Effect of Upper Airway Stimulation on Cardiovascular Dysfunction in Obstructive Sleep Apnea

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1. Title Page

Full Study Title
Effect of Upper Airway Stimulation on Cardiovascular Dysfunction in Obstructive Sleep Apnea

Short Study Title
UAS on CV Dysfunction in OSA

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Sponsors
None

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2. External collaborators

None

3. Abstract

The prevalence of obstructive sleep apnea (OSA) is significant and increasing with greater obesity and aging of populations. Patients with moderate-severe OSA carry excessive risk of cardiovascular sequelae compared to controls. The first-line treatment for OSA, positive airway pressure, has demonstrated dramatic reduction in cardiovascular risk; however, long-term acceptance of this therapy approaches 50%. The advent of hypoglossal nerve stimulation (HGNS) therapy has provided a promising option to a subgroup of patients with moderate-severe OSA. This therapy has demonstrated long-term improvement in polysomnographic and quality of life measurements with adherence rates greater than 80%. The effect of HGNS on mitigation of cardiovascular risk in this vulnerable population, however, is entirely unknown.
The cardiovascular risk from moderate-severe OSA is intimately related to sympathovascular dysfunction. Multiple methods are available to capture various elements of this physiologic process including peripheral arterial tonometry (PAT), flow mediated dilation, peripheral arterial stiffness, ambulatory blood pressure monitor, dysrhythmia monitor and serum biomarkers. Using our prospective cohort of moderate-severe OSA patients undergoing HGNS, we will evaluate the effects of hypoglossal nerve stimulation on the sympathetic nervous system. The outcome of this study will

provide a potential mechanism for cardiovascular risk reduction for this novel, physiologic therapy for OSA.

4. Introduction & Background

Obstructive sleep apnea (OSA), repetitive collapse of the upper airway during sleep, represents a growing individual and public health concern. This disease negatively impacts patients' sleep quality and daytime function, including 3-10 fold increased risk of motor vehicle accidents. Several large, longitudinal cohorts have consistently demonstrated deleterious effects of OSA on cardiovascular health, including elevated rates of incident hypertension, myocardial infarction and cerebrovascular accidents. The link between OSA and cardiovascular consequences can be largely explained by autonomic imbalance during repeated episodes of nocturnal airway obstruction. Compared to controls, patients with OSA have increased sympathetic activity when awake, with further elevation of both sympathetic activity and blood pressure during sleep. Multiple physiologic mechanisms are responsible for these autonomic changes during obstructive episodes including the interaction of baroreceptors, chemoreceptors and respiratory afferent receptors. Positive airway pressure (PAP) serves as a pneumatic stent for the airway, maintaining airway patency and normoxia. PAP therapy has demonstrated consistent, meaningful reductions in sympathetic overactivity during wake and sleep.

Though PAP therapy is highly efficacious, fewer than 50% of patients are adequately treated due to adherence difficulty. In 2014, the Federal Drug Administration approved hypoglossal nerve stimulation (HGNS) for the treatment of patients with moderate-severe OSA unable to adequately use PAP. Recently published three-year data for this therapy demonstrated stable, marked improvement in key polysomnography indices, sleepiness measures and functional outcomes with adherence greater than 80%. To date, however, no study has examined cardiovascular endpoints of HGNS therapy in OSA patients.

Our overarching aim is to evaluate the effect of HGNS therapy on autonomic and vascular function as measured by changes in peripheral arterial tonometry, flow mediated dilation, peripheral arterial stiffness, 24-hour ambulatory blood pressure, 7-day dysrhythmia monitor and serum biomarkers before, during and after treatment in this high-risk cardiovascular population. **We hypothesize that all aforementioned measurements will be significantly improved following HGNS therapy and return to baseline values following a therapy withdrawal period.**

5. Objectives

Aim 1

Determine the impact of upper airway stimulation on peripheral arterial tonometry ratio related to obstructive episodes in this cohort of patients with moderate-severe obstructive sleep apnea

Hypothesis: The peripheral arterial tonometry ratio related to obstructive episodes will be improved with increasing levels of upper airway stimulation

Aim 2a
Determine the impact of upper airway stimulation on flow mediated dilation in this cohort of patients with moderate-severe obstructive sleep apnea
Hypothesis: The flow mediated dilation parameters will be improved at therapeutic levels of upper airway stimulation and returned to pre-operative levels after 30-day withdrawal period

Aim 2b
Determine the impact of upper airway stimulation on peripheral arterial stiffness in this cohort of patients with moderate-severe obstructive sleep apnea
Hypothesis: The peripheral arterial stiffness parameters will be improved at therapeutic levels of upper airway stimulation and returned to pre-operative levels after 30-day withdrawal period

Aim 2c
Determine the impact of upper airway stimulation on 24-hour ambulatory blood pressure in this cohort of patients with moderate-severe obstructive sleep apnea
Hypothesis: The 24-hour ambulatory blood pressure will be improved at therapeutic levels of upper airway stimulation and returned to pre-operative levels after 30-day withdrawal period

Aim 2d
Determine the impact of upper airway stimulation on serum biomarker profile in this cohort of patients with moderate-severe obstructive sleep apnea
Hypothesis: The serum biomarker profile will be improved at therapeutic levels of upper airway stimulation and returned to pre-operative levels after 30-day withdrawal period

6. Study Design and Methods

Each participant will undergo three sets of blood testing. Each set of testing will require travel to the Emory Clinical Cardiovascular Research Institute (ECCRI) facility at Woodruff Memorial Research Building on Clifton Campus. The subjects will be provided directions, lunch and parking vouchers for each visit. The subject will be registered at the EECRI facility each time and undergo fasting bloodwork.

Study Timeline

- Post-operative appointment: obtain consent for study enrollment (Day 1)
- WatchPAT baseline home sleep test (Night 1)
- Baseline 24-hour ambulatory blood pressure monitoring (Day 2-3)
- Baseline serum biomarkers/vascular testing (Day 15)
- Device Activation (Day 15)
- In-lab Polysomnography Titration (Day 45)
- WatchPAT treatment home sleep test (Night 75)
- Clinic visit (Day 105)

- Treatment serum biomarkers/vascular testing, 24-hour ambulatory blood pressure monitoring (Day 105-106)
- Therapy Withdrawal (Day 106-135)
- WatchPAT withdrawal home sleep test (Night 135)
- Withdrawal serum biomarkers/vascular testing, 24-hour ambulatory blood pressure monitoring (Day 136-137)
- Therapy Reactivation (Day 137)

Risks

The risks from participating in the research include the release of confidential information.
Due to the research nature of this study there may be other risks that are currently unknown. For instance, in the future it may be possible to link genetic factors to medical problems that could possibly influence insurability and employability, either for yourself or for your immediate family. To prevent this from being a problem for you in the future, your blood samples and research results will be labeled with a study ID number and not your name. Therefore, there will be no direct linkage between your blood sample and your name. However, this code will allow researchers to link your clinical information with your blood sample, without knowing your name.

Blood testing and genetic testing: rarely, bleeding can occur around the site where we draw your blood. This is not dangerous, but, if it occurs, it could result in a small bruise. Skin tape reactions may occur in a small portion of allergic subjects, but generally well tolerated and causes no long-term side effects.

Blood flow measurements: The blood pressure inflation lasts for 5 minutes and can result in temporary feelings of numbness and pins and needles in the arm that last for one or two minutes. However, this is generally well tolerated and causes no long-term side effects. The blood flow measurement device worn for 24 hours is very well tolerated. The device is light weight and padded and does not disturb sleep or any other daily activities.

Sleep testing: The wearing of the sleep test device may result in decreased sleep quality for the night of testing.

Benefits

This study is not designed to benefit you directly. Your obstructive sleep apnea may improve while you are in this study but it may not. We expect that your symptoms will worsen (return to baseline) during the portion of the study in which your device is turned off.
This study is designed to learn more about the cardiovascular improvement with this form of treatment of obstructive sleep apnea. The study results may be used to help others in the future.

Information to be Collected

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.

Specimens to be Collected

- Blood samples (before, during and after sleep apnea treatment)

Randomization and Blinding

There will be no randomization. Interpretation of all tests (sleep tests, ambulatory blood pressure monitoring, vascular test and blood tests) will single-blinded.

7. Data Sample Information

We will obtain a blood sample (about 1/2 cup) from you and store the blood for future analysis. The blood sample may be obtained by a nurse or physician as part of other blood draws you are undergoing during your visit(s). A study ID number will be used to link your blood sample to your other information. The DNA (genetic material) in your blood sample will be isolated and stored for future studies. Permanent cells may be created. Once DNA is isolated, it can be duplicated indefinitely for future research. Serum and plasma from your blood samples will also be stored and analyzed for a variety of biochemical factors. If you are less than 60 years old an extra tube of blood (about ½ tablespoon) will be collected. This extra tube of blood will be used to look at a special type of cell in your blood. This type of blood cell may help explain the difference between young women and young men with heart disease.

8. Community Participication

Not applicable

9. Participant Selection

Requested sample size: 50 subjects
Expected refusal/withdrawal: 10 subjects
Subjects completing study: 40 subjects

Inclusion criteria: All patients are English-speaking, greater than 18 years old and able to give informed consent. HGNS inclusion criteria per FDA require an AHI >=20 on recent sleep testing, unable to use positive airway pressure therapy, BMI < 32, without circumferential collapse on drug-induced sedated endoscopy. In essence, the inclusion criteria are those patients who have undergone HGNS implantation.

Exclusion criteria: active smokers, unstable and untreated coronary or peripheral artery disease, alpha-blockers, severe and inadequately controlled arterial hypertension.

Subject recruitment plan: All patients in the cohort will have undergone implantation of hypoglossal nerve stimulator by the principal investigator, Dr. Raj Dedhia, at the Sleep Surgery Center at Emory Midtown. At their 2-week post-operative appointment, they will be approached by the research coordinator at the Emory Sleep Center regarding participation in the study.

Screening for eligibility: Eligible subjects will be identified based on a clinical chart review by the principal investigator / surgeon, Dr. Raj Dedhia.

Procedures when a subject withdraws from the study:

1. Once the subject expresses that he/she would like to withdraw, no further information will be collected from the subject
2. Existing data will be utilized for appropriate analyses
3. These changes will be reflected in the intention-to-treat analysis

10. Informed Consent Process

The consent process will be done in person by the research assistant.
The research assistant will remain in the patient room for an extended period of time to ensure the subject's patients are adequately answered. We will deliberately schedule these patients as the last slot in the morning clinic allowing greater than 30 minutes before the first patient in the afternoon clinic. The research assistant will also ask the subject to repeat the procedures and timeline involved in this study.
The informed consent will allow for the subject to "opt out" of certain aspects of the study. The choices will be captured in the informed consent layout.

11. Incidental Findings

We anticipate incidental findings for the 24-hour blood pressure monitoring. We will set the following parameters for which the patient will be notified and asked to contact his/her primary care physician:

- Systolic BP > 200mm Hg for greater than 60 minutes of recording time
- Diastolic BP > 160mm Hg for greater than 60 minutes of recording time

The consent will include wording to indicate that he/she may be contacted if these results are seen. The principal investigator and treating physician (Dr. Raj C. Dedhia) will call the patient to inform him/her of the findings. The subject will be provided the option to withdraw from the study at that time.

12. Compensation

The subject will not be offered payment for being in this study. However, we will provide mailing costs for return of sleep testing and blood pressure equipment. The subject will

also be provided lunch and parking vouchers for each time (3 in total) that he/she undergoes cardiovascular testing. The subject will not be responsible to pay for any cardiovascular testing as this is being done outside routine clinical care.

13. Statistical Analysis

With 40 subjects, we will have 89% power to detect a difference of 0.1 in the PAT ratio (primary outcome) with a standard deviation of 0.2 and alpha of 0.05.
Each subject will have a baseline PAT ratio derived from the average of the 10 obstructive events without stimulation (Aim 1). The PAT ratios at each stimulation level (5-7 stimulation levels based on previous experience) will be averaged from 5 obstructive events at each level. With greater than 30 data points per individual, linear regression will be performed for each subject with stimulation level as the main effect variable and PAT ratio as the outcome variable. We will determine if stimulation level is positively associated with PAT ratio. We will also perform linear regression, in a similar manner, from the combined values of the cohort to determine an effect at the sample level.

An interim analysis will not be performed as the primary outcome variable is largely observational (non-interventional); thus, the findings are expected during the treatment of moderate-severe obstructive sleep apnea

14. Data Safety and Monitoring Board

A DSMB will not be required. Access to this database will be restricted by a database manager and will be password protected. The only individuals who will be able to see patient identifiers, like name, address, and social security number, will be the Principal Investigator, research coordinators, recruiters and the database managers. Other investigators will have different passwords that will provide restricted access to the database. Those with restricted access will be able to query the database for scientific information/variables, but will not be able to view information on patient identifiers such as name, address, and social security number. If investigators with restricted access want to conduct studies which require them to obtain patient identifiers so that patients can be contacted for follow-up information/follow-up visits, these investigators will have to submit a separate protocol to IRB to get permission to obtain patient identifiers and contact patients.

15. Confidentiality

All information will be kept private. No current or future research results will go into the medical record. If scientific reports, publications, or educational materials are written using information from the database, patients within the database will not be identified by name.
Access to this database will be restricted by the research assistant and will be password protected. The only individuals who will be able to see patient identifiers, like name,

address, and social security number, will be the Principal Investigator and research coordinators.

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