Title:	Predictors of Obstructive Sleep Apnea in Hypertensive Patients from a Primary Care Clinic
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A. Study Purpose and Rationale

Introduction

Obstructive sleep apnea (OSA) is a prevalent[i,ii] disorder in adults that is characterized by repetitive interruption of ventilation during sleep caused by collapse of the pharyngeal airway. Patients with OSA are at increased risk for sleepiness, cognitive dysfunction, motor vehicle accidents, hypertension, and cardiovascular disease.[iii,iv,v] Continuous positive airway pressure (CPAP) is an effective treatment for OSA and its associated health effects, with the strongest evidence-based criteria for patients with moderate to severe disease (apnea–hypopnea index $\geq$ 15).[vi],[vii] Nevertheless, it has been estimated that as many as 93% of women and 82% of men with this degree of OSA may go undiagnosed.[viii] Untreated obstructive sleep apnea adds an estimated $3.4 billion annually to U.S. health care costs.[ix]

Primary care physicians can play a key role in screening patients for OSA and referring at risk individuals for polysomnography (PSG). However, community physicians are overburdened with high patient volume and patients with multiple co-morbidities, especially in an urban environment. In addition, a significant proportion of patients with OSA may not have subjective complaints of sleepiness[x] and patients with major features of OSA may not report them for many years, despite numerous encounters with health care providers [xi]. An attempt to identify cases based on only typical characteristic such as age of 40 to 70 years, male gender, and obesity might fail to identify women and normal weight patients with OSA. [xii] Even if intensive physician education programs and

accurate screening tools were instituted, sleep laboratories have a limited capacity and would likely be overwhelmed if all patients at risk for OSA were sent for PSA. Therefore, a screening instrument is necessary which will allow for the efficient stratification of patients to identify those with the greatest need for PSG and the most significant expected health benefits from treatment.

The existing evidence regarding the accuracy of OSA questionnaires is associated with promising but inconsistent results. For example, a recent study by Drager et al found that the Berlin Questionnaire, which had been validated in a primary care setting,[xiii] was highly sensitive (.93) but not specific (.59) for OSA in 99 patients from a hypertension unit. [xiv] However, metabolic syndrome was associated with a high sensitivity and specificity for OSA in this cohort (0.86 and 0.85, respectively). These findings have important implications for the efficient and accurate screening of patients for OSA given that all variables are objective and readily accessible in the electronic medical record. Further, there is promising data that good compliance to CPAP may improve insulin sensitivity, reduce systemic inflammation and oxidative stress, and reduce the global cardiovascular disease risk in patients with severe OSA and metabolic syndrome.[xv] In the present study, we will explore the predictors of OSA in consecutive patients with hypertension from a general medicine clinic. The primary objective will be to determine the accuracy of metabolic syndrome as a screening test for OSA. The secondary objective will be to compare the accuracy of metabolic syndrome as a screening test for OSA with other predictors such as the Berlin Questionnaire.

B. Study Design and Statistical Analysis

We will involve consecutive patients with established hypertension as documented in the medical record and according to current guidelines.[xvi] Detailed demographic data will be collected: age, gender, height, weight, waist circumference, triglyceride levels, HDL levels, fasting blood glucose, medications We will collect data on the relative importance of the traditional risk factors for

OSA,[7] including age of 40 to 70 years, male gender, and the presence of snoring and obesity, Berlin Questionnaire findings, and the presence of resistant hypertension and the metabolic syndrome. We will calculate the sensitivity and specificity along with the positive and negative predictive values for each of these clinical parameters as compared to data obtained from the overnight PSG, which is considered the 'gold standard' for diagnosis of OSA. We will calculate the accuracy (percentage of the total that are classified correctly) of the metabolic syndrome and Berlin Questionnaire as screening tests for OSA and compare them using the chi-square test. The quantitative variables will be expressed as the mean $\pm$ SD. The comparison of continuous variables between patients with and without OSA will be performed using the Student *t* test. Categorical variables are expressed as frequency distribution and will be compared using the chi-square test.

To determine the sample size, I used my primary objective which is to show that metabolic syndrome has an accuracy > 72%. Using data from Drager at al,[13] I estimated that the likely accuracy would be 82%. I then performed a one-sample chi-square test to calculate sample size comparing .72 to .82. My calculated sample size is 148 subjects. If 10% of patients offered PSG agree to the study, will need to screen 1480 patients

C. Study Procedures

Subjects will undergo an attended diagnostic overnight polysomnography using standard techniques and scoring criteria[xvii] (Monet SLP-Embla or Embla Titanium). Polysomnography will consist of continuous recording of EEG, electrooculography, electromyography, ECG, thoracic and abdominal impedance belts for respiratory effort, thermistors for nasal and oral airflow, pulse oximetry, and tracheal microphone for snoring. Polysomnograms will be scored manually according by a Board Certified polysomnographer using Somnologica software to established criteria. Apnea was identified by a complete cessation of airflow for $\geq$10 s; hypopnea was defined as a discernible reduction in tidal volume and

airflow accompanied by a decrease in oxyhemoglobin saturation ≥ 3% or by an EEG-recorded arousal, persisting for ≥ 10 s. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep.

This system is safe, comfortable, and permits subjects the full range of their normal nocturnal activities, including moving about in bed and using the bathroom.

D. Study Drugs

N/A

E. Medical Devices

See section C

F. Study Questionnaire

Berlin Questionnaire - See Appendix 1.

As previously described[12], predetermination of a high risk and lower risk of OSA using the Berlin Questionnaire was determined on the basis of the responses in 3 symptom categories. In category 1, high risk was defined as persistent symptoms (≥3 to 4 times/week) for ≥2 questions about snoring. In category 2, high risk was defined as persistent (≥3 to 4 times/week) daytime tiredness or fatigue. In category 3, high risk was defined as a history of high blood pressure or a body mass index ≥30 kg/m2. To be considered at high risk of OSA, a patient had to qualify for ≥2 symptom categories. Those who denied having persistent symptoms or who qualified for only one symptom category were placed in the lower risk group.

G. Study Subjects

We will involve consecutive patients with established hypertension as

documented in the medical record and according to current guidelines.[xviii] The patients will be excluded for a previous diagnosis of OSA, respiratory disorder other than OSA, neurologic lesions, and the regular use of sedative medication or alcohol.

The metabolic syndrome will be diagnosed according to the National Cholesterol Education Program, Adult Treatment Panel III, if 3 of 5 factors were present as follows: (1) waist circumference (≥102 cm in men and ≥88 cm in women); (2) triglycerides ≥150 mg/dl or patient receiving specific drug treatment; (3) high-density lipoprotein cholesterol ≤40 mg/dl in men and ≤50 mg/dl in women or receiving specific drug treatment; (4) arterial blood pressure of ≥130 or 85 mm Hg systolic and diastolic blood pressure, respectively, or receiving antihypertensive drug treatment; and (5) fasting glucose of ≥100 mg/dl or receiving specific drug treatment.[xix]

Resistant hypertension will be defined as blood pressure that remained greater than the goal of ≥140/90 mm Hg despite the concurrent use of 3 antihypertensive agents of different classes. In addition, resistant hypertension will also considered present when the blood pressure is controlled with the regular use of ≥3 medications.[xx]

H. Recruitment of Subjects

All providers will be contacted asking if they are willing to participate in the study. If a provider does not want to participate, his or her patients will be excluded. Patient will be screened near the exit of the adult Ambulatory Medicine Clinic at Columbia University. All subjects with self-reported hypertension will be screened.

Inclusion Criteria:

–Established diagnosis of HTN as documented in the medical record and according to current guidelines. [xxi]

–Age > 18

Exclusion Criteria:

–Previous diagnosis of OSA

–Respiratory disorder other than OSA

–Neurologic lesions

–The regular use of sedative medication or alcohol.

I. Confidentiality of Study Date

Each investigator will complete HIPAA training and GCP requirements. HIPAA guidelines will be explained to the subjects. All information associated with the patient will remain confidential. Patient information will be coded and stored in a secure location that is only available to the investigators.

J. Potential Conflict of Interest

None

K. Location of Study

Columbia University Ambulatory Internal Medicine Clinic

L. Potential Risks

There are no specific risks associated with the diagnostic sleep study, which is being used in accordance with the approved labeling, other than a possible breach of confidentiality, the mask may also be uncomfortable and reduce the quality of sleep initially, or allergic reaction to the medical tape of adhesive used to secure the electrodes to the patient.

M. Potential Benefits

Patients who are determined to be at high risk for OSA may obtain a definitive diagnosis and receive treatment, which may decrease their symptoms and lead to improved health outcomes.

N. Alternative Therapies

N/A

O. Compensation to Subjects

None

P. Costs to Subjects

Subjects and their insurance providers will incur the costs of the sleep study and any subsequent treatment.

Q. Minors as Research Subjects

N/A

R. Radiation or Radioactive Substances

N/A

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Appendix 1: Berlin Questionnaire

Height _____ m Weight _____ kg Age_____ Male/Female

Please choose the correct response to each question.

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Category 1

1. Do you snore?

a. Yes

b. No

c. Don't know

If you snore:

2. Your snoring is:

a. Slightly louder than breathing

b. As loud as talking

c. Louder than talking

d. Very loud—can be heard in adjacent rooms
3. How often do you snore?
a. Nearly every day
b. 3–4 times a week
c. 1–2 times a week
d. 1–2 times a month
e. Never or nearly never
4. Has your snoring ever bothered other people?
a. Yes
b. No
c. Don't know
5. Has anyone noticed that you quit breathing during your sleep?
a. Nearly every day
b. 3–4 times a week
c. 1–2 times a week
d. 1–2 times a month
e. Never or nearly never
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Category 2
6. How often do you feel tired or fatigued after your sleep?
a. Nearly every day
b. 3–4 times a week
c. 1–2 times a week
d. 1–2 times a month
e. Never or nearly never
7. During your waking time, do you feel tired, fatigued, or not up to par?
a. Nearly every day
b. 3–4 times a week
c. 1–2 times a week
d. 1–2 times a month
e. Never or nearly never
8. Have you ever nodded off or fallen asleep while driving a vehicle?
a. Yes
b. No
If yes:
9. How often does this occur?

a. Nearly every day
b. 3–4 times a week
c. 1–2 times a week
d. 1–2 times a month
e. Never or nearly never

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Category 3

10. Do you have high blood pressure?
a. Yes
b. No
c. Don't know

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Scoring Berlin Questionnaire

Adapted from table 2 in Netzer *et al*.7

The questionnaire consists of three categories related to the risk of having OSA.

Categories and scoring:

Category 1: items 1, 2, 3, 4, and 5

Item 1: If *yes* is the response, assign 1 point.

Item 2: If *c* or *d* is the response, assign 1 point.

Item 3: If *a* or *b* is the response, assign 1 point.

Item 4: If *a* is the response, assign 1 point.

Item 5: If *a* or *b* is the response, assign 2 points.

Category 1 is positive if the total score is 2 or more points.

Category 2: items 6, 7, and 8 (item 9 should be noted separately)

Item 6: If *a* or *b* is the response, assign 1 point.

Item 7: If *a* or *b* is the response, assign 1 point.

Item 8: If *a* is the response, assign 1 point.

Category 2 is positive if the total score is 2 or more points.

Category 3 is positive if the answer to item 10 is yes *or* if the BMI of the patient is greater than 30 kg/m^2.

High risk of OSA: two or more categories scored as positive

Low risk of OSA: only one or no category scored as positive [Context Link]

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