PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
David Wellman, MD, PhD

PROTOCOL TITLE
Mechanisms of Pharyngeal Collapse in Sleep Apnea

FUNDING
Dr. David Andrew Wellman Sundry Account
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February 1, 2017

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Part A (pattern of upper airway muscle activity and NED)

We hypothesize that upper airway mechanoreceptor reflexes may protect against NED. Topical oropharyngeal anesthesia has been shown to reduce phasic genioglossus activity. Thus, we also hypothesize that patients with Starling Resistor type behavior (constant inspiratory flow over a range of driving pressures) will develop NED once the reflexes have been impaired with topical anesthetic. We plan to:

1. measure upper airway muscle EMG to assess how it corresponds to the presence or absence of NED. This aim will allow us to test the hypothesis that robust upper airway muscle reflexes can protect against NED.
2. reduce upper airway muscle activity and reflexes by topical oropharyngeal anesthesia. This will allow us to test the hypothesis that attenuated upper airway muscle activity induced by topical anesthesia can induce NED.

Part B (upper airway endoscopy during flow limitation)

This part of the protocol has 3 separate steps: 1) Pharyngometry during wakefulless, 2) CPAP during sleep to induce flow limitation and 3) oral devices (oral appliance and oral pressure therapy) to observe their effect on negative effort dependence and pharyngeal collapsibility.

Pharyngometry during wakefullness: We will use a pharyngometer to estimate pharyngeal length and cross-sectional area.
CPAP to induce flow limitation: We will induce inspiratory flow limitation by dropping CPAP for 5 minutes and will simultaneously measure airway area and pressure.

Oral devices and effect on negative effort dependence and pharyngeal collapsibility: Subjects will use either an oral appliance (the subject's own oral appliance that is being used at home to treat obstructive sleep apnea) or a temporary device provided for the duration of the study or an oral pressure therapy device that we will provide.

The following hypothesis will be tested:
Aim 1: We aim to test the wave-speed theory for inspiratory flow limitation in the human pharynx. We hypothesize that this flow limiting mechanism can explain inspiratory flow limitation in OSA patients. On the other hand, we hypothesize that downstream pressure propagates upstream past the choke point when negative effort dependence can be observed, what is not expected by the wave speed theory.

Aim 2: We aim to test the influences of lung volume and low ventilatory drive on progressive expiratory narrowing (PEN). Pharyngeal cross-sectional area using endoscopy will be measured simultaneously with lung volume (magnetometers), genioglossus EMG, pharyngeal pressure, and end-tidal CO2 during 3-minute CPAP drops to subtherapeutic pressures. We hypothesize that airway area can decrease despite constant lung volume and constant or elevated ventilatory drive.

Aim 3: We aim to test the effect of oral appliance and oral pressure therapy on the pharyngeal cross-sectional area and collapsibility during sleep. We hypothesize that the both oral appliance and oral pressure therapy stabilize the soft palate and tongue and decrease negative effort dependence and improve collapsibility.

Aim 4: We aim to test the correlation between the primary structure of collapse with the change in pharyngeal collapsibility with Oral Appliance (OA) therapy. We hypothsize that non-PAP therapies like OA are inherently structure-specific and will function optimally when correctly matched to the primary structure causing collapse, and have a finite scope to improve upper airway anatomy and will be most effective in patients without severe pharyngeal collapsibility.

Part E (expiratory flow limitation)

Test of the influences of added expiratory nasal resistance on expiratory flow limitation. Recent research indicates that expiratory flow limitation occurs as the soft palate becomes inverted (prolapse) during expiration and limits expiratory flow. This can lead to a pattern of progressive expiratory and inspiratory collapse. Theoretically, applying an added expiratory resistance to provide a pressure gradient opposing soft palate prolapse may prevent this behavior. Thus, we will test whether expiratory flow limitation can be transiently improved by adding expiratory nasal resistance

Part F (oral breathing)

Test the effect of added a single-use Varnum mouthpiece on pharyngeal collapsibility and OSA severity in patients who identify themselves as mouth breathers. Research indicates that nasal breathing not only may improve sleep apnea but it also increases circulation, blood oxygen, and carbon dioxide levels, slows the breathing rate, and improves overall lung volumes (23).

Thus, we will test whether a single-use Varnum mouthpiece can improve pharyngeal collapsibility and OSA severity in mouth breathers. We will also test the Varnum mouthpiece in nose breathers to serve as a control for the effectiveness of the Varnum mouthpiece.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal collapse during sleep and is associated with increased morbidity and mortality. However, OSA remains undertreated due in part to the few treatment options available. Thus, understanding the pathophysiology of sleep apnea and developing novel therapies is of considerable importance. The mechanisms of recurrent upper airway collapse in OSA remain incompletely understood. Airflow limitation, negative effort dependence and progressive expiratory narrowing (defined below) are important characteristics of the upper airway associated with pharyngeal collapse that need further understanding.

Inspiratory flow limitation is defined as a lack of increase in flow despite increasing inspiratory effort. This phenomenon can be easily observed during polysomnography as a flattening of inspiratory flow and is frequently associated with hypopneas, which are defining events of OSA. The mechanism of flow limitation in the upper airway is not known. Several models and theories have been proposed to explain why flow limitation occurs. The Starling Resistor model is frequently used to assess pharyngeal mechanics and defines a constant airflow over a range of driving pressures. The wave-speed theory was proposed by Dawson and Elliot who stated that flow in a compliant tube could not exceed the lowest flow at which the air speed equaled the tube's "wave speed". The wave speed of a tube is the speed that a pressure pulse travels longitudinally along (and within) the wall of the tube. Flow limitation at wave speed depends on gas density, airway cross-sectional area, and airway compliance. Another flow limiting mechanism, viscous flow limitation, has been proposed to explain flow limitation in tubes of smaller areas. This mechanism of flow limitation results from the coupling between dissipative pressure losses (dependent on viscosity) and tube compliance. Since the wave-speed and viscous flow mechanisms have not been tested as flow limiting mechanisms of the human pharynx, we intend to test both these theories.

Classic Starling Resistor models suggest constant flow through a collapsible tube over a range of driving pressures. However, NED or negative effort dependence is a well recognized phenomenon whereby airflow actually decreases with increasing respiratory effort. The mechanisms underlying NED in the human upper airway remain unclear. On the other hand, the upper airway muscle dilators are modulated by locally mediated mechanoreceptive reflex mechanisms that respond to negative pharyngeal pressure. This reflex may compensate the inspiratory tendency to upper airway collapse during sleep. Moreover, muscle recruitment could potentially mitigate NED. Conversely, topical oropharyngeal anesthesia has been shown to reduce the mechanoreceptive reflex to negative pharyngeal pressure and consequently phasic upper airway muscle activity. We intend to evaluate the pattern of upper airway muscle activity and the development of NED on flow limited breaths in OSA patients during sleep. We hypothesize that upper airway mechanoreceptor reflexes may protect against NED. In addition, we also hypothesize that patients with Starling Resistor type behavior (constant inspiratory flow

over a range of driving pressures) will develop NED once the reflexes have been impaired with topical anesthesia.

A number of studies have shown that, in OSA, there is progressive narrowing of the pharyngeal airway across breaths during expiration preceding an obstructive apnea. The mechanism of this progressive expiratory narrowing (PEN) is not known, but potential causes include: falling lung volume in the breaths preceding an apnea ("lung volume hypothesis"); decreasing ventilatory drive following an arousal with ventilatory overshoot ("low drive hypothesis"); insufficient time for the airway to expand during expiration ("expansion time hypothesis"); re-expansion on expiration may not occur as easily or to the same extent as collapse on inspiration ("hysteresis hypothesis"); slow narrowing due to viscoelastic properties of the airway ("viscoelastic hypothesis"); or prolapse of the velopharynx specifically occurring during expiration ("expiratory flow limitation"). We hypothesize that PEN can occur despite constant lung volume and constant or elevated ventilatory drive. We also hypothesize that PEN can occur due to reduced time for expiratory re-expansion and also due to hysteresis and viscoelastic properties of the pharynx. In addition, we hypothesize that applying expiratory nasal resistance will minimize expiratory narrowing in patients with expiratory flow limitation.

In general, Oral Appliances (OA) devices are designed to maintain the mandible and/or tongue in a protruded posture during sleep, preventing upper airway obstruction. Limited studies in awake or sedated patients have demonstrated the effects of mandibular advancement on aspects of pharyngeal structure and function. We propose that the two major baseline determinants of OA success are the structure and severity of upper airway collapse.

In addition, mouth breathing during sleep causes the jaw to drop resulting in a reduction of pharyngeal airway diameter and contributing to sleep apnea severity. Therefore, one potential solution to this problem is to use a mouthpiece to encourage nasal breathing during sleep (and thus reduce pharyngeal collapse). We hypothesize that such a device will keep the lips from separating and thereby encourage nasal breathing.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

OSA patients with an AHI > 10 episodes/hr will be studied as well as subjects who snore with suspected obstructive sleep apnea. Subjects will be on no medications that could affect respiration or muscle control. Individuals with concurrent sleep disorders such as periodic limb movements (periodic limb movement arousal index > 10/hr), narcolepsy, or a parasomnia will be excluded. Other exclusion criteria include: periodontal disease, insufficient number of teeth, allergy to lidocaine, pregnancy, renal failure, neuromuscular disease or other major neurological disorders, uncontrolled diabetes, heart failure, central sleep apnea or Cheyne-Stokes respiration, uncontrolled hypertension, thyroid disease, or any other unstable major medical condition. The age range will be 21 – 70 years.

For each Part, Subjects will report to and be admitted into Brigham and Women's Hospital (BWH) Clinical Research Center (CRC) approximately 2 hours prior to their usual bedtime and after having been without food intake for the preceding 4 hours. For Part B there

will be three overnight studies. A history and physical examination will be performed on the night each patient is admitted to the CRC. Paste-on electrodes will then be applied to the scalp, chin, chest and face to allow monitoring of EEG, EMG, EKG and EOG. A pulse oxymeter probe will be clipped to the finger or earlobe for continuous oxygen monitoring. A nasal mask will be held in place with Velcro straps and the mask attached to a pneumotachograph and a modified CPAP device. End Tidal partial pressure of CO_2 ($PETCO_2$) and pressure in the mask will also be monitored. Pharyngeal pressure will be measured with a 5-french Millar catheter that has 6 pressure sensors 1.5cm apart starting at the tip. After nasal decongestion (0.05% oxymetazoline) and topical anesthesia (4% lidocaine), the catheter will be placed with the tip1cm below the tongue base. Once in place the catheter will be taped at the nose to ensure it does not move.

Two pairs of magnetometers will be used to monitor lung volume. The magnetometers will be placed on the front and back of the subject along the midline at the level of the sternum and just above the umbilicus. Calibration will be performed during wakefulness by comparison with tidal volumes recorded by the pneumotachograph.

If the data collected are considered insufficient, the subject may be asked to repeat the whole study or a part of it.

Part A (pattern of upper airway muscle activity and NED) (n=40):

In addition to the above described procedures, genioglossal EMG will be measured with unipolar intramuscular electrodes as follows. Two 25 gauge needles containing 30 gauge Teflon-coated stainless steel wires are inserted into the muscle after topical anaesthesia with 4% lidocaine (1-2 mL's). The needle is immediately removed leaving the wire in place. Both electrodes are referenced to a single ground producing a bipolar recording. Needle placement is as follows: the muscle is approached through the floor of the mouth with each needle being inserted about 3-5 mm lateral to the frenulum and about 12-15 mm into the body of the genioglossus near its insertion into the mandible.

After instrumentation, the patients will be asked to sleep in the supine position with the chin forward. Once asleep, CPAP will be set to the holding pressure, defined as the mask pressure required to eliminate hypopneas, snoring, and flow limitation. It will then be slowly reduced to a level that produces stable flow limitation, typically 3-5 cm H_2O below the treatment level of CPAP. If awakening occurs, the pressure will be returned to the holding pressure until stable sleep resumes.

After adequate data with flow limited breaths is obtained, the patient will be awakened and topical upper airway anesthesia will be performed. Selective oropharyngeal anesthesia will be achieved by spraying the underside of the soft palate, tonsillar pillars, posterior pharyngeal wall, and supraglottic area of the posterior oropharynx with a 4% lidocaine HCl solution repeatedly until the gag reflex is abolished. Subjects will be instructed to spit out any saliva accumulated during the procedure to minimize systemic absorption of the dose. The subject will then be allowed to sleep again and CPAP reduced to the same pressures as above to see if worsening NED develops.

Study endpoints for Part A include successful completion of all measurements in the study, at the subject's request, or by discretion of the researcher.

Part B (upper airway endoscopy during flow limitation) (Aim 1- n=20; Aim 2 – n=40; Aim 3=20):

Pharyngometry data will be collected in the CRC using the EccoVision Acoustic Pharyngometer (E. Benson Hood Laboratories, Pembrooke, MA) during wakefulness, prior to instrumentation. Each measurement consists of a plot of cross-sectional area [CSA (cm^2)] as a function of distance (cm) from the oral cavity. Each subject will be asked to breathe into the device through a mouthpiece. Oral breathing will be ensured by placing a clip on the nares. Measurements will be obtained at functional residual capacity. All measurements will be performed while subjects are awake and in the supine position.

A standardized pre-fabricated trial mandibular advancement (Blue Pro, BlueSom, Paris, France) will be adjusted for patients not currently using oral appliances. It is a thermoplastic customizable titrable oral appliance that can be easily fitted. We will set the mandible position for 70% percent of the subject's maximum possible protrusion. The device is designed to maintain the mandible in a maximally protruded posture consistent with patient comfort during sleep.

EEG, EMG, EKG, EOG, oxygen saturation, mask pressure, $PETCO_2$, airway pressure, genioglossal EMG and lung volume will be measured the same as already described. In addition, a 2.8mm pediatric fiberoptic bronchoscope with a working channel will be used to visualize the pharyngeal airway.

A small diameter (<2 mm) catheter will be introduced through the working channel of the bronchoscope. This catheter is comprised of two main assemblies: an inner core comprised of a rotating drive shaft and an optical fiber able to deliver a visible light located within the drive shaft, and a protective outer sheath. The internal core and rotational components of the catheter are sealed from communication with biological fluids and tissue at all times. The fiber is terminated at the proximal end with a commercial fiberoptic connector that permits rapid and precise connectivity to a motor drive unit and a light source. Similar catheters have been used to conduct a number of optical frequency domain imaging (OFDI) studies including the pulmonary airways at the Massachusetts General Hospital (MGH) (IRB Protocol #2008P001254). Although we will use an identical catheter as the ones being used at MGH, the present protocol will not use OFDI technology. Instead, we will use the device in the current protocol only to shine a visible light perpendicular to the catheter. No OFDI imaging will be performed. Dr. Melissa Suter, PI of the protocol that is currently running at the MGH has extensive experience with this device with no adverse events being reported to date. We have been adequately trained to operate the device safely.

The nares and nasopharynx will be topically anesthesized using no more than 1-2 ml of 4% lidocaine spray. Additionally, 4% lidocaine gel with a cotton tip will be inserted through the nares in order to assure nasal topical anesthesia. After making sure the nares and nasopharynx are numb, the scope will be inserted via a sealed hole in the mask and positioned just above the soft palate. The other end of the scope will be secured to an i.v. pole next to the bed. The visible light catheter will then be advanced through the auxiliary channel of the bronchoscope 1 to 4cm in order to highlight the region of interest to be recorded by the scope´s camera. Once the visible light catheter is in place, the inner optical core will be rotated at a speed of 100 rps.

1. **CPAP to induce flow-limitation:** After instrumentation, the patient will be asked to sleep in the supine position with the chin forward. Once asleep, CPAP will be set to the holding pressure. After several minutes of stable breathing at the holding pressure during NREM sleep, CPAP will be decreased slightly for 3-5 min in order to induce flow limitation. These maneuvers will be repeated multiple times to varying levels of suboptimal CPAP while breathing room air or while breathing the test gases for 2

consecutive respirations. If awakening occurs, the pressure will be returned to the holding pressure until stable sleep resumes.

2. **Oral devices and effect on negative effort dependence:** After instrumentation, the patient will be asked to sleep in the supine position with the chin forward in order to observe periods of spontaneous flow limitation. After a few minutes of stable sleep, the patient will be asked to wear the oral appliance or oral pressure therapy. The patient will be asked to test the oral appliance first. After a few minutes of stable sleep with oral appliance in place, the patient will be asked to change for the oral pressure therapy device.
3. **Oral appliance and effect on pharyngeal collapsibility:** The patients will be invited to participate in two additional physiological PSGs with and without OA. Those patients fitted with the temporary thermoplastic device will be asked to use it at home the night before the physiological PSG with OA. For the physiological PSGs, the instrumentation will be same described above, except the bronchoscope that will not be used. The patient will be asked to sleep in the supine position. Once asleep, CPAP will be set to the holding pressure. During the first 1-2 hours, passive upper airway collapsibility will be measured by abruptly lowering the mask pressure to subtherapeutic levels. Peak flow will be plotted against mask pressure to determine Pcrit. During the remainder of the night, patients will be monitored with standard clinical PSG to determine sleep apnea severity (apnea-hypopnea index).

Study endpoints for Part B include successful completion of all measurements in the study, at the subject's request, or by discretion of the researcher.

Part E (expiratory flow limitation) (n=30):

EEG, EMG, EKG, EOG, oxygen saturation, mask pressure, $PETCO_2$, and airway pressure will be performed the same as already described in part B. One of the following two procedures will be performed. 1) A non-rebreathing valve will be placed on the mask to enable changes in resistance to be made exclusively during expiration (providing expiratory pressure support) during sleep. 2) A single-use expiratory positive airway pressure (EPAP; Provent Sleep Therapy, Manchester, NH, USA) device will be applied to each nostril. The EPAP contains a mechanical valve with very low inspiratory resistance but low, medium, or high expiratory resistance with adhesive to provide a seal.

After instrumentation, the patients will be asked to sleep in the supine position with the chin forward.

Once asleep, during periods of reduced airflow (whether due to expiratory flow limitation or otherwise), expiratory resistance will be applied using the non-rebreathing valve (20-80 $cmH_2O/L.s$) in procedure 1 or the EPAP (low, medium, or high expiratory resistance) in procedure 2 to examine whether airflow increases. A sham expiratory resistance will operate as a control (turning the expiratory port towards a resistance of 0 cmH_2O). This data will allow us to test whether expiratory resistance increases airflow specifically in cases with expiratory flow limitation (rather than when expiratory flow limitation is absent).

Following completion of each study, all equipment will be removed, and the subject will be free to sleep in the laboratory free from equipment for the rest of the night. Alternatively, if the subject feels alert enough to leave, they may do so.

Study endpoints for Part E include successful completion of all measurements in the study, at the subject's request, or by discretion of the researcher.

Part F (oral breathing) (n=30):

Two overnight sleep studies, a baseline night and a device night, will be performed approximately one week apart in random order. On both baseline and device nights EEG, EMG, EKG, EOG, oxygen saturation, mask pressure, $PETCO_2$, and airway pressure will be performed the same as already described in part B. During the device night, in addition to these measurements, a single-use Varnum's mouthpiece, which is similar to an adhesive tape with a central opening, will be placed on a patient's mouth to encourage nasal breathing. The nostril-size central opening allows for oral breathing when necessary.

After instrumentation, the patients will be asked to sleep in the supine or lateral position with the chin forward. Following completion of each study, all equipment will be removed, and the subject will be free to sleep in the laboratory free from equipment for the rest of the night. Alternatively, if the subject feels alert enough to leave, they may do so.

Study endpoints for Part F include successful completion of all measurements in the study, at the subject's request, or by discretion of the researcher.

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

We will attempt to minimize the risk to subjects participating in these studies as follows:

1. All participants will be healthy. The obstructive sleep apnea patients have no other medically important disorders other than sleep apnea.
2. All studies will be conducted by an experienced investigator or a trained technician knowledgeable in all aspects of the procedures utilized. The investigator is an M.D. or a Ph.D. who is very knowledgeable in respiratory physiology and experienced in the procedures conducted. The trained technician will only monitor subjects during procedures equivalent to a standard or home sleep study.
3. Resuscitation equipment is immediately available should the need for it arise. However, this seems highly unlikely. If there is significant bleeding or the patient aspirates, or if any other complications occur, then the PI (David Wellman, MD, PhD) will be called (if he is not the one conducting the study) and the patient will be evaluated by a physician in the CRC or the Emergency Department on the bottom floor of the same building where the studies are conducted.

4. As subjects may be sleepy after participating in our physiology studies, several measures will be taken to combat this. After sleep studies, subjects will have the option of sleeping, without instrumentation, for as long as they would like before driving home. An additional cab voucher will be offered for the subject to return to the hospital in the case that the subject does not feel adequately rested and needs to leave his car in the garage. Last, they will only drive home if they feel adequately rested to do so. A small snack will be provided during the morning upon completion of the study.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

An adverse event is defined as untoward or unfavorable medical occurrence (e.g. abnormal physical sign/symptom or lab value) associated with the subject's participation in the research study. A serious adverse event is defined as any adverse event that results in death, is life threatening, requires hospitalization, or causes disability. The subject will be removed from the study if an adverse or serious adverse event occurs. Subjects will not be entered into the study unless they are healthy other than having obstructive sleep apnea in the patients. Specifically if any subject has uncontrolled hypertension or any cardio-respiratory problem they will not be entered into the study. If significant bleeding, swelling or vomiting are encountered during placement of the intramuscular electrodes and pressure catheter the study will be ceased although this has not been encountered in the past and so we do not expect these events. During the study the protocol will be ceased if any ECG abnormalities are noted or if any other respiratory/sleep disorder is discovered and the subject will be seen by an experienced investigator and appropriate follow-up arranged as necessary.

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

We believe that the risks associated with the procedures of the present study to be small. However, they will be individually addressed below.

Pharyngeal Pressure Determination: Pharyngeal pressure will be monitored during the studies. We have extensive experience with pharyngeal catheter placement without significant adverse reactions. However, some discomfort and potential risk may be present. There may be some discomfort passing the catheter through the nose and gagging can occur. The risk of aspiration must be considered in a subject in whom a mask is in place and pharyngeal catheter has been inserted. Although this is a potential risk, we believe the likelihood to be quite small for several reasons. First, once in place, the pharyngeal catheter causes little gagging. Second, all subjects will have fasted for four hours prior to the study and thus their stomach content is minimal. Finally, the mask can be easily removed. For these reasons we believe aspiration to be a minimal risk.

Lidocaine 4%: If the subjects have any history of lidocaine allergy, they will be excluded from the study. Excessive use of lidocaine can cause seizures, but this is reported with much higher doses than will be utilized in this study. Note: lidocaine does taste unpleasant and the subjects will be informed of this.

OxymetazolineHCl: Oxymetazoline will be sprayed twice into each nostril just prior to inserting the pressure catheters. This medicine could cause irritation to the nasal mucosa. In larger doses than used in this study, transient hypertension has been seen.
Determination of Ventilation During Sleep: The electrodes (EEG, EMG, and EOG), elastic bands, vibration sensors, mask, and oximeter used to monitor sleep and breathing may be mildly uncomfortable and could interfere with normal sleep. However, apart from the possibility of poor quality of sleep and sleepiness on the following day, no other important risk is anticipated.
Visualization of upper airway with a pediatric bronchoscope: The insertion of a pediatric bronchoscope into the nasopharynx will cause some discomfort when it is passed through the nose, and it may cause gagging when it is in the pharynx. As with the pharyngeal catheter insertion, the risk of aspiration must be considered. While this is a potential risk, we believe the likelihood to be small for the following reasons. First, the nose and pharynx will be anesthetized with lidocaine. Second, once the bronchoscope is in place, it causes little gagging. Third, all subjects will have fasted for four hours prior to the study and thus their stomach content will be minimal. For these reasons we believe aspiration to be a minimal risk.
Visible light catheter: the visible light catheter will be inserted through the working channel of the bronchoscope and kept in the pharyngeal lumen under continuous endoscopic view and therefore does not offer additional risk to the procedure.
Oral appliance: We do not expect any further risk or discomfort while using an oral appliance since the subject will be tested with his/her own custom-made device in use during the previous months.
Temporary thermoplastic oral appliance: The device may cause temporary dental sensitivity, jaw pain, dry mouth or hypersalivation. We do not expect any other significant risk once its use will be temporary.
Oral pressure therapy: this device may cause minor oral discomfort and salivation. No significant risks are expected.
Acoustic Pharyngometry: There is no risk with this procedure and no discomfort.
CPAP drops: As above, the only risks are the instrumentation described above, poor quality sleep, and transient shortness of breath when CPAP is lowered.
Magnetometers: Two pairs of magnetometers will be taped to the front and back of the patient. It does not offer any risk. However, it may lead to some discomfort since the patient will lay on the back magnetometers. After using the magnetometers in several patients, this was very infrequent.
Intramuscular EMG Determination: Needle insertion is likely to be mildly painful although the mucosa is topically anesthetized. We have found this pain to be similar to venipuncture and well tolerated. Once he needle is removed and the wire left in place, we have found the discomfort to be minimal. As we are not inserting the needle into areas where large arteries are present, we doubt quantitatively important bleeding is very probable. However, small hematomas could develop. Intramuscular or surface infection could occur as a result of the needle or wire. Although both are sterile, it is impossible to sterilize the mouth. We have, however, never encountered such a problem or heard of it happening elsewhere. However, there may be some residual soreness in the tongue for several hours after the wires are removed.
Expiratory resistance: A respiratory resistor or a single-use expiratory positive airway pressure (EPAP) will be added to which will make it slightly harder to breathe out through the nose. Although we expect this to make breathing out easier for some subjects, this may make breathing less comfortable for other subjects. By using a specialized breathing apparatus (non-rebreathing valve) it will not be any harder to breathe in through the nose, which will minimize any discomfort.
Varnum's mouthpiece: A single-use Varnum's mouthpiece will be added which will make it slightly harder to breathe in through the mouth. Although we expect this to make breathing easier

for some subjects, this may make breathing less comfortable for other subjects. By using a single-use Varnum's mouthpiece it will not be any harder to breathe in and out through the nose, which will minimize any discomfort and also can improve sleep quality and prevent dry mouth.

In conclusion, we believe the medical risks of the study to be quite small. We and other investigators have accomplished similar studies without incident. The time required to participate in this study will depend to a certain extent on how well the individual sleeps in the laboratory. However, every subject will be required to attend one overnight sleep study.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

The proposed studies offer no real benefit to the participating subjects. If unknown abnormalities of sleep are encountered, the information will be given to the subject and the subject's physician if the subject desires. However, there is no other direct benefit. The studies we propose should substantially improve our understanding of and apnea pathogenesis which will hopefully lead to new strategies for therapy. Therefore the societal benefit will hopefully be considerable.

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

In all proposed protocols, males and females will be recruited. It is also our intent to include minorities based on their representation in the patients seen at Brigham and Women's Hospital. Based on a recent assessment, the racial/ethnic mix at Brigham and Women's Hospital is 70.6% Caucasian, 12.6% African-American, 4.8% Hispanic and 2.3% Asian. American Indian and Native Hawaiian/Pacific Islander make up < 0.05% of the population and thus will not be included in these protocols. We plan to include all other groups at appropriate numbers based on these figures.

Children will not be studied as the pathophysiology of OSA is different in children and is primarily related to tonsil and adenoid hypertrophy. Pregnant women will not be studied as pregnancy will likely change respiratory control and upper airway collapsibility and therefore add considerable noise to the data.

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.

The interpreting services and the "Short Form" consent forms will be utilized to enroll any subjects who wishes to participate but does not speak English. We will provide a translator obtained from interpreter services department who is fluent in English and the subjects' native language

For guidance, refer to the following Partners policy:
Obtaining and Documenting Informed Consent of Subjects who do not Speak English
http://healthcare.partners.org/phsirb/nonengco.htm

RECRUITMENT PROCEDURES

Explain in detail the specific methodology that will be used to recruit subjects. Specifically address how, when, where and by whom subjects will be identified and approached about participation. Include any specific recruitment methods used to enhance recruitment of women and minorities.

Subjects will be recruited from our database of existing research subjects. Subjects also may be recruited through word of mouth, email, telephone, newspaper, internet and social media sites such as Facebook and Craigslist, and or bulletin fliers. Should the subject be interested in the study, they can call or email the study physician or coordinator to inquire about study participation. All email sent outside of the Partners firewall containing confidential information will be encrypted using "Send Secure" as per policy. Subjects may opt out of encrypted email communications if they have been advised of the risks associated with unencrypted email, and they indicate a preference to receive unencrypted email despite the risks.

Only patients who have stated in the initial clinical questionnaire that they are interested in hearing about research studies will be contacted by phone or email. During the phone or email interview patients will first be asked if they are willing to hear about research studies. If they aren't, the interview will be stopped. Patients will be called or emailed by one of our technicians who are not treating patients at the outpatient clinic. Therefore, patients won't feel obliged to participate because of a therapeutic relationship.

Individuals who respond and are interested in participating in this study will be given a thorough review of the risks, discomforts, potential benefits and their expected involvement during the initial phone or email conversation. Both men and women and people of all racial and ethnic backgrounds will be studied.

Provide details of remuneration, when applicable. Even when subjects may derive medical benefit from participation, it is often the case that extra hospital visits, meals at the hospital, parking fees or other inconveniences will result in additional out-of-pocket expenses related to study participation. Investigators may wish to consider providing reimbursement for such expenses when funding is available

Subjects will receive $100/night for participation in this study. Compensation for parking costs or taxi vouchers will also be provided

For guidance, refer to the following Partners policies:
Recruitment of Research Subjects

http://healthcare.partners.org/phsirb/recruit.htm

Guidelines for Advertisements for Recruiting Subjects
http://healthcare.partners.org/phsirb/advert.htm

Remuneration for Research Subjects
http://healthcare.partners.org/phsirb/remun.htm

CONSENT PROCEDURES

Explain in detail how, when, where, and by whom consent is obtained, and the timing of consent (i.e., how long subjects will be given to consider participation). For most studies involving more than minimal risk and all studies involving investigational drugs/devices, a licensed physician investigator must obtain informed consent. When subjects are to be enrolled from among the investigators' own patients, describe how the potential for coercion will be avoided.

There will be separate consent forms for Parts A, B, E, and F. Informed consent will be obtained either by the principal investigator or an experienced co-investigator prior to any participation in the study. The opportunity to talk to a licensed MD (who is readily available at the time of consent, and available overnight at the hospital) will be offered and documented in each case. After informed consent is obtained, the licensed MD will examine the subject (history and physical) to confirm whether he/she is suitable to proceed with the study. Subjects will have more than 24 hours to consider participating in the study. Prior to enrollment subjects will have all the risks of the study and details of the study procedures thoroughly reviewed. Any subject who is unable to give consent will not be studied.

NOTE: When subjects are unable to give consent due to age (minors) or impaired decision-making capacity, complete the forms for Research Involving Children as Subjects of Research and/or Research Involving Individuals with Impaired Decision-making Capacity, available on the New Submissions page on the PHRC website:
http://healthcare.partners.org/phsirb/newapp.htm#Newapp

For guidance, refer to the following Partners policy:
Informed Consent of Research Subjects
http://healthcare.partners.org/phsirb/infcons.htm

DATA AND SAFETY MONITORING

Describe the plan for monitoring the data to ensure the safety of subjects. The plan should include a brief description of (1) the safety and/or efficacy data that will be reviewed; (2) the planned frequency of review; and (3) who will be responsible for this review and for determining whether the research should be altered or stopped. Include a brief description of any stopping rules for the study, when appropriate. Depending upon the risk, size and complexity of the study, the investigator, an expert group, an independent Data and Safety Monitoring Board (DSMB) or others might be assigned primary responsibility for this monitoring activity.

NOTE: Regardless of data and safety monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for protecting the rights, safety, and welfare of subjects under his/her care.

This study is primarily a physiological investigation of the factors that lead to OSA in particular individuals. Thus, subjects will be carefully monitored with physiologic instruments (airflow, oxygen saturation, end-tidal carbon dioxide, etc.) during each of the studies. During each of the physiologic measurement, subjects will be monitored by an MD (typically the PI or sometimes a co-investigator), a PhD, a co-investigator, or a trained technician very knowledgeable in Respiratory Physiology and experienced in the procedures conducted. Each of the participants will have OSA (and be otherwise healthy). The range of possible adverse events is quite narrow and will be quickly realized by the study staff and investigator(s) performing the physiologic measurement. The study staff and investigators in this protocol will meet monthly to examine raw data and discuss any difficulties encountered. Thus, the investigators involved in this study will be responsible for overseeing the integrity of the results and monitoring for adverse events. "Stopping criteria" will consist of the patient's inability to tolerate the monitoring equipment, side effect from one of the medications, swelling of the airway, difficulty breathing, or bleeding.

Describe the plan to be followed by the Principal Investigator/study staff for review of adverse events experienced by subjects under his/her care, and when applicable, for review of sponsor safety reports and DSMB reports. Describe the plan for reporting adverse events to the sponsor and the Partners' IRB and, when applicable, for submitting sponsor safety reports and DSMB reports to the Partners' IRBs. When the investigator is also the sponsor of the IND/IDE, include the plan for reporting of adverse events to the FDA and, when applicable, to investigators at other sites.

NOTE: In addition to the adverse event reporting requirements of the sponsor, the principal investigator must follow the Partners Human Research Committee guidelines for Adverse Event Reporting

The Investigators and study staff will report any adverse events in accordance to the HRC guidelines to the IRB. The PI will email and call the Program Officer at the NHLBI as well as the IRB to report adverse and serious adverse events immediately when they occur.

MONITORING AND QUALITY ASSURANCE

Describe the plan to be followed by the principal investigator/study staff to monitor and assure the validity and integrity of the data and adherence to the IRB-approved protocol. Specify who will be responsible for monitoring, and the planned frequency of monitoring. For example, specify who will review the accuracy and completeness of case report form entries, source documents, and informed consent.

NOTE: Regardless of monitoring plans by the sponsor or others, the principal investigator is ultimately responsible for ensuring that the study is conducted at his/her investigative site in accordance with the IRB-approved protocol, and applicable regulations and requirements of the IRB.

The Principal Investigator has overall responsibility for Data and Safety Monitoring and Quality Assurance. The study staff will review the study and report to the principal investigator on a monthly basis to ensure adherence to the IRB-approved protocol and correct consenting procedures/documentation.

For guidance, refer to the following Partners policies:

Data and Safety Monitoring Plans and Quality Assurance
http://healthcare.partners.org/phsirb/datasafe.htm

Adverse Event Reporting Guidelines
http://healthcare.partners.org/phsirb/adverse_events.htm

PRIVACY AND CONFIDENTIALITY

Describe methods used to protect the privacy of subjects and maintain confidentiality of data collected. This typically includes such practices as substituting codes for names and/or medical record numbers; removing face sheets or other identifiers from completed surveys/questionnaires; proper disposal of printed computer data; limited access to study data; use of password-protected computer databases; training for research staff on the importance of confidentiality of data, and storing research records in a secure location.

NOTE: Additional measures, such as obtaining a Certificate of Confidentiality, should be considered and are strongly encouraged when the research involves the collection of sensitive data, such as sexual, criminal or illegal behaviors.

We will make every effort to maintain patient privacy and confidentiality both during and following the study. Electronic study data will be de-identified by substitution of codes for names and hospital identifiers and will be stored on a secure disk for access by co-investigators and study staff only and a hard copy will be stored in a locked cabinet. All research staff are IRB certified and it has been impressed upon them the importance of confidentiality. This study does not involve the collection of sensitive personal information from subjects. Data will be stored only at Partners sites and its use will be confined to that specified in this protocol and its approved amendments.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Specimens or data collected by Partners investigators will be sent to research collaborators outside Partners, indicate to whom specimens/data will be sent, what information will be sent, and whether the specimens/data will contain identifiers that could be used by the outside collaborators to link the specimens/data to individual subjects.

N/A

Specifically address whether specimens/data will be stored at collaborating sites outside Partners for future use not described in the protocol. Include whether subjects can withdraw

their specimens/data, and how they would do so. When appropriate, submit documentation of IRB approval from the recipient institution.

No data or specimens will be sent to collaborators outside Partners.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

When specimens or data collected by research collaborators outside Partners will be sent to Partners investigators, indicate from where the specimens/data will be obtained and whether the specimens/data will contain identifiers that could be used by Partners investigators to link the specimens/data to individual subjects. When appropriate, submit documentation of IRB approval and a copy of the IRB-approved consent form from the institution where the specimens/data were collected.

N/A