Prevalence of Obstructive Sleep Apnea in Patient's with Refractory Hypertension

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a. Specific Aims

In this project we plan to examine the prevalence of Obstructive Sleep Apnea (OSA) in Medicare patients' with refractory hypertension.

b. Background and Significance

"Uncontrolled hypertension" signifies blood pressure that is inadequately treated rather than blood pressures that is refractory to treatment, as might be observed in patient's with various co-morbidities including obstructive sleep apnea syndrome (OSAS), metabolic syndrome and obesity. Refractory hypertension is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients' with diabetes or renal disease despite adherence to at least three anti-hypertensive medications, including a diuretic (7). The majority of information regarding uncontrolled hypertension resides primarily in population-based surveys conducted by vehicles such as the Health Plan Employer Data and Information Set (HEDIS), as well as the National Center for Health Statistics who orchestrated the National Health and Nutrition Examination Survey (NHANES), which is a repository of the most comprehensive information concerning the prevalence of uncontrolled hypertension both in the general population as well as those groups at especially high risk of cardiovascular disease. Additionally, studies of hypertension control have been performed in a variety of epidemiological and practice settings such as the Framingham Heart Study cohort, the Cardiovascular Health Study and the Atherosclerosis Risk in Communities studies which have tried to ascertain the prevalence of patient's with not only goal BP but also undiagnosed, and under-treated BP in accordance with the definition recommendations of the JNC VII, American Diabetes Association and the National Kidney Foundation. It is by analyzing the data from the aforementioned studies that we can amass some insight regarding the number of patient's with refractory hypertension.

The association of OSAS with hypertension has been noted since the first description of OSAS in the medical literature (14). In a May, 2000 edition of The New England Journal of Medicine, Dr.'s Peppard and Young et al. published results from a prospective, population-based study looking at the association between objectively measured sleep-disordered breathing and hypertension (defined as a laboratory-measured blood pressure of at least 140/90 mm Hg or the use of antihypertensive medications). They found a dose-response association between sleep-disordered breathing at baseline and the presence of hypertension four years later that was independent of known confounding factors. Their finding suggested that sleep-disordered breathing is likely to be a risk factor for hypertension and consequent cardiovascular morbidity in the general population (21). Additional literature has further elucidated that the major health risk's in OSAS patients is the strong association with acute cardiovascular events (i.e. stroke,

myocardial infarction, and nocturnal sudden death) and chronic conditions such as systemic hypertension, coronary artery disease and heart failure (22).

OSAS is characterized by repeated episodes of upper airway obstruction during sleep, associated with increasing respiratory efforts, intermittent arterial oxygen desaturation, systemic and pulmonary arterial blood pressure surges and sleep disruption. The main symptoms of OSAS are nocturnal respiratory pauses interrupted by loud intermittent snoring and excessive daytime somnolence. According to recently updated International Classification of Sleep Disorders published by the American Academy of Sleep Medicine, a diagnosis of OSAS can be made if the respiratory disturbance index (RDI) is greater than or equal to 15, independent of occurrence of symptoms, or whenever an RDI greater than 5 is associated with one of the following: (a) sleep attacks, excessive daytime sleepiness (EDS), unrefreshing sleep, fatigue or insomnia; (b) awakenings with a choking sensation; or (c) witnessed heavy snoring and/or breathing pauses referred by the partner (1). The gold standard technique; however, for the diagnosis of sleep apnea is overnight polysomnography (18).

There is not yet a consensus, in fact there is still much debate surrounding the mechanisms of OSAS on BP which have been further divided into acute and chronic contributing factors. The acute cardiovascular affects of OSAS include: hypoxia, hypercapnia, and apnea, as well as negative intrathoracic pressure; while potential mechanisms linking OSA to chronic cardiovascular disease includes: sympathetic activation, vascular endothelial dysfunction, oxidative stress, inflammation, coagulation and metabolic dysregulation (24). Conversely, Calhoun et al demonstrated increased aldosterone excretion in subjects with resistant hypertension and symptoms of sleep apnea leading some to postulate that sleep apnea may contribute to the development of refractory hypertension by stimulating aldosterone excretion (5).

The next logical question surrounds identifying whether or not refractory hypertension is a pervasive enough topic to warrant further investigation which the literature appears to support. The best estimates of prevalence of refractory hypertension is provided by hypertensive outcome studies such as The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) from which we can extrapolate the prevalence of patient's with refractory hypertension by adding the number of subjects on 3 medications but whose BP remained elevated (i.e., patients who possibly should have been titrated to 4 medications) to the 8% who were on receiving 4 or more medications at the end of the study. Approximately 15% of that entire cohort could be classified as having refractory hypertension (8). In the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial 33% of subjects remained uncontrolled (BP > 140/90 mm Hg), with 18% of subjects being treated with 3 or more medications (4). Data from these two studies suggest that refractory hypertension exist among approximately twenty percent of our patient's with uncontrolled hypertension.

The problem however is not only determining the prevalence of OSAS in patient's with refractory hypertension, but also determining a mechanism by which physician's are more proactive in acting on this information. In 2001, Logan et al published results from

a small cross sectional study where 41 patients with refractory hypertension completed an overnight polysomnographic study and all but two had a 24 hour ambulatory blood pressure measurement. The results showed that the prevalence of OSAS defined in this study as an apnoea-hypopnea index of greater than or equal to 10 obstructive events per hour of sleep, was 83 percent in the 24 men and 17 men studied. Patients were generally late middle-aged, predominantly white, obese and taking a mean of 3.6 +/-.1 different antihypertensive medications daily. OSAS was more prevalent and severe in men than in women (16). This study was compelling in demonstrating a disproportionate amount of OSAS in patients with refractory hypertension. However, the small number of patients as well as homogenous group of participants makes generalizability a major shortcoming of the study. Additionally, it appears as though the major goal of the study, which presumably was to encourage physician's to potentially put OSAS higher on their differential in this subsection of patient's fell short of its intended purpose. This is supported for instance when one examines reference vehicles such as Up-to-Date, which doesn't even list OSAS as one of the possible etiologies for refractory hypertension.

It is the goal of this study to show that potentially at least one-third of patient's with refractory hypertension have OSAS, which should be significant enough to mobilize physicians into sending more patient's for polysomnography and most important decrease morbidity and mortality in this demographic. Considering that cost and or wait times for polysomnography are not trivial, there will be a corresponding questionnaire trying to elicit from individual's history whether or not they experience symptoms consistent with OSAS. Subsequently, it would be the goal of the investigator to see how well history correlates with the polysomnography results in these patients.

c. Study Design and Statistical Analysis

The study will be a longitudinal, prospective, observational study looking at the prevalence of OSA in Medicare patient's with refractory hypertension. Preliminary power analysis based on the hypothesis that at least 30 but potentially 40 percent of this demographic have this disease process leads to the inclusion of 200 patients' for the study. Medicare patient's will be the focused of the study because at one of the proposed testing center's there is no waiting time for polysomnography testing and it is covered by their insurance. Hence, if the recruitment mechanism is effective as documented below, the investigator should be able to have the testing completed in 12 months, which is the goal time frame. The subjects who agree to participate will prior to undertaking the exam be asked to fill out a questionnaire with the assistance of their partner when applicable which will investigate whether the patient has certain symptoms seen frequently in patient's with OSAS. The polysomnography results after being generated by the technician at the respective sleep labs will be sent to the investigator who will subsequently investigate the proportion of patient's with a positive test and then compare the polysomnography result with the percent of affirmative responses to the questionnaire. It is conceivable that one will then be able to say that if patient's responds in the affirmative to 75% of the OSAS symptom questionnaire than their likelihood of having polysomnography confirmed OSAS is a particular percent.

The following definitions provide additional details regarding the polysomnography scoring. Clinically speaking, an obstructive apnea is defined as a complete cessation of airflow for more than 10 seconds with persistent respiratory effort. An obstructive hypopnea is defined as a partial reduction in air flow of approximately 30% to 50% with respiratory effort and a reduction in oxygen saturation by at least 3% to 4% and/or arousal from sleep. For the purpose of this study we will use only the first definition of OSAS delineated above being a RDI, the combination of apneas and hypopneas, greater than 15 an hour. The polysomnography study will provide tangible, concrete, objective data by strictly following a RDI of 15 and will enable the investigator to clearly quantify the percentage of this refractory hypertension population who has OSAS. The questionnaire will ask ten yes/no questions and responding yes to 80 percent of the questions will be characterized as sufficient to confirm diagnosis. Relative risk calculations of the questionnaire results will be done and data will be measured on an intention to treat basis.

d. Study Procedure and Data Collection

Study participants will agree to spend one evening in the polysomnography laboratory where they will be monitored and analyzed in order to obtain a subsequent RDI thereby distinguishing the percentage of the subjects with newly diagnosed OSAS. Polysomnography is a diagnostic test during which a number of physiologic variables are measured and recorded during sleep. Physiologic sensor leads are placed on the patient to record: brain electrical activity, eye and jaw muscle movement, leg muscle movement, airflow, respiratory effort (chest and abdominal excursion), EKG, and oxygen saturation. Information is gathered from all leads and fed into a computer and outputted as a series of waveform tracings which enable the technician to visualize the various waveforms, assign a score for the test, and assist in the diagnostic process. In addition to the polysomnography test we will have the patient fill out a paper questionnaire, which should take the subject less than ten minutes to complete.

There will only be two locations for the polysomnography testing; however all data will be sent to CUMC where it will be collected and analyzed by the principle investigator in conjunction with housestaff and ancillary support services. The study procedure should be completed within a twelve month period of time with a goal turn around time of two months to collect and report upon the findings of the study.

d. Study Drugs

There are no drugs being investigated in this study; however, the participants will be allowed to remain on their current BP regimen as well as any other medications for chronic medical conditions.

e. Medical Device

No medical device is the hub of this study; however, the subject's will undergo testing on the polysomnography machine at the two participating hospital campuses in order to determine whether or not OSAS is a possible etiology in their refractory hypertension.

f. Study Questionnaires

Study participants will be asked to complete a questionnaire trying to elicit how closely we can correlate a patient's possible polysomnography confirmed OSA with their history of symptoms occurred during sleep as corroborate by a spouse or partner.

g. Study Subjects

Patients will be considered eligible for the study if they meet the definition for refractory hypertension: blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patient's with diabetes or renal disease (i.e., with a creatinine level of more than 1.5 mg per deciliter or urinary protein excretion of more than 300 mg over a 24-hour period), despite adherence to treatment with full doses of at least three antihypertensive medications, including a diuretic (7). Patient's however, in addition to falling within the criteria above must also be on Medicare so that we can ensure that the study subjects will be able to have the study conducted within twelve months which is the pre-determined period of time to complete the polysomnography testing and accompanying questionnaire which will be followed by and additional two months to amass the desired information and report its findings.

h. Recruitment of Subjects

Patients will be recruited from the AIM practice and equivalent outpatient setting at the University of Wisconsin in Madison, which is the home institution of an epidemiology specialist who published a seminal population, based OSAS study and often works with the advisory PI for this project, Dr. Pickering.

i. Confidentiality of Study Data

Confidentiality will be protected via the assignment of study identification numbers, which will be used for data processing. A list of the patient identification numbers will be kept in a separate location. All data will be kept in encrypted files on computer. Patient identities will be kept separate from these files.

j. Potential Conflict of Interest

There is no apparent conflict of interest for this study.

k. Location of Study

CUMC and University of Wisconsin Madison

l. Potential Risks

The potential risks of the study are limited to the minor side effects of polysomnography which mostly pertains to potential over-reading of EEG and potential labeling secondary to potential false positives, which again is not a direct risk to undertaking the study. There are no absolute contraindications and complications are rare with the most common complication being skin irritation caused by adhesives used to attach electrodes to the patient.

m. Potential Benefits

The potential benefits include not only being able to better define an individuals medical condition, but more importantly by uncovering a windfall of undiagnosed OSAS, physicians can in addition to using current modalities such as CPAP that have been intermittently effective in managing OSAS this study could yield credible data to support more intensive research into more consistently effective treatment regimens. Ultimately, by intervening in this capacity, physicians might be able to decrease significant morbidity and mortality associated with the downstream affects of patients with refractory hypertension not to mention greatly improving their quality of life.

n. Alternative Therapies

The diagnostic criteria for OSAS were delineated above whereby an investigator can use a combination of criteria in diagnosing OSAS. However, for the purpose of this study, the investigator decided to stay with the most objective criteria, being the RDI, noting however those alternative diagnostic criteria could have been used.

p. Compensation of Subjects

The subjects will not be compensated for participation in this study.

q. Minors as Research Subjects

This study will not involve the participation of minors.

r. Radiation or Radioactive Substances

This study will not involve radioactive substances.

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