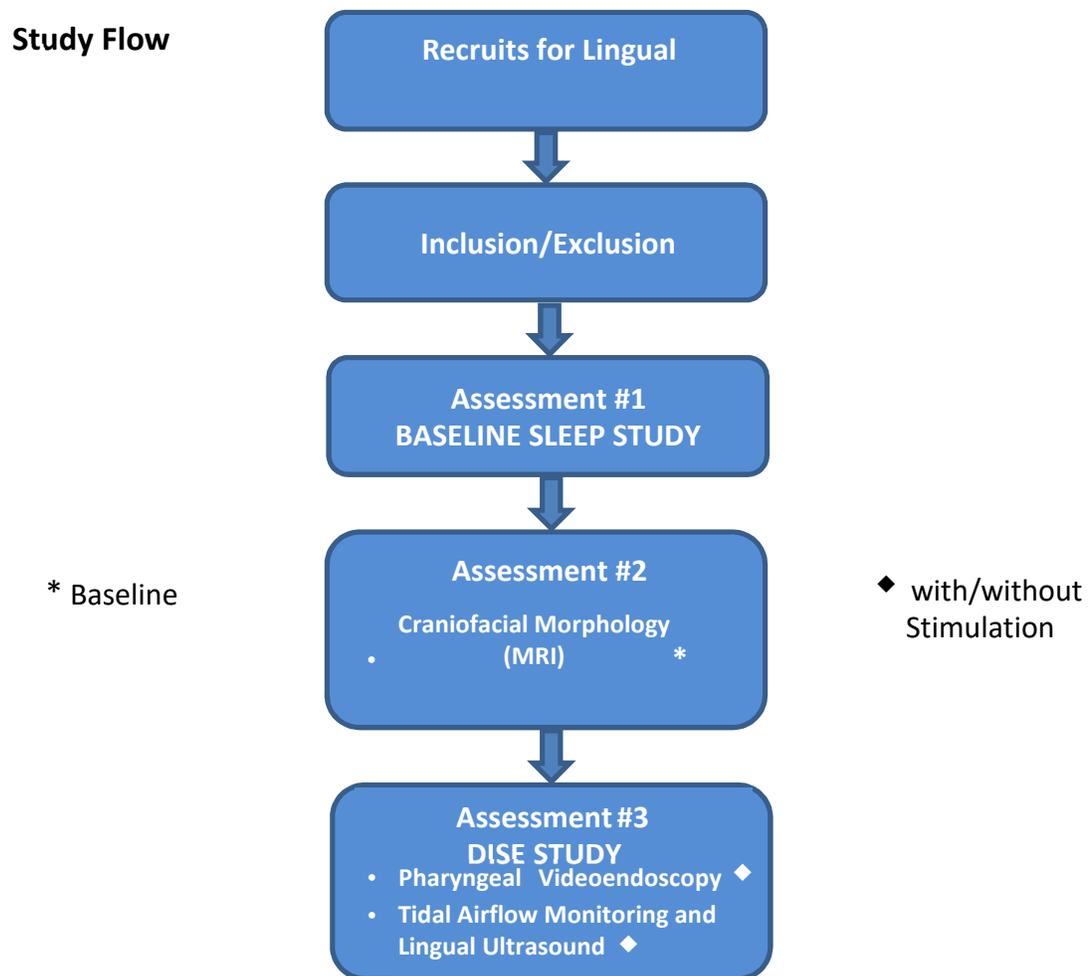
Participants will initially be consented and screened for this study with a brief medical history and physical exam. The diagnosis of moderate to severe obstructive sleep apnea will be confirmed from prior sleep study reports. If such reports are not available, the subject will undergo an overnight

home sleep study. Once all inclusion criteria have been met, participants will continue with 3 assessments.

Eligible participants will have an initial assessment (Assessment #1), where they will undergo an in lab baseline sleep study. 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.

Participants will then undergo an Assessment #2, where craniofacial morphology will be assessed with photographs and MRI measurements.

Thereafter, responses to stimulation will be assessed during DISE with ultrasound measurements of tongue morphology and with measurements of pharyngeal patency during DISE (Assessment #3). Responses in pharyngeal patency will be assessed with video endoscopy and tidal airflow monitoring while briefly stimulating each electrode during DISE.



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

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).

History & Physical Exam: Each research participant will undergo a brief history and physical exam to confirm inclusion criteria. A screening medical history and medications questionnaire will be completed on each participant. Metrics of regional adiposity (neck, waist, and hip circumferences) will be assessed on intake.

Baseline Home Sleep Study: Some participants may be asked to take home a portable home sleep testing (HST) device in order to confirm inclusion criteria. Recordings will be archived on an institutionally secured and managed network drive. Recordings will be accessed via a HIPAA secured web portal for scoring by registered polysomnographic technologists and for reviewing by project personnel. Routine scoring and analysis will provide indices of nocturnal hypoxemia and sleep apnea severity.

Ultrasound procedures: Ultrasound (SonoSite Edge: <https://www.providianmedical.com/ultrasound-machines/sonosite/sonosite-edge/>) will be performed in each study participant during wakefulness. Measurements during DISE will take about 30 minutes. Images will be acquired with and without stimulation of tongue protrudors and retractors separately and combined.

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, Erlangen, 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.

Sleep study monitoring (polysomnography): Standard monitoring of sleep will occur during Assessment #1. This will include monitoring of EEG, submental EMG, EOG, SpO₂, tidal airflow, thoraco-abdominal efforts, and body position. Overnight nocturnal recordings will be performed in our sleep laboratory. 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.

Supraglottic Manometry: In addition to standard sleep monitoring during Assessment #3, a 7 French Millar catheter (Houston, TX) marked at regular intervals will be passed perinasally to monitor supraglottic 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^{9,10}. To facilitate this process, we will administer 2% Viscous Lidocaine perinasally before passing the catheter.

Drug Induced Sleep Endoscopy (DISE): During Assessment #3, patients will be moderately sedated with Propofol (2.5mg/kg load followed by continuous drip of 6 – 12 mg/kg/hr). A fiberoptic scope will be passed through an airtight seal in the nasal mask through the nose into the pharynx. 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. Electrical stimulation will be applied in 4s bursts to protrudors with and without retractors for single breaths at each pressure level while acquiring separate sets of video-endoscopic images in both the velo- and oropharynx.

Tidal Airflow Monitoring: During Assessment #3, 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 described¹¹⁻³³.

Lingual Muscle Stimulation:

Insertion and stimulation methods:

Fine-wire stimulating electrodes (0.36mm diameter, 1.5", Natus Medical, Pleasanton, CA) will be utilized for intramuscular lingual stimulation. These wires will be connected to an EMG stimulation system (Nicolet EDX, Natus Medical)(<https://neuro.natus.com/products-services/nicolet-edx-emg-ncs-ep-iom-system>). The muscles will be stimulated with a pulse width of 40 μ S, a frequency of 30Hz, and 1s burst duration. In our extensive experience using stimulation devices to stimulate tongue muscles, we have not encountered any significant adverse events^{1,7}. The current level will then be increased stepwise. The capture threshold will be determined to be the lowest current level at which stimulation elicited tongue movement. If patients report discomfort at any point during stimulation at the capture threshold, the electrode pair will be removed and other electrodes will be inserted in another position. As stimulation current is increased further, tongue movement is expected to occur. At still higher current levels, stimulation can produce discomfort. The electrode pair that results in the greatest tongue movement without discomfort will then be utilized during DISE.

Protocol:

A transoral approach will be utilized to stimulate the lingual protrudors with and without retractors intramuscularly. Each muscle group will be stimulated with two fine-wire Teflon-coated steel electrodes (as described below). As many as four electrodes will be placed.

Stimulation during wakefulness:

- a. Retractor Muscles: electrodes will be placed under topical anesthesia (2% lidocaine gel) in the posterior gingivolabial sulcus. Single-hook wire electrodes will be directed inferoposteriorly ~2 cm below the oral mucosa under local anesthesia. Stimulating retractors will lead to tongue deviation toward the stimulated side (ipsilateral tongue deviation). The investigators have published previously utilizing such methods for selective stimulation during sleep^{1,2}.
- b. Protrudor muscles: single-hook wire electrodes will be placed just lateral to the frenulum and directed inferiorly ~2 cm below the oral mucosa under topical anesthesia (2% lidocaine gel). Protrudor stimulation will be confirmed by forward tongue movement and contralateral deviation^{1,2}.

Stimulation during DISE:

During DISE, the lingual musculature will be stimulated during the inspiratory phase of the respiratory cycle. The current level will then be increased stepwise to maximize the effect of electrical stimulation on inspiratory airflow without arousing the patient from sedation. Results

obtained at the highest level of electrical stimulation that does not arouse patients will be utilized.

Procedures to Access and Store Research Data: The results of clinically relevant tests (baseline sleep study) will be sent to the participants; urgent results and/or incidental findings will also be 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). 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 imaging (MRI) analysis.

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.

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

Each participant will be asked to participate for the duration of Assessment 1 (baseline overnight sleep study), Assessment 2 (up to 1 half day for imaging procedures), and Assessment 3 (1 half day for DISE procedure). Prior to Assessment #1, some participants may be asked to have a baseline home sleep study (1 overnight) to confirm inclusion criteria if they are unable to provide documented confirmation of their AHI. Successful placement of the fine wire stimulating electrodes will be necessary in order to obtain usable data for analysis. We anticipate that approximately 20% of participants will not be able to complete these Assessments. Participants' participation in these assessments will remain completely voluntary.

We estimate that it will take us about 3 years to collect, process, and fully analyze the ultrasound and DISE study data.

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.

Each subject's medical therapy will continue unaffected by this study with the addition of submandibular ultrasound examination and of one unscheduled polysomnography.

5. Inclusion/Exclusion Criteria

Inclusion Criteria:

- Adult patients (≥ 22 yrs) willing and capable of providing informed consent
- Moderate to severe obstructive sleep apnea ($AHI \geq 20$)
- No underlying cardiac disease
 - Clinical history of coronary artery disease (myocardial infarction, angina) arrhythmia, valvular heart disease, heart failure, or pulmonary hypertension with exacerbation or up-titration of related medications over the last 3 months before study enrollment

Exclusion Criteria:

- Significant cardiac disease, unstable or recent cardiac events
- Active pulmonary, liver, or renal disease
- Uncontrolled hypertension ($BP > 160/100$)
- Neuromuscular disease
- Major psychiatric disease
- Lifestyle considerations by the use of excessive alcohol, tobacco, or drugs, and involvement in shift work occupations that preclude study in the laboratory
- Pregnancy
 - We had not planned for subjects to take a pregnancy test, and will not require that contraception be utilized during subjects' participation in the protocol. This approach is justified by the fact that there is no risk of overnight sleep studies in pregnancy, and that the drug-induced sleep endoscopy procedure will already be undertaken for clinical purposes. The research study will add an estimated extra 10 minutes to the DISE procedure, and DISE will be provided for clinical indications.
 - If a patient becomes pregnant between the time of enrollment and study procedures (sleep study and DISE), participation in DISE will be governed by clinical indications for this procedure. The probability of enrolling pregnant or even pre-menopausal women into our protocol is low since the prevalence of clinically significant obstructive sleep apnea increases markedly after the menopause. In the unlikely event that pregnancy occurs, the study team will notify IRB.
- Anticoagulation therapy (e.g., Coumadin, Dabigatran)
- MRI contraindications (e.g., claustrophobia, presence of a ferromagnetic/MRI-contraindicated implant or foreign body, etc.)

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 supraglottic catheter and endoscope. Lidocaine will also be used during the application of the lingual fine wires to participants' tongue muscles.

A Natus Nicolet EDX UltraPro S100 unit will be used to stimulate lingual muscles with a pulse width of 40 μ S, a frequency of 30Hz, and 1s burst duration. Fine wire insulated stimulating electrodes (27 g hook wire electrodes, Natus Inc.) will be inserted into lingual muscles and connected to the EDX unit. This stimulus regimen has been utilized in previous studies by investigators with no significant adverse event^{1,7}.

WatchPAT 300 (Itamar Medical) will be used to screen patients with suspected obstructive sleep apnea for this disorder. This instrument consists of a sensor array that is worn on the finger, wrist, and manubrium. 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 WatchPAT device will be dispensed by the sleep research staff, and nocturnal recordings will be handled and scored in accordance with best clinical practice. The EDX stimulator device will be stored and operated by trained research staff for the DISE procedure.

7. Study Statistics

Our primary independent variables are stimulation electrode and intensity. 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: protruder and retractor stimulation, each isolated and combined), 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 $\sim 3.5 \pm 2.0$ cmH₂O during stimulation². This response accounts for $\sim 24\%$ of the total variance (η^2), 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^{34,35}. Using these parameters, we calculated that 15 subjects would be required to detect significant differences in responses between electrodes 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 30 subjects to complete the 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. This protocol is not a clinical trial per se, since we will examine acute effects of stimulating single breaths on markers of upper airway patency and tongue morphology. Hence, we do not anticipate a need for any stopping rules, and we have not defined any such rules. 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.

Baseline Home Sleep Testing: There is very little medical risk involved with deploying these devices, which are FDA approved for this indication. There is a small risk of inconvenience to the participant should the device malfunction and the study need repeating.

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 only risks posed by MRI relate to claustrophobia that 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 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 protocol will be certified through compliance training to work in the MRI scanner.

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. Nevertheless, we have excluded severely ill participants with underlying cardiopulmonary disease, who would ordinarily be at greatest risk for this occurrence. 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 recommended for referral to their primary care provider for an AHI \geq 30 episodes/hr or if the cumulative time spent with an SaO₂<90% is \geq 5% 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. There will be a trained rapid response team available to respond to medical emergencies in the sleep lab.

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. The thin nasal catheter and 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. The catheter will be lubricated with topical lidocaine. 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. Precautions will be taken to exclude patients with underlying cardiopulmonary disease, who might be susceptible to pneumothorax or hemodynamic compromise with alterations in airway pressure. In our previous experience, we have not had any complication resulting from negative nasal pressure administration in the ranges proposed⁹⁻³¹.

Topical Lidocaine: The risks are minimal since we will inquire beforehand about lidocaine sensitivity. Subjects may feel an initial slight burning sensation in their nostrils and an urge to swallow.

Lingual Muscle Stimulation: Each electrode will be tested during wakefulness to determine the capture threshold and submaximal stimulation level. In brief, therapy settings for each electrode, which have resulted in sufficient airflow and a decrease in sleep disordered breathing events on prior testing without evidence of causing arousal from sleep, will be selected for testing during sleep and wakefulness.

Participants may experience discomfort while the fine wire electrodes are inserted into lingual muscles. Lidocaine will be used to ease any potential discomfort. Additionally, although rare, there is a risk of:

- Transient paresthesia or tingling when stimulation is applied
- Transient pain or discomfort during stimulation
- Transient paresis (weakness of the tongue) when stimulation is applied
- Transient dysarthria (difficulty speaking) when stimulation is applied

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 flyers, and/or from existing clinic patients and research participants who have already consented to be contacted for research and/or already have a professional relationship with the PI. Participants recruited from the general population using online advertising will be directed to the REDCap study landing webpage to learn more about the study, answer basic inclusion/exclusion criteria questions, and provide contact information, so they may be contacted by a study coordinator. All ads and flyers used for recruitment purposes will be IRB approved and an IRB-approved telephone script will be used to pre-screen participants for inclusion criteria.

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.

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: The risks of this protocol are outweighed by the benefits as follows. This protocol is designed to improved therapeutic responses to lingual muscle stimulation for patients who cannot tolerate usual care with nasal CPAP. CPAP intolerant patients who are planning to undergo routine drug-induced sleep endoscopy as part of their clinical evaluation to qualify them for implantation of an Inspire Hypoglossal Nerve stimulating system will be recruited for this protocol. The risks of adding an estimated 5 to 10 minutes to routine, already-indicated clinical nasopharyngoscopy are minimal. The benefit will be significant in improving our understanding of upper airway anatomy and physiology for apneic patients, and in predicting responses to the Inspire Upper Airway Stimulation therapy. This protocol will potentially improve our ability to deliver maximally efficient, effective care for such patients.

10. Payment and Remuneration

Volunteers will receive \$75 for completing baseline polysomnography (Assessment #1), \$50 for completing intake (Assessment #2), and \$200 for completing the DISE (Assessment #3). If they are asked to repeat Assessment # 3, they will be paid an additional \$200. Some volunteers may be asked to have a home sleep study to confirm inclusion criteria. 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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